4th ESO-ESMO-RCE Clinical Update on Rare Adult Solid Cancers
Ewing Sarcoma and Osteosarcoma

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Conflict of Interest Statement

• Advisory Board/Consultancy
  Bayer, Boehringer Ingelheim, Clinigen, Ipsen, Isofol, Lilly, Pfizer, Novartis, Roche, Sensorion

• Principal Investigator (Germany)
  LOXO-TRK-15003 (Loxo => Bayer), E7080 (EISAI)
All patients with a bone lesion that is likely to be a primary malignant bone tumour on a radiological basis should be referred to a bone sarcoma centre or to an institution belonging to a specialised sarcoma network [14–15]. Children and adolescents should be referred to centres which in addition provide age-specific expertise.
Ewing sarcoma
Atypical Ewing sarcoma
PNET  
Primitive (peripheral) neuroectodermal tumor
Askin tumor

Ewing sarcoma

de Alava et al, J Clin Oncol 2001
Not everything that looks somewhat like Ewing is Ewing!

Undifferentiated small round blue cell “EWSR1-negative Ewing’s-like tumors’

• **CIC-DUX4**
  \[t(4;19) \text{ or } t(10;19)\]; soft tissue tumors

• **BCOR-CCNB3**
  X-chromosomal paracentric inversion; bone and soft tissue tumors
  • **CIC-FOXO4** \[t(X;19)\]; **FUS-NCATc2** and many others and (much) more to come
Ewing Sarcoma
standard approach

imaging/biopsy

neoadjuvant chemotherapy

surgery/radiotherapy

adjuvant chemotherapy

prim. pulm. mets: plus (surgery), adjuvant lung RT? HDT?

VCR
IFO/CYC
DOX
ActoD
ETO
Might the outlook for patients with Ewing Sarcoma be improved by treatment intensification?
HR-group: Etoposide?

YES (EVAIA)

NO (VAIA)
Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing’s Sarcoma and Primitive Neuroectodermal Tumor of Bone

49 weeks of standard chemotherapy doxorubicin, vincristine, cyclophosphamide, dactinomycin or experimental therapy these four drugs alternating with courses of ifosfamide and etoposide
Treatment intensification / diversification

- beneficial in localized (HR) disease
- **not** beneficial for metastatic disease
Ewing sarcoma
Interval-compression by G-CSF

Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children’s Oncology Group

Richard B. Womer, Daniel C. West, Mark D. Krailo, Paul S. Dickman, Bruce R. Pawel, Holcombe E. Grier, Karen Marcus, Scott Sailer, John H. Healey, John P. Dormans, and Aaron R. Weiss
Localized Ewing Sarcoma, poor response to induction chemo 
(or >200 cm³ if irradiated)

VAI: vincristine actinomycin D, ifosfamide x 7

BuMel: Busulfan-Melphalan x 1

with stem cell rescue

Randomization in R2pulm

LOC AL THER APY

Randomisation

VAI x 7
& Whole Lung Irradiation (WLI)

VAI x 1

VAI x 1

BuMel HD x 1

R 2

VIDE x 6

J Clin Oncol 37:3192-3202

Uta Dirksen, MD; Bernadette Brenna, MD; Marie-Cécile Le Deley, MD, PhD; Nathalie Cozic, MSc; Henk van den Berg, MD; Vivek Bhadri, MD, PhD; Benédicte Brichard, MD; Line Claude, MD; Alan Craft, MD; Susanne Amer, PhD; Natalie Gaspar, MD; Hans Gelderblom, MD, PhD; Robert Goldsby, MD; Richard Gorlick, MD; Holcombe E. Grier, MD; Jean-Marc Guimberteau, MD; Peter Hauser, MD, PhD; Lars Hjorth, MD, PhD; Katherine Janeway, MD; Horbent Juergens, MD; Ian Judson, MD; Mark Kailo, PhD; Jarmila Kuseva, MD, PhD; Thomas Kuehne, MD; Ruth Ladenstein, MD; Cyril Lervat, MD; Stephen L. Lessnick, MD, PhD; Ian Lewis, MD; Claude Linassier, MD; Perine Mares-Berard, MD; Neysia Marina, MD; Bruce Morland, MD; Helene Pacquement, MD; Michael Pauwesser, MD; R. L. Randall, MD; Andreas Ranft, PhD; Gwenaël Le Teuff, PhD; Keith Wheatley, DPhil; Jeremy Whealan, MD; Richard Womer, MD; Odile Oberlin, MD; and Douglas S. Hawkins, MD on behalf of the Euro-E.W.I.N.G. 99 and Ewing 2008 Investigators
Four patients died as a result of BuMel-related toxicity, and none died after VAI plus WLI. **Significantly more patients in the BuMel arm experienced severe acute toxicities than in the VAI plus WLI arm.**
VDC/IE 🇺🇸
(interval compressed)

