Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Aproximación Práctica al Tratamiento del Linfoma de Hodgkin

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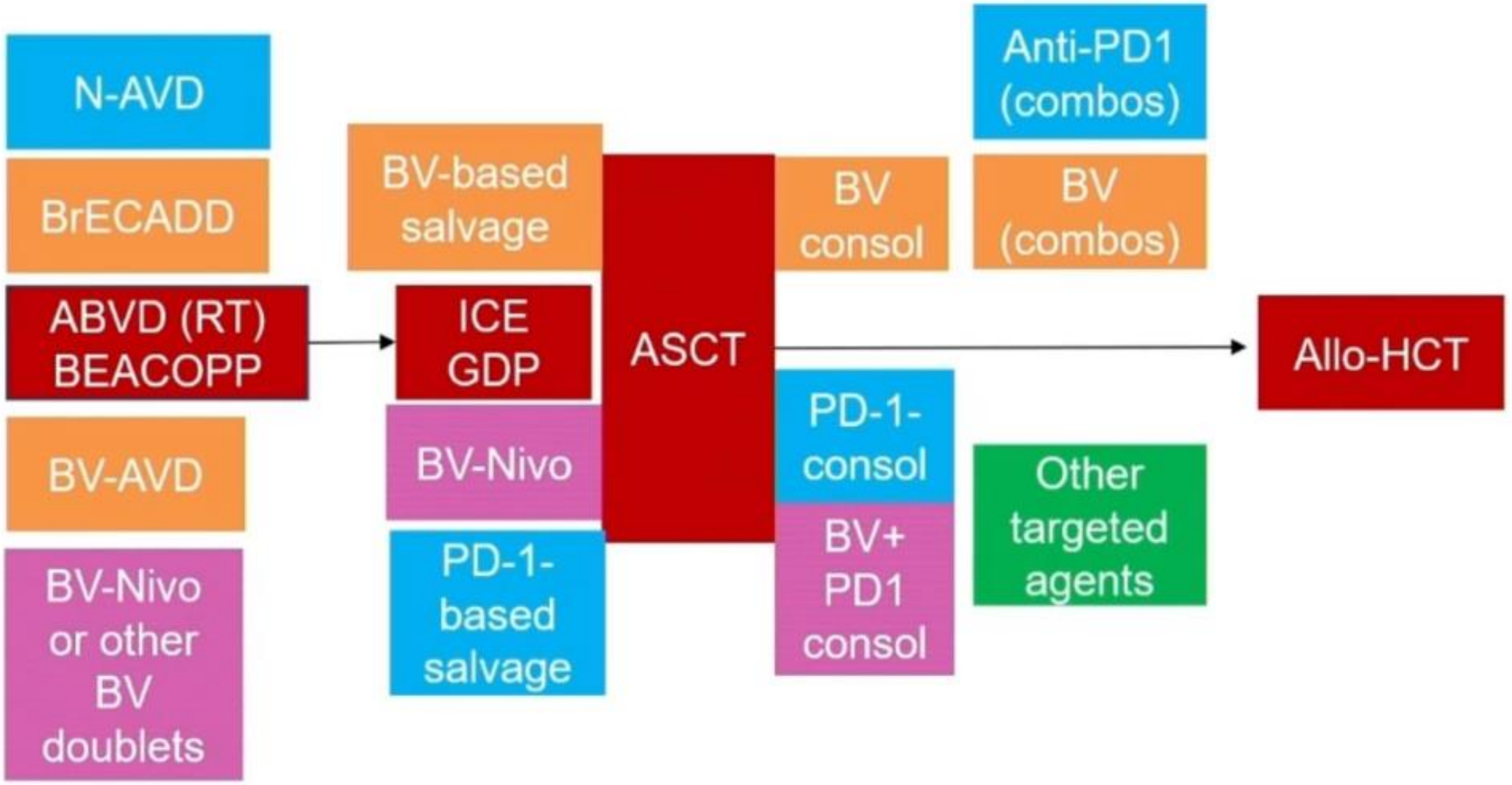
Disclosures

- Honoraria: Takeda, BMS/Celgene, MSD, Janssen, Amgen, Novartis, Gilead Kite, Sanofi, Roche, GenMab, Abbvie, Jazz Pharmaceuticals
- Consultancy: Takeda, BMS/Celgene, Novartis, Janssen, Gilead, Sanofi, GenMab, Abbvie
- Speaker's Bureau: Takeda
- Research Support: Takeda
- Non-profit organizations: Presidency of the EBMT

Hodgkin Lymphoma Management 2024



Agenda

- 1st Line Treatment Strategies
  - Early Stages
  - Advanced Stages
  - Elderly patients
- Relapsed / Refractory Setting
  - Improving salvage treatment strategies
  - Auto-HCT for all relapsed/refractory patients?
  - Allo-HCT
  - New approaches

