SYSTEMIC TREATMENT OF OSTEOSARCOMA AND EWING SARCOMA FAMILY OF TUMORS IN ADULT PATIENTS

12/12/2020

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GENERAL ASPECTS ON BONE SARCOMA

DESTRUCTIVE BONE LESION / DIFFERENTIAL DIAGNOSIS

BONE METASTASES	+++
MYELOMA	++
BONE SARCOMA	+

ESMO GUIDELINES

- 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 reference centre…
- The biopsy and the pathological diagnosis require expertise in the field and should be discussed in a multidisciplinary team (with the radiologist, the pathologist, the surgeon, the radiation oncologist and the medical oncologist).
- The biopsy should be carried out at the reference centre, with a primary biopsy under the supervision of a surgical team who will carry out the definitive tumour resection or by a dedicated interventional radiologist…

TREATMENTS (HIGH-GRADE)

HISTORICALLY

RADICAL SURGERY ALONE
DFS = 10-20%

CURRENTLY

CHEMOTHERAPY
CONSERVATIVE SURGERY
CHEMOTHERAPY
DFS > 60%

ADULT PATIENTS

- Given the peak incidence of bone sarcoma in children and adolescents and young adults,

- Much of the data for the treatment comes from pediatric studies

- Many studies excluded patients older than 50 years

2 OSTEOSARCOMA

LOCATION

- Usually arises in the metaphysis of a long bone, most commonly around the knee in children and adolescents.
- Involvement of the axial skeleton and craniofacial bones is primarily observed in older patients.
- Frequently metastasises (15-20% at diagnosis) (high-grade), the lung being the most frequent metastatic site, followed by distant bones.
- Adverse prognostic factors for conventional OS = primary metastases, axial or proximal extremity site, large size, elevated serum ALP or LDH and older age.

LOCALISED DISEASE

HUVOS GRADING

Grade	% of necrosis	Histological findings
I	0-49	Little or no apparent effect
II	50-89	Some areas of histologically viable tumor, but also areas of acellular tumor osteoid, necrotic and/or fibrotic material
III	90-99	Predominant areas of change attributable to chemotherapy, with only scattered foci of histologically viable tumor
IV	100	No histological evidence of viable tumor

Good response ≥ 90% (Grade III-IV)

Poor response ≤ 90% (Grade I-II)

- Histological responses correlated to EFS/OS

GR = EFS / OS = 68% / 51%

PR = EFS / OS = 78% / 63%

NEO-ADJUVANT CHEMOTHERAPY

DRUGS WITH PROVEN EFFICACY

Agent	Réponse objective (%)
HD MTX	**42**
Cisplatine	**33**
Ifosfamide	**33**
Doxorubicine	**26**
Actinomycine D	15
Cyclophosphamide	15
Melphalan	15
DTIC	14
Mitomycine C	13

CHILDREN / AYA

MAP = HIGH-DOSE METHOTREXATE + DOXORUBICIN + CISPLATIN

ADULTS

- >25 years = toxicity with HD-METHO

➔ DOXORUBICIN + CISPLATIN + IFOSFAMIDE

HD-MTX 12g/m²

Ferrari et al. Journal of Chemotherapy 2009

NEURO-TOXICITY
NEPHRO-TOXICITY

Etude du Rizzoli
OS localisé <40 ans
M

Maximum 8g/m² for patients > 25 years old

Age	Enfants 4-14 ans	Adolescents 15-19 ans	Adultes 20-40ans	P value
N cycles	200	312	244	
DI	0,84	0,86	0,84	NS
Retard élimination MTX(%)	0	4	11	0,005
Toxicité rénale (%)	5,2	3,5	37,5	0,001
Neutropénie G4 (%)	65	49	54	0,004
Neutropénie fébrile(%)	14	6	4	0,0004
Thrombopénie G4(%)	41	27	35	0,008

» FRENCH » API-AI / OS 2006 TRIAL

Results of API–AI based regimen in osteosarcoma adult patients included in the French OS2006/Sarcome-09 study

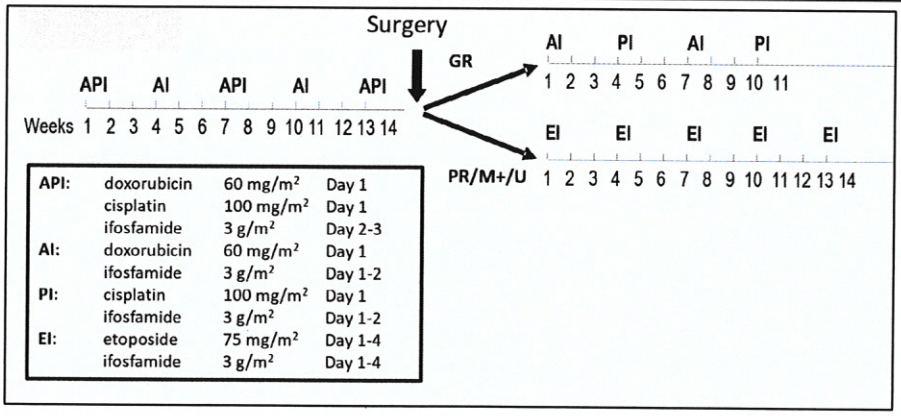
Int. J. Cancer: 146, 413–423 (2020)

Sophie Piperno-Neumann[1], Isabelle Ray-Coquard[2], Bob-Valéry Occean[3], Valérie Laurence[1], Didier Cupissol[4], Christophe Perrin[5], Nicolas Penel[6], Emmanuelle Bompas[7], Maria Rios[8], Axel Le Cesne[9], Antoine Italiano[10], Philippe Anract[11], Gonzague de Pinieux[12], Olivier Collard[13], François Bertucci[14], Florence Duffaud[15], Marie-Cécile Le Deley[3,16], Jessy Delaye[17], Laurence Brugieres[18] and Jean-Yves Blay[2]

106 pts

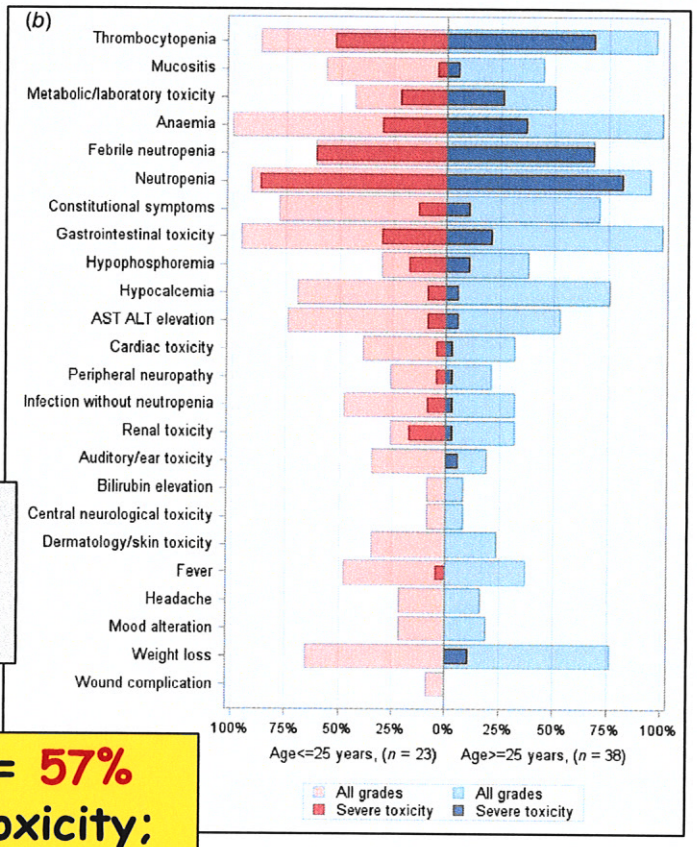
< 18 years = MTX HD
18-25 years = MTX HD or API-AI
> 25 years = API-AI

Prespecified subgroup analysis of API-AI group



API:	doxorubicin	60 mg/m²	Day 1
	cisplatin	100 mg/m²	Day 1
	ifosfamide	3 g/m²	Day 2-3
AI:	doxorubicin	60 mg/m²	Day 1
	ifosfamide	3 g/m²	Day 1-2
PI:	cisplatin	100 mg/m²	Day 1
	ifosfamide	3 g/m²	Day 1-2
EI:	etoposide	75 mg/m²	Day 1-4
	ifosfamide	3 g/m²	Day 1-4

- Median age = 30 years
- 62% > 25 years
- 92% conventional
- 74% localised disease
- 38% GR

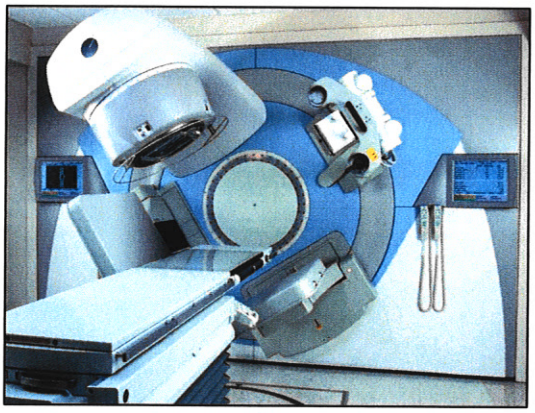


NS difference in severe acute toxicity between > or < 25 years

- 5y-EFS = 46%; 5y-OS = 57%
- API-AI = avoids MTX toxicity; feasible; no excess toxicity; favourable activity

LOCAL TREATMENT

Previously discussed by my colleagues



"Surgery went well, Mr. Moore. I had a lot of fun rebuilding your knee joint."

ADJUVANT CHEMOTHERAPY

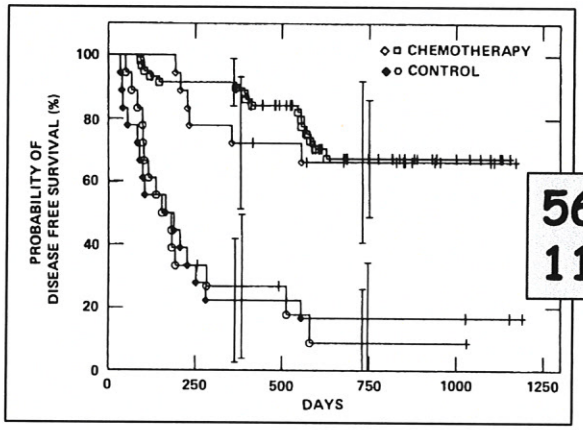
1600 THE NEW ENGLAND JOURNAL OF MEDICINE June 19, 1986

THE EFFECT OF ADJUVANT CHEMOTHERAPY ON RELAPSE-FREE SURVIVAL IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITY

MICHAEL P. LINK, M.D., ALLEN M. GOORIN, M.D., ANGELA W. MISER, M.D., ALEXANDER A. GREEN, M.D., CHARLES B. PRATT, M.D., JEAN B. BELASCO, M.D., JON PRITCHARD, F.R.C.P., JAMES S. MALPAS, F.R.C.P., ALAN R. BAKER, M.D., JOHN A. KIRKPATRICK, M.D., ALBERTO G. AYALA, M.D., JONATHAN J. SHUSTER, PH.D., HERBERT T. ABELSON, M.D., JOSEPH V. SIMONE, M.D., AND TERESA J. VIETTI, M.D.

