Gestione e Trattamento dell'Osteosarcoma

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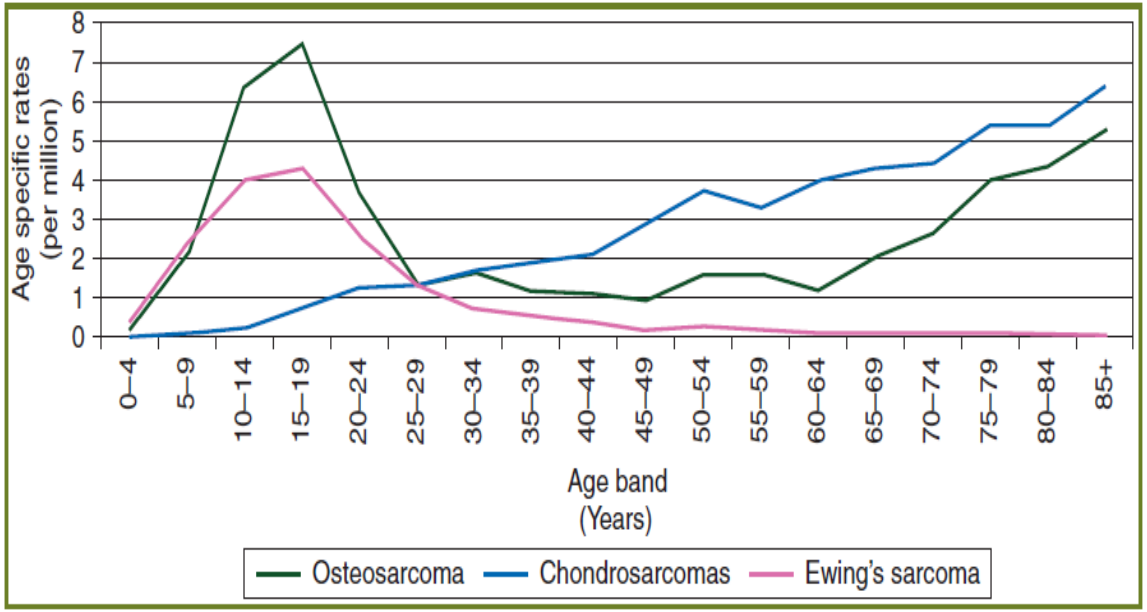
Bologna
2-4 Ottobre 2023

clinical practice guidelines

Annals of Oncology



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Osteosarcoma

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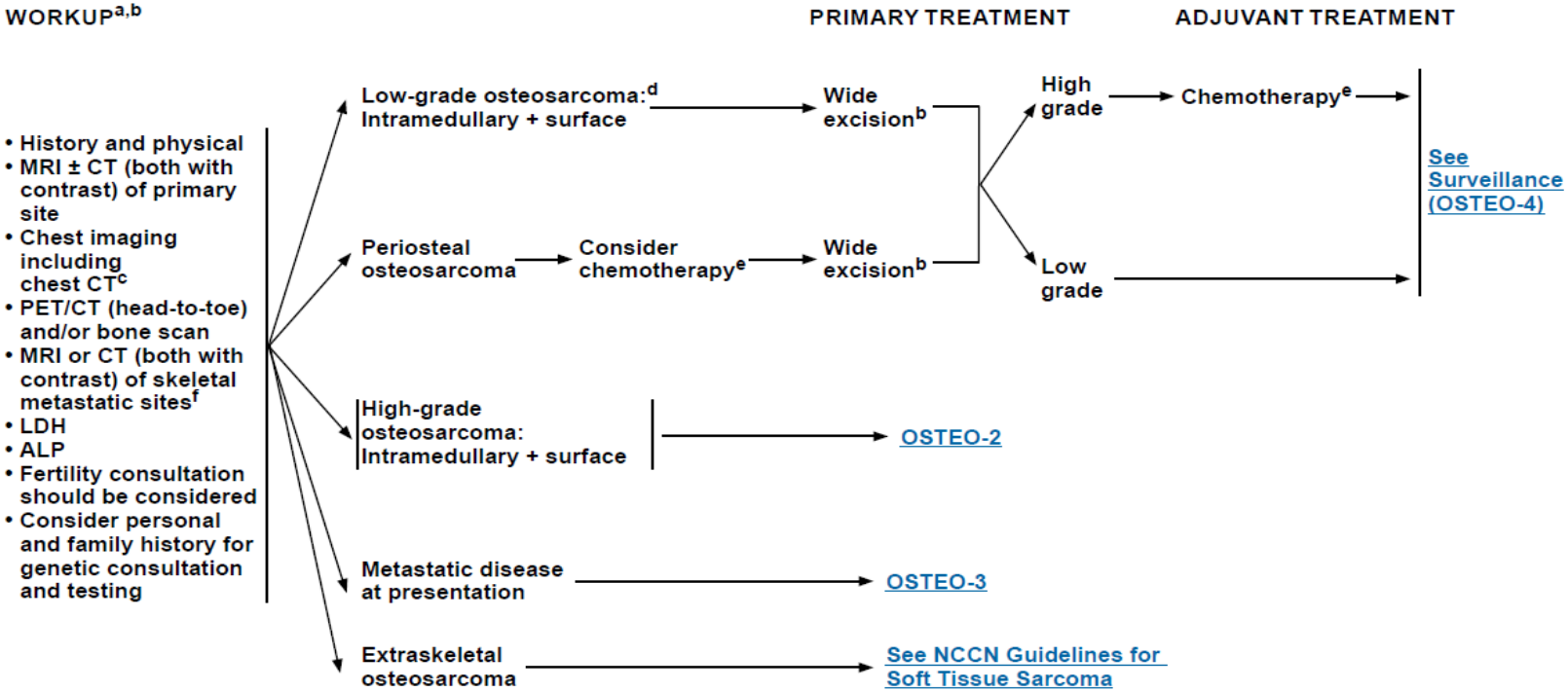

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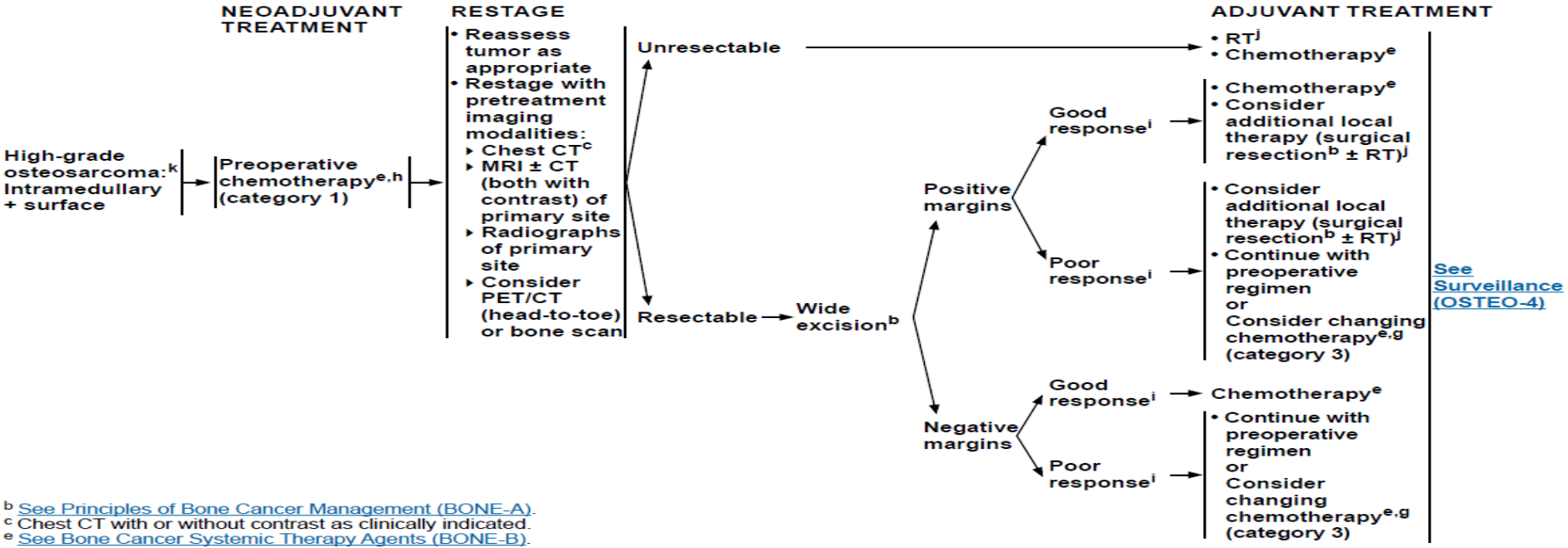


[b] See Principles of Bone Cancer Management (BONE-A).
[c] Chest CT with or without contrast as clinically indicated.
[e] See Bone Cancer Systemic Therapy Agents (BONE-B).
[g] See Discussion for further information.
[h] Selected elderly patients may benefit from immediate surgery.
[i] Response is defined by pathologic mapping per institutional guidelines; the amount of viable tumor is reported as <10% of the tumor area in cases showing a good response and ≥10% in cases showing a poor response.
[j] See Principles of Radiation Therapy (BONE-C).
[k] Other high-grade non-osteosarcoma variants such as undifferentiated pleomorphic sarcoma (UPS) of bone could also be treated using this algorithm.

