GRUPPO DI STUDIO LINFOMI: AGGIORNAMENTI ICML 2019 LINFOMA DI HODGKIN

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Novara-Italy

Linfoma di Hodgkin ICML 2019

Sessione educazionale

- Terapia di prima linea (Johnson)
- Terapia di salvataggio (LaCasce)
- Pazienti anziani (Engert)

Comunicazioni orali

- PET imaging
- Pediatric lymphomas
- New antibodies
- Early clinical data
- Hodgkin’s lymphoma
- CAR T-cells
- New drug combinations

Centro Oncologico ed Ematologico Reggio Emilia

AUSL - IRCCS TRANSLATIONAL RESEARCH LABORATORY REGGIO EMILIA - ITALY

15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 18-22, 2019

A gene expression-based model to predict metabolic response after two courses of ABVD in patients with classical Hodgkin Lymphoma

B. Donati, M. Casali, A. Fama, B. Puccini, M. Zanelli, R. Santi, A. Ruffini, V. Berti, L. Rigacci, F. Merli, A. Ciarrocchi, S. Luminari

Azienda USL – IRCCS, Reggio Emilia

AOU Careggi, Florence

Hypothesis

Biological markers predict
iPET response at diagnosis

Allowing early therapy adaptation for high risk patients

Aims

- to evaluate the biological basis of interim PET metabolic response
- to identify a gene expression signature that may anticipate chemorefractoriness

Study design

121 HL patients diagnosed at the Heamatology Unit

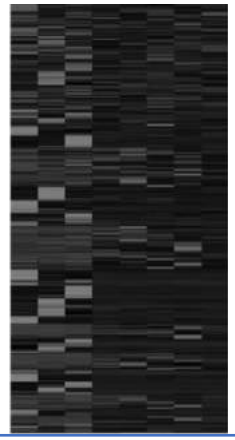
- Retrospective
- Consecutive
- All stages (I-IV)
- ABVD treated
- iPET scan available for central revision

119 FFPE tumor tissues retrieved by the Pathology Unit

111 RNA samples suitable for analysis with **PanCancer Immune Profiling Panel** by NanoString

Quality controls:

- ✓ Imaging
- ✓ Technical controls
- ✓ CodeSet content



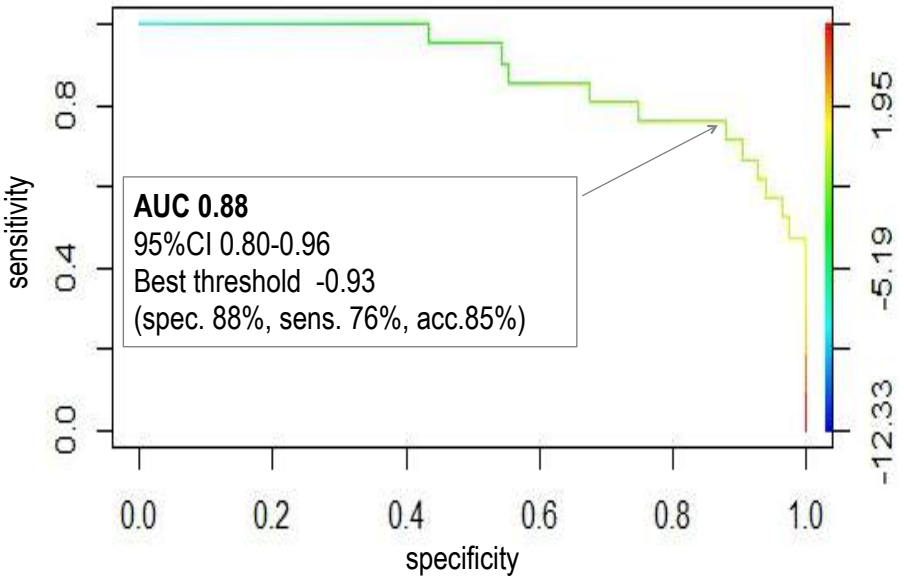
106 gene expression profiles available

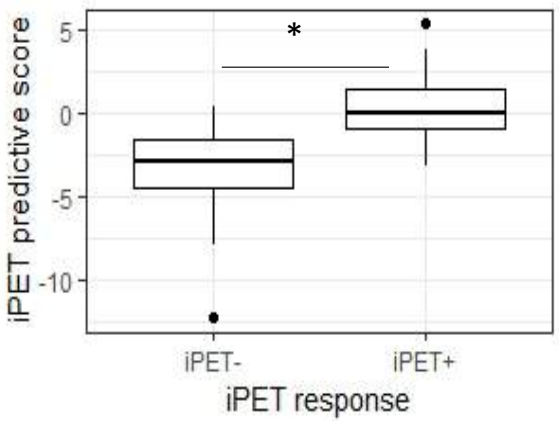
LMR

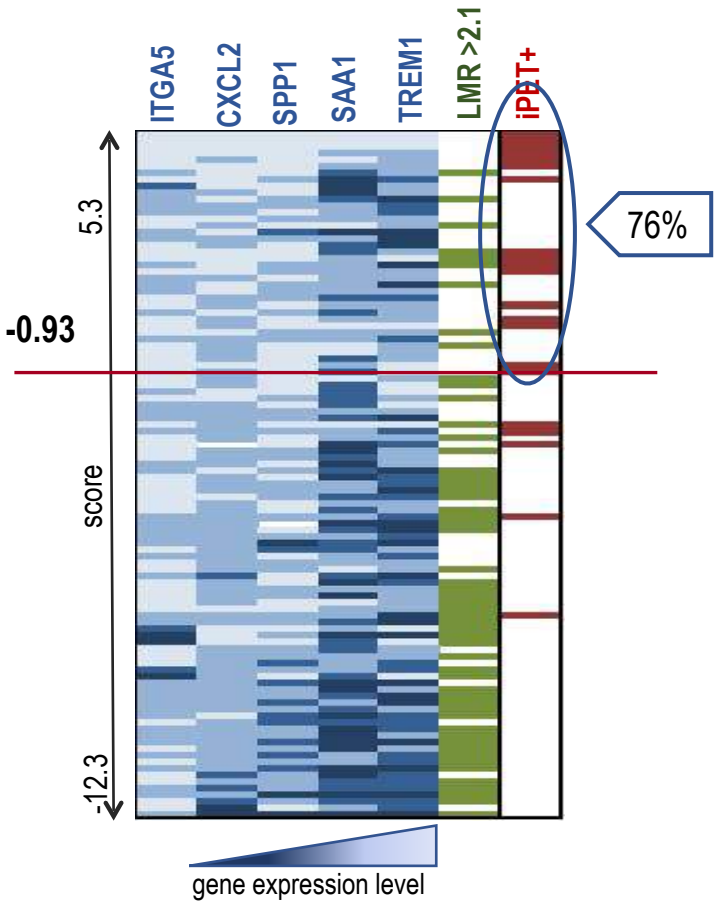
21 (19.8%) iPET positive
Deauville score IV-V*

*Cheson BD et al, JCO 2014

Gene based predictive model anticipates iPET response at diagnosis







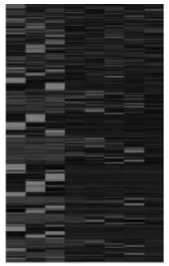
Score model validation in an independent cohort of HL patients

113 consecutive and homogeneous patients diagnosed at the Heamatology Unit

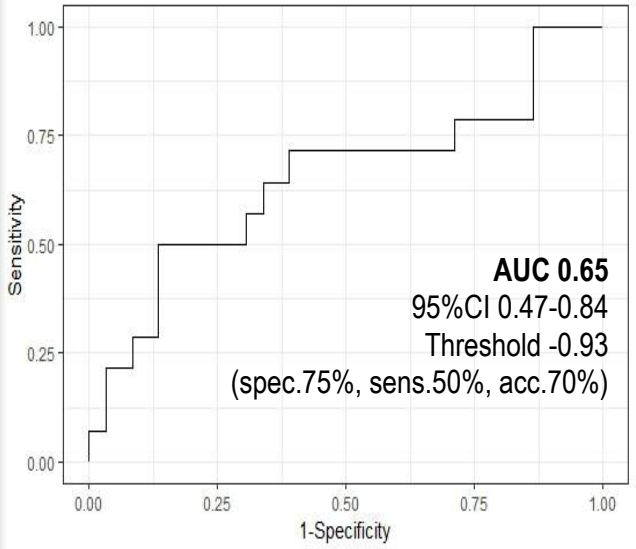
113 FFPE tumor tissues retrieved by Pathology Units of Reggio Emilia and Florence

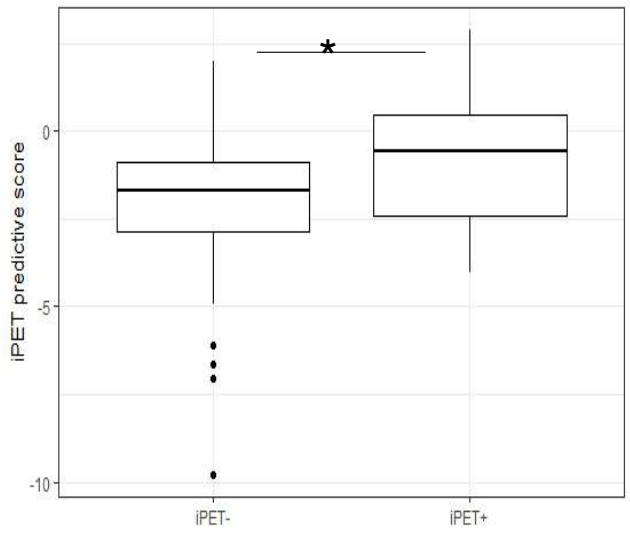
83 RNA samples suitable for NanoString analysis

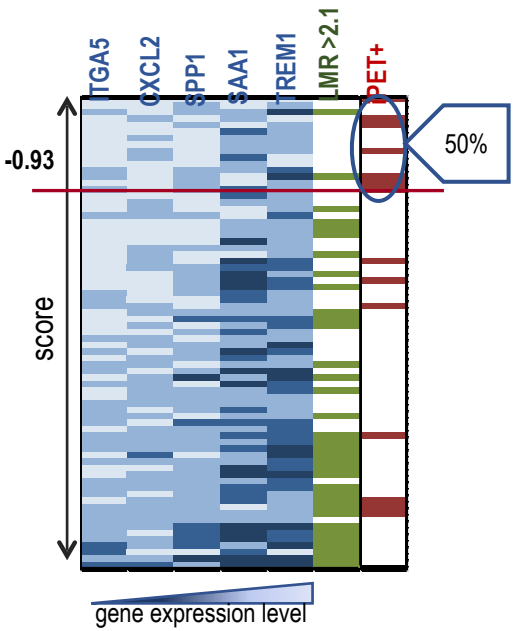
Quality controls:
- ✓ Imaging
- ✓ Technical controls
- ✓ CodeSet content



74 gene expression profiles available (19% iPET positive)

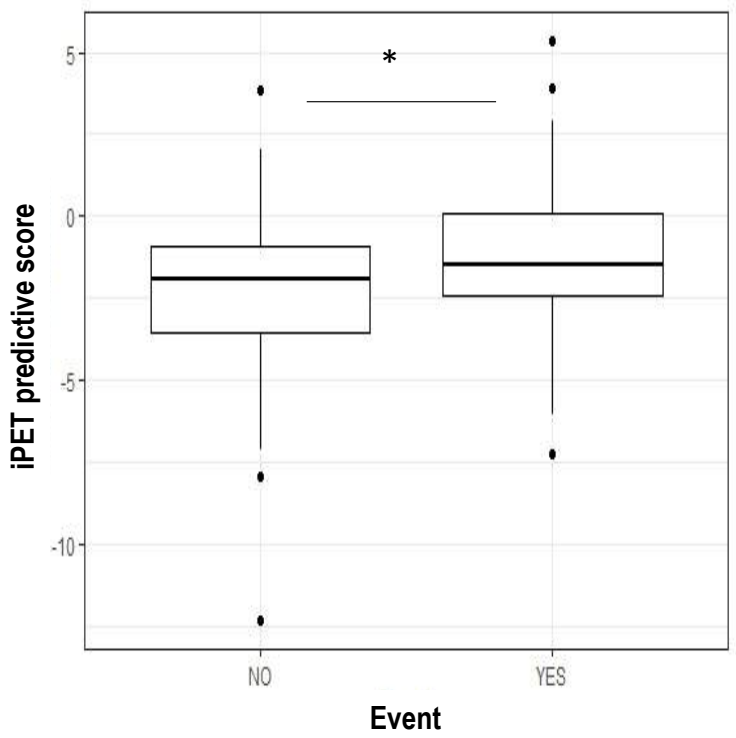


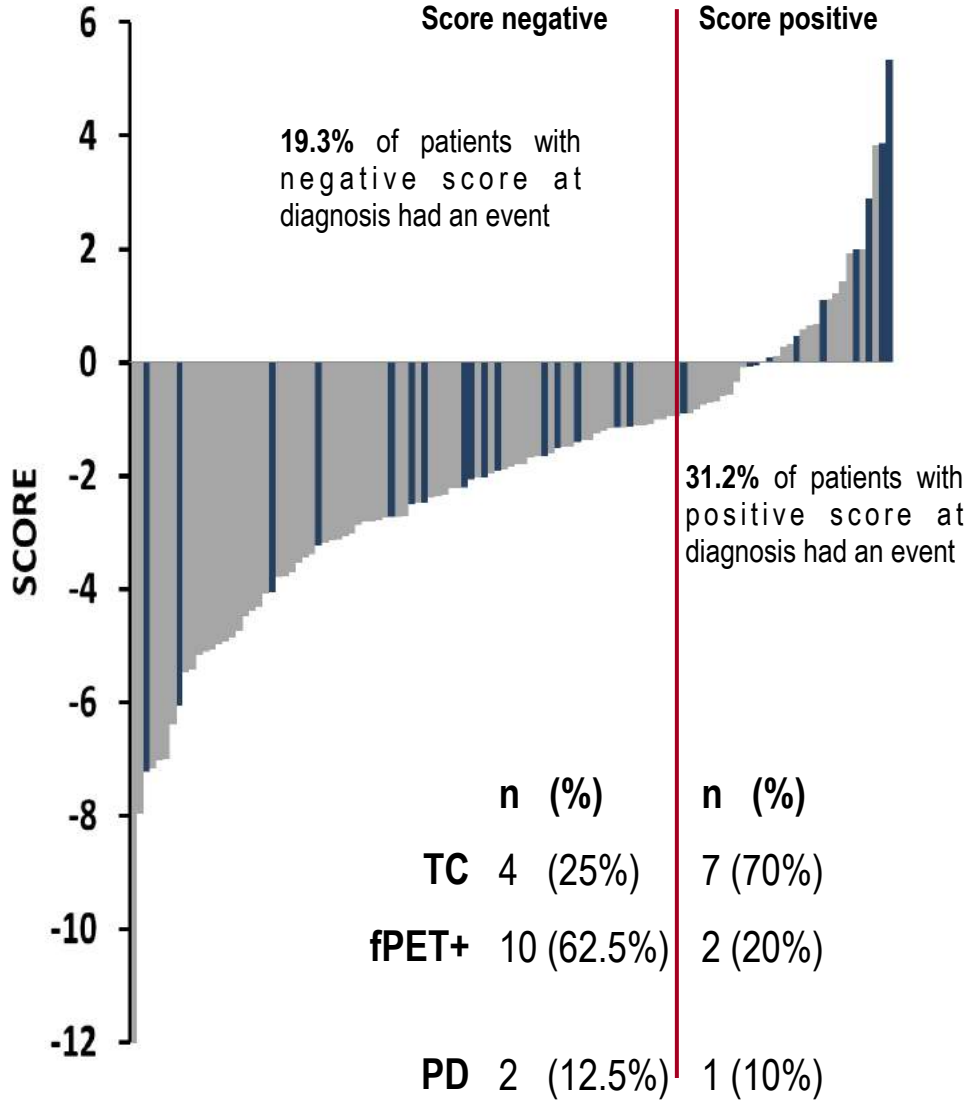




iPET predictive score and treatment failure

Treatment change (TC) or Final PET positive (fPET+) or Disease progression (PD)





Conclusion

Early metabolic response reflects biological differences in HL

We identified a gene expression signature that with a high specificity correlates with iPET positivity in HL

This signature may anticipate treatment resistance, contributing to the optimal treatment choice

Further investigations are needed considering a larger cohort of patients, other type of treatments and other phase of disease

Linfoma di Hodgkin ICML 2019

026
RESPONSE-ADAPTED TREATMENT WITH NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN YOUNG PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: CHECKMATE 744 SUBGROUP ANALYSES

K.M. Kelly[1] | S. Daw[2] | C. Mauz-Körholz[3] | M. Mascarin[4] | G. Michel[5] | S. Cooper[6] | A. Beishuizen[7] | K.J. Leger[8] | A. Garaventa[9] |

Table. CMR rates and ORR in primary refractory patients and in pediatric patients (aged <18 y) per BICR

n (%)	Overall (n=44)	Primary refractory (n=24)	Pediatric (aged <18 y) (n=31)
After nivolumab + BV induction			
CMR	26 (59)	15 (63)	18 (58)
ORR	36 (82)	19 (79)	25 (81)
Any time prior to consolidation			
CMR	38 (86)	20 (83)	27 (87)

Methods: Pts aged 5–30 y, after 1 prior tx without auto-HCT were eligible. Risk stratification was based on disease stage at diagnosis, time to relapse, B symptoms or extranodal disease at relapse, extensive disease with radiation tx (RT) contraindicated at relapse, or relapse in a prior RT field. In the standard-risk (R2) cohort, pts received 4 IND cycles with nivolumab + BV. Tumors were assessed every 2 cycles by investigators and blinded independent central review (BICR) per Lugano 2014 criteria. Pts who achieved CMR any time after cycle 4 proceeded to HDCT/auto-HCT consolidation. Pts with suboptimal response after IND received 2–4 cycles of BV + benda intensification (INT). Primary endpoint was CMR rate per BICR any time before consolidation. Efficacy and safety in primary refractory pts, and in pts aged < 18 y were post hoc analyses.

Linfoma di Hodgkin ICML 2019

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ANALYSIS OF CLINICAL DETERMINANTS DRIVING SAFETY AND EFFICACY OF CAMIDANLUMAB TESIRINE (ADCT-301, CAMI) IN RELAPSED/REFRACTORY (R/R) CLASSICAL HODGKIN LYMPHOMA (CHL)

G. Collins[1] | S. Horwitz[2] | M. Hamadani[3] | F. Samaniego[4] | A. Spira[5] | P. Caimi[6] | A. Davies[7] | T. Menne[8] | P. Fields[9] | H. Cruz[10] | S. He[11] | J. Boni[11] | J. Feingold[11] | J. Wuerthner[10] | J. Radford[12]

Results: Overall response rate (ORR) was 73.1% in the study population and 86.5% at 45 μg/kg (n=37; 43.2% complete response). **Table 1** presents subgroup analyses of response at 45 μg/kg. Of note, 3 pts improved from partial to complete response after permanent treatment discontinuation.

In PK modeling, a significant association of C_{max} to objective response was observed for the typical pt ($p=3.273 \times 10^{-8}$; **Figure 1**); mean predicted probability of Cami response was 0.84 for pts who responded to their most recent therapy vs 0.70 for refractory pts.

Autoimmune and neurologic TEAE profiles were comparable between pts with differing prior CHPi exposure. The 5 reported cases of GBS/radiculopathy did not appear related to prior CHPi (≤4 mo: 1 pt [4%]; >4 mo: 1 pt [7%]; none: 2 pts [10%]; 1 pt [20%] who received CHPi but timing information was missing).

Updated results will be presented, including response data for the ongoing 30 μg/kg cohort.

Camidanlumab Tesirine Mechanism of Action

ADC THERAPEUTICS

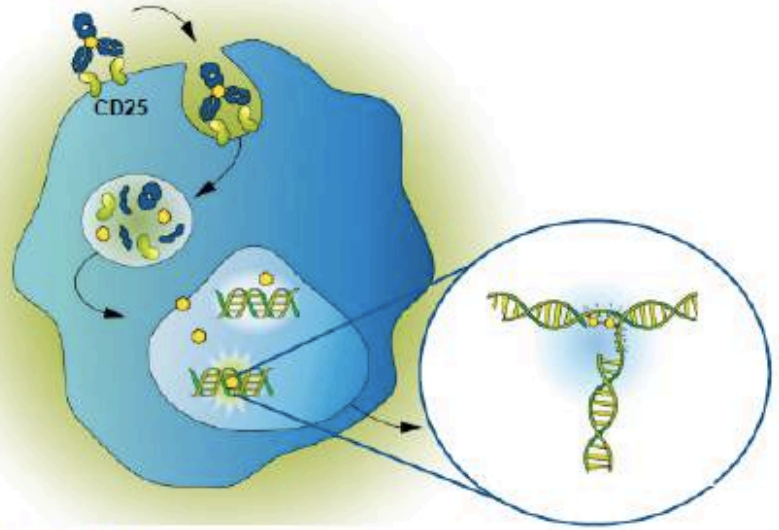
Molecular mode of action

1. **Camidanlumab tesirine binds to the CD25 antigen on the tumor cell surface**
2. **ADC internalization, linker cleavage and PBD release**
3. **Cytotoxic DNA cross-link formation**
   a) Free PBD dimers bind sequence-selectively in the minor groove of cell DNA
   b) PBD dimers form potent cytotoxic DNA cross-links
4. **Stalled DNA replication fork**

   Cross-links stall the DNA replication fork, blocking cell division and causing cancer cell death

Immunological rationale

Targeting of CD25+ Tregs may increase the Teff:Treg ratio, thus promoting immunological tumor eradication[3]



ADC, antibody drug conjugate; PBD, pyrrolobenzodiazepine; Teff, effector T cell; Treg, regulatory T cell

1. Hartley JA. *Expert Opin Investig Drugs*. 2011;20:733–744; 2. Flynn MJ, *et al. Mol Cancer Ther*. 2016;15:2709–21; 3 Sasidharan NV, *et al. Immunol Cell Biol*. 2018;96:21–33.

HL population: Selected Toxicities Summary All Grades (Safety Analysis Set),

ADC THERAPEUTICS

Potentially PBD-related toxicities (SMQ)	Dose (µg/kg)					
	≤20 (n=3)	30 (n=10)	45 (n=37)	60 (n=12)	≥80 (n=5)	Total (N=67)
Edema or effusion	1 (33.3)	3 (30.0)	10 (27.0)	2 (16.7)	1 (20.0)	17 (25.4)
Skin related	1 (33.3)	9 (90)	25 (67.6)	10 (83.3)	4 (80.0)	49 (73.1)
Liver function test	3 (100)	1 (10.0)	13 (35.1)	8 (66.7)	4 (80.0)	29 (43.3)
Selected autoimmune toxicities						
Guillain–Barré syndrome/Radiculopathy	0 (0)	1 (10.0)	3 (8.1)	1 (8.3)	0 (0)	5 (7.5)
Colitis	1 (33.3)	0 (0)	1 (2.7)	0 (0)	0 (0)	2 (3.0)
Hypothyroidism	0 (0)	0 (0)	2 (5.4)	1 (8.3)	1 (20.0)	4 (6.0)
Hyperthyroidism	0 (0)	0 (0)	2 (5.4)	0 (0)	0 (0)	2 (3.0)
Thyroiditis	0 (0)	0 (0)	0 (0)	0 (0)	1 (20.0)	1 (1.5)

TEAEs leading to treatment discontinuation occurred in 19/67 (28.4%) patients

PBD, pyrrolobenzodiazepine; SMQ, standardised MedDRA query; TEAEs, treatment-emergent adverse events

Data shown as of 16 Oct 2018

Collins et al. ASH 2018 # 1658

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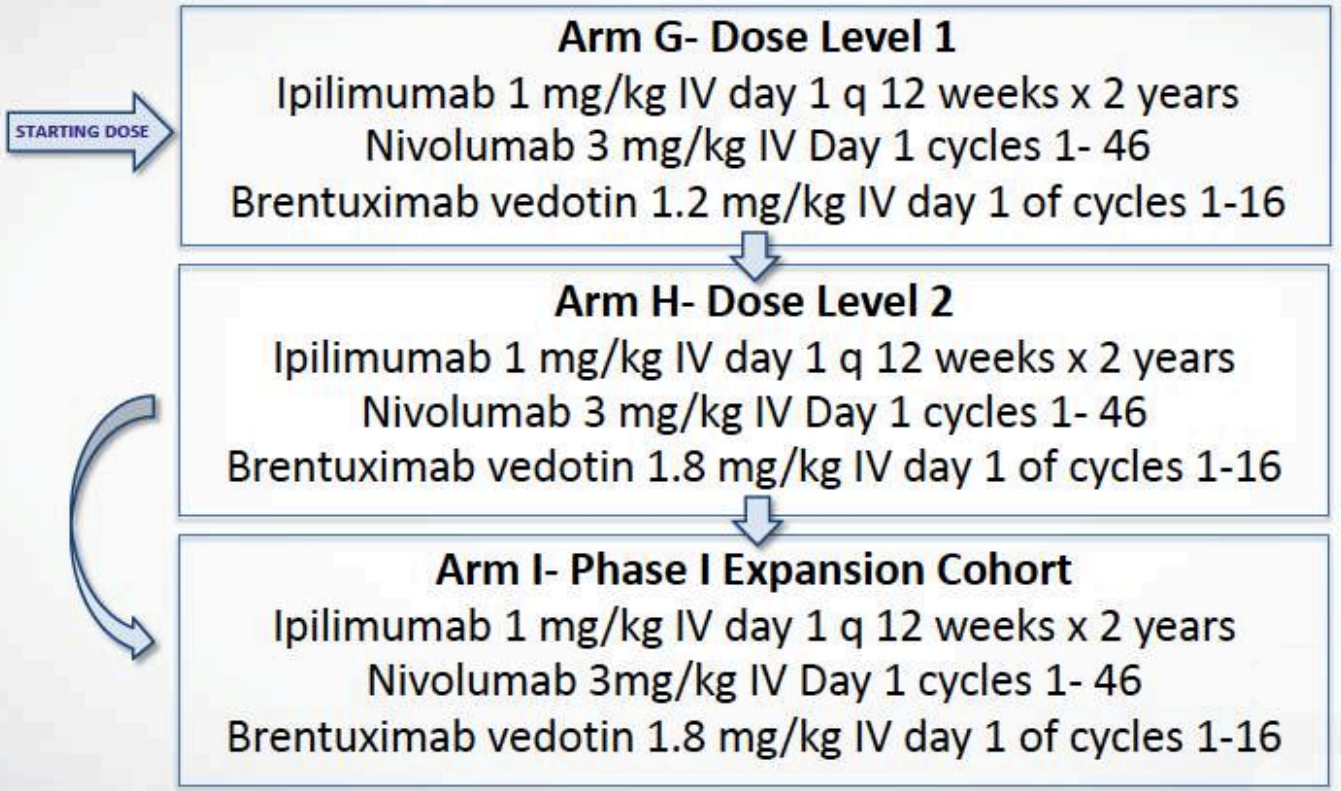
EXTENDED FOLLOW-UP OF A PHASE I TRIAL OF IPILIMUMAB, NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN RELAPSED HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN RESEARCH GROUP (E4412)

