UNIVERSITÀ DI TORINO

2023 - 2027
DEPARTMENT OF EXCELLENCE
Ministero dell'Università e della Ricerca

Choice of treatment for PMBCL

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Department of Oncology

ILROG
INTERNATIONAL LYMPHOMA
RADIATION ONCOLOGY GROUP

Progress and Challenges in Modern Lymphoma and Myeloma Management

Thursday 7th September 2023

Alexandra Suite, The Midland Hotel
16 Peter Street, Manchester, M60 2DS

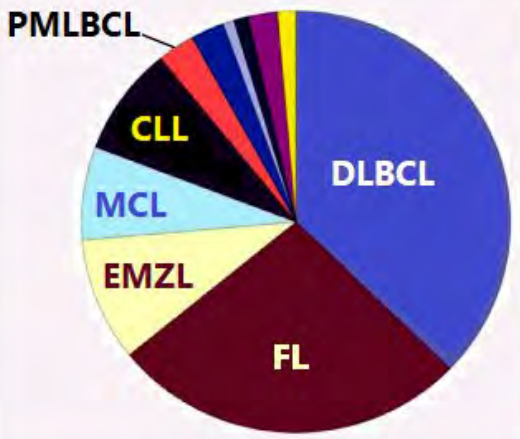
Chair: Professor Tim Illidge, *Manchester*

4th ILROG Educational Conference: Radiotherapy in Modern Management of Haematological Malignancies

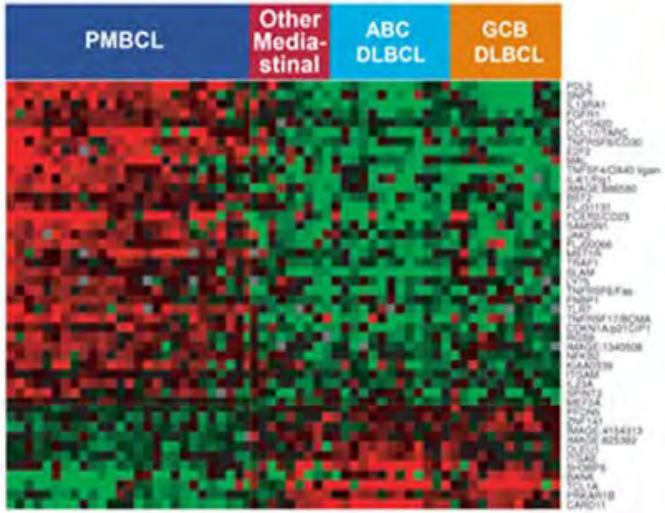
Saturday 9th & Sunday 10th September 2023

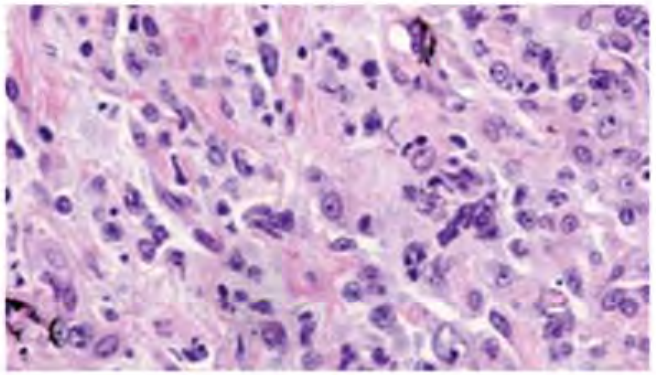
One Great George Street
Westminster, London SW1P 3AA

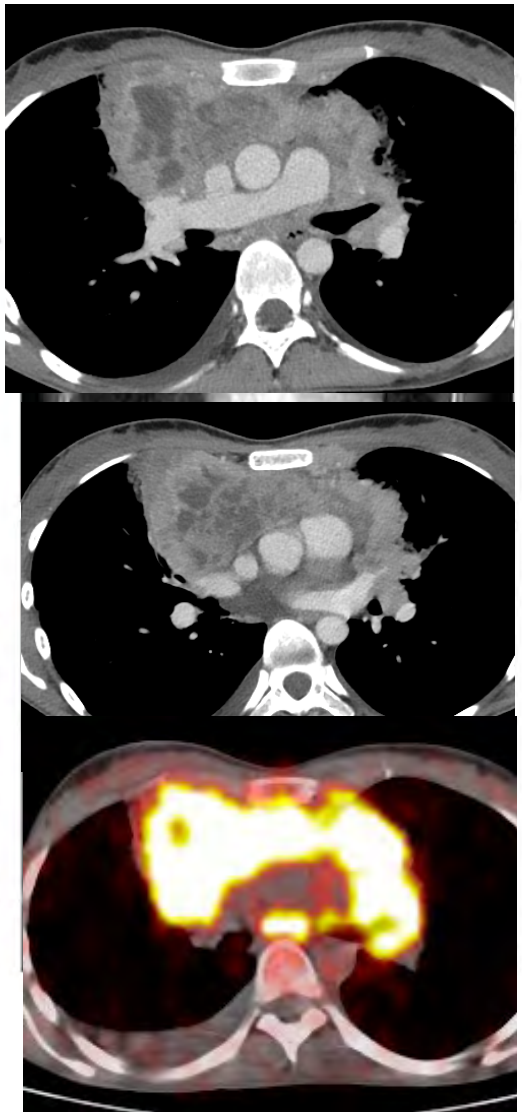
Distinctive features of PMBCL

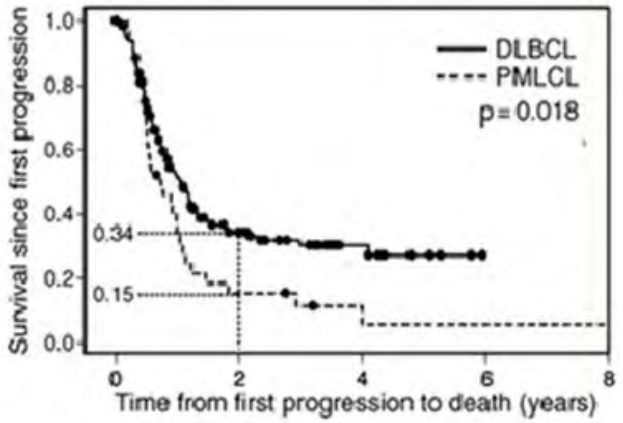


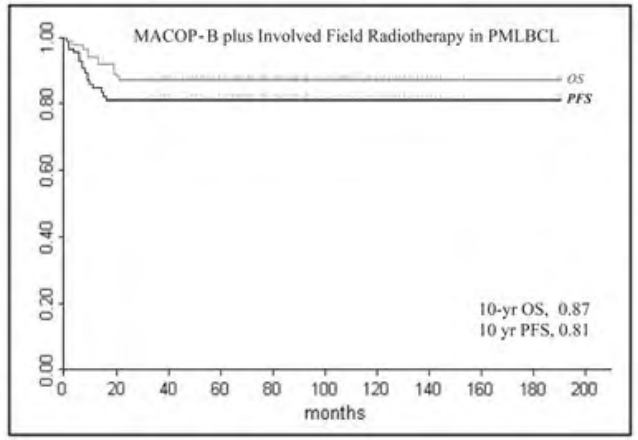
CD20	100%
CD30	87%
CD23	70%
CD15	---
Bcl-6	80%
IRF4	75%
Bcl-2	80%
BOB.1/Oct-2	80%
MAL protein	70%



