

A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of involved mediastinal radiotherapy in Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)

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PET Trial Panel

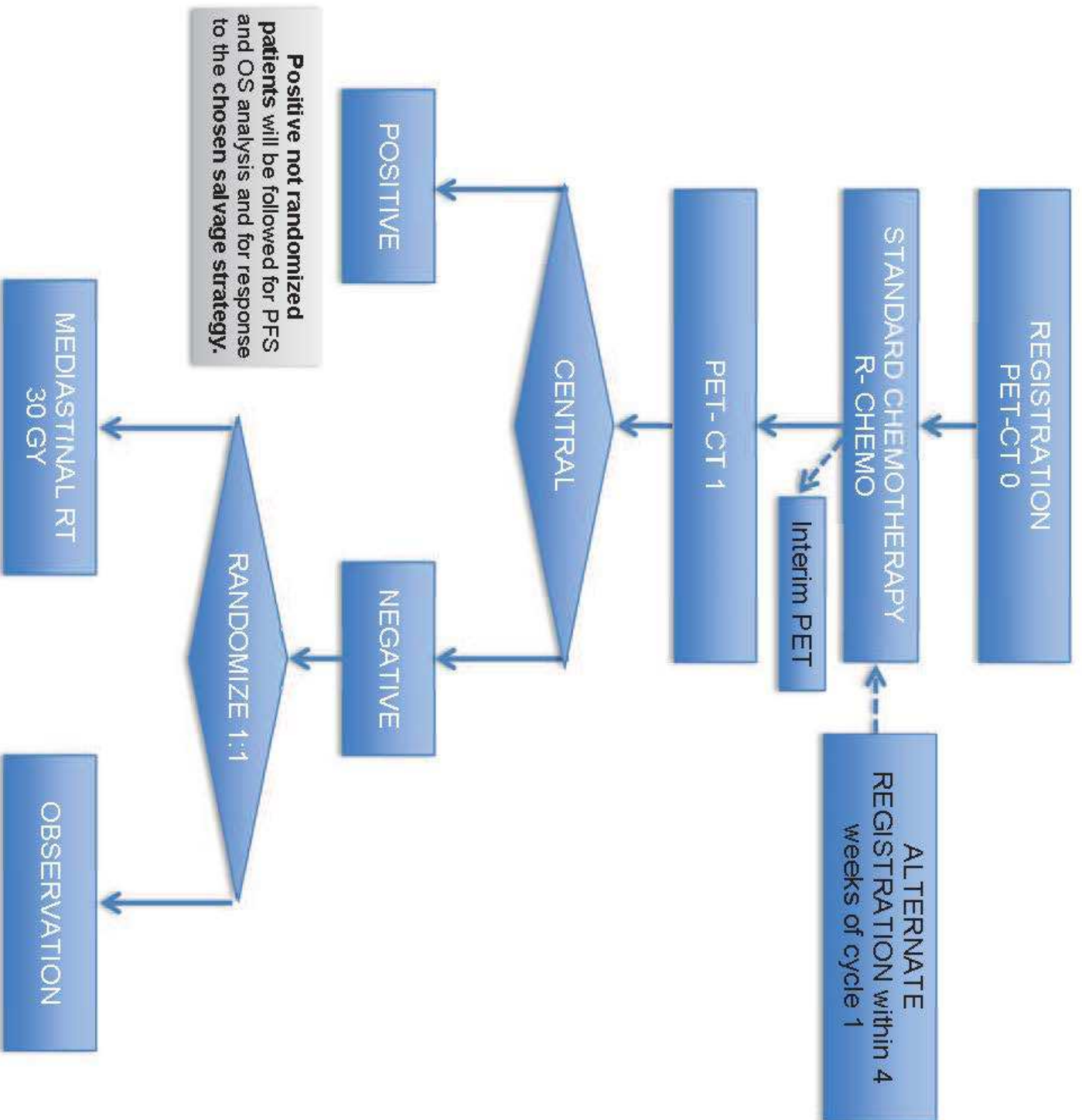
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INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

