The baseline total metabolic volume in Hodgkin lymphoma

Olivier Casasnovas

Hematologie clinique CHU Dijon France

Rational

- Tumor bulk on baseline CT was shown to impact the outcome of patients with Hodgkin lymphoma *(Gobbi P, JCO 2001)* but due to feasibility concerns was not implemented in the routine management of HL

- The total metabolic tumor volume (TMTV) assessed on the baseline FDG-PET is a novel approach of tumor burden measurement quantifying the most active part of the tumor

- TMTV has been reported to influence HL outcome in retrospective series *(Song MK, Cancer Sci2013; Kanoun S, EJNM 2014)*

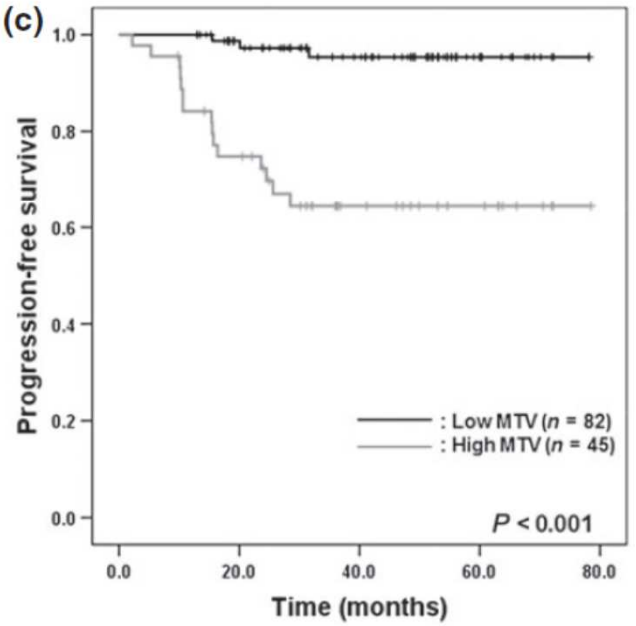
Cancer Science
The official journal of the Japanese Cancer Association

Metabolic tumor volume by positron emission tomography/computed tomography as a clinical parameter to determine therapeutic modality for early stage Hodgkin's lymphoma

Moo-Kon Song,[1] Joo-Seop Chung,[1,11] Je-Jung Lee,[2] Shin Young Jeong,[3] Sang-Min Lee,[4] Jun-Shik Hong,[5] Ari Chong,[6] Joon-Ho Moon,[7] Ji-Hyun Kim,[8] Seok-Mo Lee,[9] Seong Jang Kim[10] and Ho-Jin Shin[1]

	Total
No. patients (%)	127
Median age, (range) (years)	42 (18–78)
Sex, *n* (%)	
Male	75 (59.1)
Female	52 (40.9)
Histology, *n* (%)	
Nodular sclerosis	55 (43.3)
Lymphocyte rich	20 (15.7)
Lymphocyte depleted	11 (8.7)
Mixed cellularity	41 (32.3)
Stage, *n* (%)	
I	27 (21.3)
II	100 (78.7)
ECOG PS ≥2	11 (8.7)
B symptoms, *n* (%)	24 (18.9)
ESR, *n* (%)	
≥50 mm/L	31 (24.4)
No. involved sites (%)	
1–2	49 (38.6)
≥3	78 (61.4)
EN site involvement, *n* (%)	30 (23.6)
Mediastinum	19 (14.9)
Other	11 (8.7)
Bulky disease, *n* (%)	27 (21.3)

Median TMTV (SUVmax≥2.5) = 146 ml
Cut-off value = 198 ml



Eur J Nucl Med Mol Imaging (2014) 41:1735–1743
DOI 10.1007/s00259-014-2783-x

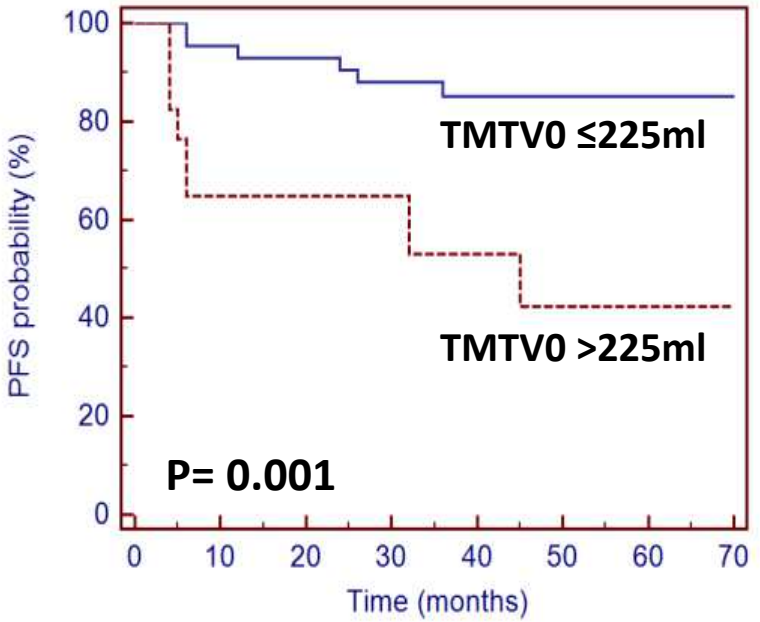
ORIGINAL ARTICLE

Baseline metabolic tumour volume is an independent prognostic factor in Hodgkin lymphoma

Salim Kanoun · Cédric Rossi · Alina Berriolo-Riedinger · Inna Dygai-Cochet · Alexandre Cochet · Olivier Humbert · Michel Toubeau · Emmanuelle Ferrant · François Brunotte · René-Olivier Casasnovas

Characteristic	TMTV0 >225 ml (n=17)	TMTV0 ≤225 ml (n=42)	p value
Age at diagnosis (years), median (range)	31 (17 – 63)	37.5 (16 – 76)	NS
Gender, n (%)			
Male	14 (82)	26 (62)	NS
Female	3 (18)	16 (38)	
Histological type, n (%)			
Lymphocyte-rich	1 (6)	4 (9)	NS
Mixed cellularity	2 (12)	5 (12)	
Nodular sclerosis	12 (70)	33 (79)	
Unclassified	2 (12)	0	
Ann Arbor stage, n (%)			
I	1 (6)	4 (10)	NS
II	2 (12)	15 (36)	NS
III	2 (12)	8 (19)	NS
IV	12 (71)	15 (36)	<0.025
Bulky tumour (diameter ≥10 cm), n (%)	7 (41)	2 (5)	<0.002
IPS ≥3, n (%)	14 (82)	22 (52)	0.04

Median TMTV (41% SUVmax) = 117 ml



Study Objective

- **To analyse the prognosis value of TMTV** in the cohort of young patients with advanced Hodgkin lymphoma included **in the AHL2011 trial** (NCT00498043)