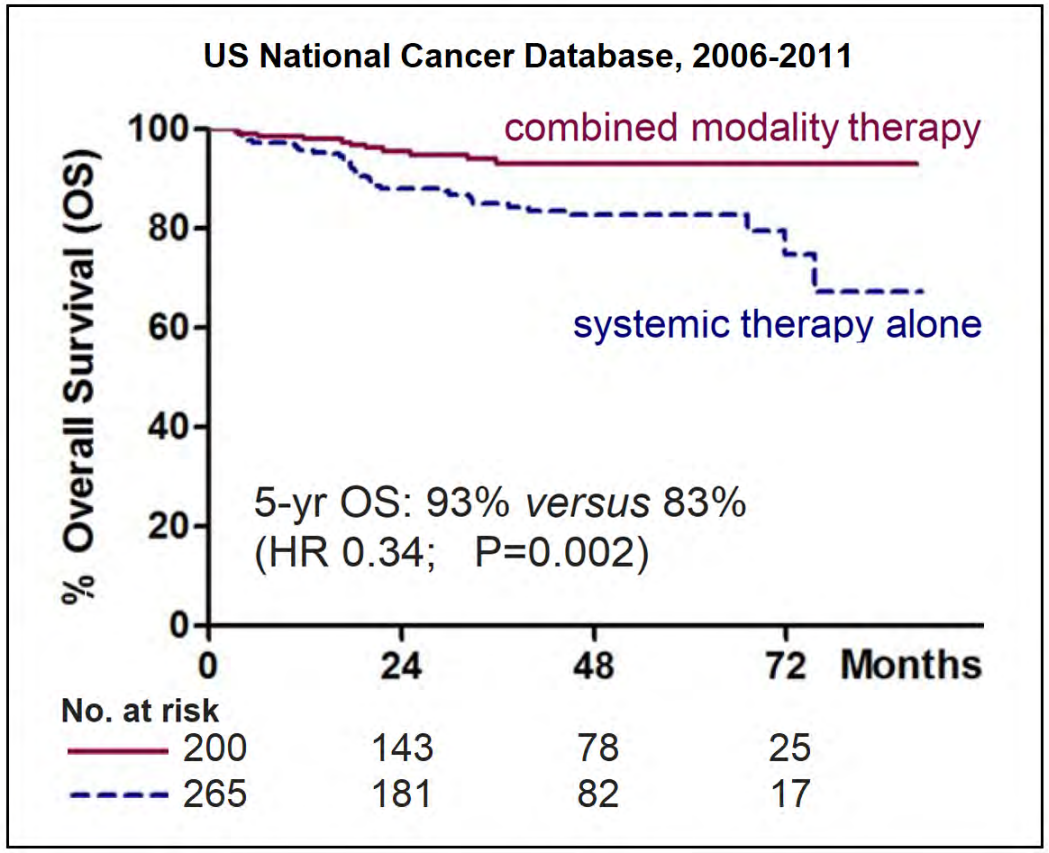




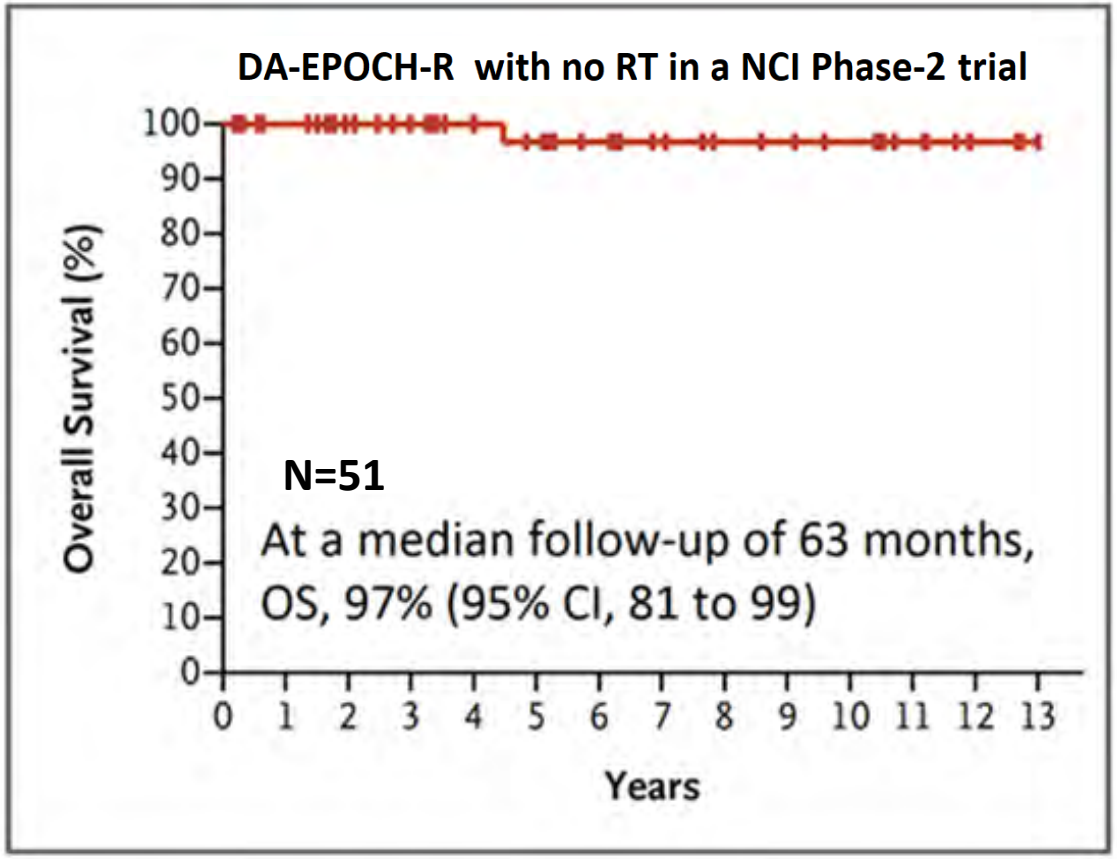




Radiotherapy in PMBCL: a therapeutic dilemma



MW Jackson et al. Am J Hematol. 2016; 91:476-80

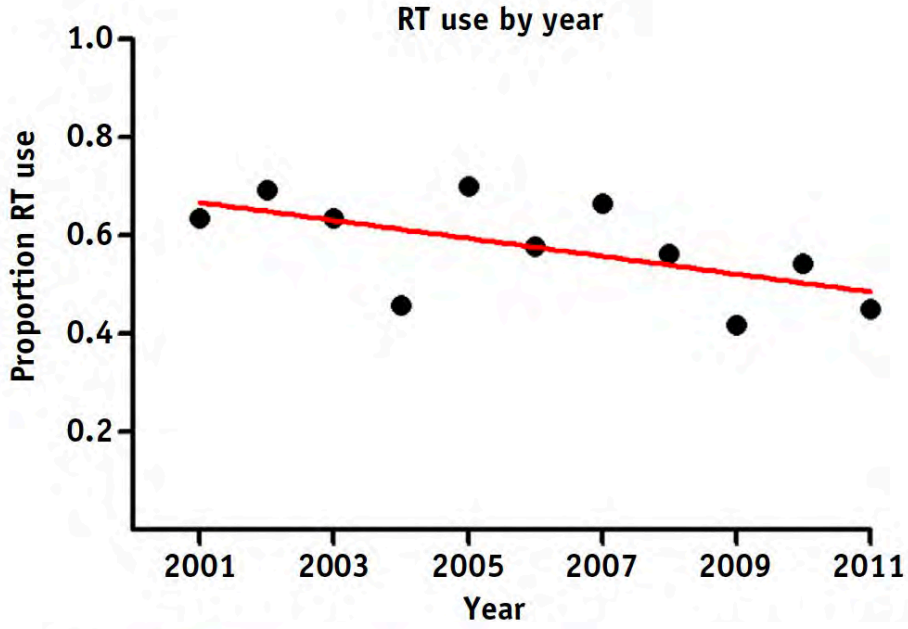


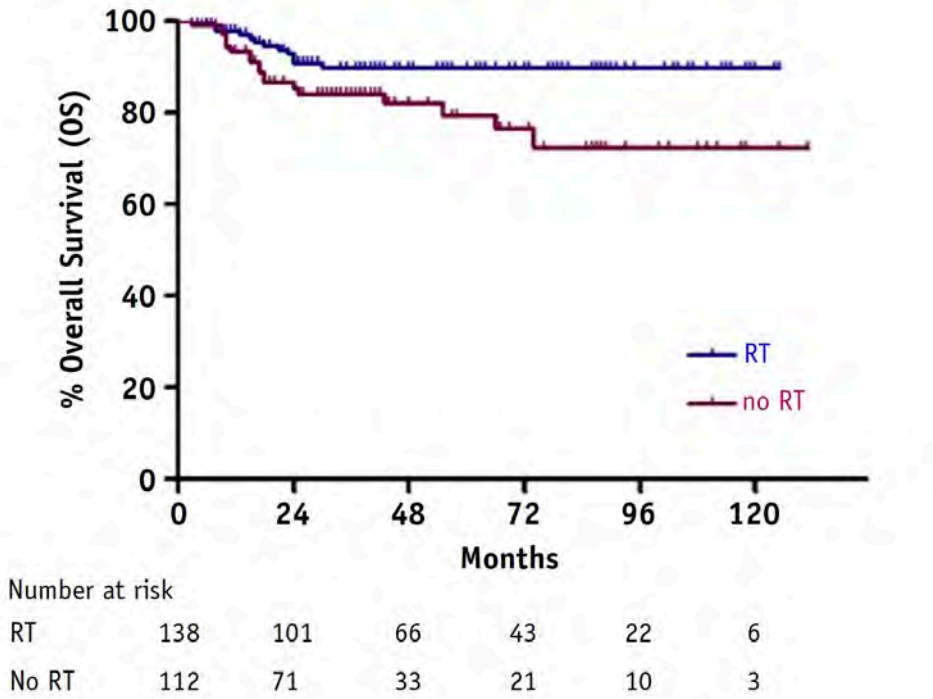
K Dunleavy et al. NEJM. 2013; 368:1408-16

Improved Survival With Radiation Therapy in Stage I-II Primary Mediastinal B Cell Lymphoma: A Surveillance, Epidemiology, and End Results Database Analysis

Summary

In this Surveillance, Epidemiology, and End Results analysis of patients with stage I-II primary mediastinal B cell lymphoma (PMBCL), the use of radiation therapy (RT) was associated with an improvement in overall survival. Patterns of care analysis reveals that nearly half of PMBCL patients treated in the United States do not receive RT, and its use appears to be declining despite a lack of randomized evidence to support its omission.





Jackson M.W., IJROBP 2016

Radiation and Dose-densification of R-CHOP in Primary Mediastinal B-cell Lymphoma: Subgroup Analysis of the UNFOLDER Trial

Primary mediastinal B-cell lymphoma (PMBCL) - a subgroup analysis of the UNFOLDER Trial
Dose-densification of R-CHOP and additive radiotherapy

131 patients with PMBCL randomized in a 2x2 factorial design
to R-CHOP-21 vs. R-CHOP-14 and
additive radiotherapy vs. observation

Key inclusion criteria

- Aged 18-60 yrs
- aaIPI = 0 and bulk (≥ 7.5 cm)
- aaIPI = 1

R-CHOP-21 vs. R-CHOP-14

Identical EFS
Identical PFS
Identical OS

Additive radiotherapy vs. observation

Significant superior 3 yrs-EFS after RTh
No superior PFS
Identical OS

- 97% 3-yrs OS after R-CHOP based therapy
- LDH > 2x upper normal value identifies as an adverse risk

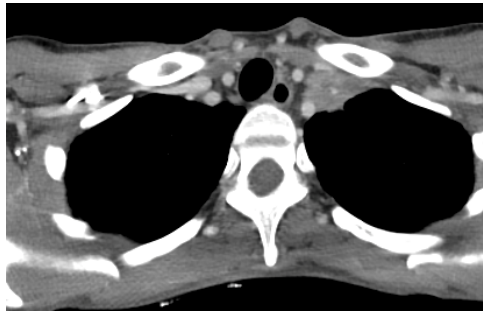
HemaSphere

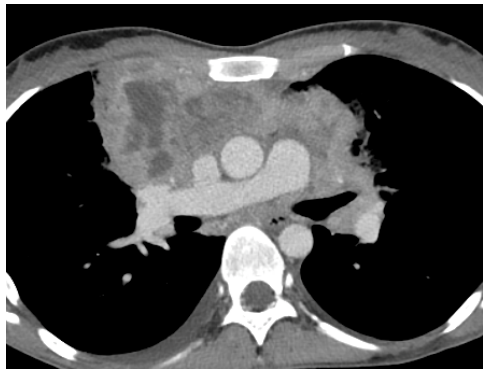
HemaSphere. 2023;7(7):e917.

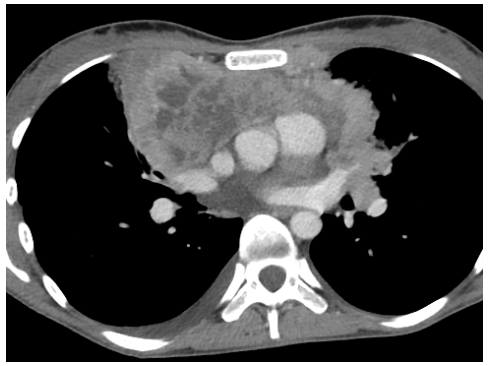
Open questions in PMBCL

Role of PET-CT scan in response evaluation after immuno-chemotherapy

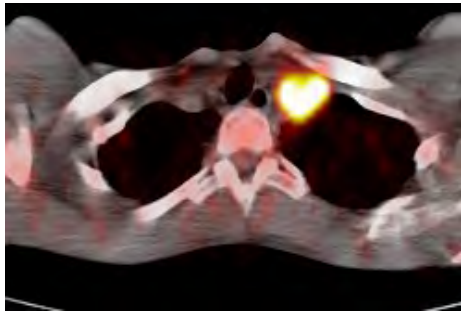
CT scan
(diagnosis)

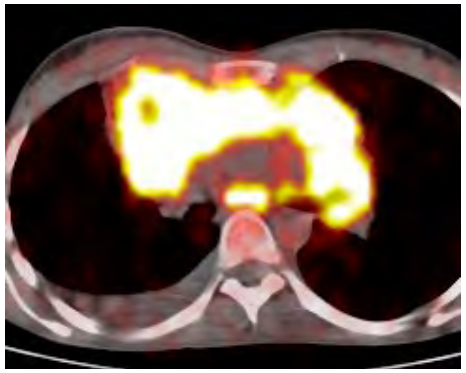


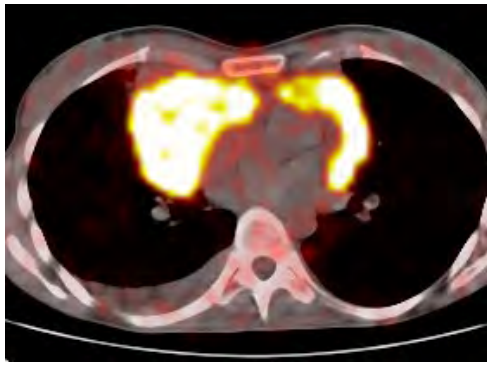




PET/CT scan
(diagnosis)

