



Princess Margaret Cancer Centre

April 8, 2026

Clinical dilemmas in primary mediastinal large B cell lymphoma

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Disclosures

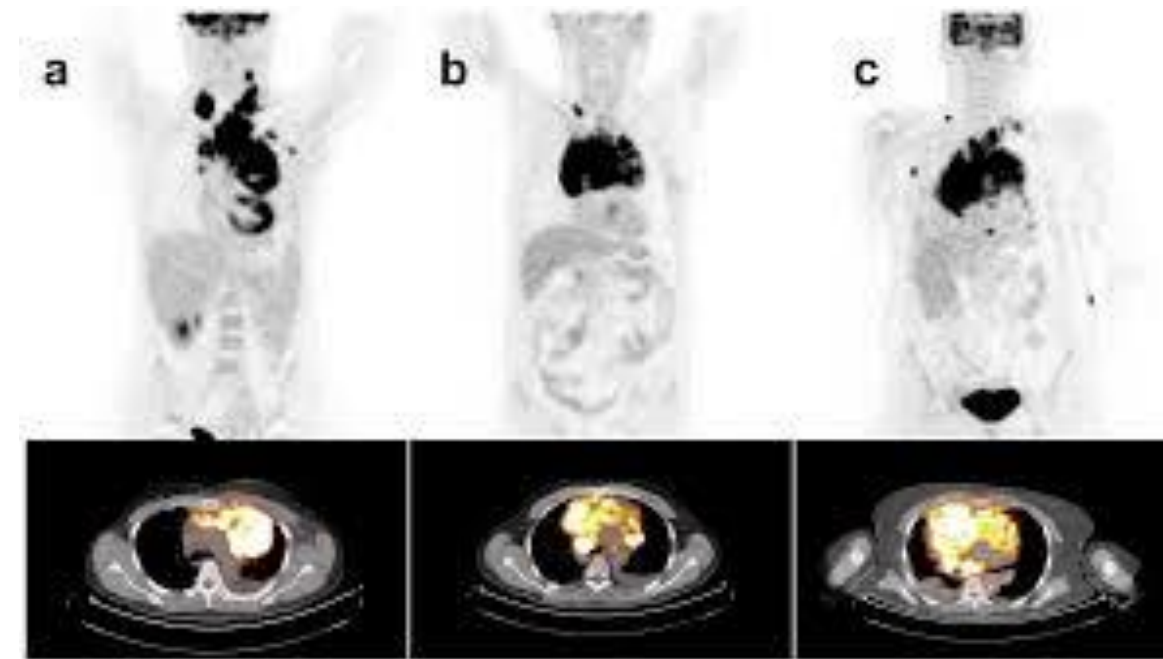
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Objectives

- Frontline regimen selection
- Interpretation of end of treatment PET response/role of radiotherapy
- Management of relapsed/refractory disease

Case vignette

- 18F 1 month history of back pain, 2 weeks of fever, progressive dyspnea
- In ED: CT chest 12.1 cm anterior mediastinal mass with mass effect on aortic arch and main pulmonary artery and compression of SVC
- Others: Pulmonary nodules 1 cm, pericardial effusion, small pleural effusion
- LDH 716
- Biopsy: diffuse medium to large lymphoid cells CD20+, BCL6+, BCL2+, MUM1+, CD23+, CD30 weakly+, CD15-
- PET: SUVmax 20.4, lung nodules SUV 3-4, hilar node



Active poll

0 8



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#PMHC09

What is the preferred frontline chemotherapy regimen for this patient with newly diagnosed PMBCL?

A. R-CHOP-21 for 6 cycles +/- radiation

0%

B. DA-R-EPOCH for 6 cycles +/- radiation

0%

C. R-CHOP-21 for 6 cycles +/- radiation

0%

D. R-CHOP-14 for 6 cycles +/- radiation

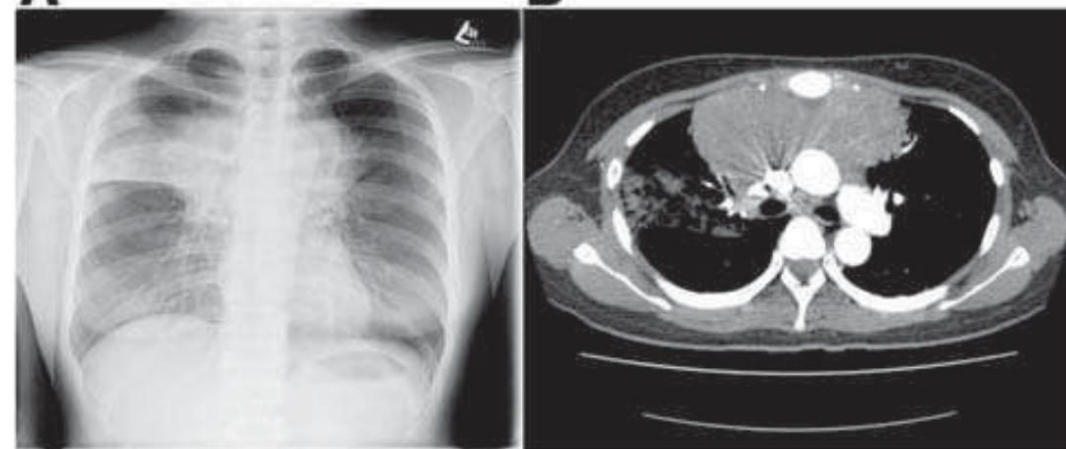
0%

E. Pola-R-CHP for 6 cycles +/- radiation

0%

PMBCL: a distinct clinical and biological entity

- 2-4% of non-Hodgkin lymphoma; 6-12% of all LBCL
- 3rd decade
- Female predominance 2:1
- Anterior mediastinal mass
 - ~70-80% stage I-II
 - 20-40% present with SVC obstruction
 - 10+cm 70-80%
 - Pleural / pericardial effusion 30-40% due to local invasion
- Marrow: rare



PMBCL histology characteristics and differential diagnosis

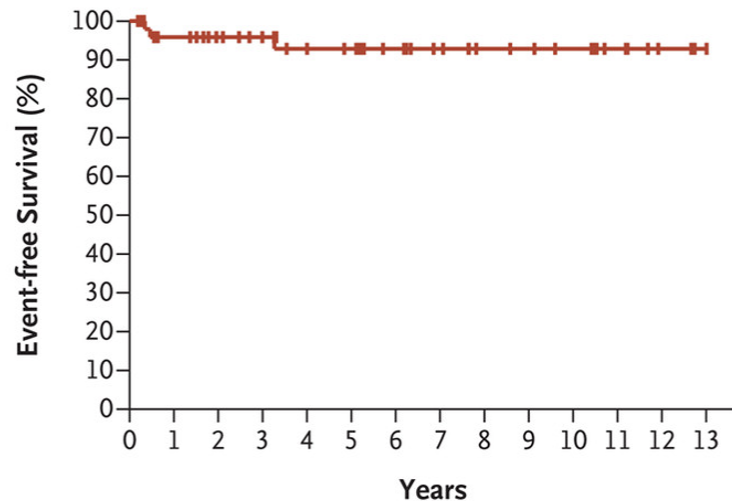
	DLBCL NOS	PMBCL	Classical HL	Mediastinal gray zone
Morphology	Diffuse/nodular infiltrate of medium-large cells, with no sclerosis	Diffuse infiltrate in clusters/sheets on fibrotic/sclerotic background, +/- HRS-like cells	Several subtypes. + HRS cells, sclerosis, mixed background	Broad appearance (DLBCL and cHL); 60-70% mediastinal [Dx of exclusion]
CD30 expression	CD30+ (weak) 19-31%	CD30+ (weak) 80%	CD30+ (strong) ~100%	CD30+ (strong) 85-100%
CD15 expression	CD15 negative	CD15 negative	CD15+ 75-85%	CD15+ 58-80%
PDL1	19%	71%	87%	80%

- WHO diagnosis: clinicopathological, anterior mediastinal mass; partial expression of CD23 and/or CD30.

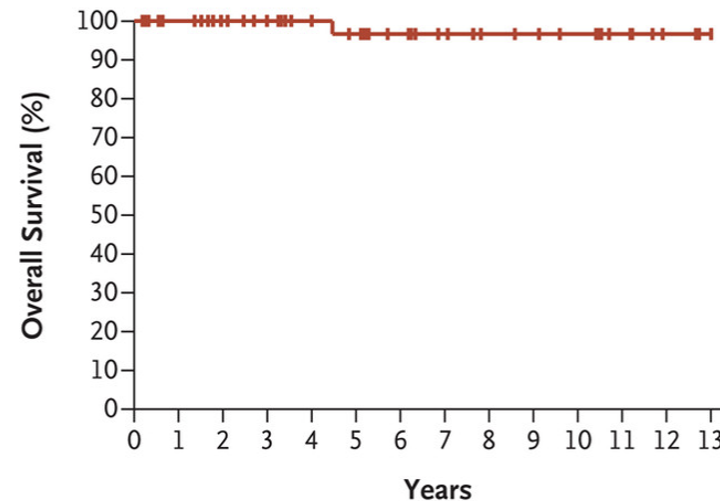
Does intensification improve outcomes?

