

LB1



Mise en place du :

# OS 2006 study

SARCOME 09/0603  
(N°EudraCT 2006-00337727)

***INTERGROUP STUDY (SFCE / GSF-GETO)  
ZOLEDRONATE - OSTEOSARCOMA  
PROTOCOL FOR TREATMENT of OSTEOSARCOMA  
in CHILDREN, ADOLESCENTS and ADULTS  
including a RANDOMISED TRIAL and  
BIOLOGICAL STUDIES***

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**Slide 1**

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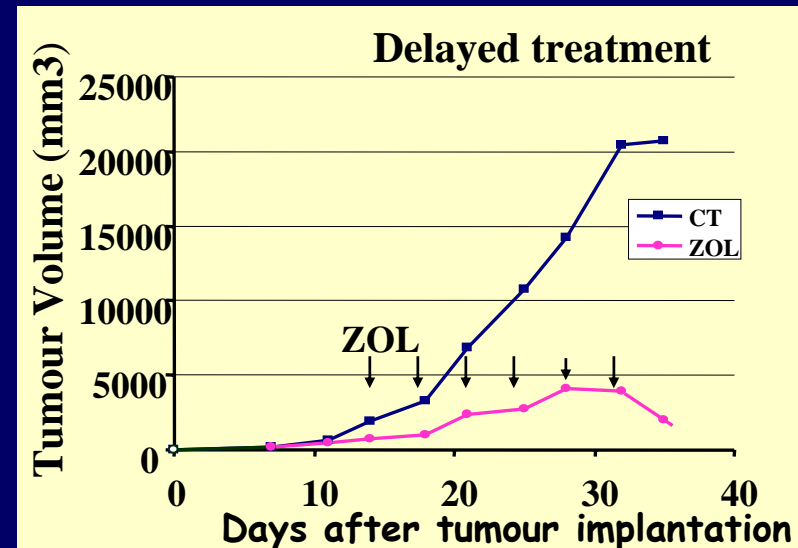
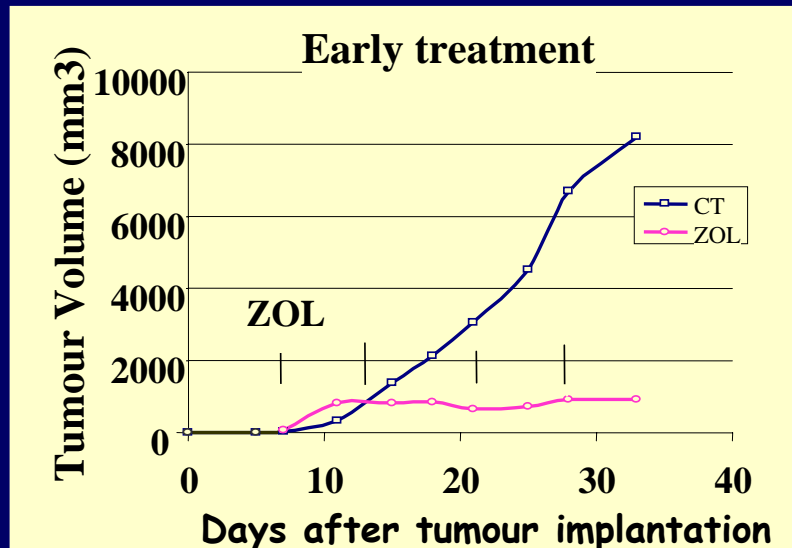
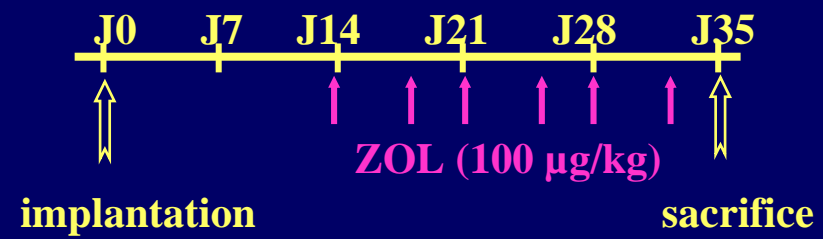
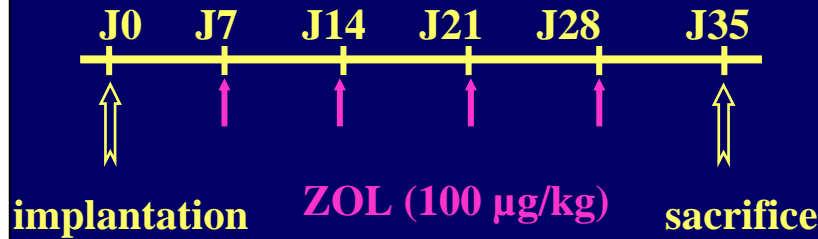
Laurence Brugieres, 13/03/2010

