Current questions in bone sarcomas

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Abstract

Purpose: Osteosarcoma and Ewing sarcoma, the most common primary bone tumours in young people, are curable in most patients. However, these tumours remain a significant challenge due to the complexity and intensity of treatment and its long-term morbidity and the significant proportion of patients in whom treatment is unsuccessful. This review addresses questions about current management and emerging therapeutic targets for patients with osteosarcoma, Ewing sarcoma and chondrosarcoma the commonest bone sarcoma but more common in older patients.

Recent findings: The largest collaborative international study in osteosarcoma, EURAMOS-1 determined that treatment of patients with resectable disease should not be altered on basis of pathological response to neo-adjuvant chemotherapy. In view of little improvement in outcome being evident in recent years, novel therapeutic approaches are required. Putative targets and clinical trials of novel agents are discussed including emerging targets such as PARP inhibition and IDH inhibition in Ewing sarcoma and chondrosarcoma respectively. Newer radiotherapy techniques including proton beam and particle ion therapy may be important for local tumour control in selected patients.

Summary: Collaborative studies are essential to answer current questions and investigate novel therapies in these malignancies to improve outcome and quality of life for patients.
Introduction

Bone sarcomas are rare primary bone malignancies, accounting for <0.2% of malignant tumours. Osteosarcoma and Ewing sarcoma have a peak incidence in adolescence, with a second peak in OS over 60 years OS (1-3). Chondrosarcoma is the most frequently occurring bone sarcoma of adulthood (1). In adolescents, OS develops most commonly in lower extremity long bones, in older patients there is an increased incidence of craniofacial (CF) and axial tumours (1). ES may involve any bone and also arise less commonly in soft tissues with about 50% of patients developing extremity tumours, and 25% pelvic primary tumours. Pain is the most common presenting symptom for patients with bone tumours, but delays in diagnosis are common and patients must be referred to specialist centres for diagnosis and management.

Osteosarcoma

Conventional high grade OS is the most common histologic type, accounting for approximately 75% of all cases, with subtypes classified according to the dominant matrix-producing cells (Table 1) (4, 5). Other rarer subtypes of high-grade central osteosarcomas include telangiectatic and small cell variants. Intermediate and low grade subtypes also exist that have a much lower rate of metastasis and greater overall survival (Table 1). All patients should be staged for bone and lung metastases.

Current Management

Chemotherapy became the mainstay of therapy for OS following a landmark study demonstrating an increase in 6-year survival from 11 to 61% with multi-agent therapy (6). Subsequently, a multitude of clinical trials have augmented therapy via dose intensification and addition of chemotherapeutic agents. However, survival rates have largely plateaued. Five year survival of patients with
Resectable disease is approximately 70% with a combination of methotrexate, adriamycin and cisplatin (MAP) considered to be the standard of care both in US and Europe (7, 8).

Complete surgical resection of the primary site and metastatic disease remains essential for cure. Primary tumour resection should be carried out by experts in surgical reconstruction to preserve function but the priority is to achieve adequate surgical margins as intralesional or marginal margins increase local recurrence rate, which is then associated with reduced overall survival (OS) (9). Limb salvage is feasible in most patients with extremity tumours, more challenging are those with pelvic and spinal tumours where complete resection may be highly morbid or not possible (10).

**What is the influence of histological response to chemotherapy on management of OS?**

Pathological response to neo-adjuvant chemotherapy is an important prognostic factor in OS and formed the basis for the global EURAMOS-1 study (9). Patients with a good response (> 90% necrosis) were randomised to the addition of pegylated interferon to MAP chemotherapy and those with a poor response a more intensive regimen incorporating ifosfamide and etoposide (MAPIE). Neither treatment improved survival, with MAPIE increasing toxicity and incidence of second malignancies (8, 11). There is therefore no evidence that chemotherapy should be changed on the basis of histological response in resectable OS treated with MAP. For patients with rarer subtypes of OS, including CF tumours, the significance of pathological response to chemotherapy is unknown.