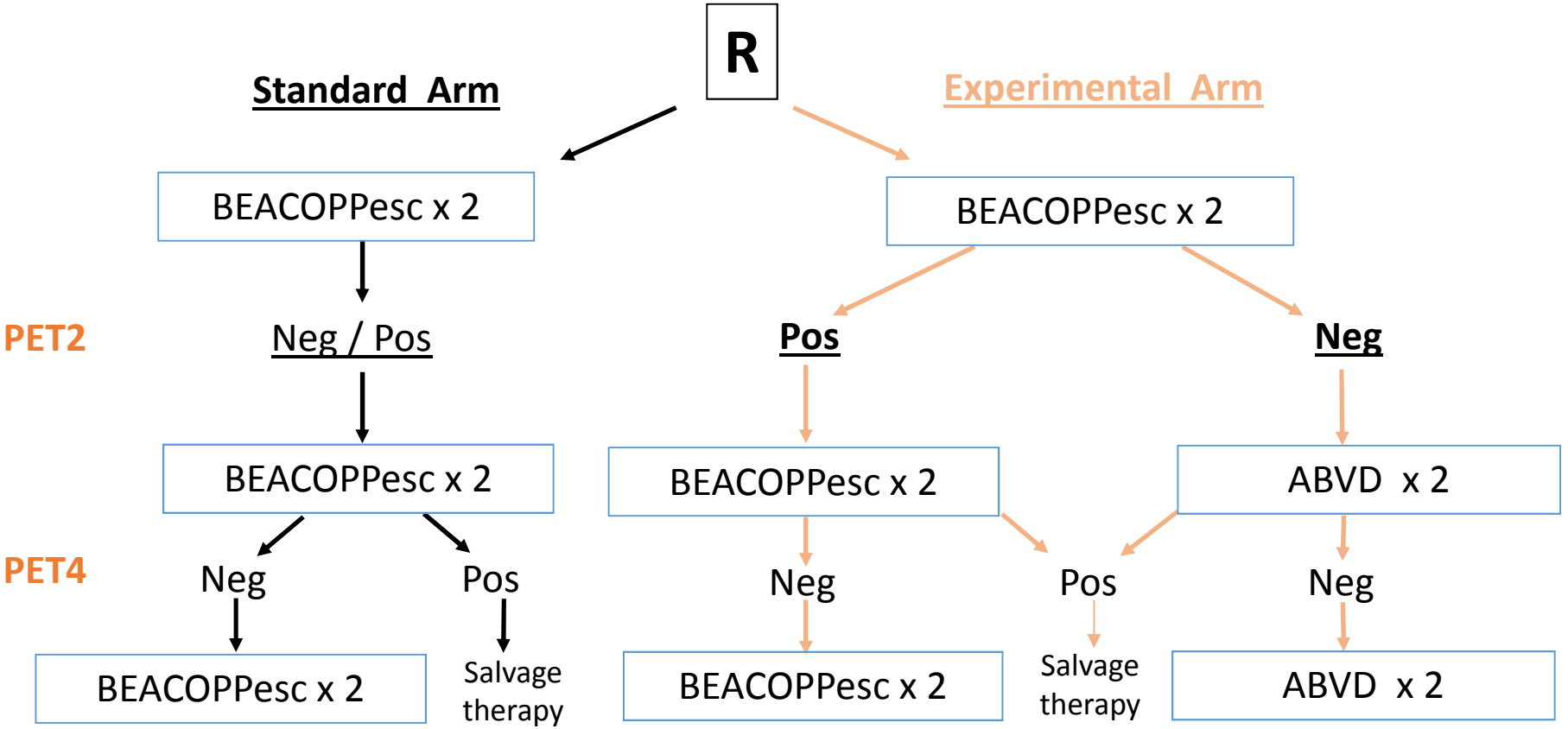
- 823 patients have been enrolled in the AHL2011 trial: 782 patients were eligible for the planned interim analysis *(Casasnovas, ASH 2015, abs 577)*

- **392 patients eligible** for the present study:
  - Pathology review with a confirmed diagnosis of HL
  - Baseline PET images available for central review and TMTV computation
  - Randomly divided in a training (n = 262) and a validation sets (n = 130) to test separately the prognosis impact of TMTV

Casasnovas RO, ASCO 2016; Abs 7509

AHL 2011: Study design

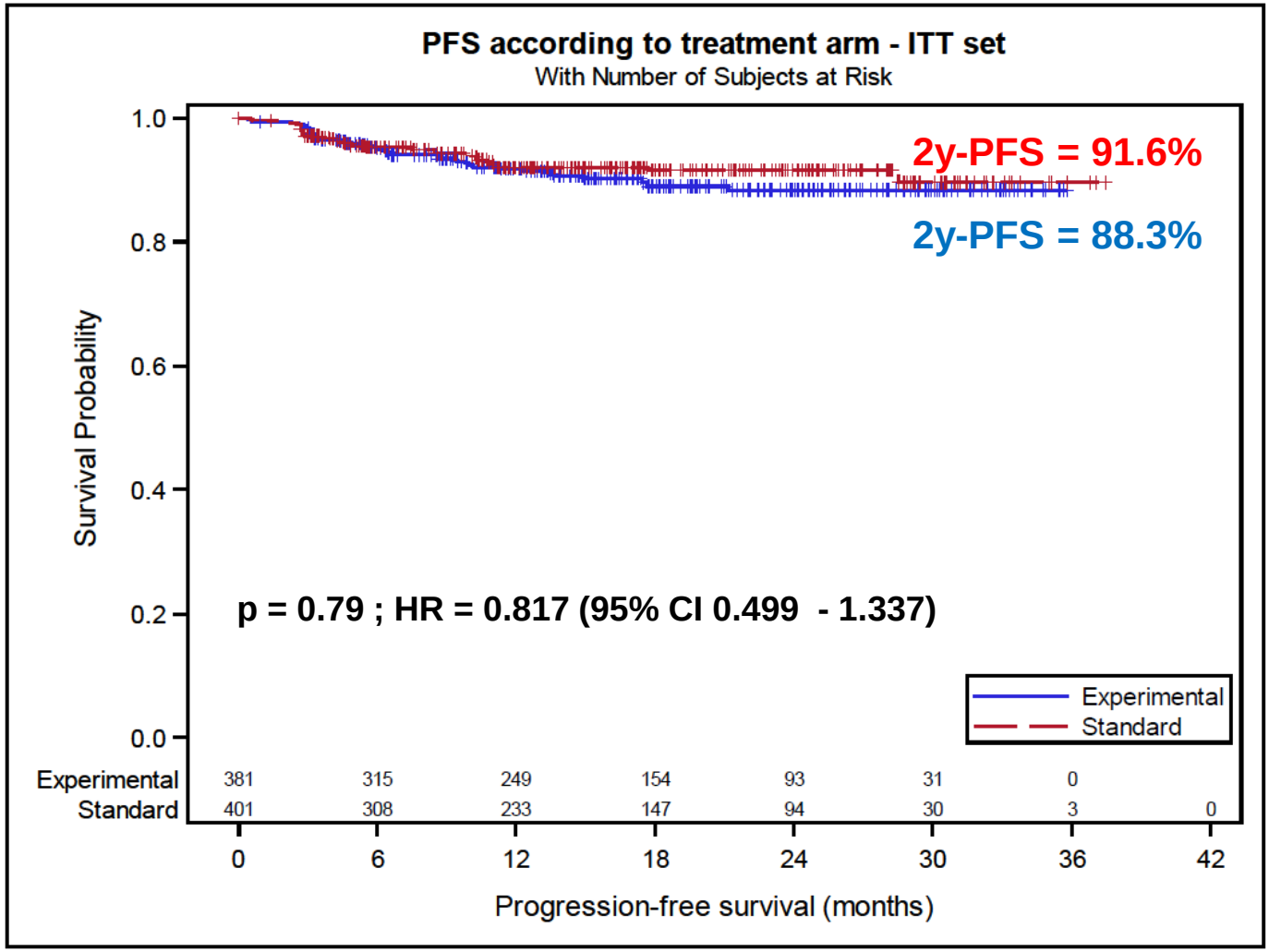
Randomized phase III
HL: 16-60y, Stage: III, IV, IIB with risk factors



