GIST et Sarcomes des tissus mous et osseux

PRESENTED AT: ASCO ANNUAL MEETING '16

Bruges, le 22 Juin 2016

GIST

Dose Escalating Study of Crenolanib Besylate in Advanced GIST Patients with *PDGFRA* D842V Activating Mutations

Margaret von Mehren, MD, Eric Tetzlaff, MD, Meghan Macaraeg, BS, Jeremy Davis, MS, Vartika Agarwal, MS, Abhijit Ramachandran, MS, Michael C. Heinrich, MD

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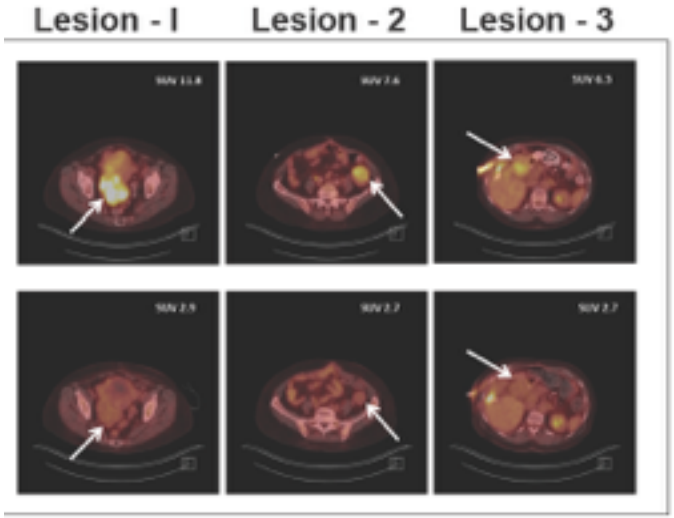
Dose Escalating Study of Crenolanib in GIST Patients with *PDGFRA* D842V Activating Mutations

Evaluable Patients (N=16*)		
Response	# of Patients	Percentage (%)
PR	2	13%
Stable Disease	3	19%
Overall clinical benefit (CR+PR+SD)	5	31%



A placebo controlled randomized phase III trial with crenolanib in patients with *PDGFRA* D842V mutated GIST is being initiated. (EudraCT Number: 2015-000287-34)

PDGFRA Exon 18 GISTs (N=71, 3 databases)

Characteristics	D842V mutated (48)	Non-D842V mutated (23)
Gender		
Male	28 (58.3%)	15 (65.2%)
Female	15 (42.9%)	8 (34.8%)
Age in years (median;range)	56 (23-80)	62 (46-87)
Tumor status at registry		
Local disease	33 (68.8%)	15 (65.2%)
Locally advanced	11 (22.9%)	2 (8.7%)
Metastasized	4 (8.3%)	6 (26.1%)
Surgery		
Yes	43 (89.6%)	21 (91.3%)
No	5 (10.4%)	2 (8.7%)
Imatinib treatment		
Yes	22 (45.8%)	14 (60.9%)
No	26 (54.2%)	9 (39.1%)
Treatment objective		
Neo-adjuvant	12 (20.8%)	3 (13.0%)
Palliative	5 (12.5%)	5 (17.4%)
Adjuvant	5 (12.5%)	6 (30.4%)
No systemic treatment	25 (54.2%)	9 (39.1%)

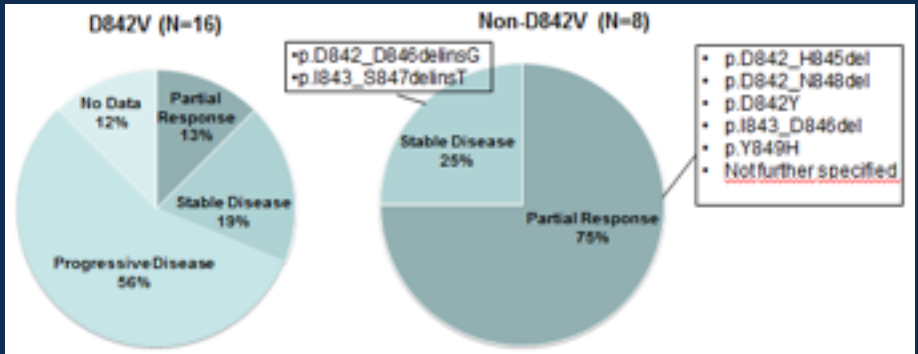


Figure 2. Radiological responses according to Choi's criteria in patients with measurable disease treated with imatinib.

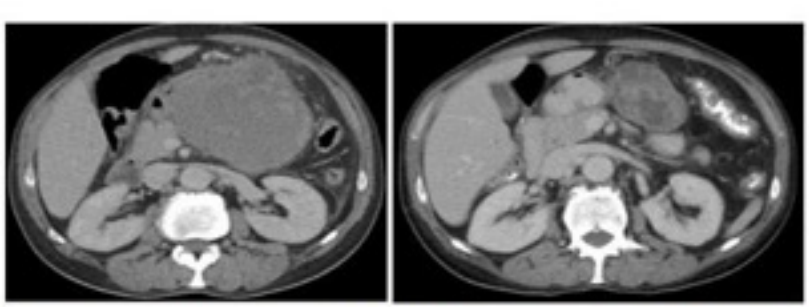


Figure 3. Partial response to imatinib seen in patient with a *PDGFRA* D842V mutated GIST.

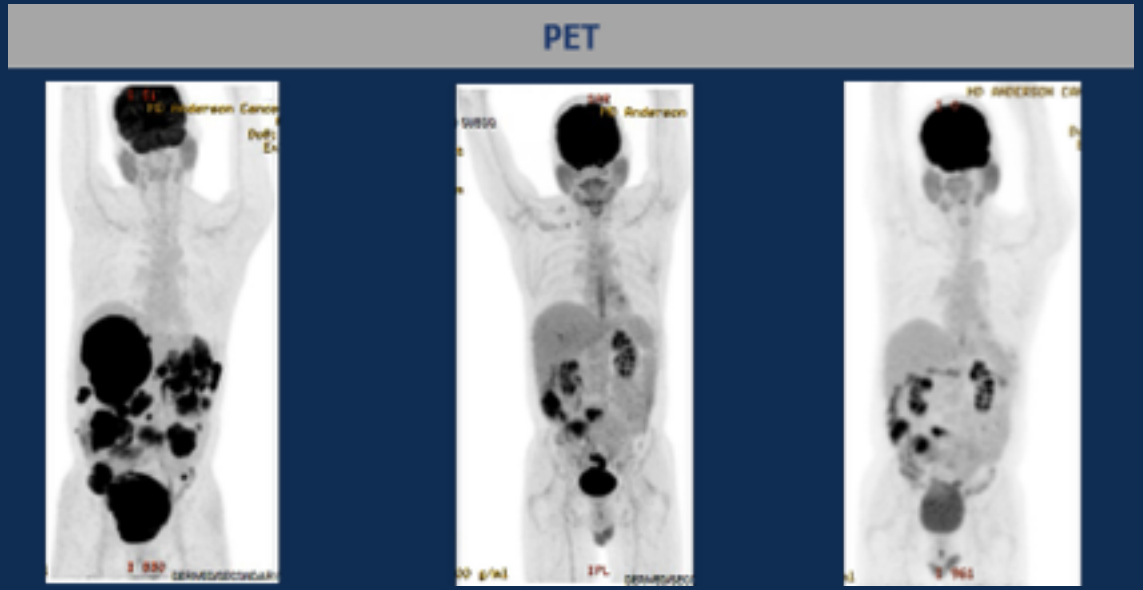
S. Farag (abstract 11011)

New Oncogenic RTK translocation in quadruple negative WT GIST

GIST classification	Fusion Panel results	SDHB IHC
Q-WT GIST	*ETV6-NTRK3*	Positive
Q-WT GIST	None detected	Positive
Q-WT GIST	None detected	Positive
Potential Q-WT GIST	*FGR1-TACC1*	Unknown
Potential Q-WT GIST	None detected	Unknown

LOX-101 (anti-NTRK3) in ETV6-NTRK3 fusion GIST

- 55 yo male with GIST progressed through imatinib, sunitinib, sorafenib, nilotinib, and regorafenib
- 150mg BID 28 day cycle
- Confirmed partial response
- Currently on study in cycle 10



David Hong MDA
AACR 2016

Sarcomes des tissus mous et osseux

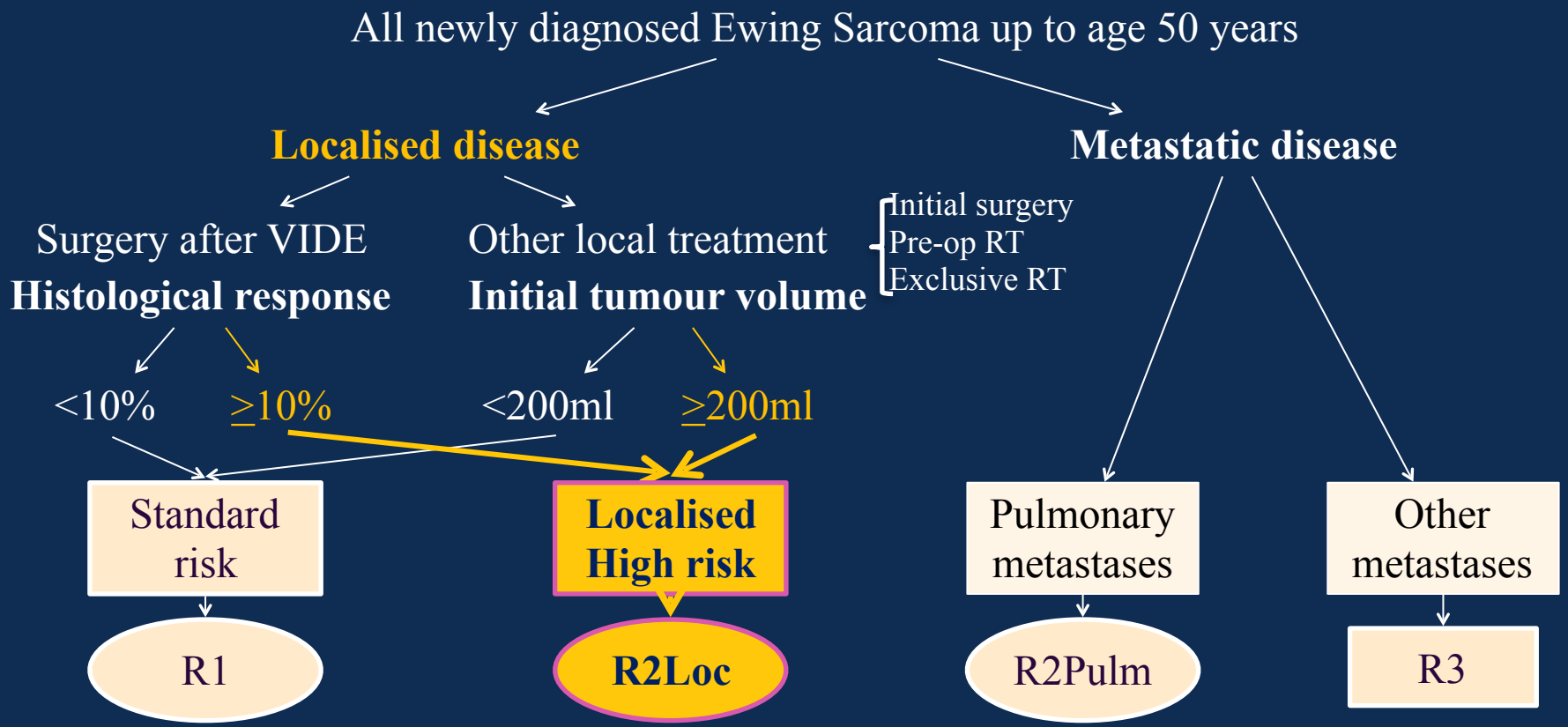
Efficacy of Busulfan-Melphalan high dose chemotherapy consolidation in localised high-risk Ewing sarcoma:

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

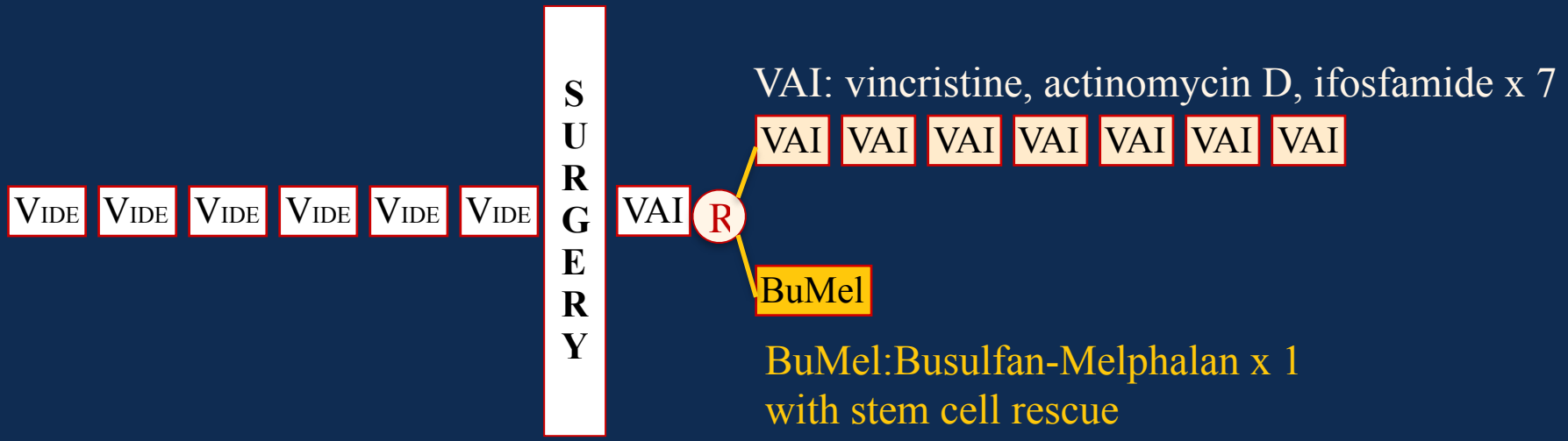
Jeremy Whelan, Marie-Cecile Le Deley, Uta Dirksen, Ian Robert Judson, Douglas S. Hawkins, Hendrik Van Den Berg, Ruth Ladenstein, Jarmila Kruseova, Andreas Ranft, Susanne Amler, Nathalie Gaspar, Valerie Laurence, Gwenael Le Teuff, Perrine Marec-Berard, Bernadette Brennan, Keith Wheatley, Bruce Morland,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

