Nouveautés 2018 autour des sarcomes des parties molles

D Orbach, au nom du comité MMT de la SFCE
Centre oncologique SIREDO
Institut Curie
Soins, innovation recherche en oncologie de l'enfant, l'adolescent et du jeune adulte

Déclaration d'intérêt

- **Conflit d'intérêt :** Activité de consultant pour Bayer (2018, *larotrectinib*)

- **Lien d'intérêt** : Novartis Pharma France (congrès GSF-GETO 2018)

Place du traitement d'entretien dans les RMS localisés de haut risque

Maintenance low dose chemotherapy in patients with high risk rhabdomyosarcoma

Gianni Bisogno on behalf of the European paediatric Soft tissue sarcoma Study Group (EpSSG)

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Gianni Bisogno 1

The EpSSG RMS2005 protocol

Eligibility criteria

a) Patients with pathologically proven RMS
b) No evidence of metastasis
c) Age 0-21
d) Previously untreated
e) Written informed consent

EpSSG Risk stratification

- Low risk
- Standard Risk
- **High Risk**
- Very high ris

•Unfavorable site
•Unfavorable histology (alveolar)
•Nodal involvement

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The RMS2005 Maintenance trial

STANDARD TREATMENT
(6-8 months)
- 9 cycles Ifosfamide, Vincristine, Actinomicyn D +/- Doxorubicine
- Surgery
-Radiotherapy

No radiological evidence of tumor

randomize

EXPERIMENTAL ARM
Maintenance
(VNL-CPM x 6 mos.)

STANDARD ARM
No Maintenance

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RMS 2005 - Maintenance Treatment Regimen

Vinorelbine: 25 mg/m² i.v. day 1,8,15 of every 28 cycle x 6

Cyclophosphamide: 25 mg/ m²/day p.o. daily for every 28 day cycle x 6

Pilot study in pretreated RMS patients (Casanova et al Cancer 2004)

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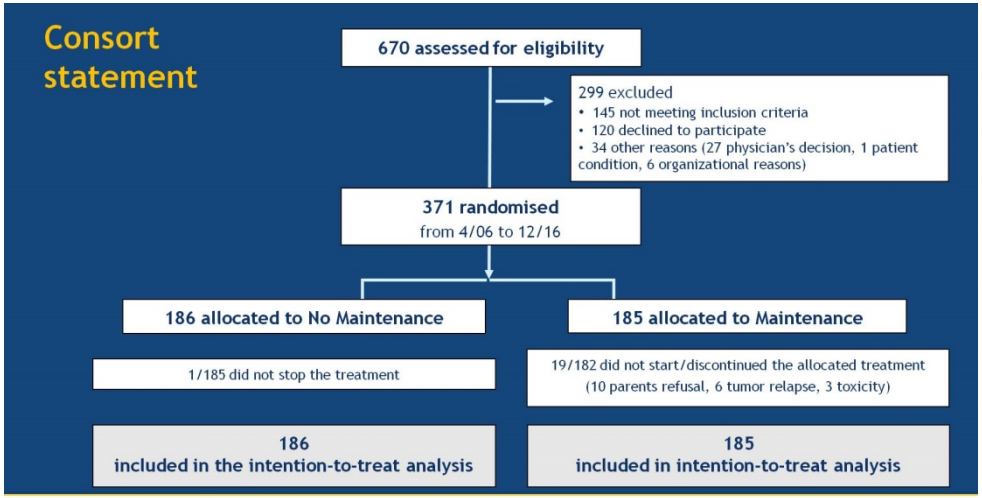
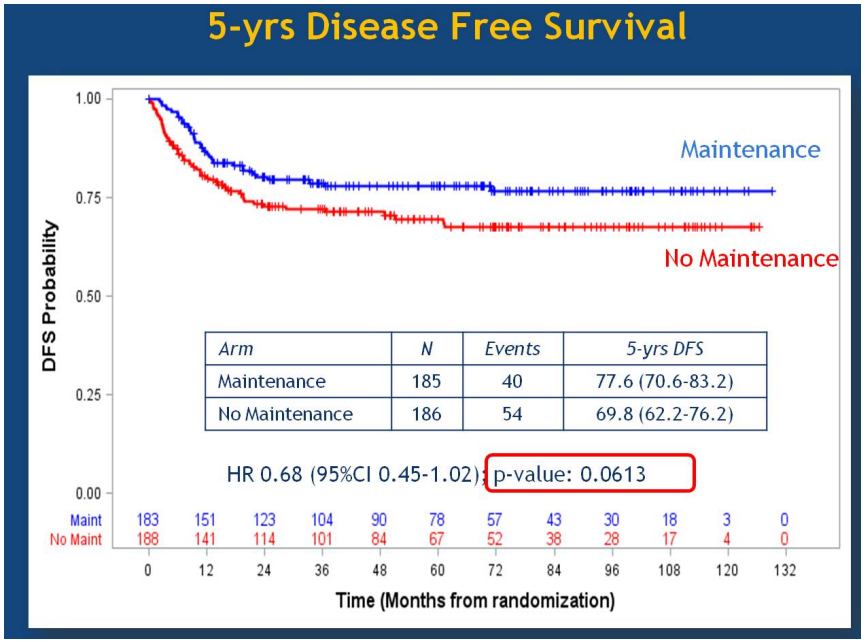
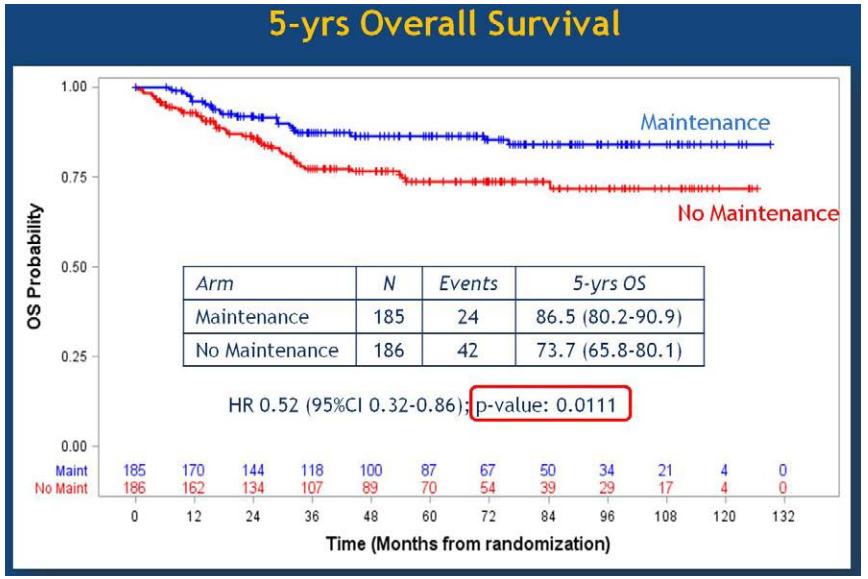




- **Amélioration globale des survies**
- **Meilleure survie avec 6 mois de vinorelbine – cyclophosphamide**
- **Prochain protocole (Far-RMS) : 6 mois vs. 12 mois ?**



EpSSG European Paediatric Soft Tissue Sarcoma Study Group

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

RMS alvéolaire avec extension ganglionnaire

Fusion Status in Patients With Lymph Node-Positive (N1) Alveolar Rhabdomyosarcoma Is a Powerful Predictor of Prognosis: Experience of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG)

Soledad Gallego, MD, PhD [1]; Ilaria Zanetti, MD[2]; Daniel Orbach, MD[3]; Dominique Ranchère, MD[4]; Janet Shipley, FRCPath[5]; Angelica Zin, MD[6]; Christophe Bergeron, MD[4]; Gian Luca de Salvo, MD[7]; Julia Chisholm, MD[8]; Andrea Ferrari, MD[9]; Meriel Jenney, MD[10]; Henry C. Mandeville, MD[8]; Timothy Rogers, MD[11]; Johannes H.M. Merks, MD [12]; Peter Mudry, MD[13]; Heidi Glosli, MD[14]; Giuseppe Maria Milano, MD[15]; Sima Ferman, MD[16]; and Gianni Bisogno, MD[2]; on behalf of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG)

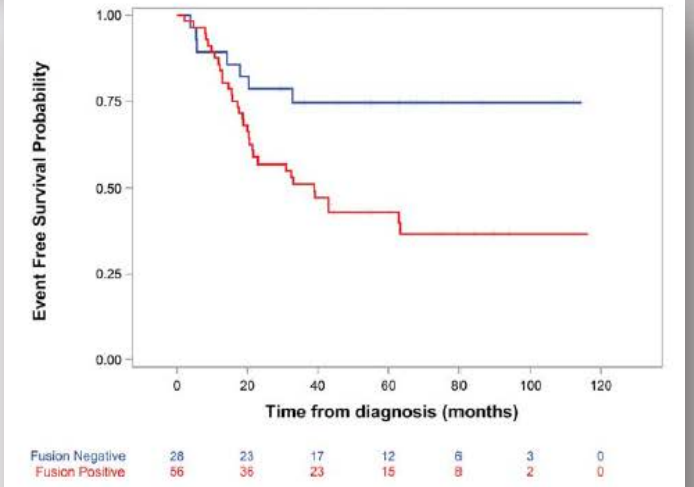


Figure 1. Kaplan-Meier curves representing 5-year event-free survival (EFS) by fusion status. The EFS rate for patients with fusion-positive tumors was 43% compared with 74.4% for those with fusion-negative tumors ($P = .01$).

- **Groupe « très haut risque » :**
- ➢ **Evaluation des aires ganglionnaires de drainage systématique (clinique/PET/IRM/Echographie/ponction)**
- ➢ **Discuter technique ganglions sentinelle systématique**
- ➢ **Importance de la biologie moléculaire**

[Cancer 2018], 103 pts

Pronostic en fonction de la réponse tumorale à 3 cures

Prognostic Relevance of Early Radiologic Response to Induction Chemotherapy in Pediatric Rhabdomyosarcoma: A Report From the International Society of Pediatric Oncology Malignant Mesenchymal Tumor 95 Study

Bas Vaarwerk, MD[1]; Johanna H. van der Lee, MD, PhD[2]; Willemijn B. Breunis, MD, PhD[1]; Daniel Orbach, MD[3]; Julia C. Chisholm, MD, PhD[4]; Nathalie Cozic, MSc[5]; Meriel Jenney, MD[6]; Rick R. van Rijn, MD, PhD[7]; Kieran McHugh, MD[8]; Soledad Gallego, MD, PhD[9]; Heidi Glosli, MD, PhD[10]; Christine Devalck, MD[11]; Mark N. Gaze, MD[12]; Anna Kelsey, MD[13]; Christophe Bergeron, MD[14]; Michael C. G. Stevens, MD[15]; Odile Oberlin, MD[16]; Veronique Minard-Colin, MD, PhD[16]; and Johannes H. M. Merks, MD, PhD[1]

