TRATTAMENTO MEDICO DEL PAZIENTE AFFETTO DA OSTEOSARCOMA

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DIPARTIMENTO DI ONCOEMATOLOGIA
SODC "TUMORI PEDIATRICI E
TRAPIANTO DI CELLULE STAMINALI".
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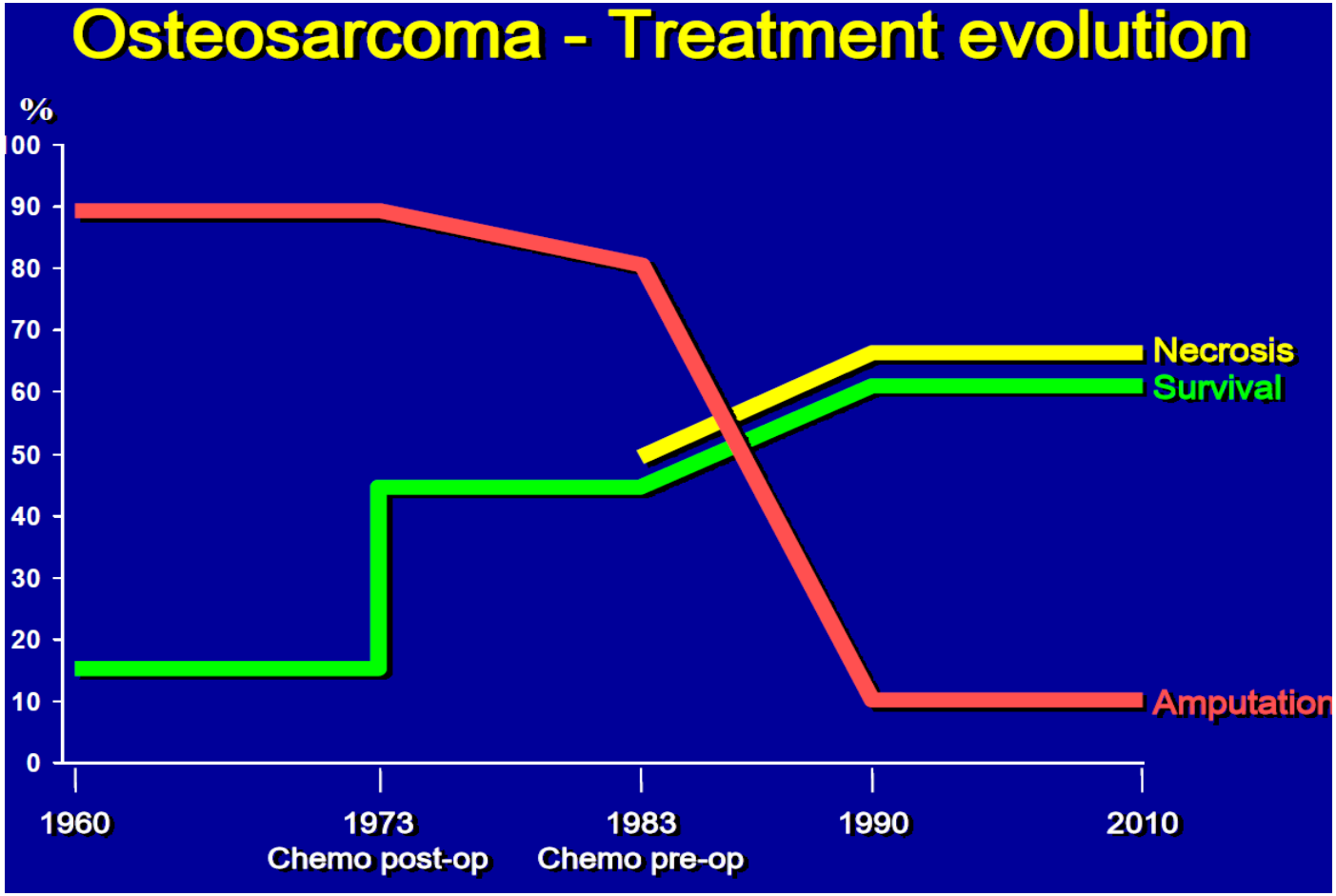
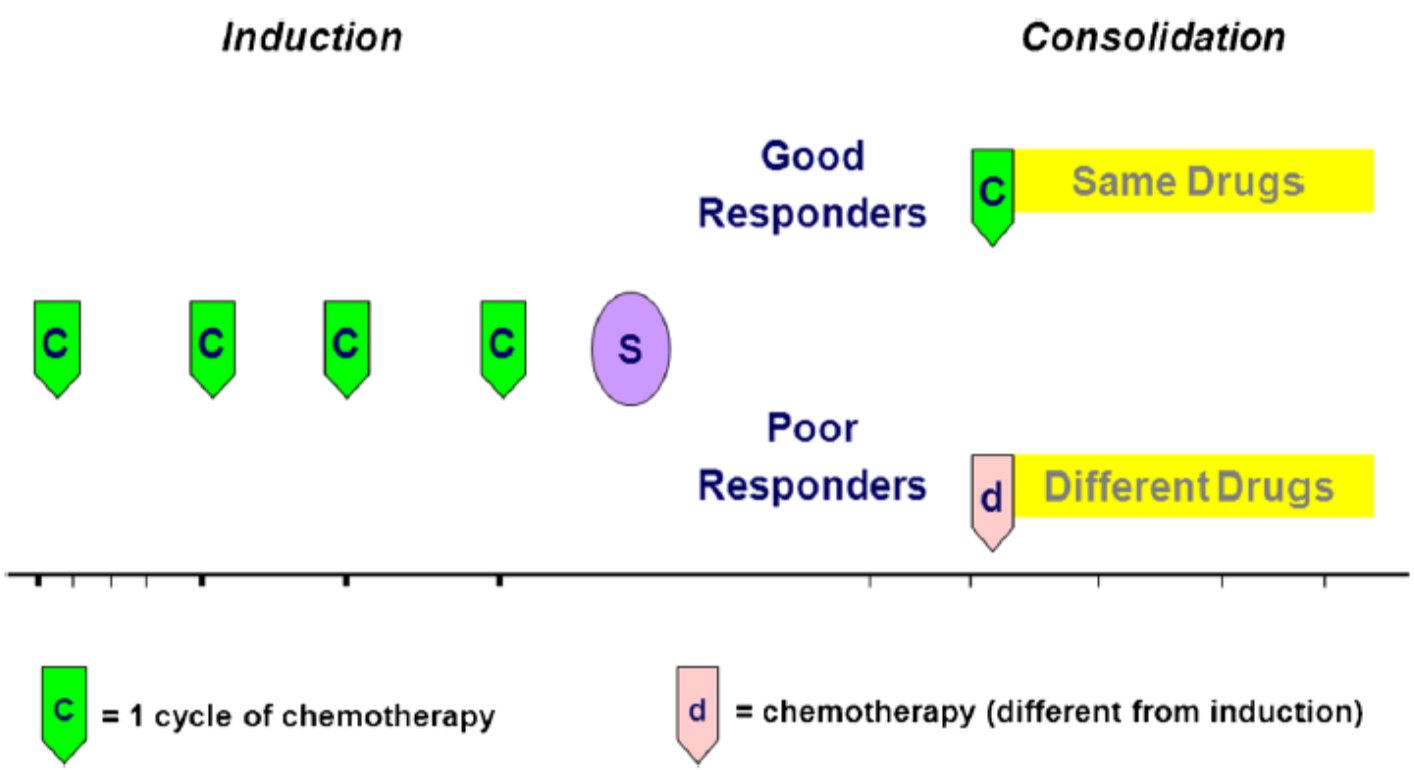
Firenze 12 Dicembre 2018


Osteosarcoma - Treatment evolution
%
100
90
80
70
60
50
40
30
20
10
0
Necrosis
Survival
Amputation
1960
1973
Chemo post-op
1983
Chemo pre-op
1990
2010

