



# Ewing sarcoma

Recommendations from the society for diagnosis and therapy of  
haematological and oncological diseases

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## **Publisher**

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# Ewing sarcoma

**Date of document:** July 2023

**Compliance rules:**

- [Guideline](#)
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## 1 Summary

Ewing sarcoma is the second most common malignant bone-associated tumor of childhood, adolescence and young adulthood. Genetic characteristics are balanced translocations between a gene of the TET family (*EWSR1*, *FUS*) with a gene of the transcription factor coding ETS family (*FLI1*, *ERG*, *ETV1*, *ETV4*, *FEV*). The previously delineated entities "Askin tumor" and "peripheral primitive neuroectodermal tumor" have now merged into the "Ewing tumor family." Many other tumors designated as "Ewing-like" are also currently treated as Ewing sarcomas. However, some of the extremely rare round cell sarcomas with other translocations are certainly not Ewing sarcoma. This, as well as inclusion in appropriate studies and registries, seems reasonable, also to better understand the entities.

Ewing sarcoma is always a highly malignant tumor. Without systemic therapy, >90% of patients die as a result of (secondary) metastatic disease. Under risk-adapted, multimodal therapy, 3-year survival rates are between 50 and 80%.

## 2 Basics

### 2.1 Definition and basic information

Classical Ewing sarcomas are histologically characterized by a so-called small-round-blue cellular picture of cells with narrow cytoplasm and rounded nuclei with uniform chromatin. Immunohistochemically, almost all Ewing sarcomas show a strong expression of the CD99 antigen; furthermore, an expression of neural markers such as synaptophysin is often detected. Particularly in young adults, (partially) CD99-positive round-blue cell tumors with translocations of *CIC* or *BCOR* or without evidence of a specific translocation are not infrequently diagnosed.

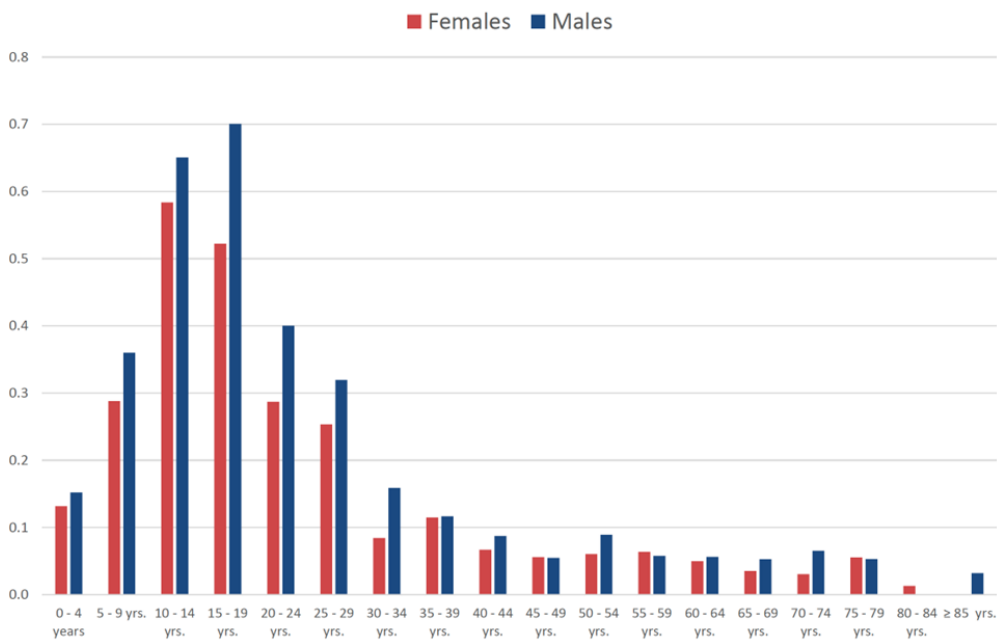
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### 2.2 Epidemiology