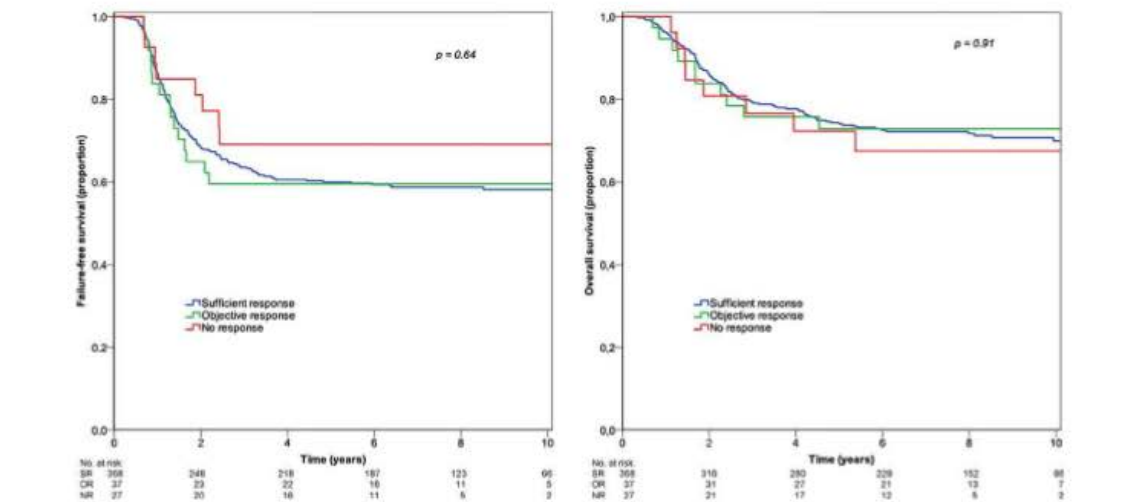


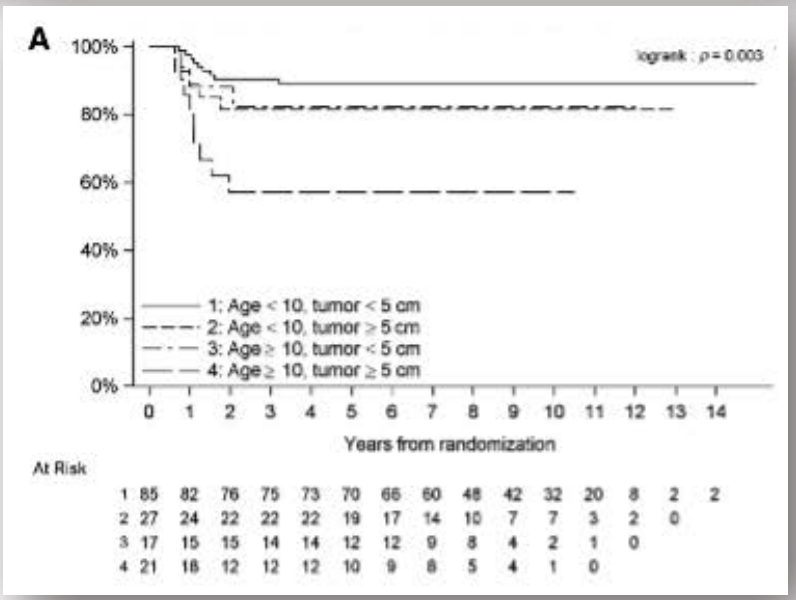
Figure 2. (A) Failure-free survival and (B) overall survival based on an early radiologic response for 432 patients included in SIOP MMT-95. MMT-95 indicates Malignant Mesenchymal Tumor 95; NR, no response; OR, objective response; SIOP, International Society of Pediatric Oncology; SR, sufficient response.

- **RMS, tumeur chimio-sensible : 85% de PR/CR**
- **Une bonne réponse précoce volumétrique n'est pas associée à une amélioration du pronostic vital**
- **Permet parfois/souvent d'envisager un traitement local plus conservateur**
- 432 patients, [*Cancer* 2018]

RMS paratesticulaires

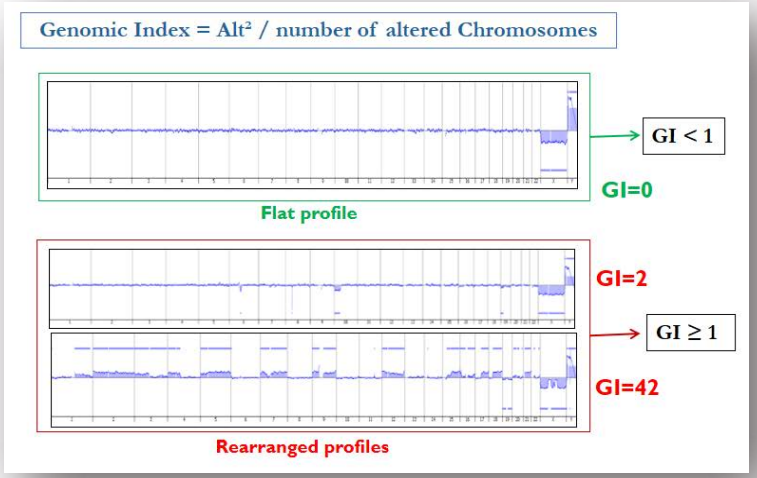
Paratesticular rhabdomyosarcoma in children and adolescents—Outcome and patterns of relapse when utilizing a nonsurgical strategy for lymph node staging: Report from the International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumour 89 and 95 studies

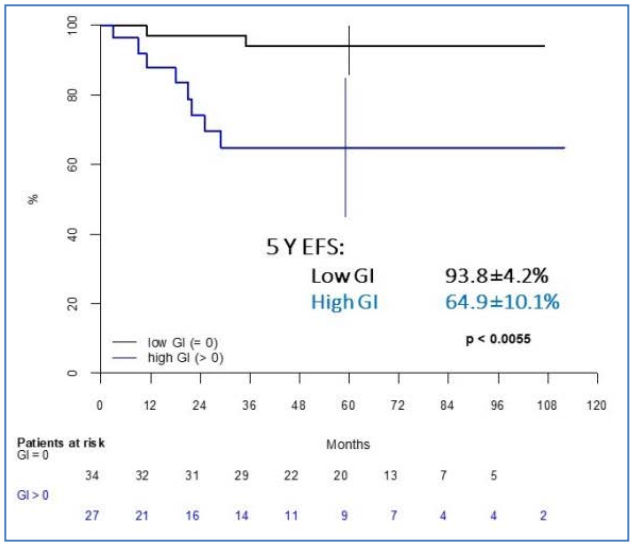
Timothy Rogers[1] | Veronique Minard-Colin[2] | Nathalie Cozic[3] | Meriel Jenney[4] | Johannes H. M. Merks[5] | Soledad Gallego[6] | Christine Devalck[7] | Mark N. Gaze[8] | Anna Kelsey[9] | Odile Oberlin[10] | Mike Stevens[11] | Richard D. Spicer[1] | Christophe Bergeron[12] | Helene Martelli[13]



- **11% des sites ; OS : 94%** (95% CI, 88.8–96.5)
- **78% des évènements tumoraux sont dans les aires ganglionnaires RP**
- ➢ **Bien explorer les aires RP : PET scan et TDM**
- ➢ **Staging ganglionnaire chirurgical : si > 10 ans et taille > 5 cm**
- ➢ **Si N+ : groupe HR (cf.) et radiothérapie RP**
- 159 pts, [*Ped Blood Cancer* 2017]

Valeur pronostique de la CGH dans les synovialosarcomes de l'enfant et l'adolescent





Taux de métastases / décès à 5 ans :

IG bas	**6.2%**	**[0.0-14.4]**
IG élevé	**25.9%**	**[8.1-43.8]**

Inhibiteurs de NTRK

Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Theodore W Laetsch, Steven G DuBois*, Leo Mascarenhas, Brian Turpin, Noah Federman, Catherine M Albert, Ramamoorthy Nagasubramanian, Jessica L Davis, Erin Rudzinski, Angela M Feraco, Brian B Tuch, Kevin T Ebata, Mark Reynolds, Steven Smith, Scott Cruickshank, Michael C Cox, Alberto S Pappo*, Douglas S Hawkins**

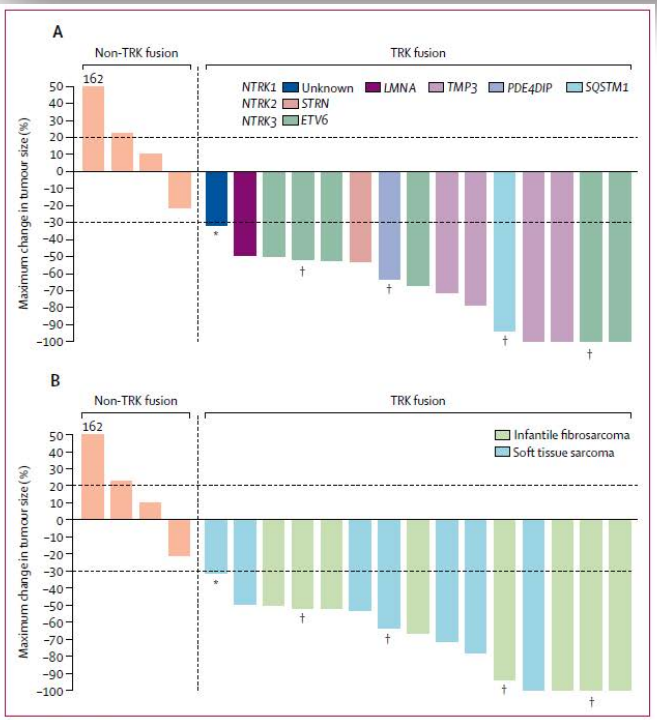


Figure 3: Waterfall plot of maximal change in tumour size

- ➢ Toxicité modérée : hépatique, hématologique, vomissements
- ➢ 14/15 cas (93%) de réponse si NTRK+
  0/7 cas (0%) si pas de fusion
- ➢ Pas de donnée sur le long terme
- Quand arrêter ?
- Inhibiteurs de seconde génération en cours

24 pts, [*Lancet Oncol* 2018]

A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion–Positive Solid Tumors

Alexander Drilon[1,2], Ramamoorthy Nagasubramanian[3], James F. Blake[4], Nora Ku[5], Brian B. Tuch[5], Kevin Ebata[5], Steve Smith[5], Veronique Lauriault[5], Gabrielle R. Kolakowski[4], Barbara J. Brandhuber[4], Paul D. Larsen[4], Karyn S. Bouhana[4], Shannon L. Winski[4], Robyn Hamor[4], Wen-I Wu[4], Andrew Parker[4], Tony H. Morales[4], Francis X. Sullivan[4], Walter E. DeWolf[4], Lance A. Wollenberg[4], Paul R. Gordon[3], Dorothea N. Douglas-Lindsay[3], Maurizio Scaltriti[6,7], Ryma Benayed[7], Sandeep Raj[7], Bethany Hanusch[1], Alison M. Schram[1], Philip Jonsson[8], Michael F. Berger[7,8,9], Jaclyn F. Hechtman[6,7], Barry S. Taylor[4,8,9], Steve Andrews[4], S. Michael Rothenberg[5], and David M. Hyman[1,2]

Small Molecule Therapeutics

Mechanisms of Resistance to NTRK Inhibitors and Therapeutic Strategies in NTRK1-Rearranged Cancers

Miho J. Fuse[1,2], Koutaroh Okada[1,2], Tomoko Oh-hara[1], Hayato Ogura[1,2], Naoya Fujita[1,2], and Ryohei Katayama[1]

Molecular Cancer Therapeutics

Tumeurs desmoïdes pédiatriques

The EpSSG NRSTS 2005 treatment protocol for desmoid-type fibromatosis in children: an international prospective case series

Daniel Orbach, Bernadette Brennan, Gianni Bisogno, Max Van Noesel, Véronique Minard-Colin, Julia Daragjati, Michela Casanova, Nadege Corradini, Ilaria Zanetti, Gian Luca De Salvo, Anne Sophie Defachelles, Anna Kelsey, Myriam Ben Arush, Nadine Francotte, Andrea Ferrari