C.S. Diefenbach[1] | F. Hong[2] | R. Ambinder[3] | J. Cohen[4] | M. Robertson[5] | K. David[6] | R. Advani[7] | T. Fenske[8] | S. Barta[9] | N. Palmisano[10] | J. Svoboda[9] | D. Morgan[11] | R. Karmali[12] | B. Kahl[13] | S. Ansell[14]

E4412 Study Schema: BV + Ipi + Nivo



Arms G-I (Triplet) Preliminary Response Data

Response Summary (Evaluable Patients n=19*)

Total	ORR	CR	PR	SD	Uneval*	PD
19	18 (95%)	16 (84%)	2 (11%)	1 (5%)	0	0

*Patients who were treated with ≥ 3 cycles of therapy and had at least 1 disease assessment

Response Summary Arms A-C BV + IPI

Total	ORR	CR	PR	SD	Uneval*	PD
21	16 (76%)	12 (57%)	4 (19.0%)	2 (9.5%)	1 (4.8%)	1 (4.8%)

Response Summary Arms D-F BV + Nivo

Total	ORR	CR	PR	SD	Uneval*	PD
18	16 (88%)	12 (66%)	4 (22%)	1 (5%)	1 (5%)	0

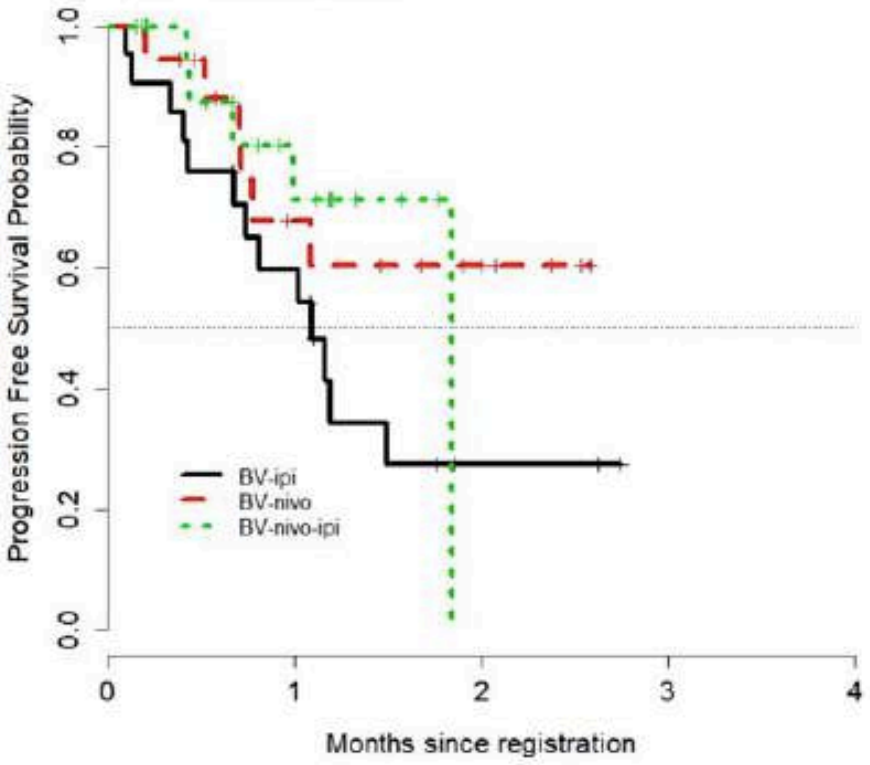
Response summary (All Patients: n=22)

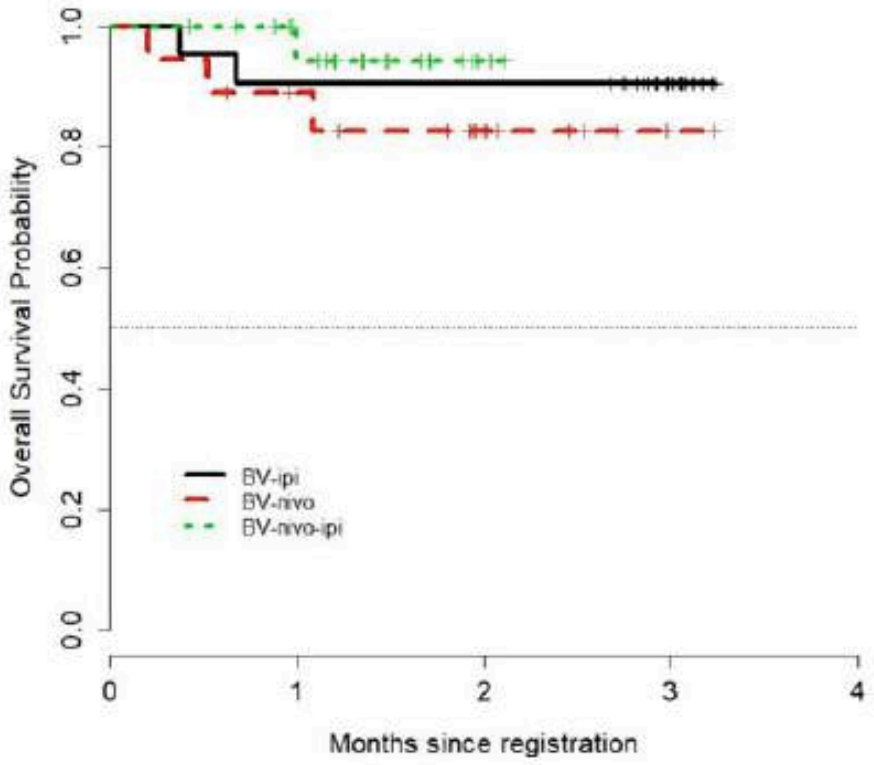
Total	ORR	CR	PR	SD	Uneval*	PD
22	18 (82%)	16 (72%)	2 (9%)	1	3	0

*Reasons for unevaluable: (went off treatment in cycle 1 week 2 with AE but not DLT); pt ended tx after C1 (n=2)

Linfoma di Hodgkin ICML 2019

Figure 1: PFS and OS





Stage I-II Nodular Lymphocyte-Predominant Hodgkin Lymphoma in the Modern Era:
a Multi-institutional Experience of Adult Patients by ILROG

15th International Conference on Malignant Lymphoma
June 21, 2019

M. S. Binkley, M.S. Rauf, S.A. Milgrom, C.C. Pinnix, R. Tsang, A. Ng, K.B. Roberts, S. Gao, U. Ricardi, M. Levis, C. Casulo, M. Stolten, C.R. Kelsey, J.L. Brady, N.G. Mikhaeel, B.S. Hoppe, S.A. Terezakis, Y. Kirova, S. Akhtar, I. Maghfoor, J.L. Koenig, C. Jackson, E. Song, S. Segal, R.H. Advani, Y. Natkunam, L.S. Constine, H. Eich, A. Wirth, R.T. Hoppe

Background

- Historically, NLPHL was characterized by multiple relapses but excellent OS[1]
- Experience with early stage NLPHL:
  - Stage II has worse PFS compared to stage I[2]
  - RT alone appears sufficient for stage I[3]
  - Active surveillance may be an option[4]
- The optimal treatment for stage I-II NLPHL remains undefined

1. Regula et al. NEJM 1988.
2. Chen et al. et al. JCO. 2010.
3. Eichenauer et al. JCO. 2015.
4. Borchmann et al. Blood. 2019.

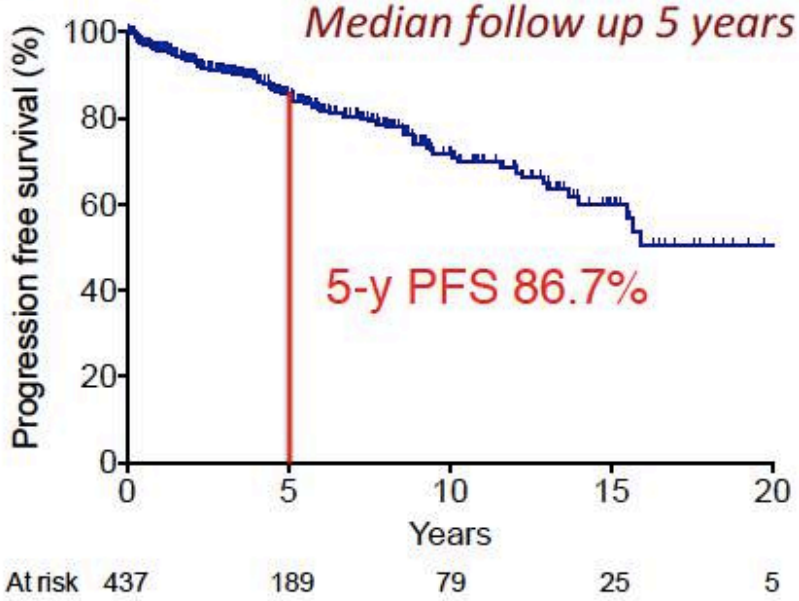
NLPHL adult cohort

Select patient characteristics

Parameter	**Total (n=437) No.**	RT (n=199) No.	CMT (n=160) No.	CT (n=37) No.	Observation (n=29) No.	Rituximab (n=12) No.
Median age, yr (range)	**38 (16-90)**	43 (17-90)	36 (17-73)	32 (17-74)	33 (16-81)	57 (20-82)
Gender						
Male	**307 (70%)**					
Female	**130 (30%)**					
Stage						
Stage I	**241 (55%)**	133 (67%)	73 (46%)	6 (16%)	27 (93%)	2 (17%)
Stage II	**196 (45%)**	66 (33%)	87 (54%)	31 (84%)	2 (7%)	10 (83%)
Median follow-up, yr (IQR)	**5 (2.4-9.8)**	5.3 (2.6-10.3)	5.1 (2.7-10.6)	4.5 (2.2-7.2)	4 (1.5-6.0)	4.7 (1.1-6.7)
Treatment dates	**1995-2018**	1995-2018	1995-2018	1996-2017	2003-2018	2000-2014

Outcomes for the entire adult NLPHL cohort

A



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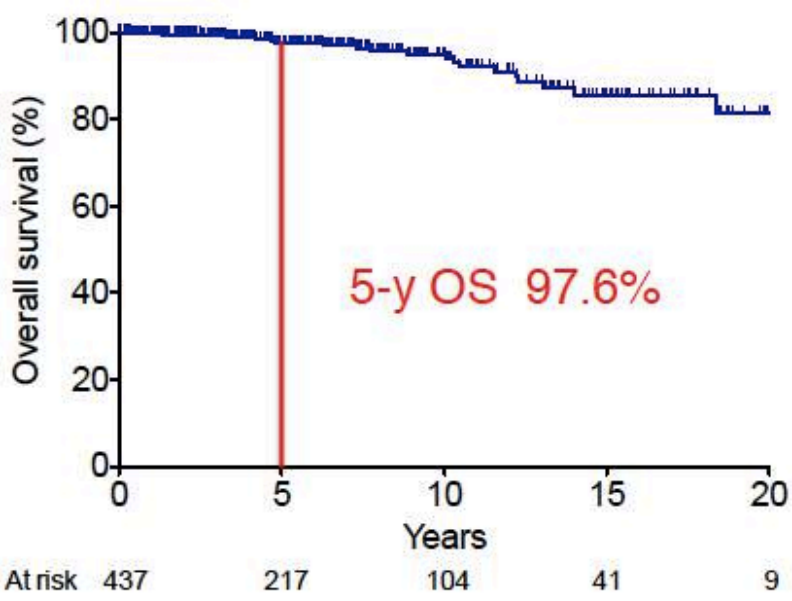
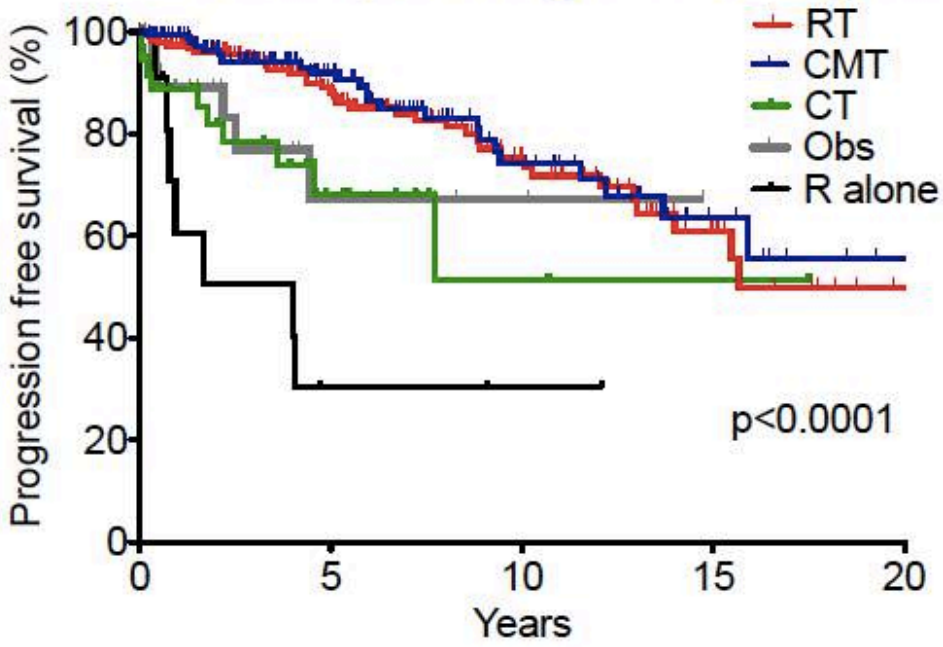


Comparing PFS by management



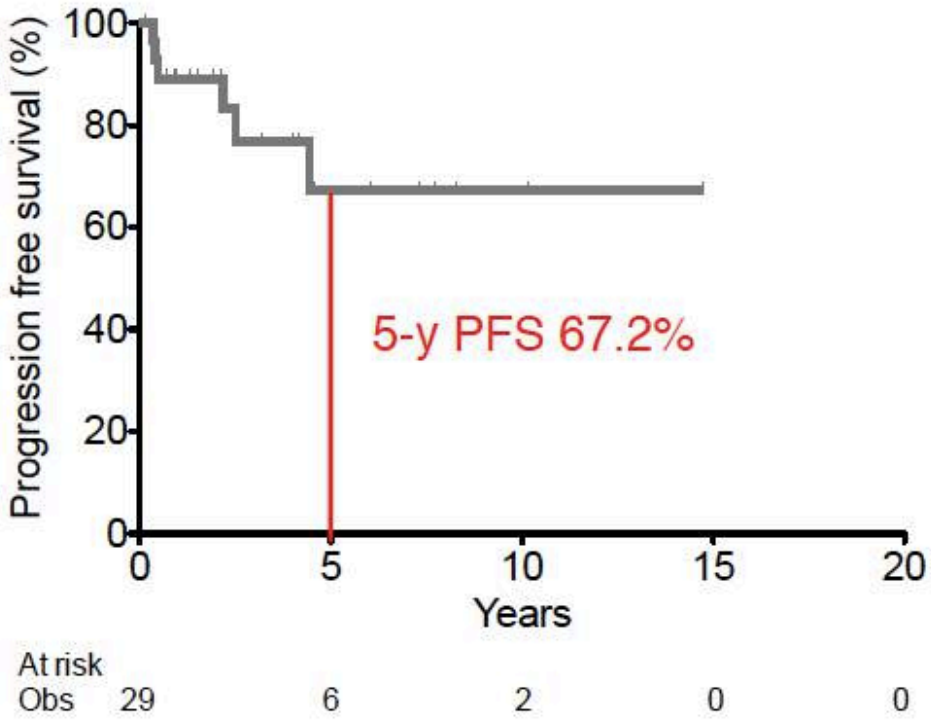
At risk					
RT	199	93	42	15	3
CMT	160	77	31	9	2
CT	37	10	3	1	0
Obs	29	6	2	0	0
R	12	2	1	0	0

- RT containing treatments had significantly improved PFS compared to all others (5-y 90% vs 61%, respectively)

- No significant difference in incidence of transformation by management

Management	Transformation No. (% of group)
CMT	4 (2.5%)
RT	7 (3.5%)
CT	2 (5.4%)
Rituximab	0 (0%)
Observation	1 (3.4%)

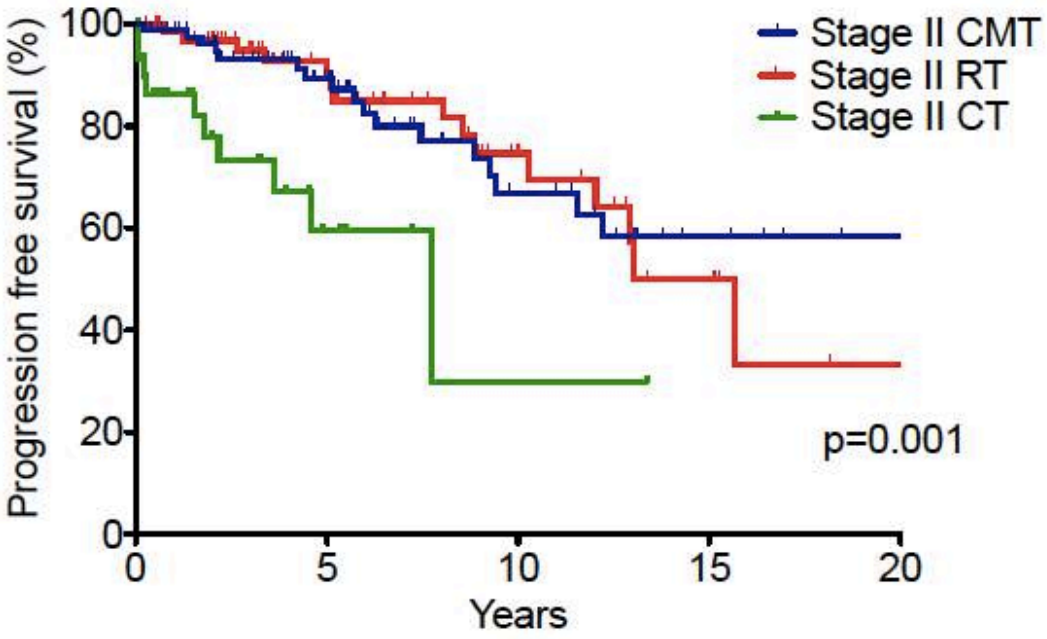
PFS in observation subgroup



Observation:

- *93% stage I*
- *90% had PET imaging*
- *93% without gross residual lymphoma after excision*
- *Median time-to-progression 5.8 mo (range, 4.1-53.3)*
- *All relapses involved initial site and 75% of NLPHL relapses were advanced stage (p=0.02)*

PFS for stage II NLPHL

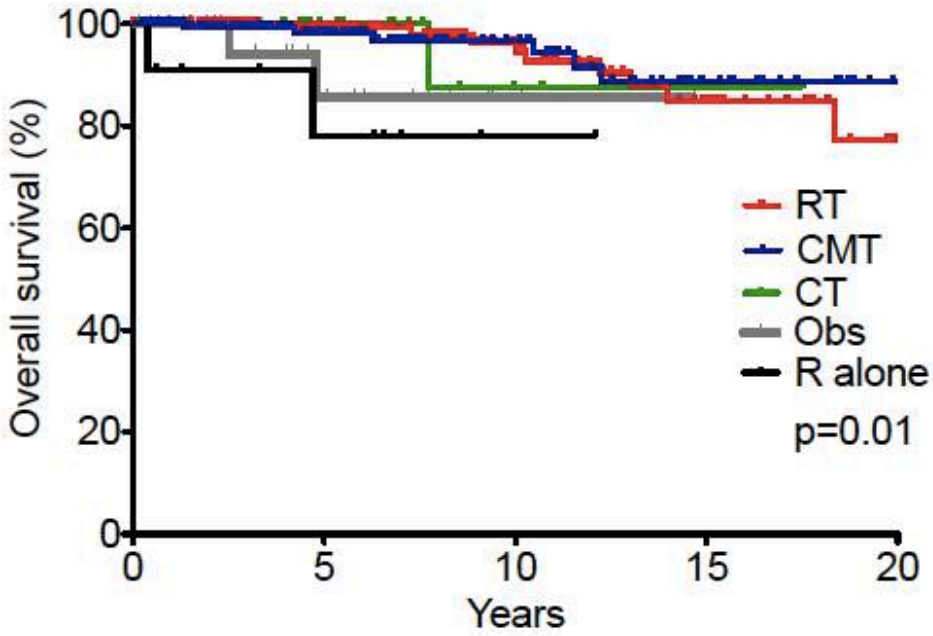


At risk					
CMT	87	45	19	6	2
RT	66	36	16	6	1
CT	31	6	1	0	0

Comparing RT vs CMT:

- No PFS difference (p=0.88)
- Number sites (p=0.23)
- Non-contiguous (p=0.75)
- B-symptoms (p=0.61)

Comparing OS by management



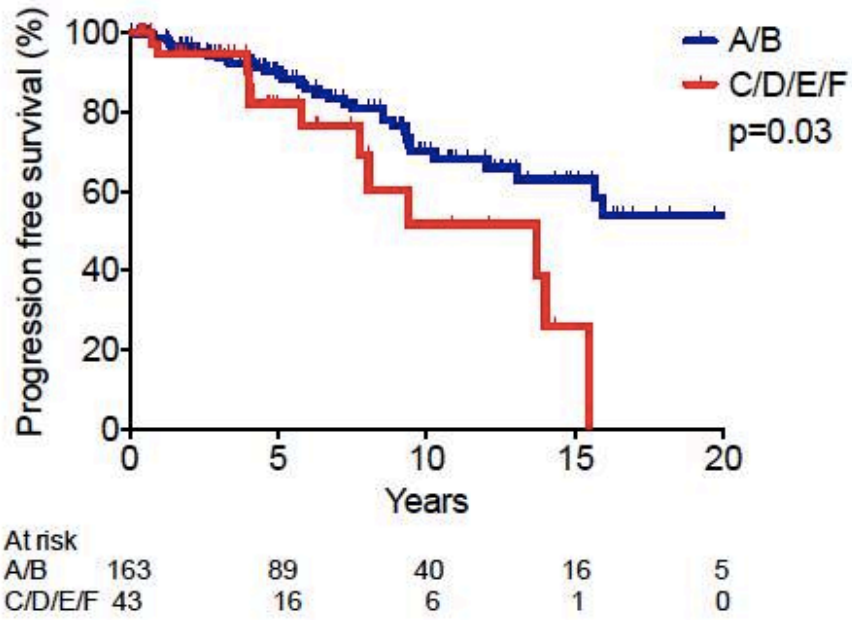
At risk					
RT	199	103	53	23	6
CMT	160	83	43	16	2
CT	37	15	5	1	0
Obs	29	10	2	0	0
R	12	5	1	0	0

No OS difference by management after adjusting for age and stage on multivariable analysis

Management	Lymphoma death No. (%)	Non-lymphoma death No. (%)
RT	3 (1.5%)	7 (3.5%)
CMT	2 (1.3%)	5 (3.1%)
CT	0 (0%)	1 (2.7%)
Observation	1 (3.4%)	1 (3.4%)
Rituximab	1 (8.3%)	1 (8.3%)

Immunoarchitectural pattern, n=206 (47%)

A



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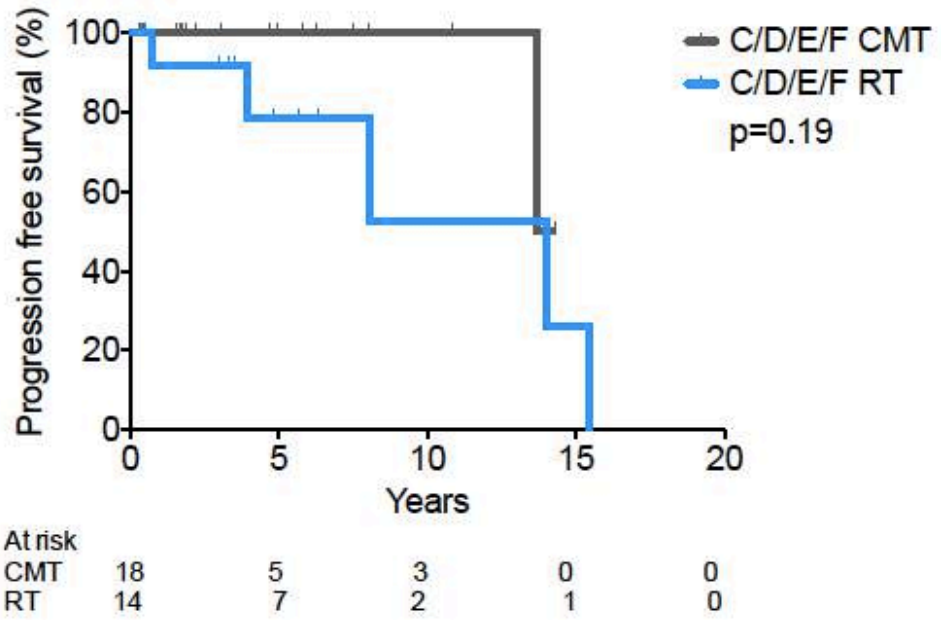


Implications and future directions

- RT-containing management has significantly better PFS vs. others
  - Prognosis is excellent, consider risk of acute and late toxicity
- Observation may be reasonable for *select* patients with stage I, staging PET, with complete excision.
  - Relapses in our data were advanced stage → local RT no longer an option
- RT alone has equivalent PFS to CMT, including for stage II NLPHL
  - CMT may have PFS benefit for variant immunoarchitectural pattern
- We continue to accrue cases for our collaborative study.