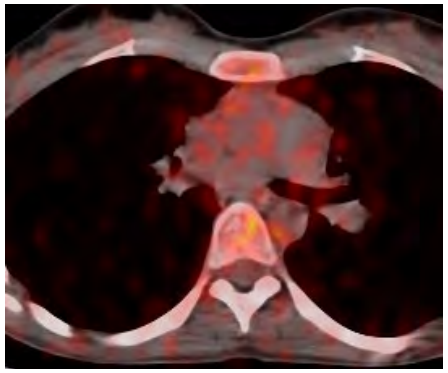






PET/CT scan
(EOT)

mCR



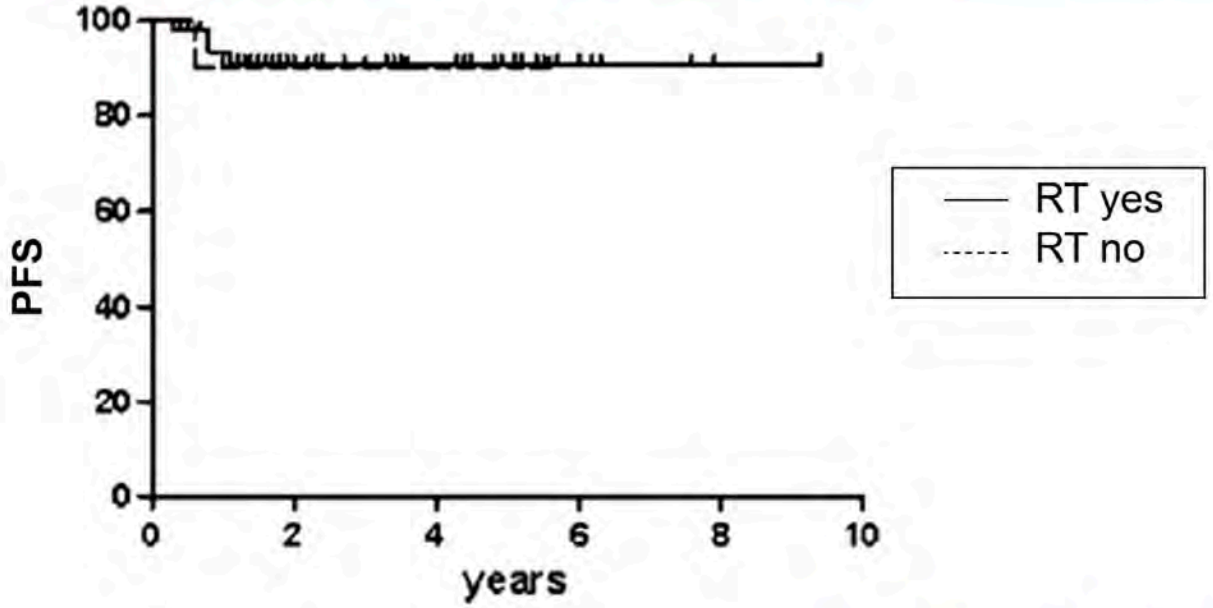
Is a negative PET-CT scan at EOT a reliable indicator of cure following immunochemo alone, making consolidation RT unncecessary?

Outcome of PMBCL: impact of a PET adapted approach

The role of rituximab and positron emission tomography in the treatment of primary mediastinal large B-cell lymphoma: experience on 74 patients

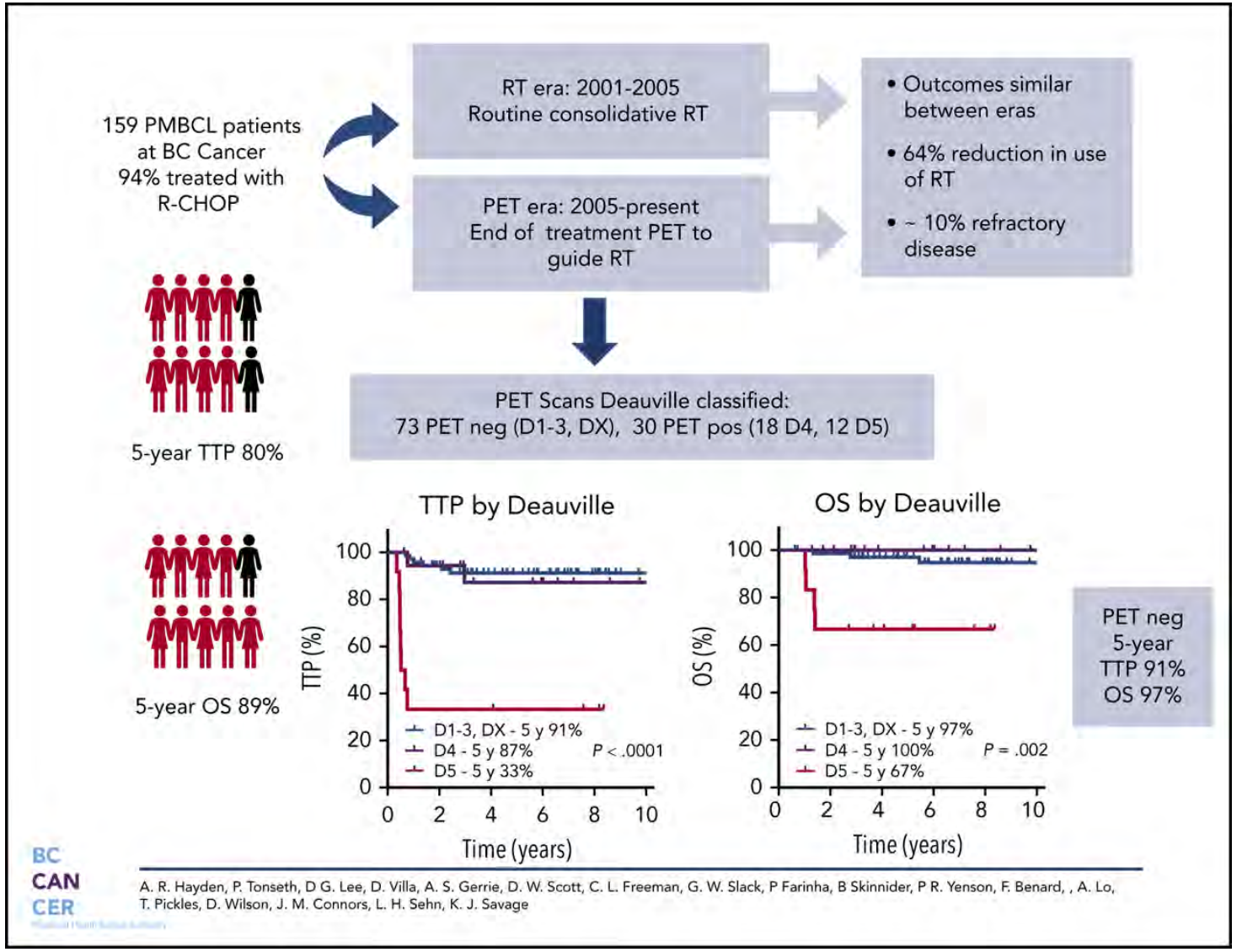
MACOP-B + rituximab

- PET negative *23 patients* → NO radiotherapy *CR rate: 100%* → PFS 90% (68 mos)
- PET positive *51 patients* → YES radiotherapy *CR rate: 75%* → PFS 91% (113 mos)

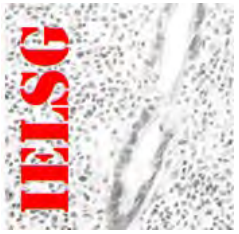


Zinzani PL. *Hematol Oncol*, 2015; 33: 145-150

Outcome of PMBCL: impact of a PET adapted approach



Hayden AR et al, Blood 2020;136:2803



INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

Observation vs. radiotherapy in PMBCL patients with complete metabolic response to standard immunochemotherapy: IELSG37 randomized trial (NCT01599559)

2023 ASCO ANNUAL MEETING

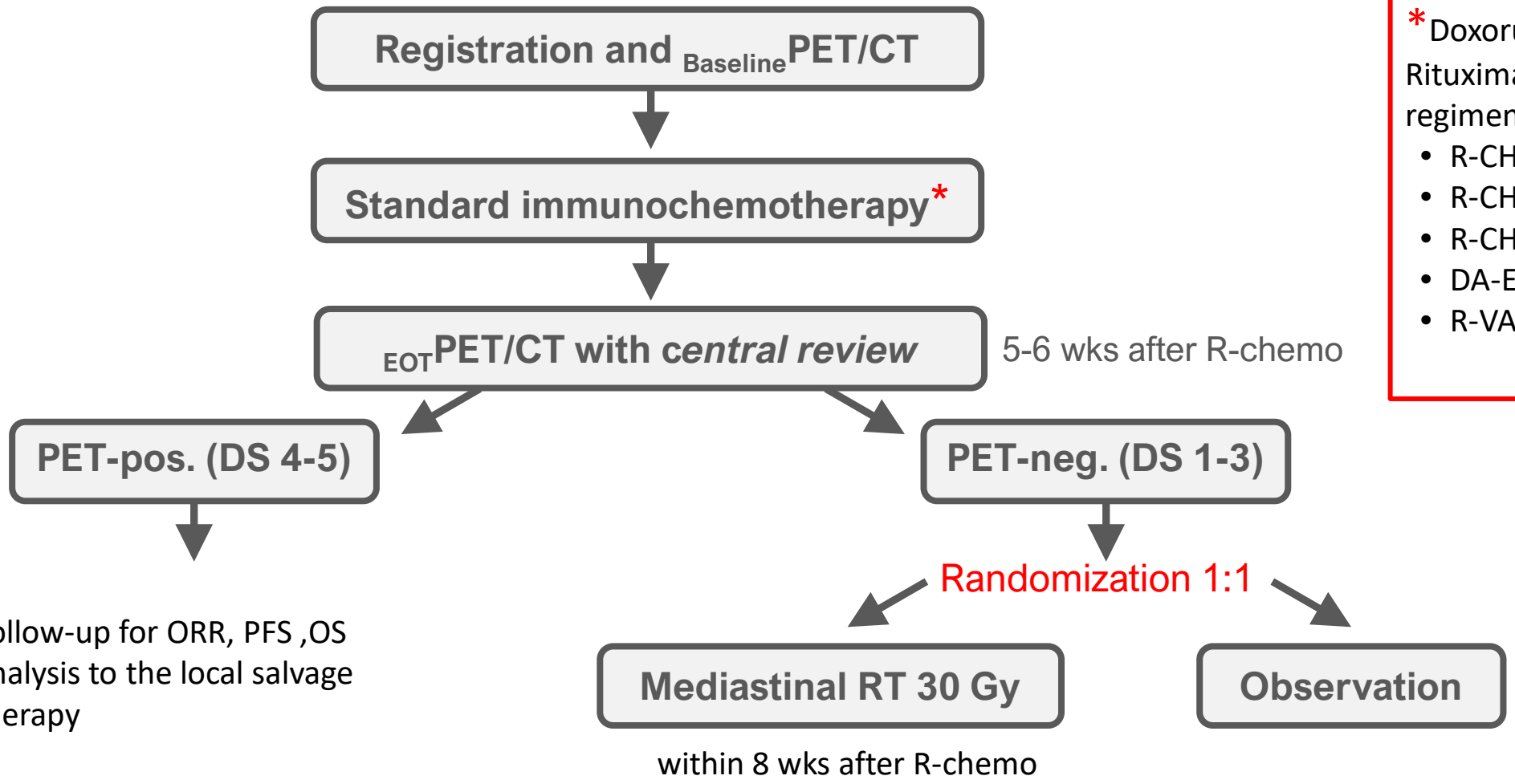
EHA2023

17th ICML International Conference on Malignant Lymphoma Lugano

IELSG 37 study: objectives

- ***Aim***
  To test whether mediastinal radiotherapy can be omitted in patients with CMR after conventional R-chemo
- ***Primary endpoint***
  PFS at 30 months from randomization in patients PET-negative at the end of induction R-chemo
- ***Secondary endpoints***
  OS at 5 years from registration; long term toxicity