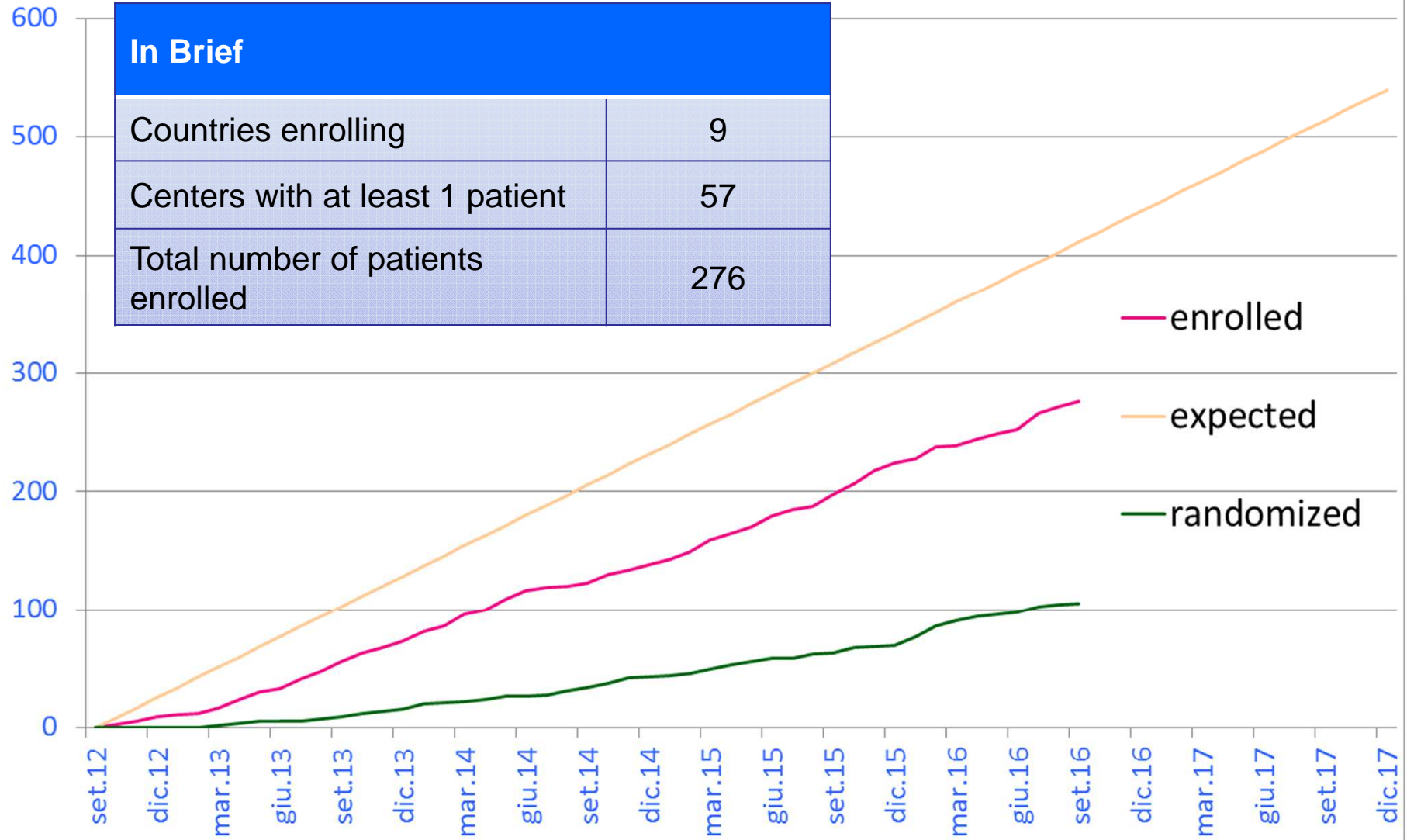


STUDY DESIGN



IELSG 37: Accrual

In Brief	
Countries enrolling	9
Centers with at least 1 patient	57
Total number of patients enrolled	276





ENROLLED PATIENTS

(September 12, 2016)

Country	# of Centres	# of Patients
Italy	33	202
UK	11	23
Ukraine	1	21
Switzerland	4	12
Canada	1	6
Poland	1	6
Norway	2	6
Sweden	1	4
USA	1	1