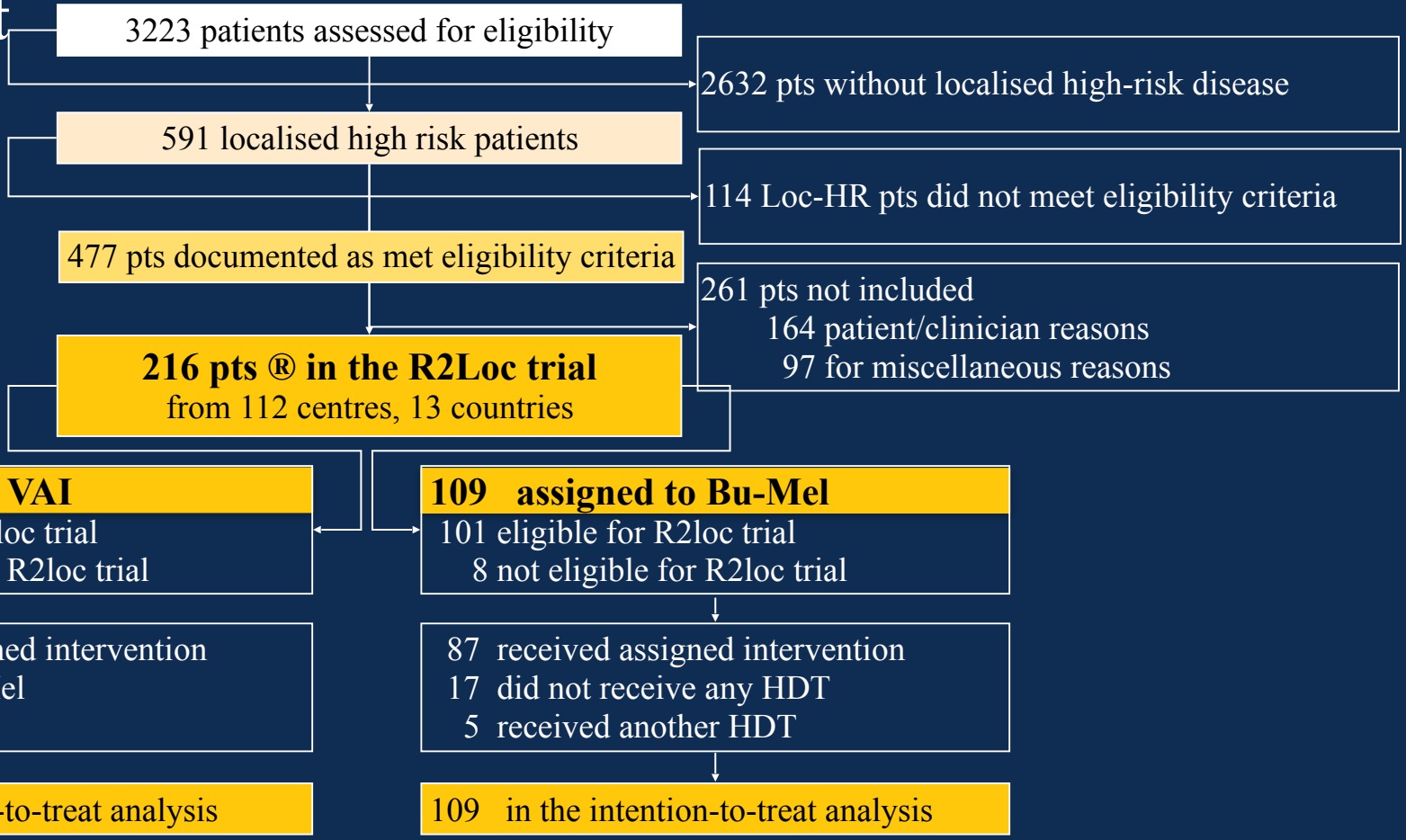
EURO-E.W.I.N.G 99 stratification



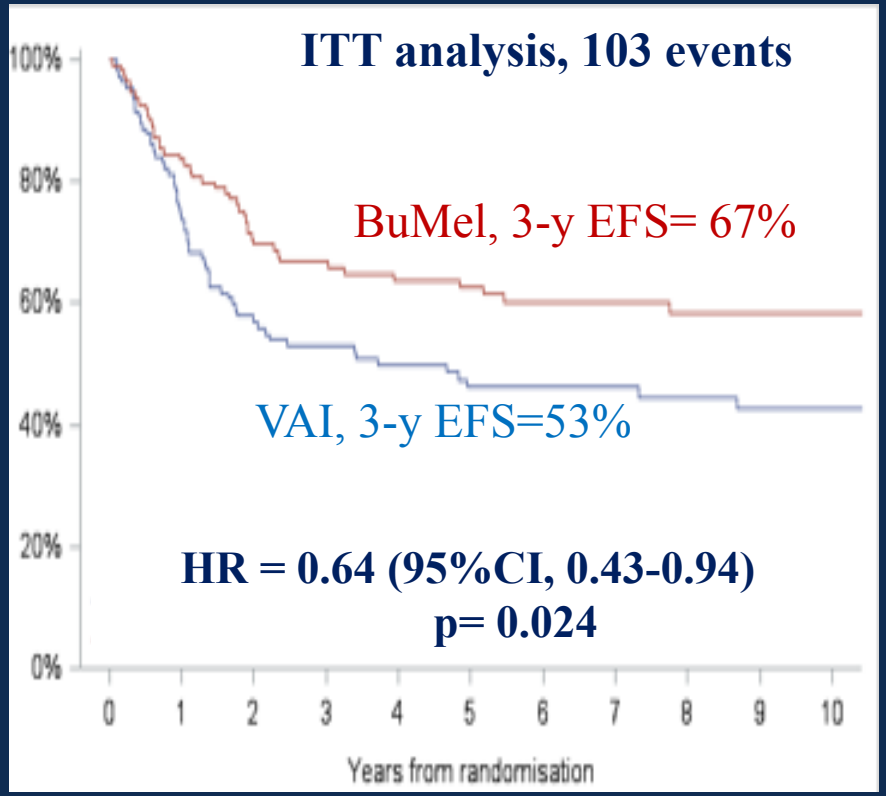
EE99- R2 Loc Scheme



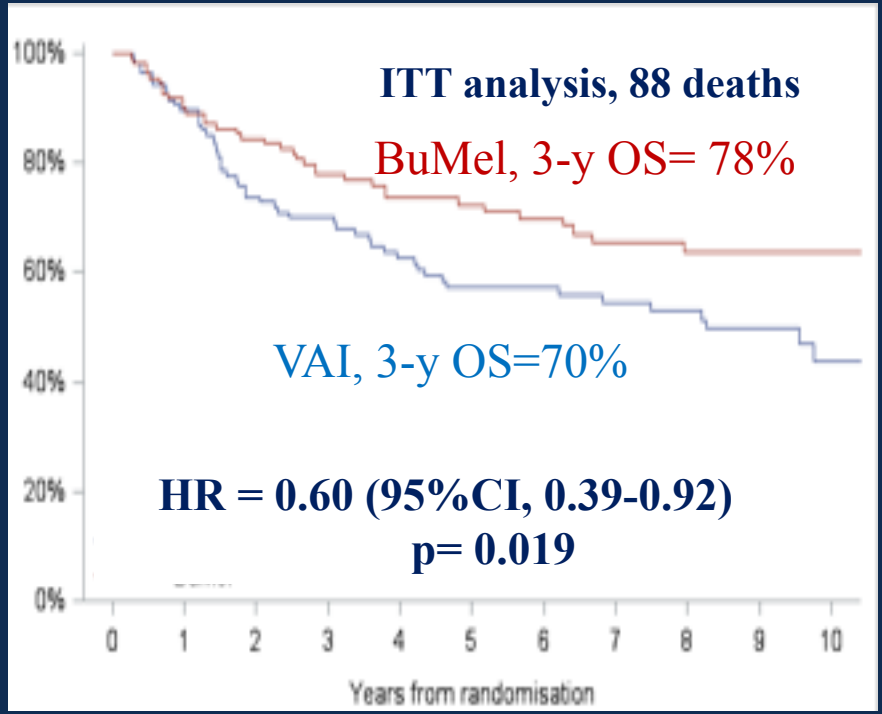
Flow chart



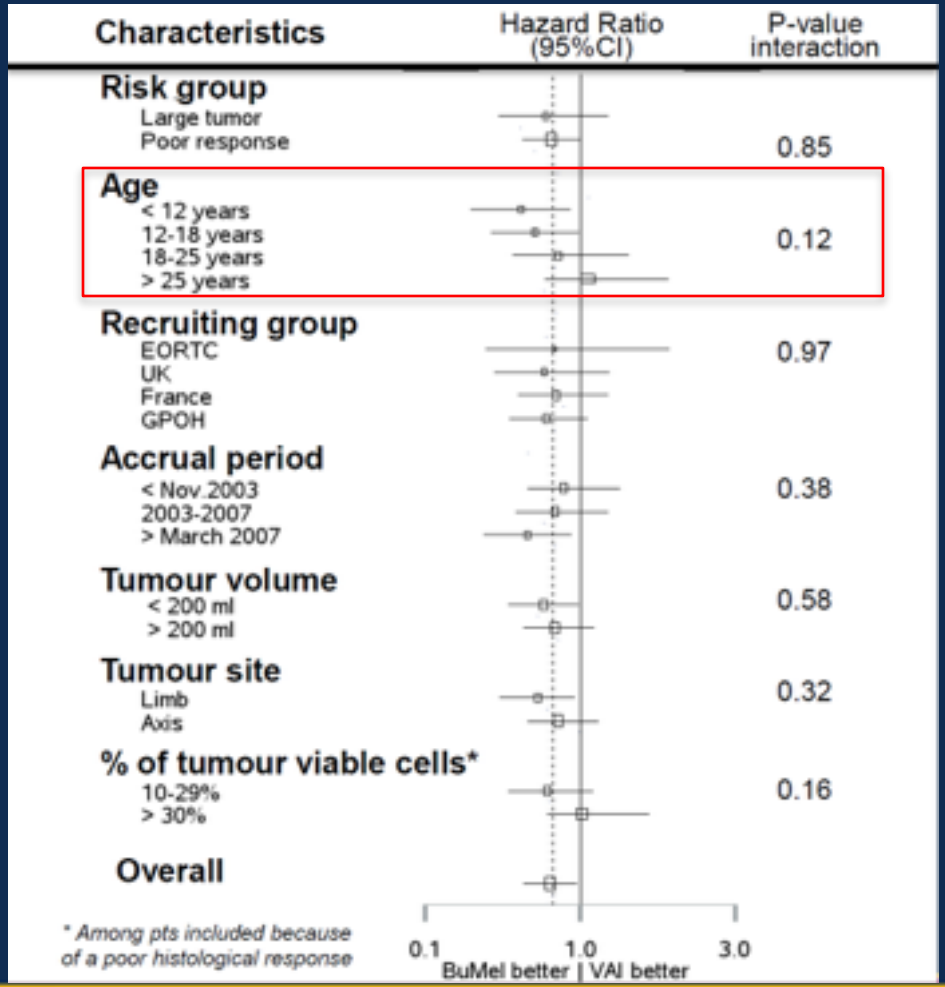
Benefit of BuMel on Event-Free Survival



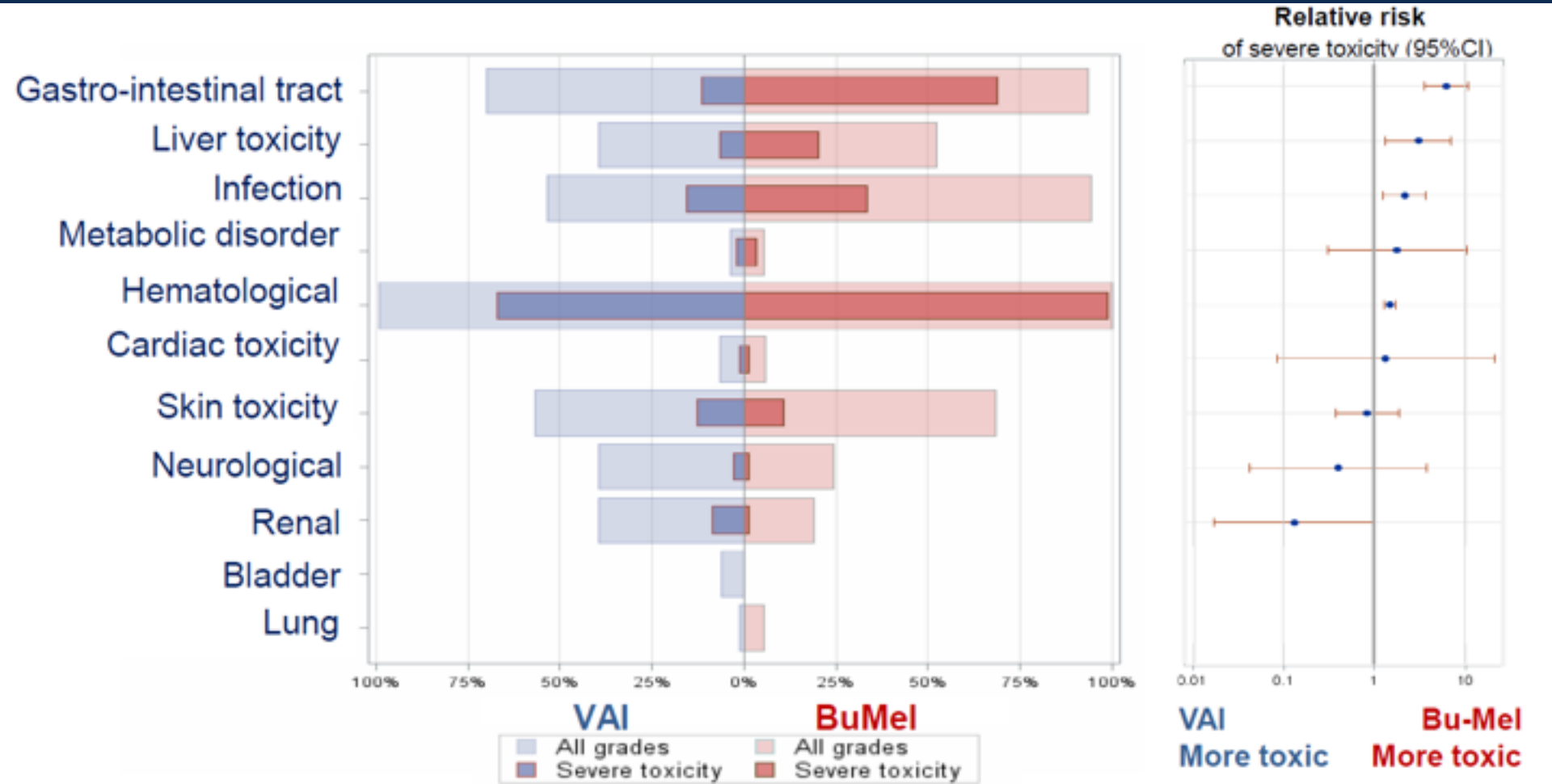
Translates into better Overall Survival



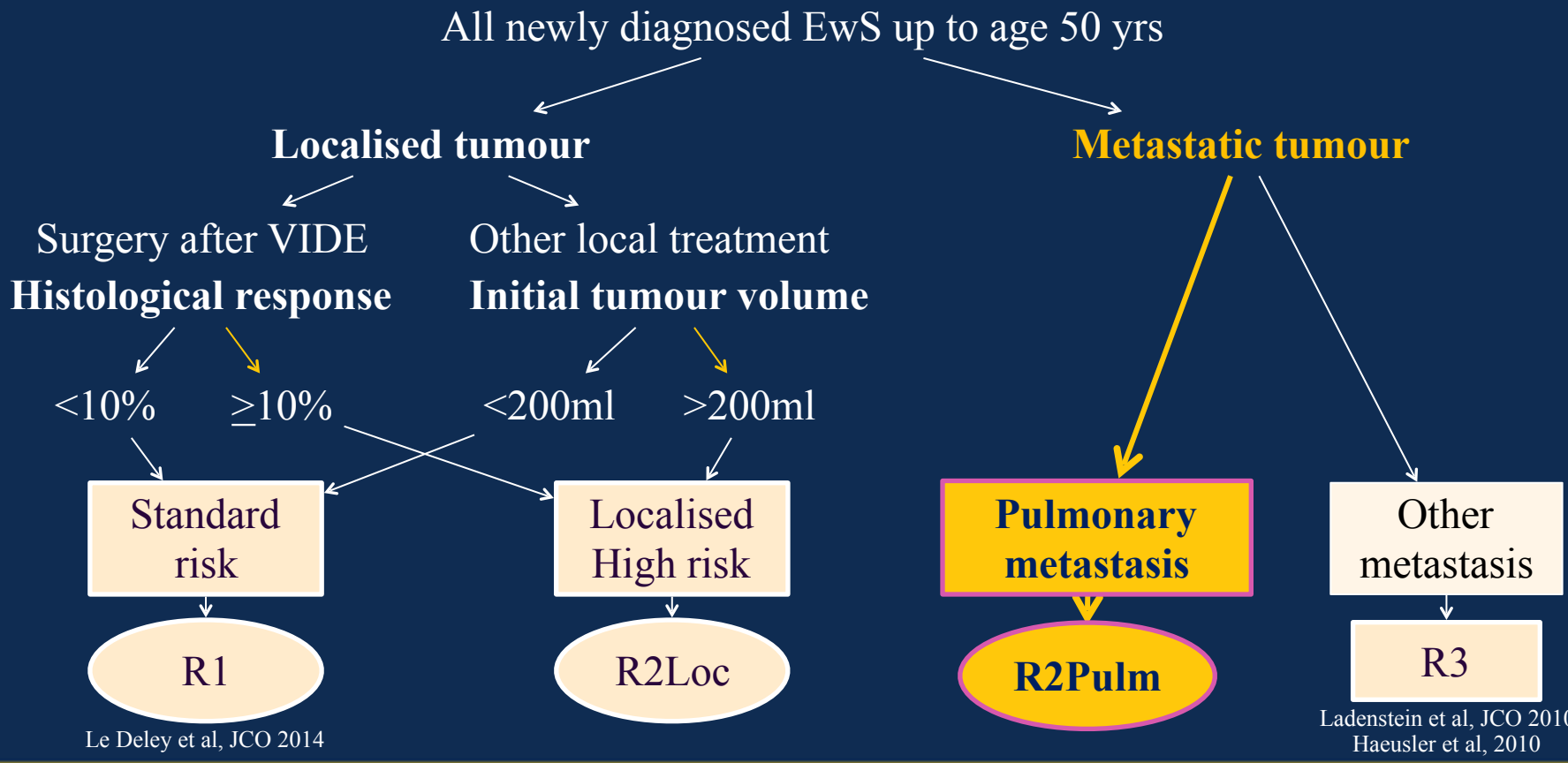
No major heterogeneity of BuMel effect on EFS across subgroups



