Hodgkin lenfoma

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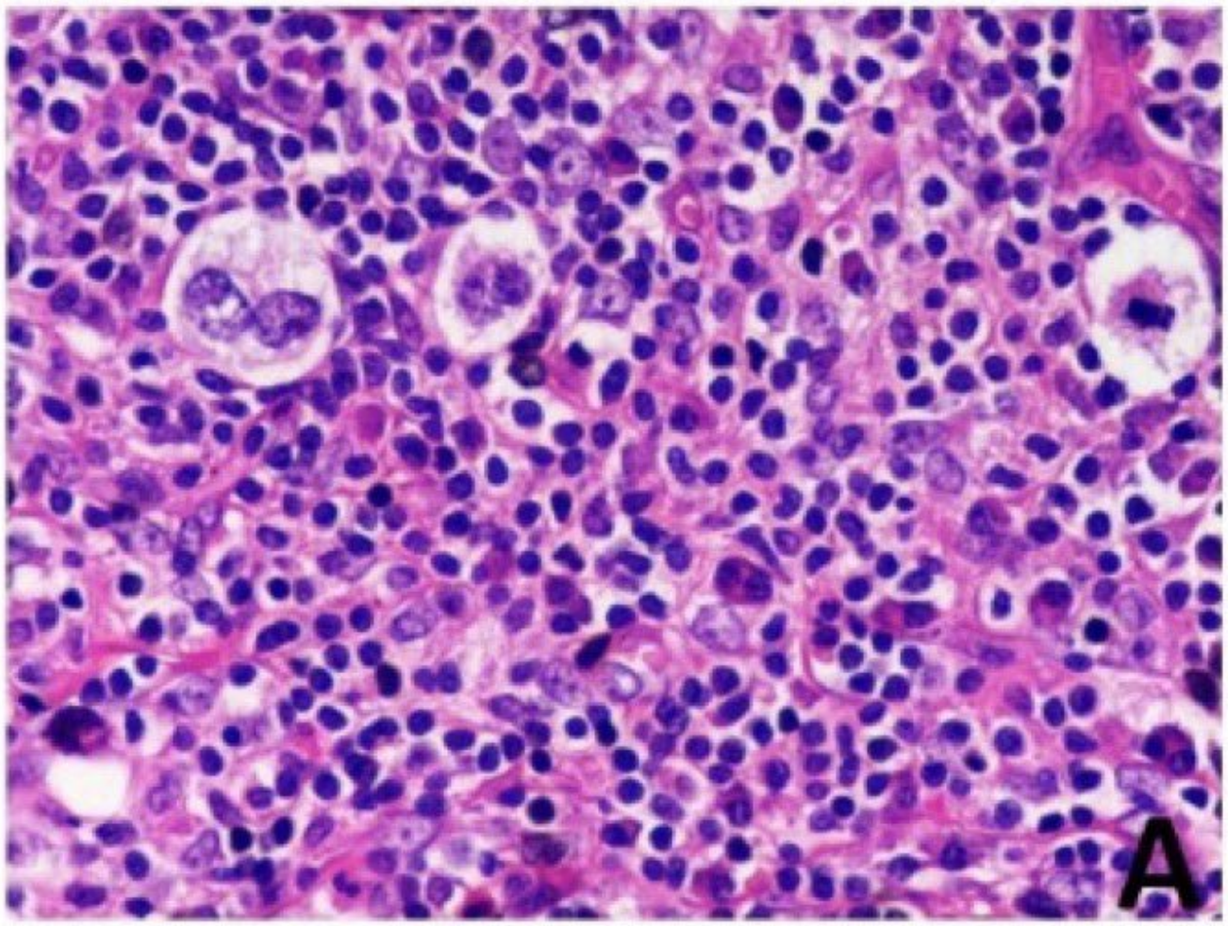
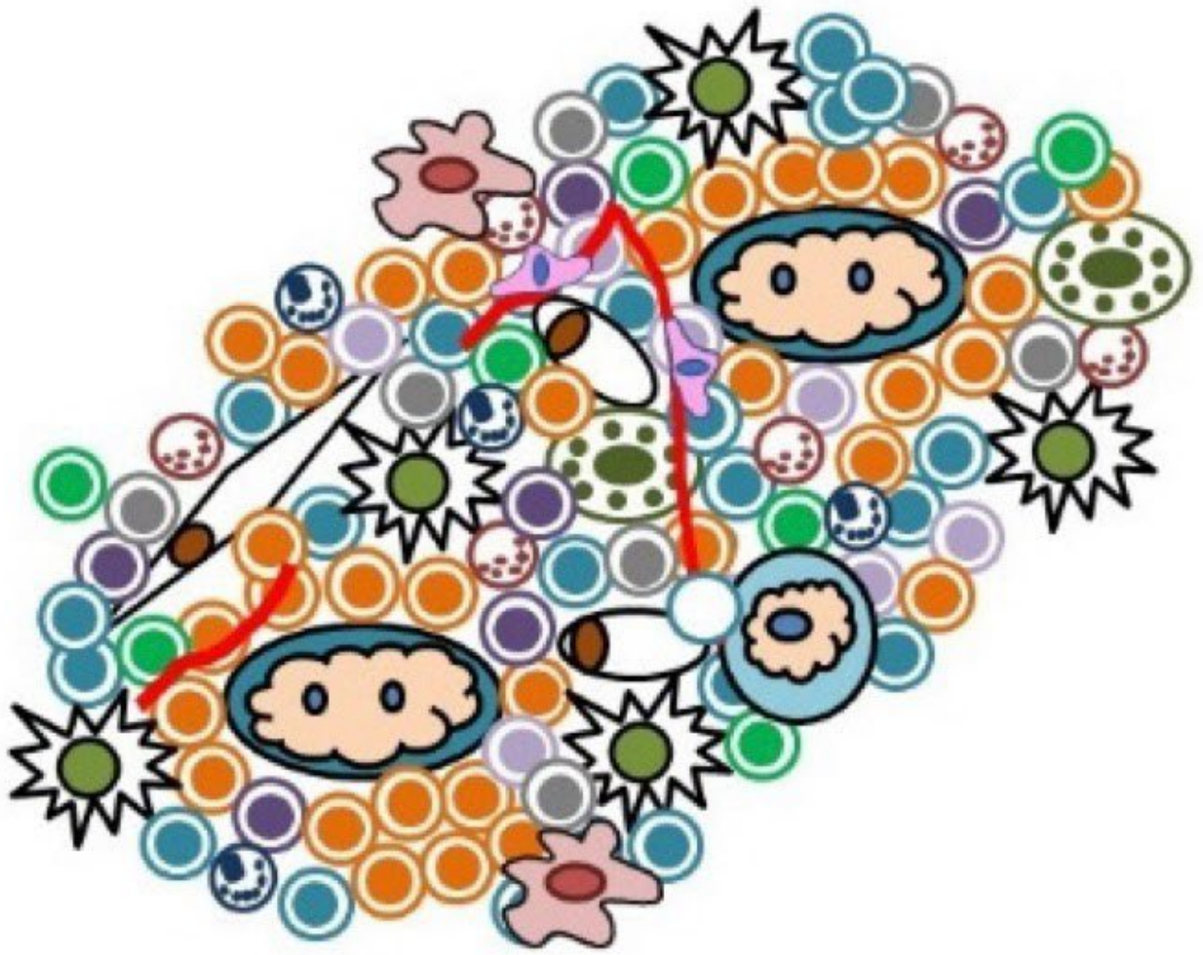
8 Ocak 2022

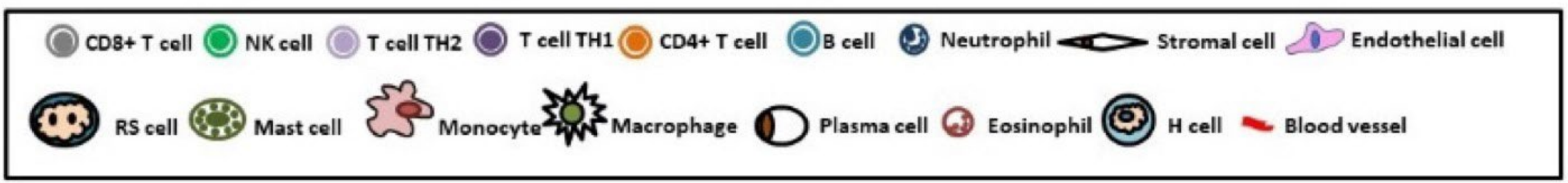
1. Hodgkin lenfomanın mutasyonel gelişimi

Hodgkin lenfomanın moleküler evrimi



%1-10





Opinto G, J Clin Med 2021

Hodgkin lenfomanın moleküler evrimi

Maura F, Univeristy of Miami, Paper: 805

Whole genome has a more comprehensive resolution than whole exome sequencing

Whole exome sequencing (WES)*

- Coding mutations
- Subclonal mutations
- Copy Number

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*Reichel et al. Blood 2015; Spina et al. Blood 2018; Tiacci et a. Blood 2018; Wienand et al. Blood Advances 2019

Hodgkin lenfomanın moleküler evrimi

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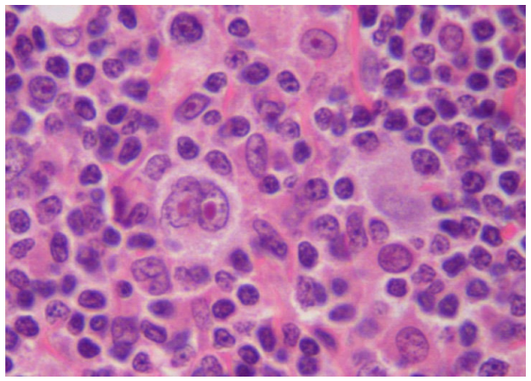
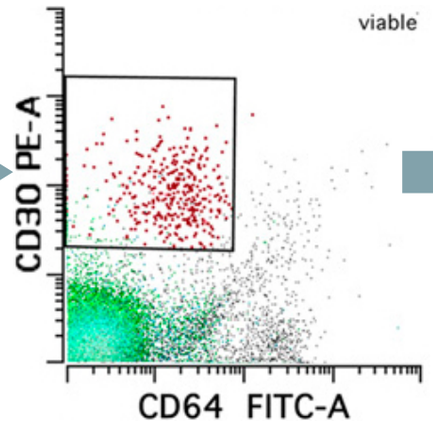
Tüm genom dizileme

Biyopsi (n=25)

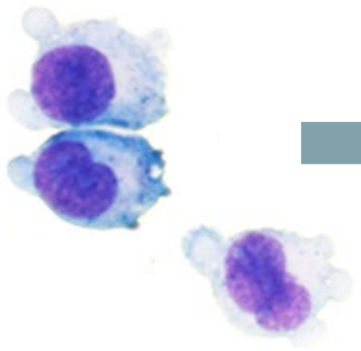


Pediatrik n=10
Adölesan=9
Erişkin=6

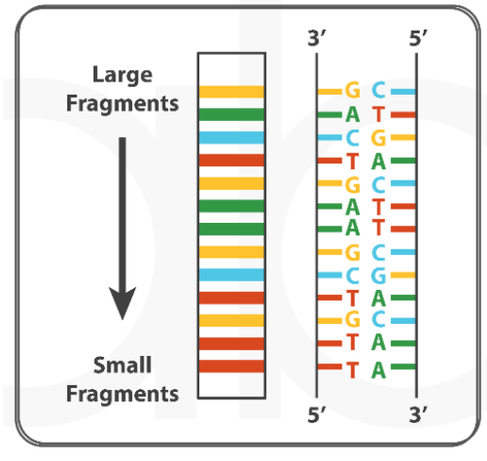
10-ab sıralama



RS DNA elde edilmesi

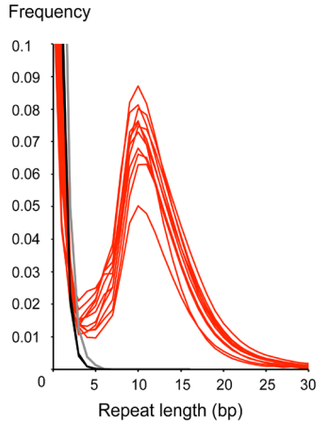


Dizileme



Amplifikasyondan kaynaklanan artefaktlar için sıkı bir kalite kontrol

Palindromik artefakt



Reichel, Blood 2018

Hodgkin lenfomanın moleküler evrimi

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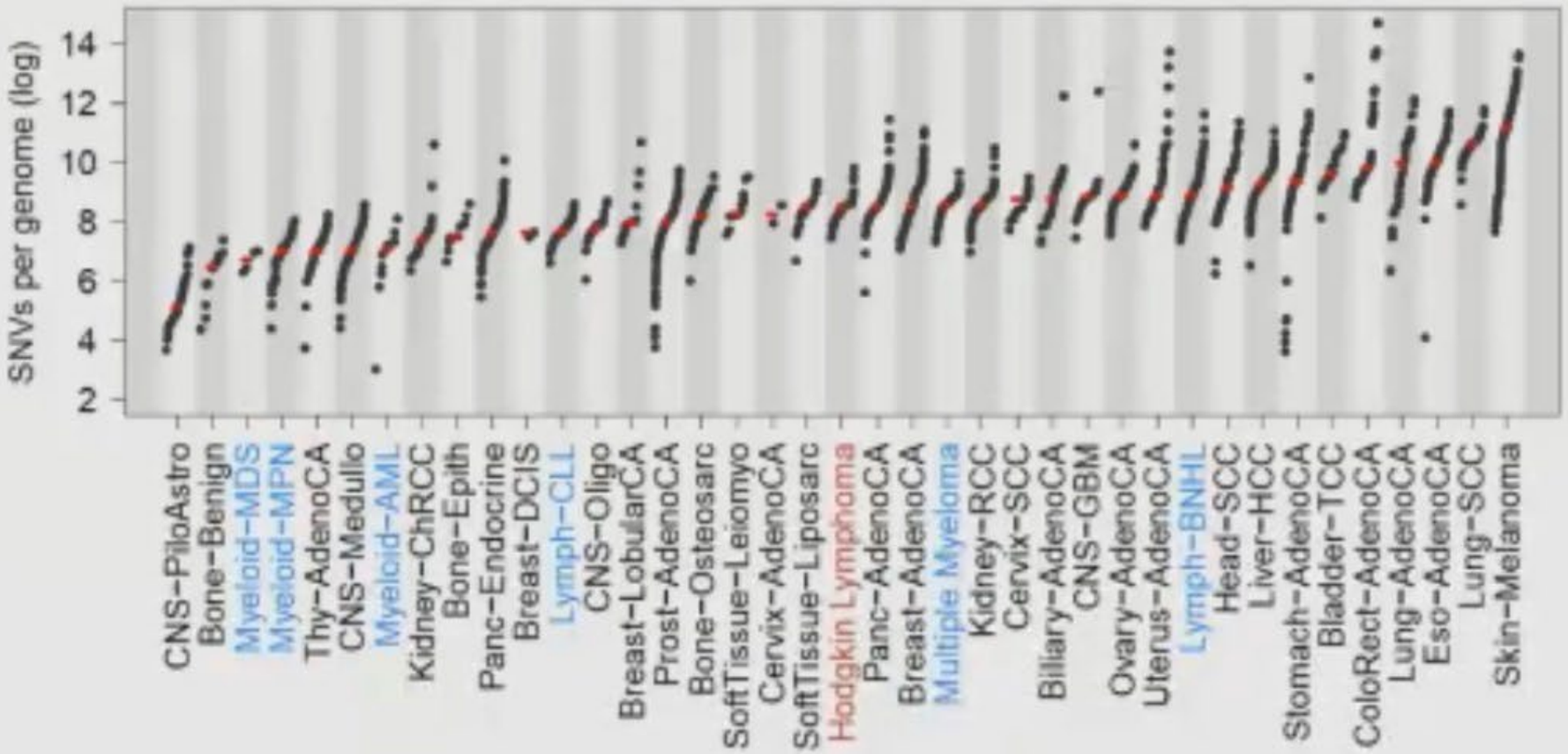
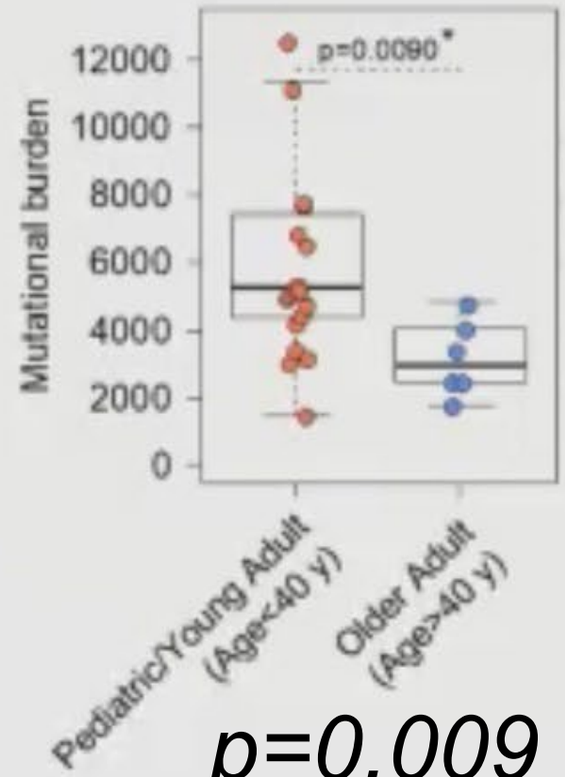
Hodgkin Lymphoma mutational burden

Ortanca 5006 SBS



5279 vs 2945



p=0.009

* Wilcoxon test

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Adapted from Alexandrov et al. Nature 2020

Hodgkin lenfomanın moleküler evrimi

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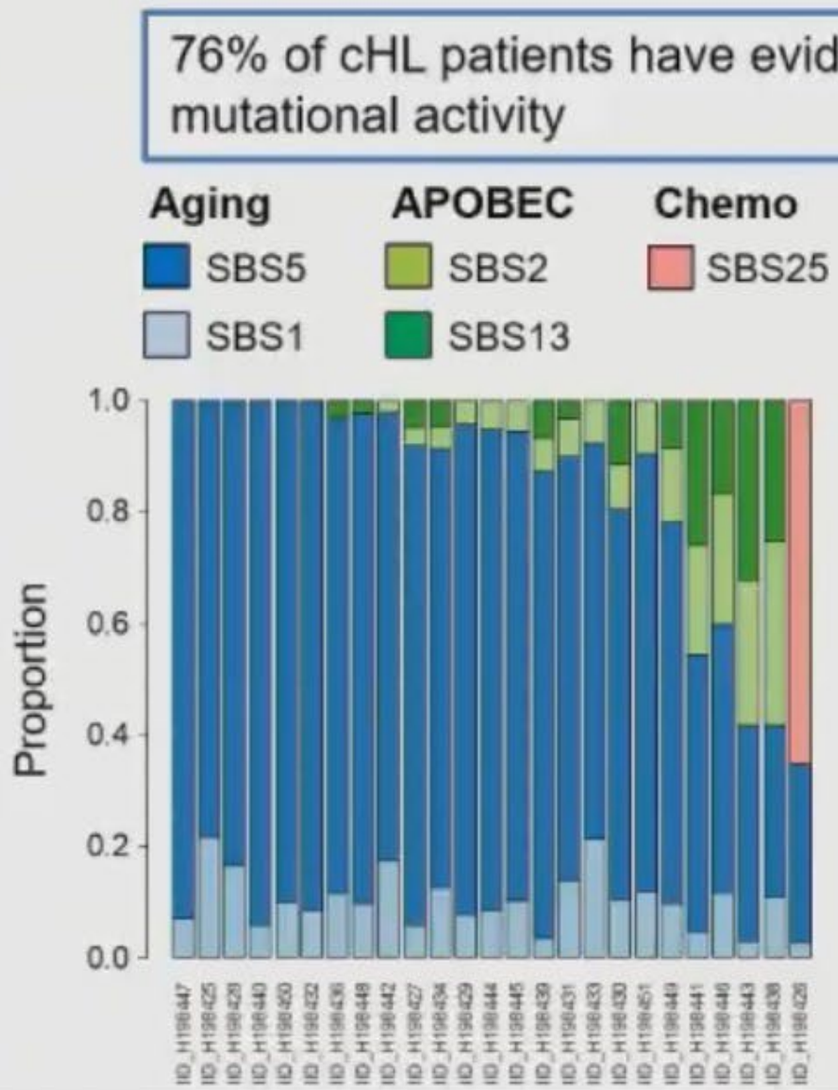
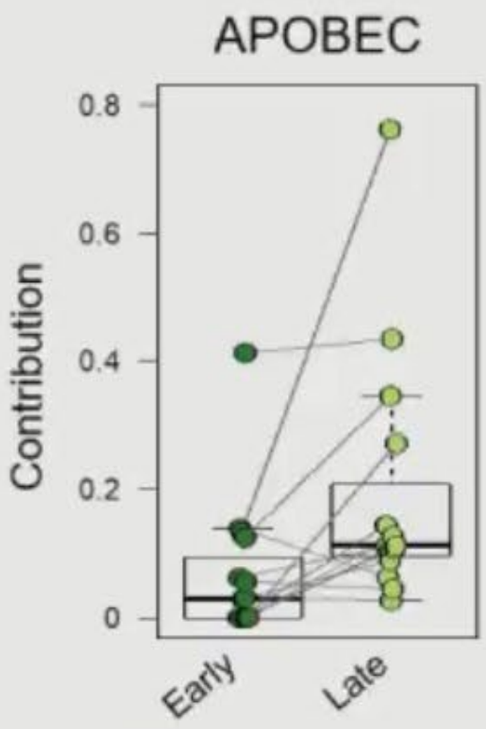
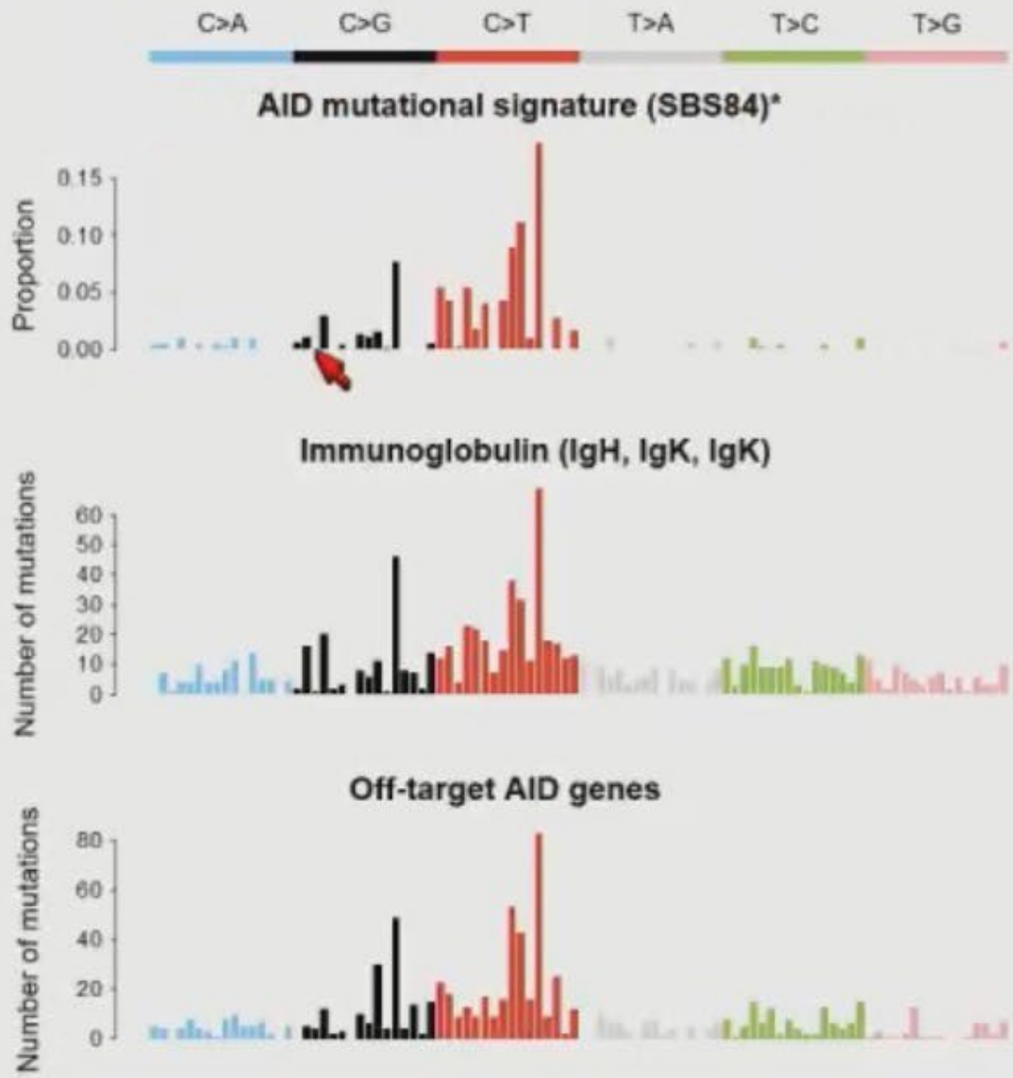
Hodgkin Lymphoma mutational signatures

76% of cHL patients have evidenced of APOBEC mutational activity







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Wienand et al. Blood Advances 2019; Maura et al. Nat Comm 2019
*https://cancer.sanger.ac.uk/signatures/sbs/; Alexandrov et al. Nature 2020

Hodgkin lenfomanın moleküler evrimi

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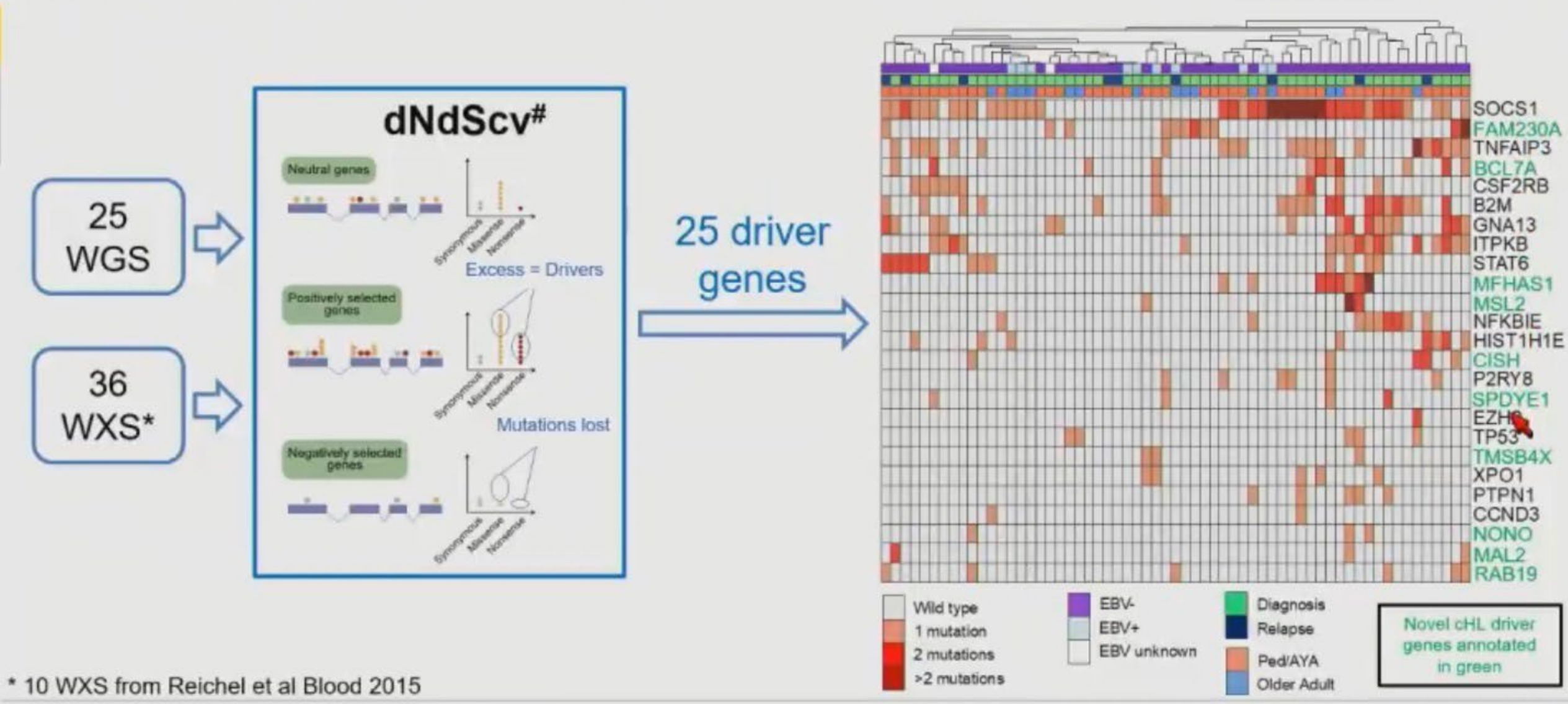
Mutations in driver genes in HL



* 10 WXS from Reichel et al Blood 2015

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\# Martincorena et al. Cell 2017