or

VIDE 🇪🇺

Preliminary data from prospective, randomized EEC trial suggest advantage for icVDC/IE (CTOS 2019)
Osteosarcoma
WHO classification 2013

- Conventional
  - chondroblastic
  - fibroblastic
  - osteoblastic
  - various unusual subtypes
- Teleangiectatic
- Small cell
- High grade surface
- Parosteal
- Periosteal
- Low grade central
Osteosarcoma
Standard approach – since early/mid 1980s

- Imaging/biopsy
  - Neoadjuvant chemotherapy
    - Surgery
      - Adjuvant chemotherapy
        - Plus surgery for primary mets

- HD-MTX
- ADR (=DOX)
- DDP
- IFOS???

Benefit of additional agents ??????
Osteosarcoma: Site & Survival

localized limb \((n=2,017)\)

axial or metastatic \((n=444)\)

Bielack et al., Cancer Treat Res 2009; based on \(n=2,464\) COSS osteosarcomas
Adult vs. pediatric osteosarcoma

More axial  More secondary
„Adult“ vs. „pediatric/adolescent“ osteosarcoma Treatment - Assumptions

the same treatment principles should apply

but

adults don‘t tolerate pediatric protocols
"Adult" vs. "pediatric/adolescent" osteosarcoma
Adults don’t necessarily experience more toxicity!

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 thrombopenia</td>
<td>children &gt; adolescents/adults</td>
</tr>
<tr>
<td>Grade 3 or 4 neutropenia</td>
<td>children &gt; adolescents/adults</td>
</tr>
<tr>
<td>Grade 3 or 4 mucositis</td>
<td>no age related difference</td>
</tr>
<tr>
<td>Death due to toxicity</td>
<td>children &gt; adolescents/adults</td>
</tr>
</tbody>
</table>

=> "true" or
- less intensive treatment?
- reporting bias?

4,403 patients ≤ 50 years
„Adult“ vs. „pediatric/adolescent“ osteosarcoma (Younger) adults & adolescents experience similar survival outcomes

Benefits and Adverse Events in Younger Versus Older Patients Receiving Neoadjuvant Chemotherapy for Osteosarcoma: Findings From a Meta-Analysis


4,403 patients ≤ 50 years
Older osteosarcoma: 41-65 years
„Adult“ vs. „pediatric/adolescent“ osteosarcoma (Only) older adults do worse

Osteosarcoma Incidence and Survival Rates From 1973 to 2004

Data From the Surveillance, Epidemiology, and End Results Program

Lisa Mirabello, PhD1, Rebecca J. Troisi, ScD2,3, and Sharon A. Savage, MD1
Are things getting better?

Type of surgery
(COSS, >2,800 extremity osteosarcomas)

5-year survival

Europe (EU & others)

North America

Stiller et al., Eur J Cancer 2006

Mirabello et al., Cancer 2009

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Osteosarcoma
Interval compression (MRC BO06 EORTC 80931)

Lewis et al., JNCI 2007
Osteosarcoma: Zoledronate added to chemo – French trial suggests potential inferiority!