- Retrospective analyses suggest intensified chemotherapy → improved outcomes (Zinzani et al. 2002).
 - 10-year PFS: CHOP 35%, MACOPB 67% and high dose +/- ASCT 78%
- Phase II (n=51) vs. retrospective Stanford cohort (n=16)
 - DA-EPOCH-R 6-8 cycles: 6 if <20% reduction in diameter
 - 93% PFS; 97% OS
 - 3/51 refractory; 2 received RT, 1 excised

A Event-free Survival (NCI Patients)

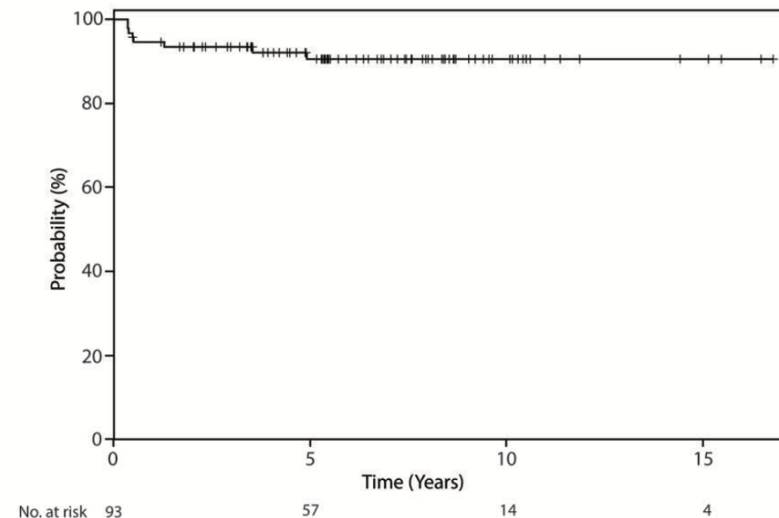


B Overall Survival (NCI Patients)



Extension cohort

A Event-free Survival (Total Cohort)



DA-EPOCH-R may allow omission of RT, but whether intensification improves outcomes remains unresolved.

- Zinzani et al. Hematologica 2002; 87:1258-1264
- Dunleavy et al., NEJM 2013; 368(15): 1408-1416

Dose intensification: R-CHOP-14 vs 21 (retrospective, LYSA)

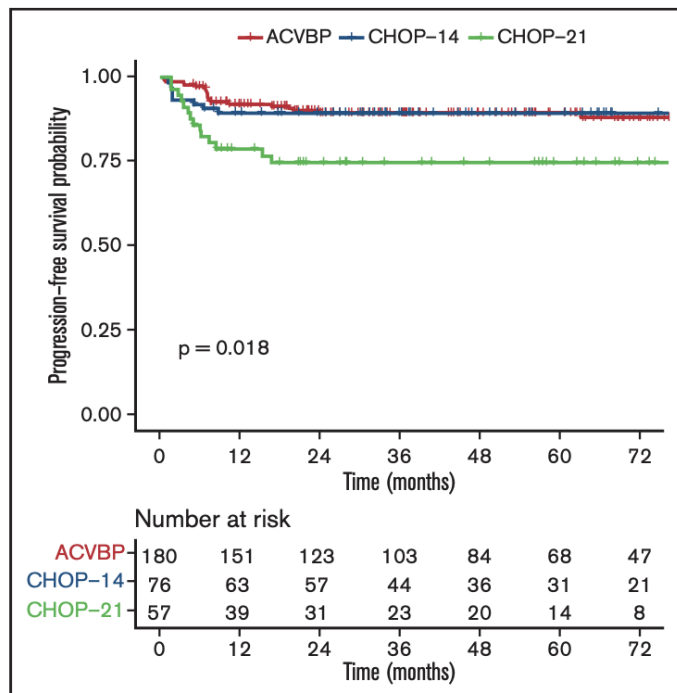


Figure 2. PFS according to ACVBP, CHOP14, and CHOP21 plus anti-CD20 treatment groups.

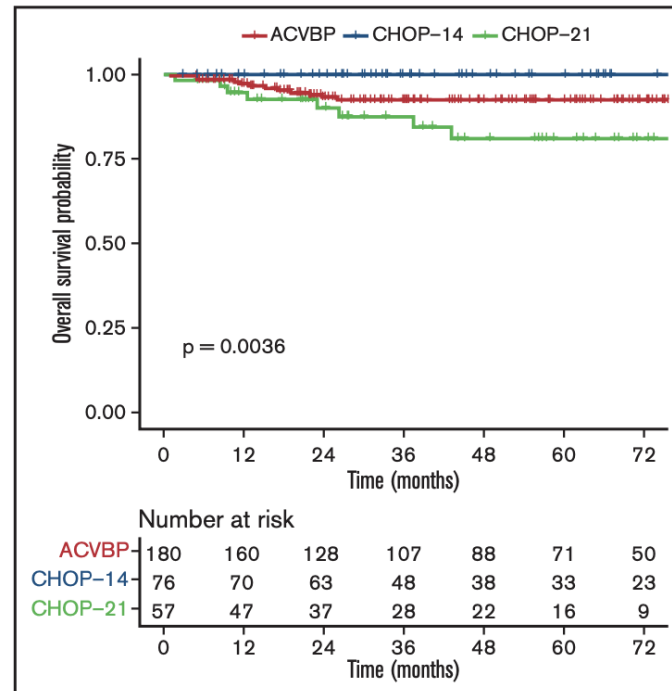


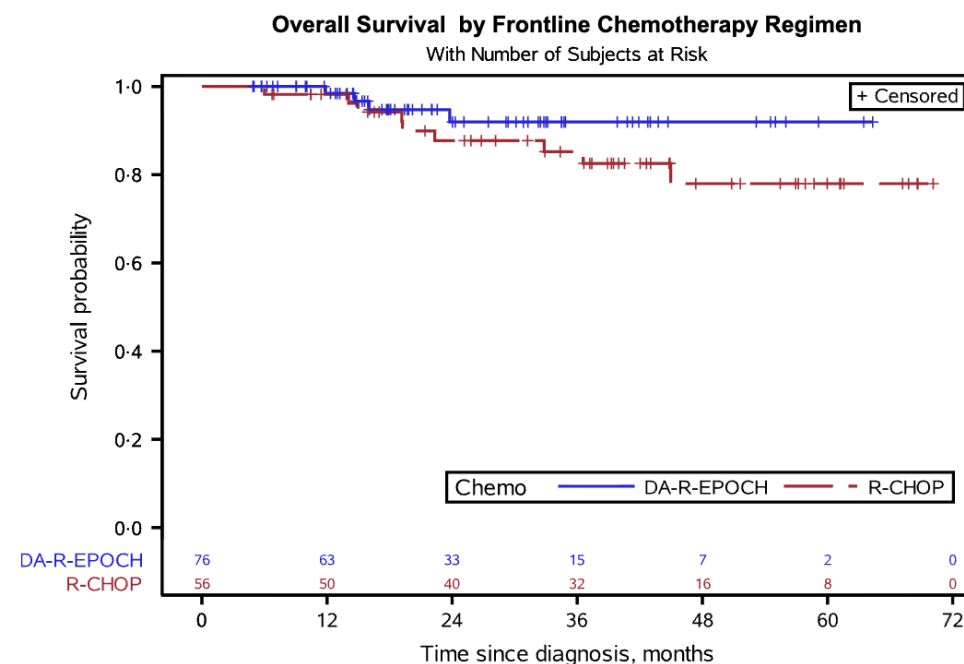
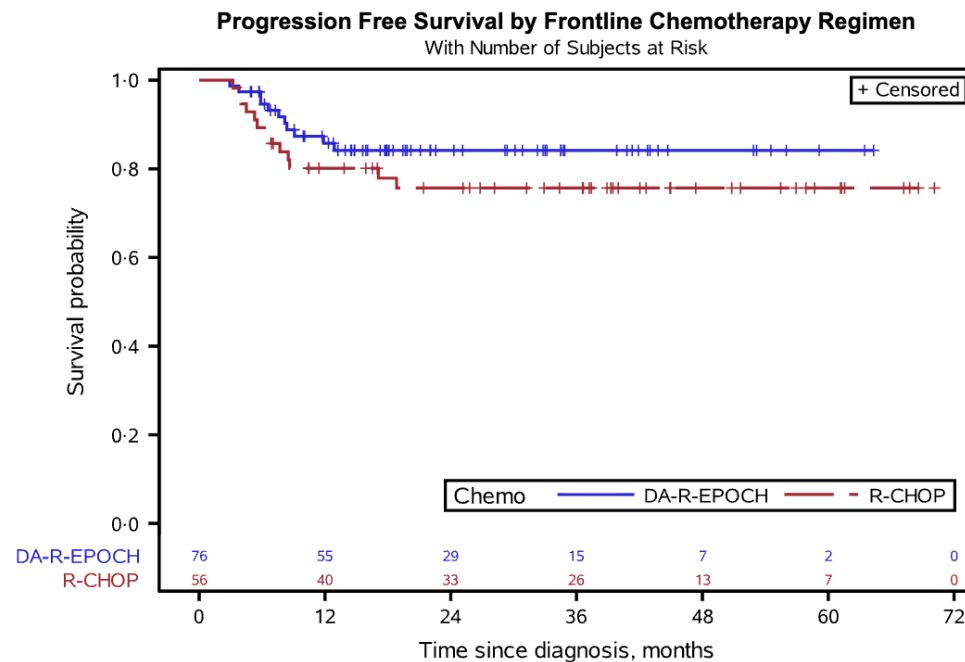
Figure 3. OS according to ACVBP, CHOP14, and CHOP21 plus anti-CD20 treatment groups.

R-ACVBP as reference		
	univariable	multivariable
PFS		
R-CHOP-14	0.90 [0.40-2.03]	0.26 [0.06-1.12]
R-CHOP-21	2.37 [1.20-4.67]	1.06 [0.41-2.76]
OS		
R-CHOP-14	NR	NR
R-CHOP-21	1.95 [0.82-4.66]	2.19 [0.28-17.2]

Apparent differences with dose intensification attenuated after adjustment, with no clear survival benefit.

R-CHOP or DA-EPOCH-R

- Retrospective (US) n=144
- No statistical significant difference in PFS or OS
- Consolidation RT: R-CHOP 59%; DA-EPOCH-R 13%



R-CHOP and DA-EPOCH-R similar outcomes, but DA-EPOCH-R may reduce the need for consolidative radiotherapy.