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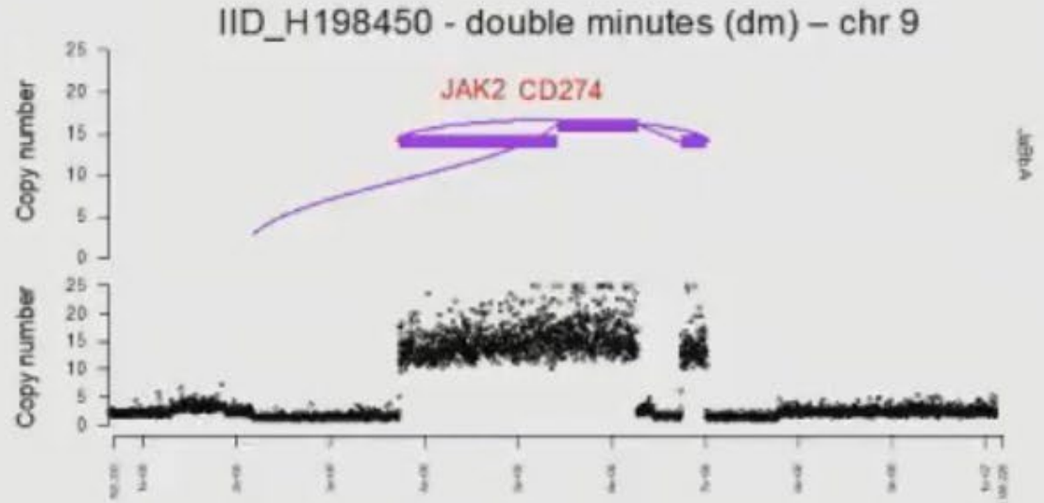
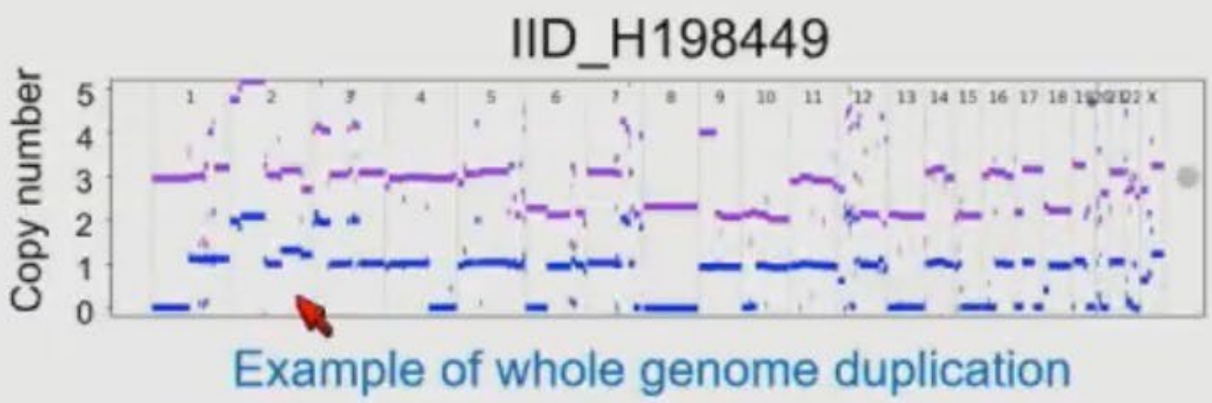
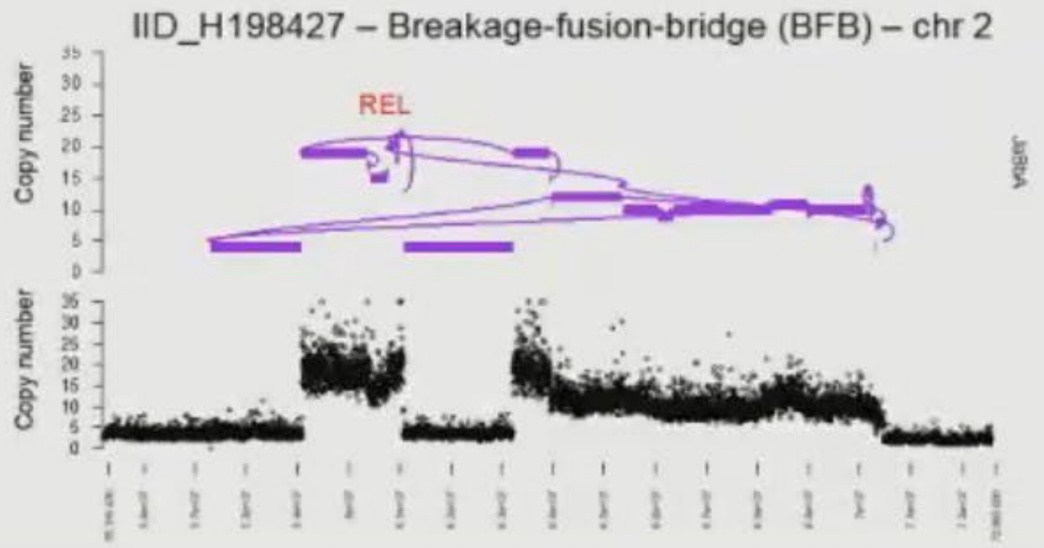
cHL high ploidy and recurrent aneuploidies

WGS and WXS were characterized by high ploidy (median 2.95, range 1.66-5.33), and 54% of patients have a whole genome duplication





Example of whole genome duplication



Hodgkin lenfomanın moleküler evrimi

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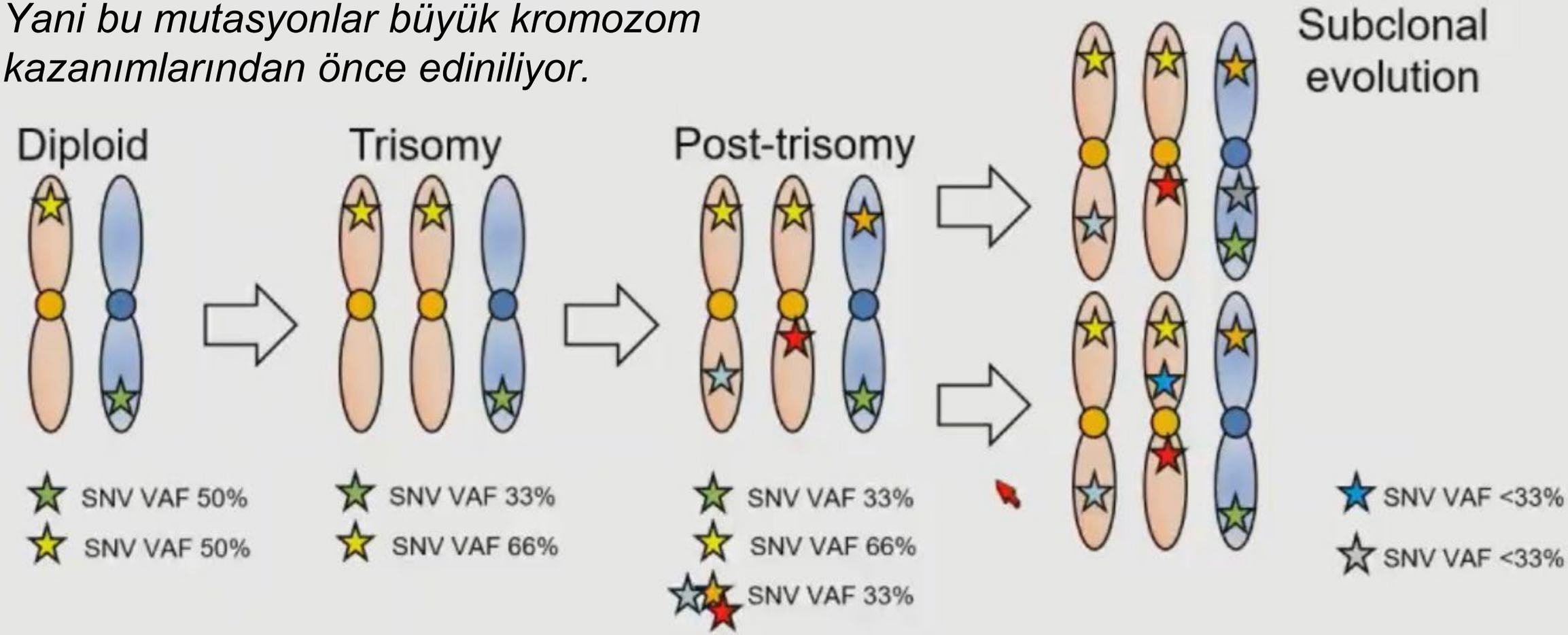
Timing the event using large chromosomal gains

Sürücü mutasyonların %61'i duplike olduğu görülmüş
Yani bu mutasyonlar büyük kromozom kazanımlarından önce ediniliyor.



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Maura et al. Nature Comm 2020
Gerstung et al. Nature 2020

Hodgkin lenfomanın moleküler evrimi

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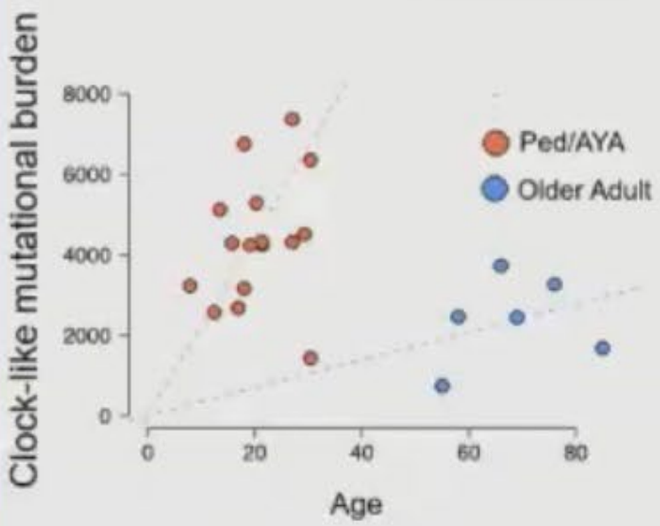
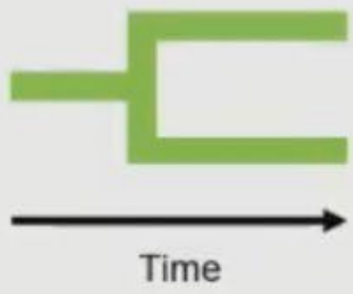
Timing large chromosomal gain events occurred

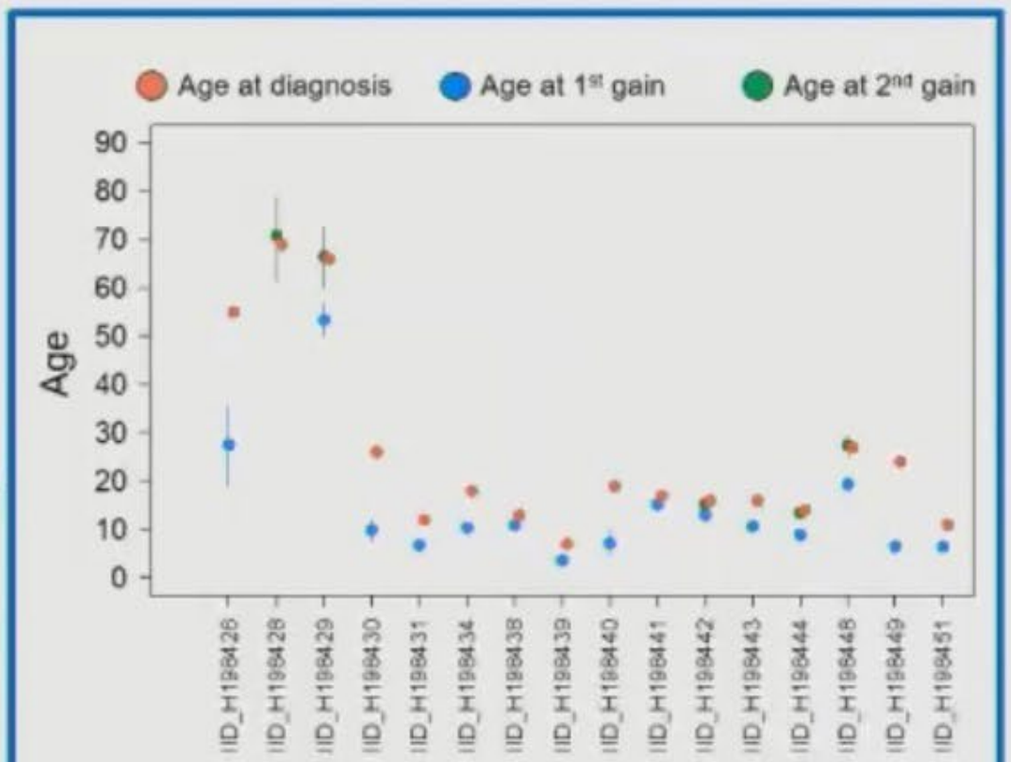
SBS1 and SBS5 mutational signatures are known to be constant over time (clock like*)



Only SBS1 and SBS5



Mol_time will be proportional to patient age



The first multi-chromosomal gain event is often acquired several years before the diagnosis [i.e., 5.6 (range 1.8-16) years in pediatric/AYA patients respectively]

Hodgkin lenfomanın moleküler evrimi

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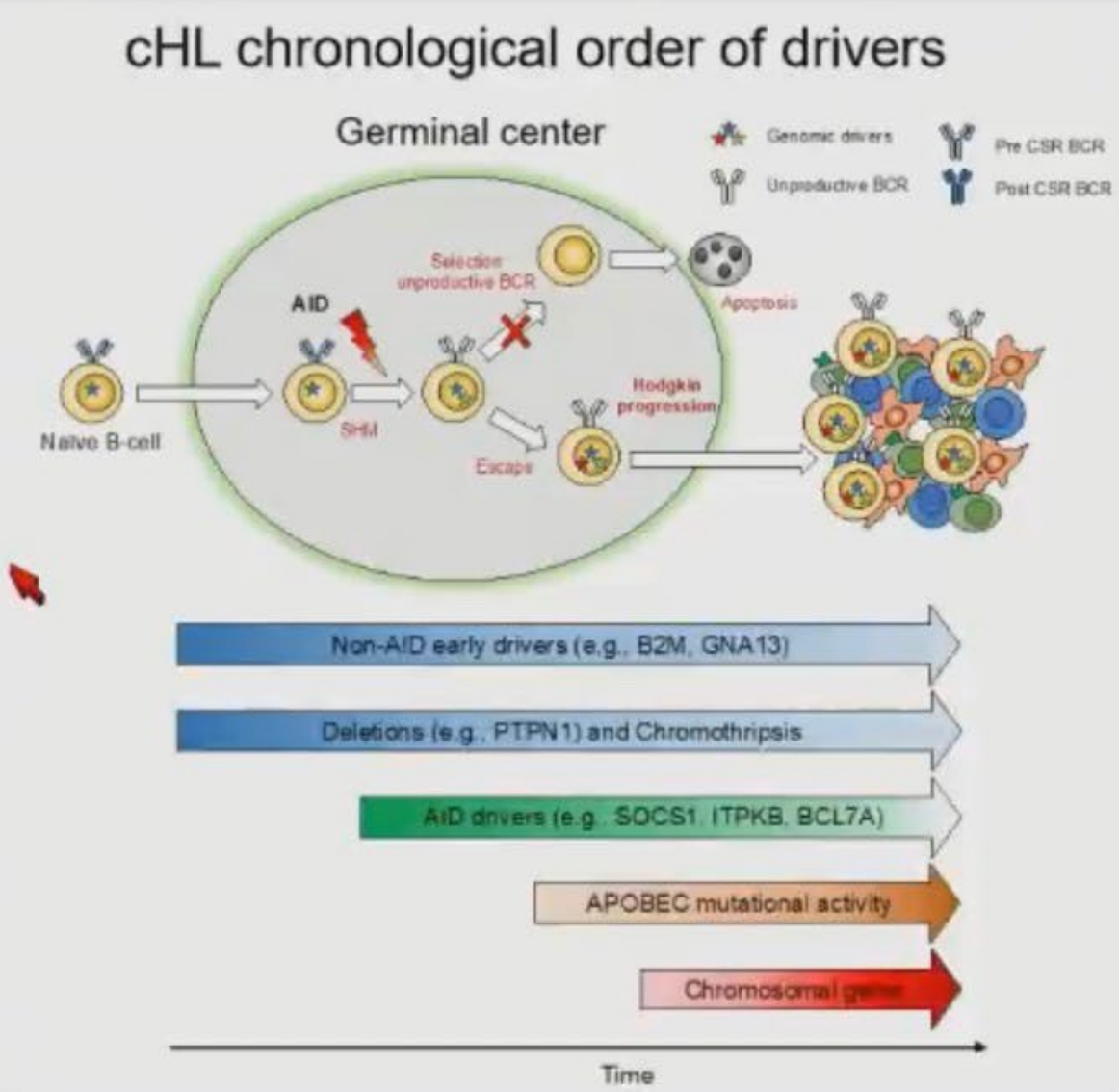
Conclusions

- Ped/AYA showed a higher mutational burden and clock-like rate (SBS1-SBS5) compared to older adults.
- Key driver mutations occurred early before large chromosomal gains
- cHL high ploidy and multiple chromosomal gains are often acquired through multiple, independent large chromosomal gain events including whole genome duplication.
- Large copy number gains are intermediate-late events in tumor history, with the first gain occurs years before the diagnosis.
- cHL genomic landscape is characterized by early several complex SV events such as double minutes, breakage-fusion-bridge, and chromothripsis often involving cHL driver genes
- APOBEC is a key cHL mutational process with an intermediate-late activity



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Pre-print available: https://www.biorxiv.org/content/10.1101/2021.11.05.467496v1

2. Prognostik faktörler: PET

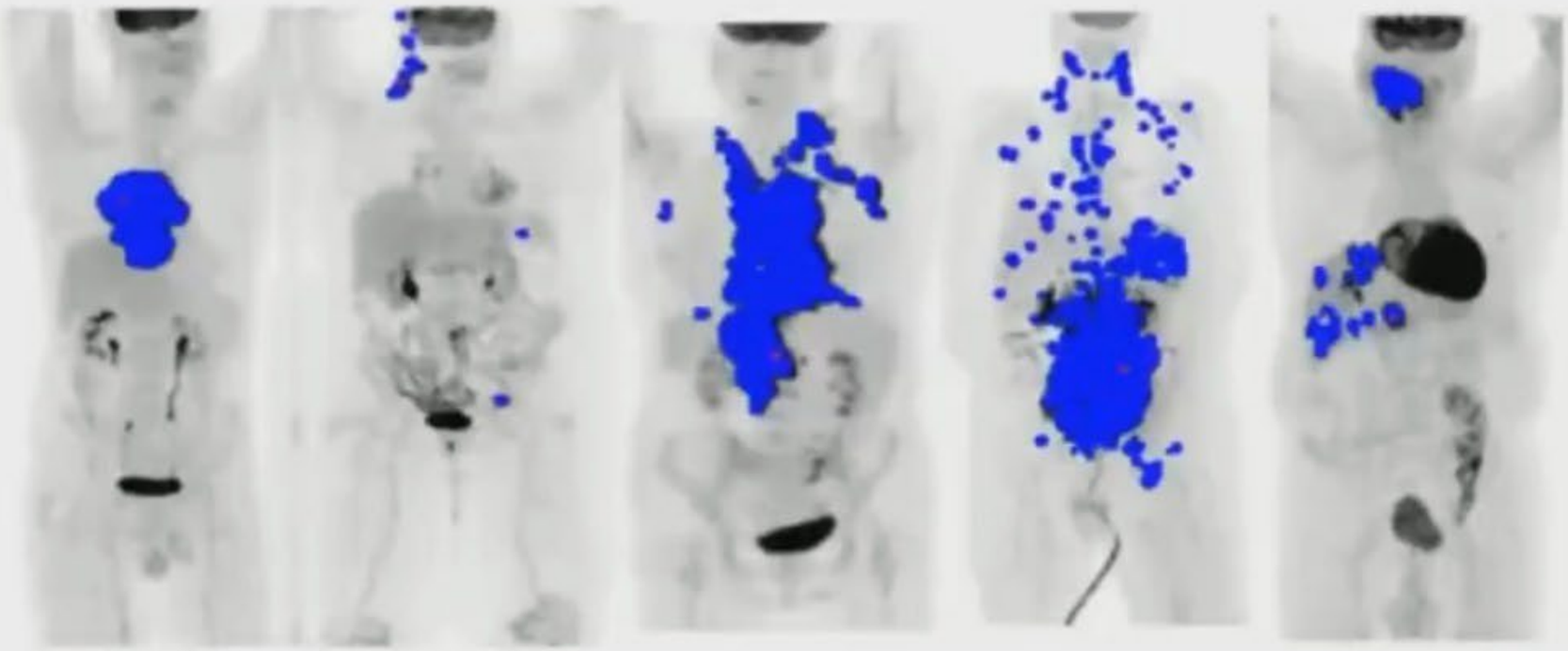
İleri evre HL'da TMTV ve tümör disseminasyonu

Kanoun S, LYSA, paper 880

Introduction

Tanı anındaki PET/BT özelliklerinin sağkalım üzerine etkisi var mı?

- TMTV : Tumor Burden Calculation



İleri evre HL'da TMTV ve tümör disseminasyonu

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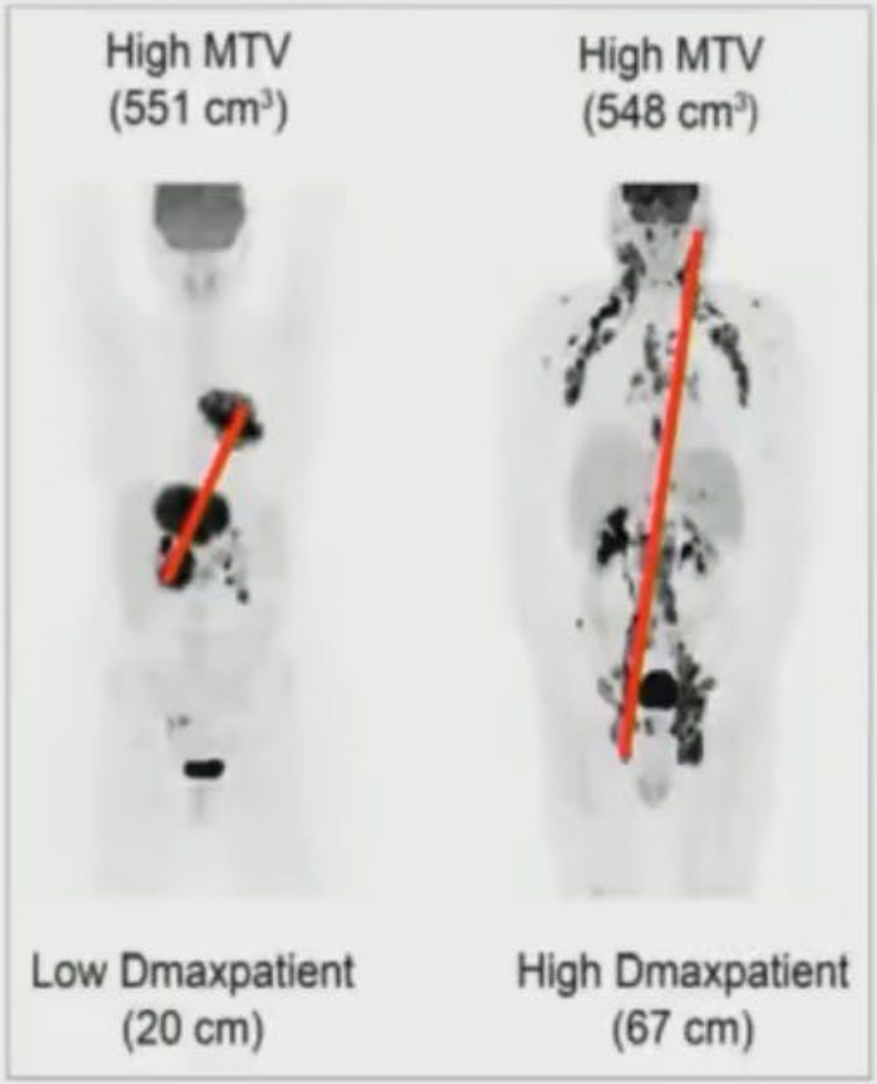
Introduction

- SDMax : Tumor Dissemination



İleri evre HL'da TMTV ve tümör disseminasyonu

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Aim

- To evaluate the prognostic value of baseline **Total Metabolic Tumor Volume** (TMTV) and **tumor dissemination** (SDmax) in **Hodgkin** Lymphoma **Ann Arbor stage III-IV** patients included in the **AHL2011** trial

İleri evre HL'da TMTV ve tümör disseminasyonu

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Material And Methods

- Ancillary study of the AHL2011 Trial
  - Ann Arbor stage **III** and **IV** subset, **634 patients included**
- TMTV calculation using 41% of SUVmax threshold on manual delineation of uptakes
- SDMax : Maximum distance between the delineated lesions normalized by body surface area
- Optimal thresholds for TMTV and SDmax were calculated using X-Tile and ROC curve approaches in a randomly assigned training (n=320) and validation sets (n=314)
- Median follow up : 5.6 years

İleri evre HL'da TMTV ve tümör disseminasyonu

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Results

- Median TMTV and SDmax were 215 ml and 0.221 m-1
- Optimal cutoffs were similar in the training and validation sets :
  - 220ml for TMTV (312 patients [49%] had High TMTV)
  - 0.330 m-1 for SDmax (149 patients [24%] had High SDmax)

İleri evre HL'da TMTV ve tümör disseminasyonu

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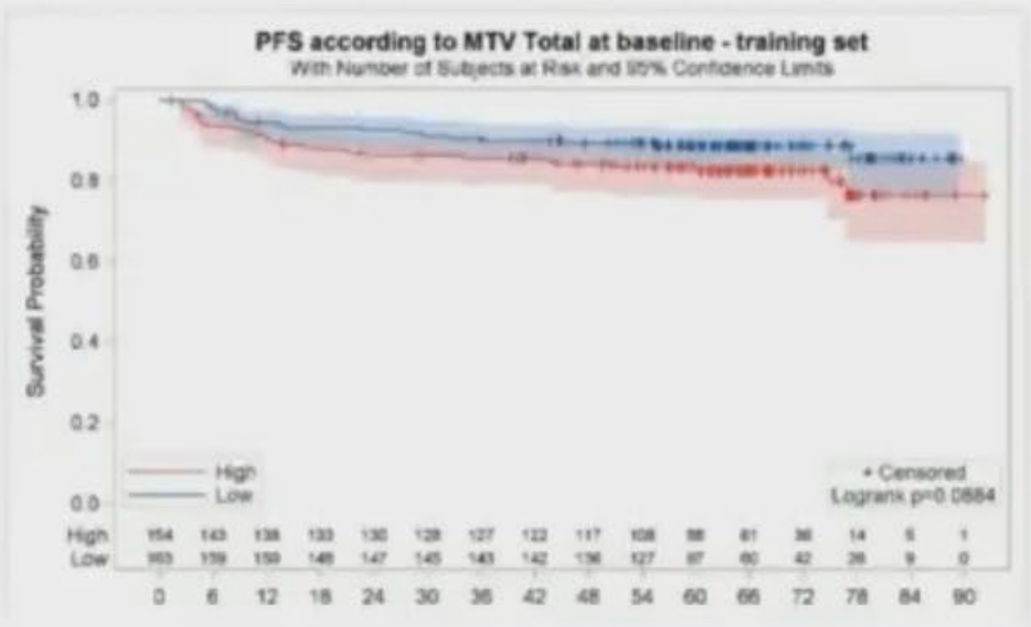
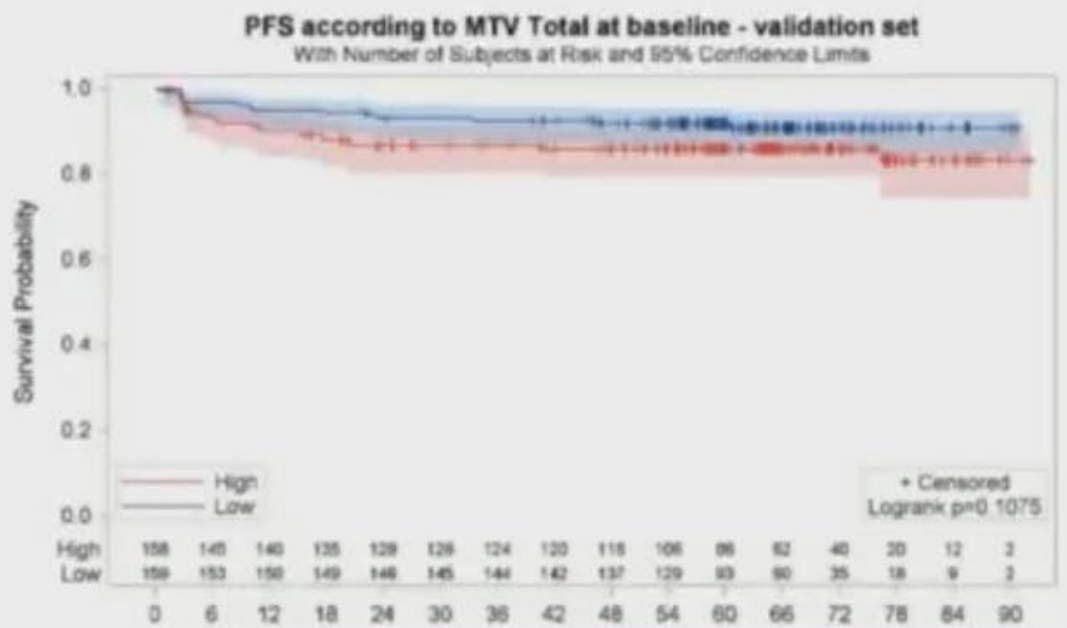
Results

- 5-year PFS for patients with TMTV>220ml was 84.1% vs 90.2% (p=0.02) in the whole population
  - Training set: 83% vs 89%, p=0.088
  - Validation set : 86% vs 92% p=0.11



