PetCT guided therapy in lymphoma (and myeloma)

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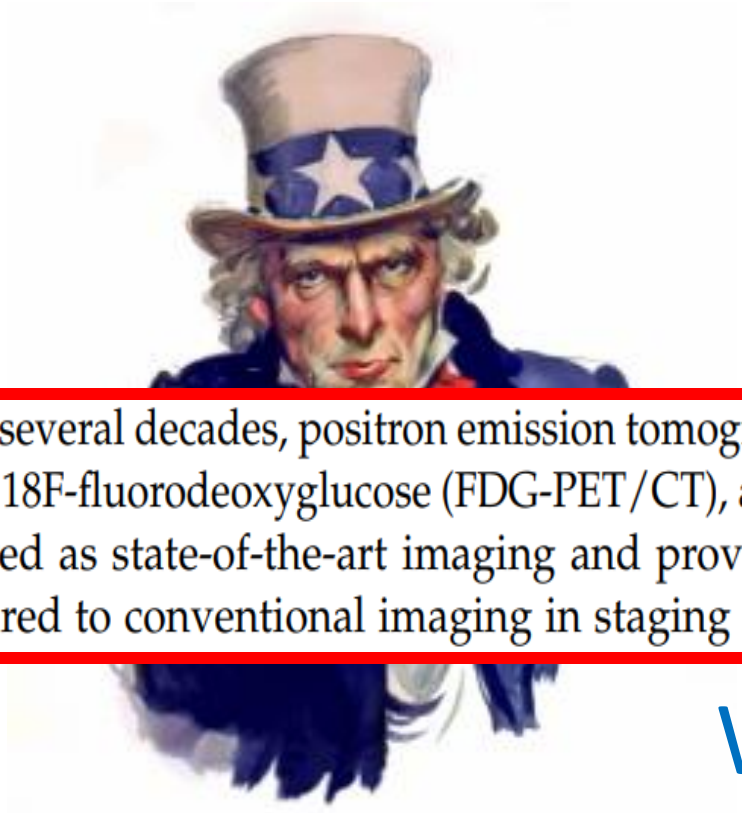
PetCT, really???

YES!



Over the past several decades, positron emission tomography coupled with computed tomography using 18F-fluorodeoxyglucose (FDG-PET/CT), a tracer of glucose metabolism, has been considered as state-of-the-art imaging and provided the most significant improvement compared to conventional imaging in staging lymphoma

We need you!

PetCT: what for?

Table 2. FDG Avidity According to WHO Classification

Histology	No. of Patients	FDG Avid (%)
HL	489	97-100
DLBCL	446	97-100
FL	622	91-100
Mantle-cell lymphoma	83	100
Burkitt's lymphoma	24	100
Marginal zone lymphoma, nodal	14	100
Lymphoblastic lymphoma	6	100
Anaplastic large T-cell lymphoma	37	94-100*
NK/T-cell lymphoma	80	83-100
Angioimmunoblastic T-cell lymphoma	31	78-100
Peripheral T-cell lymphoma	93	86-98
MALT marginal zone lymphoma	227	54-81
Small lymphocytic lymphoma	49	47-83
Enteropathy-type T-cell lymphoma	20	67-100
Marginal zone lymphoma, splenic	13	53-67
Marginal zone lymphoma, unspecified	12	67
Mycosis fungoides	24	83-100
Sezary syndrome	8	100†
Primary cutaneous anaplastic large T-cell lymphoma	14	40-60
Lymphomatoid papulosis	2	50
Subcutaneous panniculitis-like T-cell lymphoma	7	71
Cutaneous B-cell lymphoma	2	0

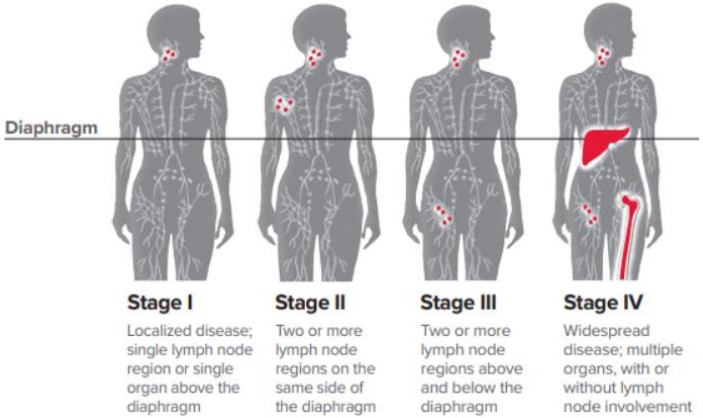
Barrington et al. JCO. 2014

PetCT: what for?

- Staging? ✓
- Diagnosis? ✓
- Prognosis? ✓
- Therapeutic strategies? ✓

PetCT: what for?

- **Staging**
  - Ann Arbor
  - Bone Marrow involvement
    - Hodgkin Lymphoma
      - N > 800: sens 95% NPV 99,9%
      - Reimbursement criteria! – Brentuximab Vedotin in stage IV
    - DLBCL → controversial
      - High NPV, Low sensibility
      - Still recommended



Voltin et al. An. Oncol. 2018
Azahrani et al. An Oncol. 2016
Kaddu-Mulindwa et al. Eur J. Nucl Med. 2021

PetCT: what for?

- **Diagnosis**
  - Richter
    - Chemotherapy era:
      - N=54 Cut off: **SUV 5** → Sens, Spe, PPV, and NPV of 91%, 80%, 53%, 97%
      - N=332 **SUV 5** → Sens 88%; NPV 92%
    - Bruton kinase inhibitors:
      - N=92

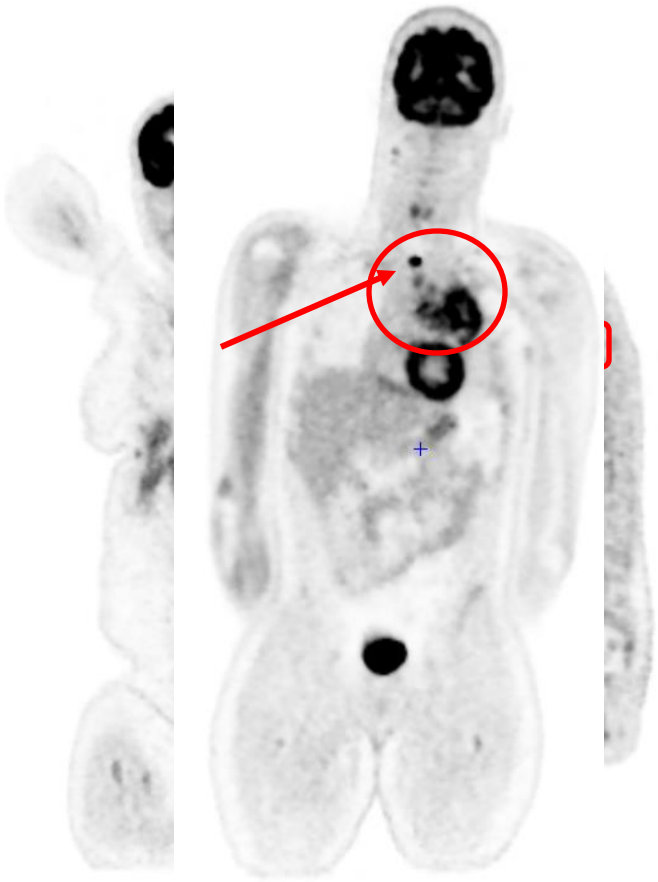
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SUVmax ≥5	96%	21%	51%	86%
SUVmax ≥6	92%	28%	52%	69%
SUVmax ≥7	84%	45%	57%	76%
SUVmax ≥8	76%	62%	63%	75%
SUVmax ≥9	72%	72%	69%	75%
SUVmax ≥10	56%	76%	67%	67%
SUVmax ≥11	52%	83%	72%	67%
SUVmax ≥12	44%	86%	73%	64%
SUVmax ≥13	40%	93%	83%	64%
SUVmax ≥14	28%	93%	78%	63%
SUVmax ≥15	28%	93%	78%	60%