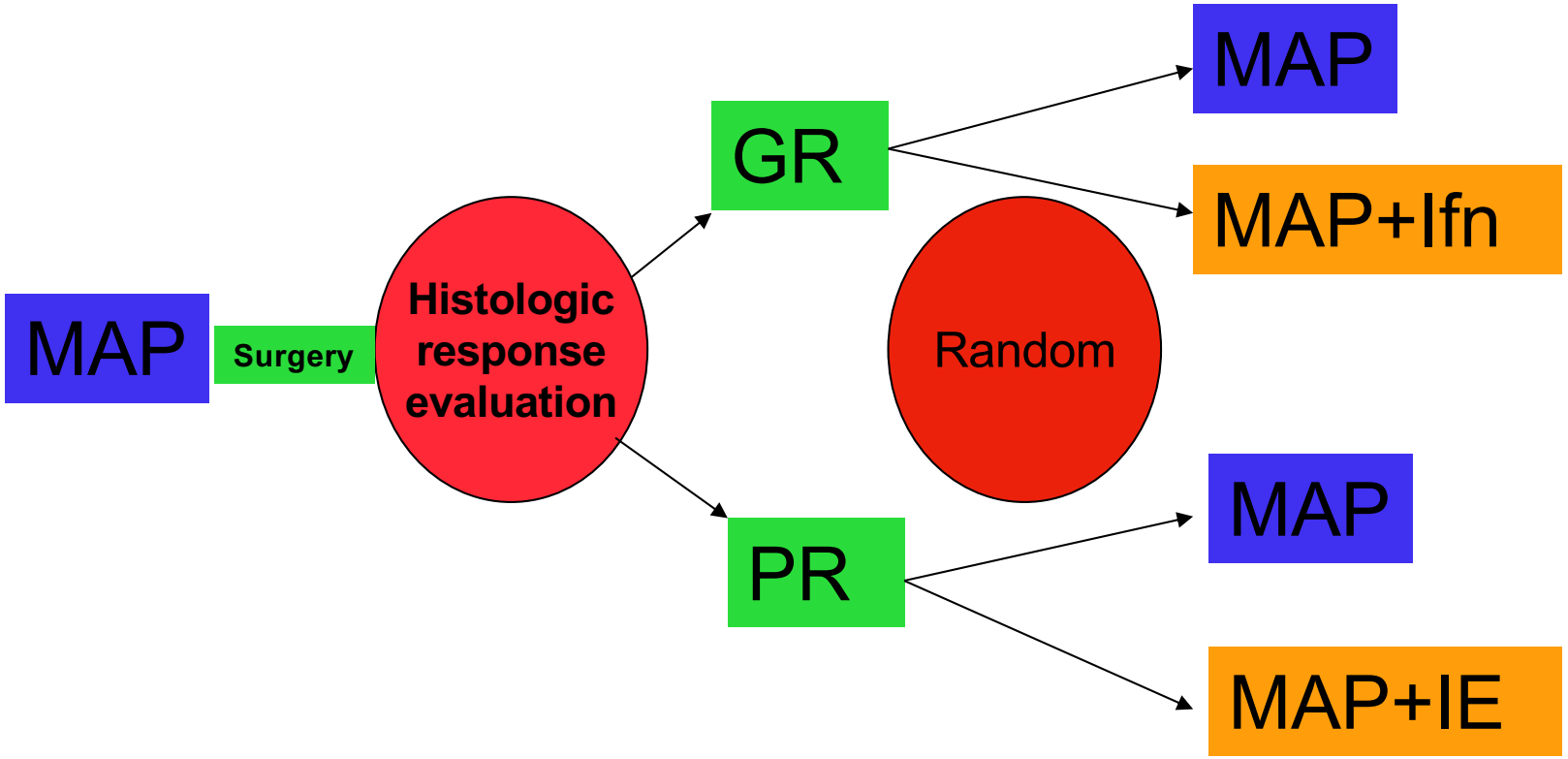

Induction
Consolidation
Good Responders
C
Same Drugs
C
C
C
C
S
Poor Responders
d
Different Drugs
C = 1 cycle of chemotherapy
d = chemotherapy (different from induction)

Selected clinical trials of neoadjuvant/adjuvant therapy in osteosarcoma.

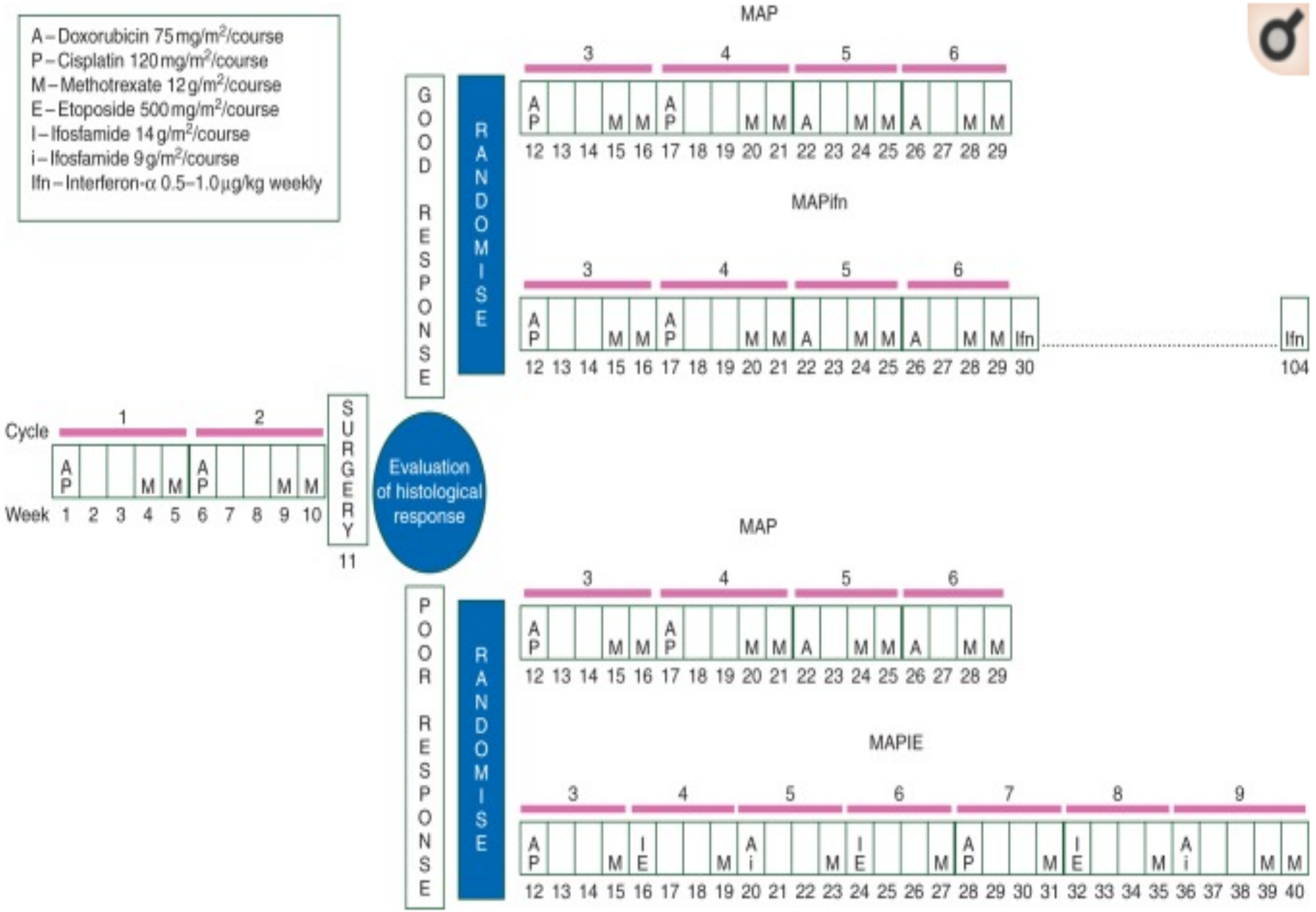
Study	N	Drugs	5-Year survival	Comments
MSKCC T-10 *single center* [48] 1975–1984	279	M (preop) GR: M + A + BCD or PR: A + P + BCD (postop)	76% (EFS) *for patients aged ⩽21 years*	Most of the current treatment strategies have evolved from the lessons learned from the T-10 protocol
SSG-II *multicenter* [75] 1982–1989	97	M (preop) GR: M + A + BCD or PR: A + P + BCD (postop)	54% (EFS) 64% (OAS)	Results of the T-10 protocol could not be confirmed
EOI-1 *multicenter, RCT* [83] 1983–86	198	A + P ± M (preop/postop)	A + P: 57% (EFS) A + P: 64% (OAS) A + P + M: 41% (EFS) A + P + M: 50% (OAS)	A brief intensive chemotherapy regimen of A + P has produced good results
COSS-86 *multicenter* [56] 1986–1988	171	*Low risk patients:* M + A + P (preop/postop) *High risk patients:* M + A + P + I (preop/postop)	10-Year survival 66% (EFS) 72% (OAS)	Use of isfosfamide for high-risk patients; intra-arterial vs. intravenous administration of cisplatin
IOR/OS-2 single center [78] 1986–1989	164	M + A + P (preop) GR: M + A + P or PR: M + A + P + I/E (postop)	65% (EFS)	I/E provided good salvage for PR
EOI-2 *multicenter, RCT* [84] 1986–1991	391	A + P or M + A + VCR (preop) A + P or M + A + VCR + BCD (postop)	44% (EFS) 55% (OAS)	No difference in survival between the two-drug and multi-drug regimen
POG-8651 *multicenter* [50] 1986–1993	100	None or M + A + P (preop) M + A + P + BCD (postop)	Immediate surgery: 69% (EFS) Neoadjuvant chemo: 61% (EFS)	No advantage of preoperative chemotherapy
SSG-VIII *multicenter* [76] 1990–1997	113	M + A + P (preop) GR: M + A + P or PR: M + A + P + I/E (postop)	63% (EFS) 74% (OAS)	Lack of benefit of modifying postoperative therapy for PR
IOR/OS-4 *single center* [79] 1993–1995	133	Preop/postop: M + A + P + I	56% (EFS) 71% (OAS)	No benefit of neoadjuvant ifosfamide
COG (INT- 0133) *multicenter, RCT* [72] 1993–1997	662	[*Regimen a*] preop: M + A + P postop: M + A + P vs. M + A + P + MTP [*regimen b*] preop: M + A + I postop: M + A + P + I vs. M + A + P + I + MTP	6-Year survival without MTP: 61% (EFS), 70% (OAS) with MTP: 67% (EFS) 78% (OAS)	Possible effects between ifosfamide and mifamurtide
EOI-3 *multicenter, RCT* [85] 1993–2002	497	Preop/postop: A + P vs. A + P + G−CSF	40% (EFS) 56% (OAS)	Histologic response as the key treatment-related predictive factor has been challenged
SFOP-OS94 *multicenter, RCT* [82] 1994–2001	234	Preop: M + I/E [*regimen a*] vs. M + A [*regimen b*] Postop [*regimen a*]: GR: M + I/E PR: A + P postop *[regimen b]*: GR: M + A PR: I/E	62% (EFS) 76% (OAS)	A preoperative chemotherapy regimen combining high-dose M + I/E improved the proportion of good histologic response compared to a regimen based on M + A
ISG/SSG-I *multicenter* [80] 1997–2000	182	Preop/postop: M + A + P + high-dose I	64% (EFS) 77% (OAS)	No advantage of neoadjuvant high-dose ifosfamide
SSG-XIV *multicenter* [39] 2001–2005	63	Preop: M + A + P postop: GR: M + A + P PR: M + A + P + I	70% (EFS) 76% (OAS)	Salvage therapy given to PR did not improve outcome to a similar degree as for GR
EURAMOS-1 *multicenter, RCT* [52,86] 2005–2011	2260	Preop: M + A + P postop: GR: M + A + P vs. M + A + P + INF-α PR: M + A + P vs. M + A + P + I/E	First results announced for 2013	Includes axial as well as extremity tumors and patients with metastatic as well as nonmetastatic disease, as long as all sites are deemed resectable

EURAMOS 1

A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to preoperative chemotherapy



The first patient was entered in April 2005. Registration closed 30 June 2011.
2260 patients have been registered and 1332 have been randomised.
326 institutions
1,108 patients from 13 European countries
1,152 patients from COG