AUTHORIZED SITES (no patients enrolled yet)

(Regulatory Authorization and PET qualification – July, 2016)

Countries (7)	# of Centers (21)
Korea	1
Italy	10
Norway	2
Sweden	1
Switzerland	1
USA	1
UK	5

Expected to join

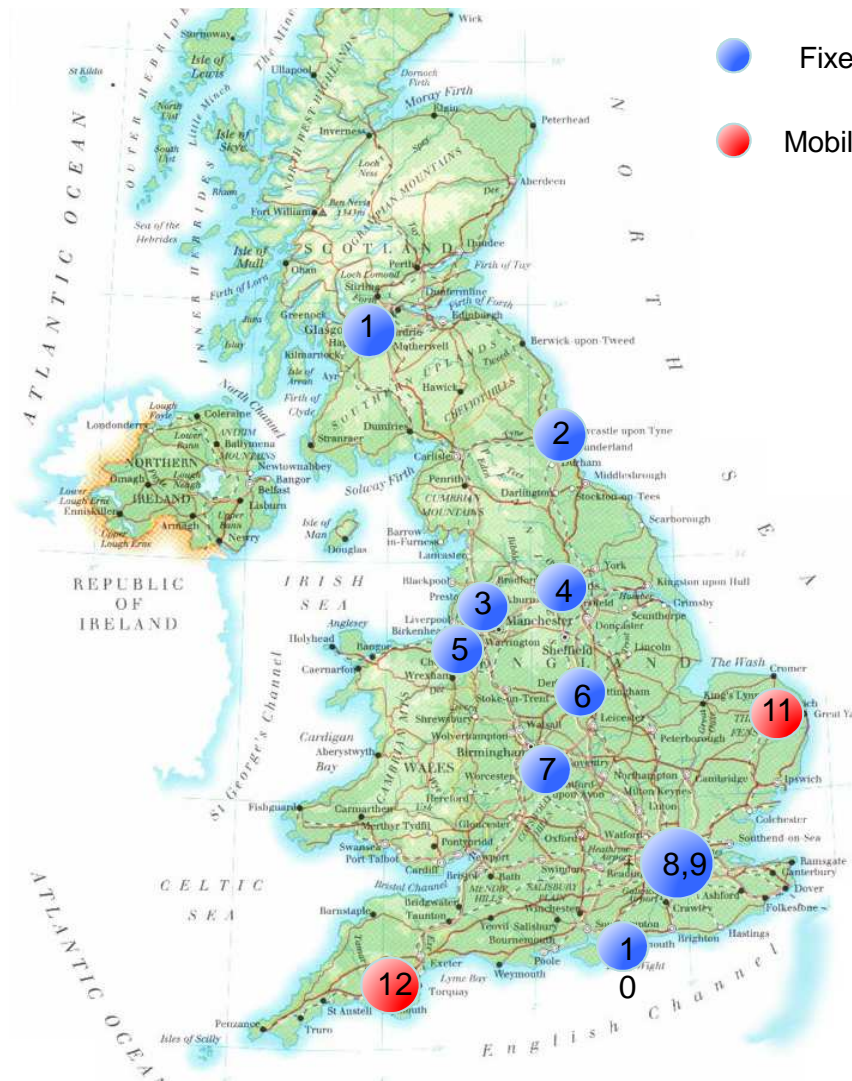
Argentina, Brazil, Germany, and a few other countries/centres with commitment