Trial design



Follow-up for ORR, PFS ,OS analysis to the local salvage therapy

*Doxorubicin- and Rituximab-containing regimen, such as

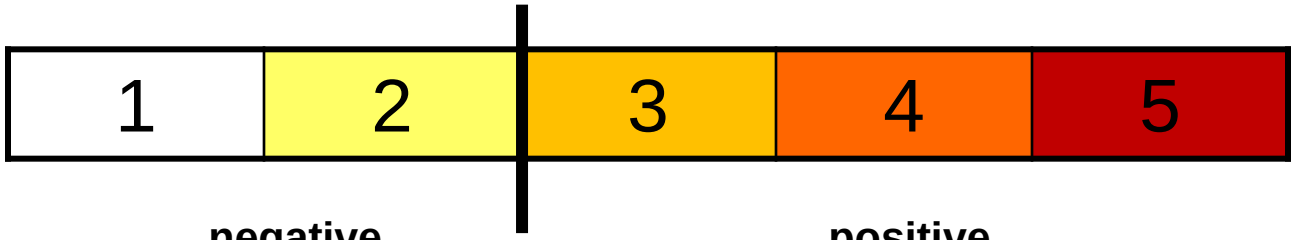
- R-CHOP21
- R-CHOP14
- R-CHOEP
- DA-EPOCH-R
- R-VACOP/MACOP-B

PET-CT response evaluation

visual analysis (Deauville score)

at 5-6 weeks after R-CHT

1. No uptake.
2. Uptake ≤ mediastinum.
3. Uptake > mediastinum but ≤ liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new disease sites



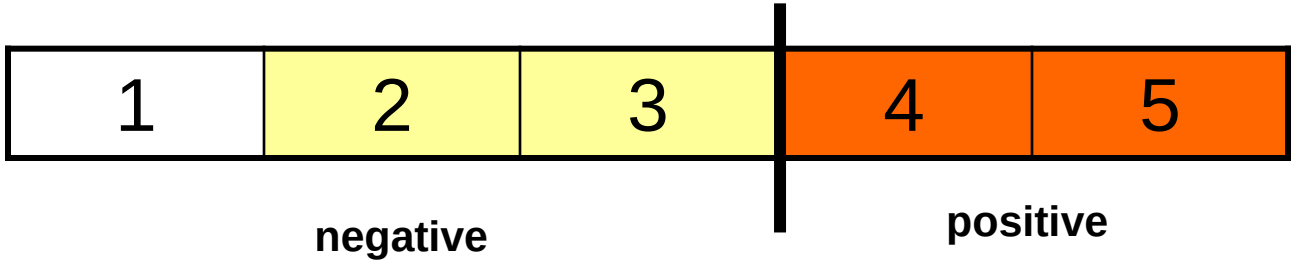
MBP cut-point

PET-CT response evaluation

visual analysis (Deauville score)

Amendment April 2014
based on IELSG 26 final results

1. No uptake.
2. Uptake ≤ mediastinum.
3. Uptake > mediastinum but ≤ liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new disease sites



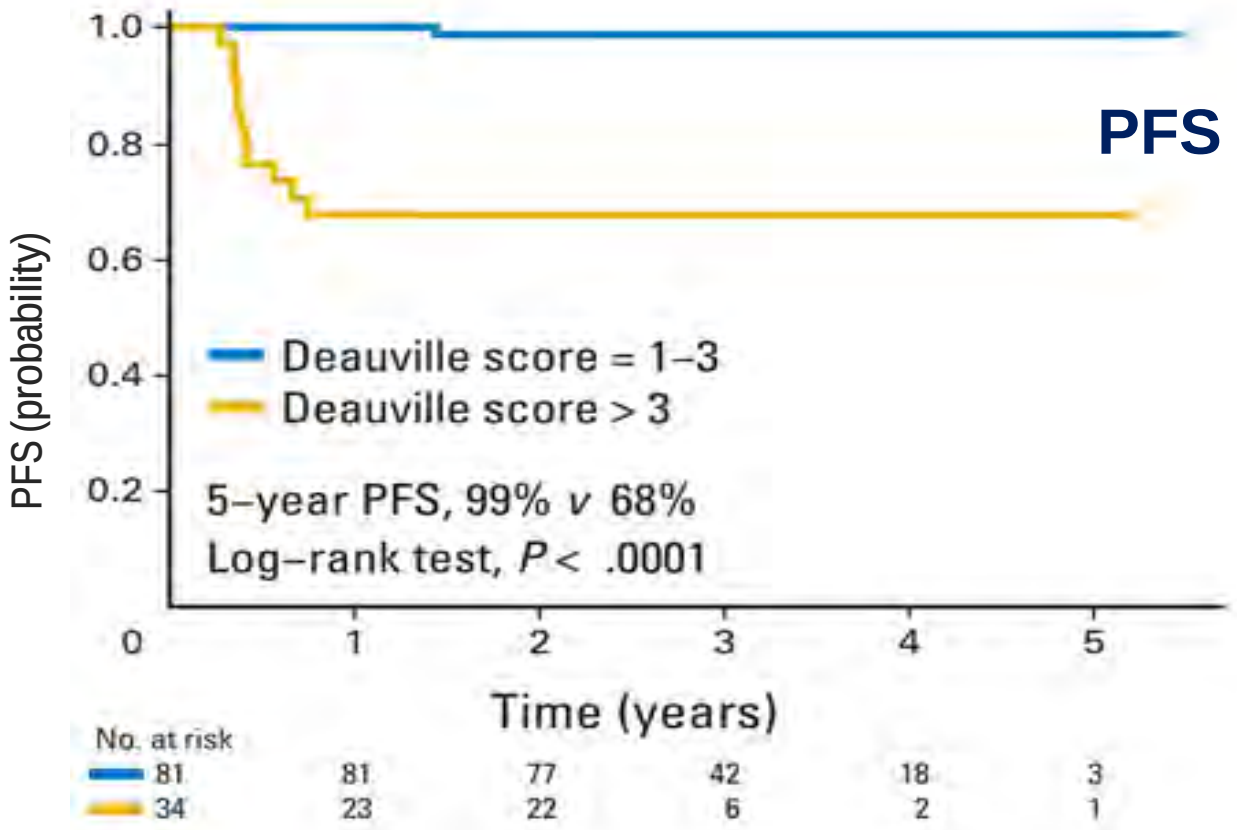
liver cut-point

Predicted to improve consensus among PET panel

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Martelli M et al. J Clin Oncol. 2014;32:1769-75

[^{18}F]Fluorodeoxyglucose Positron Emission Tomography Predicts Survival After Chemoimmunotherapy for Primary Mediastinal Large B-Cell Lymphoma: Results of the International Extranodal Lymphoma Study Group IELSG-26 Study



IELSG-26 study:

PFS better defined by liver cut-point

- DS 1-3 better discriminates patients at lower or higher risk of failure after induction therapy

- consolidation RT was given to 102 of 115 patients according to local policy, irrespectively of the DS score at the end of R-Chemo

The IELSG-26 study did not answer the question on the role of mediastinal RT

Statistical assumptions

The study was designed as a randomized non-inferiority trial comparing mediastinal radiotherapy to observation .

Sample size (n=**376)** calculated assuming a 30 months **PFS=85%** in both arms from randomization

Alternative hypothesis: non-inferiority margin corresponding to **PFS≤75% in the observation arm**

540 patients needed to be enrolled (with an expected PET-negative proportion of about 70%)

Interim analysis

- 2 planned and 1 unplanned interim analyses (IDMC requested in 2019) revealed a ***number of events much lower than expected***
- A recalculation of the sample size using these event rates showed a no longer feasible trial (N to randomize = 1821)
- **The IDMC recommended:**
  - *not to increase study size and duration to meet the planned non-inferiority margins*
  - *to complete the planned accrual of 540 patients*
  - *to perform data analysis for primary endpoint after a minimum follow-up of 30 months in >80% of patients*
  - *Include in the final analysis the absolute difference between the two arms*

Follow-up duration

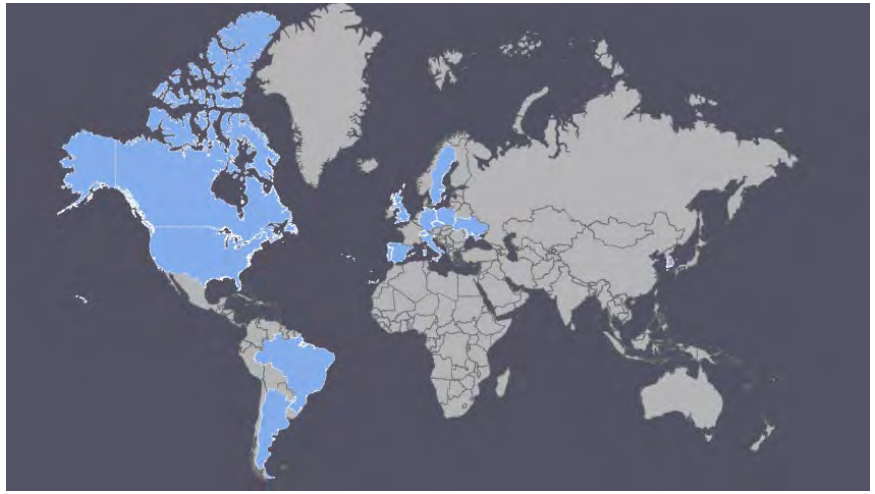
Post-randomization follow-up >30 months in **260/268 patients (97%; 95%CI 94–98)**

Study arm	Median Follow-up (95%CI)	Interquartile range
Observation	58.8 months (55.8 – 59.8)	41.9-63.4 months
Radiotherapy	58.8 months (54.4 – 60.6)	42.4-63.7 months

Huge international commitment

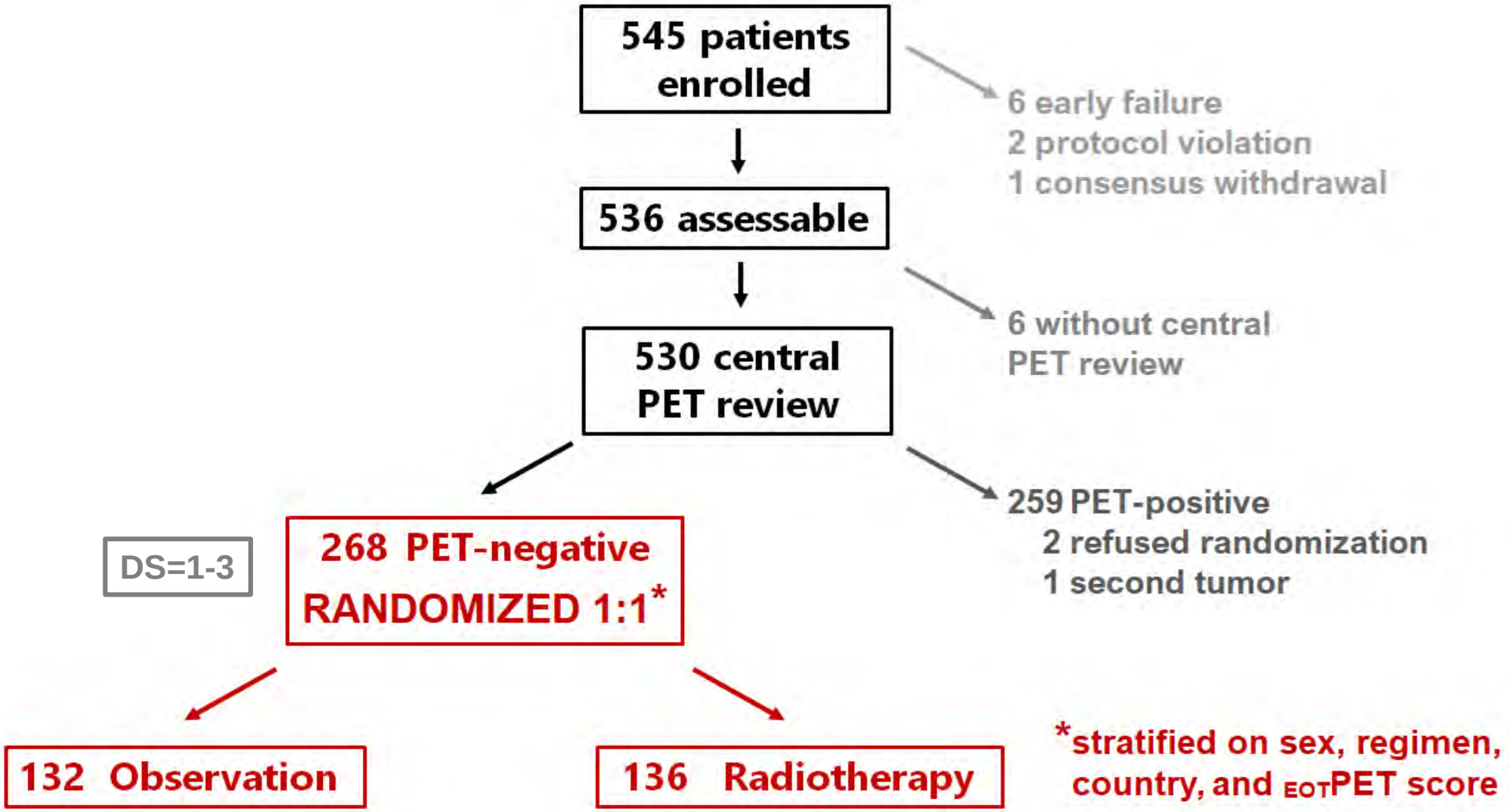
545 patients enrolled from **74 centres in 13 countries**