A – Doxorubicin 75 mg/m²/course
P – Cisplatin 120 mg/m²/course
M – Methotrexate 12 g/m²/course
E – Etoposide 500 mg/m²/course
I – Ifosfamide 14 g/m²/course
i – Ifosfamide 9 g/m²/course
Ifn – Interferon-α 0.5–1.0 µg/kg weekly
Cycle 1 2
Week 1 2 3 4 5 6 7 8 9 10
SURGERY
11
Evaluation of histological response
GOOD RESPONSE
RANDOMISE
MAP
MAPIfn
POOR RESPONSE
RANDOMISE
MAP
MAPIE
104

GR

Figure 18: Subgroup localized disease - Kaplan-Meier plot by allocated treatment

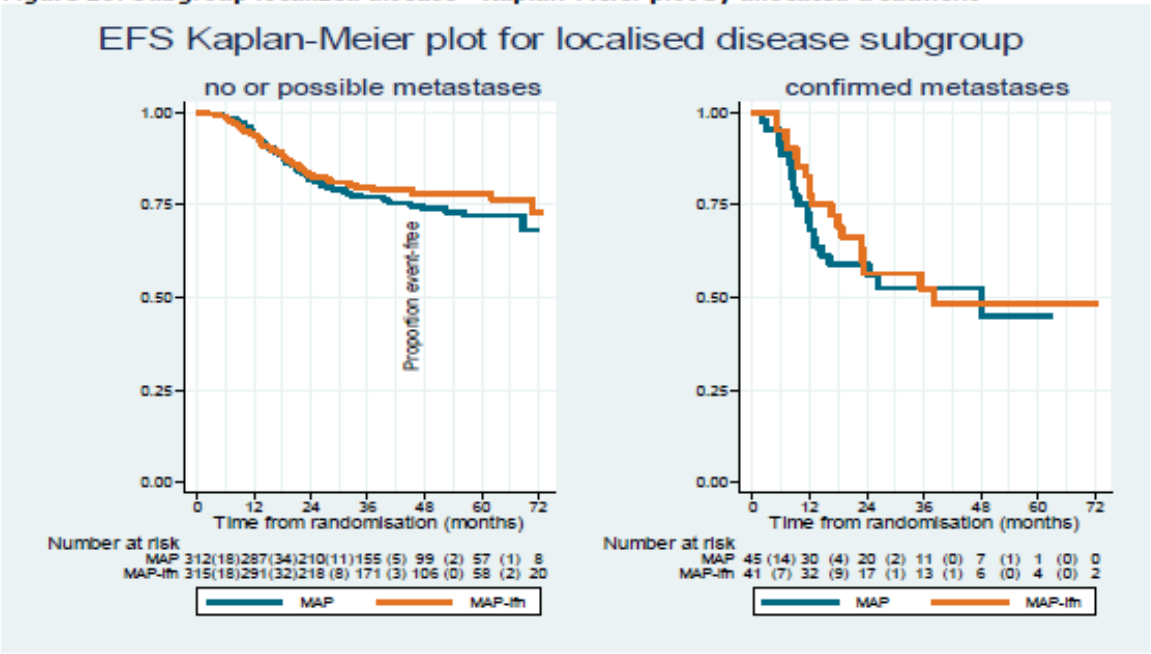


Table 19: Three-year EFS estimates by localised disease subgroup and by allocated treatment

3-year EFS	MAP	MAP-ifn
No/possible mets	77% (71%-82%)	80% (75%-84%)
Definite mets	52% (36%-67%)	52% (34%-68%)

EURAMOS 1

Figure 13.4.3: Localised disease subgroup – Kaplan-Meier plot by allocated treatment

PR

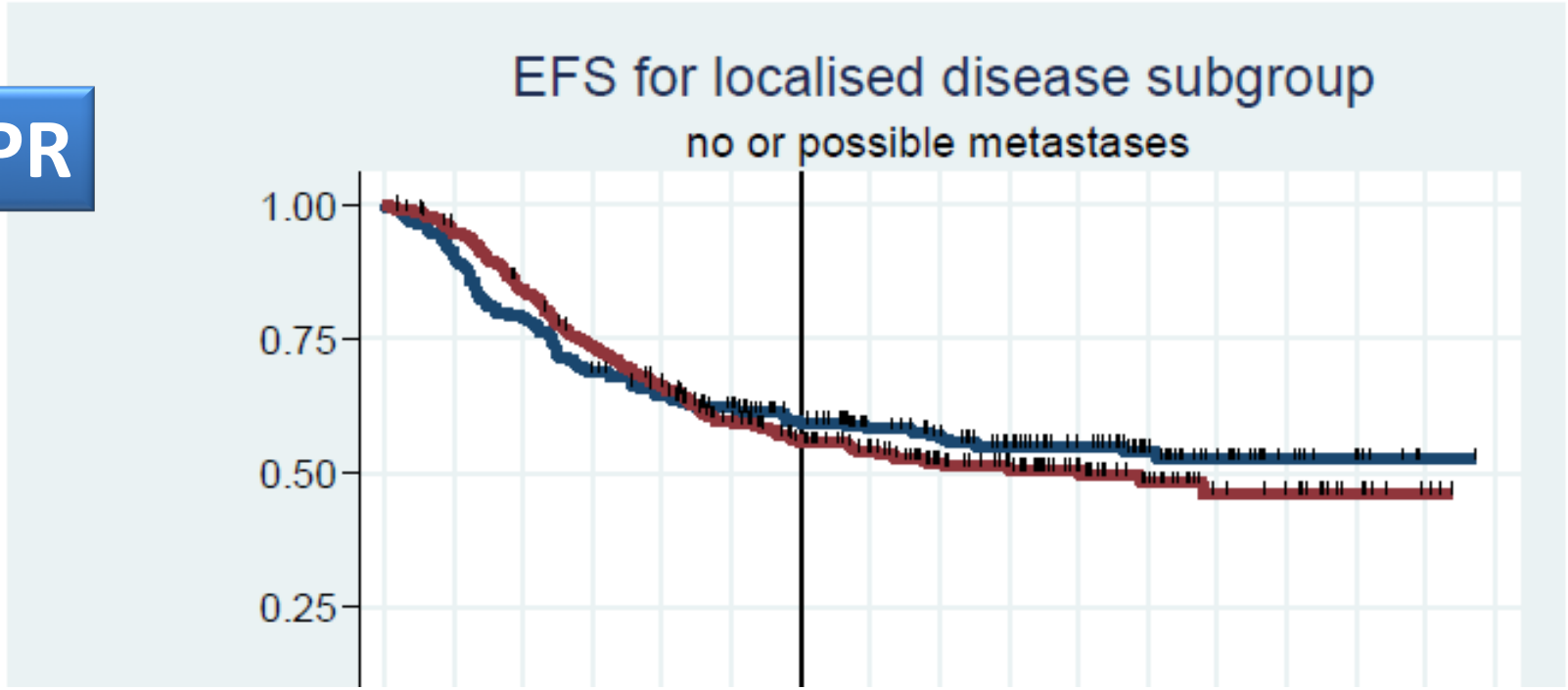


Table 13.4.4: EFS estimates with 95% CI, by allocated treatment, localised disease subgroup

EFS rates	MAP	MAPIE
EFS at 12 months, with 95%CI	79% (74%-83%)	84% (79%-88%)
EFS at 24 months, with 95%CI	64% (58%-70%)	66% (60%-72%)
EFS at 36 months, with 95%CI	59% (53%-65%)	56% (49%-61%)
EFS at 48 months, with 95%CI	57% (50%-63%)	52% (45%-58%)
EFS at 60 months, with 95%CI	55% (48%-61%)	50% (44%-57%)
EFS at 72 months, with 95%CI	53% (45%-59%)	46% (38%-54%)

European Journal of Cancer 88 (2018) 57–66

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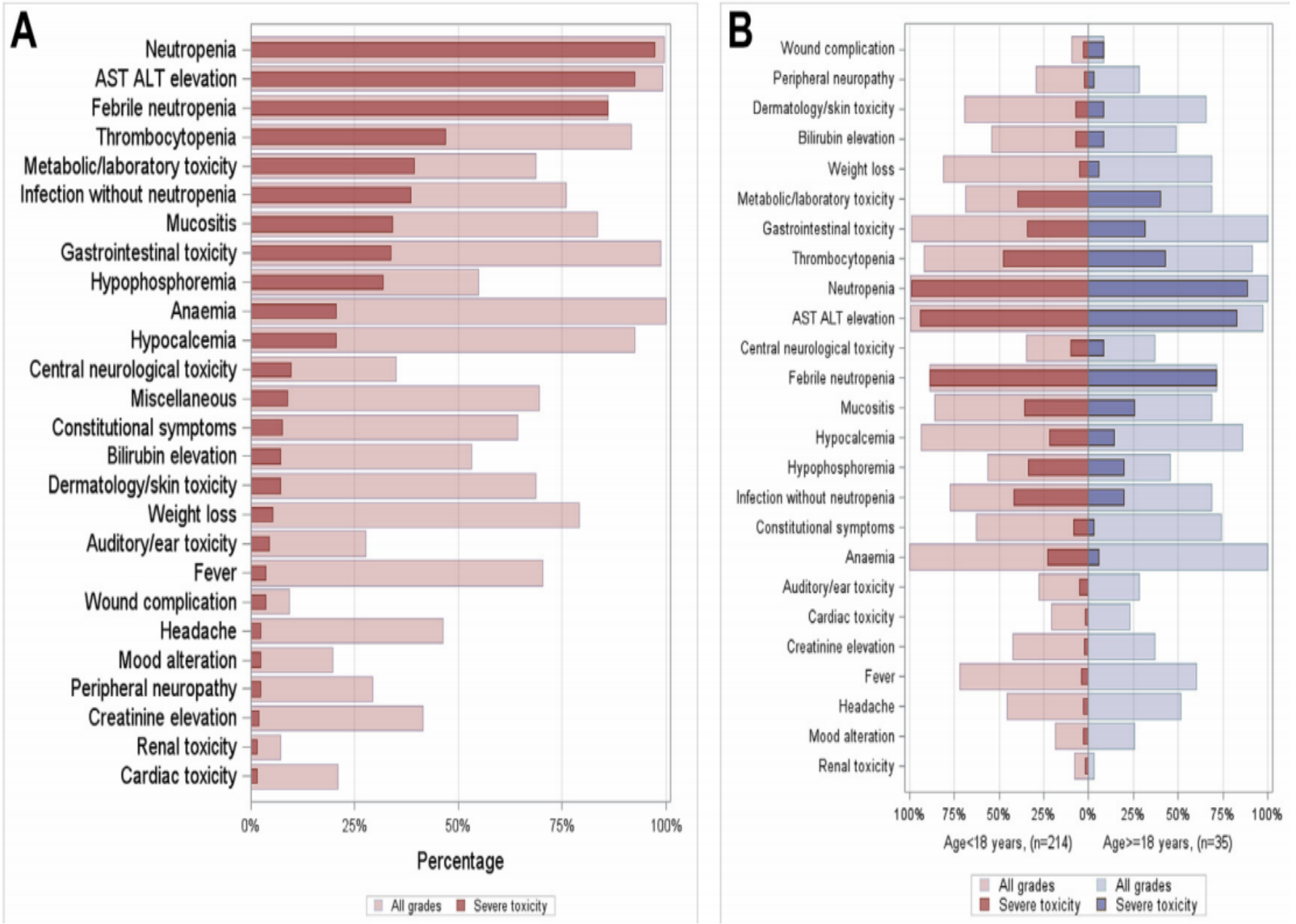
Original Research