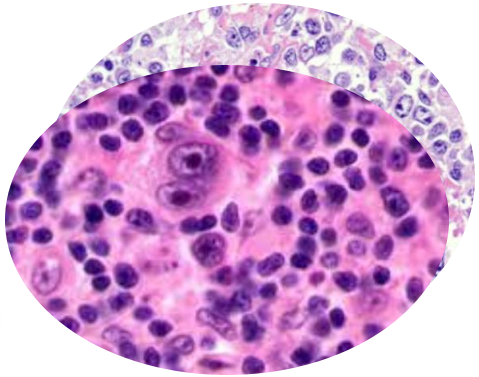
Pathology	N	Median SUV_{max} (range)	SUV_{max} <5	SUV_{max} ≥5 but <10	SUV_{max} ≥10
Richter transformation	25	11.3 (4.6-24.0)	1	10	14
Progressive CLL	18	6.4 (1.8-12.5)	5	10	3
Second malignancy*	9	8.9 (3.1-17.4)	1	5	3
Inflammation†	2	12.6 (7.4-17.7)	0	1	1
Total	54	8.6 (1.8-24.0)	7	26	21

Bruzzi et al. J. Nucl. Med. 2006
Falchi et al. Blood. 2014
Wang et al. Haematol. 2020

PetCT: what for?

- **Diagnosis**
  - Richter
  - Guiding biopsy

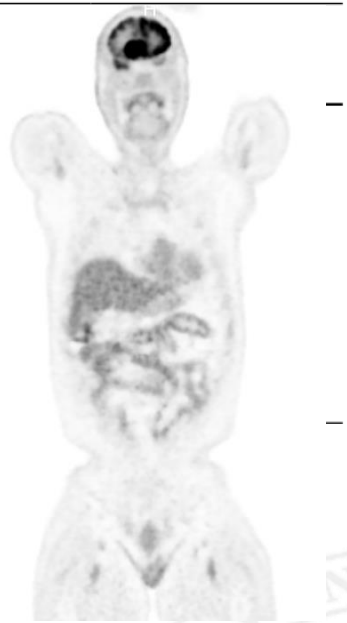




PetCT: what for?

- **Diagnosis**
  - Richter
  - Guiding biospy
  - PCNSL
    - N=300
      - DLBCL without systemic features on petCT
      - 0% of DLBCL in BM at the BM evaluation if petCT neg!
      - 8,3% with low grade lymphoma/MGUS

	All patients ($n = 300$)	PCNSL (n
Age median, years (IQR)	68.0 (60.5, 74.0)	68.0 (61.0
Male/female, n (%)	180 (60.0)/120 (40.0)	148 (58.7)
Localization, n (%)		
Supratentorial	248 (82.7)	211 (83.7)
Infratentorial	41 (13.7)	36 (14.3)
Vitreoretinal*	12 (4.0)	11 (4.4)
CSF**	33 (11.0)	21 (8.3)
Leptomeningeal involvement on MRI	10 (3.3)	6 (2.4)



Jelicic et al. Blood. 2022
Jelicic et al. An. Hematol. 2023

PetCT: what for?

- **Prognosis/Therapeutic strategies**
  - Intermediate PetCT
    - Identifying the quality of the response
      - Adapt: limiting toxicities (de-escalate) vs additional treatment (escalate)
    - Identifying early and late responders
  - End Of Treatment PetCT
  - Pitfalls – new immunotherapies

Response assessment
Deauville score/Lugano classification

Classification of Response	PET/CT Findings
CR	Deauville score of 1–3 with no new lesions, no bone marrow involvement
PR	Deauville score of 4 or 5 with reduced FDG uptake from baseline, residual bone marrow FDG uptake reduced from baseline, no new lesions
SD	Deauville score of 4 or 5 with no change in FDG uptake from baseline, no change in bone marrow involvement, no new lesions
PD	Deauville score of 4 or 5 with increased FDG uptake from baseline, new or recurrent lesions compatible with lymphoma, or appearance of bone marrow involvement based on increased FDG avidity

Meignan et al. Lymph. Leuk. 2009
Cheason et al. JCO. 2014

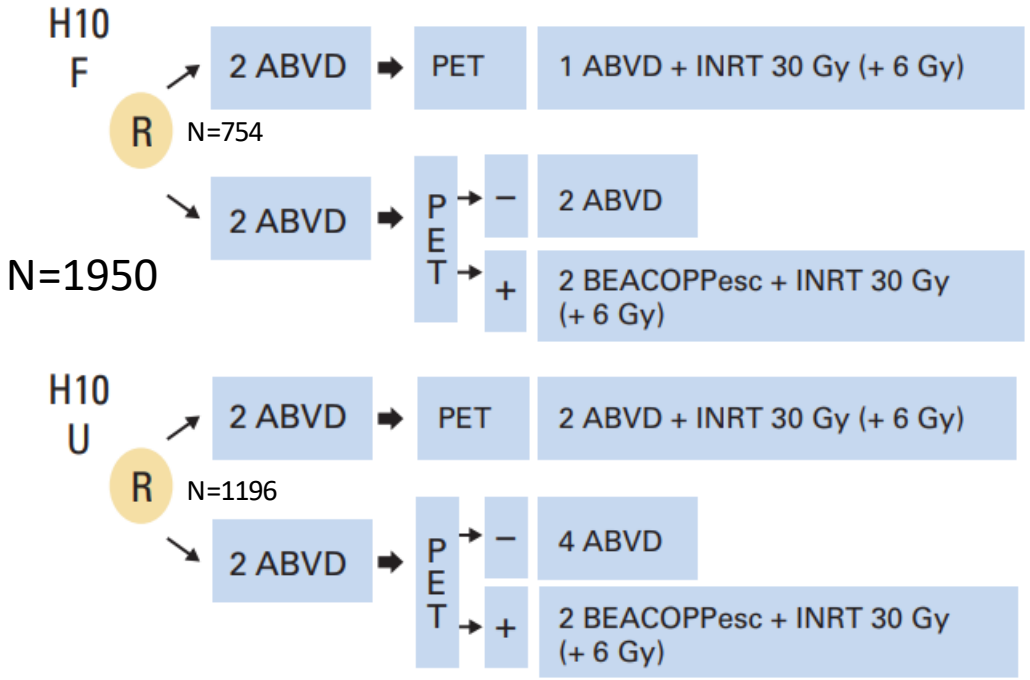
Hodgkin Lymphoma

Hodgkin Lymphoma

- Early petCT assessment has a strong pronostic value
  - High NPV 80-90%, lower PPV 50-55%
  - Lower PFS, OS whether iPET2 +