- **Italy 380**
- UK 44
- Ukraine 25
- Switzerland 17
- Poland 15
- Czech Republic 14
- China 12
- Norway 11
- Canada 10
- Sweden 7
- Germany 5
- USA 3
- Portugal 2



Accrual
September 2012
August 2019

Patient flow



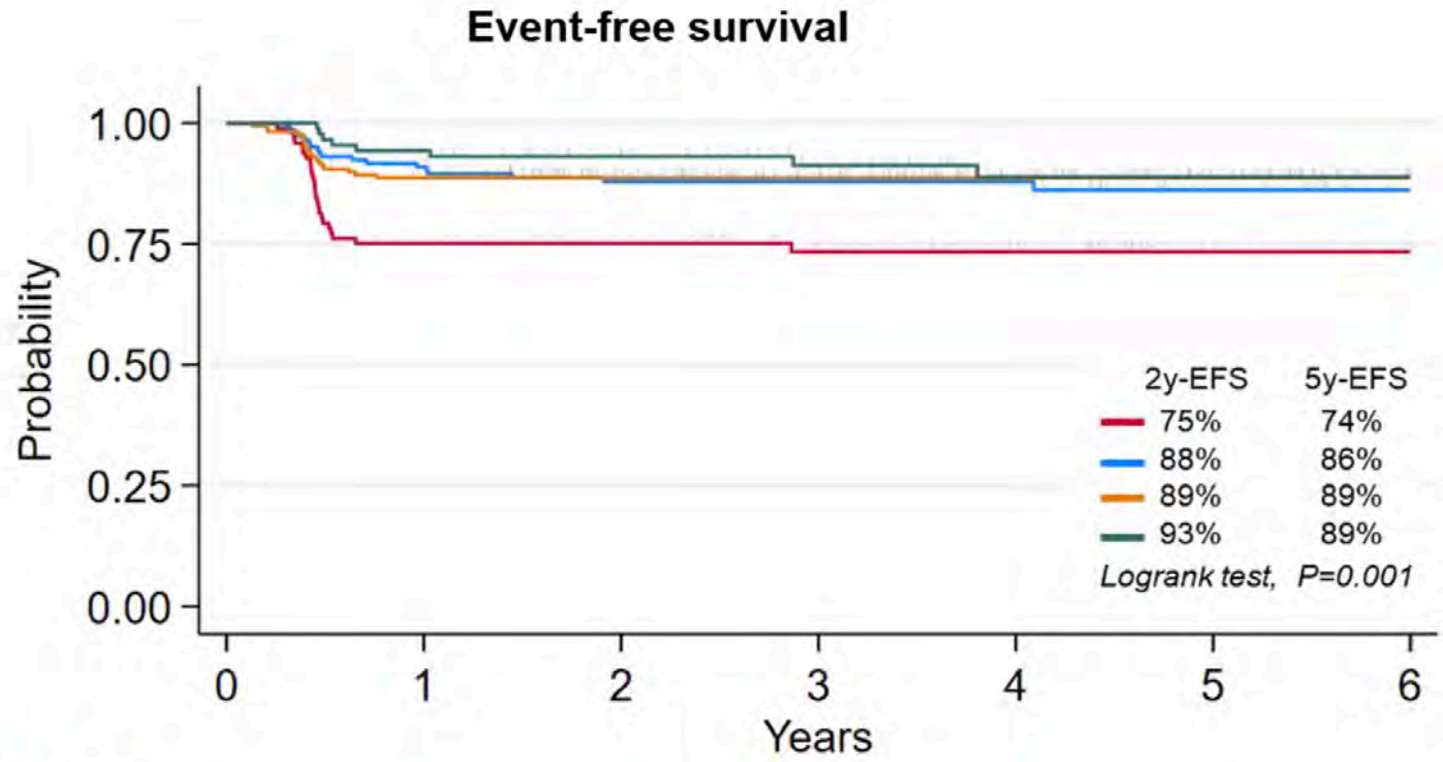
Baseline demographic and clinical features

Feature		Radiotherapy	Observation
Number of patients		**136**	**132**
Median age, years (IQR)		35.5 (29-46.5)	35.5 (29-46.5)
Sex, N (%)	Female	88 (65)	83 (63)
	Male	48 (35)	49 (37)
EGOG PS, N (%)	0	74 (54)	69 (52)
	1	50 (37)	54 (41)
	≥2	12 (9)	9 (7)
Bulky disease, N (%)	>10 cm	89 (65)	79 (60)
Elevated LDH, N (%)	>UNL	91 (67)	88 (67)
R-IPI score, N (%)	Low risk	30 (22)	31 (23)
	Intermediate risk	98 (72)	96 (73)
	High risk	8 (6)	5 (4)

Frontline regimens and Deauville Score

Feature		Radiotherapy	Observation
Number of patients		**136**	**132**
Regimen, N (%)	R-CHOP-21(-like)	20 (15)	27 (21)
	R-CHOP-14	34 (25)	33 (25)
	R-MACOP-B/VACOP-B	47 (35)	37 (28)
	R-DA-EPOCH	23 (17)	24 (18)
	Other	12 (9)	11 (8)
$_{EOT}$PET DS, N (%)	1	4 (3)	6 (5)
	2	71 (52)	67 (51)
	3	61 (45)	59 (45)

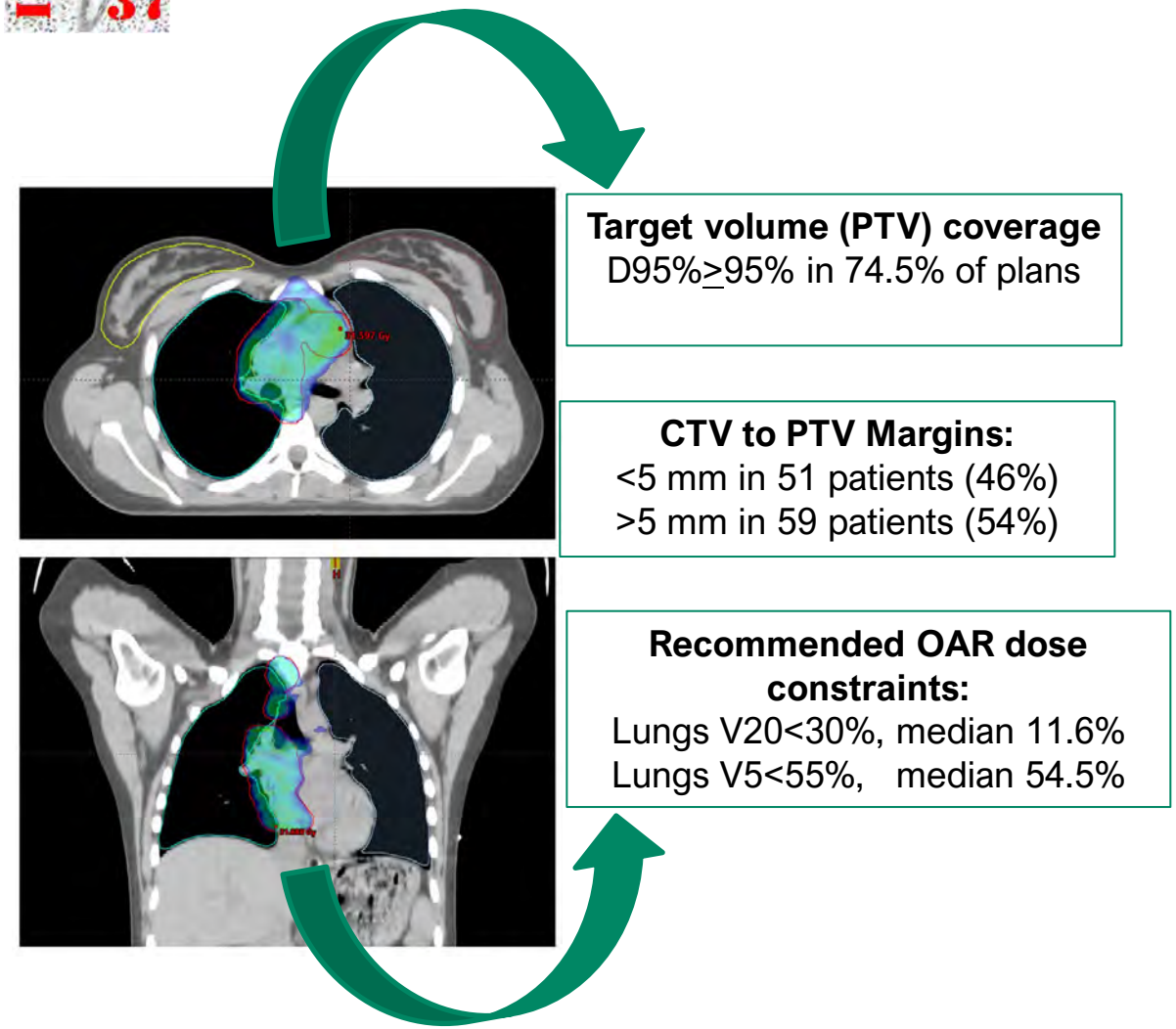
Impact of different induction regimens on the outcome of primary mediastinal B cell lymphoma (PMBCL) in the prospective IELSG37 trial



Number at risk							
R-CHOP21	98	71	58	41	26	9	1
R-CHOP14	146	126	103	81	53	36	15
R-V/MACOP-B	169	146	123	95	66	44	15
DA-EPOCH-R	88	79	61	48	35	22	15

Martelli M, Zucca E. *Hematol Oncol (16 ICML Meeting abstracts)*, 2021; 39: 049a

Radiation therapy



Target volume (PTV) coverage
D95%≥95% in 74.5% of plans

CTV to PTV Margins:
<5 mm in 51 patients (46%)
>5 mm in 59 patients (54%)

Recommended OAR dose constraints:
Lungs V20<30%, median 11.6%
Lungs V5<55%, median 54.5%

