Imaging in Lymphoma from 1999 to Lugano: What is Next?

Bruce D. Cheson, M.D.
Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, D.C., USA

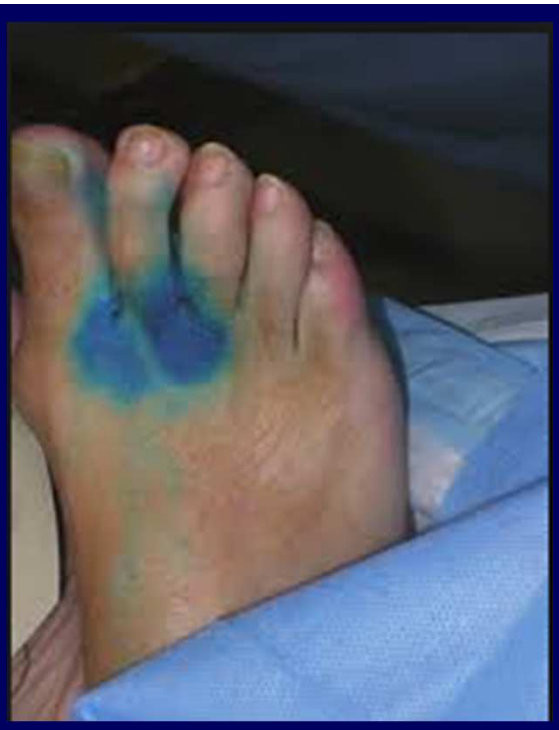
Disclosure

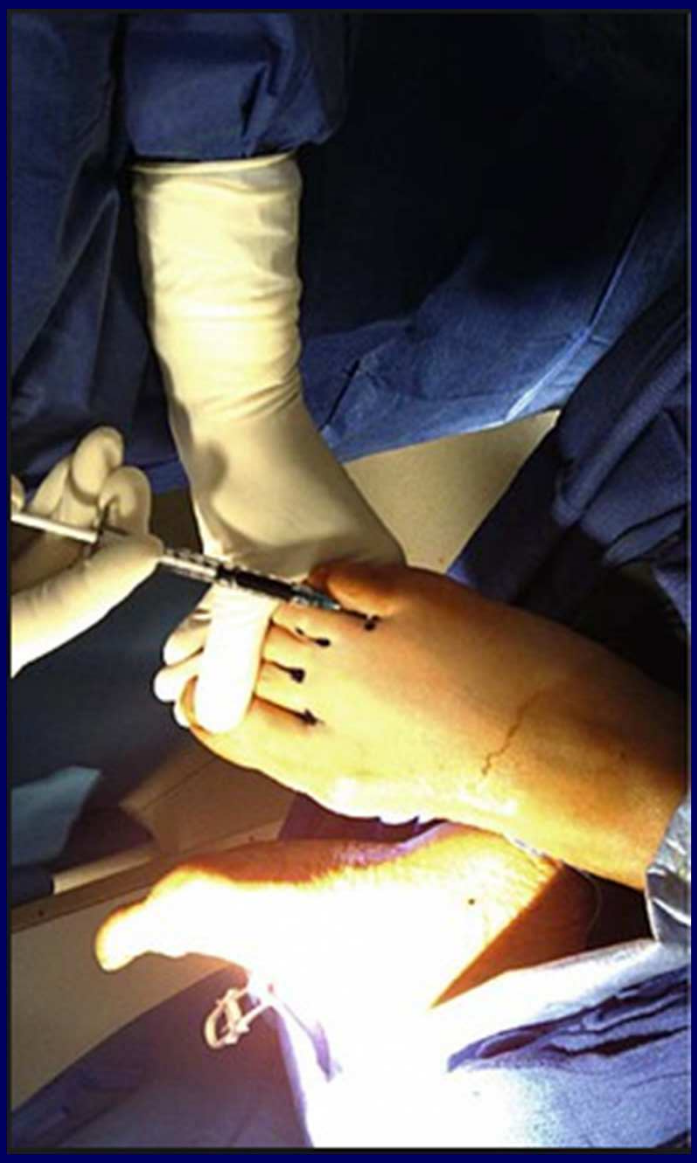
Bruce D. Cheson, M.D.

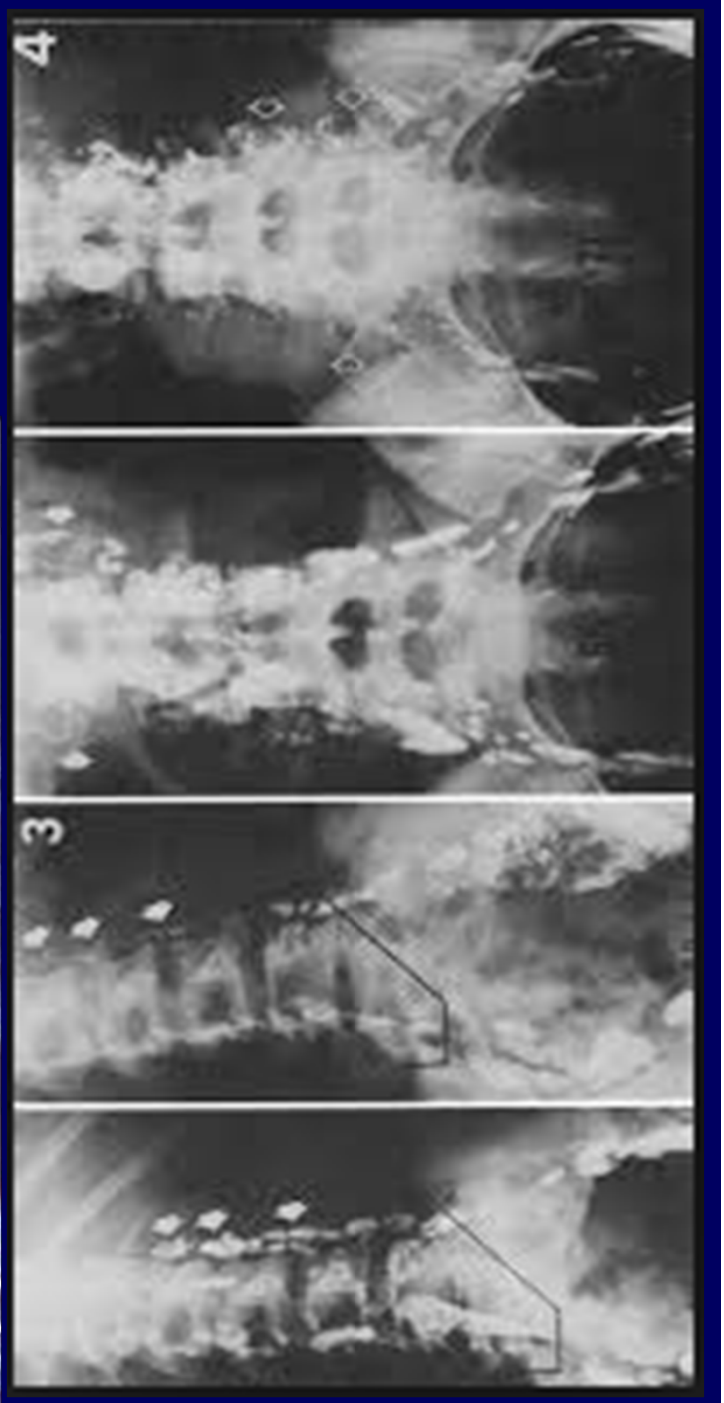
Menton PET Workshop 2016

I have a PET (Annie)

No PETs have been harmed during the preparation of this presentation






4
3

The History of Imaging

- Lymphangiogram
- IV pyelogram
- Ultrasound
- Liver/spleen scan
- CT
- Gallium scan
- MRI

International Working Group (IWG) Response Criteria for NHL: 1999

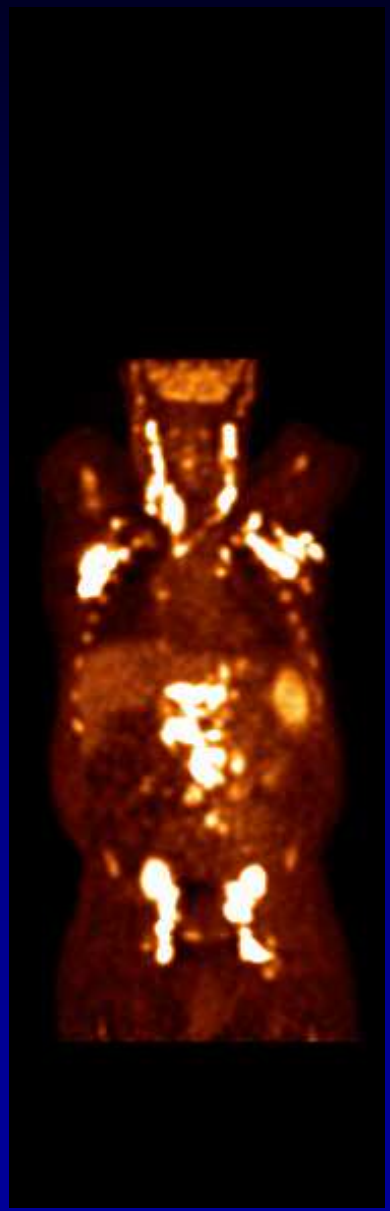
Cheson et al, J Clin Oncol 17:1244, 1999

- Complete remission (CR)
- Complete remission/unconfirmed (CRu)
- Partial remission (PR)
- Stable disease (SD)
- Relapsed disease (RD)
- Progressive disease (PD)

Limitations of IWG Response Criteria

- Unclear/misinterpretations (e.g. CRu)
- Dependent on inadequate methods
  - Physical examination
  - CXR, CT scan, MRI
  - SPECT gallium
  - Visual bone marrow evaluation

PET/CT SCANNING



Concept originated in 1974 by Hoffman and Phelps
Invented by Dr David Townsend and Dr Ron Nutt
First applied to lymphoma in 1990
Medical Invention of the year, TIME magazine 2000

Concordance of Response Classifications Between IWG and IWG/PET in DLBCL

IWG	IWG+PET: CR	CRu	PR	SD	PD	Total
CR	17	0	0	0	0	17
CRu	5	0	2	0	0	7
PR	10	0	9	0	0	19
SD	2	0	1	6	0	9
PD	1	0	0	0	1	2
Total	35	0	12	6	1	54

Juweid et al, JCO 23:4652, 2005

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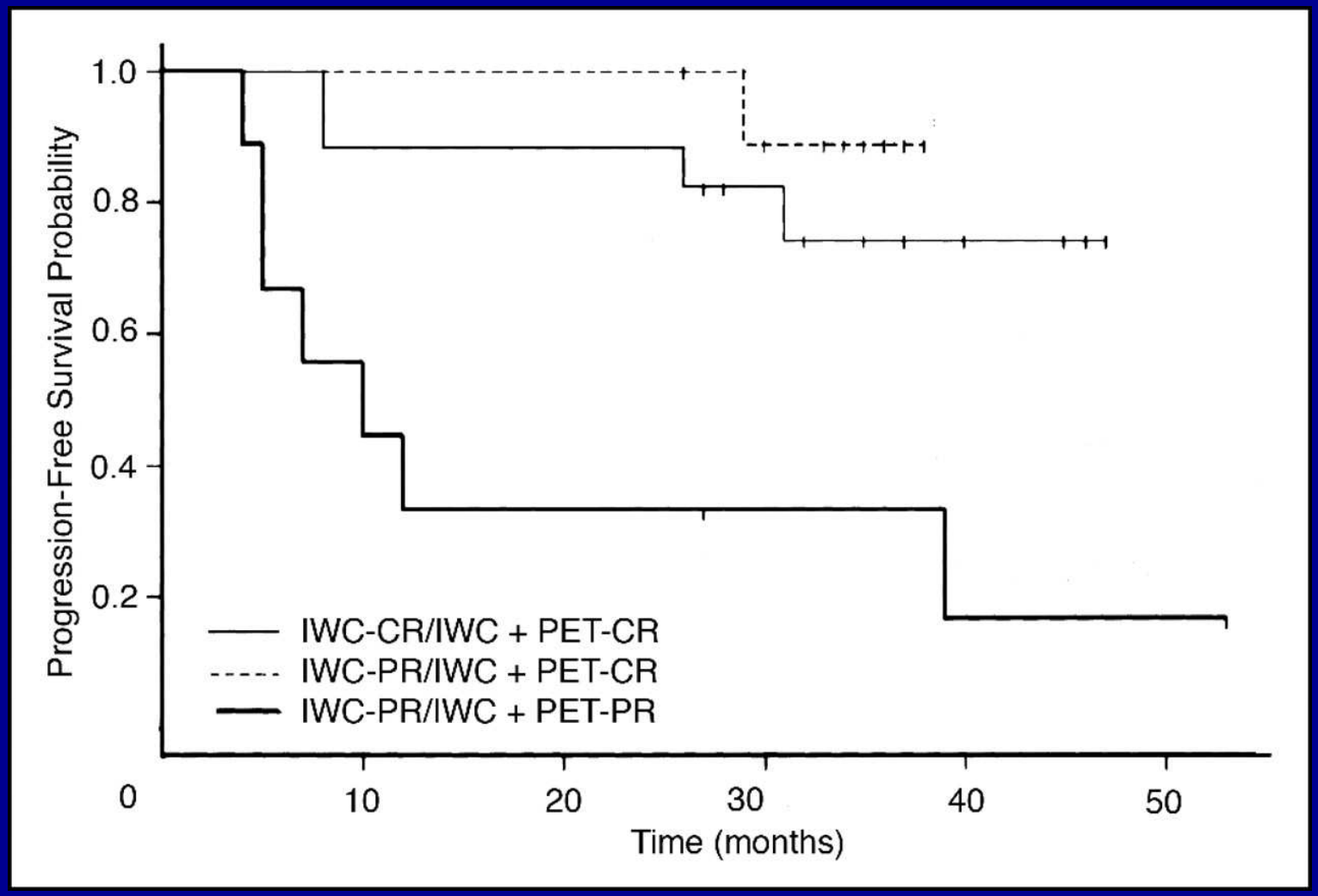
Juweid et al, JCO 23:4652, 2005

Progression-free survival by the International Workshop Criteria and IWC plus PET



Juweid M E et al. JCO 2005;23:4652-4661

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revised Response Criteria for Malignant Lymphoma

Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, Randy D. Gascoyne, Lena Specht, Sandra J. Horning, Bertrand Coiffier, Richard I. Fisher, Anton Hagenbeek, Emanuele Zucca, Steven T. Rosen, Sigrid Stroobants, T. Andrew Lister, Richard T. Hoppe, Martin Dreyling, Kensei Tobinai, Julie M. Vose, Joseph M. Connors, Massimo Federico, and Volker Diehl

From the Division of Hematology/Oncology, Georgetown University Hospital, Washington, DC; University of Cologne, Cologne; Department of Nuclear Medicine, University of Iowa, Iowa City, IA; Department of Pathology, British Columbia Cancer Agency and the University of British Columbia, Vancouver, British Columbia, Canada; Department of Oncology and Hematology, Rigshospitalet, Copenhagen University Hospital, Denmark; Division of Oncology and Department of Radiation Oncology, Stanford University, Stanford, CA; Department of Hematology, Hospices Civils de Lyon and Université Claude Bernard, Lyon, France; James P. Wilmot Cancer Center, University of Rochester, Rochester, NY; Academic Medical Center, Department of Hematology, Amsterdam, the Netherlands; Lymphoma Unit, Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; Lurie Cancer Center, Northwestern University, Chicago, IL; Department of

ABSTRACT

Purpose
Standardized response criteria are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies.

Methods
The International Working Group response criteria (Cheson et al, J Clin Oncol 17:1244, 1999) were widely adopted, but required reassessment because of identified limitations and the increased use of [^{18}F]fluorodeoxyglucose-positron emission tomography (PET), immunohistochemistry (IHC), and flow cytometry. The International Harmonization Project was convened to provide updated recommendations.

Results
New guidelines are presented incorporating PET, IHC, and flow cytometry for definitions of response in non-Hodgkin's and Hodgkin's lymphoma. Standardized definitions of end points are provided.

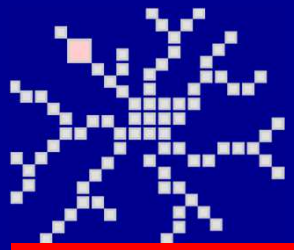
Conclusion
We hope that these guidelines will be adopted widely by study groups, pharmaceutical and biotechnology companies, and regulatory agencies to facilitate the development of new and more effective therapies to improve the outcome of patients with lymphoma.

Revised Response Criteria 2007

- FDG-PET
  - Primarily for DLBCL and Hodgkin
  - Recommended before treatment (not staging)
  - Standard for response assessment
  - Visual assessment
  - Mediastinal blood pool for background
- IHC and flow cytometry included for BM

Revised Response Criteria 2007

- CR – no FDG-avid disease in DLBCL or HL
  - Includes persistent mass
- CRu eliminated
- CT criteria used for other histologies



11th INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA
Lugano, Switzerland, June 15-18, 2011
11-ICML

Closed Workshop:
Lymphoma pretreatment assessment and response criteria in the New Millennium: Beyond Ann Arbor

Tuesday, June 14, 2011 – USI Auditorium, Lugano University

Steering Committee: B.D. Cheson, R.I. Fisher, T.A. Lister, E. Zucca
Session Co-Chair – Sally Barrington

Overarching Goals of the Lugano Classification

- ✓ Improve lymphoma patient evaluation
- ✓ Eliminate ambiguity
- ✓ Universally applicable
- ✓ Facilitate the comparison of patients and results amongst studies
- ✓ Simplify the evaluation of new therapies by regulatory agencies.

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müeller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson

See accompanying article doi: 10.1200/JCO.2013.54.8800

A B S T R A C T

Purpose
Recent advances in imaging, use of prognostic indices, and molecular profiling techniques have the potential to improve disease characterization and outcomes in lymphoma. International trials are under way to test image-based response–adapted treatment guided by early interim positron emission tomography (PET) –computed tomography (CT). Progress in imaging is influencing trial design and affecting clinical practice. In particular, a five-point scale to grade response using PET-CT, which can be adapted to suit requirements for early- and late-response assessment with good interobserver agreement, is becoming widely used both in practice- and response-adapted trials. A workshop held at the 11th International Conference on Malignant Lymphomas (ICML) in 2011 concluded that revision to current staging and response criteria was timely.

Methods
An imaging working group composed of representatives from major international cooperative groups was asked to review the literature, share knowledge about research in progress, and identify key areas for research pertaining to imaging and lymphoma.

Results
A working paper was circulated for comment and presented at the Fourth International Workshop on PET in Lymphoma in Menton, France, and the 12th ICML in Lugano, Switzerland, to update the International Harmonisation Project guidance regarding PET. Recommendations were made to optimize the use of PET-CT in staging and response assessment of lymphoma, including qualitative and quantitative methods.

Conclusion
This article comprises the consensus reached to update guidance on the use of PET-CT for staging and response assessment for [^{18}F]fluorodeoxyglucose-avid lymphomas in clinical practice and late-phase trials.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology

Sally F. Barrington and Michael J. O'Doherty, King's College London; N. George Mikhaeel, Guy's and St Thomas' National Health Service Foundation Trust, London, United Kingdom; Lale Kostakoglu, Mount Sinai Medical Center; Lawrence H. Schwartz, Columbia University Medical Center, New York, NY; Michel Meignan, Centre Universitaire Hospitalier Henri Mondor, Paris, France; Martin Hutchings, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; Stefan P. Müeller, Klinik für Nuklearmedizin, Universitätsklinikum Essen, Germany; Emanuele Zucca, Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; Richard I. Fisher, Fox Chase Cancer Center, Philadelphia, PA; Judith Trotman, Concord Hospital and University of Sydney, Sydney, New South Wales; Rodney J. Hicks, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Victoria, Australia; Otto S. Hoekstra, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; Roland Hustinx, University of Liège, Liège, Belgium; Alberto Biggi, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy; and Bruce D. Cheson, Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, DC.

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Corresponding author: Sally F. Barrington, MBBS, MSc, FRCP, FRCR, MD, Reader in Nuclear Medicine, PET Imaging Centre at St Thomas', Westminster Bridge Rd, London SE1 7EH, United Kingdom; e-mail: sally.barrington@kcl.ac.uk.

0732-183X/14/3299-1/$20.00

DOI: 10.1200/JCO.2013.53.5229

INTRODUCTION

Advances in staging and response assessment of lymphomas have occurred with the introduction of prognostic indices,[1-4] molecular profiling,[5] and more accurate imaging,[6] with the potential to improve disease characterization and treatment selection. The International Harmonisation Project (IHP) first published guidelines about the application of positron emission tomography (PET) using [^{18}F]fluorodeoxyglucose (FDG) in lymphoma[7] in 2007, and PET was integrated in revised response criteria.[8]

The field has continued to evolve. PET combined with computed tomography (CT) has replaced PET alone. Mounting evidence supports the central role of PET-CT in staging[9-18] and response assessment in Hodgkin (HL)[19-27] and non-Hodgkin lymphomas (NHL).[28-34] Multiple international studies are under way to investigate whether PET-CT response can be used to guide therapy to improve patient outcomes.[35,36] Concerted efforts have been made to standardize PET-CT methods[37-41] and interpretation in the context of trials.[42] A five-point scale (5-PS), suited to assess differing degrees of response at mid- and end of treatment, has been developed to score images.[43] This scale was recommended as the standard reporting tool at the First International Workshop on PET in Lymphoma in Deauville, France, in 2009,

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

See accompanying article doi: 10.1200/JCO.2013.53.5229

A B S T R A C T

Abstract
The purpose of this work was to modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response. As a result, fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) was formally incorporated into standard staging for FDG-avid lymphomas. A modification of the Ann Arbor descriptive terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A bone marrow biopsy is no longer indicated for the routine staging of HL and most diffuse large B-cell lymphomas. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and a number of prognostic factors. PET-CT will be used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify progressive disease. Routine surveillance scans are discouraged. These recommendations should improve evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials.

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Bruce D. Cheson, Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC; Richard I. Fisher, Fox Chase Cancer Center, Philadelphia, PA; Sally F. Barrington, St Thomas' Hospital; T. Andrew Lister, St Bartholomew's Hospital, London, United Kingdom; Franco Cavalli and Emanuele Zucca, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; and Lawrence H. Schwartz, Columbia University, New York, NY.

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Presented in part at the 10th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 16-22, 2013.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Bruce D. Cheson, MD, Georgetown University Hospital, Lombardi Comprehensive Cancer Center, 3800 Reservoir Rd, NW, Washington, DC 20007; e-mail: bdcheson@georgetown.edu.

0732-183X/14/3299-1/$20.00

DOI: 10.1200/JCO.2013.53.5229

INTRODUCTION

The availability of more effective therapies for lymphoma and the increasingly sensitive and specific technologies for disease assessment provide rationale for updated patient evaluation, staging, and response criteria. There should be unambiguous and universally applicable and facilitate the comparison of patients and results among studies and the evaluation of new therapies by regulatory agencies.