**What is the role of mifamurtide in OS?**

Mifamurtide is an immune-stimulating agent which may reduce incidence of lung metastases in OS via activation of macrophages. A large randomised study investigating the addition of ifosfamide as well as mifamurtide to MAP showed no benefit for addition of ifosfamide but an increase in overall
survival for patients treated with mifamurtide (12, 13). However, a consensus on interpretation of the data from this study has not been reached, leading to absence of regulatory approval in the US and variable use across Europe. In the metastatic setting, a limited study failed to demonstrate a significant improvement in outcome (14). The French sarcoma group are currently investigating its role in patients with high risk osteosarcoma (metastatic or localized disease with poor histologic response to neoadjuvant chemotherapy) French Sarcome13/0S2016. This randomized trial, may provide further data on the benefit of mifamurtide, at least in this patient subset.

**What is the role of radiotherapy in OS?**

Although OS is regarded as a radioreistant disease, it can be beneficial for symptom control in the palliative setting and considered when a primary tumour is unresectable, when it should be considered in combination with chemotherapy (15). Experience of proton beam (PBT) and carbon ion radiotherapy (CIRT) is increasing for those with inoperable or challenging primary sites with some encouraging results. In a series of 55 OS with inoperable OS treated with PBT, a 5 year local control rate of 72% and overall survival of 67% was observed and CIRT given to patients with inoperable osteosarcoma of the trunk, resulted in 5-year local control of 62% (16, 17).

**What is the influence of age on management of OS?**

Several series have demonstrated poor outcomes for older patients with osteosarcoma likely resulting from both chemotherapy intolerance and tumour-related factors, but few clinical trials have been conducted to inform practice (9, 18). The recent EURO-B.O.S.S study evaluated outcome in patients over 40 years who received intensive multi-agent chemotherapy that included attenuated doses of methotrexate and although significantly more chemotherapy-related toxicity
was observed, outcomes were favourable with a 5-year probability of survival of 66% for those with localised disease (19). Randomised studies are required to standardise care for these patients.

*How should less common subtypes of OS be treated?*

Craniofacial OS accounts for approximately 10% of OS, becoming more frequent in older patients. Complete resection significantly improves local control and outcome (20, 21). The role of chemotherapy is less clear however, favourable outcomes have been demonstrated with the use of standard regimens, and should be considered (20, 22). Due to the morbidity of surgery, delivery of all chemotherapy prior to surgery may be valuable with PET imaging reported to aid monitoring to ensure ongoing benefit and plan timing of surgery (23). For patients with suspected low grade OS, upfront wide resection is recommended for confirmation of biopsy results and as there is no demonstrated value for chemotherapy, patients should undergo surveillance. There is little evidence to support the use of chemotherapy in patients with periosteal OS if no high grade component is demonstrated (24).

*What is the optimal management for patients with metastatic and recurrent OS?*

Approximately 20% of patients have metastatic disease at diagnosis (9). For those with only lung metastases, cure is achievable if disease is resectable (25). Patients who develop lung metastases after completion of first line therapy, particularly if there is small volume disease and a longer disease-free internal, should be considered for resection as 5 years survival can be 40% in those who achieve a second surgical remission (26). Focal ablation techniques have been demonstrated to achieve local control of small peripheral lung metastases, however, randomised studies are required to define their role in the curative management of patients (27, 28). Patients with bone metastases have a much poorer outlook and consideration should be given to maintenance of quality of life.
Chemotherapy, usually including ifosfamide, is commonly used for patients with recurrent disease with symptomatic benefit observed in many patients and median overall survival times of approximately 1 year but at the cost of significant toxicity (29, 30). Gemcitabine alone or in combination docetaxel also has activity in OS (31, 32). Phase II studies investigating novel agents in patients with relapsed OS have rarely reported positive results. A pooled analysis of seven phase II trials conducted by Children’s Oncology Group (COG) and its collaborative groups that included strata for recurrent/refractory OS with measurable disease demonstrated a 4-month EFS of 12%; with radiographic responses observed in only 3 of the trials (33).

