Autologe Transplantation in ungewöhnlicher Indikation

SARKOME

wtz westdeutsches tumorzentrum

Universitätsklinikum Essen

Principles

HD: A **ts that may a**

TBI/TL **dose/** **marrow**

Follow **retran** **n of autologous** **hemat** **tic stem cells to reconstitute**

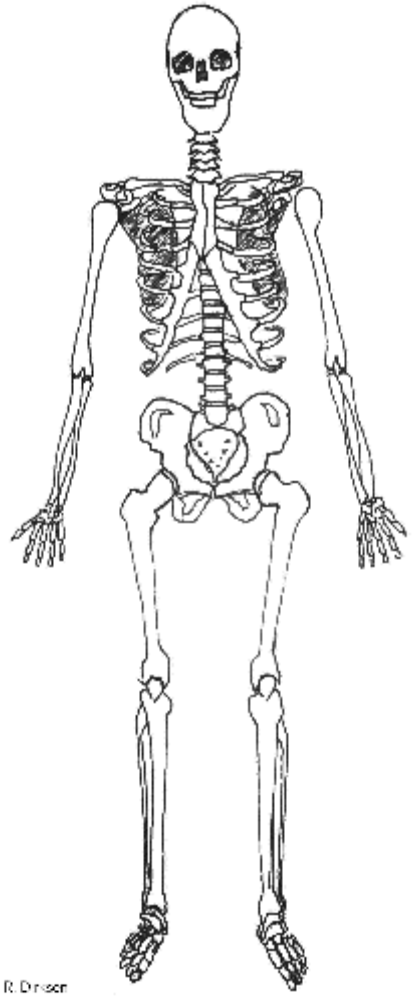
Aim: **Applic** **e** **motherapeutic agents in high d**

Today

- Ewing sarcoma
    - Disease
    - Selected overview on the literature
    - Discussion relapsed disease, localized disease, metastatic disease
- Rhabdomyosarcoma
    - Disease
    - Selected overview on the literature
    - Discussion
- Non-RMS Soft tissue sarcoma
    - Diseases
    - Selected overview on the literature
    - Discussion
- Osteosarcoma
    - Disease
    - Selected overview on the literature
    - Discussion
- CONCLUSION