Staging defines disease location and extent, suggests prognostic information, allows comparisons among studies, and provides a baseline against which response or disease progression can be compared. Initial staging criteria were designed primarily for Hodgkin lymphoma (HL)[1,2] and were superseded by the Ann Arbor classification,[3] which subdivided HL patients into four stages and subclassification A and B based on the presence of fevers to greater than 101°F (38.3°C), weight loss, and night sweats and which has been the most widely used classification since its introduction. The Cotswold classification[4] first formally incorporated computed tomography (CT) scans and introduced "X" for bulky disease and complete remission unconfirmed (CRu) to describe patients with a residual mass after treatment that was most likely fibrous tissue.

The first universally accepted response criteria for non-Hodgkin lymphoma (NHL), used also for HL, were published in 1999 by the National Cancer Institute Working Group[5] and revised in 2007 by the International Working Group (IWG)[7] to incorporate positron emission tomography (PET) and bone marrow immunohistochemistry and flow cytometry in response assessment, eliminating CRu.

Postinduction response assessment with PET-CT: limitations to these studies…

PRIMA 122 patients 2004-2010 Trotman J, JCO 2011

- Hypothesis generating.
- Retrospective analysis of local PET interpretation within a prospective study with independent CT assessment.
- Results confirmed by independent scan review of 61 patients.

Tychyj-Pinel C, EJNMMI 2014

FOLL05 202 patients 2005-2010 Luminari S, Ann Oncol 2013

- Retrospective analysis of local PET reports within a prospective study with local CT assessment.

PET Folliculaire 106 patients 2007-2009 Dupuis J, JCO 2012

- Prospective standardised PET acquisition / assessment in accordance to the 5 Point Scale (5PS), with local CT assessment.
- Shorter follow-up.

PFS according to CT response

SD/PD vs.

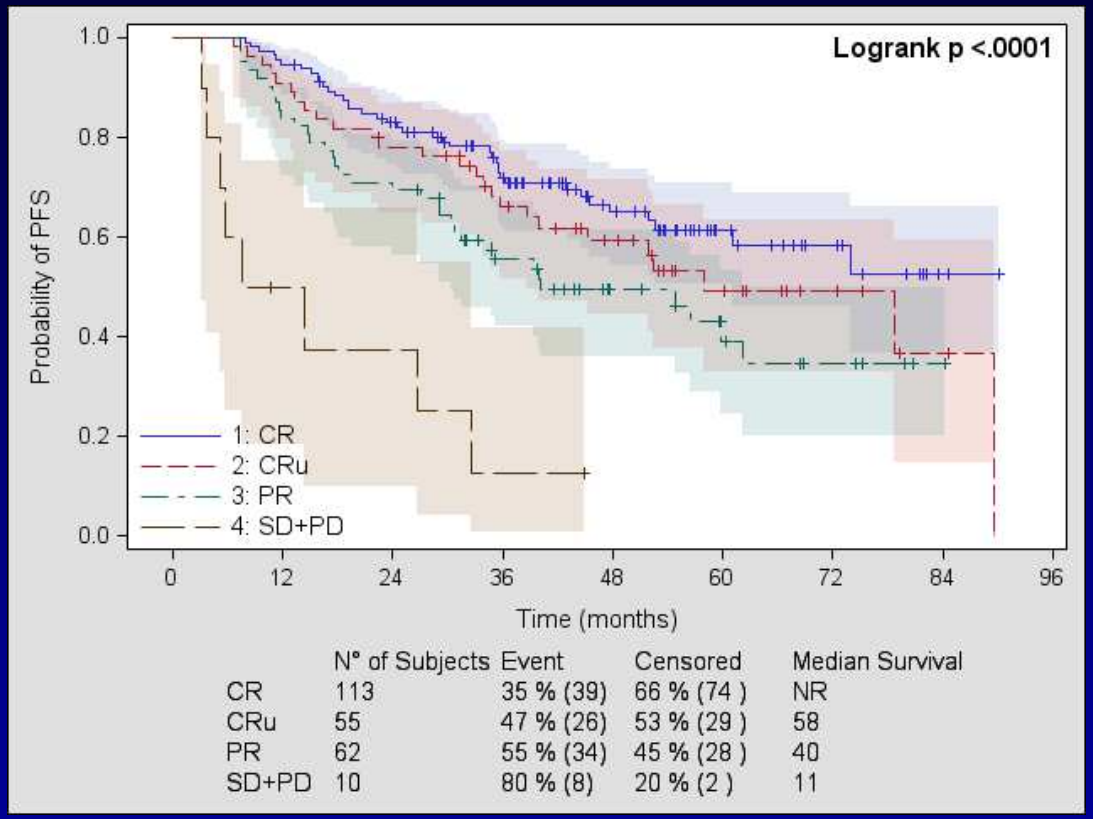
- PR, HR 4.2
- CRu, HR 5.6
- CR, HR 7.8 , p<.0001

PR vs.

- CR/CRu, HR 1.7 (1.1-2.5)
  p=0.02

CRu/PR vs.

- CR, HR 1.6 (1.1-2.4), p=0.02

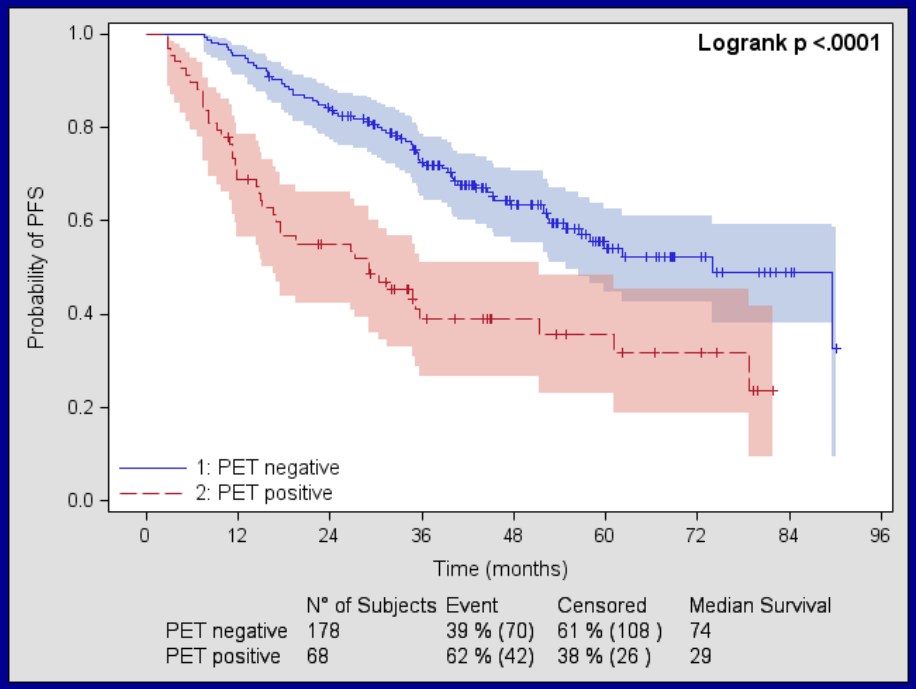


	N° of Subjects	Event	Censored	Median Survival
CR	113	35 % (39)	66 % (74)	NR
CRu	55	47 % (26)	53 % (29)	58
PR	62	55 % (34)	45 % (28)	40
SD+PD	10	80 % (8)	20 % (2)	11

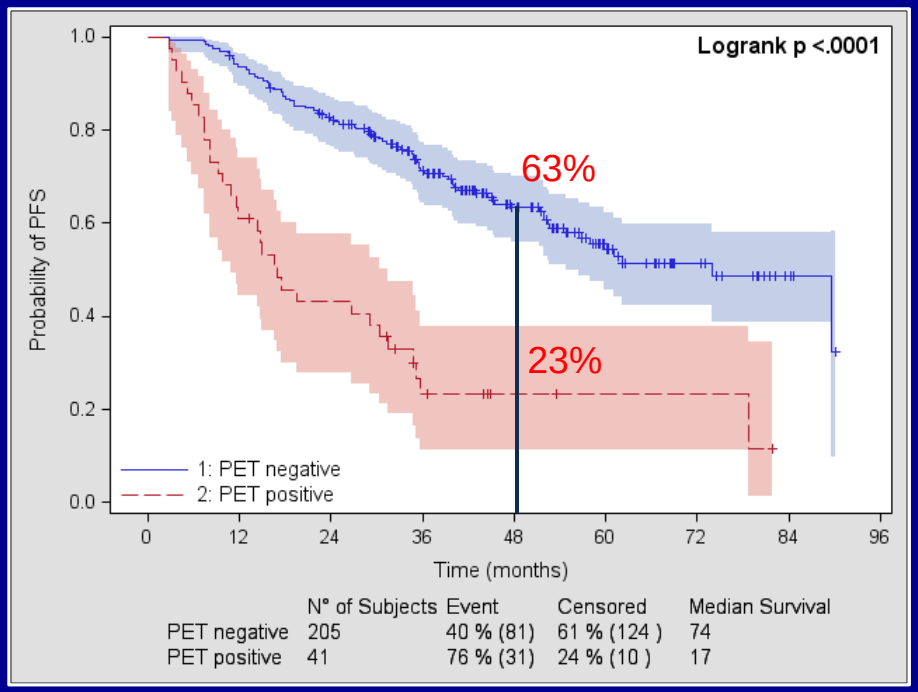
Trotman et al, Lancet Haematol, 2014

Both PET cut-offs predictive of PFS

Score ≥3



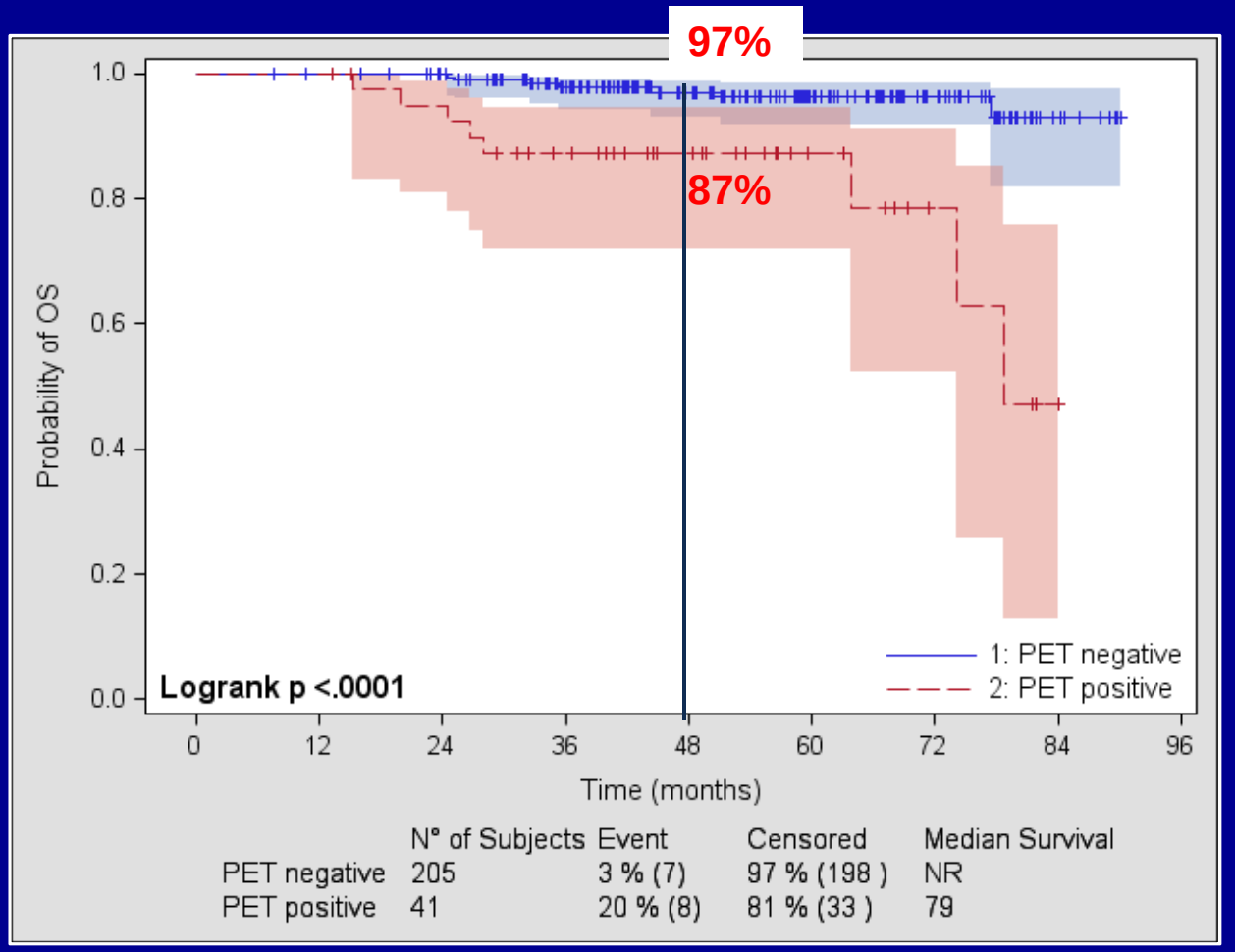
Score ≥4



HR 3.9 (95% CI 2.5-5.9, p<.0001)
Median PFS:
16.9 (10.8-31.4) vs. 74.0 mo (54.7-NR)

Trotman et al, Lancet Haematol, 2014

Postinduction PET status (cut-off ≥4) and Overall Survival



HR 6.7, 95% CI 2.4-18.5, p=0.0002
Median OS: 79 months vs. NR

Trotman et al, Lancet Haematol, 2014

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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Hodgkin Lymphoma: Protecting the Victims of Our Success

Bruce D. Cheson, *Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC*

See accompanying article on page 4508

The only saving grace of the present is that it's too damned stupid to question the past very closely.
—H.P. Lovecraft[1]

In few instances in oncology has progress been so methodical. Total nodal irradiation became subtotal, then extended field, and then involved field.[3] Randomized trials demonstrated that regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine were more

Routine Bone Marrow Biopsy in Hodgkin Lymphoma

- 454 newly diagnosed pts
- Bone marrow involvement
  - 18% focal lesions by PET
  - 8% involvement by trephine
- No pt with BM+ had CS I-II by PET
- Pts with BM+ had other evidence of stage IV
- BM Bx upstaged 5 pts from III-IV
- No treatment decisions changed by BM Bx

El-Galaly et al, J Clin Oncol 30:4508, 2012

PET-CT For Staging and Early Response in HL (n=1214)

- RATHL (ceCT) and PET-CT staging compared
- Concordance in 80%
  - PET-CT upstaged 14% (BM 92, lung 11, multiple 12)
  - Downstaged 6%
  - ceCT identified 7 PET-CT-neg lesions (bowel, Liver, spleen)
  - BMBx – positive 0.4% where PET was negative

Barrington et al, Blood 127:1531, 2016

BMBx and PET-CT in DLBCL

- 130 pts; 35 (27%) with BM involvement: 33 by PET, 14 by BMBx
- PET identified all positive BMs
- BX did not upstage any patients
- Sensitivity/specificity
  - PET-CT – 94%, 100%
  - BMBx – 40%, 100%
- Prognosis of PET+/Bx- similar to stage IV w/o BM involvement
- Pts with BM+ had other evidence of stage IV

Khan et al, Blood 122:61, 2013

PET vs BMBx in Follicular Lymphoma

	N	BMB+ PET+	BMB+ PET-	BMB- PET+	BMB- PET-	Sensitivity	Specificity	Accuracy
FL at diagnosis	57	16	8	5	28	.67	.85	.77
FL at relapse	30	8	3	2	17	.73	.89	.83

Ujjani et al, Br J Haem e-pub, 2016

BM Bx in the Staging of Lymphomas

- If PET-CT is performed, BM biopsy is no longer indicated for HL, and only for DLBCL if PET is negative and identifying discordant histology is important for patient management
- BM remains part of staging for other histologies

Staging of Lymphomas: The Lugano Classification

- PET-CT is the standard for FDG-avid lymphomas; CT is indicated for non-avid histologies (CLL/SLL, MZL, LPL, MF)
- A modified Ann Arbor staging system is recommended for disease localization; however, patients are treated according to prognostic and risk factors
- Suffixes A and B are only required for HL
- “X” for bulky disease is no longer necessary, but record the largest tumor diameter

Summary: What is New in the Lugano *Staging* Criteria?

- Splenomegaly: >13 cm
- No routine CXR
- No BMBx in HL or most DLBCL

Summary: What is New in Lugano *Response* Criteria

- PET-CT for all FDG-avid histologies
- CR includes persistent nodes that are PET-negative in FDG-avid histologies
- CT-PR retains SPD 6 nodes/extranodal lesions
- Single lesion adequate for PD
- Deauville 5-PS now the standard

5 POINT SCALE (DEAUVILLE CRITERIA)

1. no uptake
2. uptake ≤ mediastinum
3. uptake > mediastinum but ≤ liver
4. moderately increased uptake compared to liver
5. markedly increased uptake compared to liver and/or new lesions

** markedly increased uptake is taken to be uptake > 2-3 times the SUV max in normal liver

CMR/CR	PET-CT-based response	CT-based response
	Complete Metabolic Response (CMR)	**Complete Radiologic Response (ALL of the following)**
Target Nodal/ Extranodal	Score 1, 2, or 3* by 5-PS with or without a residual mass	**Nodal Disease**: ≤ 1.5 cm in LDi **Extranodal Disease**: Absent
Non-Target		
Spleen		Regress to normal
New lesions		None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

***Score of 3**

- Good prognosis with standard treatment (interim scan) for some
- De-escalation is investigated→ may consider a score of 3 as inadequate response (to avoid undertreatment).

Cheson et al, JCO 32:3059, 2014

PMR/PR	PET-CT-based response	CT-based response
	Partial Metabolic Response (PMR)	**Partial Remission (PR) (ALL of the following)**
Target Nodal/ Extranodal	Score 4,5 with reduced uptake compared with baseline and residual mass(es) of any size. • **Interim**: suggest responding disease • **EoT**: indicates residual disease	≥ 50% decrease from baseline in SPD of all Target lesions
Non-Target		No Increase
Spleen		**Spleen**: ≥ 50% decrease from baseline in enlarged portion (value over 13cm) **Liver**: no progression
New lesions		None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline Persistent focal changes in the marrow with nodal response, • Further evaluation with MRI or biopsy, or an interval scan	Not applicable

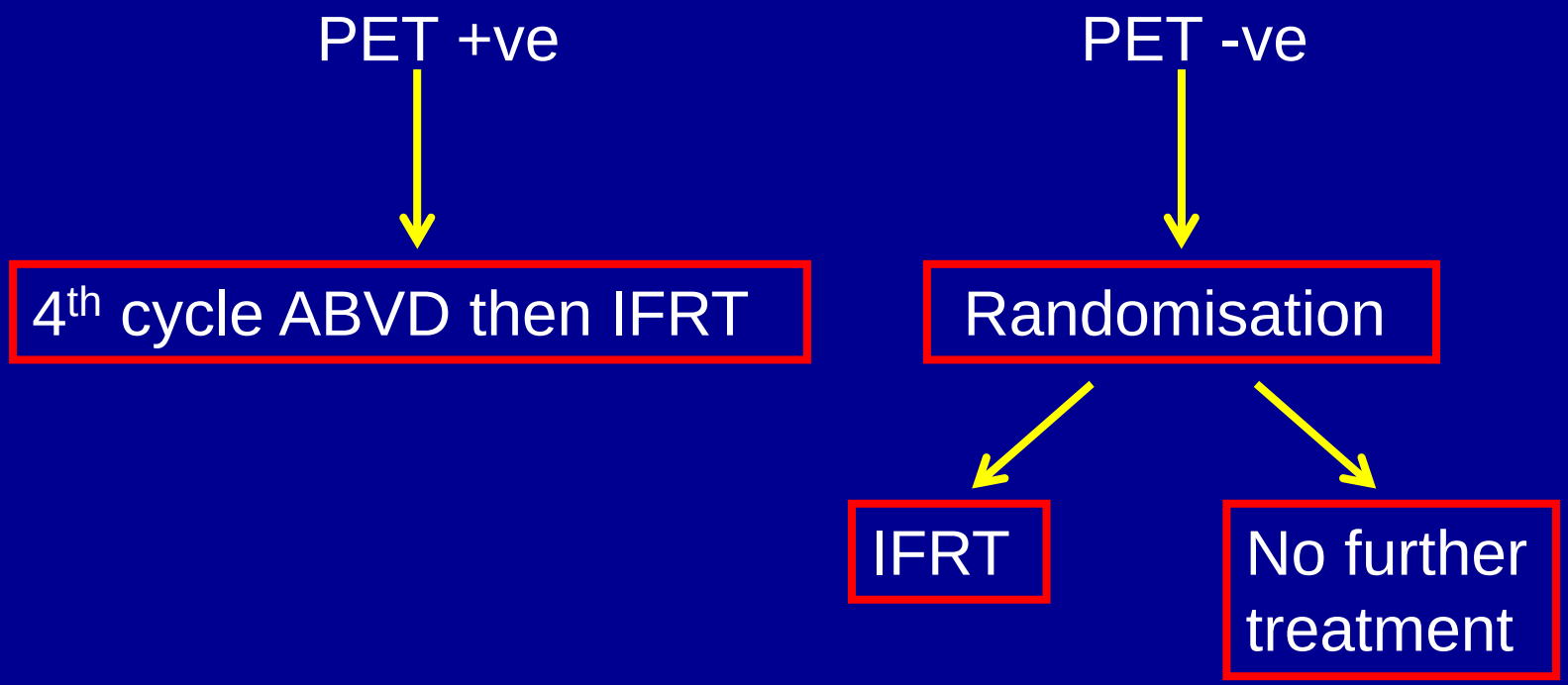
NMR/SD	PET-CT-based response	CT-based response
	No Metabolic Response (NMR)	**Stable disease**
Target Nodal/ Extranodal	Score 4 or 5 with no significant change in FDG uptake from baseline, at interim or EoT.	• < 50% decrease from baseline in SPD of all Target lesions • No criteria for PD are met
Non-Target		No progression
Spleen		No progression
New lesions		None
Bone marrow	No change from baseline	Not applicable

PMD/PD	PET-CT-based response	CT-based response
	Progressive Metabolic Disease (PMD)	**Progressive disease** **ONE of the following**
Target Nodal/ Extranodal	• Score 4, 5 with increase in intensity of uptake from baseline **and/or** • New FDG-avid foci consistent with lymphoma at interim or EoT • Consider biopsy or interval scan if etiology of new lesions uncertain	**PPD Progression:** An individual node/lesion must be abnormal with: • LDi > 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND **An increase in LDi or SDi from nadir** • ≥ 0.5 cm for lesions ≤ 2 cm • ≥ 1.0 cm for lesions > 2 cm
Non-Target		Unequivocal Progression
Spleen/Liver		Unequivocal Progression: • Progression of existing Splenomegaly • New or Recurrent Splenomegaly • New or Recurrent liver involvement
New lesions		• Regrowth of previously resolved lesions • New node > 1.5 cm in any axis • New extranodal site > 1.0 cm in any axis • New extranodal site <1.0 cm in any axis • Unequivocal/attributable to lymphoma. • Any size assessable disease unequivocal/attributable to lymphoma
Bone marrow	New/recurrent FDG avid foci	New/recurrent involvement