Rossi et al. J Nucl. Med. 2014

Hodgkin Lymphoma: Early stage



In the Pet-
5yPFS: 99 vs 87,1%
5yOS: 100 vs 97,6%

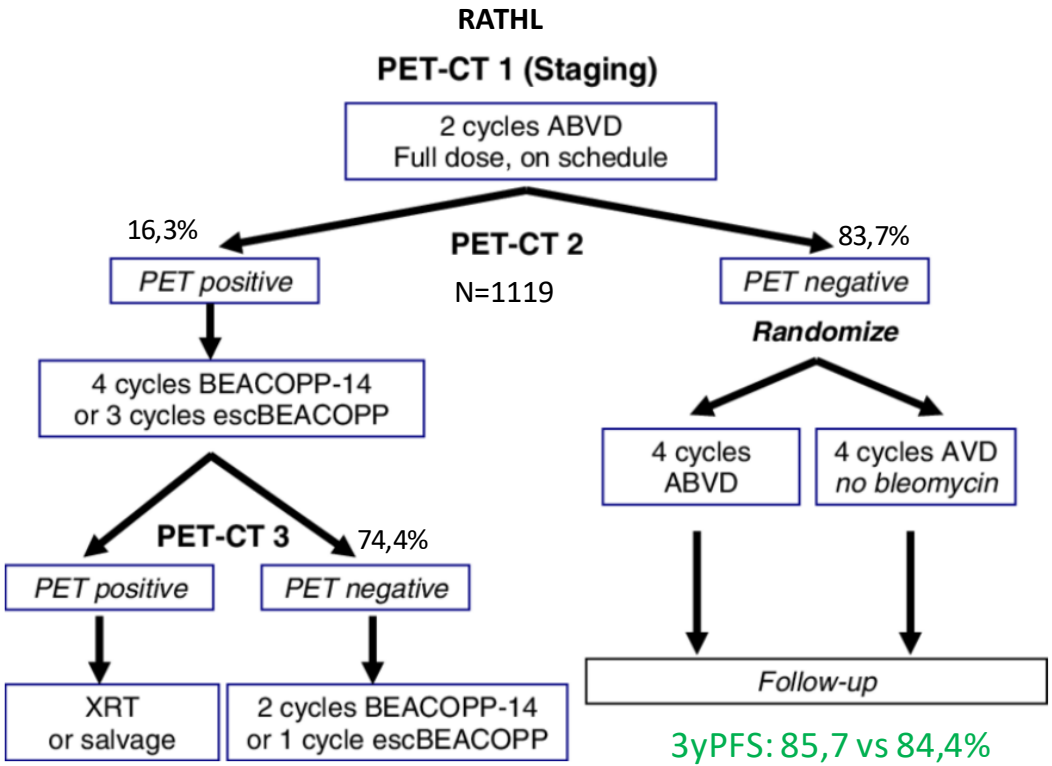
In the Pet+ (18,8%)
5yPFS: 77,4 vs 90,6%
5yOS: 89,3 vs 96%

In the Pet-
5yPFS: 92 vs 89,6%
5yOS: 96,7 vs 98,3%

iPET might overcome classic prognostic factors!

Raemakers et al. JCO. 2014
Andre et al. JCO. 2017

Hodgkin Lymphoma: Advanced stage

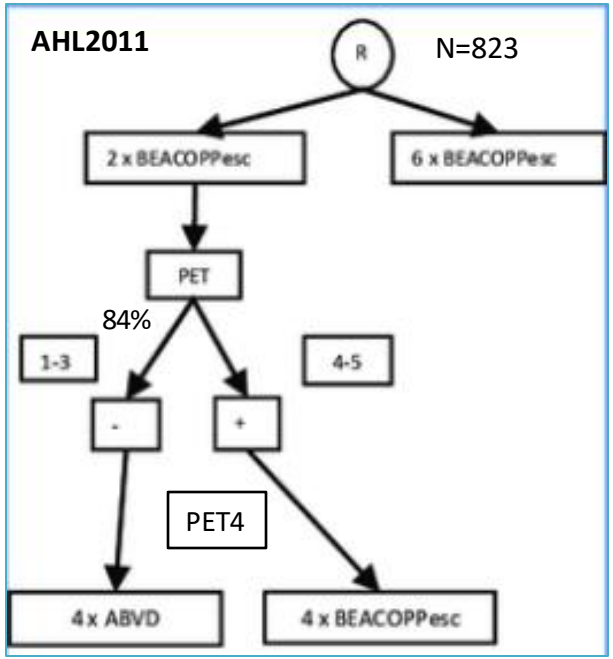


3yPFS: 65%
3yOS: 87,8%

3yPFS: 85,7 vs 84,4%
3yOS: 97,2 vs 97,6%

Johnson et al. NEJM. 2016

Hodgkin Lymphoma: Advanced stage



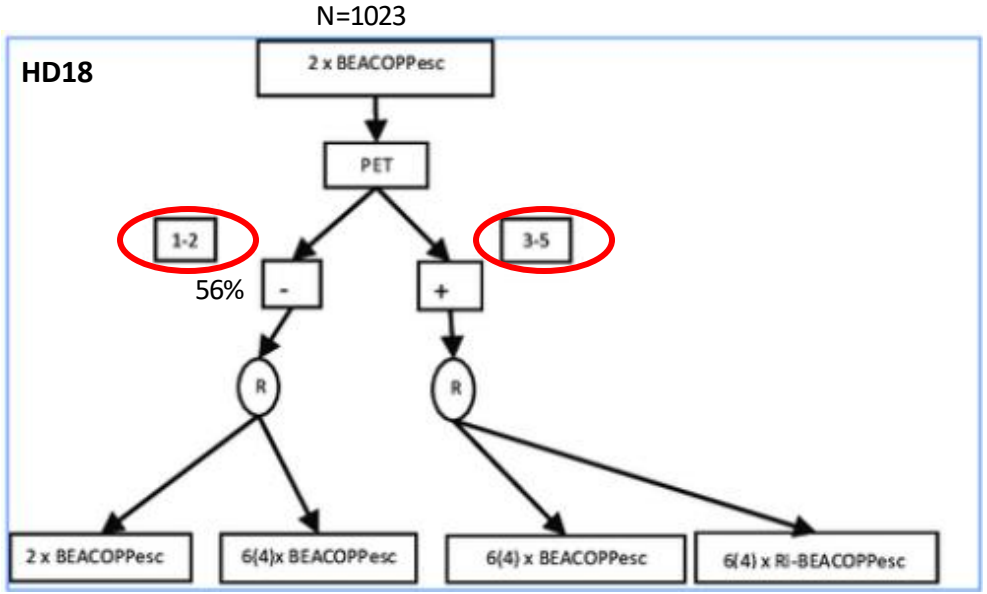
In Pet negative (SOC versus Petdriven)
5yPFS: 86,2 vs 85,7%
3yOS: 95,2 vs 96,4%

Whole Pet-driven strategy – 5yPFS
2-4- 90,9%
2+4- 75,4%
4+ 46,5%

→ Interesting stratification maybe more relevant than biological markers

Casanovas et al. Lancet. 2019

Hodgkin Lymphoma: Advanced stage



3yPFS 91,4%

3yPFS 91,4%
3yOS 96,5

3yPFS 93%
3yOS 94,4%

→ No predictive value of iPET???
< Wrong classification of DS3

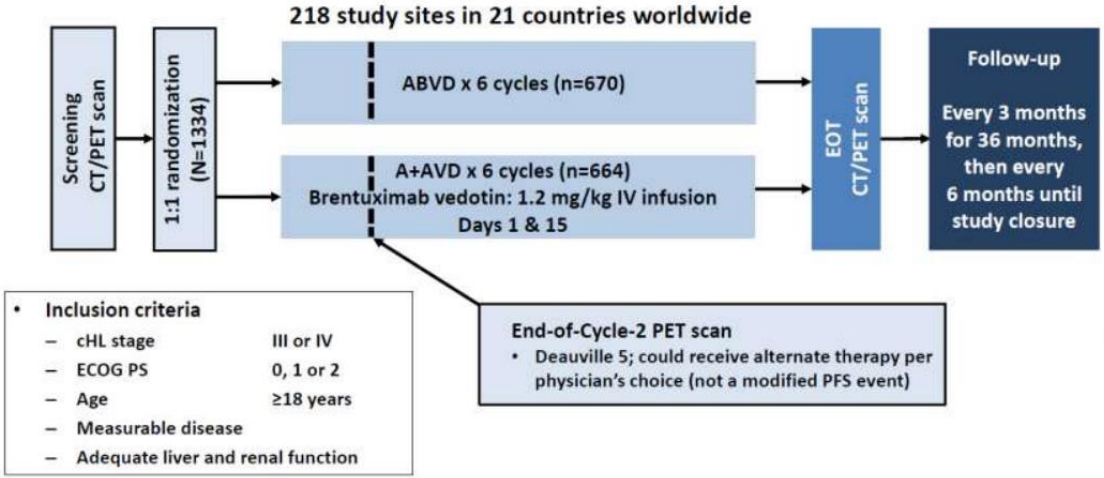
Will Rogers effect

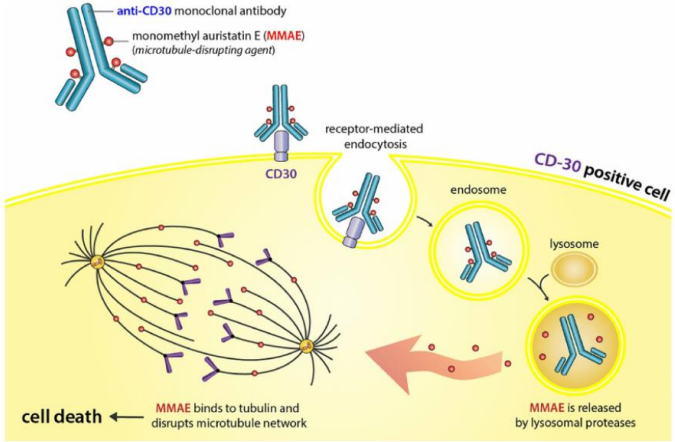
« *When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states* »