**What are the emerging targets for OS?**

Several groups have undertaken genomic sequence analysis of OS samples to further understand biology and identify molecular targets for therapy. These investigations have revealed significant genomic complexity and profound heterogeneity that makes identification of specific targets challenging. Nearly all OS have alterations of TP53 or associated pathway genes, and mutations in RB1 and deletions of CDKN2A/B are common (34, 35). Alterations of members of the PI3K/mTOR pathways were also identified in 24% of samples in one cohort (35). The largest sequencing study of OS to date identified mutations in insulin-like growth factor (IGF) signalling genes in 7% of cases and IGF1 receptor (IGF1R) amplification in 14% of tumours (36). Previous studies involving IFGR inhibitors in OS did not report significant activity but, if these findings are validated, the presence of a potential biomarker makes reconsideration a possibility. FGFR amplification is observed in 8% of OS patients, associated with a poor histological response to treatment, also providing a potential target for investigation. An exome sequencing study revealed a potential role for Poly (ADP-ribose) polymerase (PARP) inhibition in OS, with a “BRCAness phenotype” demonstrated in a cohort of patients and pre-clinical evidence of PARP inhibitor activity (37, 38) (39). These findings require independent validation but give promise for future clinical trials.
Despite a mutation rate higher than other paediatric cancers, responses to checkpoint inhibitors have been disappointing. Approximately 25% of osteosarcoma express PDL1 with expression correlating with metastasis and worse outcome (40). However, only 1 of 22 patients had a response to pembroluzimab with a progression-free survival (PFS) rate of 24% at 8 weeks (41). Combination checkpoint studies are ongoing and may reveal benefit in selected patients.

Several clinical trials have investigated oral tyrosine kinase inhibitors, particularly those that inhibit vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGR) and mTOR/PI3K. A phase II study of sorafenib demonstrated a 45% 6-month PFS in patients with recurrent, metastatic OS as did a combination of sorafenib with everolimus, whilst a recent study of gemcitabine and sirolimus demonstrated a PFS of 44% at 4 months (42-44). Correlative biomarker studies suggest that the treatment may be worth further study in selected patients. Other studies evaluating regorafenib and lenvatinib are ongoing. Denosumab, a human monoclonal antibody that targets the RANKL, is currently under evaluation for patients with recurrent osteosarcoma as is a study of an antibody to the disialogangliosid, GD2, based on evidence that OS has high GD2 expression (45) (46).

Ewing sarcoma

Ewing sarcoma is a small round cell sarcoma, the main driver being the reciprocal translocation between the EWSR1 and FLI1 genes (EWSR1-FLI1). However, in approximately 10% of patients, EWSR1 is fused with other ETS transcription factors, including ERG, ETV1, ETV4, or FEV (47). All patients require staging that includes imaging of lungs, bone and bone marrow with 20% patients having metastases.

Current Management
The incorporation of multi-agent chemotherapy with an induction regimen, local therapy (surgery, radiation therapy, or both) and consolidation therapy is based on results from clinical trials conducted by collaborative groups over several decades. Overall survival (OS) for patients with localized disease now approaches 65% to 75%, however, acute and long-term toxicities of therapy remain substantial. Outcome for patients with metastatic disease, particularly those with extra-pulmonary and recurrent ES remains poor (48, 49)

**What is the optimal first line therapy in ES?**

The standard of care for patients with newly diagnosed ES in north America is dose-compressed chemotherapy with alternating cycles of vincristine, doxorubicin, and cyclophosphamide with ifosfamide and etoposide, (VDC-IE) (50). Vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) induction with VAI (Vincristine, actinomycin ifosfamide) or VAC (Vincristine, actinomycin, cyclophosphamide) consolidation adopted from EURO-E.W.I.N.G 99 protocol, is considered the standard of care in Europe (51). The current EuroEwing consortium (EEC) study, EuroEwing2012, is comparing the two regimens and will help define an international standard of care. A second randomization is assessing the efficacy of zoledronic acid for localized and lung-only metastatic disease, a question also being addressed in the German collaborative, Ewing2008 study. On the basis of encouraging efficacy in recurrent disease, COG is assessing the value of addition of cyclophosphamide and topotecan to compressed VDC-IE in patients with localised disease (Table 2).

