

## Sarcoma Advisory Group Chemotherapy Guidelines – Bone Sarcomas

These guidelines do not include specific clinic trials, but is assumed that clinical trials should always be considered when available and clinically appropriate. In the guidelines, when several options exist, then the choice will be based on individual patient circumstances, treatment intent, co-morbidities and patient preference, and decisions will frequently be informed by MDT discussion.

Sarcoma Type	Category	1 <sup>st</sup> Line	2 <sup>nd</sup> Line	3 <sup>rd</sup> Line and Other
Osteosarcoma	Resectable < 30 years	Doxorubicin, cisplatin* methotrexate <sup>(1)</sup> +/- mifamurtide <sup>(2)</sup>  *Carboplatin/Doxorubicin if renal function does not allow for cisplatin	Ifosfamide +/- etoposide <sup>(3)</sup>	Gemcitabine and docetaxel <sup>(4)</sup> <b>or</b> Oral etoposide <sup>(5)</sup>
	Other	Doxorubicin, cisplatin* ± methotrexate <sup>(1,2)</sup>  *Carboplatin/Doxorubicin if renal function does not allow for cisplatin	Ifosfamide, etoposide ± methotrexate	Gemcitabine and docetaxel <sup>(4)</sup> <b>or</b> Oral etoposide <sup>(5)</sup> <b>or</b> Tiro sine kinase inhibitors (Regorafenib and Sorafenib) <sup>(6-8)</sup>
Ewing sarcoma (bone or soft tissue)	Localised or metastatic disease with lung or pleural metastases only	VDC/IE interval compressed regimen x 14 cycles <sup>(19)</sup>	High dose ifosfamide <sup>(11)</sup> <b>or</b> Ifosfamide and etoposide <b>Or</b> <b>or</b> Infusional ifosfamide <b>or</b> Cyclophosphamide and topotecan <sup>(12)</sup> <b>or</b> Irinotecan and temozolomide <sup>(13)</sup> <b>+/-</b> High dose chemotherapy (busulphan/melphalan or treosulphan/melphalan) with	Cyclophosphamide and topotecan <sup>(12)</sup> <b>or</b> Irinotecan and temozolomide <sup>(13)</sup> <b>or</b> Gemcitabine and docetaxel <sup>(15,16)</sup> <b>or</b> Oral etoposide <sup>(5)</sup> <b>or</b> Carboplatin and etoposide <sup>(17)</sup> <b>or</b> Infusional ifosfamide
	Metastatic disease with bone or bone marrow involvement	VDC/IE interval compressed regimen x 14 cycles <sup>(19)</sup>		

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			peripheral blood stem cell rescue <sup>(14)</sup> <b>or</b> N.B. Choice of 2 <sup>nd</sup> line therapy will depend on patient/disease specific factors (e.g. if chemo being given with curative intent) and/or patient choice	
	Localised disease – poor response to chemotherapy	High dose chemotherapy (busulphan/melphalan with peripheral blood stem cell rescue <sup>(20)</sup> )	As above	
Translocation negative or rare translocation (CIC-DUX4, BCOR small blue round cell tumours)	Treat as Ewing sarcoma but consider early evaluation given uncertainty of response/benefit			
Other high grade bone sarcomas including, leiomyosarcoma, angiosarcoma, spindle cell sarcoma, dedifferentiated chondrosarcoma, mesenchymal chondrosarcoma		Doxorubicin, cisplatin ± methotrexate <sup>(1,2)</sup> <b>or</b> Doxorubicin and ifosfamide	Ifosfamide, etoposide ± methotrexate <sup>(3)</sup>	Gemcitabine and docetaxel <sup>(4)</sup> <b>or</b> Oral etoposide <sup>(5)</sup>
Pigmented villonodular synovitis	Locally advanced unresectable/metastatic	Imatinib <sup>(21)</sup>	Pexidartinib (CSF1R inhibitor FDA approved. Compassionate access available for UK pts) <sup>(22)</sup>	
Giant cell tumour	Locally advanced unresectable/metastatic	Denosumab <sup>(23)</sup>		
Chordoma	Locally advanced, unresectable or metastatic: Non-dedifferentiated  Dedifferentiated	Imatinib 800mg <sup>(24,25)</sup>  Doxorubicin <b>or</b>	Addition of sirolimus <sup>(27)</sup> <b>or</b> Sunitinib <sup>(28)</sup>	

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		Doxorubicin and cisplatin <sup>*(26)</sup> *Carboplatin if renal function does not allow for cisplatin		
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## Sarcoma Advisory Group Chemotherapy Guidelines – Soft Tissue Sarcomas

These guidelines do not include specific clinic trials, but it is assumed that clinical trials should always be considered when available and clinically appropriate. In the guidelines, when several options exist, then the choice will be based on individual patient circumstances, treatment intent, co-morbidities and patient preference, and decisions will frequently be informed by MDT discussion.

