Hodgkin lymphoma

New options in patient management

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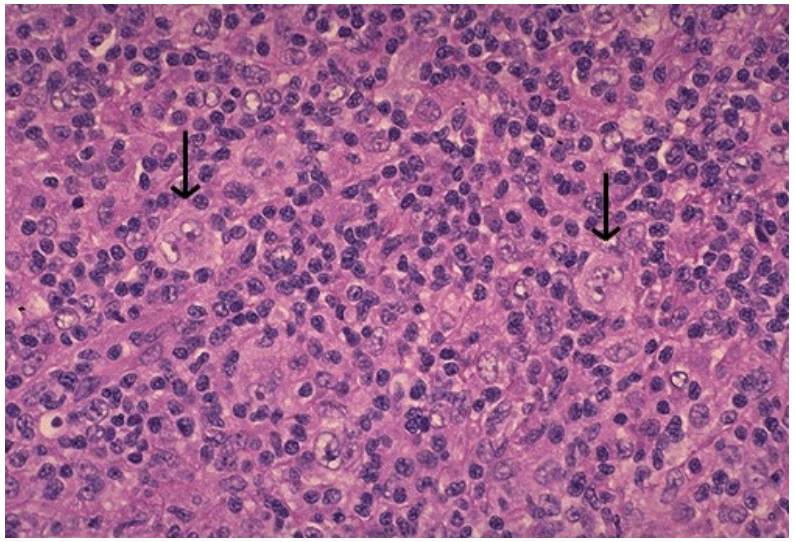
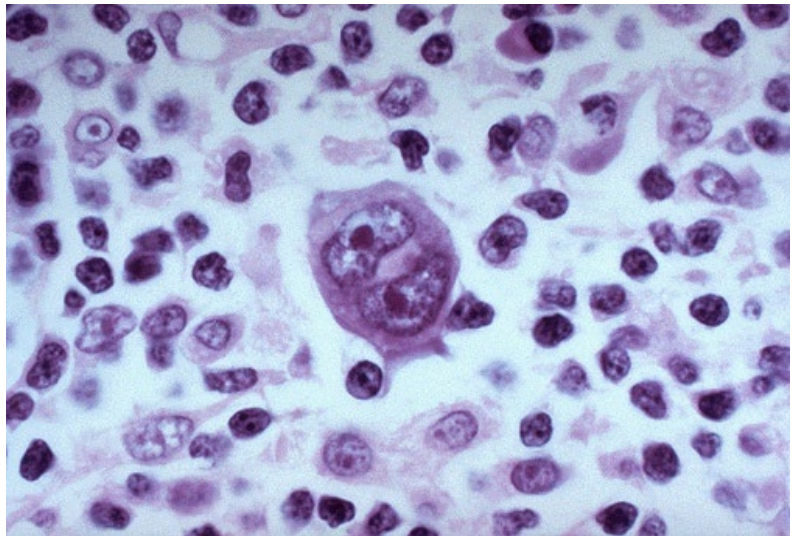
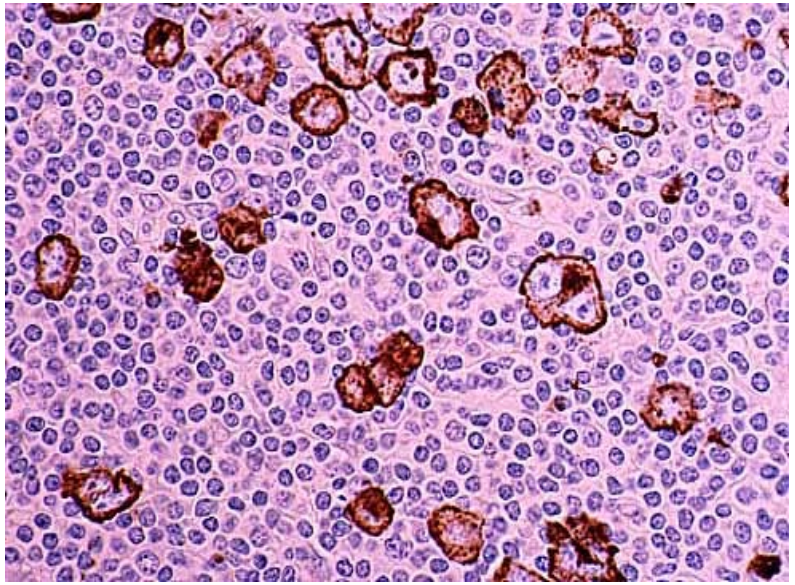
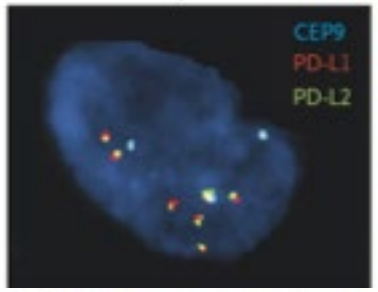
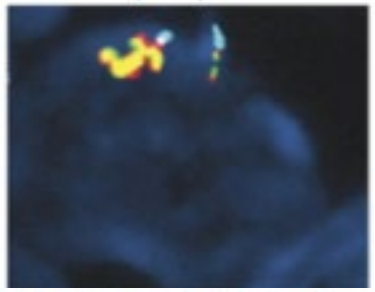
Pathology of Hodgkin Lymphoma

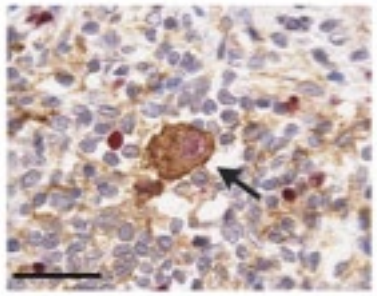


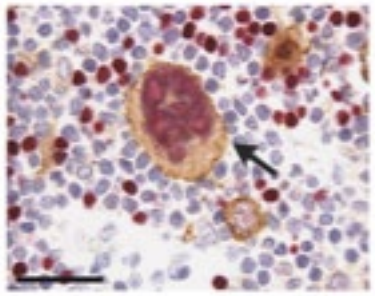












Risk Factors for Early-Stage Hodgkin lymphoma

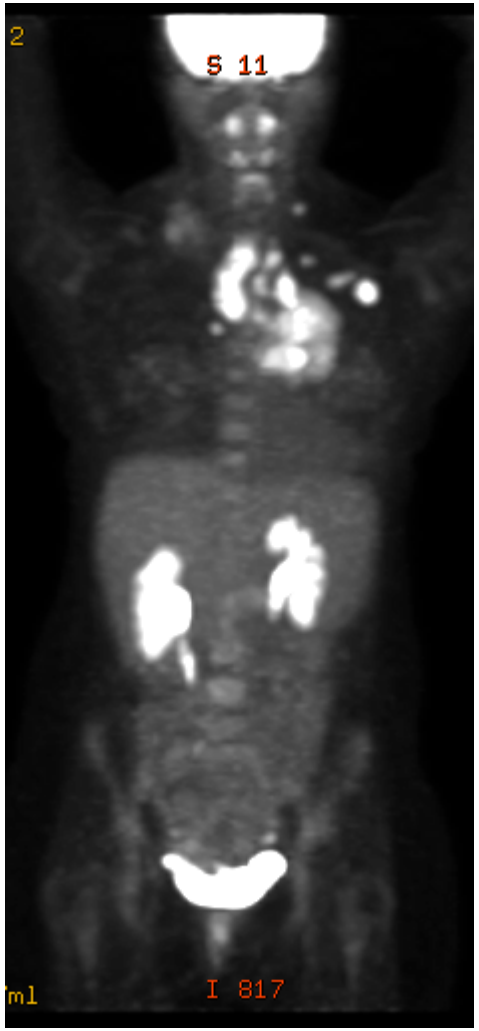


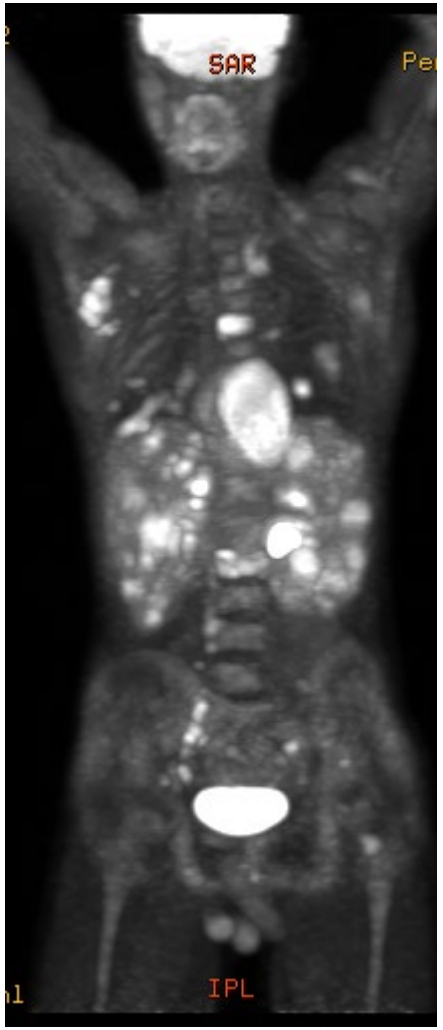
Table 1 | Definition of early stage unfavourable HL depending on the study groups*