Ewing Sarkom

Weichteil 15%



Knochen 85%

Kopf und Hals 4.0 %

Clavicula 1.0%

Humerus 4.5 %

Thoraxwand 23%

Ulna/Radius 2.0 %

Becken 23.0%

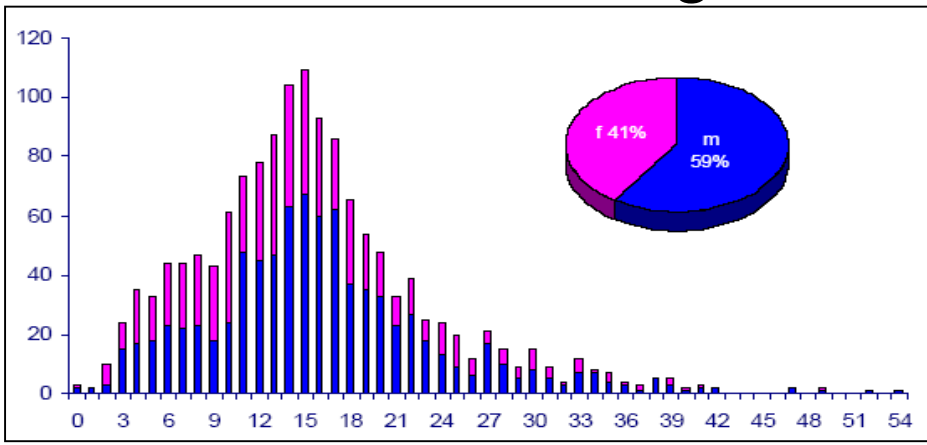
Hand 0.5%

Femur 11%

Fibula /Tibia 15%

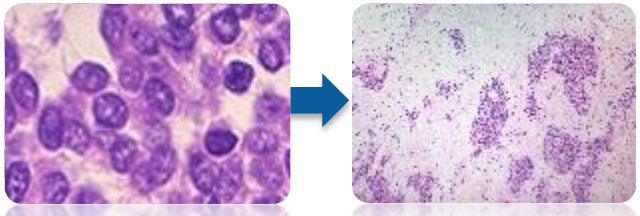
Fuß 1.0%

Alters und Geschlechtsverteilung



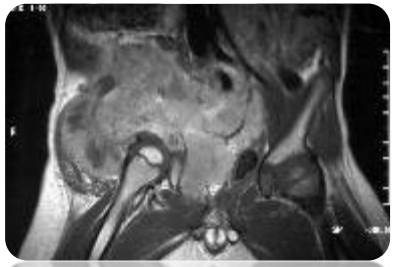
Metastases

Response

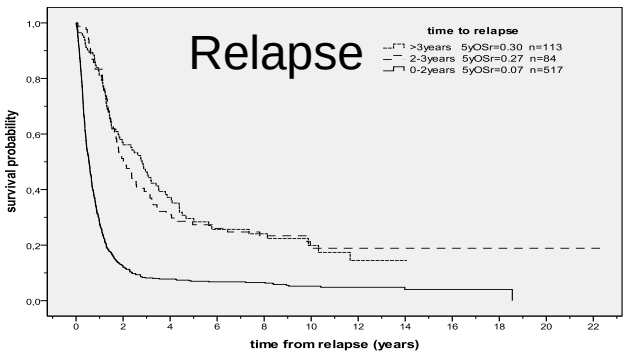


Site

Size



Age



J Clin Oncol 24:3997-4002, 006

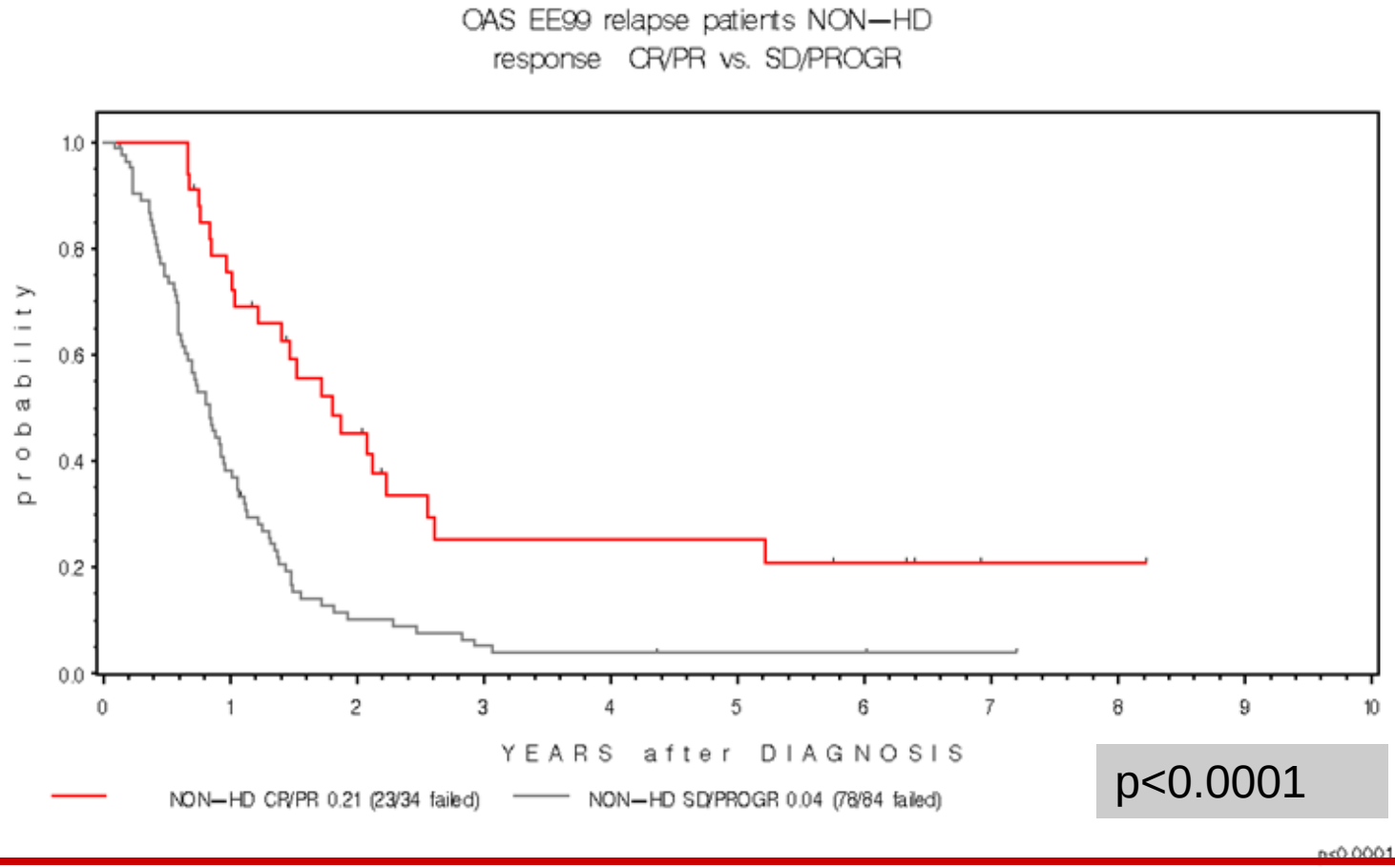
J Clin Oncol 30:4148-4154, 2012

British Journal of Cancer (2001) **85**(11), 1646–1654

Ewing Sarcoma- retrospective studies

study	patients (pts)	status at transplant	regimen	control (c) pts	survival	author
Retrosp. 84-92	79 MET 52 REL	49% CR 44% PR 5% PD 42% CR 38% PR 17% N.A.	**+TBI** MEC, ME, M, E, CYC VIC-ME **Double** ME, CyTbC Cy/Tp-BuM CyTp-ME CyTp-ME-ME **Single** MEC, ME, MC, Bu, CBME, VICE	289 cMET 105cREL	5y EFS MET/cMET 19%/27% p=0.9 5yEFS REL/cREL 11%/7%; p=0.0001	Fröhlich et al. 1999
Retrosp.92-00	54 MET/REL	N.A.	**+WB-RT** ME **ME-ME**	N.A.	5Y EFS 22% 29%	Burdach et al. 2003
Retrosp. 00-11	73 REL	CR PR 1% PD	15 BuMel 38 TreoMEL 20 other	128 cREL	5Y EFS 20%/24% REL 6% cREL	Rasper et al. 2014

Value of autologous SCT in patients with relapsed EwS

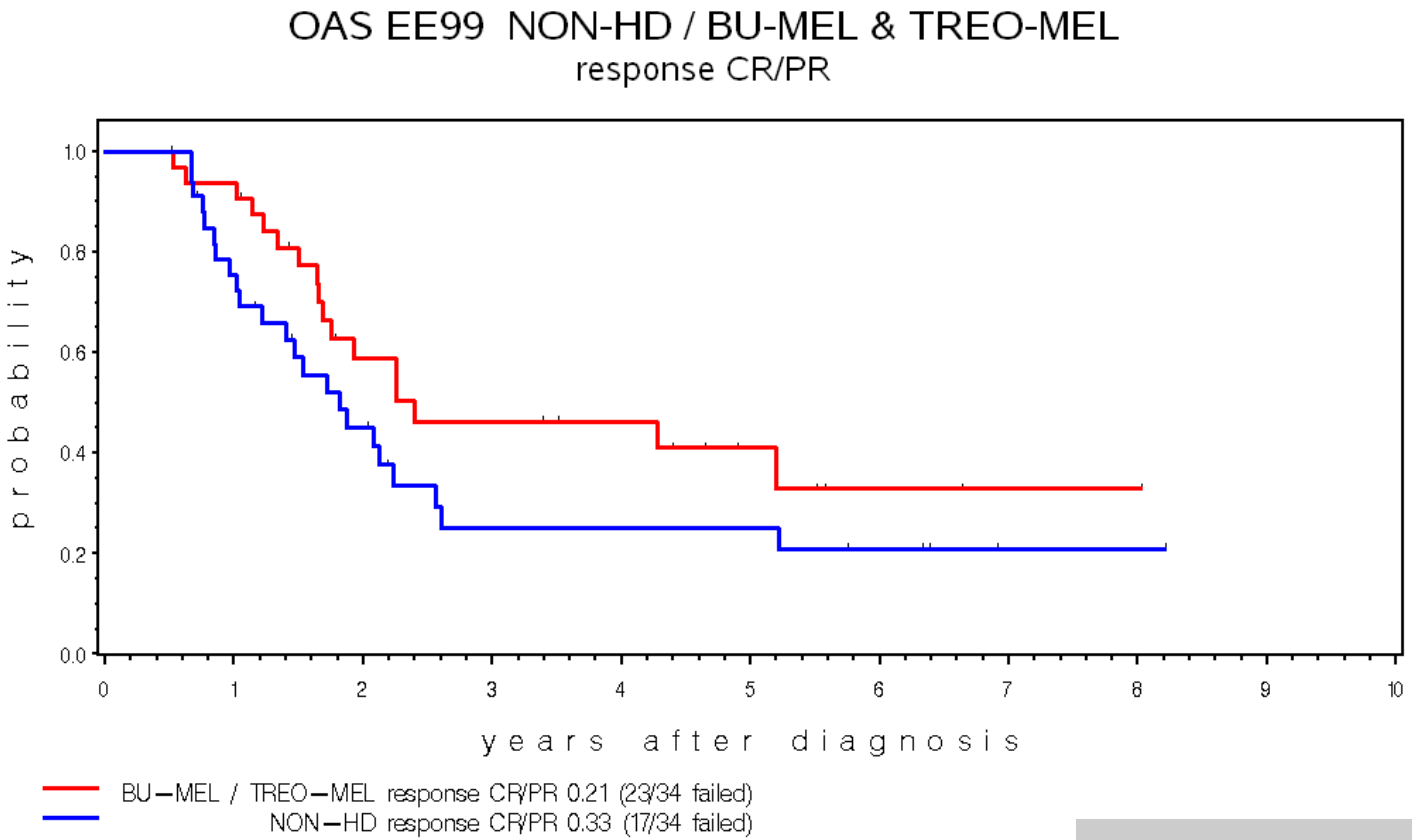


Further analysis necessary:

Non-HDtx CR/PR patients after 4-6cycles of relapse chemotherapy

vs

CR/PR Bu-Mel and Treo-Mel-HDtx-patients



p=0,1289

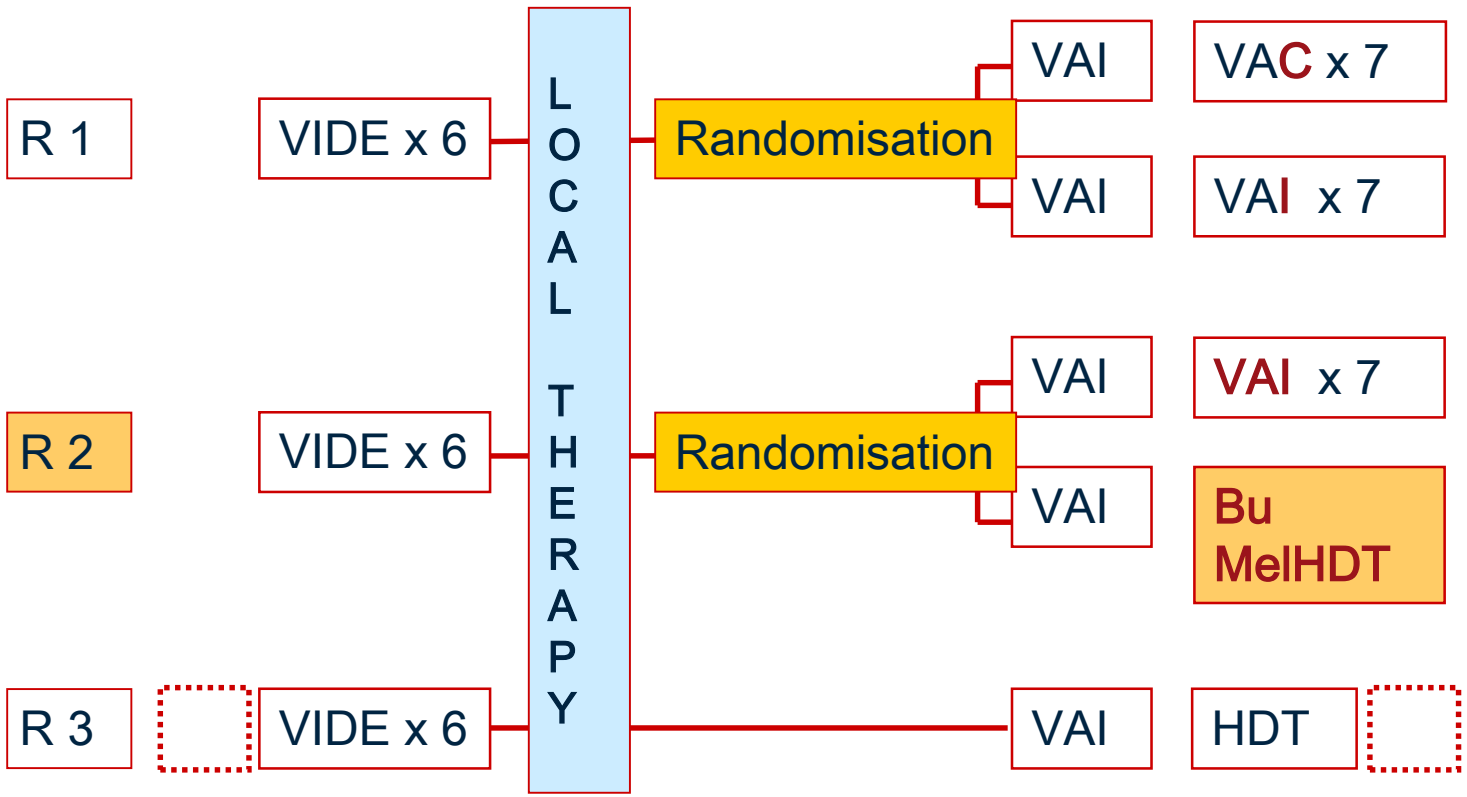
A solid prospective randomised study would be required to assess the benefit from HD in patients with relapsed disease

