POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

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Torino
Centro Congressi Lingotto
19-21 febbraio 2026

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DICHIARAZIONE Chiara Rusconi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene	x						
Takeda						x	x
Lilly						x	x
Abbvie							x

First line

- Update of randomized clinical trial for Advanced Stage: SWOG1826 and HD21
- PET driven BV+pembro+AD

Relapsed/refractory

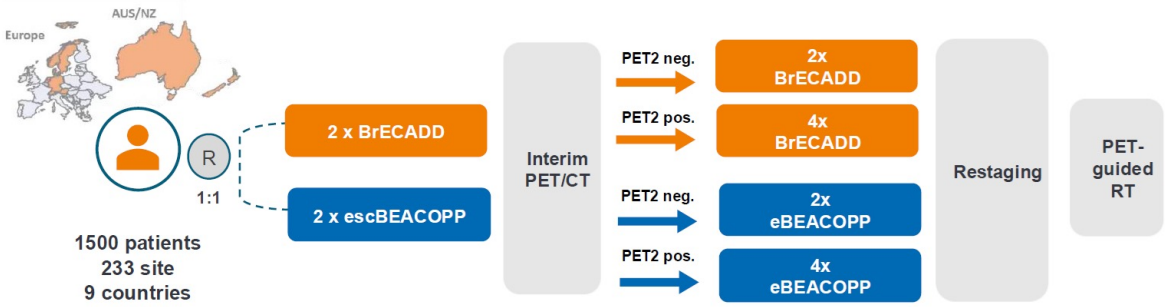
- Spacial single cell profiling on patients treated with entinostat plus pembro

New drugs

- 35C next generation targeted ADC

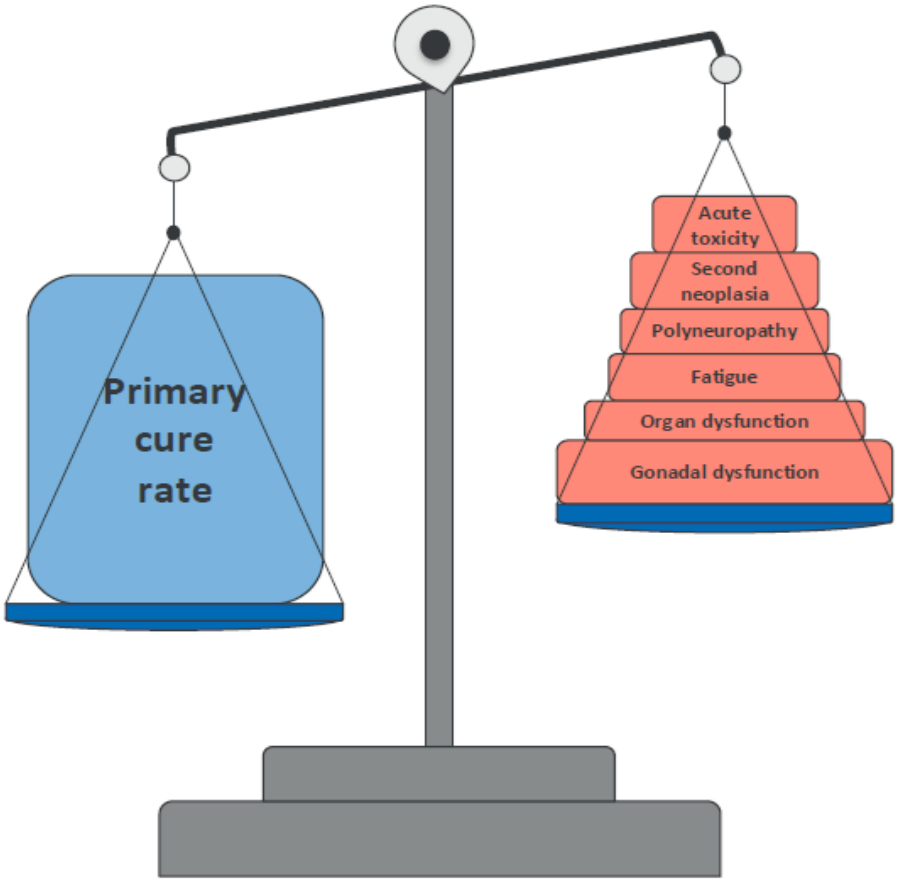
GHSG HD21 study design and primary endpoints

Randomized, open-label, Phase 3 trial of BrECADD versus eBEACOPP in patients with newly diagnosed AS-cHL

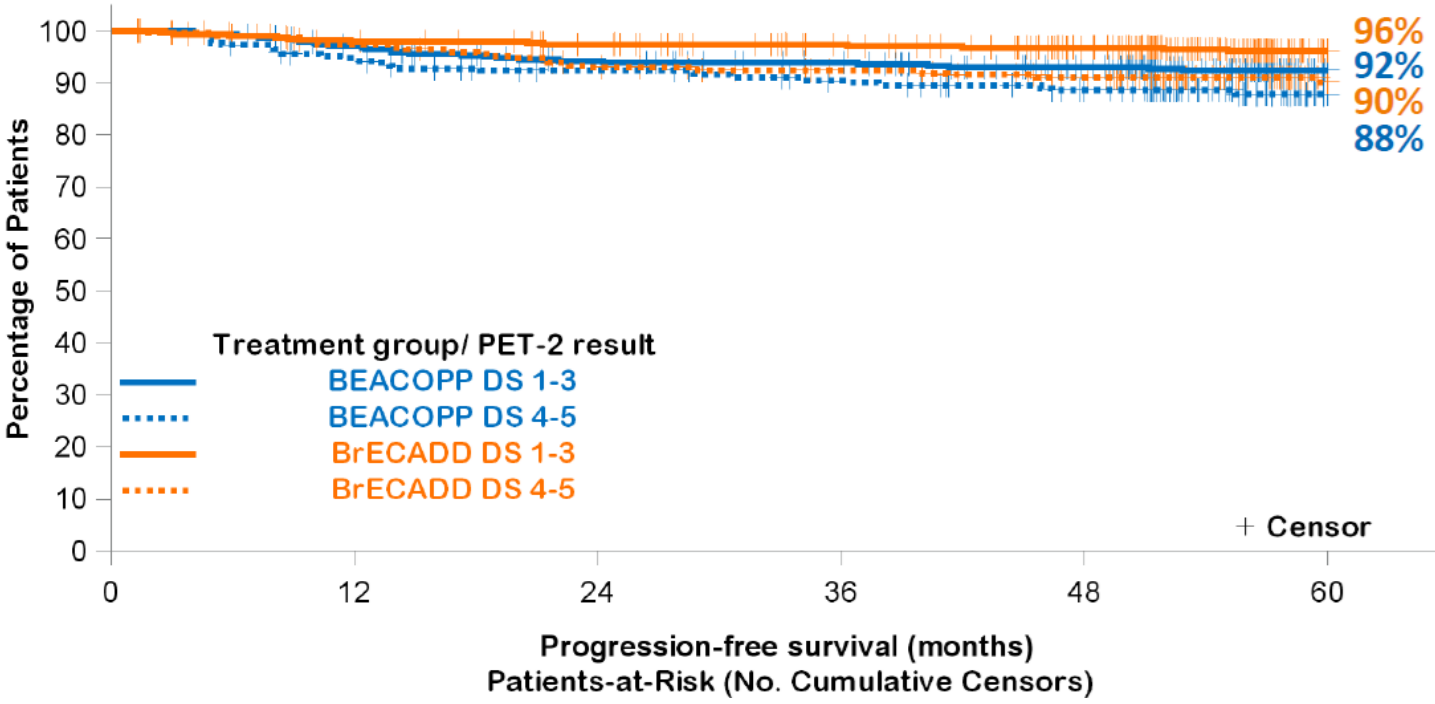


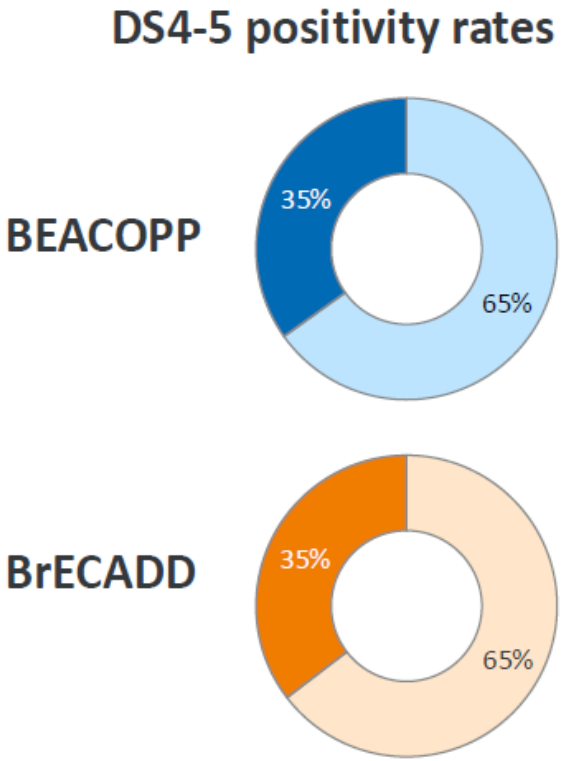
Co-primary objectives:

- **Demonstrate better acute tolerability,** i.e reduced treatment-related morbidity (TRMB) with BrECADD.
- **Demonstrate non-inferior efficacy** of BrECADD in terms of PFS