RAPID - trial design

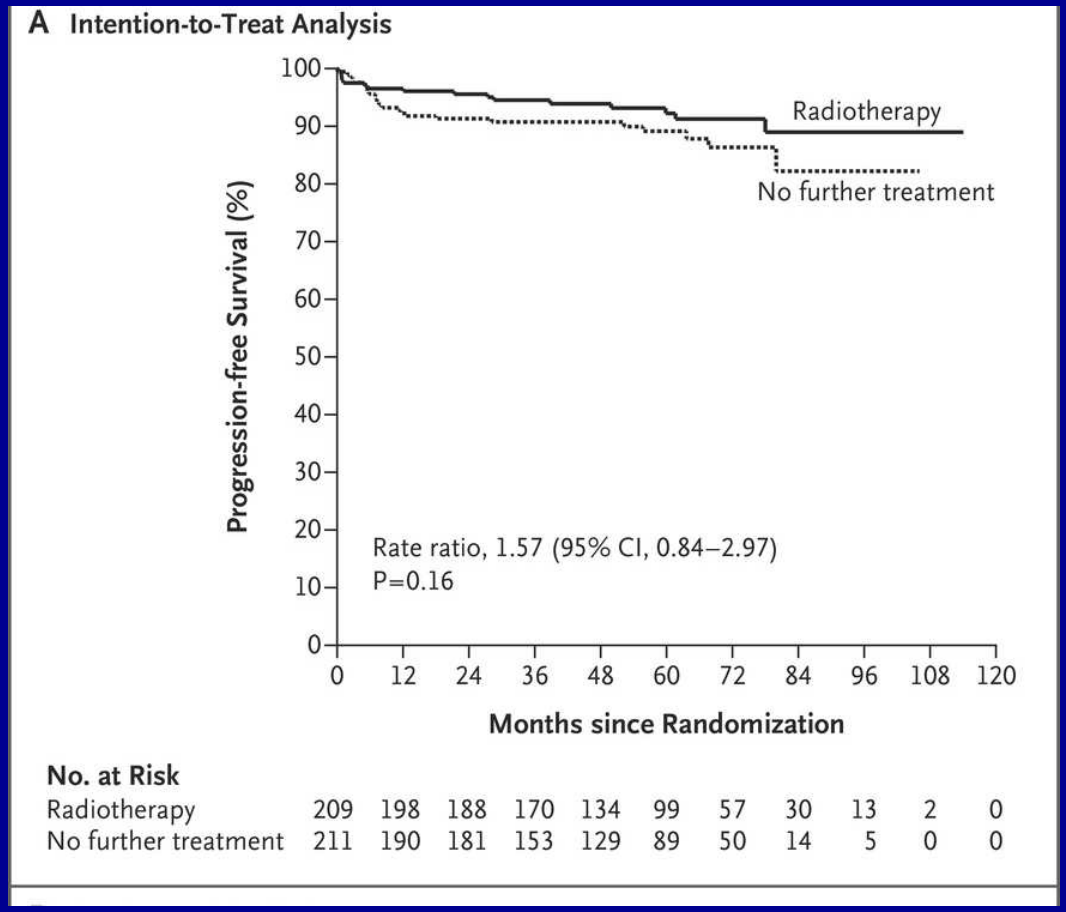
Initial treatment: ABVD x 3

Re-assessment: if NR/PD, patient goes off study
if CR/PR, FDG-PET scan performed



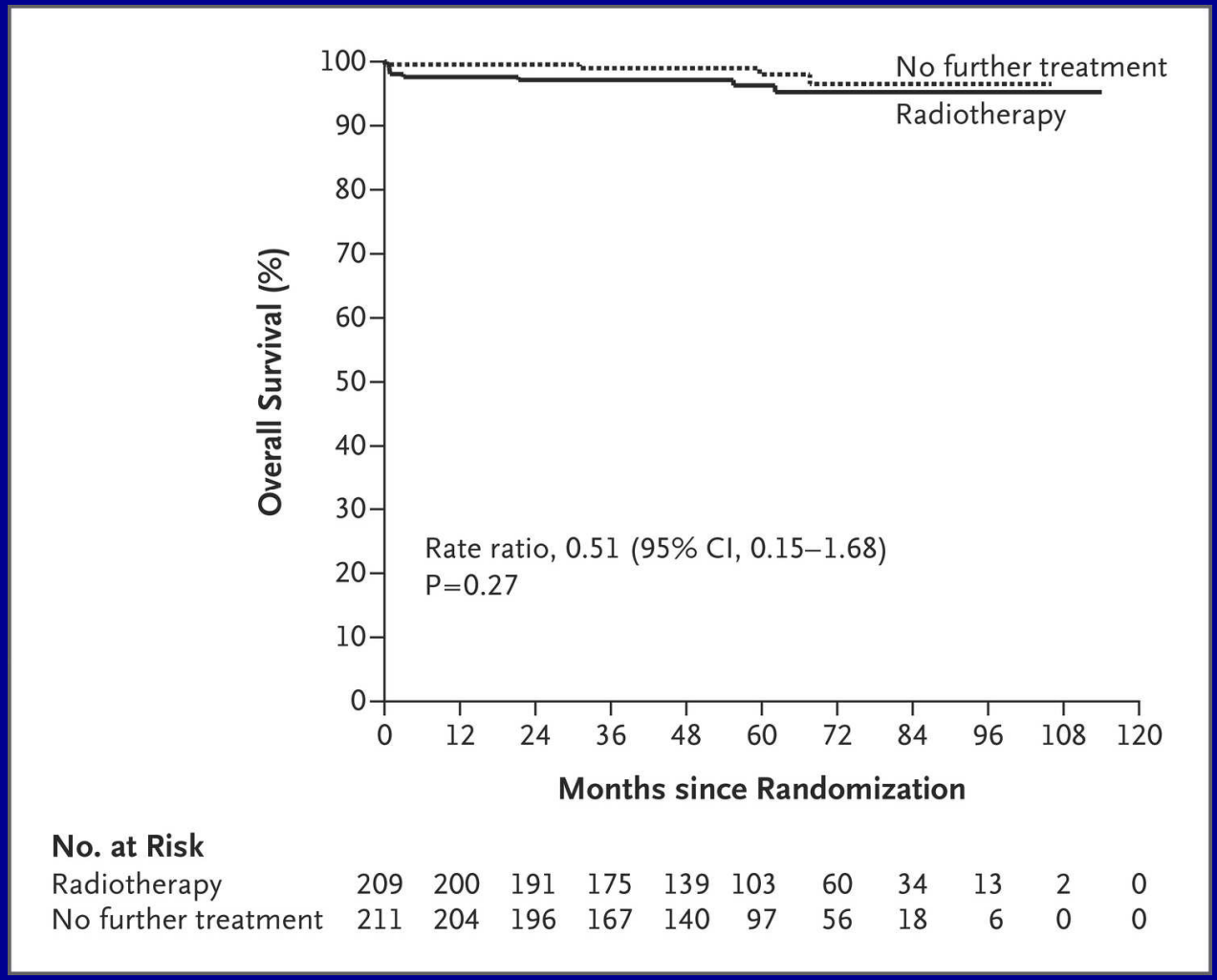
Radford et al, NEJM 372:1598, 2015

RAPID Trial: Progression-free Survival.



Radford J et al. N Engl J Med 2015;372:1598-1607.

RAPID Trial: Overall Survival.

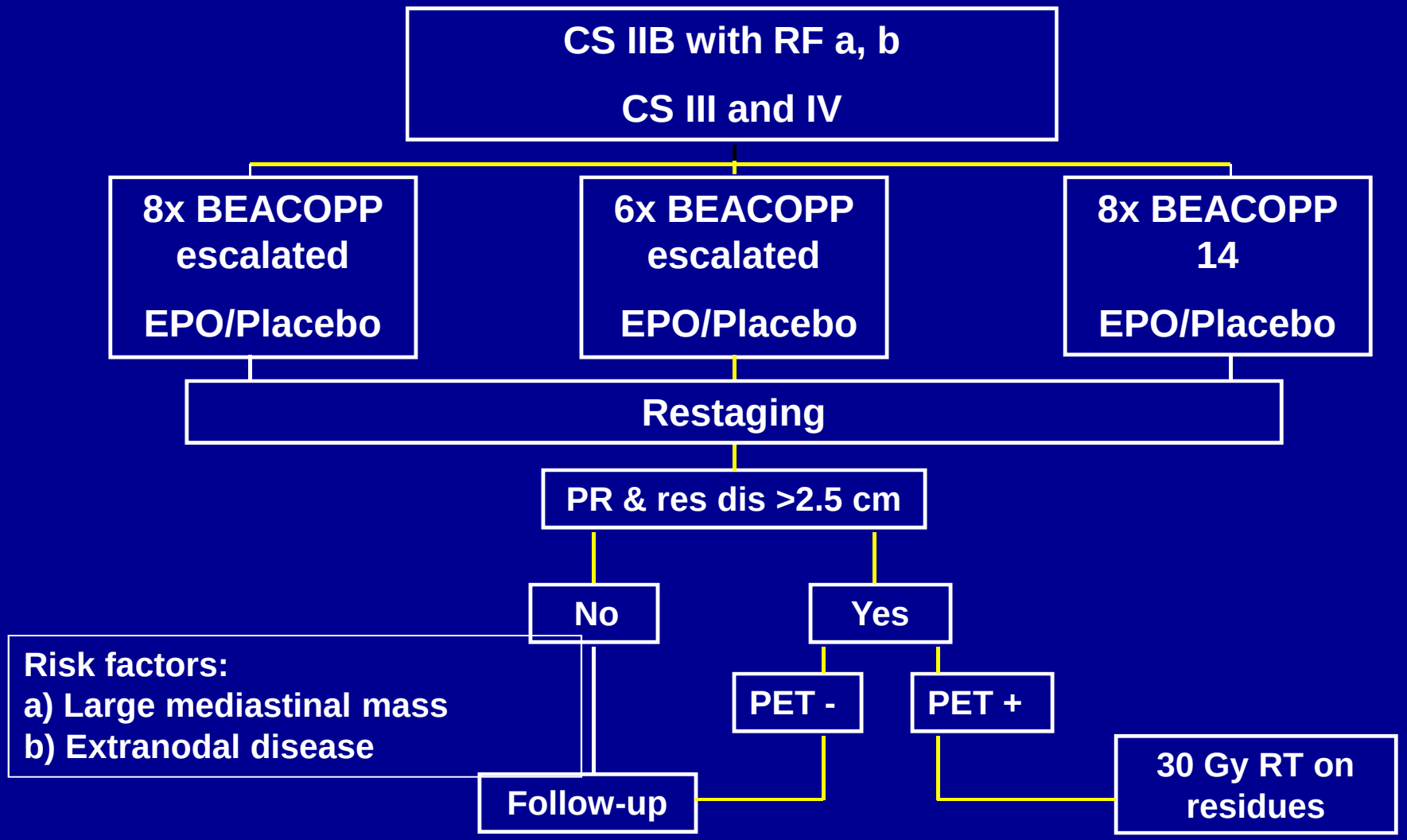


No. at Risk

Radiotherapy	209	200	191	175	139	103	60	34	13	2	0
No further treatment	211	204	196	167	140	97	56	18	6	0	0

Radford J et al. N Engl J Med 2015;372:1598-1607.

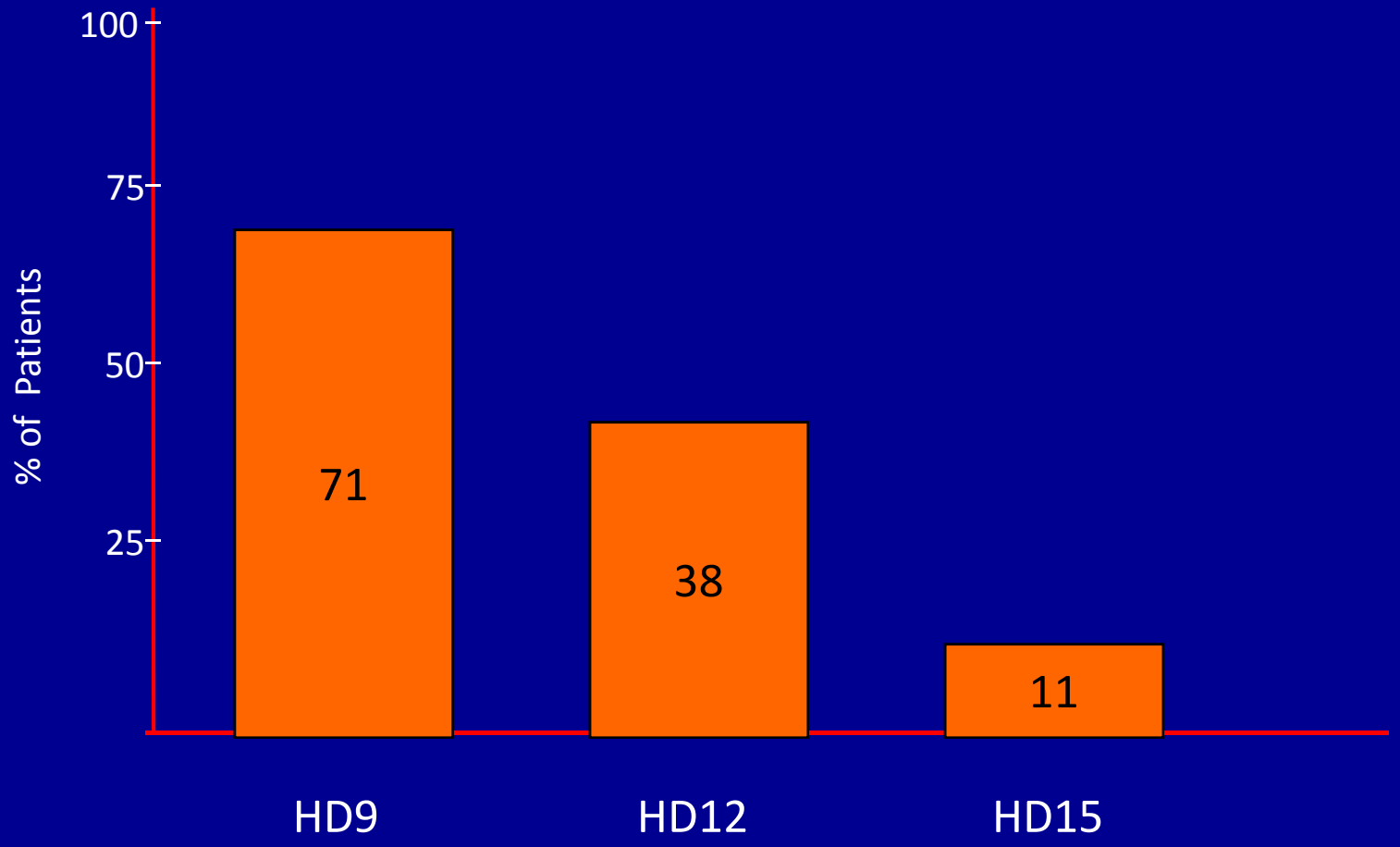
GHSG study for advanced-stage HL
(HD15; 2003-08)



Engert et al, Lancet 12:379, 2012

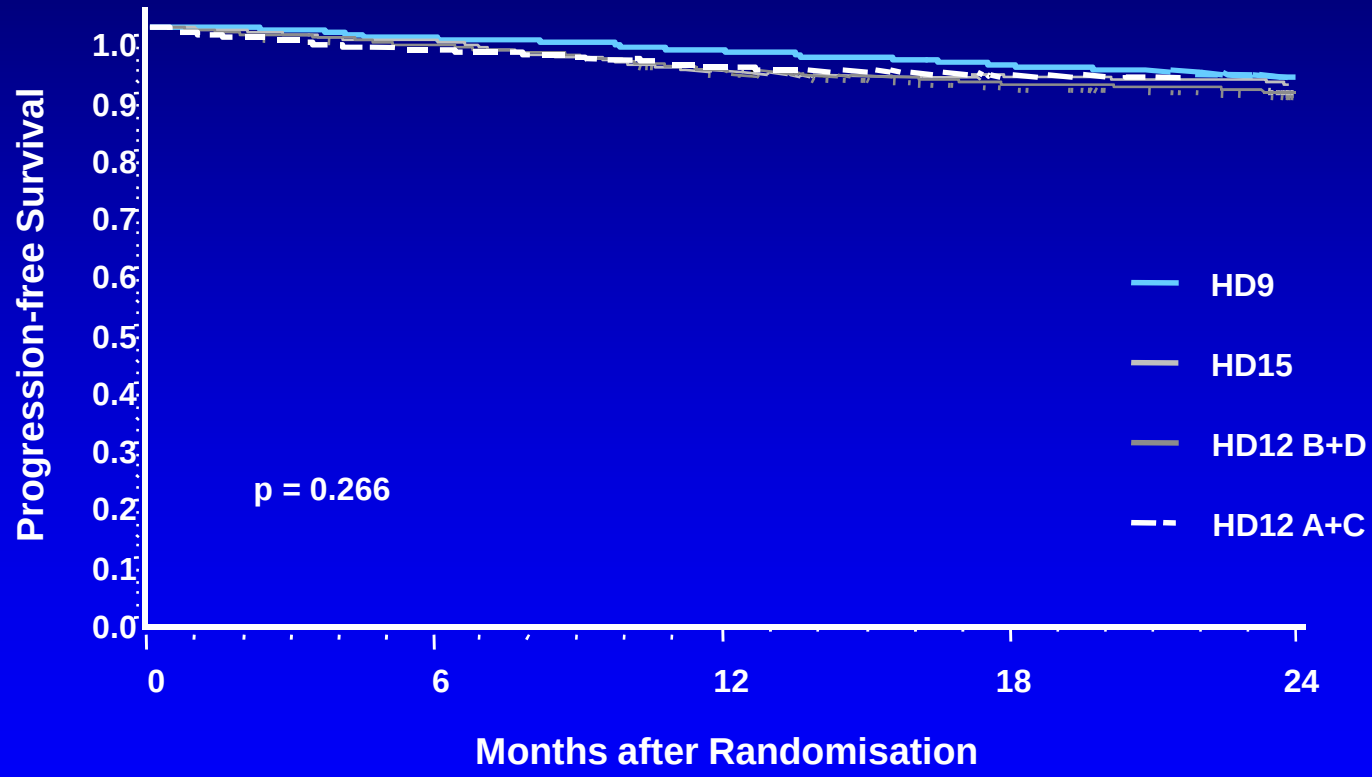
Additional RT after chemo in advanced stages

GHSG studies HD9, HD12 and HD15 (% of all pts)



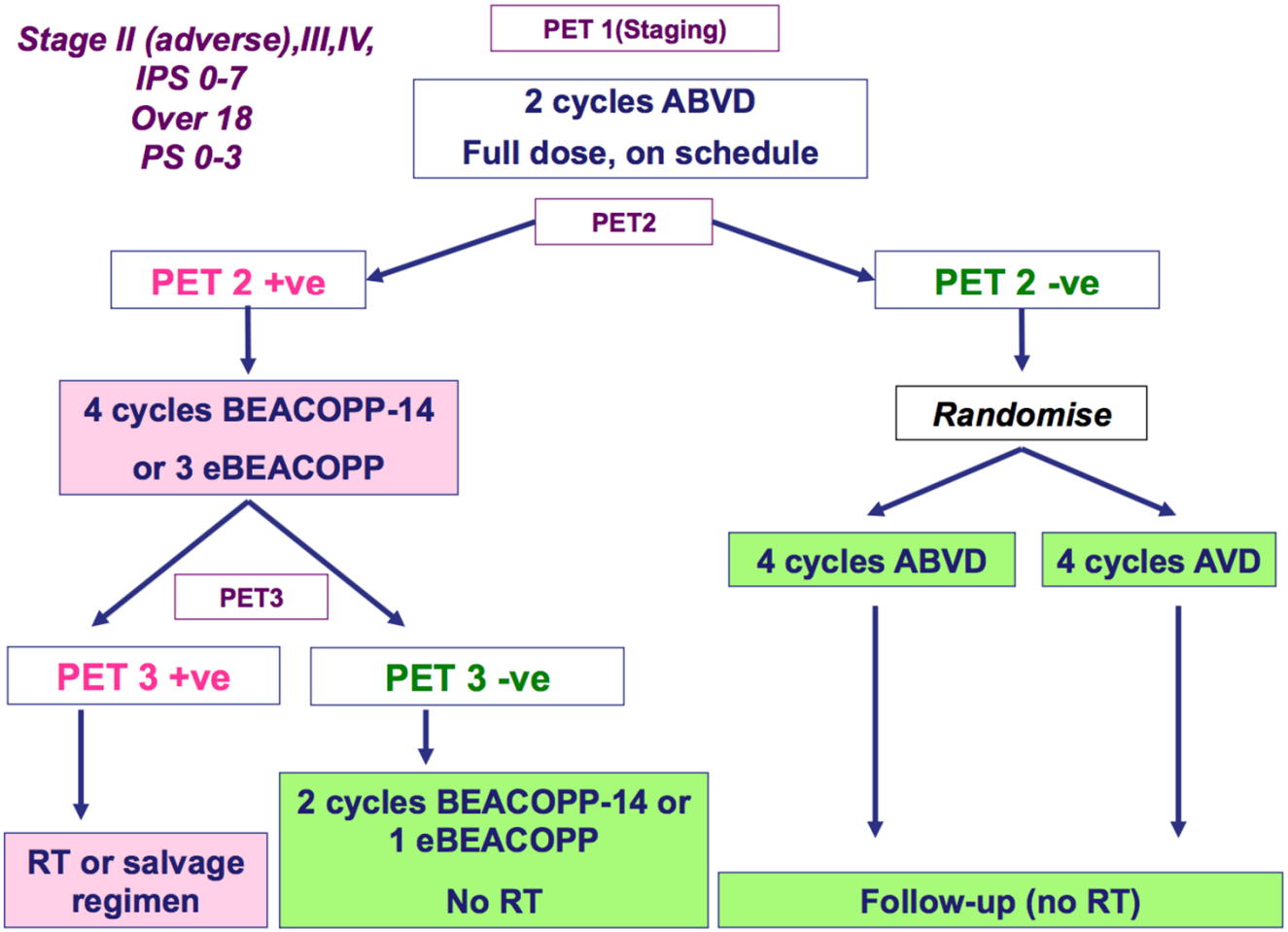
Engert et al, Lancet 12:379, 2012

Comparison of GHSG trials HD9, HD12, HD15
for advanced-stage HL (PFS)



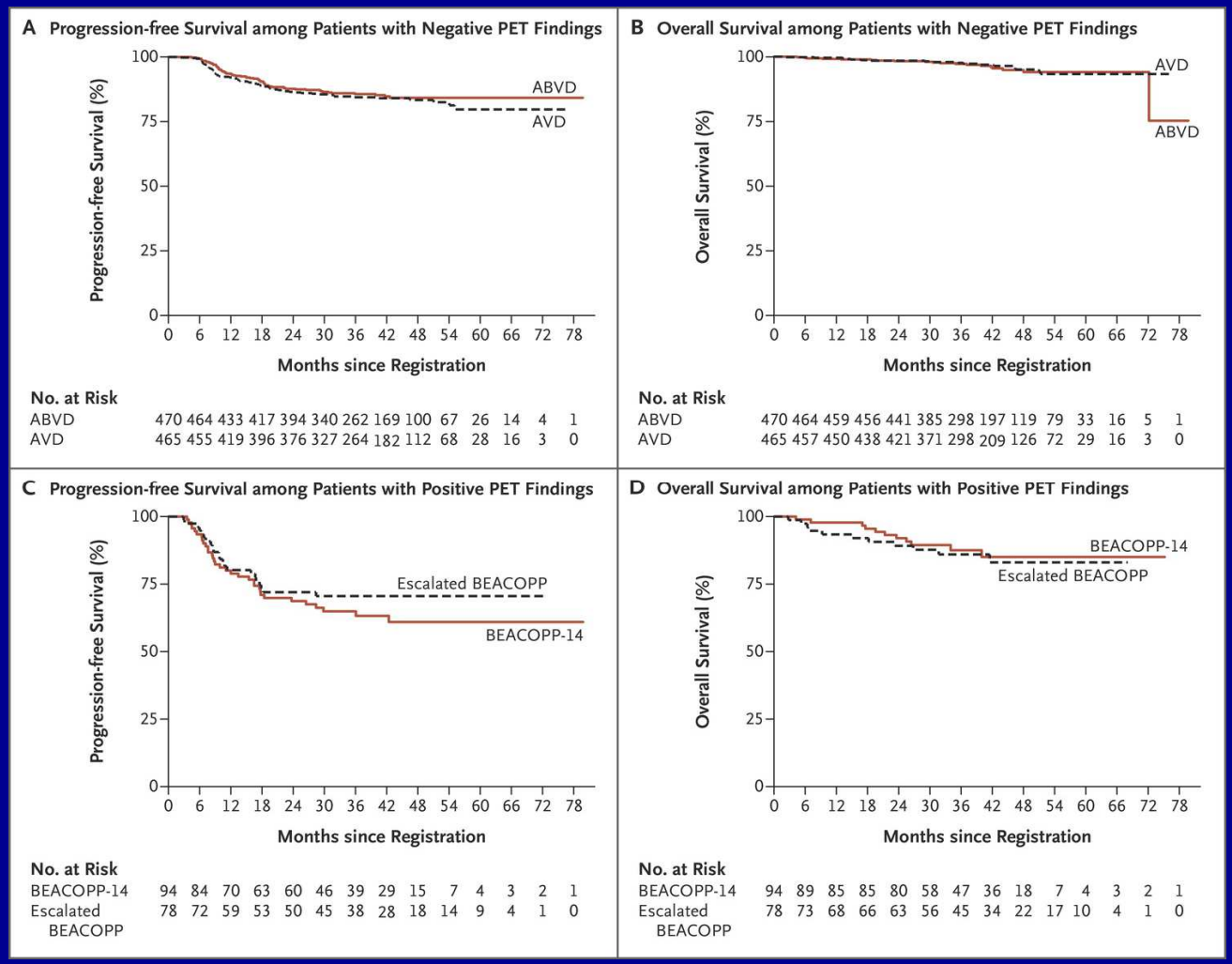
Engert et al, Lancet 12:379, 2012

RATHL: Schema



Johnson et al, NEJM 374:2419, 2016

Progression-free and Overall Survival.