Borchmann et al. Lancet. 2017

Hodgkin Lymphoma: Advanced stage
New approaches

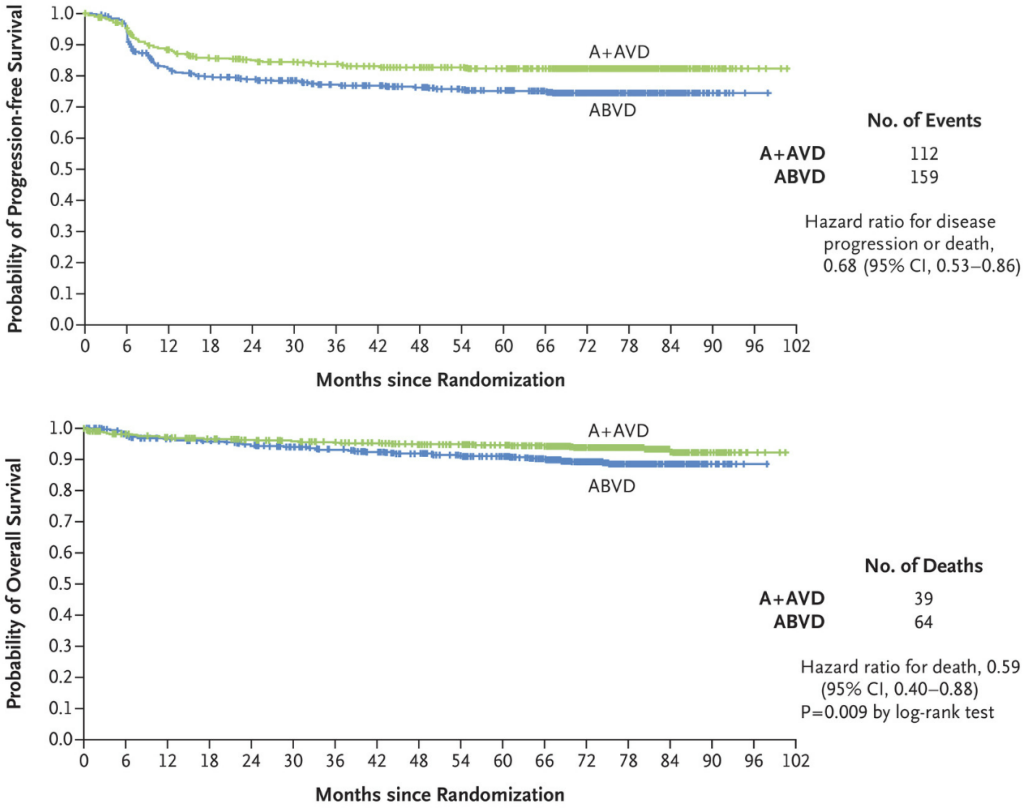
ECHELON-1





Ansell et al. NEJM. 2022

Hodgkin Lymphoma: Advanced stage
New approaches



6yPFS: 82,3 vs 72,5%
6yOS: 93,9 vs 89,4%

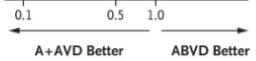
iPET wasn't decisive for strategy;
89 vs 86% were negative

6yPFS for iPET2neg: 85 vs 78%
6yPFS for iPET2pos: 61 vs 46%

Ansell et al. NEJM. 2022

Hodgkin Lymphoma: Advanced stage
New approaches

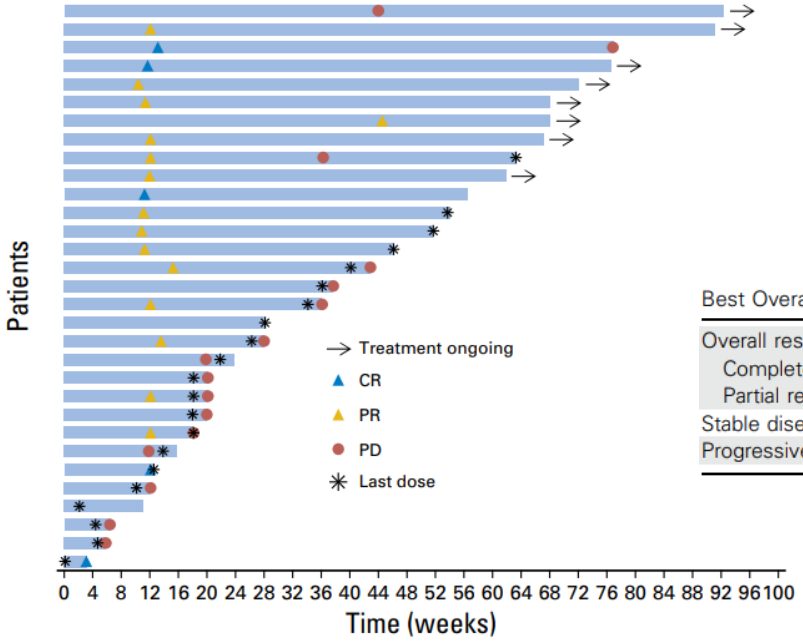
Subgroup	A+AVD	ABVD	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40–0.88)
Age			
<60 yr	19/580 (3.3)	35/568 (6.2)	0.51 (0.29–0.89)
≥60 yr	20/84 (24)	29/102 (28.4)	0.83 (0.47–1.47)
<45 yr	9/451 (2.0)	18/423 (4.3)	0.44 (0.20–0.99)
≥45 yr	30/213 (14.1)	46/247 (18.6)	0.75 (0.47–1.18)
Geographic region			
Americas	11/261 (4.2)	27/262 (10.3)	0.40 (0.20–0.80)
North America	9/250 (3.6)	26/247 (10.5)	0.33 (0.15–0.70)
Europe	26/333 (7.8)	32/336 (9.5)	0.78 (0.47–1.32)
Asia	2/70 (3)	5/72 (7)	0.37 (0.07–1.91)
No. of IPS risk factors			
0 or 1	7/142 (4.9)	7/141 (5.0)	0.97 (0.34–2.77)
2 or 3	17/355 (4.8)	26/357 (7.3)	0.62 (0.33–1.14)
4–7	15/167 (9.0)	31/172 (18.0)	0.48 (0.26–0.88)
Cancer stage at baseline			
III	17/237 (7.2)	20/246 (8.1)	0.86 (0.45–1.65)
IV	22/425 (5.2)	43/421 (10.2)	0.48 (0.29–0.80)
B symptoms at baseline			
Present	30/400 (7.5)	39/381 (10.2)	0.71 (0.44–1.14)
Absent	9/264 (3.4)	25/289 (8.7)	0.37 (0.17–0.80)
Extranodal site at baseline			
0	22/217 (10.1)	19/228 (8.3)	1.18 (0.64–2.19)
1	9/217 (4.1)	17/223 (7.6)	0.51 (0.23–1.14)
>1	8/194 (4.1)	25/193 (13.0)	0.30 (0.14–0.67)
ECOG performance-status score at baseline			
0	15/376 (4.0)	21/378 (5.6)	0.70 (0.36–1.37)
1	19/260 (7.3)	34/263 (12.9)	0.54 (0.31–0.94)
2	5/28 (18)	9/27 (33)	0.41 (0.14–1.23)
Sex			
Male	19/378 (5.0)	45/398 (11.3)	0.43 (0.25–0.73)
Female	20/286 (7.0)	19/272 (7.0)	0.96 (0.51–1.80)

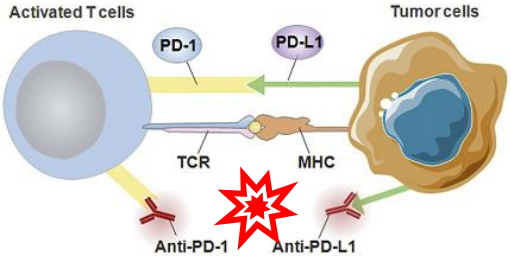


Ansell et al. NEJM. 2022

Hodgkin Lymphoma: Advanced stage
New approaches

Check-point inhibitors - Anti-PD1 approach





Best Overall Response	Total (N = 31) No.	% (90% CI†)
Overall response rate	20	65 (48 to 79)
Complete remission	5	16 (7 to 31)
Partial remission	15	48 (33 to 64)
Stable disease	7	23 (11 to 38)
Progressive disease	4	13 (5 to 27)

Armand et al. JCO. 2016

Hodgkin Lymphoma: New approaches

Anti-PD1 approach – how to assess?