UK PET Core Lab

Quality Control for PET Clinical Trials

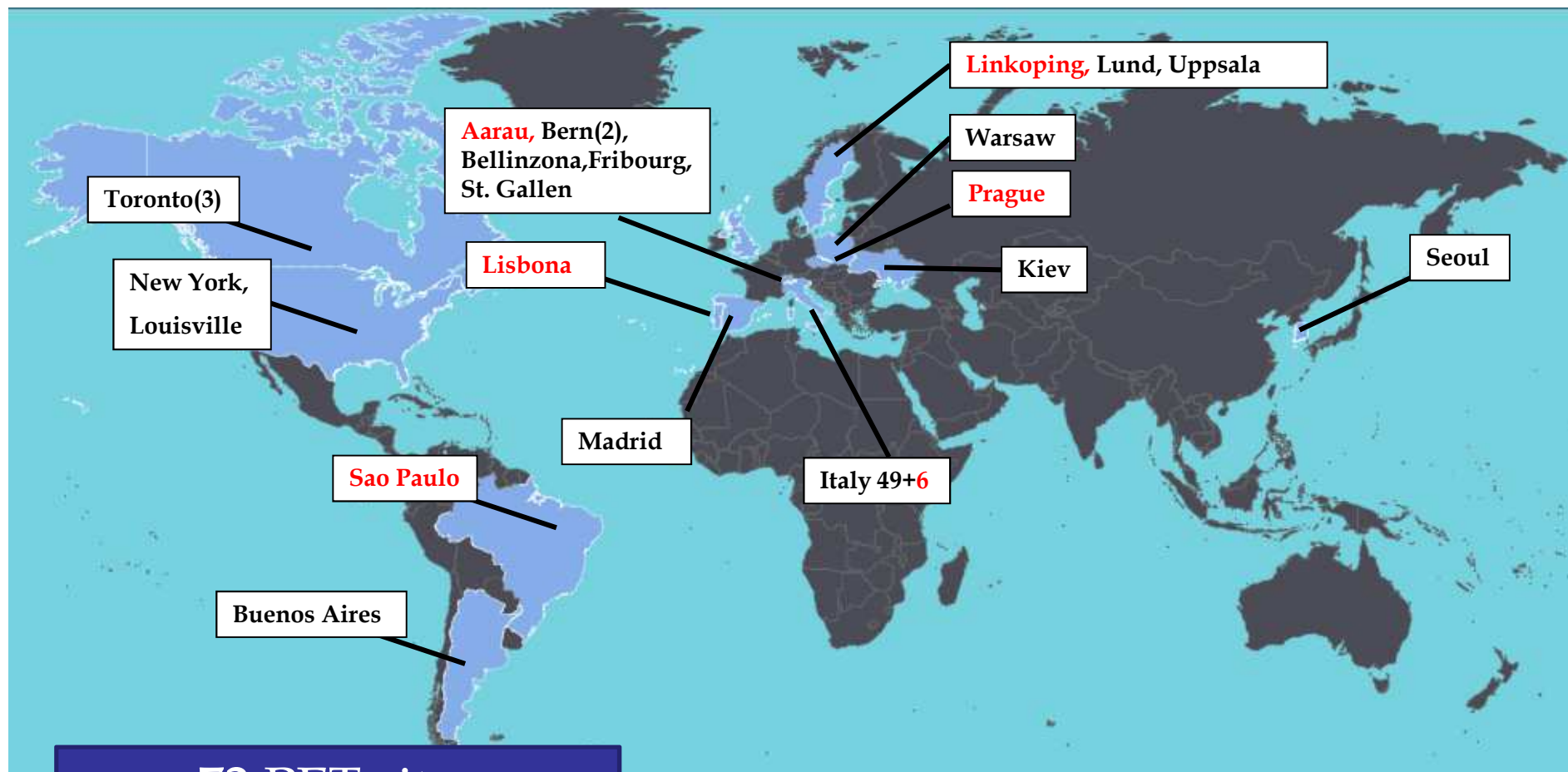
Site number	Site name	Patients scanned
1	Glasgow West of Scotland PET-CT Centre	3
2	Newcastle PET Centre	1
3	The Christie, Manchester	2
4	Leeds PET-CT Centre	1
5	Royal Liverpool University Hospital	0
6	Nottingham City Hospital	2
7	University Hospital Coventry	0
8	St Thomas' Hospital, London	2
9	University College London Hospital	2
10	Queen Alexandra Hospital, Portsmouth	4
11	Norfolk & Norwich Hospital	1
12	Derriford Hospital, Plymouth	0
	TOTAL	18