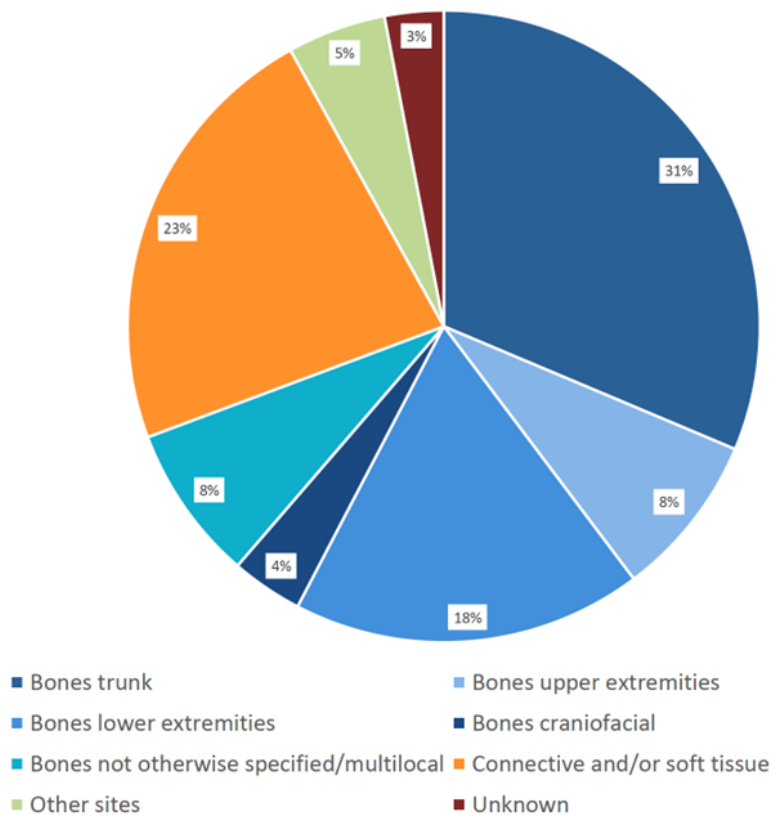
Ewing sarcoma is a rare malignant tumor with an annual incidence of approximately 0.15/100,000 individuals (crude disease rate). In Germany, 1334 cases were recorded in the state cancer registries or the German Childhood Cancer Registry nationwide between 2010 and 2019, of which 577 were in women and girls. A clear age peak is in the 2nd centile of life, males are slightly more frequently affected in all age groups ([Figure 1](#)). The median age at onset is 20 years.

A good two-thirds of the tumors originate from bone, about a quarter from connective tissue, subcutaneous and other soft tissues (Figure 2). Relative 10-year survival rates are around 62% for those under 20 years of age, 45% for those aged 20-39 years, and 34% for those over 40 years.

**Figure 1: Annual incidence rates of Ewing sarcoma in Germany by age and sex (per 100,000 persons, 2010-2019)**



**Figure 2: Localization of Ewing sarcomas (relative frequencies), Germany, 2010-2019**



## 2.3 Pathogenesis

Genetic characteristics are balanced translocations between a gene of the TET family (*EWSR1*, *FUS*) with a gene of the transcription factor coding ETS family (*FLI1*, *ERG*, *ETV1*, *ETV4*, *FEV*). In more than 85% of tumors, a t(11;22) (q24;q12) with formation of the *EWSR1-FLI1* fusion gene is present. 5-10% of tumors show a translocation t(21;22)(q22;q12) with fusion of *EWSR1* and *ERG*; the other translocation types occur less frequently. Especially in young adults, (partially) CD99-positive round-blue cell tumors with translocations of *CIC* or *BCOR* or without evidence of a specific translocation are not infrequently diagnosed.