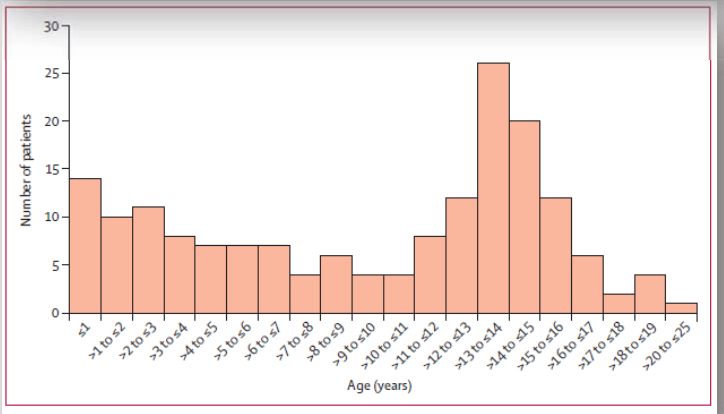


Figure 2: Age distribution of patients

Systemic therapy of aggressive fibromatosis in children and adolescents: Report of the Cooperative Weichteilsarkom Studiengruppe (CWS)

Monika Sparber-Sauer[1] | Guido Seitz[2] | Thekla von Kalle[3] | Christian Vokuhl[4] | Ivo Leuschner[4*] | Monika Scheer[1] | Marc Münter[5] | Gustaf Ljungman[6] | Stefan S. Bielack[1,7] | Felix Niggli[8] | Ruth Ladenstein[9] | Thomas Klingebiel[10] | Joerg Fuchs[11] | Ewa Koscielniak[1,12] | On Behalf of the CWS Study Group

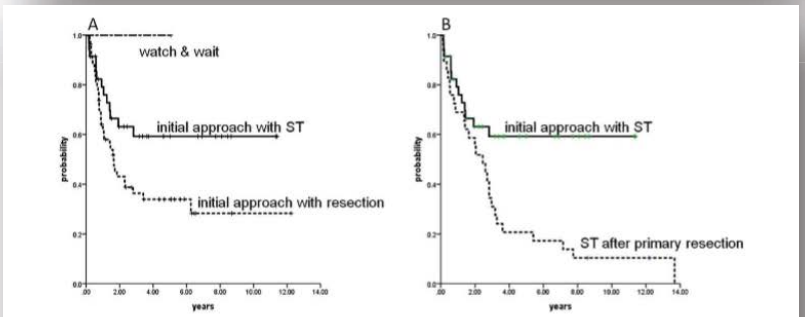


FIGURE 1 Kaplan–Meier estimates presenting EFS of (A) 90 patients with aggressive fibromatosis according to primary approach ($P = 0.08$) and (B) 64 patients with aggressive fibromatosis treated with ST ($P = 0.005$)

Pediatr Blood Cancer. 2018;65:e26943. https://doi.org/10.1002/pbc.26943

Lancet Child Adolesc Health 2017; 1: 284–92
Published Online September 11, 2017
http://dx.doi.org/10.1016/S2352-4642(17)30045-7

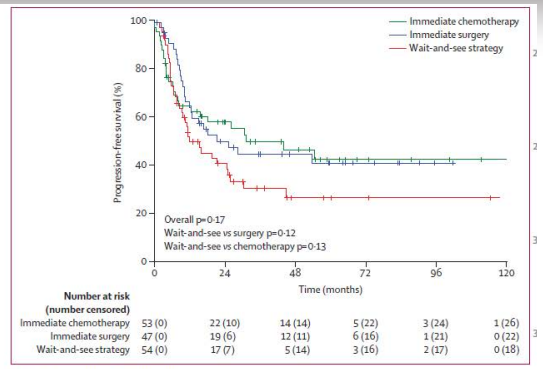


Figure 3: Progression-free survival
The p values are the log-rank test values.

- Expériences EpSSG (173 pts) et GPOH (90 pts)
- OS ≈ 100% ; EFS 36-44%
- « Efficacité » de MTX-Vinblastine : PR 35-53% ; SD 39-45%

➢ Validation de l'approche de surveillance ou médicale en 1ière ligne

Sarcomes et *DICER-1*

Review

Clinical Cancer Research

DICER1 and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies

Kris Ann P. Schultz[1,2,3], Gretchen M. Williams[1,2,3], Junne Kamihara[4], Douglas R. Stewart[5], Anne K. Harris[1,2,3], Andrew J. Bauer[6], Joyce Turner[7], Rachana Shah[8], Katherine Schneider[9], Kami Wolfe Schneider[10], Ann Garrity Carr[11], Laura A. Harney[11], Shari Baldinger[12], A. Lindsay Frazier[4], Daniel Orbach[13], Dominik T. Schneider[14], David Malkin[15], Louis P. Dehner[16], Yoav H. Messinger[1,2,3], and D. Ashley Hill[17]

Table 1. Indications for *DICER1* testing

Major:	Minor:
– Individuals with PPB (all types)	– Lung cyst(s) in adults
– Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral	– Renal cyst(s)[a]
– Thoracic ERMS[a]	– Wilms tumor
– Cystic nephroma	– Multinodular goiter or differentiated thyroid cancer
– Genitourinary sarcomas including undifferentiated sarcoma[a]	– ERMS other than thoracic or gynecologic[a]
– Ovarian SLCT	– Poorly differentiated neuroendocrine tumor
– Gynandroblastoma	– Undifferentiated sarcoma[a]
– Uterine cervical or ovarian ERMS[a]	– Macrocephaly[a]
– Genitourinary/gynecologic neuroendocrine tumors	– Consider testing for any childhood cancer in constellation with any other minor criteria
– Multinodular goiter or thyroid cancer in two or more first-degree relatives or in an index patient with a family history consistent with *DICER1* syndrome[a]	
– Childhood-onset multinodular goiter[a] or differentiated thyroid cancer[a]	
– CBME	
– NCMH	
– Pineoblastoma	
– Pituitary blastoma	

NOTE: Consider germline *DICER1* genetic testing in an individual with one major or two minor indications.

[a]Multinodular goiter, differentiated thyroid cancer (papillary or follicular carcinomas), sarcomas, Wilms tumor, neuroendocrine tumors, renal cysts, and macrocephaly may also be associated with other genetic predisposition syndromes. Consider testing for additional hereditary cancer predispositions and/or a next-generation sequencing panel that includes deletion/duplication of *DICER1* and/or other genes indicated by clinical and family history.

COG ARST14B1 Targeted Sequencing of Pediatric Rhabdomyosarcoma

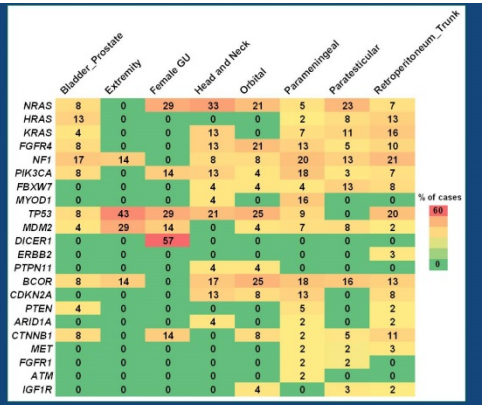
Jack Shern MD
Lasker Research Scholar
Pediatric Oncology Branch
Center for Cancer Research
National Cancer Institute

James B. Nachman Endowed ASCO Junior Faculty Award in Pediatric Oncology

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Shern 1

Percentage of cases summarized by anatomy

- *TP53* pathway mutations are common in fusion negative extremity lesions
- Female genitourinary cases account for all of the *DICER1* lesions
- *HRAS* and *KRAS* do not occur in orbital tumors
- *MYOD1* mutations are restricted to the head



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Quoi de neuf?

Sarcomes osseux pédiatriques (ou pas..)

GROUPE SARCOME FRANÇAIS

GSF-GETO 2018
P Marec-Berard pour le GROUPOS

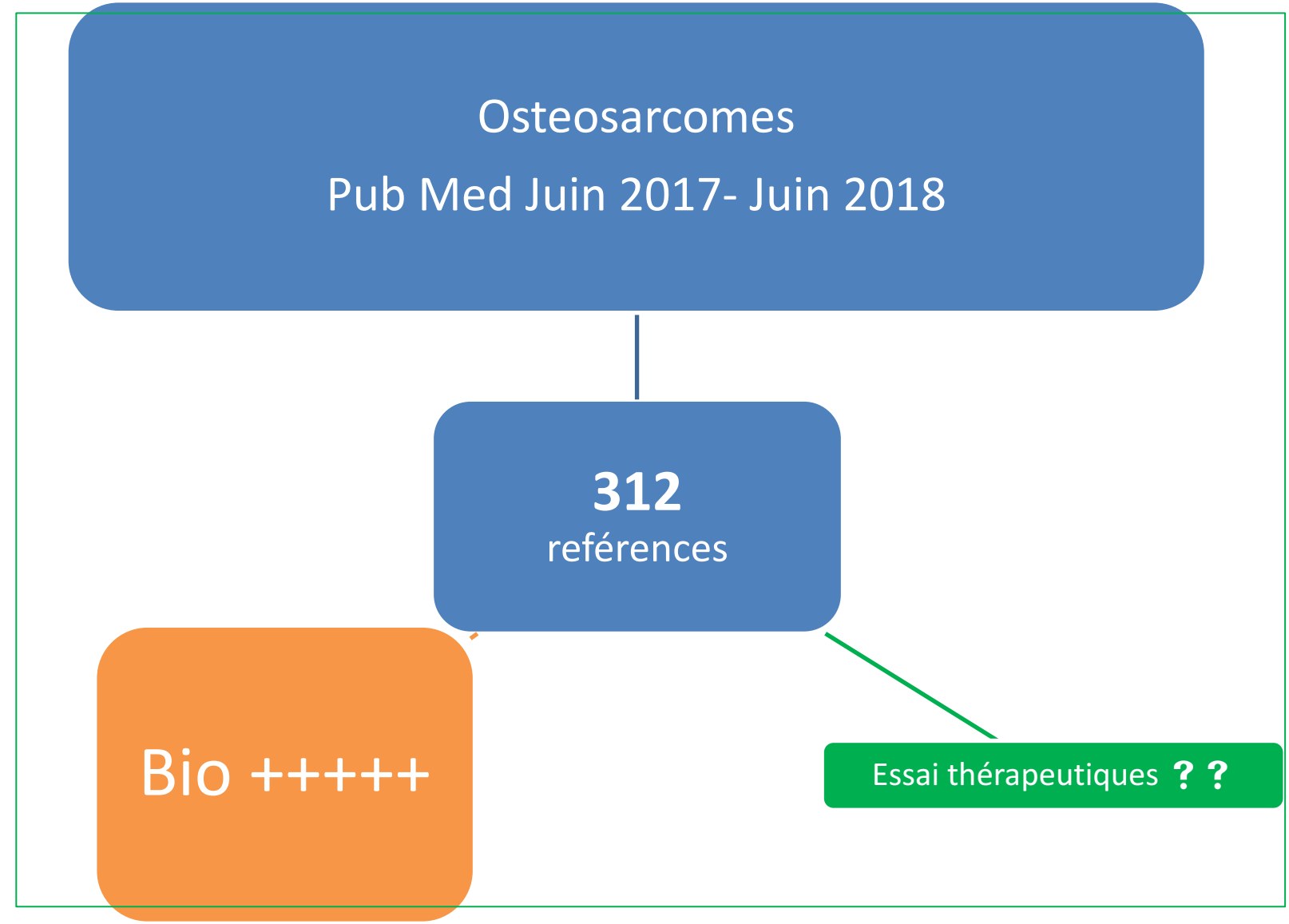
Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent

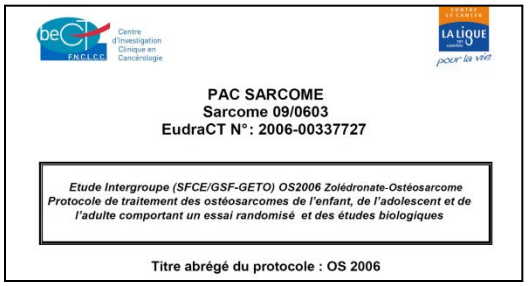
GROUPE SARCOME FRANÇAIS

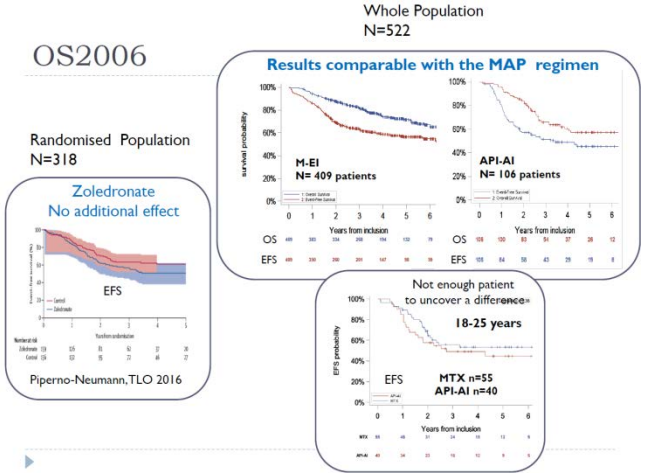
Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent

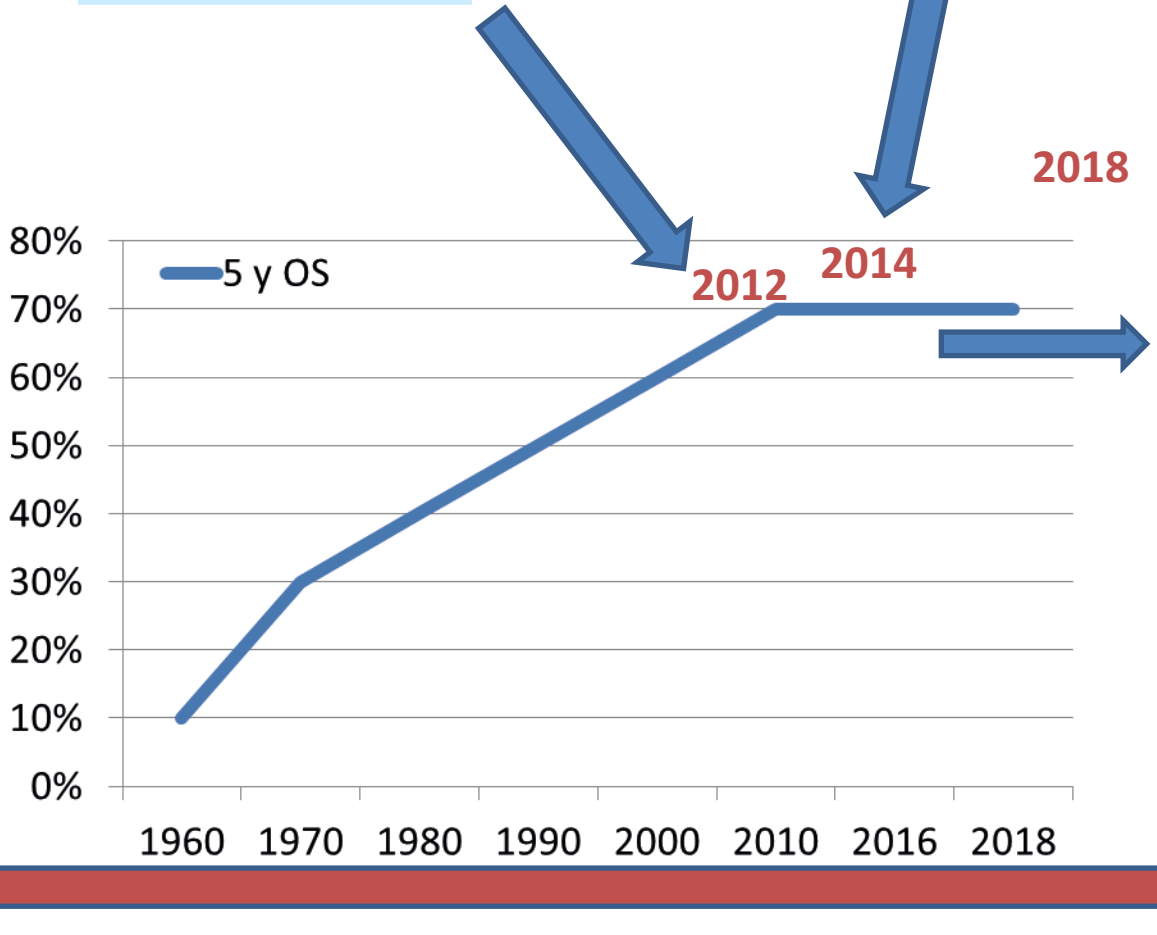
Quoi de neuf?

Ostéosarcomes


Osteosarcomes
Pub Med Juin 2017- Juin 2018
312
références
Bio +++++
Essai thérapeutiques ? ?







Sarcoma 13 / OS2016

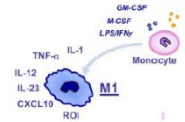
Randomised Phase 2 trial of MEPACT combined with post-operative chemotherapy for newly diagnosed high risk osteosarcoma patients (metastatic or localized disease with poor histologic response)

PI: Nathalie GASPAR, Sophie Piperno-Newman
Statisticien : Marie-Cécile Le Deley
Sponsor : UNICANCER

PHRC 2016 + Drug supply from Takeda

Anti-tumour immunity

Mepact
Anti-GD2
Anti-PD1 *(MSI+)*
Anti-IDO
Anti-CSF1R
Anti-KIR



PAC SARCOME
Sarcome 09/0603
EudraCT N°: 2006-00337727

Etude Intergroupe (SFCE/GSF-GETO) OS2006 Zolédronate-Ostéosarcome Protocole de traitement des ostéosarcomes de l'enfant, de l'adolescent et de l'adulte comportant un essai randomisé et des études biologiques

Titre abrégé du protocole : OS 2006

(2018) 57–66

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

Original Research

Results of methotrexate-etoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study

Nathalie Gaspar [a,*], Bob-Valéry Occean [b], Hélène Pacquement [c], Emmanuelle Bompas [d], Corine Bouvier [e], Hervé J. Brisse [f,x], Marie-Pierre Castex [g], Nadir Cheurfa [b], Nadège Corradini [h], Jessy Delaye [i], Natacha Entz-Werlé [j], Jean-Claude Gentet [k], Antoine Italiano [l], Cyril Lervat [m], Perrine Marec-Berard [n], Eric Mascard [o], Françoise Redini [p], Laure Saumet [q], Claudine Schmitt [r], Marie-Dominique Tabone [s], Cécile Verite-Goulard [t], Marie-Cécile Le Deley [u,v], Sophie Piperno-Neumann [w], Laurence Brugieres [a] On behalf of the SFCE (Société Française des Cancers de l'Enfant et l'adolescent), GSF-GETO (Groupe Sarcome Français), the UNICANCER sarcoma group

PAC SARCOME
Sarcome 09/0603
EudraCT N°: 2006-00337727

Etude Intergroupe (SFCE/GSF-GETO) OS2006 Zolédronate-Ostéosarcome
Protocole de traitement des ostéosarcomes de l'enfant, de l'adolescent et de l'adulte comportant un essai randomisé et des études biologiques

Titre abrégé du protocole : OS 2006

Pharmacogenomics

A Pharmacokinetic and Pharmacogenetic Analysis of Osteosarcoma Patients Treated With High-Dose Methotrexate: Data From the OS2006/Sarcoma-09 Trial

The Journal of Clinical Pharmacology
2018, 00(0) 1–9

DOI: 10.1002/jcph.1252

Gabrielle Lui, PhD[1,2,3], Jean-Marc Treluyer, MD[1,2,3,4], Brice Fresneau, MD[5,6], Sophie Piperno-Neumann, MD[7], Nathalie Gaspar, MD[5], Nadège Corradini, MD[8], Jean-Claude Gentet, MD[9], Perrine Marec Berard, MD[10,11], Valérie Laurence, MD[7], Pascale Schneider, MD[12], Natacha Entz-Werle, MD[13], Hélène Pacquement, MD[7], Frédéric Millot, MD[14], Sophie Taque, MD[15], Claire Freycon, MD[16], Cyril Lervat, MD[17], Marie Cécile Le Deley, PhD[6,18], Céline Mahier Ait Oukhatar[19], Laurence Brugieres, MD[5], Gwénaël Le Teuff, PhD[6,18], Naïm Bouazza, PhD[1,3,4], for the Sarcoma Group of UNICANCER

Original Article

Results of a Randomized, Prospective Clinical Trial Evaluating Metronomic Chemotherapy in Nonmetastatic Patients With High-Grade, Operable Osteosarcomas of the Extremities: A Report From the Latin American Group of Osteosarcoma Treatment

Andreza A. Senerchia, MD[1]; Carla Renata Macedo, MD[1]; Sima Ferman, MD[2]; Marcelo Scopinaro, MD[3]; Walter Cacciavillano, MD[3]; Erica Boldrini, MD[4]; Vera Lúcia Lins de Moraes, MD[5]; Guadalupe Rey, MD[6]; Claudia T. de Oliveira, MD[7]; Luis Castillo, MD[8]; Maria Tereza Almeida, MD[9]; Maria Luisa Borsato, MD[10]; Eduardo Lima, MD[11]; Daniel Lustosa, MD[12]; José Henrique Barreto, MD[13]; Tatiana El-Jaick, MD[14]; Simone Aguiar, MD[15]; Algemir Brunetto, PhD[16]; Lauro Greggiani, MD[17]; Hugo Cogo-Moreira, PhD[18]; Alvaro Atallah, PhD[18]; and Antonio Sergio Petrilli, PhD[1]

- Amerique du Sud
- 296 Os Loc randomisés
- MAP vs MAP + 73 sem metro
- Metro = EDX + Mtx
- 5 yrs EFS 61% vs 64%

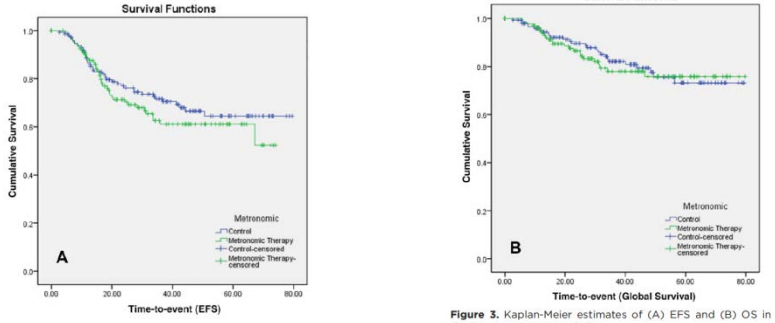


Figure 3. Kaplan-Meier estimates of (A) EFS and (B) OS in the intent-to-treat population.