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Staging at Diagnosis

	EORTC / LySA	GHSG	NCIC / ECOG	NCCN 2022
Factores de riesgo*	- Masa mediastínica >1/3 del diámetro torácico - Edad ≥50 años - Velocidad de sedimentación globular (VSG) ≥50 sin síntomas B o ≥30 con síntomas B	a) Masa mediastínica >1/3 del diámetro torácico b) Enfermedad extraganglionar c) VSG ≥50 sin síntomas B o ≥30 con síntomas B d) ≥3 áreas ganglionares	- Histología diferente a PL / EN - Edad ≥40 años - VSG ≥50 - ≥4 áreas ganglionares	- Masa mediastínica >1/3 o >10 cm -VSG ≥50 o cualquier síntoma B - ≥3 áreas nodales
Favorable	Estadios I-II supradiafragmáticos sin factores de riesgo	Estadios I-II sin factores de riesgo	Estadios I-II sin factores de riesgo	Estadios I-II sin factores de riesgo
Desfavorable	Estadios I-II supradiafragmáticos con ≥1 factor de riesgo	Estadios I o IIA con ≥1 factor de riesgo Estadio IIB con c) o d) pero sin a) y b)	Estadios I-II con ≥1 factor de riesgo	Estadios I-II con ≥1 factor de riesgo (diferenciando entre enfermedad voluminosa y otros factores de riesgo)

	EORTC / LySA	GHSG	NCIC / ECOG	NCCN 2022
Estadios avanzados	- Estadios clínicos III-IV	- Estadios clínicos IIB con masa mediastínica voluminosa o con enfermedad extranodal - Estadios clínicos III-IV	- Estadios clínicos I-II con enfermedad voluminosa - Estadios clínicos III-IV	- Estadios IIB, III y IV - Estadio IIA con enfermedad voluminosa

Guías GELTAMO, 2023

1st Line Treatment Strategies. Early Stages

Without Adverse Prognostic Factors

En los estadios localizados con pronóstico favorable se recomienda el tratamiento con 2 ciclos de ABVD seguidos de 20 Gy de IF-RT. Grado de recomendación A

En el caso de optar por una estrategia de tratamiento guiada por PET tras 2 ciclos de ABVD:

- Si PETi negativa (puntuación de Deauville 1-2), los pacientes pueden ser tratados con un total de 3-4 ciclos de ABVD sin RT (asumiendo una pérdida de eficacia relativamente pequeña).
- Si PETi es positiva (Deauville 3-5) las opciones recomendadas incluyen un total de 4 ciclos de ABVD + 30Gy IF-RT (estudio RAPID) o completar tratamiento con $BEACOPP_e$ x 2 + IF-RT 30 Gy (estudios EORTC / LySA / FIL H10 y CALGB 50604). Grado de recomendación A

Si la PETi es positiva con Deauville 5, la recomendación de los elaboradores de esta guía es realizar biopsia si es posible: en caso de no evidenciar enfermedad, proceder como en Deauville 3-4; si mostrase persistencia del LH, considerar tratamiento de rescate como enfermedad refractaria. Buena práctica clínica

With Adverse Prognostic Factors

En los estadios localizados con pronóstico desfavorable se recomienda el tratamiento combinado de ABVD durante 4 ciclos seguido de IF-RT (30 Gy). Grado de recomendación A

En el caso de optar por una estrategia de tratamiento guiada por PET:

(a) Atendiendo a los resultados del estudio EORTC / LySA / FIL H10U se recomienda 2 ciclos de ABVD seguido de PET:

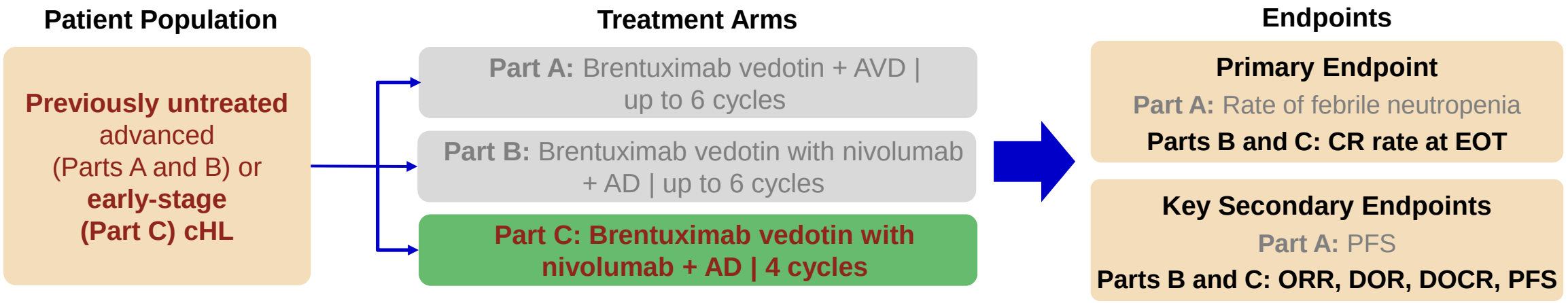
- Si PET negativa, completar tratamiento con 2 ciclos de ABVD más 30Gy IF-RT ó completar con 4 ciclos de ABVD (sin RT)
- Si PET positiva, completar tratamiento con 2 ciclos de $BEACOPP_e$ más 30Gy IF-RT