## 2.4 Risk factors

Risk factors for the development of Ewing sarcoma are not known. The ethnic background seems to be relevant, as Ewing sarcoma develops most frequently in Caucasians. Here, the incidence in the typical age group is about 1-3/1,000,000, that for the Asian population is about 0.8/1,000,000 and Ewing sarcoma is almost unknown in the African population (incidence about 0.2/1,000,000). One possible explanation for this is the binding of the EWSR-FLI1 transcription factor to specific GGAA motifs in promoter regions. In one study, an intermediate GGAT motif was shown to be converted to a GGAA motif by a specific allelic SNP variant in Ewing sarcoma patients, resulting in upregulation of *EGR2* with subsequent cell proliferation and growth. The allele for the GGAA motif is more prevalent in the Caucasian population than in the Black African population.

Various studies have shown that about 13% of patients with Ewing sarcoma carry germline mutations or genetic variants in DNA repair genes that lead to inactivation of the affected gene (example BRCA1).

Rarely, Ewing sarcoma occurs in the context of tumor disposition syndromes, such as mutations in the *TP53*, *RET*, and *PMS2* genes.

## 3 Prevention and early detection

There is no evidence for effective measures for prevention. Early detection is only possible when malignancy is included in differential diagnostic considerations, in cases of long-lasting pain (> 4 weeks), without constitutional symptoms, and often initially triggered by trivial trauma.

## 4 Clinical signs and symptoms

The typical leading symptoms are non-specific: pain - usually pain on exertion that initially increases in intensity, later also pain at rest - and occasionally palpable swelling in the bone area. If the diagnosis is made too late, a pathological fracture may occur in rare cases. The most common sites are the pelvis, femur, humerus, ribs and clavicle. In 20-25% of patients, metastases are detectable at the time of initial diagnosis. Predilection sites for metastases, in descending frequency, are the lungs, other bones, and bone marrow. Patients with rare involvement of regional lymph nodes have an increased risk of distant metastases.

## 5 Diagnosis

### 5.2 Diagnostic procedures

In addition to detailed history and physical examination, the following investigations should be performed for verification/staging. The first step is to confirm the suspected clinical and / or imaging diagnosis, see [Table 1](#).

**Table 1: Diagnostics for new-onset symptoms**

- X-ray of the affected bone and adjacent joints in 2 planes
- Magnetic resonance imaging (MRI) of the affected region with contrast medium
- Biopsy
  - Histology showing the image of a small-round-blue cell tumor
  - Immunohistochemistry to exclude other lineage differentiation (including myogenic, lymphocytic, myeloid, melanocytic, or epithelial), detect CD99, and neural marker expression, if applicable
  - Molecular pathology to detect a specific translocation (FISH, RNA sequencing or RT-PCR)
  - NGS-based methods are also already used in some specialized centers and allow to detect possibly not yet known or recently identified fusions

The biopsy should be performed by surgeons experienced in sarcoma surgery, taking into account the subsequent surgical access route. Even in case of a CT- or MRI-targeted biopsy, a specialized surgeon must be involved in the diagnosis from the very beginning.

Biopsy of metastases is strongly recommended.

If the diagnosis of Ewing sarcoma is confirmed on biopsy, staging is indicated, see [Table 2](#), focussing on the most common locations of metastases in patients with Ewing sarcoma.

**Table 2: Staging diagnostics**

- Computed tomography (CT) of thorax and abdomen
- Whole-body PET-CT or PET-MRI
- If indicated, skeletal scintigraphy
- Bone marrow puncture with biopsy and aspirate
- Further imaging procedures depending on clinical symptoms

Further diagnostic procedures in preparation of therapy are shown in [Table 3](#).

**Table 3: Further diagnostics**

#### Laboratory

- CBC and leukocyte differentiation
- Serum chemistry
- Coagulation parameters
- Urine status
- Hormone status
- Virology (Hepatitis A-C, CMV, EBV, HIV)

#### Organ function

- Echocardiography, electrocardiography
- Pulmonary function (in patients with pulmonary metastases)

Molecular analysis of bone marrow samples to detect tumor cells increases the detection rate of metastases, but is not an independent prognostic parameter.