NCT01358747

Non-inferiority assumption

AHL 2011: PFS according to treatment arm

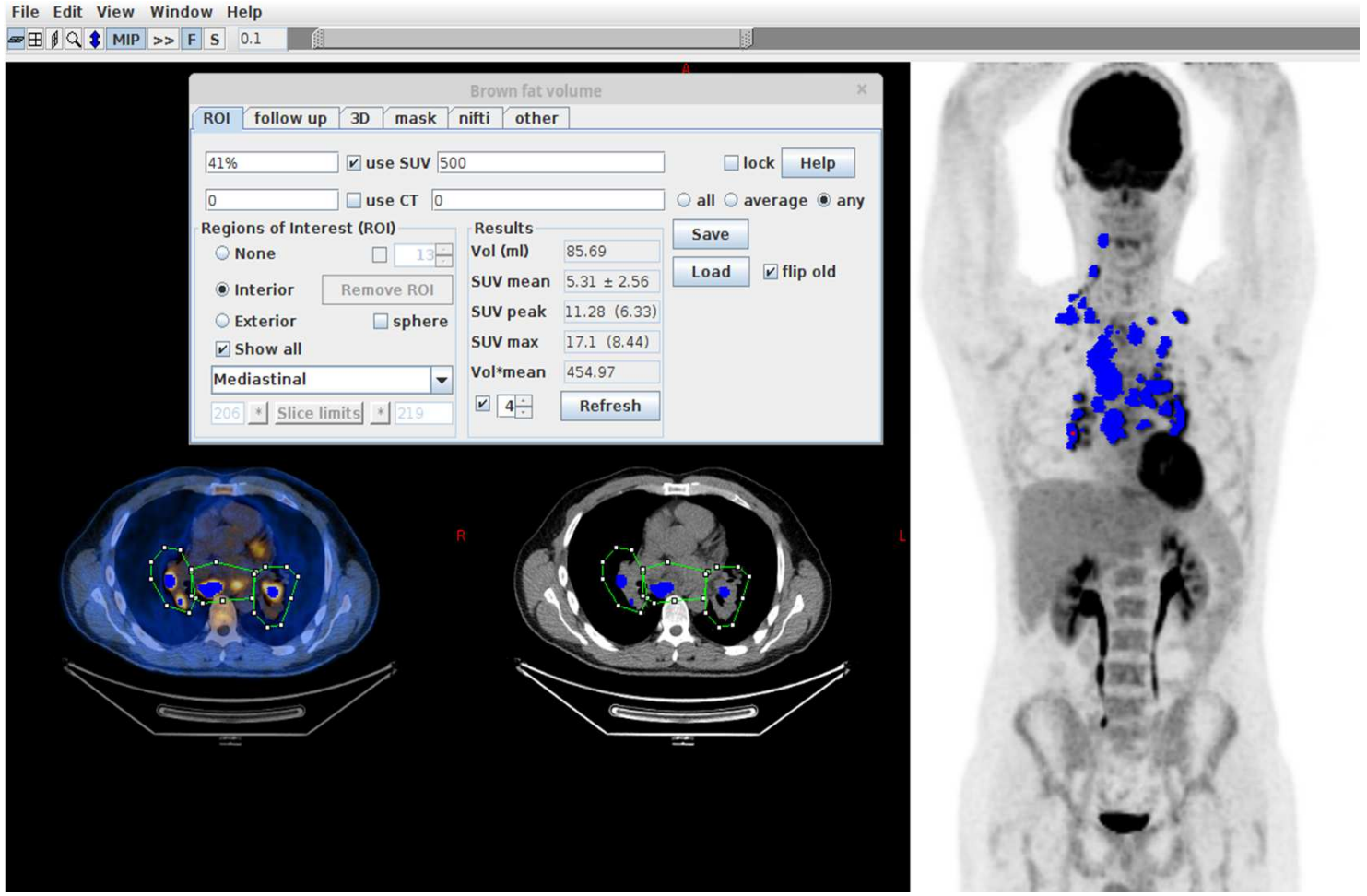


Median follow-up
16.3 months (0.1 – 37.4)

Casasnovas O, ASH 2015, abs 577

OC1

The Beth israel plug-in



Free available software

More suitable than Keosys software for TMTV computation while providing similar results