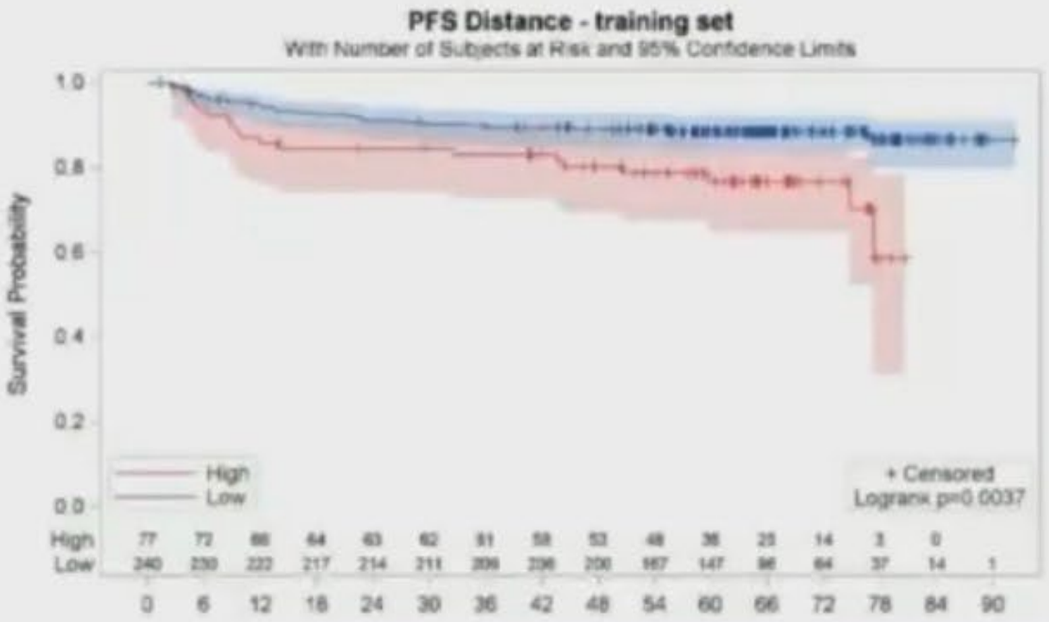


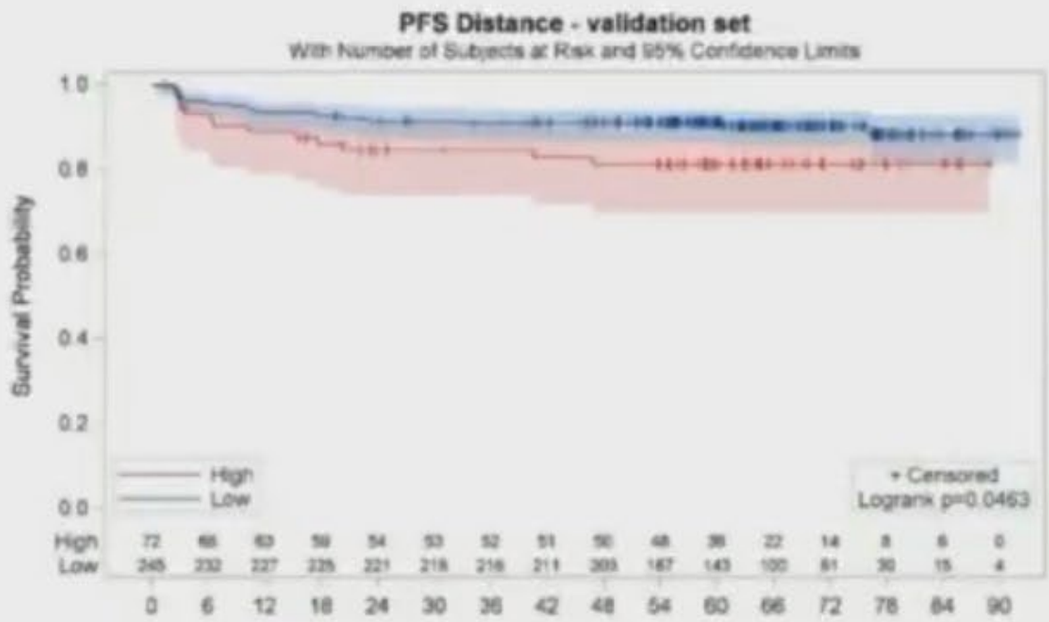
İleri evre HL'da TMTV ve tümör disseminasyonu

Kanoun S, LYSA, paper 880

Results

- 5-year PFS for patients with SDmax>0.333 m-1 was 78.8% vs 89.7%; HR=2.15 [95%CI: 1.38-3.35], p=0.0005 in the whole population
  - Training set: 77% vs 89%; p=0.0037
  - Validation set: 81% vs 91%; p=0.046





İleri evre HL'da TMTV ve tümör disseminasyonu

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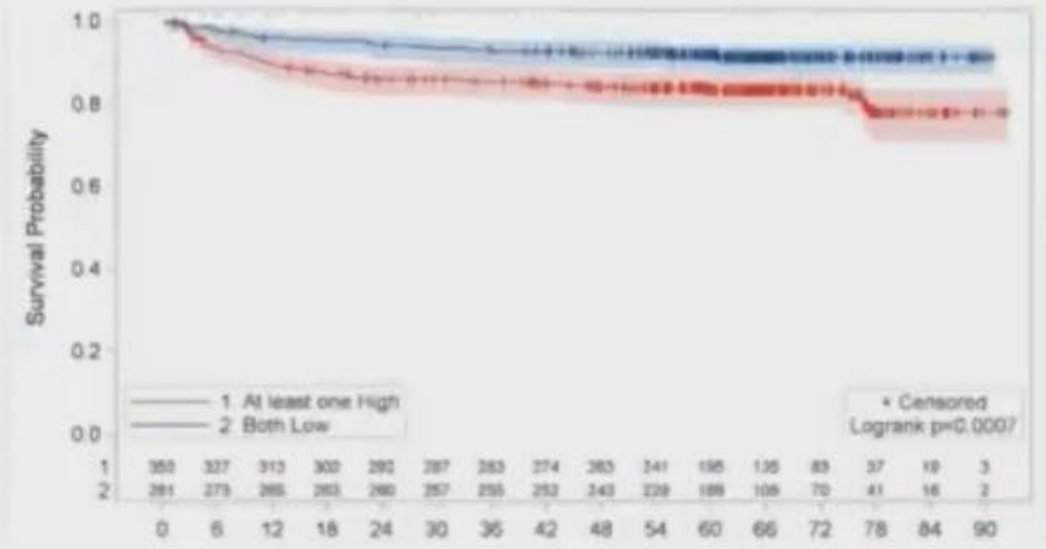
Results

- The combination of TMTV and SDmax allows to identify two subgroups of patients
  - Those having both low TMTV and low SDmax (n= 281; 44%)
  - Those having high TMTV and/or SDmax
  - 5-year PFS: 92% vs 83.4%; HR=2.24 [95%CI: 1.39-3.62], p=0.0007)



- In multivariate analysis, high TMTV (p=0.034), high SDmax (p=0.0002), PET2 (p=0.02) and PET4 (p<0.001) positivity retained independent prognostic value for predicting PFS.

İleri evre HL'da TMTV ve tümör disseminasyonu

Kanoun S, LYSA, paper 880

Discussion

- Largest series assessing the prognosis value of TMTV in advanced HL
  - TMTV predicts patients outcome in AHL2011 with a 220ml cutoff
  - TMTV was shown to predict only PET2 positivity in HD18 study but smaller series with few PFS events (n=16) (Mettler et al JNM 2018)
  - TMTV was previoulsy shown to predict outcome in early HL patients enrolled in H10 study (Cottereau et al Blood 2018)

- SDmax is new prognosis factor in advanced HL
  - First evidence in HL
  - Prognosis value independant from TMTV

- Additive prognosis value of baseline parameters (TMTV and SDMax) and interim PET response (PET2/PET4)

İleri evre HL'da TMTV ve tümör disseminasyonu

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Conclusions

- TMTV and SDMax are new prognosis factor parameters extracted from baseline PET/CT in advanced Hodgkin Lymphoma
  - TMTV quantify tumor burden
  - SDMax quantify tumor spread
- TMTV and SDMax overcome the prognosis value of IPS
- These new parameters could be integrated with interim PET evaluation to tailor new personalized therapeutic strategies

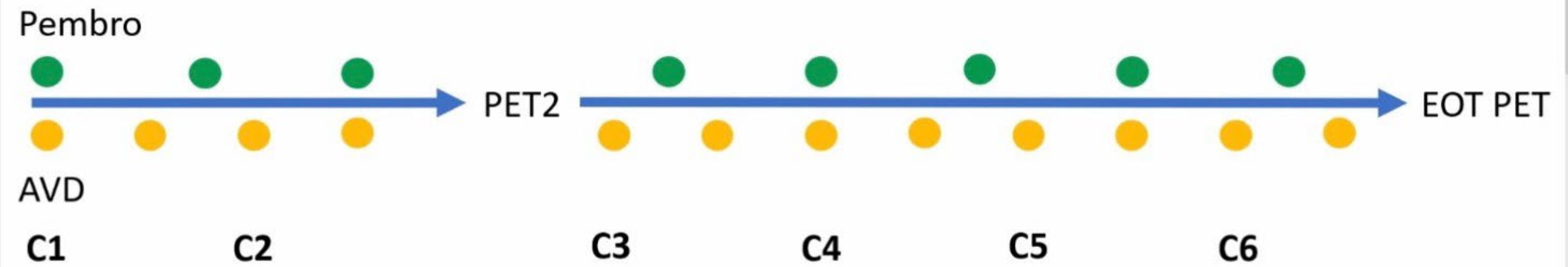
3. Birinci basamak HL tedavisi

3.1. Pembrolizumab-AVD

Yeni tanı HL’da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Study schema



Key eligibility
- Age 18+
- Stage I-IV
- Untreated CHL

Treatment dosing
Pembro 200 mg IV q21 days
AVD standard dosing q14 days
GCSF optional

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Study endpoints

- Primary endpoint: Safety
  - > 85% patients completing APVD x 2 without treatment delay
- Secondary endpoint: PET2 CR rate (5PS score from clinical read)
- Exploratory endpoints: PFS, OS, ctDNA correlates

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Baseline characteristics

Description	n = 30
Male sex, n (%)	12 (40%)
Age, median (range)	33 (18-69)
Stage	
I	1 (3%)
II	11 (37%)
III	7 (23%)
IV	11 (37%)

Description	n = 30
B symptoms, n (%)	13 (43%)
Bulk (> 10 cm), n (%)	5 (17%)
Elevated ESR (> 50)	11 (37%)
Extranodal involvment, n (%)	11 (37%)
Spleen involvement, n (%)	7 (23%)
Early stage favorable, n (%)	6 (50%)
Early stage unfavorable, n (%)	6 (50%)
IPS (advanced stage, n=18)	
0-1	6 (33%)
2-3	7 (39%)
4-7	5 (28%)

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Treatment-emergent adverse events

Grade 3-4 non-Heme AEs, N = 30

CTCAE Category	Grade 3-4
Febrile neutropenia	5 (17%)
Hyponatremia	3 (10%)
Syncope	3 (10%)
Vomiting	1 (3%)
Rash	1 (3%)
Upper respiratory infection	1 (3%)
Sepsis	2 (7%)
Conjunctivitis	1 (3%)
Colonic obstruction	1 (3%)
Colon abscess	1 (3%)

- No deaths
- SAEs in 6 (20%) patients
  - 5 patients with febrile neutropenia
  - One patient with grade 4 large bowel obstruction/abscess, no evidence of colitis
- 6 patients missed ≥ 1 dose of pembrolizumab
  - 5/6 (83%) due to grade 2+ transaminitis, all reversible
- One DLBCL 11 m after APVD

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Immune-related adverse events

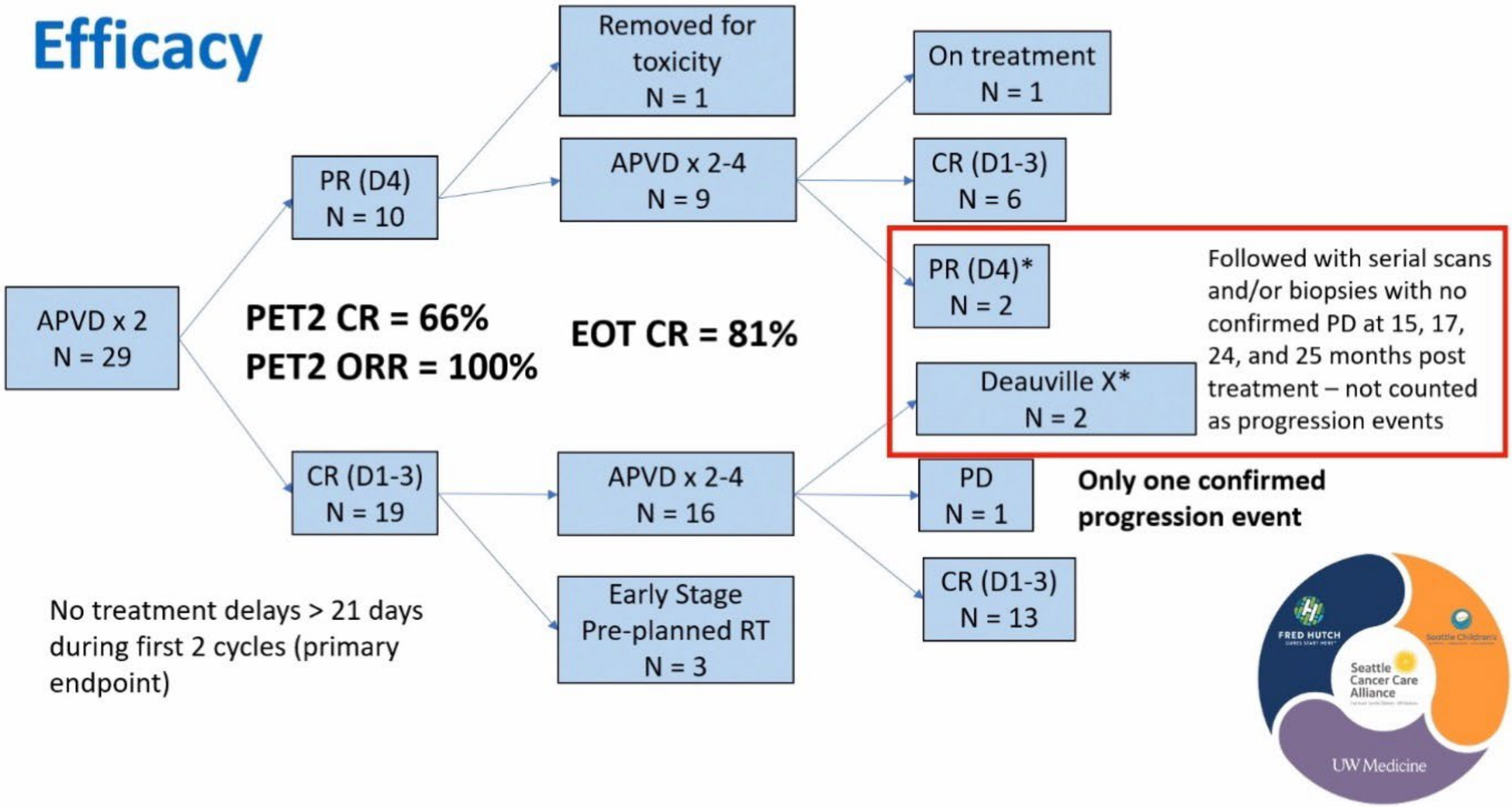
Adverse event	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Elevated ALT	20 (67%)	15 (50%)	2 (7%)	2 (7%)	1 (3%)
Elevated AST	10 (33%)	8 (27%)	1 (3%)	-	1 (3%)
Rash	13 (43%)	10 (33%)	2 (7%)	1 (3%)	-
Hypothyroidism	2 (7%)	-	2 (7%)	-	-
Arthritis	1 (3%)	-	1 (3%)	-	-
Colitis	1 (3%)	-	1 (3%)	-	-

- All successfully managed with protocol-specified therapy including corticosteroids when indicated
- Grade 4 transaminitis in one patient
  - Surreptitious high dose CBD oil use may have contributed

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Efficacy

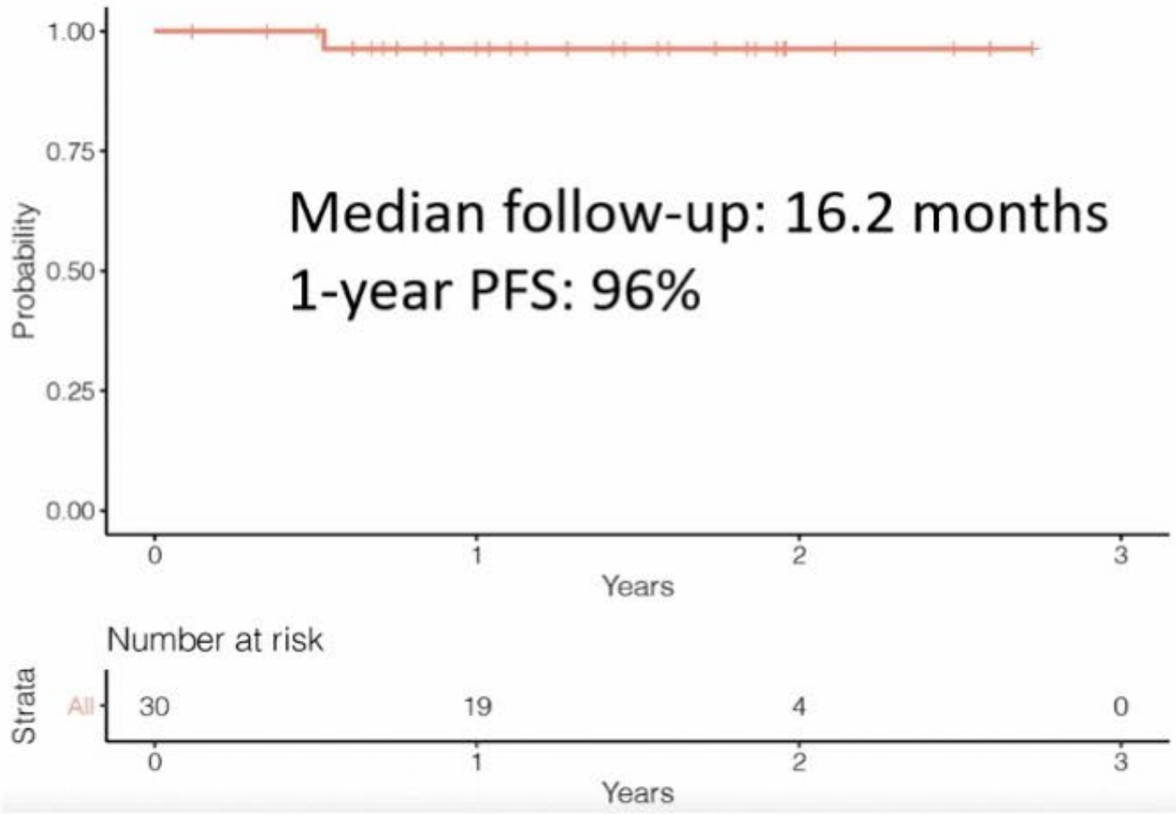


Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

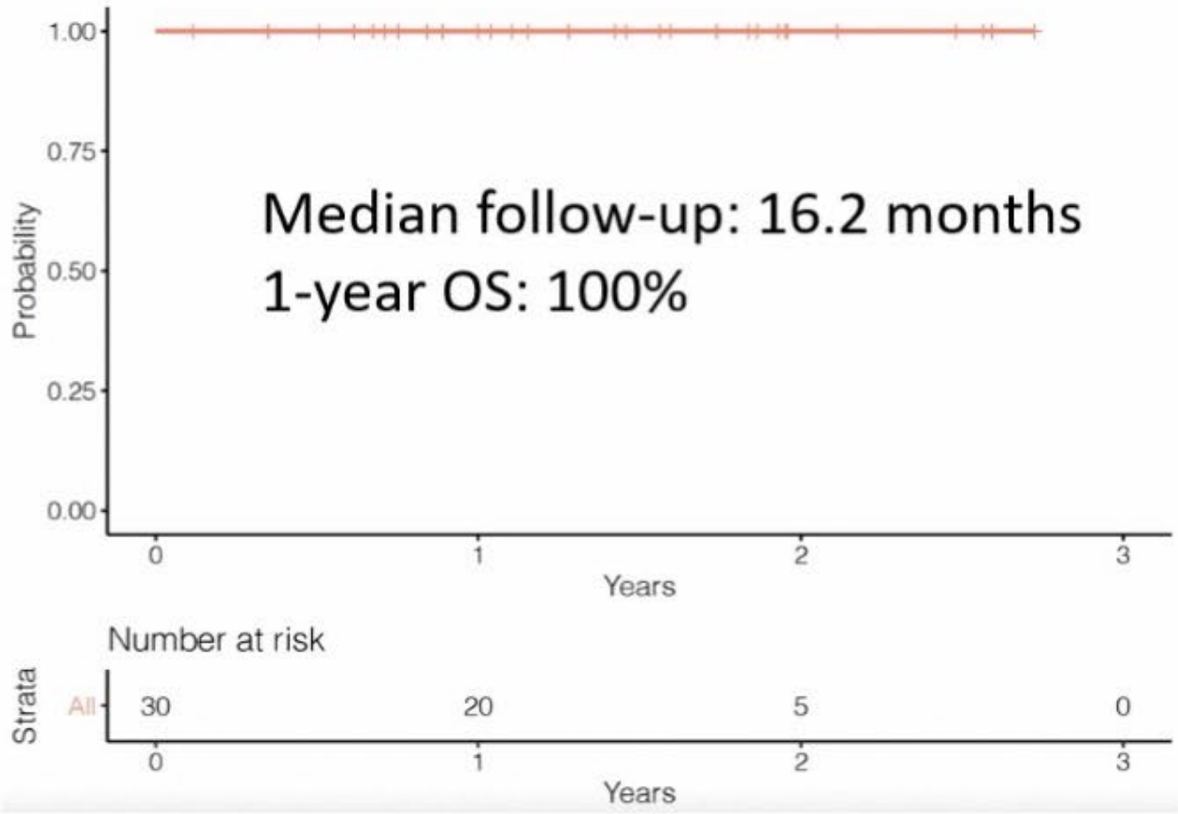
Long-term follow-up

Progression-free survival



Median follow-up: 16.2 months
1-year PFS: 96%

Overall survival



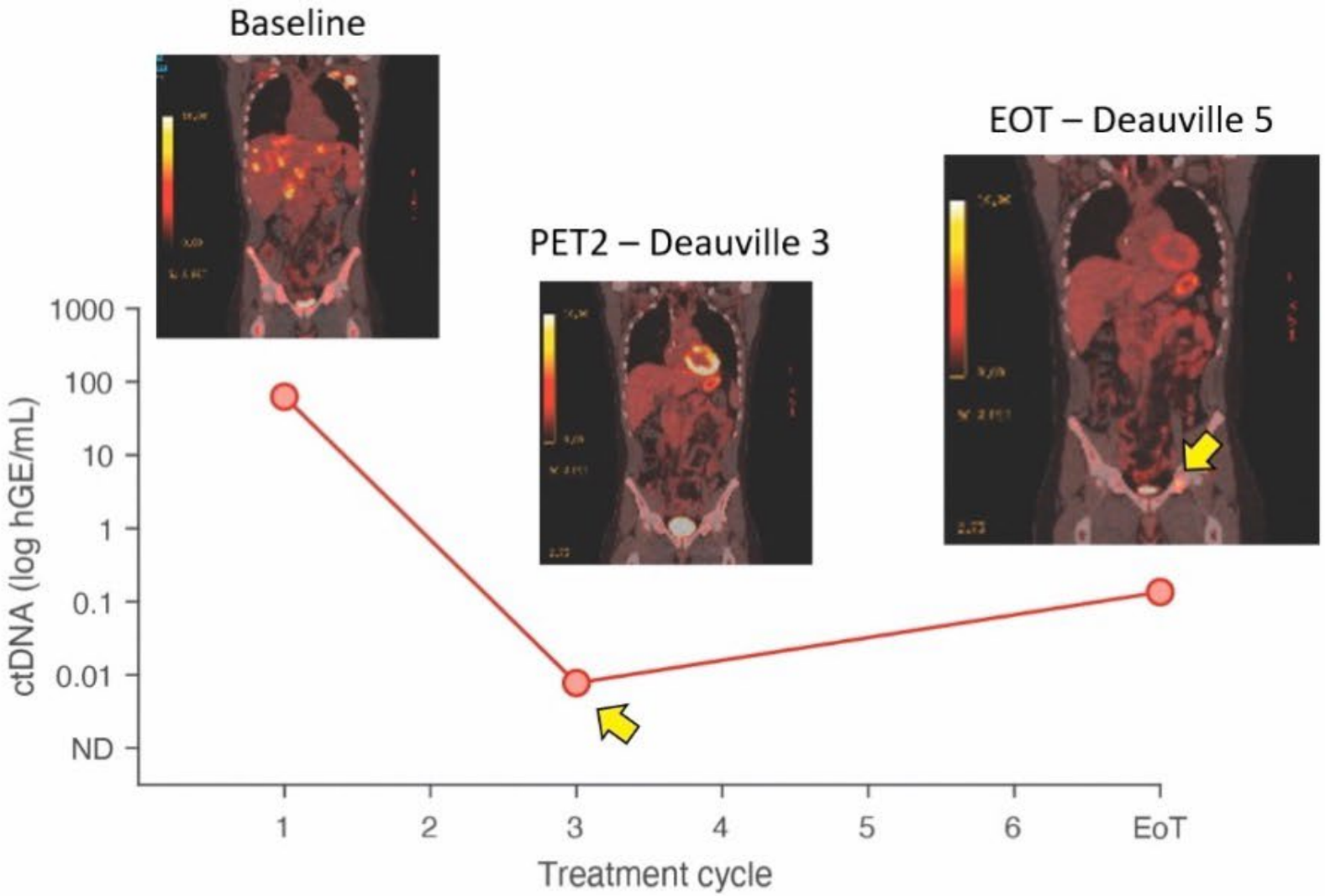
Median follow-up: 16.2 months
1-year OS: 100%

To date, no patients who interrupted or discontinued therapy due to an adverse event has progressed

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

ctDNA may be a more sensitive measure of residual disease



- PhasED-seq (Kurtz et al. Nature Biotechnology 2021)
- Stage IV, IPS - 4
  - PET2 CR (D3)
  - EOT PET – PD (D5)
  - Biopsy proven
- ctDNA
  - Post cycle 2 – detectable
  - Post cycle 6 - increased

Yeni tanı HL'da pembrolizumab-AVD

Lynch RC, Fred Hutchinson Cancer Center, paper 0233

Conclusions

- Pembrolizumab + AVD without a PD-1 lead-in safe and effective
  - 1-year PFS = 96%
- Transaminitis more common than ABVD, but reversible
  - Interrupting pembrolizumab not associated with impaired efficacy
- Utility of FDG-PET with PD1 combos undefined
  - PET2+ not associated with high risk of disease relapse
  - Only 20% of patients with positive EOT PET developed recurrent CHL

- This regimen represents a well-tolerated, and efficacious backbone that can be further evaluated in all stages of CHL.