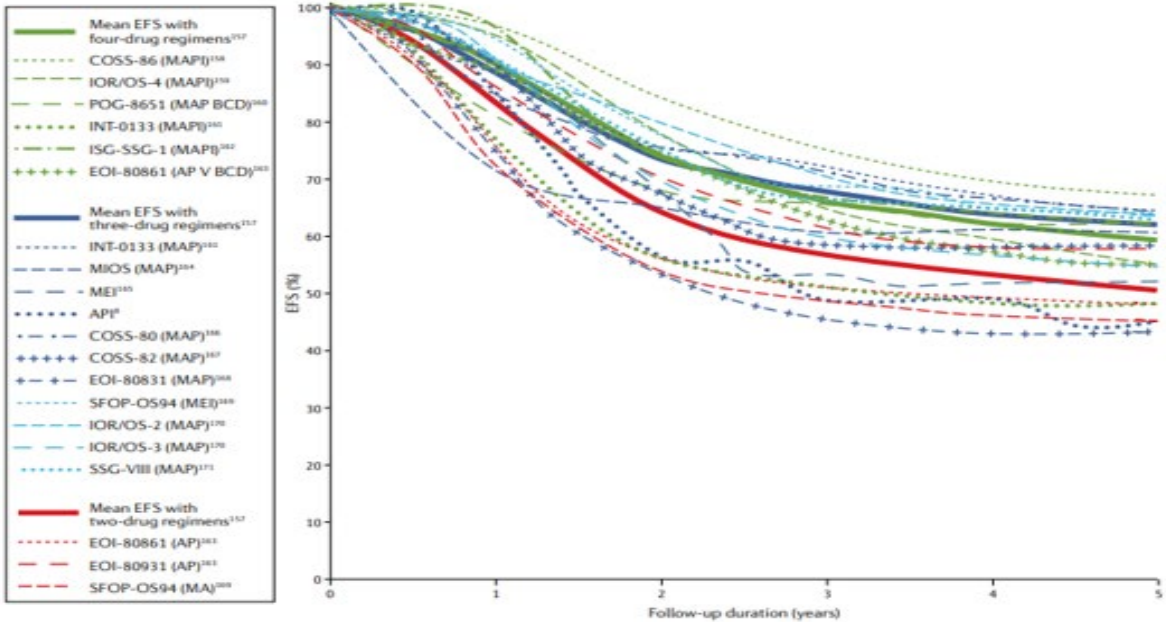
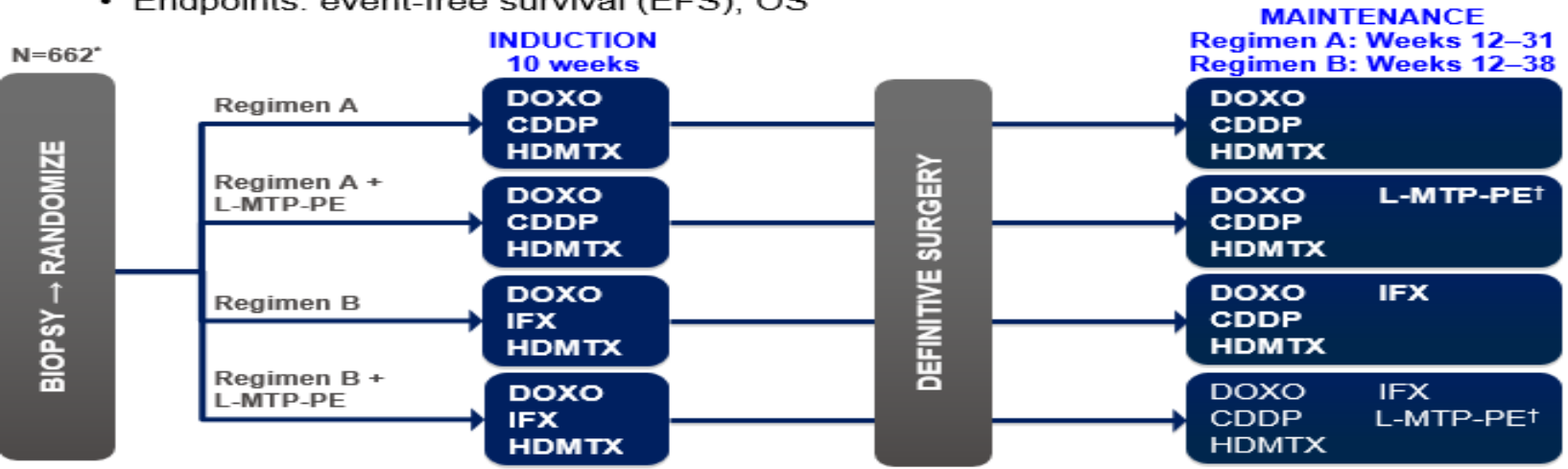


Fig. 1 | **EFS with chemotherapy regimens comprising two, three or four drugs in patients with osteosarcoma.** The dashed lines depict the event-free survival (EFS) curves from numerous large-cohort trials of various chemotherapy regimens in patients with osteosarcoma. The aggregate EFS curves of trials investigating combinations of two, three or four cytotoxic agents are shown using red, blue and green bold lines, respectively. Notably, the green EFS curves corresponding to four-drug regimens overlap substantially with the blue lines relating to three-drug regimens. Thus, the outcomes of patients treated with various three-drug or four-drug regimens are effectively the same; however, patients treated with two-drug combinations have inferior outcomes (red lines). A, doxorubicin; B, bleomycin; C, cyclophosphamide; D, dactinomycin; E, etoposide; I, ifosfamide; M, methotrexate; P, cisplatin; V, vincristine[157–171].

NATURE REVIEWS | CLINICAL ONCOLOGY

INT-0133: Phase 3 Trial - Design

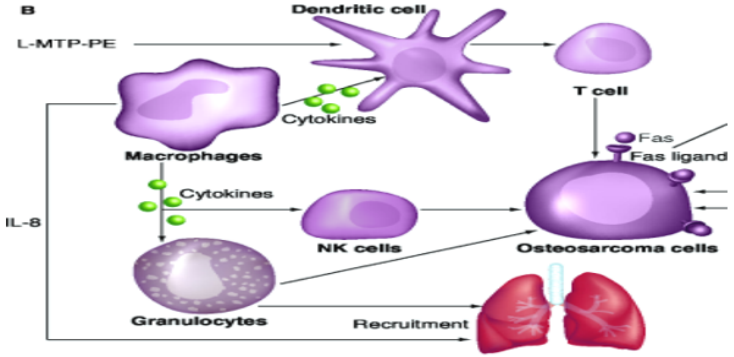
- Phase 3 trial of the addition of ifosfamide (IFX) and/or L-MTP-PE to cisplatin (CDDP), doxorubicin (DOXO) and high-dose methotrexate (HDMTX)[1,2]
- N=662 patients with osteosarcoma and no detectable metastases
- Endpoints: event-free survival (EFS), OS

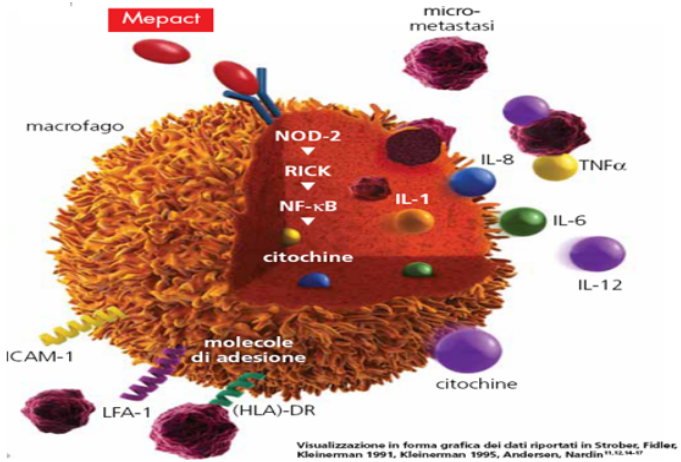


*Patients were aged ≤30 years (median 13 years).
†2 mg/m² IV twice/week for 12 weeks, then once/week for 12 weeks

