STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR EWING SARCOMA

Ewing Sarcoma Roadmap V 1.0 2021

Based on ERNPAEDCAN backbone documents. Consortium structure and basic workflow and elements are harmonized to other ERN Networks.

The ERN PaedCan received funding by the European Union's Health Programme (2014-2020), grant agreement nr. 847032.

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1-1. Background on type of disease (search term and code of ICCC)

ICD-10: C40-41
UMLS Ewing Sarcoma, Ewing`s Sarcoma, Ewing Family of Tumours
MeSH Sarcoma, Ewing [C04.557.450.565.575.650.800]
Neoplasms [C04]
Neoplasms by Histologic Type [C04.557]
Neoplasms, Connective and Soft Tissue [C04.557.450]
Neoplasms, Connective Tissue [C04.557.450.565]
Neoplasms, Bone Tissue [C04.557.450.565.575]

Ewing Sarcoma				
Site group	ICD C 40-41	C04.557.450.565.575.650.800		

Ewing sarcoma

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1-2. Summary of current treatment strategy

Ewing Sarcoma (EWS) is a highly malignant sarcoma of bone and soft tissue that arises predominately in adolescent Caucasians, with a higher incidence in males compared to females. EWS is characterized by a specific and pathognomonic TET-ETS (in 85% a EWSR1- ETS) translocation and serves as a paradigm for a translocation-positive solid malignancy with low mutation frequency. Approximately 25% of the patients present with detectable metastases at diagnosis, which in about 50% are restricted to the lung. Patients with pulmonary metastases show a more favourable outcome than patients with other metastases [1]. Patients with bone/bone marrow involvement, combined lung plus bone/bone marrow metastases or other sites show a poor outcome [2] [3]. Lymph node metastases are uncommon and, in most cases, associated with disseminated disease in elderly patients [4] [5]. The prognosis depends on the presence of metastases, age, size, and site [2]. Today more than 70% of patients with localized disease can be cured by a multimodal therapy with a multidrug chemotherapy regimen and local treatment consisting of surgery and/or radiotherapy [6] [7] [8].

While multi-agent chemotherapy is the standard of care and has been structurally evaluated in prospective clinical trials, the best approach for local control remains a matter of discussion and may depend on site and size of the tumour. Retrospective data analyses in large cohorts of EWS patients indicated that radiotherapy alone is associated with a higher rate of local recurrence and unadjusted risks of any event [9], while it is additionally associated with a risk for the development of radiotherapy-induced secondary malignancies. In a large observational studies the value of combined modality local treatment following marginal or intralesional resection in large primaries or poor histological response after induction chemotherapy has been described [10] [11] [12]. However, in differential analyses of tumour sites, the picture becomes less clear. An analysis of thoracic wall tumours showed that mainly patients with intralesional resection benefit from additional radiotherapy [13]. In patients with non-sacral pelvic primaries combined local treatment seems to be of benefit for the patients [12] [14]. Today, most groups favour surgery or combined modality local treatment for most patients. Definitive radiotherapy is recommended in patients with non-resectable tumours and patients with disseminated disease [3] [9] [12]. Local therapy techniques have rapidly evolved with time with a technology leap in the past few years. Thus, results from retrospective studies may not reflect the outcomes that would be achieved today.

1-3 Definition of Potential Special diagnostic requirements

1-3.1. Describe standard stratifying diagnostics requirements

1-3.1.1. Laboratory

Mandatory:

- Full blood count (FBC) and differential white blood count.
- Basic renal and liver serum biochemistry
- Basic Serum electrolytes (incl. phosphate).
- ECG, cardiac function tests (echocardiography or MUltiGated Acquisition scan (MUGA)) with determination of left ventricular ejection fraction or shortening fraction.

Optional (according to institutional practice):

- Additional serum biochemistry
- GFR
- Urine profile

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- Coagulation profile
- Sex hormones, gonadotropins
- Pulmonary function tests
- Serum virology.

If possible, sperm cryopreservation is recommended in male patients of appropriate age [15].

If possible, preservation of ovarian tissue is recommended in female patients of appropriate age [16].

1-3.1.2. Imaging

Primary site

Plain X-ray
MRI or CT scan as indicated by anatomic position of the lesion

Staging

Exclusion of lung metastases:
Chest CT
Preferred
Whole body imaging:
Positron emission tomography (PET) CT or PET/MRI or 99mTC bone scan. If a PET MRI or 99mTC bone scan is performed a CT scan must be performed to exclude pulmonary metastases
Minimum
Chest CT with contrast with 1 mm slice sickness.
And CT Abdomen or MRI Abdomen
99mTC bone scan

Bone marrow biopsy (optional)

1-3.1.3. Definition of metastases

Bone

The description of bone metastases must include confirmation of bone scan, PET or plain radiography findings by MRI/CT scan. **Biopsies** of unclear lesions s sites are indicated and recommended.
Skip lesions within the compartment involved by the primary tumour are considered a loco-regional extension and are NOT regarded as disseminated disease.