3. Birinci basamak HL tedavisi

3.1. Pembrolizumab-AVD

3.2. Pembrolizumab tedavisini takiben AVD

Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

NU 16H08: Sequential Pembrolizumab and AVD

Newly diagnosed early unfavorable and advanced stage classic Hodgkin lymphoma

N=30

PET1

Pembrolizumab x 3

PET2

PET negative:
FPS 1-3

AVD x 2

PET3

AVD x 2-4

End of Treatment PET

Correlatives

- Immunohistochemistry
  PD-1 pathway
- 9p24.1 alterations

Follow up every 3 months x 2 years with CT q 6 months

Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

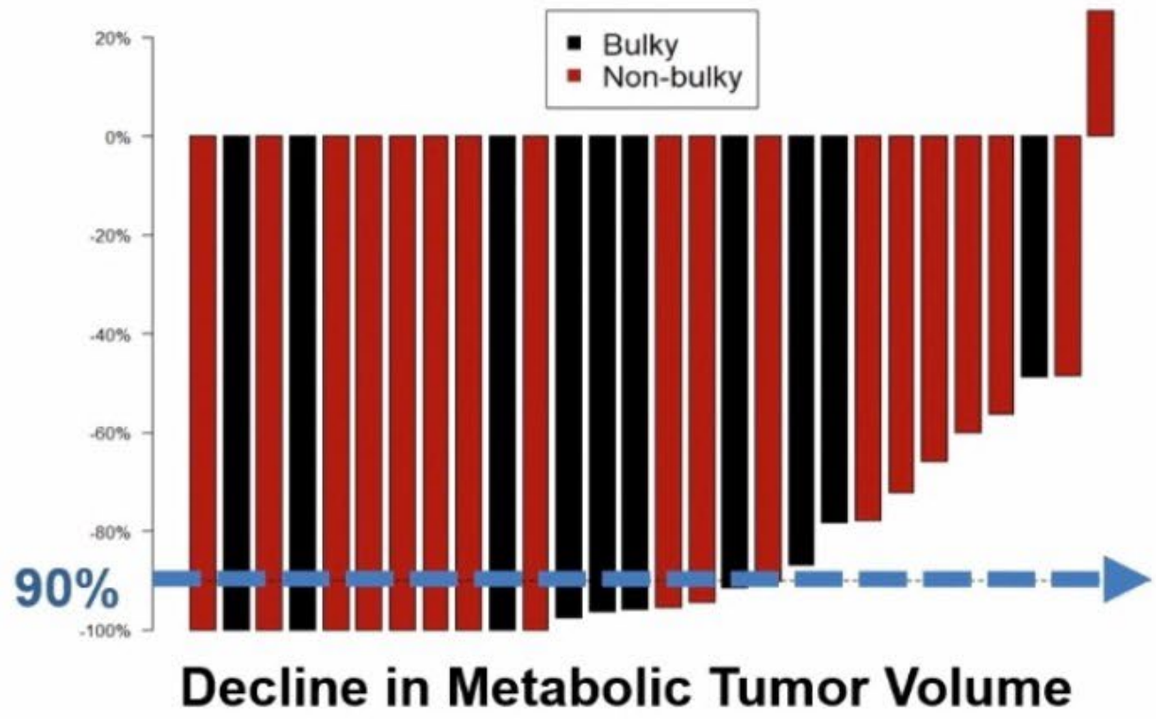
Patient Characteristics

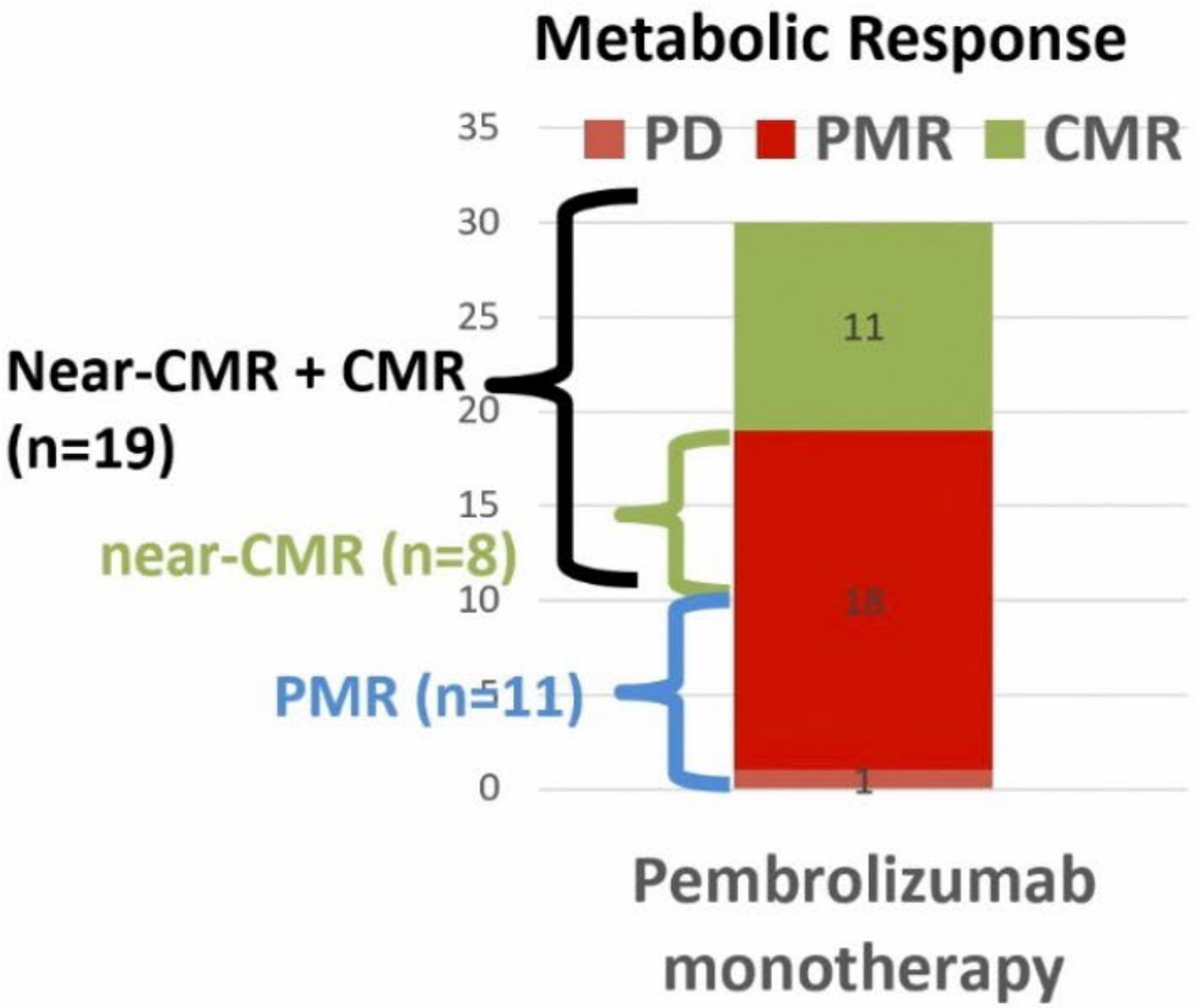
	N = 30	%
Median age, range	29, 21-77	
Age > 60	4	13%
Stage		
Early	12	40%
Advanced	18	60%
B symptoms at diagnosis	14	47%
Bulky disease (> 10 cm)	10	33%
ESR > 50	16	53%
Extranodal involvement	16	53%
Florescence in-situ hybridization	28	93%
Immunohistochemistry	29	97%

Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

Summary of Response to Single Agent Pembrolizumab





*Near-CMR = > 90% reduction in metabolic tumor volume

Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

Correlation between clinical features and depth of response to single agent pembrolizumab

	PMR n= 11	Near-CMR n = 8	CMR n= 11	p-value
Stage				0.6
Early	5 (45%)	4 (50%)	3 (27%)	
Advanced	6 (55%)	4 (50%)	8 (73%)	
Bulky				0.042
No	9 (82%)	2 (25%)	8 (73%)	
Yes	2 (18%)	6 (75%)	3 (27%)	
EBER				0.3
Negative	7 (88%)	5 (83%)	4 (50%)	
Positive	1 (12%)	1 (17%)	4 (50%)	

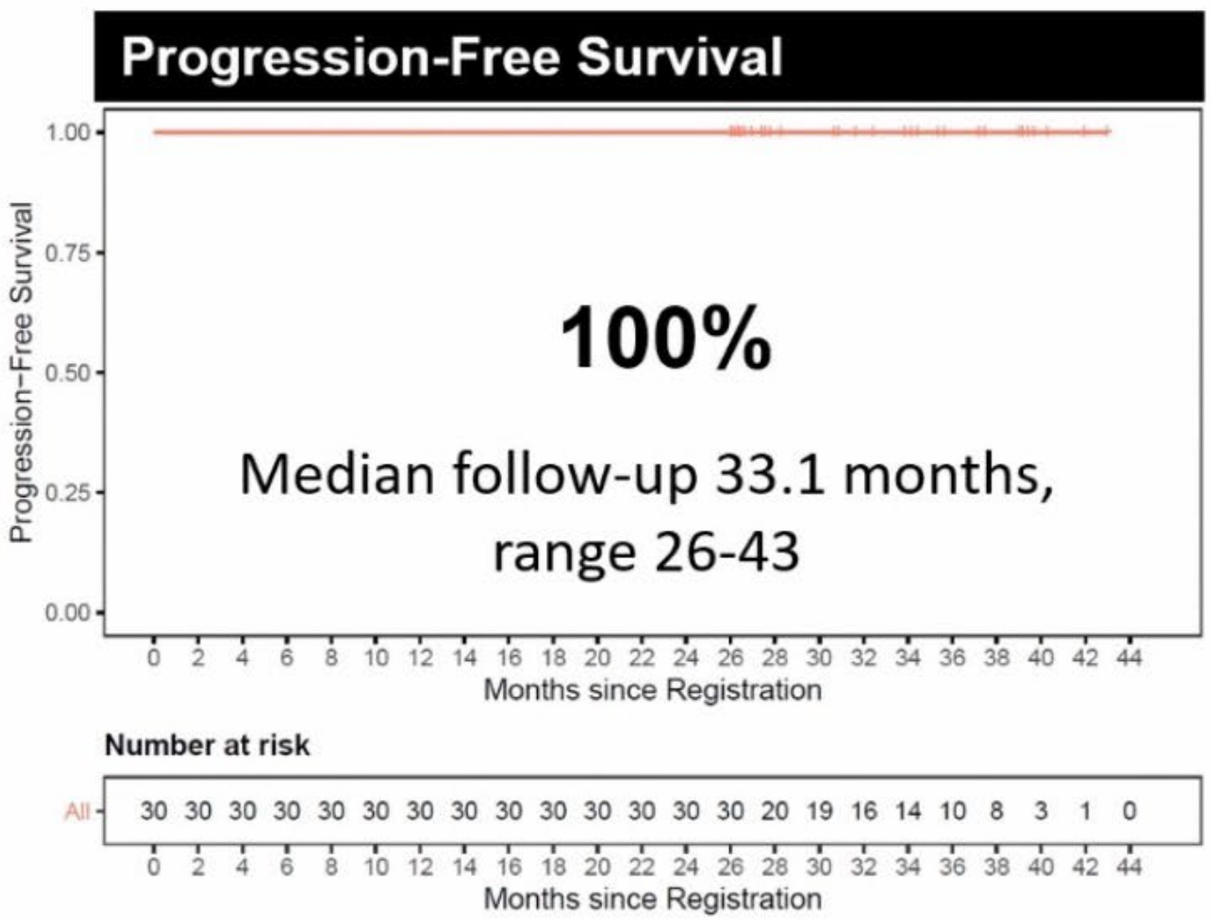
Bulky disease more commonly "near*" CMR

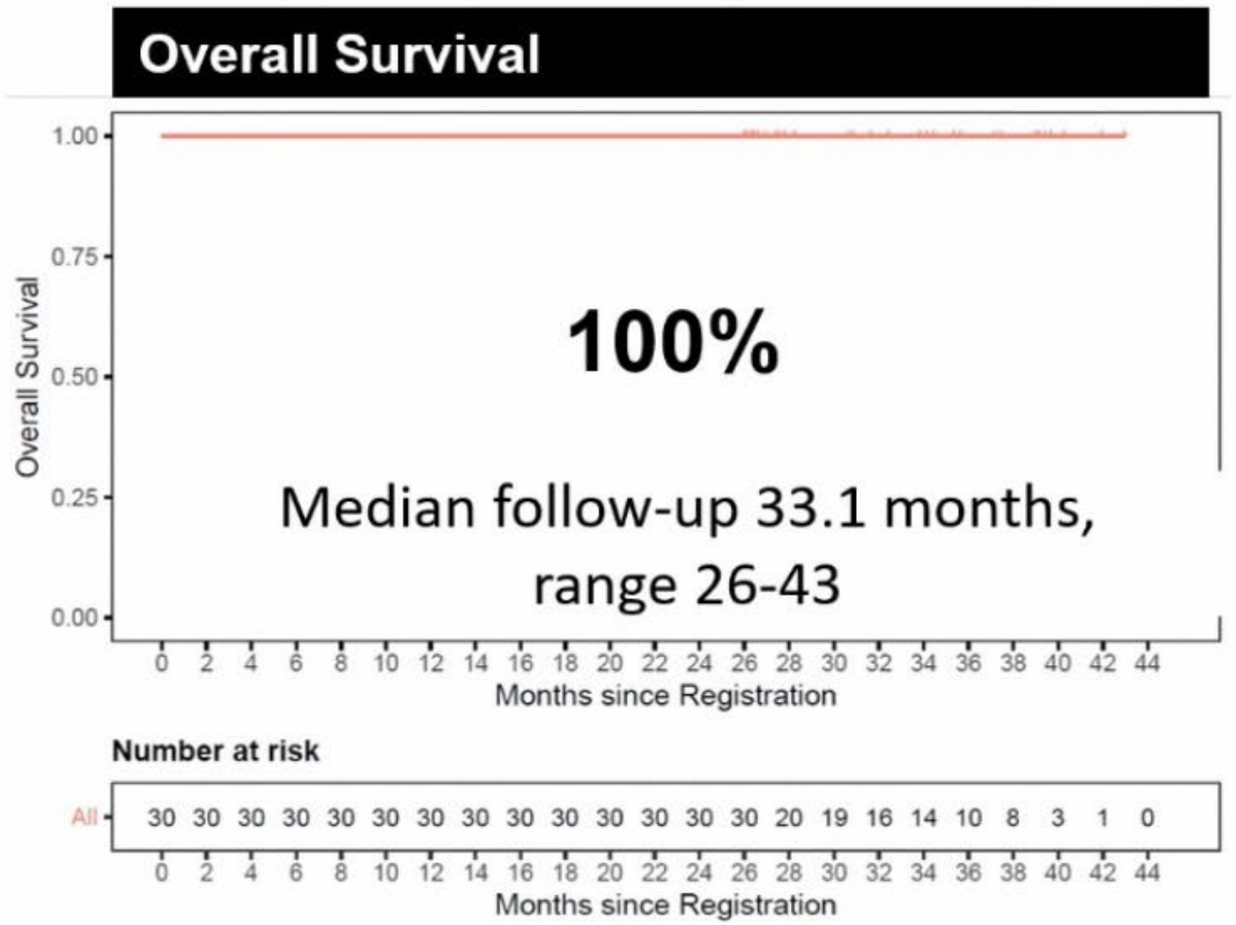
***Near-CMR = > 90% reduction in metabolic tumor volume**

Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

Sequential pembrolizumab and AVD is associated with excellent outcomes with extended follow up

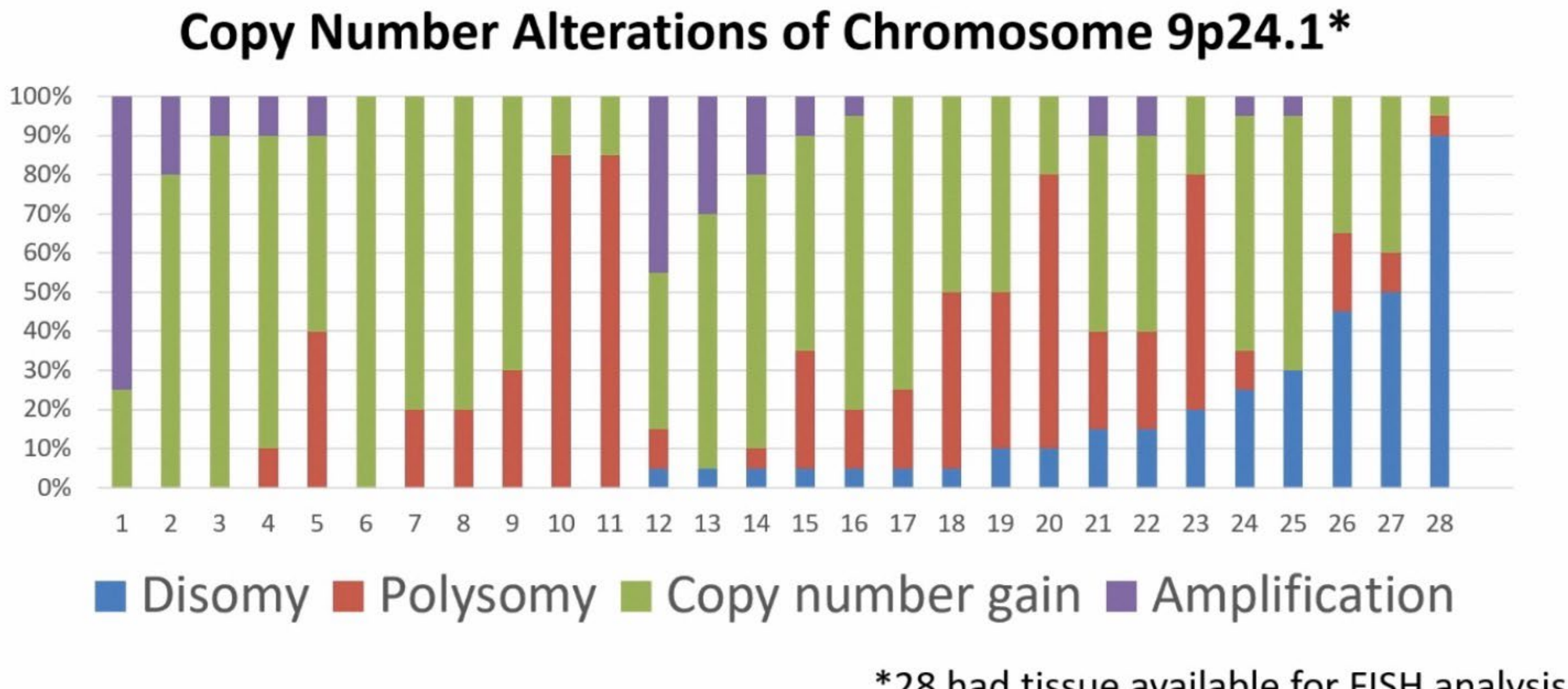




Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

All patients had alterations of 9p24.1



*28 had tissue available for FISH analysis

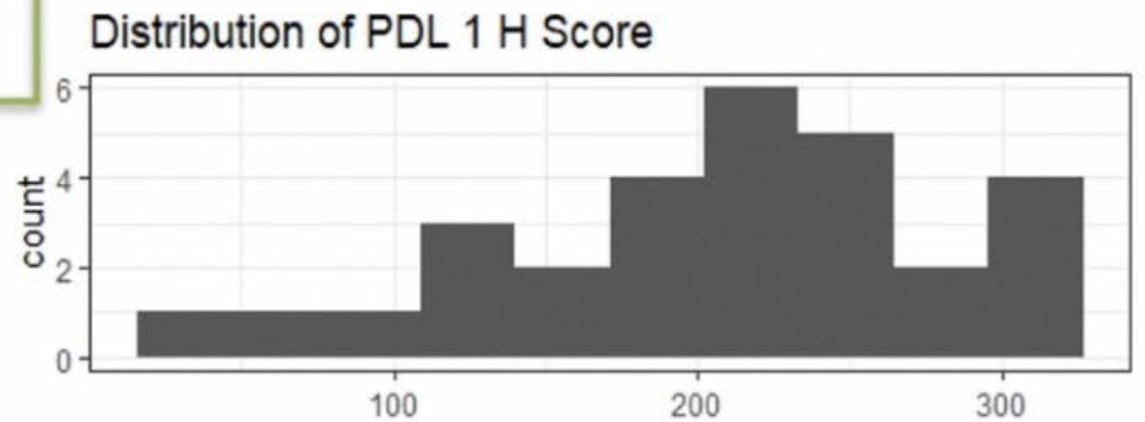
Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

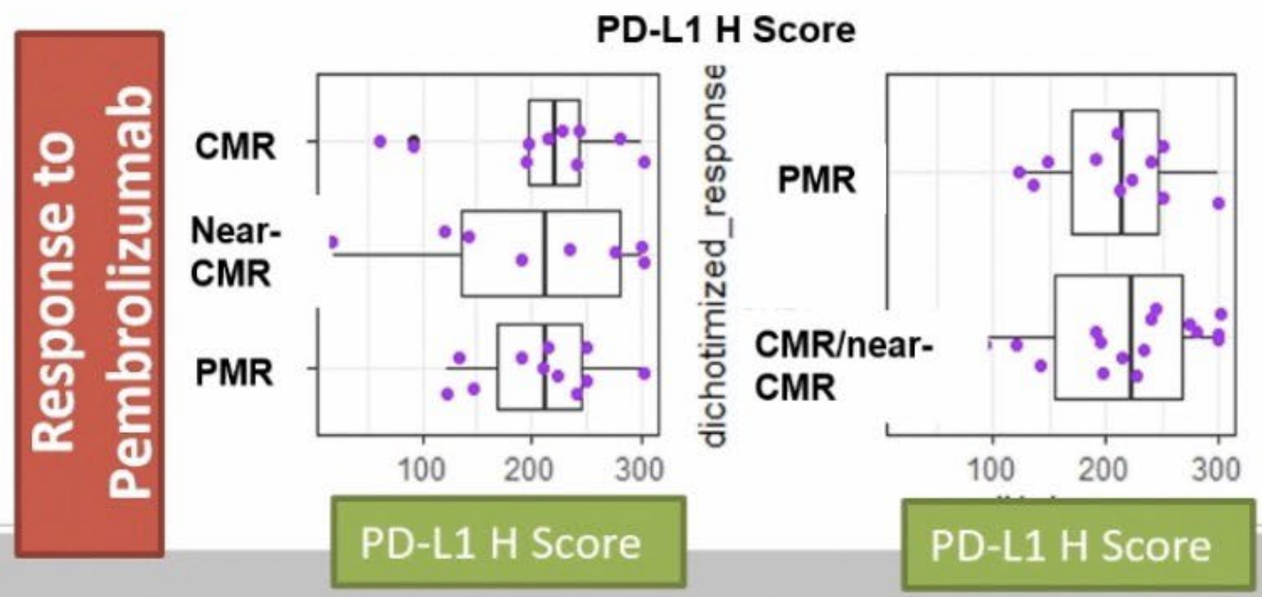
No correlation between PD-1 pathway markers and response

	CMR/near CMR (n=19)	PMR (n=11)	p-value
PD-L1 H score	221.5 (20.0-300)	213.0 (122.0-300)	>0.9
PD-L1 H score tercile			>0.9
PD-L2 H score	15.0 (0.0-180)	20.0 (0.0-135)	0.4
PD-L2 H score tercile			0.3
STAT 3 H score	300.0 (60.0-300)	300.0 (140.0-300)	>0.9
9p24.1 alteration			0.4
Polysomy or Copy gain	10 (59%)	4 (36%)	0.2
Amplification by ratio	7 (41%)	7 (64%)	

PD-L1 expression



Response to Pembrolizumab



Yeni tanı HL'da pembrolizumabı takiben AVD

Allen PB, Emory Hospital, paper 0231

Summary/Conclusions

- Previously untreated cHL is exquisitely sensitive to sequential pembrolizumab and AVD
  - 100% PFS and OS with extended follow up of 33.1 months.
- There was no correlation between PD-1 pathway markers and depth of response to single agent pembrolizumab lead-in in newly diagnosed cHL.
  - Even low levels of PD-L1 expression resulted in favorable responses to pembrolizumab

3. Birinci basamak HL tedavisi

3.1. Pembrolizumab-AVD

3.2. Pembrolizumab tedavisini takiben AVD

3.3. Yaşlı, kırılgan HL'da nivolumab

Yaşlı, kırılgan HL'da nivolumab

Lazarivici J, LYSA, paper 0232

Background

1. Elderly patients with classical Hodgkin Lymphoma (cHL) have less favorable prognosis than their younger counterparts (*Engert, J Clin Oncol 2005*)
2. Few data in frail patients:
   - ABVD: 5-y PFS 36%, OS 46% *(Evens, Blood 2016, retrospective)*
   - Brentuximab Vedotin + Bendamustine/Dacarbazine effective but toxic *(Friedberg, Blood 2017)*
3. Nivolumab effective and well tolerated in relapsed/refractory cHL (*Ansell, NEJM 2015, Younes Lancet Oncol 2016*)
4. Rationale for combining anti-PD1 and chemotherapy (*Pfirschke, Immunity 2016, Herrera, Blood 2018*)

NIVINIHO

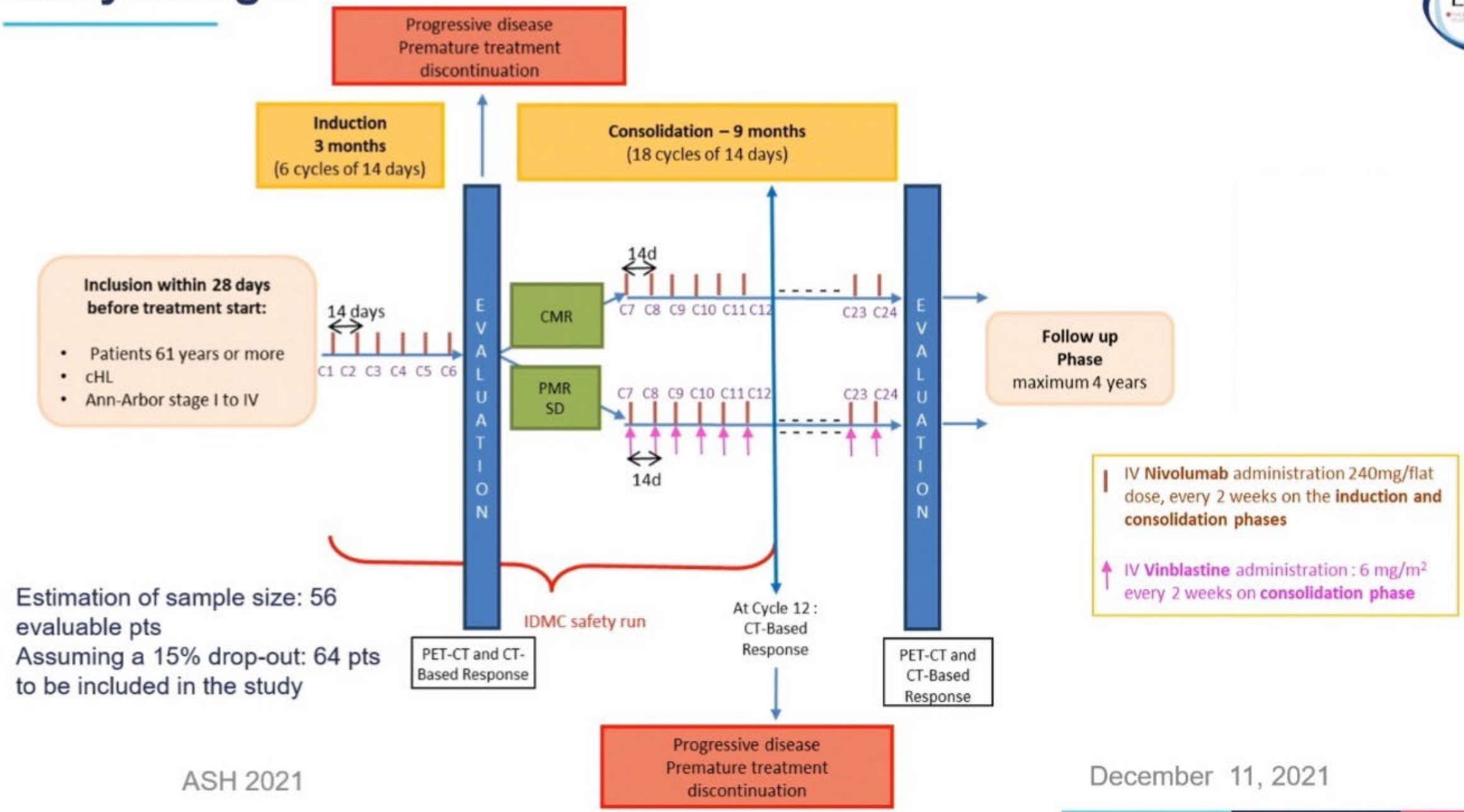
A prospective phase II study of nivolumab alone, or in combination with vinblastine in patients aged 61 years and older, with classical Hodgkin lymphoma and coexisting medical conditions

Yaşlı, kırılgan HL'da nivolumab

Lazarivici J, LYSA, paper 0232

Study design

Open-label, multi-centric phase II study – whole duration: 12 months



- Estimation of sample size: 56 evaluable pts
- Assuming a 15% drop-out: 64 pts to be included in the study

Yaşlı, kırılgan HL'da nivolumab

Lazarivici J, LYSA, paper 0232

Study objectives

- **Primary objective**: to assess the **Complete Metabolic Response (CMR)** rate by the Lugano classification 2014 (Deauville scale 1-3) based on central review assessed at the **end of treatment (EOT)**
  - Ineffective treatment will be considered if the CMR ≤ 50% (P0)
  - Effective treatment will be considered if the CMR ≥ 70% (P1)
  - α risk of 0.05 and β risk of 0.10
- **Secondary objectives**:
  - To assess the **feasibility of the protocol**, with adequate protocol adherence (adequate dose without excessive delay)
  - To assess the **safety profile** of Nivolumab alone or combined with Vinblastine including immediate toxicities and non tumor events
  - To assess progression-free survival (**PFS**), event-free survival (**EFS**), and overall survival (**OS**)
  - To assess the **CMR rate** by the Lugano classification 2014 at the **end of induction** treatment (**EOI**)
  - To perform a **geriatric assessment program (G8, Cumulative Illness Rating Score for Geriatrics, CIRS-G)**

Yaşlı, kırılgan HL'da nivolumab

Lazarivici J, LYSA, paper 0232

Baseline characteristics

Clinical characteristics	FAS/Safety Set N = 64		Efficacy Set N = 56	
Sex				
Female	25	(39.1%)	24	(42.9%)
Male	39	(60.9%)	32	(57.1%)
Median age at inclusion (years)				
Median (Min-Max)	75.0	(62 – 91)	75.0	(62 - 91)
Performance status (ECOG)				
0	17	(26.6%)	15	(26.8%)
1	31	(48.4%)	28	(50.0%)
2	10	(15.6%)	7	(12.5%)
3	6	(9.4%)	6	(10.7%)
Ann Arbor stage				
I-II	16	(25.0%)	15	(26.8%)
III-IV	48	(75.0%)	41	(73.2%)
B Symptoms	29	(45.3%)	24	(42.9%)
G8 score				
Median (Min-Max)	12.0	(5 – 17)	12.5	(6 – 17)
CIRS-G score				
Median (Min-Max)	10	(6 - 18)	10	(6 - 18)

Patients included between August 2018 and April 2020 in 31 sites in France and Belgium

Median FU: 24.4 m [20.9-25.0]

Yaşlı, kırılgan HL'da nivolumab

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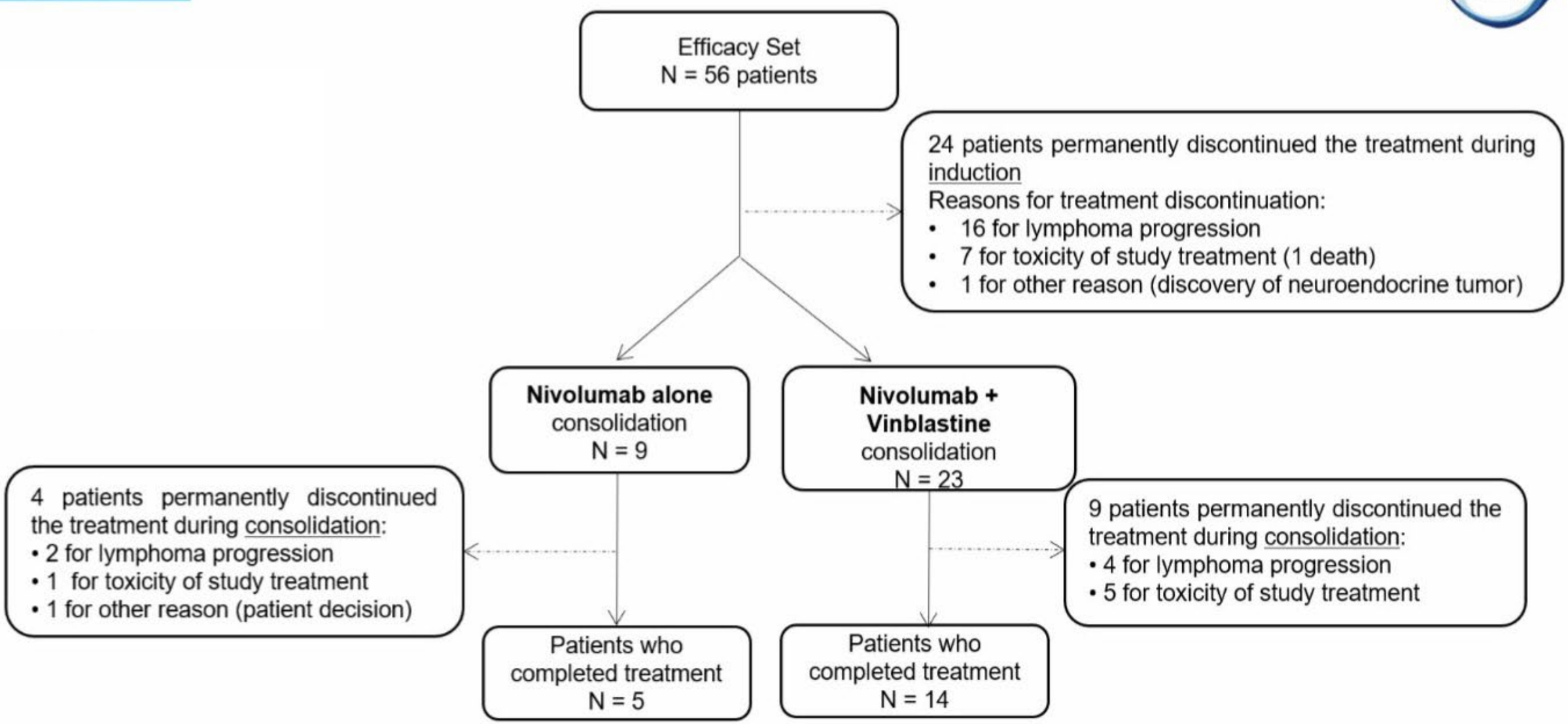
Disposition of patients - Efficacy Set