1. Meyers PA, et al. J Clin Oncol 2005;23:2004–11
2. Meyers PA, et al. J Clin Oncol 2008;26:633–8

- MTP-PE è un derivato di sintesi del muramyl dipeptide (MDP) che è un componente ad azione immunostimolante della parete di batteri Gram+/-.
- Analogamente a MDP, MTP ha proprietà di stimolazione monocitaria e macrofagica , ma in relazione alla sua elevata lipofilia risulta molto più potente ed efficace del precedente.
- Le caratteristiche lipofile di MTP ne consentono l' incapsulamento all' interno di liposomi.
- I liposomi vengono rapidamente fagocitati dal sistema macrofagico in particolare a livello toracico.
- Toll-like receptor-4 determina attivazione monociti e macrofagi e promuove attività antitumorale citotossica selettiva.
- Attivazione dei recettori intracellulari NOD-2 che induce produzione NF-kB attraverso l'attivazione del recettore RICH e quindi secrezione di citochine infiammatorie TNFa, IL6, IL8 e IL1.
- L'attivazione monociti/macrofagi e cellule dendritiche possono attivare altre cellule dell'immunità innata come NK e generare una risposta di immunità adattiva attraverso le cell T.





Visualizzazione in forma grafica dei dati riportati in Strober, Fidler, Kleinerman 1991, Kleinerman 1995, Andersen, Nardin[11,12,14-17]

ISG/OS-2 Trial, a risk-adapted study

ISG/OS-2

Non Metastatic Osteosarcoma of the extremity
Expression of ABCB1/PgP as biological stratification

Prospective cohort study

PgP-

PgP+

MTX
CDP
ADM
IFO

MTP

ISG/OS-2 Emendamento 1: Versione 28 Febbraio 2013

Espressione di ABCB1/P-glycoprotein come fattore per la stratificazione biologica dell' osteosarcoma non metastatico delle estremità: Studio prospettico. (ISG/OS-2)

Codice EUDRACT: 2011-002659-36

Clinical Trial GOV: NCT01459484

Sponsor:

Italian Sarcoma Group

c/o Istituto Ortopedico Rizzoli

Via di Barbiano 1/10 Bologna

DATA: 25 Marzo 2011

ISG/OS-2 Emendamento 1: Versione 28Febbraio 2013

con il supporto di:

Italian Sarcoma Group

1

ISG/OS-2 Trial, a risk-adapted study

Original Article

Phase 2 study for nonmetastatic extremity high-grade osteosarcoma in pediatric and adolescent and young adult patients with a risk-adapted strategy based on ABCB1/P-glycoprotein expression: An Italian Sarcoma Group trial (ISG/OS-2)

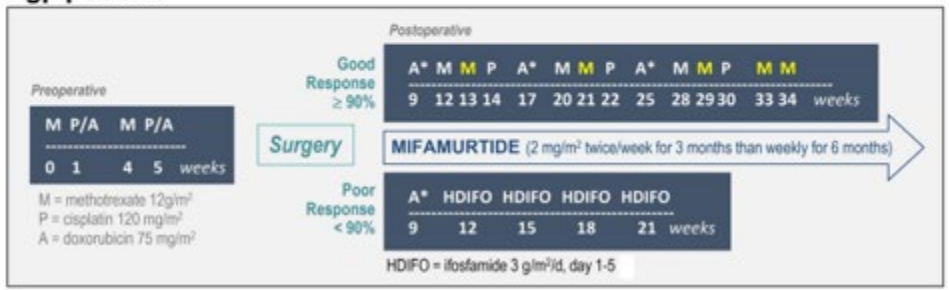
Emanuela Palmerini, MD, PhD[1]; Cristina Meazza, MD[2]; Angela Tamburini, MD[3]; Gianni Bisogno, MD[4]; Virginia Ferraresi, MD[5]; Sebastian D. Asaftei, MD[6]; Giuseppe M. Milano, MD[7]; Luca Coccoli, MD[8]; Carla Manzitti, MD[9]; Roberto Luksch, MD[2]; Massimo Serra, BSc[1]; Marco Gambarotti, MD[10]; Davide M. Donati, MD[11,12]; Katia Scotlandi, PhD[13]; Rossella Bertulli, MD[2]; Claudio Favre, MD[3]; Alessandra Longhi, MD[5]; Massimo E. Abate, MD[14]; Silverio Perrotta, MD[15]; Maurizio Mascarin, MD[16]; Paolo D'Angelo, MD[17]; Marilena Cesari, MD[1]; Eric L. Staals, MD, PhD[11,12]; Emanuela Marchesi, BSc[18]; Elisa Carretta, PhD[1]; Toni Ibrahim, MD, PhD[1]; Paolo G. Casali, MD[2]; Piero Picci, MD[18]; Franca Fagioli, MD[4,19]; and Stefano Ferrari, MD[1]

BACKGROUND: According to retrospective osteosarcoma series, ABCB1/P-glycoprotein (Pgp) overexpression predicts for poor outcomes. A prospective trial to assess a risk-adapted treatment strategy using mifamurtide in Pgp+ patients was performed. **METHODS:** This was a phase 2, multicenter, uncontrolled trial including patients 40 years old or younger with nonmetastatic extremity high-grade osteosarcoma stratified according to Pgp expression. All patients received high-dose methotrexate, doxorubicin, and cisplatin (MAP) preoperatively. In Pgp+ patients, mifamurtide was added postoperatively and combined with MAP for a good histologic response (necrosis ≥ 90%; good responders [GRs]) or with high-dose ifosfamide (HDIFO) at 3 g/m^2/d on days 1 to 5 for a histologic response < 90% (poor responders [PRs]). Pgp- patients received MAP postoperatively. After an amendment, the cumulative dose of methotrexate was increased from 60 to 120 g/m^2 (from 5 to 10 courses). The primary end point was event-free survival (EFS). A postamendment analysis was performed. **RESULTS:** In all, 279 patients were recruited, and 194 were included in the postamendment analysis: 70 (36%) were Pgp-, and 124 (64%) were Pgp+. The median follow-up was 51 months. For Pgp+ patients, 5-year EFS after definitive surgery (null hypothesis, 40%) was 69.8% (90% confidence interval [CI], 62.2%-76.2%): 59.8% in PRs and 83.7% in GRs. For Pgp- patients, the 5-year EFS rate was 66.4% (90% CI, 55.6%-75.1%). **CONCLUSIONS:** This study showed that adjuvant mifamurtide, combined with HDIFO for a poor response to induction chemotherapy, could improve EFS in Pgp+ patients. Overall, the outcomes compared favorably with previous series. Mifamurtide and HDIFO as salvage chemotherapy are worth further study. *Cancer* 2022;128:1958-1966. © 2022 The Authors. Cancer published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: adolescents and young adults (AYAs), ATP binding cassette subfamily B member 1 (ABCB1), chemotherapy, high-grade bone sarcoma, mifamurtide, osteosarcoma, pediatric bone tumors, P-glycoprotein.

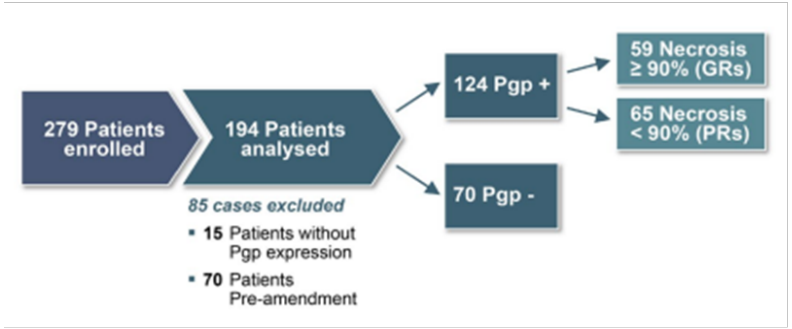
Pgp negative

Pgp positive



ISG/OS-2 Trial- Results

June 2011 to March 2018



Median age 14 yrs (4-38)

Poor Responders	Good Responders
104 pts (54%)	90 pts (46%)

No correlation between Pgp expression and histologic response

		5-y EFS %	5-y OS %
Pgp positive		**69.8**	**81.2**
	GR	**83.7**	**88.5**
	PR	**59.8**	**74.4**
Pgp negative		**66.4**	**79.4**

Median follow up 51 months

TABLE 3

High-Grade (≥3) Bone Marrow and Organ Toxicities During ISG/OS-2 Treatment in Patients With Nonmetastatic Extremity Osteos

	Pgp+ (n = 122), No. (%)	Pgp− (n = 70), No. (%)	Overall (n = 192), No. (%)
Leucopenia	107 (88)	63 (90)	170 (89)
Neutropenia	113 (93)	66 (94)	179 (93)
Thrombocytopenia	88 (72)	48 (69)	136 (71)
Anemia	70 (57)	43 (61)	113 (59)
Creatinine	1 (1)	1 (1)	2 (1)
AST	72 (59)	32 (46)	104 (54)
ALT	96 (79)	51 (73)	147 (77)
Central neuropathy	1 (1)	1 (1)	2 (1)
Peripheral neuropathy	1 (1)	2 (3)	3 (2)
Mucositis	18 (15)	15 (21)	33 (17)
Neutropenic fever	73 (60)	47 (67)	120 (63)
Cardiotoxicity	3 (2)	4 (6)	7 (4)
Multiorgan failure	1 (1)	0 (0)	1 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ISG, Italian Sarcoma Group; Pgp, P-glycoprotein.