Bone marrow (optional)

Aspirates are taken from ≥ 2 sites (2-5 ml EDTA); biopsy from ≥ 1 site: conventional cytology/histology. Please note: bone marrow biopsies must be taken from sites distant from the primary tumour. Bone marrow metastases are defined as light microscopic evidence of bone marrow involvement in any aspirate or trephine biopsy sample. Molecular evidence (i.e., by RT-PCR analysis) **alone**, is by definition **not** considered adequate for the diagnosis of metastatic bone marrow disease.

Pulmonary / pleural metastases

As a rule, one pulmonary/pleural nodule of > 1 cm is considered evidence of metastatic disease, according to RECIST criteria. Multiple nodules of > 0.5 cm are considered evidence of pulmonary/pleural metastases if there is no other clear medical explanation for these lesions. Some protocols also consider multiple nodules of >0.3 cm as questionable evidence of metastatic disease and biopsy is recommended. Pleural effusion in patients with chest wall tumours. In patients with large chest wall tumours, the value of pleura punction is unclear. Whether small effusions and no thickening of the pleura should be regarded as proof for lung/pleural metastases is also unclear. Some experts consider small effusions close to a tumour-bulk to represent loco-regional disease [17]. In an unclear situation it is recommended to consider that the respective site is affected

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by tumour cells and should be therefore included in local treatment concepts. The site(s), size, and number of involved sites are to be recorded. A tight follow up for lung lesions parallel to the systemic treatment is recommended.

Soft tissue metastases

Soft tissue lesions and regional lymph nodes may be detected by whole body FDG-PET- CT, FDG-PET-MRI or MRI and ultrasound. Please note that a FDG signal is usually only positive in lesions of more than >0.5 cm and is not tumour specific If indicated, additional abdominal CT or MRI of suspicious sites should be performed. Unclear **soft tissue lesions,** detected by clinical examination or imaging methods, should be **confirmed by biopsy.** Regional lymph node metastases are rare and additional ultrasound should be performed. In uncertain situations lymph node biopsy is recommended. Please note that a FDG-PET positive regional lymph node may be reactive. A tight follow up for soft tissue lesions parallel to the systemic treatment is recommended.

1-3.1.4. Pathology

Small round cell sarcoma

CD99 diffuse membranous expression

Gene fusion involving FET family of genes (usually *EWSR1*) and member of ETS family of transcription factors, most commonly *EWSR1-FLI1* (~85 - 90%)

1-4. Definition of Potential Special Treatment Interventions

1-4.1. Describe special disease condition and special Interventions

The current treatment of EWS is multidisciplinary. Primary EWS may present as a bone or a soft tissue tumour. Multidisciplinary management including systemic treatment and local treatment consisting of surgery, radiotherapy, or both has improved the survival of patients with localized EWS [18]. The best approach to achieve local control in sites as pelvis, thoracic wall, and multifocal tumours, however, remains controversial. Further challenging sites are spinal tumours, intracerebral tumours, and craniofacial tumours. Treatment decisions in these sites are challenging, as local treatment approaches may be associated with significant long-term sequelae. Evidence-based gold standards of local treatment approaches are not defined.
The most important goals of local treatment approaches are safety > function > cosmesis. And the large European Ewing Sarcoma study groups have agreed on basic standards for local therapy in Ewing Sarcoma. However local therapeutic approaches have been analysed retrospectively and a randomized clinical trial on local treatment procedures is lacking.

Further special treatment intervention may be high dose chemotherapy followed by re-transfusion of autologous haematopoietic stem cells in a selected group of patients. From a large phase 3 trial it is evident that patients with localized disease, poor histological response to induction chemotherapy and/or large primaries benefit from adjuvant high dose chemotherapy with busulfan and melphalan followed by re-transfusion of autologous hematopoietic stem cells.

Phase I/II clinical trials may be available for patients with Ewing sarcoma. Because phase I/II clinical trials are -per definition- not standard of care the evaluation on whether a child could and should be referred to a European centre that offers a trial must be integral part of a tumour-board discussion.