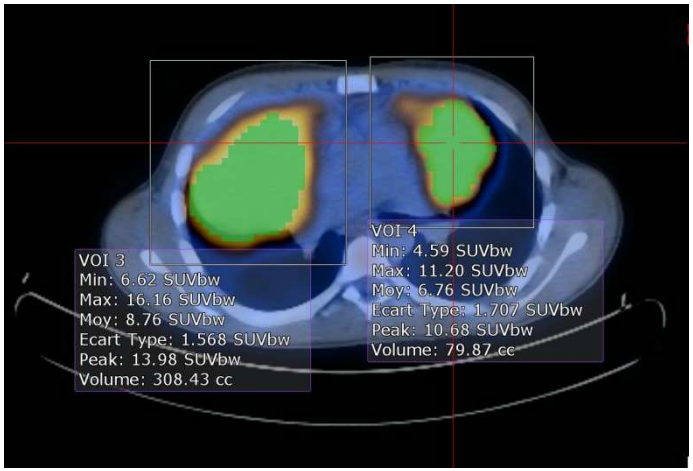
Kanoun S, PLoS One 2015

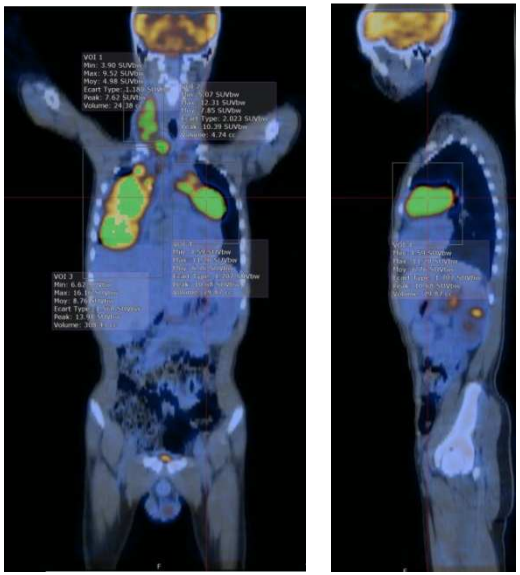
Diapositive 8

OC1 Olivier Casasnovas; 19/09/2016

TMTV Assessment

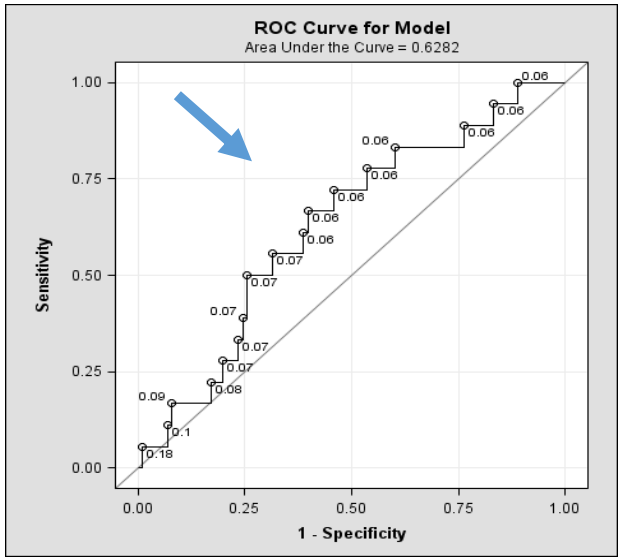
- A region of interest (ROI) was drawn around each foci FDG uptake.
- In each ROI, voxels presenting a threshold of 41% SUVmax were incorporated to define tumor volumes *(Meignan M, EJNM 2014)*
- Extranodal involvement :
  - the liver, lung and bone marrow were considered involved only if there was focal uptake,
  - Spleen involvement was considered if there was focal uptake or diffuse uptake >150 % of the liver background.
- All the individual tumors volume were added to compute the TMTV





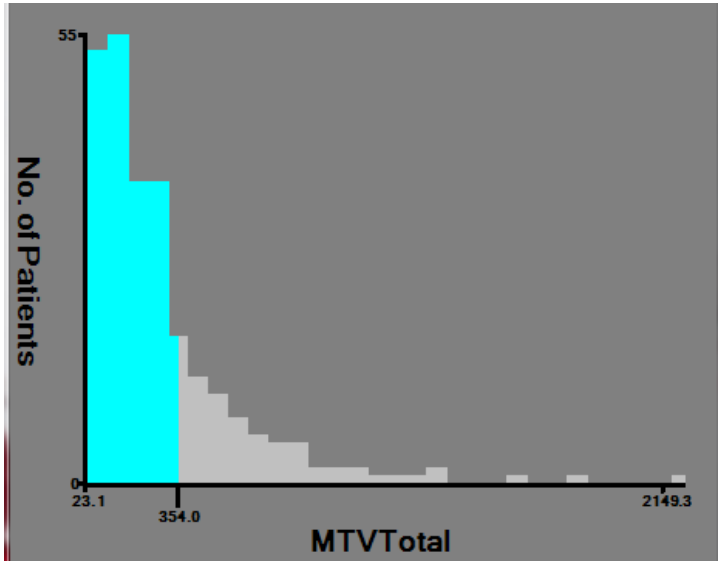
TMTV cut-off

ROC



AUC = 0.6345; p = 0.01

Xtile



Relative Risk: 2.69

<u>Cut-off 350 ml</u>
Sensitivity = 56%
Specificity = 64%

Casasnovas RO, ASCO 2016; Abs 7509

Patients characteristics in the training and validation sets

		Training set N=262		Validation set N=130		All N=392	
Age (Years)							
	Median	30		30		30	
	Min ; Max	16 ; 60		16 ; 60		16 ; 60	
Sex							
	Male	171	65%	78	60%	249	64%
	Female	91	35%	52	40%	143	36%
Performance Status (ECOG)							
	0	115	44%	70	54%	185	47%
	1	125	48%	47	36%	172	44%
	2	20	8%	13	10%	33	8%
Ann Arbor Stage IV							
	No	111	42%	53	41%	164	42%
	Yes	151	58%	77	59%	228	58%
B Symptoms							
	No	85	32%	45	35%	130	33%
	Yes	177	68%	85	65%	262	67%
LDH Level							
	Normal	157	62%	86	69%	243	65%
	> Upper Limit	96	38%	38	31%	134	36%
IPS Group							
	0-2	108	42%	51	39%	159	41%
	≥ 3	150	58%	79	61%	229	59%
Arm							
	Standard Treatment	137	52%	69	53%	206	53%
	PET-driven Treatment	125	48%	61	47%	186	47%