(b) Atendiendo a los resultados del estudio de Jonhson y cols. los pacientes con PET negativa tras 2 ciclos de ABVD pueden completar tratamiento con 4 ciclos de AVD sin RT. Grado de recomendación A

Si la PETi es positiva con Deauville 5, la recomendación es realizar biopsia si es posible: en caso de no evidenciar enfermedad, proceder como en Deauville 3-4; si mostrase persistencia del LH, considerar tratamiento de rescate como enfermedad refractaria. Buena práctica clínica

Guías GELTAMO, 2023

Introducing New Drugs in Early Stages. Study Design



- SGN35-027 is an open-label, multiple-part, multicenter, phase 2 trial
- Part C enrolled patients with Ann Arbor stage I/II cHL without bulky disease (<10 cm in diameter on CT)
- Patients received 4 cycles of AN+AD (BV 1.2 mg/kg [A] capped at 100 kg body weight, nivolumab 240 mg [N], doxorubicin 25 mg/m^2 [A], and dacarbazine 375 mg/m^2 [D]) intravenously on days 1 and 15 of each 28-day cycle
- The CR rate at EOT was measured by investigator assessment per Lugano 2014 classification[1] with incorporation of LYRIC[2]
- Additional analyses included efficacy assessments for favorable and unfavorable subgroups, defined by German Hodgkin Study Group criteria

Data cutoff: October 4, 2024

CR, complete response; CT, computed tomography; DOCR, duration of CR; DOR, duration of response; EOT, end of treatment, ORR, objective response rate; PFS, progression-free survival.

1. Cheson BD, et al. J Clin Oncol. 2014;32:3059-68. 2. Cheson BD, et al. Blood. 2016;128:2489-96.

Abramson J et al, Abstr #460, ASH2024

Patient Disposition, Demographics, and Disease Characteristics

Summary of disposition, n (%)	AN+AD N=156
Patients who received ≥1 dose of AN+AD	154 (99)
Patients on treatment	0
Patients off treatment	154 (99)
Patients in long-term follow-up	0
Reasons for treatment discontinuation[a]	
Completed treatment	147 (94)
Adverse event	4 (3)
Patient decision, non-adverse event	2 (1)
Investigator decision	1 (1)
Patients off study	156 (100)

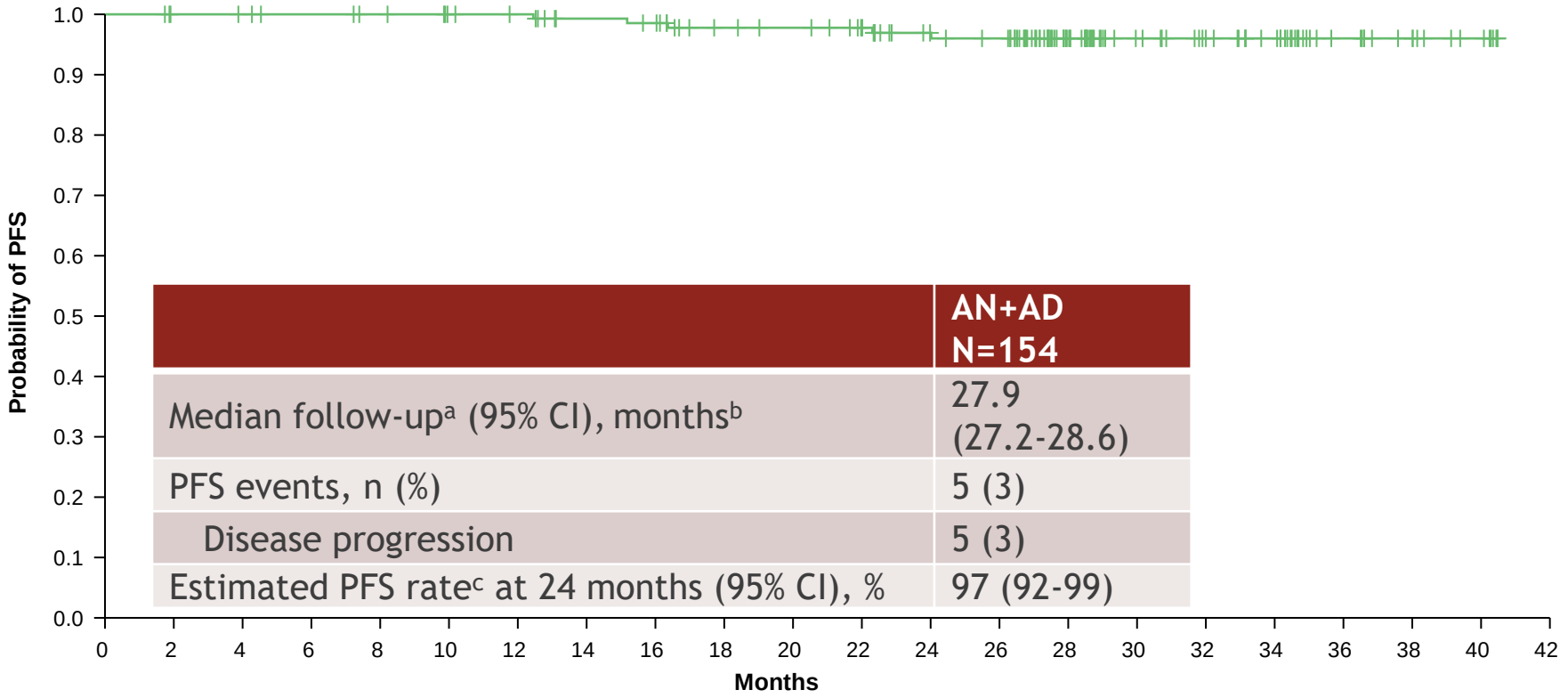
Patient demographics and disease characteristics	AN+AD N=154
Age, median (range), years	31 (18-77)
Female, n (%)	84 (55)
White, n (%)	129 (84)
Disease stage at initial diagnosis, n (%)	
I (nonbulky)	17 (11)
II (nonbulky)	137 (89)
Extranodal disease present, n (%)	17 (11)
B symptoms present at initial diagnosis, n (%)	35 (23)
Favorable/unfavorable disease per GHSG risk criteria, n (%)	
Favorable	56 (36)
Unfavorable	97 (63)
Missing	1 (1)