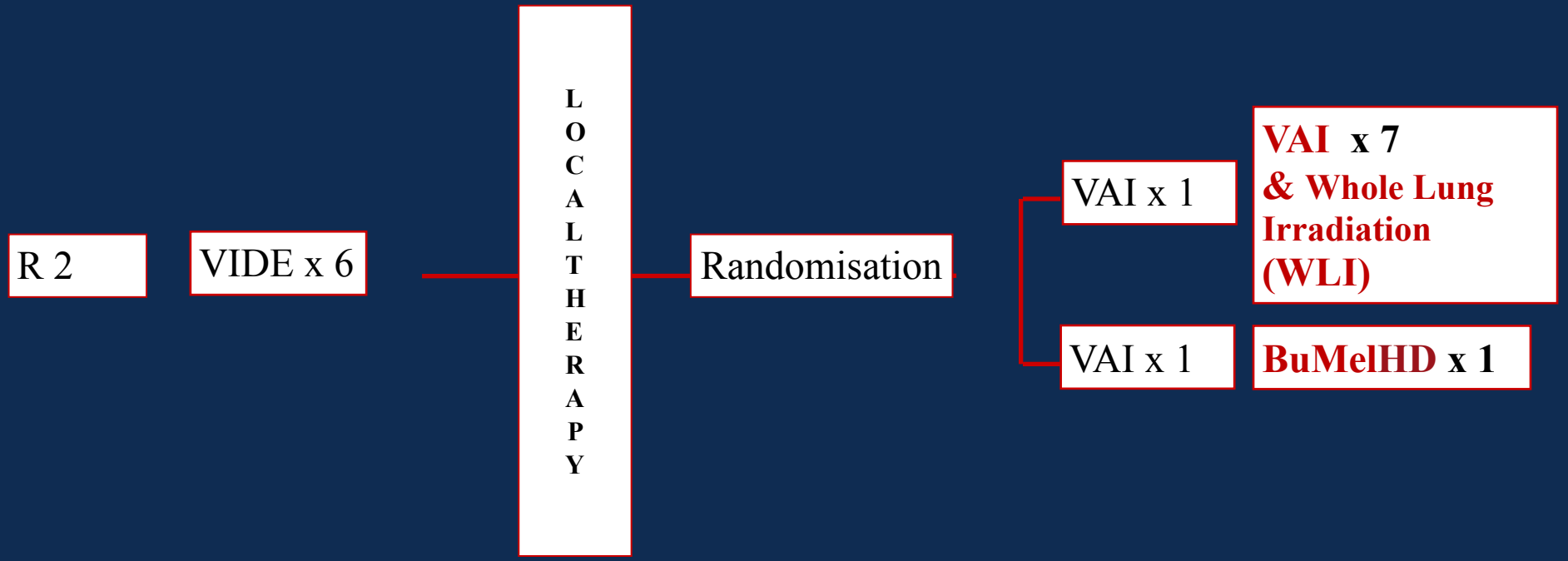
Acute toxicity analysis



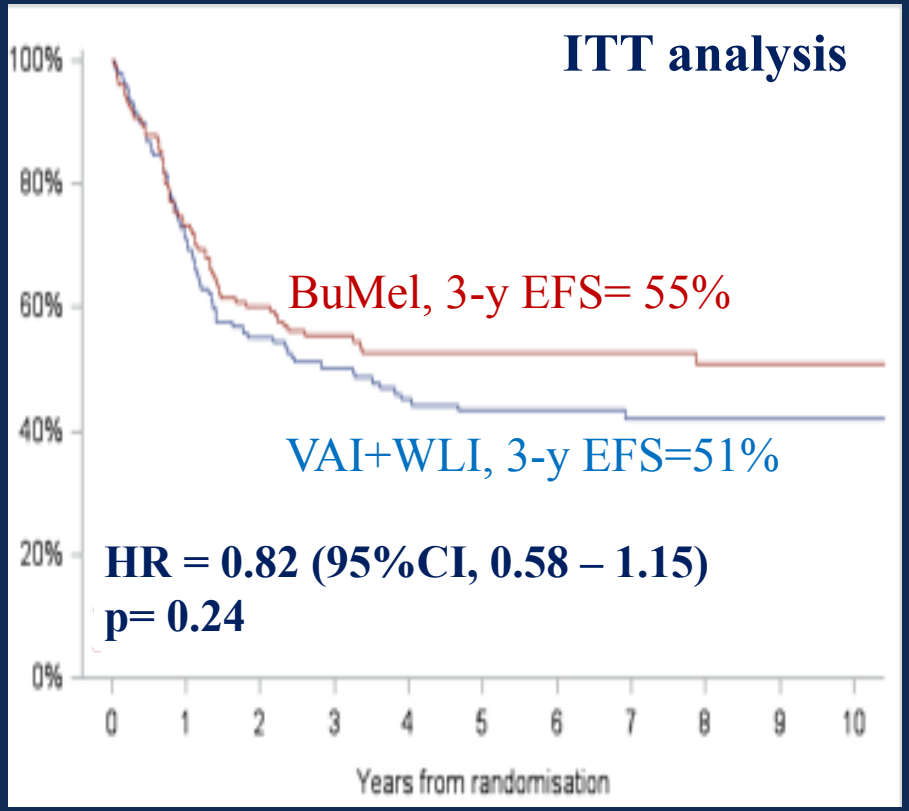
EURO-E.W.I.N.G 99 stratification

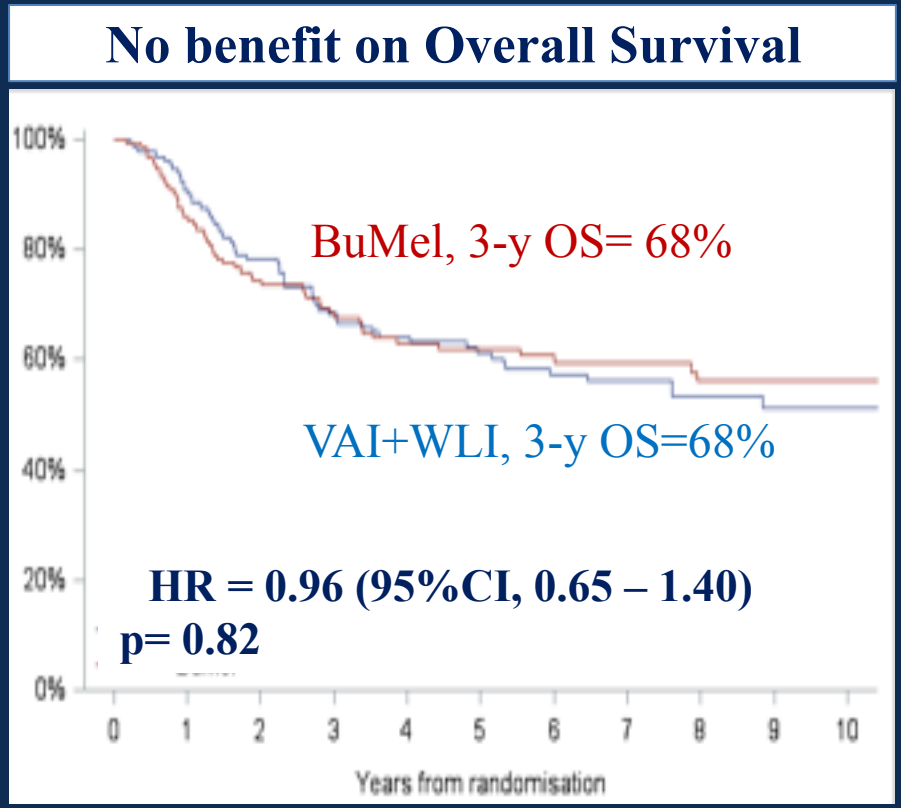


Randomization in R2 pulm



No Benefit of BuMel on Overall Survival

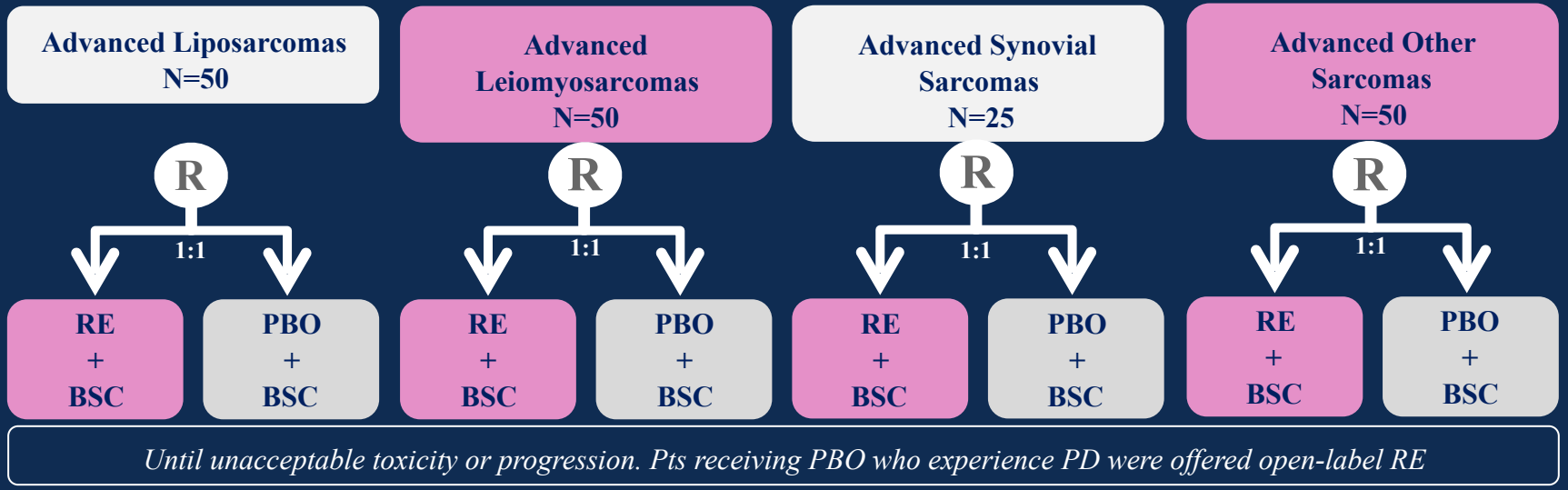




Regorafenib in doxorubicin-pre-treated patients with advanced soft tissue sarcomas: final analysis of a stratified double-blind placebo-controlled randomized phase II trial