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

M : methotrexate 12 g/m² D1
EI : etoposide 75mg/m² D1-D4
Ifosfamide 3g/m² D1-D4
AP : adriamycin 37.5 mg/m² D1-D2
cisplatinum 120mg/m² D2

GHR/L/R = Good histological response in localised resected disease
PHR/M+/U = Poor histological response or metastatic or unresectable diseases


A
Neutropenia
AST ALT elevation
Febrile neutropenia
Thrombocytopenia
Metabolic/laboratory toxicity
Infection without neutropenia
Mucositis
Gastrointestinal toxicity
Hypophosphoremia
Anaemia
Hypocalcemia
Central neurological toxicity
Miscellaneous
Constitutional symptoms
Bilirubin elevation
Dermatology/skin toxicity
Weight loss
Auditory/ear toxicity
Fever
Wound complication
Headache
Mood alteration
Peripheral neuropathy
Creatinine elevation
Renal toxicity
Cardiac toxicity
0%
25%
50%
75%
100%
Percentage
All grades
Severe toxicity
B
Wound complication
Peripheral neuropathy
Dermatology/skin toxicity
Bilirubin elevation
Weight loss
Metabolic/laboratory toxicity
Gastrointestinal toxicity
Thrombocytopenia
Neutropenia
AST ALT elevation
Central neurological toxicity
Febrile neutropenia
Mucositis
Hypocalcemia
Hypophosphoremia
Infection without neutropenia
Constitutional symptoms
Anaemia
Auditory/ear toxicity
Cardiac toxicity
Creatinine elevation
Fever
Headache
Mood alteration
Renal toxicity
100% 75% 50% 25% 0% 25% 50% 75% 100%
Age<18 years, (n=214)
Age>=18 years, (n=35)
All grades
Severe toxicity
All grades
Severe toxicity

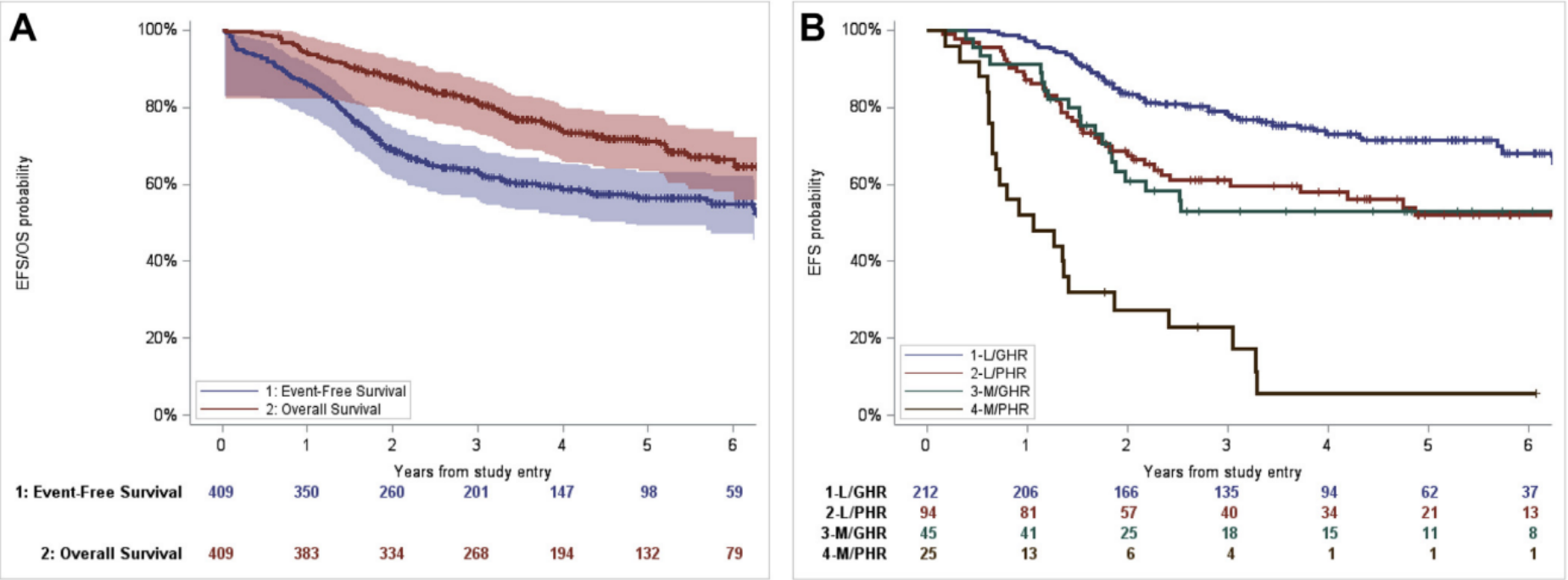


Fig. 4. **Event-free and overall survival**. (A) Kaplan−Meier estimate of event-free and overall survival of the 409 patients. The shadowed bands represent the 95% Hall−Wellner confidence bands. (B) Kaplan−Meier estimate of event-free survival according to the initial staging and the histological response, in the 376 patients who underwent surgery after neo-adjuvant chemotherapy. L, localised disease; M, metastatic disease; GHR, good histological response (<10% viable cells); PHR, poor histological response (≥10% viable cells).

Impact of initial staging and histological response on EFS and OS, in the 376 patients who underwent surgery after preoperative chemotherapy.

Patient and disease characteristics	Event-free survival analysis				Overall survival analysis			
	No of events/ no of patients	5-year EFS (95% CI)	HR (95% CI)	p-value (Wald)	No deaths/ no patients	5-year OS (95% CI)	HR (95% CI)	p-value (Wald)
Risk group				<0.0001				<0.0001
Localised disease and good histological response	57/212	71% (64−78)	1		33/212	86% (80−91)	1	
Localised disease and poor histological response	41/94	52% (41−63)	1.97 (1.32−2.95)		27/94	68% (57−78)	2.09 (1.25−3.47)	
Metastatic disease and good histological response	20/45	53% (38−67)	2.02 (1.22−3.37)		12/45	68% (52−81)	1.99 (1.03−3.85)	
Metastatic disease and poor histological response	22/25	6% (1−26)	8.19 (4.97−13.5)		17/25	24% (10−47)	9.51 (5.25−17.2)	

Good histological response: <10% viable cells; Poor histological response: ≥10% viable cells.

VOLUME 30 · NUMBER 17 · JUNE 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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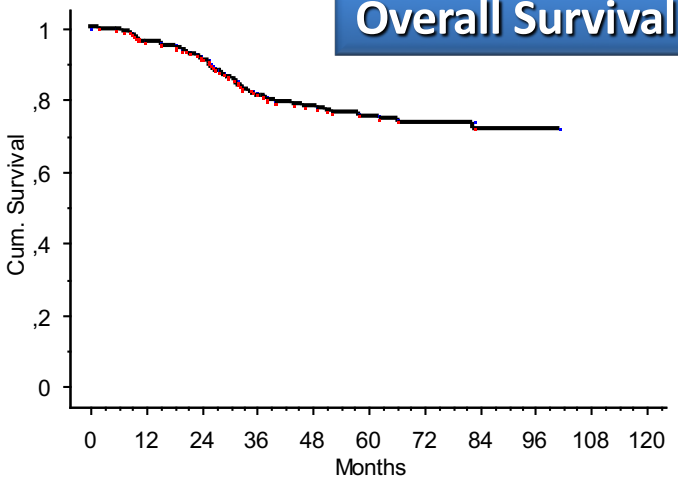
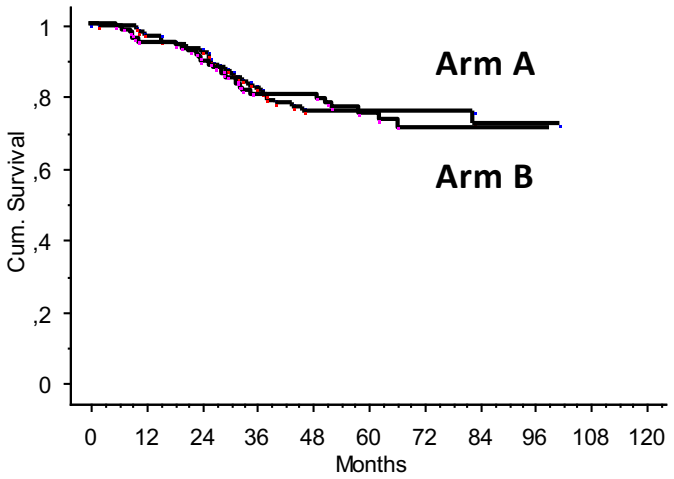
See accompanying editorial on page 2033