### 5.4 Prognostic factors

Numerous prognostic factors have been identified. The most important are metastases at initial diagnosis, tumor size ( $\geq$ / $<$  200ml), tumor location, serum LDH, age ( $>$ / $<$  15 years), general symptoms and histological response to neoadjuvant chemotherapy (vital cell count). To date,

there is no internationally accepted risk score. This complicates the comparability of clinical trials.

The results of the international Ewing2008 trial have provided the following insights. Patients with localized disease but an unfavorable histologic response to neoadjuvant induction chemotherapy benefit from adjuvant high-dose chemotherapy with busulfan-melphalan, compared to adjuvant standard chemotherapy. Patients with pulmonary metastases, on the other hand, do not benefit from busulfan-melphalan high-dose chemotherapy, compared to standard therapy with VAI combined with whole-lung irradiation. Results of a phase III trial also showed no benefit of high-dose therapy with treosulfan-melphalan in disseminated (and thus high-risk) disease, except in patients < 14 years. Thus, high-dose chemotherapy has become an integral part of the treatment plan in localized but high-risk disease.

The EuroEwing 2012 trial randomized patients to systemic treatment with VIDE versus VDC/IE. Treatment with VDC/IE was shown to be of overall benefit without more side effects, which is why the latter has become the international standard.

In the current European iEuroEwing study, patients are divided into two groups according to clinical risk factors, see [Table 4](#).

**Table 4: Risk classification according to iEuroEwing**

Risk group	Criteria	3-year OS (%)
Standard-Risk	<ul style="list-style-type: none"> <li>Localized tumor SR</li> <li>Localized tumor HR</li> </ul>	1. % 78%
High-Risk	<ul style="list-style-type: none"> <li>Disseminated disease</li> </ul>	30%-68%

## 6 Therapy

The most effective causal therapeutic procedures are systemic tumor therapy, surgery and/or radiation. These should be performed in specialized centers and, whenever possible, in the framework of clinical trials.

Since the early 1990s, the following sequence has become standard of care:

- Neoadjuvant chemotherapy
- Local therapy (surgery and/or radiotherapy)
- Adjuvant chemotherapy.

Intensification of therapy has not resulted in improved survival for high-risk tumors. The concept of intensifying therapy is therefore abandoned in the current iEuroEwing study. The total treatment duration is at least 12 months. All patients will receive a total of 9 cycles of chemotherapy, alternating 5 courses of VDC (vincristine, doxorubicin, cyclophosphamide) and 4 courses of IE (ifosfamide and etoposide), according to the iEuroEwing protocol after completed staging. During this time, patients' own hematopoietic stem cells are harvested. Further therapy is risk-adjusted in the two different therapy groups.

### 6.1 Risk-adjusted therapy

After neoadjuvant chemotherapy using VDC (vincristine, doxorubicin, and cyclophosphamide) and IE (ifosfamide and etoposide) in both risk groups, local therapy and further systemic therapy after local therapy are risk-adjusted.

### **6.1.1 Standard risk**

Induction therapy with VDC/IE regimen is followed by local surgical resection or, depending on the findings, definitive or additional radiotherapy. The iEuroEwing study is currently evaluating the effects of different radiotherapy doses on toxicity, survival, and risk of local recurrence by dividing patients into four risk groups and randomizing them to a lower and a higher dose level within each group. Following local therapy, patients receive 5 additional alternating cycles of IE and VC. The benefit of six months of oral maintenance therapy with VinoCyc (vinorelbine and cyclophosphamide) is also currently being evaluated in the iEuroEwing trial. Results from the EURO-E.W.I.N.G 99 and Ewing2008 trials have also shown that patients with a poor histologic response to neoadjuvant chemotherapy benefit from high-dose therapy with busulfan-melphalan followed by autologous stem cell transplantation.