Johnson P et al. N Engl J Med 2016;374:2419-2429.

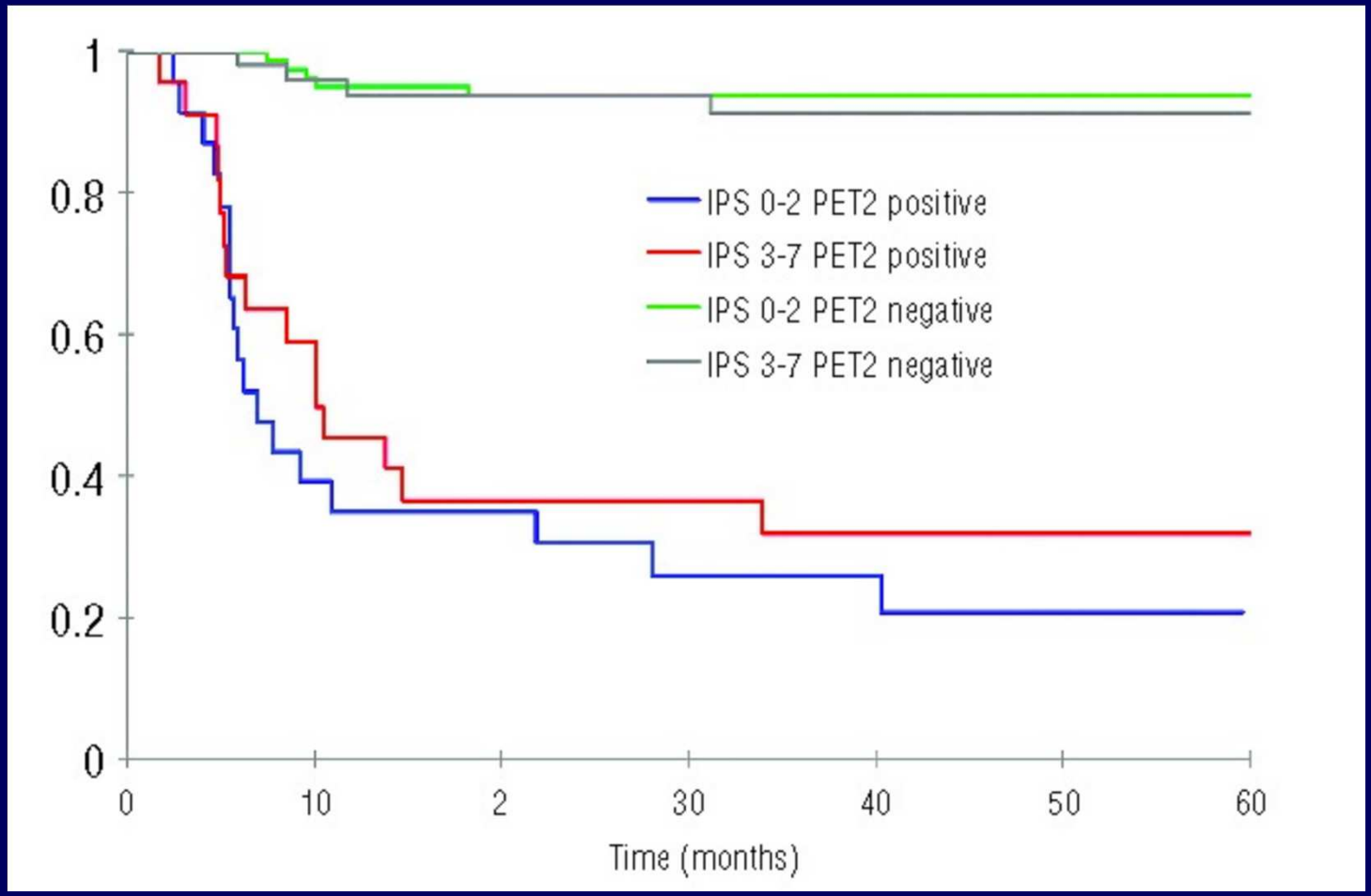
Toxicity of therapy: ABVD vs AVD

% of patients experiencing grade 3-4 events

	ABVD cycles 1-2	ABVD cycles 3-6	AVD cycles 3-6	P-value
Neutropenia	57.3	58.4	57.5	0.78
Thrombocytopenia	1.3	1.3	3.2	0.045
Neutropenic fever	2.1	4.7	2.2	0.032
Infection	6.3	14.5	10.1	0.040
Thrombo-embolism	1.4	4.9	2.6	0.061
Respiratory AEs	0.7	3.6	0.6	0.002
Any non-haematological toxicity	16	31	21	<0.001

Johnson et al NEJM 374:2419, 2016

Interim PET in HL Using the Deauville 5-PS



Gallamini, et al, Haematologica 99:1107, 2014

Risk-Adapted Studies of Increased Treatment in PET-2 Positive Patients

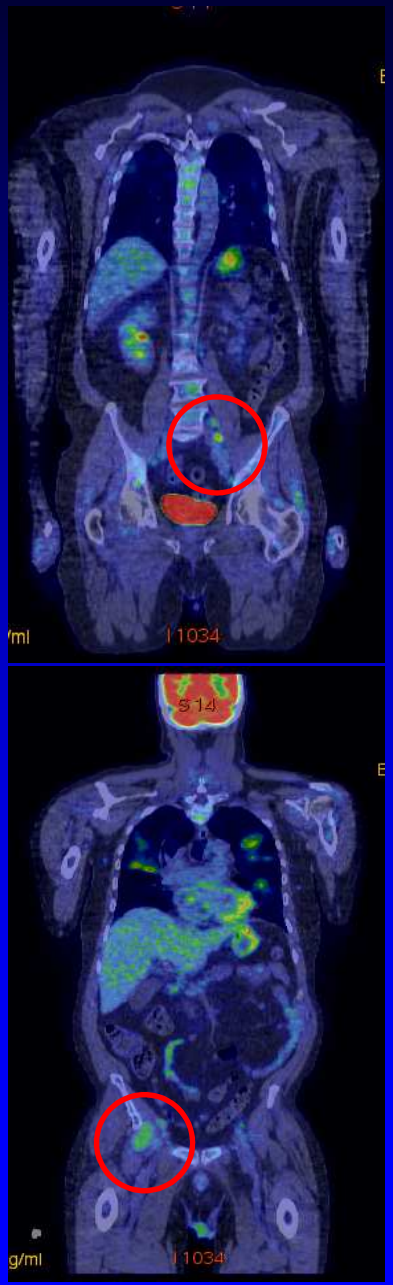
Trial	Stage	Number PET-positive	Initial therapy	% iPET positive (5PS PET score if used)	Post-PET therapy	Time to analysis	PFS %	OS %
CALGB 50604	I-II	14	2 ABVD	9	2 esc BEACOPP + IFRT	2.1 yrs	66%	N/A
EORTC H10	I-II	361	2 ABVD	19	2 ABVD + INRT 2 esc BEACOPP + INRT	5 yrs	77 91	89 96
RATHL	II with adverse features, III, IV	182	2 ABVD	16 (4-5)	4 esc BEACOPP or 6 BEACOPP-14	3 yrs	68	87
GITIL HD0607	II with adverse features, III, IV	98	2 ABVD	20 (4-5)	4 esc BEACOPP + 4 BEACOPP baseline +/- rituximab	2	66	N/A
SWOG S0816	III, IV	60	2 ABVD	18 (4-5)	6 esc BEACOPP	2	64	N/A
FIL HD0801	IIB-IV	103	2 ABVD	20 (3-5)	4 IGEV + BEAM	2	76	N/A

A New Problem

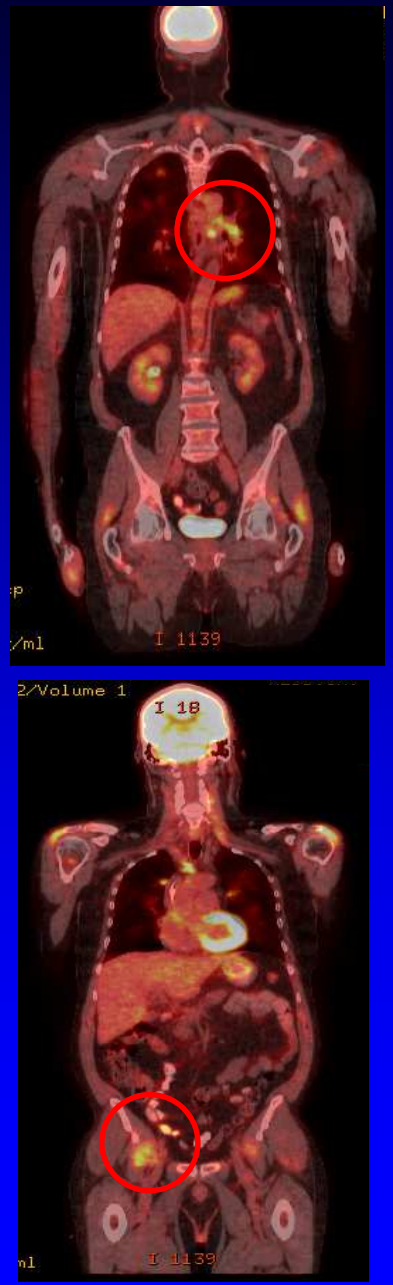
- ~15% of solid tumor pts have a flare response on immunomodulatory agents (CPIs)
- Confused with PD
- Result in premature termination
- Agents induce flare reactions in lymphoma:
  - Lenalidomide
  - Rituximab
  - Brentuximab vedotin
  - Ibrutinib
  - Check point inhibitors

May 2015

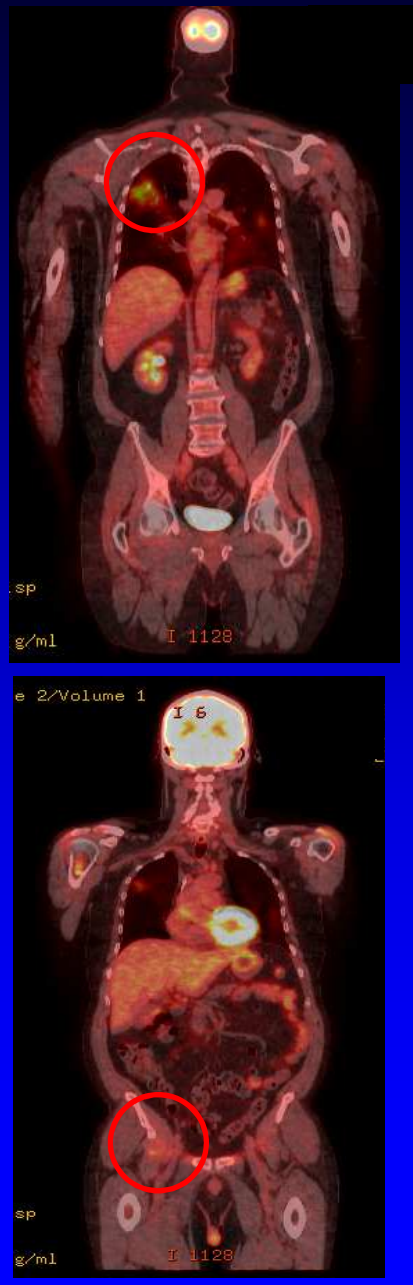
August 2015



October 2015



December 2015



Immune Response Criteria (IRC)*

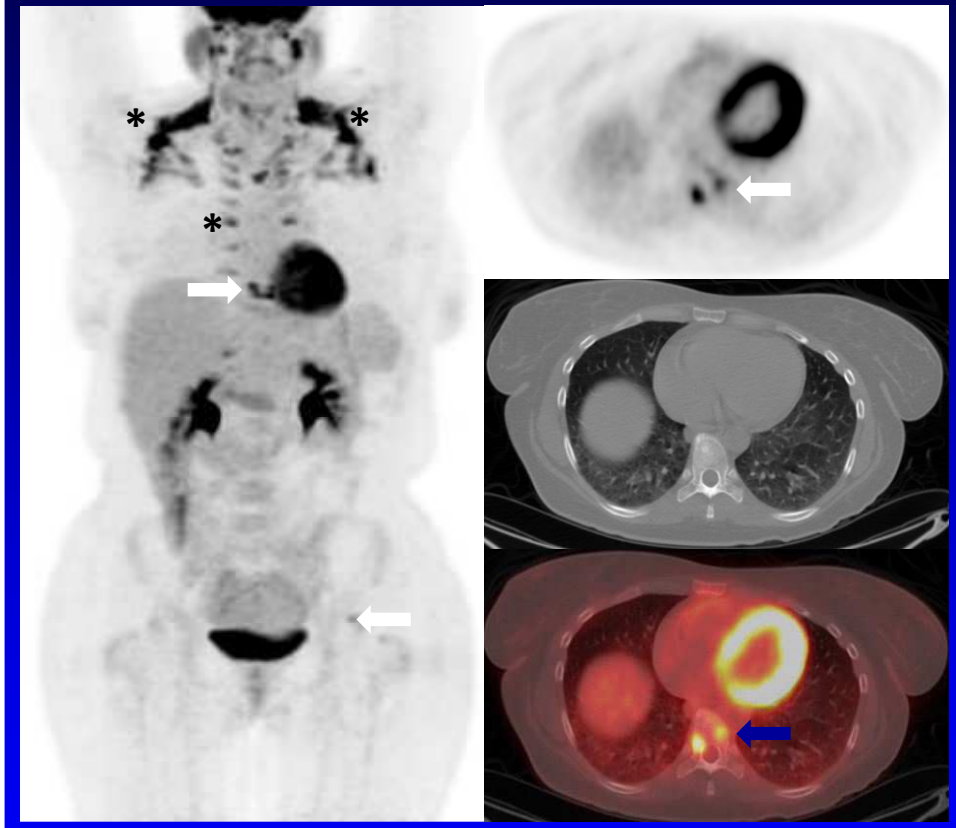
- Not applicable to lymphoma:
  - Rely on RECIST rather than Lugano
  - Timing of response assessment differs
  - Confirmatory studies not required with lymphoma
  - Definition of PD differs
  - Do not include PET-CT
  - Tumors are always abnormal; lymphomas involve nodes which are normally present
    - Normal size despite involvement
    - Enlarged despite non-involvement

* Wolchok et al, Clin Cancer Res 15:7412, 2009

Discordance Between IRC and Lugano

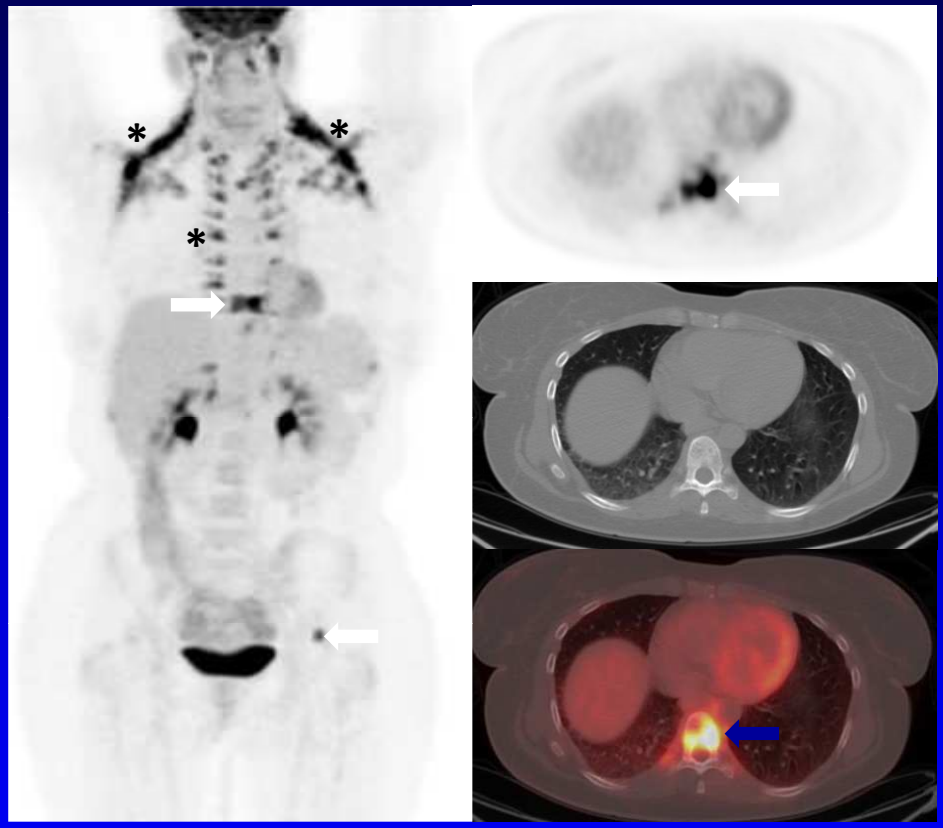
- Lymphomas often have non-measurable disease, imperceptible on CT
  - Bone marrow
  - Soft tissue involvement
- Cannot be integrated into tumor burden