Con cosa ci confrontiamo

ISG-OS-1	61% 5-year EFS	74%5-year OS
GR	71% 5-year EFS	82% 5-year OS
PR	53% 5-year EFS	70% 5-year OS
OS-2006	60% 3-year EFS	79% 3-year OS
EURAMOS PR		
MAP	60% 3-year EFS	72% 3-year OS
MAPIE	57% 3-year EFS	77% 3-year OS
EURAMOS GR		
MAP	77% 3-year EFS	81% 5-year OS
MAPIE	80% 3-year EFS	84% 5-year OS

Serra et al, J Clin Oncol 2003. EFS in 149 patients treated at the Istituto Ortopedico Rizzoli with neoadjuvant chemotherapy protocols based on **MTX-CDDP-DOX (pre-operative phase)** with the addition of **ifosfamide** in the post-operative phase for the poor responders (necrosis < 90%).
Legend: PGP = P-glycoprotein ; PR = poor responders ; GR = good responders

			%EFS at 5 years	CI 95%	*P*
All patients		149	65	57-72	
PGP+		47	40	26-54	
					0.0001
PGP-		102	76	68-85	
PGP-	GR	69	81	72-90	
					0.20
PGP-	PR	32	69	53-85	
PGP+	GR	34	50	33-67	
					0.02
PGP+	PR	13	15	0-35	

ISG/OS-2 Trial – Results. Unpublished data

Univariate analysis

		5-years EFS (95%CI)	P value
Age	< 18 y	64.4% (56.-70.9)	0.2910
	18 to 40y	55.8% (43.7-66.3)	
Gender	Male	62.7% (54.5-69.8)	0.9047
	Female	61.1% (51.0-69.8)	
Serun alcaline phosphatase	High	47.7% (36.6-57.9)	< 0.0001
	Normal	70.2% (62.3-76.8)	
Lactate dehydrogenase	High	57.5% (44.5-68.5)	0.3155
	Normal	62.6% (54.9-69.3)	
Grade	3	72.3% (59.5-81.6)	0.0481
	4	58.5% (51.1-65.2)	
Histologic Response	Good	77.8% (68.7-84.6)	< 0.0001
	Poor	50.9% (42.6-58.6)	
Pgp expression	Positive	67.5% (59.2-74.5)	0.0587
	Negative	55.0% (44.6-64.2)	
MTX cycles	5	49.3% (37.5 - 60.1)	0.0090
	10	67.7% (60.5-73.8)	

Multivariate analysis

		HR (95%CI)	P value
Pgp	Negative vs Positive	1.3 (0.8-2.0)	0.2355
Histologic Response	PR vs GR	2.5(1.5-4.0)	0.0003
ALP	High vs Normal	2.1(1.4-3.3)	0.0010
Grade	4 vs 3	2.4(1.2-4.5)	0.0088
MTX Cycles	5 vs 10	1.3(0.8-2.1)	0.2192

ISG/OS-2 Trial – Results. Unpublished data

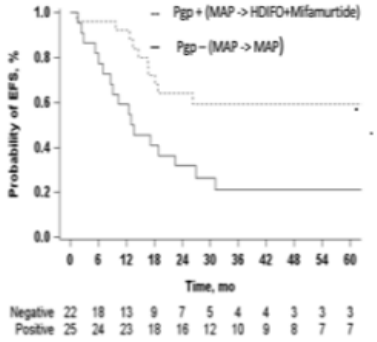
3-degree score	Necosis
Good	**≥ 90%**
Fair	**60-89%**
Very poor	**0-59%**

	5y-EFS (95%CI)	P value
GOOD	77.8% (68.7- 84.6)	<0.0001
FAIR	56.4% (46.2-65.4)	
VERY POOR	38.8% (25.1-52.2)	

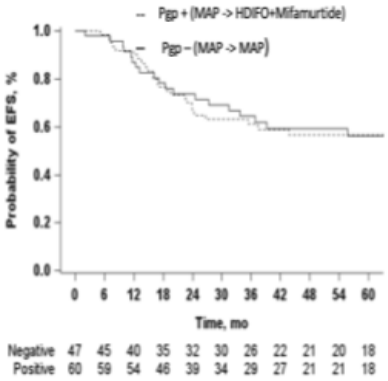
	Pgp pos	Pgp neg	P value
GOOD	80.2%	72.3%	0.4567
FAIR	56.7%	56.2%	0.9187
VERY POOR	59.1%	21.2%	0.0057

EFS in very poor respoders

a Patients with a Very Poor Histologic Response



b Patients with Fair Histologic Response



Trial record **1 of 1** for: NCT03643133 | Recruiting, Not yet recruiting Studies

Previous Study | Return to List | Next Study

Mifamurtide Combined With Post-operative Chemotherapy for Newly Diagnosed High Risk Osteosarcoma Patients (SARCOME13)

ClinicalTrials.gov Identifier: NCT03643133

Recruitment Status : Recruiting
First Posted : August 22, 2018
Last Update Posted : December 9, 2022

See Contacts and Locations

Sponsor:
UNICANCER

Information provided by (Responsible Party):
UNICANCER

Study Description

Go to

Brief Summary:
Trial evaluating the impact on efficacy of mifamurtide as add-on treatment to post-operative chemotherapy compared to post-operative chemotherapy alone in first-line treatment of patients with high-risk osteosarcoma (defined as metastatic osteosarcoma at diagnosis or localised osteosarcoma with poor histological response).

Condition or disease	Intervention/treatment	Phase
Osteosarcoma	Drug: Mifamurtide Combination Product: EI or M-API regimen depending on patient age	Phase 2

Detailed Description:

Multicentre, randomised, open-label, phase II trial, with 2 parallel groups. After pre-operative chemotherapy and surgery of the primary tumour and lung metastases (if applicable), patients presenting high-risk osteosarcoma (defined as metastatic osteosarcoma at diagnosis or localised osteosarcoma with poor histological response) will be randomised between 2 arms:

- Control arm: post-operative chemotherapy alone (with regimens adapted to the age of patient)
- Experimental arm : post-operative chemotherapy combined with mifamurtide

This randomised trial is part of a study recruiting all patients ≤50 years old with a newly diagnosed high-grade osteosarcoma.

Study Design

Go to

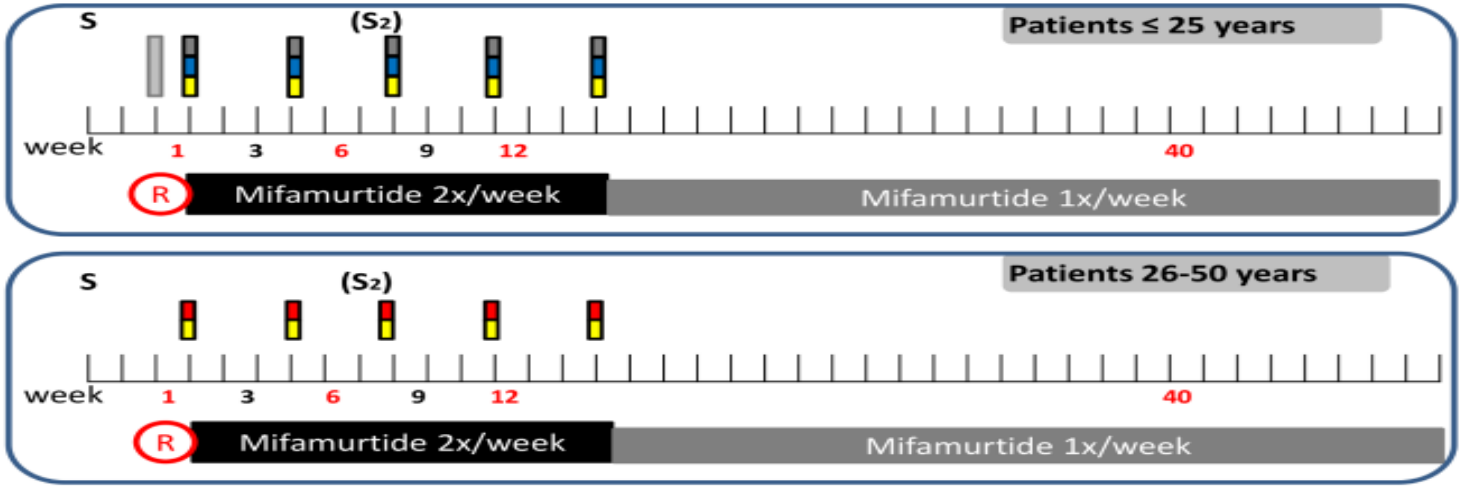
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	126 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Multicentre, Randomised, Phase 2 Trial of Mifamurtide Combined With Post-operative Chemotherapy for Newly Diagnosed High Risk Osteosarcoma Patients (Metastatic Osteosarcoma at Diagnosis or Localised Disease With Poor Histological Response)
Actual Study Start Date :	October 23, 2018
Estimated Primary Completion Date :	October 2024
Estimated Study Completion Date :	October 2033