- Fixed scanning site
- Mobile scanning site



CUNEO PET CORELAB



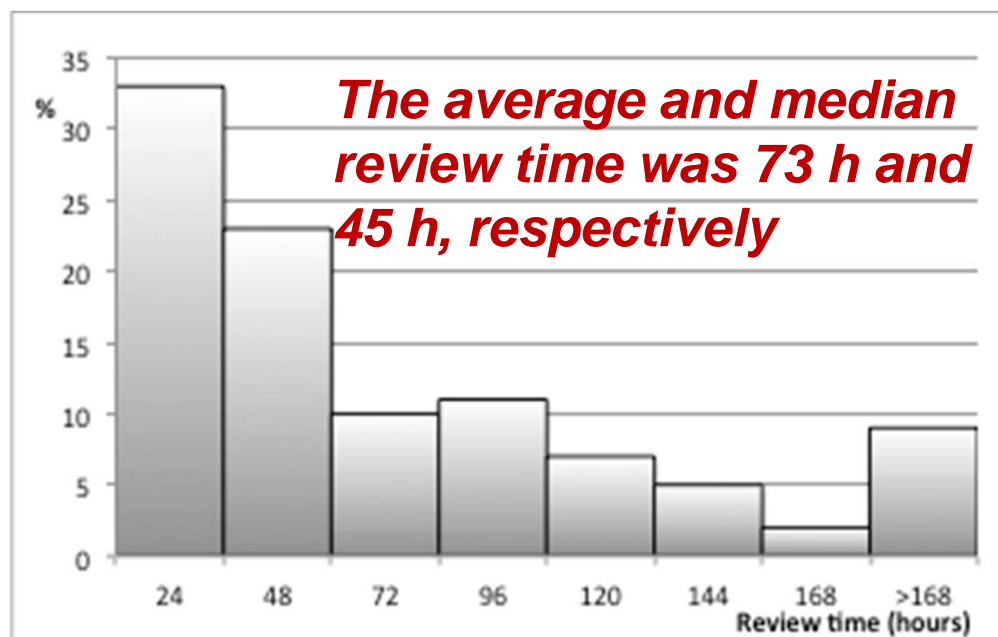
72 PET sites
77 PET scanner

Central PET Review After Chemoterapy

(September, 2016)

PET REVIEWED	PET NEGATIVE	PET POSITIVE
222	105 (47%)	117 (53%)
106 (MBP neg score 1-2)	37 (35%)	69 (65%)
116 (Liver neg score 1-3)	68 (59%)	48 (61%)

ARM A	ARM B
(RADIOTHERAPY)	(OBSERVATION)
53	52



Training improves the interobserver agreement of the expert positron emission tomography review panel in primary mediastinal B-cell lymphoma: interim analysis in the ongoing International Extranodal Lymphoma Study Group-37 study

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1) DS is precise for describing PMBCL response to therapy

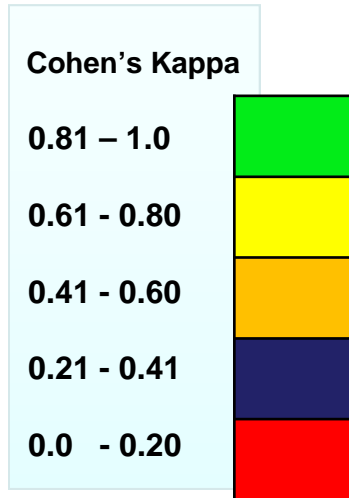
TABLE 1 Interobserver agreement in the overall population applying different thresholds using the DS

DS Cutoff	PET Negative DS1 vs PET Positive DS2, DS3, DS4, DS5	PET Negative DS1, DS2 vs PET Positive DS3, DS4, DS5 Old IELSG 27 Cutoff	PET Negative DS1, DS2, DS3 vs PET Positive DS4, DS5 New IELSG 27 Cutoff	PET Negative DS1, DS2, DS3, DS4 vs PET Positive DS5
Krippendorff α	0.25	0.65	0.72	0.71
Average Cohen κ	0.22	0.65	0.72	0.73
Cohen κ range	0.04-0.33	0.57-0.71	0.60-0.78	0.57-0.75

DS, Deauville score; IELSG, International Extranodal Lymphoma Study Group; PET, positron emission tomography.