**What is the optimal local management of ES?**

A number of factors influence the use of surgery and/or radiotherapy to treat the primary tumour including primary site, size and response to treatment. Although ES is known to be radiosensitive, radiotherapy as a single modality results in a high incidence of local recurrence (up to 30% to 35%),
particularly for large tumours and is only advised for inoperable tumours (52). Tumour resection is recommended whenever complete or marginal resection is possible. Adjuvant radiotherapy significantly reduces local recurrence in patients with large volume tumours and those with a poor histologic response (53). Preoperative radiation therapy is increasingly been used in patients who are expected to require radiotherapy as lower doses are required, which are likely to be associated with less long-term morbidity. PBT is increasingly being adopted for patients with inoperable tumours or those with tumours in challenging sites such as the spine with encouraging early local control rates (54).

**What is the role of High dose chemotherapy in ES?**

The recent EURO-E.W.I.N.G 99 study compared the use of high dose therapy incorporating busulfan and melphalan followed by stem cell rescue with standard consolidation chemotherapy in two cohorts of patients treated with induction chemotherapy and surgical resection. In the first, R2Loc, which included patients with high risk localised disease, (large tumour volume > 200mls and/or a poor response to induction chemotherapy), the study demonstrated an improvement in 3-year event-free survival (67% vs. 53%) and 3-year overall survival (78% vs. 70%) and so should be considered for this group of patients (55). No benefit was found for patients with pulmonary metastases at diagnosis (R2Pulm) and should not be recommenced in this setting (56). There are no results of randomised studies to support the use of HDT in patients with extra-pulmonary metastatic disease.

**What is the optimal therapy for patients with metastatic and relapsed ES?**

Patients with metastases at diagnosis have a less favourable outcome, particularly those with extra-pulmonary metastatic disease. Patients are treated with standard regimens, however
considerations to quality of life as well as improving outcome are required in this setting. The COG is investigating the value of addition of the IGF1R monoclonal antibody, ganitumab, to interval compressed VDC/IE in metastatic ES.

In recurrent/ refractory ES, several combination therapies have demonstrated activity, however evidence comes from retrospective analyses and small phase II studies and responses are generally short-lived. The rEECur study, the first EURO-Ewing Consortium (EEC) study for recurrent ES is comparing those most commonly used to identify the optimum therapy based on the efficacy and toxicity (Table 2). The study has a flexible, multi-arm multi-stage phase II/III trial design that allows further arms to be added to the protocol to allow randomised investigation of promising novel therapies.

What are the emerging targets and therapies in ES?

Studies describing the genomic landscape of Ewing sarcoma, have demonstrated that ES has a low mutational rate. The most common recurrent mutation is found in STAG2, found in 15% of patients. Other commonly reported genetic alterations include deletion of CDKN2A and mutations in TP53, however, to date these findings have not led to changes in therapy (57). On the basis of preclinical studies demonstrating sensitivity of ES cell lines to PARP inhibition, and potent synergy of PARP inhibitors with temozolomide and irinotecan in ES preclinical models, several international studies are investigating safety and efficacy of these combinations (58-60) (Table 3). Tyrosine kinase inhibitors also undergoing evaluation in ES with a recent study of regorafinib meeting its primary end point, with 60% patients achieving stable disease at 8 weeks (61). Other novel agents such as TK216 which directly targets the EWS-FLI1 interaction with a partner protein RNA helicase A has recently entered a phase I clinical trial (62). Inhibition of the transrepressive functions of EWSR1-FLI1 through the use of lysine-specific histone demethylase inhibitors also appears promising (63). Response to
single agent checkpoint inhibition however, has been disappointing and further work is required to determine the place of immunotherapy in ES (41).

**Chondrosarcoma**

Surgical resection of disease is the mainstay of therapy for patients with the most common subtype, conventional chondrosarcoma (Table 4). Cure rates are high if disease is low grade, where extensive intralesional curettage may be considered to reduce morbidity. Intermediate and high-grade tumours however, require wide, en-bloc resection. Dedifferentiated chondrosarcoma, which accounts for approximately 10% of chondrosarcoma, is commonly associated with development of bone and lung metastases and very poor survival. Adjuvant chemotherapy as given for OS may be considered in younger patients with localized dedifferentiated chondrosarcoma. Patients with advanced disease and good performance may benefit from the palliative use of cisplatin and doxorubicin. In mesenchymal chondrosarcoma, adjuvant chemotherapy is associated with reduced risk of recurrence and death (64).