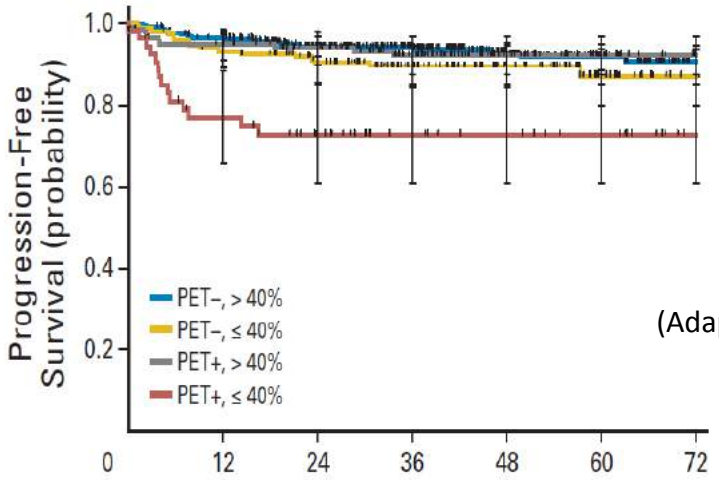
Consolidation Radiotherapy could be omitted in advanced Hodgkin Lymphoma with large nodal mass in Complete Metabolic Response after ABVD. Final analysis of the randomized GITIL/FIL HD0607 trial.

Andrea Gallamini MD[1], Andrea Rossi MD[2], Caterina Patti MD[3], Marco Picardi MD[4], Alessandra Romano MD[5], Maria Cantonetti MD[6], Sara Oppi MD[7], Simonetta Viviani MD[8], Silvia Bolis MD[9], Livio Trentin MD[10], Guido Gini MD[11], Battistini R[12], Stephane Chauvie PhD[13], Laura Bertolotti MD[14], Chiara Pavoni PhD[2], Guido Parvis MD[15], Roberta Zanotti MD[16], Paolo Gavarotti MD[17], Michele Cimminiello MD[18], Corrado Schiavotto MD[19], Piera Viero MD[20], Abraham Avigdor MD[21], Corrado Tarella MD[22] and Alessandro Rambaldi MD[2]

Lugano, Friday June 21, 2019

PET-adapted cRT in advanced-stage HL.

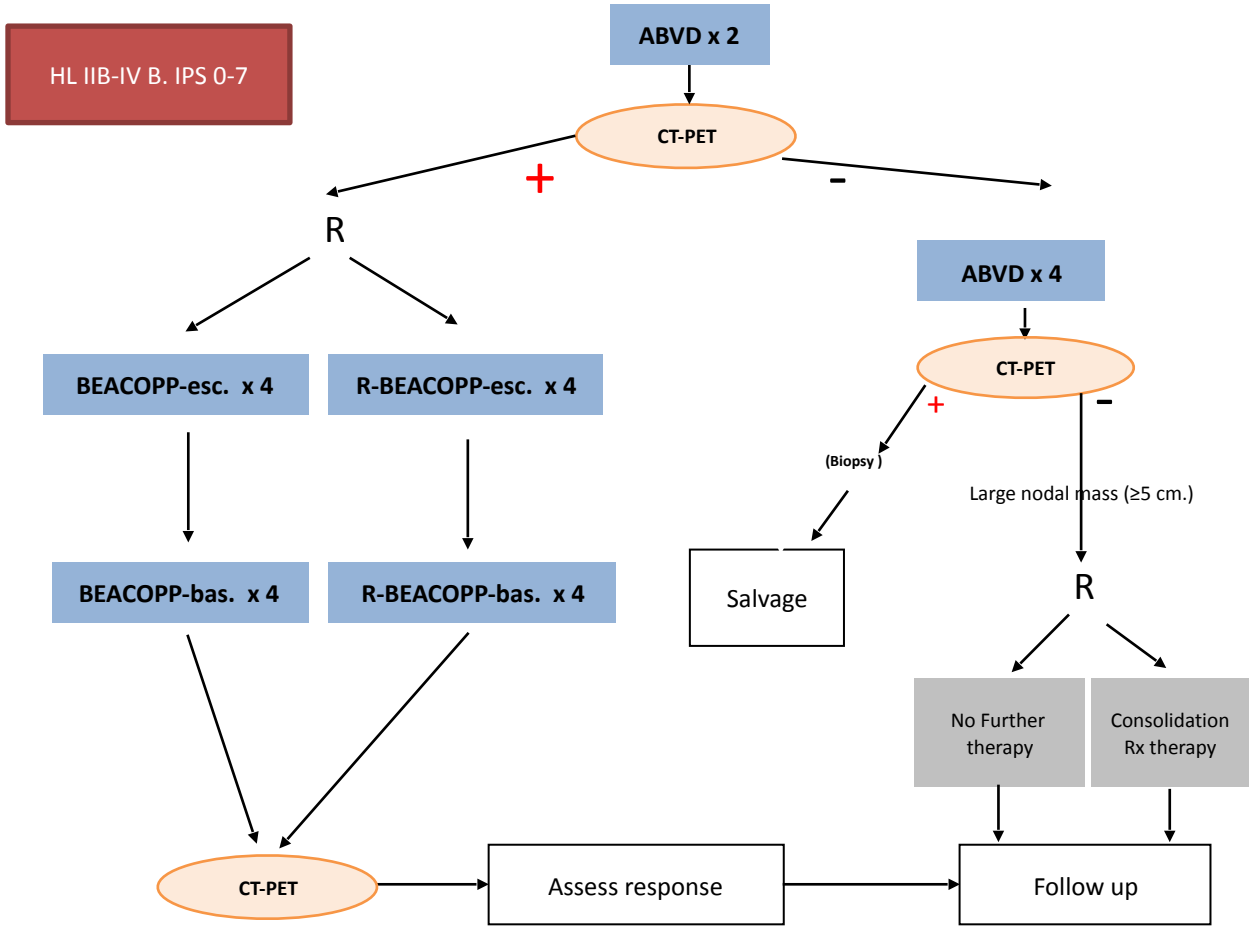
- Consolidation radiotherapy on the site of bulky nodal mass detected at baseline (cRT) was originally recommended for advanced-stage HL patients treated with ABVD[1]
- PET/CT is more accurate than CT in assessing treatment response in ABVD-treated Hodgkin lymphoma[2]
- Thus, a end-of-treatment (EoT) PET-driven strategy has been proposed in advanced-stage HL , and consolidation RT delivered in patients with a EoT positive PET[3]
- The NPV of EoT PET/CT proved quite high, depending on the CT regimen, ranging from 94% (after eBEACOPP)[4] to 89% (after ABVD)[3], to 86% (after VEBEP)[5]
- The PPV is lower and depends also on the entity of tumor size reduction after chemotherapy , with a higher risk of relapse after a tumor shrink < 40%[6]



(Adapted from Kobe C[6])

1: Bonfante V. Sem. On col 1992; 19: 38-44.
2: Cerci Jj: J clin Oncol 2010; 28: 1415-21.
3: Savage KJ: Blood 2015; 126 (23),579 [abst.].
4: Engert A: Lancet 2012; 379: 1791–99
5: Picard M: Leuk. Lymphoma 2007; 48, 1721-27.
6: Kobe C.: J Clin Oncol 2014; 32: 1776-81

GITIL/FIL HD 0607 trial (N=782)



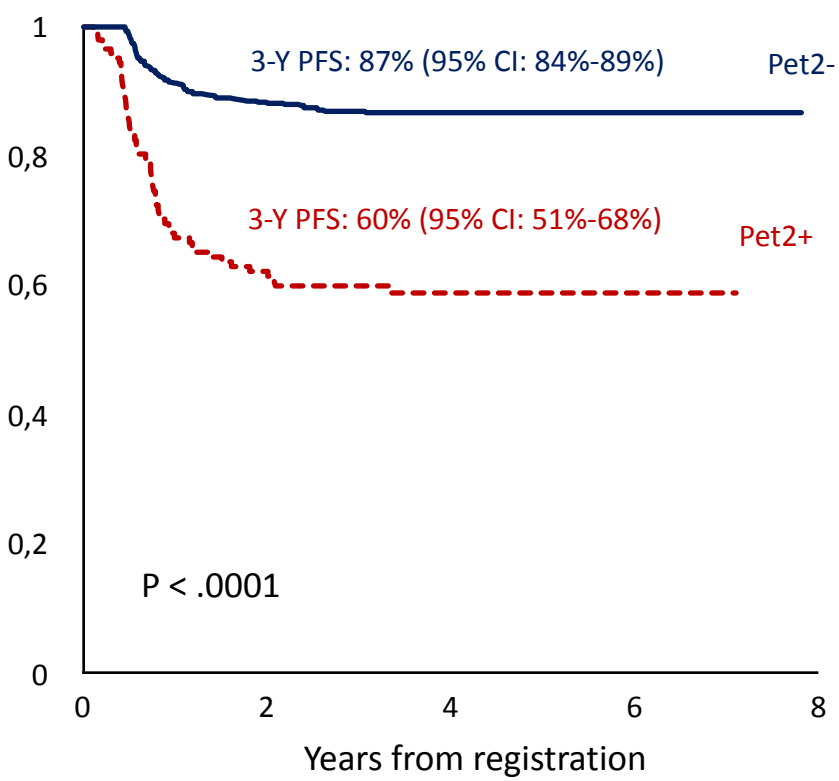
Primary endpoint:
3-Y PFS ≥ 85% for the overall strategy

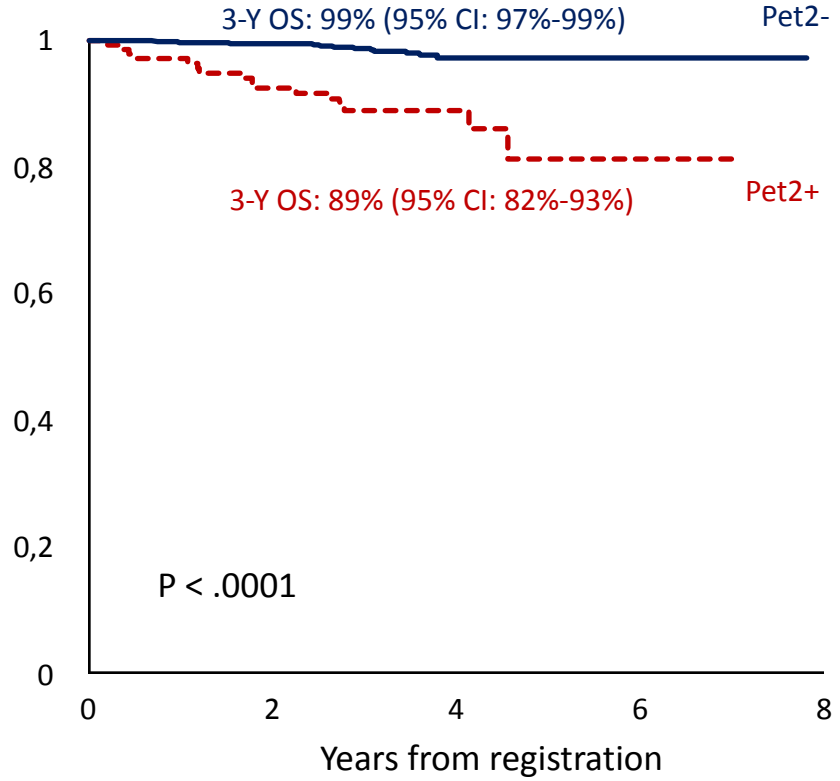
Secondary endpoints:
- Superiority in terms of 3-y PFS of the R-BEACOPP vs. BEACOPP in PET-2 positive patients
- Role of consolidation radiotherapy in patients with a negative EoT PET.

Gallamini A: J Clin Oncol. 2018; 10; 36(5): 454-462.

Gallamini A: 15° ICML, Lugano 2019

Treatment outcome based on PET-2 result



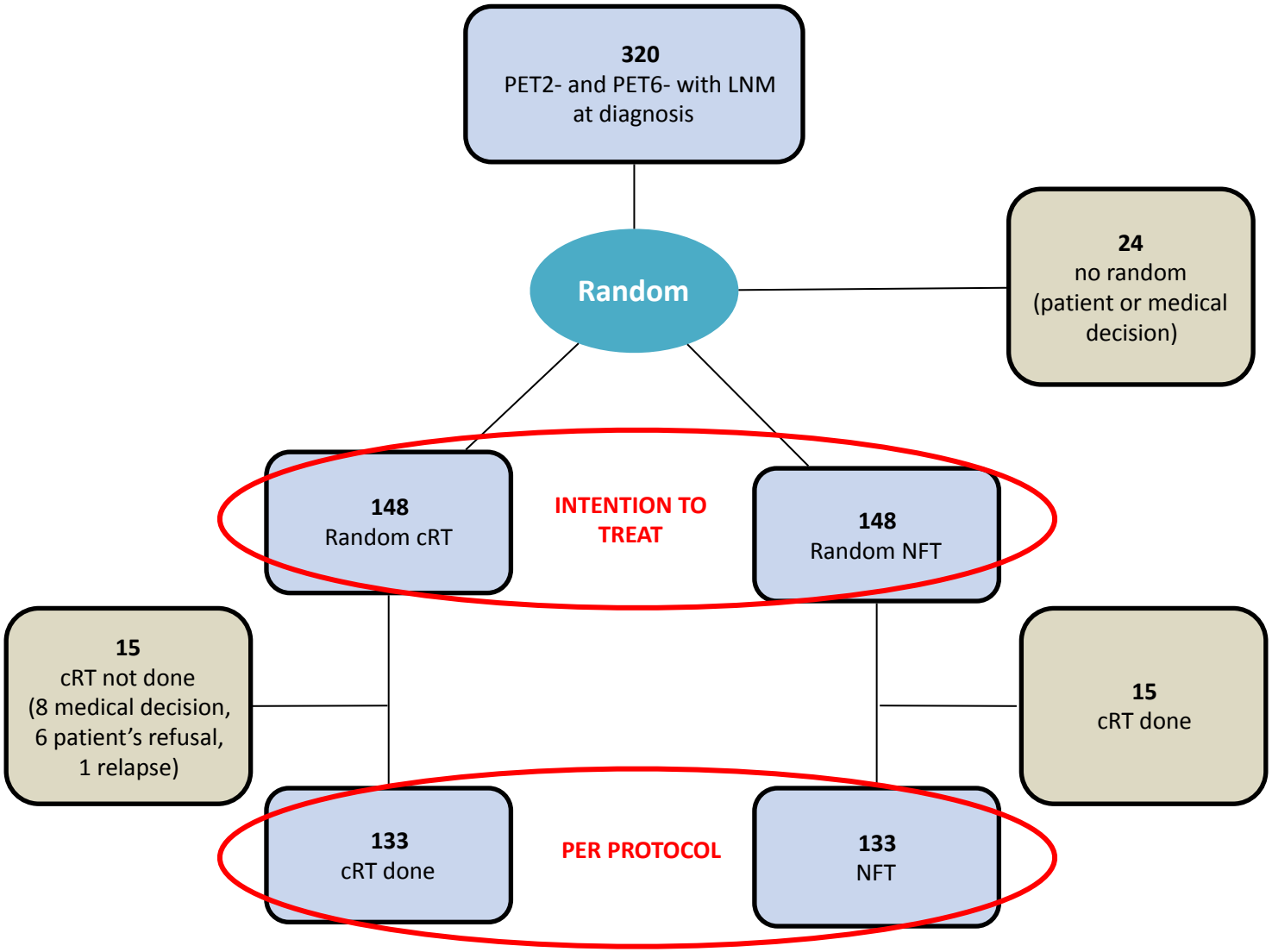


N= 782. Median f-up: 44 months

Gallamini A: J Clin Oncol. 2018; 10; 36(5): 454-462.

Gallamini A: 15° ICML, Lugano 2019

Consort diagram (N=320)

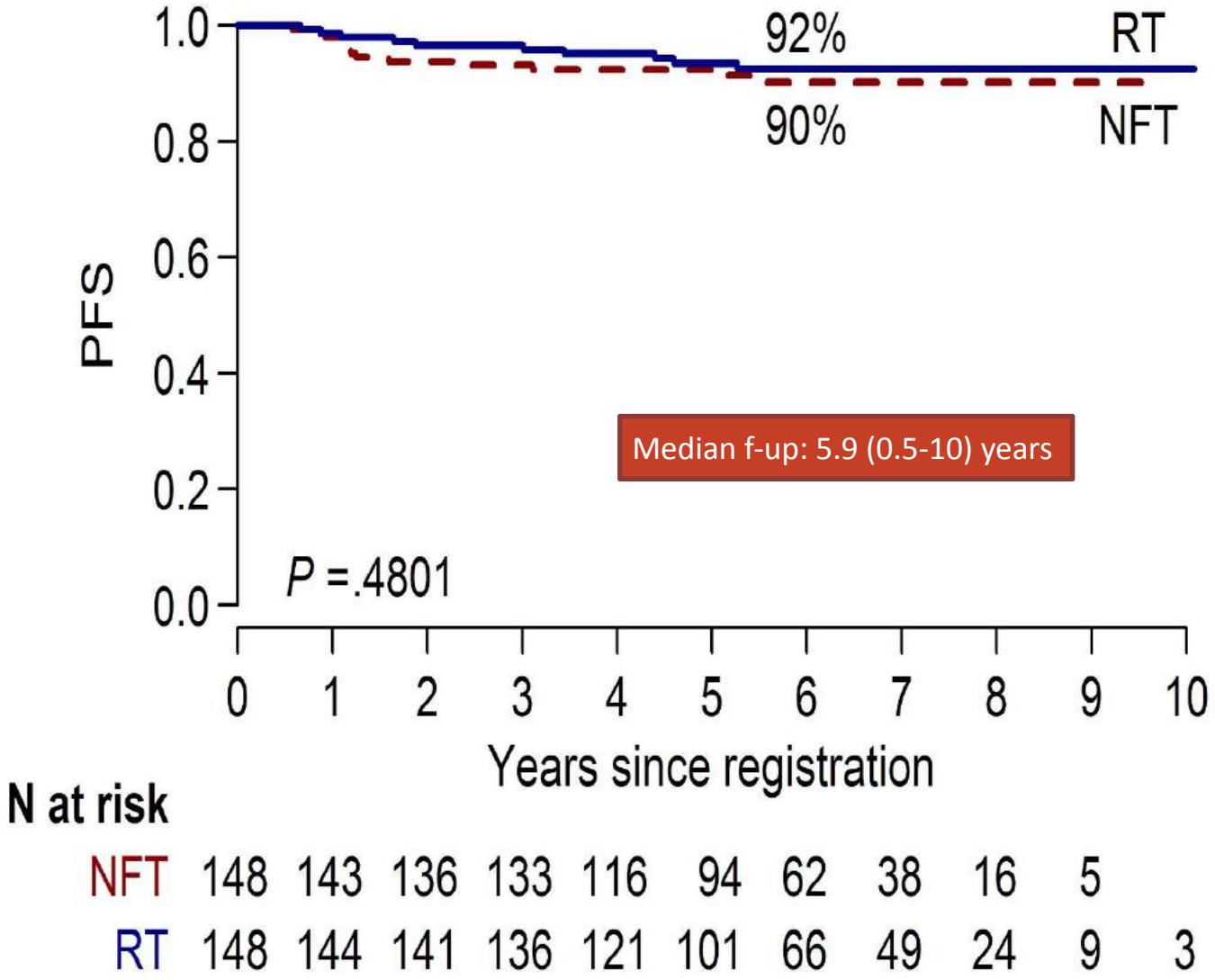


Gallamini A: 15° ICML, Lugano 2019

Demographics

Characteristics		All patients N = 296	cRT N=148	NFT N=148	P
Age (years)	median (range)	30 (16-60)	30 (18-60)	31 (16-59)	
	<50	279 (94.3)	137 (92.6)	142 (95.9)	0.6855
	≥50	17 (5.7)	11 (7.4)	6 (4.1)	
Sex, n(%)	Female	169 (57.1)	87 (58.8)	82 (55.4)	0.5571
	Male	127 (42.9)	61 (41.2)	66 (44.6)	
Ann Arbor stage, n(%)	II	140 (47.3)	68 (45.9)	72 (48.6)	0.4809
	III	79 (26.7)	44 (29.7)	35 (23.6)	
	IV	77 (26)	36 (24.3)	41 (27.7)	
B Symptoms,	n(%)	250 (84.5)	123 (83.1)	127 (85.8)	0.5210
IPS, N(%)	0-1	123 (41.6)	68 (45.9)	55 (37.2)	0.3060
	2-3	142 (48)	66 (44.6)	76 (51.4)	
	>3	31 (10.5)	14 (9.5)	17 (11.5)	
LNM size (cm), n(%)	5-7	101 (34.1)	56 (37.8)	45 (30.4)	0.3247
	7-10	96 (32.4)	43 (29.1)	53 (35.8)	
	>10	99 (33.4)	49 (33.1)	50 (33.8)	
LNM site, n(%)	Mediastinum	244 (82.4)	122 (82.4)	122 (82.4)	1.0000
	Cervical	41 (13.9)	24 (16.2)	17 (11.5)	0.2389
	Axillary	9 (3)	7 (4.7)	2 (1.4)	0.1730
	Abdominal	17 (5.7)	10 (6.8)	7 (4.7)	0.4536
	Lung hilus	4 (1.4)	3 (2)	1 (0.7)	0.6224
	Lung	4 (1.4)	1 (0.7)	3 (2)	0.6224
	Iliac	3 (1)	2 (1.4)	1 (0.7)	1.0000
	Other (<3)	7 (2.4)	4 (2.7)	3 (2.0)	1.0000

6-Y PFS (ITT analysis): N=296



Median f-up: 5.9 (0.5-10) years

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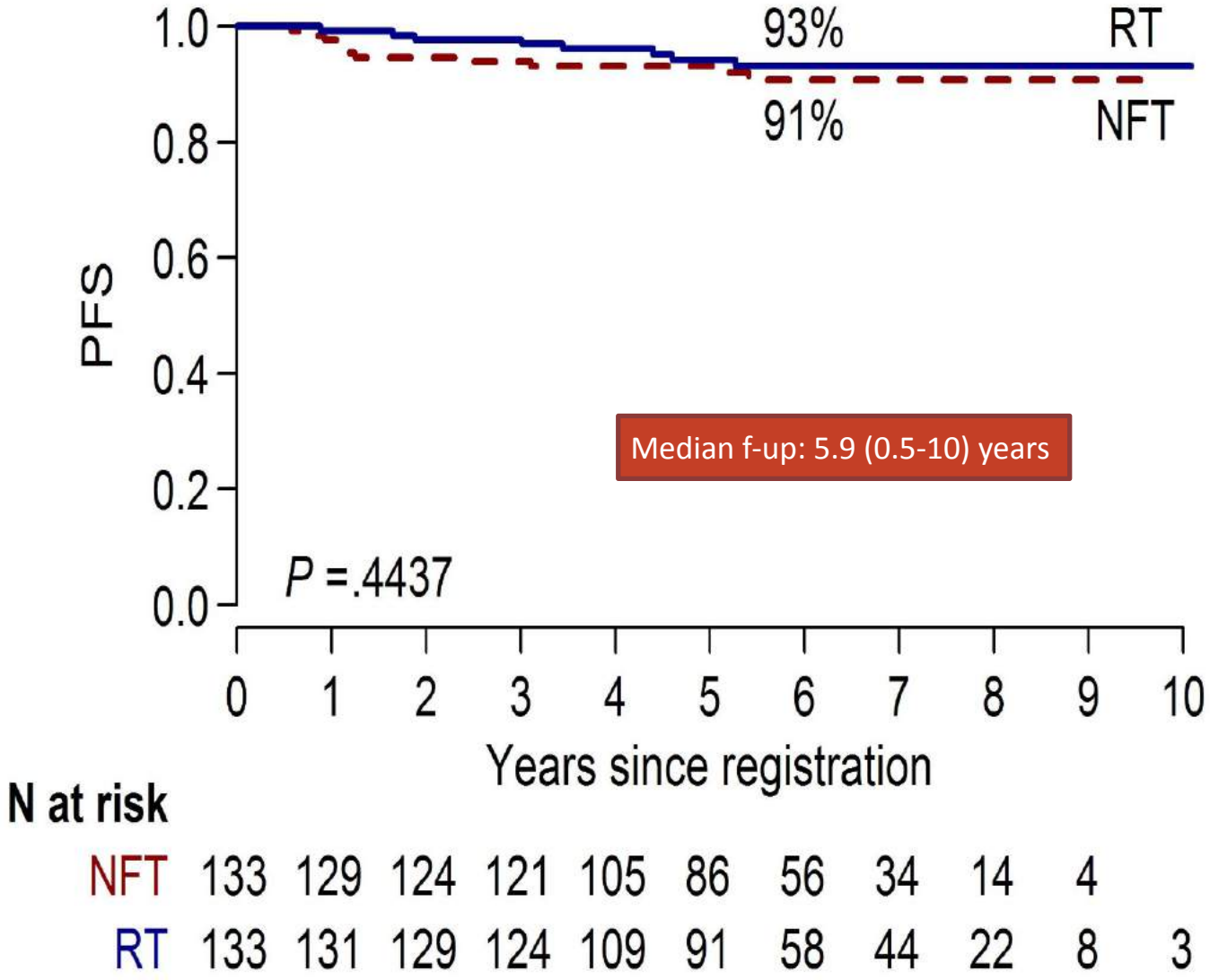
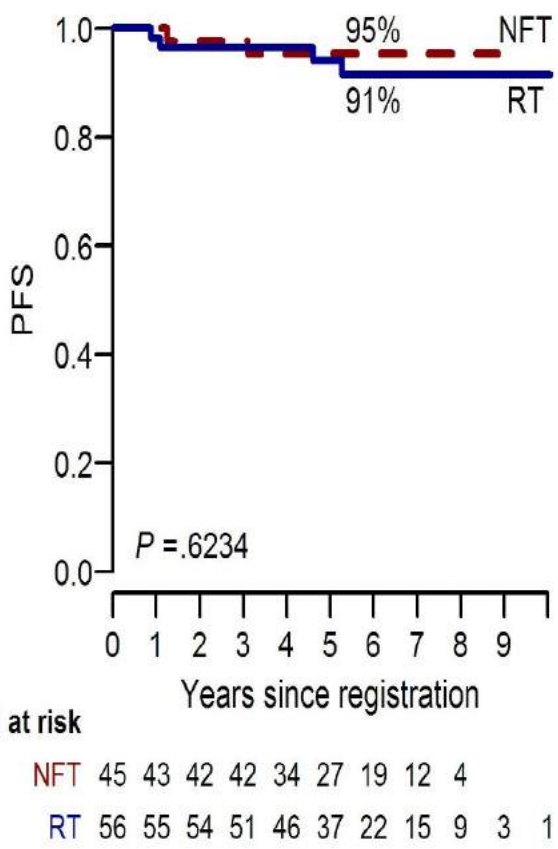
6-Y PFS (PP analysis): N= 266