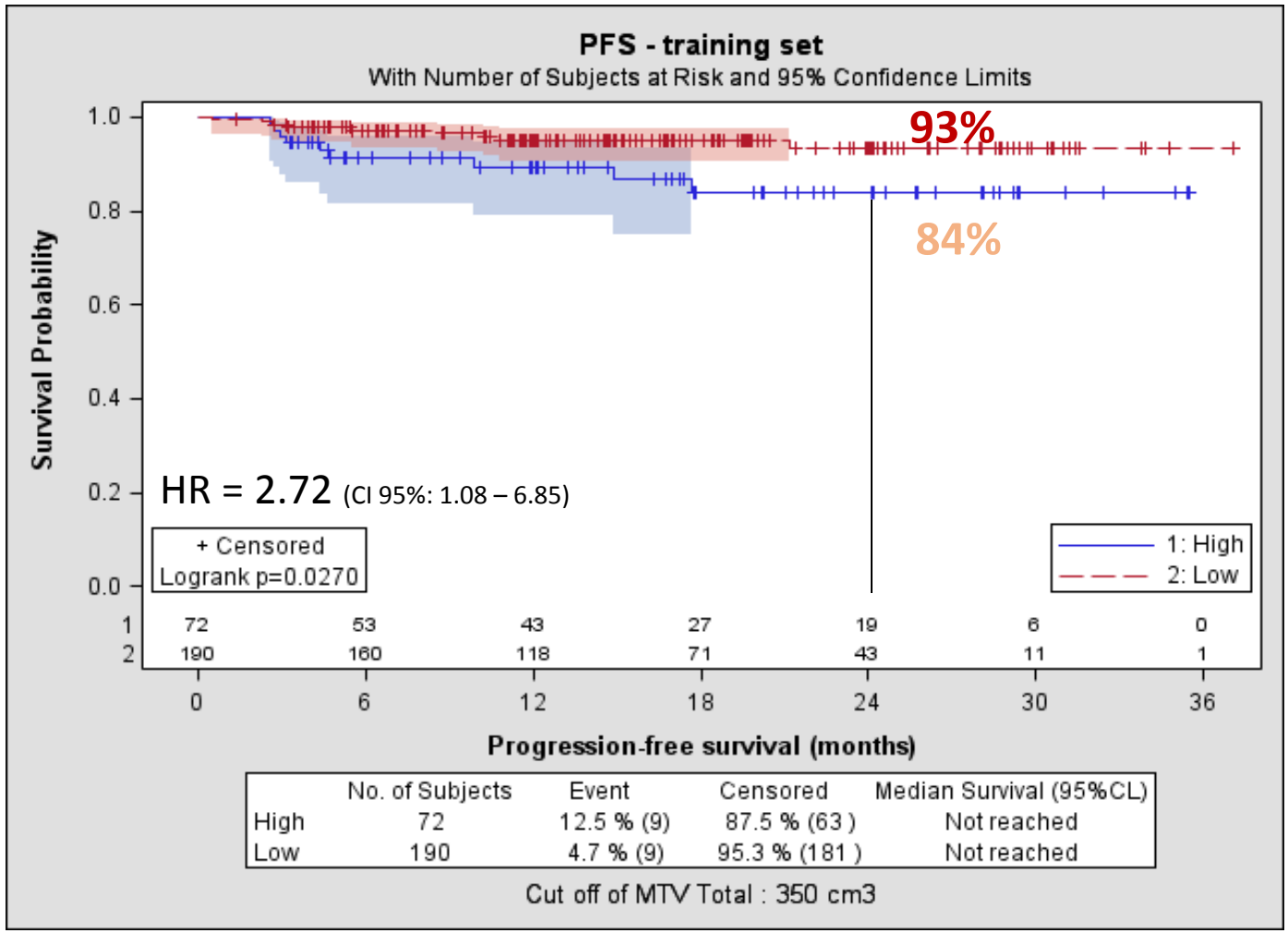
Casasnovas RO, ASCO 2016; Abs 7509

TMTV in the training and validation sets

	Training set N=262		Validation set N=130		All N=392	
TMTV						
median (range) - ml	**212 (23 - 2149)**		**171 (25 - 1861)**		**200 (23 - 2149)**	
Low	190	73%	100	77%	290	74%
High	**72**	**27%**	**30**	**23%**	**102**	**26%**