*What is the role of radiotherapy in chondrosarcoma?*

Chondrosarcomas (CS) are considered radioresistant tumours, thus high doses are required to be effective. PBT and CIRT, which are able to deliver doses over 70 Gy, are beginning to demonstrate benefit in chondrosarcoma with high local control rates for skull base and spinal CS up to 7 years after therapy with acceptable late toxicity (65, 66).

*What are the emerging targets and therapies in CS?*
Chondrosarcomas are resistant to chemotherapy, thus new therapeutic approaches are needed for unresectable or metastatic disease. IDH1 and IDH2 mutations have been identified in more than 50% of patients with conventional chondrosarcoma and offers a promising new target with several clinical trials evaluating the clinical activity of novel IDH inhibitors (67). A phase II study, investigating the efficacy and safety of pazopanib, a potent multitargeted RTK inhibitor in patients with unresectable or metastatic chondrosarcoma has recently completed accrual (NCT01330966).

**Conclusion**

Although significant advances have been made in management of bone tumours, therapy is complex and patients require management at specialist centres. Continued collaboration is essential to answer current questions and investigate novel therapies in these malignancies to improve outcome and quality of life for patients. Ideally studies should be conducted with standardised endpoints and biomarkers that better predict response and outcome are of paramount importance. Questions also remain how best to incorporating new agents into front-line therapy. For novel radiotherapy techniques, further follow is required to determine impact on long term morbidity and second malignancy.

**Key points**

1. Primary bone sarcomas require complex management that should be undertaken in specialist centres only
2. There is no evidence that altering chemotherapy on the basis of pathological response to chemotherapy improves outcome in patients with resectable osteosarcoma
3. High dose chemotherapy with stem cell support improves outcome in selected Ewing sarcoma patients with high risk localised disease
4. Collaborative studies and randomised trials are required to validate novel therapies and radiotherapy techniques

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Conflicts of interest: none
References