Gallamini A: 15° ICML, Lugano 2019

PFS by size of LNM

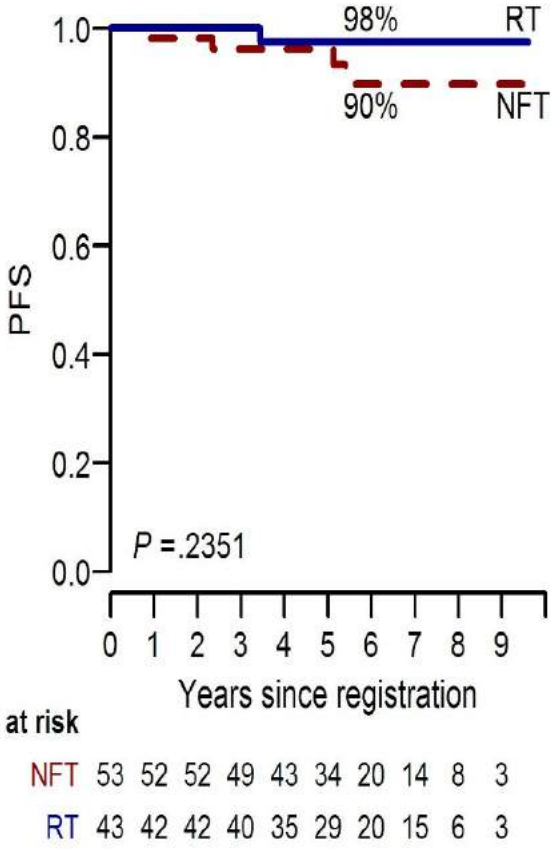
LNM 5-7 cm



N at risk

NFT	45	43	42	42	34	27	19	12	4		
RT	56	55	54	51	46	37	22	15	9	3	1

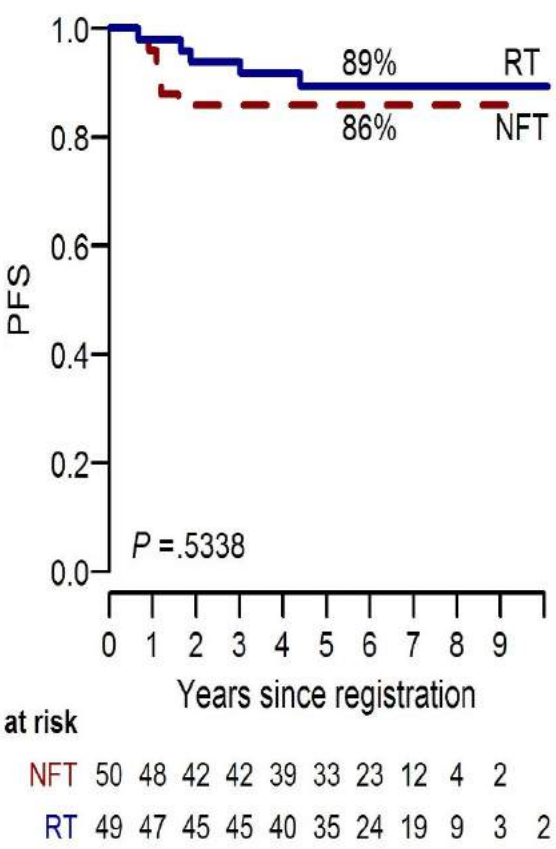
LNM 7-10 cm



N at risk

NFT	53	52	52	49	43	34	20	14	8	3	
RT	43	42	42	40	35	29	20	15	6	3	

LNM >10 cm



N at risk

NFT	50	48	42	42	39	33	23	12	4	2	
RT	49	47	45	45	40	35	24	19	9	3	2

Median f-up: 5.9 (0.5-10) years

Gallamini A: 15° ICML, Lugano 2019

Site of relapse (N=23)

Relapse site	cRT N = 10	NFT N = 13
Involved site at baseline	3	4
Involved and uninvolved site	1	2
Uninvolved site	5	4
Not known	1	3

Relapses were few, with no apparent imbalance between LNM or uninvolved site)

Results

- A post-ABVD residual mass was detected in 260 (88%) of 296 pts presenting with a LNM and in 92/99 pts with classical bulky.
- The median dose of RT was 30.6 (26.0-32.6) Gy, by involved field (88%) involved node (1%) or involved site (11%) technique.
- After a median follow-up of 5.9 (0.5-10) years the 6-year PFS for RT versus NFT in an intention to treat analysis was 92% (95% CI, 88-97%) versus 90% (95% CI, 85-95%) p = .48 and a 6-year OS 99% (95% CI, 97-100%) versus 98% (95% CI, 96-100%), respectively.
- When the analysis was limited to patients with a classical bulky lesion, the 6-year PFS was 89% (95% CI, 81-99%) for consolidation RT and 86% (95% CI, 77-96%) for NFT (p = .53).
- When the analysis was limited to those with RM, the relapse rate of patients treated or not with cRT was 7% versus 9%, with a 6-year PFS of 93% (95% CI, 88% to 97%) versus 89% (95% CI, 84% to 95%) (P = .41).

Conclusions

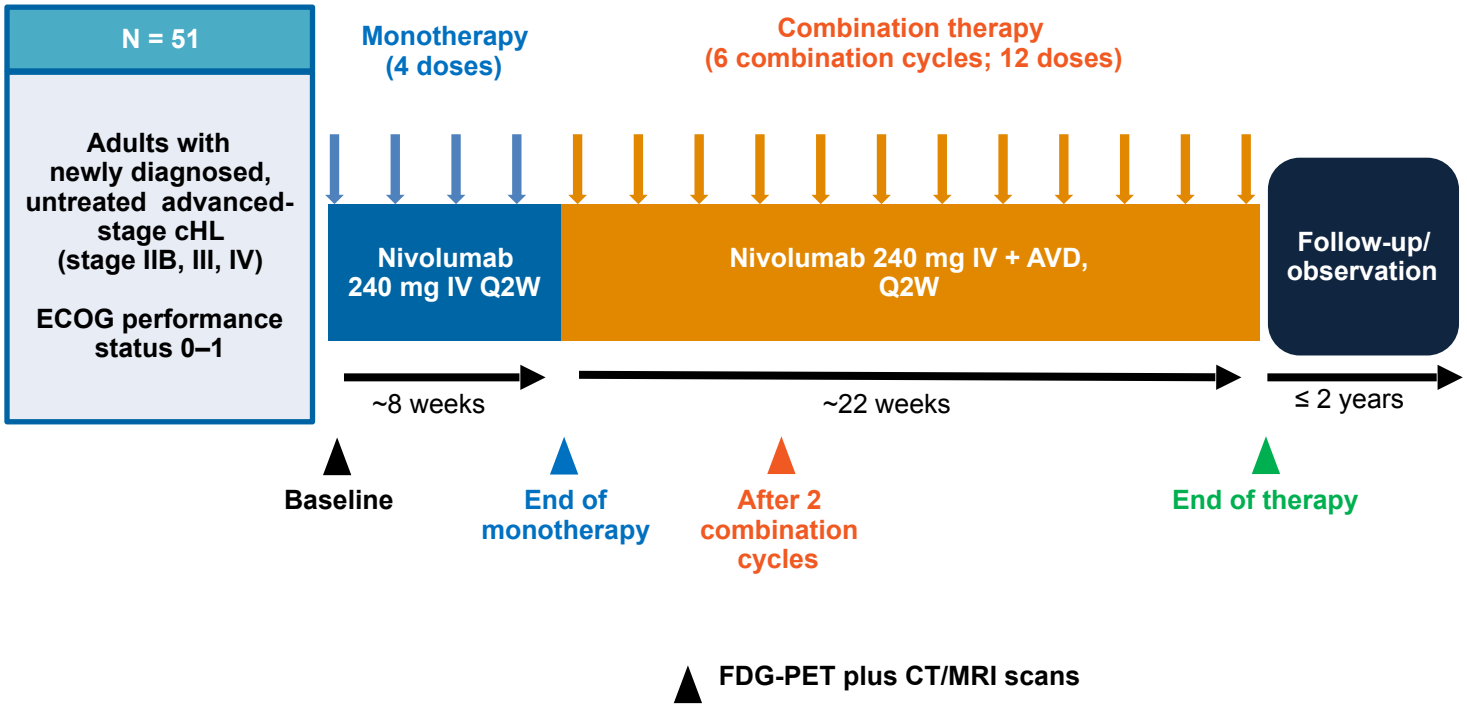
- Consolidation Radiotherapy could be safely omitted in advanced-stage HL pts presenting with a LNM and both a negative PET-2 and EoT-PET, irrespective from the LNM size.
- No differences in the pattern of (rare) relapse between irradiated and non-irradiated patients
- As in more than 80% of the pts the site of LNM at baseline was in mediastinum, this could translate in a significant reduction of late-onset treatment related mortality for secondary tumours and coronary arterial disease.

Nivolumab Plus Doxorubicin, Vinblastine and Dacarbazine for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma: CheckMate 205 Cohort D 2-Year Follow-Up

Stephen Ansell,[1] Radhakrishnan Ramchandren,[2] Eva Domingo-Domènech,[3] Antonio Rueda,[4] Marek Trněný,[5] Tatyana Feldman,[6] Hun Ju Lee,[7] Mariano Provencio,[8] Christian Sillaber,[9] Jonathon Cohen,[10] Kerry J. Savage,[11] Wolfgang Willenbacher,[12] Anne Sumbul,[13] Mariana Sacchi,[13] Philippe Armand[14]

[1]Mayo Clinic, Rochester, MN, USA; [2]University of Tennessee, Knoxville, TN, USA; [3]Institut Català d'Oncologia (ICO), Barcelona, Spain; [4]Costa del Sol Hospital, Marbella, Spain; [5]Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic; [6]Hackensack University Medical Center, Hackensack, NJ, USA; [7]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Hospital Universitario Puerta de Hierro, Madrid, Spain; [9]Medical University of Vienna, Vienna, Austria; [10]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [11]British Columbia Cancer Center for Lymphoid Cancer, Vancouver, Canada; [12]Innsbruck University Hospital & OncoTyrol - Center for Personalized Cancer Medicine, Innsbruck, Austria; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]Dana-Farber Cancer Institute, Boston, MA, USA

Phase 2 CheckMate 205 Cohort D Study Design



Endpoints included:

Primary

Safety and tolerability (G3–5 treatment-related AEs)

Additional

- Discontinuation rate
- CR and ORR by IRC and investigator at EOM, A2C, and EOT
- mPFS by IRC

Post hoc analysis:

- Deauville assessment by IRC
- PFS by investigator

- Per protocol, IRC assessments of response used the IWG 2007 criteria
- Post hoc, metabolic response was assessed by IRC, using the 5-point Deauville scale
  - PET negativity was a Deauville score of ≤ 3
- Median follow-up was 25.3 months

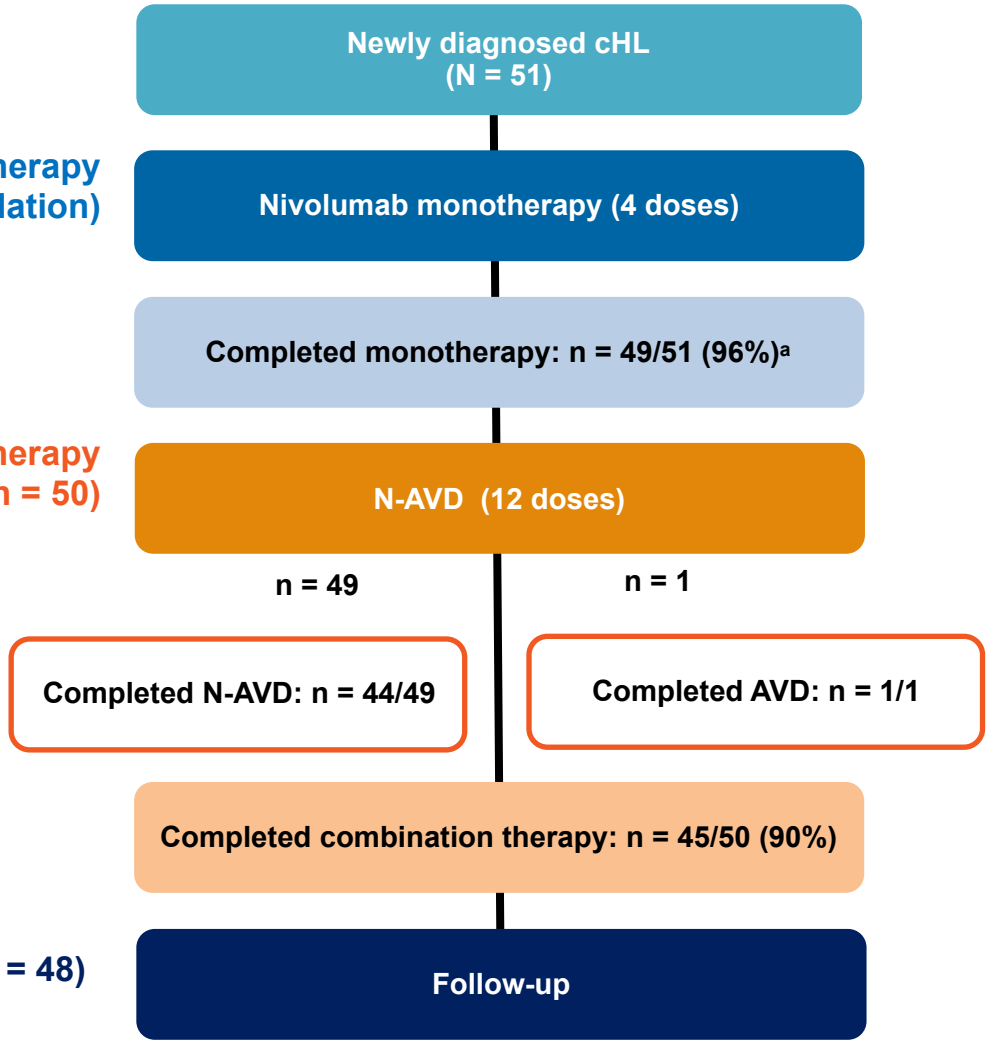
AVD dosage: doxorubicin (25 mg/m^2)/vinblastine (6 mg/m^2)/dacarbazine (375 mg/m^2)
A2C, after 2 combination cycles; AE, adverse event; ECOG, Eastern Cooperative Oncology Group; EOM, end of monotherapy; EOT, end of therapy; FDG-PET, fluorodeoxyglucose–positron emission tomography; G, grade; ORR, objective response rate.

Baseline Characteristics

Characteristic	Newly diagnosed cHL (N = 51)
Age, median (min–max), years	37 (18–87)
Male	32 (63%)
International Prognostic Score at diagnosis 0–1 2–3 ≥ 4 Not reported	 12 (24%) 21 (41%) 13 (25%) 5 (10%)
Disease stage at diagnosis II III IV	 10 (20%) 12 (24%) 29 (57%)
B symptoms at diagnosis	41 (80%)
Bulky disease[a]	16 (31%)
Extranodal involvement	25 (49%)

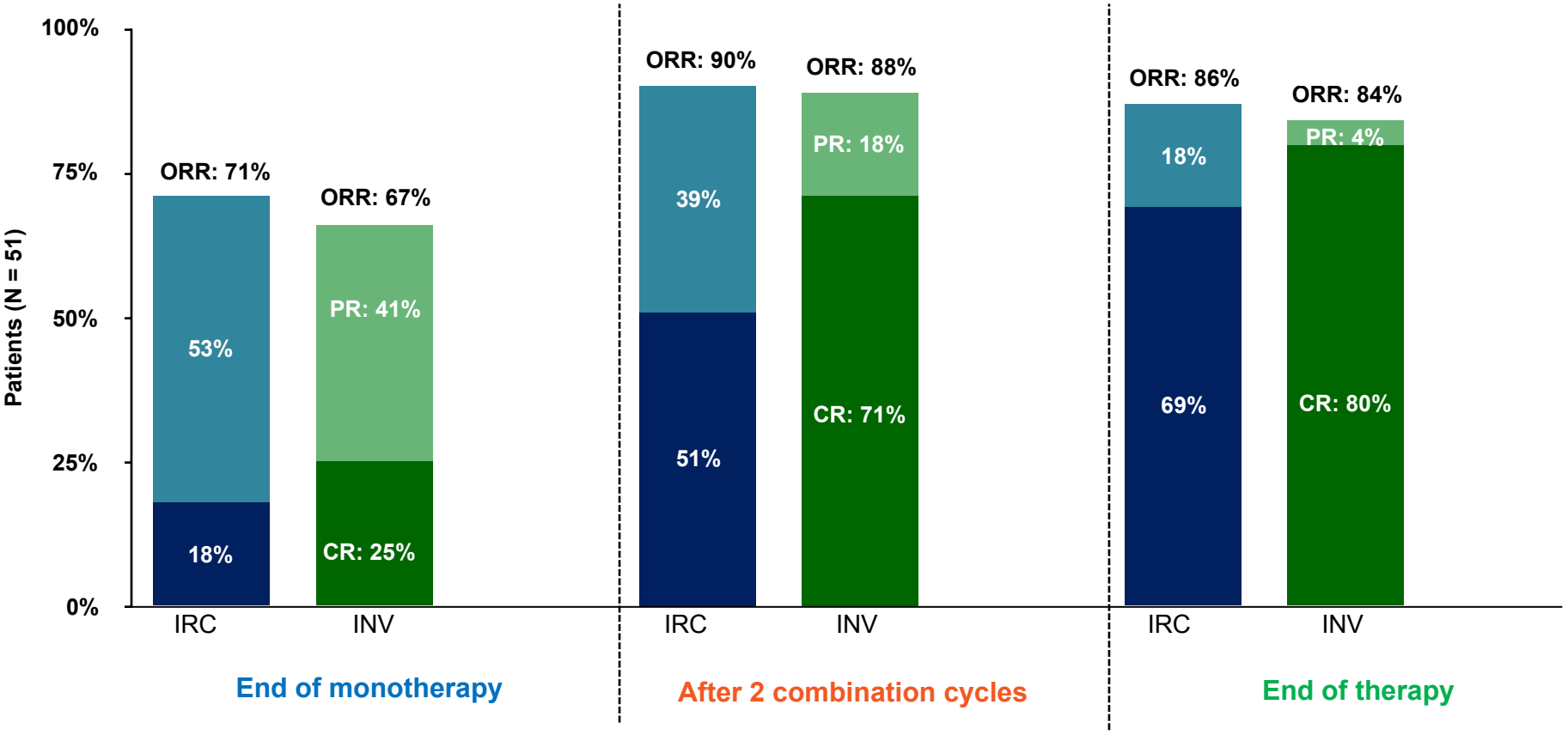
[a]A node or nodal mass > 10 cm, or a mediastinal mass with a maximum width of ≥ 1/3 of the internal transverse diameter of the thorax at the level of T5/6.

Patient Disposition



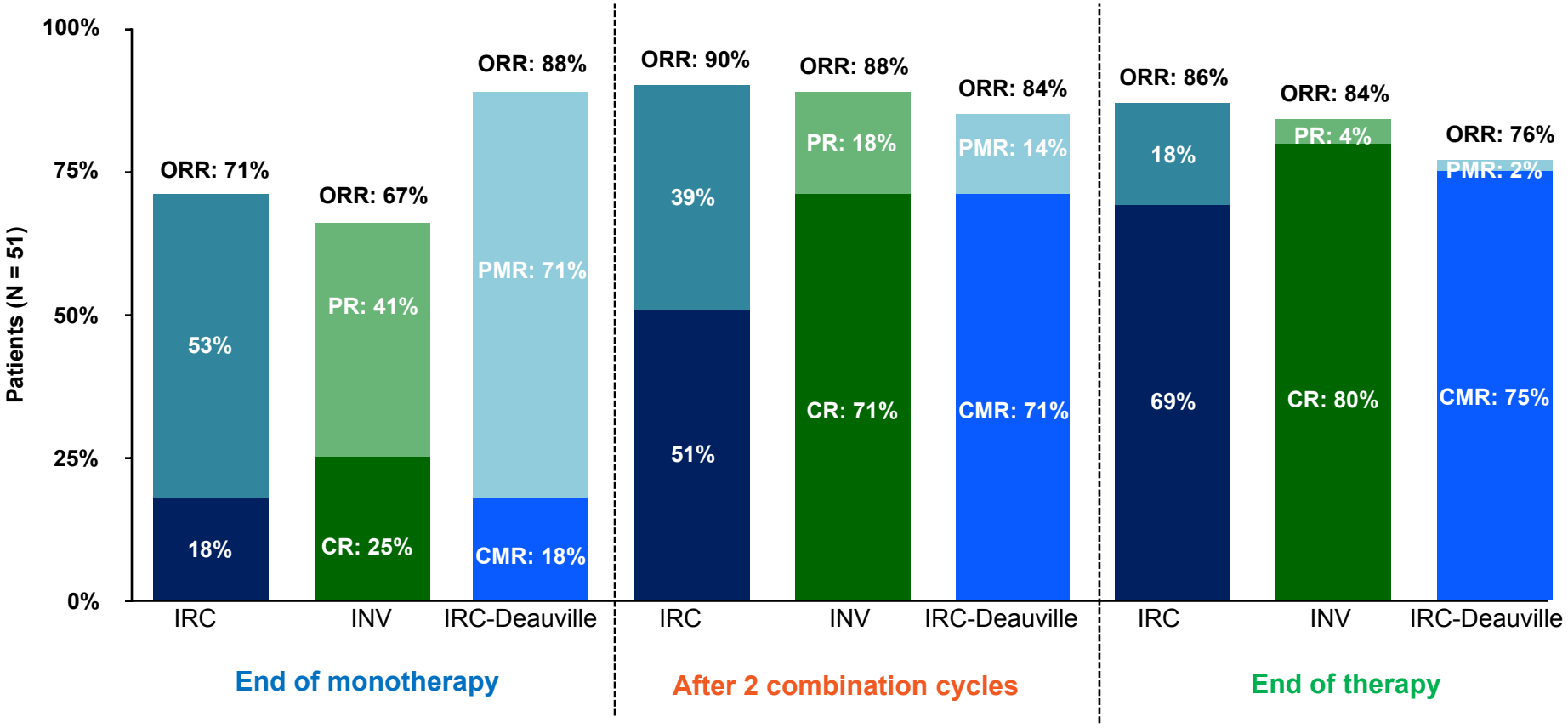
[a]One patient experienced study drug toxicity during the monotherapy phase and received AVD only during combination therapy.
ITT, intention to treat.

Response Per IRC and Investigator – ITT Population



Response assessed using IWG 2007 criteria. Four and 5 patients were non-evaluable at EOT per IRC and investigator, respectively. Values may not total ORR due to rounding.
INV, investigator, PR, partial remission.

Response Per IRC and Investigator – ITT Population



- At EOT, ORR per IRC was 86% (69% CR) and CMR rate per IRC-Deauville was 75%
  - At EOT, 3 patients (6%) had PD

Response assessed using IWG 2007 criteria. Four, 5, and 6 patients were non-evaluable at EOT per IRC, investigator, and IRC-Deauville, respectively. Values may not total ORR due to rounding.
CMR, complete metabolic response (Deauville ≤ 3); INV, investigator; PD, progressive disease; PR, partial remission; PMR, partial metabolic response.