Risk factors	EORTC	GHSG	NCIC/ECOG	NCCN 2010
Large mediastinal mass (>1/3)	Yes	Yes	No	Yes or >10 cm
Histology other than LP/NS	No	No	Yes	No
Age	≥50 years	No	≥40 years	No
Extranodal disease	No	Yes	No	>1 lesion
ESR ≥50 mm/h without B-symptoms or ≥30 mm/h with B-symptoms	Yes	Yes	Yes, if ≥50	Yes, if ≥50 or any B-symptoms
Number of nodal areas involved	≥4 nodal areas	≥3 nodal areas	≥4 nodal areas	≥3 nodal areas

*All patients must have stage I or II disease according to the Ann–Arbor classification (that is, involved lymph node regions only on one side of the diaphragm). Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin Lymphoma; LP, lymphocyte predominance; NCCN, National Comprehensive Cancer Network; NCIC, National Cancer Institute of Canada; NS, nodular sclerosis.

Nat Rev Clin Oncol 2012 Aug; 9(8): 450-459

Prognostic Factors in Advanced Stage Hodgkin Lymphoma



Age ≥ 45 years
Stage IV
Male sex
White blood count ≥ 15,000 cells/μl
Lymphocyte count < 600 cells /μl or <8%
Albumin < 4.0 g/dL
Hemoglobin < 10.5 g/dL

Hasenclever et al. NEJM 1998; 339: 1506-1514

Primary Therapy for Hodgkin Lymphoma

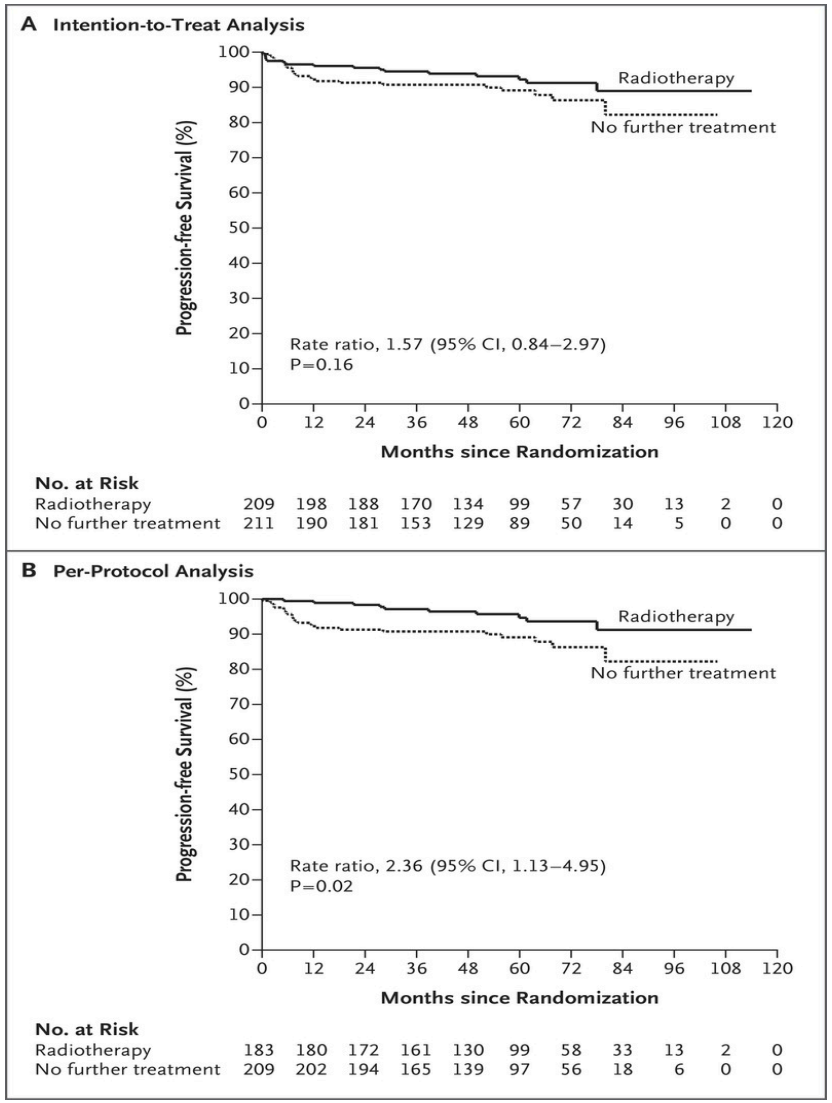
Early stage (I and IIA) favorable disease-
2 cycles of ABVD chemotherapy plus 20 cGy involved field radiotherapy

Early stage – interim PET negative – ABVD x 3 cycles

Early-stage unfavorable disease –
4 cycles of ABVD chemotherapy plus 30 cGy involved field radiotherapy

Advanced disease - Combination chemotherapy –
A+AVD, A(B)VD or escalated BEACOPP (high risk patients)

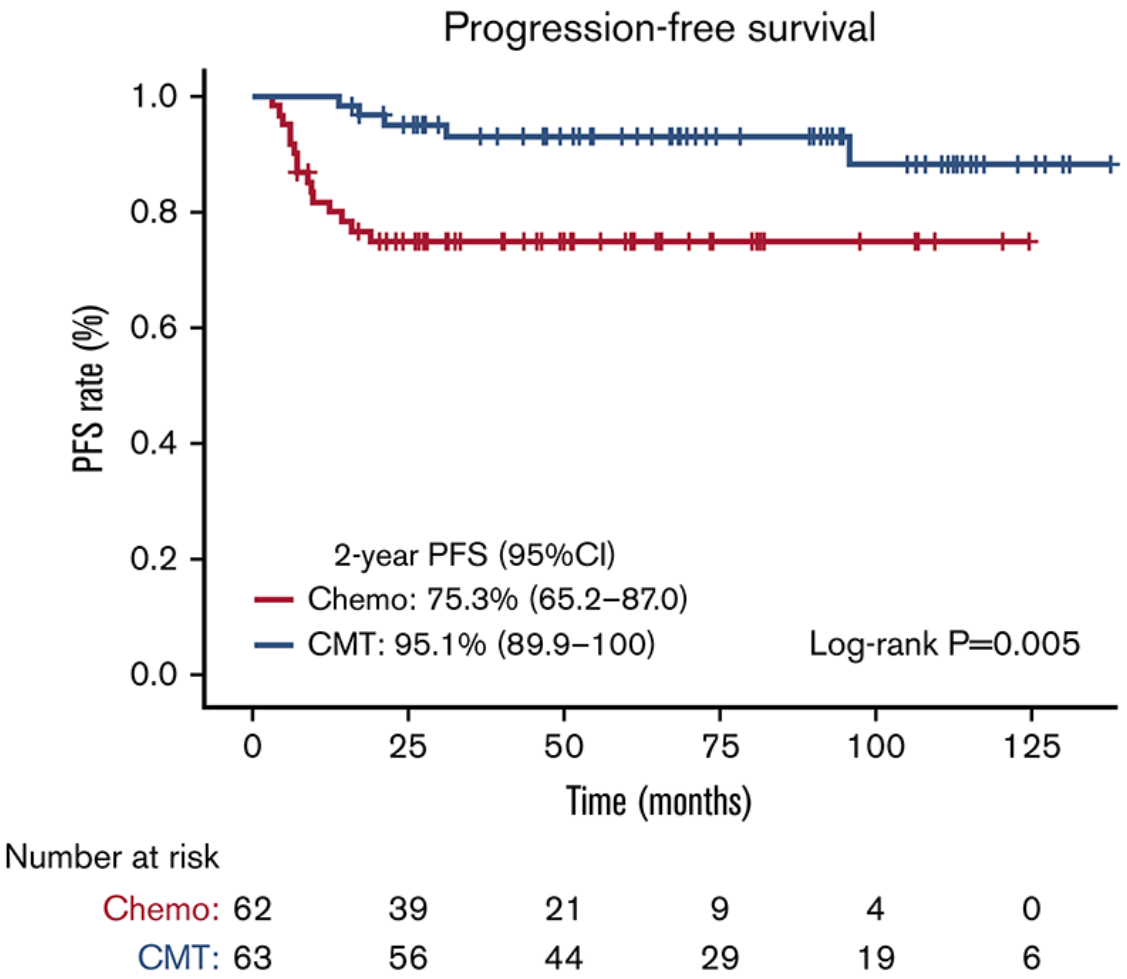
RAPID trial of PET-directed therapy for *early-stage* Hodgkin's lymphoma



PET negative –
ABVD x3 versus ABVD x3 + IFRT

Radford et al. N Engl J Med. 2015 Apr 23;372(17):1598-607.