GHSG, German Hodgkin Study Group.

[a]Treatment discontinuation includes all study drugs.

Abramson J et al, Abstr #460, ASH2024

Progression-Free Survival: All-Treated Patients



	AN+AD N=154
Median follow-up[a] (95% CI), months[b]	27.9 (27.2-28.6)
PFS events, n (%)	5 (3)
Disease progression	5 (3)
Estimated PFS rate[c] at 24 months (95% CI), %	97 (92-99)

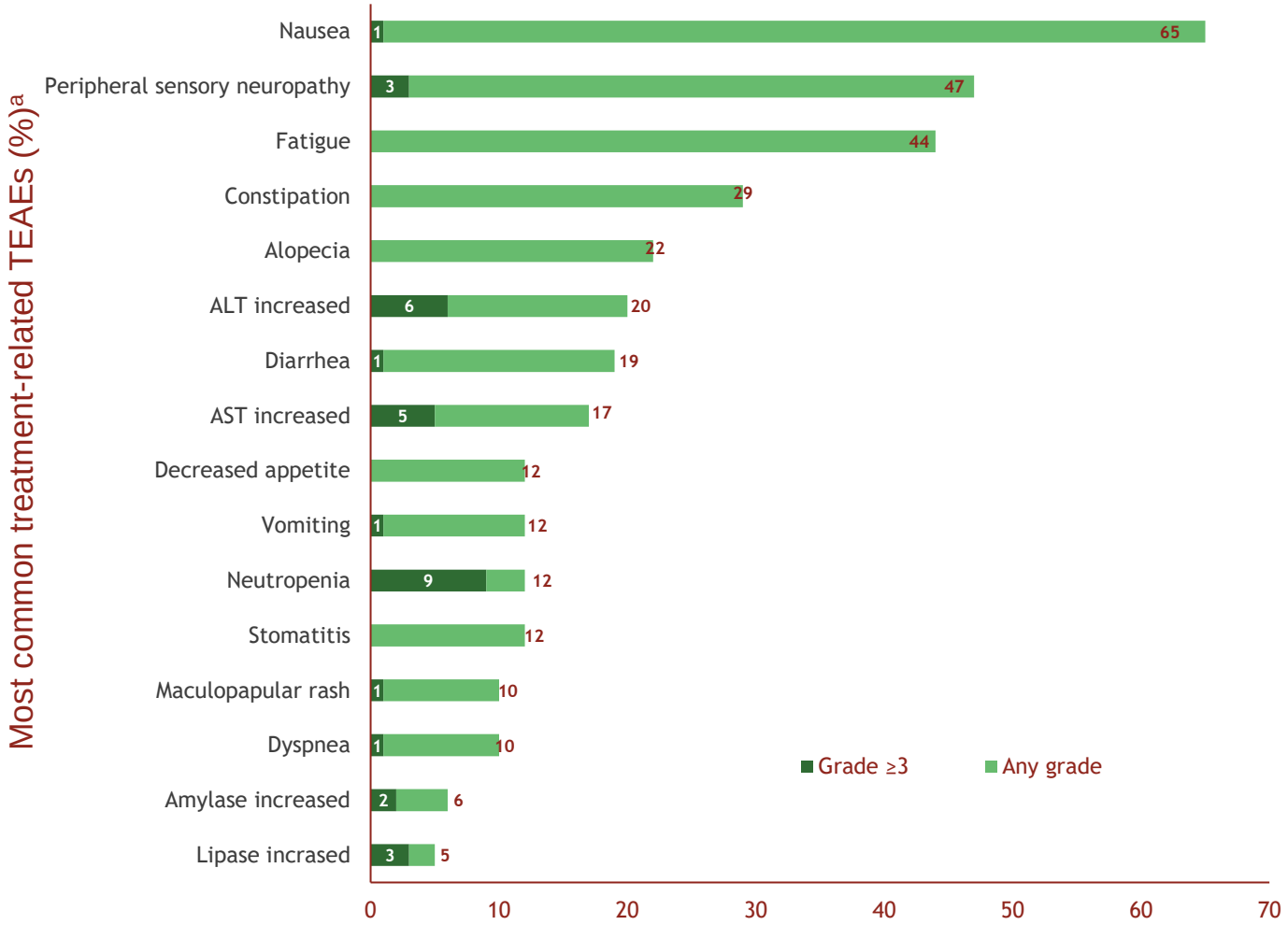
No. of patients at risk (no. of events)