Status of IRC Non-CR Patients at EOT

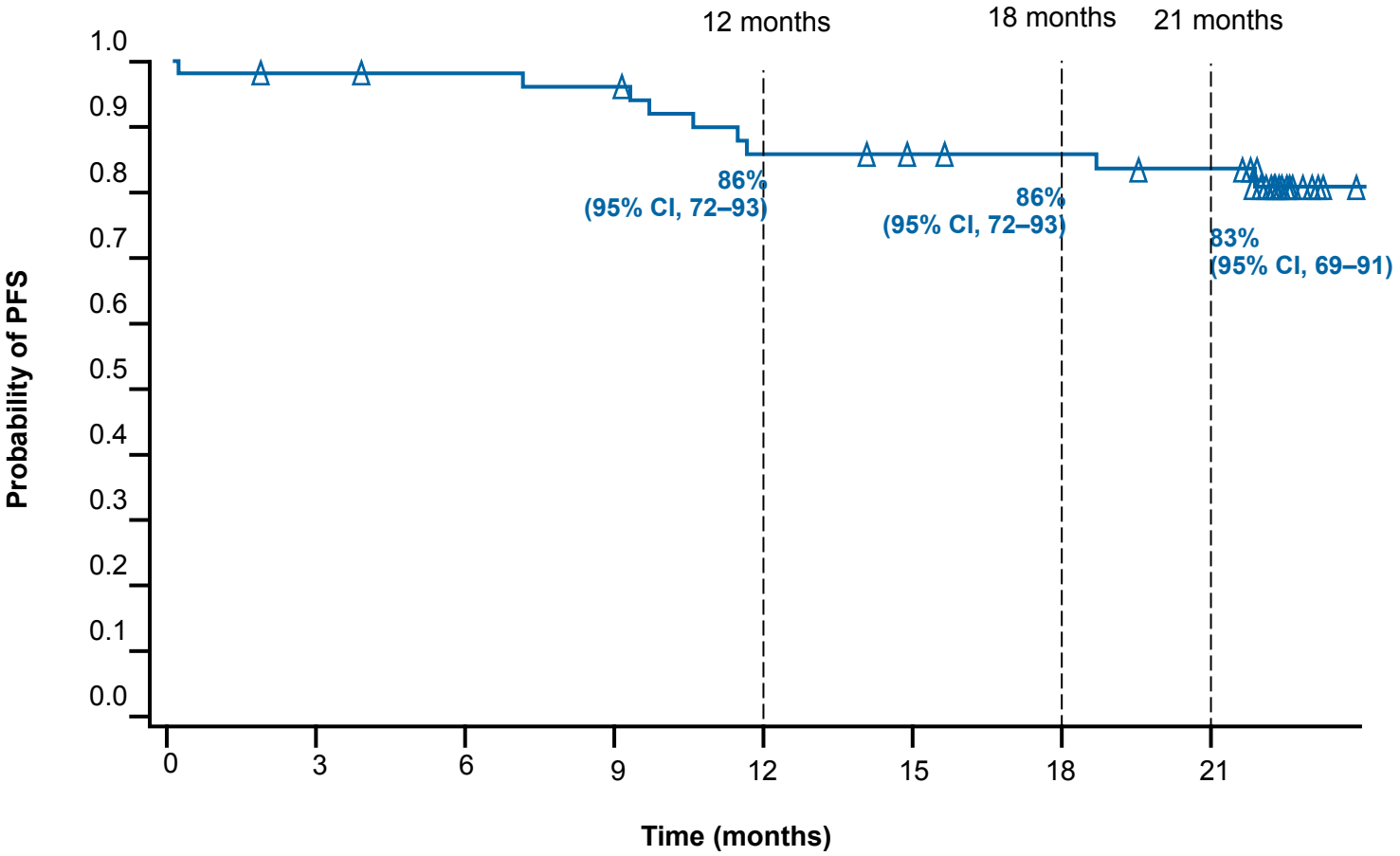
Patient	IRC	IRC-Deauville	INV	Subsequent Therapy
1	PR	CMR*	CR	None
2	PR*	CMR*	CR	None
3	PR	CMR	CR	None
4	PR*	CMR*	CR	Radiotherapy, bendamustine (on relapse)
5	PR*	CMR*	CR	None
6	PR*	CMR*	CR	None
7	NE[a]	CMR	CR	Nivolumab (commercial)
8	PR*	PMR*	PR	None
9	PR	PMD*	PR	ESHAP, BV, radiotherapy
10	PR*	PMD	PD	ESHAP, radiotherapy
11	PD	PMD*	PD	ESHAP, auto-HCT, BV, allo-HCT
12	PD	PMD	PD	Radiotherapy
13	PD	NA	NA	None
14	NA (CR at Week 60)	NA	NA (CR at Week 60)	None
15	NA	NA	NA	None
16	NA	NA	NA	None

*Adjudication required

- 16 patients did not achieve CR per IRC IWG 2007 criteria per protocol
  - 7 achieved both CMR per IRC-Deauville and CR per investigator

Three patients did not have an EOT IRC assessment reported.
[a]Patient's EOT assessment (CR) occurred after initiating subsequent therapy of nivolumab monotherapy..
Allo-HCT, allogeneic hematopoietic cell transplantation; auto-HCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; NA, not available; NE, not evaluable; PMD, progressive metabolic disease.

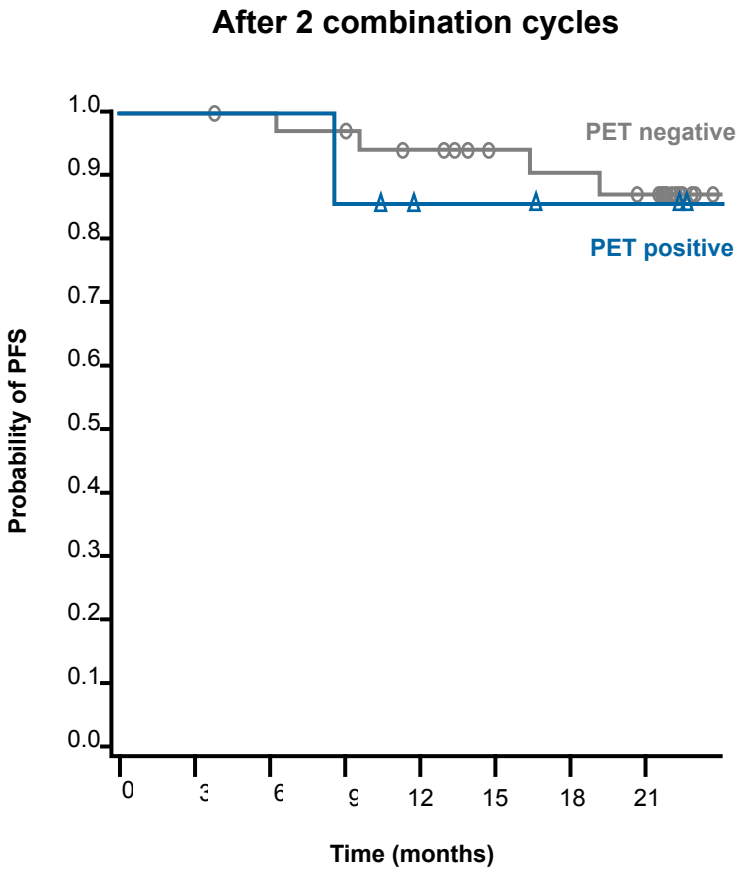
PFS Per Investigator



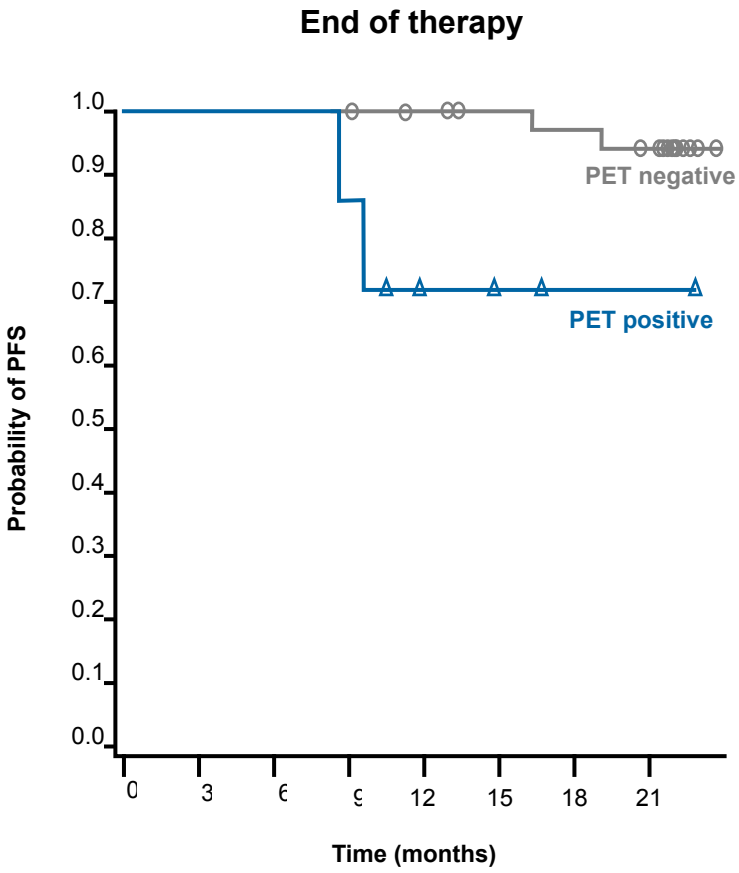
Patients at risk (events: 9)	51	49	48	47	41	39	38	36

Traditional PFS per IRC was not analyzed because tumor scans were not centrally collected in the study after patients receiving subsequent therapy.

PFS by Deauville PET Status



Patients at risk								
PET positive (events: 1)	7	7	7	6	4	4	3	3
PET negative (events: 5)	36	36	35	34	31	27	26	24



Patients at risk								
PET positive (events: 2)	7	7	7	6	3	2	1	1
PET negative (events: 3)	38	38	38	38	36	34	33	31

Treatment-Related AEs

Treatment-related AEs (N = 51)	Any grade, n (%)	Grade 3–4, n (%)
Total patients with treatment-related AEs	**49 (96)**	**30 (59)**
Hematologic/investigations (≥ 5% patients)		
Neutropenia	24 (47)	21 (41)
Decreased white blood cell count	7 (14)	1 (2)
Decreased neutrophil count	6 (12)	6 (12)
Febrile neutropenia	5 (10)	5 (10)
Increased alanine aminotransferase	4 (8)	2 (4)
Anemia	4 (8)	1 (2)
Increased amylase	3 (6)	0
All others (≥ 10% patients)		
Nausea	18 (35)	1 (2)
Infusion-related reaction	16 (31)	0
Fatigue	13 (25)	0
Pyrexia	7 (14)	1 (2)
Constipation	7 (14)	0
Hypothyroidism	7 (14)	0
Vomiting	7 (14)	0
Arthralgia	6 (12)	0
Stomatitis	6 (12)	0

Includes AEs reported between first dose and 30 days after last dose of study therapy.

Immune-Mediated AEs and Deaths

Immune-mediated AEs (N = 51)	Any grade, n (%)	Grade 3–4, n (%)
Rash	3 (6)	0
Increased alanine aminotransferase	2 (4)	2 (4)
Increased aspartate aminotransferase	1 (2)	1 (2)
Infusion-related reaction	2 (4)	0
Pneumonitis	1 (2)	0

- No grade 5 treatment-related AEs occurred within 30 days of last dose of study therapy
- Two patients died after the last dose of N-AVD
  - 1 patient (age 68 years) died 38 days after last dose due to study drug toxicity (3 grade 4 treatment-related SAEs followed by acute respiratory failure [due to N-AVD])
    - Duration of treatment was 175 days
  - 1 patient (age 85 years) died 451 days after last dose due to disease progression
    - Duration of treatment was 209 days

Includes AEs reported between first dose and 100 days after last dose of study therapy.
SAE, serious adverse event.

Summary/Conclusion

- In this 2-year extended follow-up of CheckMate 205 Cohort D, nivolumab followed by N-AVD at the end of therapy was associated with:
  - ORR per IRC of 86%
  - CMR rate per IRC-Deauville of 75%
  - PFS rate per investigator of 83% at 21 months
- Incorporation of Deauville scoring improved the concordance of CR between IRC- and investigator-assessed responses
  - Further analysis of PET status at EOT as a predictor of PFS is warranted
- Nivolumab monotherapy followed by N-AVD was well tolerated, with no new safety signals with extended follow-up
- Nivolumab followed by N-AVD may provide a promising alternative treatment option to standard-of-care multi-agent chemotherapy for patients with newly diagnosed, advanced-stage cHL

CD30-CAR T Cells for Therapy of Hodgkin Lymphoma

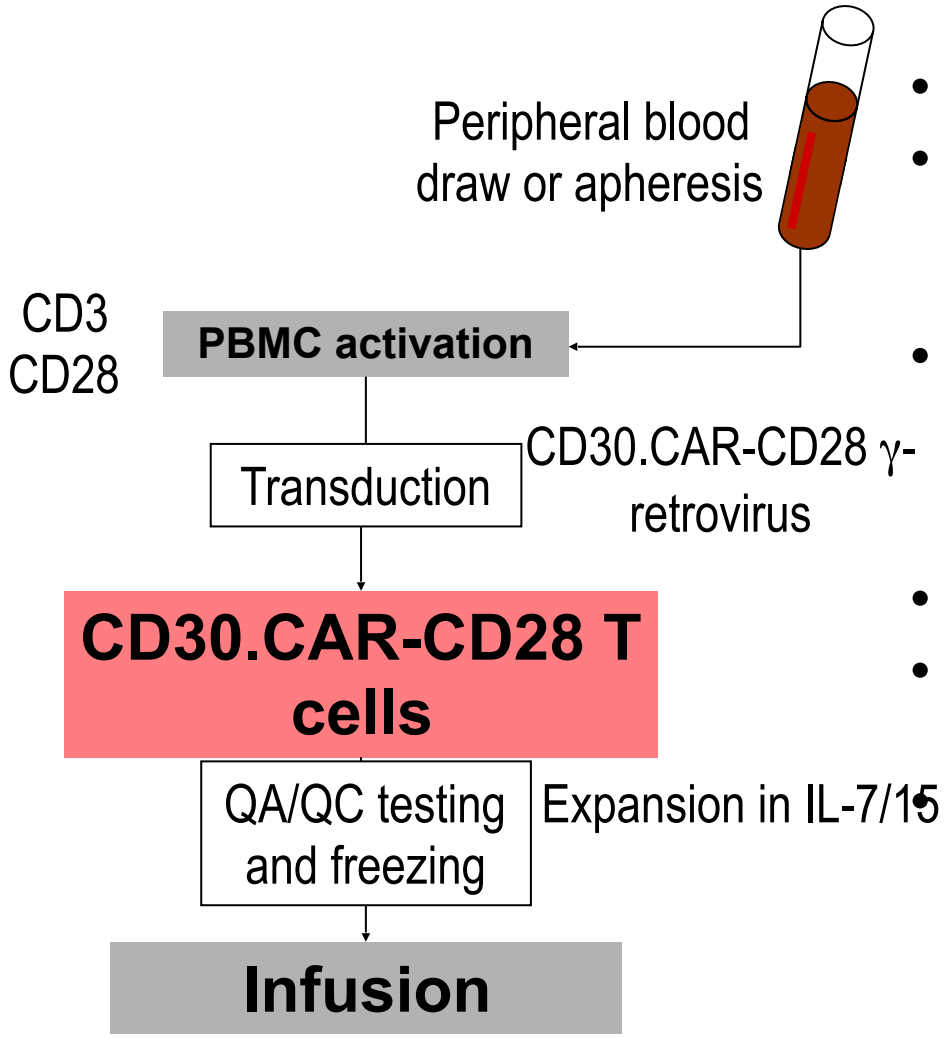
C.A. Ramos, M. Bilgi, C. Gerken, O. Dakhova, Z. Mei, M.-F. Wu, B. Grilley, A.P. Gee, C.M. Rooney, G. Dotti, B. Savoldo, H.E. Heslop & M.K. Brenner

15-ICML, June 2019

Targeting CD30 with a CAR

- CD19-specific CAR-T cells are highly successful against B-cell NHL and ALL
- Targets for other lymphoproliferative disorders have lagged behind
- CD30 has been validated as a immune target (e.g. brentuximab vedotin)
- A CD30-specific CAR (CD30.CAR) has activity in pre-clinical models of HL (Hombach, Ca Res 1998; Savoldo, Blood 2007)

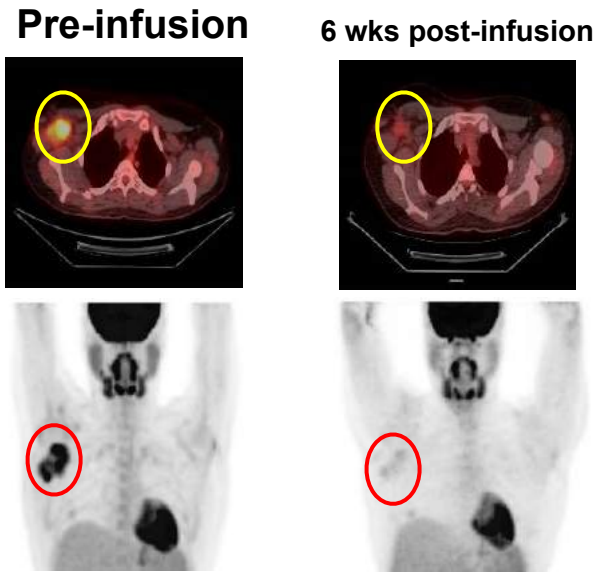
CART CD30 trial (NCT01316146)

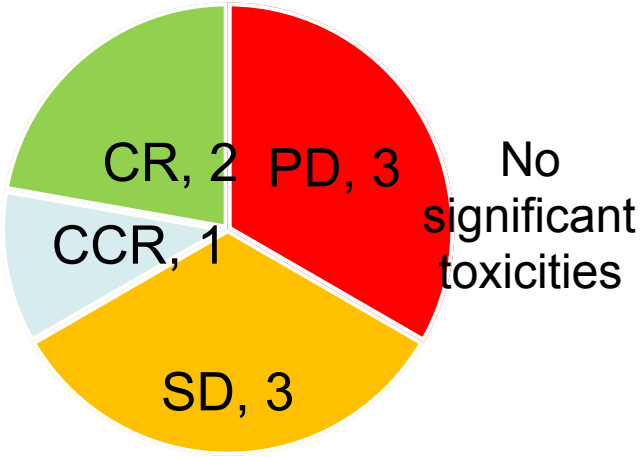


- Phase 1 trial
- $CD30^+$ malignancies
  - Active disease
  - Failure of standard treatment
- Dose escalation by continual reassessment
  - 2×10^7 (DL1), 1×10^8 (DL2), 2×10^8 (DL3) CAR^+ cells/m^2
- Repeat infusions possible
- Off experimental therapy > 6 weeks
- No lymphodepleting chemotherapy prior to CART infusion

Previous CD30.CART trial summary

- Gender
  - 4 F
  - 5 M
- Diagnoses
  - HL
    - NS (6)
    - MC (1)
  - ALCL
    - ALK$^+$ (1)
    - ALK$^-$ (1)
- Age
  - Median 30 yrs (range 17-69 yrs)
- Prior treatments
  - Median 5 regimens (range 3-9)
  - Brentuximab vedotin used in 7 patients
  - HDT/ASCT used in 6 patients

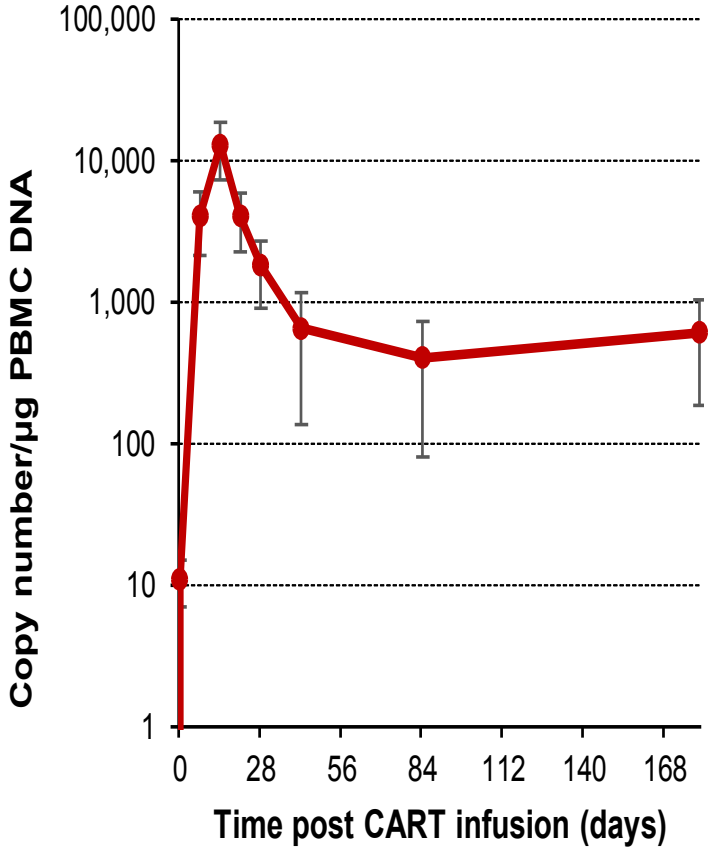




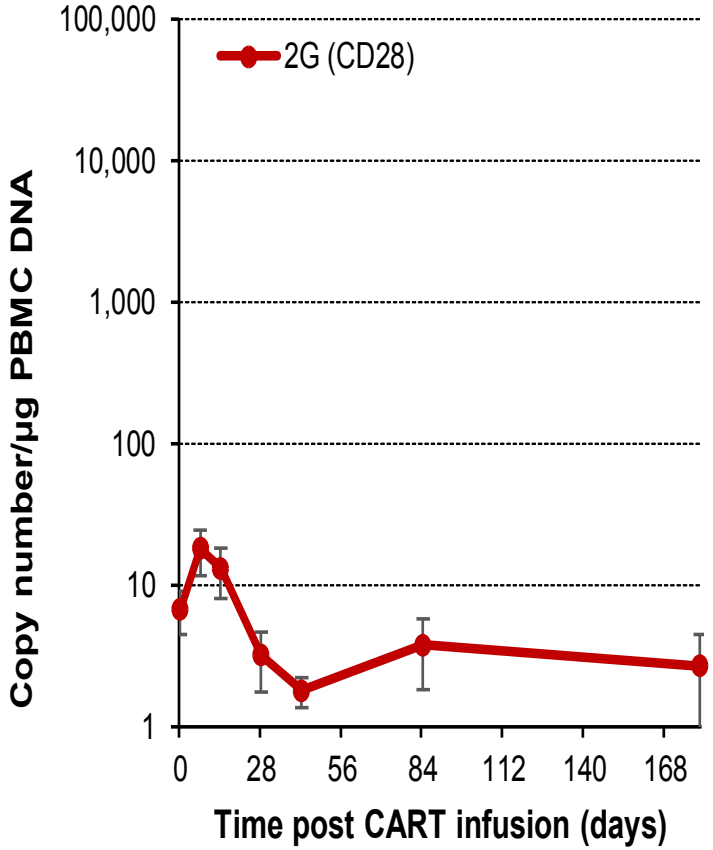
(Ramos *et al.*, J Clin Invest 2017)

Lymphodepleting chemotherapy improves CAR-T expansion

Cyclophosphamide + fludarabine

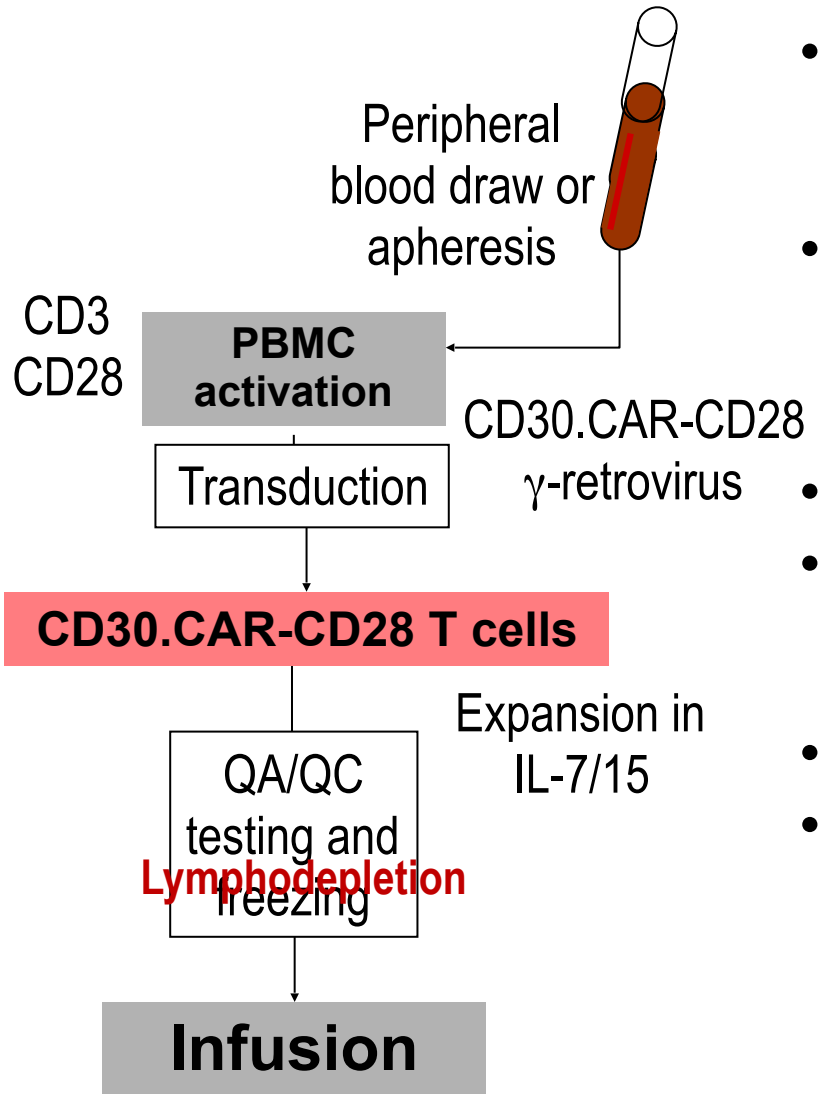


No preceding chemotherapy



(Ramos et al., Mol Ther 2018)

RELY-30 trial (NCT02917083)