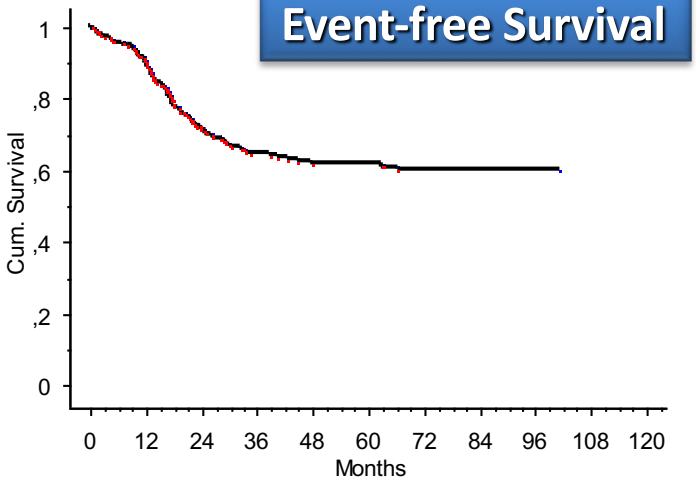
Arm A : MTX CDP ADM ± IFO
Arm B : MTX CDP ADM IFO

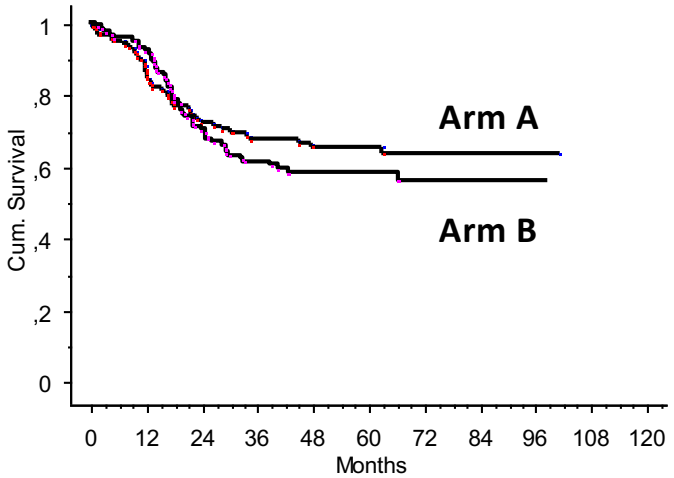
Overall Survival





Event-free Survival





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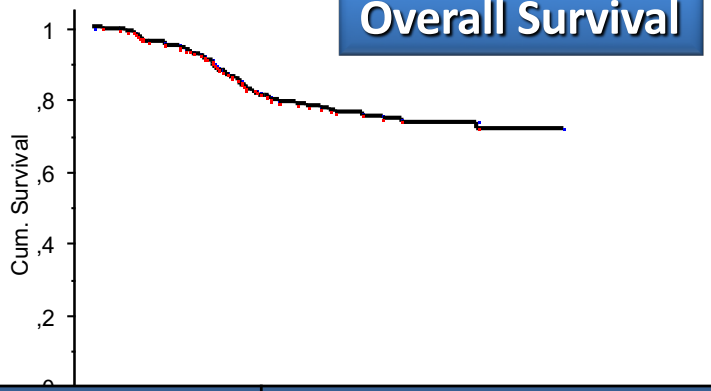
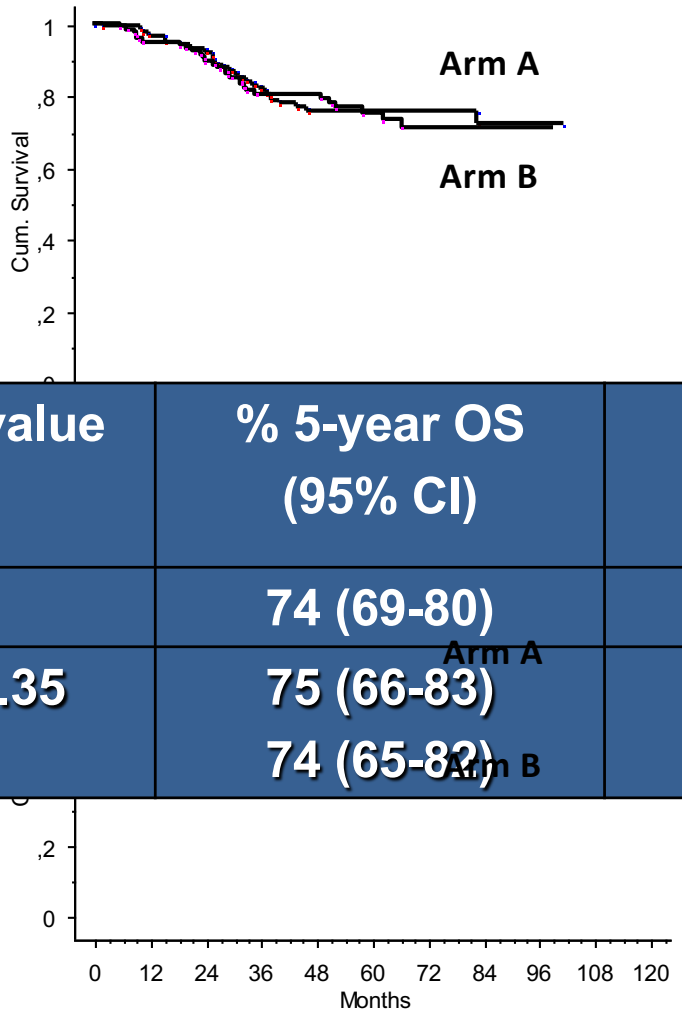
Arm A : MTX CDP ADM ± IFO
Arm B : MTX CDP ADM IFO

Overall Survival





ISG/OS-1	% 5-year EFS (95% CI)	P-value	% 5-year OS (95% CI)	P-value
All	61 (54-67)		74 (69-80)	
Arm A	65 (56-73)	0.35	75 (66-83)	0.6
Arm B	57 (47-66)		74 (65-82)	

ISG/OS1 (2001- 2007)

Lo scopo dello studio era quello di valutare l' efficacia (in termini di EFS, MFS, DFS) e la tossicità di due protocolli chemioterapici che utilizzavano HDMTX, CDP, ADM e IFO. Un braccio prevedeva l'utilizzo dei quattro farmaci in tutti i soggetti e sin dalla fase preoperatoria (braccio B); nell'altro erano somministrati solo HDMTX, CDP e ADM, mentre IFO veniva aggiunto nella fase post operatoria nei soli pazienti che presentano una necrosi tumorale, indotta dalla chemioterapia primaria, inferiore al 90% (braccio A).

Non e stata evidenziata differenza di sopravvivenza in funzione dei diversi schemi terapeutici adottati mentre e stata documentata una maggiore tossicità per i pazienti che ricevettero ifosfamide (Braccio B) sin dalla fase preoperatoria.

I risultati ottenuti con ISG OS 1 riportano percentuali di sopravvivenza libera da eventi a 5 anni del 61% (IC 95% 54-67) e sopravvivenza globale del 74% (IC 95% 69-80), non differenti rispetto a precedenti protocolli e rispetto ad altri studi riportati in letteratura .

ISG-Oss/OS/A (2007- 2011)

In considerazione dei dati ottenuti con ISG-OS 1 e nell' attesa di un nuovo protocollo di studio basato su nuovi farmaci e approcci innovativi, è stato successivamente attivato uno studio clinico osservazionale per i pazienti con osteosarcoma non metastatico delle estremità basato sul braccio A del protocollo ISG-OS 1.

Unica differenza fra ISG/OS-1 e lo studio osservazionale ISG-Oss/Os/A è il numero di cicli di methotrexate, 5 nello studio osservazionale e 10 nel braccio A di ISG/OS-1.