154 (0) 151 (0) 150 (0) 148 (0) 146 (0) 142 (0) 140 (0) 134 (1) 132 (2) 123 (3) 121 (3) 116 (3) 106 (4) 103 (5) 71 (5) 50 (5) 42 (5) 34 (5) 19 (5) 13 (5) 7 (5) 0 (5)

[a]Median follow-up is calculated using the Kaplan-Meier method switching the PFS event/censored status, ie PFS event as censored and censored as PFS event. [b]Calculated using the complementary log-log transformation method. [c]Estimated using Kaplan-Meier methods.

Abramson J et al, Abstr #460, ASH2024

Summary of Adverse Events



ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

[a]≥10% of patients with all grades or ≥2% of patients with grade ≥3.

- Any-grade and grade ≥3 TEAEs occurred in 99% and 44% of patients, respectively
  - No event of febrile neutropenia was reported
- Any-grade and grade ≥3 treatment-related TEAEs occurred in 97% and 34% of patients, respectively
- Serious TEAEs occurred in 19% of patients
  - Treatment-related serious TEAEs occurred in 12% of patients, with the most common being pyrexia (3%)
- 4 of 154 patients (3%) had TEAEs leading to BV discontinuation
- There was 1 death reported after the safety reporting period

Abramson J et al, Abstr #460, ASH2024

1st Line Treatment Strategies. Advanced Stages

En caso de optar por un plan terapéutico **NO guiado por *PET interim*:**

- El tratamiento recomendado en pacientes con LHc en estadios avanzados en nuestro medio es 6 ciclos de ABVD. **Grado de recomendación A**
- Puede considerarse la utilización de 6 ciclos de $BEACOPP_e$ en pacientes <60 años y con un IPS de alto riesgo. **Grado de Recomendación A**
- A-AVD 6 ciclos es una alternativa adecuada (considerando la situación actual de aprobación por la EMA para estadios IV y la no financiación en nuestro país). **Grado de recomendación A**

En caso de optar por un plan terapéutico **guiado por *PET interim*:**

(a) Para los pacientes que inician tratamiento con ABVD:

- Si PETi negativa (DS 1-3) tras 2 ciclos, desescalar a 4 ciclos de AVD. **Grado de recomendación A**
- Si PETi positiva (DS 4, 5) tras 2 ciclos, escalar a 3 ciclos de $BEACOPP_e$. Si la PET después de estos 3 ciclos es negativa, recibirán 1 ciclo más del mismo esquema. Si la PET después de 3 ciclos es positiva, deberían ser tratados con esquemas de segunda línea (en caso de lesión única residual cabe plantearse RT). **Grado de recomendación B**

(b) Para los pacientes que inician tratamiento con $BEACOPP_e$:

- Si PETi negativa (DS 1-3) tras 2 ciclos, administrar sólo 2 ciclos más de $BEACOPP_e$ o desescalar a 4 ciclos de ABVD. **Grado de recomendación A**
- Si PETi positiva (DS 4-5) tras 2 ciclos, administrar 4 ciclos más de $BEACOPP_e$ o pasar a estrategias de 2ª línea (especialmente en casos de DS 5 y con datos radiológicos de progresión de la enfermedad). La RT puede ser una opción en caso de lesiones residuales únicas. **Grado de recomendación B**