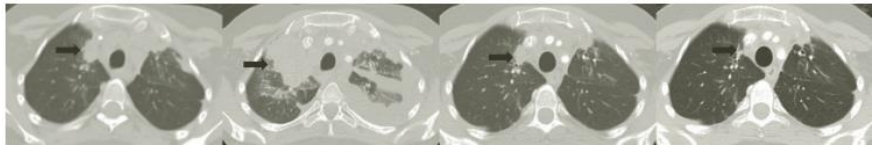
LYRIC – Lymphoma Response to Immunotherapy Criteria

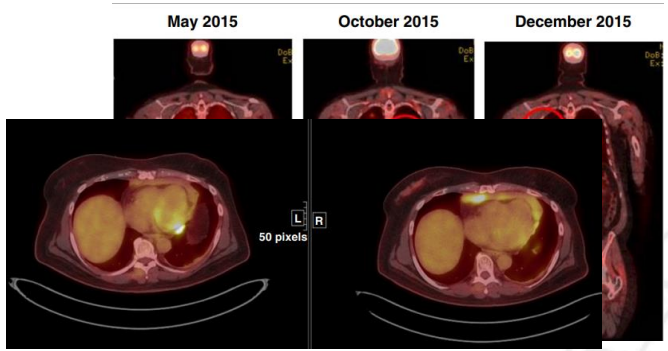
→ Introduction of **Intermediate Response** (IR)

1. Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration [IR(1)] (Figure 3). This pattern may be seen as a con-

2. 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, as measured by SPD of up to 6 lesions at any time during the treatment [IR(2)] (Figure 4). This

3. Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number [IR(3)] (Figure 5).

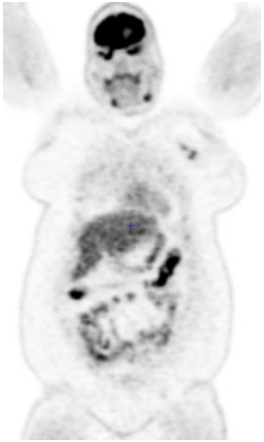




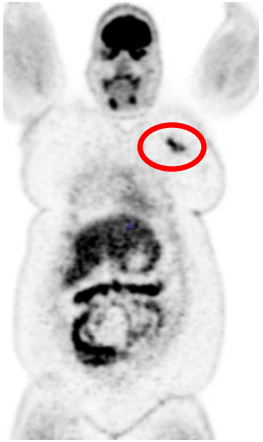
Cheson et al. Blood. 2016

Hodgkin Lymphoma: New approaches

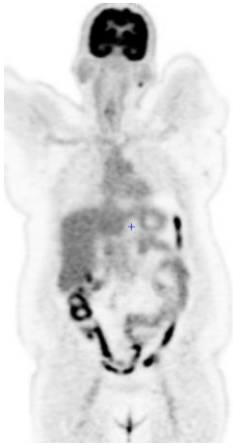
Anti-PD1 approach



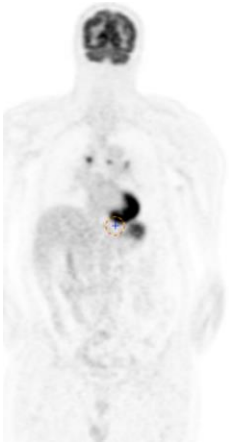
baseline



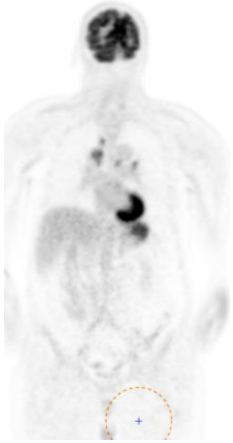
8w
Pembrolizumab



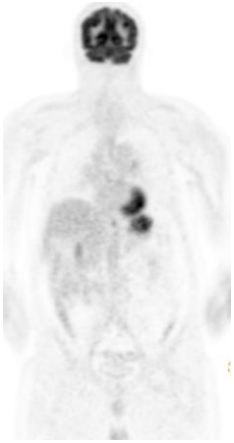
16w
Pembrolizumab



PD
8th line



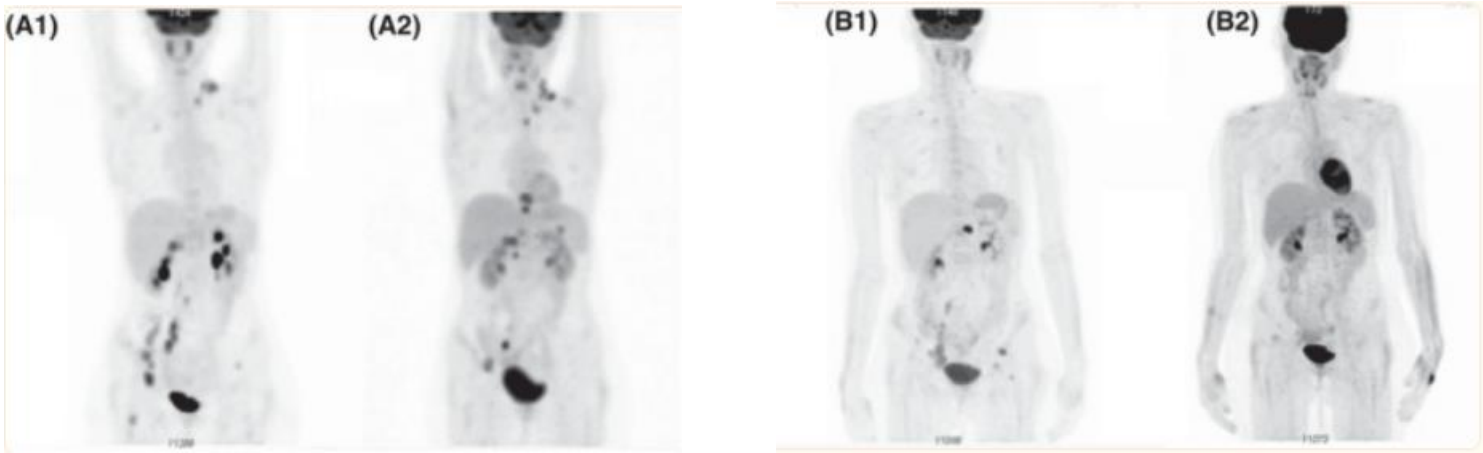
15w
Nivolumab



12w
Nivolumab + Gemci

Hodgkin Lymphoma: New approaches

Anti-PD1 approach – restoring chemo-sensitivity!



ORR 93% - CR 82%

How long? → Bridge to alloSCT?

Calabretta et al. Br. J. Haematol. 2022

Hodgkin Lymphoma: Advanced stage
New approaches

Anti-PD1 approach – First Line

APembroVD: 30 patients enrolled with only 1 PD after 2,1 years of follow-up!

BUT:

- PETneg in only **57%**
- EOT PETneg in only **87%**

→ False positive PetCT < Fitter T cells??