N Penel, O Mir, A Italiano, J Wallet, JY Blay, F Bertucci, C Chevreau, S Piperno-Neumann, E Bompas, S Salas, C Perrin, C Delcambre, B Liegl-Atzwanger, M Toulmonde, S Dumont, T Ryckewaert, I Ray-Coquard, S Clisant, A Le Cesne, T Brodowicz from the French Sarcoma Group and Austria Sarcoma Platform

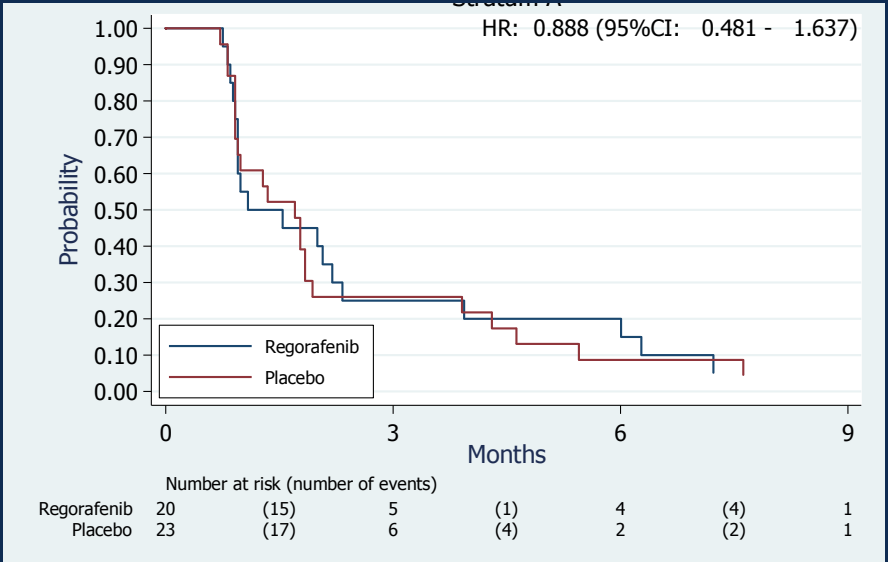
Study Design



- Randomized, double-blind, placebo-controlled, multi-center phase II trial with 4 parallel cohorts in pts with refractory STS – Preliminary results presented at last ASCO meeting
- Pts were assigned in a 1:1 ratio to receive either regorafenib plus BSC or placebo plus BSC

Liposarcoma

Progression-free survival



Regorafenib 1.1 (0.9-2.3)

Placebo 1.7 (0.9-1.8)

HR = 1.13 [0.48-1.63]

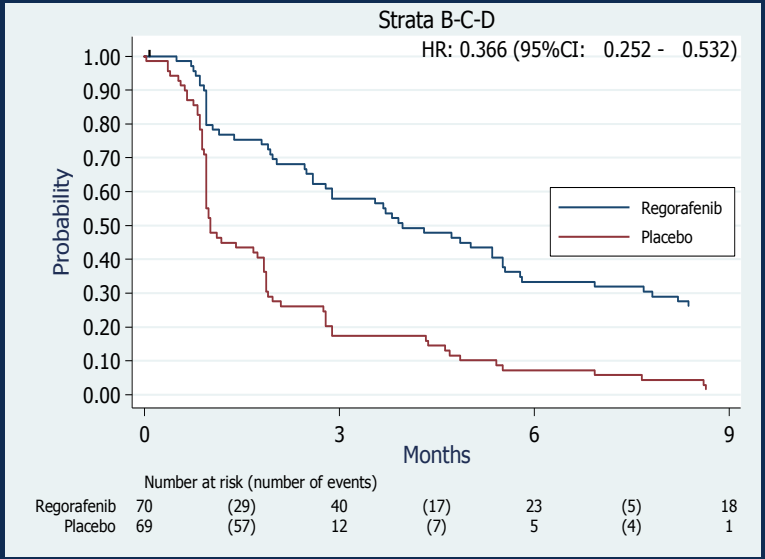
P=0.700

Same results observed with Pzb

Non-Adipocytic sarcoma: pooled analysis

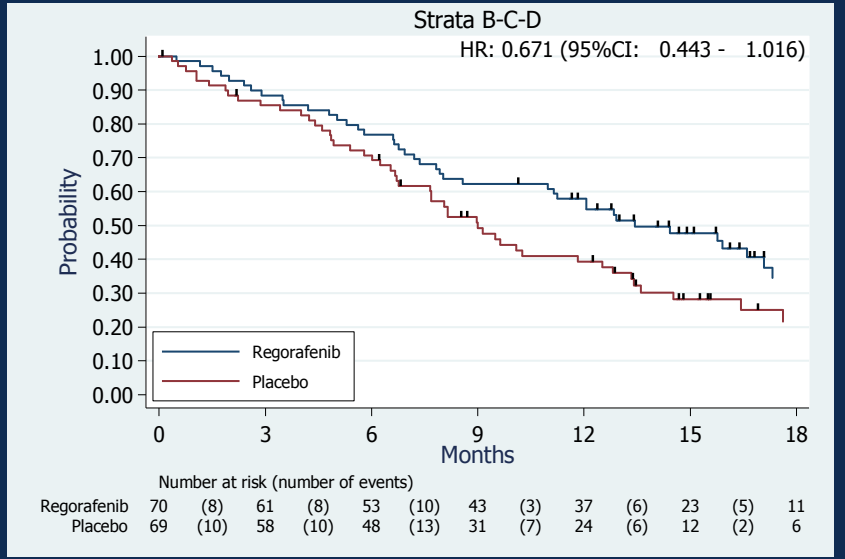
PFS

Regorafenib 4.0 (2.6-5.5)
Placebo 1.0 (1.0-1.8)
HR = 0.36 [0.26-0.53] **p<0.0001**



OS

Regorafenib 13.4 (8.6-17.3)
Placebo 9.0 (6.8-12.5)
HR = 0.67 [0.44-1.02] **p=0.060**

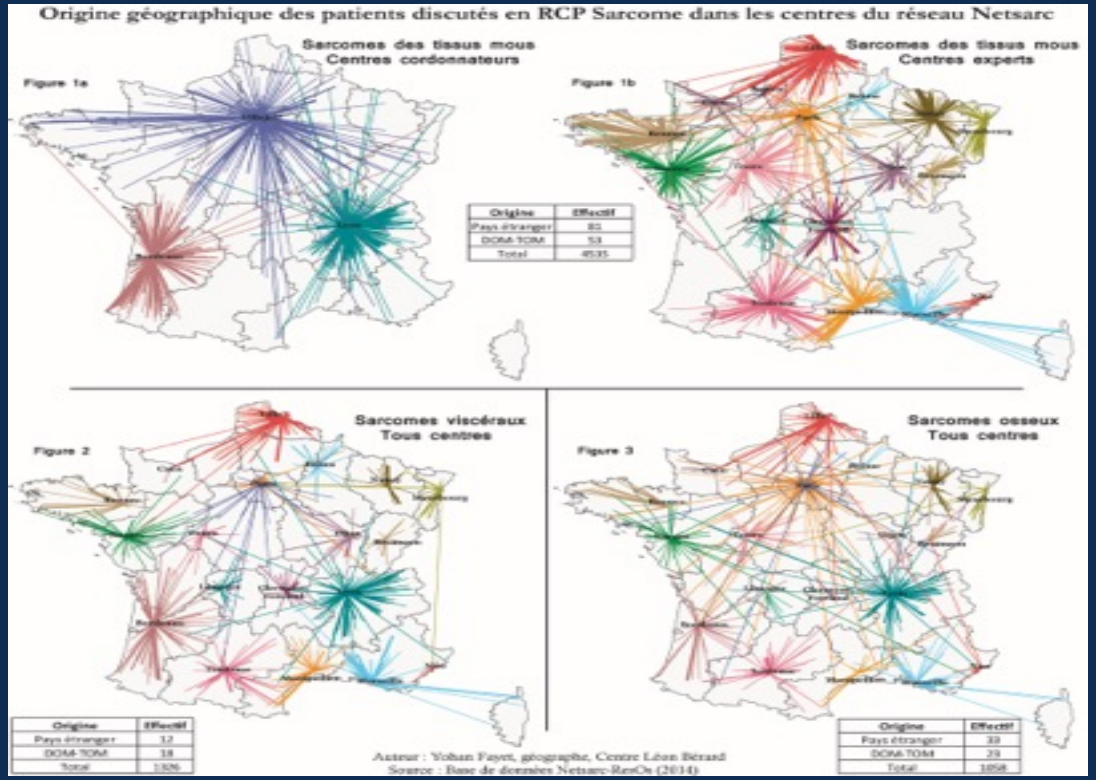


Improved sarcoma management in a national network of reference centers: Analysis of the NetSarc network on 13.454 patients treated between 2010 and 2014

Jean-Yves Blay, Axel Le Cesne, Nicolas Penel, Emmanuelle Bompas, Florence Duffaud, Christine Chevreau, Maria Rios, Pierre Kerbrat, Didier Cupissol, Philippe Anract, Jean-Emmanuel Kurtz, Celeste Lebbe, Nicolas Isambert, Francois Bertucci, Antoine Thyss, Sophie Piperno-Neumann, Pascale Dubray-Longeras, Francoise Ducimetiere, Jean-Michel Coindre, Antoine Italiano from the French Sarcoma Group

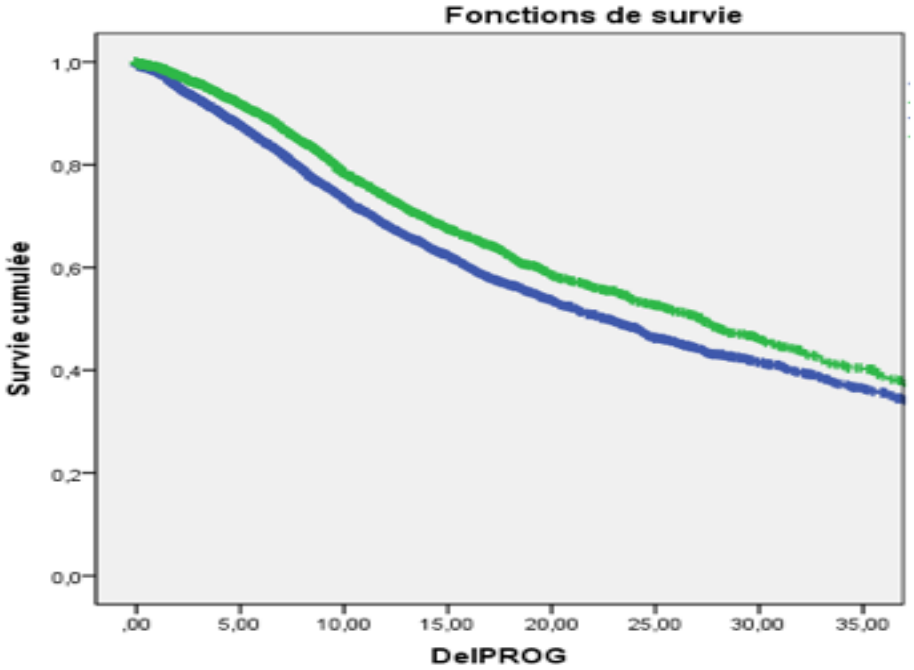
Origin of patients in MDT of NetSARC

These represent an estimated 78% of sarcoma case in France in 5 years.