Guías GELTAMO, 2023

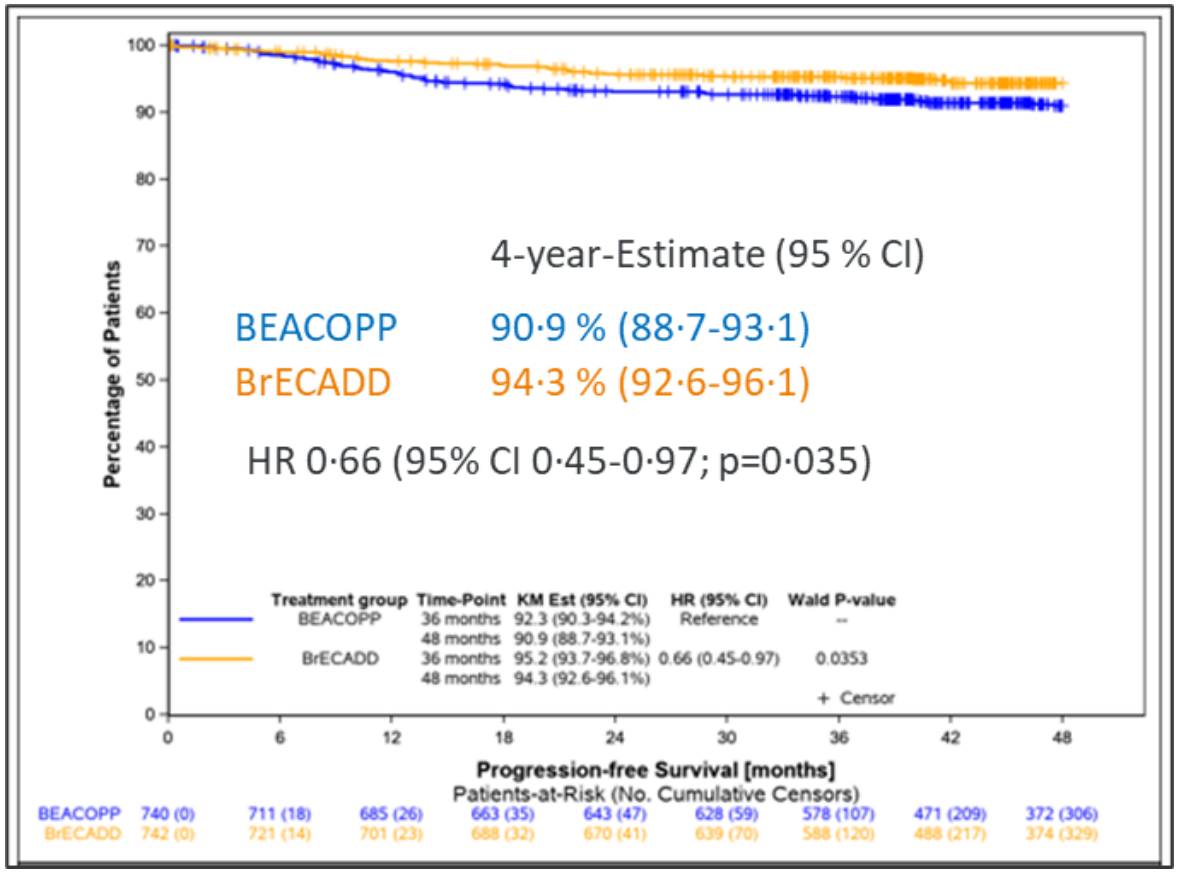
HD21 final analysis: BrECADD is superior to eBEACOPP (mFU 48 m)

GHSG

Borchmann P et al, ASCO2024, EHA2024, ISHL2024

HD21 final analysis: BrECADD is superior to eBEACOPP (mFU 48 m)