# Background

## Zoledronate and cancer

- Biphosphonate
- Given for the treatment of osteoporosis, osteolytic bone lesions and hypercalcemia
- Efficacy demonstrated several years ago for the **prevention of complications linked to bone metastases**
- Efficacy through the inhibition of osteoclasts mediated bone resorption
- **Direct antitumoral effect by**
  - inhibition of apoptosis
  - inhibition of growth, attachment and invasion of cells in culture

## Background : Zoledronate and osteosarcoma

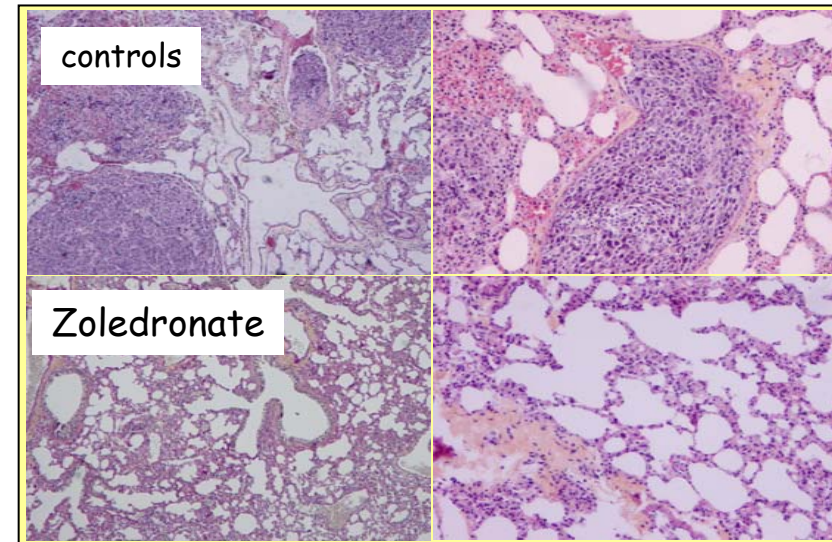
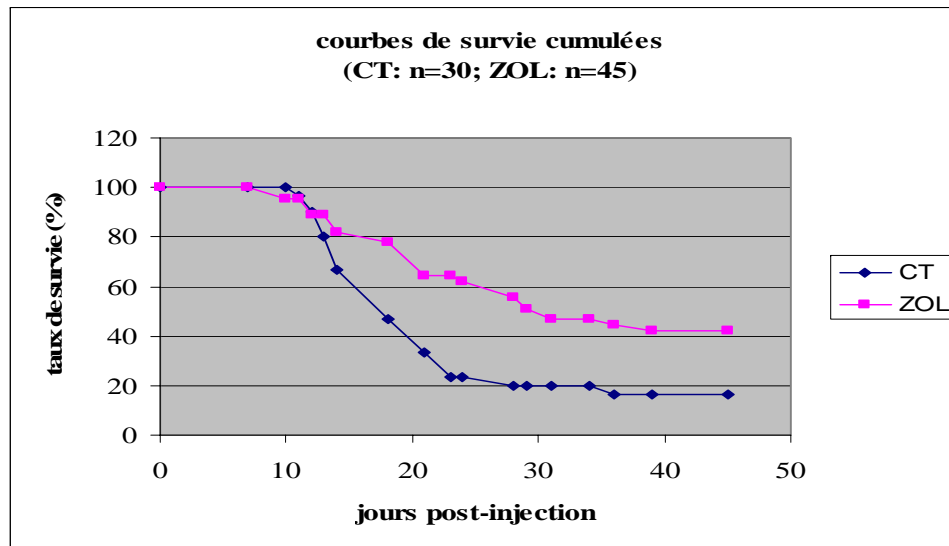