Adjuvant CT (BLEO + HD-MTX + CISPLATIN + DOXO)
vs
SURVEILLANCE

56pts



56 pts = 2y-EFS = 17 / 66%
113 pts = 6y-EFS = 11 / 61%

EILBER ET AL., JCO 1987

Neo-adjuvant CT (DOXO)
and Adjuvant CT (BLEO + HD-MTX + DOXO)
vs
SURVEILLANCE

59pts

59 pts = 2y-EFS = 20 / 55%

Very few patients but very significant differences

NEO- or ADJUVANT CHEMO ??

POG 8651 TRIAL / GOORIN JCO 2003

100pts

	Schéma	N	Taux d'amputation	5-y EFS	5-y OS
R	CT-CHIR	45	50 %	65 %	78 %
	MTX-AP-BCD			p = 0.8	p = 0.6
	CHIR-CT	55	45 %	69 %	79 %

NO DIFFERENCE in EFS, OS and CONSERVATIVE SURGERY

SoC = NEO-ADJUVANT because
- **surgery planning**
- **personalization of conservative surgery**
- **histological response evaluation**

ALTERING THERAPY BASED ON HISTOLOGICAL RESPONSE IMPROVED OUTCOME ?

EURAMOS-1 TRIAL

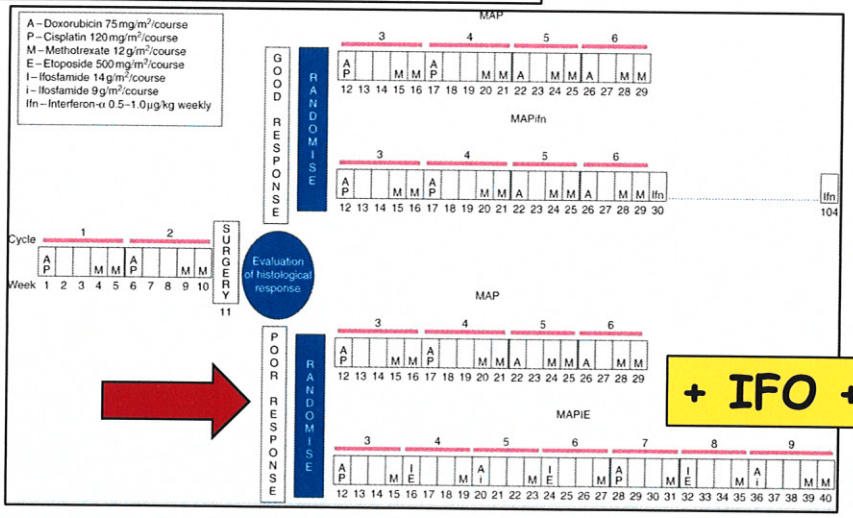
Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial

Lancet Oncol 2016; 17: 1396-408

Neyssa M Marina, Sigbjørn Smeland, Stefan S Bielack, Mark Bernstein, Gordana Jovic, Mark D Krailo, Jane M Hook, Carola Arndt, Henk van den Berg, Bernadette Brennan, Bénédicte Brichard, Ken L B Brown, Trude Butterfass-Bahloul, Gabriele Calaminus, Heike E Daldrup-Link, Mikael Eriksson, Mark C Gebhardt, Hans Gelderblom, Joachim Gerss, Robert Goldsby, Allen Goorin, Richard Gorlick, Holcombe E Grier, Juliet P Hale, Kirsten Sundby Hall, Jendrik Hardes, Douglas S Hawkins, Knut Helmke, Pancras C W Hogendoorn, Michael S Isakoff, Katherine A Janeway, Heribert Jürgens, Leo Kager, Thomas Kühne, Ching C Lau, Patrick J Leavey, Stephen L Lessnick, Leo Mascarenhas, Paul A Meyers, Hubert Mottl, Michaela Nathrath, Zsuzsanna Papai, R Lor Randall, Peter Reichardt, Marleen Renard, Akmal Ahmed Safwat, Cindy L Schwartz, Michael C G Stevens, Sandra J Strauss, Lisa Teot, Mathias Werner, Matthew R Sydes, Jeremy S Whelan**

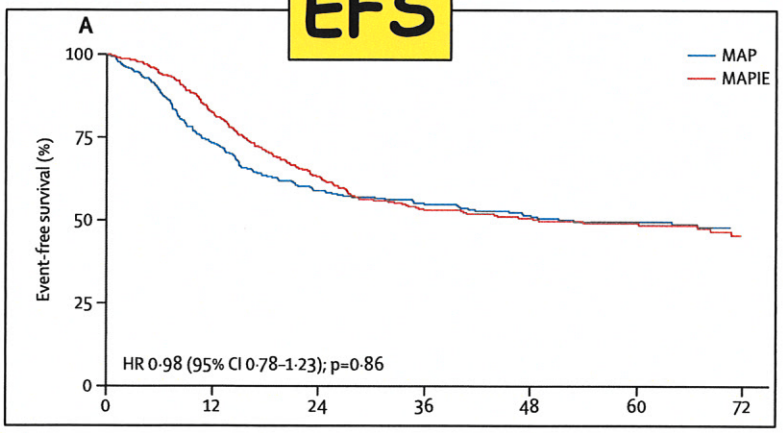
618 pts

POOR RESPONDERS



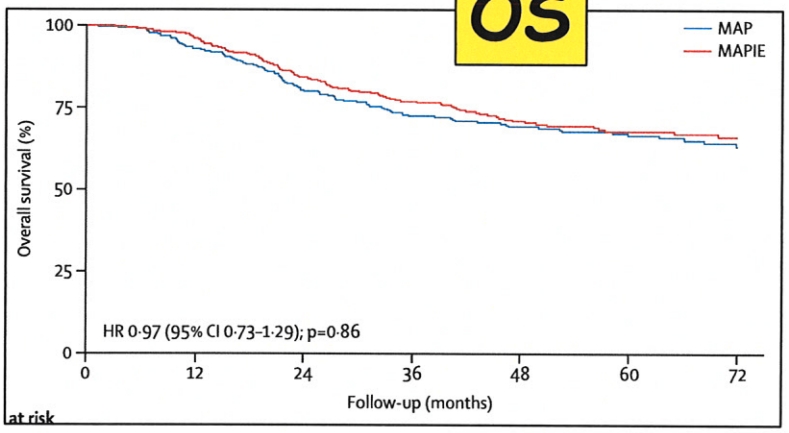
+ IFO + ETOPOSIDE ??

EFS



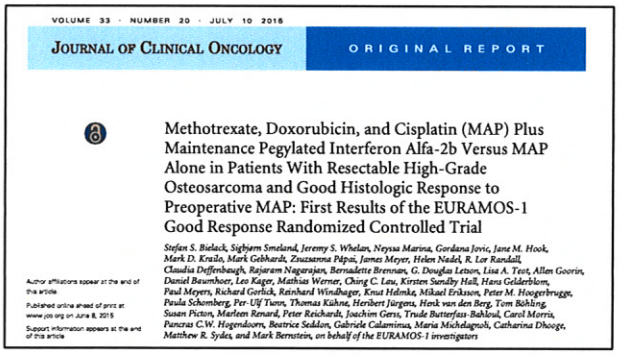
NO DIFFERENCE

OS



HIGHER TOXICITY

EURAMOS-1 TRIAL



VOLUME 33 · NUMBER 20 · JULY 10 2015

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial

Stefan S. Bielack, Sigbjørn Smeland, Jeremy S. Whelan, Neyssa Marina, Gordana Jovic, Jane M. Hook, Mark D. Krailo, Mark Gebhardt, Zsuzsanna Pápai, James Meyer, Helen Nadel, R. Lor Randall, Claudia Daffenbaugh, Rajeram Nagarajan, Bernadette Brennan, G. Douglas Letson, Lisa A. Teot, Allen Goorin, Daniel Baumhoer, Leo Kager, Mathias Werner, Ching C. Lau, Kirsten Sandby Hall, Hans Gelderblom, Paul Meyers, Richard Gorlick, Reinhard Windhager, Knut Helmke, Mikael Eriksson, Peter M. Hoogerbrugge, Paula Schomberg, Per-Ulf Tunn, Thomas Kühne, Heribert Jürgens, Henk van den Berg, Tom Böhling, Susan Picton, Marleen Renard, Peter Reichardt, Joachim Gerss, Trude Butterfass-Bahloul, Carol Morris, Pancras C.W. Hogendoorn, Beatrice Seddon, Gabriele Calaminus, Maria Michelagnoli, Catharina Dhooge, Matthew R. Sydes, and Mark Bernstein, on behalf of the EURAMOS-1 investigators

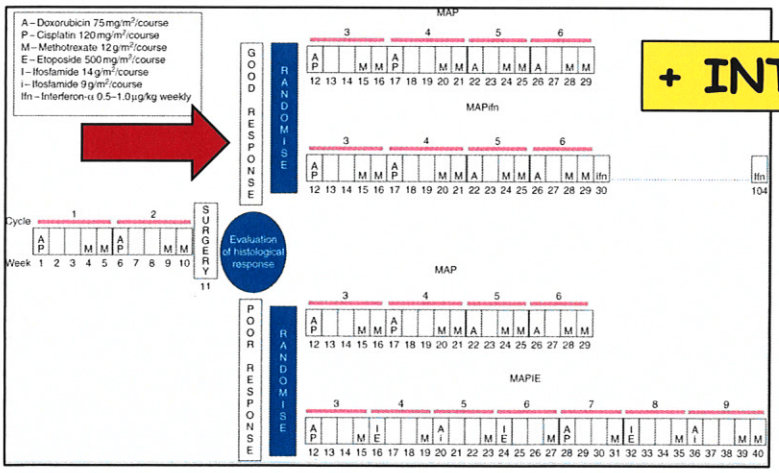
Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on June 8, 2015

Support information appears at the end of this article.

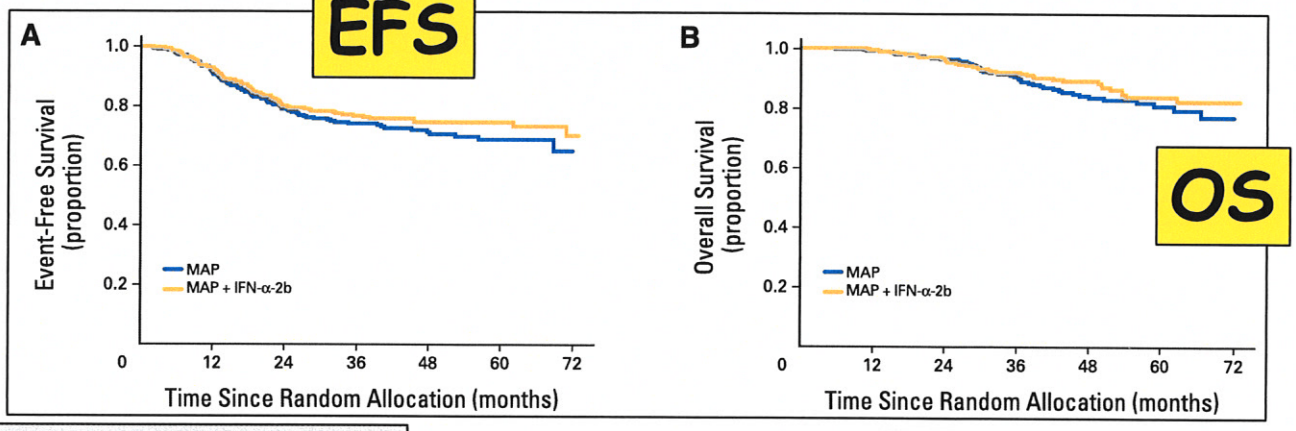
716 pts

GOOD RESPONDERS



+ INTERFERON ??