Relapse free survival n=13454 pts

Patients whose primary surgery was performed in Netsarc centers
had R0, R1, R2 surgery in 49%, 27%, 7%
vs 24%, 31%, 21% in centers outside Netsarc (p<0.000001).



Logrank
p=0.0008

Inside (green) vs outside (blue) NETSARC

Patterns of care and outcome of metastatic soft-tissue sarcoma (STS) patients (pts) according to histological subtype and treatment setting: the METASARC study

Antoine Italiano, Axel Le Cesne, Jean-Yves Blay, Isabelle Ray Coquard, Olivier Mir, Maud Toulmonde, Philippe Terrier, Dominique Ranchere-Vince, Pierre Meeus, Eberhard Stoeckle, Charles Honoré, Paul Sargos, Marie-Pierre Sunyach, Cécile Le Péchoux, Antoine Giraud, Carine Bellera, Marion Savina, Jean-Michel Coindre

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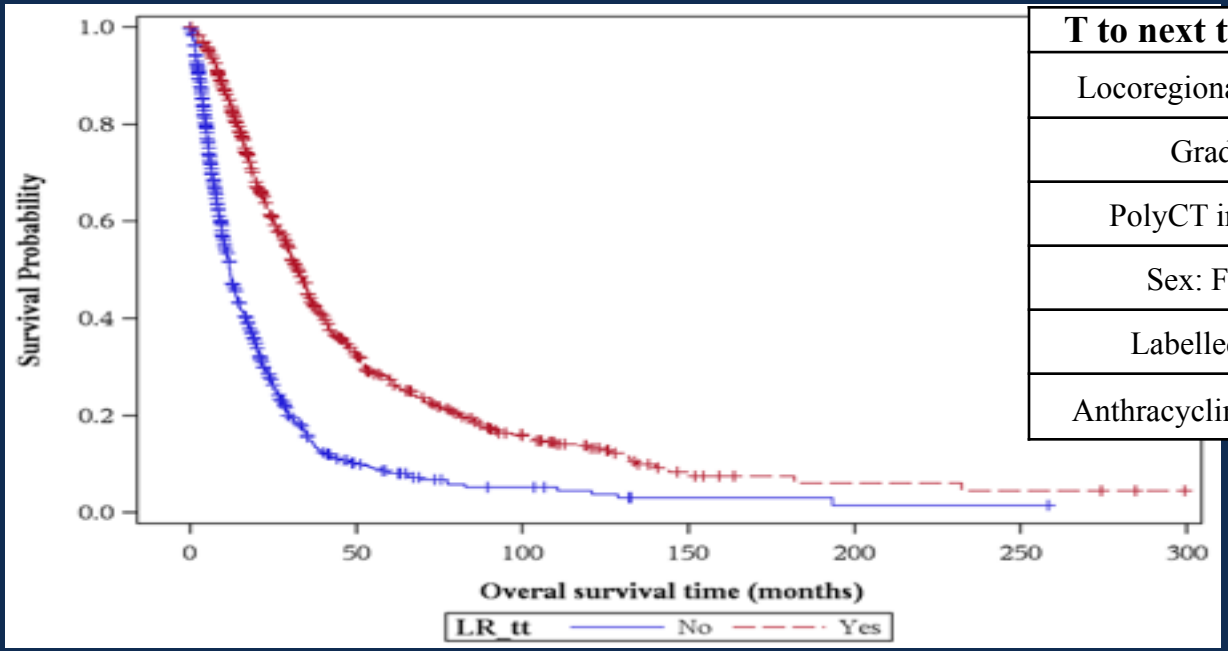
Patients with advanced STS: the METASARC study

	N = 2225	Comments
No treatment	625 (28%)	elderly
1st line	1600 (72%)	
2nd line	950	Lost: 41%
3rd line	650	Lost: 32%
4th line	496	Lost: 24%
5th line	232	
6th line	134	

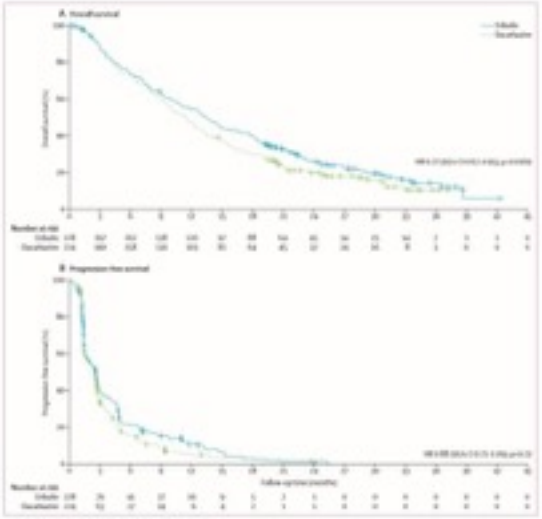
Impact of locoregional treatment of metastases on OS (patients treated with systemic treatment, n=1600)

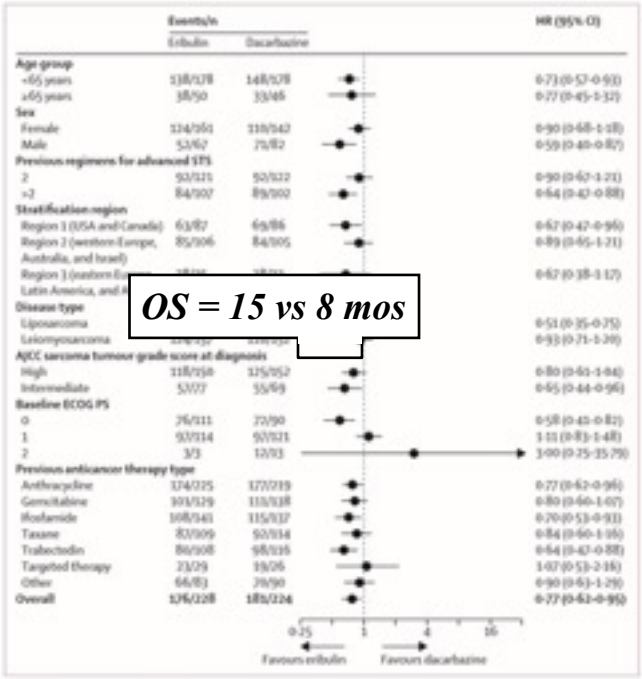


T to next tt (n=1600)	p	HR [IC95%]
Locoregional tt of mets	<.0001	0.485 [0.430; 0.547]
Grade: 3	<.0001	1.380 [1.226; 1.554]
PolyCT in 1st line	0.0048	0.821 [0.716; 0.942]
Sex: Female	0.0032	0.837 [0.744; 0.942]
Labelled drugs	0.0022	0.728 [0.594; 0.892]
Anthracycline in 1st line	0.0090	0.828 [0.718; 0.954]

Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial

Patrick Schöffski, Sant Chawla, Robert G Maki, Antoine Italiano, Hans Gelderblom, Edwin Choy, Giovanni Grignani, Veridiana Camargo, Sebastian Bauer, Sun Young Rha, Jean-Yves Blay, Peter Hohenberger, David D'Adamo, Matthew Guo, Bartosz Chmielowski, Axel Le Cesne, George D Demetri, Shreyaskumar R Patel



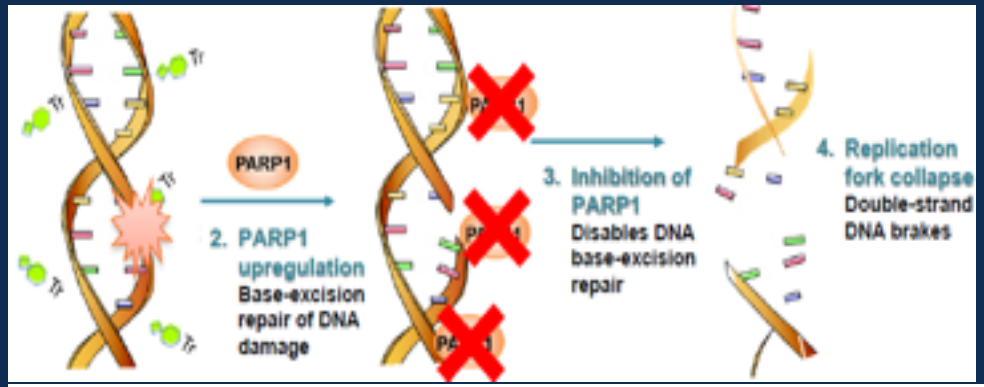


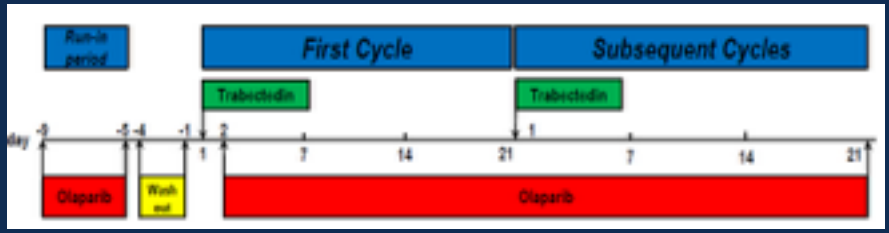
OS = 15 vs 8 mos

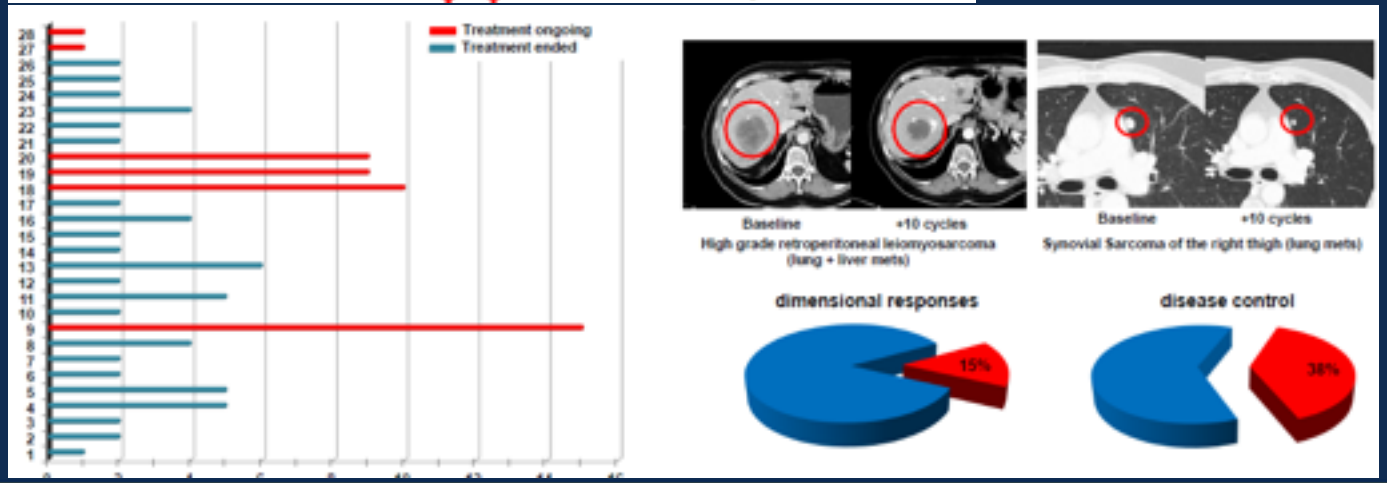
Lancet 2016 Feb 10 [Epub]