### **6.1.2 High-Risk**

Patients with disseminated disease at diagnosis also receive the alternating 9 courses of VDC/IE. This is followed by local therapy (surgery and/or radiotherapy). Concurrent to the first three cycles of the subsequent systemic therapy, consisting of five alternating courses of IE and VC, radiotherapy is continued. The iEuroEwing study is also evaluating the benefit of six months of oral maintenance therapy with VinoCyc in this patient group. Results of the completed Ewing2008 trial showed no benefit of high-dose therapy with busulfan-melphalan followed by autologous stem cell therapy over standard therapy with VAC in this patient group.

## **6.2 Treatment modalities**

### **6.2.1 Systemic therapy**

Multicenter, international studies have established combinations of four or five drugs as the standard. They are applied at intervals of two weeks +/- 3 days. The most active substances are cyclophosphamide, doxorubicin, etoposide, ifosfamide and vincristine. Etoposide has been shown to improve the prognosis of patients with primarily non-metastatic disease. Oral maintenance therapy with VinoCyc is given over a period of 6 months.

All patients will receive a total of 9 cycles of chemotherapy, alternating 5 courses of VDC (vincristine, doxorubicin, cyclophosphamide) and 4 courses of IE (ifosfamide and etoposide), according to the iEuroEwing protocol. During this time, autologous hematopoietic stem cells are harvested for eventual high-dose therapy and stem cell transplantation.

Further improvement of long-term results can possibly be achieved by shortening the treatment intervals. Intensification of chemotherapy by increasing the dose of alkylating agents does not improve the results.

### **6.2.2 Autologous stem cell transplantation**

Autologous stem cell transplantation allows intensification of myelosuppressive chemotherapy and may lead to an increase in remission rates in cancer patients. It was shown in a randomized phase III study that Ewing sarcoma patients with a localized large tumor (> 200ml) and poor histological response benefit from high-dose chemotherapy with busulfan-melphalan followed by autologous stem cell transplantation.

### **6.2.3 Side effects of systemic tumor therapy**

The most frequent severe side effects (grade 3/4) result from bone marrow toxicity with leukocytopenia, neutropenia, thrombocytopenia and anemia. To reduce the risk of infections in neutropenia, prophylactic administration of G-CSF is possible.

Severe non-hematologic side effects are mainly nausea/vomiting, mucositis, cardio-, nephro-, and neurotoxicity. Elderly patients often develop significantly more severe side effects than children. In case of ifosfamide-induced encephalopathy, preventive intravenous administration of methylene blue should be given before the next cycle.

Side effects of radiotherapy depend on the localization and size of the irradiation field.

Patients with Ewing sarcoma have an increased risk of secondary neoplasms, especially as a consequence of antineoplastic therapy. Increased incidence of sarcomas (non-Ewing) and carcinomas in the irradiation field, as well as myeloid neoplasms (AML, MDS) after high-dose therapy with alkylating agents and topoisomerase inhibitors have been reported.

### **6.2.4 Bisphosphonates**

In secondary osseous manifestations of malignancies, bisphosphonates or RANKL antibodies may reduce the risk of osseous complications and delay the progression of osseous metastasis. The Ewing2008 trial assessed whether adjunctive bisphosphonate therapy improves survival for patients with localized disease. No impact of bisphosphonates on survival was observed.

### **6.2.5 Local therapy of the primary tumor**

Surgery and radiotherapy are effective measures for local control. Retrospective analyses show an advantage for surgery the combination of surgery and radiotherapy.

#### **6.2.5.1 Surgical resection**

The goal of surgery is R0 resection. The technique and extent depend on the location and size of the primary tumor. Since the operation has a very high value in the treatment of the disease, it should be performed only by surgeons who have a great experience with these operations. Tumor debulking surgery should not be performed except in a few emergency cases. A challenge remains as to which imaging, initial or subsequent, should be used to guide resection margins. Primary localization in the pelvis is a particular multidisciplinary challenge.