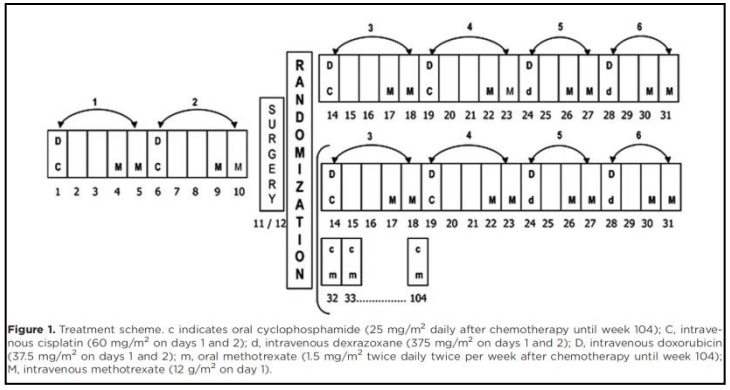


Figure 1. Treatment scheme. c indicates oral cyclophosphamide (25 mg/m^2 daily after chemotherapy until week 104); C, intravenous cisplatin (60 mg/m^2 on days 1 and 2); d, intravenous dexrazoxane (375 mg/m^2 on days 1 and 2); D, intravenous doxorubicin (37.5 mg/m^2 on days 1 and 2); m, oral methotrexate (1.5 mg/m^2 twice daily twice per week after chemotherapy until week 104); M, intravenous methotrexate (12 g/m^2 on day 1).

BACKGROUND: Metronomic chemotherapy (MC) consists of the administration of a low dose of chemotherapy on a daily or weekly basis without a long break to achieve an antitumoral effect through an antiangiogenic effect or stimulation of the immune system. The potential effect of MC with continuous oral cyclophosphamide and methotrexate in patients with high-grade operable osteosarcomas (OSTs) of the extremities was investigated. **METHODS:** Patients with high-grade OSTs who were 30 years old or younger were eligible for registration at diagnosis. Eligibility for randomization included 1) nonmetastatic disease and 2) complete resection of the primary tumor. The study design included a backbone of 10 weeks of preoperative therapy with methotrexate, adriamycin, and platinum (MAP). After surgery, patients were randomized between 2 arms to complete 31 weeks of MAP or receive 73 weeks of MC after MAP. The primary endpoint was event-free survival (EFS) from randomization. **RESULTS:** There were 422 nonmetastatic patients registered (May 2006 to July 2013) from 27 sites in 3 countries (Brazil, Argentina and Uruguay), and 296 were randomized to MAP plus MC (n = 139) or MAP alone (n = 157). At 5 years, the EFS cumulative proportions surviving in the MAP-MC group and the MAP-alone group were 61% (standard error [SE], 0.5%) and 64% (SE, 0.5%), respectively, and they were not statistically different (Wilcoxon [Gehan] statistic = 0.724; *P* =.395). The multivariate analysis showed that necrosis grades 1 and 2, tumor size, and amputation were associated with shorter EFS. **CONCLUSIONS:** According to the current follow-up, EFS with MAP plus MC is not statistically superior to EFS with MAP alone in patients with high-grade, resectable OSTs of the extremities. *Cancer* 2017;123:1003-10. © *2016 American Cancer Society.*

IJC
International Journal of Cancer

A phase II trial evaluating the feasibility of adding bevacizumab to standard osteosarcoma therapy

Fariba Navid [1,2], Victor M. Santana[1,2], Michael Neel[3], M. Beth McCarville[4,5], Barry L. Shulkin[4,5], Jianrong Wu[6], Catherine A. Billups[6], Shenghua Mao[6], Vinay M. Daryani[7], Clinton F. Stewart[7], Michelle Kunkel[1], Wendene Smith[1], Deborah Ward[8], Alberto S. Pappo[1,2], Armita Bahrami[9], David M. Loeb[10], Jennifer Reikes Willert[11], Bhaskar N. Rao[3,12] and Najat C. Daw[13]

Increased vascular endothelial growth factor (VEGF) expression in osteosarcoma correlates with a poor outcome. We conducted a phase II trial to evaluate the feasibility and efficacy of combining bevacizumab, a monoclonal antibody against VEGF, with methotrexate, doxorubicin and cisplatin (MAP) in patients with localized osteosarcoma. Eligible patients received two courses of MAP chemotherapy before definitive surgery at week 10. Bevacizumab (15 mg/kg) was administered 3 days before starting chemotherapy then on day 1 of weeks 3 and 5 of chemotherapy. After surgery, patients received MAP for a total of 29 weeks; bevacizumab was added every 2 or 3 weeks on day 1 of chemotherapy at least 5 weeks after surgery. Group sequential monitoring rules were used to monitor for unacceptable bevacizumab-related targeted toxicity (grade 4 hypertension, proteinuria or bleeding, grade 3 or 4 thrombosis/embolism, and grade 2–4 major wound complications). Thirty-one patients (median age 12.8 years) with localized osteosarcoma were enrolled. No unacceptable targeted toxicities were observed except for wound complications (9 minor and 6 major), which occurred in 15 patients; none required removal of prosthetic hardware or amputation. The estimated 4-year event-free survival (EFS) rate and overall survival rate were 57.5 ± 10.0% and 83.4 ± 7.8%, respectively. Eight (28%) of 29 evaluable patients had good histologic response (<5% viable tumor) to preoperative chemotherapy. The addition of bevacizumab to MAP for localized osteosarcoma is feasible but frequent wound complications are encountered. The observed histologic response and EFS do not support further evaluation of bevacizumab in osteosarcoma.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2994–2999, 2017
doi:10.1093/annonc/mdx536
Published online 25 September 2017

ORIGINAL ARTICLE

Gemcitabine plus sirolimus for relapsed and progressing osteosarcoma patients after standard chemotherapy: a multicenter, single-arm phase II trial of Spanish Group for Research on Sarcoma (GEIS)

J. Martin-Broto[1,2*], A. Redondo[3], C. Valverde[4], M. A. Vaz[5], J. Mora[6], X. Garcia del Muro[7], A. Gutierrez[8], C. Tous[2], A. Carnero[2,9], D. Marcilla[10], A. Carranza[1], P. Sancho[1], J. Martinez-Trufero[11], R. Diaz-Beveridge[12], J. Cruz[13], V. Encinas[14], M. Taron[2], D. S. Moura[2], P. Luna[15], N. Hindi[1,2] & A. Lopez-Pousa[16]

- 35 patients OS rechutes
- Gemcitabine + Rapa
- ➔ PFSR 4 mois = 44%
- 2 PR + 14 MS

Background: Patients with relapsed unresectable osteosarcoma represents an unmet need, so active and safe systemic treatments are required. Fas cell surface death receptor and mammalian target of rapamycin pathways are implicated in progressing osteosarcoma, and we had preclinical and clinical experience with a scheme that targets both pathways. Therefore, we designed a phase II trial with gemcitabine plus rapamycin, to determine the efficacy and safety, in this subset of patients.

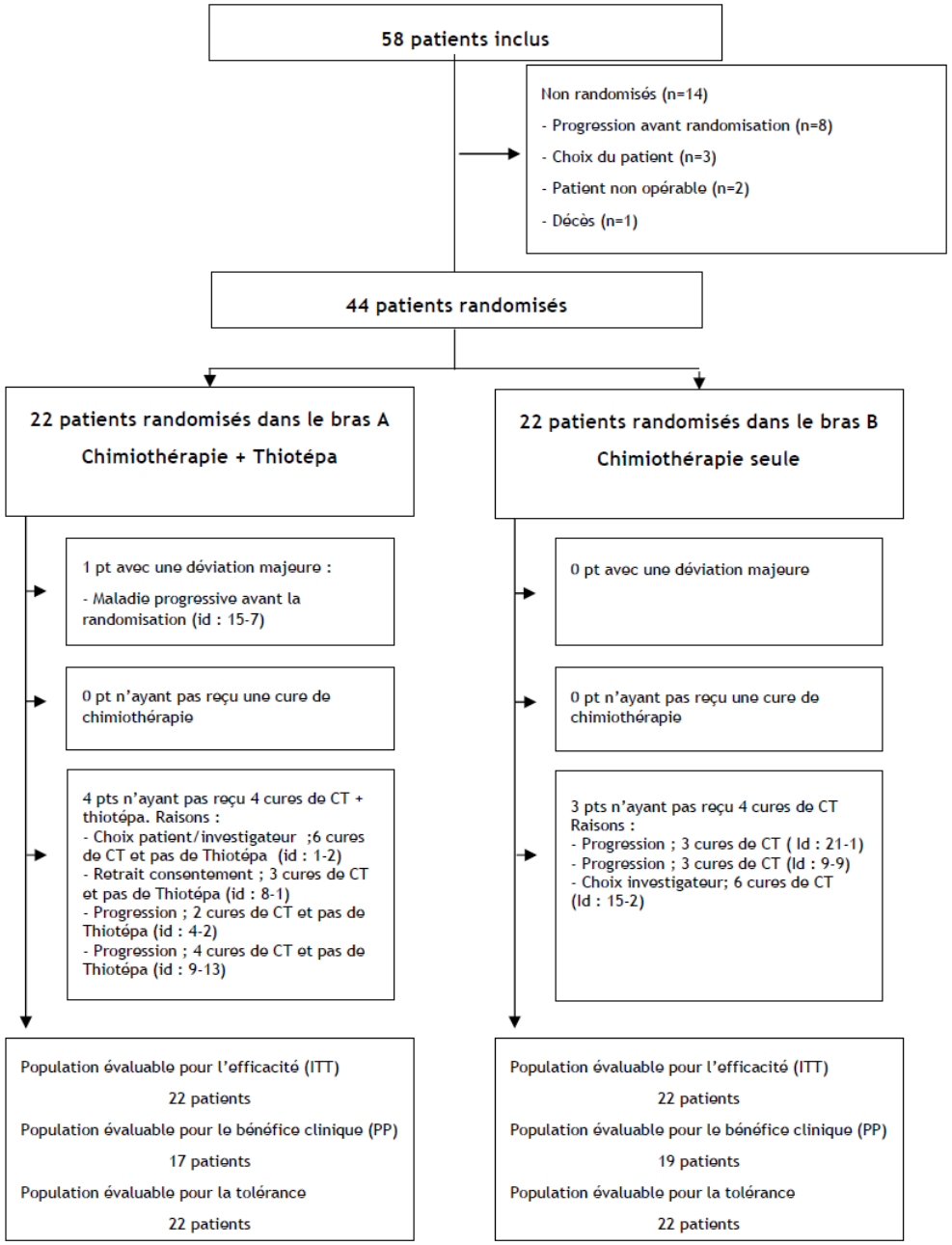
Patients and methods: A multicenter, single-arm phase II trial was sponsored by the Spanish Group for Research on Sarcoma. Osteosarcoma patients, relapsed or progressing after standard chemotherapy and unsuitable for metastasectomy received gemcitabine and rapamycin p.o. 5 mg/day except for the same day of gemcitabine administration, and the day before. The main end point was 4-month progression-free survival rate (PFSR), with the assumption that rates higher than 40% would be considered as an active regimen. Translational research aimed to correlate biomarkers with the clinical outcome.

Results: Thirty-five patients were enrolled and received at least one cycle. PFSR at 4 months was 44%, and after central radiologic assessment, 2 partial responses and 14 stabilizations (48.5%) were reported from 33 assessable patients. The most frequent grade 3–4 adverse events were: neutropenia (37%), thrombocytopenia (20%), anemia (23%), and fatigue (15%); however, only three patients had febrile neutropenia. Positive protein expression of RRM1 significantly correlated with worse PFS and overall survival, while positivity of P-ERK1/2 was correlated with significant better overall survival.