EFS



OS

EFS = 77 vs 80%
HR = 0.83
CI, 0.59-1.17
P = 0.284

NO DIFFERENCE

OS = 81 vs 84%
HR = 0.77
CI, 0.50-1.19
P = ...

- Considerable proportion of patients allocated to IFN never started or did not complete treatment with the drug, which complicates interpretation of the efficacy data
- Reported toxicity in patients who started IFN did not seem excessive

ZOLEDRONATE / OS 2006 TRIAL

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

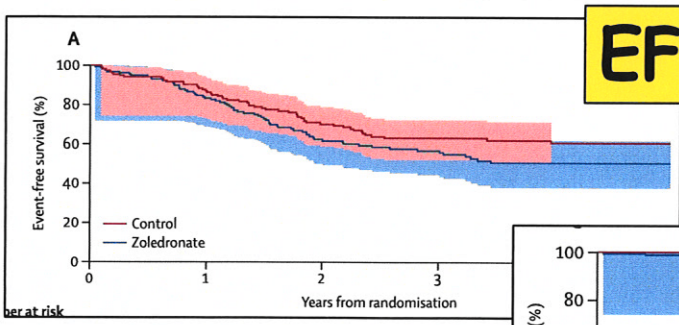
Sophie Piperno-Neumann, Marie-Cécile Le Deley, Françoise Rédini, Hélène Pacquement, Perrine Marec-Bérard, Philippe Petit, Hervé Brisse, Cyril Lervat, Jean-Claude Gentet, Natacha Entz-Werlé, Antoine Italiano, Nadège Corradini, Emmanuelle Bompas, Nicolas Penel, Marie-Dominique Tabone, Anne Gomez-Brouchet, Jean-Marc Guinebretière, Eric Mascard, François Gouin, Aurélie Chevance, Naima 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)

Lancet Oncology 2016

318 pts

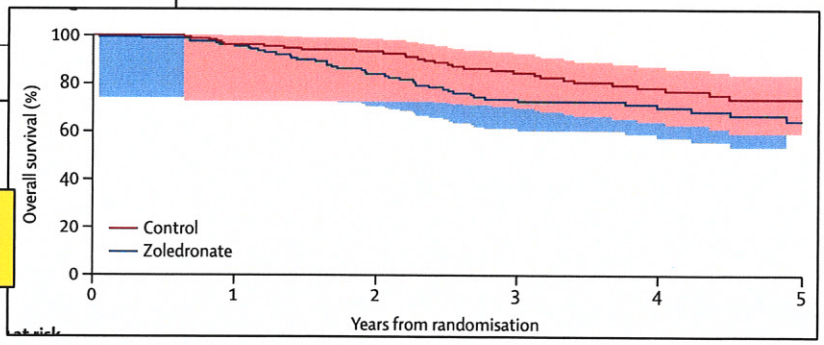
ZOLEDRONATE = 10 monthly (4 PRE-OP / 6 POST-OP)

EFS



NO DIFFERENCE

OS



MURAMYL TRIPEPTIDE (MTP) / INT-0133 TRIAL

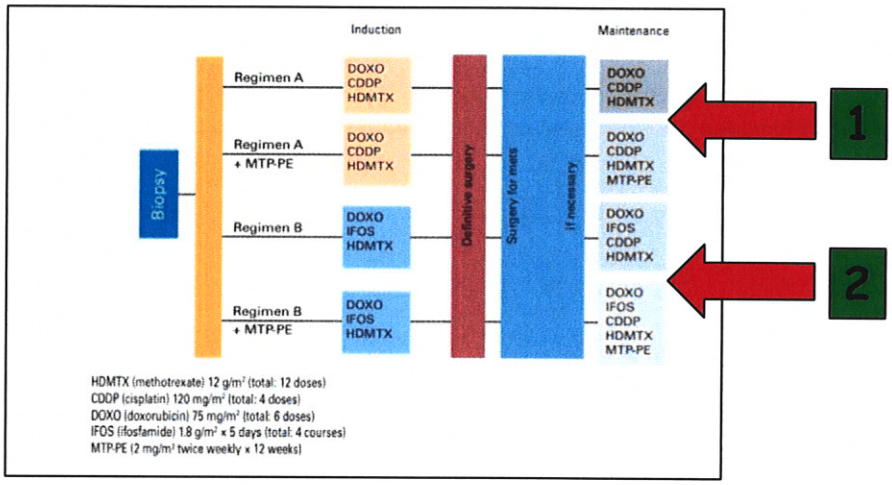
VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

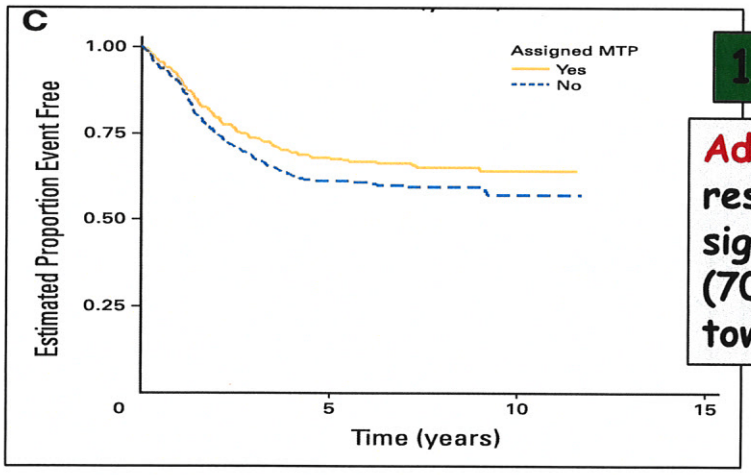
Osteosarcoma: The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival—A Report From the Children's Oncology Group

Paul A. Meyers, Cindy L. Schwartz, Mark D. Krailo, John H. Healey, Mark L. Bernstein, Donna Betcher, William S. Ferguson, Mark C. Gebhardt, Allen M. Goorin, Michael Harris, Eugenie Kleinerman, Michael P. Link, Helen Nadel, Michael Nieder, Gene P. Siegal, Michael A. Weiner, Robert J. Wells, Richard B. Womer, and Holcombe E. Grier

677 pts

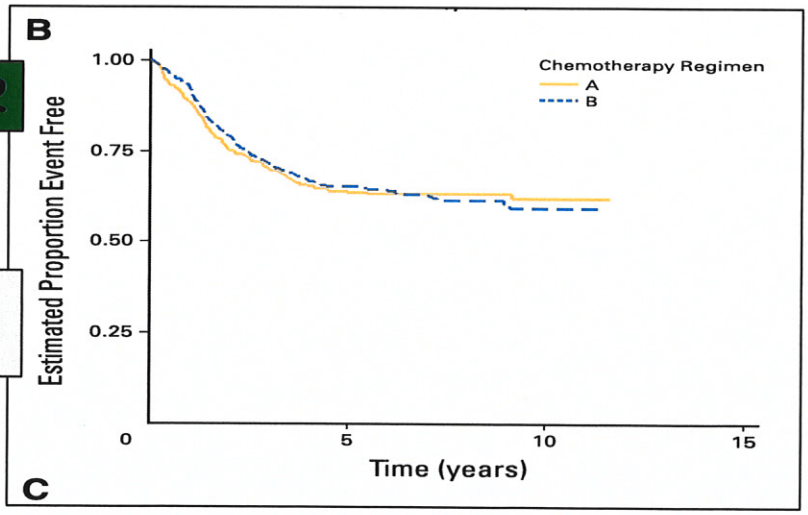
IMMUNO-STIMULATOR





1

Addition MTP to MAP resulted in a statistically significant improvement in OS (70 to 78%) and a trend toward better EFS



2

Addition IFO to MAP did not enhance EFS or OS

PRIMARY METASTATIC DISEASE

10 - 20%

- Prognosis factors = number of M+ at diagnosis; complete surgical resection of all clinically detected tumour sites

- Treated following the same principles of non-metastatic disease

- Long-term survival rates were higher for patients whose M+ were excised following CT and surgery of the primary tumor compared to those patients whose M+ could not removed (48 / 5%)...

RECURRENT DISEASE

TREATMENT DECISION TAKING INTO ACCOUNT

- The timing of recurrences/metastases
- The number of metastases
- The metastatic sites

ISOLATED LUNG M+

- Complete removal of all metastases must be attempted; >30% of patients with a complete second surgical remission survive for 5 years

- For lung metastases, stereotactic RT, radiofrequency ablation or cryotherapy might be used as alternative options in patients unfit for surgery

CHEMOTHERAPY DRUGS

IFOSFAMIDE (HIGH-DOSE) OR CYCLOPHOSPHAMIDE +/- ETOPOSIDE +/- CARBOPLATIN

CYCLOPHOSPHAMIDE + TOPOTECAN OR ETOPOSIDE

GEMCITABINE

DOCETAXEL + GEMCITABINE

HIGH-DOSE MTX

LIMITED DATA

- Despite second-line treatment, the prognosis of recurrent disease has remained poor, with a long-term post-relapse survival rate of < 20%...

EMERGING DRUGS

cancers

MDPI

Review

Molecular Biology of Osteosarcoma

Cancers 2020

Anna M. Czarnecka [1,2], Kamil Synoradzki [1], Wiktoria Firlej [2,3], Ewa Bartnik [4,5], Pawel Sobczuk [2,6], Michal Fiedorowicz [7,8,*], Pawel Grieb [1,†] and Piotr Rutkowski [2,†]

Comparison of altered genes in pediatric and adolescent vs adult patients

Process	Pediatric	Adolescent/Adult
Control of cell cycle and apoptosis	*TP53, RB1, CDKN2A, CDK4, MDM2, MYC, CARD11, CTNND1, BLM, CCNE1, COPS3, PRKCA*	*TP53,*
PI3K-mTOR and RAS-signaling pathways	*EGFR, GNAQ, GNAS, ALK, PDGFRA, PDGFRB, PIK3CA, AKT2, PIK3R1, PTEN, TSC2, VHL, CBL*	*PIK3CA,*
Notch-signaling pathway	*NOTCH1-4, MAML2, FBXW7, PDPK1, AKT1, E1F4B*	*AKT1,*
DNA damage repair	*BRCA1, BRCA2, MLH1, BAP1, ATM, WRN*	*SETD2, FBXW7*
Chromatin modification	*ATRX, FANCE, RECQL4, ARID1A, EP300*	*H3F3A*
Regulation of transcription	*Runx1, GAS7, MLLT3*	
Angiogenesis		*TIE1* and *KDR*

HETEROGENEOUS DISEASE

List of protein targets and potential drugs in targeted therapies of OS

Protein	Potential Drug
DNMT1 (DNA (cytosine-5)-methyltransferase 1)	azacytidine (Vidaza), decitabine (Dacogen)
ERBB2 (receptor tyrosine–protein kinase erbB-2)	trastuzumab (Herceptin), lapatinib (Tycerb), afatinib (GIOTRIF/GILOTRIF), pertuzumab (PERJETA)
GSR (mitochondrial glutathione reductase	carmustine (GLIADEL® WAFER)
HDAC1 (histone deacetylase 1)	vorinostat (Zolinza)
HDAC2 (histone deacetylase 2)	romidepsin (Istodax)
KIT (mast/stem cell growth factor receptor kit)	imatinib (Gleevec), sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), dasatinib (Sprycel), axitinib (Inlyta), nilotinib (Tasigna)
FGFR1 (fibroblast growth factor receptor 1)	lenvatinib (Lenvima)
MET (hepatocyte growth factor receptor)	cabozantinib (COMETRIQ), crizotinib (XALKORI)
MTOR (serine/threonine protein kinase mTOR)	temsirolimus (Torisel), everolimus (Afinitor)
PARP1 (poly (ADP–ribose) polymerase 1)	olaparib (AZD2281)
PDGFR α (platelet-derived growth factor receptor alpha)	imatinib (Gleevec), sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), nilotinib (Tasigna), axitinib (Inlyta) and dasatinib (Sprycel)
PSMC2 (26S protease regulators subunit 7)	bortezomib (Velcade)