Casasnovas RO, ASCO 2016; Abs 7509

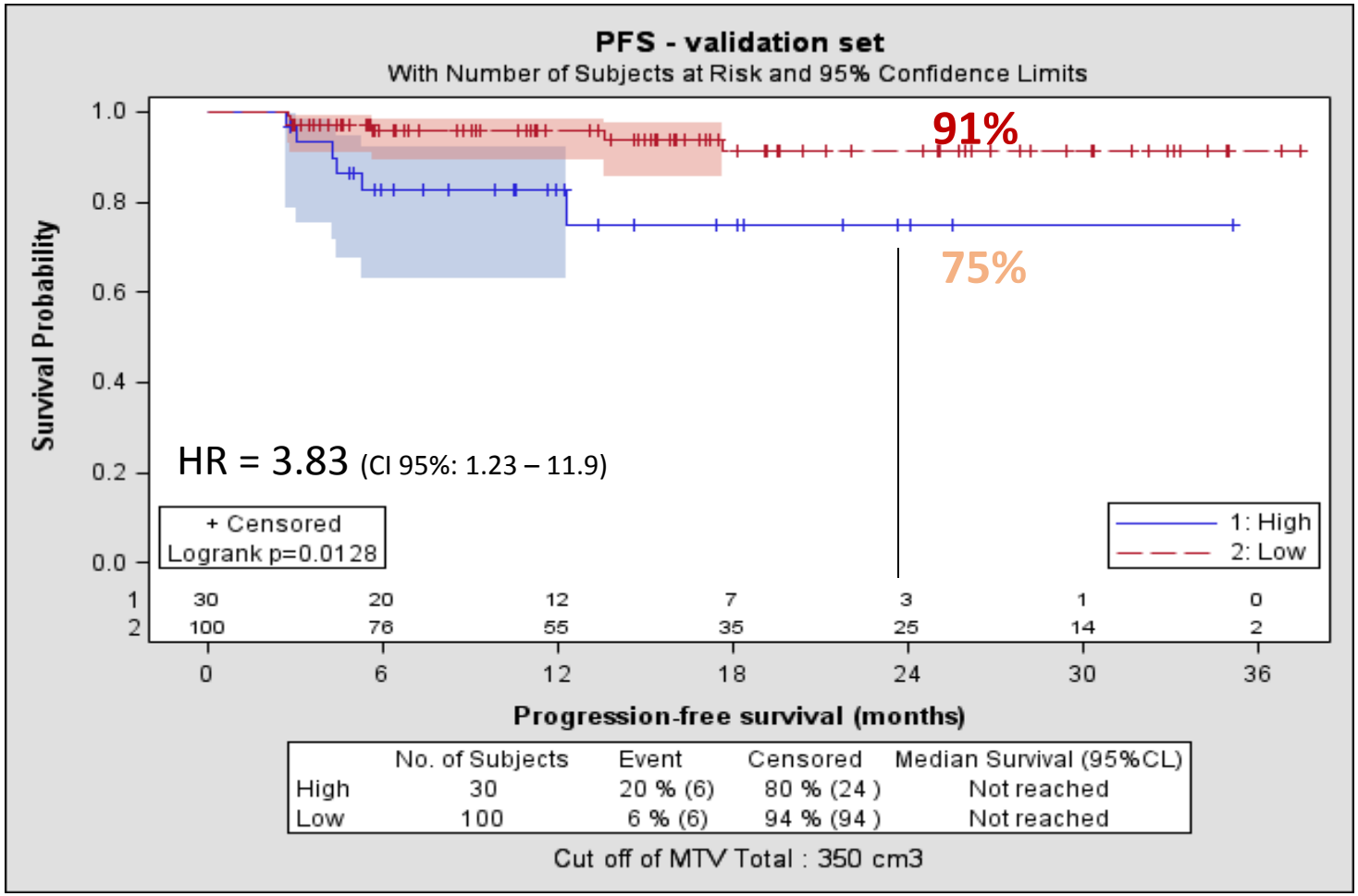
PFS according to the TMTV: training set



27% High TMTV

Casasnovas RO, ASCO 2016; Abs 7509

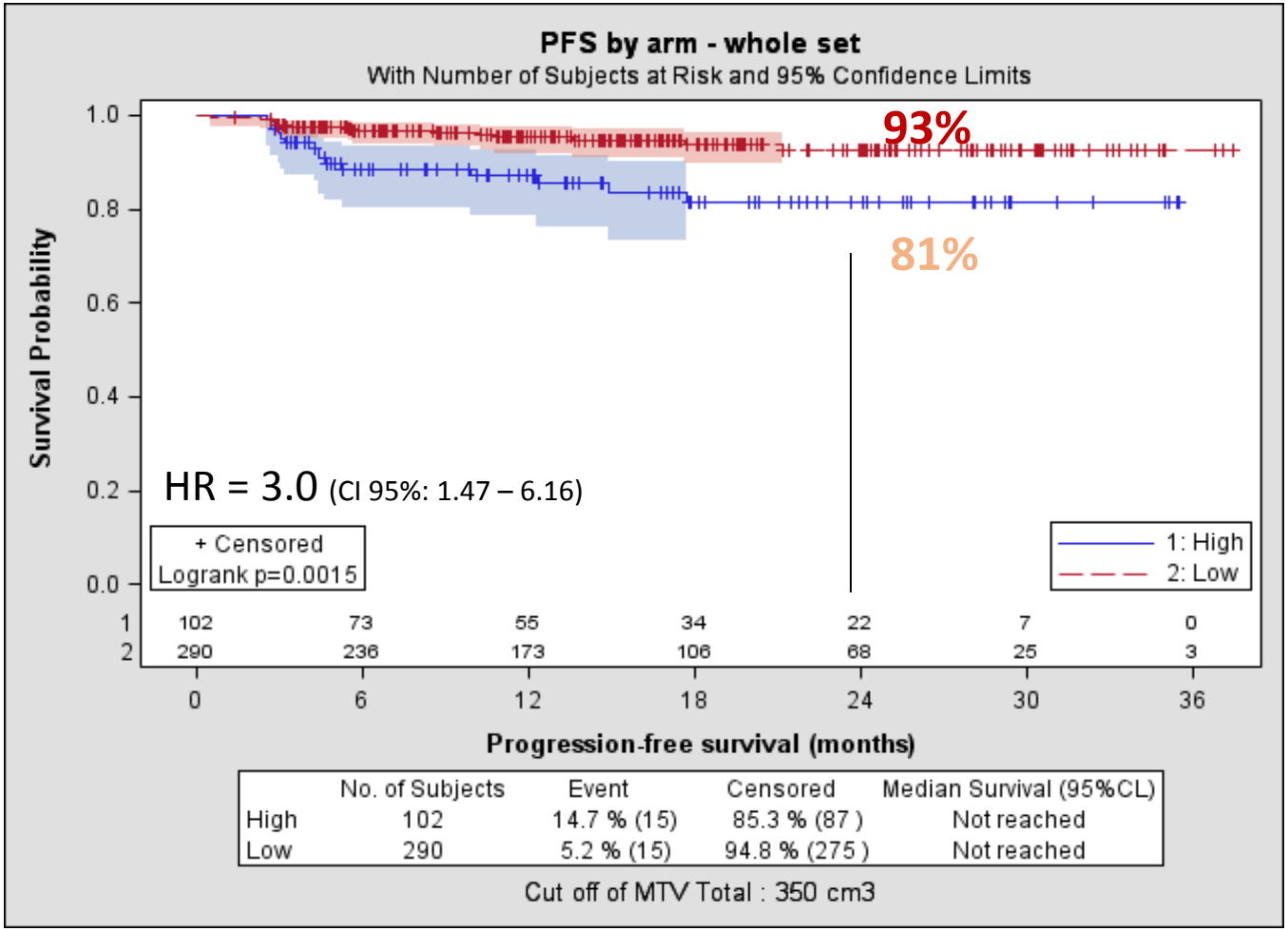
PFS according to the TMTV: validation set



23% High TMTV

Casasnovas RO, ASCO 2016; Abs 7509

PFS according to the TMTV: whole cohort



26% High TMTV

Casasnovas RO, ASCO 2016; Abs 7509

Patients characteristics according to TMTV

		Low TMTV N=290		High TMTV N=102		p
Gender	**Male**	**167**	**58%**	**82**	**80%**	**<0.00003**
	Female	123	42%	20	20%	
Performance Status: ECOG	**0**	146	50%	39	38%	
	1	116	41%	56	55%	NS
	2	26	9%	7	7%	
Ann Arbor Stage IV	**No**	138	48%	26	25%	
	Yes	**152**	**52%**	**76**	**75%**	**0.0001**
B Symptoms	**No**	114	39%	16	16%	
	Yes	**176**	**61%**	**86**	**84%**	**<0.00001**
LDH Level	**Normal**	199	72%	44	44%	
	> Upper Limit	**79**	**28%**	**55**	**56%**	**0.00003**
IPS Group	**0-2**	136	47%	23	23%	
	≥ 3	**151**	**53%**	**78**	**77%**	**< 0.00002**
Arm	**Standard Treatment**	158	55%	48	47%	
	PET-driven Treatment	132	45%	54	53%	NS
PET2 result	**Negative**	261	90%	78	77%	
	Positive	**25**	**9%**	**23**	**23%**	**0.0011**
	Missing	**4**	**1%**	**1**	**1%**	

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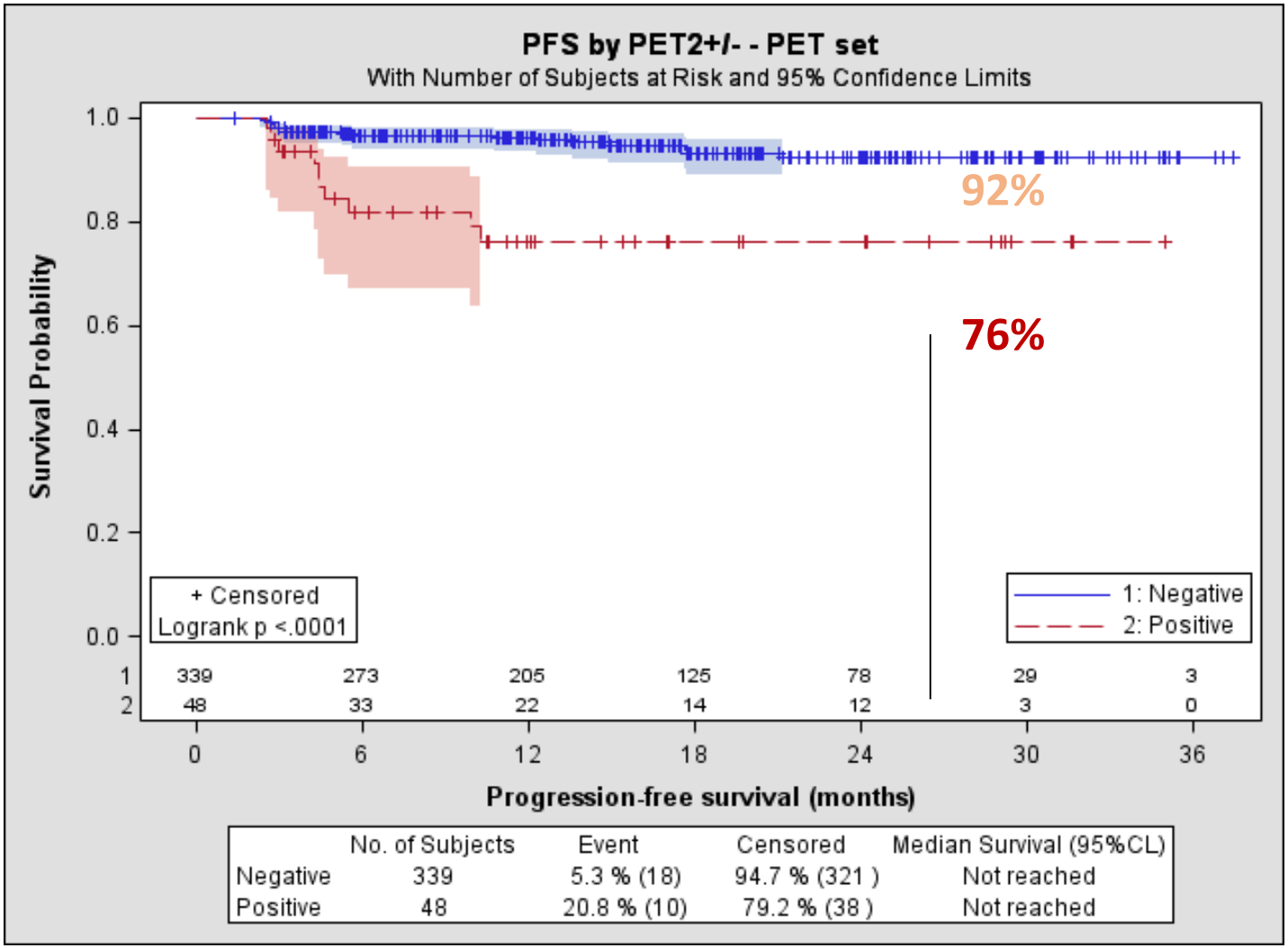
PFS according to PET2 results: whole cohort