Ferdinandus J et al, abs 14210

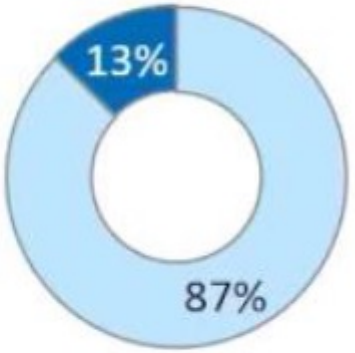




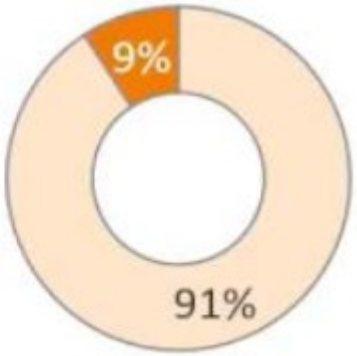
Ferdinandus J et al, abs 14210

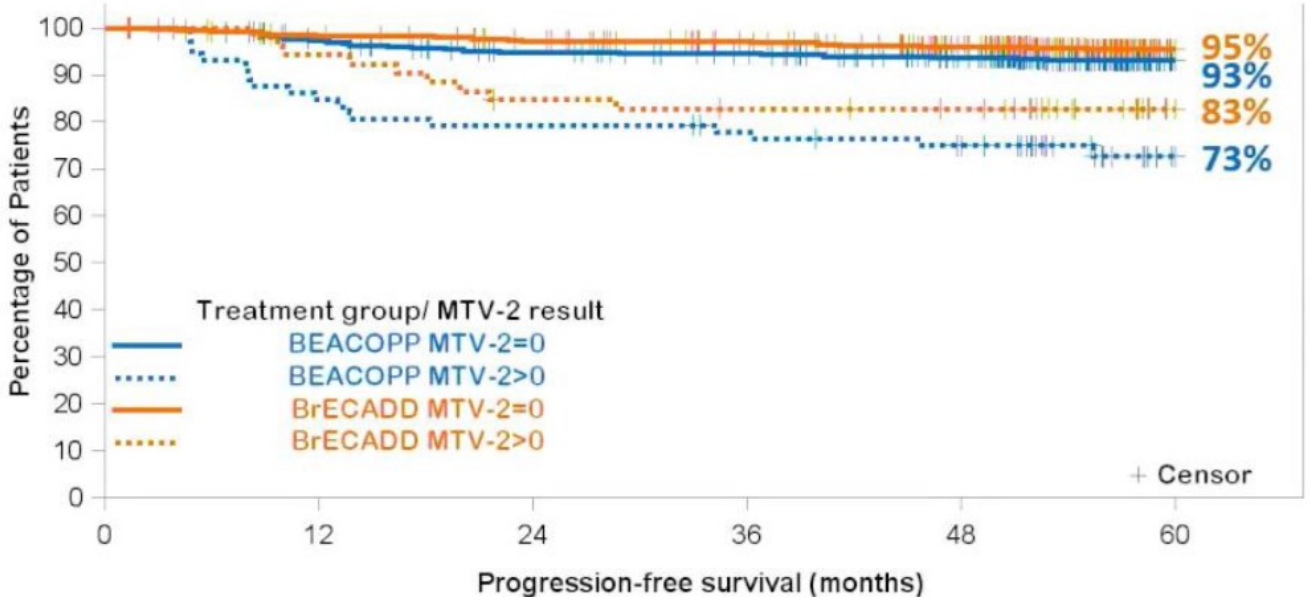
MTV-2 positivity rates

BEACOPP



BrECADD



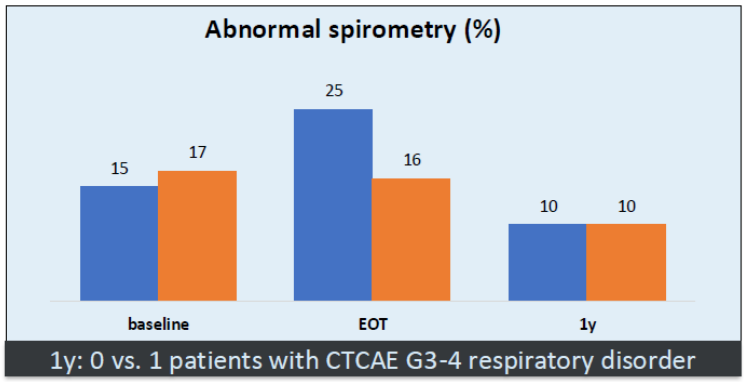


Ferdinandus J et al, abs 14210

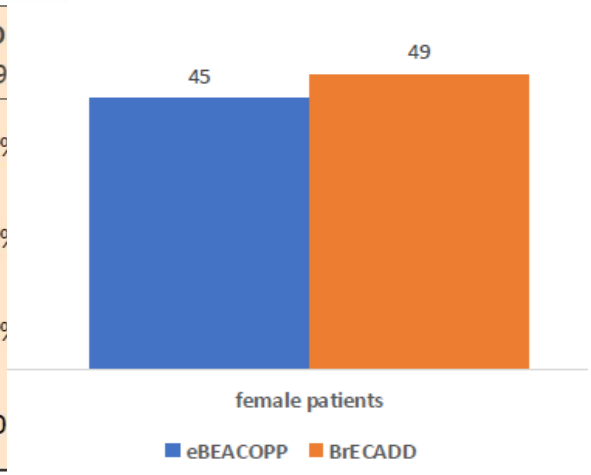
Ferdinandus J et al, abs 14210

HD21: treatment related morbidity

		eBEACOPP N=734	BrECADD N=739	ITT N=1473
Second malignancy		19 (3%)	21 (3%)	40 (3%)
Type of malignancy	AML/MDS	6 (1%)	1 (<1%)	7 (<1%)
	NHL	2 (<1%)	8 (1%)	10 (1%)
	Solid tumor	9 (1%)	11 (1%)	20 (1%)
	Other hematological malignancy	2 (<1%)	1 (<1%)	3 (<1%)
Year of event	2016-2023 (pre-publication)	16/19 (84%)	21/21 (100%)	37/40 (93%)
	2024	**3/19 (16%)**	**0/21 (0%)**	3/40 (8%)



	eBEACOPP N=734	BrECAD N=739
Any PNP during treatment	368 (50%)	294 (36%
No PNP at EOT	452 (62%)	540 (73%
No PNP or resolved	724 (99%)	724 (98%
Resolved to ≤ G1	733 (100%)	735 (100



GHSG HD21 Final Analysis (5y mFU): Summary and Author's Conclusions

Very high primary cure rate with BrECADD

5y PFS 94% for all patients

PET-2 guided approach:

- Allows for short treatment for most patients with 5y-PFS 96% after 4 cycles
- Negates risk from higher lymphoma burden with 5y-PFS 90% after 6 cycles

Low rate of long-term side effects with BrECADD

Omission of problematic drugs led to

- improvements in organ function
- lower AML/MDS rate and
- high childbirth rate

Almost all patients recovered from peripheral neuropathy and any other toxicity during FU

Individualized BrECADD sets a new benchmark for the primary cure rate of AS-cHL with minimal long-term side effects

S1826 Study Design

Newly diagnosed Stage III-IV Hodgkin lymphoma

RANDOMIZE 1:1

N-AVD x 6 cycles
Nivolumab 240mg days 1,15[a]
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
*G-CSF optional
470 pts

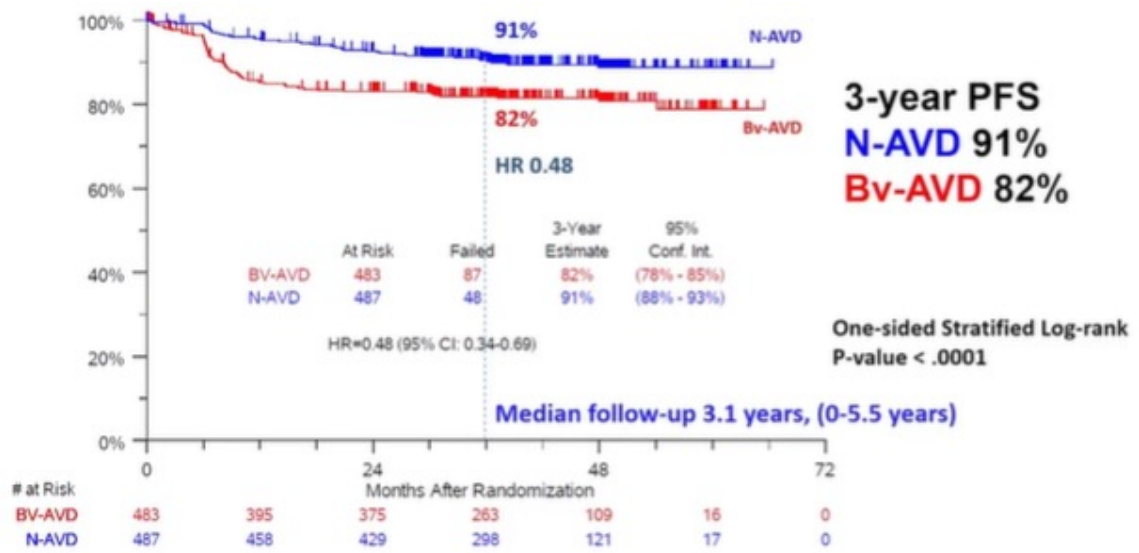
Bv-AVD x 6 cycles
Bv 1.2mg/kg days 1,15
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
*G-CSF required
470 pts

EOT RT (residual FI

Stratification:
- Age (12-17/18-60/>60)
- IPS (0-3/4-7)
- EOT RT intended (Y/N)

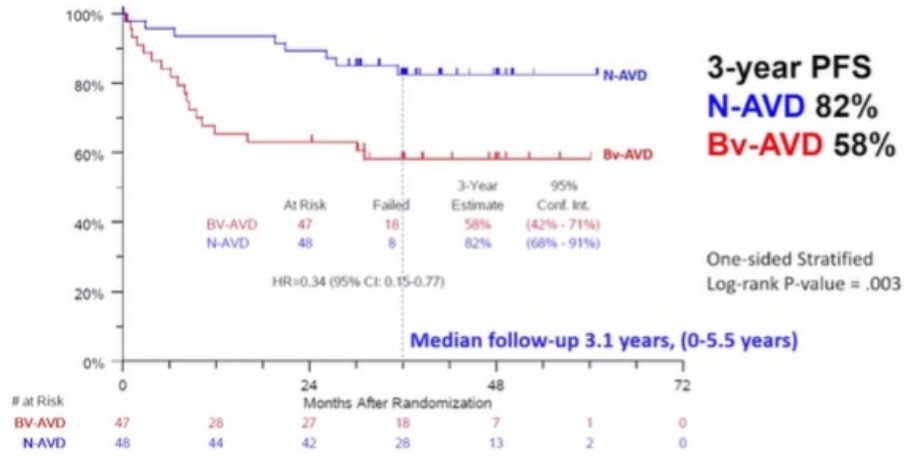
- **Primary endpoint: PFS**
- Secondary endpoints: EFS, OS, EOT CMR rate, PROs

Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
Age, median (range)	**27 (12-83)**	**26 (12-81)**
12-17 years	118 (24%)	118 (24%)
18-60 years	321 (66%)	318 (66%)
≥ 61 years	48 (10%)	47 (10%)



Herrera AJ et al, abs 10450

N-AVD prolongs PFS in older adults

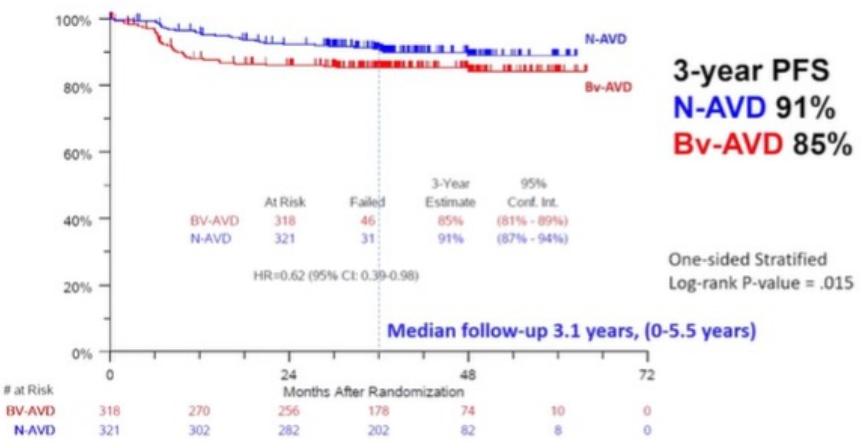


3-year PFS
N-AVD 82%
Bv-AVD 58%

One-sided Stratified
Log-rank P-value = .003

Median follow-up 3.1 years, (0-5.5 years)

N-AVD prolongs PFS in 18-60 year-old adults



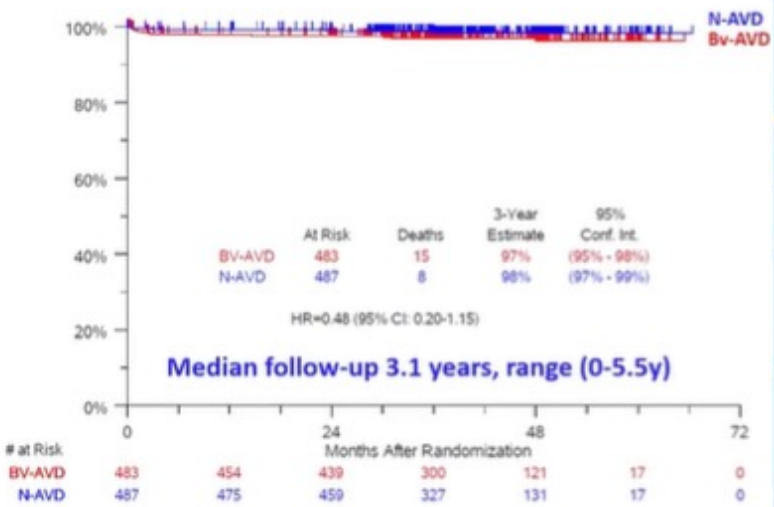
3-year PFS
N-AVD 91%
Bv-AVD 85%

One-sided Stratified
Log-rank P-value = .015

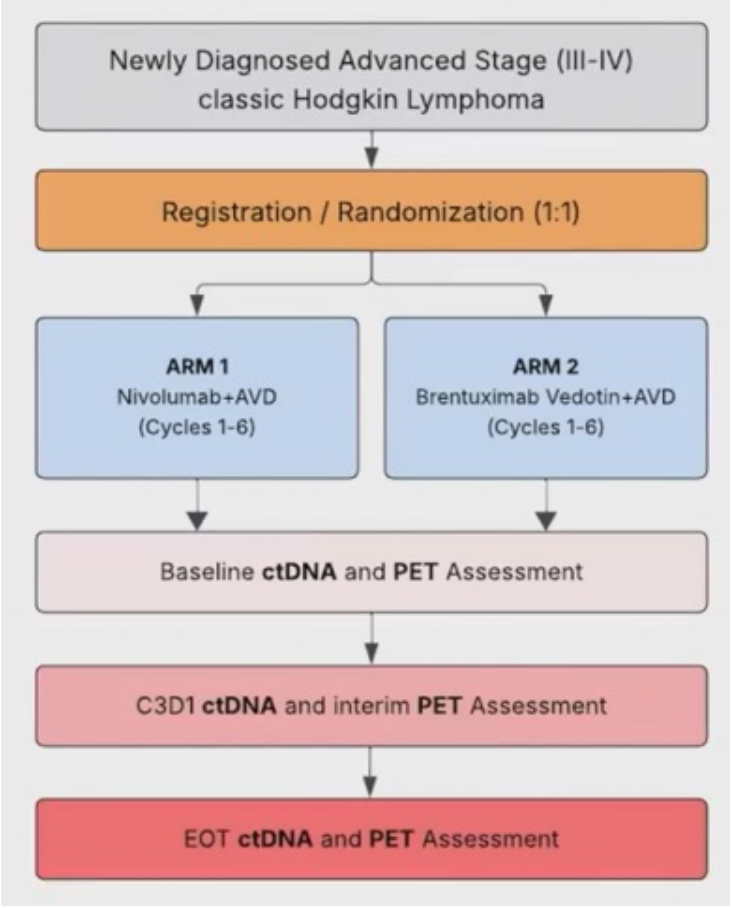
Median follow-up 3.1 years, (0-5.5 years)

Herrera AJ et al, abs 10450

Overall Survival

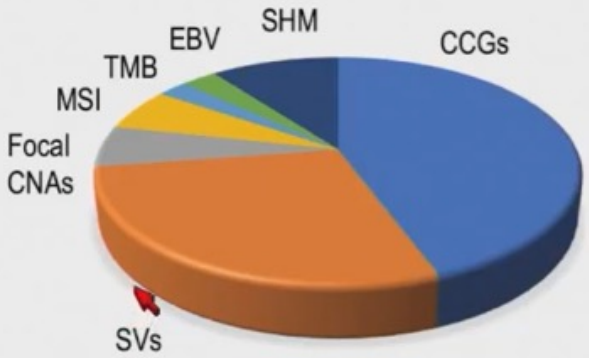


Second Cancer Type	N-AVD N=487	BV-AVD N=483
Non-Hodgkin Lymphoma	4	3
Skin Cancer	1	0
Multiple Myeloma	0	1
Solid tumors	1	7
Total	6 (1.2%)	11 (2.3%)



Targeted sequencing assay

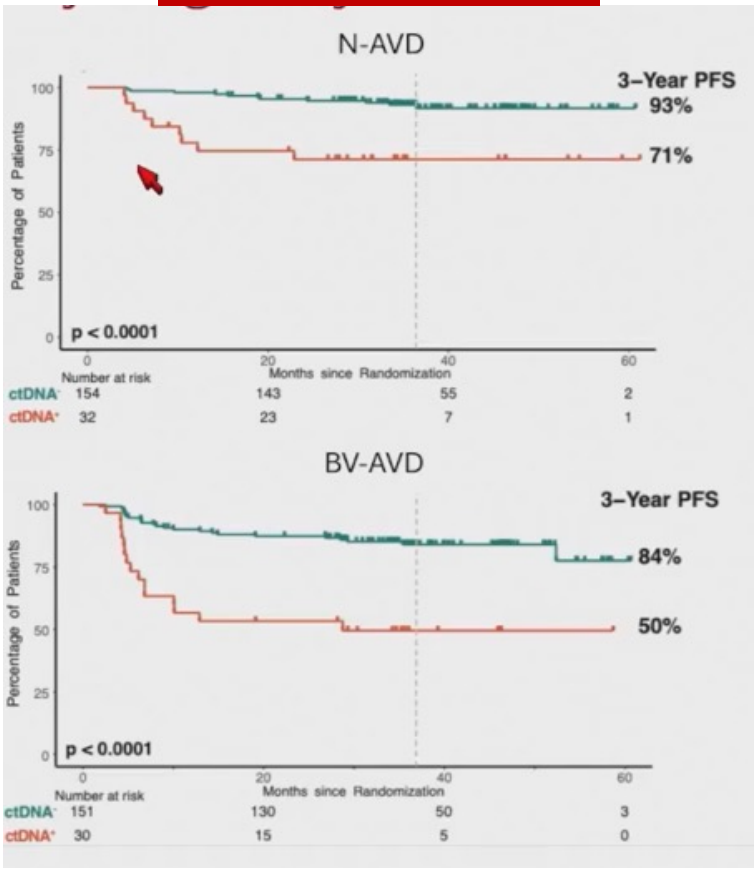
- ~300KB, ~1200 targets, based on our earlier genomic analyses
- Sites of physiologic and aberrant somatic hypermutation (SHM)
- Baits for EBV detection
- Captures recurrent mutations, copy number alterations and structural variants
- Assesses molecular tumor burden (MTB) with a new tool, MTB Tracker