RT technique	N	%
3D CRT	31	28.2
IMRT	78	70.9
Proton therapy	1	0.9

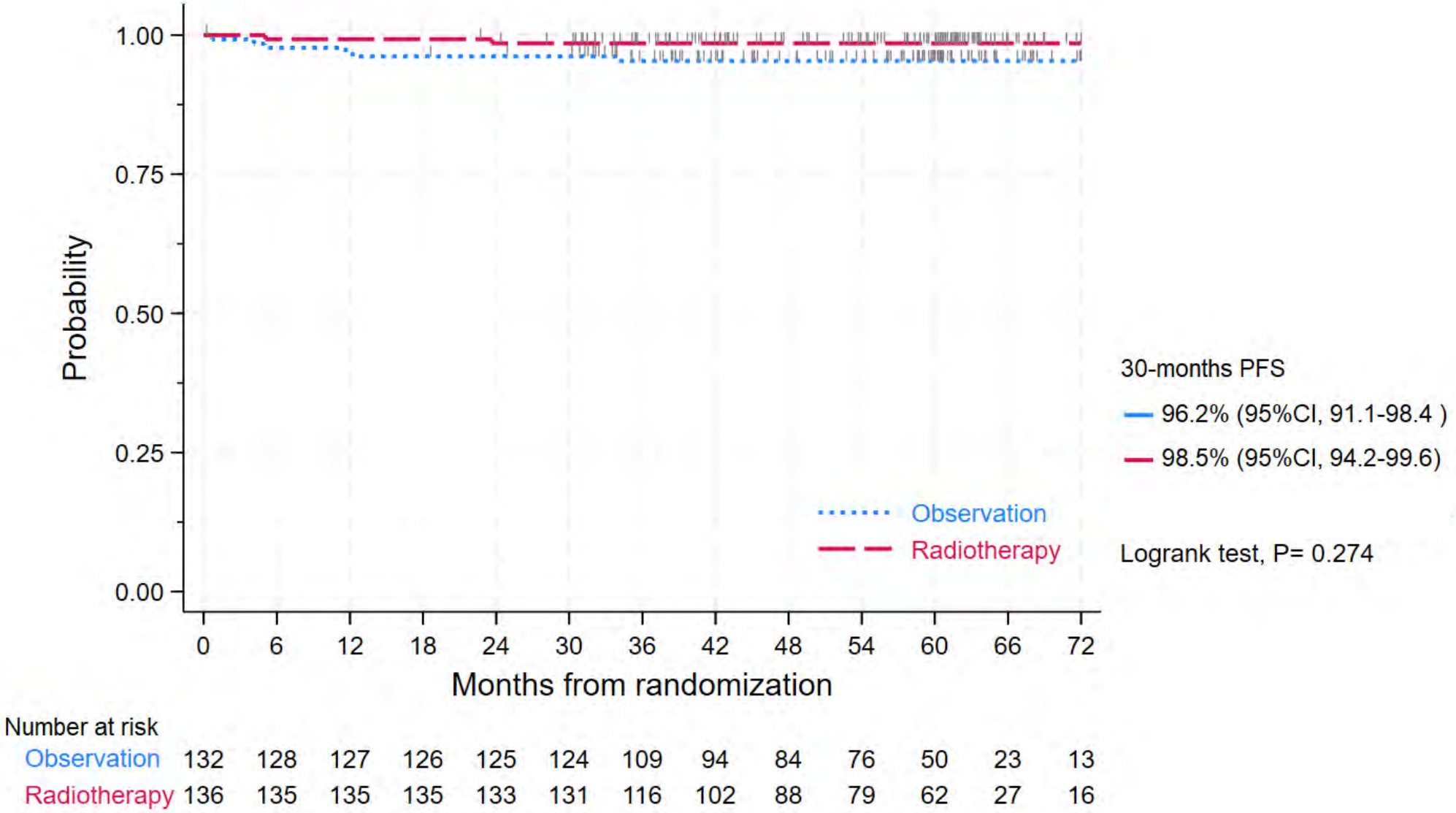
RT characteristics	Median	Range
Total dose delivered	30 Gy	29.9-30.6
Daily fractionation	2 Gy	1.5-2
Time from the end of R-chemo to start of RT	8.7 weeks	4.3-19.1
Overall treatment time	21 days	17-35

Follow-up duration

Post-randomization follow-up >30 months in **260/268 patients (97%; 95%CI 94–98)**

Study arm	Median Follow-up (95%CI)	Interquartile range
Observation	58.8 months (55.8 – 59.8)	41.9-63.4 months
Radiotherapy	58.8 months (54.4 – 60.6)	42.4-63.7 months

Progression-free survival: primary endpoint



PFS: relative vs absolute effects

Analysis type	Relative effect of RT vs. observation	Absolute difference between RT and observation	N. Needed to Treat
	HR (95%CI)	Δ (95%CI)	N
Unadjusted	0.47 (0.12-1.88)	2.3% (-1.5 to 6.2)	42.6
Stratified*	**0.68 (0.16-2.91)**	**1.2% (-3.2 to 7.0)**	**126.3**

*on sex, chemotherapy (CHOP 14/21, VACOP//MACOP-B, DA-EPOCH, other), country (Italy, UK, other), and $_{EOT}$PET/CT (DS1,2 or 3)

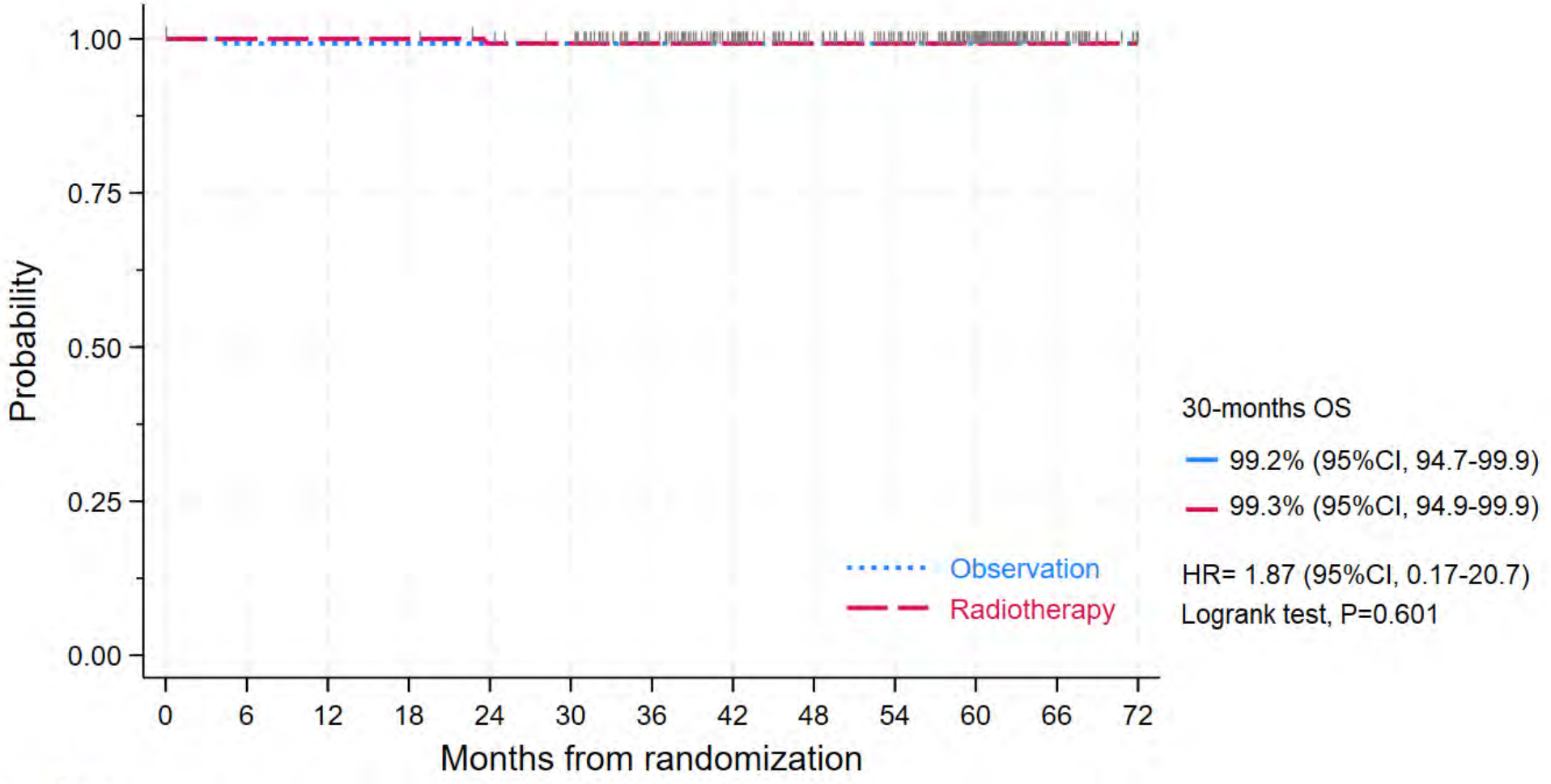
Statistical power of the trial to detect RT superiority

ASSUMPTIONS FOR POWER ESTIMATION	
Sample size	**N = 268**
Randomization ratio	1:1
Alpha error (2-tails)	0.05
Observed 30-m PFS for the radiotherapy arm	**98%**

CALCULATED STATISTICAL POWER		
Expected 30-m PFS Observation arm	**Absolute Δ (RT-Obs.)**	**Statistical Power**
93%	5%	74.2%
92%	**6%**	**86.1%** ←
91%	**7%**	**93.4%**
90%	**5%**	**97.2%**
89%	**9%**	**99.0%**
88%	**10%**	**99.7%**

The IELSG-37 trial has a statistical power of more than 85% for detecting an absolute PFS difference at 30 months $\geq$ 6%

Overall survival: secondary endpoint



Number at risk

Observation	132	130	130	130	129	128	114	98	88	80	54	24	13
Radiotherapy	136	136	136	136	134	132	117	103	89	80	62	27	16

Severe cardiac adverse events and 2nd cancers

Event	Grade*	Arm	Time from randomization	Outcome	PMBCL status at last visit
Left ventricular systolic disfunction*	3	RT	during chemotherapy	Resolved	Continuous CR
Acute Heart failure**	4	RT	18 months	Resolved	
Hypertension**	3	RT	8 months	Resolved	Continuous CR
Metastatic melanoma	4	RT	22 months	Death from concurrent sepsis	Continuous CR
Glioblastoma	3	RT	>55 months	Death	Continuous CR
Acute Myeloid Leukemia	4	RT	15 months	CR after allotrasplant	Continuous CR