### Table 1: Subtypes of osteosarcoma

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Grade</th>
<th>Incidence (% of OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional chondroblastic, fibroblastic, osteoblastic</td>
<td>High</td>
<td>Common (&gt;75)</td>
</tr>
<tr>
<td>Telangectatic</td>
<td>High</td>
<td>Rare</td>
</tr>
<tr>
<td>Small cell</td>
<td>High</td>
<td>Rare (4%)</td>
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<tr>
<td>High grade surface</td>
<td>High</td>
<td>Rare (&lt;1)</td>
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<tr>
<td>Periosteal</td>
<td>Intermediate</td>
<td>Rare (1-2)</td>
</tr>
<tr>
<td>Low Grade central</td>
<td>Low</td>
<td>Rare (1-2)</td>
</tr>
<tr>
<td>Parosteal</td>
<td>Low</td>
<td>Rare (4)</td>
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### Table 2: Current Randomised Clinical trials in Ewing sarcoma
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Disease cohort</th>
<th>Treatment</th>
<th>No patients</th>
<th>Primary Outcome measure</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Newly diagnosed Disease</strong></td>
<td></td>
<td></td>
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<tr>
<td>EuroEwing2012</td>
<td>SR: Localised HR: pulmonary metastases (R2) Extra-pulmonary metastases (R3)</td>
<td>VIDE x 6 VAI /VAC x 8: +/-Sx +/-RT vs VDC/IE +/-Sx +/-RT (Randomisation 1) +/-Zol (Randomisation 2)</td>
<td>600</td>
<td>EFS</td>
<td>ISRCTN92192408</td>
</tr>
<tr>
<td>Ewing 2008</td>
<td>Localised SR (continued from EE99)</td>
<td>VIDE x 6 VAI/VAC x 8: +/-Sx +/-RT vs +/-Zol</td>
<td>1163</td>
<td>EFS</td>
<td>NCT00987636</td>
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<tr>
<td>Ewing 2008</td>
<td>Lung only metastases</td>
<td>VIDE x 6 VAC x 8: +/-Sx +/-RT vs Bu/Melphalan</td>
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<td></td>
<td></td>
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<tr>
<td>Ewing 2008</td>
<td>Metastatic</td>
<td>VIDE x 6 VAC x 8: +/-Sx +/-RT vs Bu/Treosulphan</td>
<td></td>
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<tr>
<td>AEWS 1031</td>
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<td>VDC/IE +/- C/T</td>
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<td>EFS</td>
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<td>AEWS 1221</td>
<td>Metastatic</td>
<td>VDC/IE +/- Ganitumab</td>
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<td>EFS</td>
<td>NCT02306161</td>
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<tr>
<td>Italy ISG/AIEOP EW-1</td>
<td>Localised</td>
<td>Standard treatment (as per protocol ISG SSG III) vs. dose-intensification and shorter length of treatment</td>
<td>220</td>
<td>EFS</td>
<td>NCT02063022</td>
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<tr>
<td><strong>Recurrent Disease</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>rEECur</td>
<td>Recurrent, refractory</td>
<td>C/T vs IT vs G/D vs High Dose Ifos</td>
<td>275 for phase II 390 for phase III</td>
<td>ORR</td>
<td>ISRCTN36453794</td>
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AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; Bu, busulphan; C/T, cyclophosphamide plus topotecan; COG, Children’s Oncology Group; G/D, gemcitabine plus docetaxel; EFS, Event Free Survival; HR, high risk; IE, ifosfamide plus etoposide; ISG, Italian Sarcoma Group; IT, irinotcan plus temozolomide; ORR, Objective Response Rate, RT, radiotherapy; SR, Standard risk; Sx, surgery; VAC, vincristine, dactinomycin, cyclophosphamide; VAI, vincristine, dactinomycin, and ifosfamide; VC, vincristine plus cyclophosphamide; VDC, vincristine, doxorubicin, and cyclophosphamide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide; Zol, zoledronic acid.
<table>
<thead>
<tr>
<th>Study Sponsor</th>
<th>Indication, age entry criteria</th>
<th>No. patients with ES entered</th>
<th>PARP inhibitor, (schedule if detailed)</th>
<th>Cytotoxic Agent, (schedule)</th>
<th>Reference</th>
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<td>COG</td>
<td>Paediatric phase 1 &gt;12 months ≤ 21 yrs</td>
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<td>Talazaparib (D1-6)</td>
<td>Temozolomide (D2-6)</td>
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<tr>
<td>MGH</td>
<td>ES Age ≥ 16 years</td>
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<td>Olaparib (D 1-7)</td>
<td>Temozolomide (D1-7)</td>
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<tr>
<td>SARC Arm 1</td>
<td>ES Age ≥ 13 years</td>
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<td>Niraparib (D1-7; D1-14; Continuous)</td>
<td>Temozolomide (D2-6)</td>
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<td>SARC Arm 2</td>
<td>ES Age ≥ 13 years</td>
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<td>Niraparib (D1-7)</td>
<td>Irinotecan (D2-6)</td>
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<td>St Jude Children's Research Hospital</td>
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<td>ESMART Paediatric phase I Cohort D: Age: &gt;12 months ≤ 18 years</td>
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COG- Children’s Oncology Group; MGH - Massachusetts General Hospital; SARC-Sarcoma Alliance for Research through Collaboration; ITCC; ESMART, European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors
<table>
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<th>WHO classification</th>
<th>Grade</th>
<th>Incidence, %</th>
<th>Indication for systemic chemotherapy</th>
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<td>Conventional central</td>
<td>I / atypical cartilaginous tumour, II, III</td>
<td>Common &gt;75</td>
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<tr>
<td>Conventional peripheral</td>
<td>I / atypical cartilaginous tumour, II, III</td>
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<td>No defined role</td>
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<tr>
<td>Periosteal</td>
<td>Low</td>
<td>&lt; 1</td>
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<tr>
<td>Dedifferentiated</td>
<td>High</td>
<td>10</td>
<td>Consider adjuvant chemotherapy in younger patients with localised disease and for palliation in good PS</td>
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<tr>
<td>Mesenchymal</td>
<td>high</td>
<td>&lt;2</td>
<td>Recommended as adjuvant chemotherapy and for palliation</td>
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<tr>
<td>Clear cell</td>
<td>Low</td>
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PS, performance status