Zoledronate in combination with chemotherapy and surgery to treat osteosarcoma (OS2006): a randomised, multicentre, open-label, phase 3 trial

Sophie Piperno-Neumann, Marie-Cécile Le Deley, Françoise Rédini, Hélène Pacquement, Perrine Marec-Bérard, Philippe Petit, Hervé Brisse, Cyril Lervat, Jean-Claude Gentet, Natacha Entz-Werle, Antoine Italiano, Nadège Corradini, Emmanuelle Bompas, Nicolas Penel, Marie-Dominique Tabone, Anne Gomez-Brouchet, Jean-Marc Guinebretière, Eric Mascard, François Gouin, Aurélie Chevance, Naïma Bonnet, Jean-Yves Blay, Laurence Brugières, on behalf of the Sarcoma Group of UNICANCER, the French Society of Pediatric Oncology (SFCE), and the French Sarcoma Group (GSF-GETO)
Can outcomes be improved for poor responders?
**EURAMOS1-POOR RESPONSE: Design**

**Induction MAP**
- AP MM x2
- Primary tumor resection
- wk 1-10
- wk 11
- Poor Response
- wk 12-29

**MAP**
- AP MM
- AP MM
- A MM
- A MM

**MAPIE**
- AP MM
- IE M
- Ai M
- IE M
- AP MM
- IE M
- Ai MM
- wk 12-40

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**European and American Osteosarcoma Study**

<table>
<thead>
<tr>
<th>COG</th>
<th>Childrens’ Oncology Group</th>
</tr>
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<tbody>
<tr>
<td>COSS</td>
<td>Cooperative Osteosarcoma Study Group</td>
</tr>
<tr>
<td>EOI</td>
<td>European Osteosarcoma Intergroup</td>
</tr>
<tr>
<td>SSG</td>
<td>Scandinavian Sarcoma Group</td>
</tr>
</tbody>
</table>

**Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial**

- 2,260 patients from 326 institutions in 17 countries
- eligible: ≤40 years at osteosarcoma diagnosis

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Poor Response - **MAPIE vs. MAP**

**Event-Free Survival**

- **HR** 1.00
- 95% CI 0.81 – 1.24
- P-val 0.993

**Overall Survival**

- **HR** 1.06
- 95% CI 0.81 – 1.39
- P-val 0.674

Janeway et al., CTOS 2019
MAPIE more toxic than MAP

- Grade III/IV non-hematological toxicity
  \[ p = 0.0024 \]

- SMNs: 6 MAP vs. 14 MAPIE

5-yr survival (SMN):
- MAP: 99%
- MAPIE: 96%

HR: 2.425
95% CI: 0.92 – 6.48
P-val: 0.028

Janeway et al., CTOS 2019
Interventions

Primary tumor resection

R ifn

MAP MAP MA MA

wk 1-10 wk 11 wk 12-29 wk 30-104

M Methotrexate 12gm/m²
A Doxorubicin 75mg/m²
P Cisplatin 120mg/m²

Pegylated interferon α-2b

Timing
Weekly after chemo until wk 104

Dosing
Starting at 0.5 μg/kg/wk (max. 50 μg) x 4 wks if well tolerated
Escalation to 1.0 μg/kg/wk (max. 100 μg)

Protocol guidelines for
Monitoring, mandatory tests, supportive care, dose adaptation
EURAMOS-1: Conclusions

- Evidence from EURAMOS-1 does **NOT** support adaptation of postoperative chemotherapy based on histological response!
And how about recurrent bone sarcomas?
Osteosarcoma recurrence (COSS, n=576)

Survival

Bielack et al., J Clin Oncol 2009

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Recurrent Osteosarcoma Surgery!!!

Surgery, CR2
- n=275
- 71%

Surgery, no CR2
- n=95
- 18%

No surgery
- n=53
- 8%

p=.038

p<.001
Osteosarcoma recurrences: Surgery!