Investigators

Principal Investigator:	Nathalie MD GASPAR, PhD	Gustave Roussy Cancer Campus
Principal Investigator:	Sophie MD PIPERNO-NEUMANN, PhD	Institut Curie

High-Risk osteosarcomas
- Metastasis at diagnosis
- Or Localised disease and poor histological response

Sarcoma 13



S: Surgery (primary +/- met)
S2: Second surgery if needed (bilateral lung metastases)

MTX 12g/m2 x 1d

A : Adriamycine 60 mg/m² x 1d
P : Cisplatinum 100 mg/m² x 1d
I : Ifosfamide 3 g/m² x 2d

E : Etoposide 75 mg/m² x 4d
I : Ifosfamide 3 g/m² x 4d

Figure 2 Individual historical data, from Sarcome-09/OS2006 subgroup of patients who fulfilled the planned Sarcome-13/OS2016 eligibility criteria, on the control arm of the current trial.

Nell'era della medicina di precisione anche in oncologia pediatrica, la difficoltà di progettare e validare nuove terapie più mirate nel caso OS si basa su due livelli di complessità:

•un'**elevata eterogeneità genomica** e un **tasso mutazionale alto** che determinano eventi oncogenici scarsamente definiti (mutazioni ricorrenti TP53, RB, MDM2, ATRX e DLG2; cromotripsi; kataegis) : effetto fioco di neve

•un **microambiente** attivo e reattivo composto da cellule dinamiche, interconnesse e intensamente comunicanti attraverso secrezione paracrina di fattori solubili ed vescicole extracellulari, con una complessa interazione con le cellule tumorali.

Fra le possibili strategie terapeutiche attuali da testare verso questo complesso ecosistema dell'OS, sicuramente spiccano gli inibitori multi-chinasi (MKI) che interagiscono con le cellule tumorali e quelle del microambiente.

La maggior parte delle MKI non sono considerati farmaci di precisione poiché agiscono su più chinasi in misura variabile e non solo su cellulle OS. Hanno come target recettori di chinasi ad attività angiogenica (VEGFR1-3, TIE-2), stromale (PDGFR-β, FGFR) e oncogenica (KIT, RET e RAF) e per questo possono agire a più livelli.

Table 1. Multi-kinases inhibitors (MKI) in Osteosarcoma (OS): Molecular and Cellular Targets and Clinical Trials.

MKI	Targets		Clinical Trials
	Molecular	Cellular	ClinicalTrials.gov
Sorafenib	RAF, KIT, FLT3, RET VEGFR1-3 PDGFRβ	Tumor Endothelial Stromal	NCT 00889057 [125] NCT 01804374 [126]
Regorafenib	KIT, RET, RAF VEGFR1-3, Tie-2 PDGFRβ FGFR	Tumor Endothelial Stromal	NCT 0238244 [159] NCT 02048371 [158]
Pazopanib	KIT, FMS VEGFR1-3 PDGFRαβ FGFR	Tumor Endothelial Stromal	[160]
Cabozantinib	MET, KIT, RET VEGFR-2, Tie-2	Tumor Osteoblasts Endothelial	NCT02243605 [162]
Lenvatinib	KIT, RET VEGFR-1, 2, 3 PDGFR-α FGFR1-4	Tumor Endothelial Stromal	NCT04154189

Inibitori delle tirosin chinasi

Overespressione di VEGF, IGF1, PDGF, HER2, MET

frontiers in Oncology

Receptor Tyrosine Kinases in Osteosarcoma Treatment: Which Is the Key Target?

Zhichao Tian*, Xiaohui Niu† and Weitao Yao**

- Sorafenib → 4-month PFS of 46%
- Regorafenib → 4-month PFS of 44%
- Cabozantinib → 4-month PFS of 71%
- Lenvatinib → 4-month PFS of 33%
- Apatinib → 4-month PFS of 57%
- Pazopanib → median PFS of 5.5 months

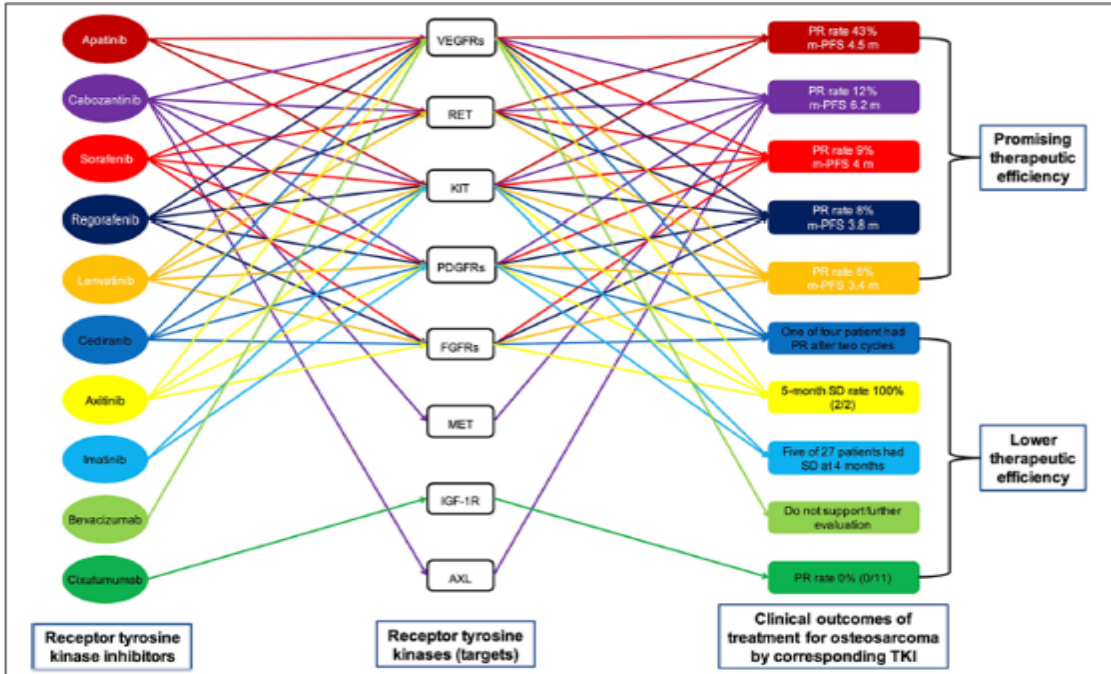


FIGURE 3 | A visual interaction map of the different targets of the different drugs. Preclinical data indicate that all eight targets shown in the figure play an important role in the progression of osteosarcoma. However, clinical trials in osteosarcoma have demonstrated the low efficacy of single-target therapy by inhibiting VEGFs (by bevacizumab), KIT and PDGFRs (by imatinib), and IGF-1R (by cixutumumab). The results of these clinical trials suggest that the inhibition of one type of targets in the treatment of osteosarcoma is not feasible. PFS, progression-free survival; TKI, tyrosine kinase inhibitor; PR, partial response; VEGFR, vascular endothelial growth factor receptor; KIT, stem cell factor receptor; RET, rearranged during transfection; FGFR1, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; SD, stable disease.