Ewing Sarcoma- prospective studies

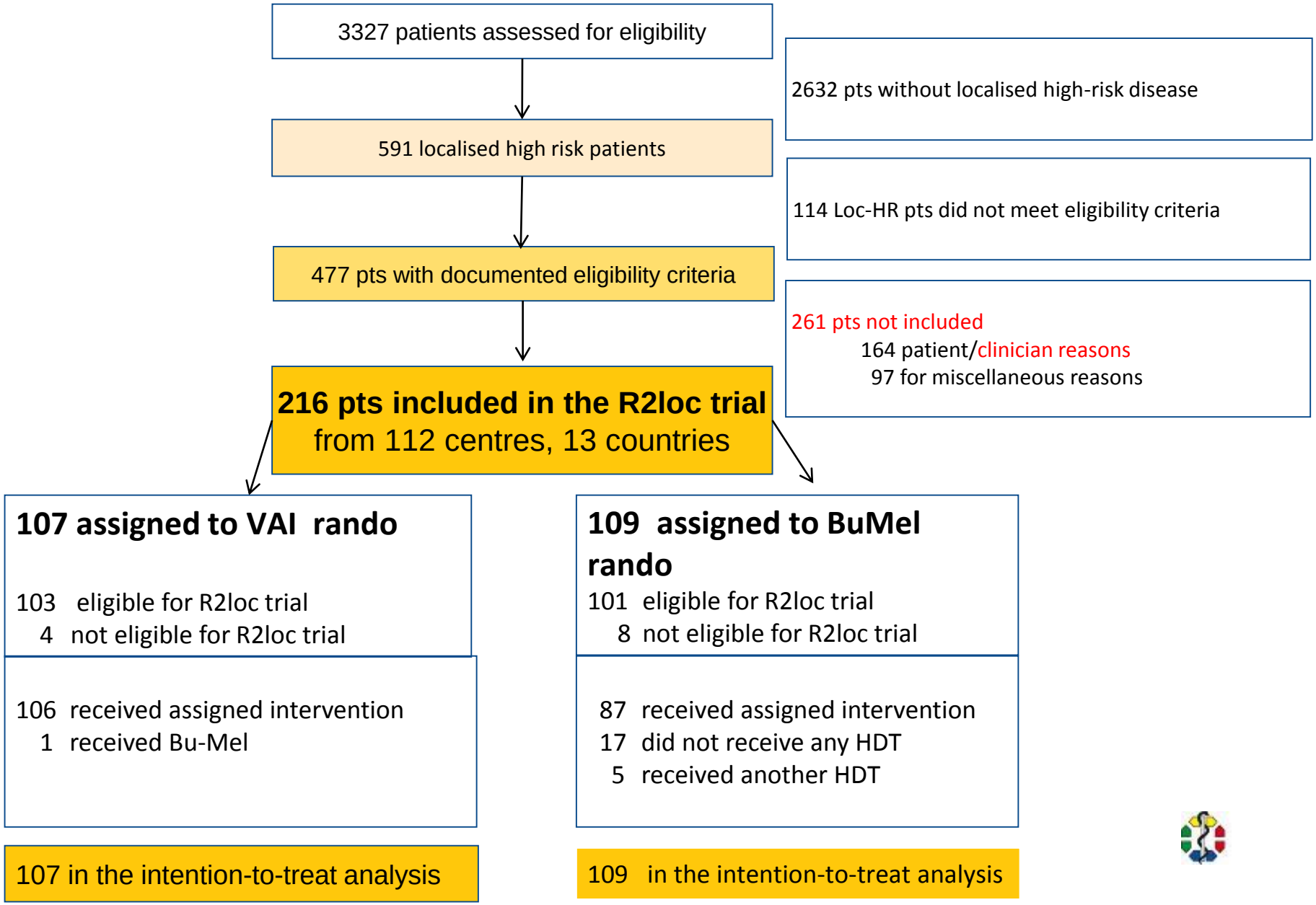
study	patients (pts)	status at transplant	regimen	control (c) pts	survival	author
Prosp. 99-08	103 MET	N.A.	BuMel	N.A.	5Y EFS 43%	Luksch et al. 2012
Prosp. 02-09	18 MET	CR vgPR	BuMel-BuMEl	N.A. (5 noHD/PD)	3Y EFS 11%	Loschi et al. 2015
Prosp. 91-99	75 MET	CR vgPR	BuMel	N.A.	5Y EFS 47% (52%) pMets	Oberlin et al. 2006
Prosp. 99-05	169 MET	CR vgPR SD/PD	136 BuMel 13 ME-ME 20 other	N.A. noHD PD 44 noHD other 68	3Y EFS/ Status prior HD 52% (in CR) 32% (in PR) 24% (in SD/PD)	Ladenstein et al. 2010
Prosp. 99-09	154 Loc. Poor resp	N.A.	BuMel	N.A. (28 noHD/PD)	5Y EFS 72% 33%	Ferrari et al. 2011