S. Hudgens (abstract 11015)

Trabectedin + olaparib: ISG phase 1b of trial







Recommended dose:
T: 1.3 mg/m2
O: 150 mg BID

Immunotherapy in Sarcoma: Where Do We Go From Here?

Breelyn A. Wilky, MD

Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine

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Timeline of Immunotherapy in Sarcoma

1890s

William Coley

1980 - 2005

Cytokines +/- chemo
- IL-2 (high dose)
- IFN-α/β
- mifamurtide

2005 - 2012

Vaccines
- Autologous tumor cells
- Dendritic cells
- GVAX

2010

Adoptive T cell therapy – NY-ESO-1^{+} synovial sarcoma

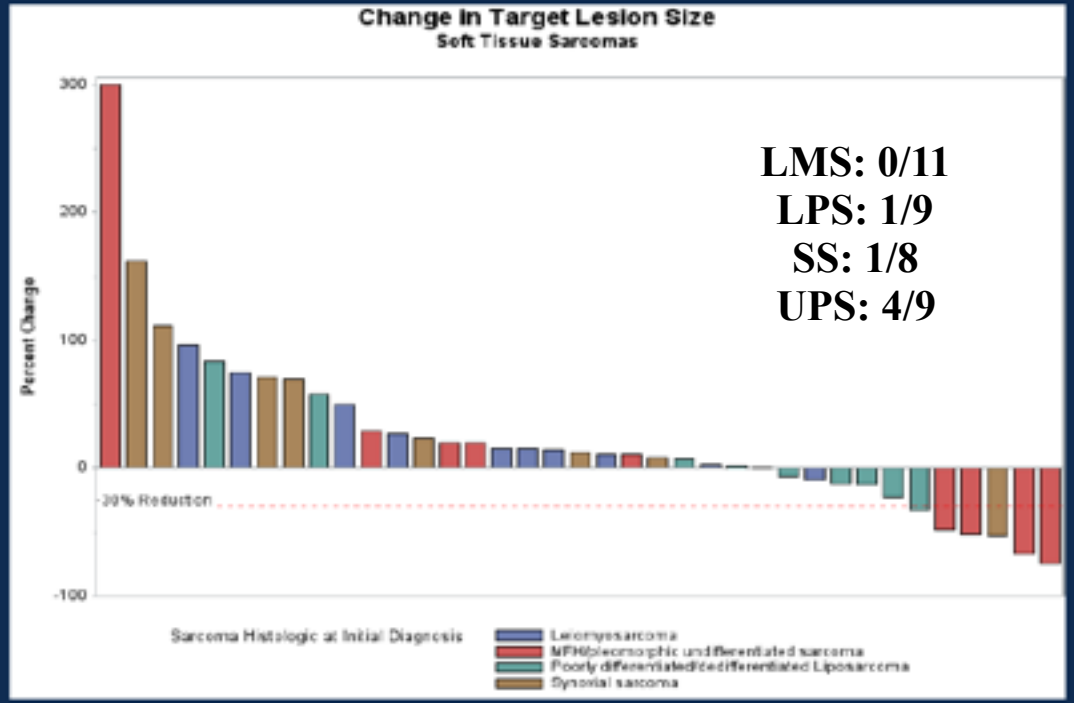
2013 - today

Checkpoint inhibitors

Wilky and Goldberg, Discov Med 2014

Abstract 1 – SARC 028 Pembrolizumab

- 11/37 with tumor regressions, UPS, dedifferentiated LPS, and synovial sarcoma
- Overall 19% ORR rate by RECIST, additional 40% of patients with best response of stable disease
  - Melanoma 33%
  - NSCLC 19%
  - >20% ORR gastric, bladder, head and neck

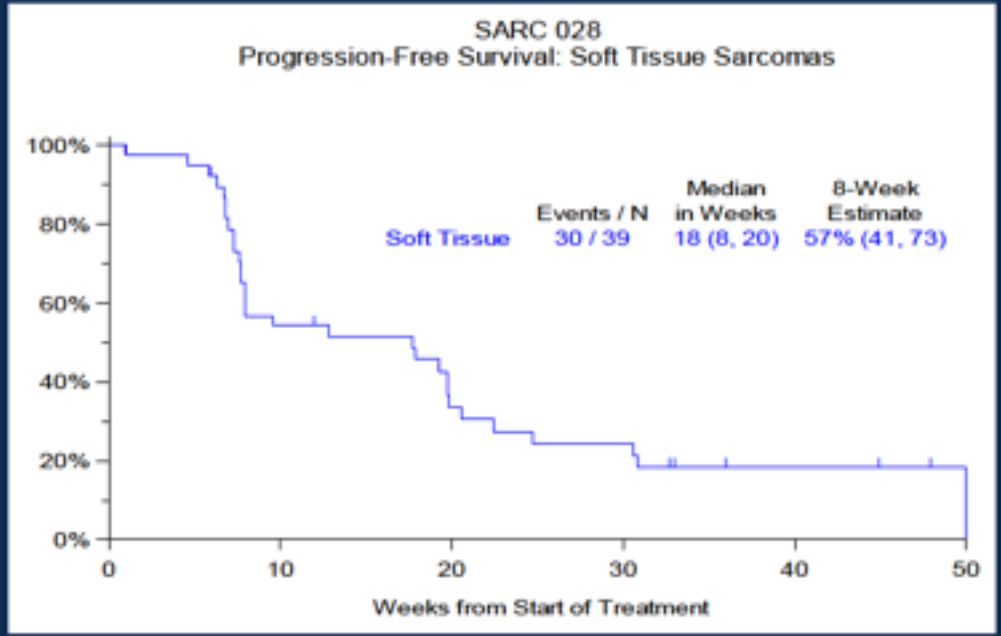


LMS: 0/11
LPS: 1/9
SS: 1/8
UPS: 4/9

Tawbi (abstract 11006)

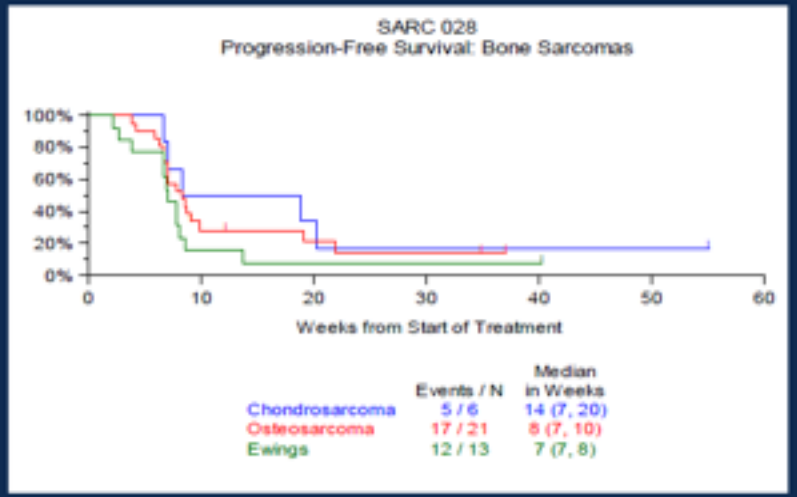
Abstract 1 – SARC 028 Pembrolizumab

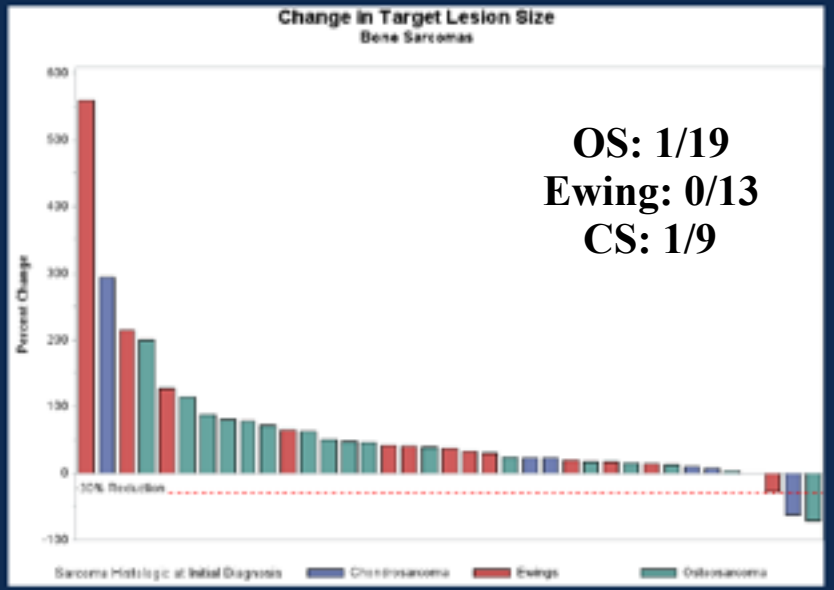
- Median F/U- 7.5 months
- **4-months PFR 44% [C.I., 22%-66%] statistically significant improvement relative to historical control PFR rate (20%)**