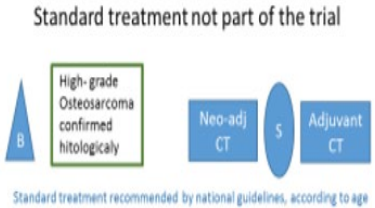
FOSTER CabOS

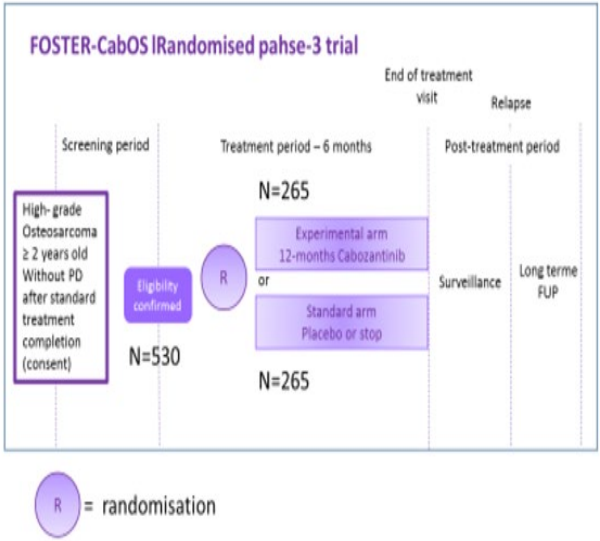
FIGHT OSTEO-SARCOMA THROUGH EUROPEAN RESEARCH

ATTRACT
Accelerate Together Rare Cancer Treatment

Study phase/type	**Randomised phase-3**
Objective	**Co-primary objective** To assess efficacy, in terms of event-free survival (EFS), of Cabozantinib compared to placebo as maintenance therapy after first-line chemotherapy in patients treated for osteosarcoma, considering both -patients in complete remission (CR) at the end of first-line therapy, -the whole randomised dataset, including also patients with residual disease after first-line treatment (non-resectable primary tumour, or metastatic disease). **Secondary objectives** To evaluate in this setting: -compliance to Cabozantinib treatment -efficacy of Cabozantinib in terms of overall survival -safety of Cabozantinib -Cabozantinib impact on Quality-of-Life -benefit/risk ratio associated with Cabozantinib-versus-control using the Q-TWiST approach (Quality-adjusted Time Without Symptoms of disease recurrence or Toxicity of treatment) -net treatment benefit, combining efficacy and safety endpoints, of Cabozantinib-versus-control -whether the treatment effect of Cabozantinib on EFS is homogeneous in the study population, or differs between subgroups of patients (clinical risk groups based on initial staging and histological response; biological subgroups; type of first line treatment) -the prognostic and predictive value of biological and imaging biomarkers

Appendix 1: Study design





FIGHT OSTEO-SARCOMA THROUGH EUROPEAN RESEARCH

Efficacy of Regorafenib Combined With Best Supportive Care as Maintenance Treatment in High Grade Bone Sarcomas Patients (REGOMAIN)

This is a randomized, double-blinded, 2 arms study concerning patients with high-grade bone sarcoma (HGBS) without complete remission after standard treatment at diagnosis or first relapse.

In the first arm, patients will be treated with regorafenib + best supportive care (BSC) for a maximum of 12 months as maintenance therapy after standard line therapy completion, whereas in th second arm, patients will be treated with placebo + BSC (standard of care).

The comparison between this two arms will allow to determine whether or not regorafenib and BSC is efficient for disease control, in terms of Progression-Free Survival improvement.

INCLUSION CRITERIA:

I1. Age ≥ 12 years at the day of consenting to the study;

I2. Patients must have histologically confirmed high-grade sarcomas of bone primary localisation, including but not limited to: Osteosarcomas, Ewing sarcomas, Chondrosarcomas, Undifferenciated Pleomorphic Sarcomas (UPS), Leiomyosarcomas (LMS) and Angiosarcomas

I3. Measurable residual disease not amenable to resection after multimodal treatment principles either at diagnosis (after standard multimodal treatment based on the histological subtype) or at relapse (chemotherapy)

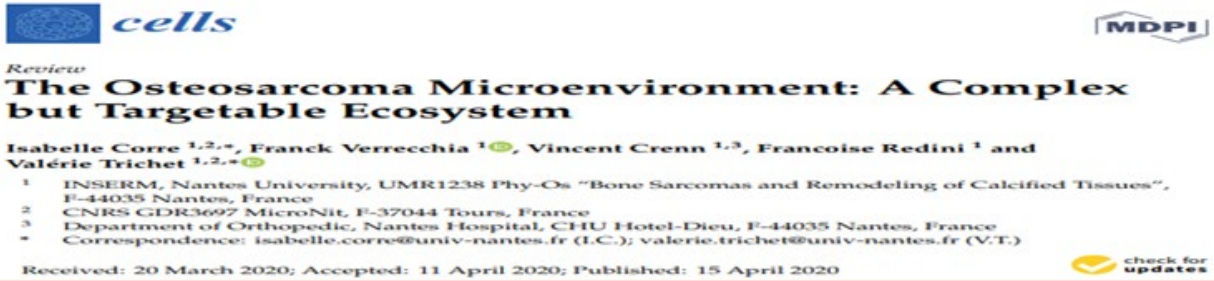
I4. Non progressive disease (defined by the investigator according to the RECIST version 1.1 Appendix 1) at study entry;

I5. Interval between the date of last anticancer treatment (chemotherapy or surgery) and the date of randomization: at least 4 weeks but no longer than 2 months;

I6. Life expectancy of greater than 6 months;

I7. Eastern Cooperative Oncology Group (ECOG) performance status < 2 (Karnofsky ≥ 70%) (Appendix 2);

Microambiente osseo è un ambiente molto specializzato, complesso e altamente dinamico composto da cellule ossee (osteoclasti, osteoblasti, osteociti), cellule stromali (MSC, fibroblasti), cellule vascolari (cellule endoteliali e periciti), cellule immunitarie (macrofagi, linfociti) e una matrice extracellulare mineralizzata. In condizioni fisiologiche, un'attività orchestrata coordinata e messa a punto dalle cellule ossee, vascolari e stromali attraverso intense comunicazioni paracrine e cellulari garantisce l'omeostasi ossea. Secondo la teoria di Paget , le cellule tumorali trovano in questo microambiente un terreno fertile, una nicchia in cui seminare, sfruttando i percorsi fisiologici dell'osso a proprio vantaggio per sopravvivere, crescere e metastatizzare. L'interazione tra OS e microambiente osseo coinvolge numerosi segnali ambientali, indotti da molteplici citochine, chemochine e fattori di crescita solubili o veicolati da vescicole extracellulari, considerate oggi efficaci vettori di comunicazione tra cellule .



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Review

The Osteosarcoma Microenvironment: A Complex but Targetable Ecosystem

Isabelle Corre [1,2,*], Franck Verrecchia [1], Vincent Crenn [1,3], Francoise Redini [1] and Valérie Trichet [1,2,*]

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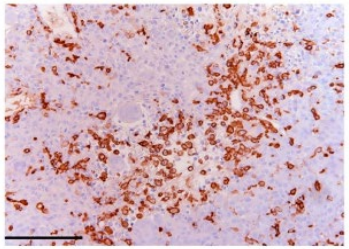
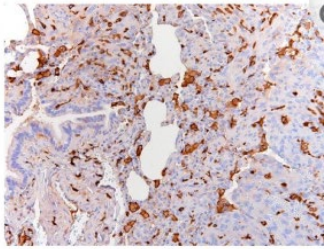
Tumor-Associated Macrophages in Osteosarcoma: From Mechanisms to Therapy

Francesca Cersosimo,[1] Silvia Lonardi,[2] Giulia Bernardini,[1] Brian Telfer,[3] Giulio Eugenio Mandelli,[2] Annalisa Santucci,[1] William Vermi,[2,4] and Emanuele Giurisato[1,5,*]





(a) (b)