Yaşlı, kırılgan HL'da nivolumab

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Response

Primary endpoint: CMR at end of study treatment (EOT) (central review)

Metabolic response according to Lugano Classification (PET-CT-Based)	Efficacy Set N=56	
Complete Metabolic Response	16	(28.5%)
Partial Metabolic Response	10	(17.9%)
No Metabolic Response	10	(17.9%)
Progressive Metabolic Disease*	20	(35.7%)

**3 patients without central review*

CMR at the EOT = 28.6%

Secondary endpoint: CMR at end of induction (EOI) (local review)

Metabolic response according to Lugano Classification (PET-CT-Based)	Efficacy Set N=56	
Complete Metabolic Response	9	(16.1%)
Partial Metabolic Response	20	(35.7%)
No Metabolic Response	9	(16.1%)
Progressive Metabolic Disease	16	(28.5%)
Not Evaluated	2	(3.6%)

ORR at the EOI= 51.8%

Yaşlı, kırılgan HL'da nivolumab

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Feasability

- Median delay between 2 cycles: 14 days (Q1-Q3: 14 -14) is the same for induction and both consolidation arms
- The median number of cycles administered was:
  - 6 [Q1-Q3: 5 - 6] during induction (Nivolumab) (n=56)
  - 16 [Q1-Q3: 8 - 18] during consolidation for Nivolumab (n=32)
  - 17 [Q1-Q3: 12 - 18] for Vinblastine (n=23)
- Mean of Percentage of Planned Dose:
  - Nivolumab: 99%
  - Vinblastine: 100%
- Among the 56 patients of the efficacy Set, 34% of patients completed treatment

Yaşlı, kırılgan HL'da nivolumab

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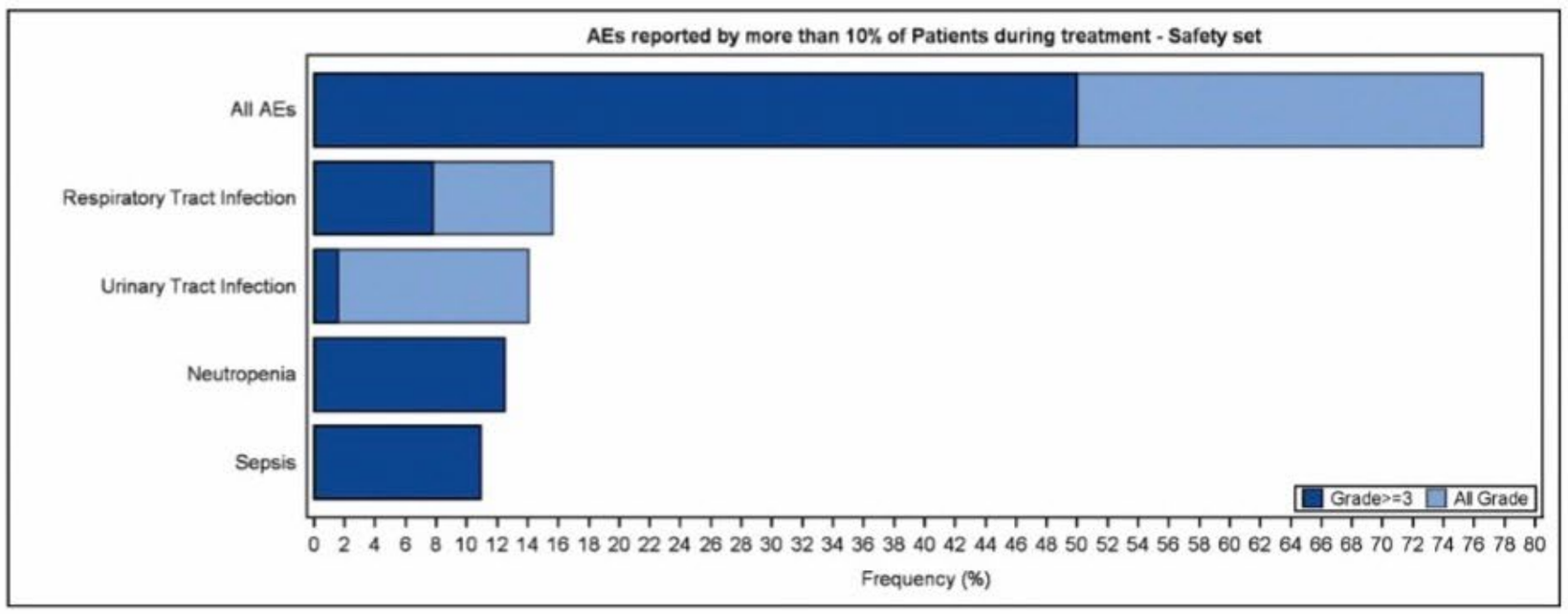
Safety

Patients	Induction phase N=64		Consolidation phase N=34	
with at least one Adverse Event (AE)	37	(57.8%)	27	(79.4%)
with at least one AE of highest grade >= 3	14	(21.9%)	16	(47.1%)
with at least one SAE	14	(21.9%)	11	(32.4%)
with at least one fatal AE	2	(3.1%)	0	(0.0%)
AEs leading to Nivolumab discontinuation	11	(17.2%)	8	(23.5%)
AEs leading to Vinblastine discontinuation	1	(1.6%)	5	(14.7%)



Deaths :

- 2 deaths during induction phase (one AESI)
- no death during consolidation phase
- 16 deaths during FU (1 aseptic meningitis linked to study treatment)

AEs: Adverse Event
AESI: Adverse Event of Special Interest
EOT : End of treatment
SAE : Serious Adverse Event
FU : Follow Up

Yaşlı, kırılgan HL'da nivolumab

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Adverse Events of Special Interest

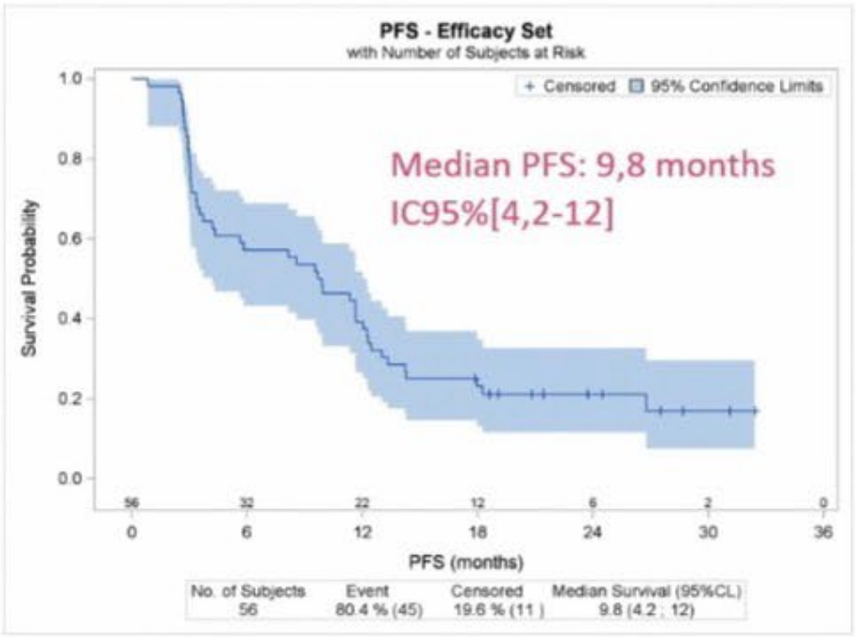
AESI group	N = 36 (%)
Immune-related endocrinopathies	8 (22.2)
Immune-related rash	7 (19.4)
Immune-related pneumonitis	4 (11.1)
Immune-related nephritis or renal dysfunction	2 (5.6)
Immune-related colitis	1 (2.8)
Immune-related hepatitis	1 (2.8)
Other immune-related adverse reactions	9 (25.0)
Infusion reactions	4 (11.1)

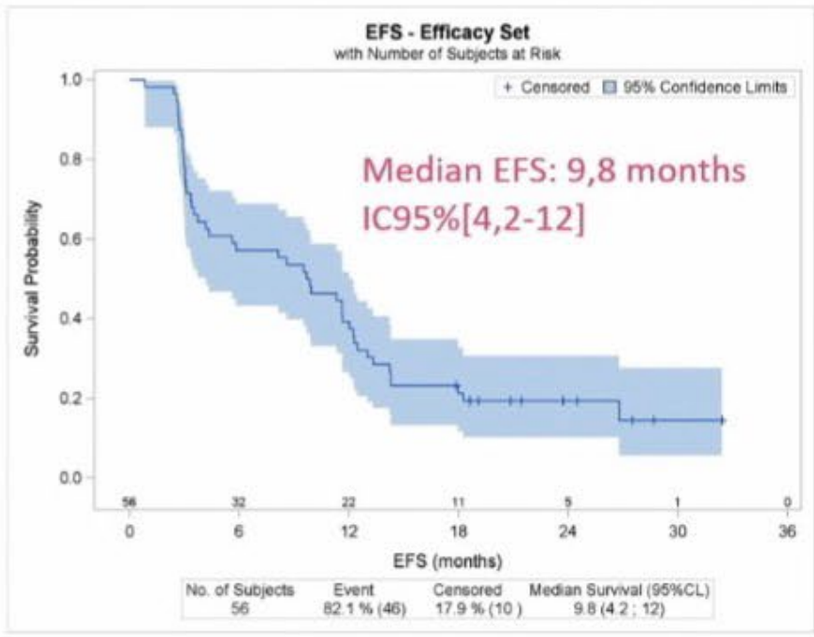
- 24 patients presented 36 AESI
- 12 AESI -> stop of Nivolumab
- 1 fatal AESI (pneumonitis) after only one Nivolumab injection

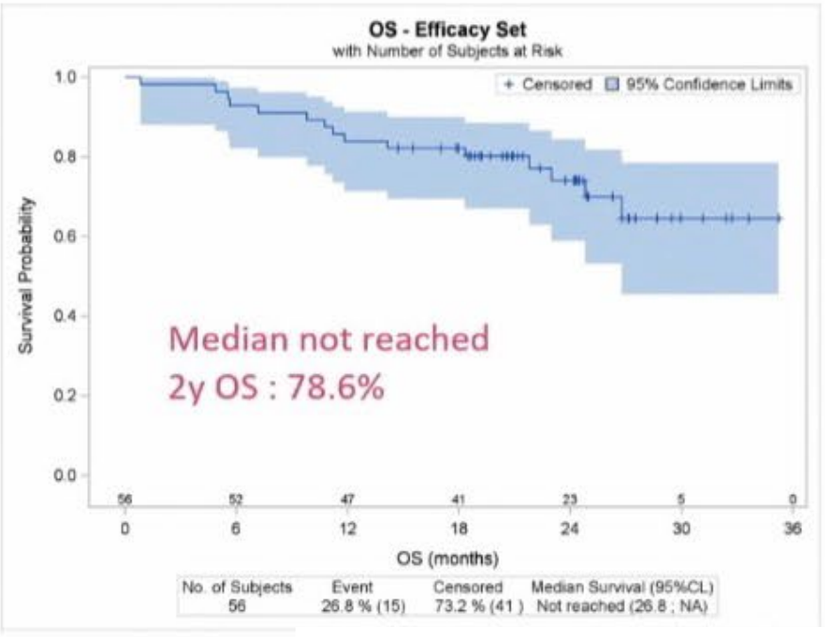
Yaşlı, kırılgan HL'da nivolumab

Lazarivici J, LYSA, paper 0232

Survival







Yaşlı, kırılgan HL'da nivolumab

Lazarivici J, LYSA, paper 0232

Conclusion

- NIVINIHO is one of the first studies designed to evaluate the efficacy and safety of Nivolumab in frontline setting in elderly, frail patients with classical Hodgkin Lymphoma
- With a 28.6% Complete Metabolic Response (CMR) rate at end of study treatment, NIVINIHO did not reach its pre-specified endpoint
- However, ORR 51.8% at end of induction, including 9 pts (16.1%) with CMR, after Nivolumab monotherapy (5 pts still with CMR at end of study)
- Toxicity comparable to the published data in elderly patients treated with anti-PD(L)-1 for cancer (Baldini et al., Eur J Cancer 2020)
- Biological studies awaited to better identify patients who may benefit from this approach

4. Nüks/dirençli HL tedavisi

4.1. OKİT öncesi nüks

4.1.1. Brentiksumab-kemoterapi

4.1.2. Pembrolizumab-ICE

4.1.3. Br-Nivo/Br-Benda

4.3. PD-1 blokerleri sonrası nüks

4.3.1. Nivolumab-ruksolutinib

4.3.2. Pembrolizumab-vorinostat

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Literature search of clinical trials in R/R cHL

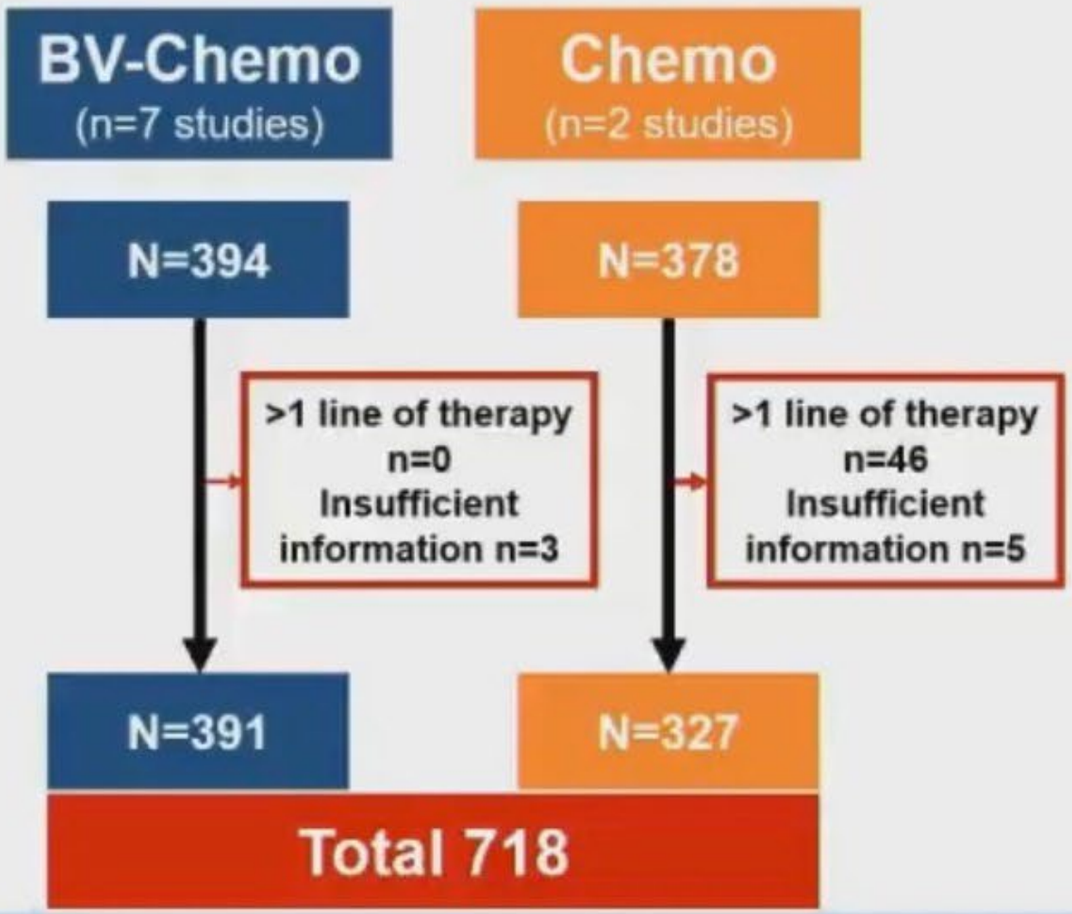
Study	Subgroup	Regimen	N	Included in this analysis
Moskowitz, 2017	BV	BV + ICE (sequential)	65	Yes
Herrera, 2018	BV	BV + ICE/GVD (sequential)	57	Yes
Cole, 2018	BV	BV + gemcitabine	45	Yes
LaCasce, 2018	BV	BV + bendamustine	55	Yes
Garcia-Sanz 2019	BV	BV + ESHAP	66	Yes
Broccoli 2019	BV	BV + bendamustine	40	Yes
Abuelgasim, 2019	BV	BV + IGEV	28	No (retrospective)
Kersten, 2020	BV	BV + DHAP	67	Yes
Advani, 2021	BV	BV + nivolumab	91	No (no chemo)
Josting, 2010	Chemo	DHAP (BEAM vs cyclo/eto/MTX+BEAM)	279	Yes
Moskowitz, 2010	Chemo	ICE	105	No (different Tx for subgroups)
Moskowitz, 2012	Chemo	ICE + GVD (sequential)	99	Yes
Labrador, 2014	Chemo	ESHAP	82	No (retrospective)
Santoro, 2016	Chemo	BeGEV	58	No (request ongoing)

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Study characteristics

Flow-chart of inclusion



Study characteristics

Study	Regimen	N	Primary refractory	PD	Death
Kersten, 2020	BV-DHAP	65	39%	20%	5%
Garcia-Sanz, 2019	BV-ESHAP	65	60%	25%	9%
Broccoli, 2019	BV-Benda	40	70%	35%	5%
LaCasce, 2018	BV-Benda	55	51%	36%	9%
Cole, 2018	BV-Gem	45	64%	36%	18%
Herrera, 2018	BV-ICE (seq)	57	54%	46%	14%
Moskowitz, 2017	BV-ICE (seq)	64	53%	25%	13%
Moskowitz, 2012	ICE/GVD (seq)	94	43%	32%	22%
Jostings, 2010	DHAP	233	5%	28%	19%

- Definition of primary refractory disease: no complete response to first-line treatment

Seq, sequential; PD, progressive disease

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Patient characteristics (whole cohort)

	BV (N=391)	Chemo (N=327)	Total (N=718)	*P* value
Sex = Female	53%	43%	49%	0.013
Age (median; range)	31 (5 - 68)	34 (18 - 72)	32 (5 - 72)	0.028
Refractory disease	55%	16%	37%	< 0.001
Stage at relapse = III/IV	50%	48%	49%	0.594
B symptoms at relapse	27%	23%	25%	0.295
Extranodal disease	37%	34%	36%	0.480
Bulky disease	37%	32%	34%	0.134
Prior treatment				< 0.001
ABVD	90%	67%	78%	
BEACOPP	6%	25%	16%	
OTHER	4%	8%	6%	
Prior radiotherapy	23%	54%	39%	< 0.001

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Matching of BV and Chemo cohorts

Variable	BV (N=205)	CHEMO (N=205)	Total (N=410)	P-val
Female	*111 (54%)*	*93 (45%)*	*204 (50%)*	*0.075*
Age (median; range)	*32 (12-66)*	*33 (18-72)*	*32 (12-72)*	*0.760*
Primary refractory	51 (25%)	51 (25%)	102 (25%)	1.000
Stage III/IV	85 (50%)*	100 (49%)	185 (50%)	0.850
B-symptoms	59 (29%)	53 (26%)	112 (27%)	0.506
Extranodal disease	87 (42%)	82 (40%)	169 (41%)	0.616
Bulky disease	79 (39%)	75 (37%)	154 (38%)	0.683
Prior treatment = BEACOPP	15 (7%)	15 (7%)	30 (7%)	1.000

- Patients were excluded if >1 matching variable was unknown
- Stage at relapse was unknown for 1 study (n=35 patients in BV-cohort*)

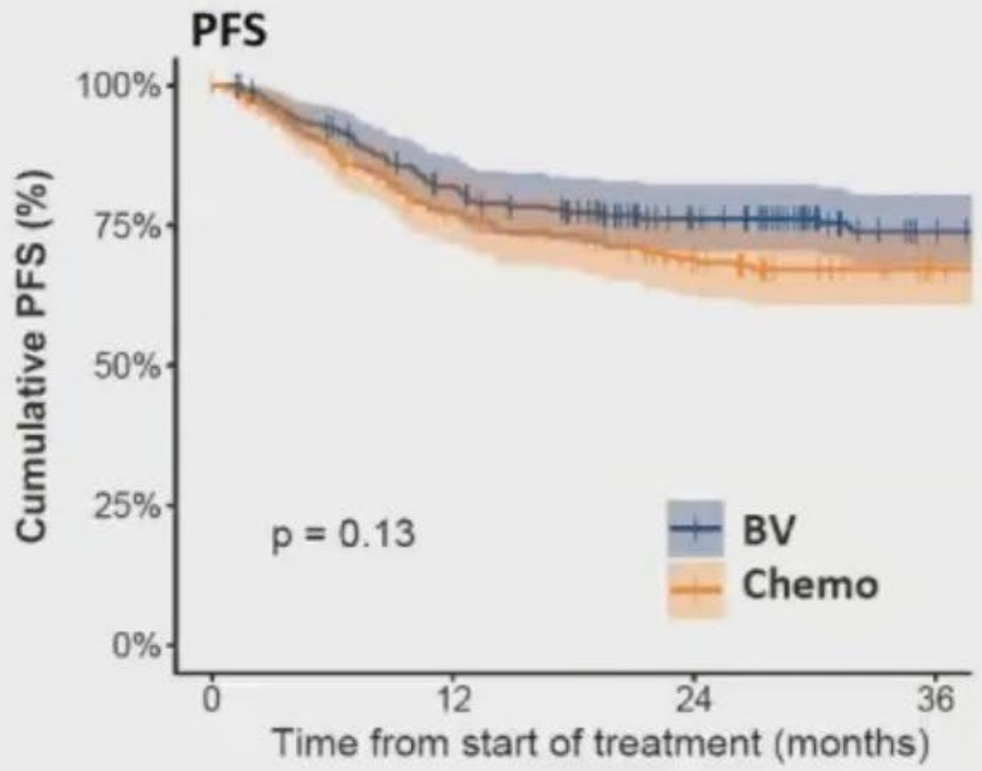
- Matching by propensity score, nearest neighbors method, ratio 1:1
- Equal distribution of variables across groups

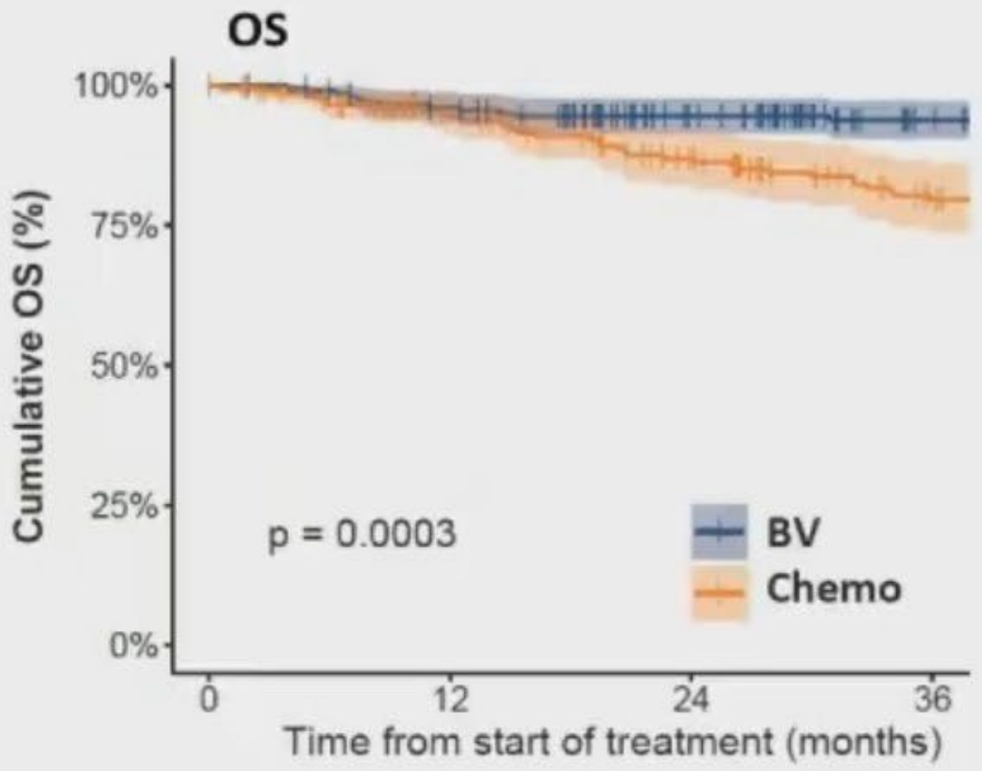
- Primary refractory disease is limiting factor for group size
  - Only n=51 primary refractory patients in Chemo-cohort

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Matched cohort: 3-year PFS and OS





3-year PFS (95% CI)	BV	74% (68 – 80)	P=0.13
3-year PFS (95% CI)	Chemo	67% (61 – 74)	
HR (95% CI)	Chemo vs BV	1.33 (0.92 - 1.92)	P=0.13

3-year OS (95% CI)	BV	94% (90 – 97)	P=0.0003
3-year OS (95% CI)	Chemo	80% (74 – 86)	
HR (95% CI)	Chemo vs BV	3.15 (1.63 - 6.06)	P=0.0002

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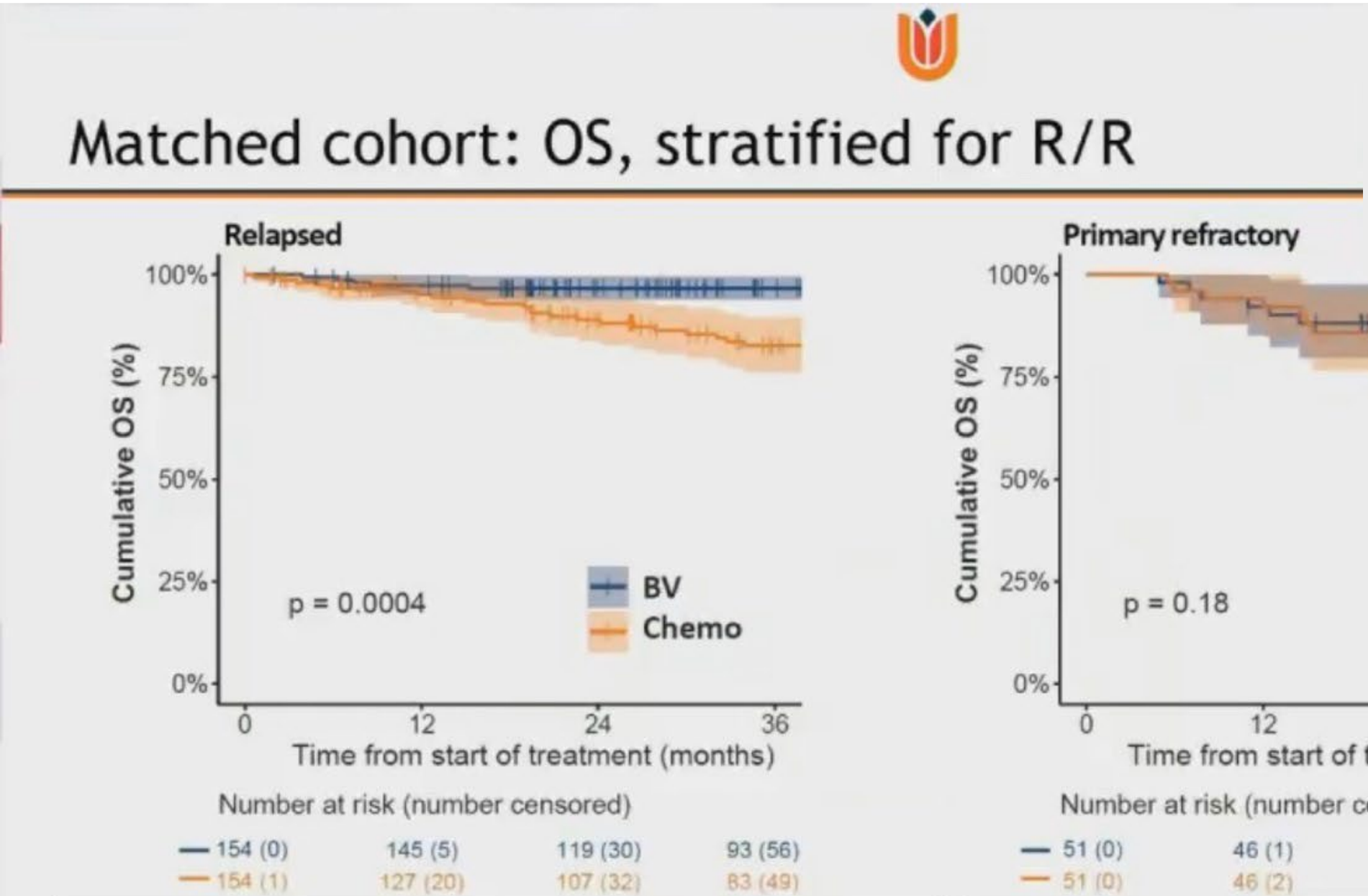
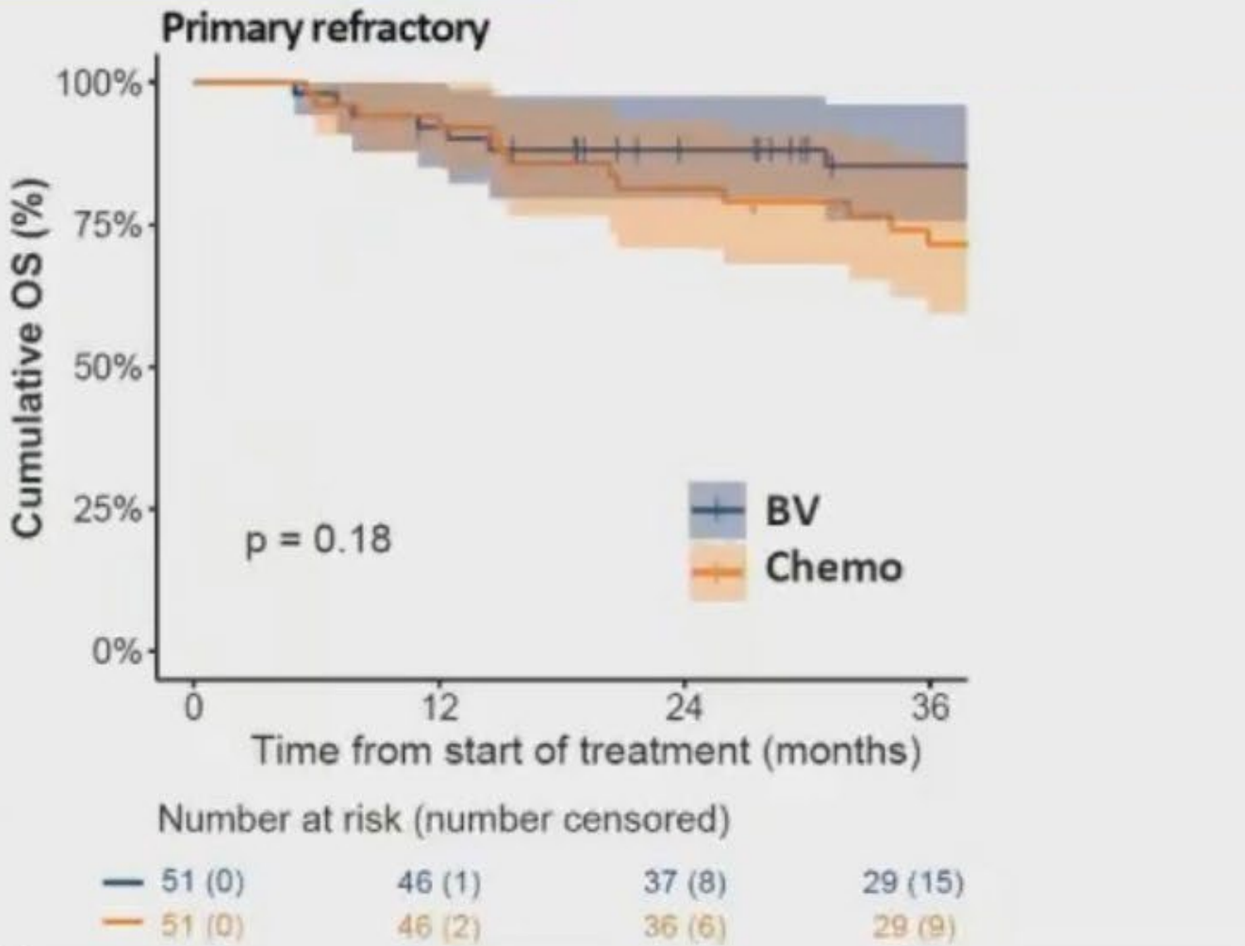
Matched cohort: OS, stratified for R/R