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1-5. Current European Standard Treatments as used within or recommended by the Euro Ewing Cooperative Ewing Sarcoma Study Group

Large randomized international clinical trials have been conducted in EUROPE by the EURO EWING group, the Cooperative Ewing Sarcoma Study Group, and the Italian Sarcoma Group/Scandinavian Sarcoma Groups. Members of these cooperative groups are part of the Ewing Sarcoma Roadmap team. Within this cooperation treatment guidelines have been defined:
If available, patients should be registered in one of the open multinational, multicentre clinical trials or registries, whenever feasible. We are aware that major hurdles are the enormous costs/involved country and administration and this document aims to provide guidance if clinical trial infrastructure is not available

A way to optimize treatment for patients in these countries is to offer recommendations by the reference networks.

1-5.1 Surgery- Guidelines

In order to diagnose a Ewing sarcoma a biopsy is mandatory
Rules for biopsy:
The biopsy may be performed as an open biopsy or needle biopsy. The biopsy channel must be in the planned operation field or radiotherapy field. A biopsy should be performed by an experienced surgeon or radiologist. If no open biopsy is performed a core needle should be used to get enough material for the diagnosis four core needle biopsies (at least 16G) are required to have enough material for histopathology and molecular analysis.
Surgery-general rules
Definitive surgery is to follow induction chemotherapy. This rule must not be violated, unless emergency surgical procedures are mandatory at diagnosis, e.g., in case of spinal cord compression. Careful planning of surgery is strongly recommended. **Patients should be referred to an experienced centre for their surgical treatment**. The European (Ewing) Sarcoma Reference Network offers central guidance in the planning of local therapy based on interdisciplinary tumour board discussions [12].

1-5.1.1 General rules for surgery

- Limb sparing surgery is achievable in most patients at least in specialized centres
- In all cases, adequate surgical removal (wide resection according to ENNEKING [19] is the appropriate goal.
- The biopsy channel must should be completely included in the surgical specimen
- "Debulking" intralesional manoeuvres are strongly discouraged.
- Wide excision with negative histological margins is necessary to optimize local control. Margins must be wide enough for optimal oncological control and narrow enough to maximize function.
- Resect all tissue which was originally **invaded** by tumour.
- Reconstructive surgical techniques should be applied wherever possible
- The surgeon should consider the putative comorbidity with chemotherapy and radiotherapy. Therefore, the treatment plan for the patient should be worked out in an interdisciplinary oncology core group.
- Surgery may be combined with additional radiotherapy before or usually after surgery in case of large tumour volume with extensive soft tissue extension, (expected) narrow margins, non-sacral pelvic primary tumours and/or poor histological response (≥ 10% viable tumour cells in the specimen). Postoperative radiotherapy should also be discussed if not all tissue contaminated by the tumour at diagnosis could be removed.
- The surgical specimen must be examined in cooperation by the surgeon and pathologist to define surgical margins and histopathological response.
- In case of residual lung disease after induction chemotherapy, surgical biopsies and/or removal of such lesions should be considered.

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- In patients with oligometastatic disease (2-5) surgical removal of extrapulmonary metastases may be considered individually[3].

1-5.2 Radiotherapy - Guidelines

Surgery is favoured whenever feasible. Radiotherapy as an active modality for assuring local control is used as definitive radiotherapy in inoperable tumours or in combination with surgery either pre- or postoperatively.

1-5.2.1 General rules for radiotherapy

- Preoperative radiotherapy is indicated in case of clinical progression of tumour extension or anticipated marginal or intralesional resection. In some centres preoperative radiotherapy is performed in patients with large primaries when the need of additional radiotherapy is expected. According to the results of a large European clinical trial patients with large primaries where histological response cannot be used for stratification high dose chemotherapy with busulfan and melphalan is recommended. Early radiotherapy should only be considered if the patient is expected to have a major benefit from such a procedure, e.g., in emergencies like spinal cord compression or in tumour progression under chemotherapy.

- Postoperative radiotherapy should be considered if not all tissue contaminated by the tumour at diagnosis could be removed.
  - Poor histological response to induction chemotherapy.
  - Marginal resection.
  - Intralesional resection - after second-look surgery (if feasible).
  - Surgery at the time of diagnosis even if this was considered R0, unless a wide second-look operation is feasible.
  - In large tumours (> 200 mL/ 8cm) and wide resections post-operative radiotherapy could be considered and should be discussed in a multidisciplinary team with the surgeons.
  - Patients with non-sacral pelvic tumours.
  - If a tumour of the spine was resected additional radiotherapy is mandatory as for anatomical reasons wide margins cannot be achieved in the vertebra
- In Spine definite radiotherapy should be considered as treatment of choice. Special attention should be paid on the dose of the myelon (< 50Gy) for toxicity reasons.