Ewing sarcoma- randomized study

EURO-E.W.I.N.G. 99

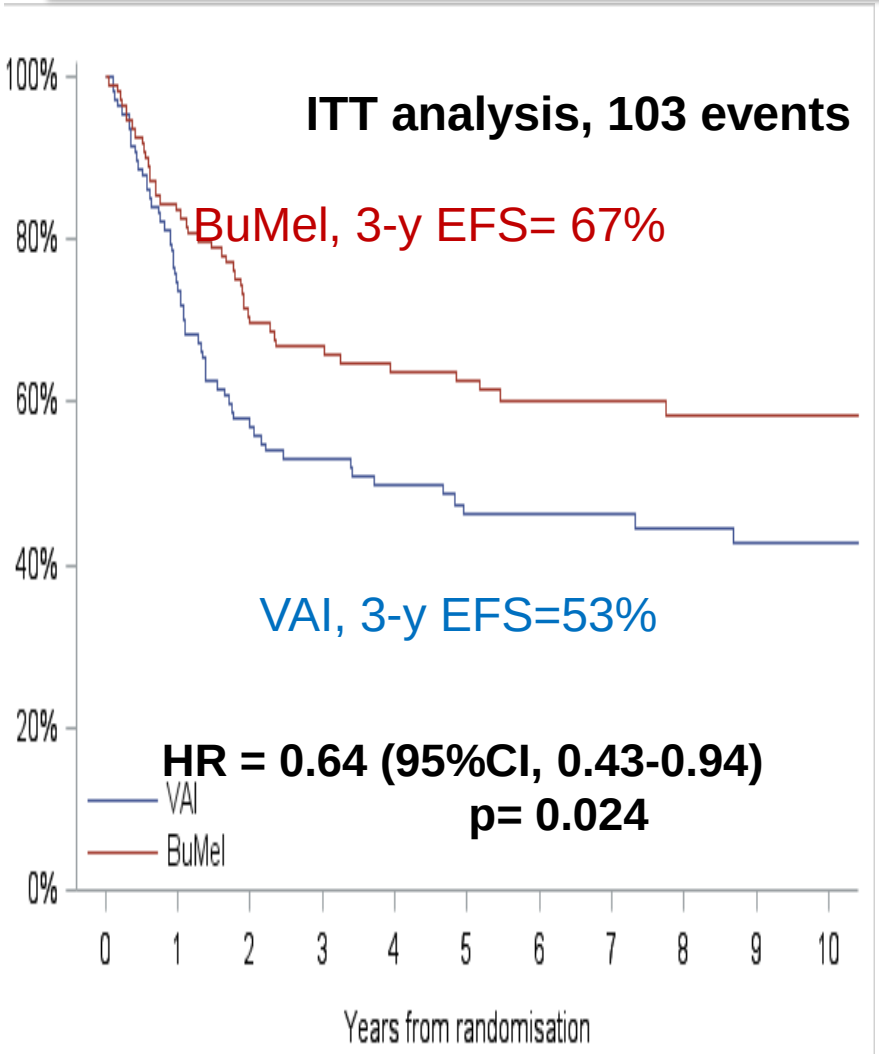


R2loc: HR localized disease; VAI vs BuMel HD

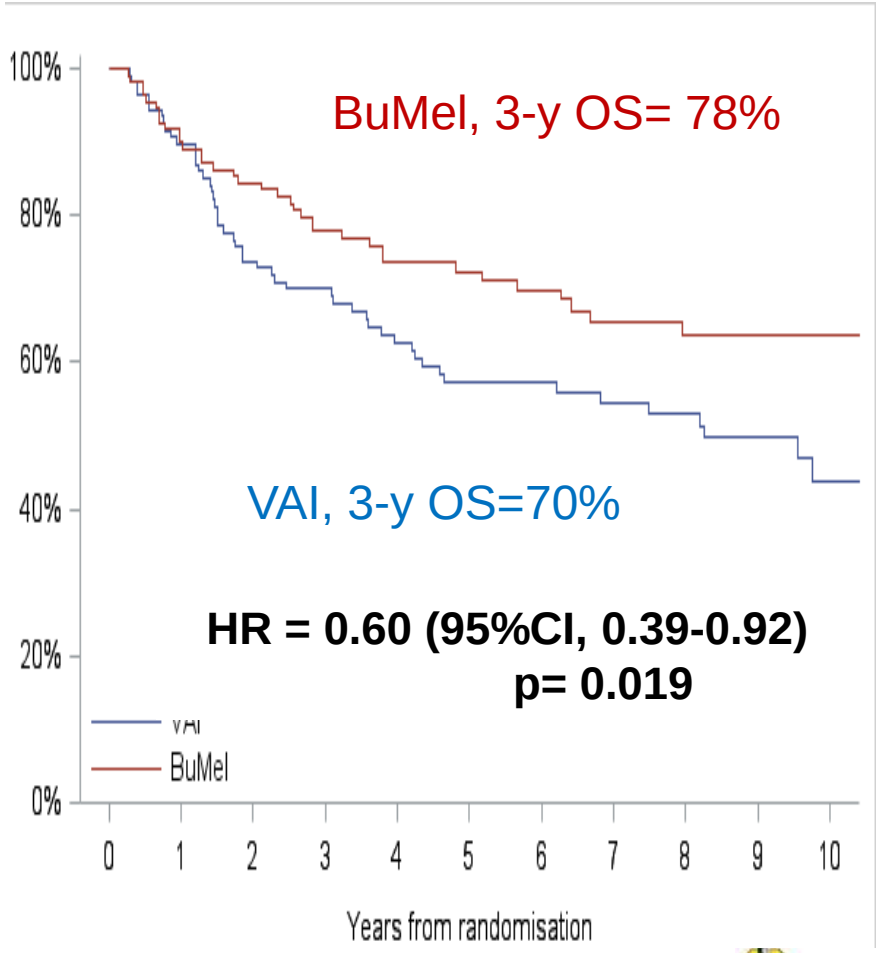


Benefit of BuMel in a subgroup

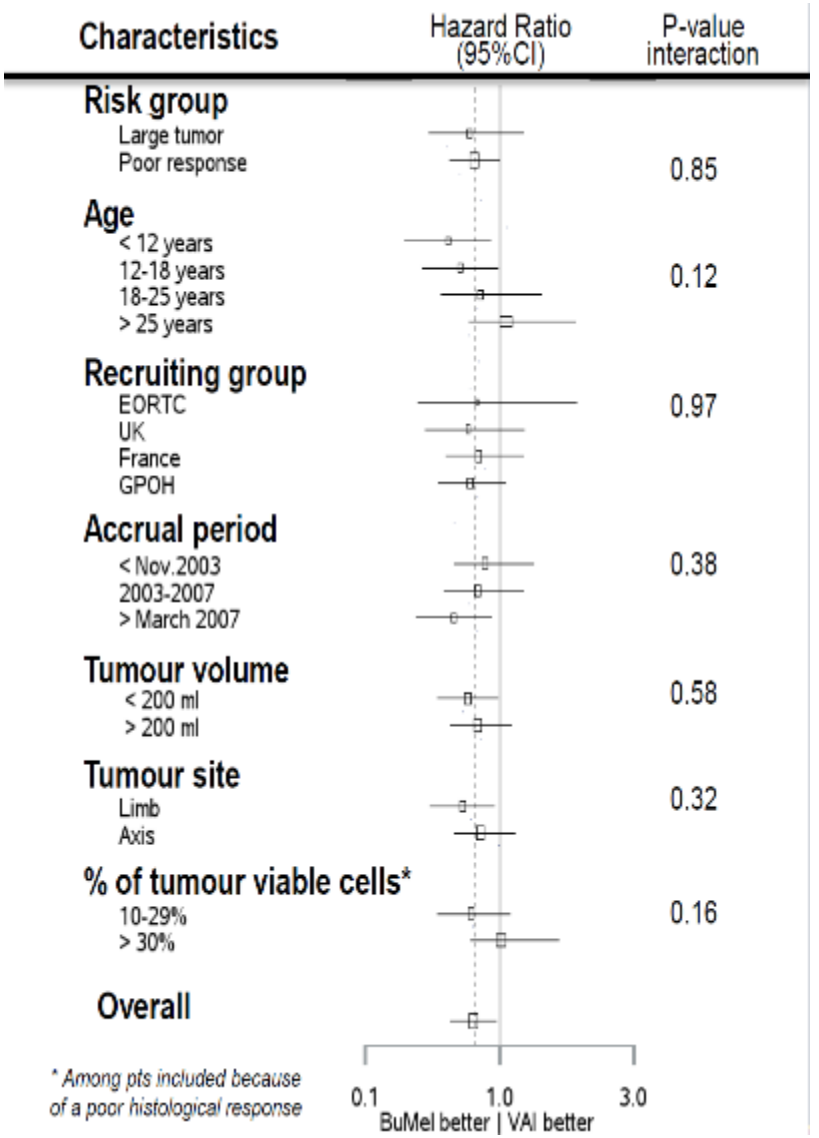
Event Free Survival



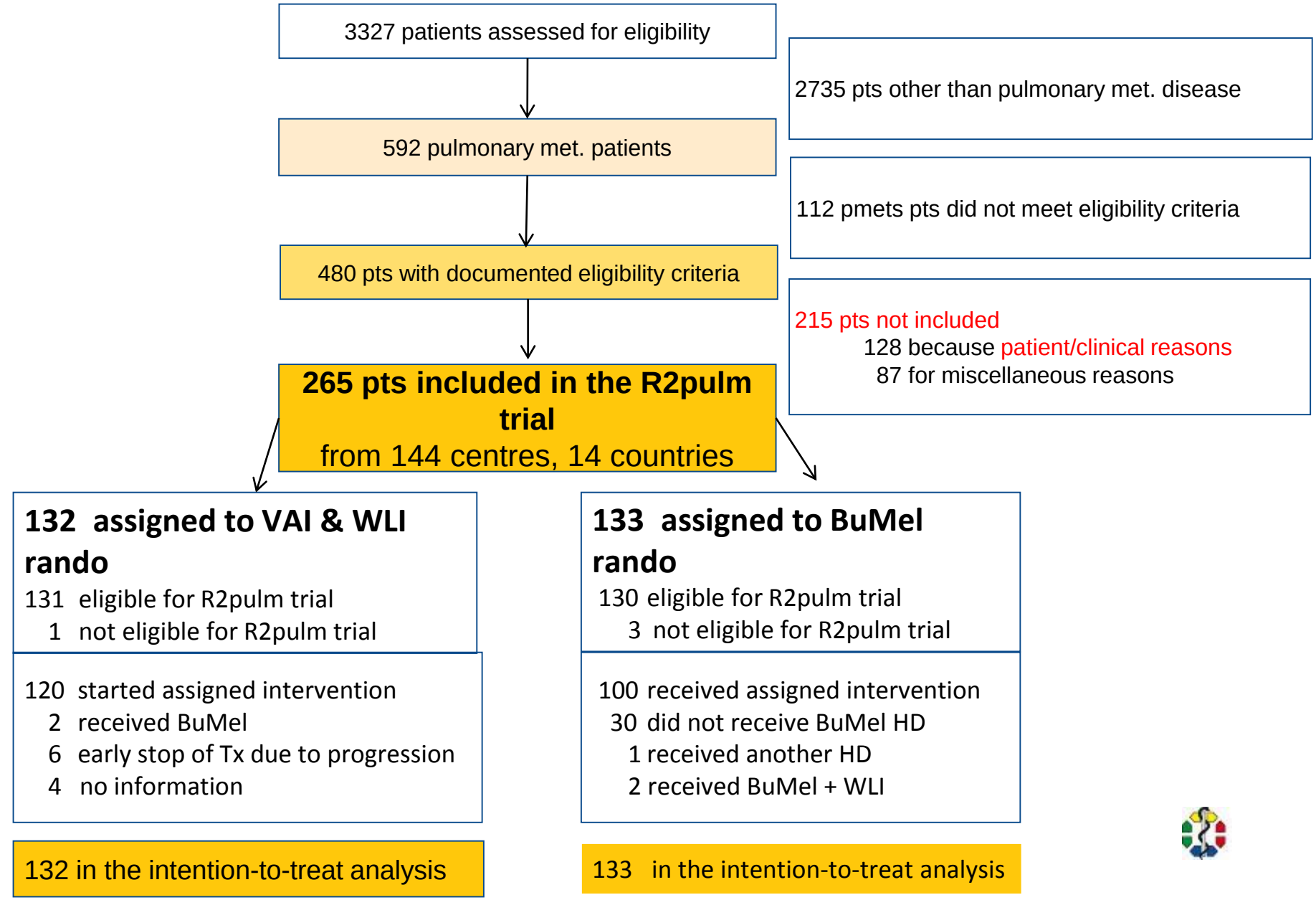
Overall Survival



No heterogeneity

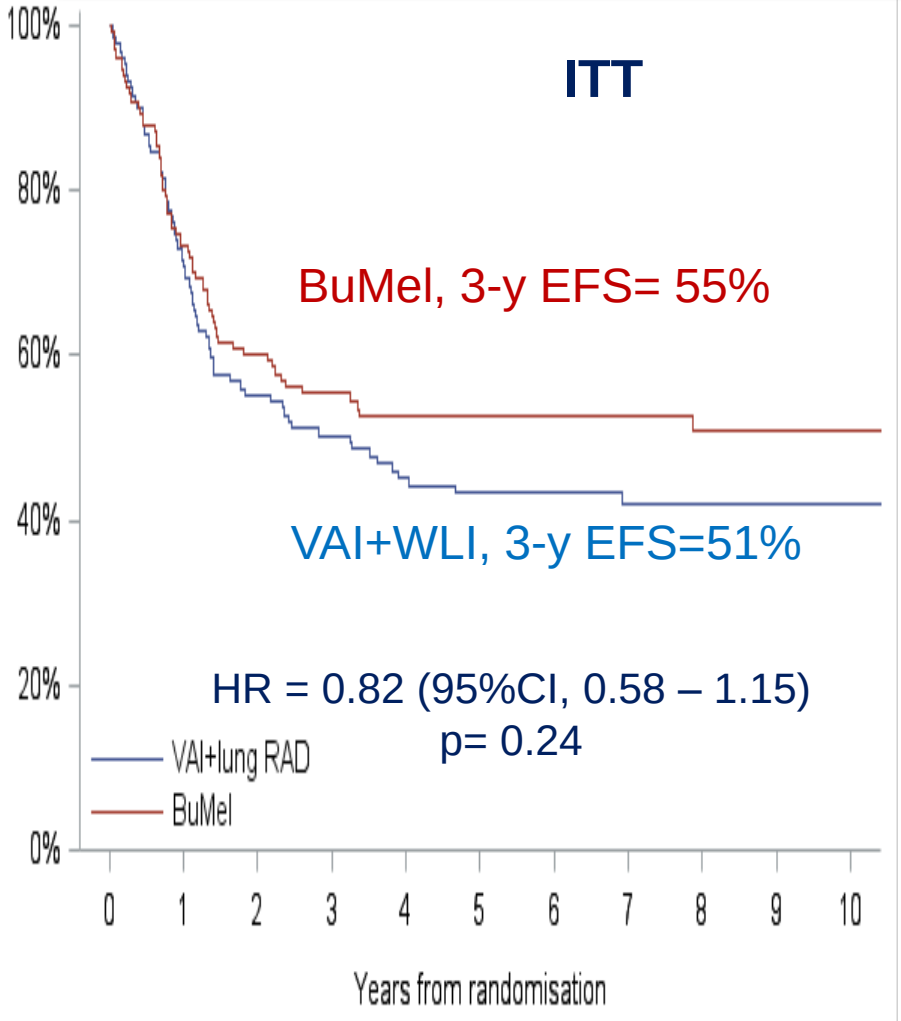