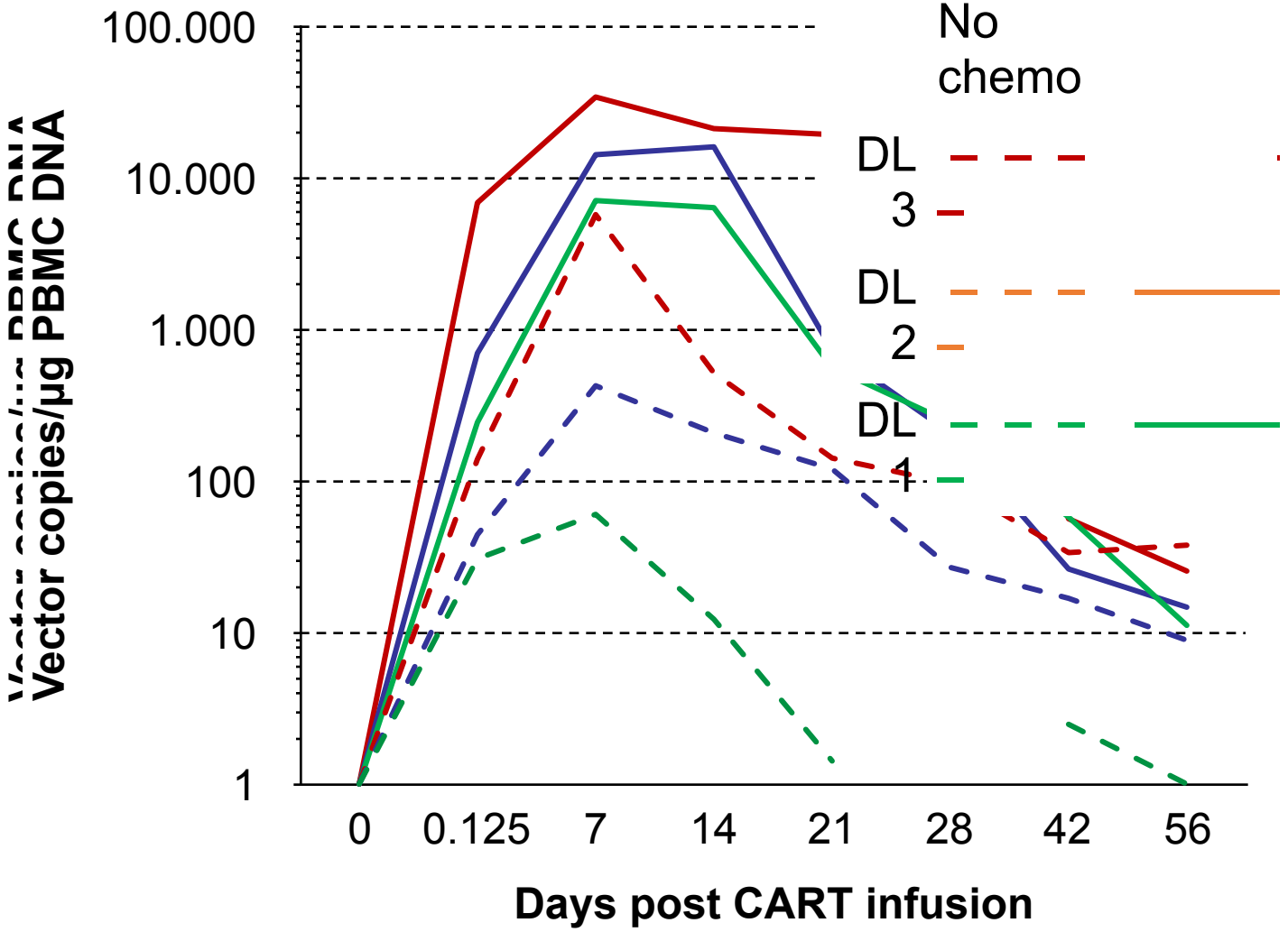


- Phase 1 trial
- $CD30^+$ malignancies
  - Active disease
  - Failure of standard treatment
- Dose escalation by continual reassessment
  - 2×10^7 (DL1), 1×10^8 (DL2), 2×10^8 (DL3) CAR^+ cells/m^2
- Single infusion
- Cyclophosphamide and fludarabine prior to CART infusion
- Primary objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 6

RELY-30 patients characteristics

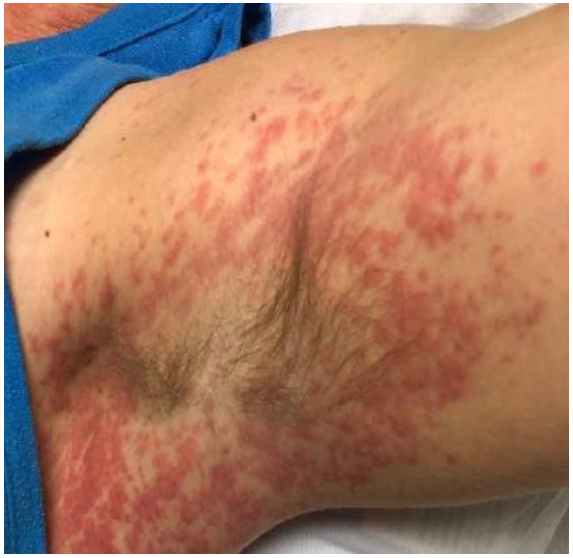
- Gender
  - 7 F
  - 8 M
- Diagnoses
  - HL
    - NS (14)
    - “NOS” (1)
- Age
  - Median 30 yrs (range 17-69 yrs)
- Prior treatments
  - Median 5 regimens (range 2-9)
  - PD-1 inhibitor in 14 patients
  - Brentuximab vedotin in 12 patients
  - HDT/ASCT in 10 patients

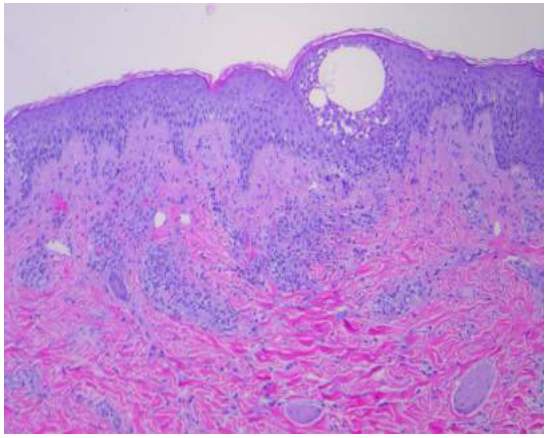
CD30.CART expansion is increased by lymphodepleting chemotherapy

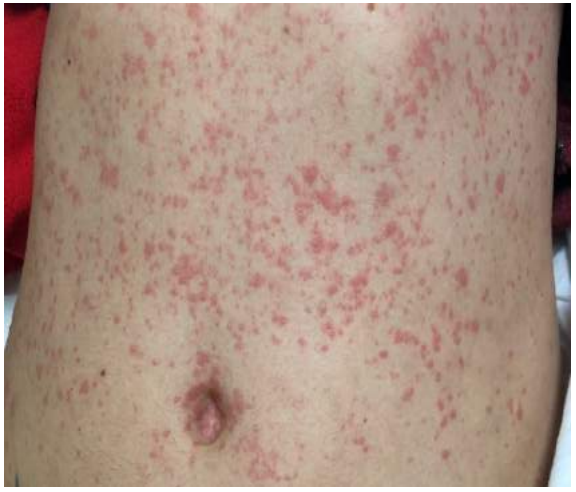


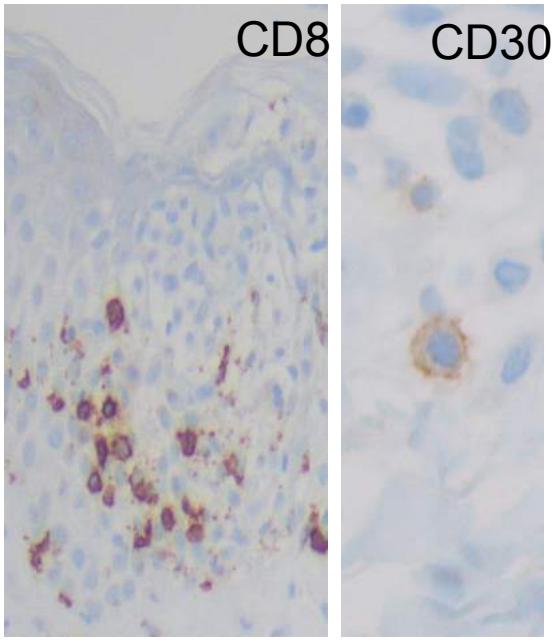
CD30.CART toxicities (patient #9)

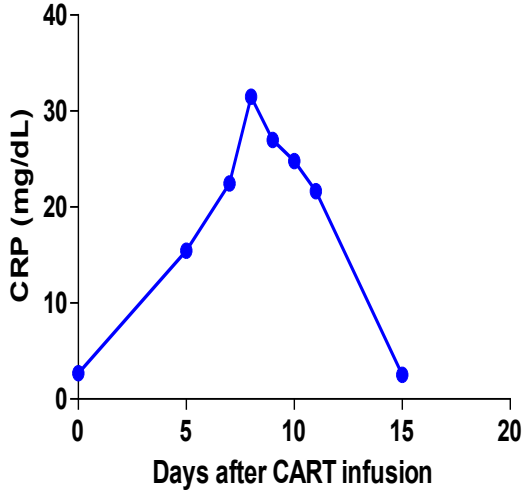
- Mild CRS (grade 1)
- Maculopapular rash
- Transient cytopenias, nausea, alopecia (related to chemo)





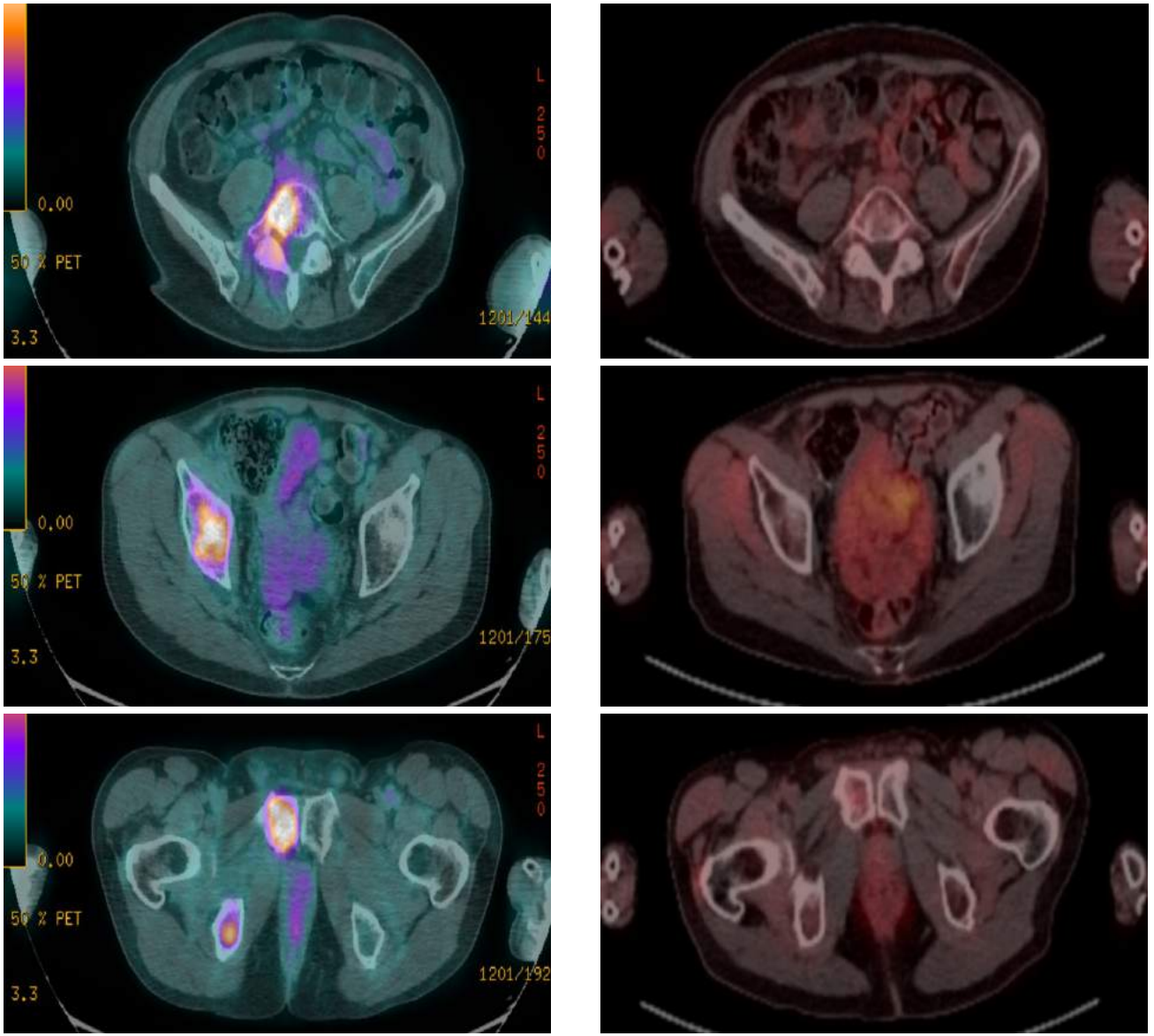






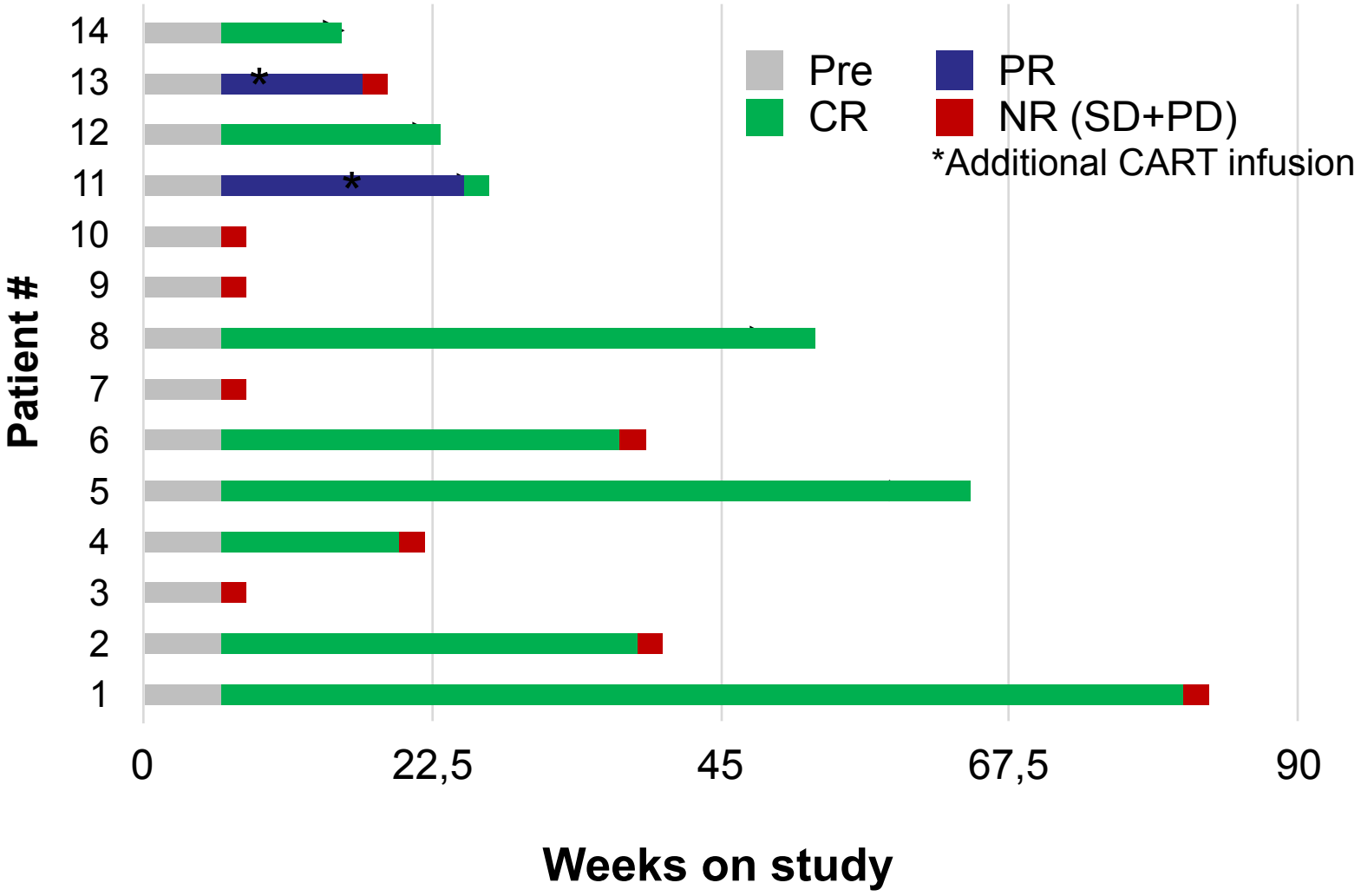
CD30.CART tumor response (patient #1)

Pre-infusion



6 wks post-infusion

RELY-30 outcomes



Conclusions

- Adoptive transfer of CD30.CAR-T cells is safe
- Expansion and persistence is dose-dependent
- Responses are improved with lymphodepleting chemotherapy
- Increased expansion may be associated with CRS and limited skin toxicity
- Follow-up is limited: response duration unknown
- Expansion cohorts are planned

Linfoma di Hodgkin ICML 2019

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INVESTIGATING SAFETY AND PRELIMINARY EFFICACY OF AFM13 PLU PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER BRENTUXIMAB VEDOTIN FAILURE

S.M. Ansell[1] | N.L. Bartlett[2] | R.W. Chen[3] | A. Herrera[3] | E. Domingo-Domenech[4] | A. Mehta[5] | A. Forero-Torres[5] | R. Garcia-Sanz[6] | P. Armand[7] | S. Devata[8] | A. Rodriguez Izquierdo[9] | I.S. Lossos[10] | C.B. Reeder[11] | T. Sher[12] | C. Choe-Juliak[13] | K. Prier[14] | S.E. Schwarz[14] | A. Strassz[14] | L. Alland[13]

Background: AFM13 is a bispecific, tetravalent NK cell-engaging antibody construct binding to CD30 on Hodgkin Lymphoma (HL) cells and CD16A on NK cells [1]. Pembrolizumab is a PD-1 blocking antibody that induces high response rates in patients (pts) with relapsed or refractory HL (RRHL) [2]. AFM13 has shown clinical activity in pts with RRHL in a Phase 1 study [3]. Preclinical data of the combination of AFM13 with PD-1 inhibition suggest synergism [4].

Conclusions: The combination of AFM13 and pembrolizumab is well-tolerated with most AEs mild to moderate in nature. The ORR of 88% compares favorably to the historical data of pembrolizumab in a similar RRHL population, with the CR rates of 42% and 46% by local and independent assessment, respectively, approximately doubling that of pembrolizumab (CR rates 22-25%) [2].

Options for first line therapy of Hodgkin lymphoma

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Overall results of therapy

≥90% cures with first line therapy
(90-95% in early stages, 85-90% in advanced disease)

More than 85% alive at 10 years

Recent trials show more deaths from other causes than Hodgkin lymphoma: disease control and survival are not the same thing

Primary focus of research is to

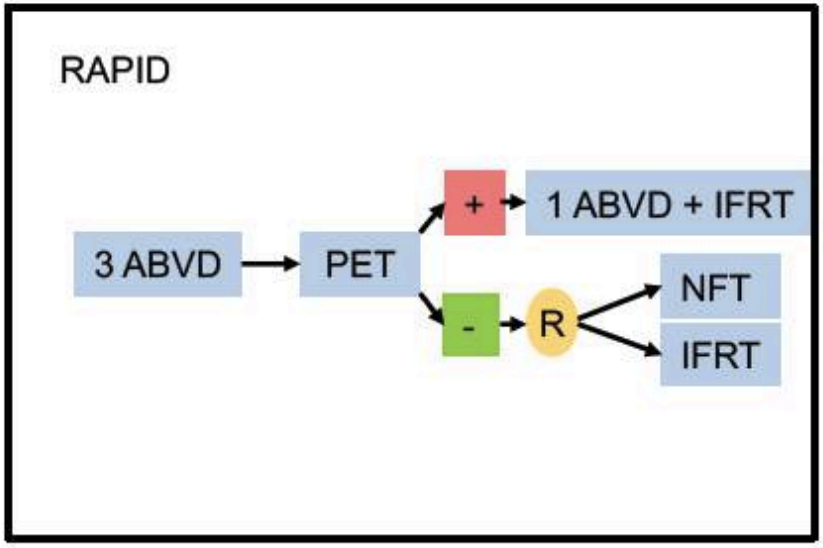
- improve this result
- minimise toxicity

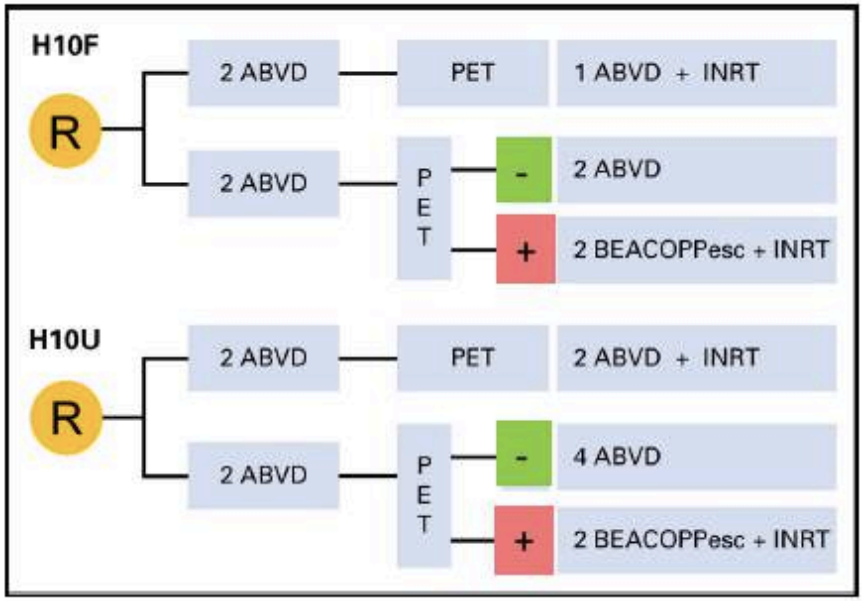
Some questions in 2019

- How to select patients with early stage disease for combined modality or chemotherapy alone?

- How to select first line chemotherapy for patients with advanced stage disease?
  - Whether to add brentuximab vedotin?
  - Will the anti-PD1 antibodies be helpful ?