* according to CTCAE v5.0

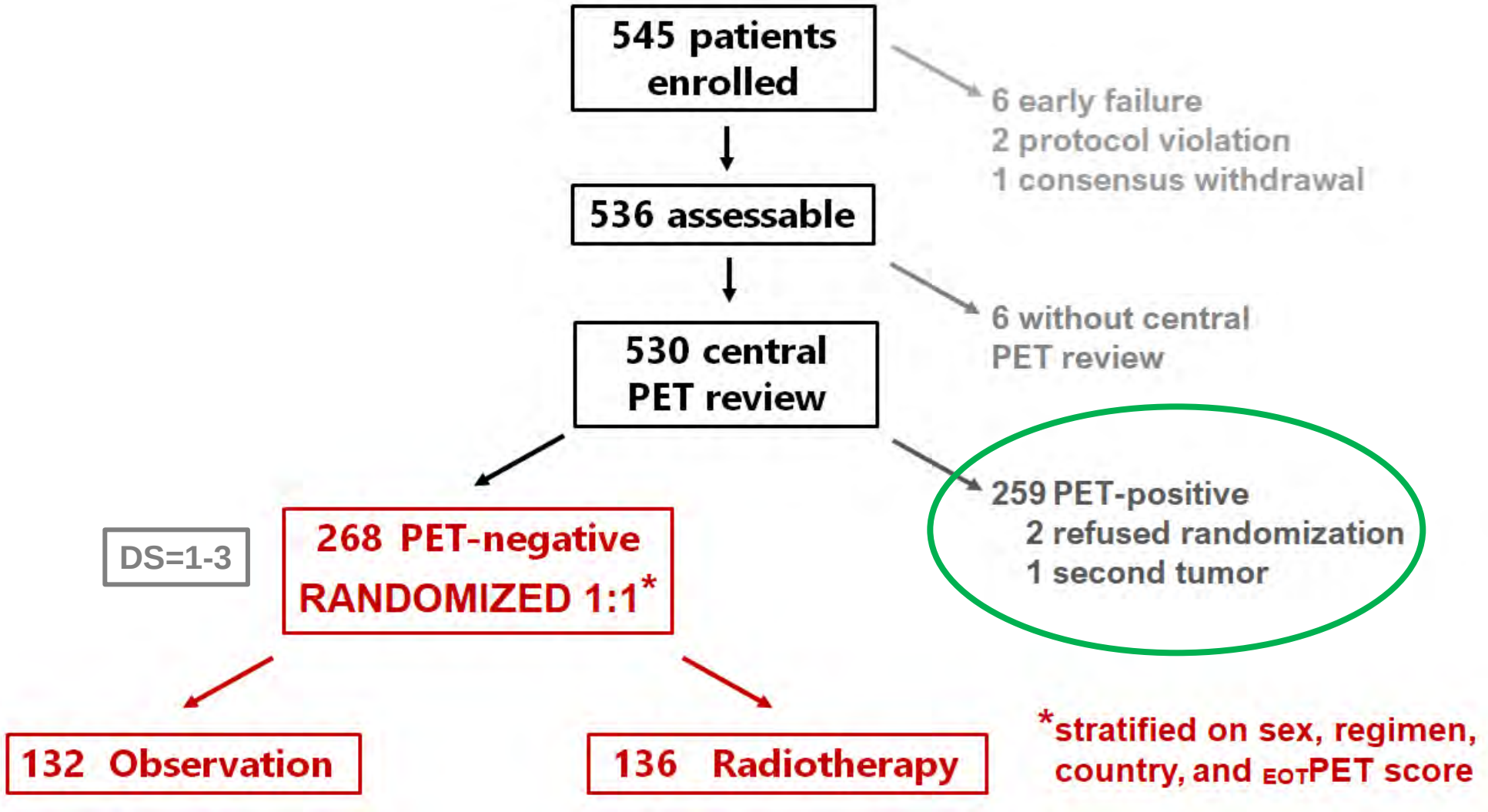
**occurred in the same patient

Conclusions

- IELSG-37 is the largest randomized trial of PMBCL ever conducted.
- ***Mediastinal RT may be safely omitted*** in patients with CMR (DS=1-3) after front-line immunochemotherapy
- This is in keeping with the results reported in single-institution retrospective studies with a PET driven approach*
- A longer follow-up is needed to properly evaluate the long term toxicity

*Hayden AR et al, Blood 2020;136:2803 Zinzani PL et al. Hematol Oncol 2015;33:145

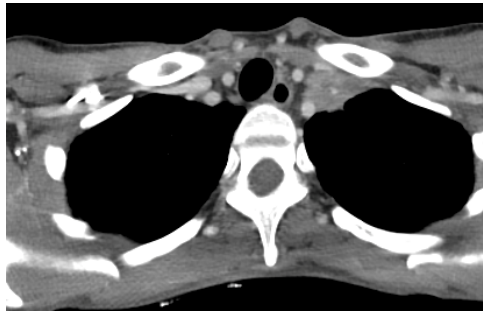
Patient flow

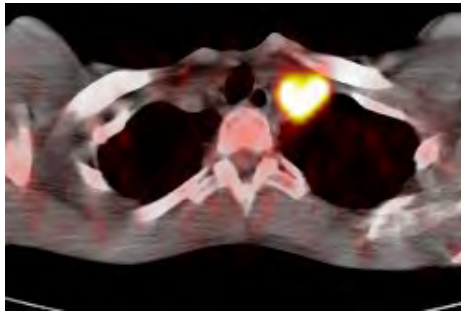


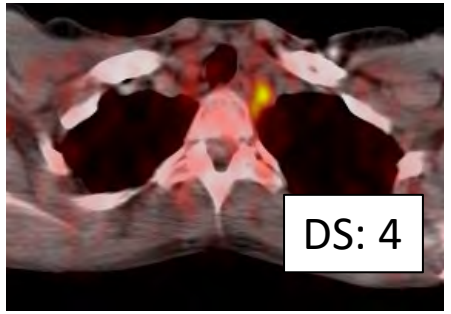
CT scan
(diagnosis)

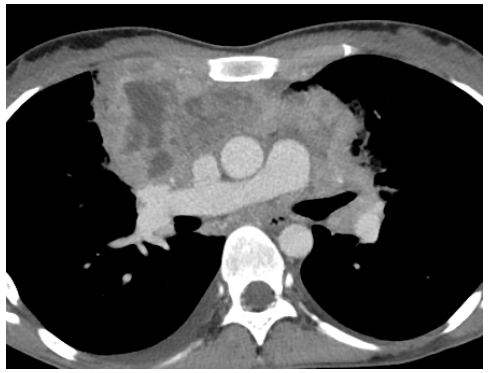
PET/CT scan
(diagnosis)

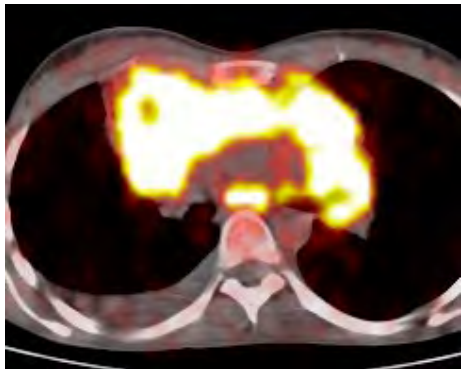
PET/CT scan
(after 6 R-CHOP14)

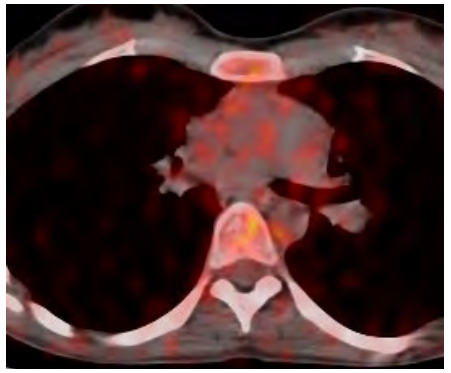


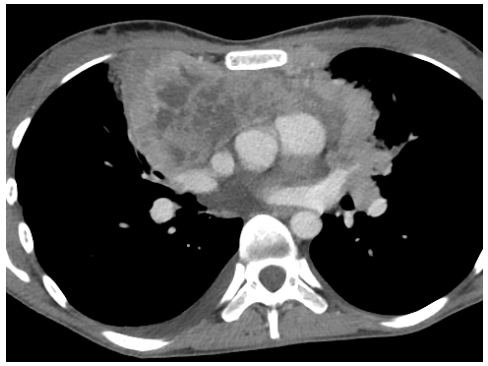


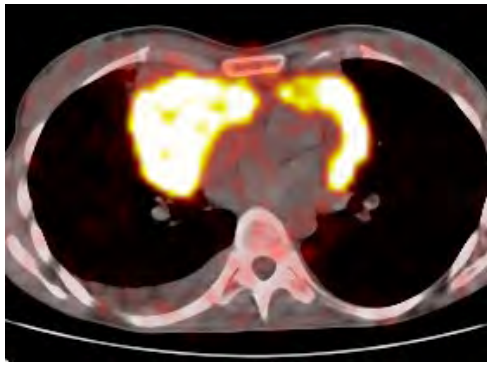


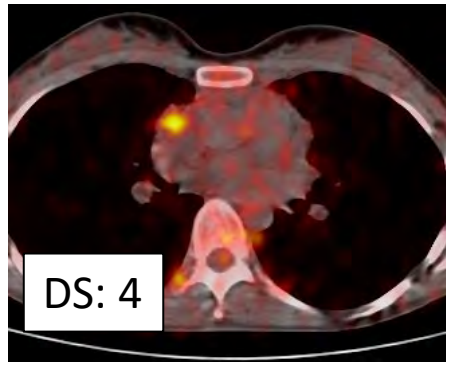






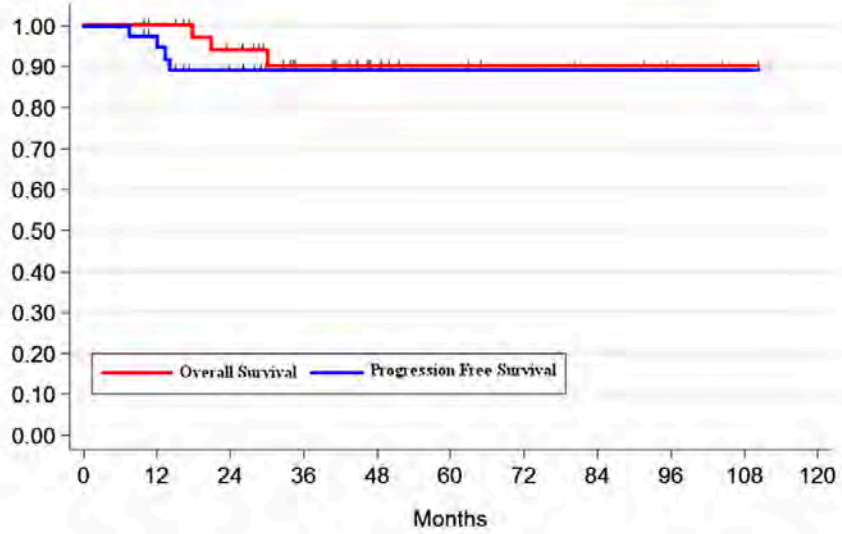


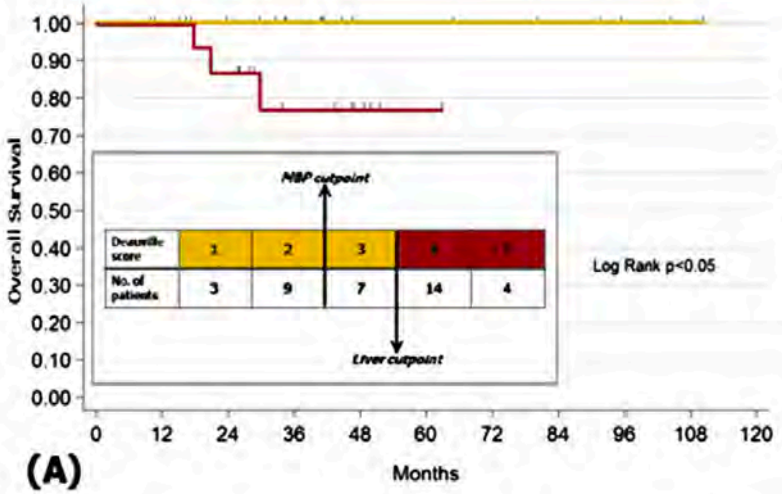


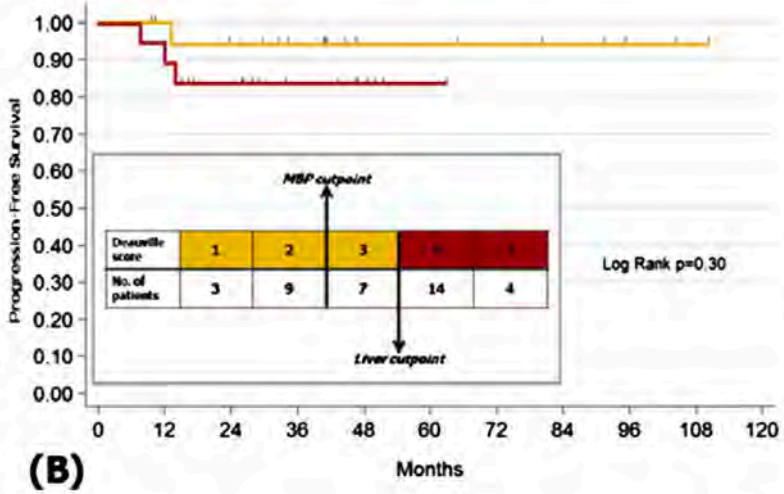


Radiation Therapy in Primary Mediastinal B-Cell Lymphoma With Positron Emission Tomography Positivity After Rituximab Chemotherapy