Meta analysis comparing outcomes following frontline treatment

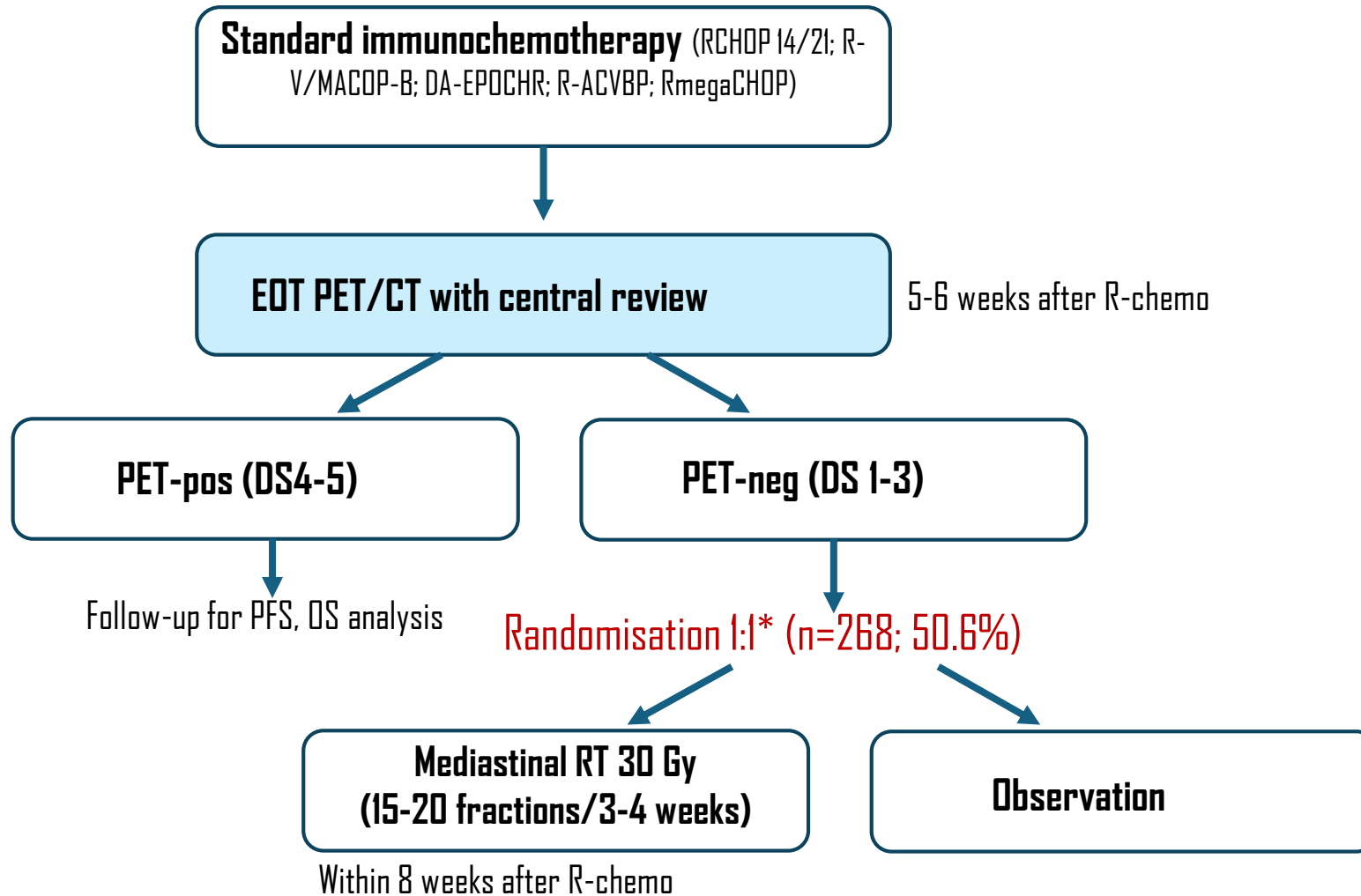
- 52 studies: n=4068 (62% high intensity)
- Dose intensive regimens:
 - R-CHOP-14
 - DA-EPOCH-R
 - V/MACOP-B
- Standard regimens:
 - R-CHOP/CHOP-21
- Overall OS 88% vs. 80%
- DA-EPOCH-R 90% vs. R-CHOP-21 86% (p<0.25)

Table 3. Primary and secondary outcomes.

Treatment cohort	Overall survival, % (95% CI)	Meta-regression P
DI-CIT, N=2,234	88 (85-90)	< 0.01
S-CIT, N=1,440	80 (74-85)	
da-EPOCH-R, N=636	90 (88-93)	< 0.25
R-CHOP21, N=1,032	86 (82-89)	
R-DI-CIT, N=1,279	91 (89-93)	0.03
R-S-CIT, N=1,032	86 (82-89)	
Progression-free survival, % (95% CI)		
DI-CIT, N=1,501	83 (79-86)	< 0.01
S-CIT, N=1,200	72 (65-79)	
da-EPOCH-R, N=276	83 (78-87)	0.18
R-CHOP21, N=957	77 (72-82)	
Consolidative radiation, % (95% CI)		
DI-CIT, N=2,050	22 (15-31)	<0.01
S-CIT, N=1,202	55 (43-65)	
da-EPOCH-R, N=670	13 (7-21)	<0.01
R-CHOP21, N=894	57 (43-70)	

Primary and secondary outcome data for different treatment cohorts. Meta-regression analysis was performed for each endpoint, compared dose-intensive chemoimmunotherapy (DI-CIT) versus standard approach chemoimmunotherapy (S-CIT), da-EPOCH-R versus R-CHOP21 and rituximab-containing DI-CIT versus S-CIT only. da-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

IELSG 37: secondary analysis evaluating frontline regimen

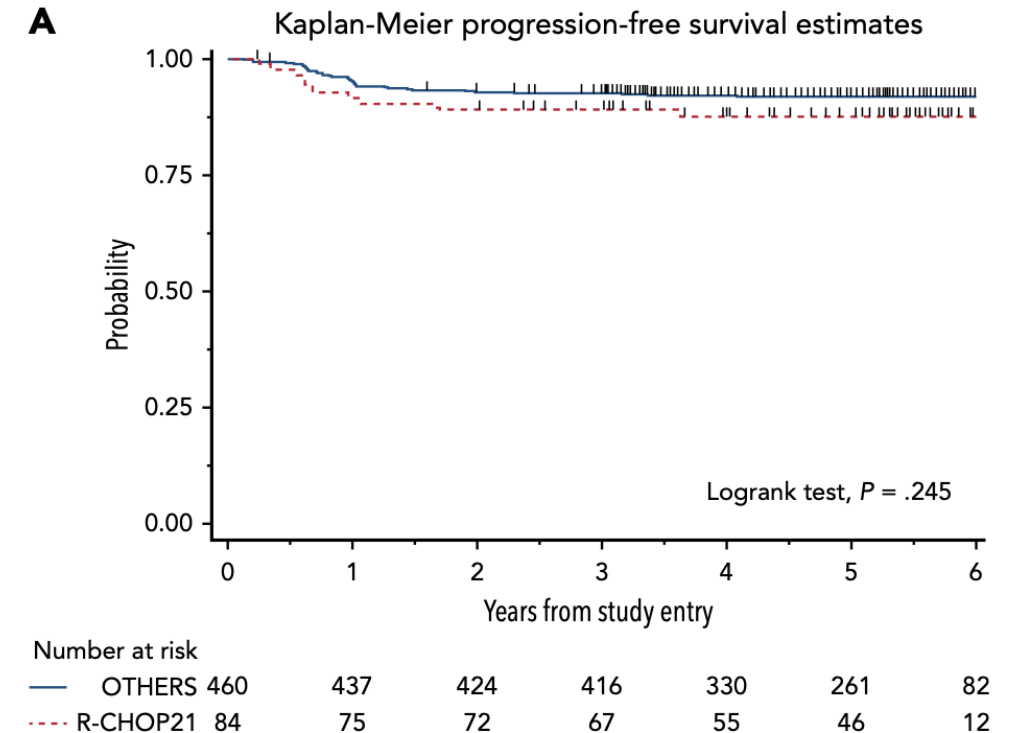


* Stratification for randomisation

- Sex
- Country
- Chemotherapy-type (CHOP/CHOP-like, V/MACOP-B, DA-EPOCH, other)
- PET response (DS1,2,3)

PET response differences did not translate to survival differences

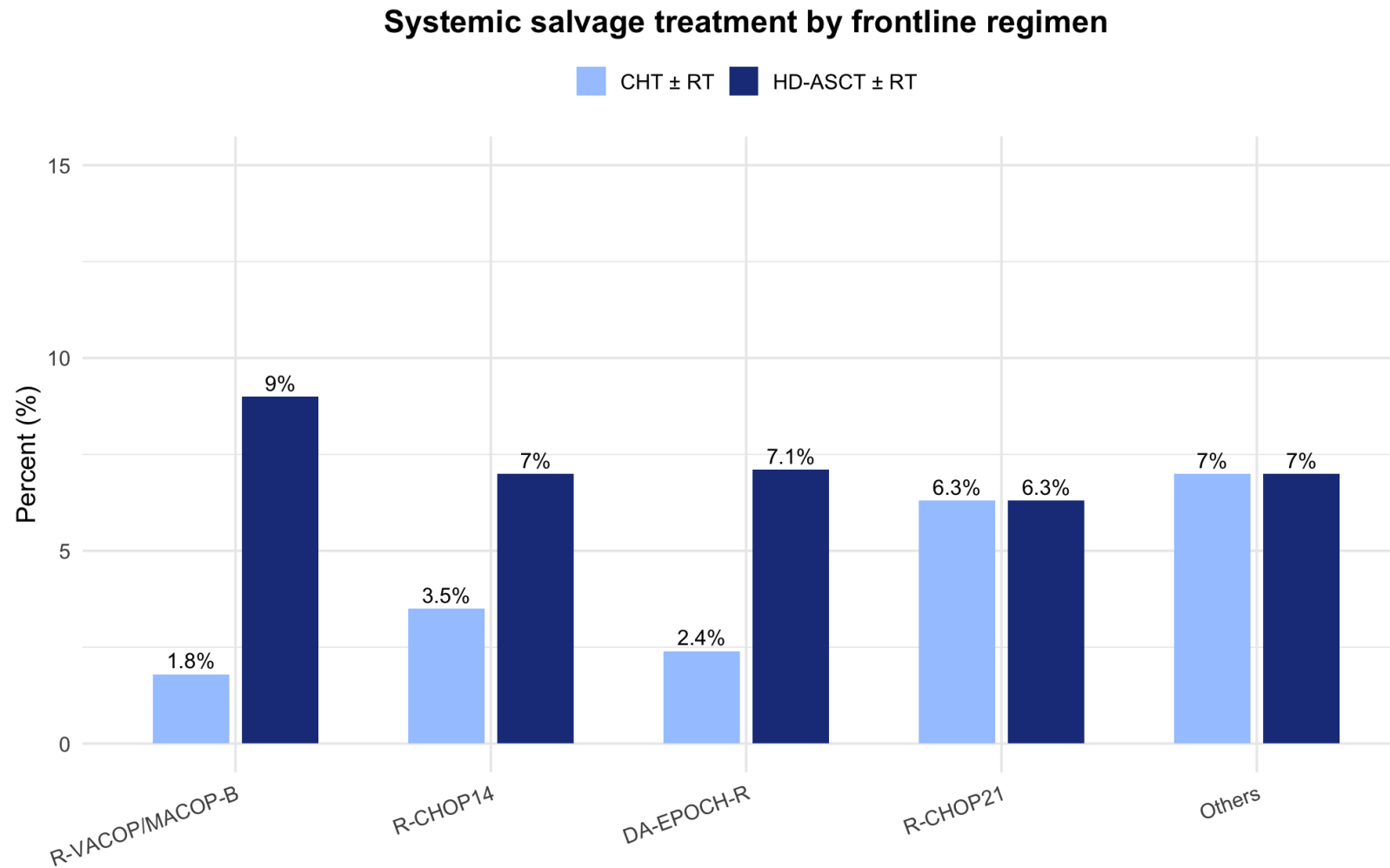
Regimen	DS 4	DS 5
R-VACOP/MACOP-B	36.8	9
R-CHOP14	37.1	8.4
DA-EPOCH-R	29.8	5.9
R-CHOP-21	23.8	23.7
Others	28.1	8.8
Total	32.8	10.6