2) all DS are equals but some DS are more equals than other

Agreement evolution in first 100 patients



1. Training (20 pts)

	Mean	1	2	3	4	5	6
1	0.51		0.40	0.80	0.58	0.50	0.29
2	0.51	0.40		0.60	0.46	0.78	0.32
3	0.55	0.80	0.60		0.40	0.76	0.20
4	0.53	0.58	0.46	0.40		0.78	0.43
5	0.64	0.50	0.78	0.76	0.78		0.38
6	0.32	0.29	0.32	0.20	0.43	0.38	

Krippendorff's alfa = 0.42

2. Early clinical (10 pts)

	Mean	1	2	3	4	5	6
1	0.55		0.40	0.80	0.60	0.53	0.40
2	0.49	0.40		0.58	0.40	0.76	0.29
3	0.57	0.80	0.58		0.40	0.76	0.29
4	0.51	0.60	0.40	0.40		0.76	0.40
5	0.63	0.53	0.76	0.76	0.76		0.32
6	0.34	0.40	0.29	0.29	0.40	0.32	

Krippendorff's alfa = 0.45

3. Late clinical April '14 (50 pts)

	Mean	1	2	3	4	5	6
1	0.81		0.74	0.84	0.91	0.74	0.84
2	0.66	0.74		0.66	0.67	0.61	0.64
3	0.73	0.84	0.66		0.77	0.54	0.84
4	0.75	0.91	0.67	0.77		0.65	0.76
5	0.67	0.74	0.61	0.54	0.65		0.80
6	0.78	0.84	0.64	0.84	0.76	0.80	

Krippendorff's alfa = 0.59

4. Clinical April – August '14 (40 pts)

	Mean	1	2	3	4	5	6
1	0.77		0.77	0.79	0.84	0.76	0.67
2	0.65	0.77		0.69	0.71	0.63	0.43
3	0.73	0.79	0.69		0.62	0.86	0.69
4	0.70	0.84	0.71	0.62		0.59	0.72
5	0.69	0.76	0.63	0.86	0.59		0.63
6	0.63	0.67	0.43	0.69	0.72	0.63	

Krippendorff's alfa = 0.69

- Our experience to date indicates that the agreement among expert nuclear physicians in reporting PMBCL, even using standardized criteria, was only moderate when the study began.
- However, improved agreement in PET reporting was rapidly obtained using a training process which involved revision and discussion of practical rules in the application of commonly adopted interpretation.

Dycothomic score on the first 100 patients

DS 3

Reliability for all reviewers together: **Alpha**
0.65

Cohen's Kappa:

1	0.61	0.76	0.84	0.64	0.67
0.61	1	0.53	0.60	0.59	0.51
0.76	0.53	1	0.70	0.67	0.67
0.84	0.60	0.70	1	0.70	0.70
0.64	0.59	0.67	0.70	1	0.64
0.67	0.51	0.67	0.70	0.64	1

DS4

Reliability for all reviewers together: **Alpha**
0.72

Cohen's Kappa:

1	0.76	0.80	0.80	0.69	0.59
0.76	1	0.84	0.84	0.70	0.60
0.80	0.84	1	0.84	0.73	0.63
0.80	0.84	0.84	1	0.81	0.63
0.69	0.70	0.73	0.81	1	0.56
0.59	0.60	0.63	0.63	0.56	1

Inter-observer variability among pathologies

<u>K's alpha - DS 4 (+/-)</u>			
Pathology	Trial	alpha	PET
HD	IVS	0.76	interim 2
HD	HD0607	0.77	interim 2
HD	PLRG	0.72	interim 1
PMBCL	IELSG37	0.72	EoT
FL	FOLL12	0.63	EoT
DLBCL	DLCL10	0.63	EoT

<u>K's alpha – DS 4 (+/-)</u>				
Pathology		alpha pre	alpha post	PET
HD	CC	0.45	0.76	interim 2
HD	PLRG	0.58	0.72	interim 1
PMBCL	IELSG37	0.53	0.72	EoT

Training
matters

Thanks to IELSG Staff



***International Extranodal Lymphoma Study
Group (IELSG)***