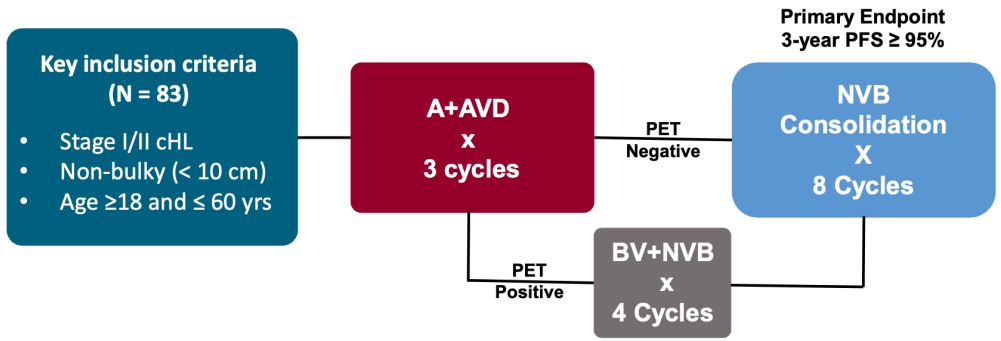
A real-world study of combined modality therapy for early-stage Hodgkin lymphoma: too little treatment impacts outcome

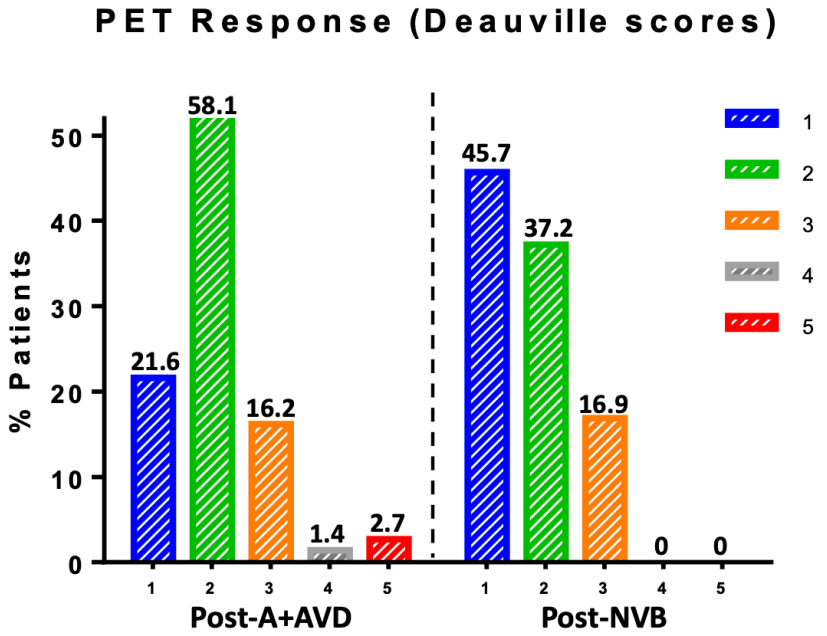


- In the real-world setting, CMT improved outcomes for patients with PET2-positive and unfavorable disease.
- Similar to clinical trials, favorable, non-bulky, and PET2-negative subgroups had comparable survival outcomes with chemotherapy alone.

Chohan KL, et al. Blood Adv. 2022 Jul 26;6(14):4241-4250.

Frontline PET-Directed Therapy with BV Plus AVD Followed By Nivolumab in Patients with *Limited Stage* Hodgkin Lymphoma

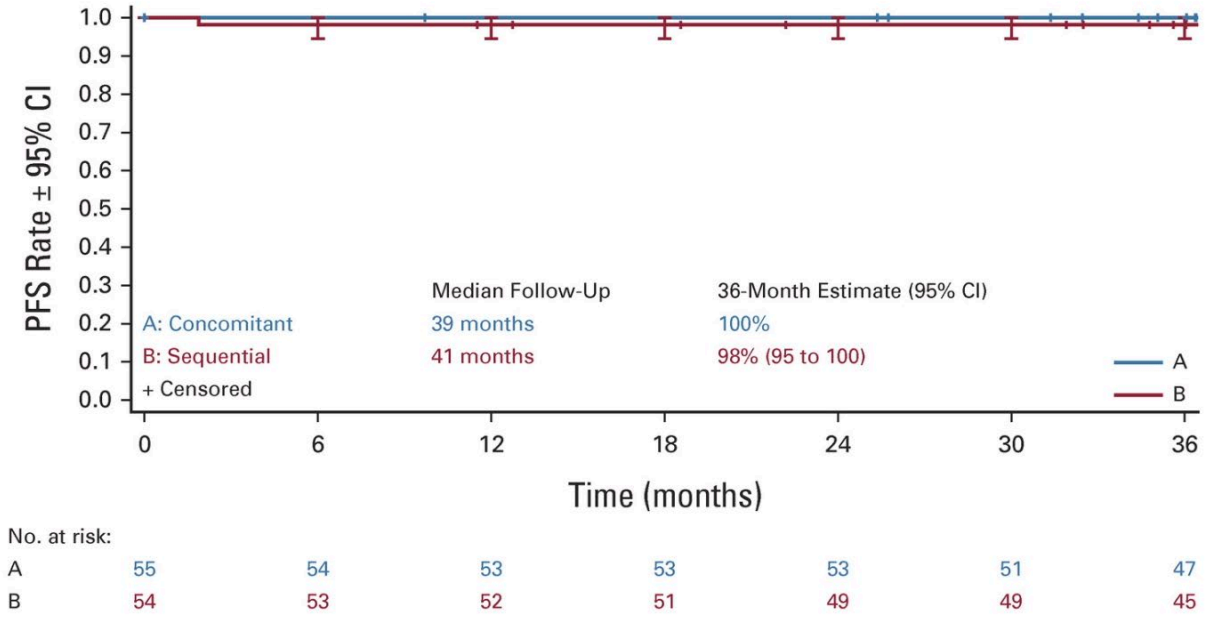




83 patients Limited stage cHL
97% negative interim PET scan
2 patients came off study and got RT
100% remained progression free after nivolumab consolidation

Park S et al. ASH 2022; #728

Nivolumab and AVD in *Early-Stage* Unfavorable Hodgkin Lymphoma: GHSG Nivahl Trial

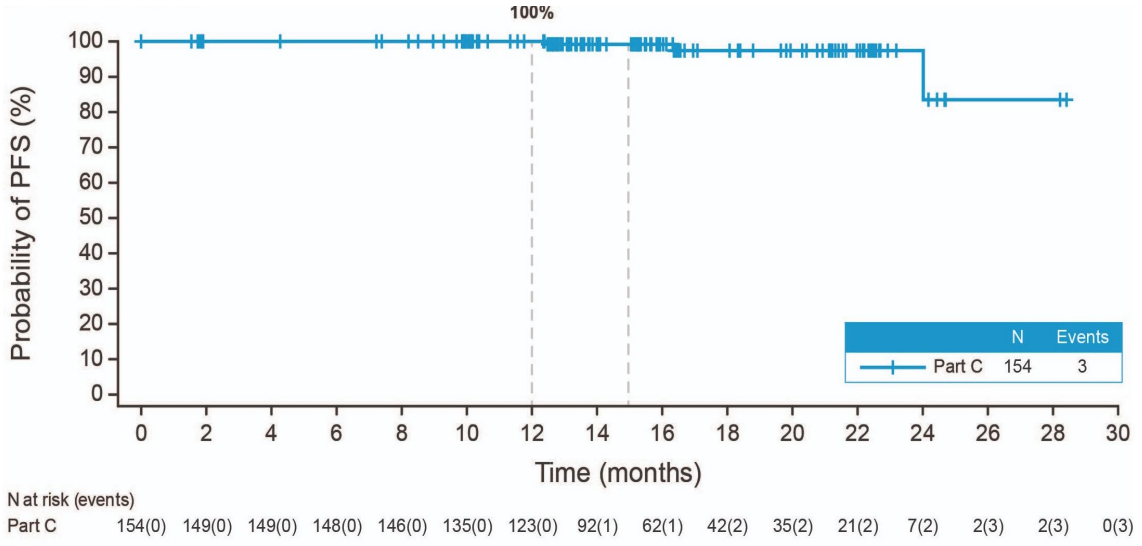


- 109 patients aged 18-60 years with early-stage unfavorable HL.
- Patients received concomitant (4xnivo-AVD; arm A) or sequential (4xnivolumab, 2xnivo-AVD, 2xAVD; arm B) treatment
- Each followed by 30Gy involved-site radiotherapy (IS-RT).