Experimental model of transplantable rat osteosarcoma



## Background : Zoledronate and osteosarcoma

- Model of lung metastases after IV injection of osteosarcoma POS-1 cells in mice
- Treatment by zoledronate

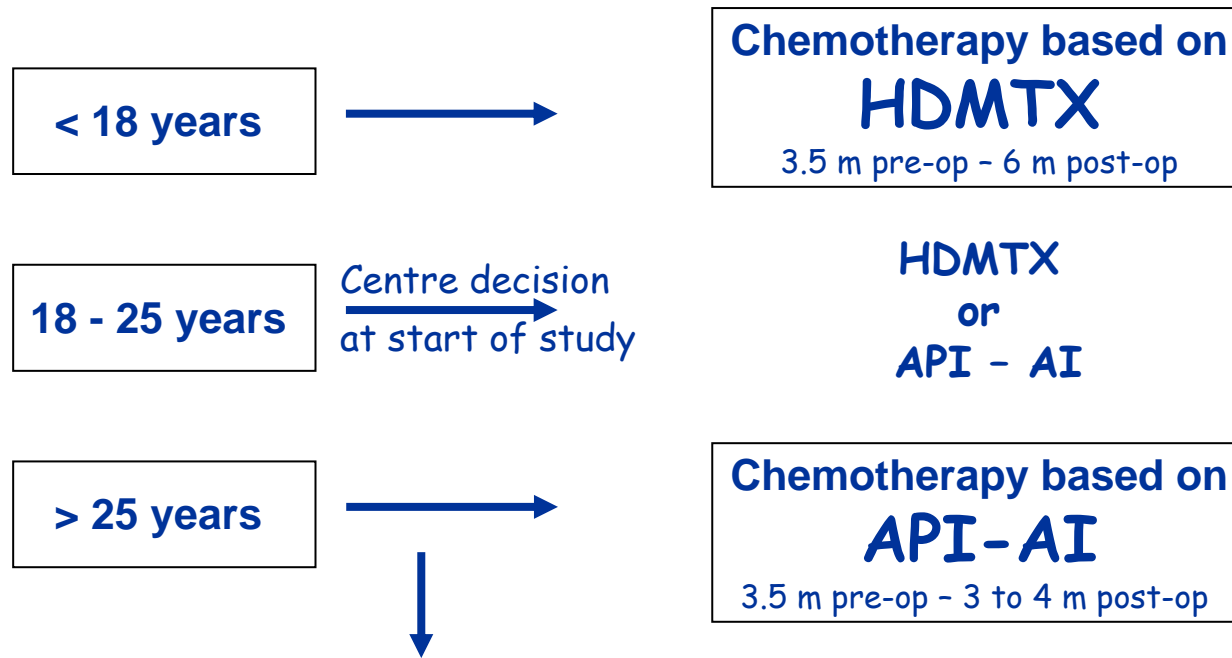


**Zoledronate improves survival of mice after IV injection of OS cells**

## DESIGN of the Randomised trial

- Primary objective : To assess whether the addition of a 10-month treatment of Zoledronate to chemotherapy and surgery improves event-free survival of patients with osteosarcoma
- Design: Randomised, open, phase III trial
- Date of activation : april 2007
- Number of centres: 51