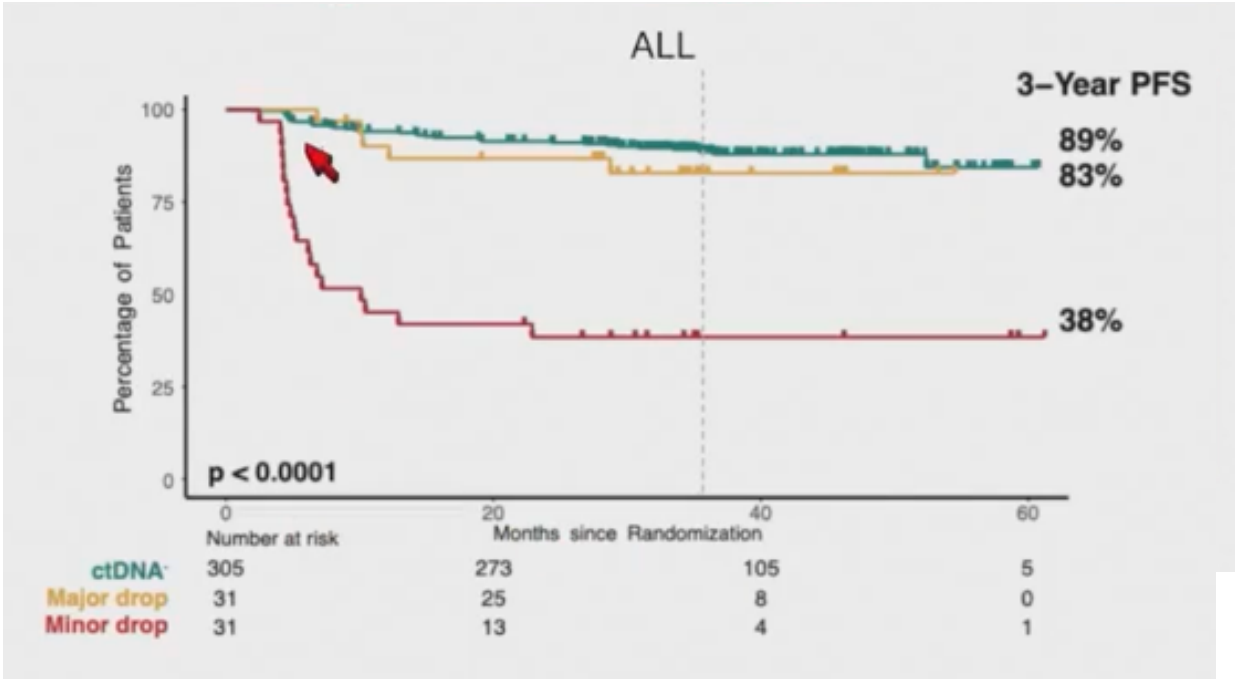


Targeted Panel (300 kb)

Paczkowska J et al, abs 8300

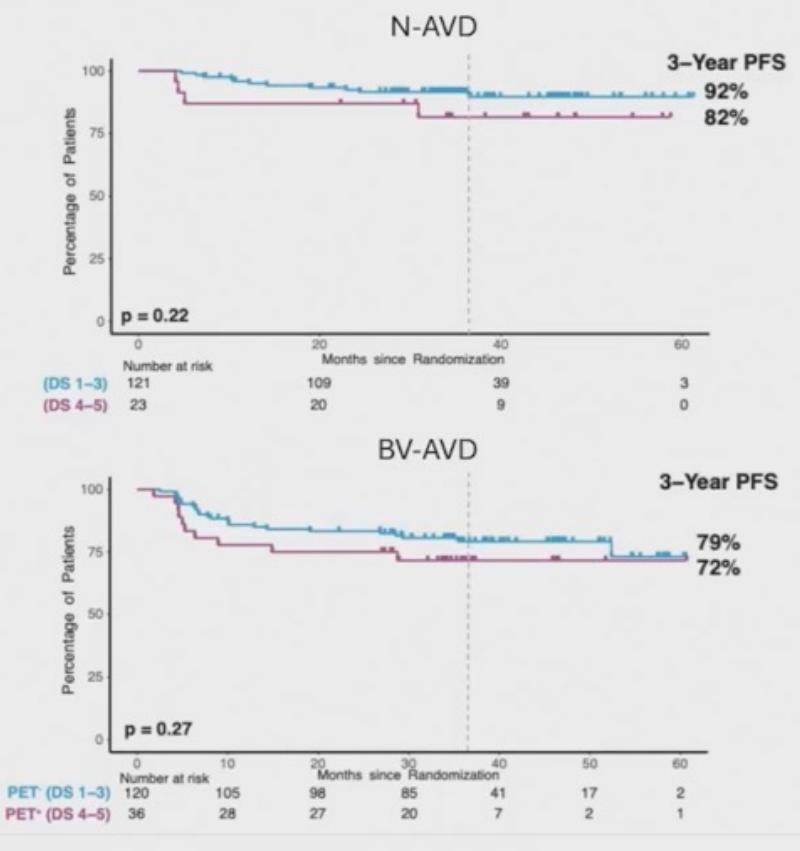
CtDNA C3D1



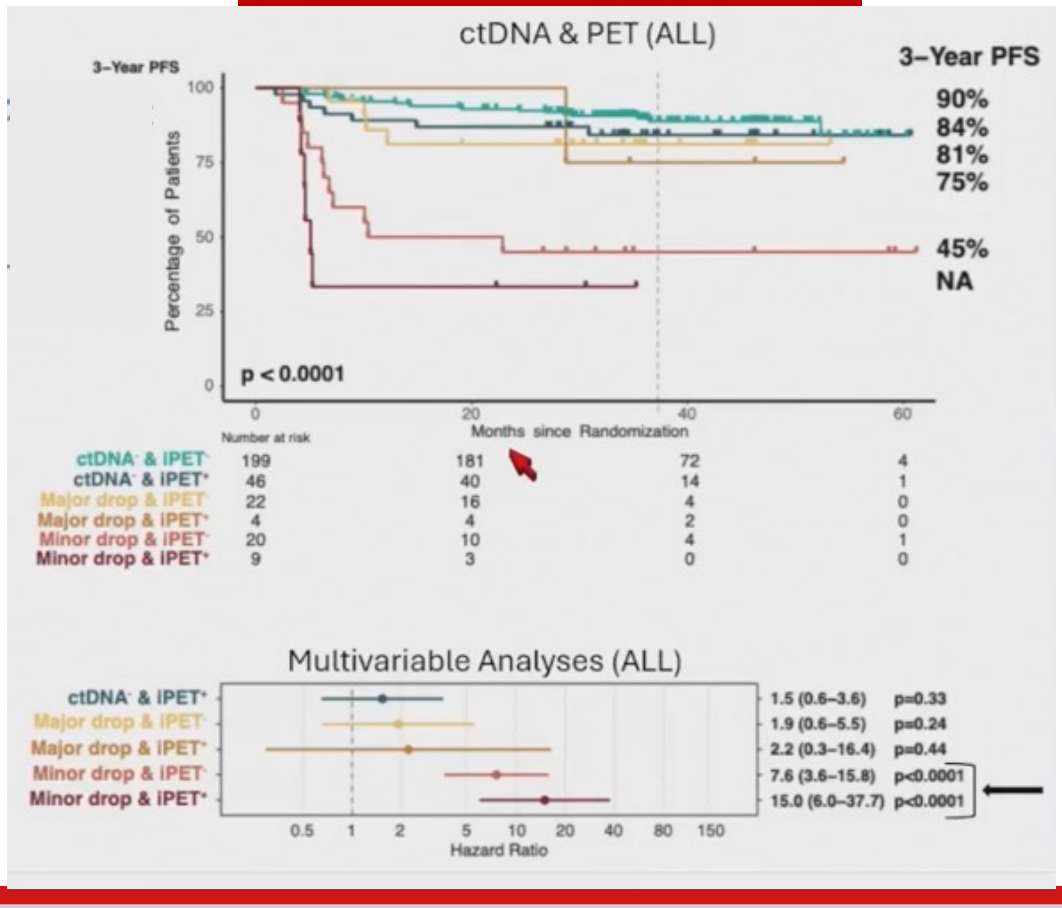


Paczkowska J et al, abs 8300

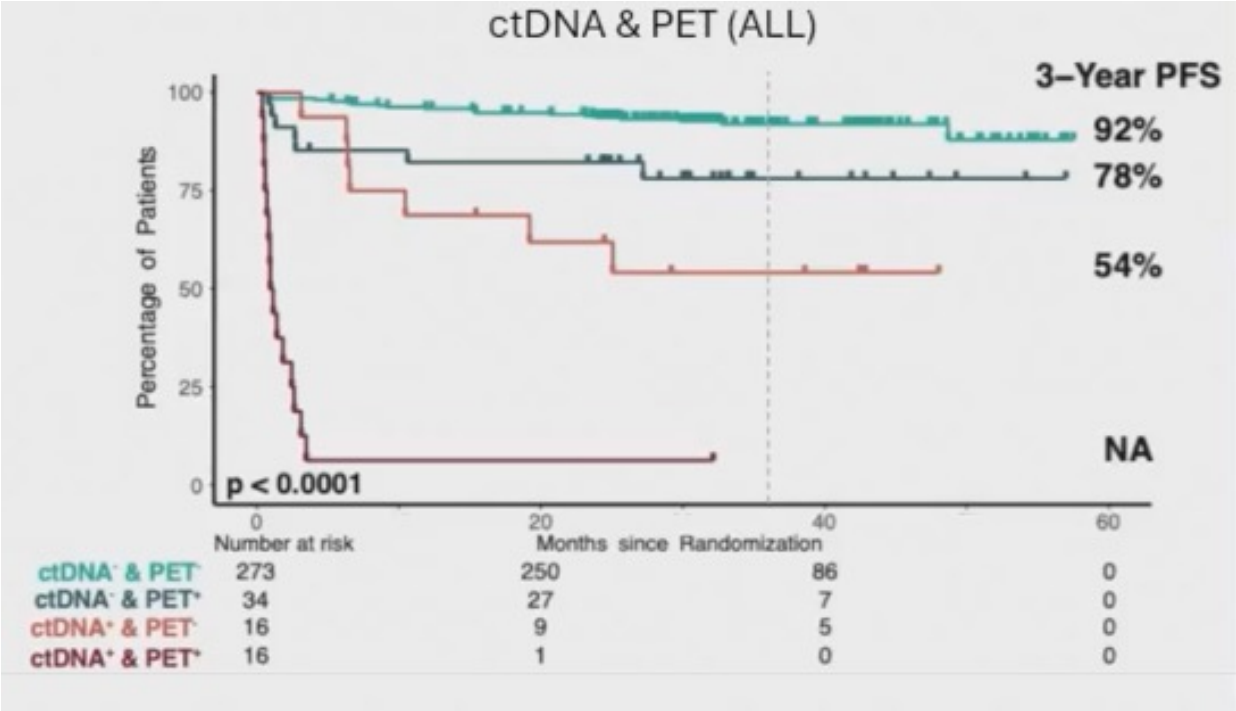
iPET C3D1

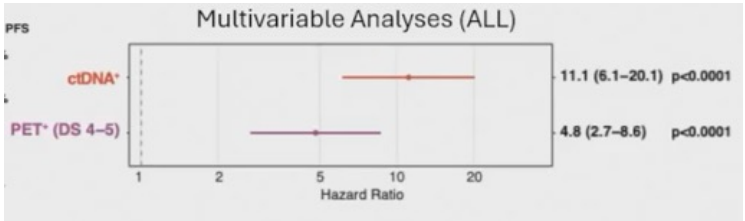


iPET&CtDNA C3D1



CtDNA&PET EOT





Paczkowska J et al, abs 8300

Novel Study Desgin

KEY ELIGIBILITIES

- Newly Diagnosed cHL
- Advanced Stage (III or IV) or ES Bulky (>10cm)