Open thoracotomy with palpation

Questionnaire sent to 16 experts & collaborative groups. Carrle et al., Cancer Treat Res 2009

16
100%
Recurrent osteosarcoma
Chemotherapy & overall survival

multidrug chemo $n=333$
none or single agent $n=216$

$p=.012$
## Osteosarcoma & TKIs
### Phase 2 & retrospective studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pts</th>
<th>PFS</th>
<th>Reference</th>
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<tbody>
<tr>
<td>• Apatinib</td>
<td>n=37</td>
<td>5 mo</td>
<td>Xie 2019</td>
</tr>
<tr>
<td></td>
<td>n=27</td>
<td>3 mo</td>
<td>Tian 2019</td>
</tr>
<tr>
<td>• Cabozantinib</td>
<td>n=42</td>
<td>6 mo</td>
<td>Italiano 2018 (abstr.)</td>
</tr>
<tr>
<td>• Lenvatinib</td>
<td>n=32</td>
<td>3 mo</td>
<td>Gaspar 2018 (abstr.)</td>
</tr>
<tr>
<td>plus IFOS/ETO</td>
<td>n=32</td>
<td>11 mo</td>
<td>Gaspar 2019 (abstr.)</td>
</tr>
<tr>
<td>• Pazopanib</td>
<td>n=15</td>
<td>6 mo</td>
<td>Longhi 2018</td>
</tr>
<tr>
<td>• Regorafenib</td>
<td>n=43 (38)</td>
<td>4 mo</td>
<td>Duffaud 2018</td>
</tr>
<tr>
<td>vs. Placebo</td>
<td></td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td>Regorafenib vs. Placebo</td>
<td>n=47</td>
<td>4 mo</td>
<td>Davis 2019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mo</td>
<td></td>
</tr>
<tr>
<td>• Sorafenib</td>
<td>n=35</td>
<td>4 mo</td>
<td>Grignani 2011</td>
</tr>
</tbody>
</table>
Recurrent Ewing Sarcoma Survival

Risk of Recurrence and Survival After Relapse in Patients With Ewing Sarcoma

Martin Stahl, MD,1 Andreas Ranft,1 Michael Paulussen, MD,2 Tobias Bölling, MD,3 Volker Vieth, MD,4 Stefan Bielack, MD,5 Irene Görtitz, MD,6 Gabriele Braun-Munzinger,1 Jendrik Hardes, MD,7 Heribert Jürgens, MD,1 and Uta Dirksen, MD1*
Recurrent Ewing sarcoma: Achieving CR2 is good!

Post-Relapse Survival in Patients With Ewing Sarcoma

Stefano Ferrari, MD,1* Roberto Luksch, MD,2 Kirsten Sundby Hall, MD, PhD,3 Franca Fagioli, MD,4 Arcangelo Prete, MD,5 Angela Tamburini, MD,6 Amelia Tienghi, MD,7 Stefania DiGirolamo, MD,1 Anna Paioli, MD,1 Massimo Eraldo Abate, MD,1 Marta Podda, MD,2 Silvia Cammelli, MD, PhD,8 Mikael Eriksson, MD,9 and Adalberto Brach del Prever, MD10

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Recurrent Ewing sarcoma
Chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide/irinotecan:</td>
<td>[41, 43–45]</td>
</tr>
<tr>
<td>Topotecan/cyclophosphamide</td>
<td>[14, 43]</td>
</tr>
<tr>
<td>Gemcitabine/docetaxel</td>
<td>[46]</td>
</tr>
<tr>
<td>Oral cyclophosphamide/vinorelbine</td>
<td>[47]</td>
</tr>
<tr>
<td>Ifosfamide+Mesna</td>
<td>[48–50]</td>
</tr>
</tbody>
</table>

Support the Euro-EWING-Consortium:
Participate in rEECur
to help determine the „best“ chemo!
Recurrent Ewing sarcoma

High-dose chemo with auto-PBSCT

ISG/SSG, Ferrari et al. PBC 2015

London, Mc Tiernan et al. Sarcoma 2006

CESS, Rasper et al. PBC2014
Bone Sarcoma
Conclusions

• **Multidisciplinary approach!**
  - Always multidrug chemo (except low-grade osteosarcoma variants)
    - **Ewing** - intensive, dose-dense chemo
      - HDT/PBSCT in (very) selected cases
    - **Osteo** - same chemo backbone as ever
      - response strongly prognostic, but not to guide chemo decisions
  - Discussion of best local treatment would require at least 20 more minutes, particularly for Ewing’s
• Will the ever increasing knowledge about tumor biology lead to better and more effective treatments?
Thank you!

CLINICAL PRACTICE GUIDELINES

Bone sarcomas: ESMO–PaedCan–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†