- Definitive radiotherapy is advised only in inoperable lesions. Inoperability is given in tumours that cannot be resected completely and in tumours of critical sites where complete surgery would result in unacceptable mutilation or is associated with a high risk of serious complications.

- Dose constraints in organs of risk must be respected

In patients eligible for busulfan-high dose chemotherapy the treatment must be discussed upfront with the radiotherapist as a combination of busulfan and radiotherapy may lead to severe adverse events. If radiotherapy of central axial sites involving critical organs is mandatory and the patient qualifies to receive busulfan melphalan high dose, radiotherapy planning should be discussed with the ERN expert centres. Radiation doses planned or administered involving the spinal cord or brain must not exceed 30 Gy and for all sites time.

Metastatic disease
In patients with metastatic disease radiotherapy should be considered whenever feasible.

- If surgery is not considered to the primary tumour, radiotherapy should be performed in metastatic disease

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- In patients with oligometastatic disease, radiotherapy to all metastatic sites should be performed if surgery is not considered possible
- In patients with multiple metastases, radiotherapy may be considered individually and discussed in a multidisciplinary team
- In patients where radiotherapy to all metastatic sites is not feasible for toxicity reasons palliative radiotherapy (i.e. hypofractionated) to the primary tumour, to symptomatic sites and to sites where risk of fracture or other complications are envisioned (i.e. trochanter, vertebra,etc.)
- Whole lung irradiation is recommended in patients with pulmonary metastases after remission

1-6 Refer to guidelines (if any) including publications

1-6.1 Refer to active first line treatment trials

1-6.1.1. Link to Clin Trial Gov or Eudra-CT Number (Synopsis of respective Clin Trial traceable)

There are currently no active clinical trials for first line treatment in Europe
The EURO EWING CONSORTIUM will open two clinical trials, soon.

iEUROEWING
Please contact: ieuroewing@uk-essen.de; for clinical question please use itb-ewing@uk-essen.de

INTEREWING 1
Please contact: INTER-EWING1@trials.bham.ac.uk

Furthermore, an international registry is open for patients not eligible or willing to participate in the randomized trials and also for countries where it is currently difficult to open randomized clinical trials. The registry is also open for other small blue round cell sarcoma, including DSRCT but excluding RMS.
Please contact: registry-ewing@uk-essen.de

1-6.2 Summary of recently closed European clinical trials

NCT00987636 EWING 2008 randomized multinational, multicentre phase 3 open label trial for patients with localized and metastatic Ewing Sarcoma

Primary objectives:
Standard Risk R1: in a randomised trial, to examine whether add-on treatment with zoledronic acid in addition to induction and maintenance chemotherapy improves event-free survival in patients with localised Ewing sarcoma and good histological response or with initial tumour volume <200 mL compared to no add-on treatment. All patients received 6 cycles VIDE induction and 8 cycles VAI (male) or 8 cycles VAC (female) consolidation. Zoledronic acid treatment started parallel to the 6th consolidation cycle and 284 pts were randomized. The event-free survival was not significantly different between the zoledronic acid and the no add-on arm in the adaptive design (HR 0.74, 95% CI 0.43-1.28, p=0.27, intention-to-treat). The 3-year event free survival was 84.0% (95% CI 77.7-90.8%) with add-on zoledronic acid versus 81.7% (95% CI 75.2-88.8%) for no add-on. Results were

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similar in the per-protocol collective. The 3y- overall survival was 92.8% (95% CI 88.4-97.5%) with add-on zoledronic acid and 94.6% (95% CI 90.9-98.6%) for no add-on. Noticeable more renal, neurological and gut toxicities were observed for zoledronic acid ($p<0.05$) and severe renal toxicities occurred more often in the zoledronic acid arm ($p=0.003$). **CONCLUSION: the outcome in standard localized disease is excellent and zoledronic acid is not recommended in the treatment of localized Ewing Sarcoma [20].**

High Risk R2: this randomised trial examined whether high-dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion (BuMel), compared with standard chemotherapy, improves event-free survival in patients with localised Ewing sarcoma and poor histological response or tumour volume ≥200 mL (R2loc). 240 patients were randomly assigned to VAI or BuMel. The risk of event was significantly decreased by BuMel compared with VAI: HR, 0.64 (95%CI, 0.43 to 0.95; P = .026); 3- -year EFS was 69.0% (95% CI, 60.2% to 76.6%) versus 56.7% (95%CI, 47.6%to 65.4%). Overall survival (OS) also favoured BuMel: HR, 0.63 (95% CI, 0.41 to 0.95; P = .028). **CONCLUSION: BuMel improved EFS and OS when given after vincristine, ifosfamide, doxorubicin, and etoposide induction in localized EWS with predefined high-risk factors. For this group of patients, BuMel may be an important addition to the standard of care [21].**