#### **6.2.5.2 Radiotherapy**

Ewing sarcoma is a radiosensitive tumor. The indication for radiotherapy, using photons or protons, is based on the result of surgical resection and the histologic response to preoperative systemic therapy. Radiotherapy is often given as part of a trimodal treatment approach. In cases of inoperability, definitive radiotherapy is an alternative local therapy. Preoperative radiotherapy is given if surgical resection with close margins is expected or if tumor progression occurs under primary chemotherapy. Postoperative radiotherapy is indicated after R1 or R2 resection, as well as in the case of R0 resection when >10% vital tumor cells are found in the resected tumor tissue, or a tumor volume of >200ml at the time of diagnosis in a large primary tumor. Other situations in which patients benefit from postoperative radiotherapy include surgery of the tumor prior to chemotherapy or in the presence of pathologic fractures. Furthermore, postoperative irradiation is performed in primary pelvic tumors and often also in specific

locations such as ribs and pleura, as well as spinal, paraspinal, parameningeal and craniofacial sites.

Especially in complex situations, highly conformal radiation techniques such as intensity-modulated radiotherapy (IMRT) or proton therapy (PT) are used because they allow high intensity and good normal tissue sparing. Also in localized stages, radiotherapy is usually combined with systemic therapy. For radiotherapy, total cumulative doses of 45 Gray (Gy) to about 60 Gy are common. Higher doses appear to show improved tumor control, but are currently not the standard of care. In addition to the actual tumor area, safety margins of 1-2 cm are now usually included to also target subclinical lesions. Field reductions to the high-risk area such as tumor bed or residual tumor are then often performed during the treatment series. The current iEuroEwing study is evaluating the effect of different radiation doses, or dose escalation of radiation, on toxicity, survival, and risk of local recurrence. Patients are divided into four risk groups and randomized within the groups to a standard and a higher dose level.

### **6.2.6 Local therapy of metastases**

Resection of pulmonary metastases is associated with an improved prognosis. Resection of pulmonary metastases is recommended in patients with primary pulmonary metastases, if pulmonary metastases are still detectable after induction chemotherapy. The Euro E.W.I.N.G. 99 and Ewing2008 studies failed to show an advantage of high-dose chemotherapy with busulfan/melphalan in patients with pulmonary metastases compared to standard VAI therapy combined with whole-lung irradiation. Patients with multiple bone metastases also benefit from the most extensive local therapeutic treatment possible.

## **6.3 Special situations**

### **6.3.1 Recurrence**

Prognosis in recurrence is unfavorable. The 5-year survival rates are less than 20%. The most important prognostic factor is the time from initial diagnosis to recurrence. Patients with an interval < 2 years have a 5-year survival rate of 7%, in contrast to 29-30% with an interval > 2 years. Positive prognostic parameters include local recurrence only, isolated pulmonary recurrence, young age, and low serum LDH.

An experimental curative therapeutic approach in relapse is intensification of chemotherapy followed by autologous or allogeneic stem cell transplantation, while a survival benefit has not yet been shown with allogeneic stem cell transplantation.

The randomized rEECur trial tested chemotherapy approaches for relapsed disease. The initial interim analyses of the rEECur trial showed that high-dose ifosfamide was more effective in terms of survival without causing increased toxicity. The already closed study arms irinotecan/temozolomide, gemcitabine/docetaxel, and topotecan/cyclophosphamide were also effective therapeutic agents, but they should not be used first-line ([EudraCT no. 2014-000259-99](#)). Molecularly targeted therapies, for example a phase I trial with TK216, a molecular inhibitor of the downstream effect of EWS-FLI1, are also the subject of current research.

Another therapeutic approach is the administration of anti-GD2 antibodies, since GD2 is partially expressed in Ewing sarcomas. Other studies in Europe are looking at metformin as maintenance therapy (NCT04758000), administration of the tyrosine kinase inhibitor regorafenib (NCT05395741) or anti-GD2 CAR T cells (NCT03373097) in relapse.