ISG/OS-2

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

Prospective cohort study

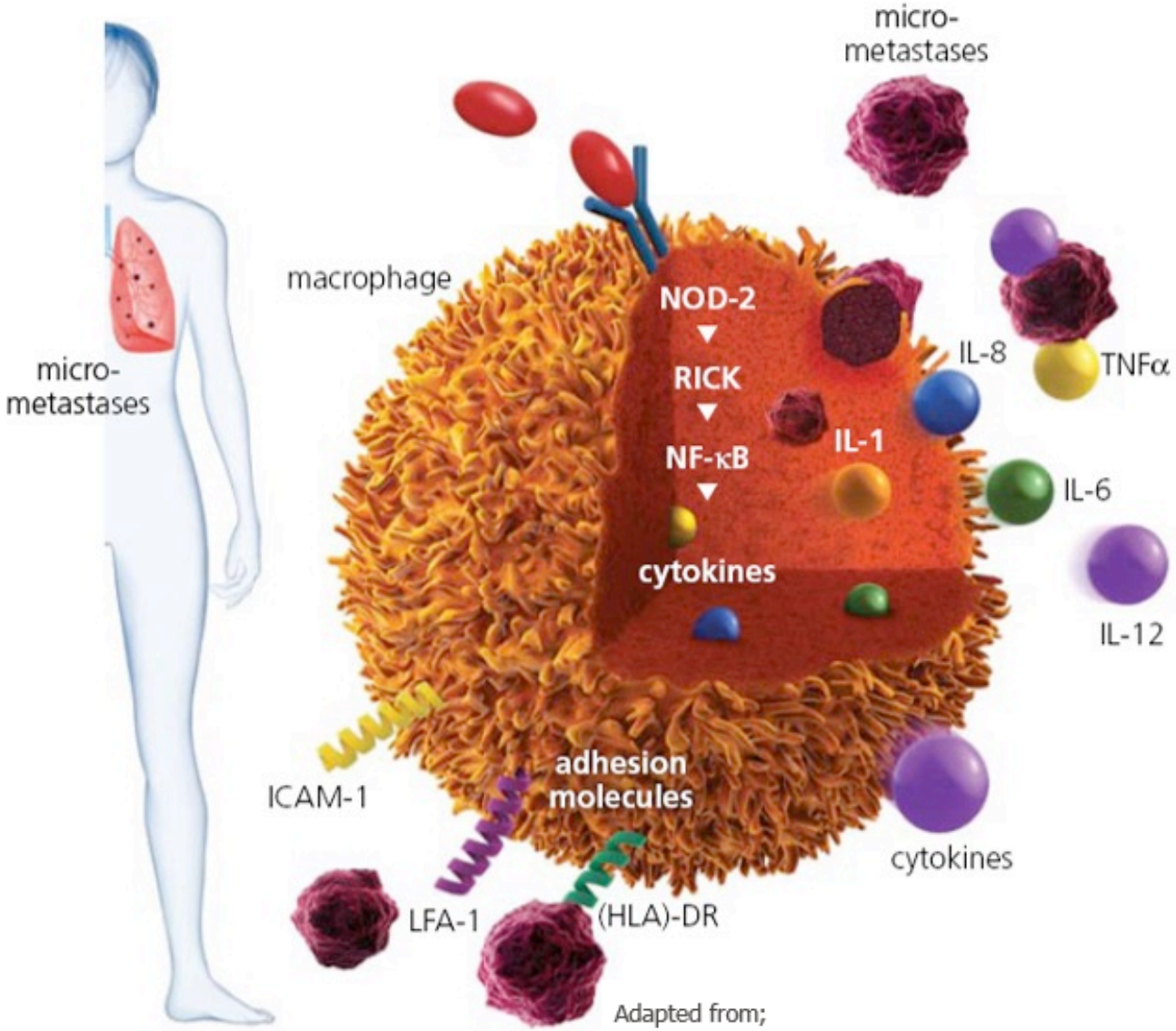
PgP-

PgP+

MTX
CDP
ADM
IFO

MTP

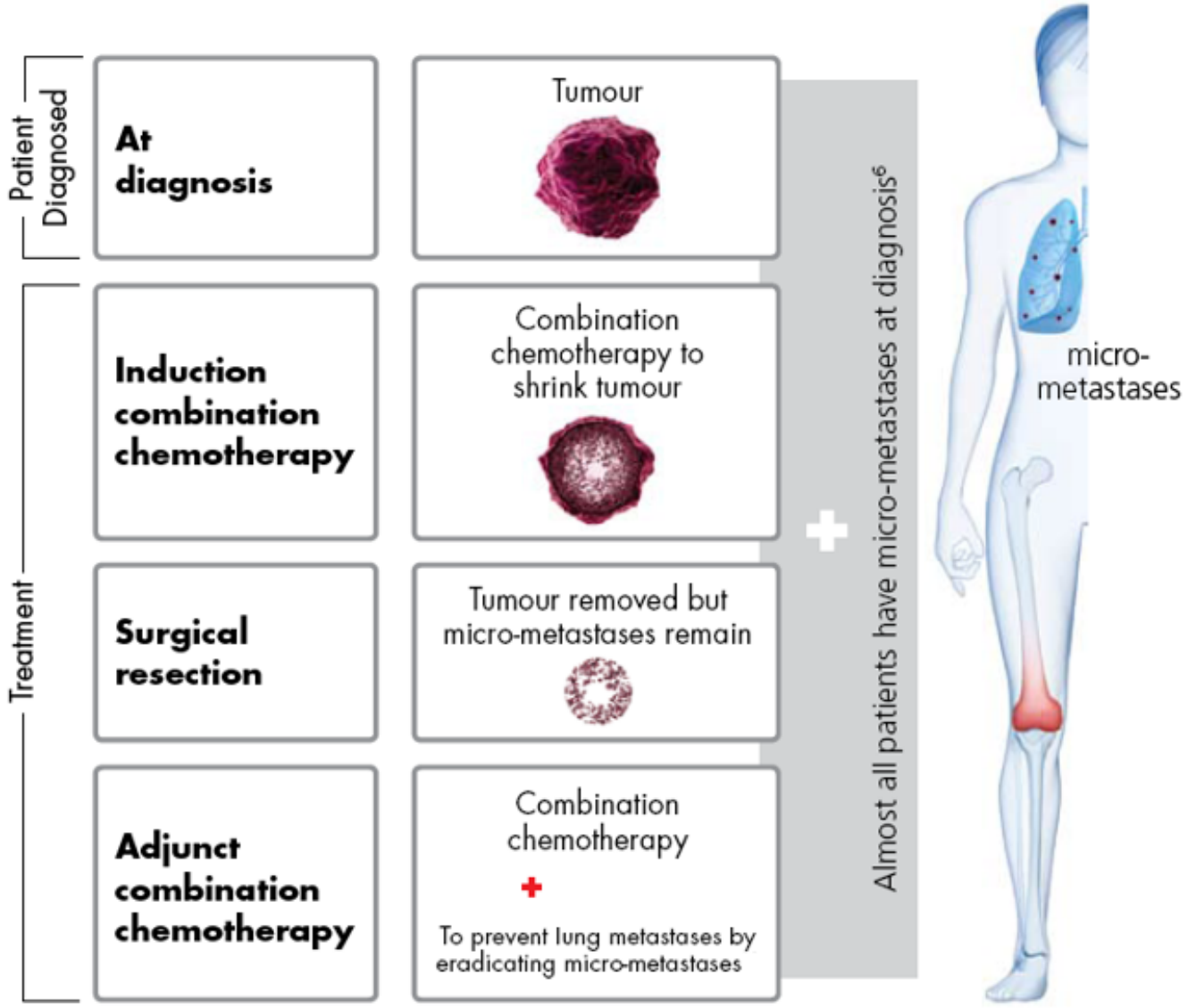
L'attività antitumorale del MTP è mediate dalla attivazione del sistema immune dell'ospite



Fidler IJ et al. Proc. Natl Acad. Sci. USA. 1981;78:1680-1684
Anderson A. Future Oncol. 2006;2:333-334
Kleinerman ES et al. J Clin Oncol. 1991;9:259-267

Adapted from;
Strober W et al. Nature Rev Immunol. 2006;6:9-20
Nardin A et al. Current Cancer Drug Targets. 2006;6:123-133
Kleinerman ES et al. Cancer Res. 1989;49:4665-4670
Kleinerman ES et al. J Immunotherapy. 1995;17:181-193

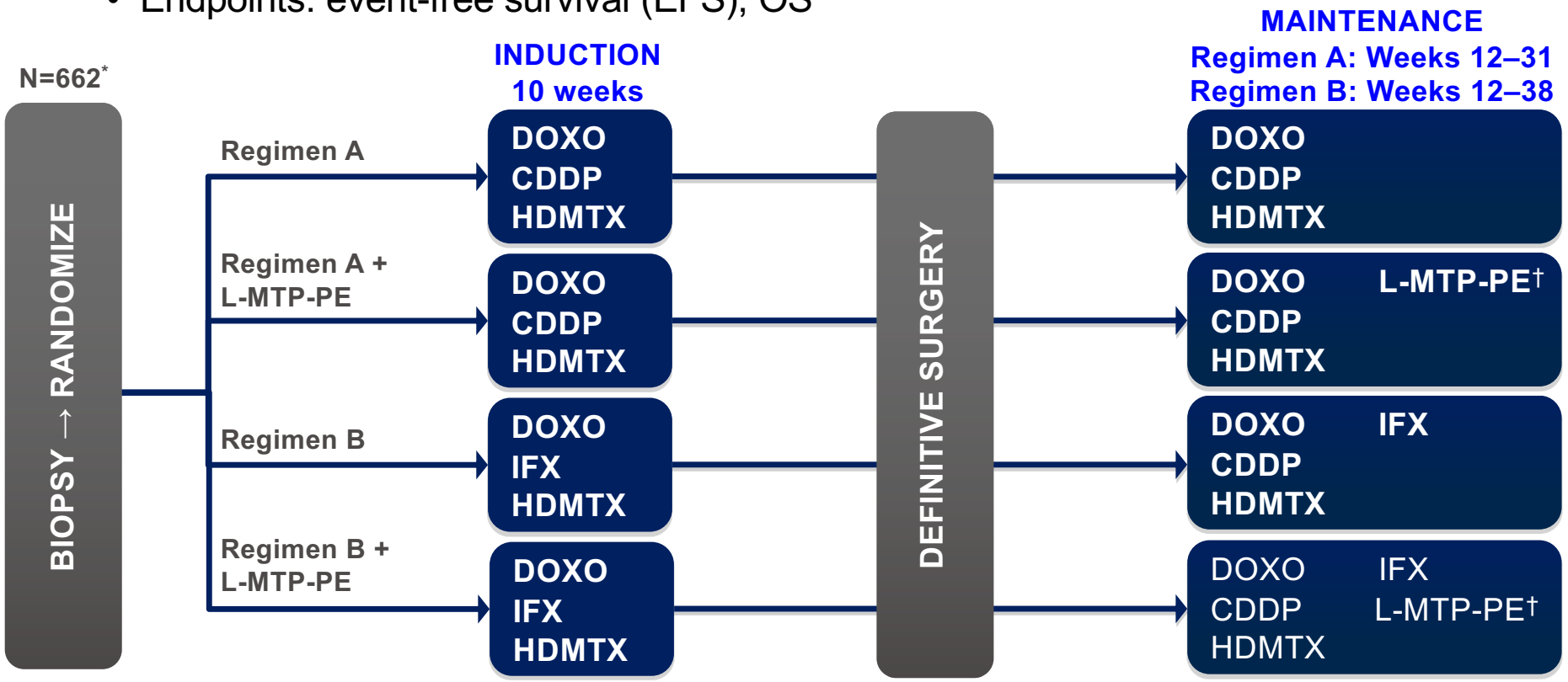
MTP effetto sinergico con la chemioterapia



Mori K et al. Expert RevAnticancer Ther. 2008;8(2):151-159
Fidler IJ, Sone S, Fogler WE et al. Proc. Natl Acad. Sci. USA. 1981;78:1680-1684