In patients with pulmonary metastases high dose busulfan-melphalan chemotherapy with autologous stem cell reinfusion was randomised versus standard chemotherapy plus whole lung irradiation (R2pulm) and 543 patients were randomly assigned to VAI+WLI or BuMel. The study did not observe any significant difference in survival outcomes between these treatment groups. EFS was 50.6% versus 56.6% at 3 years for VAI+WLI and BuMel patients, respectively Significantly more patients in BuMel-arm experienced severe acute toxicities than in the VAI+WLI arm.
Conclusion: In EWS with pulmonary or pleural metastases, there is no clear benefit from BuMel compared to conventional VAI+WLI [22].

Very High Risk R3: in a randomised trial, to examine whether the addition of high dose chemotherapy using treosulfan-melphalan followed by autologous stem cell reinfusion (TreoMel) to eight cycles of standard adjuvant chemotherapy, compared to eight cycles of standard adjuvant chemotherapy alone, improves event-free survival in patients with primary disseminated disease. 109 patients were randomized to receive additional TreoMel or no additional treatment. There was no significant difference in EFS between TreoMel and control. The 3-year-EFS was 20.9 % (95% CI 11.5-37.9%) in TreoMel and 19.2% (95% CI 10.8-34.4%) in control patients. Patients aged <14 benefited from TreoMel with 3y-EFS 39.3% (95% CI 20.4-75.8%) vs 9% (95% CI 2.4-34%); p=0.016; HR 0.40 (0.19-0.87). **Conclusion: There is no benefit from TreoMel high dose chemotherapy in patients with disseminated Ewing Sarcoma. However, children < 14 years may benefit from the additional high dose chemotherapy [23]. The observation is supported by comparable results from the non-randomized trial EE99R3 [2].**

NCT02063022
Efficacy of Dose Intensification in Patients with Non-metastatic Ewing Sarcoma (EW-1)
Purpose
Controlled, randomized phase III study, with the intent of optimizing the treatment of not metastatic Ewing Sarcoma. The patients will be randomized into 2 arms: standard treatment vs intensive treatment. They were randomized to receive 4-courses induction therapy - 1 every 21 days - with a standard arm (arm A) as per ISG/SSGIII protocol (Ferrari S, et at, Ann Oncol.

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2011;22(5):1221) or with an intense arm B, consisting of vincristine, doxorubicin, ifosfamid for each course. After induction, patients underwent surgery and/or radiotherapy, followed by an adaptive treatment. Good responders received standard courses chemotherapy: arm A pts received 9 courses, while arm B pts received 5 courses. Poor responders in both arms received 4 courses followed by high-dose BuMel with autologous stem cell rescue. Good responders in arm A and in arm B and poor responders in arm B had comparable results: 5-year EFS (95% CI) was 80% (71-91%), 77% (67-88%), and 72% (59-86%), respectively, while poor responders in arm A showed a worse, not statistically significant (p = 0.164) performance (63%; 50-78%) [24].

NCT02727387 Protocol for the Treatment of Metastatic Ewing Sarcoma (EW-2)
Purpose
Study for the treatment of metastatic Ewing sarcoma. Patients received temozolomide and irinotecan as front-line treatment followed by VDI and CE courses and BuMel high-dose chemotherapy, radiotherapy and maintenance therapy using celecoxib and cyclophosphamide. The 3-year event-free survival (EFS) and overall survival (OS) were 21% (95% CI 6–35%) and 36% (95% CI: 18–54%), respectively [25]. **Conclusion: compared to other trials [7] the addition of temozolomide and irinotecan and celecoxib and cyclophosphamide did not improve outcome in metastatic disease.**

EuroEwing 2012 – no identifier in clinicaltrials.gov.
http://www.euroewingconsortium.eu