Bröckelmann et al. J Clin Oncol. 2023 Feb 20;41(6):1193-1199.

Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine (AN+AD) for *Early-Stage* Classical Hodgkin Lymphoma

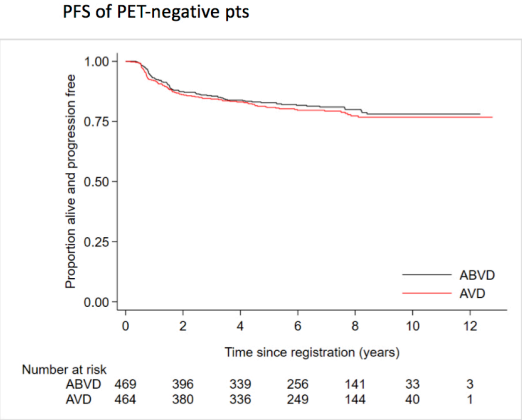
Overall Response at EOT per Investigator, n (%)	All Treated N = 154	Efficacy Evaluable N = 150
ORR (CR+PR)[a,b]	147 (95)	147 (98)
95% CI[c] for ORR	(90.9, 98.2)	(94.3, 99.6)
CR[a,b]	139 (90)	139 (93)
95% CI[c] for CR rate	(84.4, 94.4)	(87.3, 96.3)
PR[a,b]	8 (5)	8 (5)
95% CI[c] for PR rate	(2.3, 10.0)	(2.3, 10.2)
SD[a,b]	0	0
PR[a,b]	0	0
IR[d]	3 (2)	3 (2)
NE[b]	4 (3)	Not applicable

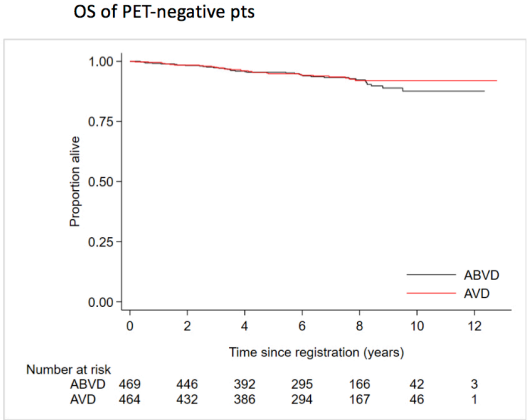


Abramson et al. ASH 2023, abstract 611

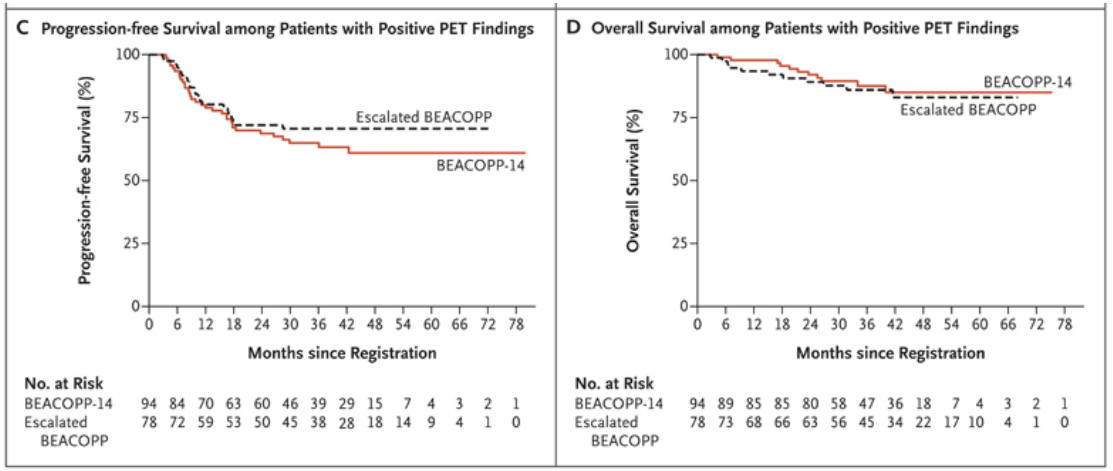
Treatment Guided by PET in *Advanced* Hodgkin Lymphoma: RATHL Trial

PET-2 negative





PET-2 positive



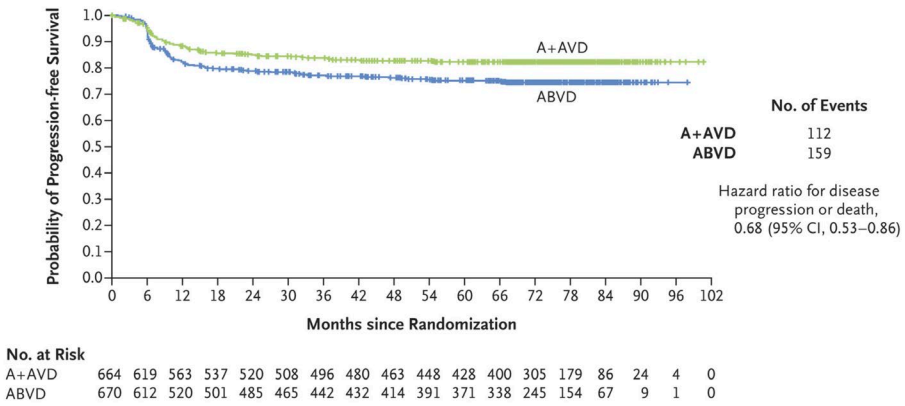
If you start with ABVD, you can drop the bleomycin if PET-2 negative

Not clear that escalating therapy in PET-2 patients improves outcome

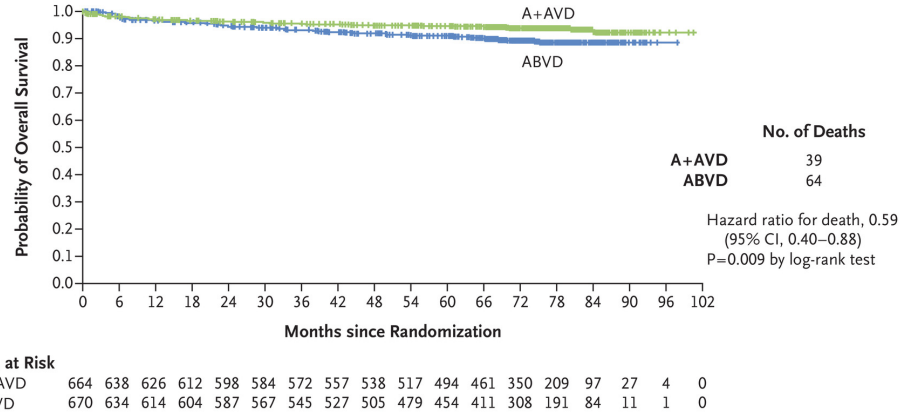
Johnson et al. N Engl J Med. 2016 Jun 23;374(25):2419-29.
Luminari et al. ASH 2022; #315

Outcomes with Brentuximab Vedotin + AVD vs. ABVD in *Stage III or IV* Hodgkin's Lymphoma

PFS



Overall Survival



Ansell SM et al. N Engl J Med. 2022 Jul 28;387(4):310-320.