R2 pulm: VAI&WLI vs.BuMelHD

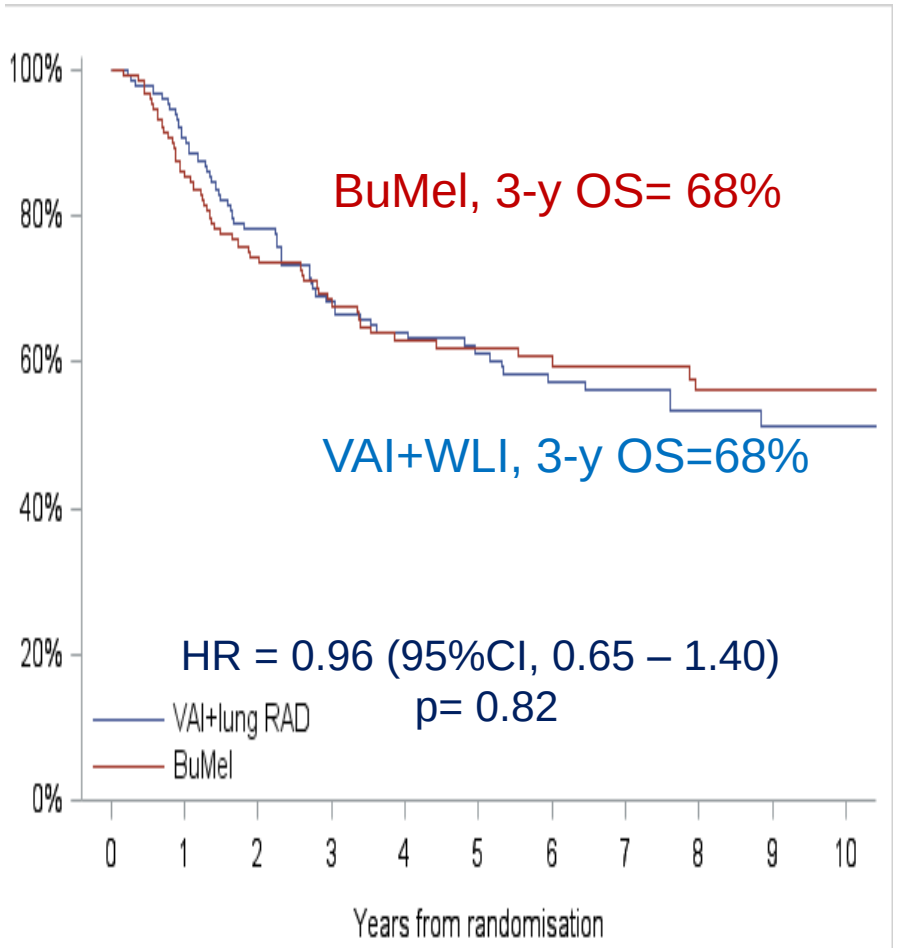


No difference

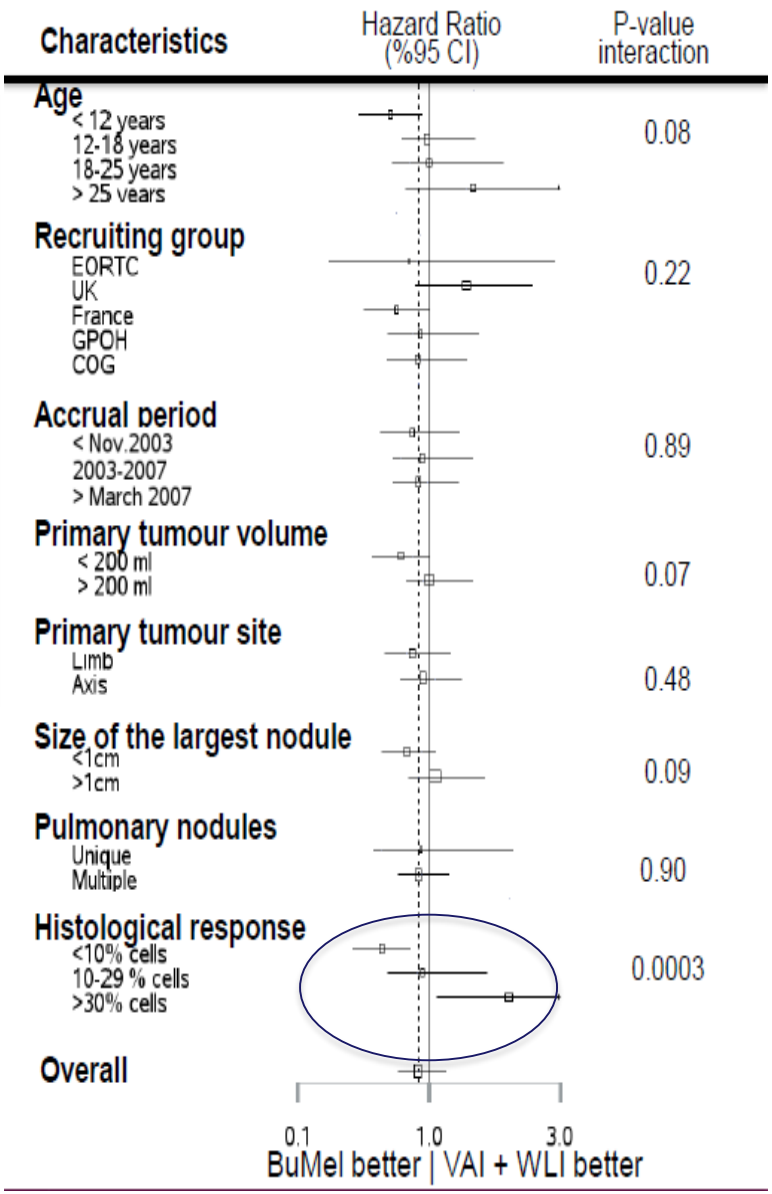
Event Free Survival



Overall Survival



Subgroup effect



Discussion

HD in localized disease

Prospective Study; ISG/SSG group
Prospective, randomized; EE99 group

Benefit from BuMel- HD
in a subgroup of patients with poor histological response