- EudraCT number: 2012-002107-17
- ISRCTN reference number: ISRCTN 92192408

The objective of the induction/consolidation chemotherapy randomisation (R1) is to compare the VIDE strategy (VIDE induction and VAI/VAC consolidation) with the VDC/IE strategy (compressed VDC/IE induction and IE/VC consolidation). The event-free survival (EFS) of the two chemotherapy regimens will be compared, and the relative toxicity experienced by patients both before and after local control of the primary tumour. The objective of the zoledronic acid randomisation (R2) was to determine whether the addition of zoledronic acid to consolidation chemotherapy, as assigned at R1, is associated with improved clinical outcome in patients with localised EWS or with pulmonary and/or pleural metastases only at diagnosis. **Conclusion: VDC/IE was superior to VIDE. VDC/IE is the new backbone standard. Results from the R2 randomization are pending.**
Cancer Research UK Clinical Trials Unit at the University of Birmingham EE2012@trials.bham.ac.uk at

1-6.3 Refer to relapse /refractory treatments

1-6.3.1. Link to clinical trials listed in Clin. Trial Gov.

https://clinicaltrials.gov/ct2/results?cond=Ewing%27s+Sarcoma+Recurrent&term=&cntry=&state=&city=&dist=

rEECur – no identifier in clinicaltrials.gov.

- EudraCT number: 2014-000259-99
- ISRCTN reference number: ISRCTN 36453794

rEECur - International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma

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The aim of the rEECur trial is to compare different chemotherapy regimens to determine which is most effective and/or has fewest side effects. It is a randomised trial and is open to patients with a diagnosis of recurrent or primary refractory EWS from the ages of four to 49 years old.
The objectives of the study are to compare chemotherapy regimens in recurrent/refractory EWS starting with cyclophosphamide & topotecan, irinotecan & temozolomide, gemcitabine & docetaxel, and high dose ifosfamid, to identify the best one for use as a backbone in future treatment with respect to efficacy (imaging response and survival), toxicity and acceptability to patients. In 2021 a new arm with carboplatin and etoposide was added, [26].. When 50 patients were recruited to each arm, the gemcitabine and docetaxel arm was dropped based on activity and/or toxicity. The second stage was a 3-way randomisation between the remaining arms. When 25 additional patients were recruited to each arm, the irinotecan and temozolomide arm was dropped as it was unlikely that the arm would outpace the other arms. The next arm to be dropped was topotecan and cyclophosphamide as a new arm. Carboplatin and etoposide were added. If you have any questions about this trial, please contact the Cancer Research UK Clinical Trials Unit at the University of Birmingham reecur@trials.bham.ac.uk*** Please note in the rEEcur trial arms are excluded when it is unlikely that they outspace the other arms. Thus, the use of other the arms still can be considered.

Furthermore, patients with relapsed or refractory Ewing sarcoma may be included in the E-Smart https://clinicaltrials.gov/ct2/show/NCT02813135 , iTHER https://www.trialregister.nl/trial/5728, MAPPYACT (https://imagineformargo.org/en/mappyacts-trial/) or INFORM https://www.kitz-heidelberg.de/klinische-studien/diagnostik-studien/inform/ studies or other trials https://clinicaltrials.gov/ct2/results?cond=Ewing%27s+Sarcoma+Recurrent&term=&cntry=&state=&city=&dist=

1-6.4. Reference to local treatment guidelines

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1-7. Current identified tumour entity Ewing Sarcoma and other translocation-positive rare small blue round cell tumours (i.e., CIC-DUX, BCOR etc.) – Euro-Ewing Sarcoma ERN Structure

Through our joint initiative we will ultimately improve the medical care of patients with Ewing sarcoma and associated bone and soft tissue sarcoma. Treatment of this kind of cancer is challenging, mainly in the planning and performing of appropriate local treatment. Consequently, close cooperation among highly specialized centres and the caring physician is crucial. We will create a network connecting internationally visible experts and professionals from multiple specialties institutions for treatment and support. Furthermore, we will create a network with parents and parental organizations. Our network will provide a hub to facilitate European cooperation among lay persons and groups. Another major aim of this group is to promote collaborative clinical and translational research.

The EUROEWING ERN has identified expert centres across Europe (see table). Furthermore, we are joining with centres that are experienced in the treatment of Ewing Sarcoma but where specialized expertise on modules of the multimodal treatment is lacking. In a joint effort, these centres will guide medical care for Ewing Sarcoma patients in Europe. Though this, optimal medical care can be provided to every single patient in Europe.