REGORAFENIB

Lancet Oncology 2018

Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study

38 pts

Florence Duffaud, Olivier Mir, Pascaline Boudou-Rouquette, Sophie Piperno-Neumann, Nicolas Penel, Emanuelle Bompas, Corinne Delcambre, Elsa Kalbacher, Antoine Italiano, Olivier Collard, Christine Chevreau, Esma Saada, Nicolas Isambert, Jessy Delaye, Camille Schiffler, Corinne Bouvier, Vincent Vidal, Sylvie Chabaud, Jean-Yves Blay, for the French Sarcoma Group

- Progressed after 1-2 previous lines of CT for M+ disease
- REGO ARM = 17/26 pts non-progressive at 8 weeks
- PLACEBO ARM = 0/10 pts

CABOZANTINIB

Lancet Oncology 2020

Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial

45 pts (OS)

Antoine Italiano, Olivier Mir, Simone Mathoulin-Pelissier, Nicolas Penel, Sophie Piperno-Neumann, Emmanuelle Bompas, Christine Chevreau, Florence Duffaud, Natacha Entz-Werlé, Esma Saada, Isabelle Ray-Coquard, Cyril Lervat, Nathalie Gaspar, Perrine Marec-Berard, Hélène Pacquement, John Wright, Maud Toulmonde, Alban Bessede, Amandine Crombe, Michèle Kind, Carine Bellera, Jean-Yves Blay

- 5 / 42 pts = 12% ORR
- 33% = 6 months non-progressive

RARE SUB-TYPES

LOW-GRADE

INTRA-MEDULLARY / SURFACE (PAROSTEAL)

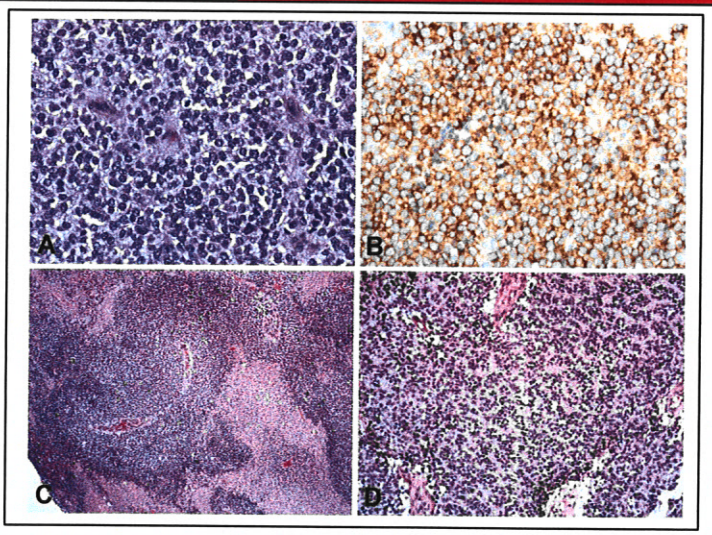
SURGERY ALONE

INTERMEDIATE-GRADE

PERIOSTEAL

SURGERY ? CT FOLLOWED BY SURGERY ?
RETROSPECTIVE ANALYSES
NO STRONG DATA

3 EWING SARCOMA FAMILY OF TUMORS



LOCATION

- vary with age
- most common primary site = extremity bones (50%), followed by pelvis, ribs and vertebra
- older AYA patients (20–24 years of age) had more pelvic and axial primary tumours, larger tumours and worse outcomes than children (0–9 years of age)
- in older patients tend to occur more frequently in soft tissues

2013 WHO CLASSIFICATION

- defines these tumours as ES, characterized by pathognomonic *FET-ETS* gene fusions.
- also includes the term « Ewing-like sarcomas (ELS) » = small round cell sarcomas with morphologically similar appearances to ES but characterized by different fusion genes and clinical and pathological features; …biologically distinct from *FET-ETS* ES.

EWSR1–non-ETS fusions	EWSR1–NFATc2
	EWSR1–POU5F1
	EWSR1–SMARCA5
	EWSR1–PATZ
	EWSR1–SP3
Non-TET–non-ETS fusion	BCOR–CCNB3

CIC-fused sarcomas
This group of ELSs includes sarcomas with *CIC–DUX4*, *CIC–FOXO4* and *CIC–NUTM1* fusions[206,207].

BCOR-rearranged sarcomas
This group of ELSs includes sarcomas with *BCOR–CCNB3*, *BCOR–MAML3* and *ZC3H7B–BCOR* fusions and sarcomas with *BCOR* internal duplications[7,208].

NFATC2 sarcomas
This group of ELSs includes sarcomas with *EWSR1–NFATC2* fusions, which commonly show an *EWSR1* amplification pattern on fluorescence in situ hybridization[209].

- Genetically well characterized: its main driver mutations = specific chromosomal translocations fusing

-a member of the FET family of proteins (encoded by *FUS*, *EWSR1* and *TAF15*), RNA-binding proteins involved in transcription and splicing,
-different members of the ETS family of transcription factors, involved in cell proliferation, cell differentiation, cell-cycle control, angiogenesis and apoptosis — most commonly *FLI1* (85% of cases)

FET part	*ETS* part	Fusion gene	Chromosomal translocation	Frequency
FUS	*FEV*	*FUS–FEV*	t(2;16)(q35;p11)	<1%
	ERG	*FUS–ERG*	t(16;21)(p11;q22)	<1%
EWSR1	*FLI1*	*EWSR1–FLI1*	t(11;22)(q24;q12)	≈85%
	ERG	*EWSR1–ERG*	t(21;22)(q22;q12)	≈10%
	ETV1	*EWSR1–ETV1*	t(7;22)(p22;q12)	<1%
	ETV4	*EWSR1–ETV4*	t(17;22)(q21;q12)	<1%
	FEV	*EWSR1–FEV*	t(2;22)(q33;q12)	<1%
	ETV5 (?)	*EWSR1–ETV5*	?	?
TAF15	?	?	?	?

STAGING AND RISK CLASSIFICATION

- The clinical stage at diagnosis is one of the major predictors of survival. The accurate determination of tumour burden at diagnosis is a critical factor in planning treatment and predicting outcome.

- Tumour volume (*TV*) = a × b × c × F, where a, b and c represent the maximum tumour dimensions in three planes, with F = 0.52 for spherical tumours or F = 0.785 for cylindrical tumours. Large tumours >200 ml = associated with worse outcome.

Standard risk
- Patients with localized disease, small tumours and good histological response (<10% vital tumour cells)
- Patients with small tumours <200 ml in whom histological response cannot be assessed
- In European trials, histological response to induction chemotherapy has been reported as a significant biomarker in the group of patients with localized disease[70,214–216]

High-risk localized
- Unfavourable histological response
- More than 10% vital tumour cells
- Patients with large tumours (≥200 ml) in whom histological response cannot be assessed are also stratified in the high-risk group in European trials[70,144,217]
- The North American study groups do not substratify patients with localized disease[147]

Very high-risk metastatic
- Disseminated disease
- Patients with lung metastases have been reported to have a better outcome than patients with other metastases[142]

LOCALISED DISEASE

NEO-ADJUVANT CHEMOTHERAPY

VINCA ALKALOIDS + ALKYLATING + ANTHRACYCLINES AGENTS

AMERICAN

VDC/IE

VINCRISTIN + DOXORUBICIN + CYCLOPHOSPHAMIDE alternating with IFOSFAMIDE and ETOPOSIDE

EUROPEAN

VIDE

VINCRISTIN + IFOSFAMIDE + DOXORUBICIN + ETOPOSIDE

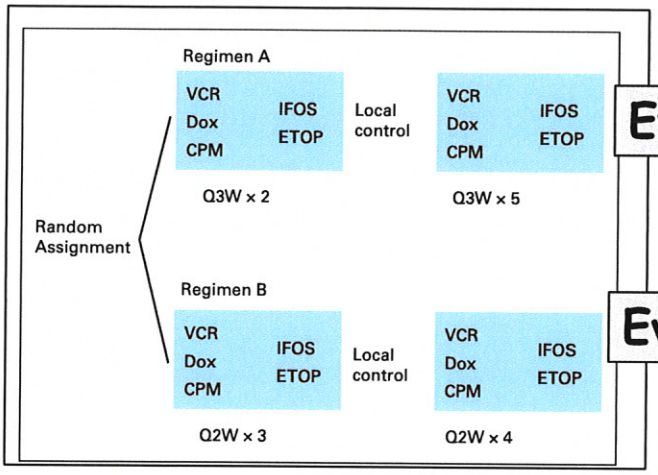
INTERVAL- COMPRESSED CT ?

VOLUME 30 · NUMBER 33 · NOVEMBER 20 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

587 pts

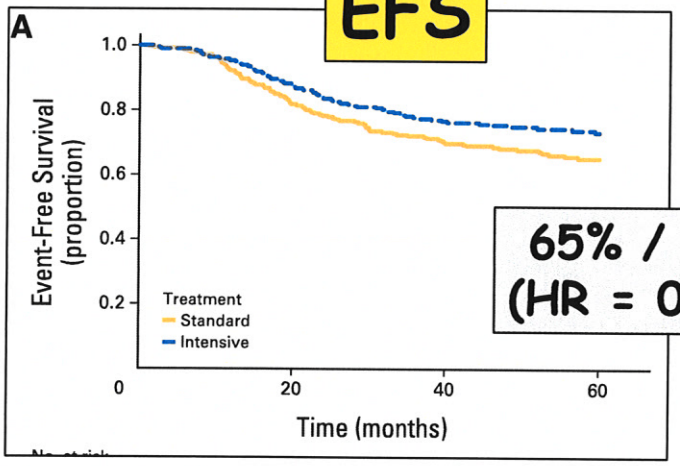


Every 3 weeks

Every 2 weeks

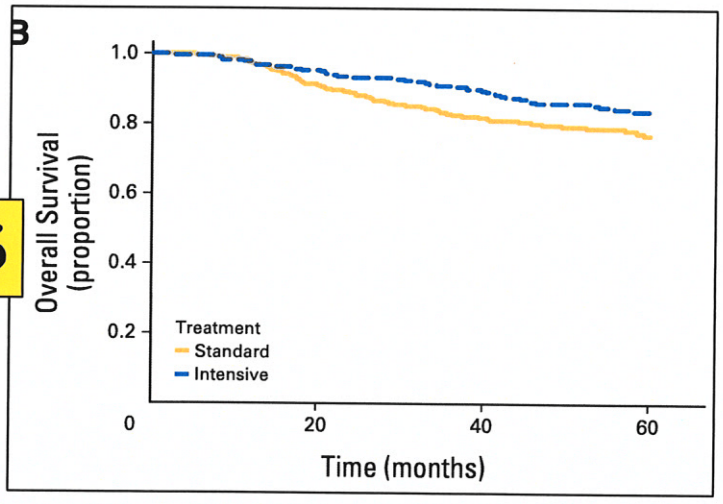
< 50 years
67 pts (12%) = > 18 years

EFS



65% / 73% (p = 0.048)
(HR = 0.74, 95%CI 0.54-0.99)