Disseminated disease, stratification criteria

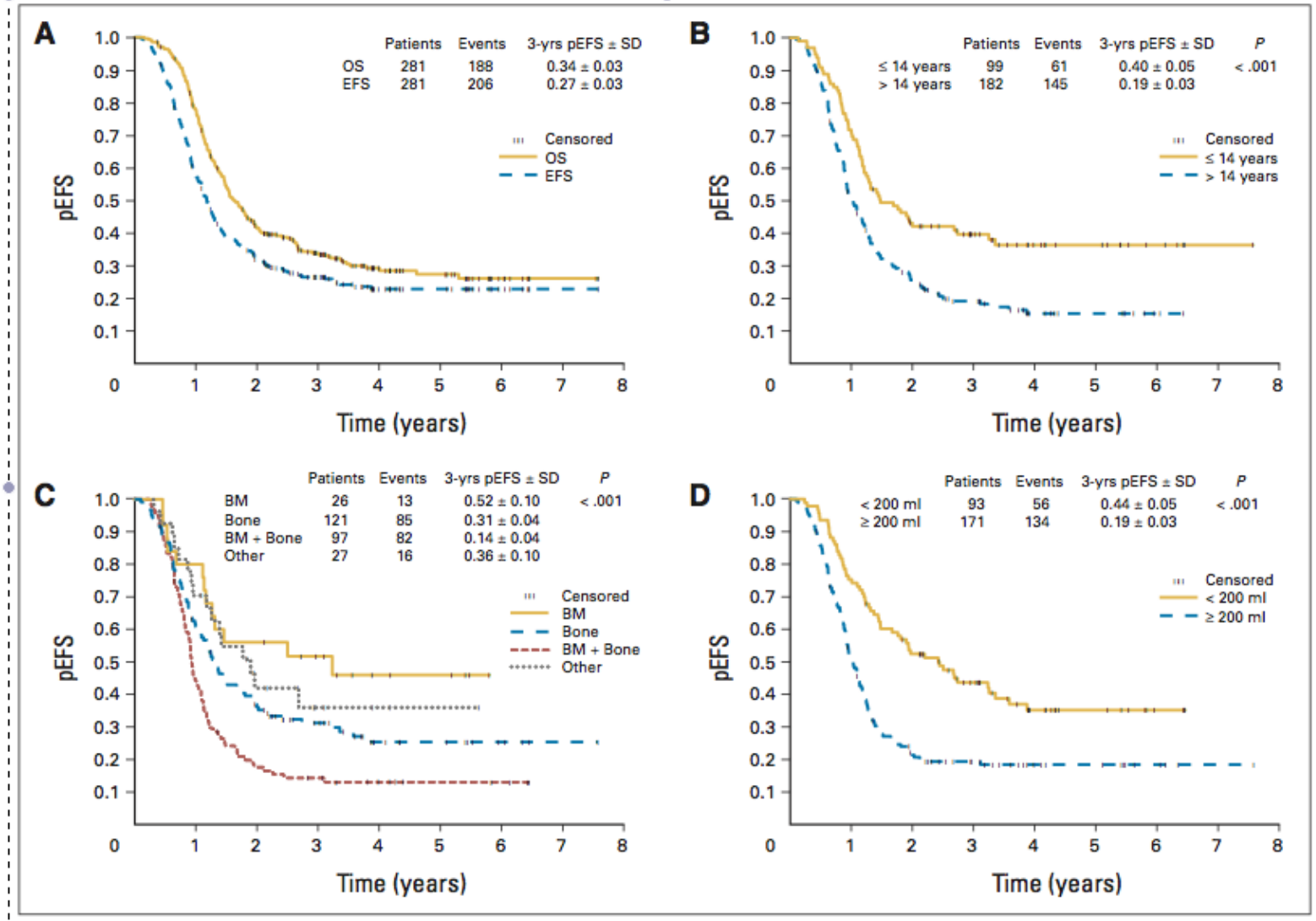
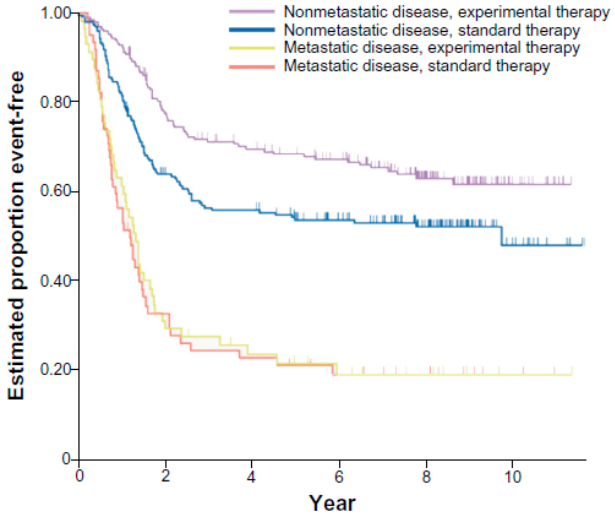


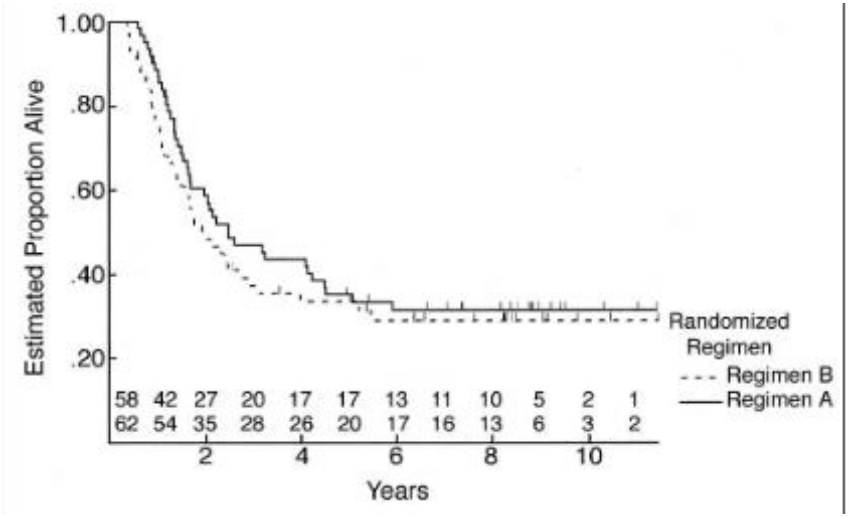
Fig 2. Outcome according to univariate parameters at diagnosis in the unselected patients with primary disseminated multifocal Ewing sarcomas. OS, overall survival; EFS, event-free survival; BM, bone marrow; pEFS, probability of event-free survival.