3-year OS (95% CI)	BV	97% (94-100)	<0.001
3-year OS (95% CI)	Chemo	83% (76-90)	
HR (95% CI)	Chemo vs BV	4.83 (1.83 - 12.8)	<0.001



3-year OS (95% CI)	BV	85% (76-96)	0.18
3-year OS (95% CI)	Chemo	72% (60-86)	
HR (95% CI)	Chemo vs BV	1.86 (0.74 - 4.67)	0.17

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Influence of BV salvage regimen on PFS

Study	N	Regimen	Chemo	Sequential	BV cycles	Cumulative dose
Moskowitz, 2017	64	BV-ICE	Multiple	Seq	6; 1.2mg/kg	7.2 mg
Herrera, 2018	57	BV-ICE	Multiple	Seq	4; 1.8mg/kg	7.2 mg
Garcia-Sanz, 2019	65	BV-ESHAP	Multiple	Combi	4; 1.8mg/kg	7.2 mg
Kersten, 2020	65	BV-DHAP	Multiple	Combi	3; 1.8mg/kg	5.4 mg
LaCasce, 2018	55	BV-benda	Mono	Combi	2-6 + 14x; 1.8mg/kg	3.6 – 36 mg (median 9)
Broccoli, 2019	40	BV-benda	Mono	Combi	4-6; 1.8mg/kg	10.8 mg
Cole, 2018	45	BV-gem	Mono	Combi	8; 1.8mg/kg	14.4
Cox univariate	391	HR; 95% CI; P-value	0.77 (0.54 - 1.11) p=0.16	1.048 (0.72 - 1.53) p=0.80	0.937 (0.66 - 1.34) p=0.72	1.298 (0.9 - 1.87) p=0.16
Cox (corrected for refractory disease)	391	HR; 95% CI; P-value	0.845 (0.59 - 1.22) p=0.36	1.096 (0.75 - 1.6) p=0.63	0.868 (0.61 - 1.24) p=0.44	1.184 (0.82 - 1.71) p=0.18

No significant differences in PFS between studies within the BV-cohort with different regimens

kemoterapi

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Prognostic factors for 3-year PFS

Multivariable Cox regression for 3-year PFS

	PFS from enrollment *Whole cohort*			Post-ASCT PFS *Studies with PET data*		
	HR	95% CI	*P value*	HR	95% CI	*P value*
PET status = Positive	-	-	-	**1.96**	**1.15 – 3.35**	**0.013**
Refractory	**2.76**	**1.84 – 4.16**	**<0.0001**	**2.61**	**1.56 – 4.37**	**0.0002**
B symptoms	**1.90**	**1.26 – 2.86**	**0.0022**	**1.63**	**0.96 – 2.78**	**0.07**
Stage III/IV	**2.31**	**1.43 – 3.74**	**0.0007**	**2.80**	**1.52 – 5.12**	**0.0009**
Extranodal	1.15	0.72 – 1.82	0.56	1.41	0.80 – 2.47	0.24
Bulky	**1.52**	**1.03 – 2.24**	**0.035**	1.25	0.77 – 2.03	0.36
BEACOPP	0.81	0.32 – 2.03	0.65	0.76	0.23 – 2.49	0.65

kemoterapi

Driessen J, University of Amsterdam, paper: 879

Conclusions

1. The addition of BV to salvage chemotherapy followed by ASCT seems to increase PFS in relapsed, but not in primary refractory cHL patients
   - *Include more Chemo-studies (BeGeV) with more primary refractory patients and PET-data*

2. OS was increased in the BV-cohort, however this could be due to advances in treatment over time for patients who fail ASCT

4. Nüks/dirençli HL tedavisi

4.1. OKİT öncesi nüks

4.1.1. Brentiksumab-kemoterapi

4.1.2. Pembrolizumab-ICE

4.1.3. Br-Nivo/Br-Benda

4.3. PD-1 blokerleri sonrası nüks

4.3.1. Nivolumab-ruksolutinib

4.3.2. Pembrolizumab-vorinostat

ICE

Locke JB, Augusta University, paper: 229

Hypothesis:

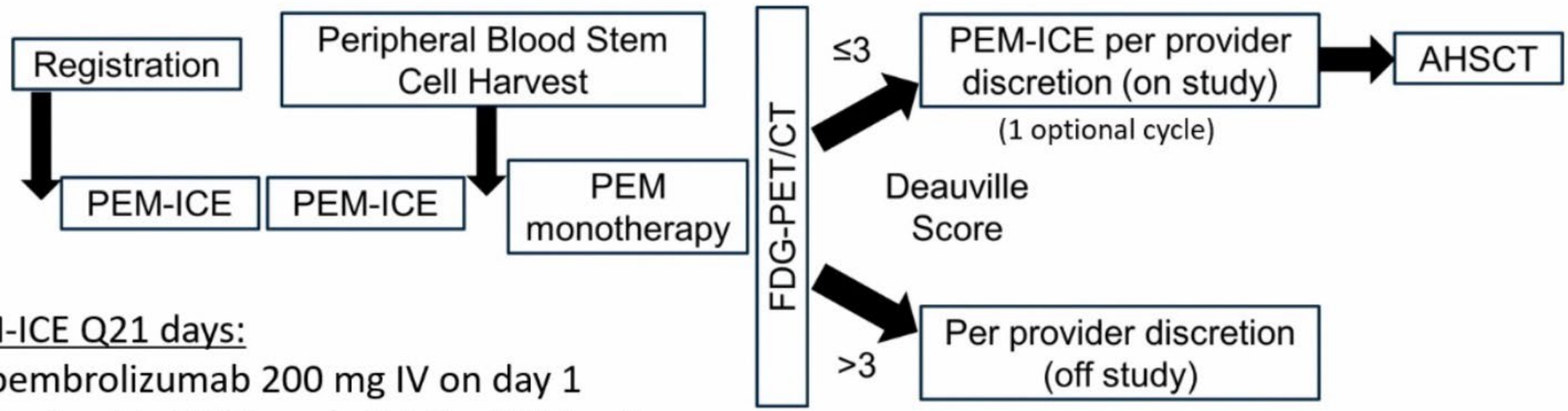
- Combination of PEM + ICE chemotherapy will be a safe and effective regimen to improve the CMR rate prior to autoSCT
  - Primary Endpoint - Improve CMR to 70%

ICE

Locke JB, Augusta University, paper: 229

Trial Schema:

Key enrollment criteria:
Age >18 years
Medically fit for AHSCT
Relapsed/refractory classic Hodgkin lymphoma
Exclusions: >2 prior regimens, prior PD-1 inhibitor exposure, history of autoimmune disease, known CNS involvement.



PEM-ICE Q21 days:

- pembrolizumab 200 mg IV on day 1
- ifosfamide 5000 mg/m2 24hr CIV day 2
- carboplatin AUC 5 IV day 2
- etoposide 100 mg/m2 IV days 1-3

NCT03077828

ICE

Locke JB, Augusta University, paper: 229

Results:

43 patients enrolled

- Ineligible by h/o pericarditis
  - Never treated on protocol
- Deemed ineligible following path review (NLPHL)
- Allergy to etoposide
- Pt withdrew following cycle #1
- Received TLI prior to PET/CT
- Grade 5 event during stem cell collection

Patient Characteristics (n = 37)	n	(%)
Age: median age (range)	37	(19-70)
Sex		
Female	25	(68)
Male	12	(32)
Race		
White	26	(70)
African American	6	(16)
Asian	1	(3)
Not Reported / Unknown	4	(11)
Treatment History		
Received ABVD as Front-line Therapy	34	(92)
Primary Refractory Disease	14	(39)
Relapsed Disease within 1 yr	12	(32)
Bulky Disease (>10 cm) at Enrollment	6	(16)

ICE

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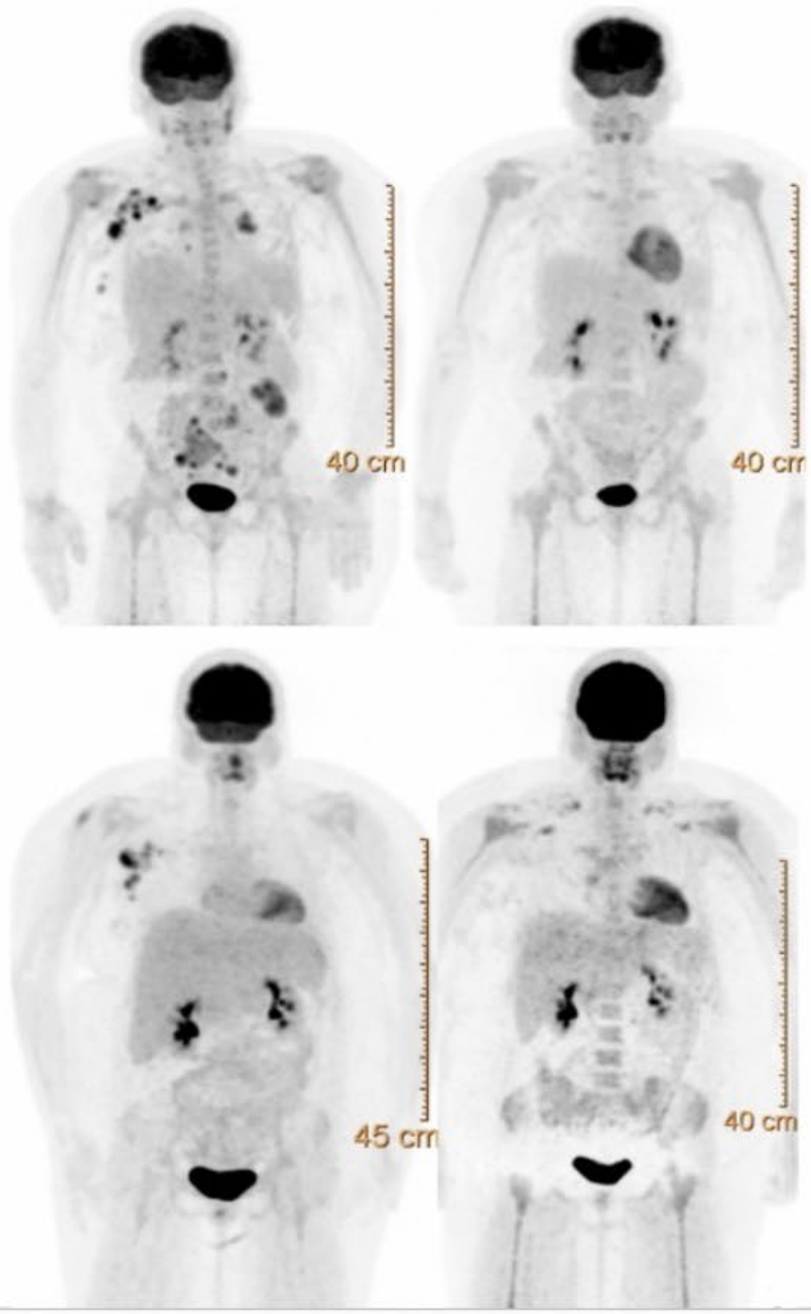
Results: Primary Endpoint

PET/CT Response Assessment (n = 37)		
Complete Response Rate	**86.5%**	(71 - 96)
PET2 Response	n	(%)
Deauville Score 1	17	(45)
Deauville Score 2	10	(27)
Deauville Score 3	3	(8)
Deauville Score 4	*5	(14)
Deauville Score 5	*2	(5)

* 2 cases with follow up biopsies confirmed noncaseating granuloma and EBV positive cells without evidence of lymphoma



ICE

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Results:

Transplant Related Therapy (n = 37)	n	(%)
3rd cycle of PEM-ICE (optional)	5	(14)
Underwent autoSCT		
Yes	35	(95)
No	2	(5)
Radiation Therapy		
Treatment with AutoSCT conditioning	7	(19)
Post-transplant consolidation	4	(11)
AutoSCT conditioning Regimens		
BEAM (carmustine, etoposide, cytarabine, melphalan)	25	(68)
CCE (carboplatin, cyclophosphamide, etoposide) + TLI	7	(19)
BCV (busulfan, cyclophosphamide, etoposide)	3	(8)
Cyclophosphamide + TBI	1	(3)
CBV (cyclophosphamide, carmustine, etoposide	1	(3)

ICE

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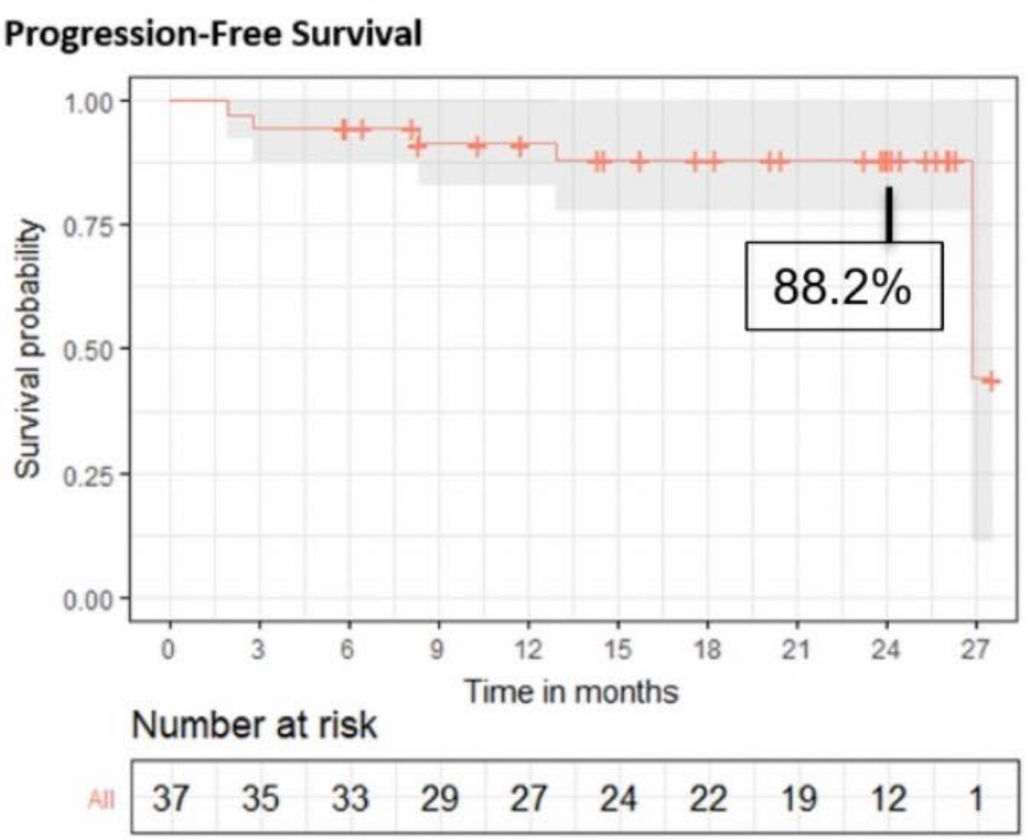
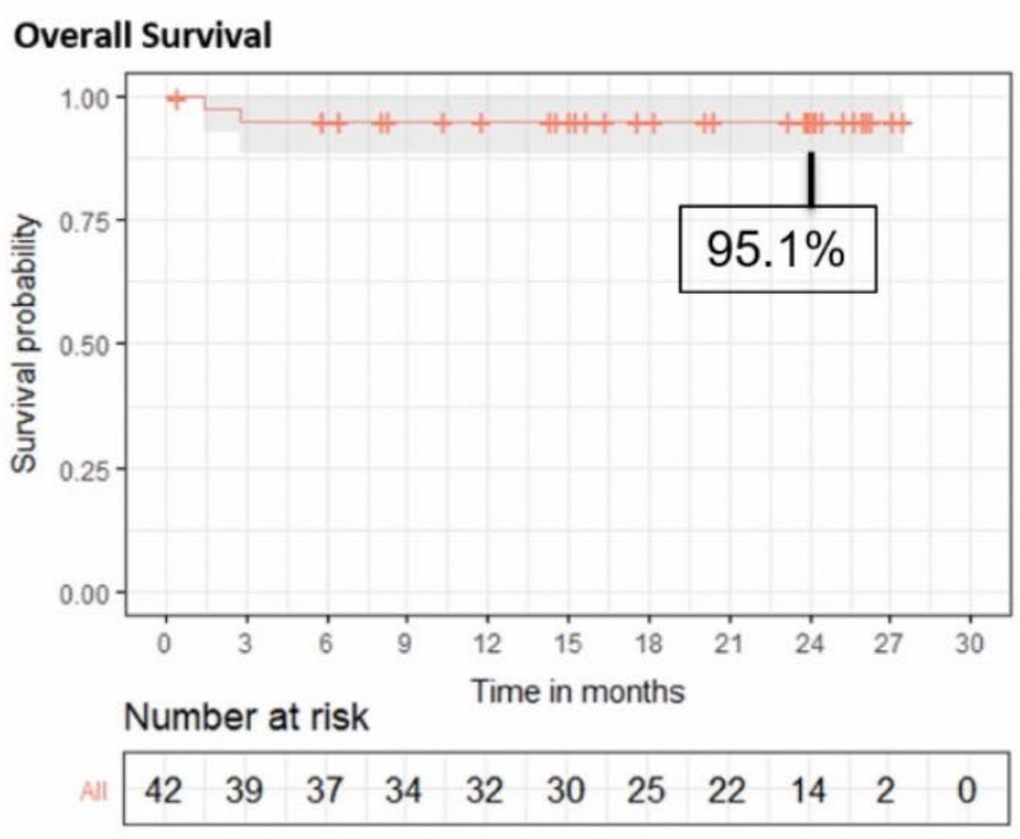
Results: Outcomes





ICE

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Results: Secondary Endpoints

Stem Cell Mobilization / Collection (n = 40)		
Mean Number of Apheresis Sessions	1.6	(1 - 7)
Cell Collected (million cells/kg)	9.6	(1.6 - 46.1)

Engraftment (n = 40)	days (range)	
Absolute Neutrophil Count Recovery	11	(9 - 24)
Platelet Count Recovery	12	(8 - 23)

ICE

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Results:

Safety and Tolerability (n = 42)	n	(%)
Grade 3-4 Hematologic Toxicity		
Thrombocytopenia	39	(93)
Anemia	32	(76)
Febrile Neutropenia	12	(29)
Grade 3-4 Non-hematologic Toxicity		
Hypokalemia	15	(36)
Hypophosphatemia	11	(26)
Oral Mucositis	10	(24)
Attribution to PEM		
PEM-related Autoimmune Events	1*	

Grade 5 Toxicities
Cardiac arrest during stem cell collection
*ARDS following autoSCT – engraftment syndrome

ICE

Locke JB, Augusta University, paper: 229

Conclusions:

- Pembrolizumab + ICE chemotherapy
  - Tolerable and efficacious regimen
  - High CMR rate as assessed by PET/CT
  - Acceptable salvage regimen for patients fit for autoSCT
  - With short follow up, excellent PFS and OS

- Future Direction
  - Expect to see this regimen in upcoming trial for relapsed/refractory cHL

4. Nüks/dirençli HL tedavisi

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4.3.1. Nivolumab-ruksolutinib

4.3.2. Pembrolizumab-vorinostat

Benda

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12 merkez, retrospektif, OKİT yapılan hastalar

Patient Characteristics

Patient Characteristics*	Number (%) (Total 853)
Age (median, range)	33 (18-72) years
Male	446 (52%)
Advanced Stage	257 (30%)
Extranodal disease	271 (32%)
B symptoms	369 (43%)
Primary refractory disease	142 (17%)
Early (<1 yr) relapse	307 (36%)
Number of Salvage therapy before ASCT:	
1	853 (100%)
2	245 (29%)
3	71 (8%)
4	26 (3%)
BV maintenance after ASCT	164 (19%)

* At relapse

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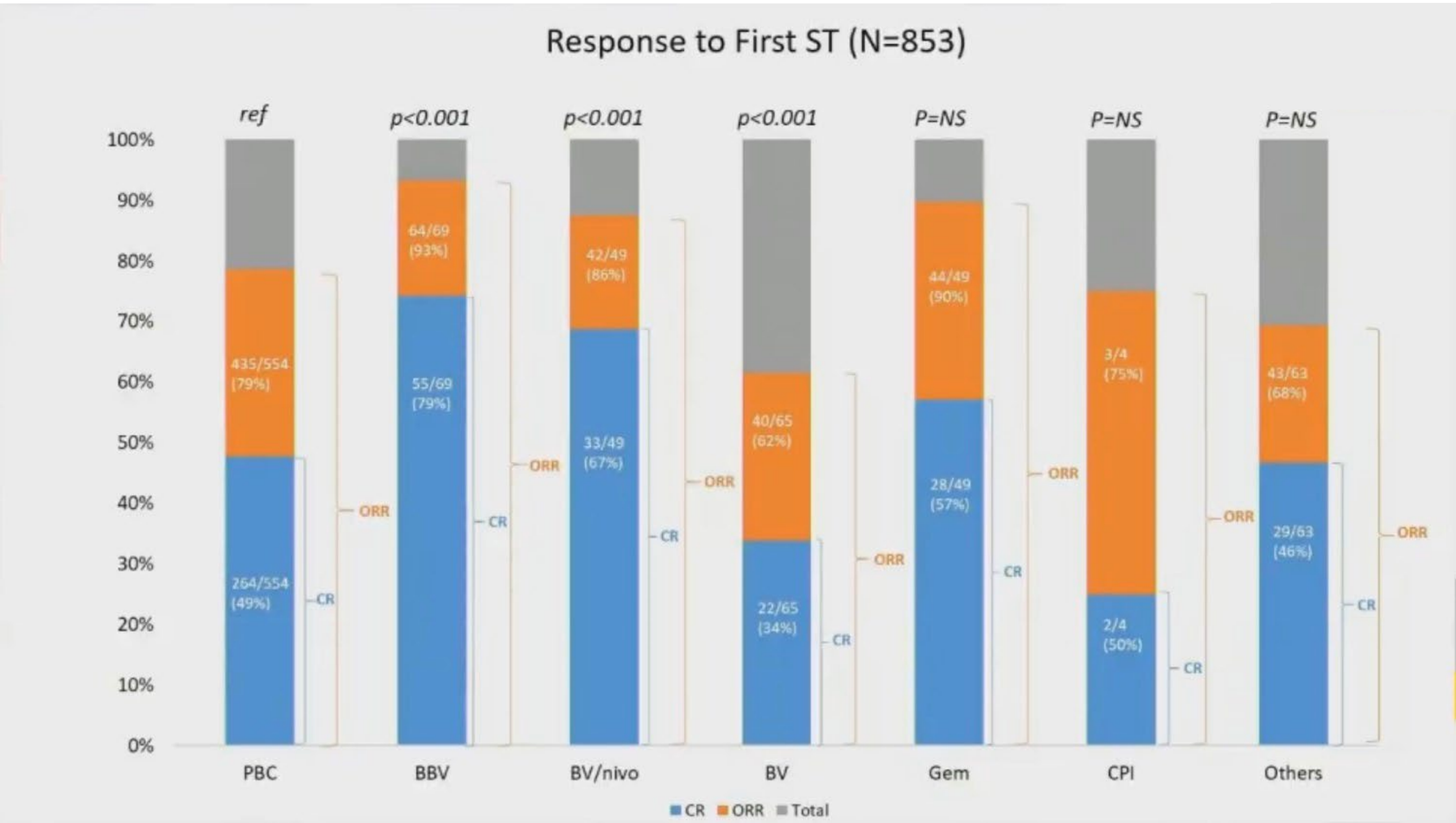
12 merkez, retrospektif, OKİT yapılan hastalar



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12 merkez, retrospektif, OKİT yapılan hastalar

Predictors of response

Variable	ORR (Odds ratio, CI_{95})	P	CR (Odds ratio, CI_{95})	P
BV/Nivo*	2.1 (0.8 -5.1)	NS	***2.6 (1.3-4.8)***	***0.005***
BBV*	***3.48 (1.3-8.0)***	***<0.001***	***4.4 (2.4-8.2)***	***<0.001***
BV*	***0.4 (0.2-0.7)***	***0.002***	***0.5 (0.3-0.9)***	***0.03***
B symptoms	0.4 (0.2-0.8)	<0.05	0.1 (0.3-0.8)	<0.05
Early relapse	0.3 (0.05-0.5)	<0.05	0.3 (0.05-0.5)	<0.05
Primary refractory	0.6 (0.3-0.9)	<0.05	0.4 (0.2-0.8)	<0.05

* With Platinum based chemotherapy (PBC) as a reference

Benda

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12 merkez, retrospektif, OKİT yapılan hastalar

Pre-ASCT Salvage therapy

- Salvage therapy received right before ASCT.