OS



The Oncologist®

Sarcomas

The Oncologist 2017

Localized Adult Ewing Sarcoma: Favorable Outcomes with Alternating Vincristine, Doxorubicin, Cyclophosphamide, and Ifosfamide, Etoposide (VDC/IE)-Based Multimodality Therapy

67 pts

Jennifer L. Pretz,[a] Constance M. Barysauskas,[e] Suzanne George,[d] Jason L. Hornick,[b] Chandrajit. P. Raut,[c,d] Yen-Lin E. Chen,[f] Karen J. Marcus,[a,d] Edwin Choy,[f] Francis Hornicek,[f] John E. Ready,[d] Thomas F. DeLaney,[c,f] Elizabeth H. Baldini[a,d]
Departments of [a]Radiation Oncology, [b]Pathology, and [c]Surgical Oncology, [d]Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute and Brigham & Women's Hospital, Boston, Massachusetts, USA; [e]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [f]Center for Sarcoma and Connective Tissue Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Median age = 28 years
19% = > 40 years

5-y LRFS non-pelvic / pelvic = 96% / 64%
5-y PFS = 66%
5-y OS = 79%

Survival for adults with localized ES appaers to be better than historical data
and similar to excellent outcomes in children

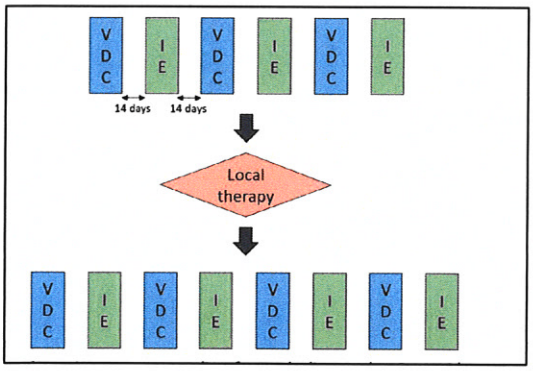
The Oncologist 2020;25:150–155

The Oncologist®

Sarcomas

Feasibility of Treating Adults with Ewing or Ewing-Like Sarcoma with Interval-Compressed Vincristine, Doxorubicin, and Cyclophosphamide Alternating with Ifosfamide and Etoposide

Eric Lu,[a] Christopher W. Ryan,[a] Solange Bassale,[b] Jeong Youn Lim,[b] Lara E. Davis[a,c]



Characteristic (*n* = 24)	Value
Age, years	
Median (range)	28.6 (18.7–60.6)
Age, *n* (%), years	
18–29	15 (62.5)
30–49	4 (16.7)
50+	5 (20.8)
Sex, *n* (%)	
Male	15 (62.5)
Female	9 (37.5)
Race, *n* (%)	
White	23 (95.8)
Multiracial	1 (4.2)
Ethnicity, *n* (%)	
Non-Hispanic	21 (87.5)
Hispanic	3 (12.5)
Largest tumor dimension, cm	
Median (range)	7.2 (2.2–15.5)
Anatomic site, *n* (%)	
Extremity	9 (37.5)
Soft tissue	6 (25.0)
Pelvis	4 (16.7)
Head and neck	2 (8.3)
Thorax	2 (8.3)
Spine	1 (4.2)
Metastatic at diagnosis, *n* (%)	
No	16 (66.7)
Yes	8 (33.3)

- Early discontinuation = 17%
- Doses reduction = minimal with mean cumulative dose comparable to original planned dose

EURO-EWING 2012 PROTOCOL

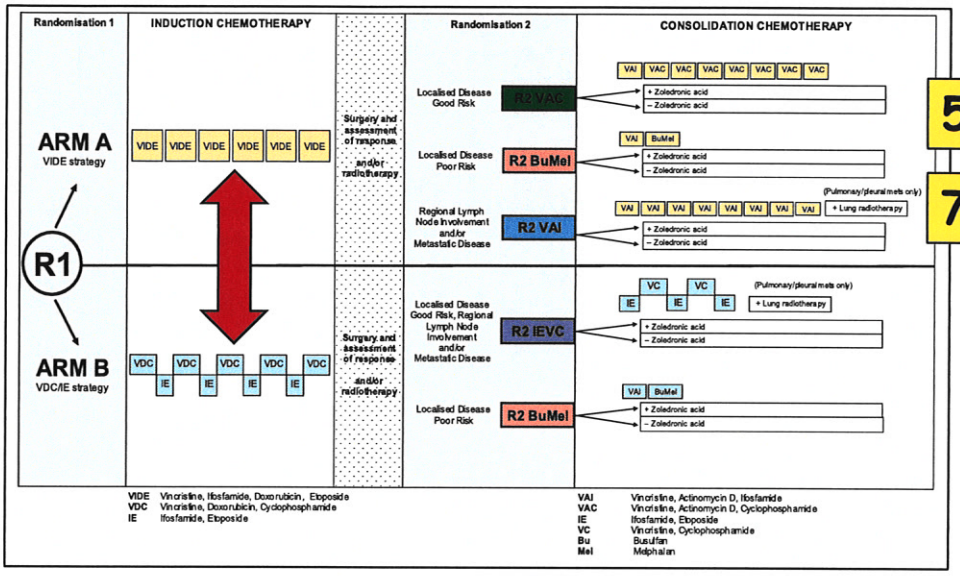
Comparison of two chemotherapy regimens in Ewing sarcoma (ES): Overall and subgroup results of the Euro Ewing 2012 randomized trial (EE2012).

Bernadette Brennan, Laura Kirton, Perrine Marec-Berard, Javier Martin -Broto, Hans Gelderblom, Nathalie Gaspar, Sandra J Strauss, Ana Sastre Urgelles, Jennifer Anderton, Valerie Laurence, Jeremy Whelan, Keith Wheatley

On behalf of the EE2012 collaborative group

ASCO 2020

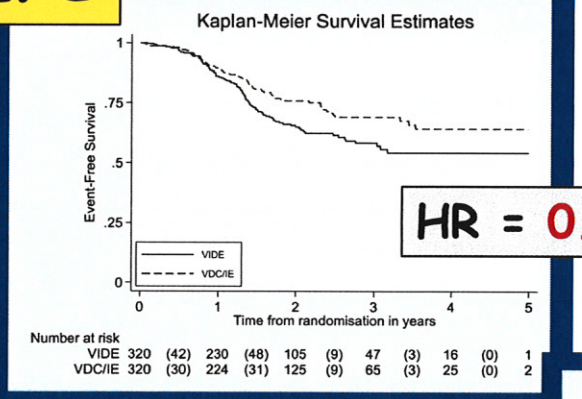
640 pts



59% >14 years

74% LOCALISED

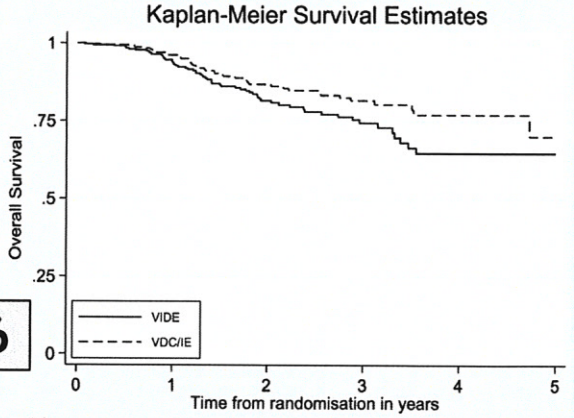
EFS



IN FAVOR OF VDC/IE !!!

HR = 0.70; 95% CI 0.51-0.95

OS



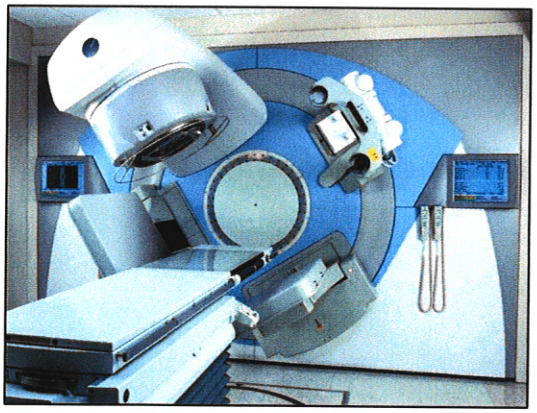
HR = 0.64; 95% CI 0.42-0.96

GRADE 3-5 ADVERSE EVENTS

Patients with grade 3-5 adverse events (%)		VIDE	VDC/IE
Induction:	Any event	91	90
Specific AEs (occurring in >10% of patients):			
	Haematological	85	77
	Gastrointestinal	35	39
	Infections	19	20
	Febrile neutropenia	73	57
Consolidation:	Any event	65	65

LOCAL TREATMENT

Previously discussed by my colleagues



"Surgery went well, Mr. Moore. I had a lot of fun rebuilding your knee joint."

ADJUVANT or MAINTENANCE CHEMOTHERAPY

STANDARD-RISK

CYCLOPHOSPHAMIDE OR IFOSFAMIDE ??

EURO-EWING 99-R1 PROTOCOL

VOLUME 32 · NUMBER 23 · AUGUST 10 2014

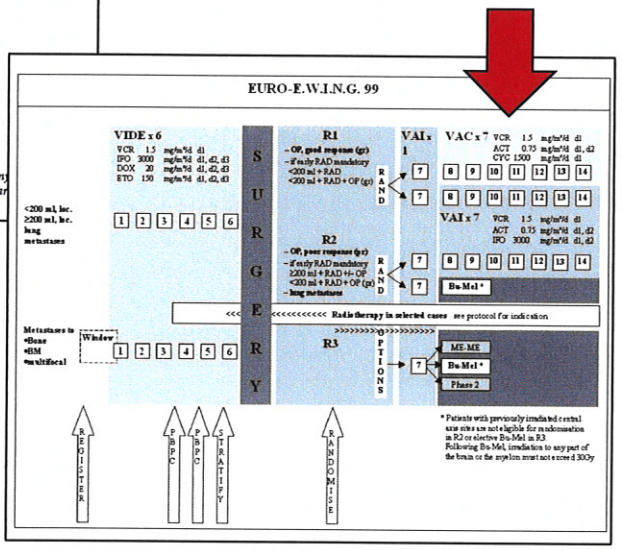
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

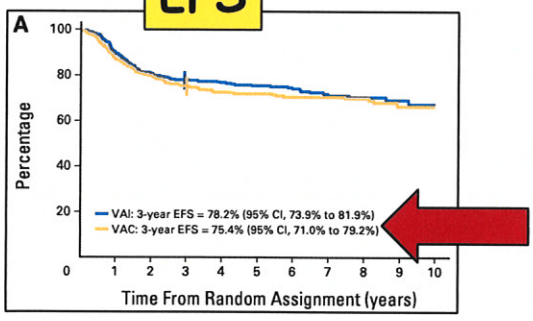
Cyclophosphamide Compared With Ifosfamide in Consolidation Treatment of Standard-Risk Ewing Sarcoma: Results of the Randomized Noninferiority Euro-EWING99-R1 Trial