Dose intensity in patients with disseminated disease

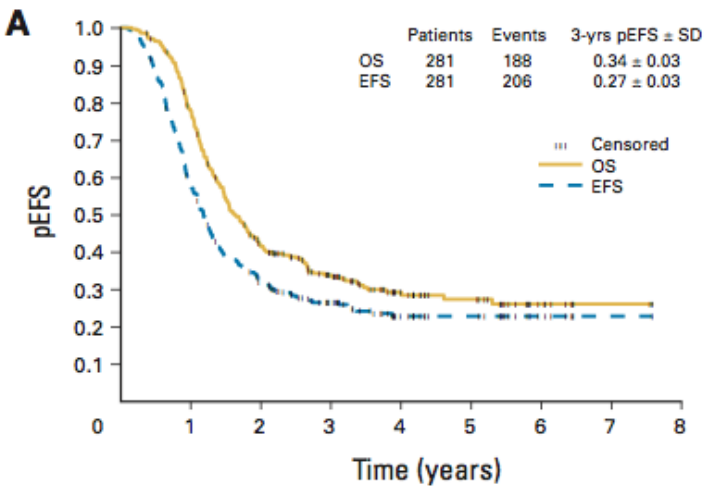
INT- 0091
VAVA vs VACA/IE

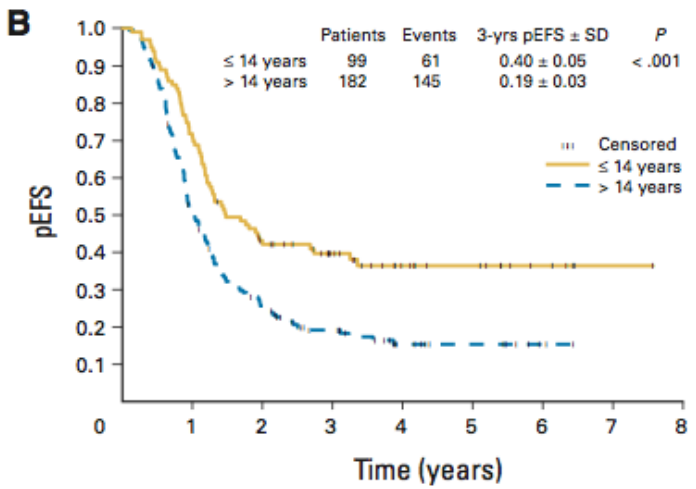


AEWS0031
VDC/IE vs VDC/IE compressed

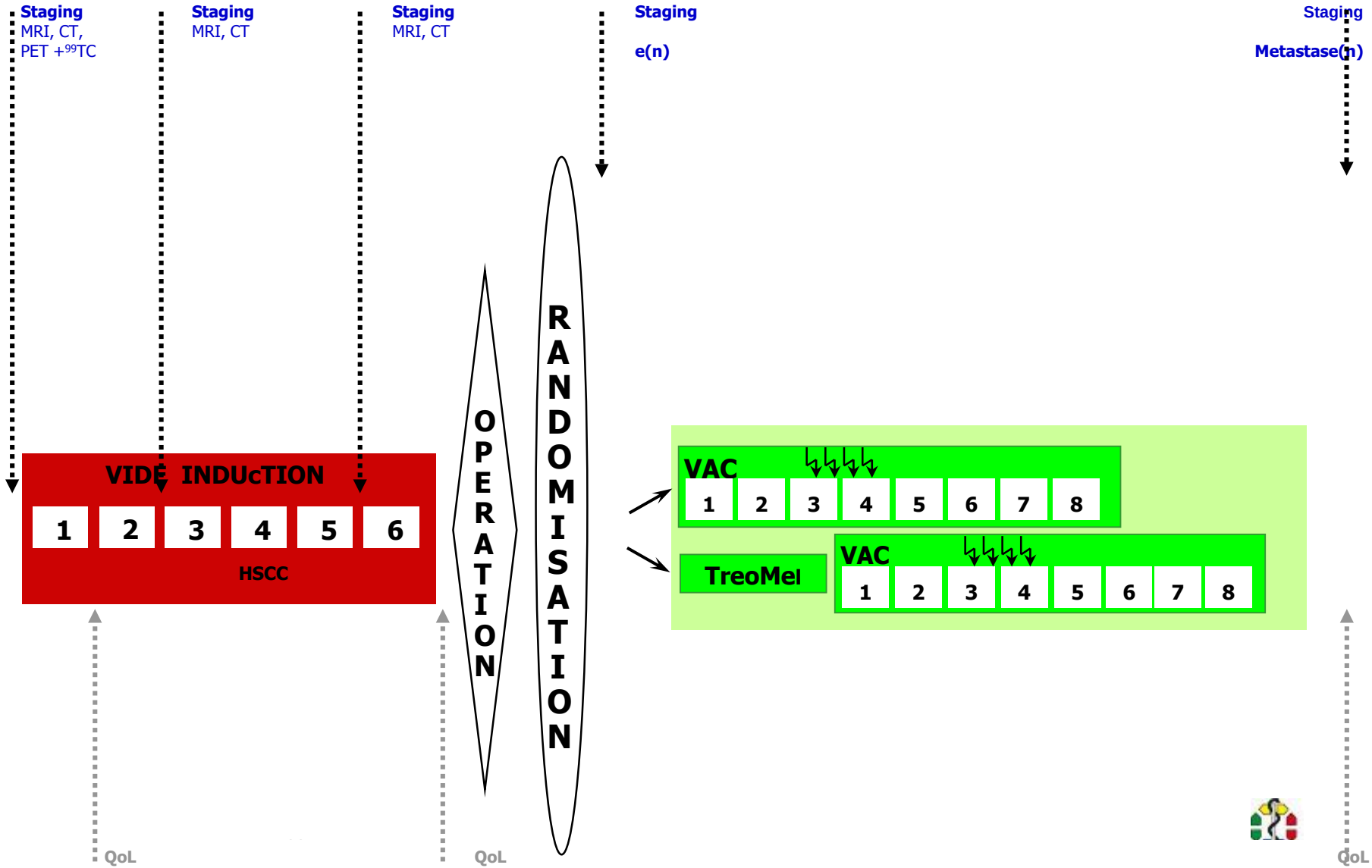


EE 99





Prospective randomized clinical trial



Discussion

HD in disseminated disease

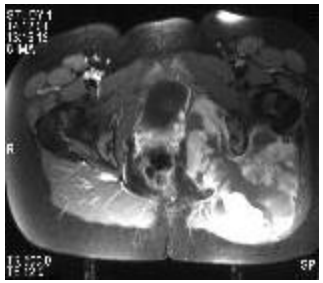
Experimental, benefit not proven

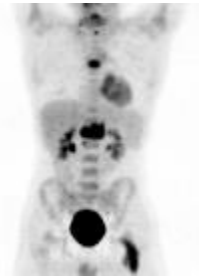
Randomized clincial trial ongoing; results pending

Rhabdomyosarcoma

4 years, embryonales RMS: 85%

14 years, alveolar metastatic RMS <10%





Risk group	Sub-groups	Pathology	Post surgical stage (IRS group)	Site	Node stage	Size & Age
Low	A	Favourable	I	Any	N0	Favourable
Standard	*B*	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High	*E*	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable	I, II, III	Any	N0	Any
Very High	*H*	Unfavourable	II, III	Any	N1	Any

Rhabdomyosarcoma

study	patients (pts)	status at transplant	regimen	Control (c) pts	survival	author
Retrosp 84-94	27 MET 9 REL	100%CR CR PR N.A.	**+WB-RT** MEC **+TLI** CyBu **Single** MEC /BCNU	N.A. N.A	2Y EFS 36%	Koscielniak et al. 1997
Prosp.	70 MET	N.A.	consecutive courses of high dose TpMel CyTp Mel	N.A.	3Y OS 42%	Bisogno et al. 2006
Prosp not randomized	96 MET RMS & RMS-like	N.A.	45 TpCY-ME	51 oTIE	5Y OS 27% pts 52% cpts	Klingebiel et al. 2008
89-02	112 MET	N.A:	N.A.	N.A.	5y OS 32%	Stiff et al. 2010

NON-RMS

Soft tissue sarcoma ; Non-RMS

study	patients (pts)	status at transplant	regimen	control (c) pts	survival	author
Prosp.. Rando. 84-94	38 various	N.A.	**CaEI**	45	3Y OS Pts 32% cpts 49 %	Bui-Nguyen et al. 2012
Retrosp. 88-94	24 Various	N.A.	VIC	N.A.	NR	Blay et al. 2000
Retrosp. 97-02	10 DSRCT	PR	various	N.A.	3 Y OS 20%	Bertuzzi et al. 2003
Retrosp. 99-08	14 DSRCT	PR	consecutive courses of high dose TpMel CyTp Mel	N.A.	3Y OS 48%	Bisognio et al. 2010
Retrosp. 99-07	36 DSRCT	REL/PR	various	N.A.	3Y OS 40%	Cook et al. 2012
Retrosp. 95-06	14 DSRCT	PR	various	N.A.	2Y OS 51%	Phillipe et al.2012
Retrosp. 91-12	41 DSRCT		Various NON High dose	N.A.	2Y EFS 42%	Wong et al. 2013