CLINICAL TRIALS AND OBSERVATIONS | MAY 25, 2023

The next frontier: enter PD-1 and exit PET scans?

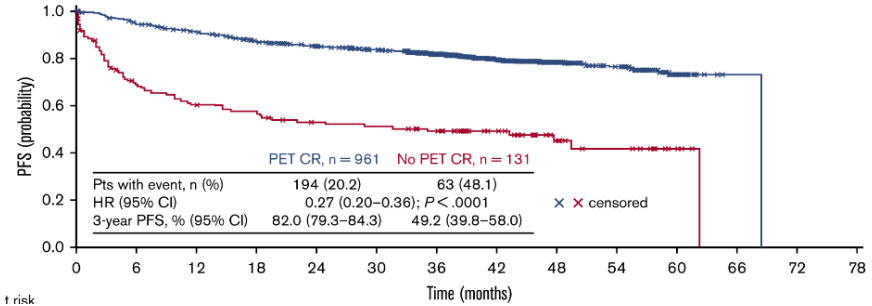
Clinical Trials & Observations

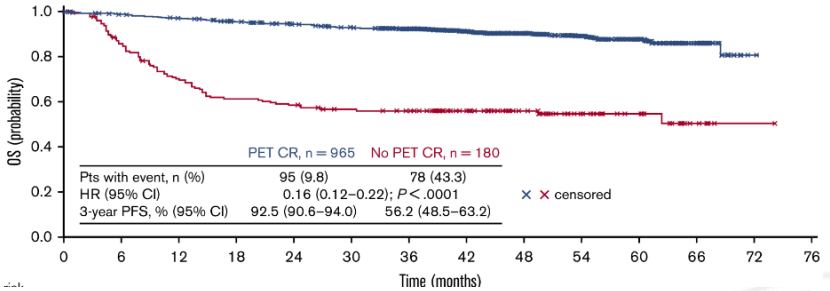
Lynch et al. Blood. 2023

Non-Hodgkin Lymphoma

Diffuse Large B Cell Lymphoma

N= 1346 ND DLBCL (GOYA)
O-CHOP/R-CHOP X 6-8
Evaluation of correlation between **EOT PetCT** and **outcomes**





NPV 83,5%

→ EOT PetCT could be a surrogate for PFS/OS

Kostakoglu et al. Blood Adv. 2021

Diffuse Large B Cell Lymphoma

Meta analysis from PETRA database to determine the **optimal timing** and pet **positivity criteria** for iPet to predict **outcomes - 1977 ND DLBCL**
iPet done after 1-4 cycles of R-CHOP/R-DA-EPOCH
Deauville score scale (cut off DS 1-3 vs 4-5 vs 5)
Cut off of ΔSUV after 1-3 cycles: 66% ; after 4: 70%

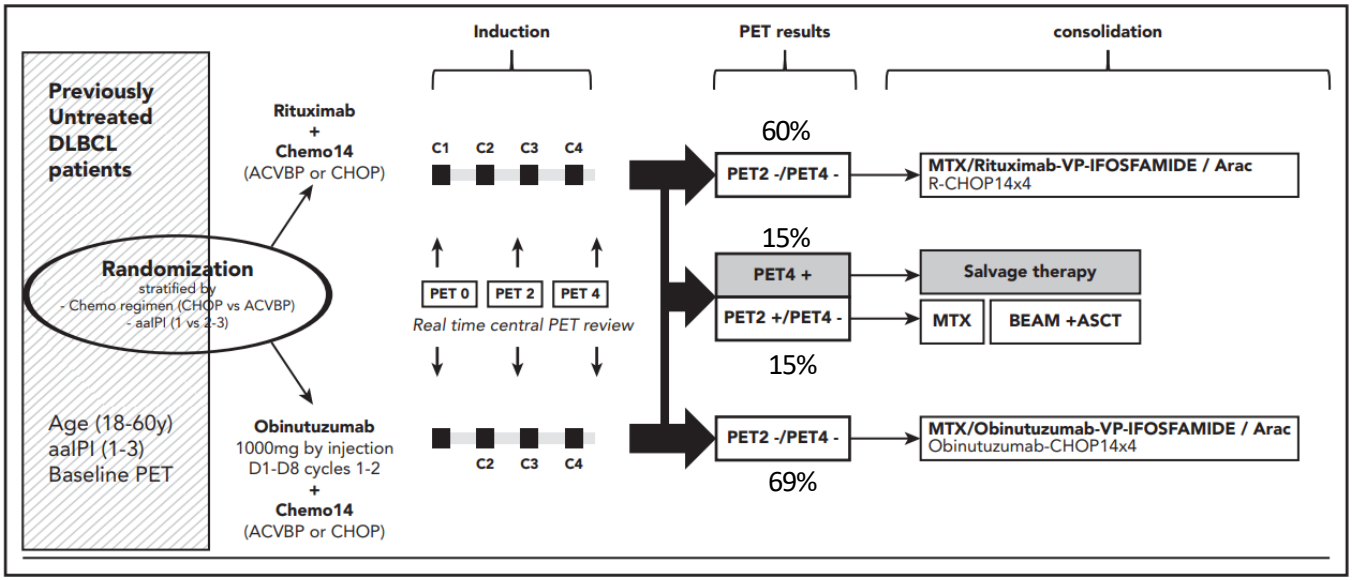
	DS4-5		DS5		ΔSUV	
	24 months PFS (no of patients)	HR vs I-PET 2	24 months PFS (no of patients)	HR vs I-PET 2	24 months PFS (no of patients)	HR vs I-PET 2
I-PET2 neg	83% (711)	1	81% (1134)	1	81% (1064)	1
I-PET1 neg	72% (23)	1.7	71% (50)	1.60	68% (29)	1.89
I-PET3 neg	80% (49)	1.16	82% (59)	0.96	79% (48)	1.15
I-PET4 neg	82% (379)	1.07	80% (462)	1.07	80% (281)	1.07
I-PET2 pos	73% (504)	1	46% (81)	1	61% (153)	1
I-PET1 pos	64% (40)	1.43	49% (13)	0.93	66% (19)	1.19
I-PET3 pos	62% (15)	1.52	20% (5)	2.05	64% (9)	0.91
I-PET4 pos	62% (107)	1.52*	30% (24)	1.53	44% (29)	1.68*

→ Room for treatment strategy petCT-guided?

Eertink et al. Blood. 2019

Diffuse Large B Cell Lymphoma

GAINED

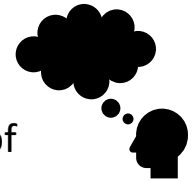


ΔSUVmax 66% @PET2
ΔSUVmax 70% @PET2

4yPFS:
- Pet2neg Pet4neg: 83%
- Pet2posPet4neg: 83,9%
- Pet2posPet4pos: 60,9%

Le Gouill et al. Blood. 2021
Casanovas et al. Blood. 2011

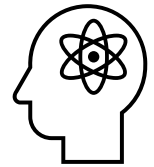
Diffuse Large B Cell Lymphoma



What about a first line Pet-guided strategy to catch quickly bad responders (high risk of progression/relapse) and select them for next line of treatment (CAR-T treatment)?

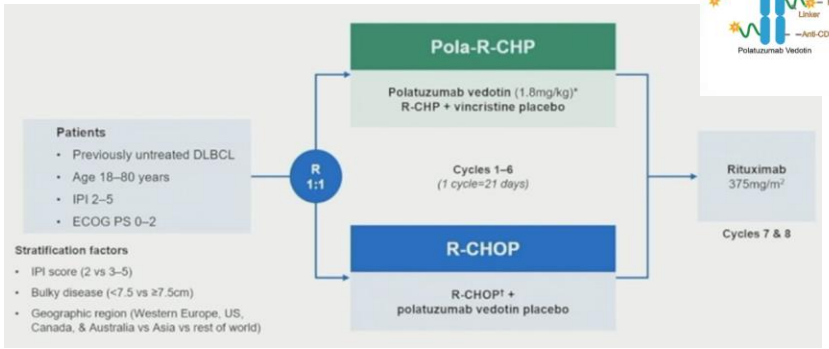
- late responders? PET2+PET4- (gained-like strategy) // 2y PFS 42%

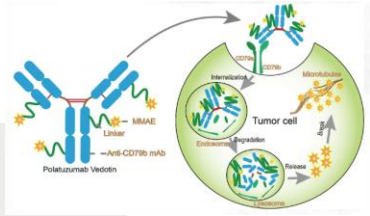
→ if PET4 only: waste of time? Unecessity of chemo?