Discrepancy Between Lugano and Immune Response Criteria



Restaging FDG-PET/CT 1

12 weeks



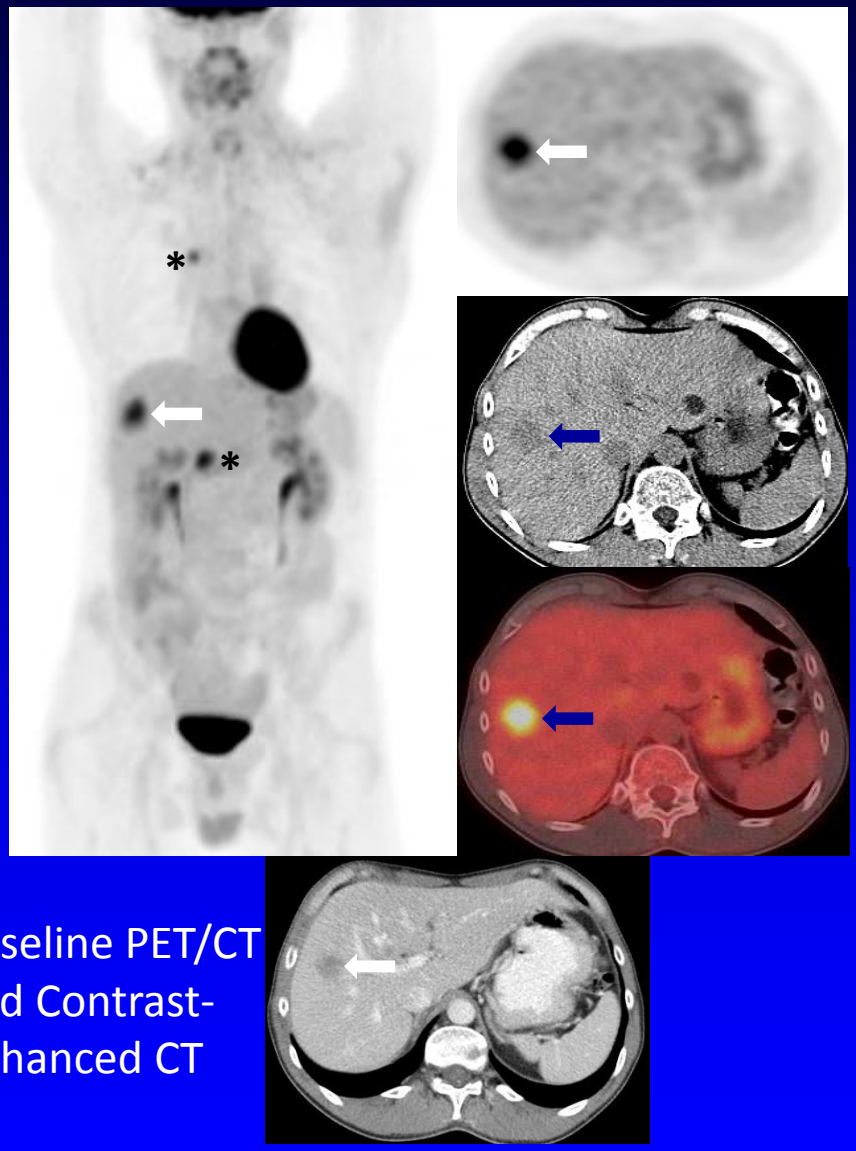
Restaging FDG-PET/CT 2

20 weeks

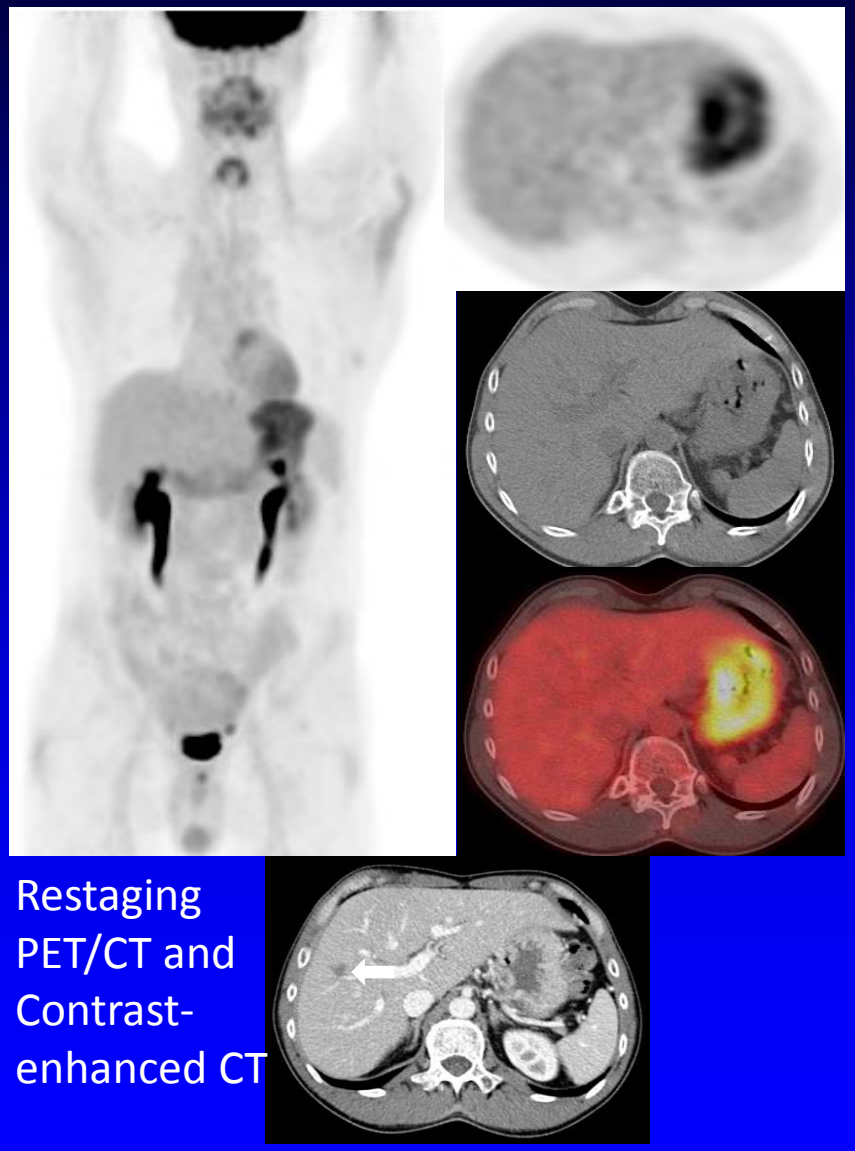
Discordance Between IRC and Lugano

- Restaging PET-CT shows resolution of lesions
- If persistent CT lesions would be considered a PR by IRC
- Considered CR by Lugano if no longer FDG avid

Dicrepancy Between Lugano and IRC



Baseline PET/CT and Contrast-enhanced CT



Restaging PET/CT and Contrast-enhanced CT

LRF Sponsored Workshop 20.11.15: Assessment of Response in Patients On Immunmodulatory Agents

LYMPHOMA RESEARCH · FOUNDATION

CANCER RESEARCH INSTITUTE

Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents Including Immune Checkpoint Inhibitors

Overview:	The *Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents Workshop* (the workshop) will allow leading clinicians and pharmaceutical researchers to share their experience with immune regulating agents which may induce an immune flare reaction in lymphoma. Lymphoma is one of the major cancer types for which new immune-based cancer treatments are currently in development.
Objective:	The objective of the workshop is to address the unique patient response to this class of drugs and recommend appropriate adaptations of current lymphoma response criteria
Logistics:	One-day program on November 20; the workshop will be held in Washington, DC.

Immune Response Workshop

- Included presentations from investigators and industry representatives on experience with check point inhibitors
- Discussed the relevance of solid tumor IRC to lymphoma
- Determined lymphoma-specific criteria were needed
- Developed Lymphoma Response to Immunomodulatory Therapy Criteria (LyRIC)

Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy

Bruce D. Cheson, Stephen Ansell, Larry Schwartz, Leo I. Gordon, Ranjana Advani, Heather A. Jacene, Axel Hoos, Sally F. Barrington, Philippe Armand

Blood 2016 :blood-2016-05-718528; doi:10.1182/blood-2016-05-718528

Indeterminate Response (IR)

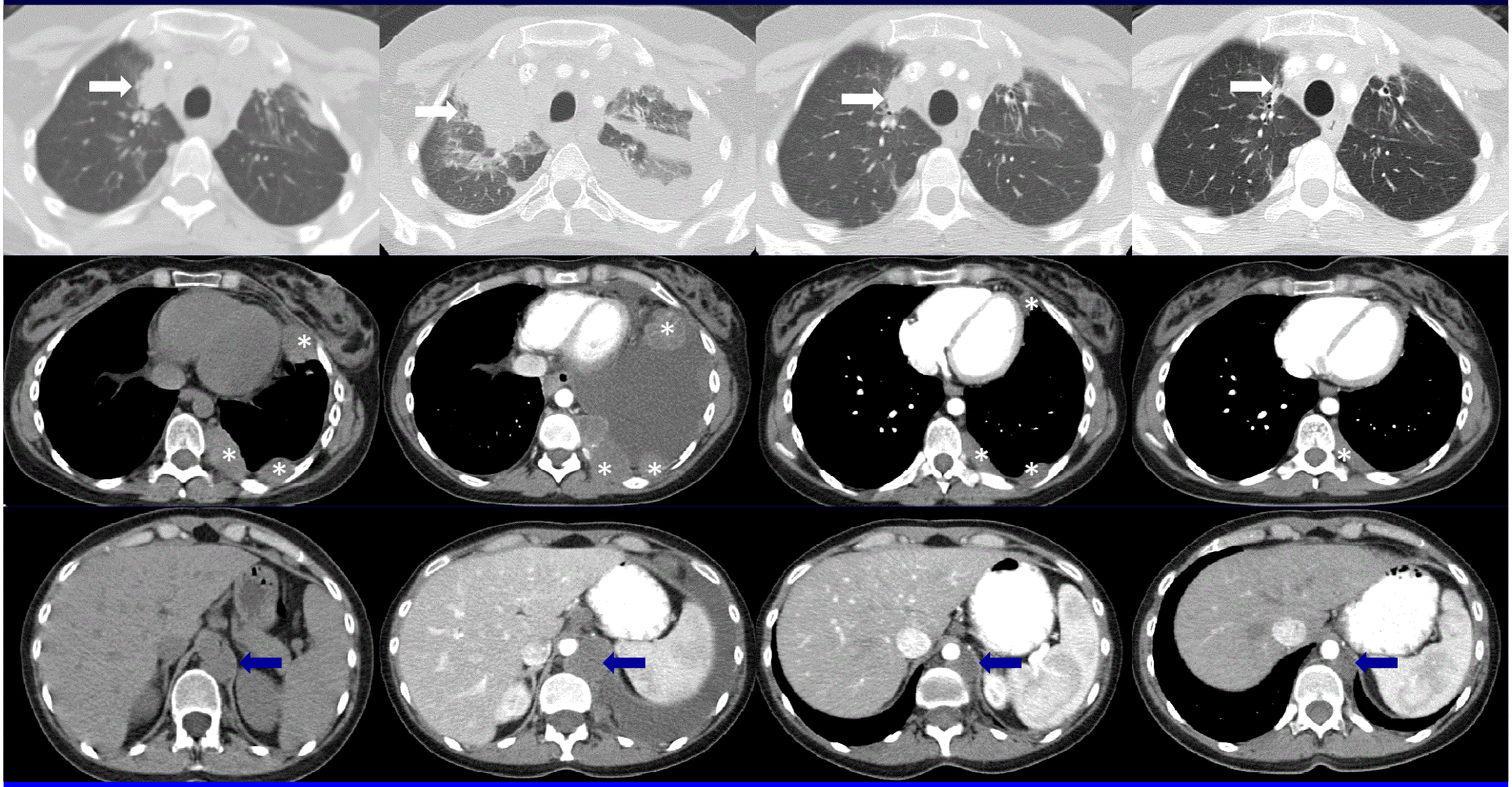
- Provisional term
- To identify lesions that may be flare vs PD
- Does not make direct reference to underlying mechanism
- Allows appropriate patients to remain on treatment
  - until reassessment to confirm or refute PD
  - or biopsy proven disease

Definitions of Types of IR

IR1: Increase in overall tumor burden (by SPD) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration

Cheson et al, Blood, e-pub online, Sept 2016

IR1

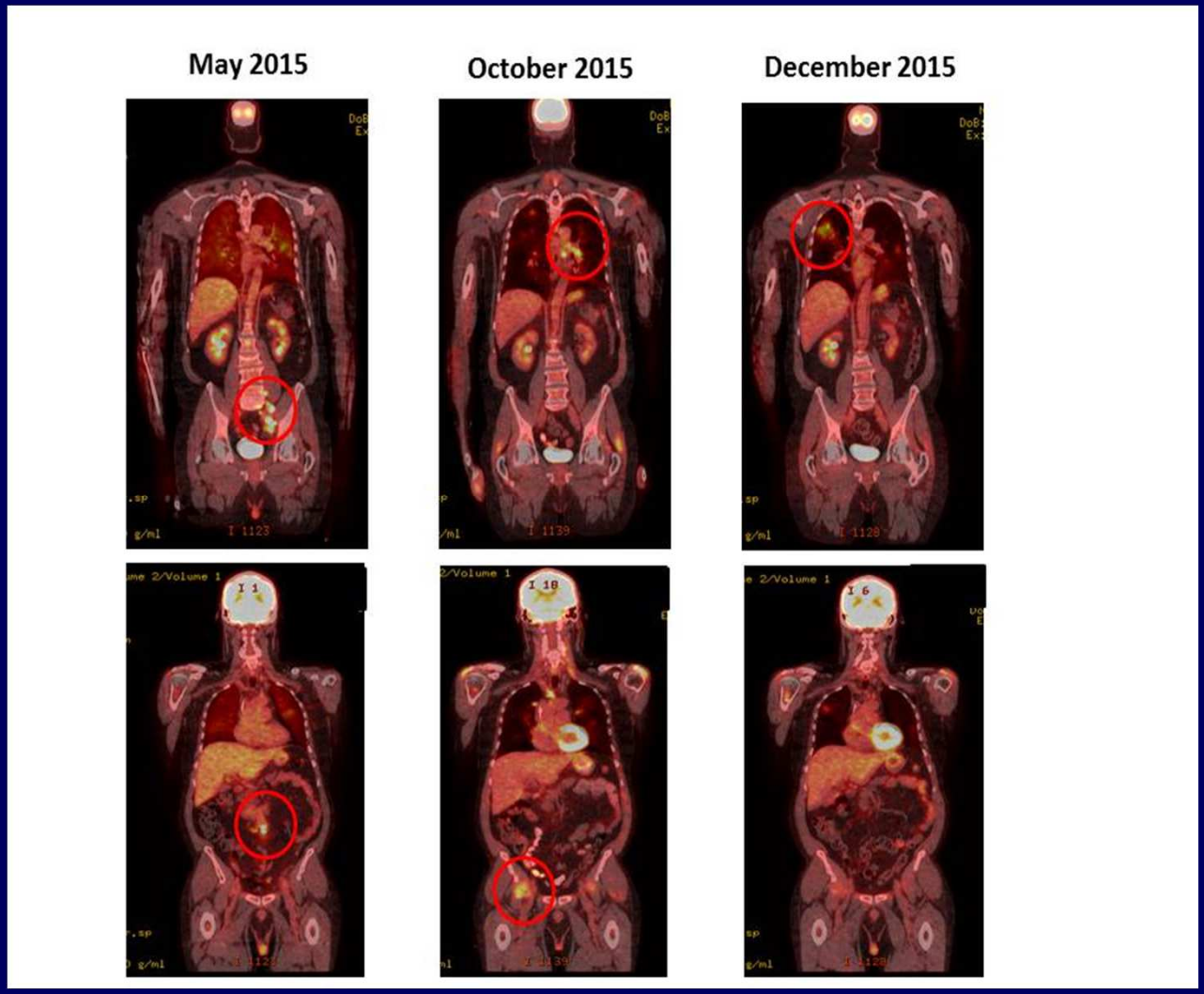


Baseline CT | Restaging CT 1- 3 wks | Restaging CT 2- 7 wks | Restaging CT 3-13 wks

Definitions of Types of IR

IR2: Appearance of new lesions; or growth of one or more existing lesion(s) ≥50%; at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, by SPD of up to 6 lesions at any time during the treatment.

IR2



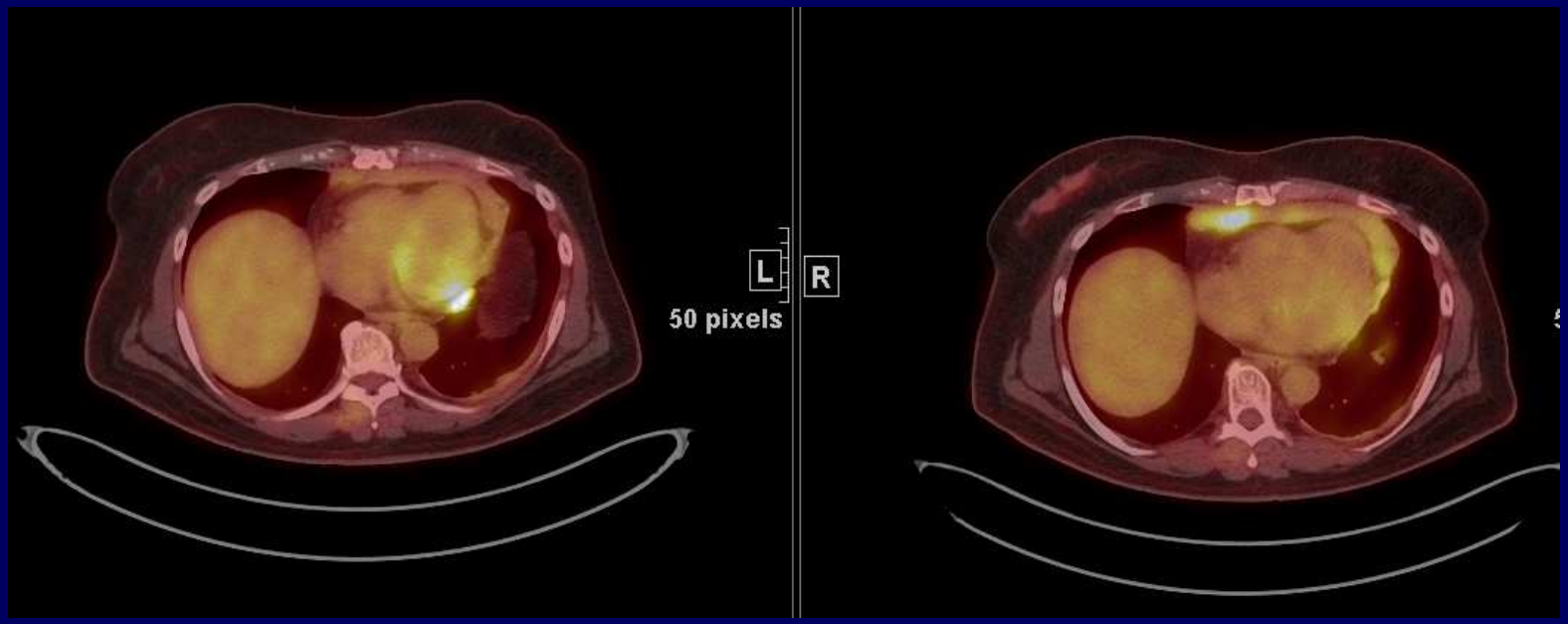
Definitions of Types of IR

IR3: Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number

IR(3) an increase in FDG uptake of one or more lesions suggestive of lymphoma without a concomitant increase in size of those lesions meeting PD

July 2, 2014

Sept 3, 2014



Follow-up of IR

- Repeat scan in 12 wks (earlier if indicated)
- PD if:
  - IR1 – further increase in SPD
  - IR2 – new lesion added to SPD (unless benign) and, if ≥50% increase – PD
  - IR3 – PD if increase in size or new lesions

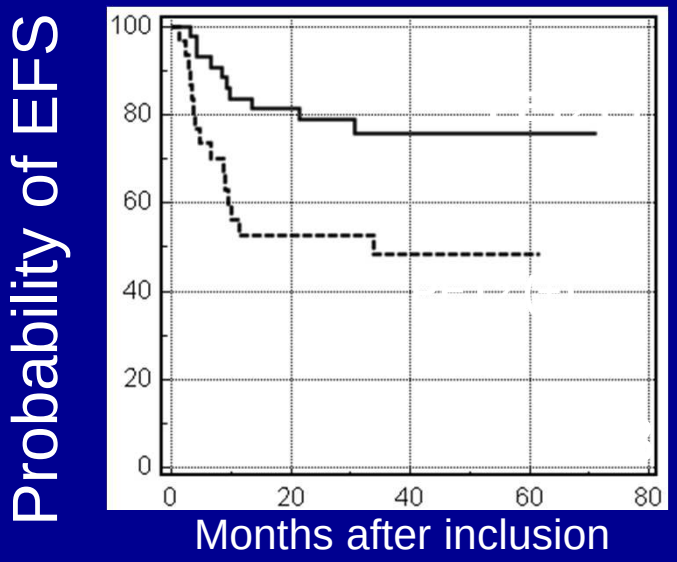
Future Directions

- Quantitative assessment of response
  - Δ SUV
  - Total tumor glycolysis
  - Metabolic tumor volume
- Combined modality approaches
- Understand contribution of the microenvironment
- Stratify patients pre-treatment

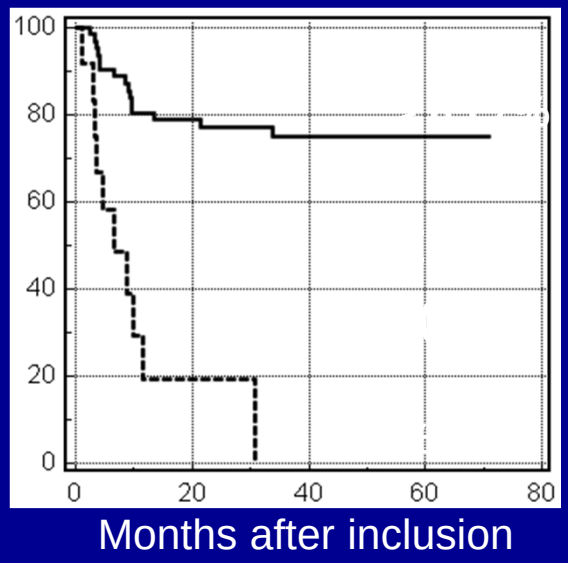
Visual *vs* SUV analysis

Early response assesment (2 cycles), n=92

Visual Analysis
(positive or negative)



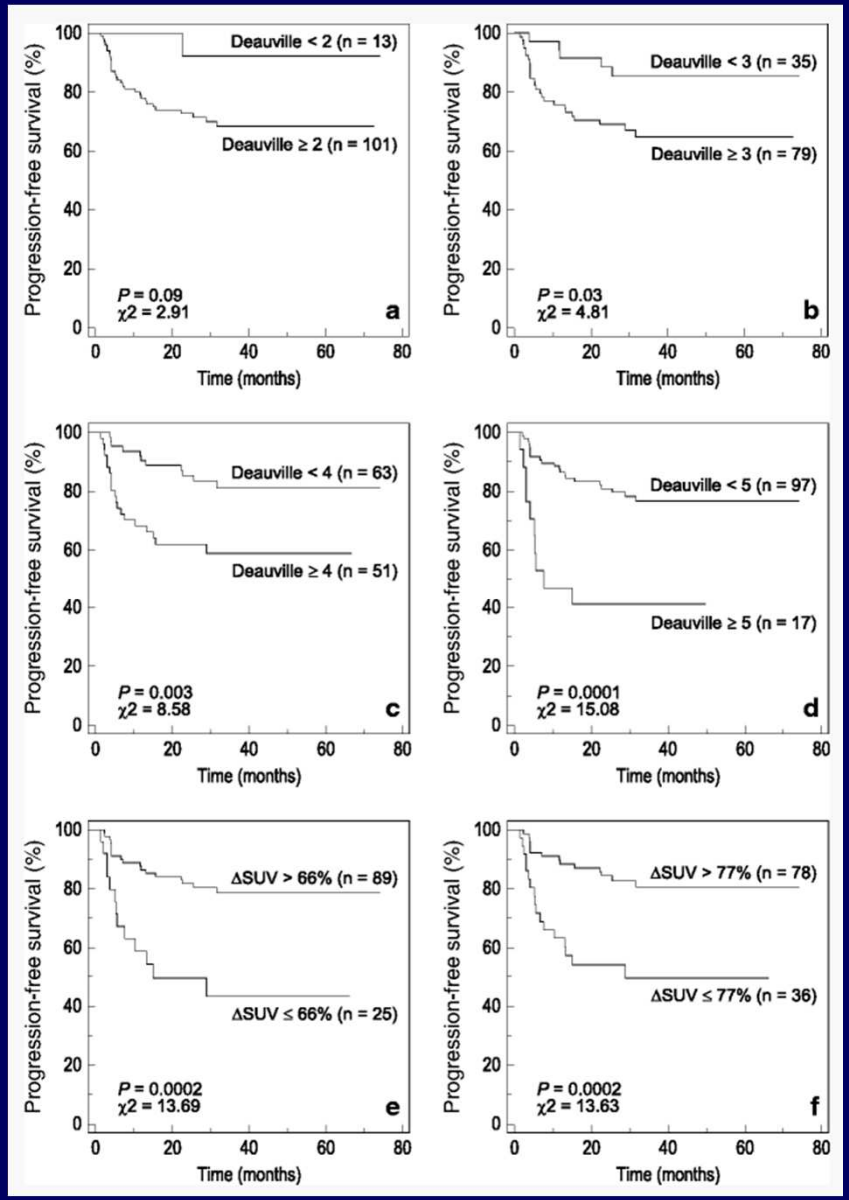
SUV Analysis
(ΔSUVmax PET0/PET2)



- Decreases the number of false positive studies
- 14/17 « false positive » patients reclassified with ΔSUVmax
- 2 cycles: ΔSUV better than visual assessment