Children and adolescents with relapsed disease can be enrolled in the INFORM (INdividualized Therapy FORe Relapsed Malignancies in Childhood) program for molecular workup. There, tumor

samples are molecularly characterized according to current standards. Physicians treating the patients may use the information obtained for targeted recurrence therapy. In addition to the INFORM study, the NCT Master Program for adults is offered in Heidelberg.

### **6.3.2 Extraosseous manifestations**

Extraosseous manifestations are less common, but account for 20-25% of Ewing sarcomas in adults. A painless swelling is typical. Other symptoms result from infiltration of adjacent structures.

The median age at onset is 20 years. Common primary sites are thorax (synonym: Askin tumor), lower extremities, paravertebral region, and retroperitoneum. Extraosseous Ewing sarcomas can occur in almost any part of the body.

At initial diagnosis, pulmonary and / or osseous metastases are often already present. The therapeutic concepts are identical to those of primary osseous Ewing sarcoma.

## **7 Rehabilitation**

Surgery, radiotherapy and systemic tumor therapy may have sequelae of varying severity, which require targeted rehabilitative measures. In addition, there are the special psychological and social effects of cancer in children and adolescents or adolescents and young adults.

Patients should be informed at an early stage of treatment about the various options of outpatient and inpatient rehabilitation as well as other claims arising from social law. With regard to the rehabilitation clinic, the patient's preferences should be taken into account (§9 SGB IX). Nevertheless, a recommendation should be made for a clinic with an oncological focus, which has special experience in the age group of Ewing sarcoma patients. Furthermore, experience with patients after major tumor surgery of the skeletal system is useful in order to ensure targeted physiotherapy.

## **8 Follow-up**

The follow-up of patients with Ewing sarcoma is structured. The goals are early diagnosis of recurrence with the aim of increasing the chance of cure, detection of side effects of therapy and prevention. Long-term side effects of tumor therapy include endocrinopathies including fertility, cardiotoxicity, nephrotoxicity, neurotoxicity, neurocognitive deficits, osteoporosis, psychosocial problems, and second neoplasms. The individual risk for clinically relevant late effects depends on the type and intensity of therapy administered, as well as individual risk factors including lifestyle.

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## 10 Active studies

- iEuroEwing: International Randomised Controlled, Phase 3 Trial for the Treatment of Newly Diagnosed Ewing Sarcoma Family of Tumors (EudraCT number: 2019-004153-93).
- Italy: Observational Study on Skeletal Ewing's Sarcoma (EWOss) (NCT04845893).
- France: Long Term Brain Toxicity of Chemotherapy in Patients Treated for a Bone Tumor During Childhood or Adolescence (NCT05071001).
- Italy: Dietary Habits, Metabolome, Immune Profile and Microbiota in Patients With Bone Sarcoma (NCT04735289).
- France: Combination of Pembrolizumab and Cabozantinib in Patients With Advanced Sarcomas (PEMBROCABOSARC) (NCT05182164).
- Sweden: Use of GnRHa During Chemotherapy for Fertility Protection (NCT05328258).
- France: A Phase II Study Evaluating Efficacy and Safety of Regorafenib in Patients With Metastatic Bone Sarcomas (REGOBONE) (NCT02389244).
- France: Efficacy and Safety of Regorafenib as Maintenance Therapy After First-line Treatment in Patients With Bone Sarcomas (REGOSTA) (NCT04055220).
- Spain: Multicohort, Phase II Trial of Trabectedin and Low-dose Radiation Therapy in Advanced/Metastatic Sarcomas (SYNERGIAS) (NCT05131386).
- France: A Post-treatment Program to Identify and Manage Complications Related to Oncology or Hematology Treatments in Cancer Survivors. (PASCA) (NCT04671693)
- Registries
  - iEuroEwing: International Randomised Controlled, Phase 3 Trial for the Treatment of Newly Diagnosed Ewing Sarcoma Family of Tumors.
  - INFORM: INdividualized therapy FORe Relapsed Malignancies in Childhood
- Current phase II/III relapse studies in Germany:

- rEECur: An international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (EudraCT Number: 2014-000259-99).
- CAMPFIRE: A Study of Abemaciclib (LY2835219) in Participants With Ewing's Sarcoma NCT05440786).
- Study Of Palbociclib Combined With Chemotherapy In Pediatric Patients With Recurrent/Refractory Solid Tumors NCT03709680 *in Germany starting 2023*
- Current phase I/II relapse studies in Europe:
  - Italy: Anti-GD2 CAR T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma or Other GD2-positive Solid Tumors (NCT03373097).
  - Italy: Metformin as Maintenance Therapy in Patients With Bone Sarcoma and High Risk of Relapse (Metform-Bone) (NCT04758000).
  - Poland: Regorafenib in Patients With Refractory Primary Bone Tumors (Regbone) (NCT05395741).

## 14 Links

The Cooperative Ewing Sarcoma Study Center (CESS) offers counseling for affected individuals, family members and treating physicians: <https://kinderklinik3.uk-essen.de/patienten-angehoerige/haemato-onkologie/studien/>

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**16 Disclosure of Potential Conflicts of Interest**

according to the [rules of DGHO, OeGHO, SGH+SSH, SGMO](#)

Author	Employer <sup>1</sup>	Consulting / Expert opinion <sup>2</sup>	Shares / Funds <sup>3</sup>	Patent / Copyright / License <sup>4</sup>	Fees <sup>5</sup>	Funding of scientific research <sup>6</sup>	Other financial relations <sup>7</sup>	Personal relationship with authorized representatives <sup>8</sup>
Hardes, Jendrik	Universitätsklinikum Essen	No	No	No	No	Yes Implantcast, Buxtehude	Yes Implantcast, Buxtehude, Vereinigung Kinderorthopädie, LMU München, Arbeitsgemeinschaft Endoprothetik	No
Brodowicz, Thomas	Medizinische Universität Wien	No	No	No	No	No	No	No
Dirksen, Uta	Universitätsklinikum Essen	No	No	No	No	No	No	No
Hartmann, Wolfgang	Universitätsklinikum Münster	No	No	No	No	No	No	No
Hummel, Yvonne	Kantonärztlicher Dienst Kanton Solothurn Kantonärztlicher Dienst Kanton Aargau	Yes Leiterin des Vertrauensärztlichen Dienstes der Krankenversicherung Sanitas, Schweiz, bis 12/2019	No	No	No	No	No	No
Kersting, Josephine	Universitätsklinikum Essen	No	No	No	No	No	No	No
Kraywinkel, Klaus	Robert Koch-Institut, Berlin	No	No	No	No	No	No	No
Reichardt, Peter	Helios Klinikum Berlin-Buch GmbH	Yes Bayer, Novartis, Roche, Deciphera, Mundibio-pharma, Pharma-Mar, Blueprint Medicines, GSK, Boehringer Ingelheim	No	No	Yes Clinigen, Deciphera, Pharma-Mar, Boehringer Ingelheim	No	No	No
Timmermann, Beate	Westdeutsches Protonentherapiezentrum Essen (WPE)	No	No	No	No	No	No	No

Legend:

<sup>1</sup> - Current employer, relevant previous employers in the last 3 years (institution/location).

<sup>2</sup> - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care

*industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.*

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<sup>4</sup> - *Relates to drugs and medical devices.*

<sup>5</sup> - *Honoraria for lecturing and training activities or paid authors or co-authorships on behalf of a company in the health care industry, a commercially oriented contracting institute or an insurance company.*

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<sup>7</sup> - *Other financial relationships, e.g., gifts, travel reimbursements, or other payments in excess of 100 euros outside of research projects, if paid by an entity that has an investment in, license to, or other commercial interest in the subject matter of the investigation.*

<sup>8</sup> - *Personal relationship with an authorized representative(s) of a healthcare company.*