Conclusion: Gemcitabine plus sirolimus exhibits satisfactory antitumor activity and safety in this osteosarcoma population, exceeding the prespecified 40% of 4-month PFSR. The significant correlation of biomarkers with clinical outcome encourages further prospective investigation.

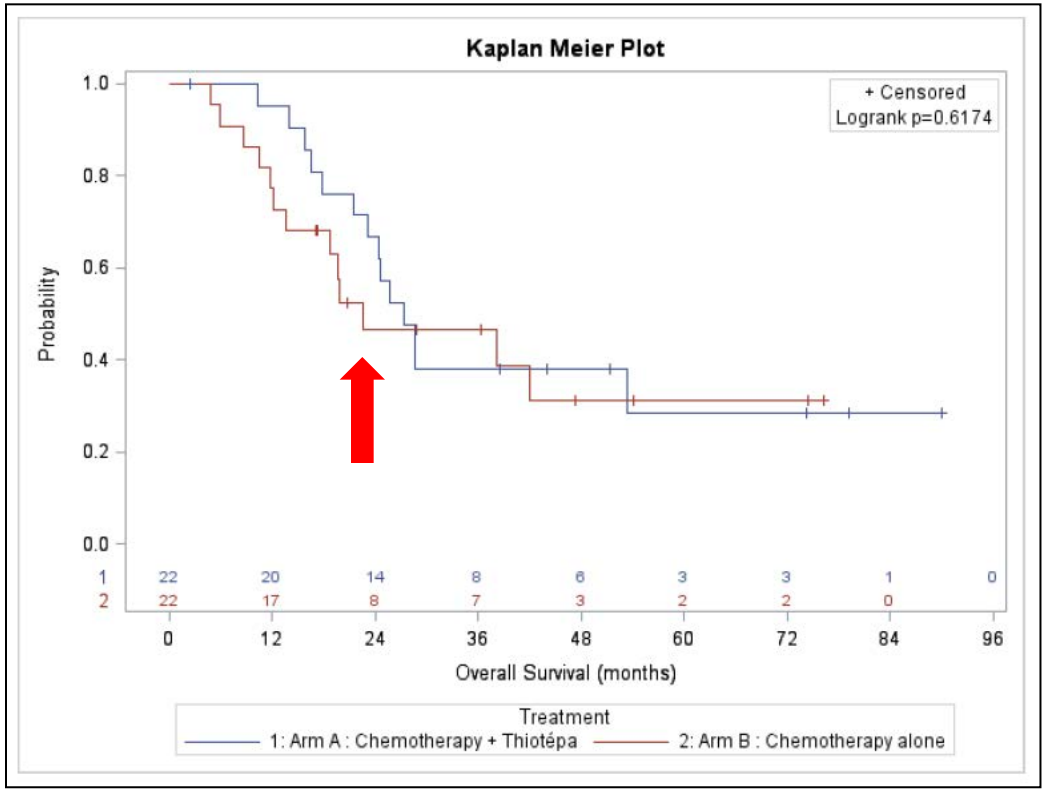
- **Arrêt des inclusions en Mars 2017**
- **44 patients / 66 attendus**

Figure : Consort Flow Diagram



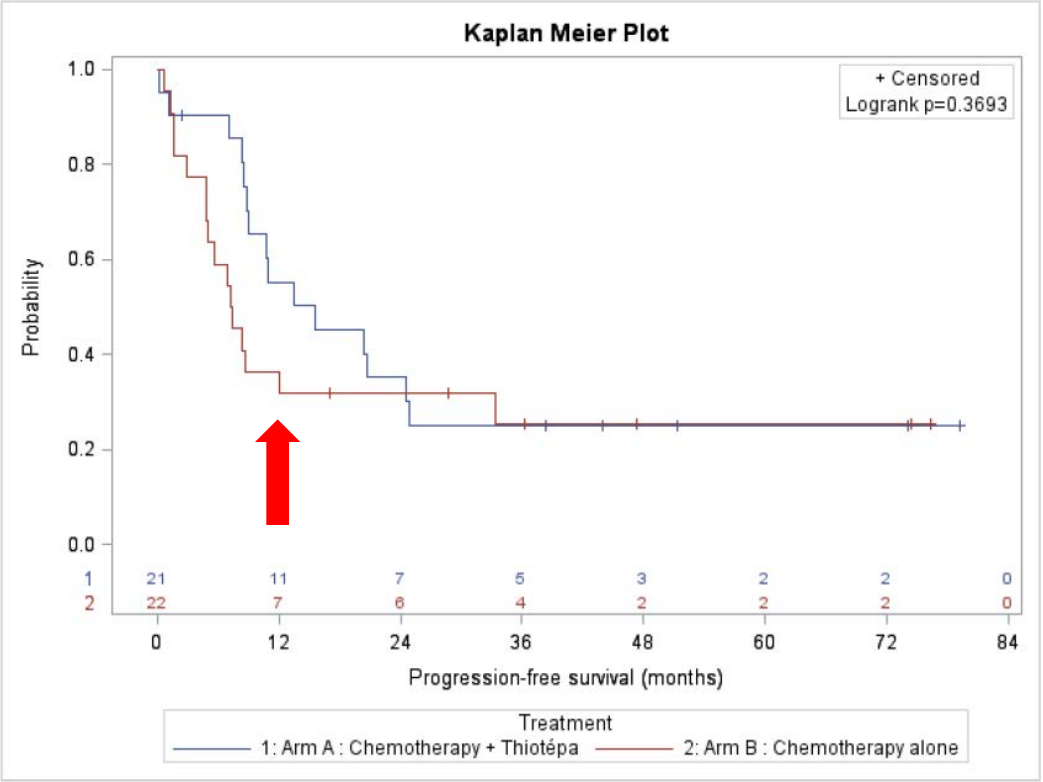
	Bras A : Chimio + Thiotépa N=22	Bras B : Chimio seule N=22
Evènements (décès) : n (%)	14 (63.6%)	13 (59.1%)
Médiane de survie globale (IC95%)	27.4 mois [21.5; NA]	22.5 mois [12.1; NA]
Taux de survie globale à 1 an (IC95%)	95.2% IC95% [70.7; 99.3]	77.3% IC95% [53.7; 89.8]
Taux de survie globale à 2 ans (IC95%)	66.7% IC95% [42.5; 82.5]	46.6% IC95% [24.2; 66.3]
Test du Log-rank exploratoire (non stratifié)	p=0.6174	
HR bras A vs bras B (IC95%) (non ajusté)	0.825 [0.387 ; 1.759]	
HR bras A vs bras B (IC95%) (ajusté sur le critère lésions uniques vs multiples)	0.823 [0.385; 1.756]	

OS



	Bras A : Chimio + Thiotépa N=21	Bras B : Chimio seule N=22
Evènements (progression ou décès) : n (%)	15 (71.4%)	16 (72.7%)
Médiane de survie globale (IC95%)	15.6 mois [8.9; 24.9]	7.2 mois [4.8; 33.3]
Taux de survie à 1 an (IC95%)	55.3% IC95% [31.6; 73.7]	31.8% IC95% [14.2; 51.1]
Taux de survie à 2 ans (IC95%)	35.2% IC95% [15.8; 55.4]	31.8% IC95% [14.2; 51.1]
Test du Log-rank exploratoire (non stratifié)	p=0.3693	
HR bras A vs bras B (IC95%) (non ajusté)	0.724 [0.356 ; 1.471]	

PFS



OS II TTP

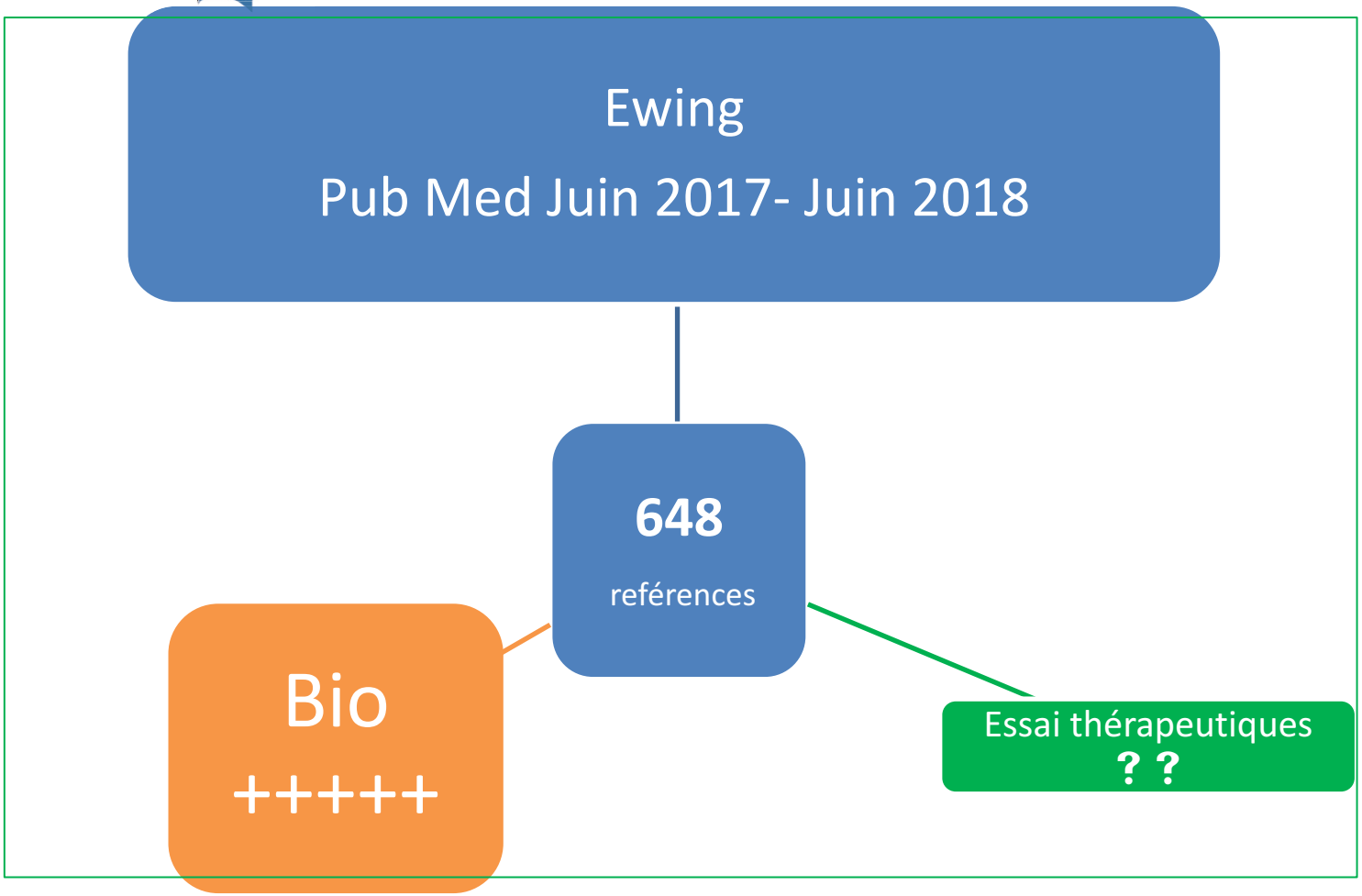
- Tendance en faveur du bras SCT+HDT
  - OS 2 ans = 66, 7% versus 46,6% (p= 0,36)
  - median OS de 27.4 versus 22.5 months (HR: 0.823, 95% CI 0.385-1.756; p=0.6174)
- Toxicité acceptable (délai médian hospitalisation pour HDCT = 15 jours)

- Mais étude non significative
  - manque de puissance ➔ nombre d'évenements requis non atteint (27 / 37 attendus).
  - hypothèses initiales = 20 % de survie à 2 ans = versus 45 % dans le bras expérimental ≠taux de survie à 2 ans bras contrôle = 47% donc bien au-delà de l'hypothèse initiale
  - Explications possibles =
    - sur sélection de la population incluse (quelquesoit le bras de traitement)
    - Effet « essai clinique »
    - changement de pratique apparu en cours d'étude du fait de la longueur du recrutement

➔ TTP haute dose = alternative possible en traitement rechute dans population sélectionnée en attendant preuves efficacité thérapeutiques ciblées et AMM pédiatriques

Quoi de neuf?