Lin, Itti et al. *J Nucl Med* 2007;48:1626-32

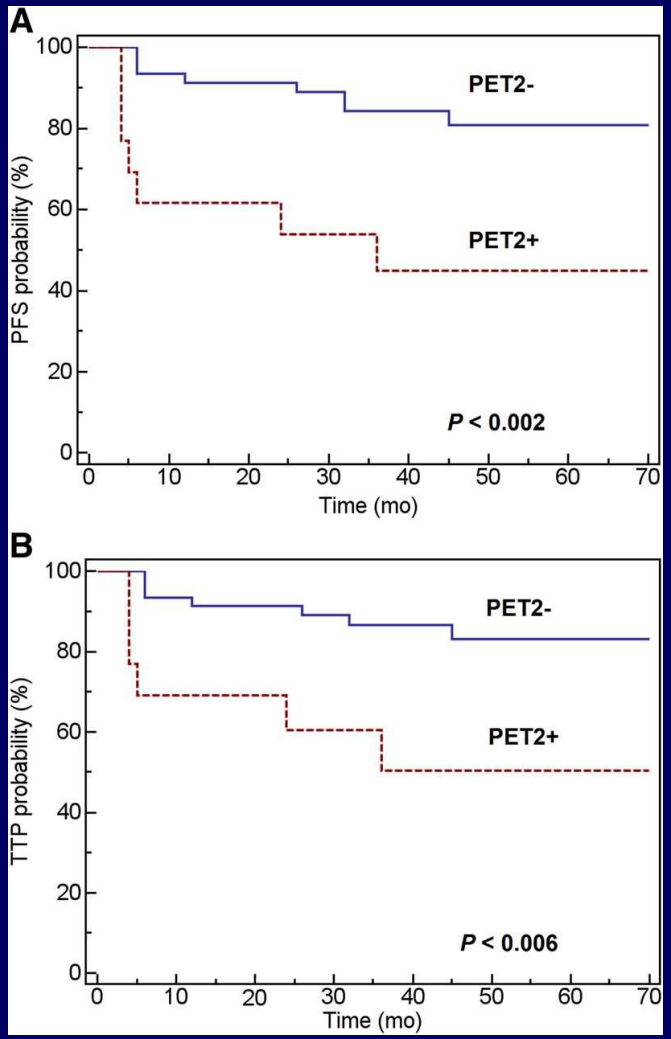
Interim PET and SUVmax Reduction in DLBCL



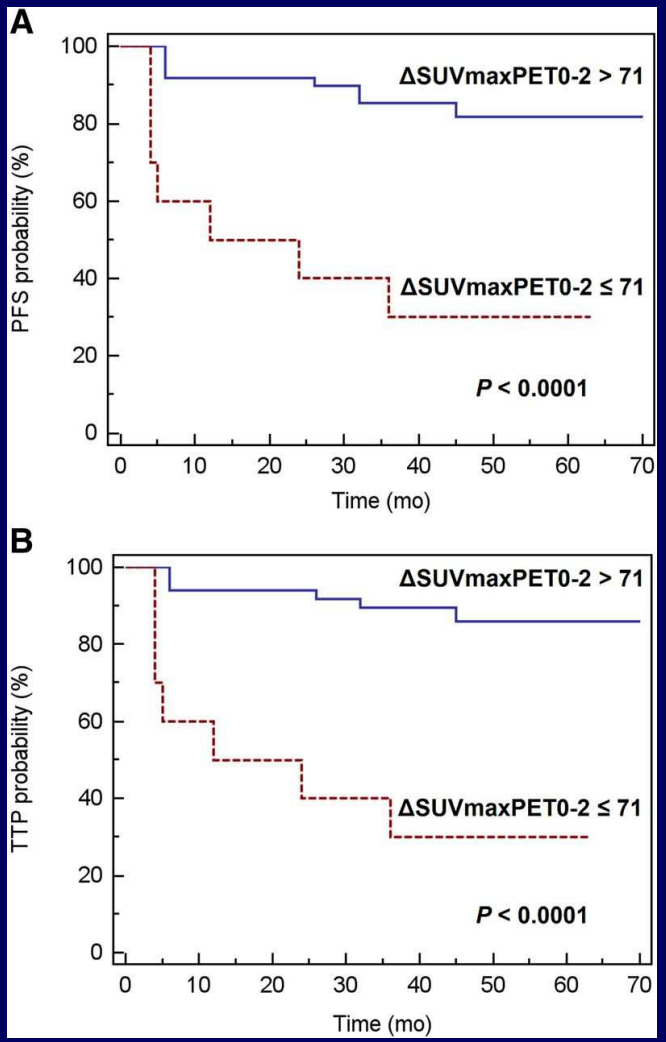
Itti et al Eur J Nucl Med Mol Imaging 40:1312, 2013

Interim PET vs SUVmax in HL

DS 5PS



ΔSUVmax



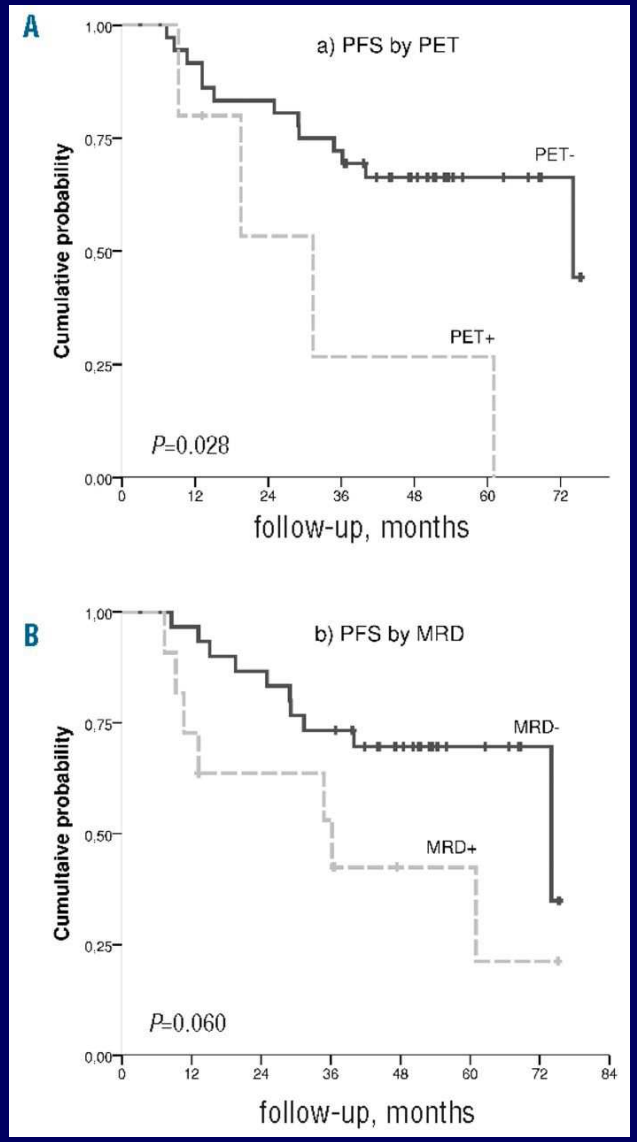
Rossi et al. J Nucl Med 2014;55:569-573

Combining PET with MRD in FL

- Subset analysis of FOLLO5 study
- MRD by BM aspirate for *BCL2/IGH* fusion gene at diagnosis and, if possible, EOT
- Positive scan – DS $\geq$ 4
- 41 patients had both PET and MRD data EOT
- PET/MRD concordance 76%

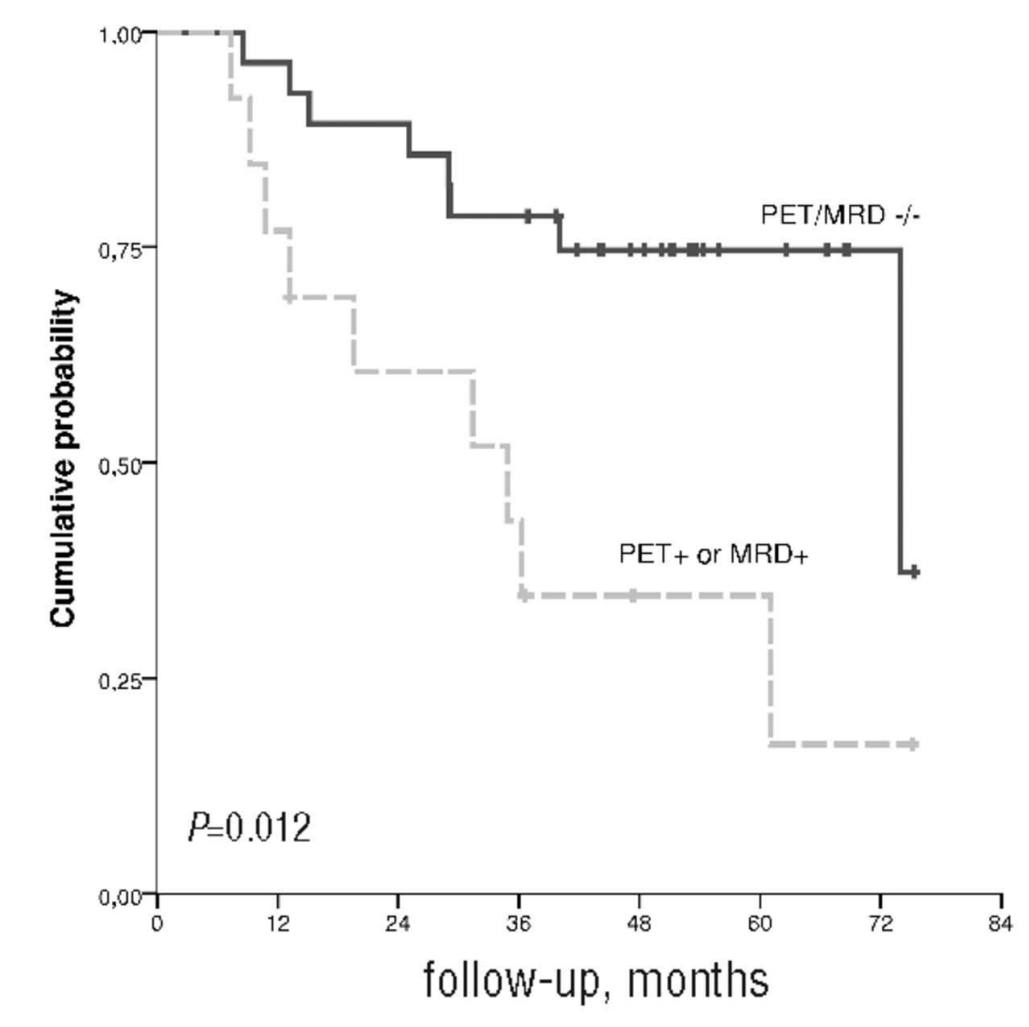
Stefano Luminari et al. Haematologica 2016;101:e66-e68

(A) PFS by PET. (B) PFS by MRD.



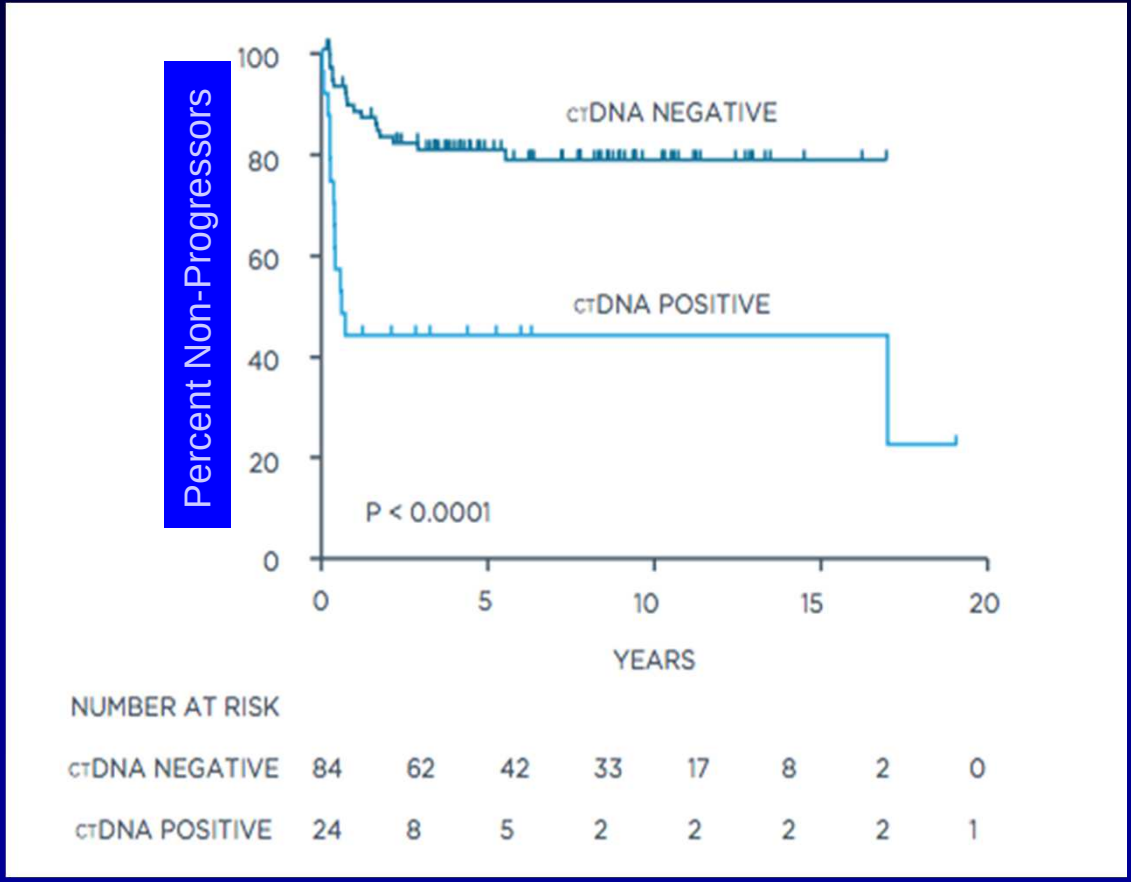
Stefano Luminari et al. Haematologica 2016;101:e66-e68

PFS in FOLLO5 according to combination of PET and MRD results.



Stefano Luminari et al. Haematologica 2016;101:e66-e68

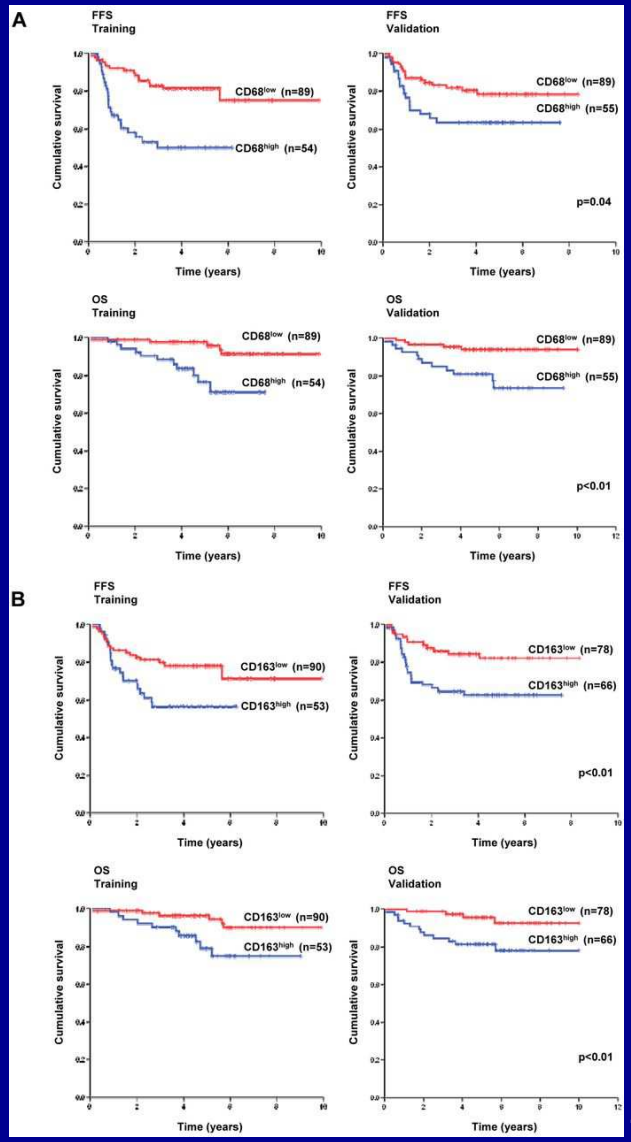
Detection of ctDNA During Treatment of DLBCL (Cycle 3, Day 1) Predicts Relapse



PPV	62.5 %
NPV	79.8 %
Sensitivity	46.9 %
Specificity	88.2 %

Roschewski, *et al. Lancet Oncol* 2015; 5:541-9.

Survival analysis based on macrophage content



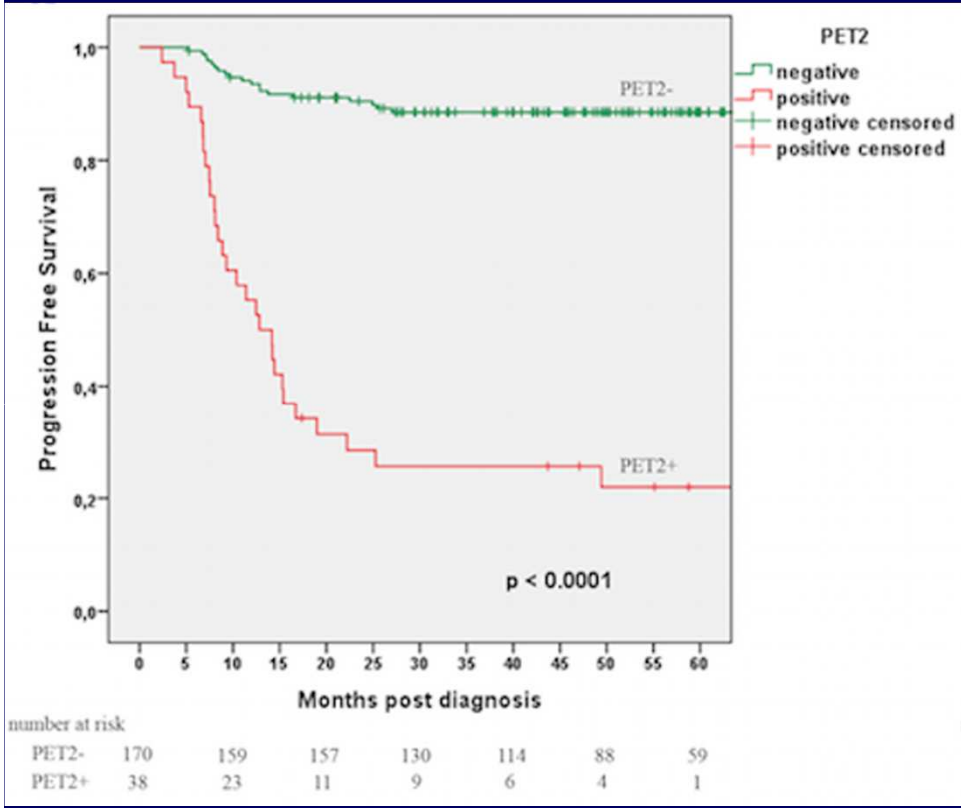
Tan et al. Blood 2012;120:3280-3287

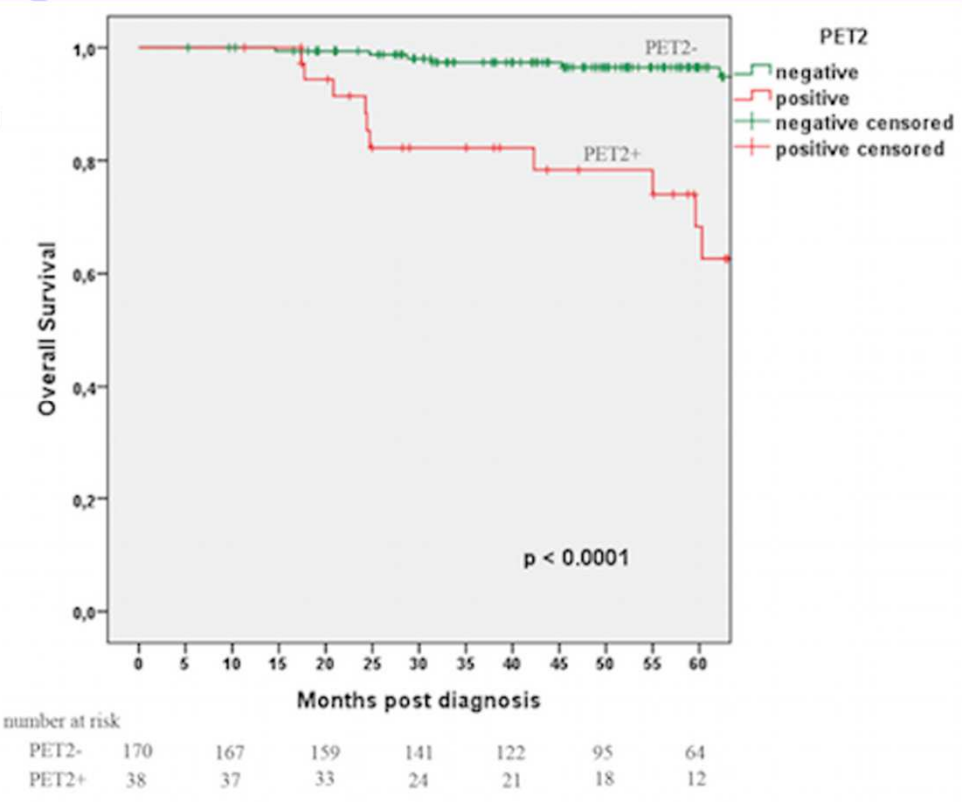
Biomarkers and the Microenvironment in HL

- PET-2 strong predictor of outcome.
- NPV suboptimal: ~12% still relapse.
- Retrospective test in 208 pts with cHL treated with ABVD, validated in 102 pts.
- Assessed biomarkers on neoplastic cells.
- Evaluated biomarkers in microenvironmental cells from TMAs.
- Classification and Regression Tree (CART)