Marie-Cécile Le Deley, Michael Paulussen, Ian Lewis, Bernadette Brennan, Andreas Ranft, Jeremy Gwénaël Le Teuff, Jean Michon, Ruth Ladenstein, Perrine Marec-Bérard, Henk van den Berg, Lars Keith Wheatley, Ian Judson, Heribert Juergens, Alan Craft, Odile Oberlin, and Uta Dirksen

856 patients



EFS



TOXICITY

Toxicity	VAI Arm No.*	VAI Arm %	VAC Arm No.*	VAC Arm %	Odds Ratio VAC/VAI	95% CI	Nominal P
Severe hematologic toxicity, grade ≥ 4	319 of 406	79	343 of 408	84	1.49	1.03 to 2.2	.03†
Anemia, grade 4	44 of 406	11	46 of 408	11	1.05	0.68 to 1.62	.84‡
Leucopenia, grade ≥ 4	256 of 406	63	283 of 408	69	1.36	1.01 to 1.85	.04†
Neutropenia, grade ≥ 4	291 of 383	76	313 of 386	81	1.43	0.99 to 2.1	.06†
Thrombocytopenia, grade ≥ 4	143 of 406	35	183 of 408	45	1.53	1.15 to 2.0	< .001†
Infection, grade ≥ 2	168 of 404	42	176 of 409	43	1.08	0.81 to 1.44	.62†
Other toxicity	215 of 408	53	207 of 410	50	0.92	0.70 to 1.22	.56†
General condition, grade ≥ 3	34 of 395	9	23 of 400	5.8	0.65	0.37 to 1.12	.12†
Stomatitis, grade ≥ 3	12 of 404	3.0	11 of 408	2.7	0.91	0.40 to 2.1	.83†
Vomiting, grade ≥ 3	26 of 405	6.4	19 of 407	4.7	0.72	0.39 to 1.32	.29†
Diarrhea, grade ≥ 3	8 of 404	2.0	5 of 408	1.2	0.61	0.20 to 1.89	.40‡
Skin toxicity, grade ≥ 3	13 of 404	3.2	6 of 407	1.5	0.45	0.17 to 1.20	.11‡
Creatinine, grade ≥ 2	8 of 403	2.0	8 of 408	2.0	0.99	0.37 to 2.7	.98‡
Proteinuria, grade ≥ 2	7 of 345	2.0	5 of 354	1.4	0.69	0.22 to 2.2	.53‡
Hematuria, grade ≥ 2	8 of 357	2.2	8 of 362	2.2	0.99	0.37 to 2.7	.98‡
Glomerular function, grade ≥ 2	12 of 314	3.8	4 of 308	1.3	0.33	0.11 to 1.04	.06‡
Tubular function, grade ≥ 2	71 of 229	31	34 of 208	16	0.41	0.26 to 0.67	< .001†
Hyperbilirubinemia, grade ≥ 3	9 of 386	2.3	6 of 391	1.5	0.65	0.23 to 1.85	.42†
Transaminase elevation, grade ≥ 3	14 of 402	3.5	16 of 402	4.0	1.15	0.55 to 2.4	.71‡
Cardiac toxicity, grade ≥ 2	4 of 332	1.2	3 of 313	1.0	0.79	0.18 to 3.6	.76‡
LV-SF impairment, grade ≥ 2	13 of 283	4.6	7 of 249	2.8	0.68	0.26 to 1.77	.43†
Central neurotoxicity, grade ≥ 2	7 of 404	1.7	3 of 406	0.7	0.42	0.11 to 1.64	.21‡
Peripheral neurotoxicity, grade ≥ 2	26 of 403	6.5	28 of 406	6.9	1.08	0.62 to 1.89	.79†

LOCALIZED HIGH-RISK

CLASSIC CT versus HIGH-DOSE CT ???

EURO-EWING 99 and 2008 PROTOCOLS

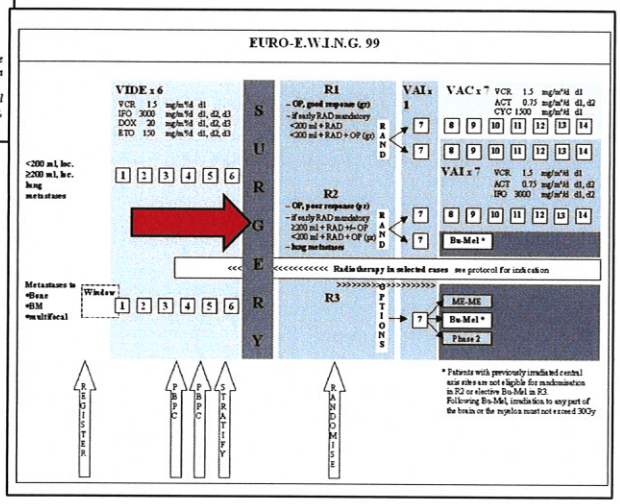
VOLUME 36 · NUMBER 31 · NOVEMBER 1, 2018

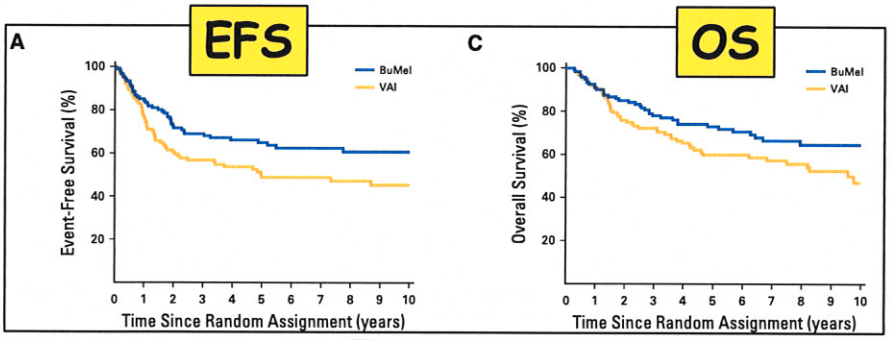
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

240pts

High-Dose Chemotherapy and Blood Autologous Stem-Cell Rescue Compared With Standard Chemotherapy in Localized High-Risk Ewing Sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008

Jeremy Whelan, Marie-Cecile Le Deley, Uta Dirksen, Gwénaël Le Teuff, Bernadette Brennan, Nathalie Gaspar, Douglas S. Hawkins, Susanne Amler, Sebastian Bauer, Stefan Bielack, Jean-Yves Blay, Stefan Burdach, Marie-Pierre Castex, Dagmar Dilloo, Angelika Eggert, Hans Gelderblom, Jean-Claude Gentet, Wolfgang Hartmann, Wolf-Achim Hassenpflug, Lars Hjorth, Marta Jimenez, Thomas Klingebiel, Udo Kontny, Jarmila Kruseova, Ruth Ladenstein, Valerie Laurence, Cyril Lervat, Perrine Marec-Berard, Sandrine Marreaud, Jean Michon, Bruce Morland, Michael Paulussen, Andreas Ranft, Peter Reichardt, Hendrik van den Berg, Keith Wheatley, Ian Judson, Ian Lewis, Alan Craft, Heribert Juergens, and Odile Oberlin, on behalf of the Euro-E.W.I.N.G.99 and EWING-2008 Investigators



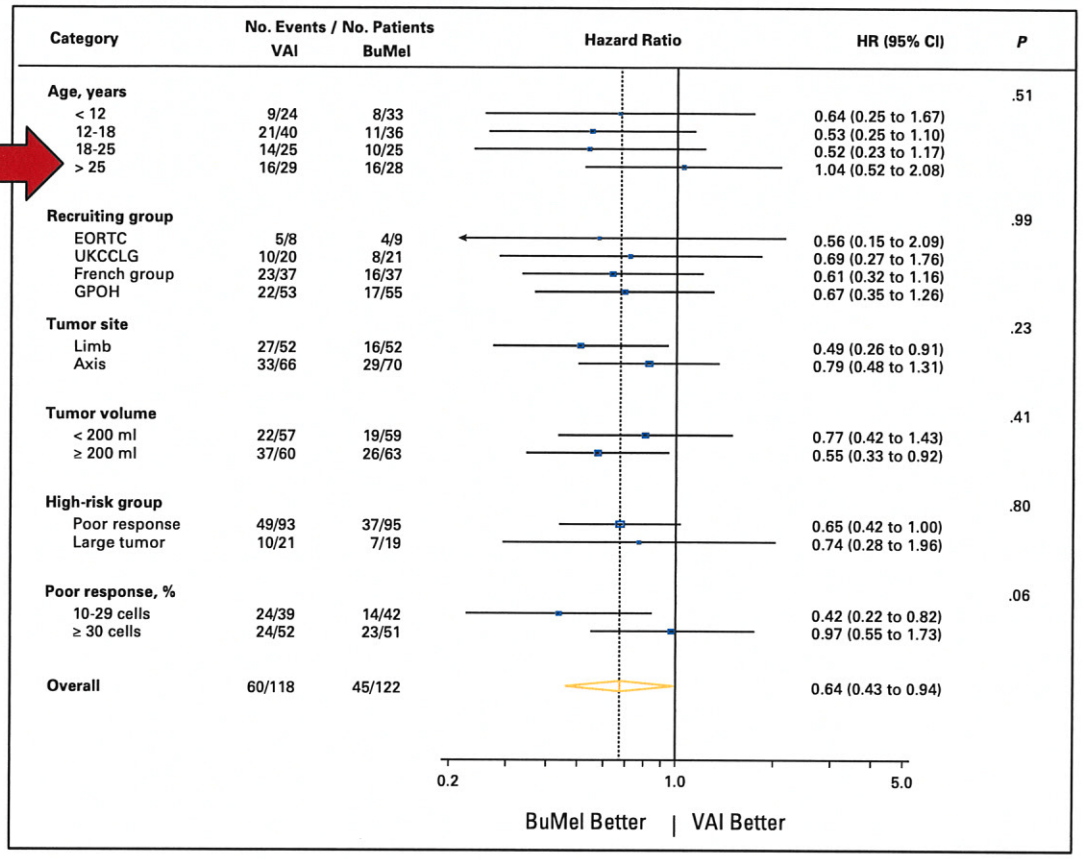


Outcome	Intention-To-Treat Analysis		As-Treated Population*	
	VAI Arm (n = 118)	BuMel Arm (n = 122)	VAI Arm, n = 116	BuMel Arm (n = 93)
EFS				
No. and type of events	60	45	60	33
Progression/relapse	56	37	56	27
Local progression or relapse	8	5	8	4
Without metastases	48	32	48	23
Distant metastases				
With or without local progression or relapse				
Secondary malignancy	3	2	3	2
Death as first reported event†	1	6	1	4
Treatment-related death	0	3‡	0	2
Death from other cause	1	2§	1	1
Death from unknown cause	0	1	0	1
3-year EFS since randomization, % (95% CI)	56.7 (47.6 to 65.4)	69.0 (60.2 to 76.6)	56.0 (46.8 to 64.8)	71.7 (61.8 to 79.9)
8-year EFS since randomization, % (95% CI)	47.1 (37.7 to 56.8)	60.7 (51.1 to 69.6)	46.3 (36.8 to 56.0)	62.8 (51.9 to 72.6)
HR of event (95% CI)‖	1	0.64 (0.43 to 0.95)¶	1	0.57 (0.37 to 0.88)
P		.026#		.010
Adjusted HR of event (95% CI)#	1	0.65 (0.44 to 0.96)	1	0.58 (0.38 to 0.89)
P		.032		.012
Overall survival				
No. and cause of deaths	53	37	53	28
Due to progression/relapse	48	31	48	24
Treatment-related death	0	3§	0	2
Secondary malignancy	4	0	4	0
Other cause	1	2‖	1	1
Unknown cause		1		1
3-y OS from randomization, % (95% CI)	72.2 (63.3 to 79.6)	78.0 (69.6 to 84.5)	71.7 (62.8 to 79.2)	79.2 (69.8 to 86.3)
8-y OS from randomization, % (95% CI)	55.6 (45.8 to 65.1)	64.5 (54.4 to 73.5)	55.0 (45.1 to 64.5)	65.4 (54.1 to 75.3%)
HR of death (95% CI)‖	1	0.63 (0.41 to 0.95)	1	0.58 (0.37 to 0.92)
P		.028		.019
Adjusted HR of death (95% CI)#	1	0.64 (0.42 to 0.97)	1	0.59 (0.37 to 0.93)
P		.035		.022

EFS

OS

SUB-GROUP ANALYSIS



PRIMARY METASTATIC DISEASE

20%-25% of patients diagnosed with metastatic disease

LUNG	10%
BONE / BONE MARROW	10%
COMBINATIONS / OTHERS	5%

- Treated with the same treatment as patients with localised disease but
- Worse prognosis

ONLY LUNG METASTASES

CLASSIC CT versus HIGH-DOSE CT ???