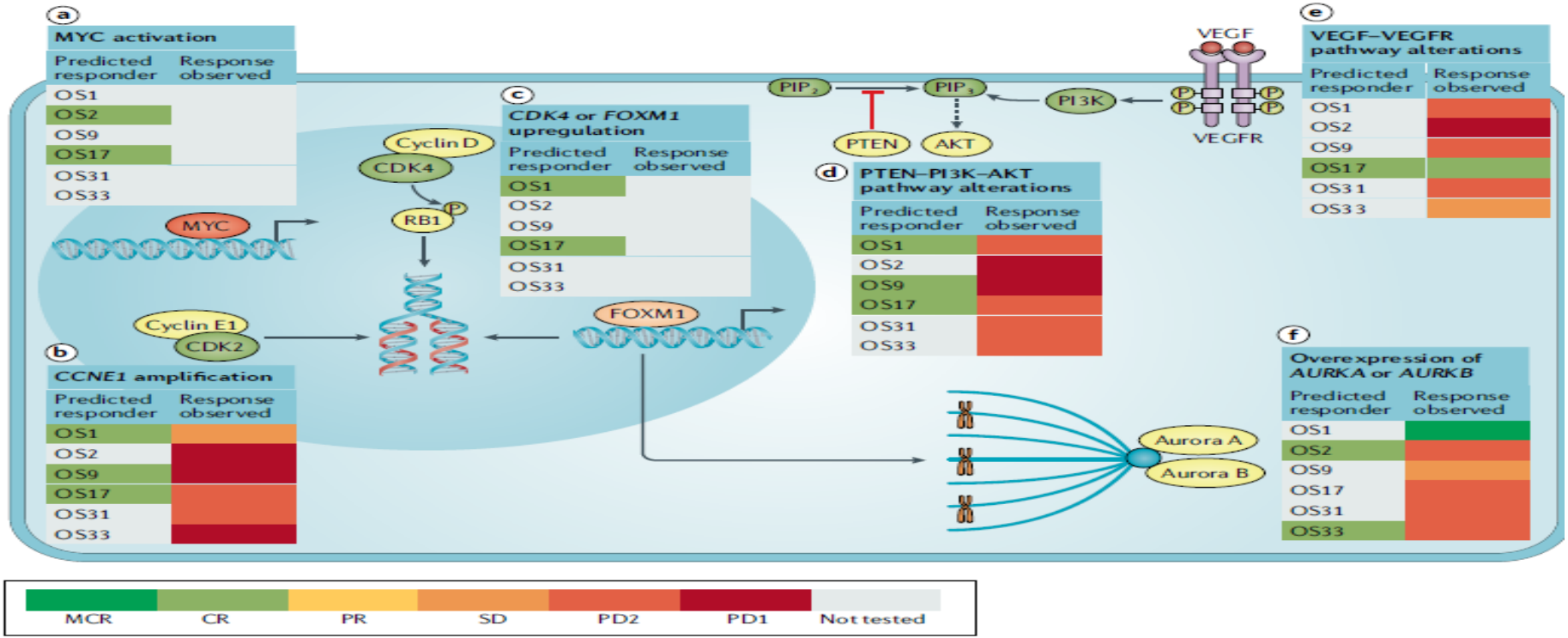
Therapeutic agents targeting TAMs for OS treatment.

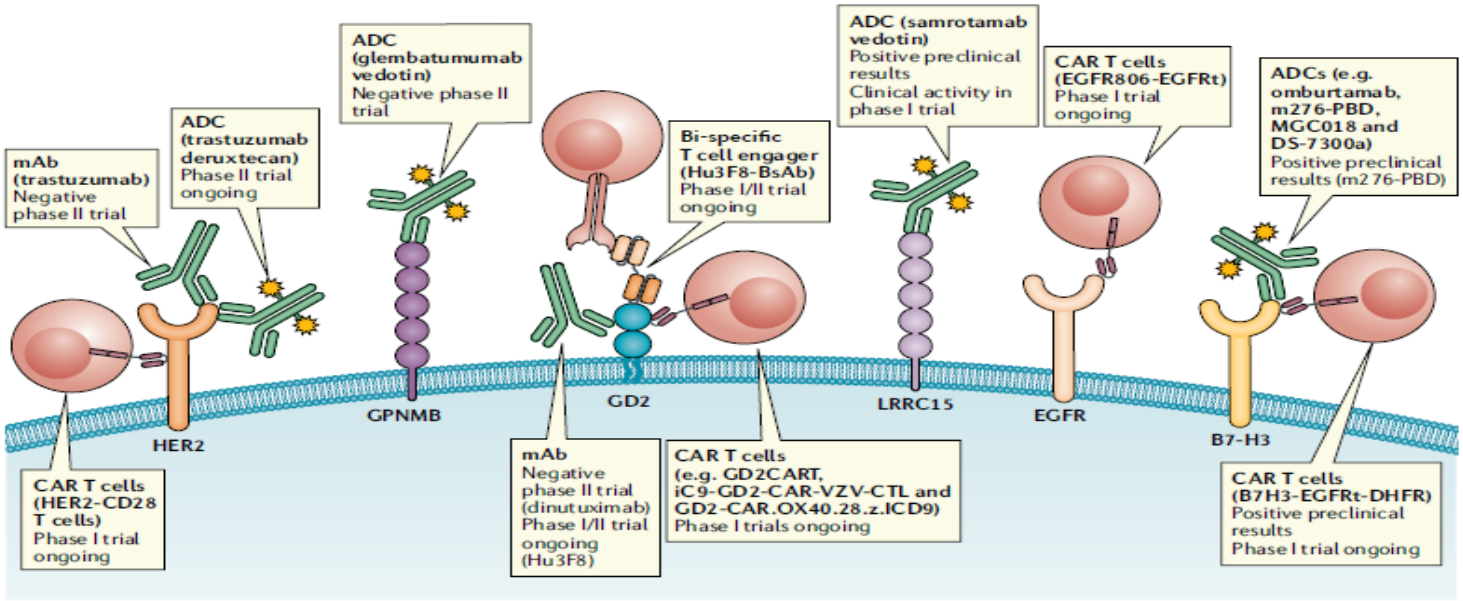
Biomarkers associated with tumor-associated macrophages in OS.

Biomarkers	Function	Ref.
MMP-9	Matrix metalloproteinase	[5]
COX2	Proinflammatory enzyme	[5]
STAT3	Transcription factor	[5]
CD163	Scavenger receptor hemoglobulin	[6]
CCL18	Chemokine	[98]
CD209	Leptin receptor	[99]
IL-6	Interleukin	[100]
CCL22	Chemokine	[101]
IL-10	Interleukin	[101]
TGFB2	Cytokine	[101]
CD206	Mannose receptor	[102]

Agent	Mechanism	Phase	Ref.
All trans retinoic acid	Reduces polarization of M2-like	Pre-clinical	[8]
Mifamurtide	Induces M1-like activation	3	[145]
Esculetin	Inhibits TAMs differentiation	Pre-clinical	[150]
Zoledronate	Polarizes TAMs to M1-like	3	[151]
Natalizumab	Interferes cross-talk between cancer cells and TAMs	NCT03811886	[157]
Nivolumab	mAbs anti-PD-1	NCT02304458	[158]
Pembrolizumab	mAbs anti-PD-1	NCT02301039	[158]

Categorie molecolari dell'osteosarcoma e risposte relative a trattamenti target nei modelli PPTC PDX





Varie molecole di superficie cellulare sono comunemente sovra-espresse sulle cellule dell'osteosarcoma.
Sono in fase di studio una serie di approcci basati su anticorpi e/o terapie cellulari che hanno come target queste molecole.
Per le sperimentazioni in atto, sono riportati la fase dello studio e i risultati finora ottenuti.
ADC, anticorpo-farmaco coniugato; CAR, recettore dell'antigene chimerico; mAb, anticorpo monoclonale

Negli ultimi quattro decenni sono stati compiuti progressi limitati nel migliorare i risultati di sopravvivenza nei pazienti con osteosarcoma.

Grazie ai progressi nella comprensione biologica, allo sviluppo di robusti modelli preclinici, alla fattibilità di test clinici rapidi e a nuovi concetti di trattamento come :

- **Attacco al microambiente**
- **Tecniche di caratterizzazione molecolare** (hanno rivelato sottocategorie di osteosarcoma e potrebbero consentire un approccio di medicina di precisione con agenti che inibiscono le vie di segnalazione attivate)
- **Terapie Target immuno-mediate (**anticorpi monoclonali, anticorpi farmaco-coniugati e CAR T)

nel prossimo futuro si prevedono miglioramenti tanto attesi nel trattamento medico dell'osteosarcoma.

Una caratteristica importante dei tumori OS è la loro eterogeneità, sia a livello intra che inter tumorale. Pertanto, i comuni processi biologici che danno inizio all'osteosarcomagenesi non sono ancora stati identificati. La complessità delle alterazioni somatiche del genoma dell'OS è una delle principali cause di eterogeneità intratumorale caratterizzata :

- aneuploidia cromosomica,
- alterazione dei geni mediante mutazione e/o variazione del numero di copie,
- instabilità genomica caratterizzata da massiccio riarrangiamento (cromotripsi),
- presenza di pattern di regioni ipermutate localizzate (kataegis).

Sappiamo che un piccolo insieme di geni presenta mutazioni ricorrenti nell'OS (TP53, RB, MDM2, ATRX e DLG2) .

Un sottogruppo di OS è stato descritto con alterazioni nei geni delle vie di riparazione del DNA, che ricordano i tumori con deficit di BRCA1/2 .