Each of the topics dealt by EUROEWING are the subject of expertise of more than one major referral centre. This provides an opportunity for leading, generalizing and synergizing their expertise with the other participants with less experience in the context of the network. These centres provide guidance and/or coverage of all Ewing sarcoma and other translocation-postive small blue round cell sarcoma patients (except of RMS) in their respective countries and they are referral centres for training and consultation at a global level. Some of them are leaders in different fields of Ewing sarcoma care. Many partners have participated and participate in EU initiatives including European Reference Network for Paediatric Oncology (ERN PAEDCAN) https://paedcan.ern-net.eu/; PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) http://www.pancaresurfup.eu/; PanCare LIFE http://www.pancarelife.eu/; EuroEwing Consortium; http://www.euroewing.eu/

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1-8. Main contact point (WEB –Address (Siope or ECTG or Centre/Help Desk)

CENTRAL E- MAIL (SIOP-E)

CENTRAL WEB PAGE (SIOP–E)

Group Chair:
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Group vice chair:
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Princess Máxima Center for Pediatric Oncology,
Department of Solid tumors,
Heidelberglaan 25,
3584 CS, Utrecht, The Netherlands

Paediatric oncology
Ruth Ladenstein, A
Martin McCabe; (associated, UK)
Anna Raciborsca; P
Maria Otth, CH (Chair, Young SIOPE)
Ivana Radulovic, D (Young SIOPE)
Stefan Zoellner, D (Young GPOH)

Medical oncology
Sebastian Bauer; D
Hans Gelderblom, NL
Sandra Strauss (associated, UK)

Pathology
Enrique de Alava, E

Wolfgang Hartmann, D

Radiology/Nuclear medicine
Ken Herrmann, D
Volker Vieth, D

Radiotherapy
Beate Dieckmann, A
Line Claude, F
Beate Timmermann; D (EEC - radiotherapy)

Surgery
Dimosthenis Andreou, D (EEC- surgery)
Jos Bramer, NL

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Lee Jeys, Craig Gerrand (associated, UK)
Andreas Leithner; A
Arne Streitbürger, D/ Jendrik Hardes, D

Late Effects/QoL
Gabriele Calaminus/Thorsten Langer; D
Lars Hjorth; S
Katrin Scheineman, CH

Patient Advocats
Helene Loewen (EEC)
Kathrin Schuster (SPAEN)
Yasmin Uhlenbruch (EEC)
Markus Wartenberg (German Sarcoma Foundation)

1-9. Governance structure of the EUROEWING

The aim of the project is to provide cross border healthcare for Ewing sarcoma patients. The EUROEWING group is partner in the ERN PaedCan and participates in the general Assembly of the network. The EUROEWING group includes members from the Patient Advocacy Group. The EUROEWING group is represented by a chair and vice chair and an executive board including the chair, vice-chair, coordinator, and vice coordinators. The structure of the EUROEWING group consists of work packages (WP). Work Package leaders are expected to submit and present an annual report to the board for approval. A yearly group meeting is envisioned to present the updates and perform a general assembly with the partners. The use of an official dedicated platform for the activities of the group is being elaborated. The group is not a legal entity. The structure of the group is governed by an agreed bylaws document that is described below.

Board
Protects and carries out the aims of and sets the direction for the group. The Board should include the leaders of the different WPs, including paediatric and medical oncologists, surgeons, pathologists, other specialist, and representatives from patient advocates. The Board should strive for gender equality and geographic reach.
Full membership will be recognized to those professionals interested in Ewing Sarcoma who devote at least part of their professional time to the care of patients with Ewing Sarcoma or perform research related to this tumour. Chair functions: In addition to leading the work of the board, the chair represents the group in external functions, e.g., at the EU and with other networks or groups. In the absence of the chair, the vice chair carries out this function.

Interaction with patients and parents
Interaction with patient organizations. One work package is led by patients/parents organizations. The EUROEWING cooperates with SPAEN.

1-9.1. Should be able to direct request into the respective advisory structure in place

Requests for patient consultations initiated by physicians of the group will be accepted. The consultation may be initiated by any member of the team of each participating institution and all

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collaborators from that institution will be notified instantly. Patients are not allowed to directly contact the advisory.

All the group documents will be in English.
An advisory virtual office will initially receive the submitted request. The request may be submitted by the virtual platform (see below). Cases that require an interdisciplinary tumour board are submitted to itb-ewing@uk-essen.de. The ITB will manage the request confirming the completeness of the material is provided, including informed consents. After the documentation process is completed (target time 48 hours), the consultation will be discussed in a virtual interdisciplinary tumour board by the group. The final recommendation letter will be signed by all who participated in the discussion and approved and signed by the WP leader, or a formally delegated member of the committee in case of non-availability, in a time frame described for each clinical situation, usually within two weeks of receipt of all documents needed. E- signature is allowed.