# OVERALL TREATMENT PLAN

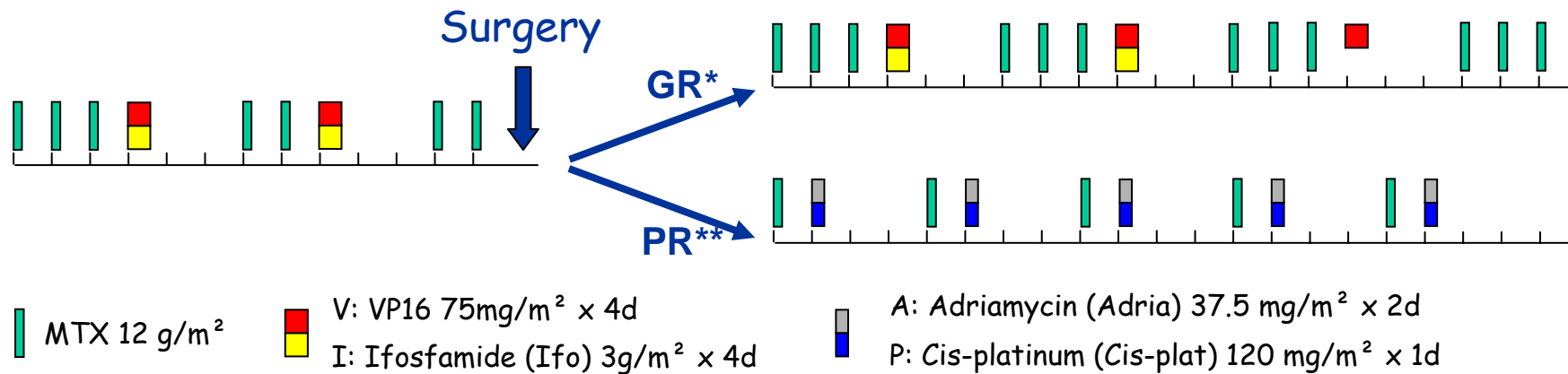


Randomisation at diagnosis  
to receive or not Zoledronate®

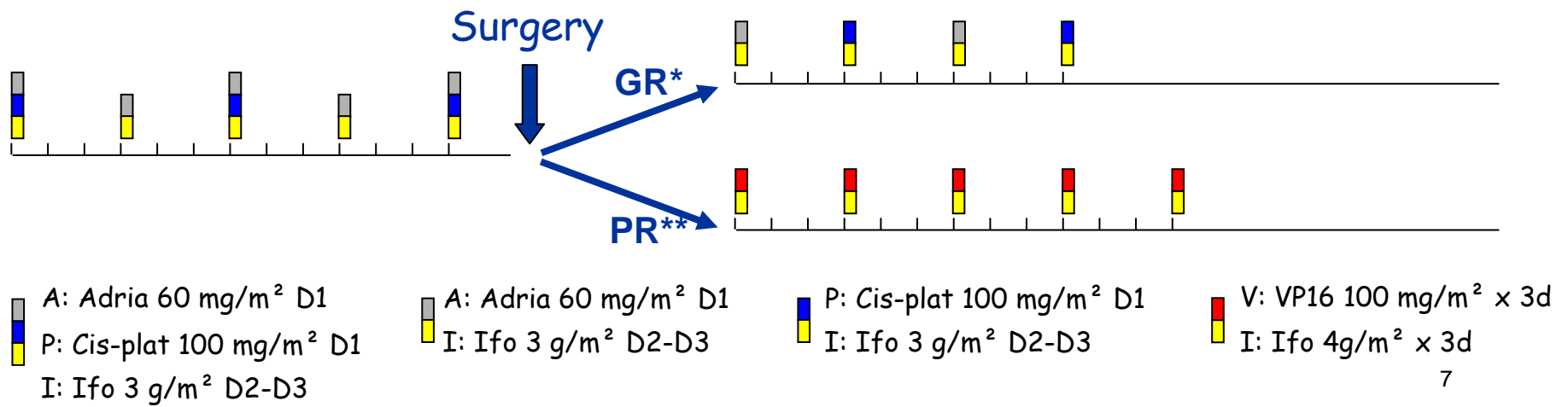
For patients randomised with  
Zoledronate®:

- 10 injections every 4 weeks
- 4 before surgery
- 6 after surgery

# CHEMOTHERAPY REGIMEN



\* : GR = Good histological response (<10% viable cells)  
 \*\* : PR = Poor histological response (≥10% viable cells)  
 and patients with not resectable tumour or metastatic disease