Agostinelli et al, Lancet Haem e-pub online

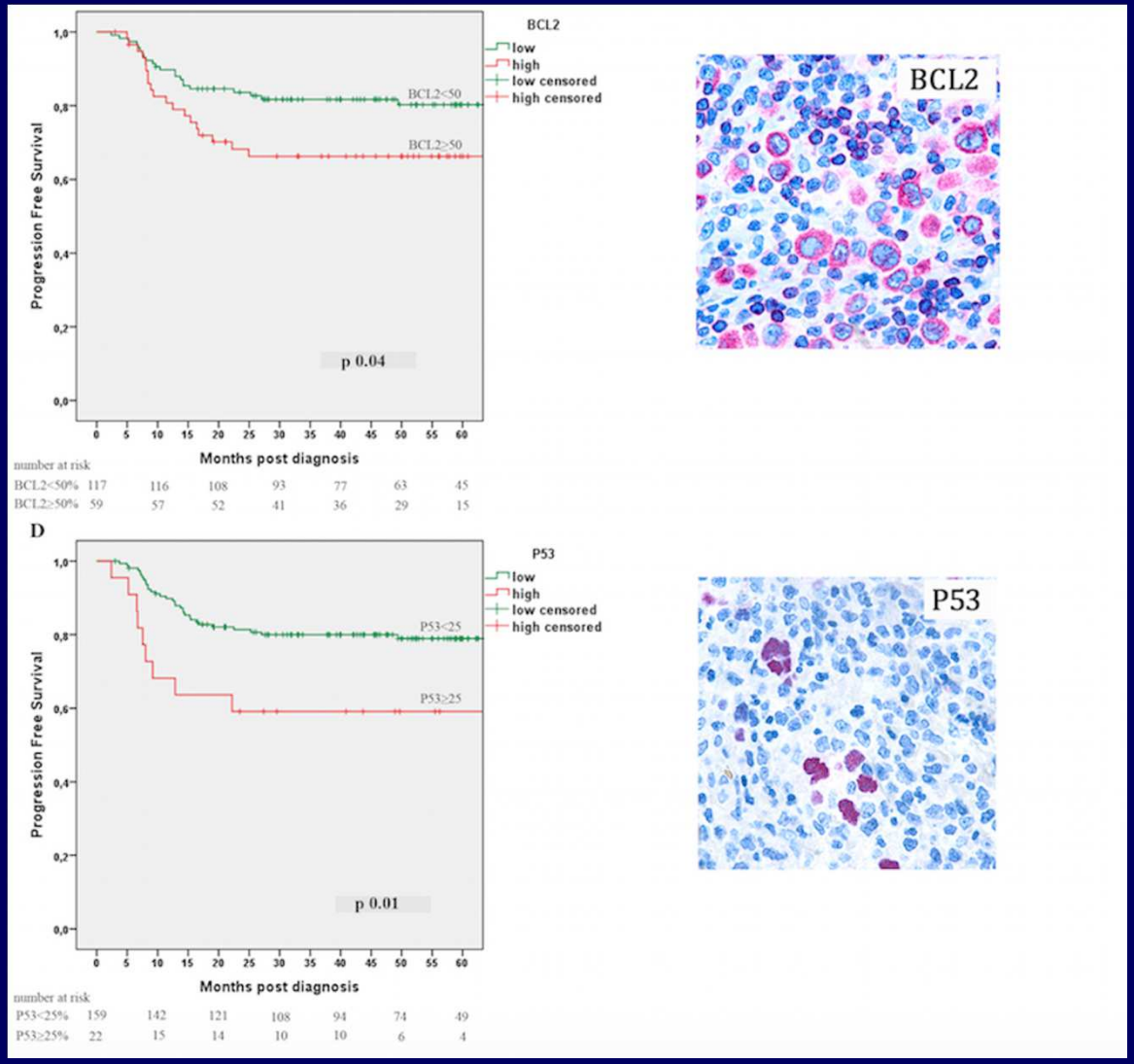
PET and Outcome in cHL





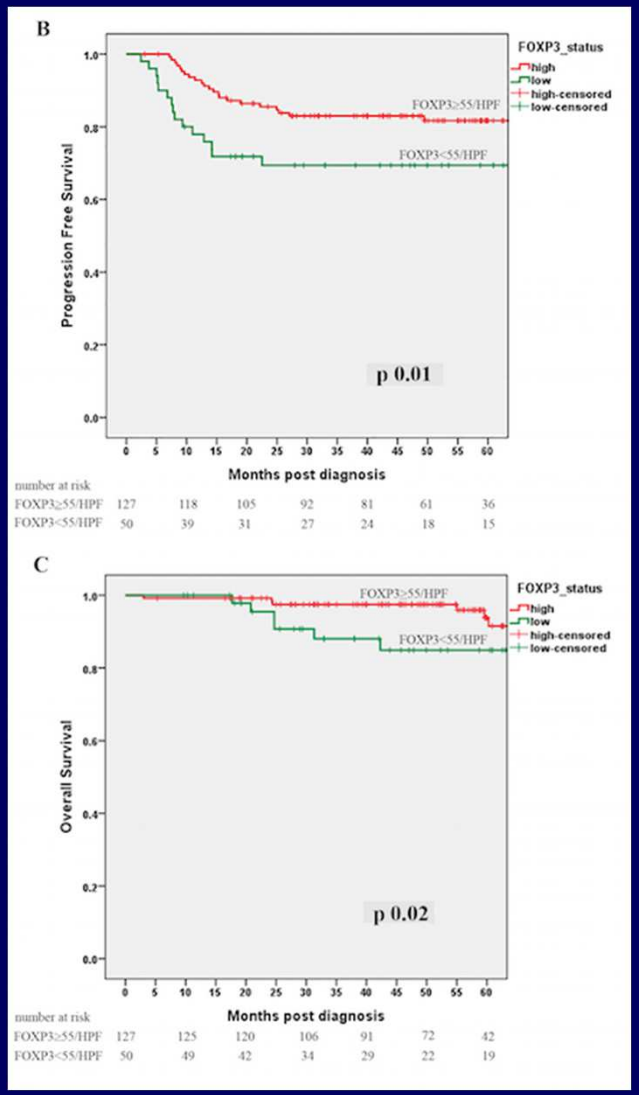
Agostinelli et al, Lancet Haematol e-pub on line

Biomarkers on HRS Cells and Outcome in cHL



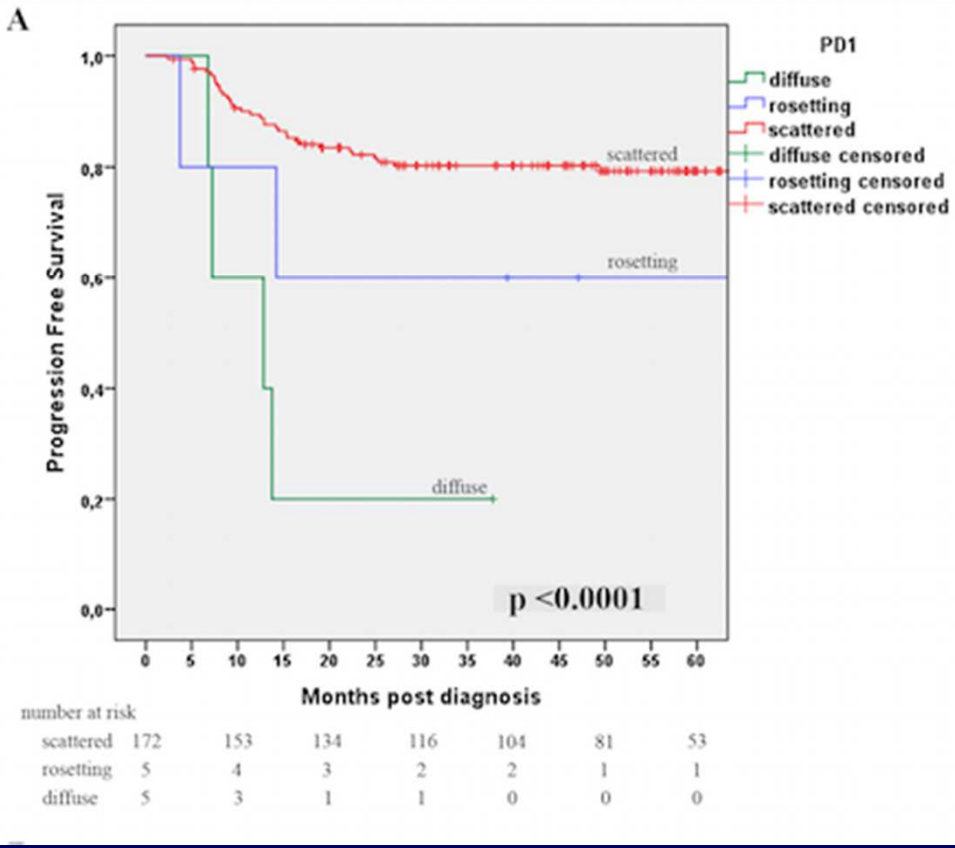
Agostinelli et al, Lancet Haematol e-pub on line

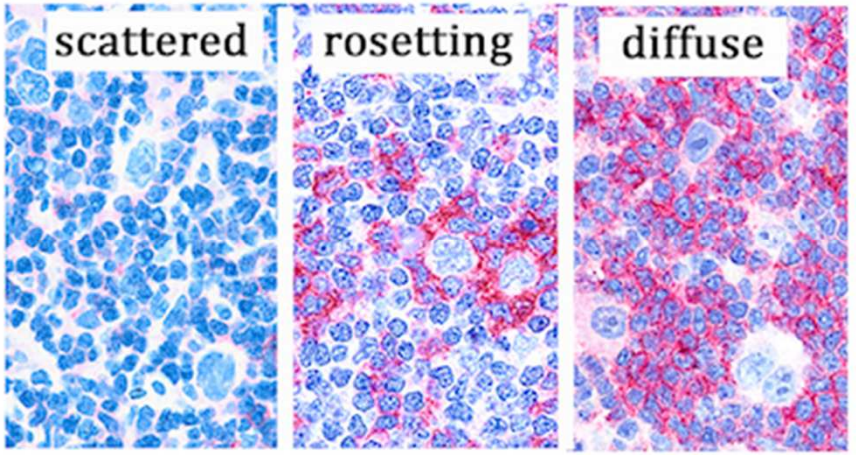
FOXP3 and Outcome in cHL



Agostinelli et al, Lancet Haematol e-pub on line

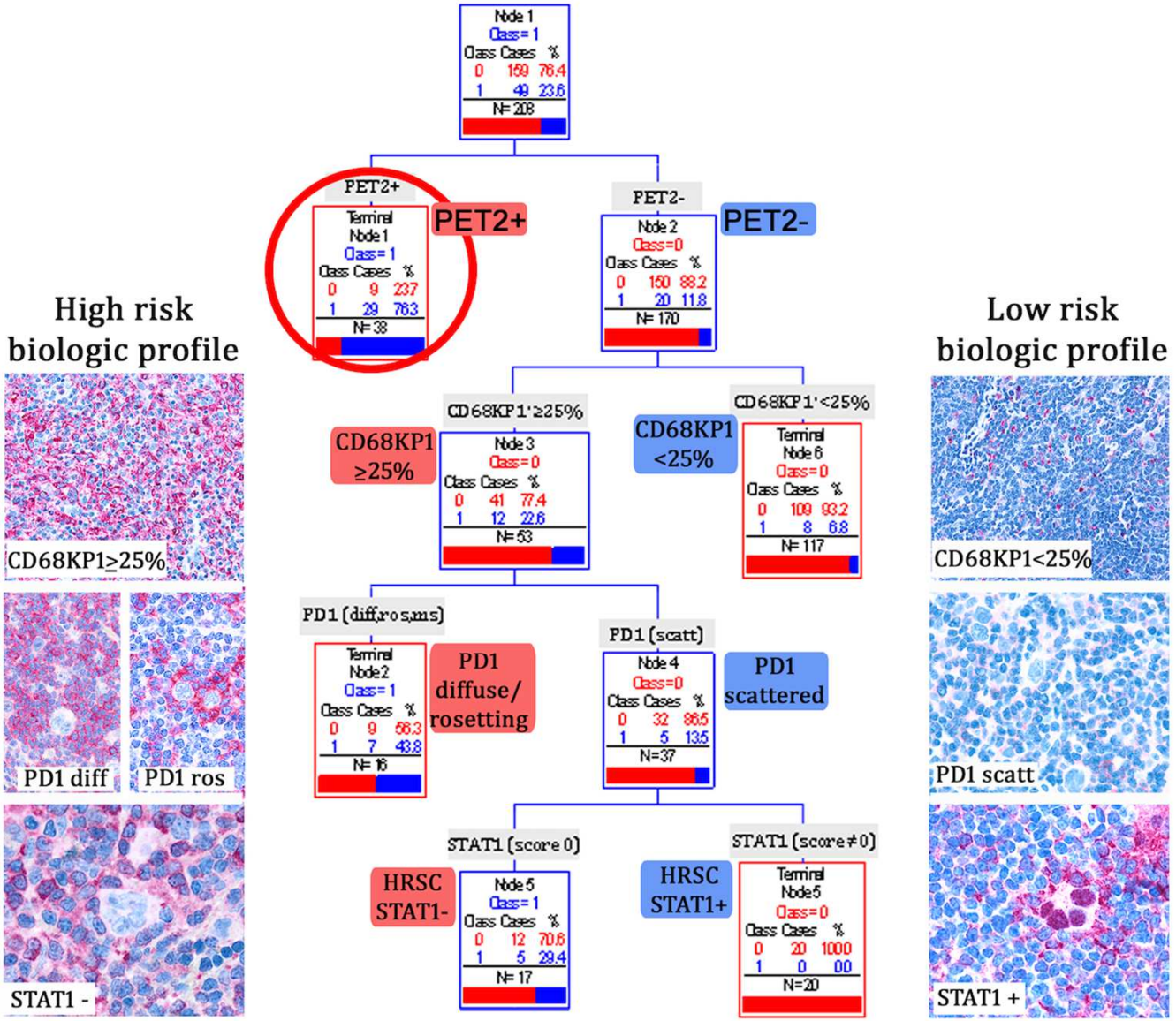
PD1 and Outcome in cHL





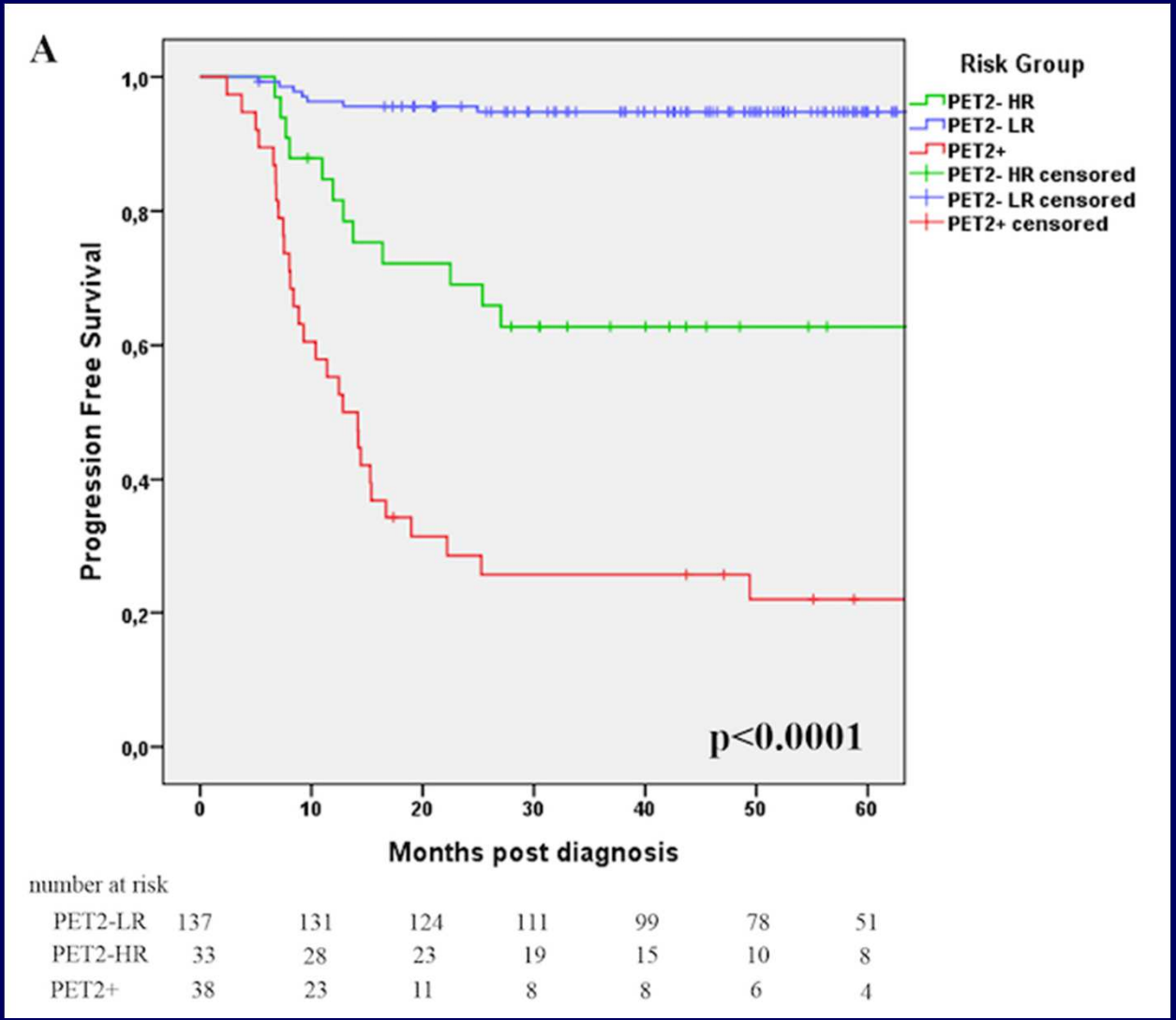
Agostinelli et al, Lancet Haematol e-pub on line

Classification tree for relapse/progression, learning set: 208 patients



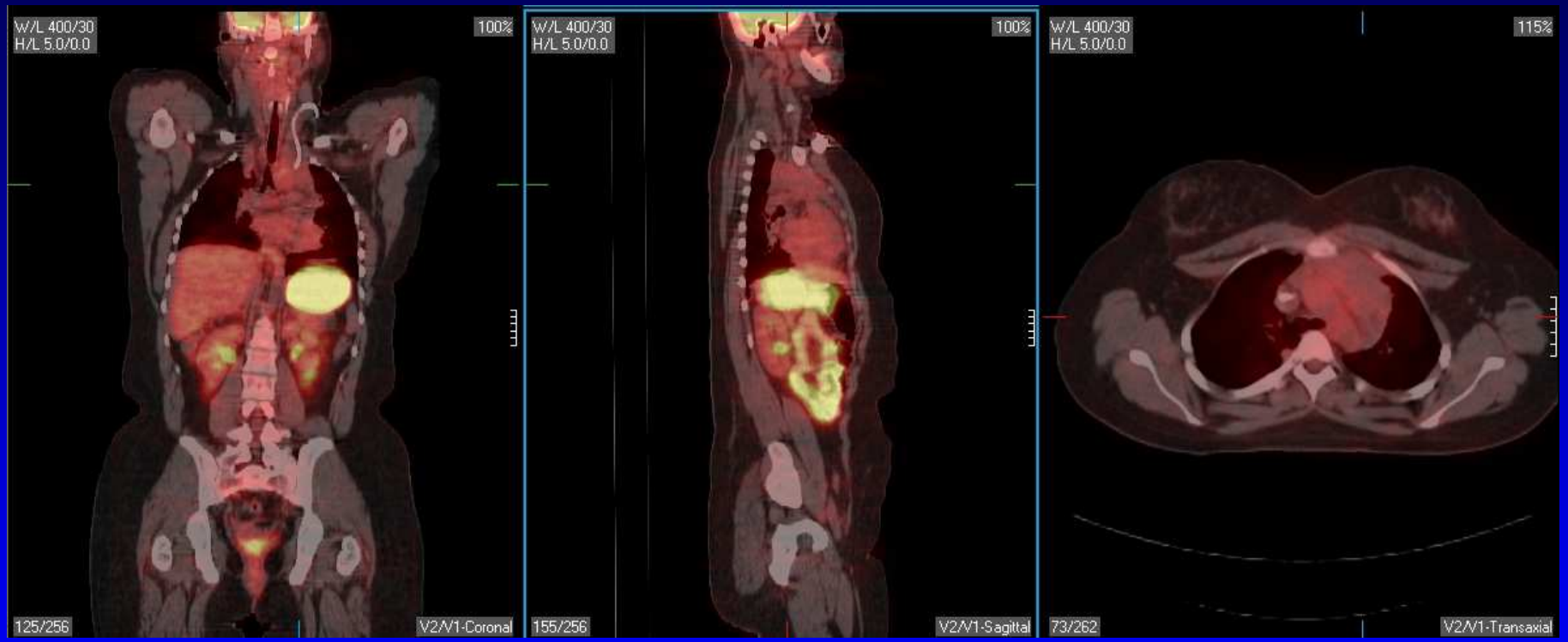
Agostinelli et al Lancet Haematol e-pub online

PFS By Biomarkers

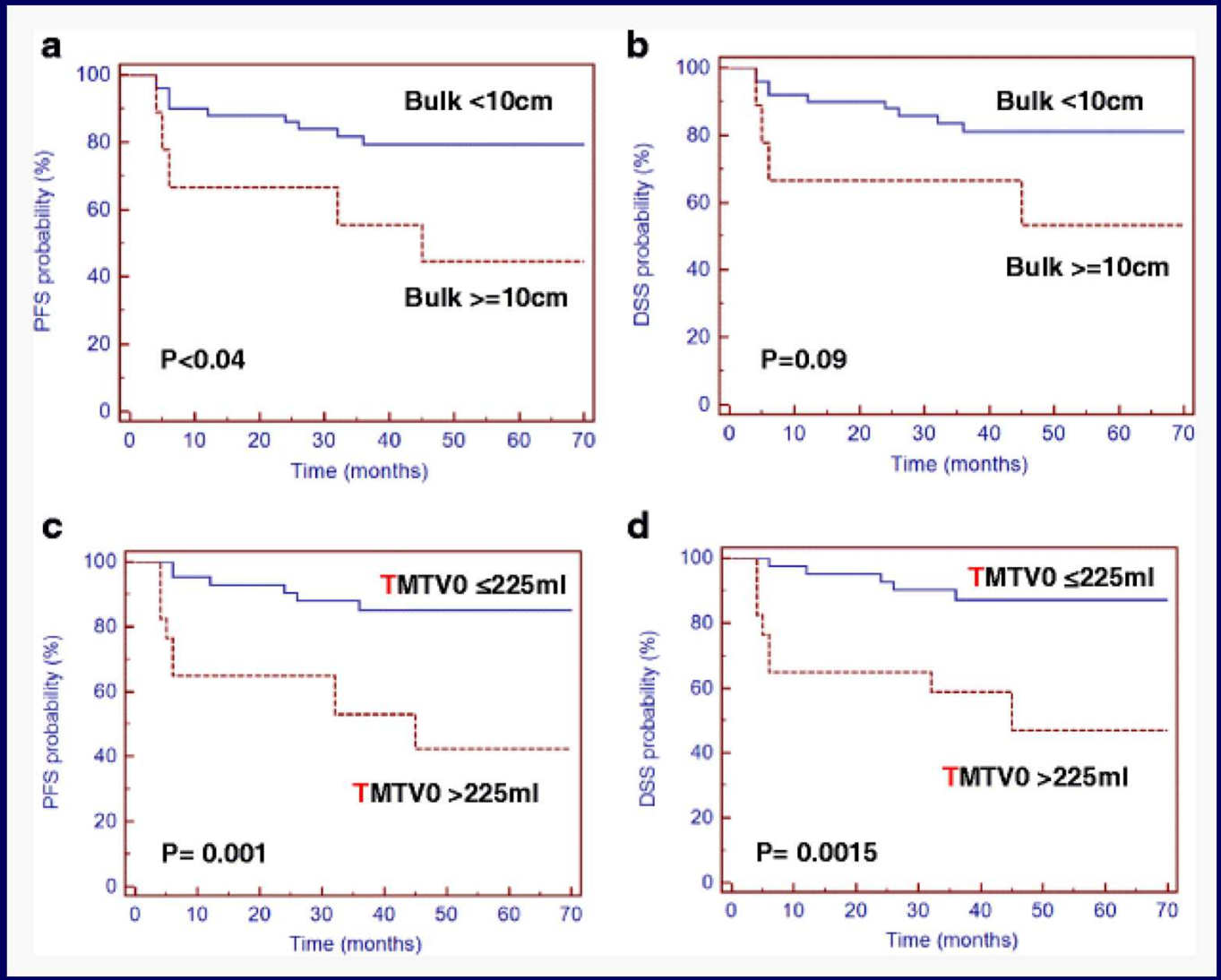


Agostinelli et al, Lancet Haematol e-pub on line


W/L 400/30
H/L 5.0/0.0
100%
118/256
V2/V1-Coronal
W/L 400/30
H/L 5.0/0.0
Sup
100%
231x470
Post
Ant
142/256
Inf
V2/V1-Sagittal
W/L 400/30
H/L 5.0/0.0
Ant
102%
391x445
R
79/262
183 (232,179)
Post
V2/V1-Transaxial