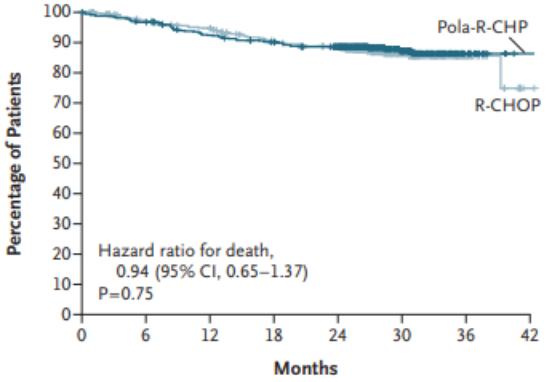


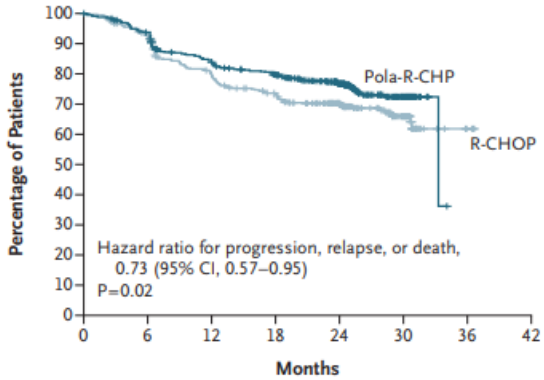
Diffuse Large B Cell Lymphoma

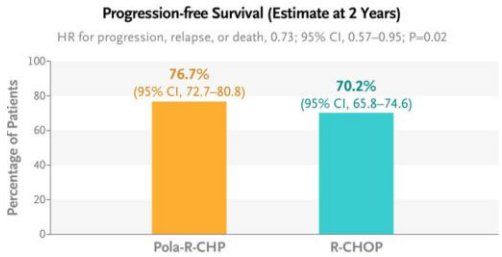
Will that be necessary?







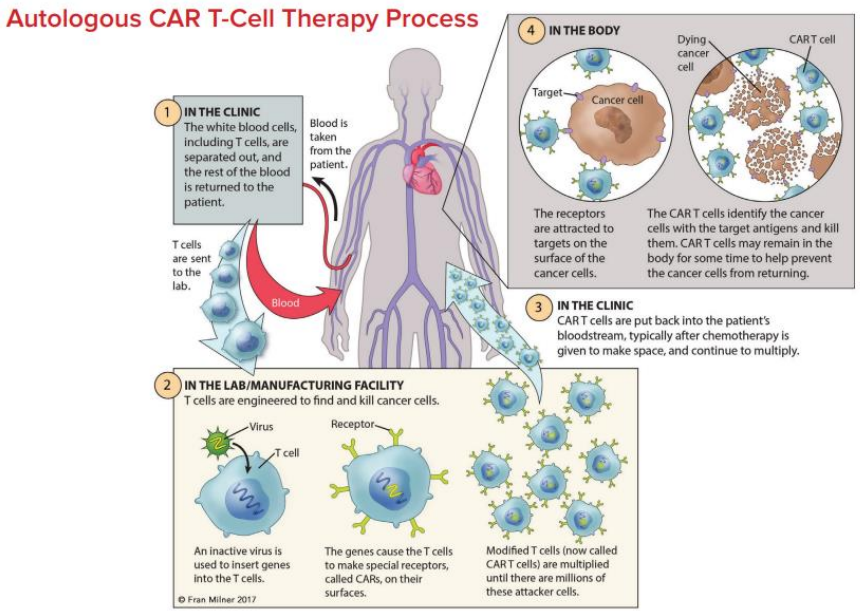


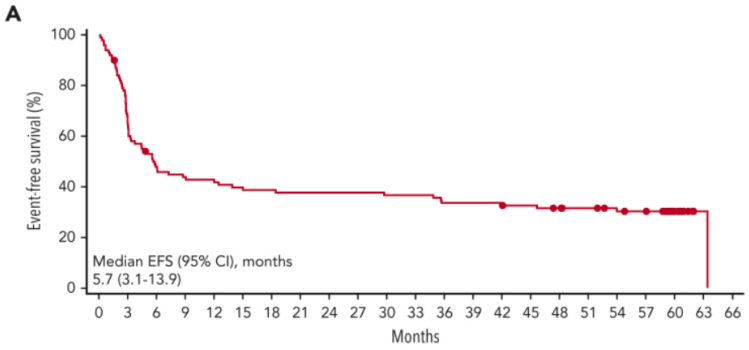


Tilly et al. NEJM 2022

Diffuse Large B Cell Lymphoma

Chimeric Antigen Receptor T-Cell therapy





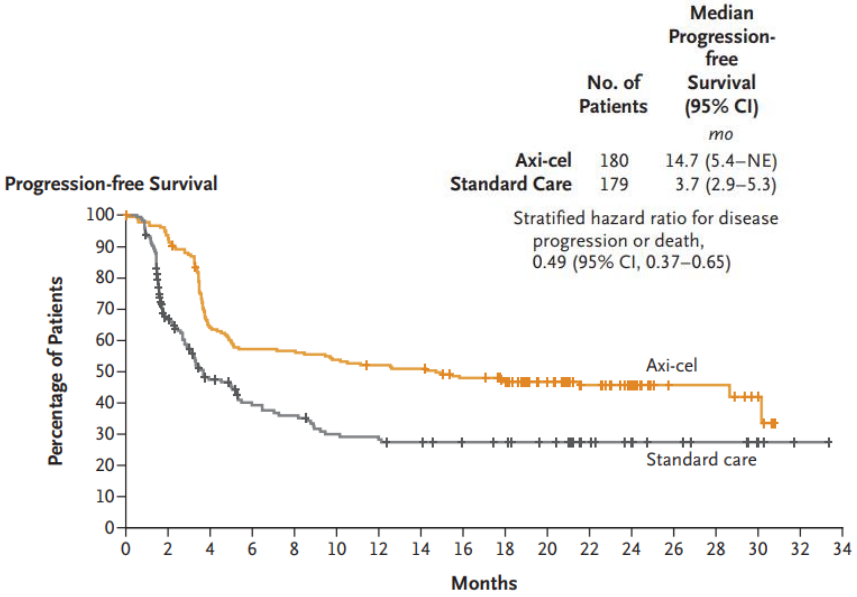
ORR 84%, 58% CR

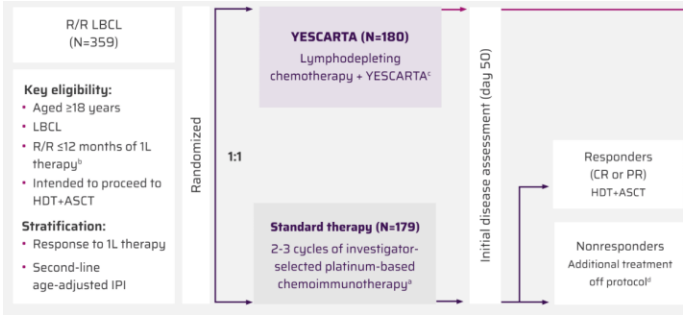
→ mDOR in CR 62,2 months!

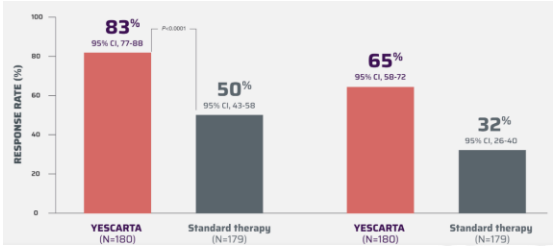
Neelapu et al. Blood. 2023

Diffuse Large B Cell Lymphoma

Chimeric Antigen Receptor T-Cell therapy **in second line**!