PART A

PEMBROLIZUMAB AND BRENTUXIMAB + AD — X3 CYCLES — $iPET_3$

CYCLE WILL CONSIST : DRUG ADMINISTERED (C1-C3)	DAY 1	DAY 15
Doxorubicin (A) (25 mg/m2)	x	x
Dacarbazine (D) (375 mg/m2)	x	x
Brentuximab vedotin (Bv) (1.2 mg/kg)	x	x
Pembrolizumab (P) (400mg) IV every 6wks	C1 D01	C2 D15

Primary ENDPOINT: CR rate at EOT

SECONDARY ENDPOINT: ORR, PFS, DOR

PART B, DE-ESCALATION ARM

Must achieve one of the following on $iPET_3$
DS 1
DS 2
DS 3 AND ≥90% reduction in TMTV.

CYCLE WILL CONSIST : DRUG ADMINISTERED (C4-C6)	DAY 1	DAY 15
Brentuximab vedotin (Bv) (1.2 mg/kg)	x	x
Pembrolizumab (P) (400mg) IV every 6wks	C4 D01	C5 D15

PEMBROLIZUMAB AND BRENTUXIMAB — X3 CYCLES

Key Metrics

- 28 days per cycle
- EOT PET performed 4 week post last infusion
- Follow up every 6 months with CT first 2 years

PEMBROLIZUMAB AND BRENTUXIMAB + AD — X3 CYCLES

PART C, STANDARD RISK ARM

Showing the following on $iPET_3$:
DS 3 with less than 90% reduction in TMTV.
DS 4
DS 5

CYCLE WILL CONSIST : DRUG ADMINISTERED (C4-C6)	DAY 1	DAY 15
Doxorubicin (A) (25 mg/m2)	x	x
Dacarbazine (D) (375 mg/m2)	x	x
Brentuximab vedotin (Bv) (1.2 mg/kg)	x	x
Pembrolizumab (P) (400mg) IV every 6wks	C4 D01	C5 D15

Lee H et al, abs 15096

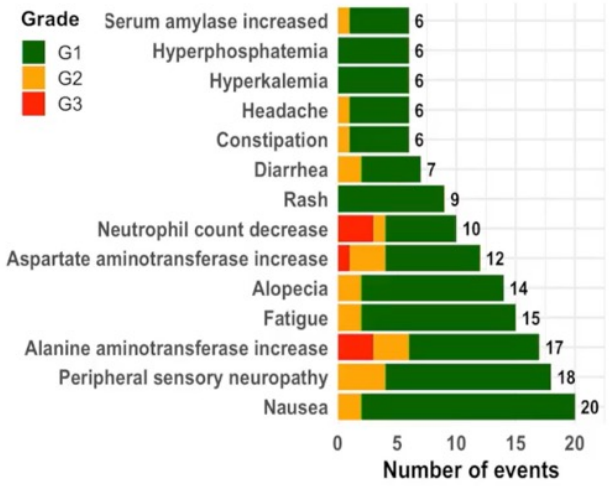
BV-pembro-AD

Patient Demographics and Disease Characteristics	N=25 (%)
Age, median years (range)	**35** (19-78)
Sex, Female, n (%)	**12** (48)
Race, White, n (%)	**16** (64)
Disease stage at initial diagnosis, n (%)	
II Bulky	**8** (32)
III	**5** (20)
IV	**12** (48)
Extranodal disease present, n (%)	**13** (52)
B symptoms present at initial diagnosis, n (%)	**8** (32)
International Prognostic Score, n (%)	
0-1	**12** (48)
2-3	**11** (44)
4-7	**2** (8)

End Of Therapy CR	Frequency (n)	Percentage (%)
DS 1	5	20%
DS 2	14	56%
DS 3	3	12%
DS 4	3	12%
DS 5	0	0%
Total	**25**	**100%**

CR RATE at EOT : 88%

Treatment related adverse events (Any grade)

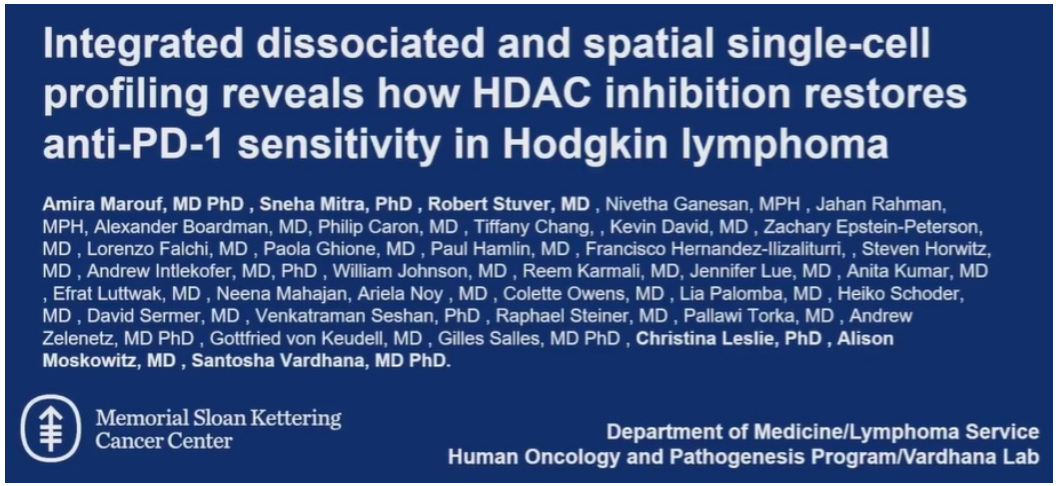


Lee H et al, abs 15096

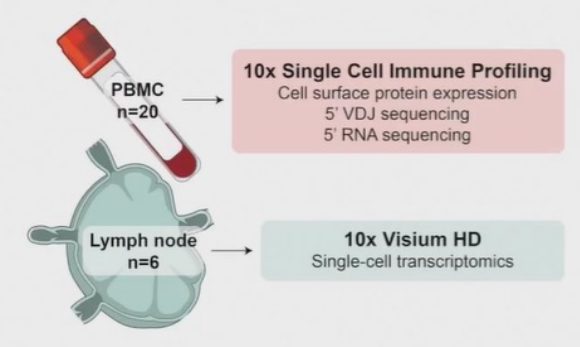
3053 Final Response and Survival Results from a Phase II Trial of Pembrolizumab and Entinostat in Relapsed/Refractory Hodgkin Lymphoma

- Treatment consisted of **pembrolizumab 200 mg every 21** days plus **entinostat 5-7 mg on days 1, 8 and 15** of each 21-day cycle. Treatment was continued until progression of disease (POD), unacceptable toxicity, or death, for a maximum of 35 cycles (two years)
- 39 R/R cHL
- median number of prior therapies was 5 (range: 2-18)
- median PFS was 12.1 months (95% CI 7.3-24.5)

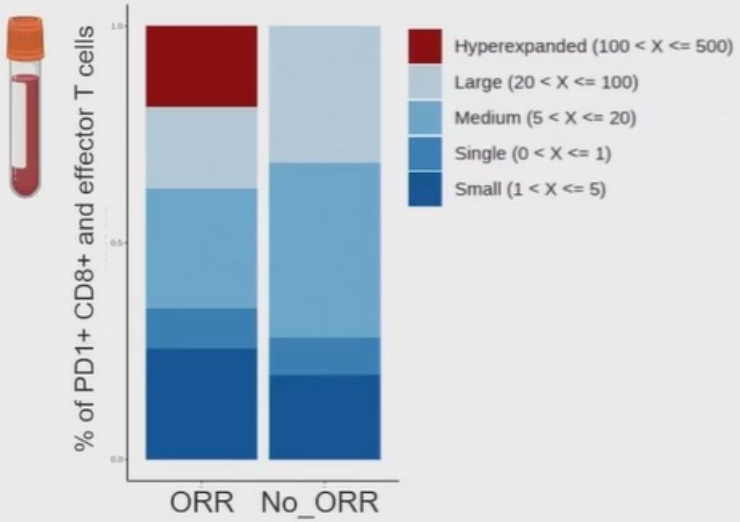
Stuver A et al, ASH 2024



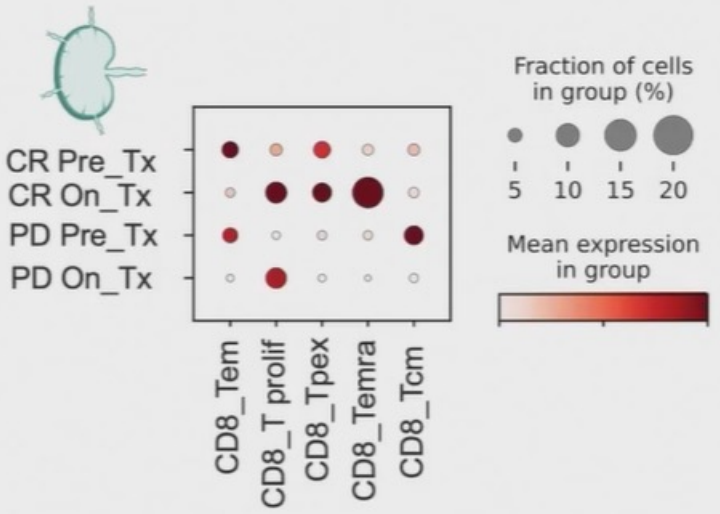
Hypothesis: HDAC inhibition can restore anti-PD1 sensitivity in cHL by reversing myeloid cell-driven immunosuppression.