Sarcoma Type	Category	1 <sup>st</sup> Line	2 <sup>nd</sup> Line	3 <sup>rd</sup> Line and Other
All	Adjuvant (in selected high risk patients)	Doxorubicin and ifosfamide <sup>(29)</sup>	NA	NA
	Neoadjuvant	Doxorubicin and ifosfamide <sup>(30)</sup>	NA	NA
	Metastatic/Locally advanced	Doxorubicin <sup>(31)</sup> + or +/- ifosfamide <sup>(32)</sup> (consider combination chemotherapy for fit patients e.g. PS 0/1, age ≤60 years) or Oral cyclophosphamide and prednisolone <sup>(33)</sup> (consider for elderly patients of good PS but not suitable for doxorubicin) or Pegylated liposomal doxorubicin (for patients with cardiac impairment requiring an anthracycline in 1 <sup>st</sup> or 2 <sup>nd</sup> line indication) or	Ifosfamide (bolus or infusional) <sup>(34,35)</sup> or Trabectedin <sup>(36,37)</sup> or Oral cyclophosphamide and prednisolone <sup>(33)</sup> or Gemcitabine +/- docetaxel <sup>(38)</sup>  N.B. Choice of chemotherapy will depend on disease factors (histiological subtypes) and patient factors (PS, patient choice)	Ifosfamide (bolus or infusional) <sup>(34,35)</sup> or Trabectedin <sup>(36,37)</sup> or Oral cyclophosphamide and prednisolone <sup>(33)</sup> or Gemcitabine +/- docetaxel <sup>(38)</sup> or Dacarbazine <sup>(39)</sup>  N.B. Choice of chemotherapy will depend on disease factors (histiological subtypes) and patient factors (PS, patient choice)
Leiomyosarcoma	Metastatic/Locally advanced	As for STS or Aromatase inhibitor (if ER/PR positive) (for uterine leiomyosarcoma) <sup>(40)</sup> Or	As for STS Or Gemcitabine and dacabazine <sup>(39)</sup> Or gemcitabine +/- docetaxel <sup>(38)</sup>	As for STS

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Endometrial stromal sarcoma	Metastatic/Locally advanced	Aromatase inhibitor <sup>(41)</sup> <b>or</b> As for STS	Medroxyprogesterone <sup>(41)</sup> <b>or</b> steroidal aromatase inhibitor/exemestane As for STS	As for STS
Liposarcoma	Metastatic/locally advanced (high grade)	As for STS	As for STS Eribulin (compassionate use program available for eligible pts) <sup>(42)</sup>	
Dedifferentiated liposarcoma	Metastatic/locally advanced	Infusional ifosfamide <sup>(34,35)</sup> <b>or</b> As for STS	Infusional ifosfamide <sup>(34,35)</sup> <b>or</b> As for STS	As for STS
Angiosarcoma	Metastatic/Locally advanced Cutaneous angiosarcoma	As for STS <b>or</b> Paclitaxel <sup>(43,44)</sup>	As for STS <b>or</b> Paclitaxel <sup>(43,44)</sup>	As for STS
Desmoplastic small round cell tumour	All	VDC/IE 2 weekly x 14 or VIDE, maintenance VAC <sup>(45)</sup> <b>or</b> Vinorelbine and cyclophosphamide <sup>(46)</sup>	Trabectedin <sup>(36,37)</sup> <b>or</b> Gemcitabine +/- docetaxel <b>or</b> Irinotecan and temozolomide <sup>(47)</sup>	
Alveolar soft part sarcoma	Metastatic/locally advanced	Standard STS chemotherapy not effective Consider for Clinical trials	Crizotinib <sup>(48)</sup> Cediranib <sup>(49)</sup> Sunitinib <sup>(50,51)</sup> Pazopanib <sup>(52)</sup> or Sorafenib <sup>(53)</sup>	
Malignant Peripheral Nerve Sheath Tumour		As for STS	As for STS <b>or</b> Ifosfamide and etoposide <sup>(54)</sup>	As for STS
Haemangiopericytoma/Malignant solitary fibrous tumour	Metastatic/Locally advanced	As for STS	As for STS Or Pazopanib <sup>(55)</sup>	As for STS
Desmoid Tumor/ Fibromatosis	Unresectable	Nonsteroidal anti-inflammatory (e.g. sulindac, naproxen) <sup>(56)</sup> <b>and/or</b> Tamoxifen <sup>(57)</sup>	Tamoxifen <sup>(57)</sup> <b>or</b> Vinblastine and methotrexate <sup>(58)</sup> <b>or</b> Vinorelbine and methotrexate <sup>(59)</sup>	Sorafenib 400-mg <sup>(61)</sup> Imatinib <sup>(62)*</sup>

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		Consider clinical trials	<b>or</b> Doxorubicin <sup>(60)</sup> <b>Or</b> Imatinib <sup>(62)*</sup> <b>Or</b> Vinorelbine, oral	
PEComa	Locally advanced/metastatic disease	As for STS <b>or</b> Sirolimus <sup>(63)</sup>		
Gastrointestinal stromal tumour	Adjuvant - high risk of recurrence	Imatinib 400mg <sup>(64)</sup> for 3 years. Genotyping mandatory (not indicated in PDGFRA exon 18 D842V and KIT, BRAF, SDH deficient and NF1)		
Gastrointestinal stromal tumour	Locally advanced/metastatic disease	Imatinib 400mg <sup>(65,66)</sup>  Avapritinib in PDGFRA exon 18 mutation, including <i>PDGFRA</i> D842V mutations (FDA approved - based on results from the phase I NAVIGATOR trial)	Sunitinib <sup>(67)</sup>	Regorafenib <sup>(68)</sup>
Dermatofibrosarcoma protuberans	Locally advanced, unresectable or metastatic	Imatinib <sup>(69)</sup> 800mg		
Inflammatory myofibroblastic tumour	all	Crizotinib in ALK positive <b>Or</b> Corticosteroids	As for STS for aggressive/metastatic disease	
Mesenchymal chondrosarcoma	(neo)-adjuvant	Doxorubicin + ifosfamide	As per STS	
Rhabdomyosarcoma	See separate guidelines			

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