High dose treatment in soft tissue sarcoma

Author`s conclusions

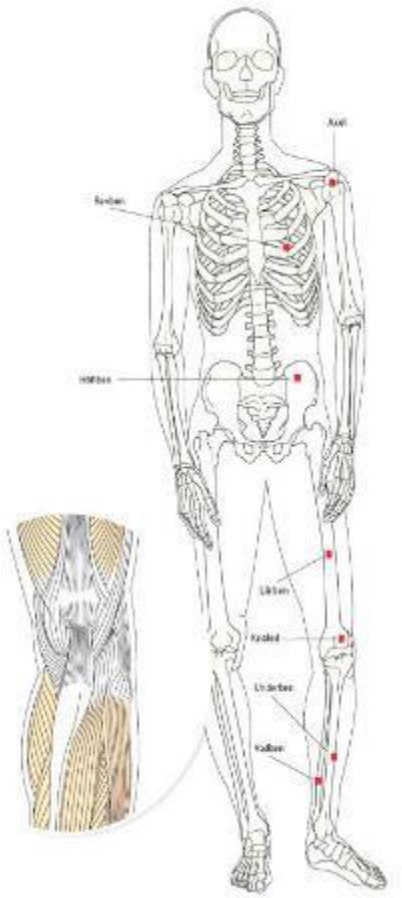
No benefit from high dose chemotherapy in RMS and NON-RMS soft tissue sarcoma in children and adolescents

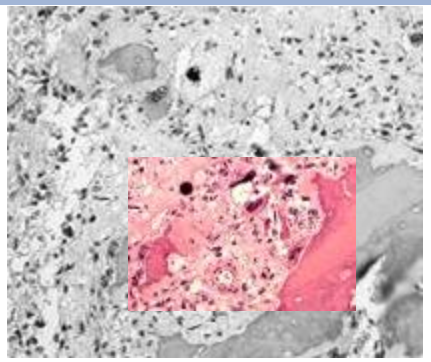
No benefit from high dose chemotherapy in adult type soft tissue sarcoma

Most studies were done without any control arm

One prospective randomized study showed no benefit from hugh dose chemotherapy

Osteosarcoma



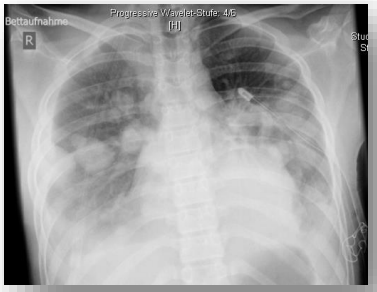


Adolescents and young adults

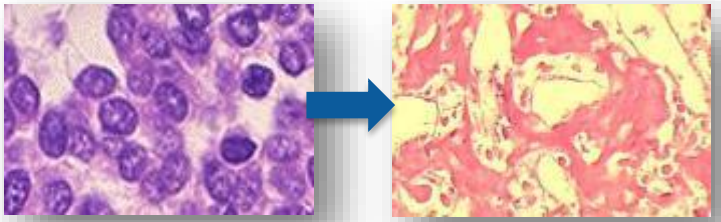
Elderly

OSTEOSARCOMA

Metastases



Response to induction chemotherapy

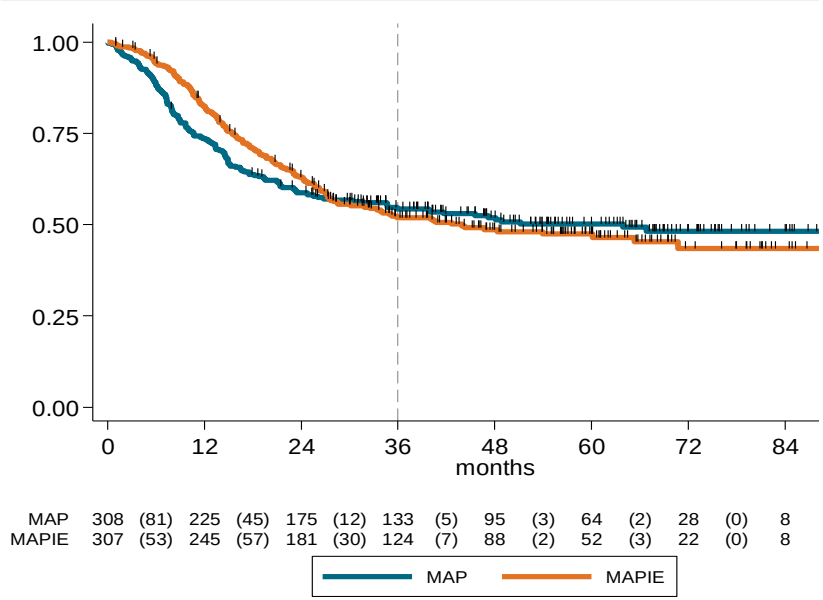


Resectablility

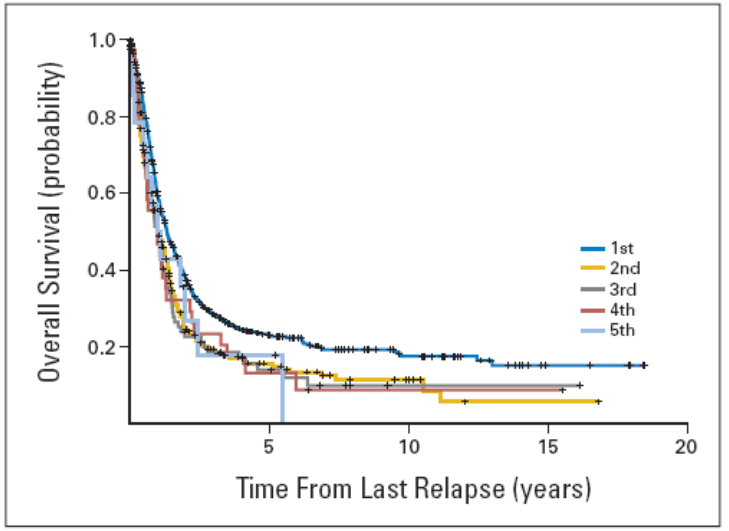
Age

Osteosarcoma

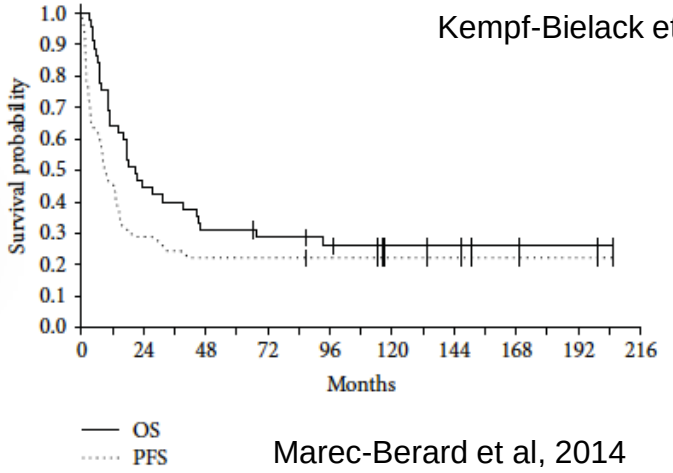
study	patients (pts)	status at transplant	regimen	control (c) pts	survival	author
Retrosp 92-04	53 REL/Ref	N.A.	**Tp**	N.A.	5Y OS 52%	Marec-Berard et al. 2013
Prosp.	19 MET	N.A.	MECa	N.A.	3Y OS 42%	Hong et al. 2015



EURAMOS-1; Marina et al., 2014



Kempf-Bielack et al, 2006



Marec-Berard et al, 2014

Discussion

High dose chemotherapy is an experimental treatment
Many retrospective studies
Lack of clinical data
i.e. status prior transplant missing

Selection Bias
Reporting Bias
Various baseline characteristics
Heterogenous groups of patients

A high risk experimental treatment should be assessed in a controlled clinical trial setting

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Oscar Martinez

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Lars Hjorth
Jukka Kanerva

Tschechien
Ian Stary
Jarmila Kruzeova

Ungarn
Peter Hauser

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Bernadette Brennan
Sue Burchill
Alan Craft
Bass Hassan
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