Progression-free survival



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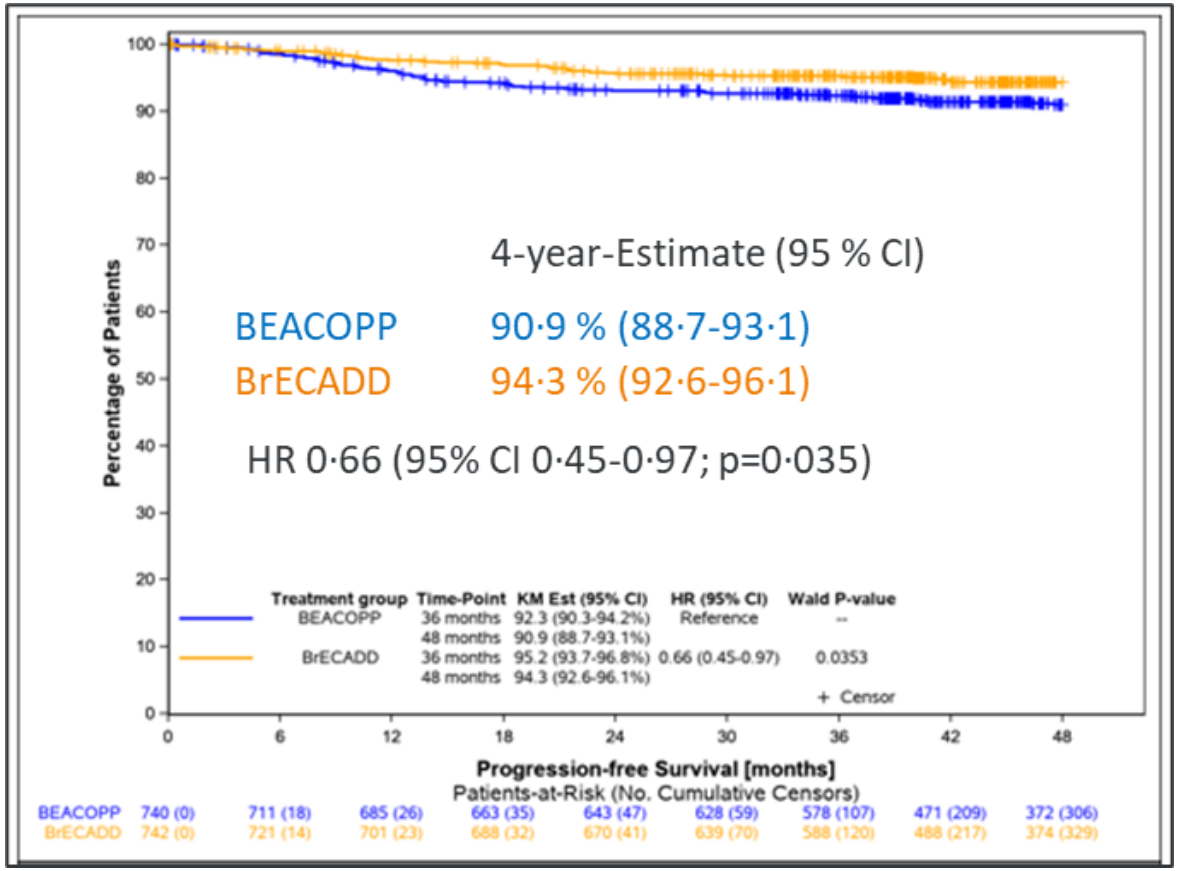
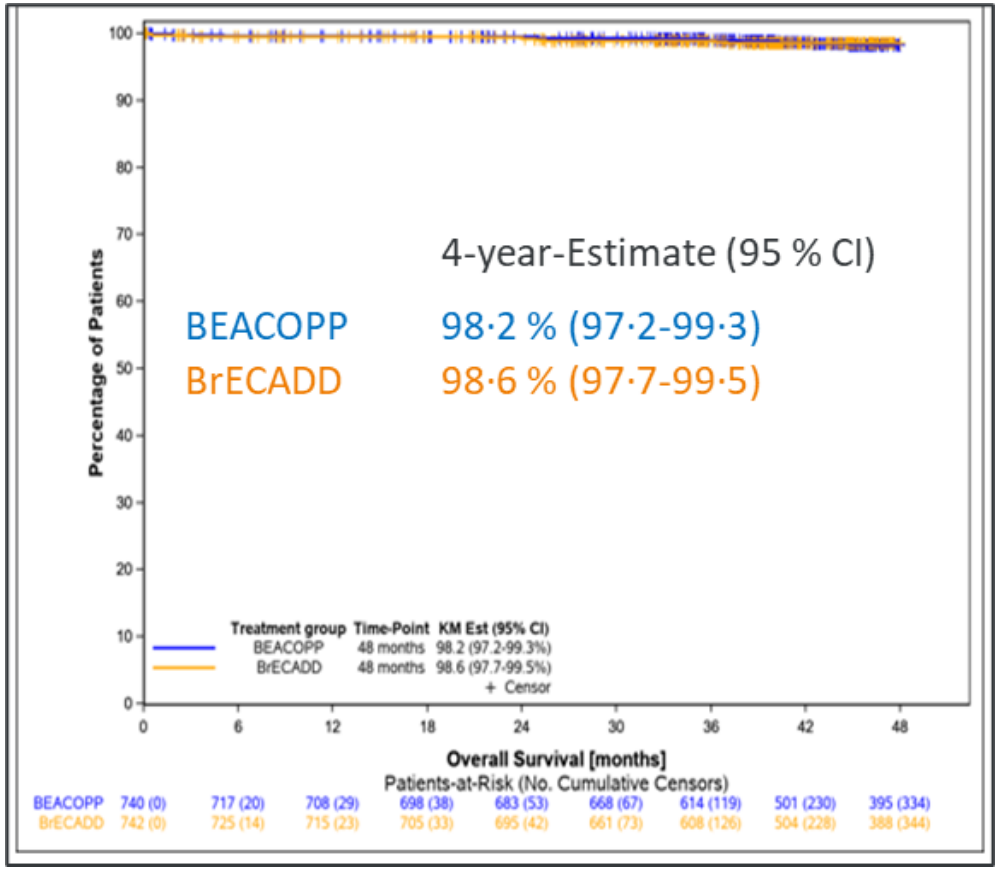