BrECADD Proves Non-inferior to eBEACOPP in *Advanced* Classical Hodgkin Lymphoma (HD21 trial)

BrECADD - brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone

1500 patients, 749 were randomly assigned to eBEACOPP and 751 were assigned to BrECADD.

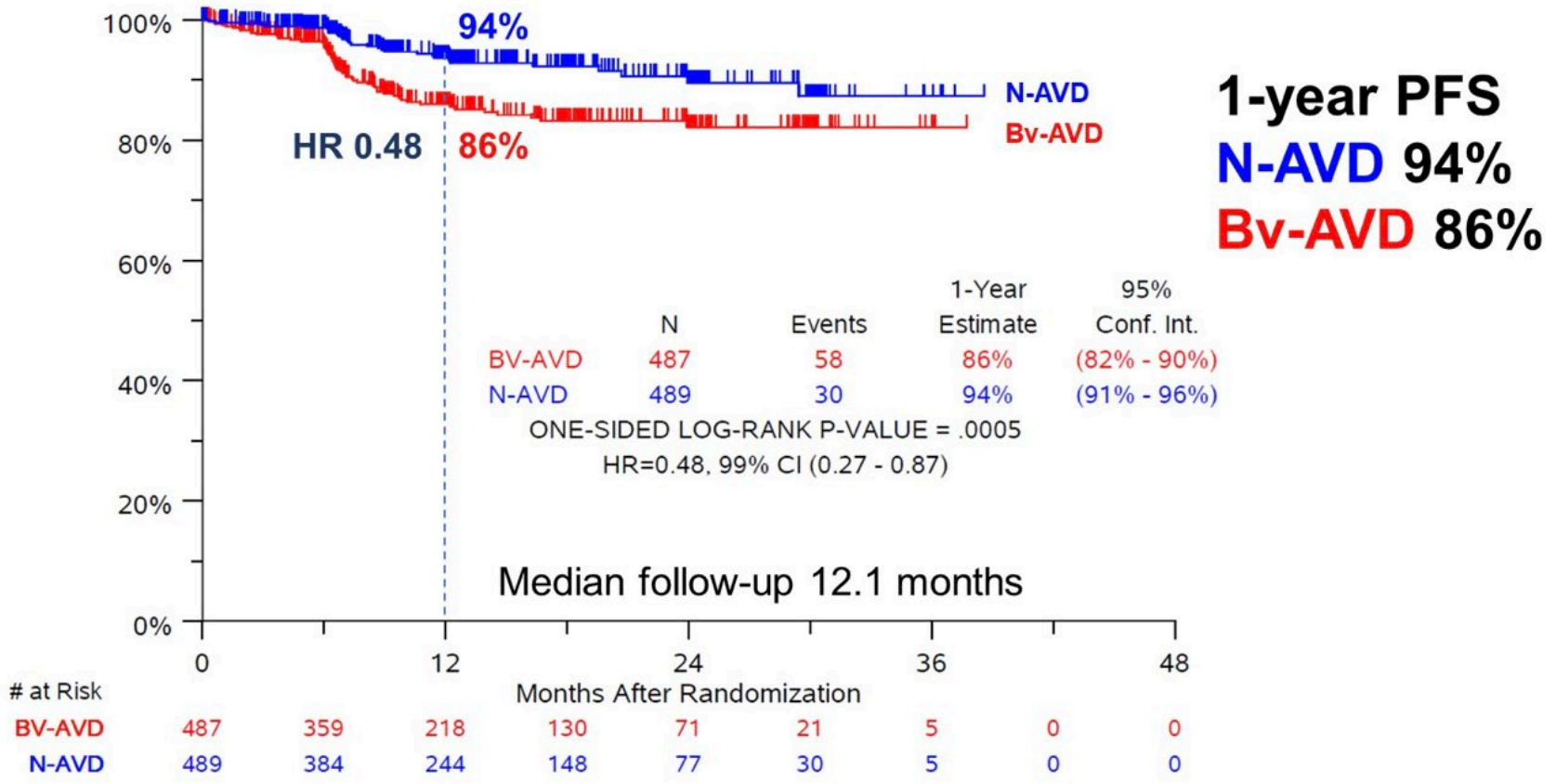
At a median follow-up of 40 months, the estimated 3-year PFS rate with BrECADD (n = 740) was 94.9% (99% CI, 92.8%-97.1%) vs 92.3% (99% CI, 89.7%-94.9%) with eBEACOPP (n = 742) in the intention-to-treat (ITT) population (HR, 0.63; 99% CI, 0.37-1.07).

The 1-year PFS rate with BrECADD was 97.5% (99% CI, 96%-99%).

The estimated 3-year OS rate was 98.5% in both the BrECADD and eBEACOPP arms

Borchmann P, et al. *Hematol Oncol*. 2023;41(suppl 2):881-882. doi:10.1002/hon.3196_LBA5

Nivolumab+AVD for Newly Diagnosed *Advanced-Stage* cHL



1-year PFS
N-AVD 94%
Bv-AVD 86%

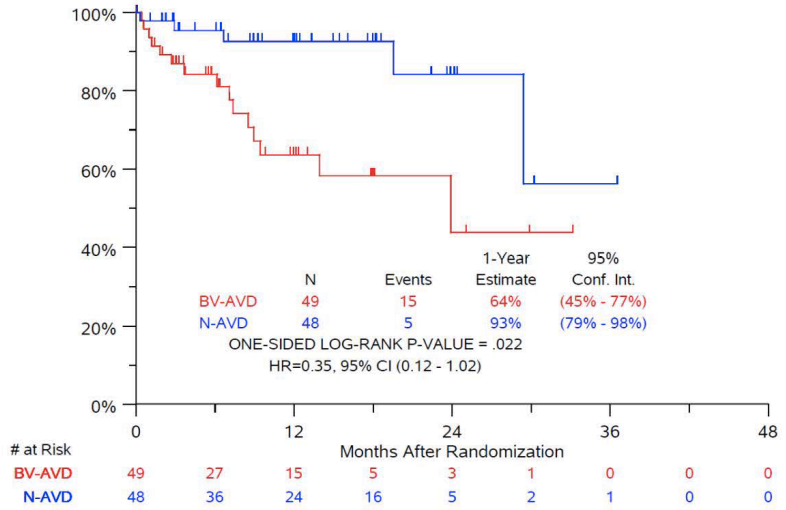
Herrera et al. J Clin Oncol 41, 2023 (suppl 17; abstr LBA4).

Nivolumab-AVD Is Better Tolerated and Improves PFS Compared to Bv-AVD in Older Patients (Aged ≥60 Years) with *Advanced Stage* Hodgkin Lymphoma

Table: Key Adverse Events by Treatment Arm (Any Grade and Grade ≥3).