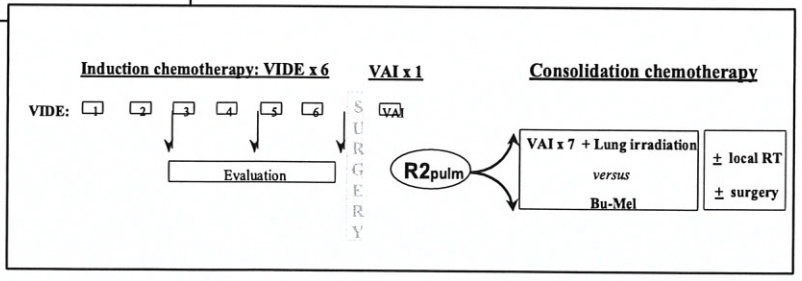
EURO-EWING 99 and 2008 PROTOCOLS

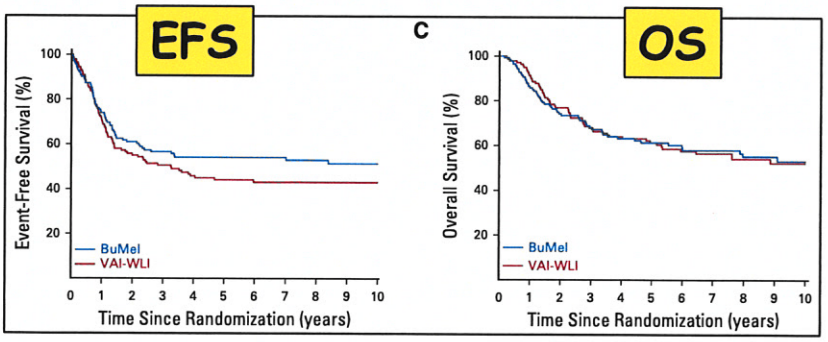
287pts

original report

High-Dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases: Results of the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008

Uta Dirksen, MD[1]; Bernadette Brennan, MD[2]; Marie-Cécile Le Deley, MD, PhD[3]; Nathalie Cozic, MSc[4]; Henk van den Berg, MD[5]; Vivek Bhadri, MD, PhD[6]; Bénédicte Brichard, MD[7]; Line Claude, MD[8]; Alan Craft, MD[9]; Susanne Amler, PhD[10]; Natalie Gaspar, MD[4]; Hans Gelderblom, MD, PhD[11]; Robert Goldsby, MD[12]; Richard Gorlick, MD[13]; Holcombe E. Grier, MD[14]; Jean-Marc Guinbretiere, MD[15]; Peter Hauser, MD, PhD[16]; Lars Hjorth, MD, PhD[17]; Katherine Janeway, MD[14]; Heribert Juergens, MD[18]; Ian Judson, MD[19]; Mark Krailo, PhD[20]; Jarmila Kruseova, MD, PhD[21]; Thomas Kuehne, MD[22]; Ruth Ladenstein, MD[23]; Cyril Lervat, MD[24]; Stephen L. Lessnick, MD, PhD[25]; Ian Lewis, MD[26]; Claude Linassier, MD[27]; Perrine Marec-Berard, MD[28]; Neyssa Marina, MD[29]; Bruce Morland, MD[30]; Hélène Pacquement, MD[31]; Michael Paulussen, MD[32]; R. Lor Randall, MD[33]; Andreas Ranft, PhD[34]; Gwénaël Le Teuff, PhD[35]; Keith Wheatley, DPhil[36]; Jeremy Whelan, MD[37]; Richard Womer, MD[38]; Odile Oberlin, MD[4]; and Douglas S. Hawkins, MD[39] on behalf of the Euro-E.W.I.N.G. 99 and Ewing 2008 Investigators





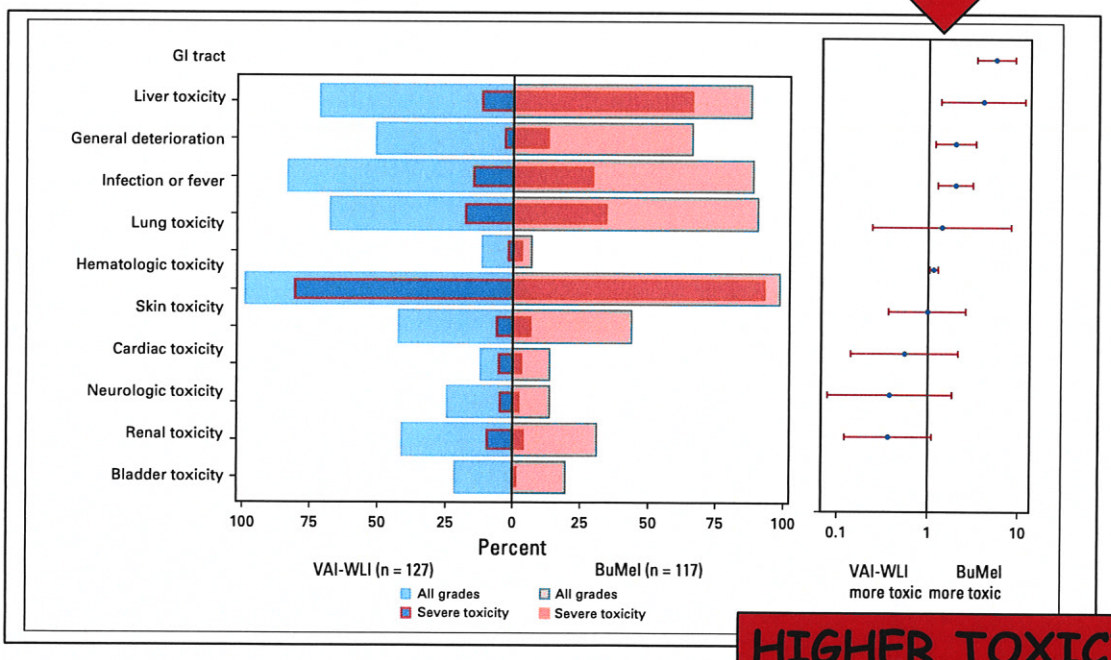
NO DIFFERENCE

EFS

OS

Outcome	Intention-to-Treat Analysis: VAI Plus WLI Arm (n = 143)	Intention-to-Treat Analysis: BuMel Arm (n = 144)	As-Treated Population*: VAI Plus WLI Arm (n = 131)	As-Treated Population*: BuMel Arm (n = 123)
EFS, No.				
No. and type of events	78	66	72	56
Progression/relapse	77	59	71	49
Local progression or relapse without metastases	14	6	13	5
Distant metastases with or without local progression or relapse	63	52	58	43
Site of progression missing	0	1	0	1
Secondary malignancy	1	1	1	1
Death as first reported event†	0	6	0	6
Treatment-related death	0	4	0	4
Death from other cause	0	1	0	1
Death from unknown cause	0	1	0	1
3-year EFS from randomization, % (95% CI)	50.6 (42.3 to 58.8)	56.6 (48.3 to 64.6)	51.5 (43.0 to 60)	57.7 (48.8 to 66.2)
8-year EFS from randomization,% (95% CI)	43.1 (34.9 to 51.6)	52.9 (44.5 to 61.2)	43.6 (35.2 to 52.4)	53.6 (44.5 to 62.4)
Unadjusted HR of event (95% CI)‡	1	0.79 (0.56 to 1.10)§	1	0.80 (0.56 to 1.13)
		P = .16		*P* = .21
Adjusted HR of event (95% CI)‖		0.81 (0.58- to 1.12)		0.78 (0.55 to 1.11)
		P = .1998		*P* = .17
Overall survival, No.				
Total/cause of death	60	58	57	49
Due to progression/relapse	58	49	55	40
Treatment-related	1	6	1	6
Secondary malignancy	0	1	0	1
Other	1	1	1	1
Unknown	0	1	0	1
3-year OS from randomization, % (95% CI)	68.0 (59.7 to 75.2)	68.2 (60.0 to 75.4)	67.4 (58.8 to 74.9)	69.1 (60.3 to 76.7)
8-year OS from randomization, % (95% CI)	54.2 (45.3 to 62.8)	55.3 (46.1 to 64.0)	53.7 (44.5 to 62.6)	57.2 (47.6 to 66.3)
Unadjusted HR of death (95% CI)‡	1	1.00 (0.70 to 1.44)	1	0.95 (0.65 to 1.39)
		P = .99		*P* = .77
Adjusted HR of event (95% CI)‖		0.99 (0.68 to 1.42)		0.91 (0.62 to 1.35)
		P = .93		*P* = .65

TOXICITY



HIGHER TOXICITY

RECURRENT DISEASE

- associated with very poor outcomes
- patients who relapse within 24 months after diagnosis 5-year survival of <10%

- Favourable prognostic factors at relapse are local relapse, younger age, isolated pulmonary recurrence and low LDH levels

- Few clinical trials completed
- The vast majority of the value of different therapeutic approaches is drawn from retrospective analyses

NO STANDARD TREATMENT !!