Pre-ASCT ST (N)
Platinum based chemotherapy (PBC=451)
Bendamustine/brentuximab (BBV=76)
Brentuximab/Nivolumab (BV/Nivo = 48)
Brentuximab Vedotin (BV=87)
Checkpoint inhibitors (CPI=24)
Gemcitabine based therapy (Gem=90)
Other miscellaneous agents (Others=64)

Benda

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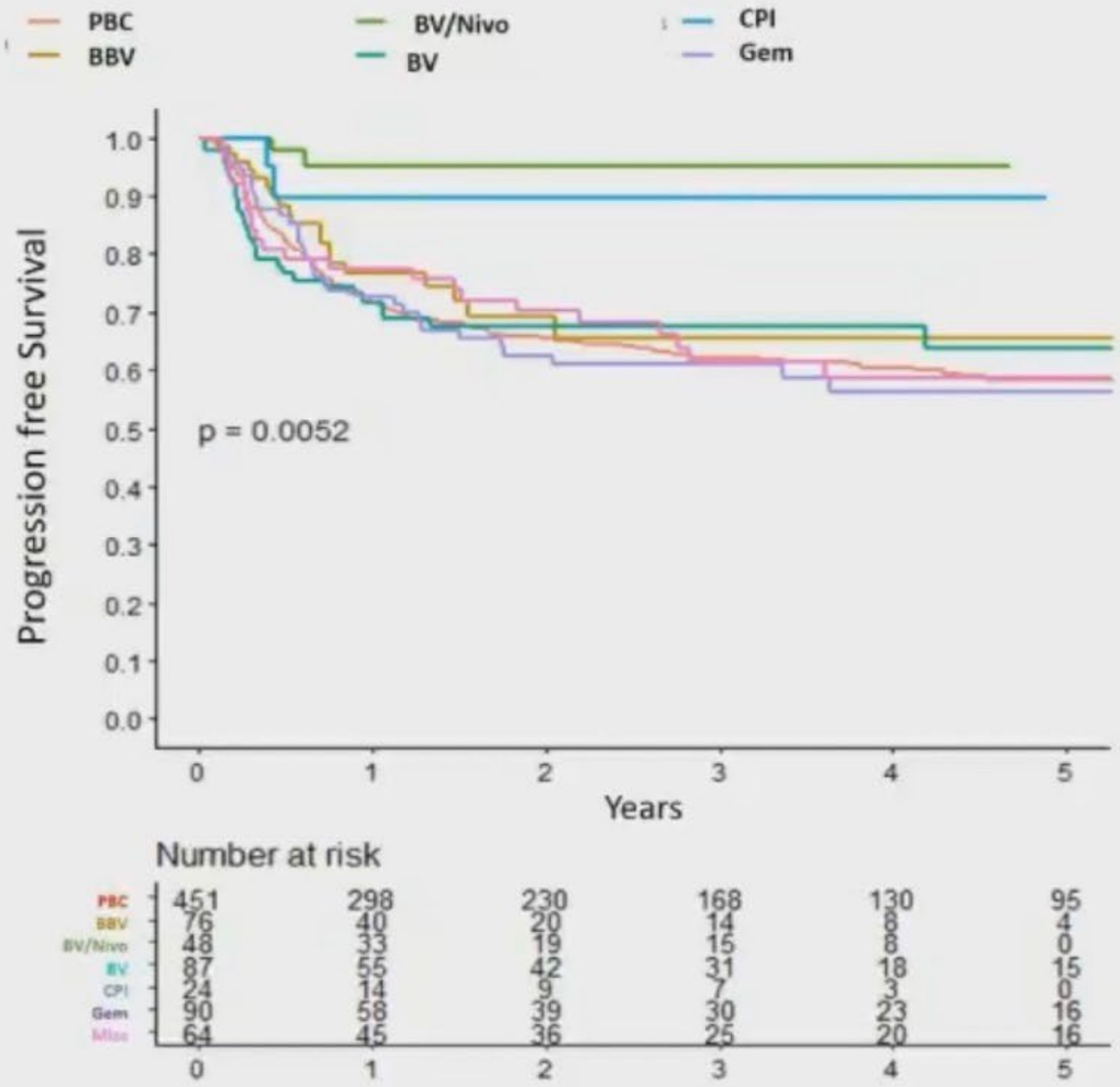
12 merkez, retrospektif, OKİT yapılan hastalar

Progression Free Survival by pre-ASCT salvage therapy

Pre-ASCT ST (N)	2 Year PFS % (CI_{95})	P value
PBC (451)	65.4 (61.9-68.9)	ref
BBV (76)	69.3 (60.2-78.4)	NS
BV/Nivo (48)	***95.2 (91.7-98.7)***	***<0.01***
BV (87)	67.6 (60-75.2)	NS
CPI (24)	***89.7 (82.1-97.3)***	***<0.01***
Gem (90)	62.6 (54-71.2)	NS
Others (64)	70.3 (62-78.6)	NS



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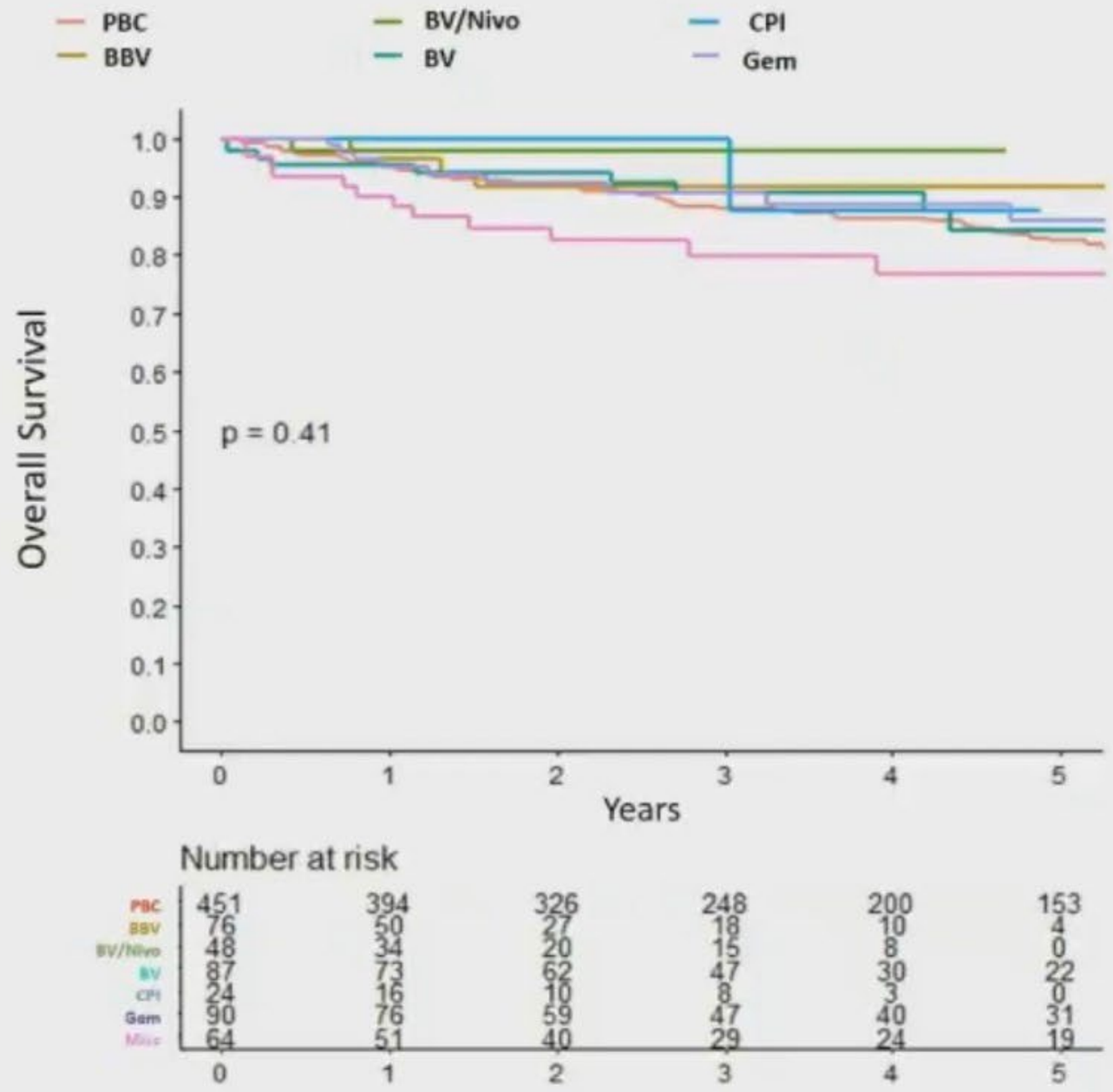
12 merkez, retrospektif, OKİT yapılan hastalar

Overall Survival by pre-ASCT salvage therapy

Pre-ASCT ST (N)	2 Year OS% (CI_{95})	P value
PBC (451)	91.8 (90.3-93.3)	ref
BBV (76)	91.8 (87.5-96.1)	NS
BV/Nivo (48)	***97.7 (95.3-100)***	***NS***
BV (87)	94.4 (91.7-97.1)	NS
CPI (24)	***100 (-)***	***NS***
Gem (90)	92.4 (89.2-95.6)	NS
Others (64)	82.5 (76.4-88.6)	NS



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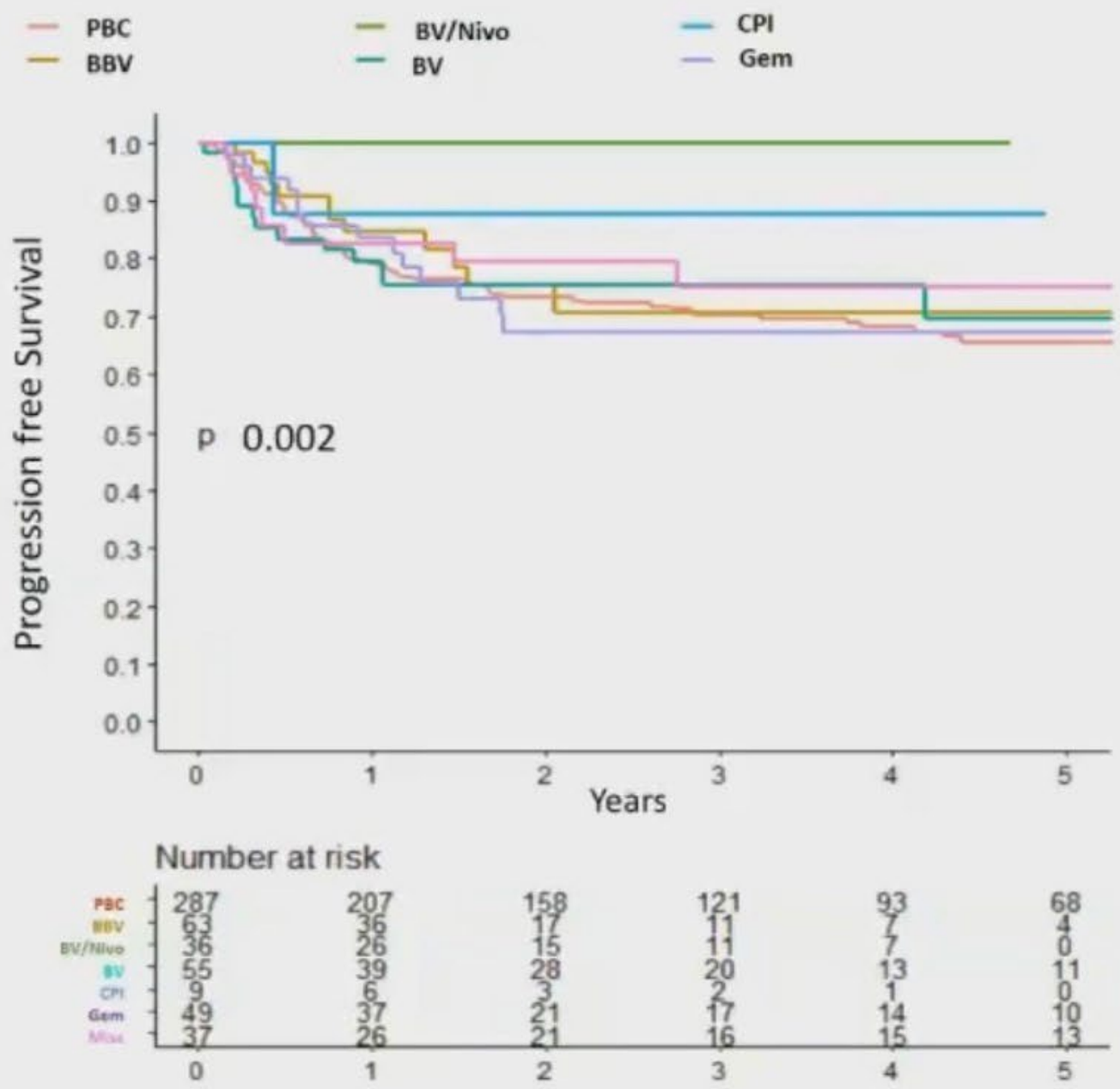
12 merkez, retrospektif, OKİT yapılan hastalar

Subgroup of CR:
PFS by pre-ASCT salvage therapy

Pre-ASCT ST (N)	2 Year PFS % (CI_{95})	P value
PBC (287)	73.2 (69.5-76.9)	ref
BBV (63)	75 (66-84)	NS
BV/Nivo (36)	***100 (-)***	***0.002***
BV (55)	75.2 (67.3-83.1)	NS
CPI (9)	***87.5 (86.2–88.8)***	***0.002***
Gem (49)	67.2 (56.3-78.1)	NS
Others (37)	79.3 (70.5-88.1)	0.02



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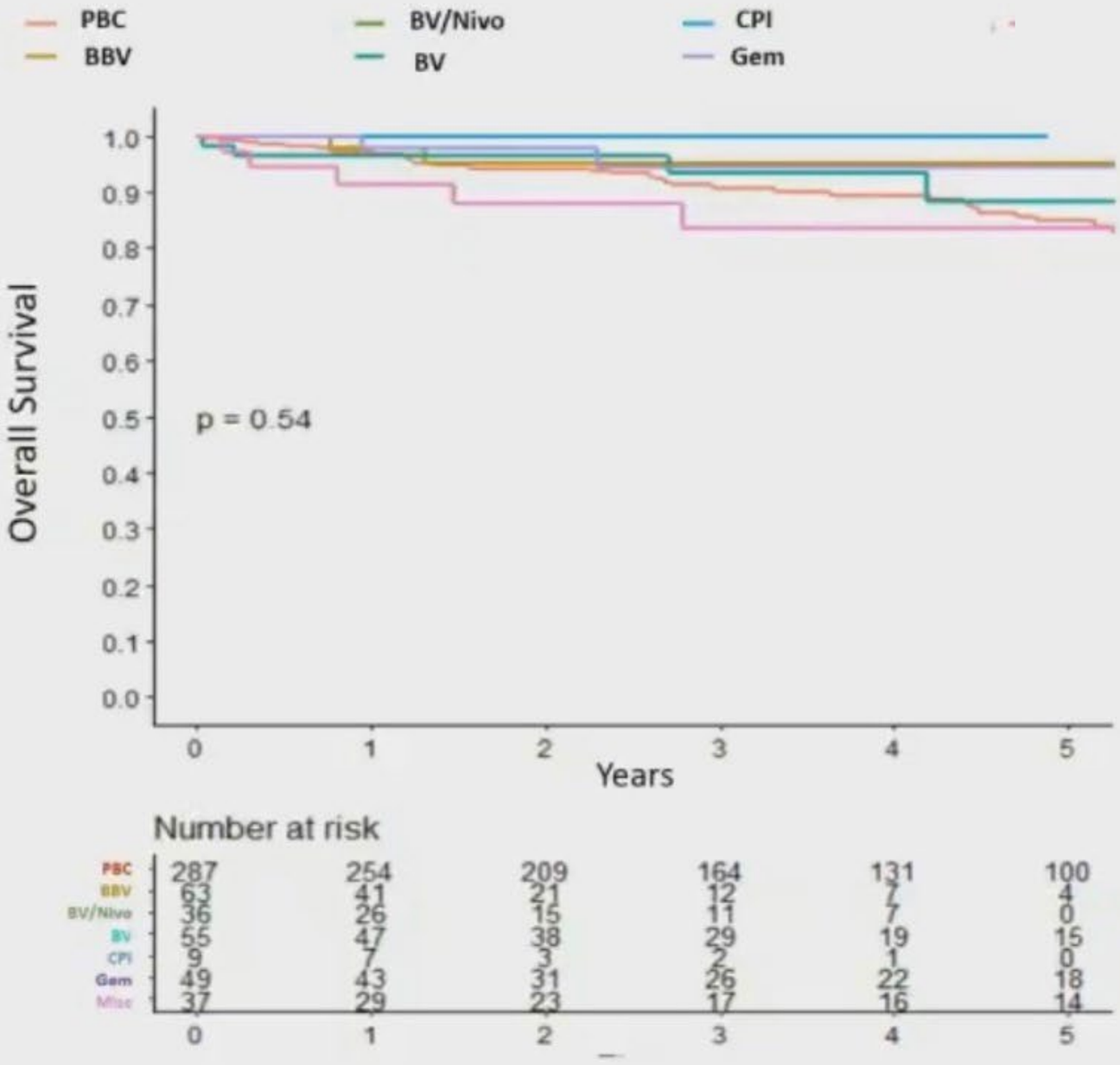
12 merkez, retrospektif, OKİT yapılan hastalar

Subgroup of CR
OS by pre-ASCT salvage therapy

Pre-ASCT ST (N)	2 Year OS % (CI_{95})	P
PBC (451)	94.2 (92.7-95.7)	ref
BBV (76)	94.9 (91.2-98.6)	NS
BV/Nivo (48)	***100 (-)***	***NS***
BV (87)	96.3 (93.7-98.9)	NS
CPI (24)	***100 (-)***	***NS***
Gem (90)	97.8 (95.6-100)	NS
Others(64)	88.0 (81.6-94.4)	NS



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12 merkez, retrospektif, OKİT yapılan hastalar

Predictors of survival

Variable	PFS (HR, CI_{95})	P
BV/Nivo*	***0.1 (0.03 -.0.4)***	***0.002***
CPI*	***0.2 (0.05-0.8)***	***<0.05***
Pre-ASCT PR	4.3 (2.7-6.8)	<0.001
Pre-ASCT PD	1.4 (1.2-2.3)	<0.001
Early relapse	1.7 (1.3-2.1)	<0.001
Primary refractory	2.0 (1.4-2.7)	<0.001
BV maintenance	0.4 (0.3-0.8)	<0.05

* With Platinum based chemotherapy (PBC) as a reference

Benda

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12 merkez, retrospektif, OKİT yapılan hastalar

Conclusion:

- BV/Nivo has a higher CR rate and better post-ASCT PFS compared to conventional chemotherapy.
- BV/Nivo led to durable remissions in pts with pre-ASCT CR suggesting cure.
- BBV had a higher response rate and similar post-ASCT survival to conventional chemotherapy.
- BV had lower response rates compared to PBC.
- Novel ST such as BV/Nivo and BBV may be preferable to conventional chemotherapy in R/R cHL.

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4.3.1. Nivolumab-ruksolutinib

4.3.2. Pembrolizumab-vorinostat

PD-1 blokerden sonrası nüks: **Nivolumab Ruksolutinib**

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Study Design and Eligibility

- This is a Phase I multicenter, open-label, dose escalation/dose-expansion study to evaluate the safety, tolerability and preliminary efficacy of ruxolitinib when combined with nivolumab in patients with relapsed or refractory classical Hodgkin Lymphoma
- Continuous re-assessment method (CRM) was used to assign dose level
- Ruxolitinib starts at day 1 at q28-day cycle. Three dose levels were tested:
  - **10 mg orally twice a day (bid)**
  - **15 mg bid**
  - **20 mg bid**
- Nivolumab 480 mg IV started at day 8 and was infused every 4 weeks
- Treatment was continued until disease progression, unacceptable toxicity or planned HCT
- **Planned duration of therapy was 2 years.**

B1G CANCER RESEARCH CONSORTIUM

63rd ASH® Annual Meeting and Exposition

Ruksolutinib

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All Enrolled Patients Failed Prior CPI

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Variable	Frequency Patients (%)
Prior Check-point Inhibitor (CPI) Detail available for 15 pts	19 (100%)
Pembrolizumab Nivolumab	5 (33%) 10 (67%)
Progressed while on CPI	11 (73%)
Duration of remission with prior CPI Median (range in months)	4.3 (0.9-46.3)
Time from last CPI to enrollment Median (range, in months)	**1.7 (0.7-36.4)**

B1G Cancer Research Consortium

Ruksolutinib

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Patient and Disease Characteristics

University of Minnesota
Driven to Discover

Variable	All patients (n=19)
Age (median; range)	38 (22-76)
Gender : Male n (%)	13 (68)
Race: White n (%)	17 (89)
Time from Dg to enrollment Median (range in years)	3.4 (0.9-16.7)
Stage at Diagnosis II n (%) III-IV	2 (11%) 17 (88%)
Prior Lines of therapy Median (range)	4 (2-11)
Prior HCT: Autologous HCT only n (%) Allogeneic HCT only Both auto and allo HCT	13 (69) 8 (42) 2 (11) 3 (16)

B1G Cancer Research Consortium

PD-1 blocking small molecules: **Nivolumab**

Ruksolutinib

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Tolerability and Adverse Events

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- Median number of cycles was 8 (range 3 – 28 cycles)
- No DLTs were observed
- Most AEs were grade 1 and 2
  - Fatigue, GI (nausea), anemia and heme toxicity
- Two patients required hospitalization for therapy related SEA
  - Both patients had pneumonia (one auto-immune)
- Immune mediated adverse events n= 5 (27%)
  - LFT elevation: Gr 1 (n=3) and Gr 2 immune hepatitis (n=1)
  - Pneumonitis Gr 3 (n=1)
  - All were reversible

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Disease Control Rate and Overall Response

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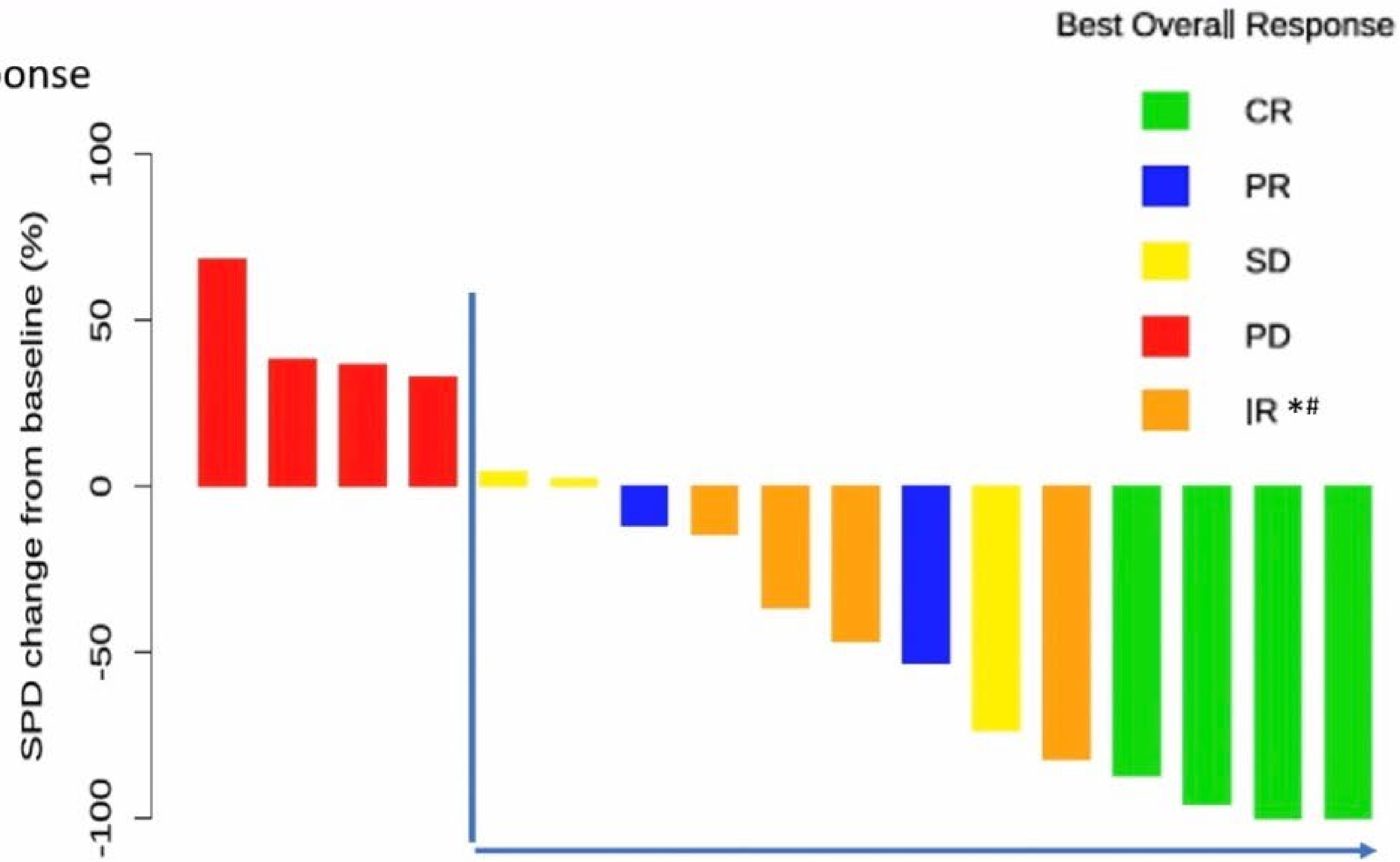
17 subjects were evaluable for response

Response	n (%)
DCR	**13 (77)**
ORR	8 (48)
CR	4 (24)
PR	2 (12)
SD*	3 (36)
IR#	4 (24)
PD	4 (24)



. *15-47% SPD reduction. #Two patients with indeterminate response had negative biopsy of increased PET activity area
2 subjects were not evaluable for response (1 patient who received < 1 month of therapy due to rapid disease progression and Gr 2 immune hepatitis)

Ruksolutinib

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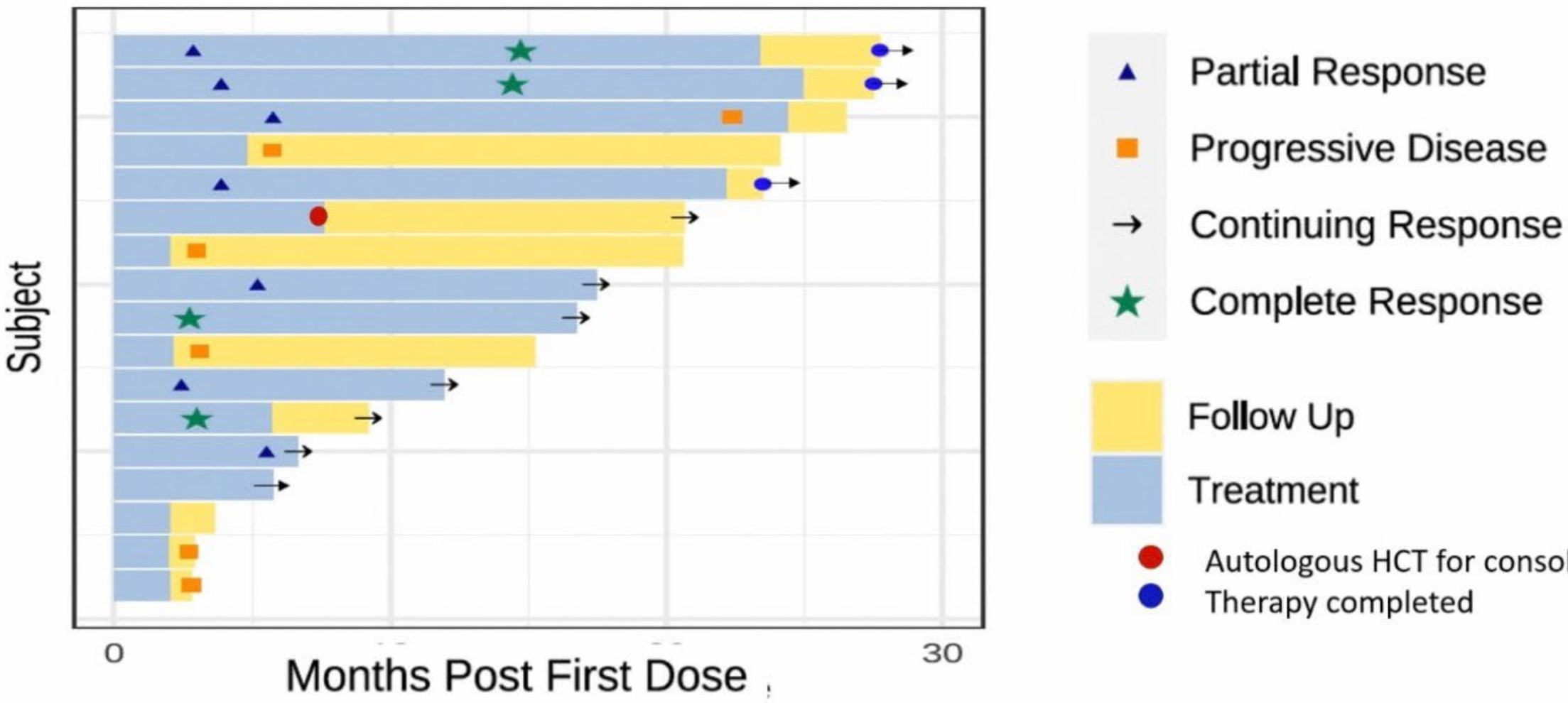
Duration of Response



Median duration of response is 12.5 months (3.7-20.4 months)

11 (64%) patients are alive without progression

PD-1 blocken sonrası nüks: **Nivolumab**

Ruksolutinib

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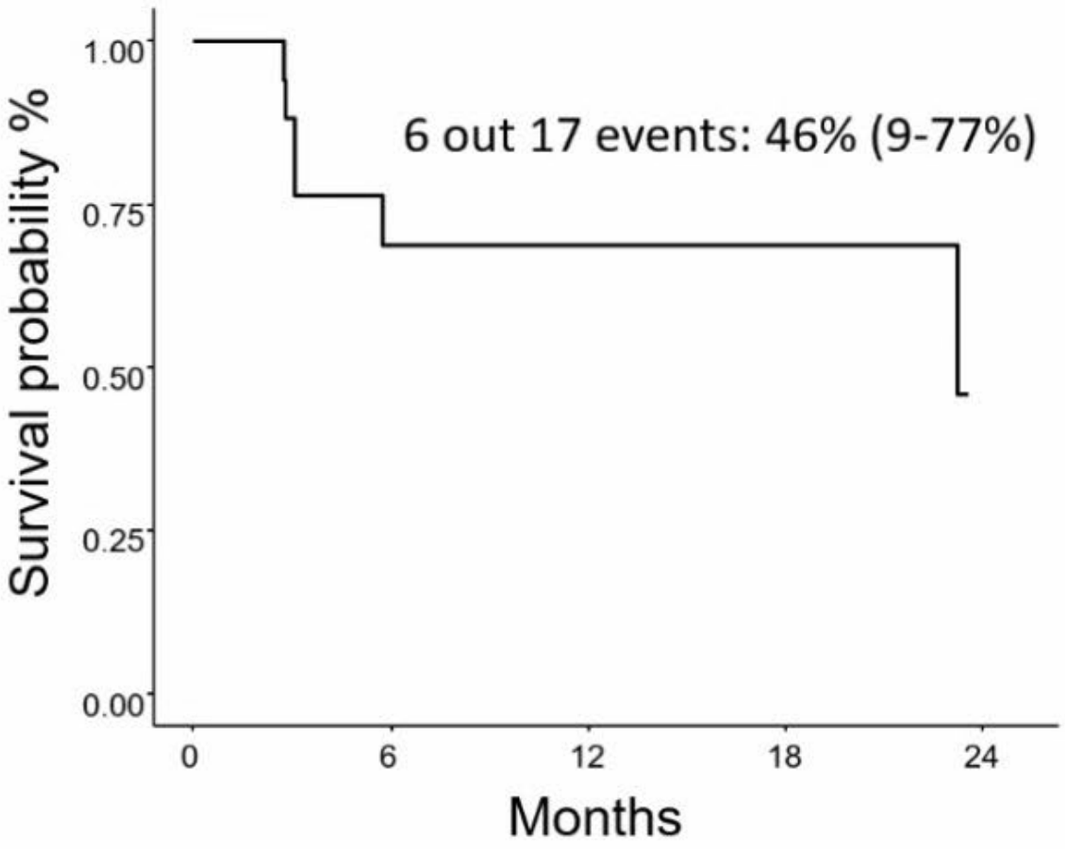
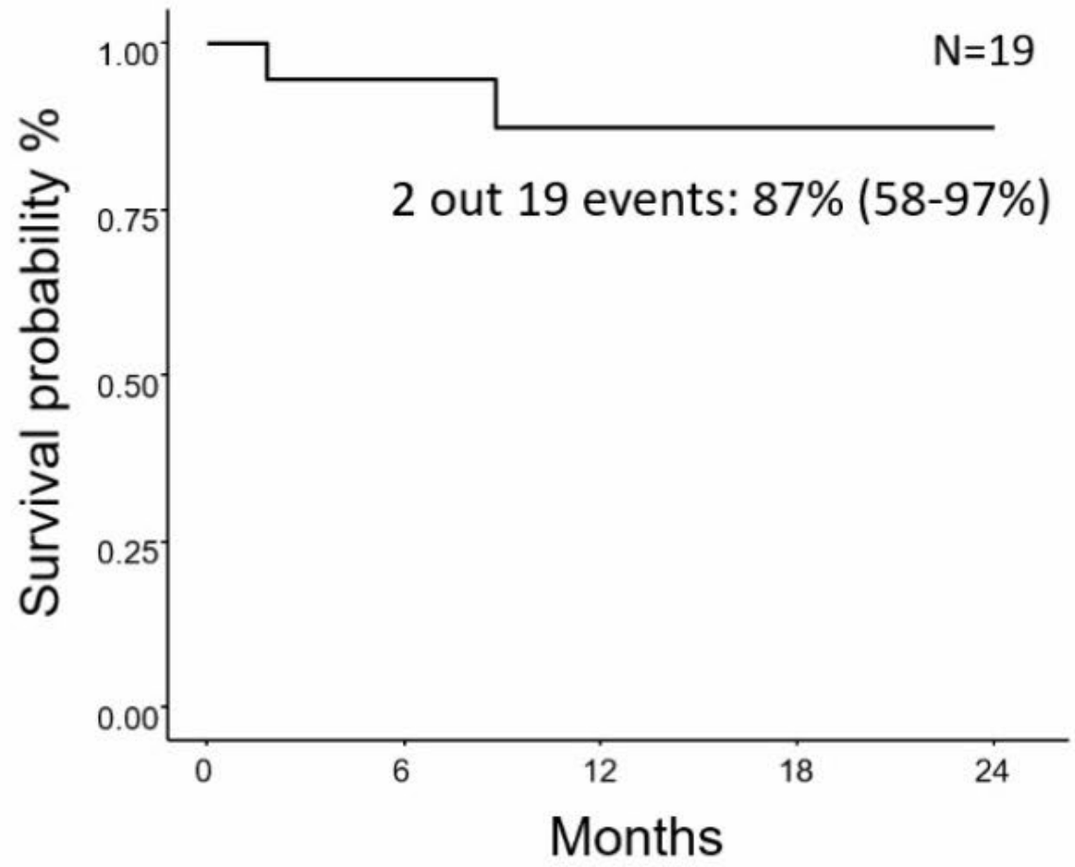
PFS and OS at 2 years





Median follow-up is 16.8 months (2.8-28 months)

One death is related to disease progression; one is related to toxicity from subsequent therapy

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Ruksolutinib

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Conclusions

- Therapy combining ruxolitinib at dose 20mg BID daily with nivolumab 480mg IV monthly is well tolerated with infrequent and reversible immune mediated adverse reaction (27%).