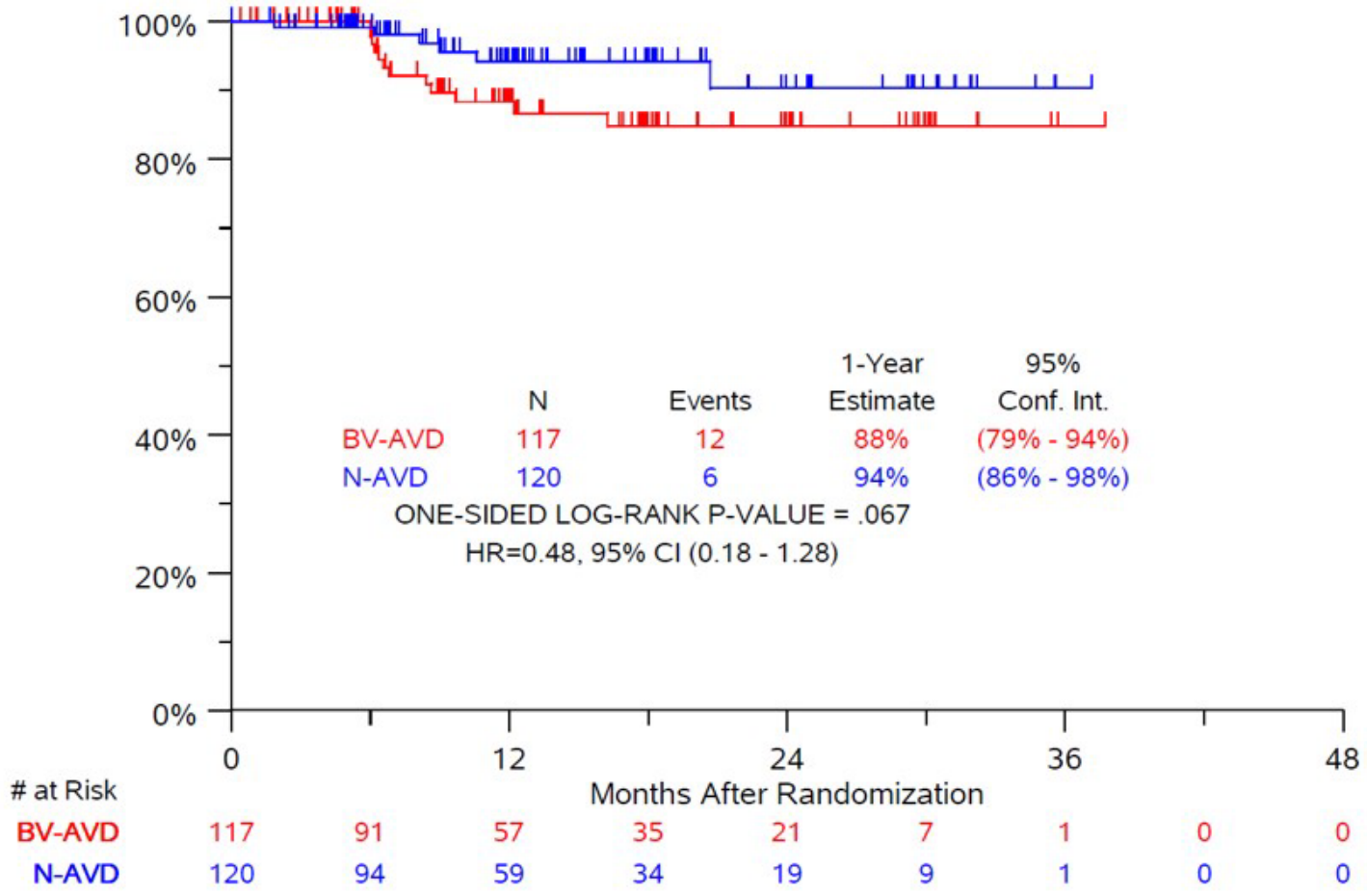
	N-AVD (N=48)	Bv-AVD (N=47)		N-AVD (N=48)	Bv-AVD (N=47)	
Adverse Event	Any Grade	Any Grade	p-value[3]	Grade ≥3	Grade ≥3	p-value[3]
Febrile neutropenia	6 (13%)	9 (19%)	0.42	6 (13%)	9 (19%)	0.42
Sepsis	3 (6%)	10 (21%)	0.04	3 (6%)	10 (21%)	0.04
Infections and infestations	9 (19%)	16 (34%)	0.11	3 (6%)	10 (21%)	0.04
Peripheral sensory neuropathy[1]	15 (31%)	31 (66%)	0.001	1 (2%)	5 (11%)	0.11
Peripheral motor neuropathy[2]	4 (8%)	7 (15%)	0.36	0 (0%)	1 (2%)	0.49

Figure: Progression-Free Survival for Patients Aged ≥60 years Enrolled on S1826.



Rutherford et al. ASH 2023, abstract 181

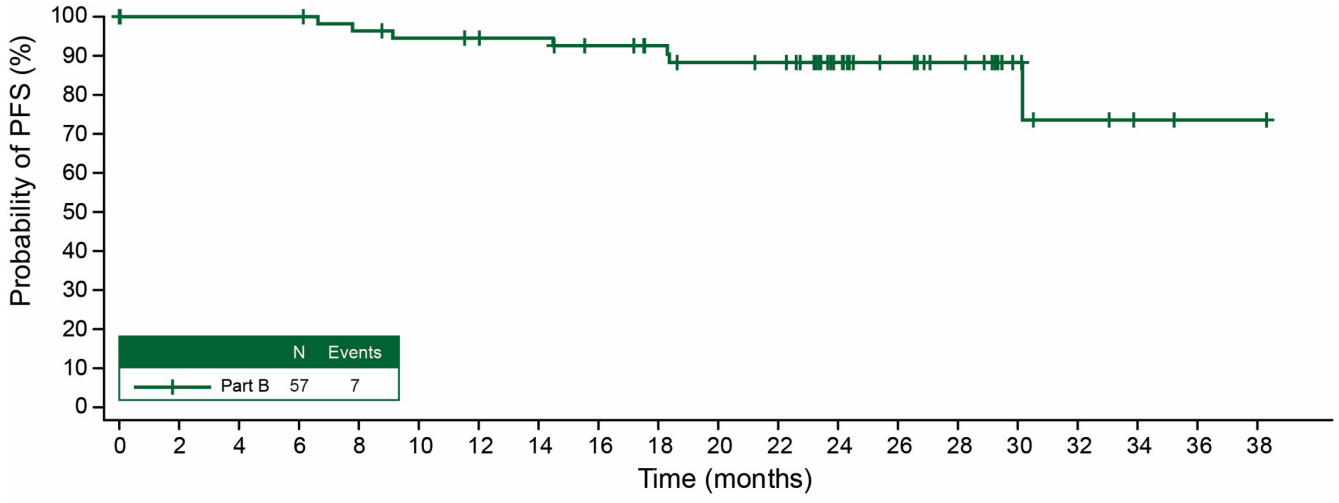
PFS and Toxicity with Nivolumab-AVD Compared to BV-AVD in Pediatric *Advanced Stage* cHL, Results of SWOG S1826



Castellino et al. ASH 2023, abstract 610

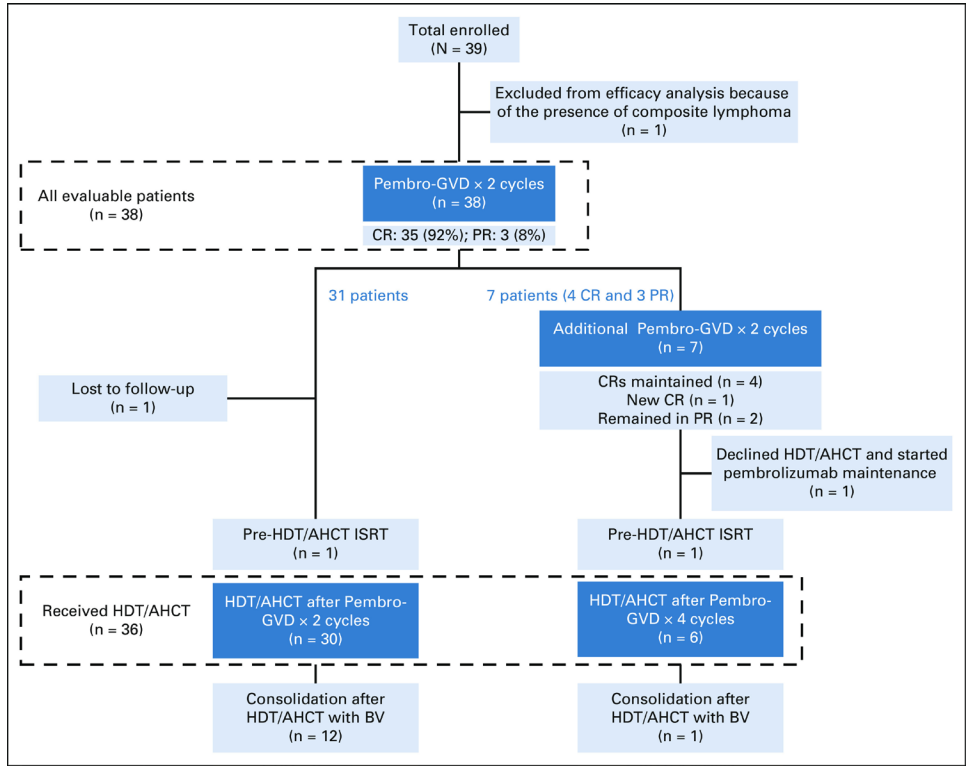
Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for *Advanced Stage* Classical Hodgkin Lymphoma

Overall Response at EOT per Investigator, n (%)	Part B N = 56, Efficacy Evaluable
ORR at EOT (CR+PR)[a,b]	53 (95)
95% CI for ORR	(85.1, 98.9)[c]
CR	50 (89)
95% CI for CR	(78.1, 96.0)[c]
PR	3 (5)
95% CI for PR	(1.1, 14.9)[c]
SD	0
PD	2 (4)
IR[d],	1 (2)