Virtual platform (Martin Schalling)
The EUROEWING Group uses a virtual case consultation by the EU, provided free of charge, Clinical Patient Management System (CPMS) https://cpms.ern-net.eu/login/ platform. This web-based clinical software application was designed to support ERNs in diagnosis and treatment. It enables highly specialized healthcare providers to give virtual advice on specific complex patient cases. Upon submission of the requests, the physicians will have a list of available consultants and chose a number of experts from that list. Local treatment decisions are always made by a group of reference local therapist that discuss the patient together in an analogue or virtual conference setting (ITB).
The expert or group of experts who accepts to review the case will do it within the time frame specified for the clinical situation
HELPDESK
ERN PaedCAN Helpdesk located at CCRI
martin.schalling@ccri.at
+43 1 40470-4991

The platform is ready to use
It allows a secure data upload, compliant with up-to-date EU data protection laws of various medical documents, including a wide variety of imaging files. The system de-identifies patient data is used for all consultations. The cloud-based solution is approved by the EC Data Protection officers. The data is stored on secured servers within the EU (Microsoft Azure Germany). Additional security for patient data is provided by using a 2-factor authentication login procedure.
The core systems that enable HCPs to interact and exchange information are the ERN Collaborative Platform (ECP) and the Clinical Patient Management System (CPMS).
For more details about ERNs and their work, click here.

Timelines
Management of initially diagnosed patients. Within 7 business days
Consultation of management of local treatment. Within 7 business days
Consultation about management of relapse. within 7 business days
Consultation about late effects. Within 10 business days
Consultation about rehabilitation. Within 10 business days

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1-9.1.1. Should give written guidance how to address the Tumor board

The EUROEWING will use the itb-service with the option of a joint tumor board (1-9.1.4.) And also the ECP AND CPMS SYSTEM.

The following information was provided by the CPMS support desk.

How to access ECP and CPMS?

Users must request access to the system in order to be authenticated
o First, an EU login must be created (click https://webgate.ec.europa.eu/cas/eim/external/register.cgi).
o To request access to the ECP, click https://webgate.ec.europa.eu/ern/.
o Click on the button "Search & join Networks" and select PaedCAN.
o After the ERN coordinator has granted access, you can interact with other members of the network.
o In order to be able to use 2-factor authentication for CPMS, a working mobile phone number needs to be linked to the EU account.
o Then, access to CPMS can be requested (click: https://webgate.ec.europa.eu/cas/).
Important! If guest access is requested, "0000 Guest Access" needs to be chosen as the healthcare provider
o Upon correct admission of the request, the ERN coordinator can grant access.
Extensive documentation and written as well as video-guides are available
o Requests for trainings and documentation can be directed at the ERN PaedCAN CPMS Helpdesk (martin.schalling@ccri.at).
o Upon login to CPMS, all resource material will be easily accessible.
To login and start using CPMS, click https://cpms.ern-net.eu/login/

1-9.1.2. Should state what is needed for a proper request

The information needed for a proper request will vary depending of the type of consultation.
Documents are uploaded to the CPMS platform

Case Sheet completed with a pertinent clinical information and precise question
Physician´s report
Initial imaging
Initial pathology report
Treatment plan (if applicable)
Radiotherapy plan (if applicable)
Follow up imaging (if applicable)
Surgeon´s report (if applicable)
Follow up (Post OP) pathology report (if applicable)
Post-operative imaging (if applicable)

At relapse
Initial imaging
Initial pathology report
Actual pathology report (if applicable)
Follow up and actual imaging
Initial treatment plan (if applicable)
Initial radiotherapy plan (if applicable; in case of an in-field relapse of a relapse close to the initial radiation field)
Surgeon´s report (if applicable)
Follow up (Post OP) pathology report (if applicable)
Post-operative imaging (if applicable)

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1-9.1.3. Section on ERN document if you want to use the itb- videoconference option (Templates, ICF)

Sheet for every occasion
The case sheet and a checklist and an upload link are sent upon request: itb@uk-essen.de

Patient	Initials
	Sex
	DOB – or year of birth or age
	Trial ID :

Centre (physician): **Address:** **Fax:** **Tel:**		
Diagnosis: **Primary tumour site**		
Date of diagnosis:		
Metastasis: **Number and site:**		
Relapse(s): **Date and site:**		
Relevant finding **of initial imaging:**		
Relevant finding of **latest (current) imaging:**		
Systemic treatment (protocol, **number of cycles, relevant remarks):**		
Surgery (other than biopsy):		
Radiotherapy:		
Relapse treatment:	---	
Relevant secondary diagnoses:	---	
Question:		
Tumour Board recommendation from **DATE**		

Follow up document: (recommendation followed, patient alive..)

1-9.1.4. Should have a statement on cost

This can vary by member states.

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