TOPOTECAN + CYCLOPHOSPHAMIDE

TEMOZOLOMIDE + IRINOTECAN

GEMCITABINE + DOCETAXEL

IFOSFAMIDE HIGH-DOSE

rEECur TRIAL

FIRST INTERIM

Results of the first interim assessment of rEECur, an international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma

ASCO 2019

MG McCabe, V Moroz, M Khan, U Dirksen, A Evans, N Fenwick, N Gaspar, J Kanerva, T Kühne, A Longhi, R Luksch, C Mata, M Phillips, K Sundby Hall, CM Valverde Morales, AJ Westwood, M Winstanley, J Whelan, K Wheatley

SECOND INTERIM

ASCO 2020

Results of the second interim assessment of rEECur, an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES)

MG McCabe, L Kirton, M Khan, N Fenwick, U Dirksen, N Gaspar, J Kanerva, T Kuehne, A Longhi, R Luksch, C Mata, M Phillips, A Safwat, SJ Strauss, K Sundby Hall, CM Valverde Morales, AJ Westwood, M Winstanley, J Whelan, K Wheatley

1st ENDPOINT = OBJECTIVE RESPONSE

Treatment Overall Response	GD	IT	TC or IFOS	Overall
Complete response	1	4	2	7 (2%)
Partial response	6	14	27	47 (15%)
Stable disease	16	27	29	72 (23%)
Progressive disease	4	14	11	29 (9%)
Discontinued before cycle 4	36	28	53	117 (38%)
Not evaluable	1	1	4	3 (1%)
Missing	1	16	15	35 (11%)
Total	65	**104**	**141**	**310 (100%)**

Treatment Overall Response	GD	IT	TC or IFOS	Overall
Non responder	57 (89%)	70 (80%)	97 (77%)	224 (81%)
Responder	7 (11%)	18 (20%)	29 (23%)	54 (19%)
Total	64	**88**	**126**	**278**

FIRST INTERIM

GD less effective than IT, TC or IFO

SECOND INTERIM

IT less effective than TC or IFO but more grade 3 GI toxicity, less FN

NEXT

Adding PLATINUM + ETOPOSIDE
1st endpoint = PFS

EMERGING DRUGS

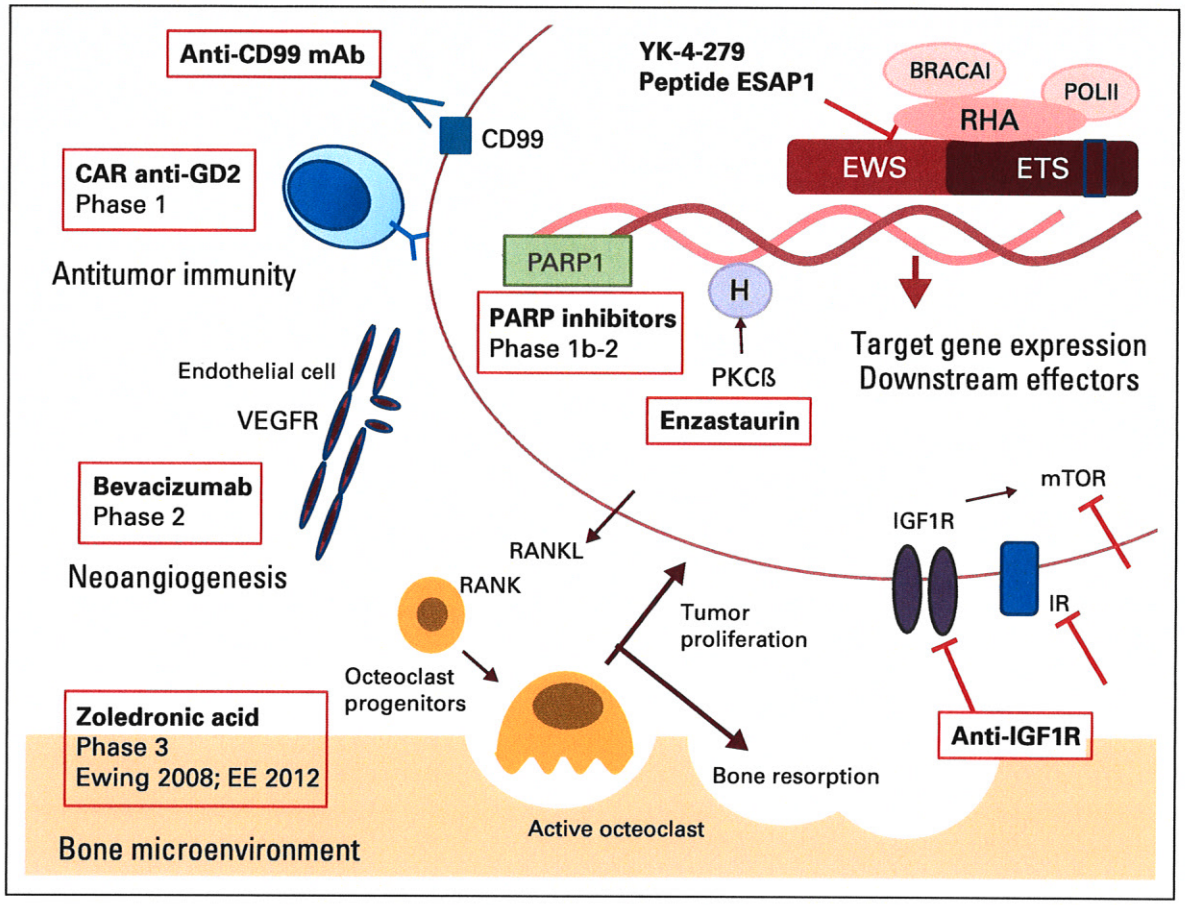
MULTI-TARGETED KINASE INHIBITORS

	Sorafenib[1]	Lenvatinib[2]	Regorafenib[3]	Regorafenib[4]	Cabozantinib[5]	Apatinib[6]
N	35	30	26	22	42	37
PR	9%	7.7%	7.7%	14%	11.9%	43%
4 month PFS 95% CI	46% (28-63%)	33% (17-54%)	62% (40-77%)	44% NA	NA	57% (39-71%)
Median PFS (mos) 95% CI	4 (2-5)	3.4 (1.8-6.5)	4 (2-6.5)	3.6 (2-7.6)	6.2 (5.4-8.2)	4.5 (3.5-6.3)
Median OS (mos) 95% CI	7 (7-8)	NA	11.3 (5.9-23.9)	11 (4.7-26.7)	10.6 (7.2-13.2)	9.9 (8-18.9)

[1]Grignani et al 2012; [2]Gaspar et al. 2018; [3]Duffaud et al. 2019, [4]Davis et al. 2019, [5]Italiano, CTOS 2018 [6]Xie et al. Oncologist, 2018; NA=Not Available

ASCO 2019

RESULTS:	Apatinib + Camrelizumab	Apatinib
PFS at 4 mos	62% (46%, 76%)	57% (39, 71%)
PFS at 6 mos	44% (28%, 59%)	37% (21%, 52%)
ORR (CR+PR)	9 (22%)	16 (43%)
CBR (CR+PR+SD x 6 mos)	18 (44%)	13 (35%)
First Imaging Timepoint	8 weeks	4 weeks
Apatinib Dose	500 mg	750 mg
Lung only disease	42%	73%
Grade ¾ AEs	70%	



RARE SUB-TYPES

EWING-LIKE SARCOMA ?

- For some of them (CIC-,NFATC2,…), higher rate in adult patients
- Currently, patients presenting with these variants are treated with Ewing-like regimens, although their best treatment and even their natural history are poorly known

- Inclusion in prospective registries is worthwhile…

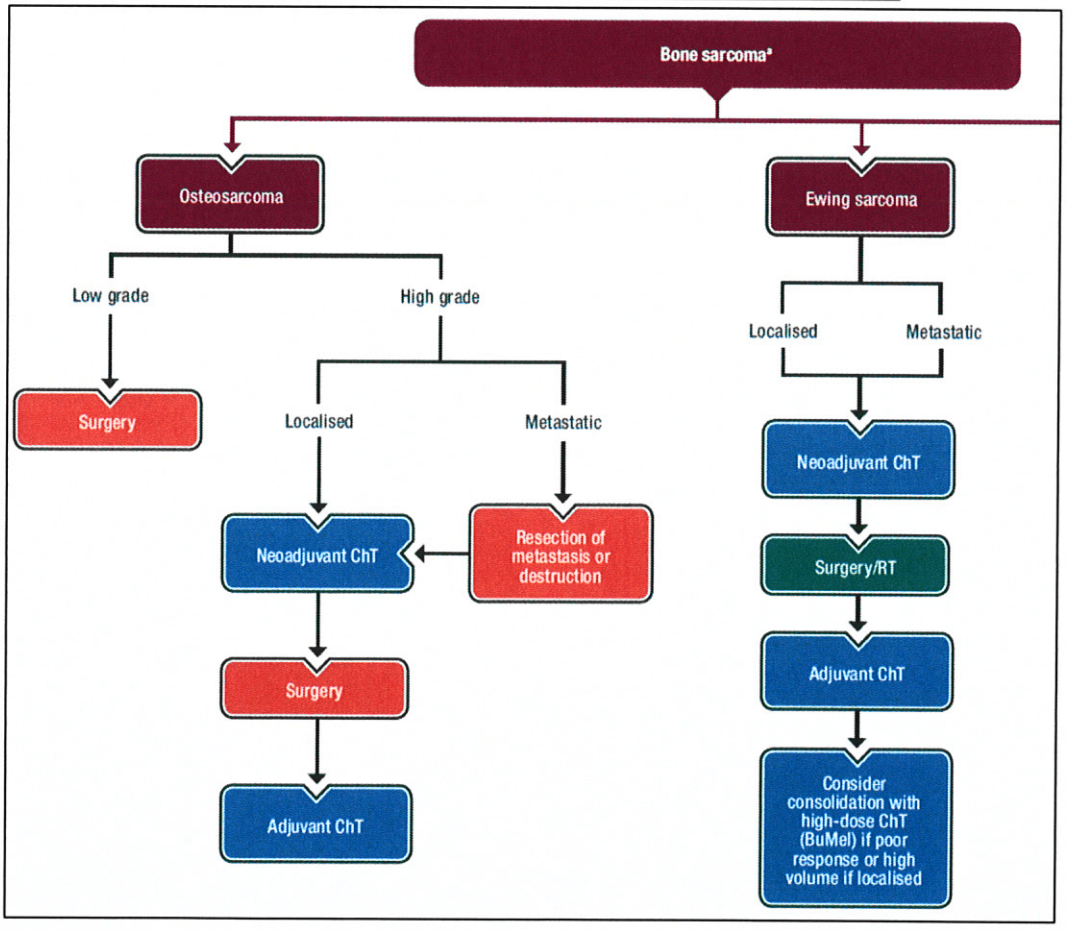
4 CONCLUSIONS

GLOBAL MANAGEMENT

- requires a **multidisciplinary team** including

- Paediatric and Medical oncologists
- Radiation oncologists
- Orthopaedic surgeons
- General surgeons
- Anatomopathologists
- Geneticists
- Nurses
- ...

GLOBAL MANAGEMENT



OSTEOSARCOMA

NEOADJUVANT CT

> 18 years

WITHOUT MTX

API X 3 + AI X2

WITH MTX

MAP X 2

OSTEOSARCOMA

ADJUVANT CT

GOOD RESPONDERS

WITHOUT MTX

API X 2 + AI X2

WITH MTX

MAP X 4

POOR RESPONDERS

WITHOUT MTX

EI X 5

WITH MTX

MAP X 4

RECURRENT SETTING

NO STANDARD TREATMENT !!!

IFOSFAMIDE (HIGH-DOSE) OR CYCLOPHOSPHAMIDE +/- ETOPOSIDE +/- CARBOPLATIN

CYCLOPHOSPHAMIDE + TOPOTECAN OR ETOPOSIDE

GEMCITABINE

DOCETAXEL + GEMCITABINE

HIGH-DOSE MTX

EWING SARCOMA

NEOADJUVANT CT

VDC X 5 + IE X 4 every 2 weeks

ADJUVANT CT

GOOD RISK

VC X 2 + IE X 3 every 2 weeks

RT in case of lung M+

POOR RISK

< 25 years

VAI x 1 + BU-MELPHALAN

> 25 years

VC X 2 + IE X 3 every 2 weeks

RECURRENT SETTING

NO STANDARD TREATMENT !!

TOPOTECAN + CYCLOPHOSPHAMIDE

IFOSFAMIDE HIGH-DOSE

IRINOTECAN + TEMOZOLOMIDE

GEMCITABINE + DOCETAXEL

THANKS !!!