INT-0133: Phase 3 Trial - Design

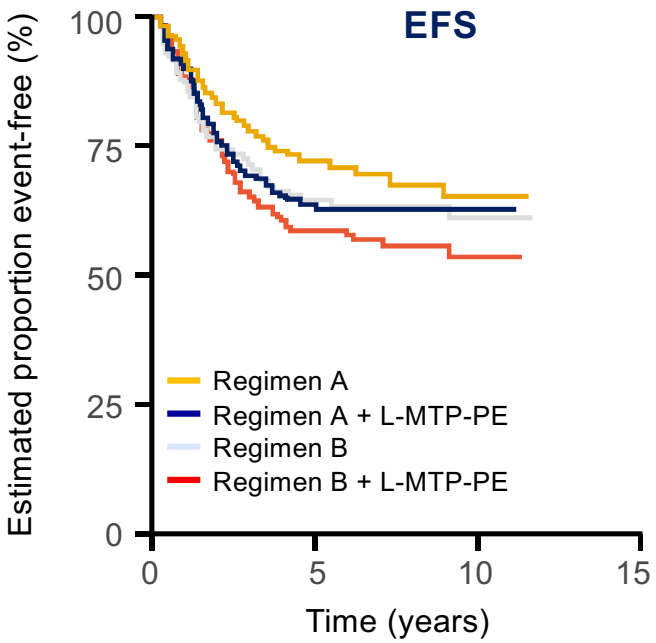
- Phase 3 trial of the addition of ifosfamide (IFX) and/or L-MTP-PE to cisplatin (CDDP), doxorubicin (DOXO) and high-dose methotrexate (HDMTX)[1,2]
- N=662 patients with osteosarcoma and no detectable metastases
- Endpoints: event-free survival (EFS), OS

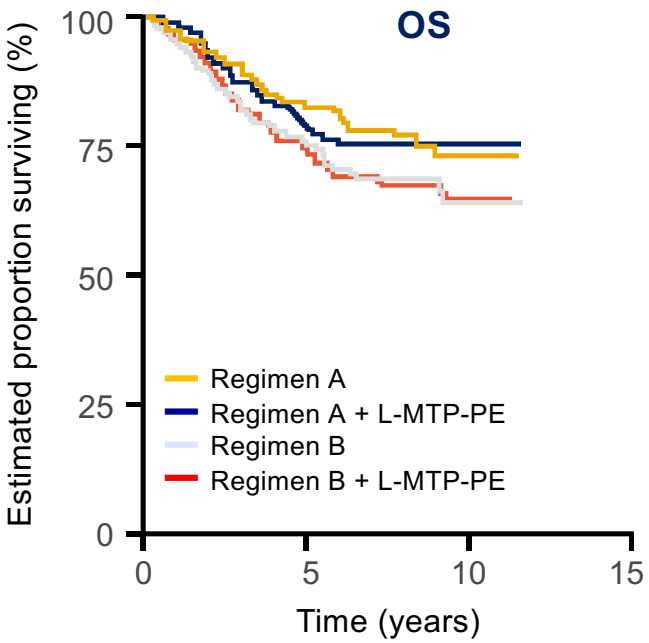


*Patients were aged ≤30 years (median 13 years).
†2 mg/m^2 IV twice/week for 12 weeks, then once/week for 12 weeks

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

INT-0133: Pivotal Phase 3 Trial - EFS and OS





- 6-year EFS was 61% in patients who did not receive L-MTP-PE and 67% in patients who did receive L-MTP-PE (p=0.08)
- 6-year OS was 70% in patients who did not receive L-MTP-PE and 78% in patients who did receive L-MTP-PE (p=0.03)

Meyers PA, et al. J Clin Oncol 2008;26:633–8

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

Localized osteosarcoma of the extremities
Biologic Stratification based on P Glycoprotein expression

Prospectic cohort Study

PgP-

PgP+

MTX
CDP
ADM
IFO

MTP

Riunione finale di consenso: 2 marzo 2011 Bologna

Sottomissione CE : Aprile 2011

Attivazione : Maggio 2011

Primo paziente : Luglio 2011

Primo Emendamento Sostanziale : Marzo 2013

Chemioterapia

Pazienti ABCB1/P-GLYCOPROTEIN negativi

MTX	CDP/ADM	MTX	CDP/ADM	Chirurgia	ADM*	MTX	MTX	CDP	ADM*	MTX	MTX	CDP	ADM*	MTX	MTX	CDP	MTX	MTX	
0	1		4	5		8		9	12	13	14		17	20	21		22	25	28	29		30	33	34	settimane

MTX 12g/m2 CDP 120mg/m2 ADM 75mg/m2 ADM*90mg/m2

Pazienti ABCB1/P-GLYCOPROTEIN positivi e buona risposta istologica (GR)

MEPACT →

MTX CDP/ADM MTX CDP/ADM Chirurgia ADM* MTX MTX CDP ADM* MTX MTX CDP ADM* MTX MTX CDP MTX MTX

0 1 4 5 8 9 12 13 14 17 20 21 22 25 28 29 30 33 34 44

MTX 12g/m2 CDP 120mg/m2 ADM 75mg/m2 ADM*90mg/m2 MEPACT 2 mg/m^2 2 volte la settimana per i primi tre mesi (sett 9-20), 1 volta la settimana per i sei mesi successivi (sett 21-44)

Pazienti ABCB1/P-GLYCOPROTEIN positivi e scarsa risposta istologica (PR)

MEPACT →

MTX CDP/ADM MTX CDP/ADM Chirurgia ADM* HDIFO HDIFO HDIFO HDIFO

0 1 4 5 8 9 12 15 18 21 44

MTX 12g/m2 CDP 120mg/m2 ADM 75mg/m2 ADM*90mg/m2 HDIFO 15g/m2 la settimana MEPACT 2 mg/m^2 2 volte la settimana per i primi tre mesi (sett 9-20), 1 volta la settimana per i sei mesi successivi (sett 21-44)

ISG-GEIS/OS-2

322 patients registered
(July 2011-March 2018)

78
preamendment

1 excluded
Site

77
Evaluable for survival

40 (52%) Events
24 (32%) Deaths
Median observation time : 48 months (1-82)

244
postamendment

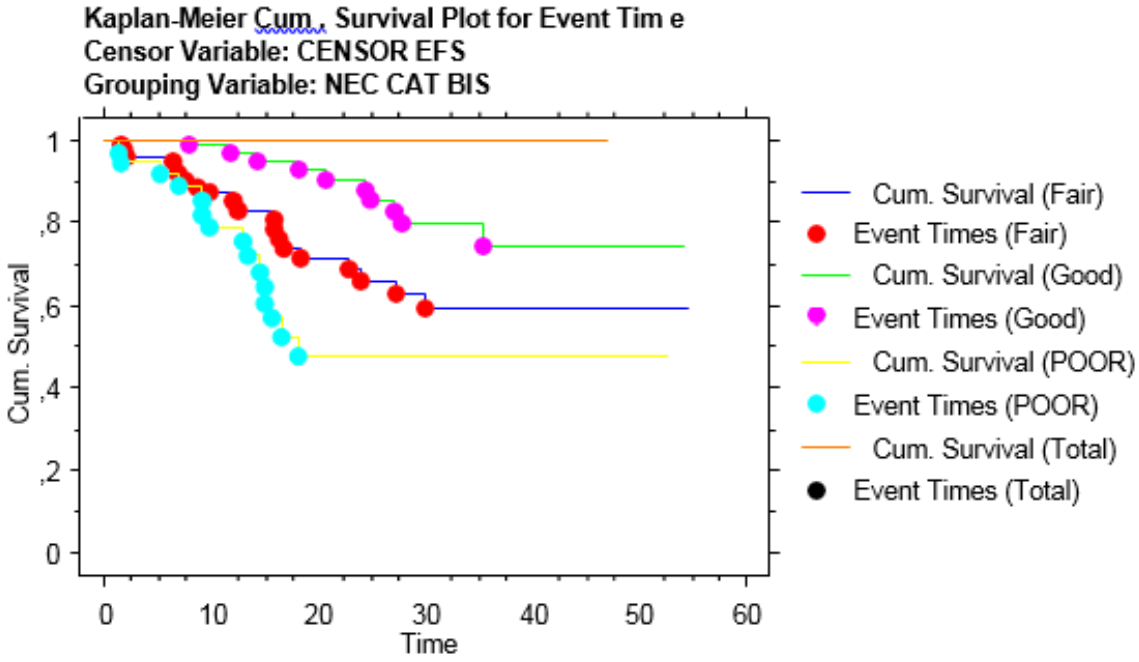
5 excluded
(Site 2, stage 2, histology 1

239
Evaluable for survival

48 (20%) Events
10 (4%) Deaths
Median observation time : 26 months (1-62)

March 2013-March 2018: 49 pts/year

ISG-GEIS/OS-2 PA



% Necrosis	3 years % EFS (95% CI)
Total	100
90-99	75 (59-89)
60-89	60 (45-75)
<60	48 (28-67)

55 (43-67)

DATI STORICI

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	**70% 3-year EFS**	**81% 3-year OS**
	60% 5-year EFS	**75% 5-year OS**
EURAMOS PR		
MAP	**60% 3-year EFS**	**72% 3-year OS**
MAP-IE	**57% 3-year EFS**	**77% 3-year OS**
EURAMOS GR		
MAP	**77% 3-year EFS**	**81% 5-year OS**
MAP-ifn	**80% 3-year EFS**	**84% 5-year OS**

GRAZIE
DELL' ATTENZIONE

Dott.ssa Angela Tamburini
DIPARTIMENTO DI ONCOEMATOLOGIA
SODC "TUMORI PEDIATRICI E
TRAPIANTO DI CELLULE STAMINALI".
AZIENDA OSPEDALIERO UNIVERSITARIA A.MEYER

Firenze 12 Dicembre 2018

INT-0133: Pivotal Phase 3 Trial - EFS and OS by Regimen

Regimen	EFS probability (%) 4 year	EFS probability (%) 6 Year	OS probability (%) 4 Year	OS probability (%) 6 Year	Impact of L-MTP-PE on 6-year OS rate HR	Impact of L-MTP-PE on 6-year OS rate 95% CI
All patients	66	64	81	74		
Chemotherapy						
Without L-MTP-PE	63	61	78	70		
With L-MTP-PE	69	67	84	78	0.71*	0.52, 0.96
Regimen A	65	63	80	73		
Without L-MTP-PE	66	64	78	71		
With L-MTP-PE	65	63	82	75	0.76	0.49, 1.2
Regimen B	67	64	82	75		
Without L-MTP-PE	60	58	77	70		
With L-MTP-PE	74	71	86	81	0.66	0.43, 1.0