Lee et al. ASH 2023, abstract 608

Pembrolizumab Plus GVD As Second-Line Therapy for *Relapsed or Refractory* cHL



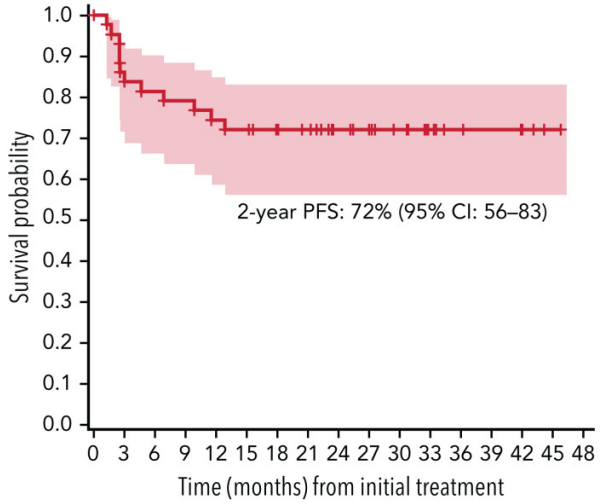
- 39 patients enrolled, 41% had refractory disease and 38% relapsed within 1 year of frontline treatment.
- ORR and CR rates after pembro-GVD were 100% and 95%, respectively.
- 36 (95%) patients proceeded to ASCT, 13 (33%) received post-ASCT brentuximab vedotin maintenance.
- All 36 transplanted patients were in remission at a median post-transplant follow-up of 13.5 months.

Moskowitz et al. J Clin Oncol. 2021 Oct 1;39(28):3109-3117.

Nivolumab Plus ICE As First Salvage Therapy in High-Risk *Relapsed/Refractory* Hodgkin Lymphoma

Characteristics	n (%)
Total	43 (100)
Male sex	26 (60)
Age (median, range), y	35 (18-70)
Stage at diagnosis	
I-II	17 (40)
III-IV	26 (60)
Frontline regimen	
A(B)VD	37 (86)
BV+AVD	2 (5)
BV→ABVD (sequential)	1 (2.3)
ABVD/BV+AVD	1 (2.3)
ABVE+PC	1 (2.3)
BEACOPP escalated	1 (2.3)
Stage at baseline	
I-II	17 (40)
III-IV	26 (60)
B symptoms at baseline	15 (35)
Extranodal disease at baseline	16 (37)
Bulky disease at baseline (>5 cm)	8 (19)
Prior radiation	5 (12)
Primary refractory	19 (44)
Relapsed	24 (56)

- After nivolumab, the ORR was 81%, and the CR rate was 71%.
- At the end of protocol therapy, the ORR and CR rates were 93% and 91%.
- Thirty-three patients were bridged directly to AHCT, including 26 after Nivo alone.
- The 2-year PFS and OS were 72% and 95%, respectively.



Mei et al. Blood. 2022 Jun 23;139(25):3605-3616.

PD-1 Blockade before Autologous Stem Cell Transplantation Improves Outcomes in *Relapsed/Refractory* cHL

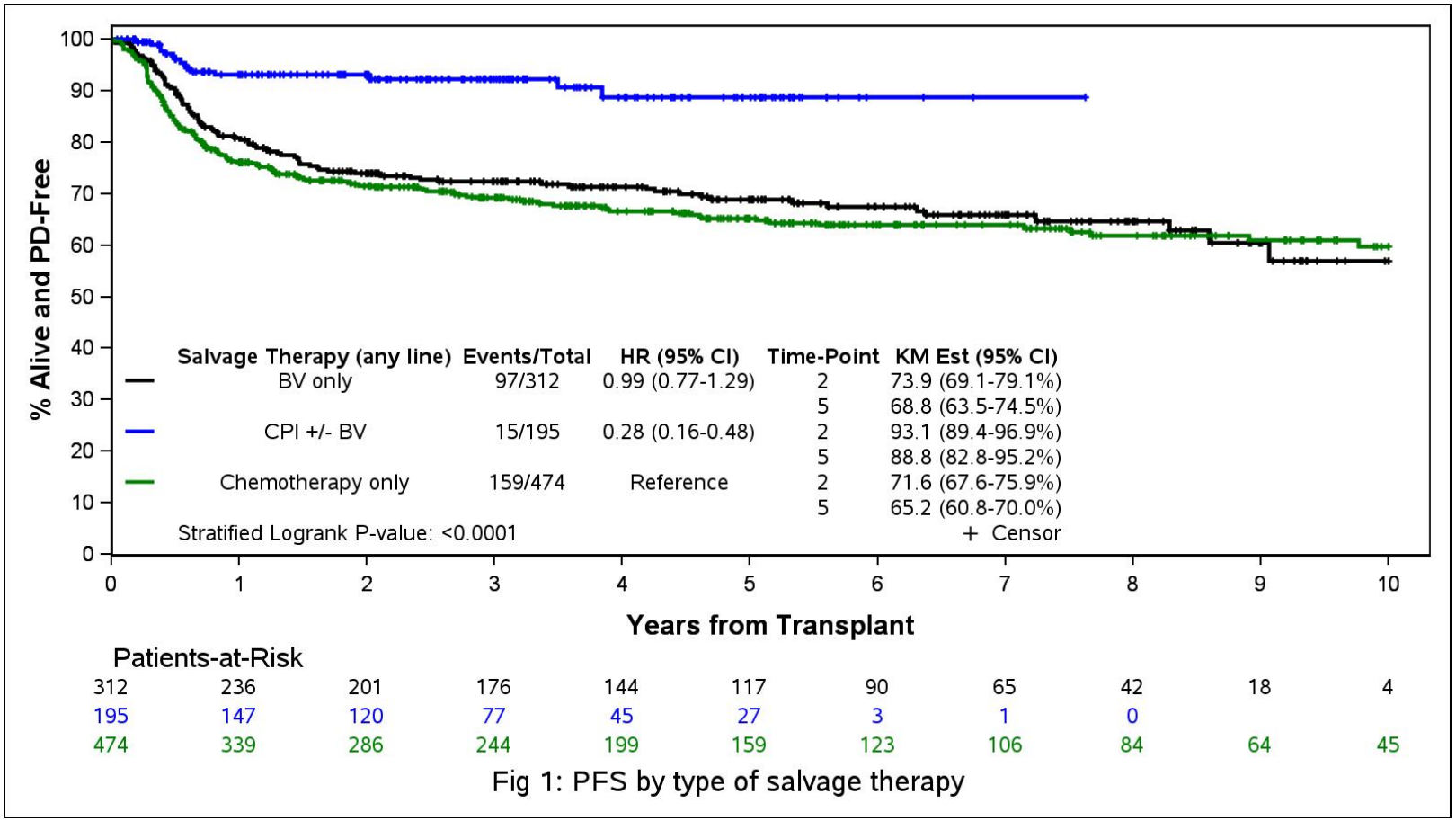
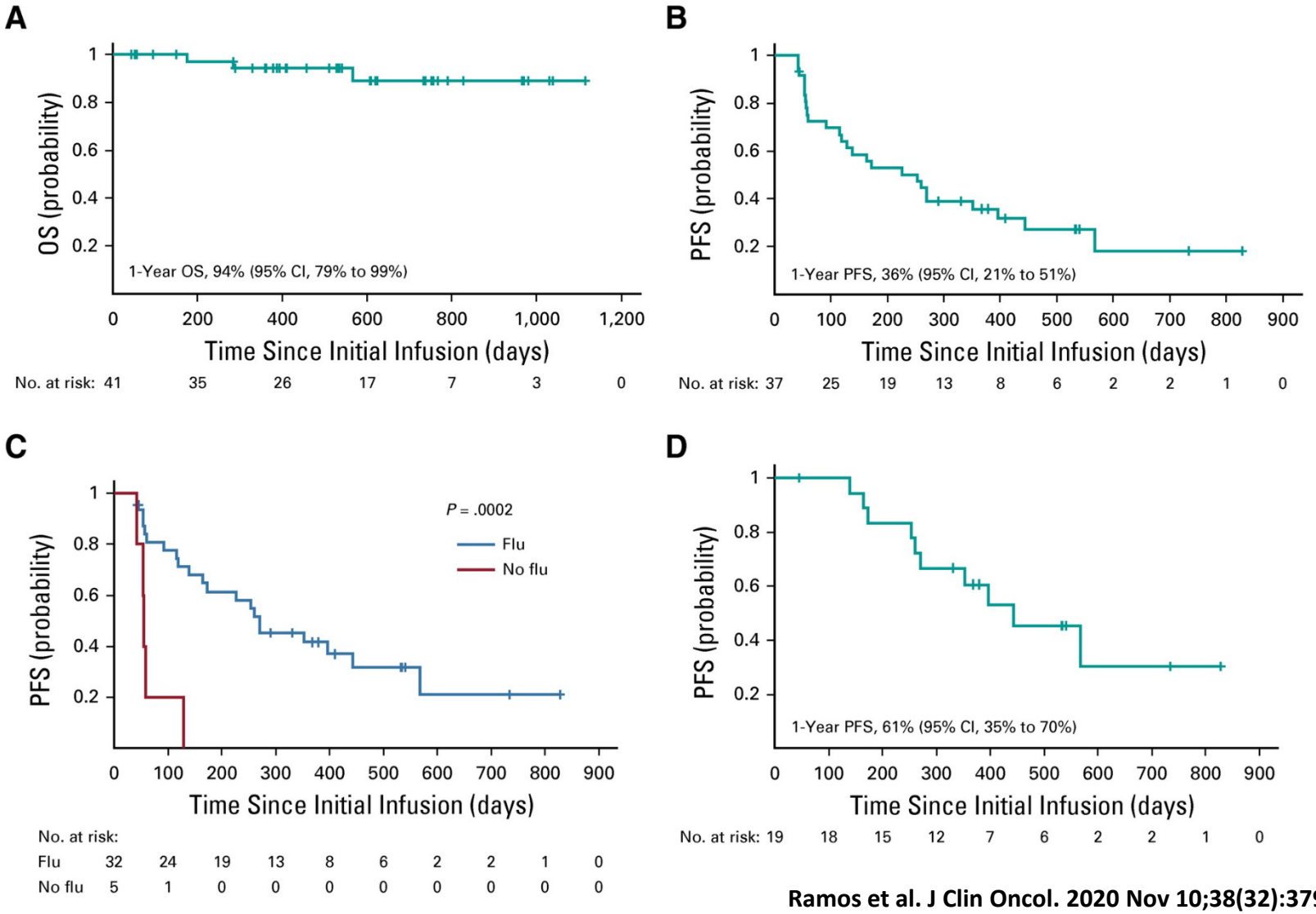