No conclusions regarding inferiority can be drawn from this non-randomized analysis.

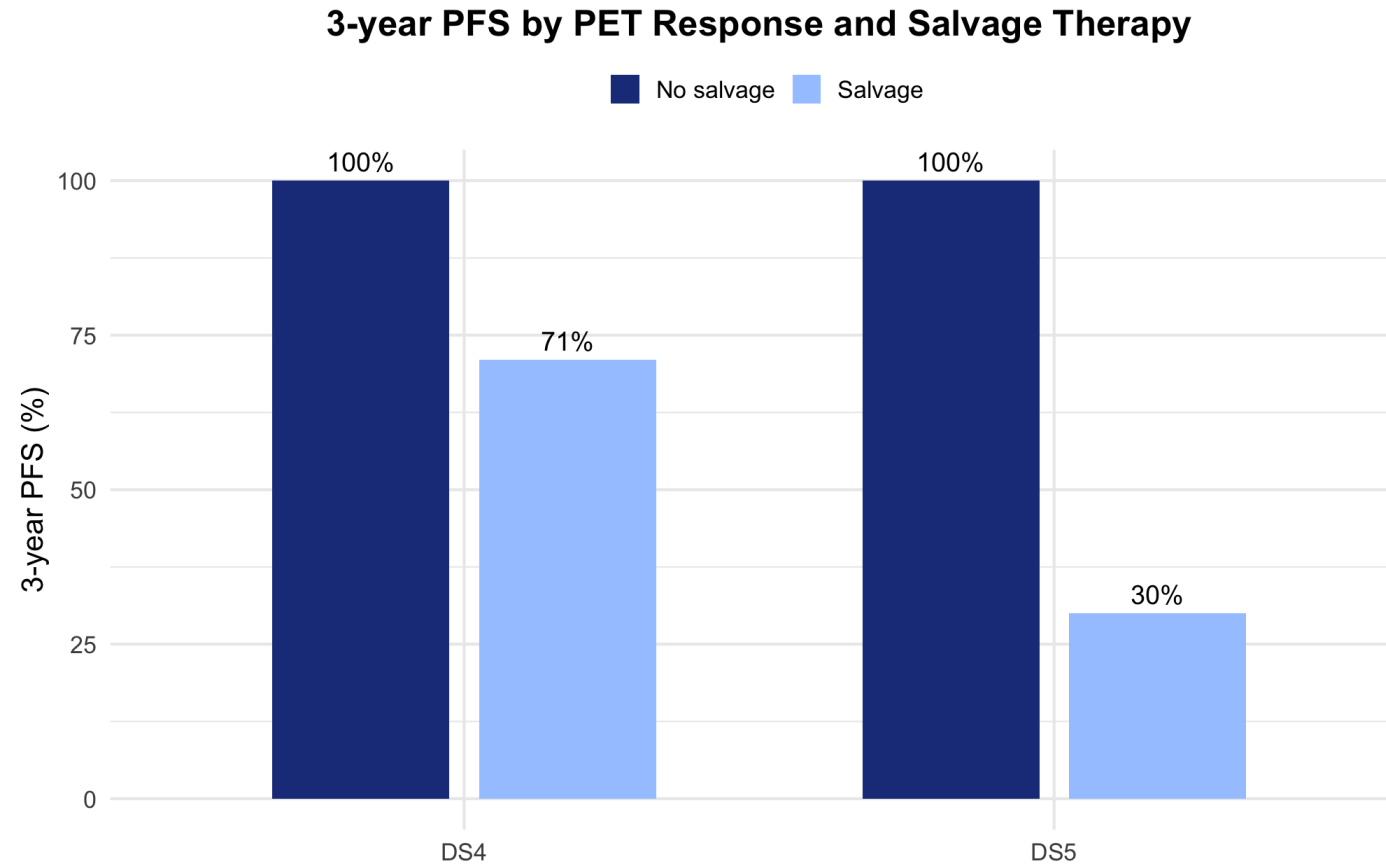
*Caution: study not designed/powerd to detect differences in CIT strategies

Patients who required 2L treatment did not differ across regimens



*Caution: study not designed/powerd to detect differences in CIT strategies

Outcomes driven by need for 2L treatment



*Caution: study not designed/powerd to detect differences in CIT strategies

Summary: frontline regimen selection

- R-CHOP-21 was associated with higher DS5 rates (~24% vs ~8%), but this did not translate into 2L treatment or inferior survival
 - Poor outcomes in patients selected to receive 2L
- While no survival advantage between regimens, intensified regimens may be preferred when omission of RT is a priority: R-CHOP-14 / DA-EPOCH-R*

* Tradeoff: increased toxicity (ALLIANCE; infection/FN, mucositis, neuropathy)

Case Vignette: Part II

- She received R-CHOP-14 achieving PMR SUV 20 → 6.8 (liver 3.1)
- Morphologically: 12 cm → 5 cm



Does she need consolidative radiotherapy?

1. Yes
 0%

2. No
 0%

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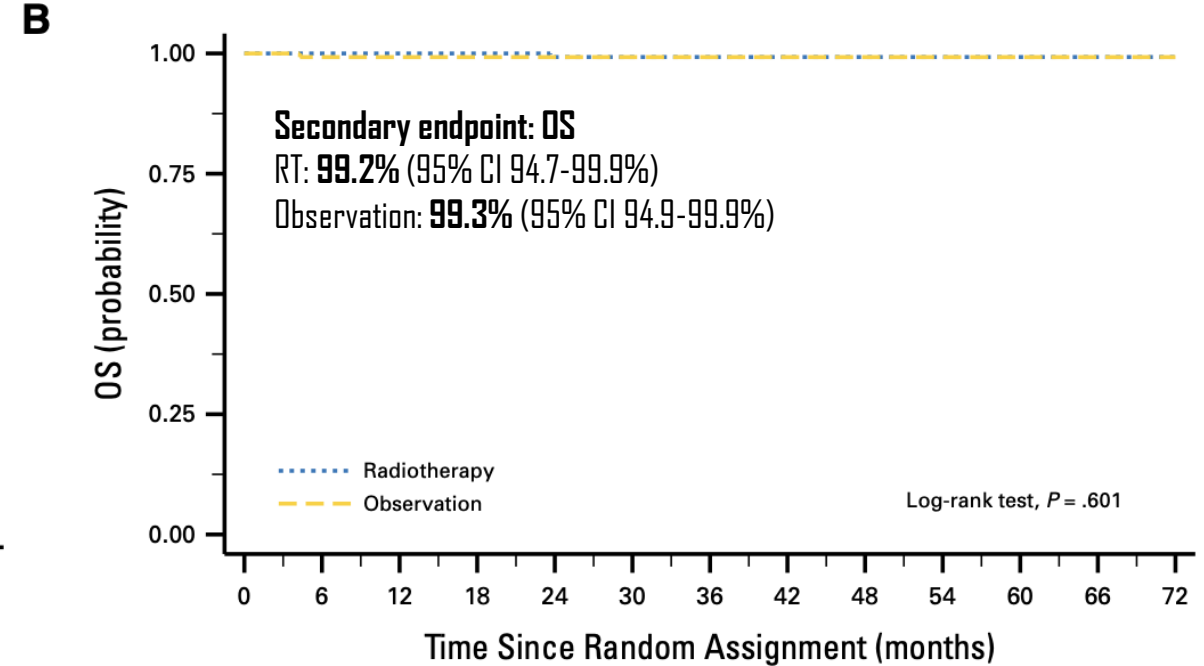
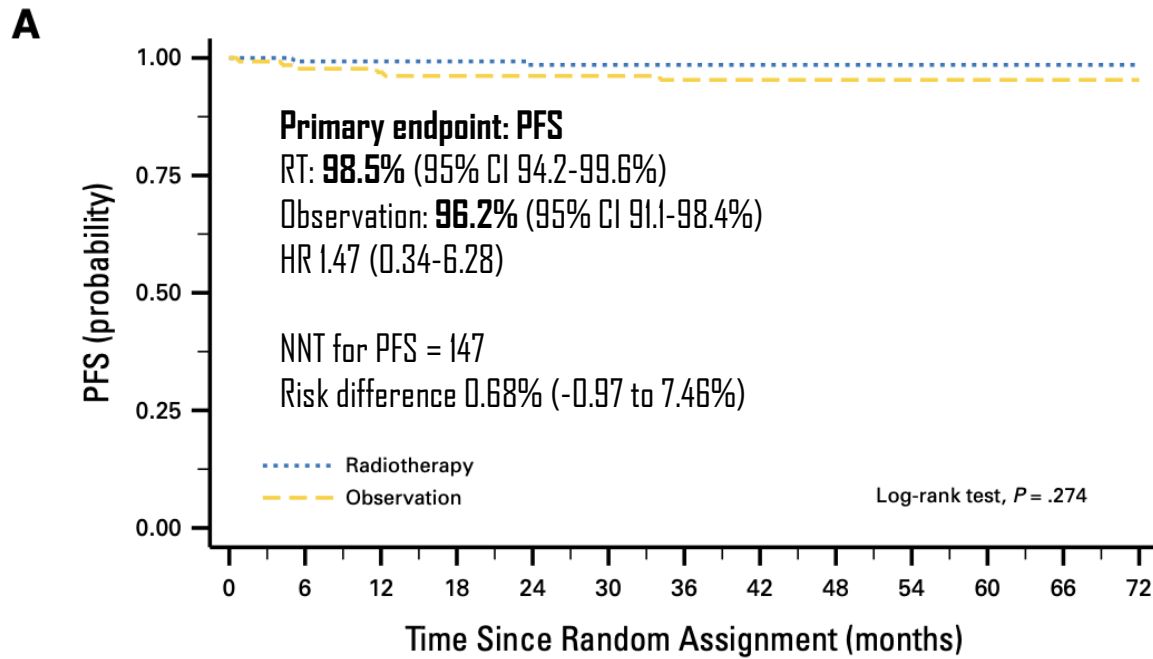