W/L 400/30
H/L 5.0/0.0
100%
125/256
V2/V1-Coronal
W/L 400/30
H/L 5.0/0.0
100%
155/256
V2/V1-Sagittal
W/L 400/30
H/L 5.0/0.0
115%
73/262
V2/V1-Transaxial

TMTV in Hodgkin Lymphoma



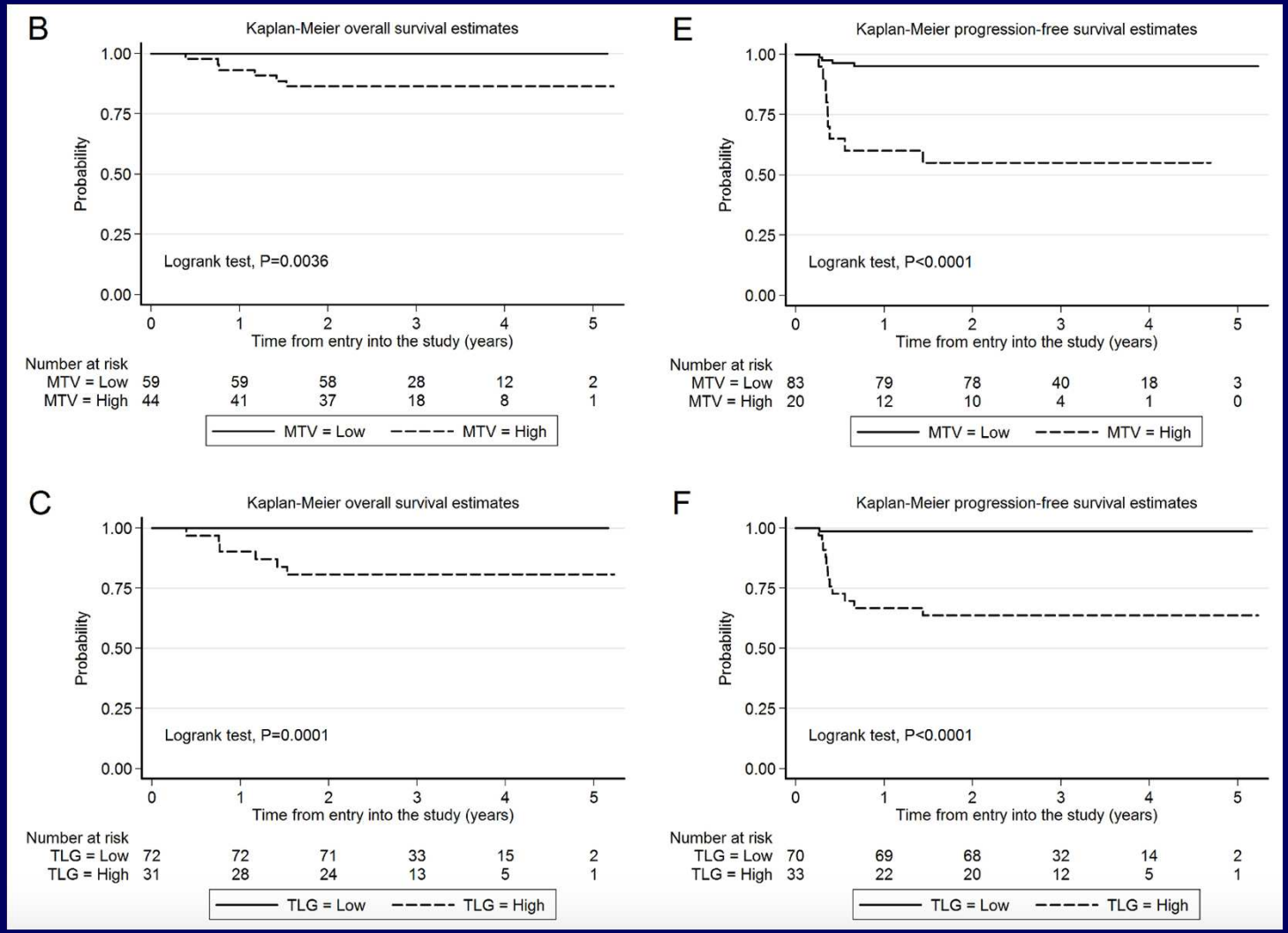
Kanoun et al Eur J Nucl Med Mol Imaging 41:1735, 2014

SUV_{max}, MTV and TLG in PMBCL in IELSG-26 Trial

- Prospective study of 103 pts with PMBCL
- All treated with R-doxorubicin; 90% with RT
- Median follow-up – 36 months
- Overall PFS/OS – 87%/94%
- Outcome correlated with functional imaging at diagnosis

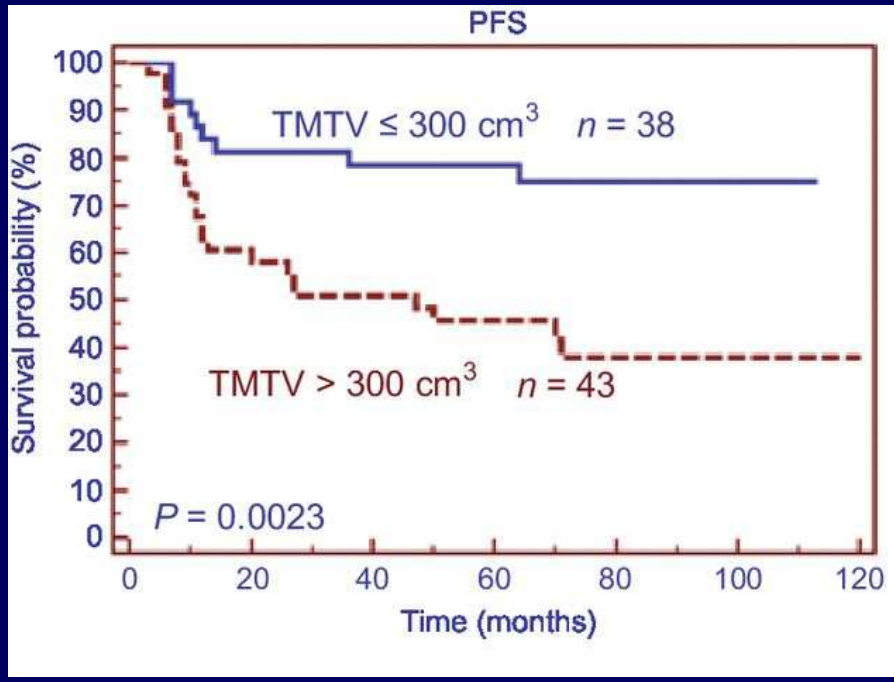
Ceriani et al, Blood, e-pub on line 2015

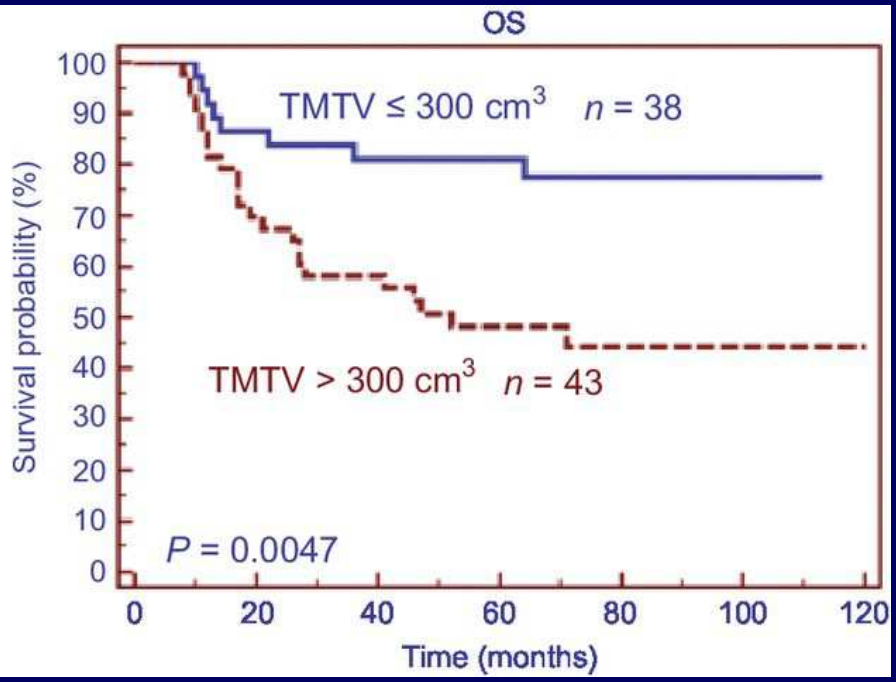
MTV and TLG in PMBCL



Ceriani et al, Blood 126:950, 2015

Kaplan–Meier estimates of PFS and OS according to baseline TMTV in DLBCL





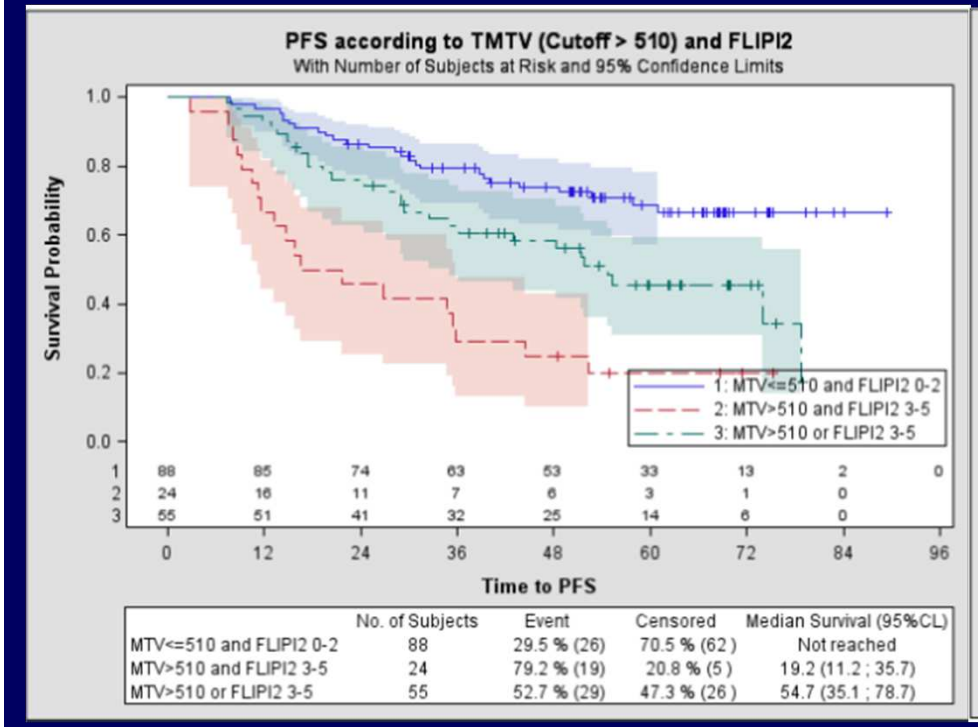
Cottereau et al. Clin Cancer Res 2016;22:3801-3809

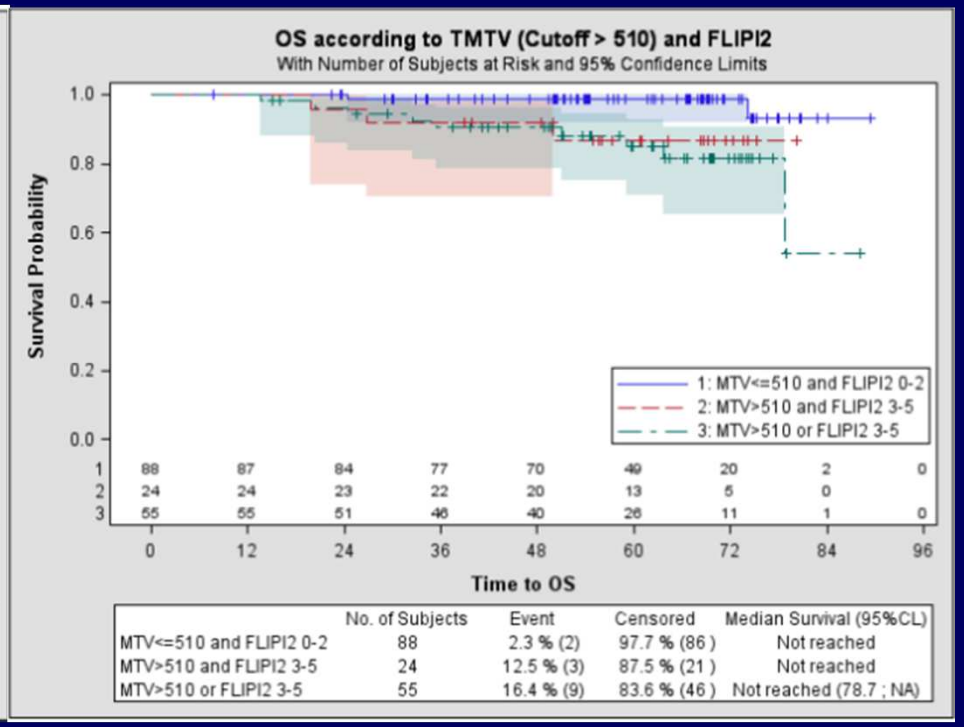
Baseline TMTV and Outcome in Patients with Untreated FL

- Pooled analysis from 3 R-chemo trials
- N = 185
- Median age 55 yrs
- 92% advanced disease; 37% FLIPI 3-5
- Median f/u 64 mos
- Used cut off of 510 cm^3

Meignan et al, JCO, in press

Pre-Treatment TMTV in FL



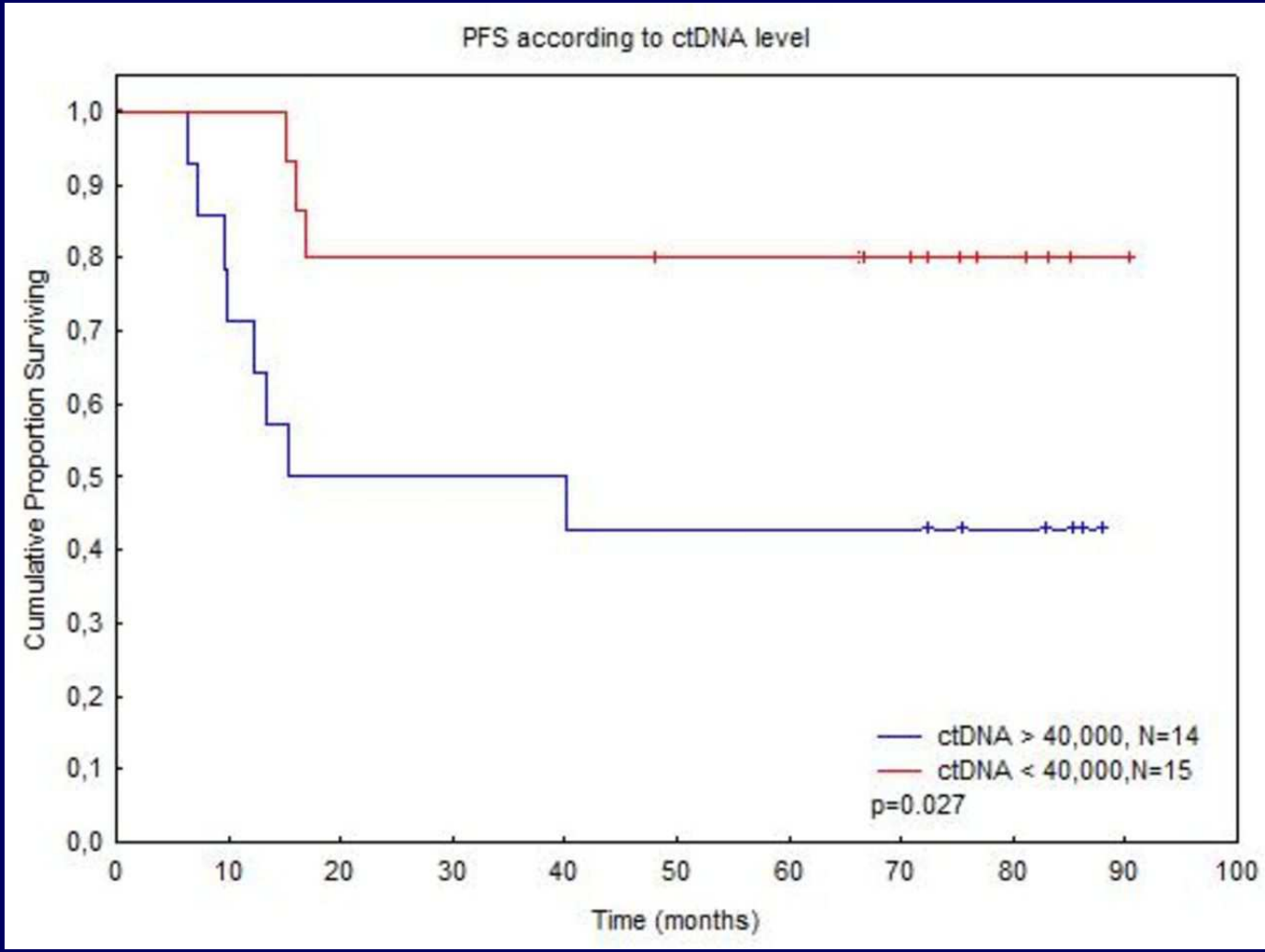


Meignan et al, JCO, in press

Issues With TMTV

- Retrospective nature of the studies
- Various cut-offs in different studies
- Various therapies
- Variable equipment
- Variable time to imaging
- Threshold may vary with primary tumor SUV or location
- Need to merge with more biological indicators

PFS of FL according to the level of pre-tx circulating tumor DNA (Clonoseq)

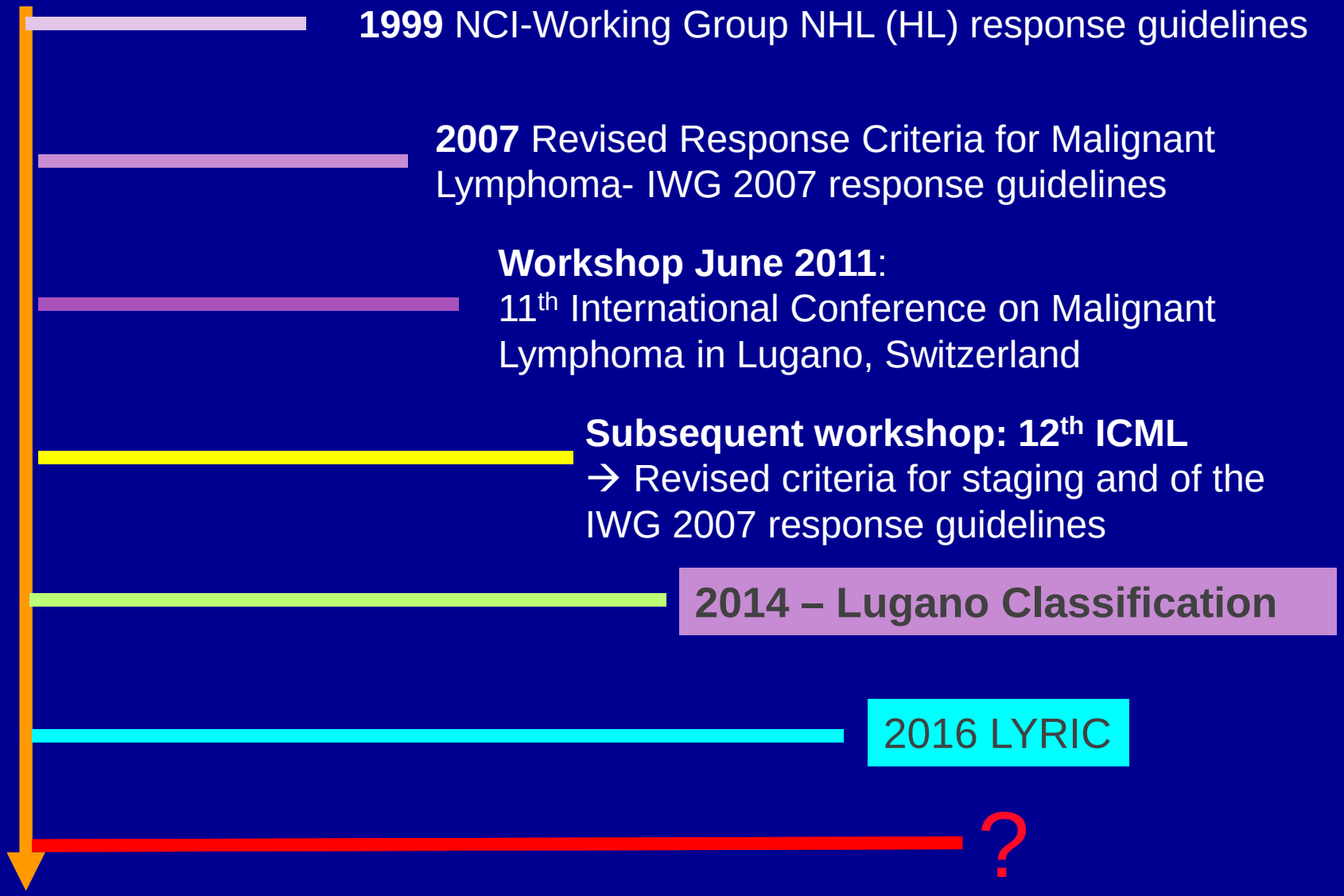


Clémentine Sarkozy et al. Blood 2015;126:2675

Conclusions

- PET-CT has revolutionized the staging and response assessment in lymphoma
  - Fewer patients overtreated
  - Fewer patients undertreated
  - Fewer patients trephined
- Response adapted approaches decrease toxicity and improve efficacy in HL
- PET-CT may be useful in pretreatment stratification
- Combined modality approaches should be explored
- Continued study will improve patient outcome

1999……TO LUGANO AND……..



1999 NCI-Working Group NHL (HL) response guidelines

2007 Revised Response Criteria for Malignant Lymphoma- IWG 2007 response guidelines

Workshop June 2011:
11th International Conference on Malignant Lymphoma in Lugano, Switzerland

Subsequent workshop: 12th ICML
→ Revised criteria for staging and of the IWG 2007 response guidelines

2014 – Lugano Classification

2016 LYRIC

?

Menton: 6th International Workshop on PET in Lymphoma 19-21.9.2016

14th ICML~ 14-17 June, 2017