## INCLUSION CRITERIA for the randomised trial

- ❖ High grade osteosarcoma (local pathology report) including
  - ❖ Patients with non resectable primary tumour
  - ❖ Patients with metastases (if metastases 'resectable')
- ❖ Age at diagnostic  $\geq 5$  years and  $\leq 50$  years
- ❖ No medical contra-indication to planned treatment
- ❖ No previous treatment with chemotherapy or radiotherapy
- ❖ Patient fit to undergo protocol treatment and follow-up
- ❖ Efficient contraception for women in age of procreation
- ❖ Written informed consent
- ❖ Affiliation to a social insurance regimen

## NON INCLUSION CRITERIA

- ❖ Low grade osteosarcoma
- ❖ Small cell variant osteosarcoma
- ❖ Osteosarcoma of the jaws
- ❖ Primary resected osteosarcoma
- ❖ Osteosarcoma with multiple metastases for whom complete removal is expected not to be feasible even after shrinkage with chemotherapy
- ❖ Extra-osseous osteosarcoma
- ❖ Recent dental problem  
(including infection, traumatism or surgery)
- ❖ Any medical condition precluding treatment with protocol chemotherapy (listed in the protocol)

# RANDOMISATION

**Randomisation at diagnosis:** before the start of treatment or within 3 days following the 1st course of chemo.

**Centralised, stratified on:**

- age and type of chemotherapy => 4 strata
  - < 18 years - MTX
  - 18-25 years - MTX
  - 18-25 years - API
  - > 25 years - API
- risk group : non metastatic and resectable *versus* metastatic or not resectable (primary tumor)
- centre