IELSG37: is radiotherapy consolidation required?

Characteristic	Radiotherapy (N=136)	Observation (N=132)	Total (N=268)
Sex, N (%)			
Female	88 (65)	83 (63)	171 (64)
Male	48 (35)	49 (37)	97 (36)
Median age, years (interquartile range)	35.5 (29-46.5)	35.5 (28.5-46)	35.5 (29-46)
EGOG PS, N (%)			
0	74 (54)	69 (52)	143 (53.4)
1	50 (37)	54 (41)	104 (38.8)
≥2	12 (9)	9 (7)	21 (7.8)
Bulky disease, >10 cm N (%)	89 (65)	79 (60)	168 (62.7)
Elevated LDH, >UNL N (%)	91 (67)	88 (67)	179 (66.8)
R-IPI score, N (%)			
Low risk	30 (22)	31 (23)	61 (22.8)
Intermediate risk	98 (72)	96 (73)	194 (72.4)
High risk	8 (6)	5 (4)	13 (4.9)
Frontline regimen			
R-CHOP-21/R-COMP	20 (14.7)	27 (20.5)	47 (17.5)
R-CHOP-14	34 (25.0)	33 (25.0)	67 (25.0)
R-V/MACOP-B	47 (34.6)	37 (28.0)	84 (31.3)
R-DA-EPOCH	23 (16.9)	24 (18.2)	47 (17.5)
Others	12 (8.8)	11 (8.3)	23 (8.6)
Response at central PET/TC review (Deauville Score)			
1	4 (2.9)	6 (4.5)	10 (3.7)
2	71 (52.2)	67 (50.8)	138 (51.5)
3	61 (44.9)	59 (44.7)	120 (44.8)

RT consolidation can be safely omitted in DS 1-3 after R-chemo

- ~50% achieve CMR post-induction



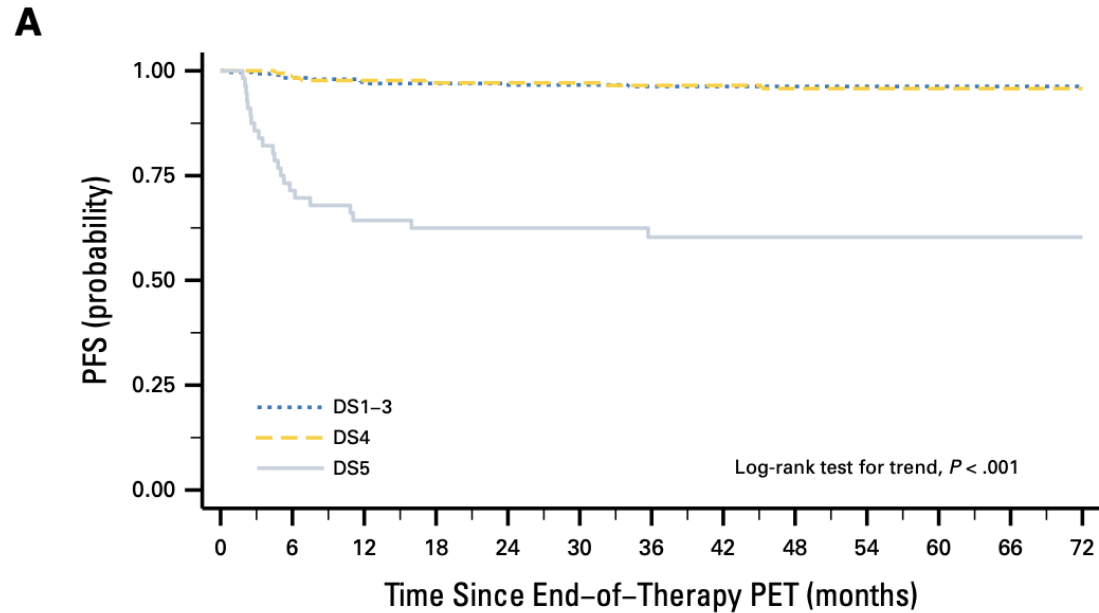
Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Radiotherapy	136	135	135	135	133	131	116	102	88	79	62	27	16
Observation	132	128	127	126	125	124	109	94	84	76	50	23	13

Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Radiotherapy	136	136	136	136	134	132	117	103	89	80	62	27	16
Observation	132	130	130	130	129	128	114	98	88	80	54	24	13

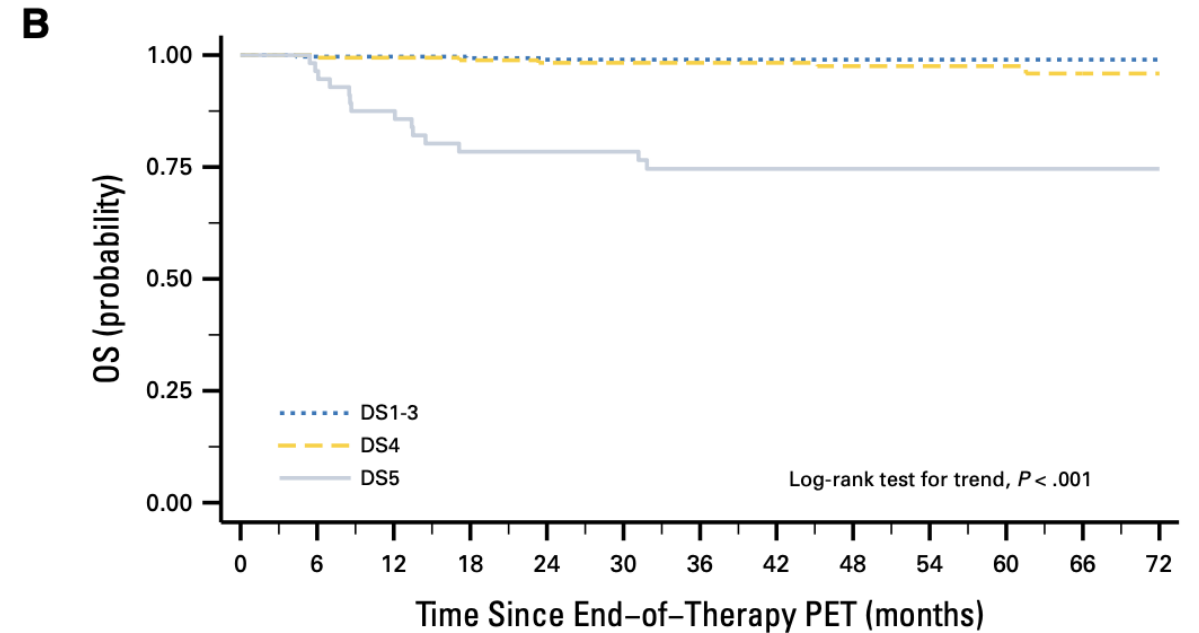
RT can be safely omitted in DS1-3 without compromising PFS or OS.

DS 4 at EOT had comparable outcomes to DS1-3 when RT given

- DS4 PFS 96% vs. 97.5% (DS 1-3); 86% DS 4 received RT
- DS5 PFS 60%



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
DS1-3	300	293	290	288	284	280	250	221	197	178	130	60	38
DS4	174	172	170	169	169	165	150	137	121	107	69	35	24
DS5	56	40	36	34	34	34	28	26	24	21	10	2	2

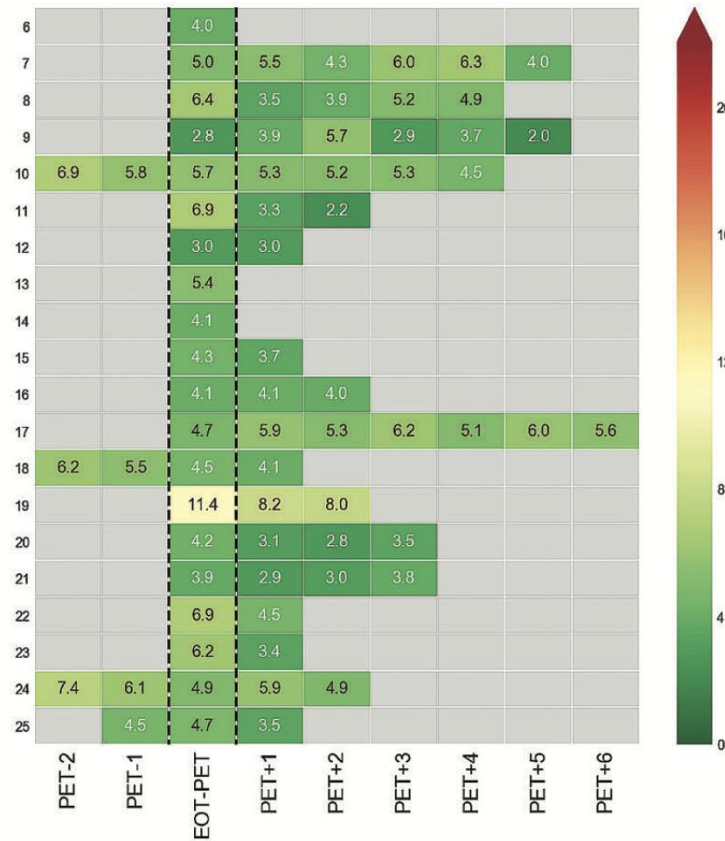


Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
DS1-3	300	297	297	295	291	287	257	227	203	184	134	61	38
DS4	174	173	173	172	171	167	153	139	123	109	71	35	24
DS5	56	54	49	43	43	43	35	33	30	26	14	2	2