*p=0.03

- Test for interaction between chemotherapy and L-MTP-PE: p=0.102 (EFS), p=0.60 (OS)†

†A p-value of ≤0.10 was considered evidence of a significant interaction
CI = confidence interval; HR = hazard ratio

Meyers PA, et al. J Clin Oncol 2008;26:633–8

INT-0133: Phase 3 trial (osteosarcoma) results in patients with metastases

Patients with metastases* (n=91)

Regimen	5-year EFS probability (%)	5-year OS probability (%)
All patients	34	47
Chemotherapy		
Without L-MTP-PE	26	40
With L-MTP-PE	42	53
Regimen A		
Without L-MTP-PE	29	53
With L-MTP-PE	41	50
Regimen B		
Without L-MTP-PE	23	30
With L-MTP-PE	44	57

- There were no differences among the 4 regimens for EFS (p=0.55) or OS (p=0.60)†
- Relative risk in patients who received L-MTP-PE:
  - 0.72 (95% CI: 0.42–1.20; p=0.23) for AEs
  - 0.72 (95% CI: 0.40–1.30; p=0.27) for death
- Test for interaction between chemotherapy and L-MTP-PE: p=0.20 (EFS), p=0.39 (OS)

*Patients with metastatic disease were treated and analyzed separately using the same protocol (n=91);
†Log-rank test

Chou AJ, et al. Cancer 2009;115:5339–48

Only post amendement

239 patients (March 2013-March 2018)

Median observation time 26 months (1-62)

	% 3-yrs OS (95% CI)	% 5-yrs OS (95% CI)	P value
All	**90% (85-95)**	**83% (73-93)**	
ABCB1-PGP			0.9
Negative	**91 (83-100)**	**87 (76-98)**	
Not evaluable	**93 (79-100)**	**93 (79-100)**	
Positive	**89 (82-96)**	**79 (63-95)**	
Necrosis			0.007
Good	**97 (94-100)**	**97 (94-100)**	
Poor	**85 (77-94)**	**72 (55-89)**	
Only PGP negative			
Necrosis			
Good	**100**	**100**	
Poor	**84 (70-99)**	**75 (53-96)**	
Only PGP positive			
Necrosis			0.02
Good	**98 (94-100)**	**94 (94-100)**	
Poor	**83 (71-95)**	**65 (38-91)**	

Only post amendement
239 patients (March 2013-March 2018)

	% 3-yrs EFS (95% CI)	% 5-yrs EFS (95% CI)	P value
All	66 (58-73)	66 (58-73)	
ABCB1-PGP			0.7
Negative	66 (53-79)	66 (53-79)	
Not evaluable	36 (0-73)		
Positive	68 (58-77)	68 (58-77)	
Necrosis			0.0001
Good	79 (68-91)	79 (68-91)	
Poor	55 (45-66)	55 (45-66)	
Only PGP negative			
Necrosis			0.04
Good	75 (53-96)	75 (53-96)	
Poor	59 (42-76)	59 (42-76)	
Only PGP positive			
Necrosis			0.001
Good	82 (68-95)	82 (68-95)	
Poor	58 (45-71)	58 (45-71)	

PRE vs POST amendement

	% 3-yrs EFS (95% CI)	% 5-yrs EFS (95% CI)	P value
PRE	55 (44-66)	47 (36-58)	0.02
POST	66 (59-74)	66 (58-73)	
	% 3-yrs OS (95% CI)	% 5-yrs OS (95% CI)	P value
PRE	78 (69-88)	63 (52-74)	0.008
POST	90 (85-95)	83 (73-93	

Expected patients: 225 – 5 year enrollment

	ABCB1-PGP-	ABCB1-PGP+
Planned/expected 5-year EFS	75%	40%
Planned/expected 5-year OS	85%	50%

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
MAPint	80% 3-year EFS	84% 5-year OS

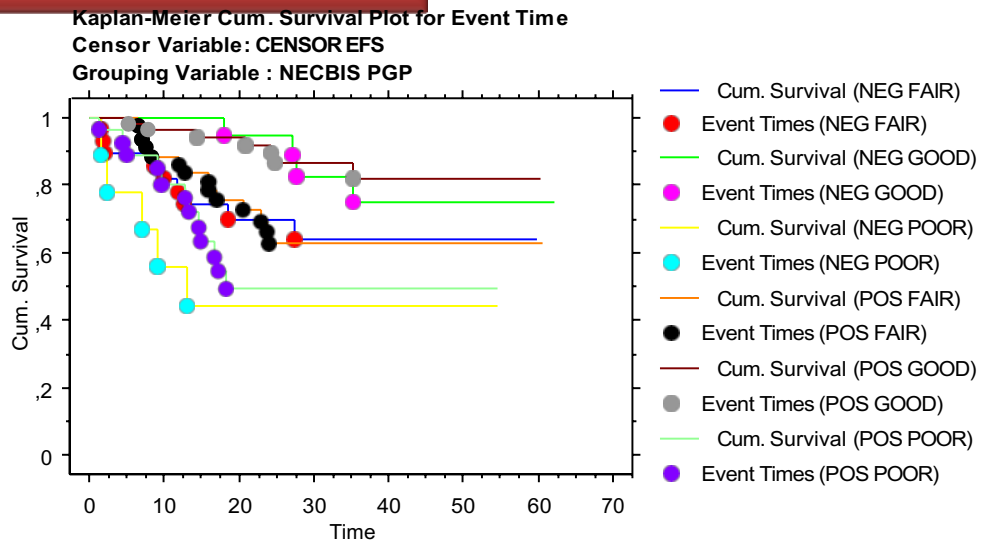
316 patients (July 2011-March 2018)
Event-free survival

	% 3-yrs EFS (95% CI)	% 5-yrs EFS (95% CI)	P value
All	**62% (56-69)**	**57% (50-64)**	
ABCB1-PGP			0.4
Negative	**59 (49-69)**	**51 (40-63)**	
Not evaluable	**56 (29-82)**	**56 (29-82)**	
Positive	**65 (57-74)**	**63 (54-71)**	
Necrosis			0.0001
Good	**80 (71-89)**	**76 (66-86)**	
Poor	**51 (43-59)**	**46 (37-55)**	
Only PGP negative			
Necrosis			0.001
Good	**83 (69-97)**	**74 (57-91)**	
Poor	**48 (35-61)**	**39 (25-53)**	
Only PGP positive			
Necrosis			0.002
Good	**80 (69-92)**	**76 (63-89)**	
Poor	**56 (45-67)**	**54 (42-65)**	

316 patients (July 2011-March 2018)
Overall survival
Median observation time 30 months (1-82)

	% 3-yrs OS (95% CI)	% 5-yrs OS (95% CI)	P value
All	86% (81-90)	73% (65-80)	
ABCB1-PGP			0.4
Negative	81 (73-90)	69 (57-81)	
Not evaluable	86 (68-100)	86 (68-100)	
Positive	88 (82-95)	73 (61-85)	
Necrosis			0.001
Good	97 (93-100)	92 (85-99)	
Poor	79 (72-86)	62 (51-72)	
Only PGP negative			
Necrosis			0.004
Good	96 (89-100)	90 (77-100)	
Poor	73 (61-85)	58 (43-73)	
Only PGP positive			
Necrosis			0.009
Good	98 (95-100)	94 (86-100)	
Poor	83 (73-92)	61 (45-75)	

ISG-GEIS/OS-2 PA



Logrank (Mantel-Cox) Tes t for Eve nt Tim e
Censor Variable : CENSOR EFS
Grouping Variable : NECBIS PGP

Chi-Square	DF	P-Value
21,220	5	,0007

ABCB1/NECROSIS (No.)	3 year % EFS (95% CI)
NEG/≥ 90% (27)	75 (53-97)
NEG/60-89% (28)	64 (44-83)
NEG/< 60%(10)	44 (12-77)
POS/≥ 90% (56)	82 (68-95)
POS/60-89% (46)	63 (47/79)
POS/< 60% (27)	49(29-70)

ISG/OS-2

Final consensus ISG Meeting: March 2011 Bologna

IRB Submission : April 2011

IRB Approval : May 2011

First patient : July 2011

First substantial amendment : March 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: 2011-001659-36

Clinincal Trial GOV: NCT01459484

Sponsor:

Italian Sarcoma Group

c/o Istituto Ortopedico Rizzoli

Via di Barbiano 1/10 Bologna

March 2013 1° substantial amendment

13 Sep 2013
Meeting with GEIS delegation
ISG/GEIS OS-2

DATA: 25 Marzo 2011

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

con il supporto di:

Italian Sarcoma Group

Osteosarcoma metastatico all'esordio

Vi è indicazione ad un trattamento chemioterapico associato, ove possibile, alla chirurgia radicale della lesione primitiva e di quelle metastatiche.

I farmaci utilizzati sono gli stessi usati per le forme localizzate (MAP). Vi sono segnalazioni controverse di efficacia della combinazione di alte dosi di Ifosfamide.

L'uso di trattamenti con alte dosi e recupero di cellule staminali periferiche ha dato risposte di breve durata.

Vi sono segnalazioni in letteratura in favore dell'uso di Muramyl-tripeptide, sempre associato a polichemioterapia e chirurgia delle metastasi dove possibile.

Vi sono segnalazioni anche recenti di risultati validi con altre forme di immunoterapia (IL2)

Osteosarcoma metastatico all'esordio la resezione chirurgica completa di tutti i siti di malattia e' predittiva di buona prognosi e indispensabile per la sopravvivenza.

Tutte le combinazioni chemioterapiche sono indicate per il raggiungimento della radicalità ottenuta.

Quando questa è stata ottenuta, attualmente l'immunoterapia può essere indicata a consolidare una possibile guarigione.

Quando non si riesce ad ottenerla e/o in caso di malattia multimetastatica i pazienti dovrebbero essere avviati ad approcci terapeutici innovative (immunoterapia cellulare con CIK).

Da considerare il ruolo della radioterapia in caso di lesioni piccole, se la chirurgia è controindicata (cyber-knife o tecnica di radioterapia stereotassica polmonare in caso di M+ polmonari sia la tecnica di prima scelta).

Mancanza di nuove terapie dal 1980