HDACi enables effector CD8+ T cell expansion and tumor infiltration in responders



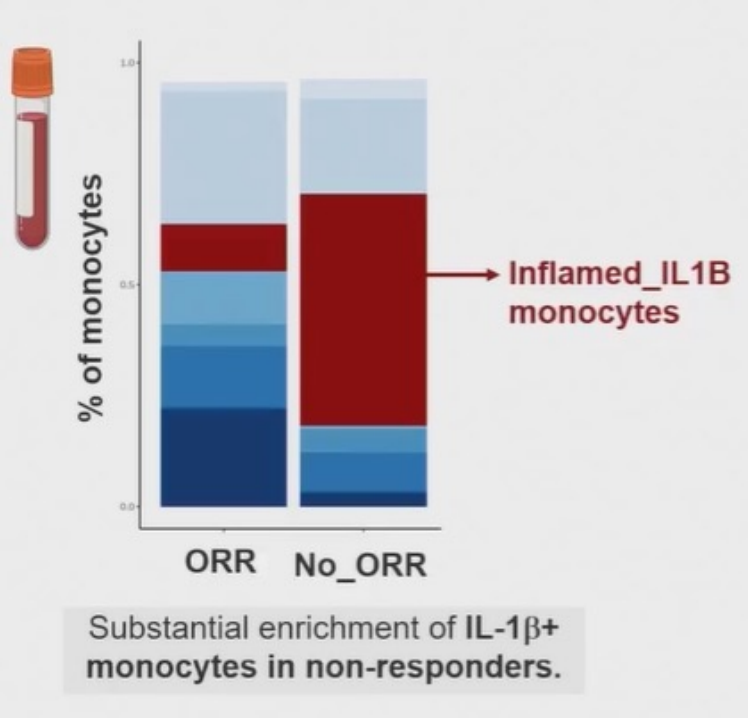
Peripheral CD8⁺ T-cell clonal expansion restricted to responders.

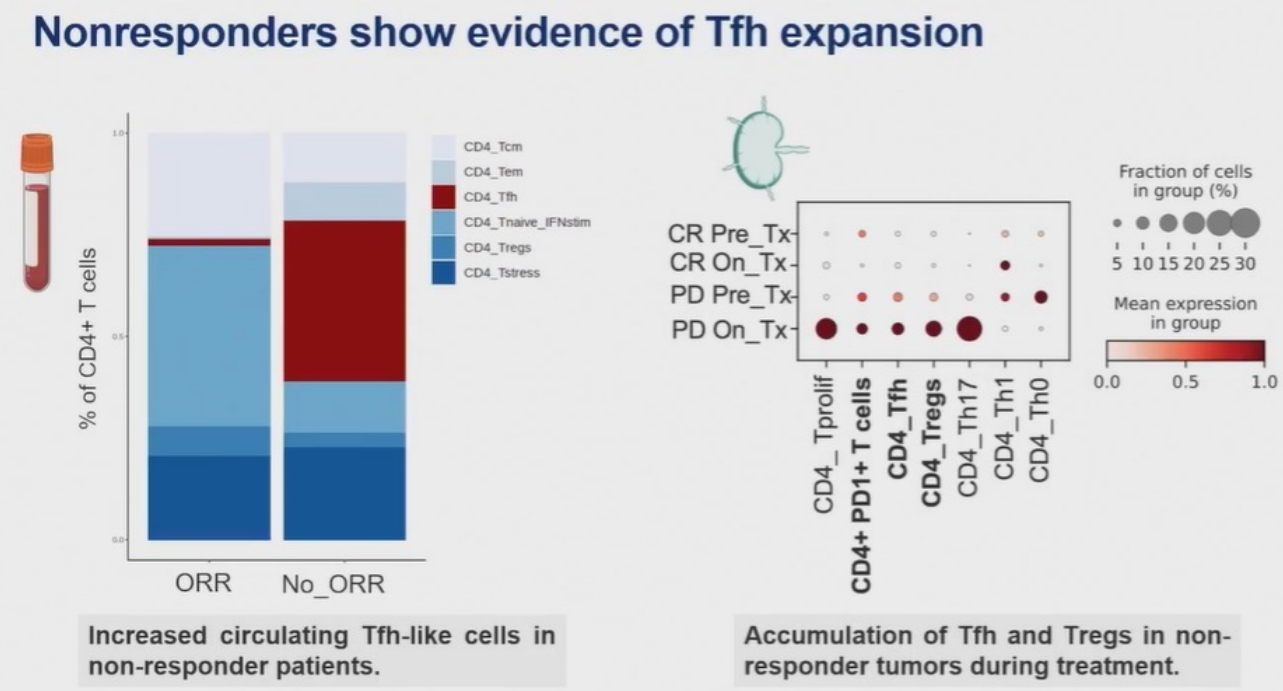


Enhanced effector and terminally differentiated T cell infiltration in the responder on-treatment.

Marouf A et al, abs 150

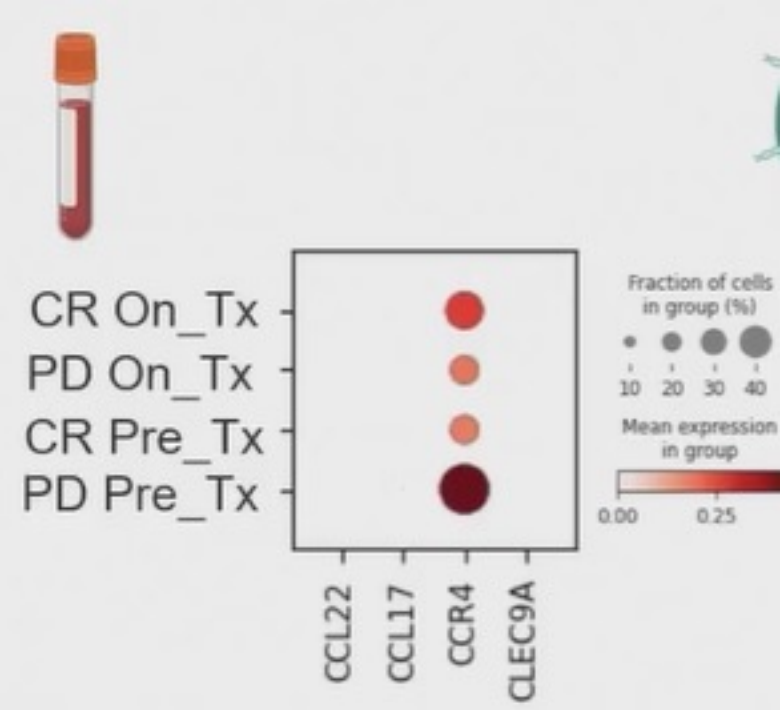
Non-responders characteristics



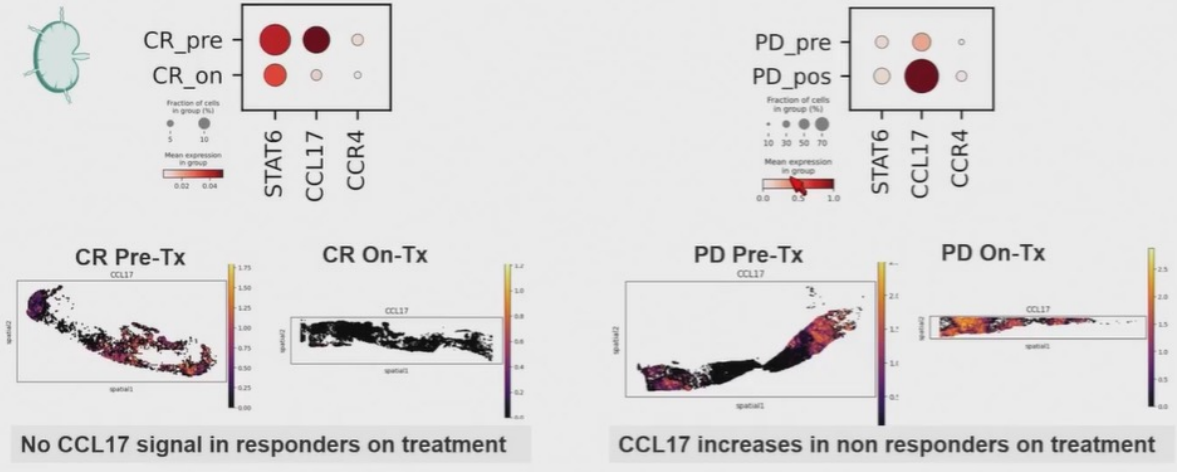


Marouf A et al, abs 150

CCR4+ CD4 T cells' niches depend on STAT6-driven CCL17 chemokine production by HRS cells.



HDAC inhibition restores anti-PD1 sensitivity by locally disrupting CCL17-CCR4 HRS-CD4 interactions.