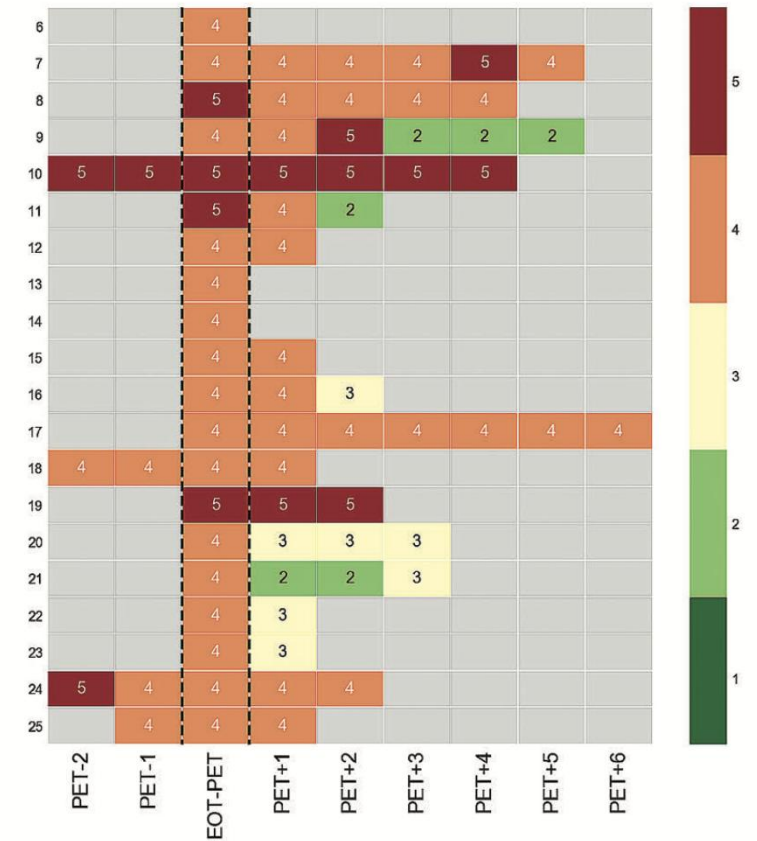
Serial PET in patients with DS 4 with no progression

- N=17 serial imaging
- SUVm static in majority (76%)
- Increased 24%

A SUVmax in EOT FDG-PET+ Non-Progressors

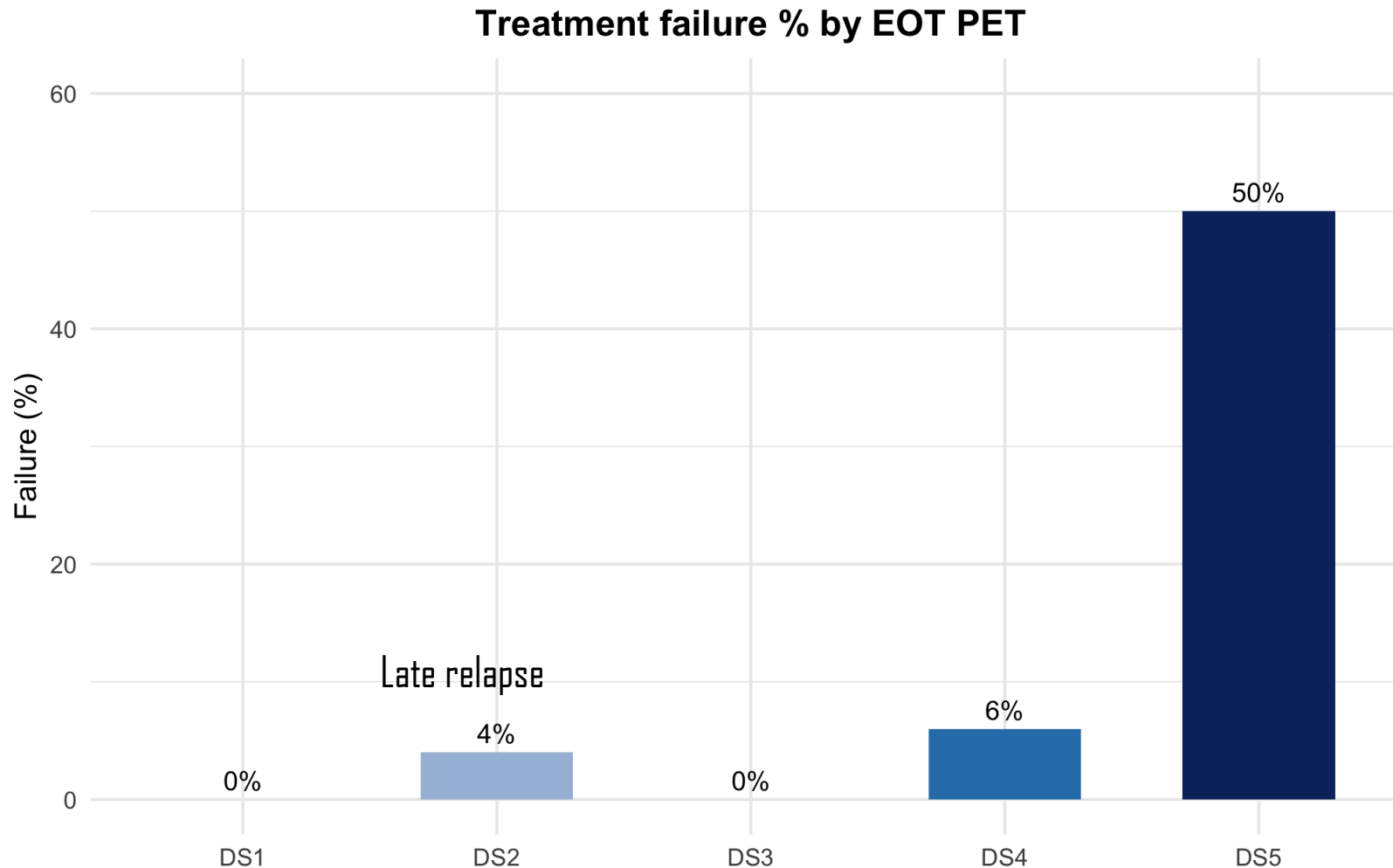


B Deauville Score in EOT FDG-PET+ Non-Progressors



Median SUVmax = 4.7

Serial PET imaging after DA-EPOCH-R suggest DS4 may be observed



DS 4: 1/17 (6%)

DS 5: 4/8 (50%)

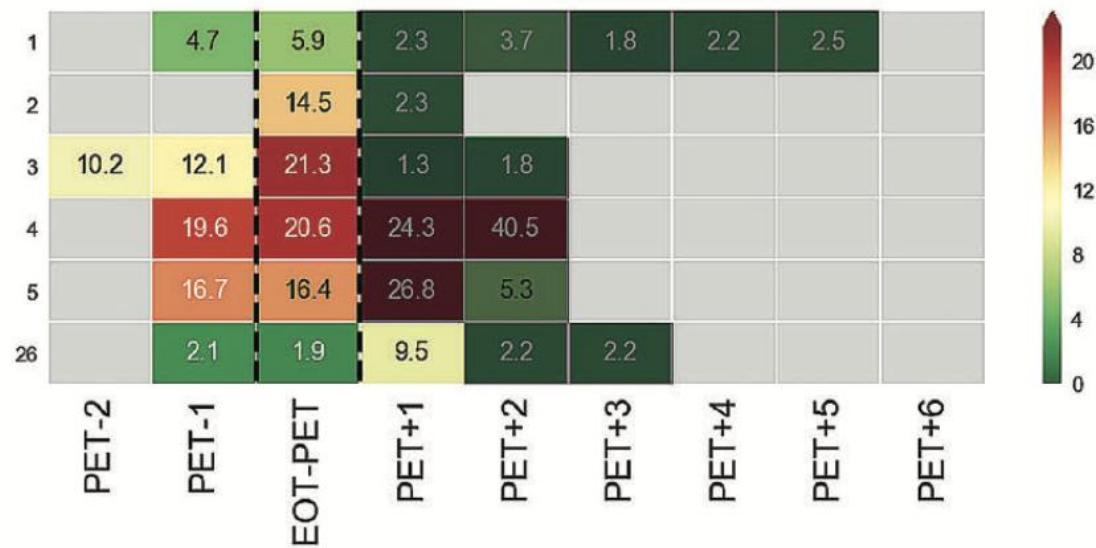
4/6 treated successfully

- 2 RT alone (DS 5)
- 1 resection
- 1 chemo/auto/RT

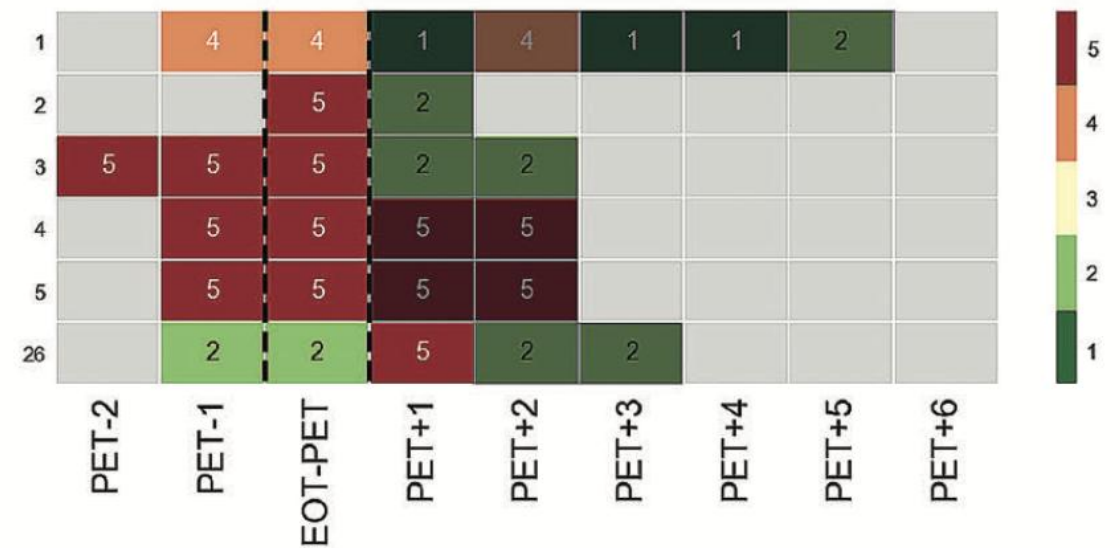
2 pts died of PD (DS 5)