Dans les Ewing


Ewing
Pub Med Juin 2017- Juin 2018
648
références
Bio
+++++
Essai thérapeutiques
? ?

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

Centre Léon Bérard
LYON ET RHÔNE-ALPES

International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

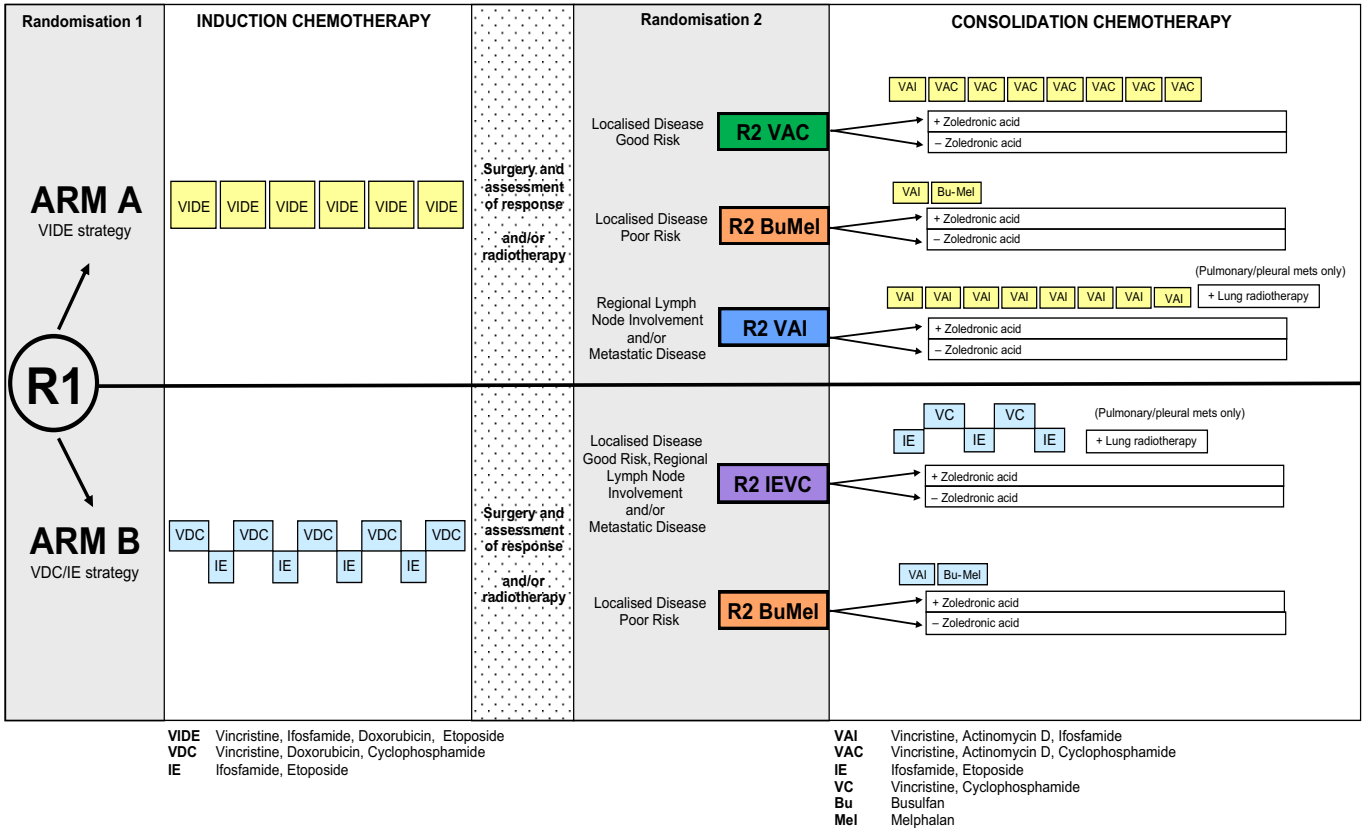
Euro Ewing 2012

EURO EWING Consortium EEC

Arret Sept 2019

Euro-Ewing 20xx

- Local treatment
- New drug



VIDE Vincristine, Ifosfamide, Doxorubicin, Etoposide
VDC Vincristine, Doxorubicin, Cyclophosphamide
IE Ifosfamide, Etoposide

VAI Vincristine, Actinomycin D, Ifosfamide
VAC Vincristine, Actinomycin D, Cyclophosphamide
IE Ifosfamide, Etoposide
VC Vincristine, Cyclophosphamide
Bu Busulfan
Mel Melphalan

Efficacy of Busulfan-Melphalan high dose chemotherapy consolidation in localised high-risk Ewing sarcoma:

Results of EURO-E.W.I.N.G 99 R2Loc randomised trial

Jeremy Whelan, Marie-Cecile Le Deley, Uta Dirksen, Ian Robert Judson, Douglas S. Hawkins, Hendrik Van Den Berg, Ruth Ladenstein, Jarmila Kruseova, Andreas Ranft, Susanne Amler, Nathalie Gaspar, Valerie Laurence, Gwenael Le Teuff, Perrine Marec-Berard, Bernadette Brennan, Keith Wheatley, Bruce Morland, Sandrine Marreaud, Heribert Juergens, Odile Oberlin

Gesellschaft für Pädiatrische Onkologie und Hämatologie (**GPOH**); French Society of Pediatric Oncology, French Sarcoma Group and Sarcoma Group of UNICANCER (**SFCE/GSF/UNICANCER**); UK Childrens Cancer and Leukaemia Group (**UKCCLG**); European Organisation for Research and Treatment of Cancer (**EORTC**)

PRESENTED AT: ASCO ANNUAL MEETING '16

Comparison of VAI standard chemotherapy & whole lung irradiation and Busulfan-Melphalan high dose chemotherapy in Ewing sarcoma (EwS) patients with pulmonary metastases:

Results of EURO-E.W.I.N.G. 99 R2pulm randomised trial

On behalf of the international EURO- E.W.I.N.G 99 group

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Uta Dirksen- NO CONFLICT OF INTEREST

BJC

British Journal of Cancer (2017) 117, 767–774 | doi: 10.1038/bjc.2017.252

Keywords: gemcitabine; docetaxel; Ewing sarcoma; adolescent and young adult sarcomas; minimal residual disease management

GEIS-21: a multicentric phase II study of intensive chemotherapy including gemcitabine and docetaxel for the treatment of Ewing sarcoma of children and adults: a report from the Spanish sarcoma group (GEIS)

J Mora*[,1], A Castañeda[1], S Perez-Jaume[1], A Lopez-Pousa[2], E Maradiegue[1], C Valverde[3], J Martin-Broto[4,11], X Garcia del Muro[5], O Cruz[1], J Cruz[6], J Martinez-Trufero[7], J Maurel[8], M A Vaz[9], E de Alava[10] and C de Torres[1]

- 43 patients < 40 ans (med = 17 ans)
- Haut Risque (MTS, Axial, Moelle+)
- Gem/Tax x 2 windows
- 70% OR (7PR + 5 SD)
- 5 yrs OS = 55% EFS = 50%

Background: First Spanish trial of Ewing sarcoma (ES) including adults and children with the aim to test the efficacy of Gemcitabine and Docetaxel (G/D) in newly diagnosed high-risk (HR) patients.

Methods: This was a prospective, multicentric, non-randomised, open study for patients ⩽40 years with newly diagnosed ES. HR patients (metastatic, axial-pelvic primaries or bone marrow micrometastasis) received 2 window cycles of G/D. Patients with an objective response (OR) to G/D received 12 monthly cycles of G/D after completion of mP6. The primary end point was the OR rate to the G/D window phase and the event-free survival (EFS) and overall survival (OS) for all patients. The study is registered at ClinicalTrials.gov (identifier: NCT00006734).

Results: Forty-three patients were enroled, median age 17 years (range, 3–40). After a median follow-up of 43.4 months, the 5-year OS rate is 55.0% (95% CI, 41–74%) with an EFS of 50.0% (95% CI, 36–68%). The 5-year OS and EFS rates for standard risk (SR) patients was 76.0% (95% CI, 57–100%) and 71.0% (CI, 54–94%); for HR 36.0% (CI, 20–65%) and 29.0% (CI, 15–56%). Twelve of 17 (70.6%) high-risk (HR) patients showed an OR (7 PR and 5 SD) to G/D window therapy. The 5-year OS rate for patients ⩽18 years of age was 74.0% (CI, 56–97%) and 31.0% for >18 years (95% CI, 15–66%), $P<0.001$. Grade 4 adverse events during mP6 occurred in 28/39 of patients (72%) and did not correlate with age. Multivariate survival analyses with <18 *vs* ⩾18 and risk groups significant differences, $P<0.00001$. Using a Cox model for OS, both age and risk group were statistically significant ($P=0.0011$ and $P=0.0065$, respectively).

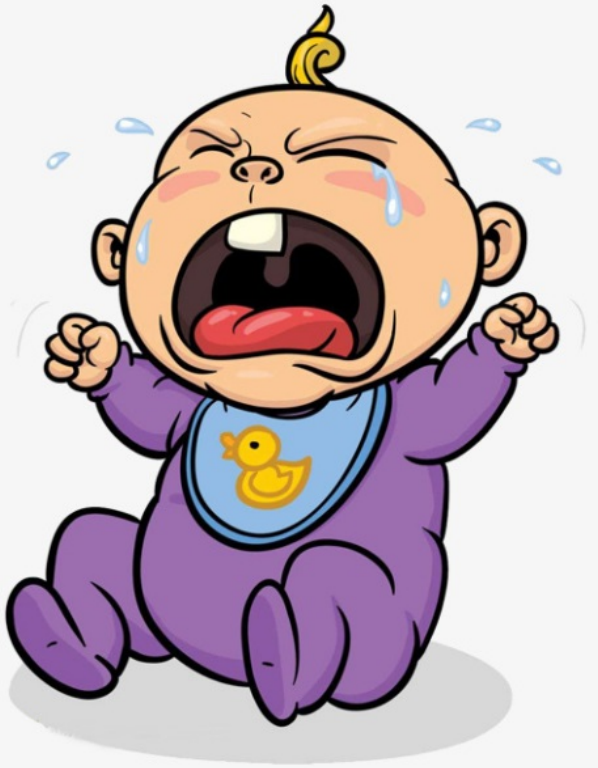
Conclusions: Age at diagnosis is an independent prognostic factor superior to the presence of metastases with 18 years as the strongest cut-off. The mP6 regimen provided survival curves that plateau at 3 years and G/D produced significant responses in HR-ES that is worth further exploring.