Fig 1: PFS by type of salvage therapy

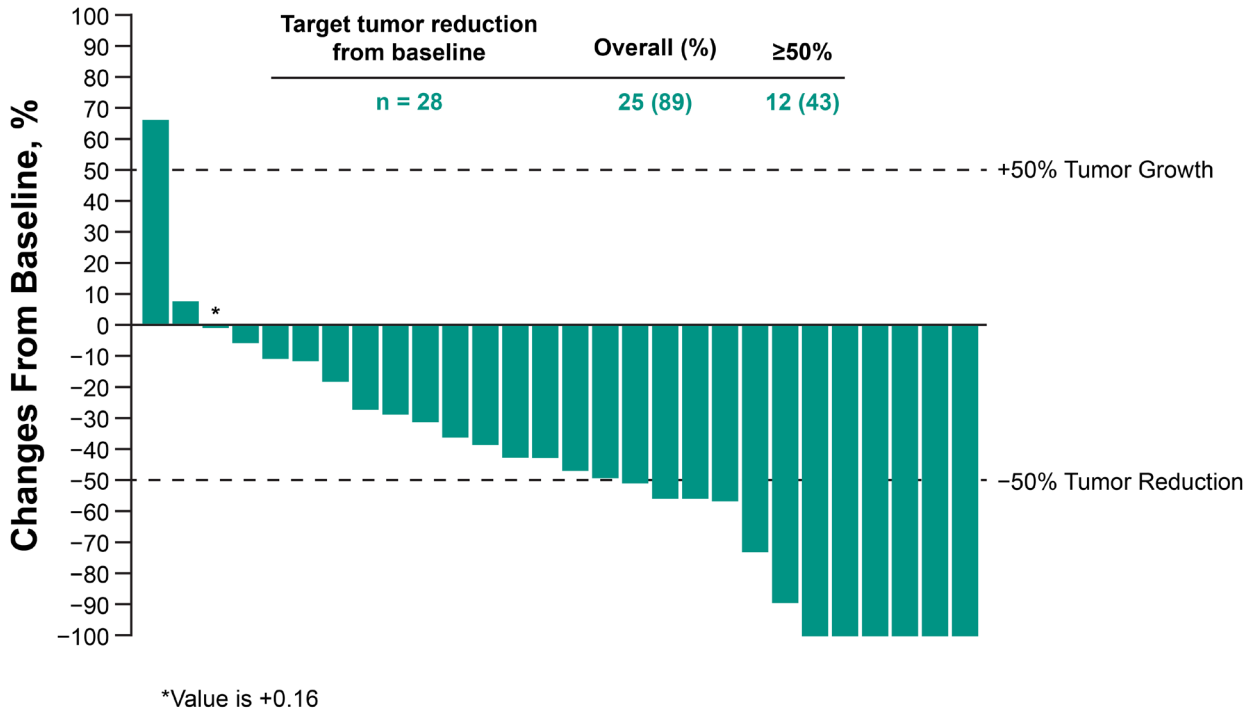
Desai et al. ASH 2023, abstract 182

Relapse post transplant - CD30 directed CAR T-cells are promising



Ramos et al. J Clin Oncol. 2020 Nov 10;38(32):3794-3804.

Favezelimab (anti–LAG-3) Plus Pembrolizumab in *R/R* Classical Hodgkin Lymphoma after Anti–PD-1 Treatment



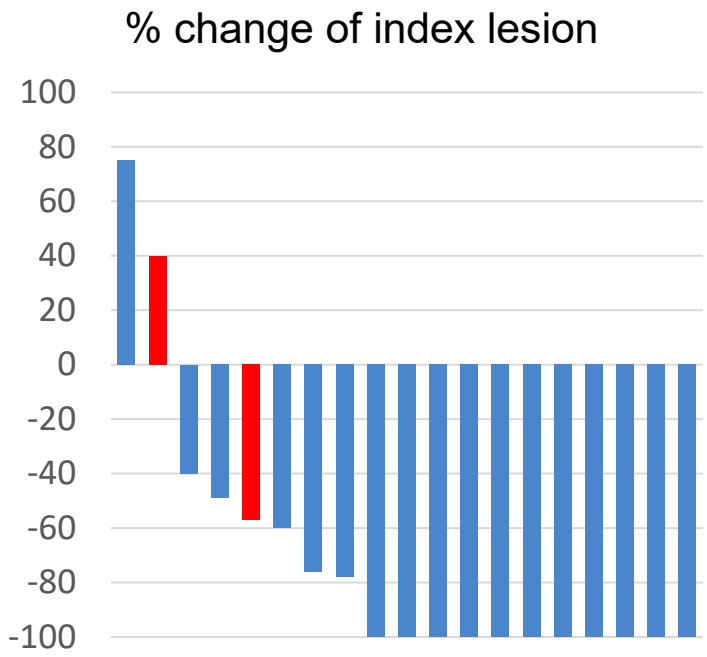
34 patients
10 pts had objective response (ORR, 29%; CR 3 [9%]; PR 7 [21%]).
Median PFS was 9.7 months

Timmerman et al. ASH 2023; #4440

AFM13 Combined with Preactivated and Expanded Cord Blood-Derived NK Cells for *R/R* CD30+ Lymphoma

42 patients
ORR and CR were 92.8% and 66.7%, respectively (94.4% and 72.2%, respectively, in 36 pts treated at the RP2D). Nine pts had a response consolidated with SCT (5 allo, 4 auto).
At median follow-up of 14 (6-34) months, the EFS/OS rates are 31%/76%

Baseline patient characteristics	N=42
Age, median (range)	43 (20–75)
Gender (male/female)	27 / 15
Diagnosis (HL / NHL)	37 / 5
No. prior lines therapy, median(range)	7 (1–14)
Prior brentuximab vedotin	42
Prior anti-PD-1	39
Prior SCT (autologous / allogeneic)	32 (22 / 10)
Prior CD30.CAR-T	4



Nieto et al. ASH 2023; #774

New options for classical Hodgkin lymphoma patients

1. To include new agents (particularly PD-1 blockade) in initial therapy
2. To add PD-1 antibodies to salvage therapy prior to autologous stem cell transplantation
3. To consider clinical trials testing novel agents for patients relapsing post transplant