Patients with progression had higher median EOT SUV_{max} 15.4

C SUVmax in Treatment Failures

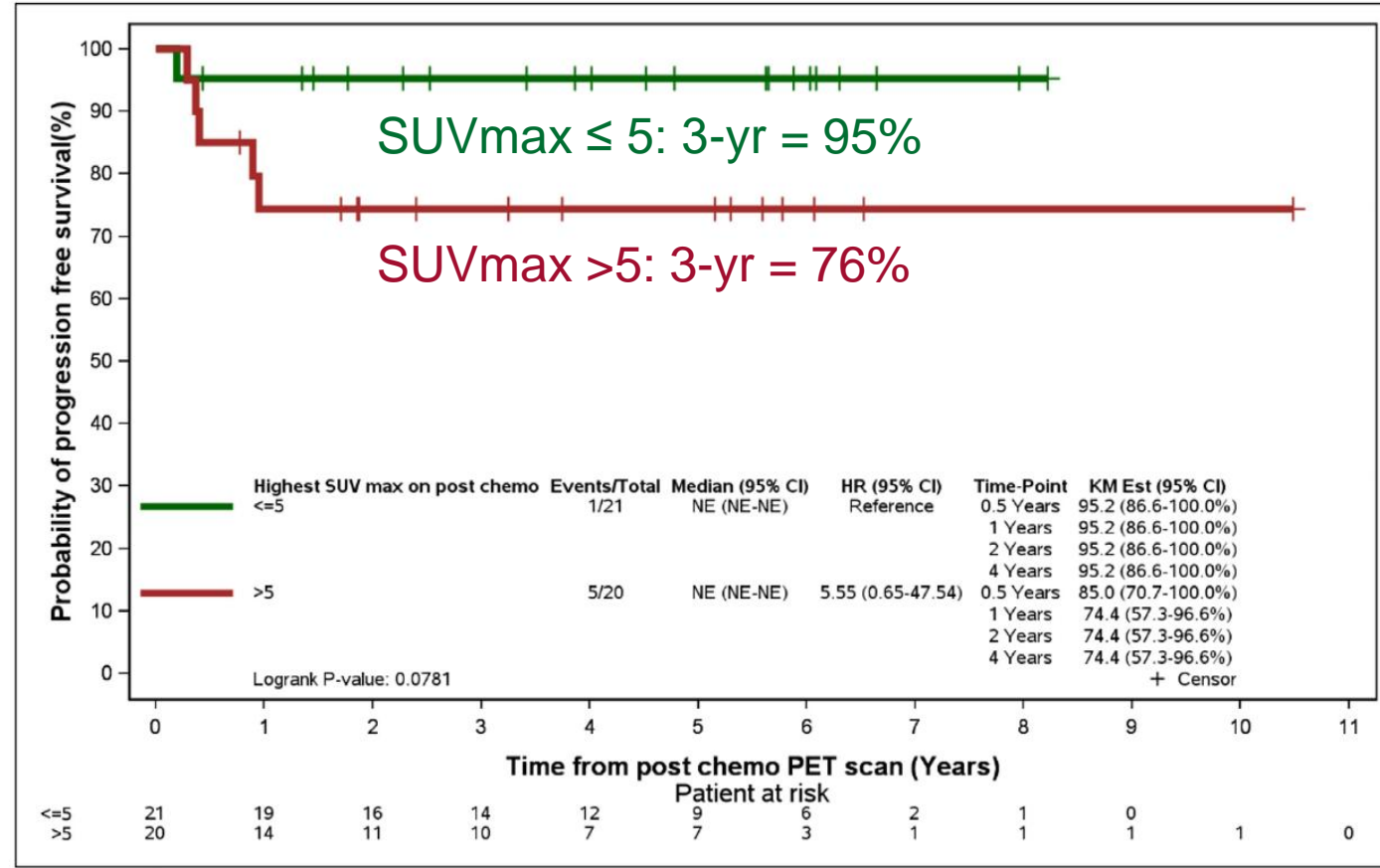


D Deauville Score in Treatment Failures

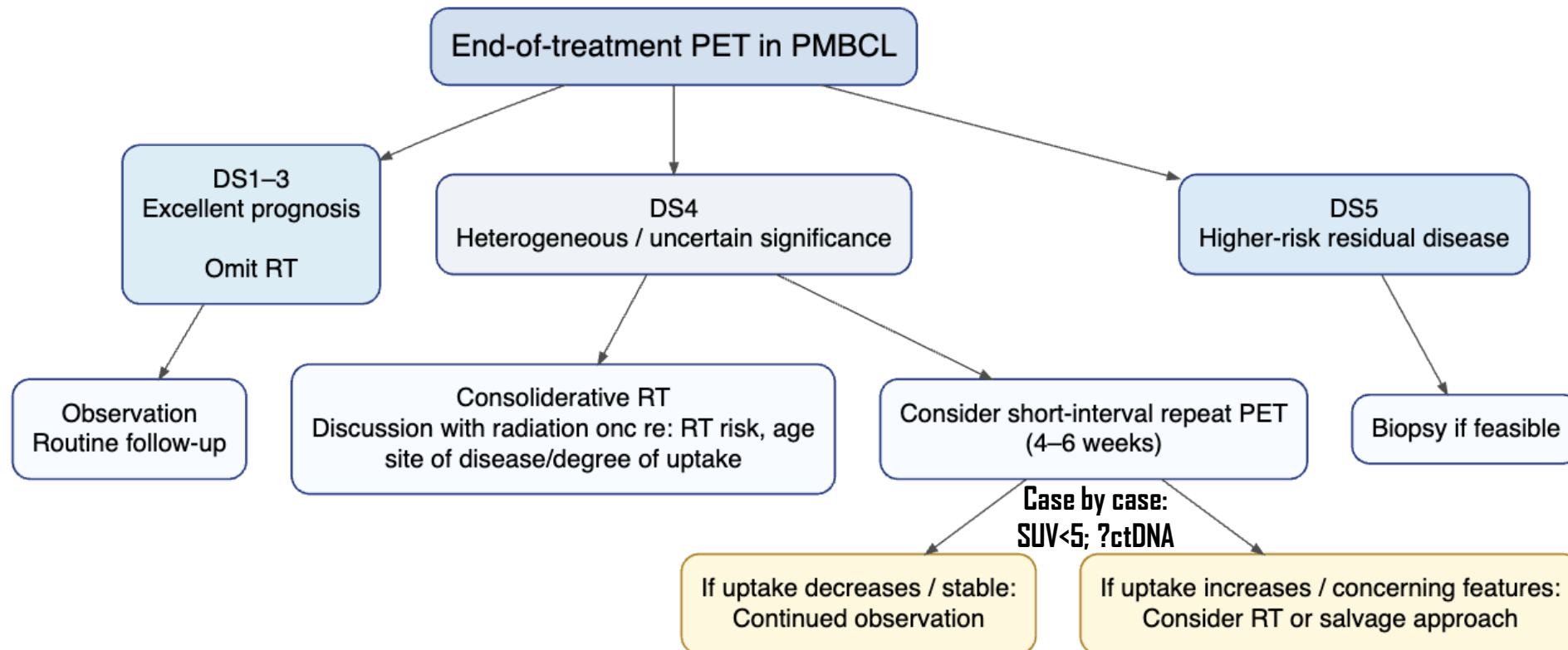


PFS in DS 4 PMR with EOT $SUV_{max} \leq 5$ vs >5

- 1L regimen: RCHOP21 88%, DA-EPOCH-R 9.5%
- PMR n=42/151 (28%)
- 86% involved site RT
- 4-year PFS: 83% overall; 89% RT



Clinical management



Case Vignette: part III

- 6 months later, she presents with left arm paresthesia
- Urgent MRI shows C6 paraspinal mass and compression

- Biopsy: consistent with PMBCL

Relapsed/refractory PMBCL

- Median time to progression: 8 months (90% within 12 months)
- Extra-nodal sites are commonly involved at relapse (30%)

Response to salvage chemotherapy is substantially lower in PMBCL compared to DLBCL