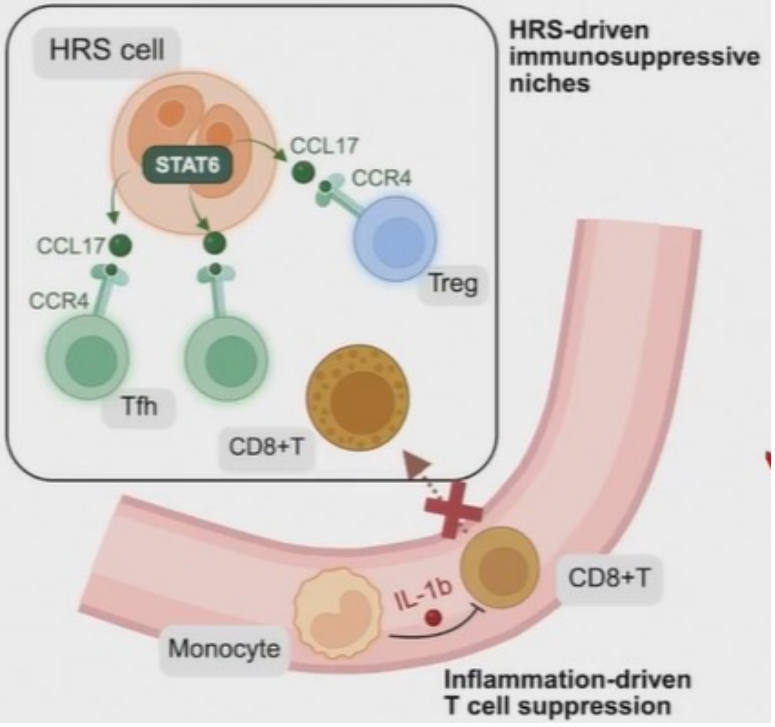
No CCL17 signal in responders on treatment

CCL17 increases in non responders on treatment

Marouf A et al, abs 150

Conclusion

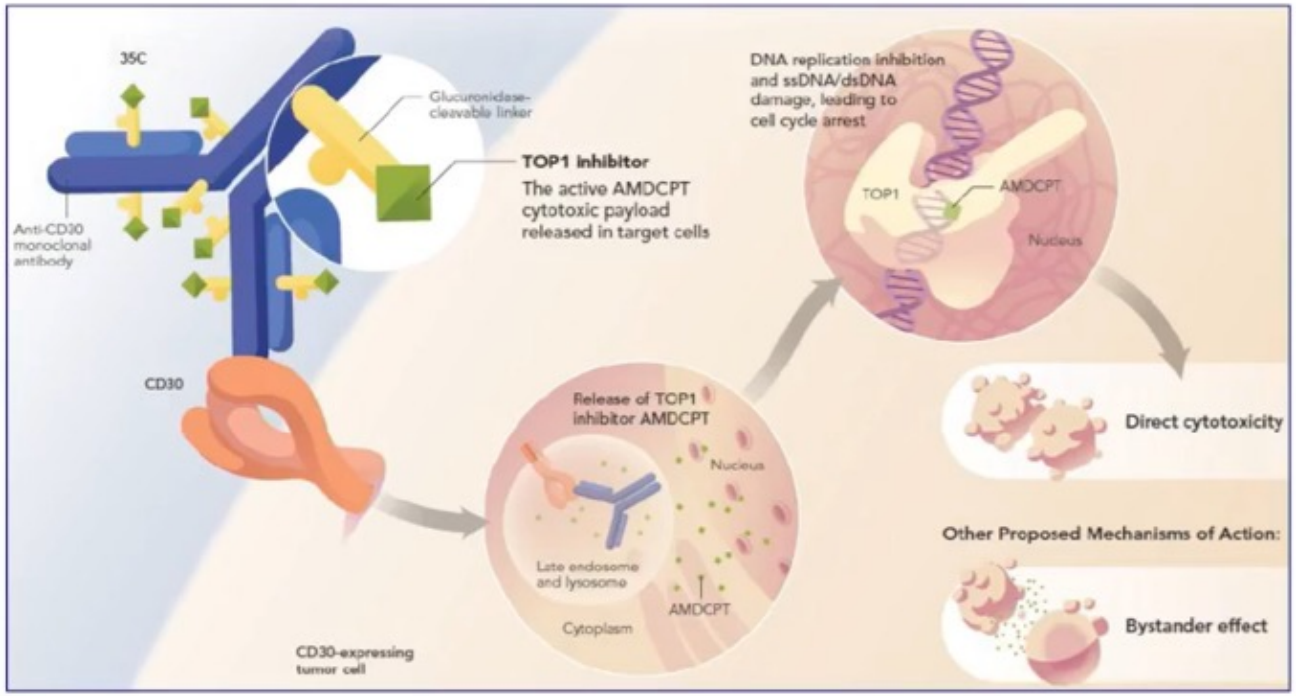
- Entinostat restores clinical sensitivity to anti-PD-1 therapy in patients with refractory HL.
- 2 layers **foster resistance to immune checkpoint blockade** in HL.
  - ✓ Sustained **myeloid inflammation**, which limits CD8 T cell expansion and infiltration
  - ✓ Local **HRS-CD4 immunosuppressive niches** driven by STAT6-dependent **CCL17 -CCR4** signaling.



Marouf A et al, abs 150

PF-08046044 (35C) Is a Next Generation CD30 Targeted ADC

- 35C comprised of a CD30-directed monoclonal antibody, conjugated to a camptothecin-derived topoisomerase 1 inhibitor payload[1]
- Direct tumor cell killing via internalization of the CPT cytotoxic payload
- Bystander effect enables killing of neighboring tumor cells that do not express CD30
- Potential for innate immune activation, Treg targeting, and T cell stimulation
- 35C induces cytotoxicity in cHL BV-resistant cell lines and inhibits tumor growth in animal models[2]



Thiruvengadam S et al, abs 155

Study Design and Inclusion Criteria

Part A
Dose escalation
35C administered IV Q3W based on TBW
0.6 – 4.0 mg/kg

→

Part B
Dose optimization (optional)

→

Part C
Disease-specific dose expansion
(R/R cHL, PTCL, and DLBCL)

Inclusion criteria: Parts A and B

- Age ≥ 18 years
- ECOG PS of 0 or 1
- Adequate organ function
- Measurable disease per Lugano criteria (2014)

Diagnosis and prior therapy:

- R/R cHL ≥ 3 prior therapies, including ASCT or PD-1 inhibitor, or 2 if no other appropriate treatment
- R/R PTCL (excluding sALCL) ≥ 2 prior therapies or 1 if no other appropriate treatment
- R/R sALCL ≥ 2 prior therapies including BV or 1 with BV-CHP
- R/R DLBCL ≥ 2 prior therapies, including ASCT or CAR-T cell therapy, if eligible
- For patients with PTCL or DLBCL - CD30 expression level of ≥ 1% in tumor biopsy

Endpoints

- **Primary** – Safety and tolerability; to establish MTD and RDE
- **Secondary** – PK, immunogenicity and preliminary antitumor activity
- **Exploratory** – Biomarker assessments

Baseline Demographics and Disease Characteristics

	0.6 mg/kg (n = 2)	1.2 mg/kg[a] (n = 12)	2.0 mg/kg (n = 15)	2.5 mg/kg (n = 13)	3.2 mg/kg (n = 8)	4.0 mg/kg (n = 3)	Total (N = 53)
Age, years, median (range)	41.5 (41–42)	34.0 (28–87)	63.0 (24–81)	47.0 (27–79)	59.0 (28–75)	37.0 (37–42)	43.0 (24–87)
Male sex, n (%)	1 (50.0)	8 (66.7)	9 (60.0)	7 (53.8)	4 (50.0)	0	29 (54.7)
Disease diagnosis, n (%)							
cHL	**2 (100.0)**	**7 (58.3)**	**9 (60.0)**	**10 (76.9)**	**6 (75.0)**	**3 (100.0)**	**37 (69.8)**
PTCL	0	3 (25.0)	5 (33.3)	1 (7.7)	1 (12.5)	0	10 (18.9)
sALCL	0	3 (100.0)	1 (20.0)	1 (100.0)	1 (100.0)	0	6 (60.0)
PTCL, not otherwise specified	0	0	4 (80.0)	0	0	0	4 (40.0)
DLBCL	0	2 (16.7)	1 (6.7)	2 (15.4)	1 (12.5)	0	6 (11.3)
ECOG PS, n (%)							
0	0	7 (58.3)	8 (53.3)	8 (61.5)	3 (37.5)	2 (66.7)	28 (52.8)
1	2 (100.0)	5 (41.7)	7 (46.7)	5 (38.5)	5 (62.5)	1 (33.3)	25 (47.2)
Ann Arbor Staging at study entry, n (%)							
Stage II	0	0	2 (13.3)	0	1 (12.5)	0	3 (5.7)
Stage III	0	3 (25.0)	3 (20.0)	2 (15.4)	4 (50.0)	0	12 (22.6)
Stage IV	2 (100.0)	9 (75.0)	10 (66.7)	11 (84.6)	3 (37.5)	3 (100.0)	38 (71.7)
Prior lines of therapy, median (range)	8.5 (4–13)	6.5 (2–10)	4.0 (2–14)	5.0 (3–15)	5.0 (1–7)	10.0 (3–10)	**5.0 (1–15)**
Prior treatment with BV, n (%)	2 (100.0)	11 (91.7)	13 (86.7)	12 (92.3)	5 (62.5)	2 (66.7)	**45 (84.9)**
Prior treatment with PD-1 inhibitor, n (%)	2 (100.0)	8 (66.7)	10 (66.7)	11 (84.6)	6 (75.0)	3 (100)	**40 (75.5)**
Prior ASCT, n (%)	1 (50.0)	4 (33.3)	7 (46.7)	6 (46.2)	5 (62.5)	2 (66.7)	**25 (47.2)**

cHL Population Characteristics (N=37)

- Median (range) prior lines of therapy: 6 (2–15)
- Prior BV: 35/37 (94.6%)
- Prior PD-1 inhibitor: 35/37 (94.6%)
  - Nivolumab 26/37 (70.3%)
  - Pembrolizumab 28/37 (75.7%)
- Prior ASCT: 23/37 (62.2%)

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Safety

	0.6 mg/kg (n = 2)	1.2 mg/kg (n = 12)	2.0 mg/kg[a] (n = 15)	2.5 mg/kg (n = 13)	3.2 mg/kg (n = 8)	4.0 mg/kg (n = 3)	Total (N = 53)
Any treatment-related TEAE	0	11 (91.7)	13 (86.7)	13 (100.0)	7 (87.5)	3 (100.0)	47 (88.7)
Nausea	0	9 (75.0)	7 (46.7)	7 (53.8)	4 (50.0)	3 (100.0)	30 (56.6)
Neutropenia	0	1 (8.3)	3 (20.0)	9 (69.2)	5 (62.5)	2 (66.7)	20 (37.7)
Anemia	0	4 (33.3)	0	7 (53.8)	6 (75.0)	2 (66.7)	19 (35.8)
Fatigue	0	3 (25.0)	5 (33.3)	5 (38.5)	1 (12.5)	1 (33.3)	15 (28.3)
Thrombocytopenia	0	0	2 (13.3)	5 (38.5)	2 (25.0)	1 (33.3)	10 (18.9)
Alopecia	0	0	4 (26.7)	3 (23.1)	1 (12.5)	1 (33.3)	9 (17.0)
Constipation	0	2 (16.7)	1 (6.7)	3 (23.1)	1 (12.5)	1 (33.3)	8 (15.1)
Rash maculopapular	0	2 (16.7)	4 (26.7)	0	0	1 (33.3)	7 (13.2)
Diarrhea	0	2 (16.7)	1 (6.7)	2 (15.4)	0	1 (33.3)	6 (11.3)