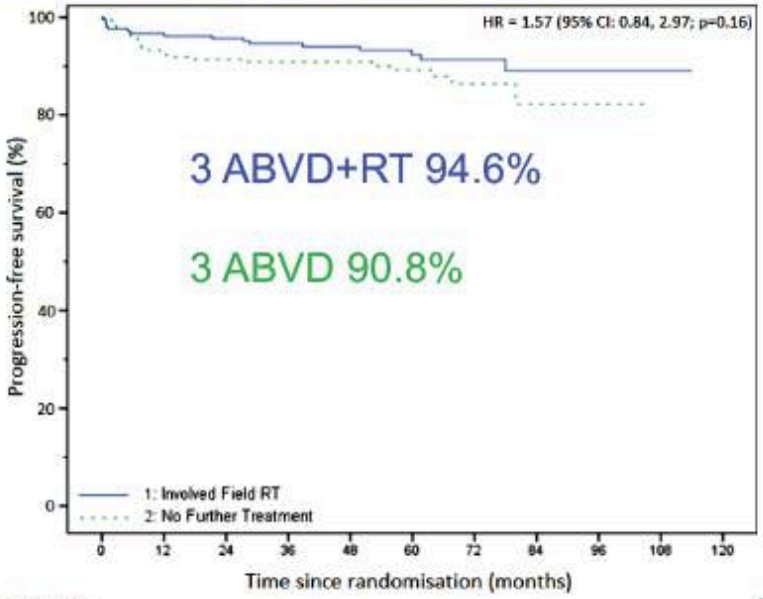
PET-driven studies in early stage disease





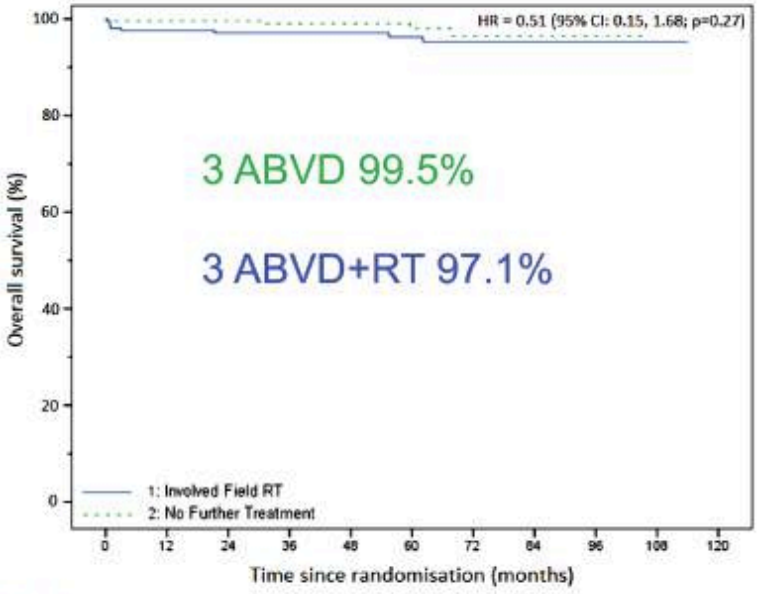
RAPID: Progression-free and overall survival at 3 years:
Interim PET negative

Intention to treat analysis



Number at risk:

IFRT	209	198	188	170	134	99	57	30	13	2	0
NFT	211	190	181	153	129	89	50	14	5	0	0

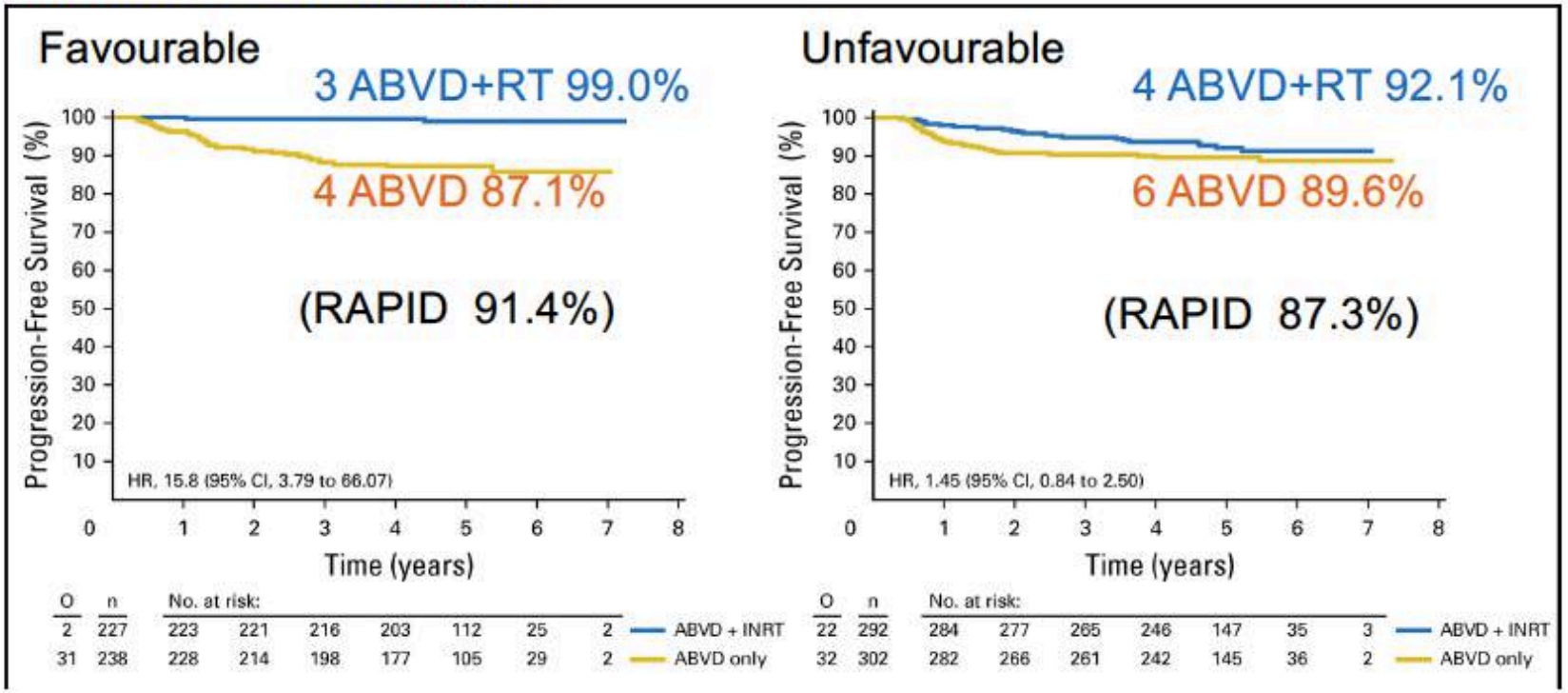


Number at risk:

IFRT	209	200	191	175	139	103	60	34	13	2	0
NFT	211	204	196	167	140	97	56	18	6	0	0

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

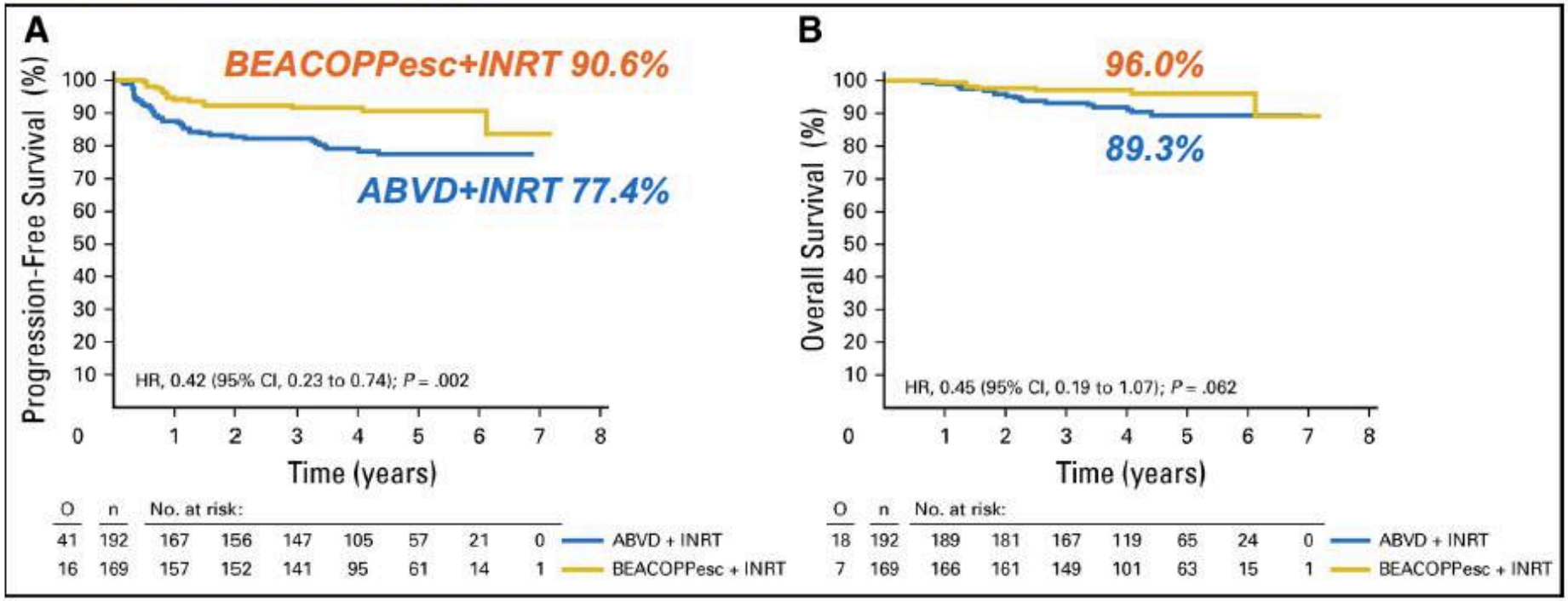
H10: Progression-free survival at 5 years:
Interim PET negative
Intention-to-treat analysis



Marc Andre et al., J Clin Oncol 2017: 35(16):1786-1794

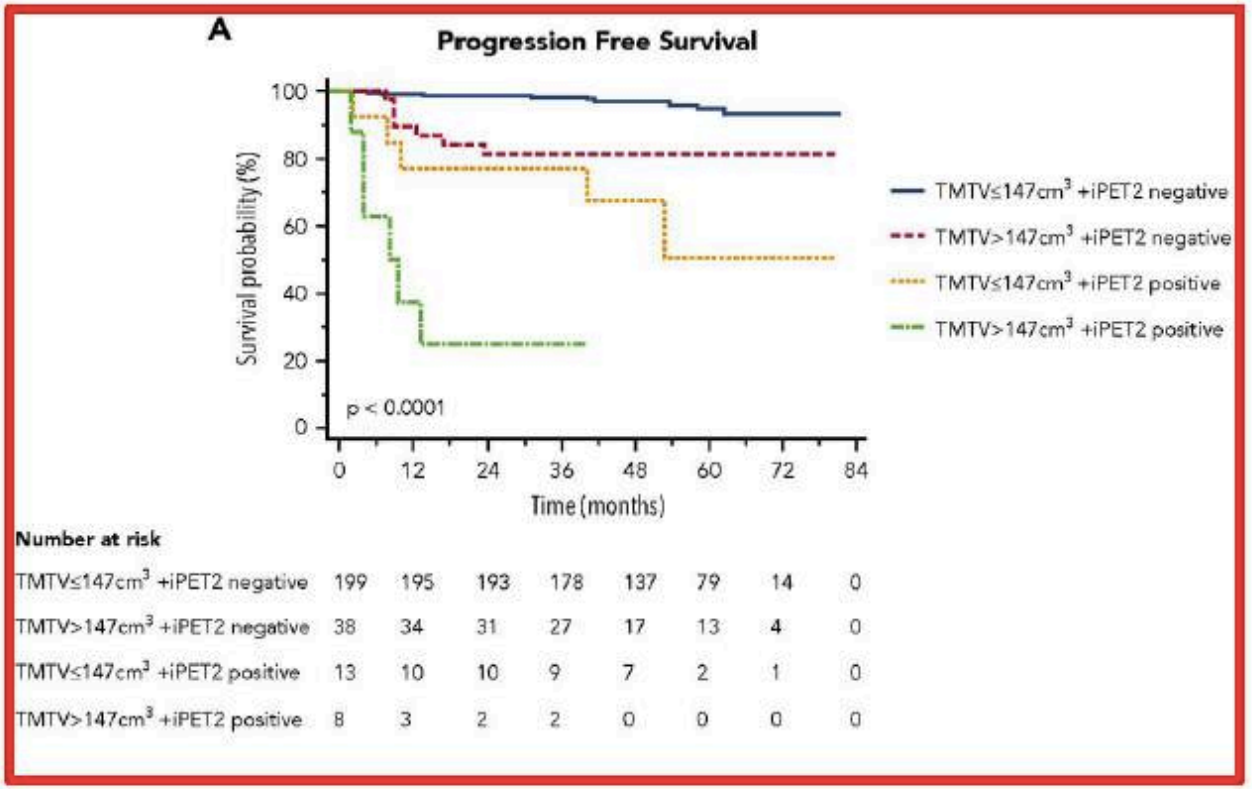
H10: Interim PET+:
Progression-free and overall survival at 5 years

Intention-to-treat analysis



Marc Andre et al., J Clin Oncol 2017: 35(16):1786-1794

PFS according to TMTV and early PET response



Number at risk

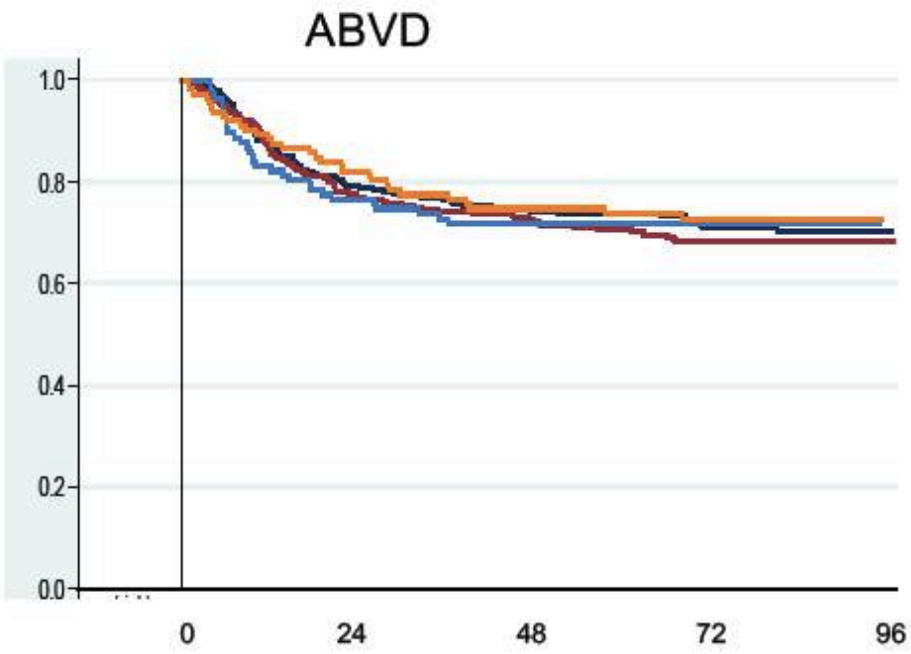
TMTV≤147cm³ +iPET2 negative	199	195	193	178	137	79	14	0
TMTV>147cm³ +iPET2 negative	38	34	31	27	17	13	4	0
TMTV≤147cm³ +iPET2 positive	13	10	10	9	7	2	1	0
TMTV>147cm³ +iPET2 positive	8	3	2	2	0	0	0	0

Anne-Ségolène Cottereau et al. Blood 2018;131:1456-1463

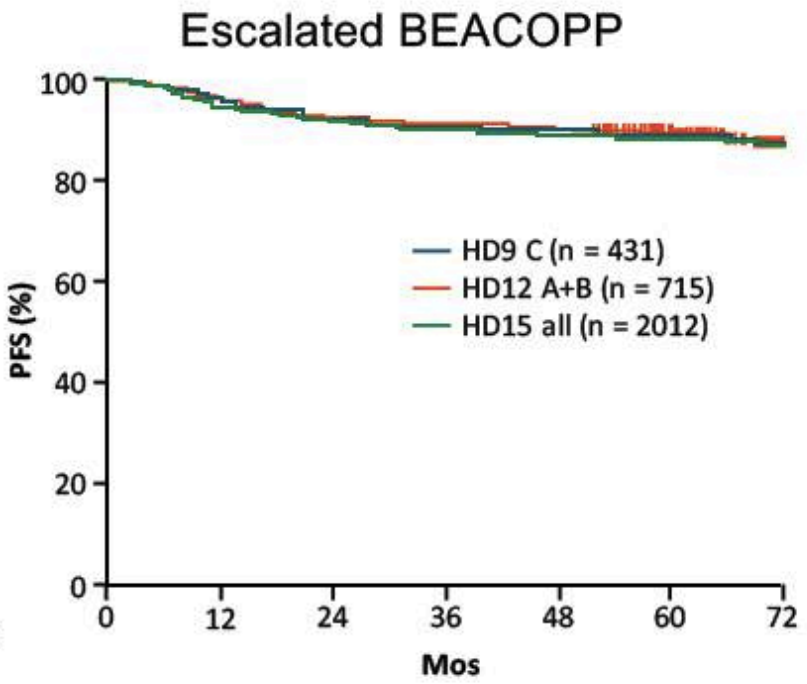
Putting the evidence together: Early stage disease

- Combined modality therapy is standard, but...
- Therapy adapted by iPET after 2 ABVD is reasonable
- Chemotherapy alone approaches can be considered:
  - For people with low MTV at presentation (no bulk)
  - For people at high risk of second cancer/cardiac damage from IFRT
  - If the iPET after 2 ABVD is negative (DFPS 1-3)
- Escalation to escBEACOPP before INRT should be considered:
  - For those with an iPET DFPS of 5
  - For those with iPET DFPS 4 if the MTV was high at presentation

Standard of care in advanced disease?



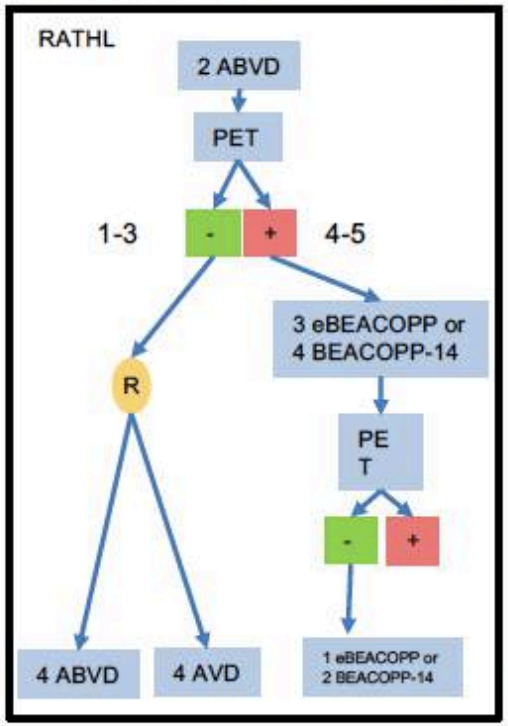
Johnson, P. J Clin Oncol. 2005; 23:9208



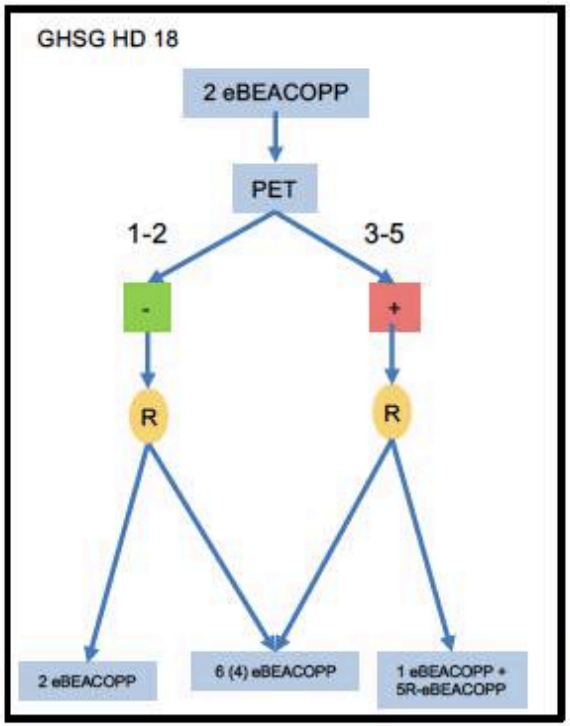
Engert, A. Lancet. 2012;379:1791.

Randomised trials to test the role of interim FDG-PET
Advanced stage disease

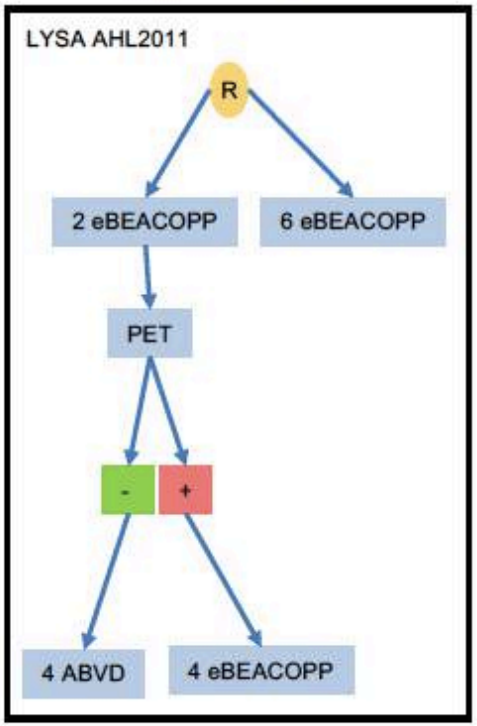
Johnson P. et al., 2016
New Engl J Med,. 374:2419-29



Borchmann P et al., 2017
Lancet (17): 32134-73



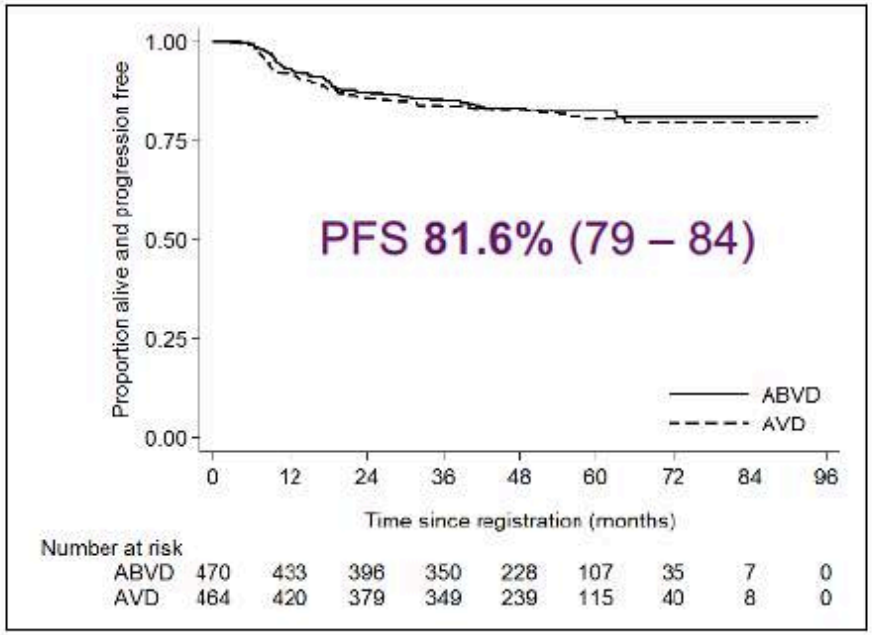
Casasnovas RO, 2019. Lancet
Oncology 20:202-215



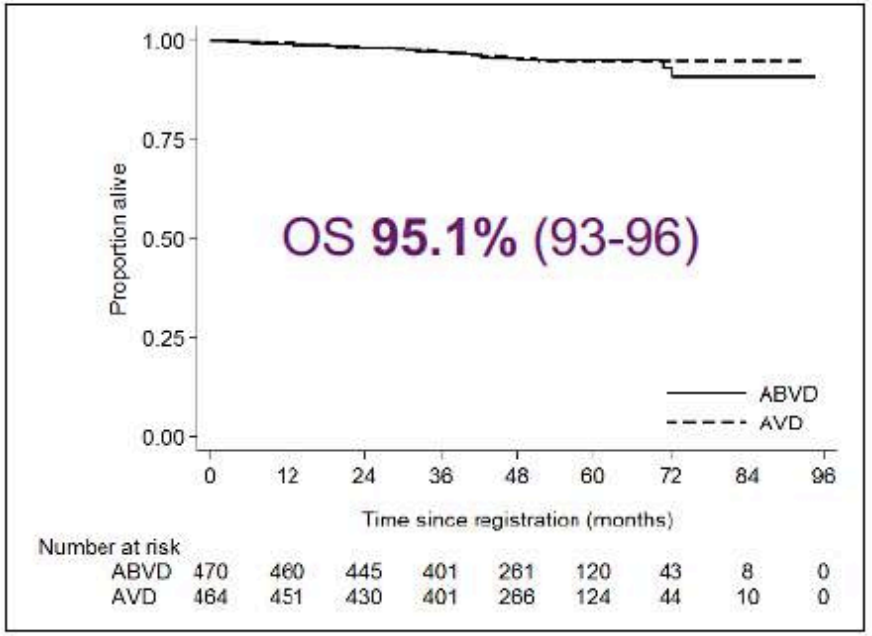
RATHL: Progression-Free and Overall Survival at 5 years for interim PET-negative patients

(median follow up 52 months)

PFS

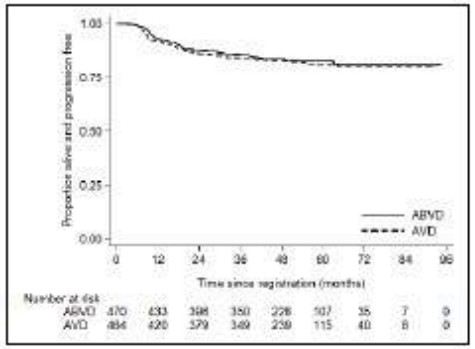


OS

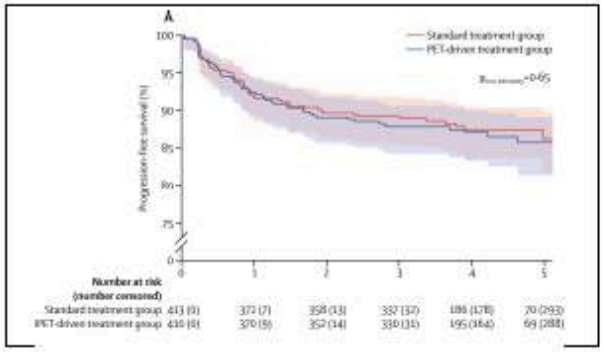


Control of lymphoma after de-escalation in PET-negative groups

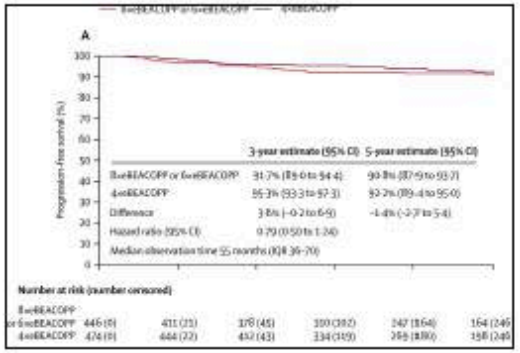
RATHL **5 Year PFS 81.6%**



LYSA **5 Year PFS 89.4% vs 88.4%**



HD18 **5 Year PFS 91.7 vs 90.8%**



N Engl J Med, 2016. 374:2419-29
Lancet Oncol 2019. 20:202-215
Lancet 2017; 6736(17)32134-7

Choice of initial chemotherapy: advanced disease

- Initial therapy with escBEACOPP:
  - Improves negative predictive value of iPET, especially in high risk disease
  - Results in higher PFS...
  - ...but influence on OS is less clear, and it is more toxic
- De-escalation after negative iPET retains efficacy and *should* reduce morbidity
  - no RT
  - no bleomycin
  - reducing to ABVD
  - less cycles of BEACOPP
- Escalation ABVD -> BEACOPP appears to improve disease control and may improve survival

Can we do better? Probably, yes

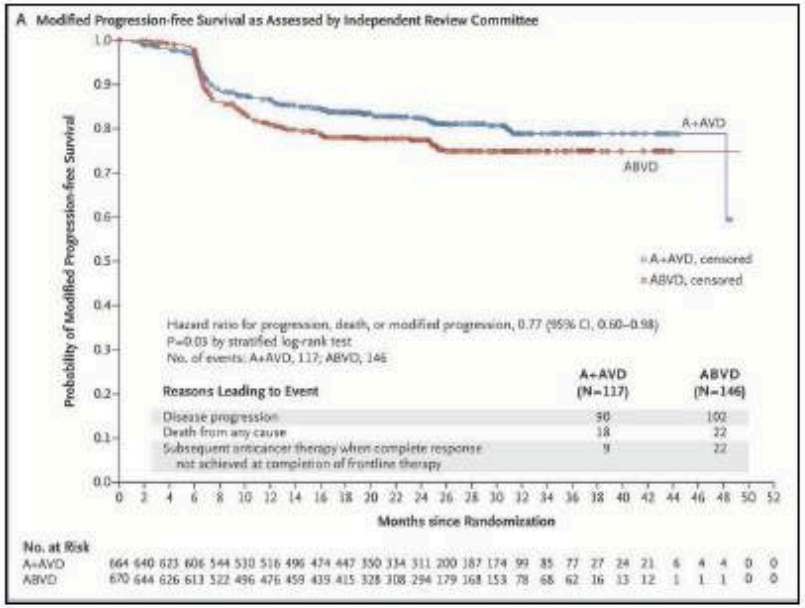
1. The results with ABVD in patients with high risk disease are less good, even after a negative iPET