In conclusion, we show that the G/D regimen provides clinical benefit to newly diagnosed HR-ES patients. The G/D schema provides a backbone regimen for managing minimal residual ES disease that is worth further exploring.

Quoi de neuf?

2018

Reference Abstract	Titres	Inforamtions
P Meyers et al, abstract 10533 Memorial Sloan Kettering (MSK)	**Addition of cycles of irinotecan/temozolomide (i/T) to cycles of VDC/IE for the treatment of Ewing sarcoma.**	• irinotecan 20 mg/m2/day for 10 days with TMZ 100 mg/m2/day for 5 days + VDC/IE • 22 loc ➔ 3y EFS = 95% OS = 95% (median FU = 14 m) • 16 MTS ➔ 3y EFS = 55% OS = 70% (median FU = 20 m)
Lu Xie et al Abstract 11550 Pekin	**Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: an open label phase 2 clinic trial**	77m (95%
Algunik et al Abstract 11520	**A phase II study of pazopanib with o topotecan in patients with metastati and non-resectable soft-tissue and bone sarcomas**	a 28-day (18-71)
J Livingstonet al, abstract 11018 Texas MD Anderson Cancer Center, Houston, TX	**Parallel genomic and immune profili of relapsed and metastatic osteosarcoma to reveal bases of low immunogenicity**	ith high- profiling der ➔subset of patients exhibit increased PD-L1 expression associated with lower levels of T-cell clonality, for which immune checkpoint blockade may be beneficial.



Single-agent Expansion Cohort of Lenvatinib (LEN) and Combination Dose-finding Cohort of LEN + Etoposide (ETP) + Ifosfamide (IFM) in Patients (pts) Aged 2 to ≤ 25 Years With Relapsed/Refractory Osteosarcoma (OS)

Poster No. 11527

Nathalie Gaspar,[1] Michela Casanova,[2] Francisco José Bautista Sirvent,[3] Rajkumar Venkatramani,[4] Bruce Morland,[5] Marion Gambart,[6] Estelle Thebaud,[7] Sandra J. Strauss,[8] Franco Locatelli,[9] Soledad Gallego Melcon,[10] Adela Canete Nieto,[11] Stefan Bielack,[12] Claudia Rossig,[13] Isabelle Aerts,[14] Perrine Marec-Berard,[15] Silvija Kraljevic,[16] Seiichi Hayato,[17] Coin He,[18] Corina Dutcus,[19] Quentin Campbell-Hewson[20]

Phase 1: Single-agent dose-finding

Cohort 1: All solid tumors
Subjects 6 to <18 yr
- 12 - 24 subjects

N=2
3

Dose level	Le
–1	9 mg/m²
1 (starting dose)	11 mg/m²
2	14 mg/m²
3	17 mg/m²

After 6 subjects

Assess DLT

Include subjects 2 to <6 yr
- Run-in period for 3 weeks at 5 mg/m²

Phase Ib

International PI: N.GASPAR, Gustave Roussy
Five countries: France, UK, Italy, Spain, Germany, US

HOPE

Eisai

ITCC Innovative Therapies for Children with Cancer European Consortium

Lenvatinib

VEGFR1-2-3 (FLT1-4), FGFR1-2-3-4, PDGFRα; KIT; RET

Pediatric and AYA < 25y

Phase 1 : EW 2SD/ 4pts

Phase-II single agent

Phase-Ib combo VP/Ifo

Tolerance in combination with chemotherapy

Tolerance Lenvatinib + VP16/Ifo = VP16/Ifo alone

LEN was administered daily and continuously throughout all treatment cohorts.
- For the combination treatment, IFM + ETP was administered on days 1–3 of each 21-day cycle, for a total of 5 cycles.

Quoi de neuf?

Sarcome osseux pédiatriques tout venant

Received: 15 March 2018 | Revised: 13 May 2018 | Accepted: 15 May 2018

DOI: 10.1002/cam4.1602

ORIGINAL RESEARCH

WILEY Cancer Medicine Open Access

Increased risk of bone tumors after growth hormone treatment in childhood: A population-based cohort study in France

Amélie Poidvin[1,2] | Jean-Claude Carel[1,2] | Emmanuel Ecosse[3] | Dominique Levy[4] | Jean Michon[4] | Joël Coste[3,5]

- Etude de cohorte
- 111875 persons-years
- Observation moy 17,5 ans
- Jusque age moyen 28,4 ans

Abstract

The association between growth hormone (GH) treatment and cancer risk has not been thoroughly evaluated and there are questions about any increased risk of bone tumors. We examined cancer risk and especially bone tumor risk in a population-based cohort study of 6874 patients treated with recombinant GH in France for isolated GH deficiency, short stature associated with low birth weight or length or idiopathic short stature. Adult mortality and morbidity data obtained from national databases and from questionnaires. Case ascertainment completeness was estimated with capture-recapture methods. Standardized mortality and incidence ratios were calculated using national reference data. 111 875 person-years of observation were analyzed and patients were followed for an average of 17.4 ± 5.3 years to a mean age of 28.4 ± 6.2 years. For cancer overall, mortality and incidence were not different from expected figures. Five patients developed bone tumors (chondrosarcoma, 1, Ewing sarcoma, 1, osteosarcoma, 3) of whom 3 died (Ewing sarcoma, 1, osteosarcoma, 2), whereas only 1.4 case and 0.6 deaths were expected: standardized mortality ratio, 5.0 and standardized incidence ratio from 3.5 to 3.8 accounting or not accounting for missed cases. Most patients received conventional doses of GH, although one patient with osteosarcoma had received high dose GH (60 µg/kg/d). This study confirms an increased risk of bone tumors but not overall cancer risk in subjects treated with GH in childhood for isolated GH deficiency or childhood short stature. Further work is needed to elucidate the mechanisms involved.

Twenty-four cancer events were identified in this group through the different sources, including one case which was not validated (Table 2). The most common cancers were bone tumors (n = 5), lymphoma (n = 4), and acute leukemia (n = 3). Overall, the patients were treated with con-

Eur J Nucl Med Mol Imaging (2017) 44:1712–1720
DOI 10.1007/s00259-017-3698-0

ORIGINAL ARTICLE

The role of ^{18}F-FDG PET/CT in the detection of osteosarcoma recurrence

Andrea Angelini[1] · Francesco Ceci[2] · Paolo Castellucci[2] · Tiziano Graziani[2] · Giulia Polverari[2] · Giulia Trovarelli[1] · Emanuela Palmerini[3] · Stefano Ferrari[3] · Stefano Fanti[2] · Pietro Ruggieri[1]

Pediatr Radiol (2017) 47:1800–1808
DOI 10.1007/s00247-017-3963-1

ORIGINAL ARTICLE

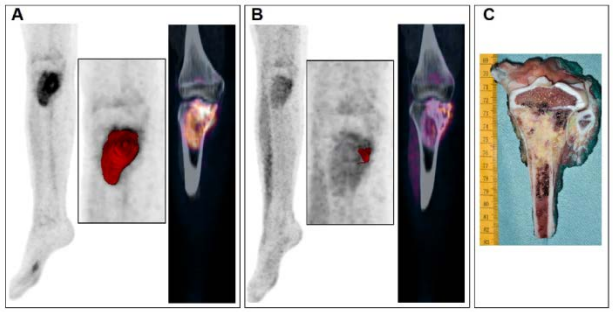
FDG PET/CT appearance of local osteosarcoma recurrences in pediatric patients

Susan E. Sharp[1] · Barry L. Shulkin[2] · Michael J. Gelfand[1] · M. Beth McCarville[2]

RESEARCH ARTICLE

Prognostic value of FDG-PET indices for the assessment of histological response to neoadjuvant chemotherapy and outcome in pediatric patients with Ewing sarcoma and osteosarcoma

Clement Bailly[1,2], Rodolphe Leforestier[1], Loic Campion[3], Estelle Thebaud[4], Anne Moreau[5], Francoise Kraeber-Bodere[1,2], Thomas Carlier[1,2]*, Caroline Bodet-Milin[1,2]*



ELSEVIER

Seminars in NUCLEAR MEDICINE

The Role of ^{18}F-FDG-PET/CT in Pediatric Sarcoma

Douglas J. Harrison, MD, MS,* Marguerite T. Parisi, MD, MS,† and Barry L. Shulkin, MD, MBA‡

Conclusion ^{18}F-FDG-PET/CT showed valuable results for detecting recurrence(s) in osteosarcoma patients with suspicious of relapse after treatment, particularly in the detection of local relapse and lung metastasis.

The role of ^{18}F-FDG
recurrence

Andrea Angelini[1] · Francesco Ceci[2] · Paolo Castellucci[2] · Tiziano Graziani[2] · Giulia Polverari[2] · Giulia Trovarelli[1] · Emanuela Palmerini[3] · Stefano Ferrari[3] · Stefano Fanti[2] · Pietro Ruggieri[1]

RESEARCH ARTICLE
Prognostic

Conclusion

Only elongation determined on initial FDG-PET has a potential interest as a prognostic factor of PFS and OS in pediatric OST patients. Unlike recent studies of the literature realized in adult population, all the metrics reveal limited additional prognostic value in pediatric EWS patients. This seems to reinforce the question of whether children experience different subtypes of the same pathologies than older patients, with different outcomes.

Estelle Thebaud[4], Thomas Carlier[1,2,4], Caroline Bodet-

Pediatr Radiol (2017) 47:1800–1808
DOI 10.1007/s00247-017-3963-1

CrossMark

ORIGINAL ARTICLE

FDG PE
in pediat

Susan E. Sharp[1]

Conclusion Local osteosarcoma recurrences are well visualized by FDG PET/CT, demonstrating either solid or peripheral/nodular FDG uptake with a wide range of maximum SUVs. FDG PET/CT demonstrates the full extent of local recurrences, while MRI can be limited by artifact from metallic hardware. PET/CT appears to be more sensitive than bone scan in detecting local osteosarcoma recurrences.

ELSEVIER

The Role of ^{18}F

Seminars in
NUCLEAR

Recent data have shown that ^{18}F-FDG-PET/CT in osteosarcoma may be of use in the identification of recurrent disease after completion of therapy.[18,19] A study performed in

Conclusion ^{18}F-FDG-PET/CT showed valuable results for detecting recurrence(s) in osteosarcoma patients with suspicious of relapse after treatment, particularly in the detection of local relapse and lung metastasis.

The role of ^{18}F-FDG
recurrence

Andrea Angelini[1] · Francesco Ce
Giulia Polverari[2] · Giulia Trovar
Stefano Fanti[2] · Pietro Ruggieri[1]

RESEARCH ARTICLE
Prognostic va

FDG-PET/CT en 2018➔

- Valeur confirmée dans diagnostic et extension **Ewing**
- Encore controversé dans **osteosarcomes** en particulier staging initial
- Mais ++ argument pour diagnostic **rechutes** osteo

- Evaluation réponse histo ➔ plus d'arguments pour Osteo que pour Ewing

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ORIGINAL ARTICLE

FDG PE
in pediat

Susan E. Sharp[1]

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local recurrences, while MRI can be limited by artifact from metallic hardware. PET/CT appears to be more sensitive than bone scan in detecting local osteosarcoma recurrences.

ELSEVIER

The Role of ^{18}F

Seminars in
NUCLEAR

Recent data have shown that ^{18}F-FDG-PET/CT in osteosarcoma may be of use in the identification of recurrent disease after completion of therapy.[18,19] A study performed in

Le GROUPOS

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- Merci..