- This therapy yields encouragingly high remission rates (DCR 77%, CR 24%) and durable responses (median DOR 12.5 months) in R/R Hodgkin lymphoma patients who had failed previous check-point inhibitors.

- Pharmacodynamic and correlative analyses on the mechanism of synergism suggest preservation of T cell function and alteration in host MDSCs

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4.3.2. Pembrolizumab-vorinostat

PD-1 blokeren samen met: **Pembrolizumab**

Vorinostat

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Rationale

- HDAC inhibition has multiple immunologic effects
  - Recruit T cells into the tumor microenvironment
  - Upregulate PD-L1 expression in multiple tumor types *(Woods et al. Cancer Immunol Res 2015)*

- HDACi and PD-1 blockade are synergistic in enhanced anti-tumor activity pre-clinical lung, colorectal, and breast cancer models.

- Monotherapy HDAC inhibition has modest anti-tumor activity in cHL

Hypothesis: Pembrolizumab + HDAC inhibition with vorinostat will be safe and effective in pts with RR cHL

PD-1 blokeri sonrası nüks: **Pembrolizumab Vorinostat**

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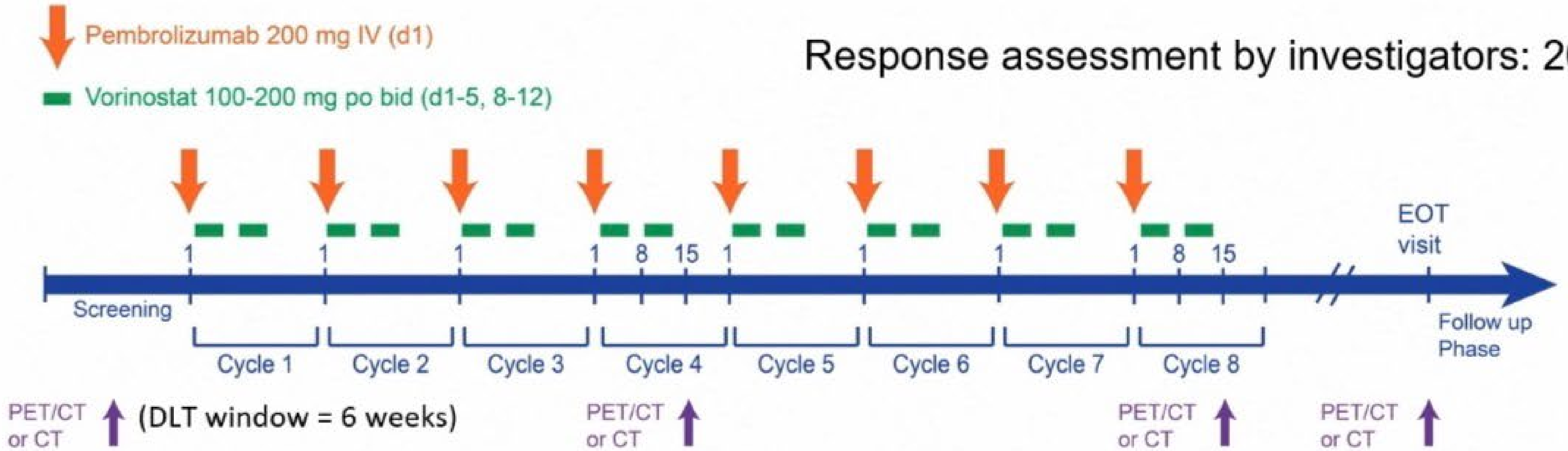
Study Design and Treatment Plan

Response assessment by investigators: 2014 Lugano



- Dose escalation: enrollment according to Rolling six design, n=12 (mixed cHL, FL, DLBCL)

Dose Level	Vorinostat (PO)	Pembrolizumab (IV)
1 (Starting)	100mg BID, d1-5, 8-12	200mg, d1
2	200mg BID, d1-5, 8-12	200mg, d1

❖ Amendment to add n=10 anti PD-1 refractory cHL

- Expansion cohort treated at RP2D (DL2), n=30 (mixed cHL, FL, DLBCL)

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PD-1 blokkeren sonrası nuks: **Pembrolizumab**

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Baseline Characteristics

Baseline Characteristics	N (%)
Total	32 (100)
Stage I-II	8 (25)
Stage III-IV	24 (75)
B symptoms	4 (13)
Bulky disease (> 5cm)	6 (19)
Extranodal involvement	14 (44)
EBV+	4 (13)
Primary refractory	22 (69)
Refractory to most recent therapy	17 (53)
Median # of prior therapies (range)	4 (1-12)
Prior BV	30 (94)
BV refractory	21 (66)
Prior PD1 blockade	25 (78)
Anti-PD1 refractory	18 (56)

PD-1 blokeren sonrası nuks: **Pembrolizumab**

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Disposition (n=32)

Status	N (%)
DL1	2 (6)
DL2	30 (94)
Median # of cycles (range)	8.5 (1-36)
Vorinostat dose reduction (↓ANC)	1 (3)
Ongoing treatment	8 (25)
Discontinued treatment	24 (75)
Disease progression	13 (41)
Stem cell transplant	6 (19)
Patient preference	2 (6)
Completion of 2y therapy	2 (6)
AE (skin rash)	1 (3)

PD-1 blokkeren sonrasi hiks: **Pembrolizumab**

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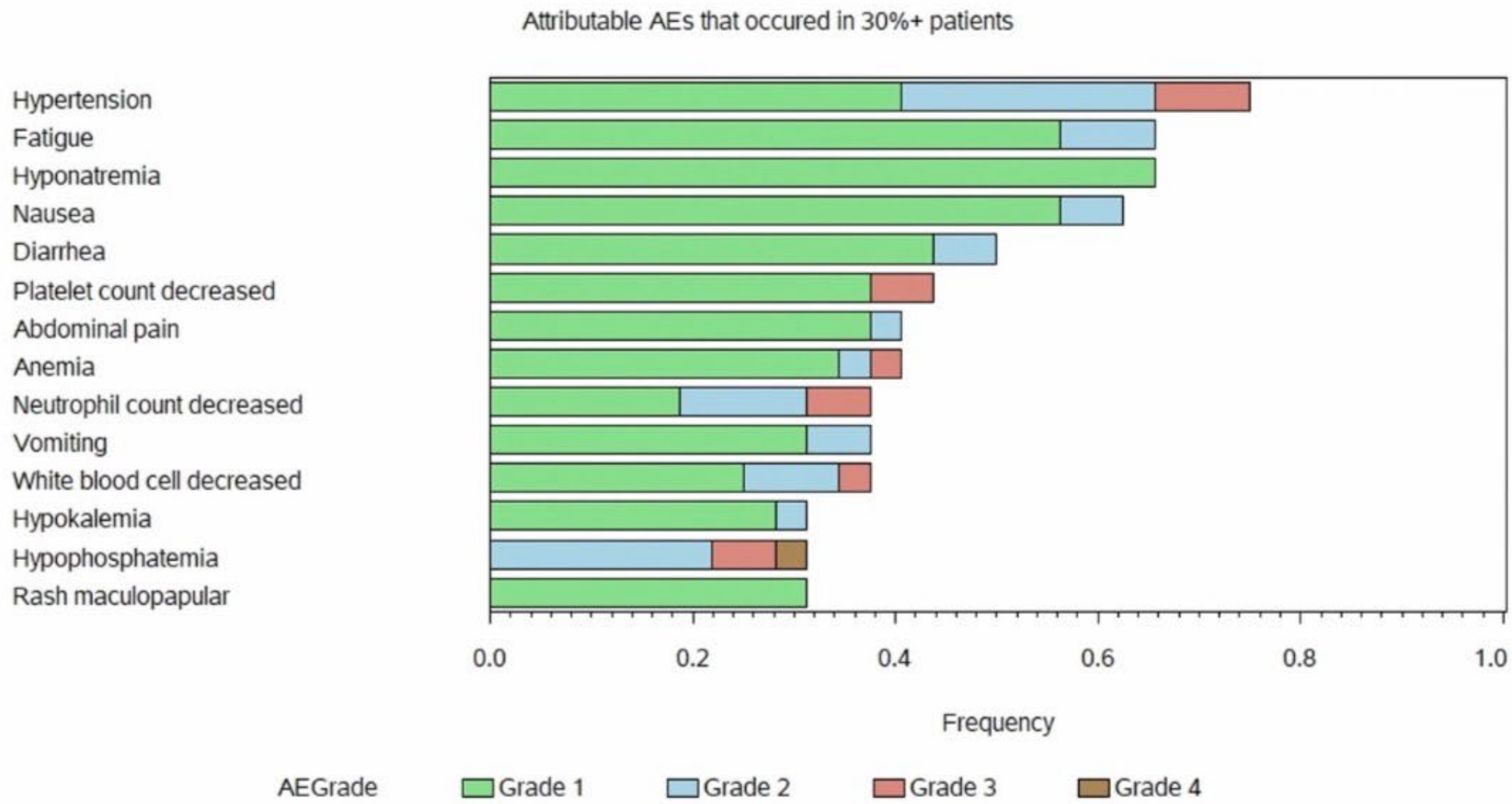
Most Common Treatment-Related AEs



PD-1 blokeren sonrasi nuks: **Pembrolizumab**

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Immune-Related AEs

- N=4 with Gr 1-2 thyroiditis
- N=2 with Gr 1 rash
- N=1 with Gr 3 esophagitis/duodenitis
  - Treated with steroids was able to resume and completed 34 cycles

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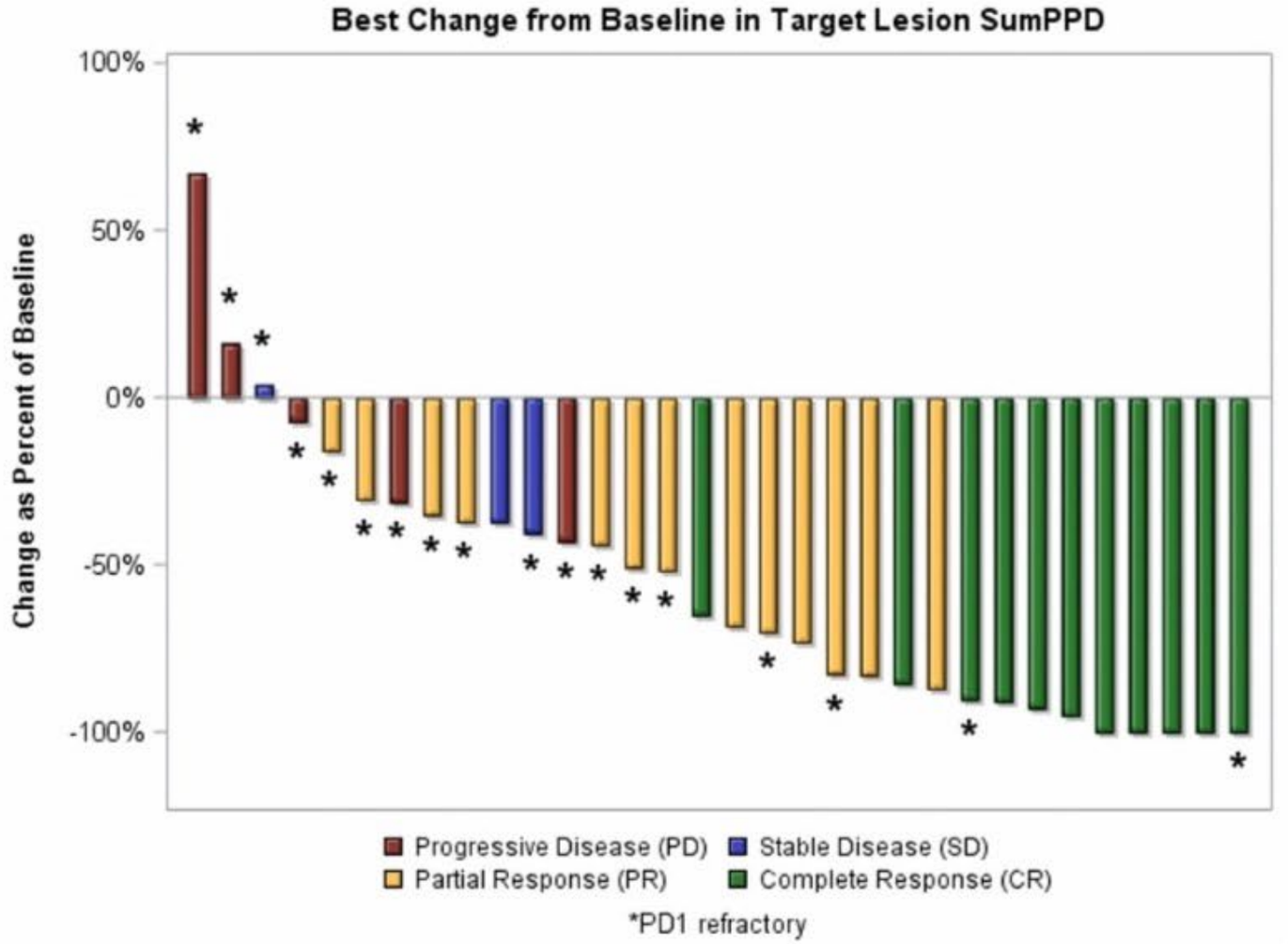
Best response to Pembro+Vorinostat

N=32
ORR 75%, CR 34%

Response	N (%)
Overall	**24 (75)**
CR	**11 (34)**
PR	13 (41)
SD	3 (9)
PD	5 (16)



PD-1 blokeren sonrası nüks: **Pembrolizumab**

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Best Response to Pembro+Vorinostat

Disease	Response	N (%)
Anti-PD1 Naïve (n=7)	**Overall**	**7 (100)**
	CR	**4 (57)**
	PR	3 (43)
	SD	0 (0)
	PD	0 (0)
Anti-PD1 Exposed Sensitive (n=7)	**Overall**	**6 (86)**
	CR	**5 (71)**
	PR	1 (14)
	SD	1 (14)
	PD	0 (0)
Anti-PD1 refractory (n=18)	**Overall**	**11 (61)**
	CR	**2 (11)**
	PR	9 (50)
	SD	2 (11)
	PD	5 (28)

PD-1 blokeren sonrası nuks: **Pembrolizumab**

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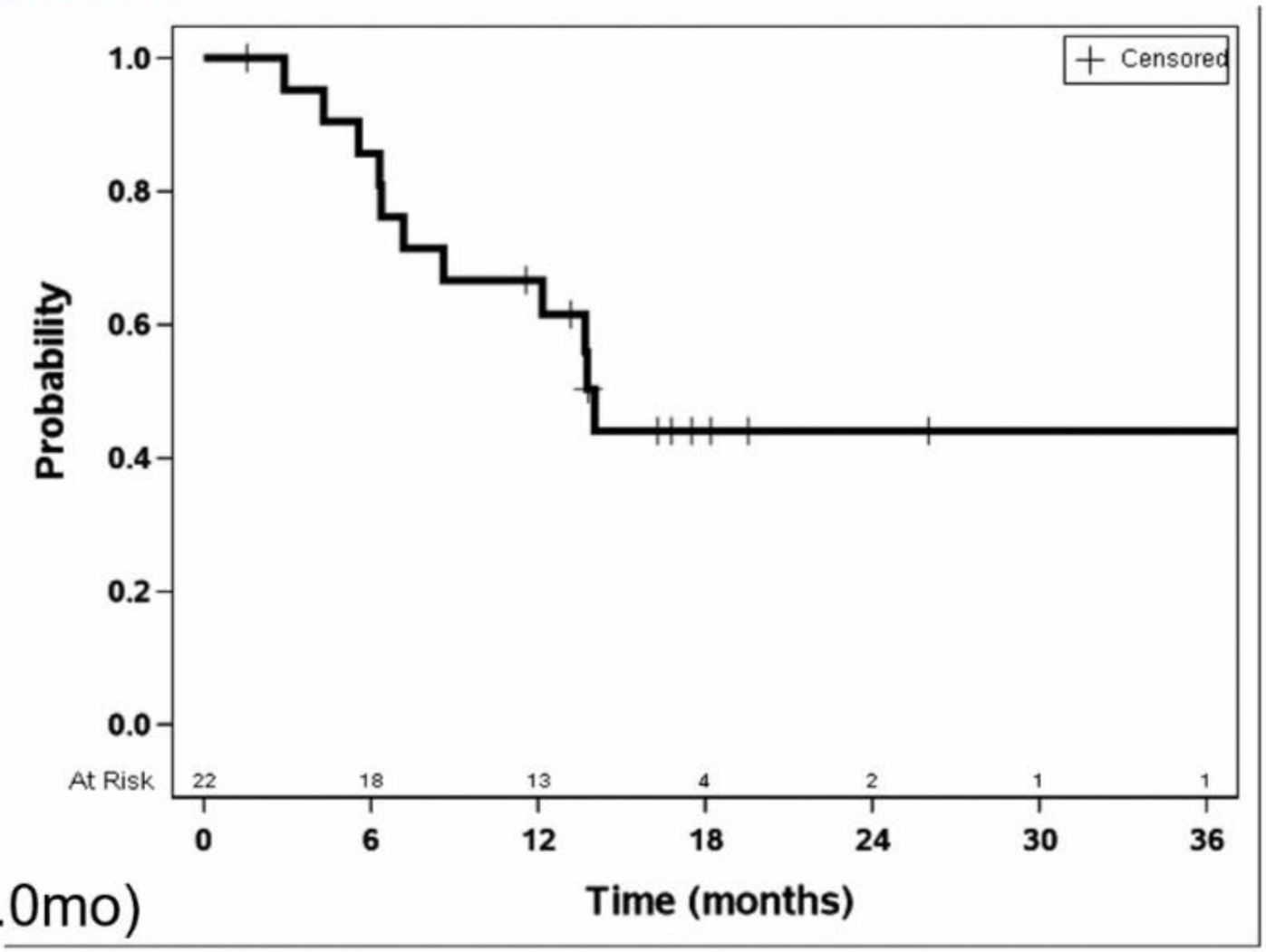
Duration of Response

Median: 14 months

- PD1 naïve/sens: NR
- PD1 refractory: 11.1mo

1y DOR: 67%

- PD1 naïve/sens: 77%
- PD1 refractory: 50%



Median FU time 19.8 mo (2.1-41.0mo)

PD-1 blokeren sonrası nüks: **Pembrolizumab Vorinostat**

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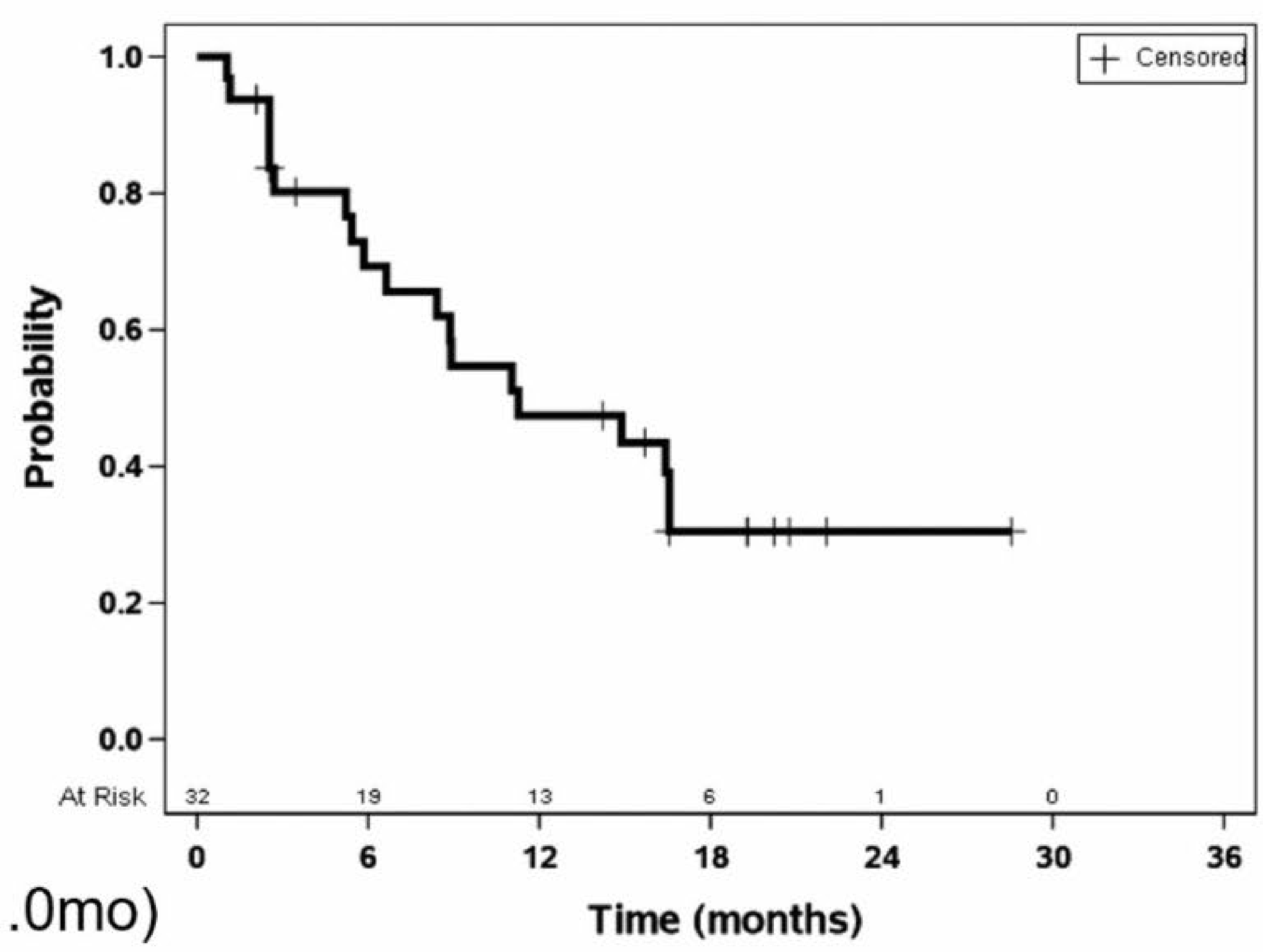
Progression-Free Survival

Median: 11 months

- PD1 naïve/sens: NR
- PD1 refractory: 5.8mo

1y PFS: 47%

- PD1 naïve/sens: 71%
- PD1 refractory: 24%



Median FU time 19.8 mo (2.1-41.0mo)

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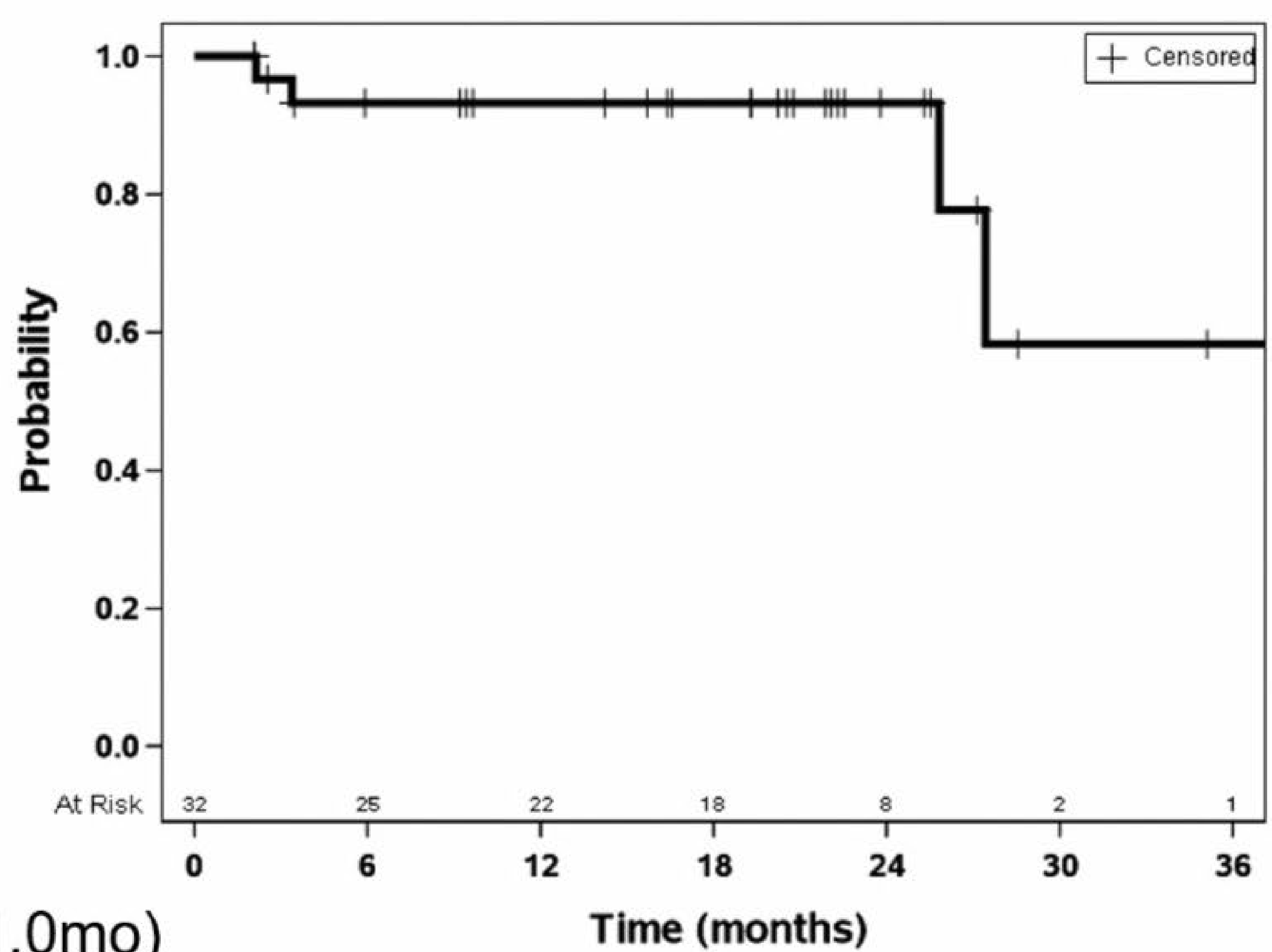
Overall Survival

1y OS: 93%
Median: not reached



Median FU time 19.8 mo (2.1-41.0mo)

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Conclusions

- Pembrolizumab + vorinostat was tolerable and led to high ORR and CR rate in pts with anti-PD1 naïve/sensitive cHL
- Majority of anti-PD1 refractory pts responded to pembro + vorinostat
  - 67% ORR in pts progressing on PD1 blockade as most recent tx
- DOR nearly 1y in anti-PD1 refractory pts
  - 50% in ongoing response at 1y
- PD1 blockade + HDACi should be explored further in cHL

“Teşekkürler”