Response and ASCT rates

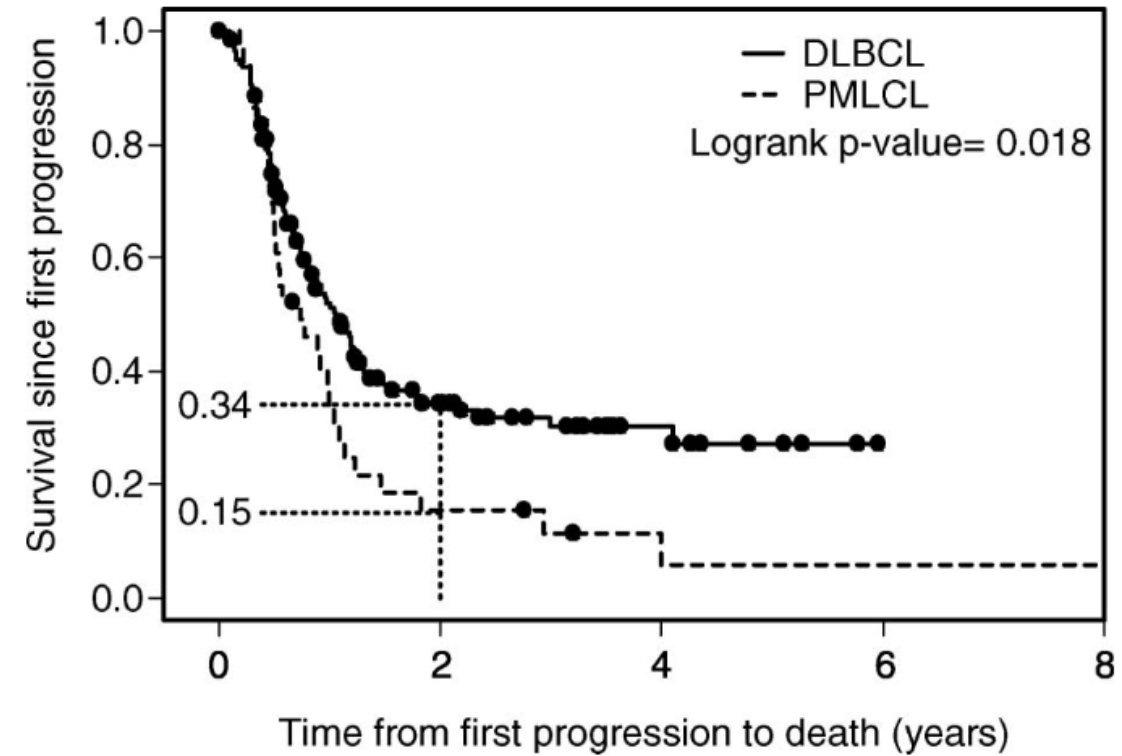
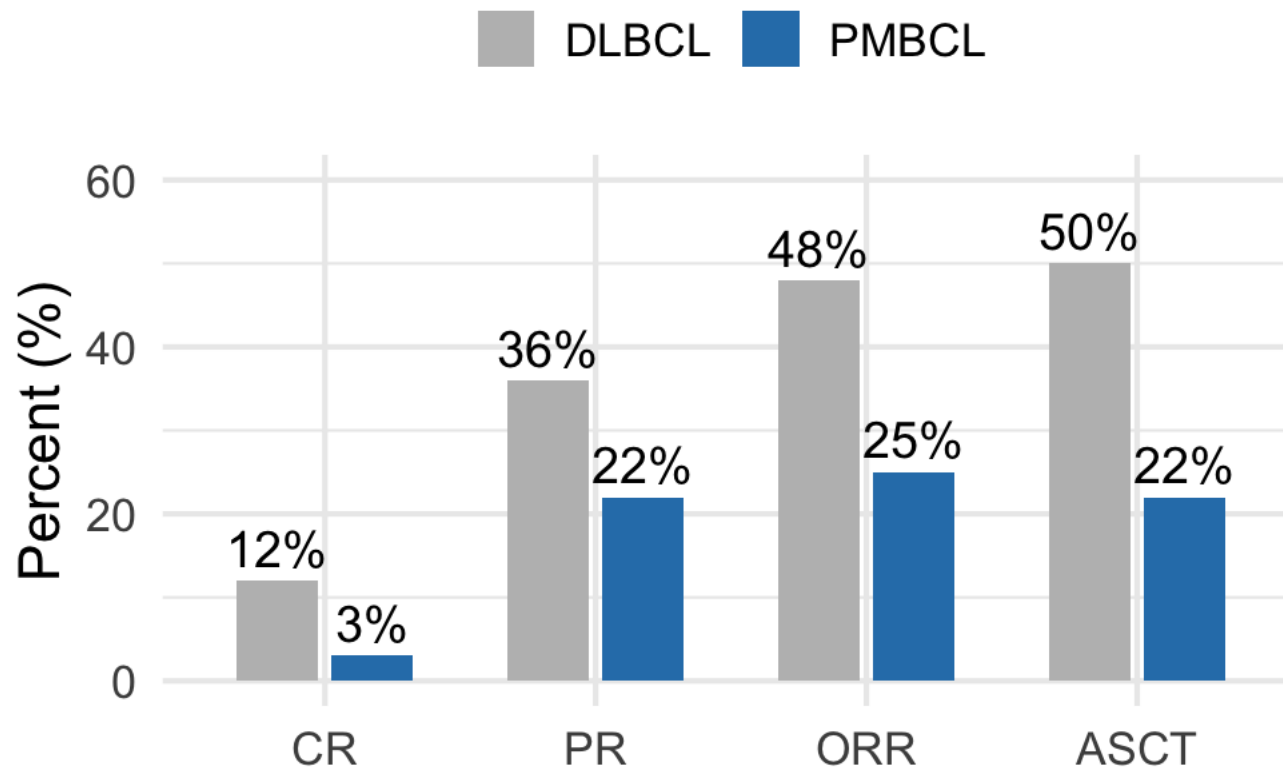
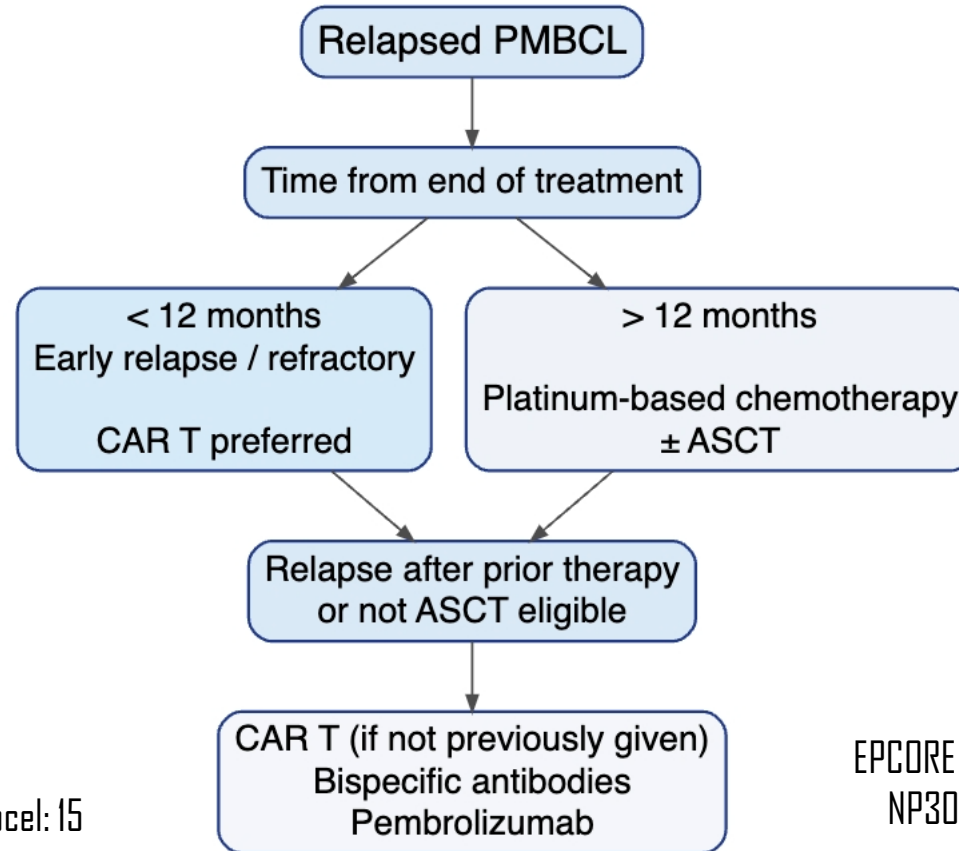


Figure 1. OS from first progression.

Treatment for R/R PMBCL

ZUMA-7 excluded but CCO funded
 TRANSFORM: 8 in lisocel, 10 in SOC (6 crossed to lisocel)

ZUMA-1: 8
 TRANSCEND lisocel: 15



EPCORE NHL-1: 4
 NP30179: 6

Pembrolizumab II KEYNOTE-170 (*approved not funded)
 ORR 41.5% (CR 20.8%)
 Median PFS 4.3; median OS 22.3

CAR T outcomes: PMBCL vs. LBCL

Study	Product(s)	Histology subset	n	ORR	CR rate	Landmark PFS	Landmark OS
Crombie et al., Blood Advances 2023	Axi-cel	PMBCL	33	78%	69%	2-yr 64%	2-yr OS 78%
Schubert et al., Blood Advances 2023 (GLA/DRST registry)	Axi-cel	PMBCL	13	71%	42%	2-yr 54%	2-yr OS 75%
CART-SIE, Leukemia 2024 (Italy)	Axi-cel, tisa-cel	PMBCL	70	78%	50%	12-mo 62%	12-mo 86%
		LBCL	190	75%	53%	12-mo 48%	12-mo 71%
Bourlon et al., Haematologica 2024	Axi-cel, tisa-cel	PMBCL	27	-	-	12-mo 53%	12-mo 80%
		LBCL	529	-	-	12-mo 42%	12-mo 50%
Gauthier CIBMTR	Axi-cel or tisa-cel	PMBCL	135	79%	68%	2-year 59%	2-year 81%

Conclusion

- Current frontline approach
 - No clear survival benefit with intensified regimens over R-CHOP-21
 - Intensified regimens may be preferred when RT avoidance is a priority
 - Evolving frontline strategies: pembrolizumab + R-CHOP
 - Omission of RT for DS 1-3
- Refining response assessment (DS4)
 - PET alone insufficient to distinguish residual lymphoma vs inflammation
 - Integration of ctDNA: ?guide RT decisions ?early intervention
- Relapsed disease
 - Limited response to salvage chemotherapy
 - 2L CAR T preferred for early relapse

THANK YOU!