Filippi et al., IJROBP 2013



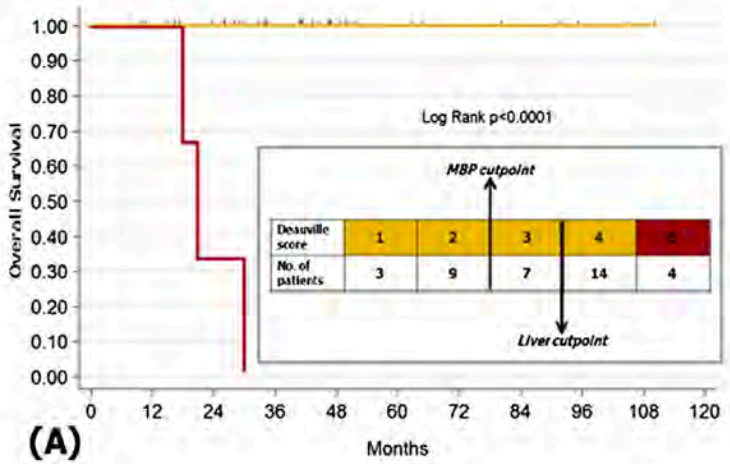


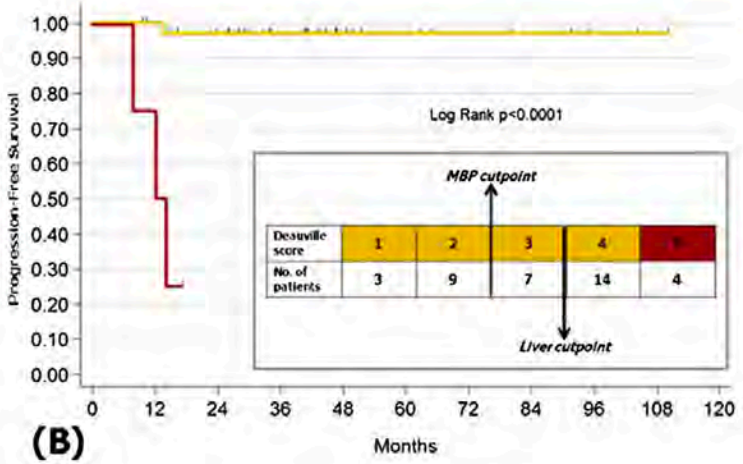


Approximately 50% of PMBCL patients show residual disease at ^{18}FDG-PET scan after R-CT

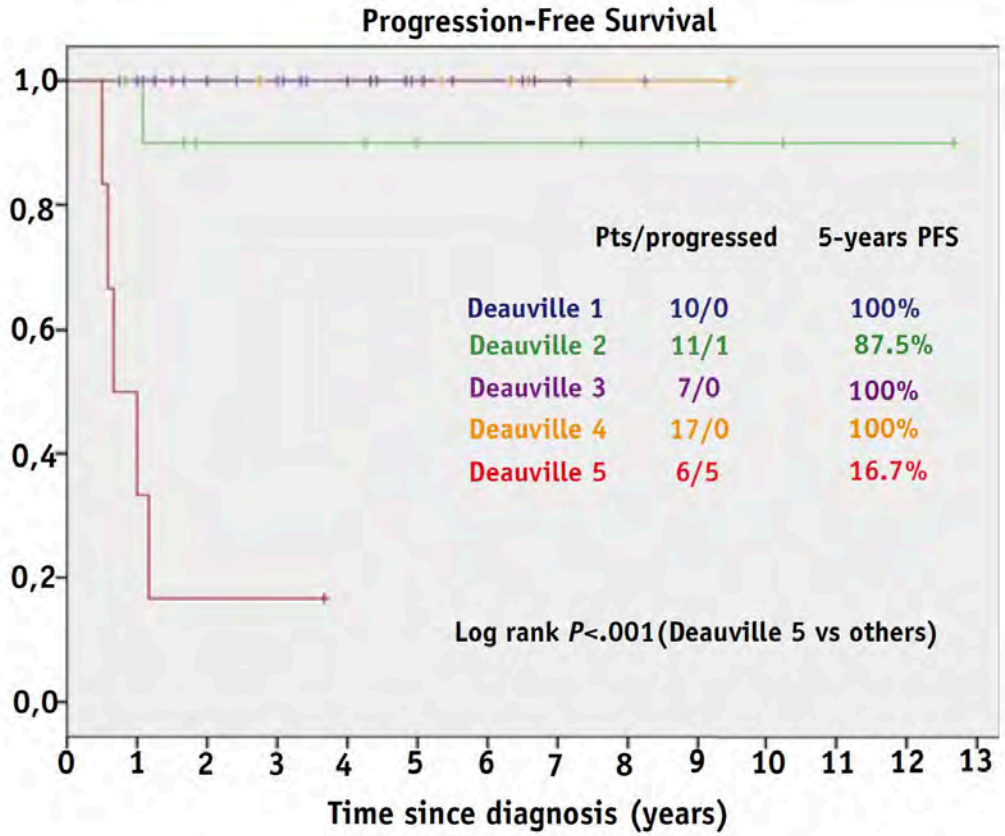
RT is able to convert to CR approximately 85% of these patients

Pts with a D5PS (10%) appear at high risk of progression and death





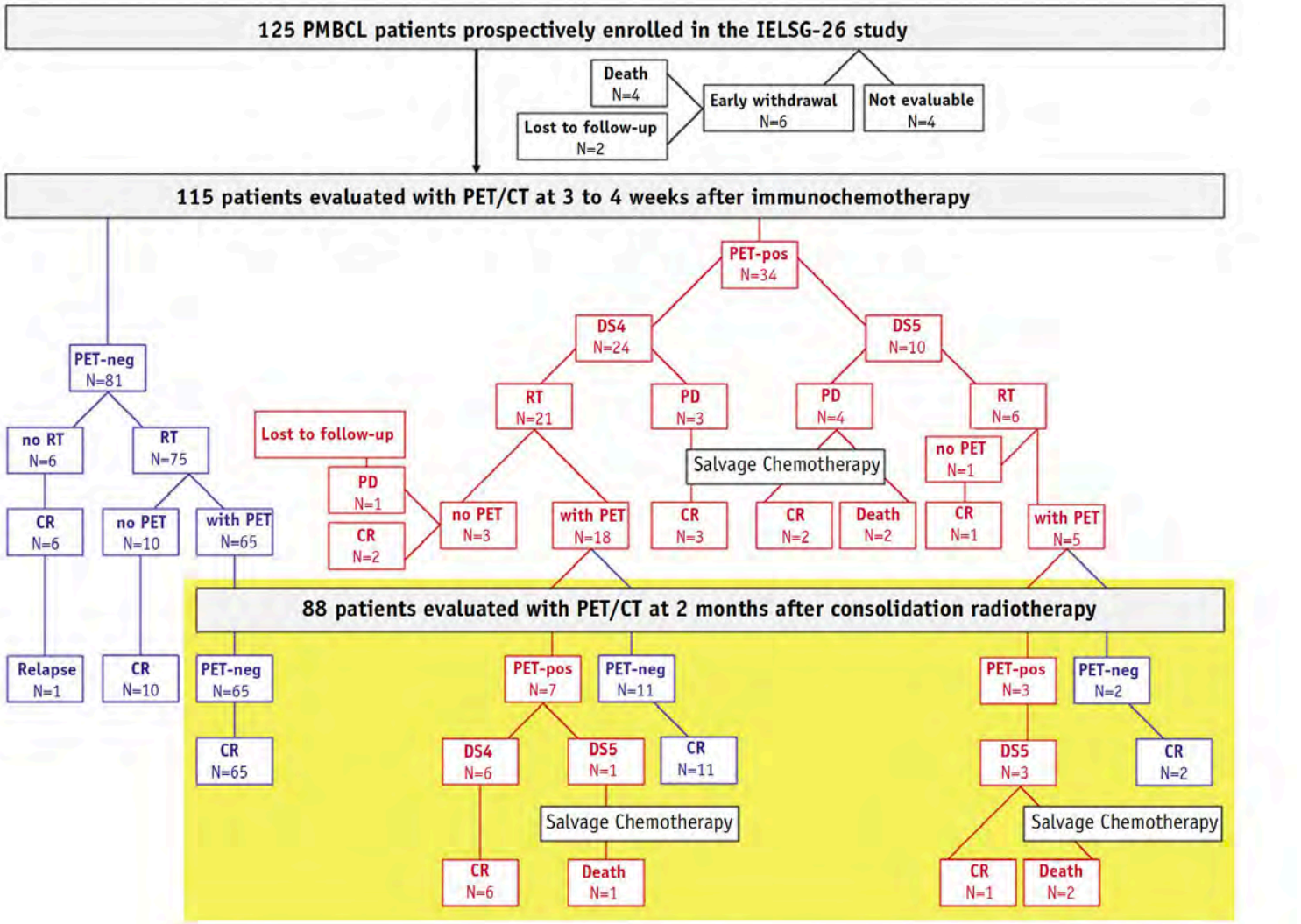
Prognostic Role of Pre—Radiation Therapy ^{18}F-Fluorodeoxyglucose Positron Emission Tomography for Primary Mediastinal B-Cell Lymphomas Treated with R-CHOP or R-CHOP-Like Chemotherapy Plus Radiation



Filippi et al., IJROBP 2016

Positron Emission Tomography/Computed Tomography Assessment After Immunochemotherapy and Irradiation Using the Lugano Classification Criteria in the IELSG-26 Study of Primary Mediastinal B-Cell Lymphoma

Ceriani L. et al., IJROBP 2016



All the patients with DS 4 after RT achieved a longlasting complete remission (CR)

r/r PMBCL

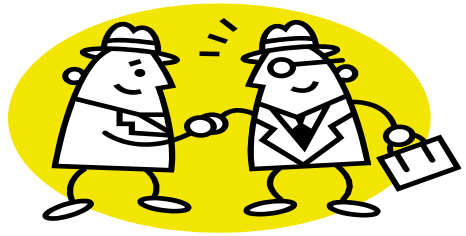
- Single-agent PD-1 inhibitor pembrolizumab has demonstrated high and durable remission rates
- Despite the expression of CD30, the CD30 antibody drug-conjugate brentuximab vedotin (BV) as a single agent has been deemed inactive in this disease
- On the contrary, the combinations of BV and PD-1 inhibitor has shown higher response rates than PD-1 inhibitor alone
- Moreover, anti-CD19 chimeric antigen receptor T-cell (CAR T-cell) therapy has been positioned as another successful strategy for patients with rrPMBCL
- **Radiotherapy role: depending on first line therapy**

Radiotherapy still has a role in PMBCL

- 50% of patients do not achieve MCR after immunochemotherapy

- New imaging criteria for response evaluation at EOT (false positivity for some DS 4 findings?)

A special thank to



- The patients and their families
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- Co-chairs: E. Zucca (Bellinzona, CH), M. Martelli (Rome, IT) and A. Davies (Southampton, UK)
- Study statistician: G. Ciccone (Turin, I)
- PET panel: L. Ceriani (Bellinzona, CH), S. Barrington (London UK), A. Biggi (Cuneo, I), B. Malkowski (Bydgoszcz, PL), U. Metser (Toronto, CA), A. Versari, (Reggio Emilia, I)
- Medical Physicist: S. Chauvie (Cuneo, I)
- Radiotherapy, U. Ricardi (Turin, I)
- IDMC members: C. Gisselbrecht (Paris, F), L. Trümper (Göttingen, D), V. Torri (Milan, I),
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