Anche diverse sindromi ereditarie come i tumori familiari di Li-Fraumeni, Rothmund-Thomson, Werner, Bloom e retinoblastoma sono state associate a una predisposizione allo sviluppo di OS . Tuttavia nel 95% dei casi gli OS si presentano come eventi sporadici.

Nel complesso, eventi oncogenici scarsamente definiti associati all'elevata eterogeneità delle cellule tumorali rendono difficile lo sviluppo di terapie mirate molecolari.

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Review

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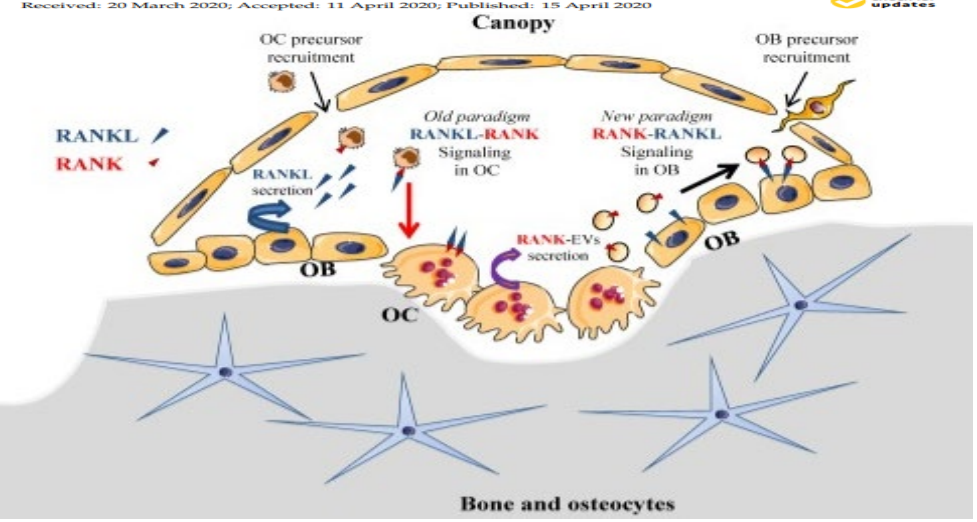

L'interazione RANK-RANKL sembra essere bidirezionale, duplice e complementare nell'accoppiamento tra riassorbimento e formazione ossea: la trasduzione di RANK su osteoclasti e precursori attiva l'osteolisi, mentre la trasduzione di RANKL su osteoblasti e precursori attiva l'osteogenesi.

Nel contesto dell'OS, il rimodellamento osseo è legato a un circolo vizioso tra osteoclasti e cellule tumorali , che si instaura attraverso il rilascio di fattori di crescita dalla matrice ossea degradata. Questo circolo vizioso può essere ulteriormente rafforzato dagli EV secreti dagli osteoclasti e dalle cellule OS.

EV secreti dalle cellule OS sono stati in grado di migliorare l'osteolisi, mentre i RANK-EV secreti dagli osteoclasti possono attivare il RANKL espresso sulle cellule OS, suggerendo segnalazione inversa RANK-RANKL nell'OS, come nella normale fisiologia ossea

- ZOL è stato il primo agente anti-riassorbimento ad essere esplorato come trattamento combinato per l'OS.Risultati deludenti ottenuti nello studio clinico OS2006.
- DENOSUMAB, un anticorpo umanizzato diretto contro il RANKL, non è più considerato un potenziale trattamento combinato per i pazienti con OS. Infatti, se la segnalazione RANK trasduce il segnale in diversi tipi di cellule, inclusi osteoclasti, cellule stromali, cellule endoteliali e cellule dendritiche, non è direttamente implicata nella divisione cellulare e nella sopravvivenza dell'OS.

POSSIBILI APPROCCI VERSO TERAPIE MIRATE:

sostegno del segnale proliferativo (IGFR, SHH/GLI, PDGFR, c-KIT),

elusione dei soppressori della crescita cellulare (p53 , RB, CDK),

resistendo alla morte cellulare (attivazione di ERK, inibizione della molecola proapoptotica, attivazione della molecola antiapoptotica Bcl2, sindecan-2),

consentendo l'immortalità replicativa,

aumentando l'angiogenesi (VEGFR, IGFR, PDGFR, HIF1α) e attivando l'invasione e la metastasi, il genoma instabilità (p53, GADD45), elusione della distruzione immunitaria (IFN) o

interazione con il microambiente osseo (RANK/RANKL/OPG)

Negli osteosarcomi vengono identificate numerose anomalie molecolari che conferiscono alle cellule tumorali alcune caratteristiche particolari:

- segnali proliferativi (PDGFR, IGFR, c-KIT),
- resistenza ai segnali di retroazione (p53, RB),
- resistenza alla morte cellulare (ERK, Bcl-2),
- angiogenesi (VEGFR, PDGFR),
- resistenza alla distruzione immunitaria (IFN).

I potenziali TT potrebbero inibire le vie di segnalazione dei fattori di crescita, o migliorare l'apoptosi, o inibire il processo metastatico, o modulare la risposta immunitaria antitumorale, o modulare il microambiente osseo per aumentare il controllo locale del tumore primario, limitare la diffusione metastatica e infine migliorare la sopravvivenza del paziente . Vedi art5

Table 2: Univariate Event-free survival (EFS) and Overall Survival (OS) in patients with non-metastatic extremity osteosarcoma treated in ISG/OS-2 trial.

	5-year EFS (95%CI)	P value	5-year OS (95%CI)	P value
Age				
< 18 years	64.4% (56.-70.9)	0.2910	74.9% (67.2-81.1)	0.7362
18 to 40 years	55.8% (43.7-66.3)		72.1% (59.7-81.3)	
Gender				
Male	62.7% (54.5-69.8)	0.9047	74.5% (66.3-81.1)	0.9637
Female	61.1% (51.0-69.8)		73.0% (60.0-79.9)	
Serum alkaline phosphatase (ALP)				
High	47.7% (36.6-57.9)	< 0.0001	63.3% (51.2-73.2)	0.0091
Normal	70.2% (62.3-76.8)		79.3% (71.1-85.4)	
Lactate dehydrogenase (LDH)				
High	57.5% (44.5-68.5)	0.3155	65.8% (51.6-76.7)	0.1955
Normal	62.6% (54.9-69.3)		76.0% (68.4-82.0)	
Grade				
3	72.3% (59.5-81.6)	0.0481	85.4% (72.5-92.5)	0.0254
4	58.5% (51.1-65.2)		70.4% (62.7-76.7)	
Histologic Response (2-degree score)				
Good response (GR)	77.8% (68.7-84.6)	<0.0001	79.3% (71.1-85.5)	0.0002
Poor response (PR)	50.9% (42.6-58.6)		67.3% (56.3-76.1)	
Histologic Response (3-degree score)				
Good response (GR)	77.8% (68.7-84.6)	<0.0001	79.3% (71.1-85.5)	0.0002
Fair response (FR)	56.4% (46.2-65.4)		68.0% (57.2-76.6)	
Very poor response (VPR)	38.8% (25.1 - 52.2)		59.2% (42.8-72.4)	
Pgp				
Positive	67.5% (59.2-74.5)	0.0587	79.3% (71.1-85.5)	0.0648
Negative	55.0% (44.6-64.2)		67.3% (56.3-76.1)	
Amendment				
Pre-amendment	49.3 % (37.5-60.1)	0.0090	61.6% (49.5-71.7)	0.0025
Post-amendment	67.7 % (60.5-73.8)		79.9% (72.4-85.6)	

Table 3: Univariate Event-free survival (EFS) and Overall Survival (OS) according to histological response to induction chemotherapy and Pgp expression.

		EFS			OS	
	Number of patients	**Number of events**	**5-year EFS (95 % CI)**	**P value**	**Number of events**	**5-year OS (95 % CI)**
Pgp in GR (2 and 3-degree score)						
Positive	69	13	80.2% (68.2-88.0)	0.4567	7	88.9% (76.2-95.0)
Negative	41	10	72.3% (54.3-84.2)		5	84.8% (66.8-93.4)
Pgp in PR (2-degree score)						
Positive	85	35	57.3% (45.7-67.3)	0.1259	23	71.4% (59.3-80.5)
Negative	69	36	45.0% (32.4-56.7)		27	57.9% (44.0-69.5)
Pgp in FR (3-degree score)						
Positive	60	25	56.7% (42.7-68.5)	0.9187	18	70.3% (55.9-80.8)
Negative	47	19	56.2% (40.0-69.6)		14	65.0% (47.0-78.2)
Pgp in VPR (3-degree score)						
Positive	25	10	59.1% (37.1-75.6)	0.0057	5	73.8% (46.6-88.6)
Negative	22	17	21.2% (7.0-40.4)		13	43.8% (22.7-63.2)