Abstract 1 – SARC 028 Pembrolizumab

- 3 patients with partial responses



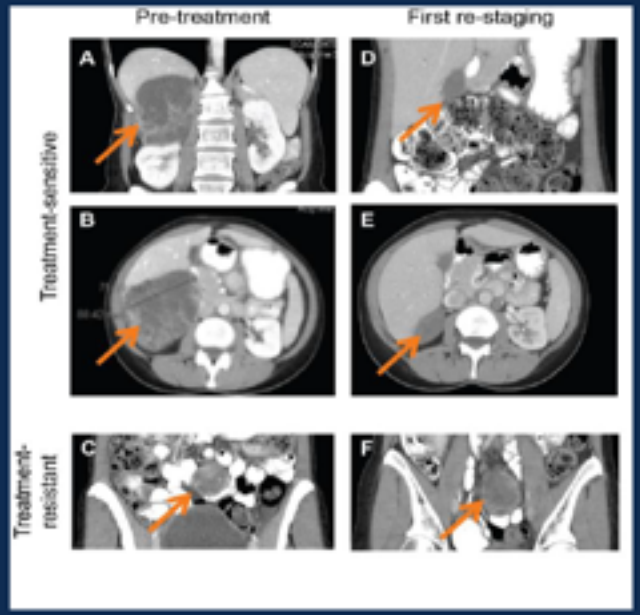


OS: 1/19
Ewing: 0/13
CS: 1/9

Tawbi (abstract 11006)

Abstract 2 – Phase 2 Nivolumab for uLMS

- 12 patients – small numbers
- All with progressive disease at 3 month scans
- Consistent with lack of response for LMS in SARC 028
- However one exceptional responder reported separately



S. George (abstract 11007)

Integrative assessment of expression/levels and prognostic value of PD-L1, IDO1 and Kynurenine in 328 Primary Soft Tissue Sarcomas with Genomic Complexity

Maud Toulmonde, Julien Adam, Alban Bessède, Dominique Ranchère-Vince, Valérie Velasco, Véronique Brouste, Jean-Yves Blay, Olivier Mir and Antoine Italiano, on behalf of the GSF-GETO French Sarcoma Group

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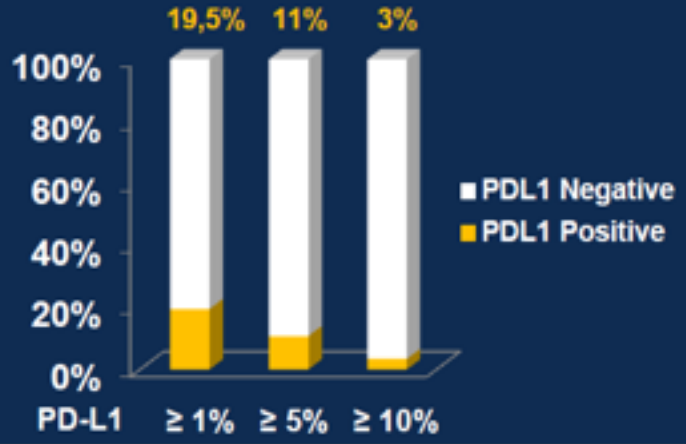
PD-L1 Expression in Sarcoma

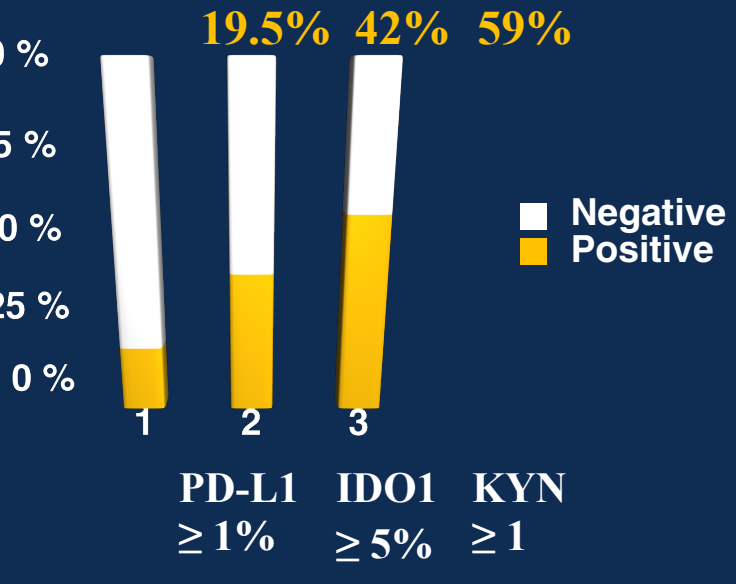
- About 20% positivity in sarcomas
- Problems with PD-L1 as biomarker (staining, transient expression, heterogeneity)
- May not be required for response
- Await analysis of responders in Tawbi trial

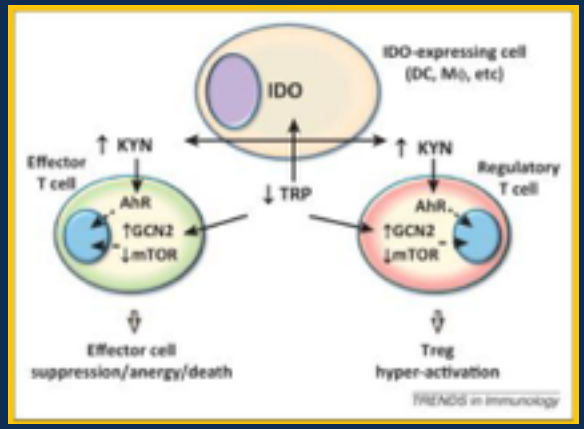


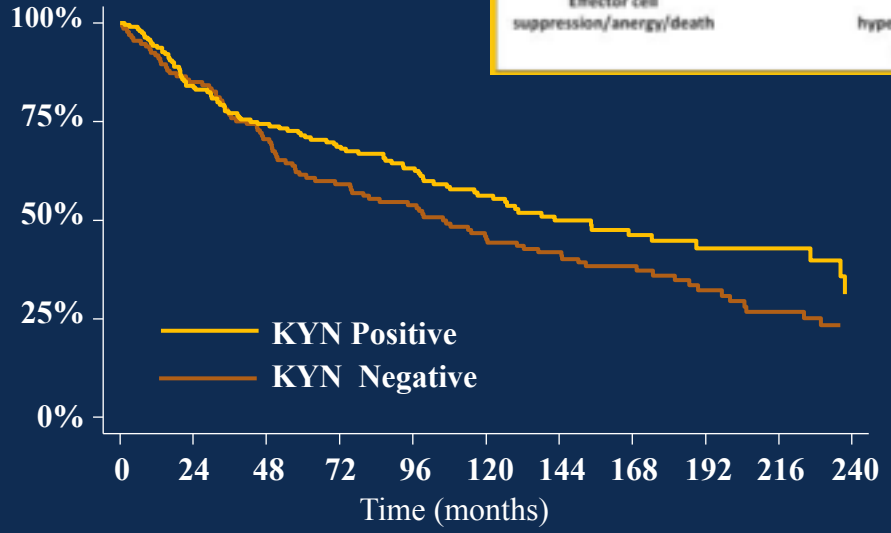
	IHC PDL1 % positive		IHC PD1 % positive		IHC PDL2 % positive	
	malignant cells	non-malignant cells	malignant cells	non-malignant cells	malignant cells	non-malignant cells
7	0	NA	0	NA	90	na
9	0	20	0	0	80	0
2	1	2	0	0	20	5
6	0	10	0	0	40	0
1	0	5	0	0	90	0
10	0	na	0	0	80	na
8	0	20	0	0	10	0
11	0	20	0	5	30	0
3	10	1	0	0	20	0
5	20	0	0	5	90	0

Results – Prognostic Factors

Potential role of Kynurénine on OS







IDO1 was more expressed in UPS than LMS (48% vs 30% p=0.01)

Potential Predictive Biomarkers for Checkpoint Blockade

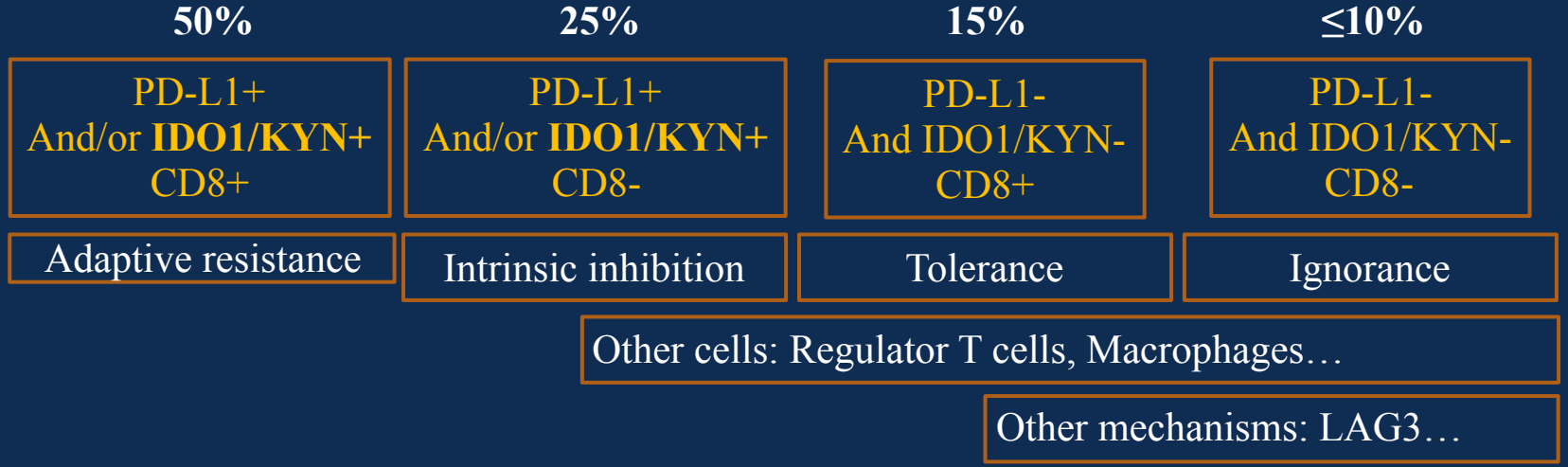
- Tumor PD-L1 expression? Most tumors, but some responders even in PD-L1 negative tumors (RCC, melanoma, squamous NSCLC)
- PD-1/PD-L1 expression on TIL (Bladder, melanoma)
- Presence of $CD8^+$ TIL, particularly at tumor invasive margin (melanoma)
- High somatic mutation burden (MMR deficient colorectal cancer, melanoma, NSCLC)
- Low Tregs/MDSC in tumor OR peripheral blood (melanoma)
- Elevated IDO1/2 and KYN (linked to anti-CTLA4 activity in melanoma)
- And many more…

Meng et al, Cancer Treat Rev 2015; Hamid et al J Transl Med 2011

Results – Prognostic Factors

Potential role of IDO1/Kyn and CD8 effector cells?

- STS with genomic complexity have heterogeneous immune infiltrates.



Additional biomarker / immunocorrelative studies are critical for future trials to further delineate immunoactive sarcomas (Breeklin A. Wilky, discutant)

Adapted from Snolz et al. *Clin Cancer Res.*, 2013

Merci