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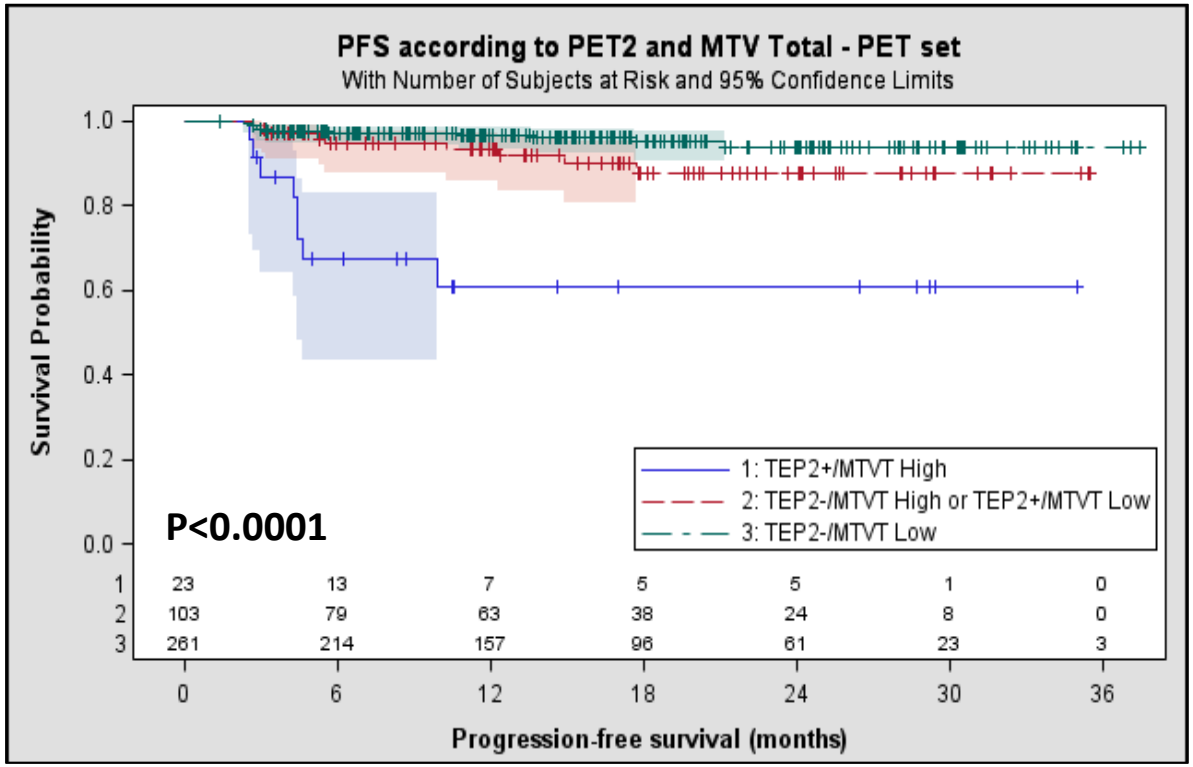
AHL2011: PFS according to TMTV and PET2 results