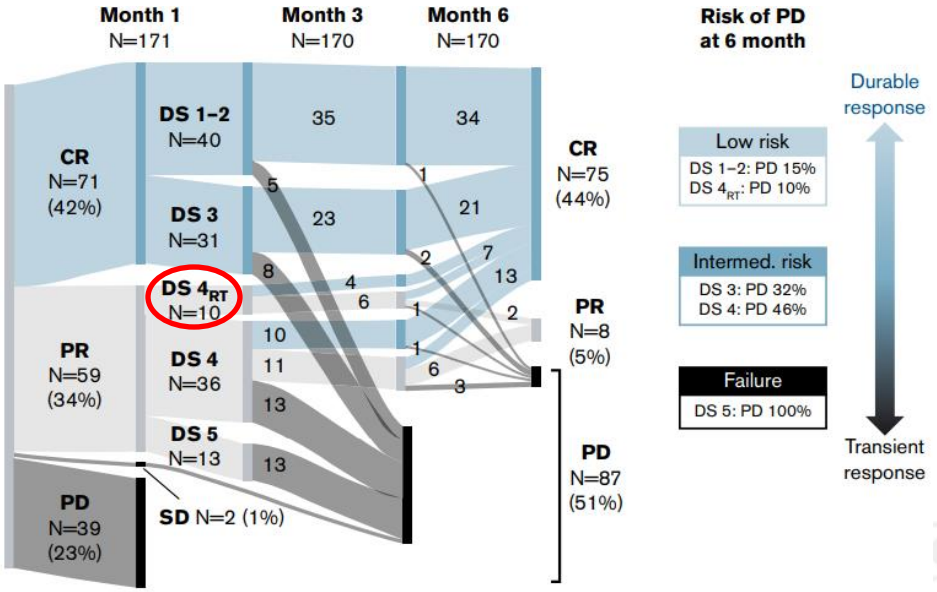
Locke et al. NEJM. 2021

Diffuse Large B Cell Lymphoma

Chimeric Antigen Receptor T-Cell therapy

Retrospective study
171 DLDBL with CAR-T
PetCT @ **1, 3 and 6 months** post-infusion

	HR (95% CI)	5 month* PD rate
DS 1–2/4$_{RT}$	1.00	14.0% (6.9–27.1)
DS 3	2.47 (0.99–6.13)	29.0% (16.3–48.4)
DS 4	3.53 (1.51–8.36)	38.9 (25.2–56.7)
DS 5	19.78 (7.77–49.7)	100%



PetCT@30d good surrogate of outcomes
DS1-2/4infl vs 3 vs 4 vs 5

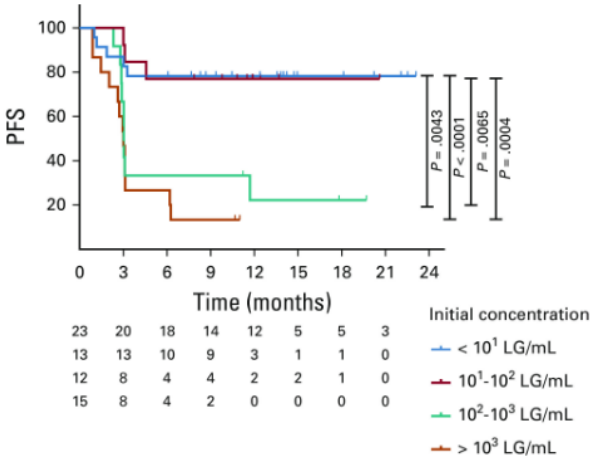
→ Combined strategy for DS3-4?
→ Other more precise surrogate: ctDNA?

Kuhln et al. Blood Adv.. 2021

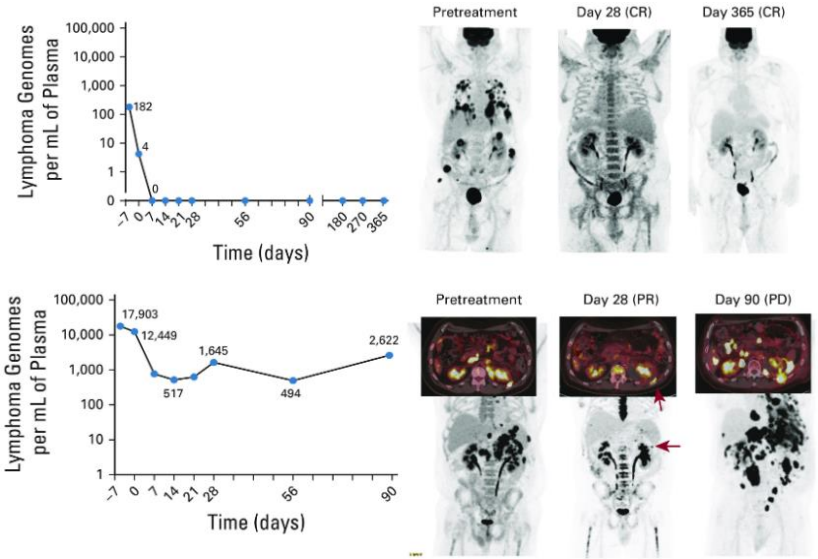
Diffuse Large B Cell Lymphoma

Chimeric Antigen Receptor T-Cell therapy

→ ctDNA might be an accurate tool for prognosis/treatment strategy - MRD



// CRS and ICANS



Franck et al. JCO. 2021

Follicular Lymphoma

Bispecific antibodies (Epcoritamab/Mosunetusumab/Glofitamab/Odronextamab…)

R/R FL ; N=128 ; med prior line: 3
ORR: 82% - CR 63%
medDOR not reached!
Est PFS@12m: 85% ; @18m: 74%

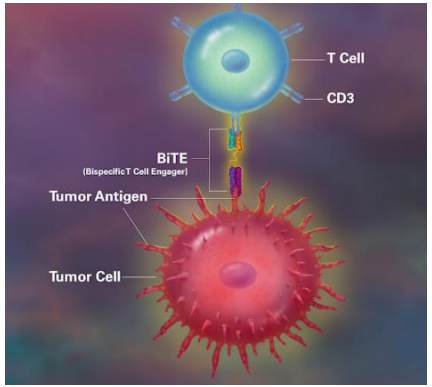
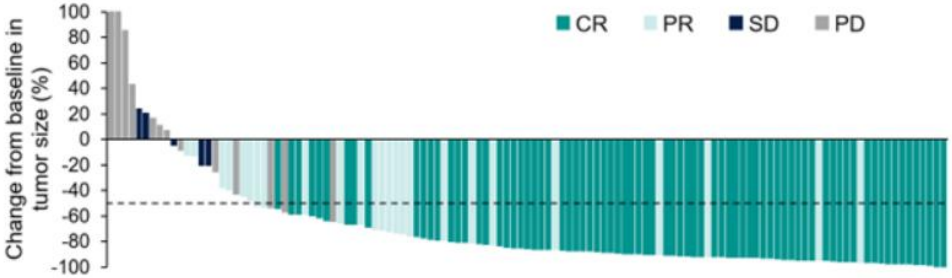


Figure. Antitumor activity

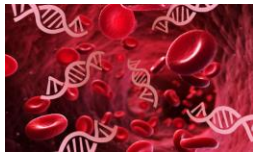


Two patients had a change from baseline in tumor size of >100%. Seven patients were not evaluable for change from baseline in tumor size.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Linton et al. ASH meeting. 2023

Conclusions

- PetCT remain … homa
  - Staging/Dia…
- PetCT-guided … ndard of care in Hodgkin lympl…
  - What abou… ?
    - Would ctD…
- PetCT is and re… n-Hodgkin lymphoma
  - Time for pe… ??
  - Even more … with some friends!



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Thank you for your attention!