- [a]**Primary antiemetic prophylaxis** was instituted at 2.0 mg/kg
- **No peripheral neuropathy** was observed

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90% of Patients Experienced a Reduction in Tumor Size

Efficacy

	0.6 mg/kg (n = 2)	1.2 mg/kg (n = 12)[a]	2.0 mg/kg (n = 15)	2.5 mg/kg (n = 13)	3.2 mg/kg (n = 8)	4.0 mg/kg (n = 3)	Total (N = 53)
ORR, n (%) [95% CI]	1 (50.0)	9 (75.0)	11 (73.3)	9 (69.2)	8 (100.0)	3 (100.0)	**41 (77.4)** [63.8–87.7]
CR, n (%) [95% CI]	0	3 (25.0)	4 (26.7)	3 (23.1)	3 (37.5)	0	**13 (24.5)** [13.8–38.3]
PR, n (%)	1 (50.0)	6 (50)	7 (46.7)	6 (46.2)	5 (62.5)	3 (100.0)	28 (52.8)
SD, n (%)	0	2 (16.7)	2 (13.3)	1 (7.7)	0	0	5 (9.4)
PD, n (%)	1 (50.0)	0	2 (13.3)	3 (23.1)	0	0	6 (11.3)

- **cHL Population** (N=37): **ORR 81.1%** and **CR rate 18.9%**

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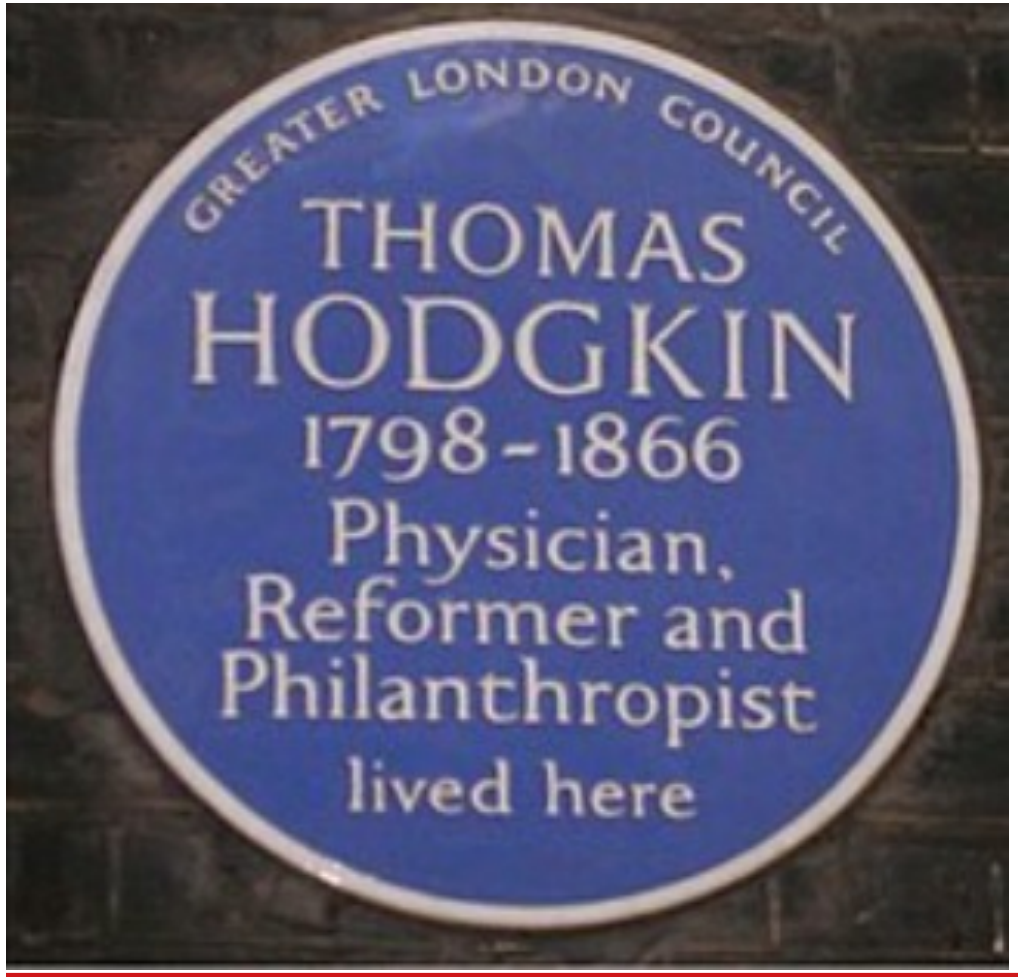
cHL @ ASH 2025: Summary

- BrECADD is the regimen who provides the highest cure rate in AS cHL and, if PET2 negative, with a short treatment duration
- Nivo-AVD confirmed at 3-ys follow-up to be more effective than BV-AVD with low toxicity and candidates as a potential new standard of care, expecially for elderly patients
- Promising preliminary data on C35, a new CD30 ADC, phase 1 trial



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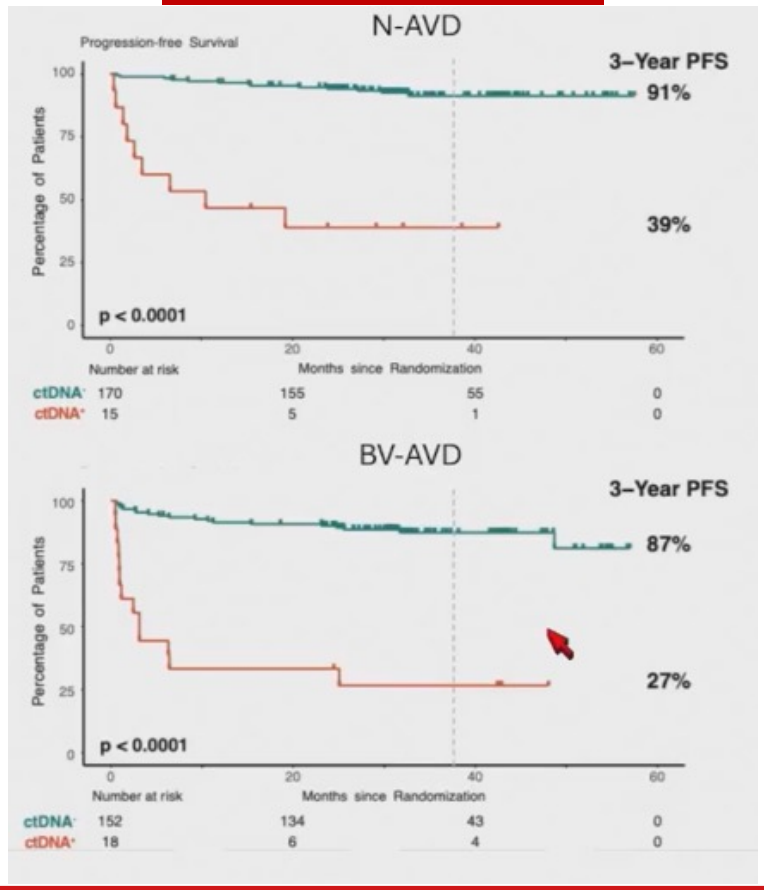
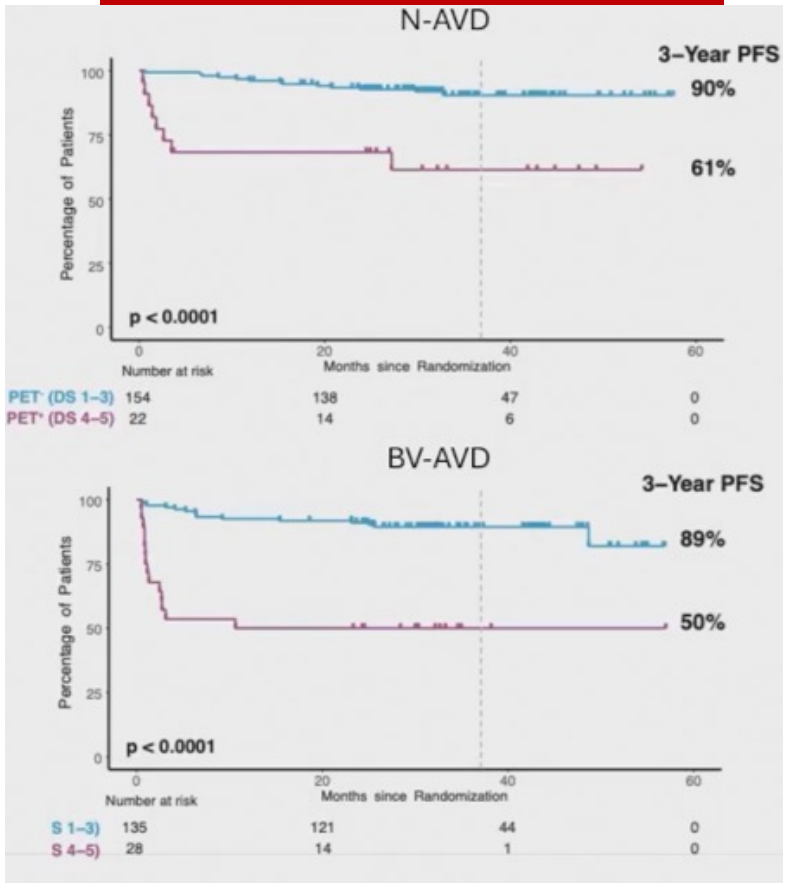
Grazie per l'attenzione!

Back up

CtDNA EOT



iPET EOT



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