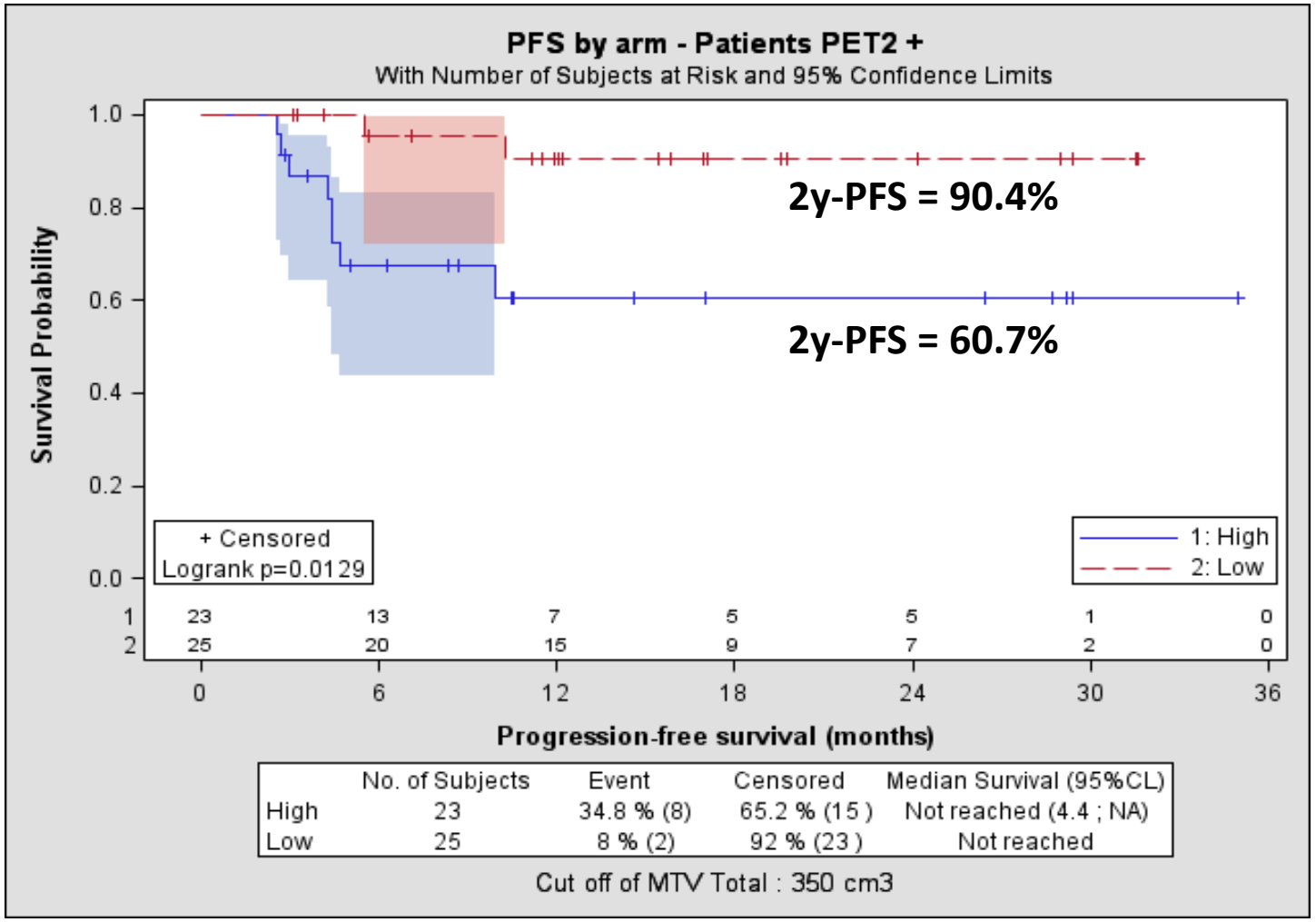


	2y-PFS	HR
TMTV ≤ 350 ml and negative PET2 (n = 261; 67%)	93.8%	1
TMTV > 350 ml or positive PET2 (n = 103; 26%)	87.9%	2.08 (95%CI: 0.86 – 5.03)
TMTV > 350 ml and positive PET2 (n = 23; 6%)	60.7%	10.9 (95%CI: 4.38 – 27.32)

Casasnovas RO, ASCO 2016; Abs 7509

AHL 2011

PFS according to **TMTV in PET2+ patients**



48% of High TMTV (cut-off = 350 ml)

Conclusions

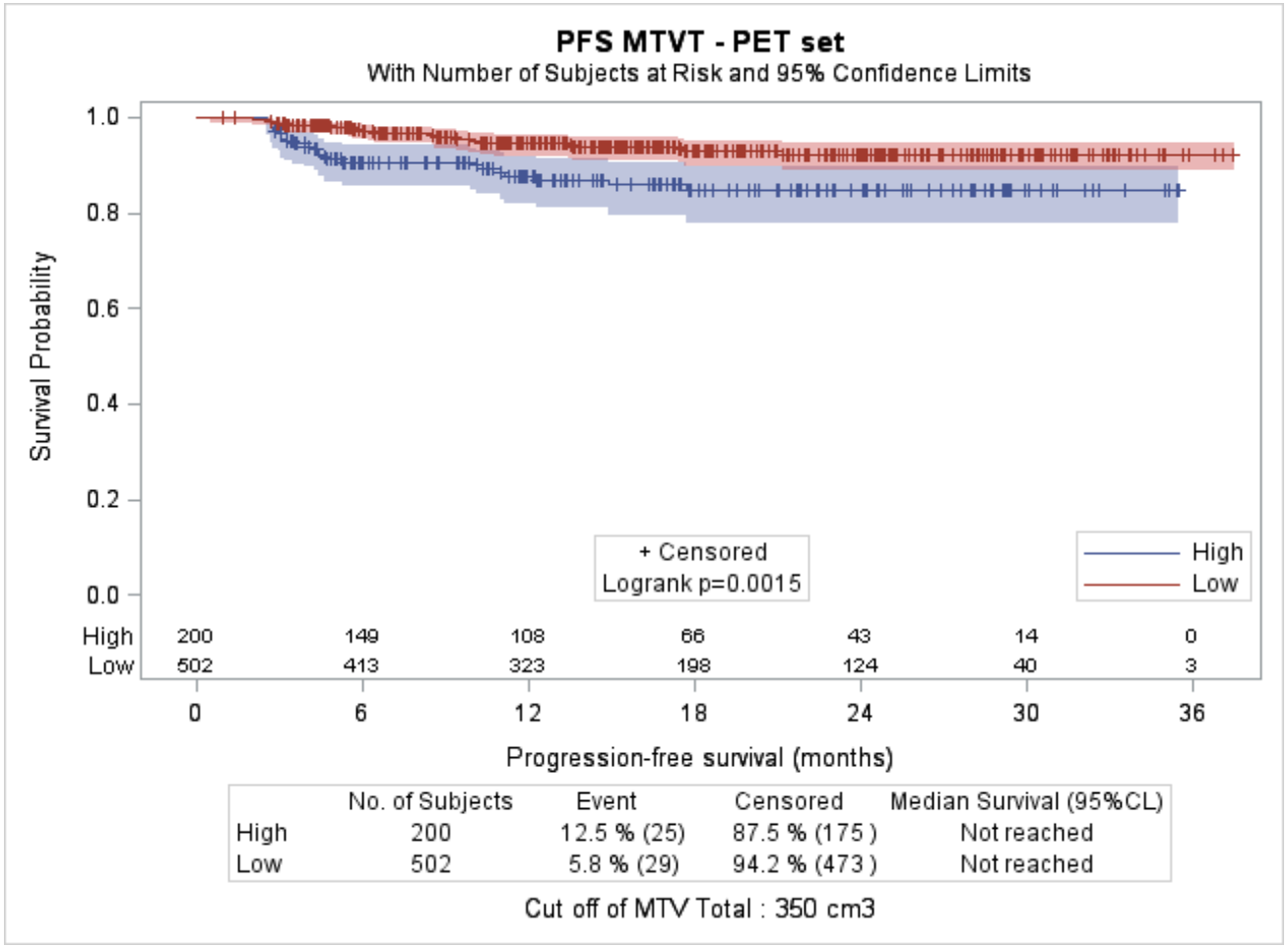
- About **25% of patients have a baseline high TMTV** (>350ml) and a higher risk of positive PET2

- **TMTV predicts the outcome of young advanced HL pts** independently of the early metabolic response to treatment

- The combination of **TMTV and PET2 allows identifying 3 subsets of HL pts with significantly different outcome** that may help clinician to better tailor therapy

- These first results on 392 patients are now validated on the remaining patients of the AHL2011 cohort

The 350 ml cut-off value now validated in 310 additionnal patients



28% high TMTV

AHL 2011

PET Team

- Salim Kanoun, Alina Berriolo-Riedinger (Dijon, France)
- Ilan Tal (Boston, USA)
- Véronique Edeline (St Cloud, France)
- Anne-Ségolène Cottereau, Michel Meignan (Créteil, France)

The Beth Israel free plugin for FIJI from the Beth Israel Deaconess Medical Center, Division of Nuclear Medicine and Molecular Imaging is available at: http://sourceforge.net/projects/bifijiplugins/

AHL 2011 Statistics

- Bénédicte Gelas-Dore (LYSARC, Lyon, France)
- Sami Boussetta (LYSARC, Lyon, France)