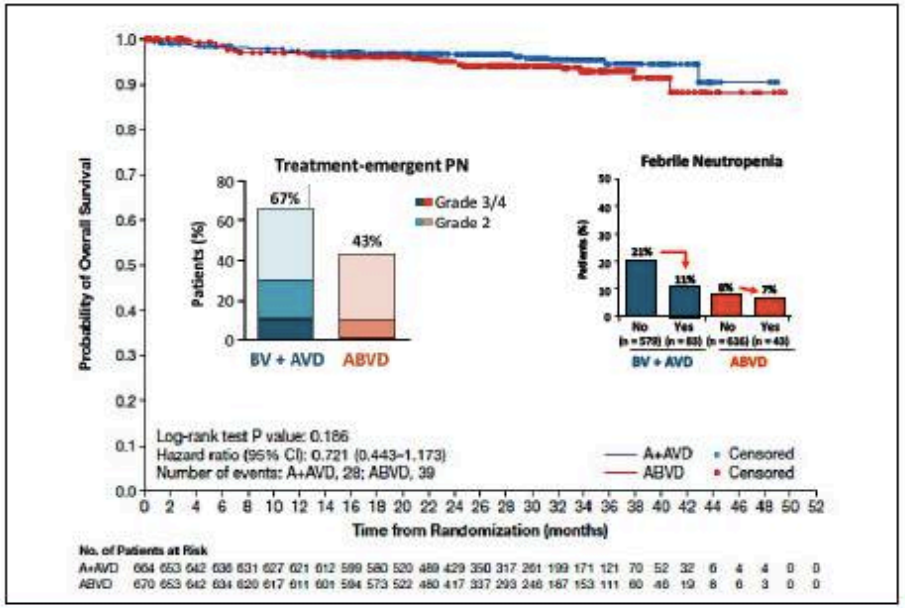
2. We could find better forms of initial therapy

3. We could find better approaches for those with positive iPET

ECHELON-1 results

Modified PFS and OS with median follow up 25 months

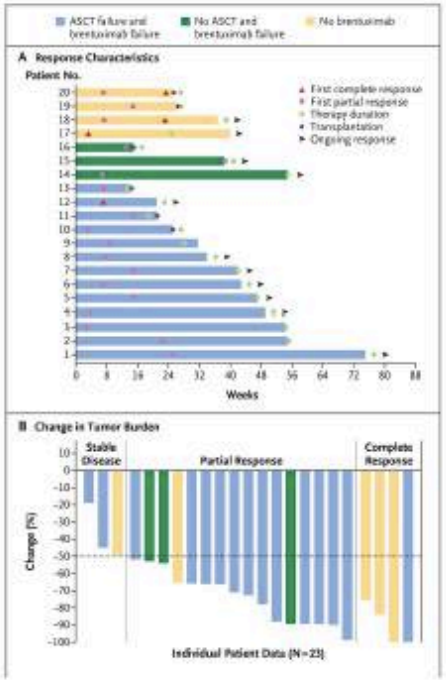




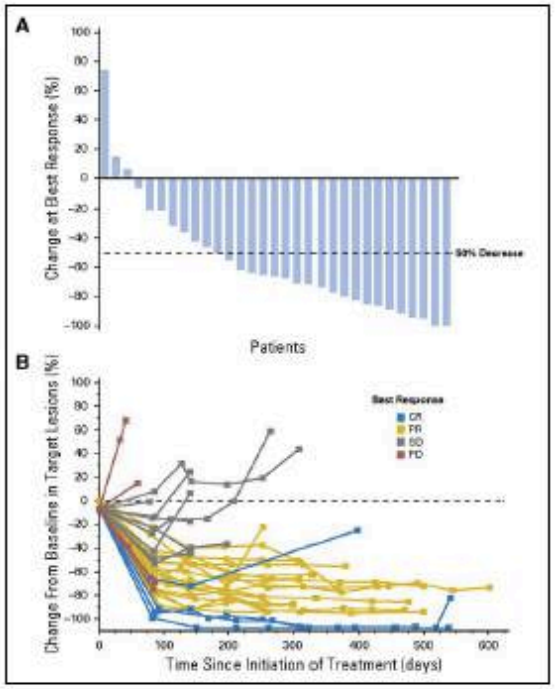
Baseline Ann Arbor stage			
Stage III	40/237 (16.9)	43/246 (17.5)	0.92 (0.60–1.42)
Stage IV	77/425 (18.1)	102/421 (24.2)	0.71 (0.53–0.96)

Connors JM et al. N Engl J Med. 2018 Jan 25;378(4):331-344

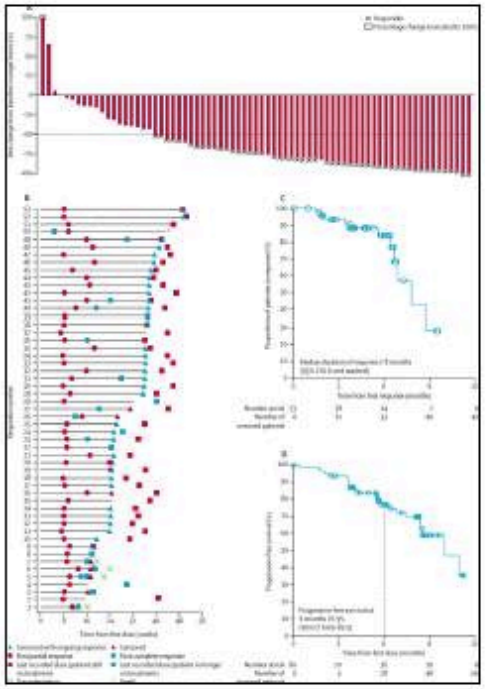
Activity of Nivolumab & Pembrolizumab in relapsed/refractory disease



Ansell SM et al. N Engl J Med 2015;372:311-319

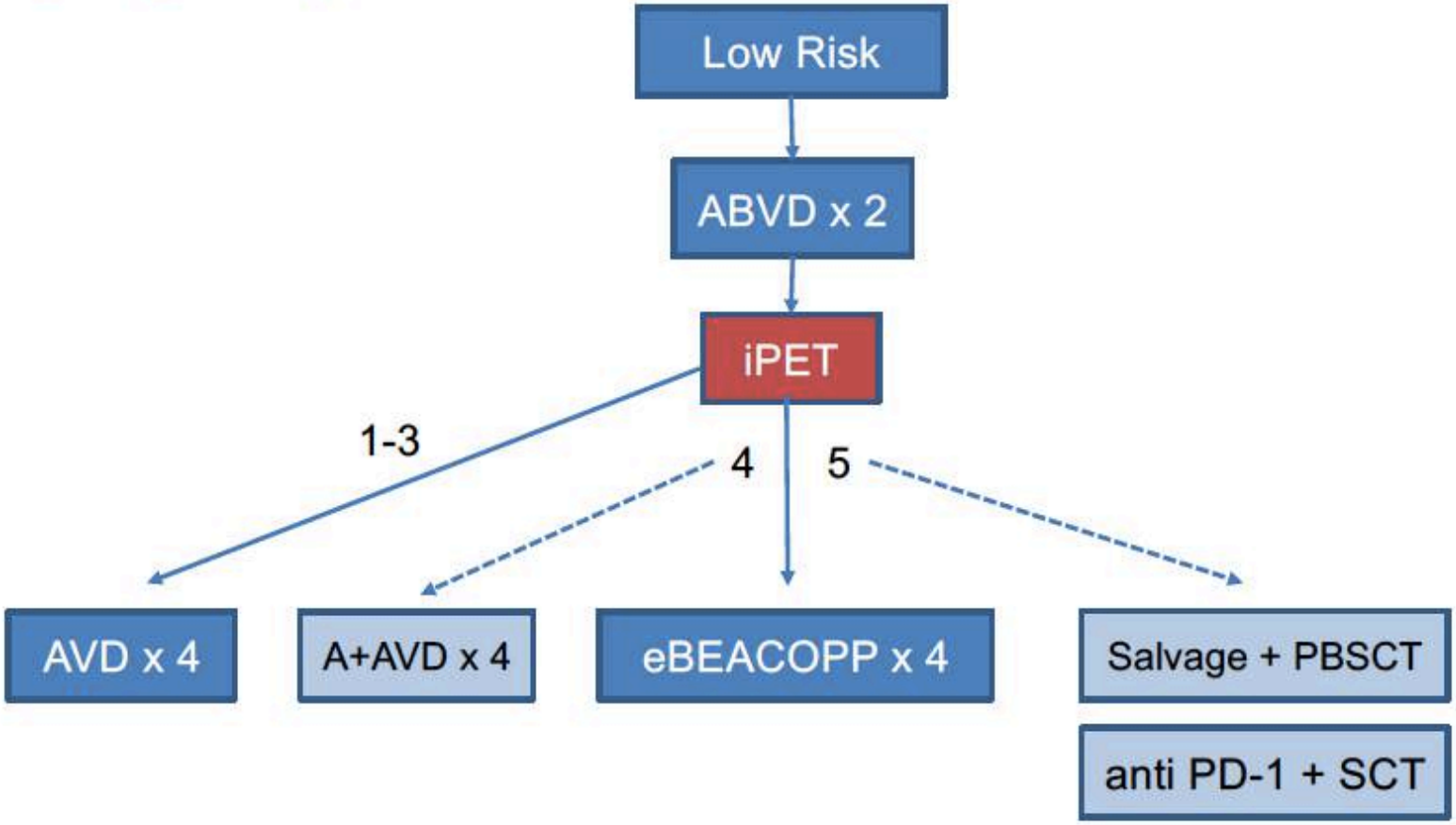


Armand et al. J Clin Oncol. 2016;34:3733-3739



Younes et al, Lancet Oncology 2016, 17: 1283–1294

Trying to synthesise the current data



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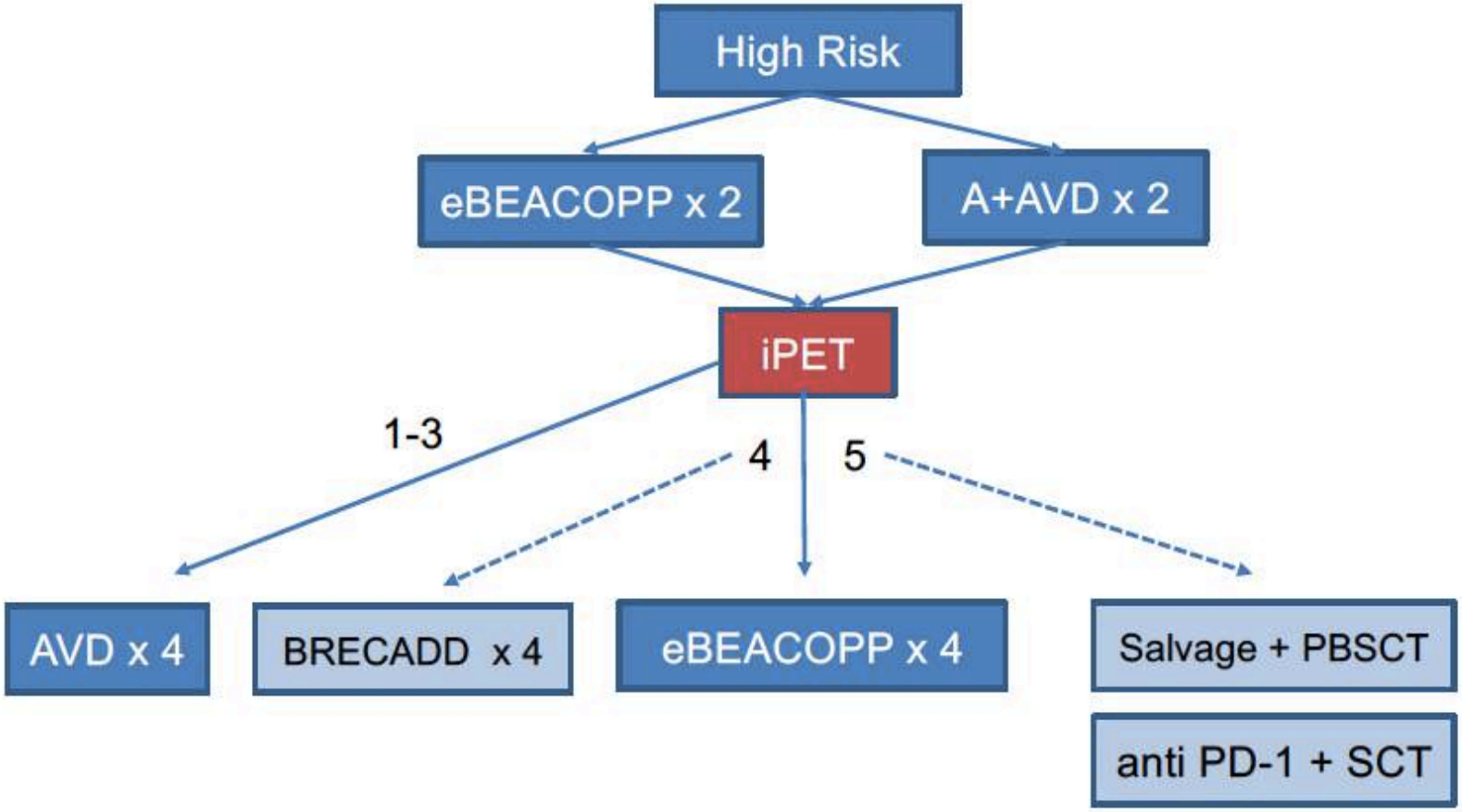
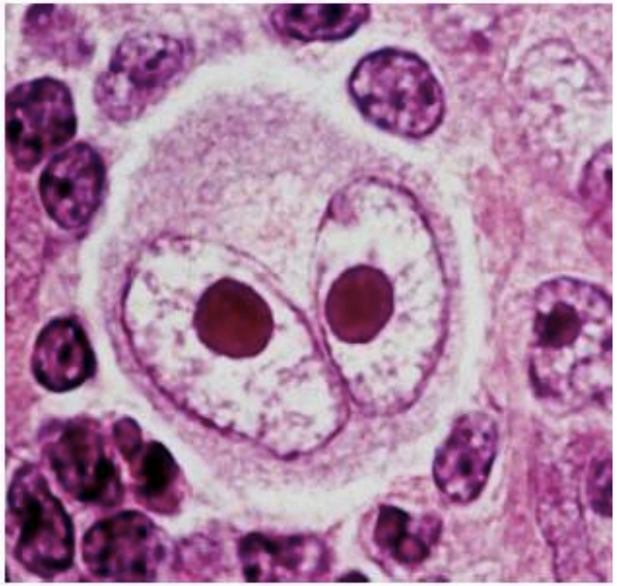


DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Treating Hodgkin Lymphoma in the New Millennium: Relapsed and Refractory Disease



June 19, 2019

Ann LaCasce, MD, MMSc

PET after salvage predicts of PFS in ASCT

n	PET – PFS		PET + PFS		ref
105	4 yr PFS	77%	4 yr PFS	33%	Moskowitz BJH 2010
153	5 yr PFS	75%	5 yr PFS	31%	Moskowitz Blood 2010
97	4 yr PFS	80%	4 yr PFS	29%	Moskowitz Blood 2012
111	5 yr PFS	79%	45yr PFS	31%	Devillier Hematologica 2012

CR rates 50-70% with salvage chemotherapy

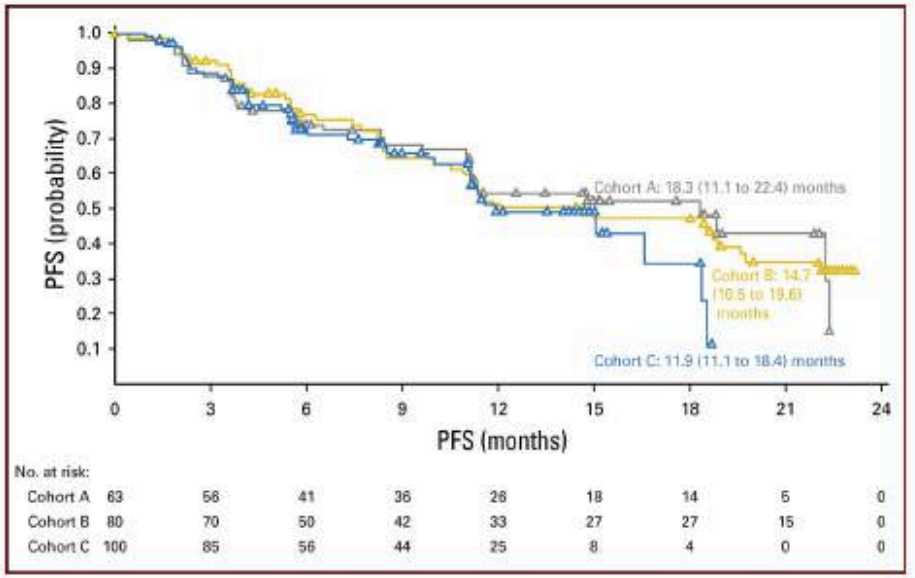
Regimen	n	CR	ref
ICE	97	60%	Moskowitz Blood 2012
DHAP	102	21% (CT)	Josting Ann Onc 2002
ESHAP	82	50%	Labrador Ann Hematol 2014
BeGV	59	73%	Santoro Blood 2018

BV containing salvage regimens with high CR rates

Regimen	n	CR	2 year PFS	ref
BV augmented ICE	45	27% BV 76% total	80% (EFS)	Moskowitz Lancet Onc 2015
BV bendamustine	82	73%	63%	LaCasce Blood 2018
BVDHAP	12	92%	100%	Hagenbeek Hematologica 2019
BV ESHAP	66	70%	71%	Garcia-Sanz Ann Onc 2019

Nivolumab approved in R/R HL after ASCT and BV

	Cohort A N=63 (BV naïve)	Cohort B N=80 (BV s/p ASCT)	Cohort C N=100 (BV before +/- after ASCT)
ORR	65%	68%	73%
CR	29%	13%	12%
PR	37%	55%	61%
SD	24%	21%	15%
PD	11%	8%	10%

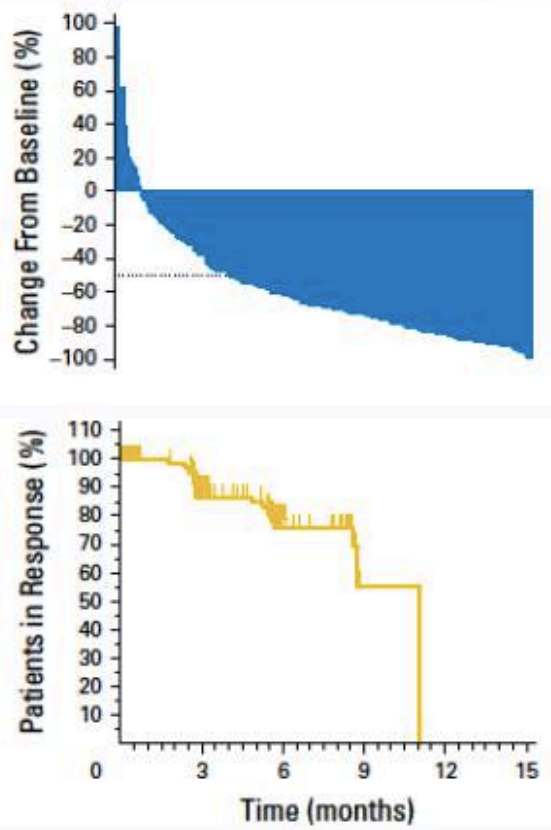


Armand et al J Clin Oncol 2017

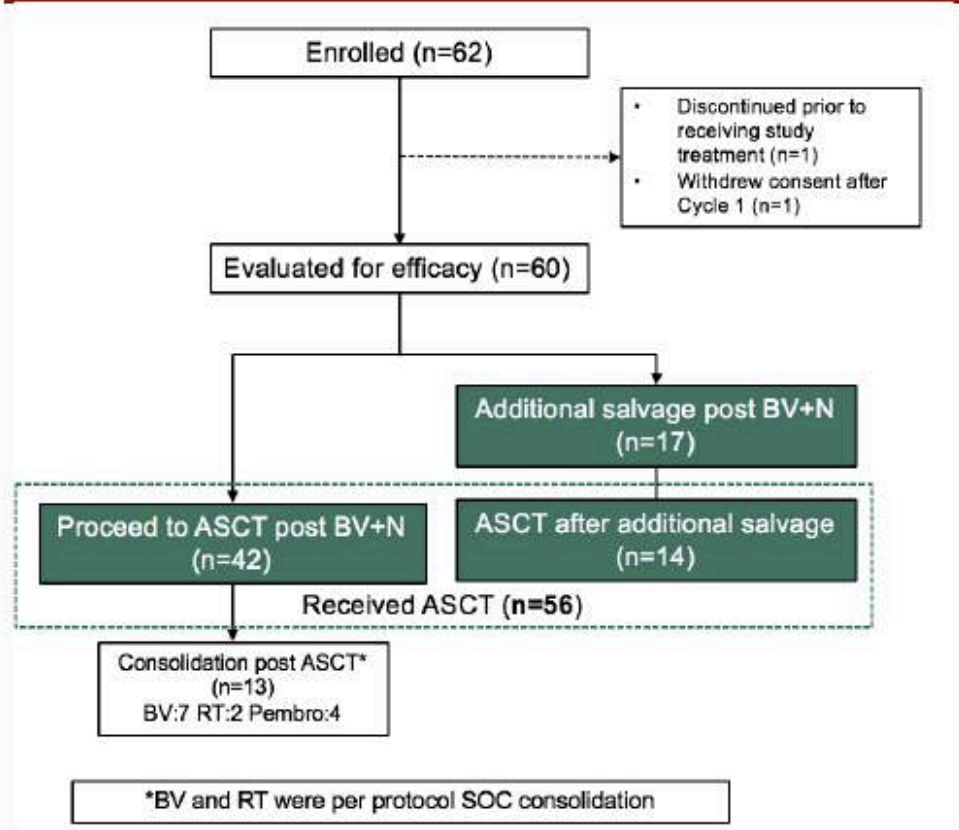
Pembrolizumab approved in relapsed/refractory HL after 3 prior regimens

	Cohort 1 (ASCT/BV) N=69	Cohort 2 (ASCT ineligible) N=81	Cohort 3 (ASCT no BV post) N=60
ORR	74%	64%	70%
CR	22%	25%	20%
PR	52%	40%	50%
SD	16%	12%	17%
PD	7%	21%	13%

Chen et al. JCO 2017



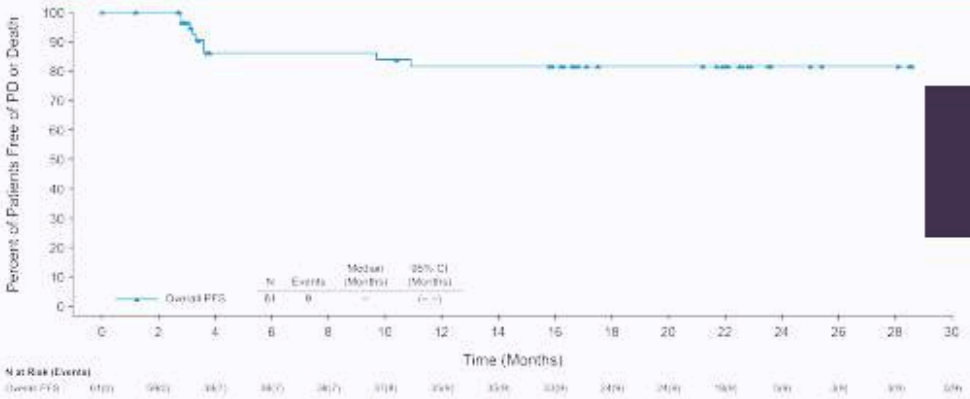
Brentuximab vedotin plus nivolumab in first relapse cHL



80% ORR 61% CR

Herrera et al. ASH 2018 #1635

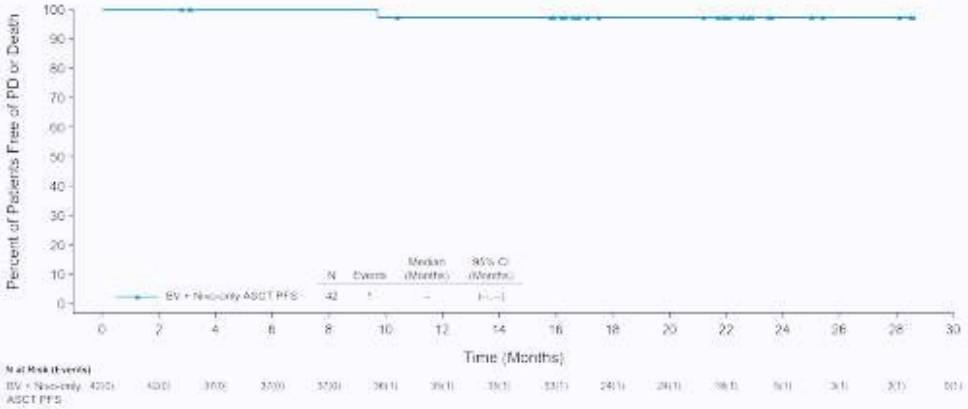
Patients who proceed to ASCT with excellent PFS



all patients: 82% at 21 m

97% relapsed 65% 1° ref

direct to ASCT in CR: 97% at 21 m



Herrera et al. ASH 2018 #1635

Grazie per l’attenzione