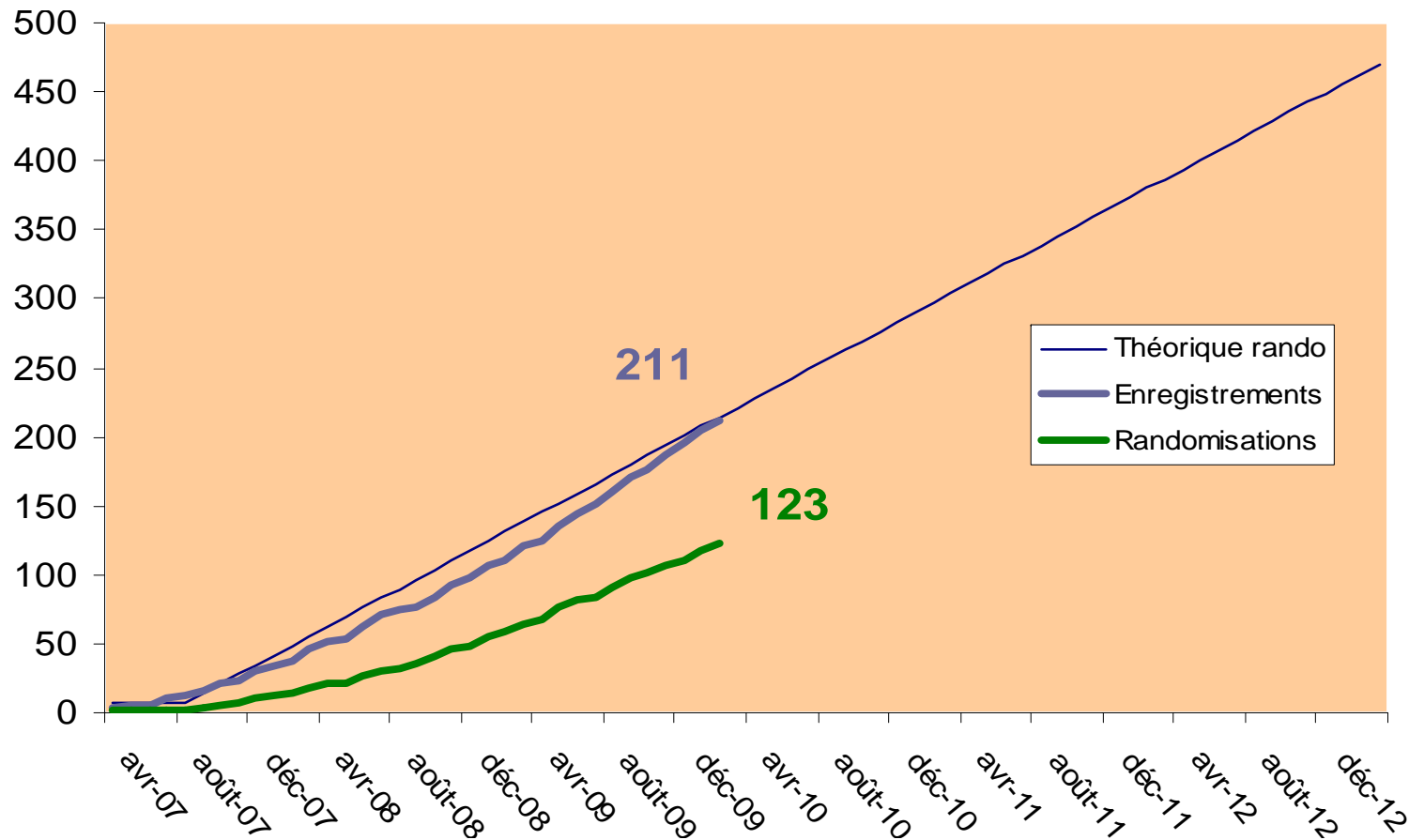
## STATISTICAL CONSIDERATIONS

- **Primary endpoint: event-free survival**
- **Sample size :**
  - Assuming a 3 year-EFS of 55% with the reference treatment, a total number of 440 patients (169 events) is required to be able to show a 13% difference between both arms ( $\alpha=5\%$  -  $\beta=20\%$ )
  - Considering planned interim analyses (3 interim analyses) and possible secondary exclusion (2%), **470 patients are requested (235 in each arm).**
  - This calculation may be reviewed after estimation of the actual EFS in the reference arm (without Zoledronate) after interim analysis.

# Accrual

Inclusions in the study on 28/2/2010:

- $\approx 60$  pts/ y in the randomised trial (15% M+ or unresectable)
- $\approx 60$  pts /y registered but not randomised ( $\approx 50\%$  non eligible)



## Safety

- Studied on the first 36 patients given zoledronate (> 100 courses)
- No major problem apart from hypocalcemia > grade 2 in 75% of the patients
- Consequence on growth after the end of treatment still to be evaluated

## Thiotepa study

- Randomised phase 2 study in relapsed patients
  - Objective : to assess the impact of HD thiotepa on the 3y survival of patients with relapsed osteosarcoma
  - Open to inclusion since june 2009
  - Inclusion criteria : 1<sup>st</sup> or second relapse
  - Study design :
    - All patients receive 4 courses of chemotherapy and surgery
    - Patients are randomised after the 1<sup>st</sup> course to receive or not HD Thiotepa after the 4th course
  - Nb of patients required : 66
  - Main end point : 3 year survival

# Combination of MTP-PE and zoledronate : pre-clinical studies

- Model of transplantable osteosarcoma (rat) and pulmonary metastases (mouse)
- Two steps
  - Study of dose-effect MTP-PE: 4 groups (3 doses + 1 CT)
  - Study of the combination of an optimal dose of MTPPE with ZOL (100 mg/kg, twice/wk)
- Parameters :
  - tumor volume, number of tumor nodules at the necropsy
  - histological: presence of osteoclasts (TRAP staining), macrophage infiltrating the tumors, apoptosis quantification
  - bone remodelling parameters in the serum

# ZOMEPACT study

- ❖ **Objective** : To assess toxicity and possible interaction of the combination of zoledronic acid and liposomal mifamurtide
- ❖ **Inclusion criteria** : relapsed osteosarcoma
- ❖ **Regimen** :
  - Zoledronic acid D1 every 4 weeks (10 injections).
  - MTP PE beginning at week 2, twice weekly for 12 weeks then weekly for 36 weeks
- ❖ **Number of patients** : 10 to 15
- ❖ **Evaluation criteria** :
  - Toxicity
  - Biological parameters of bone modeling and immunomodulation
  - Survival

## Next steps

- **Decision for MTP**
  - Either add it to post-operative CT for all patients
  - Or add it as a second randomisation (factorial design)
- **Proposal :**

MTX-VP IFO

API-AI

MAP or MAPIE

1st randomisation at diagnosis  
to receive or not Zoledronate®

2nd randomisation after  
surgery  
to receive or not MTP PE