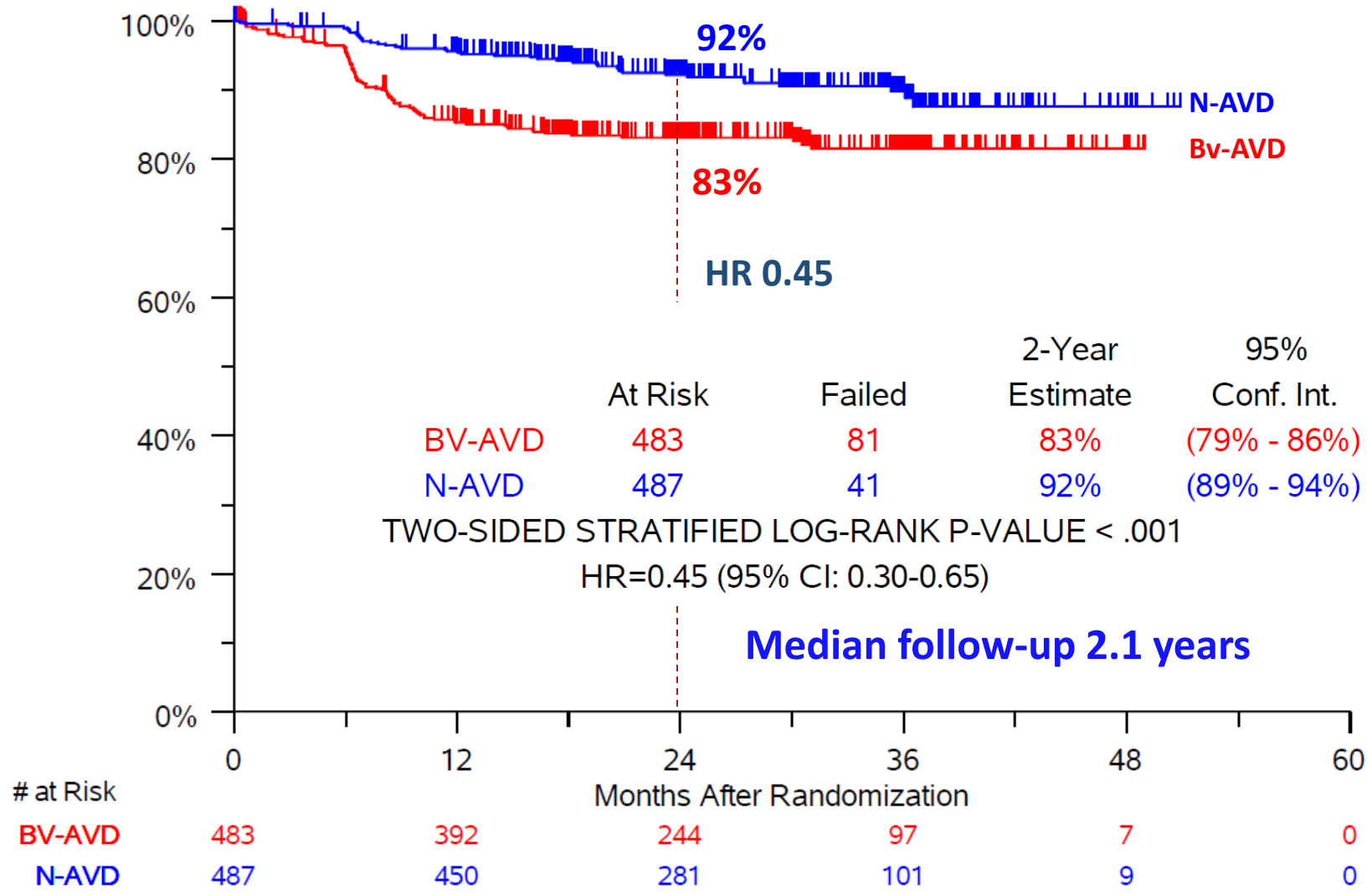
Overall survival



GHSG

Borchmann P et al, ASCO2024, EHA2024, ISHL2024

PFS Benefit of N-AVD Sustained With 2y Follow-Up



2-year PFS
N-AVD 92%
Bv-AVD 83%

Presented by: Alex F. Herrera, MD

Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138.

1st Line Treatment Strategies. Elderly Patients

En los pacientes con LH y edad avanzada debe realizarse una adecuada evaluación de la función cardiaca y pulmonar, así como una evaluación geriátrica exhaustiva. Grado de recomendación C

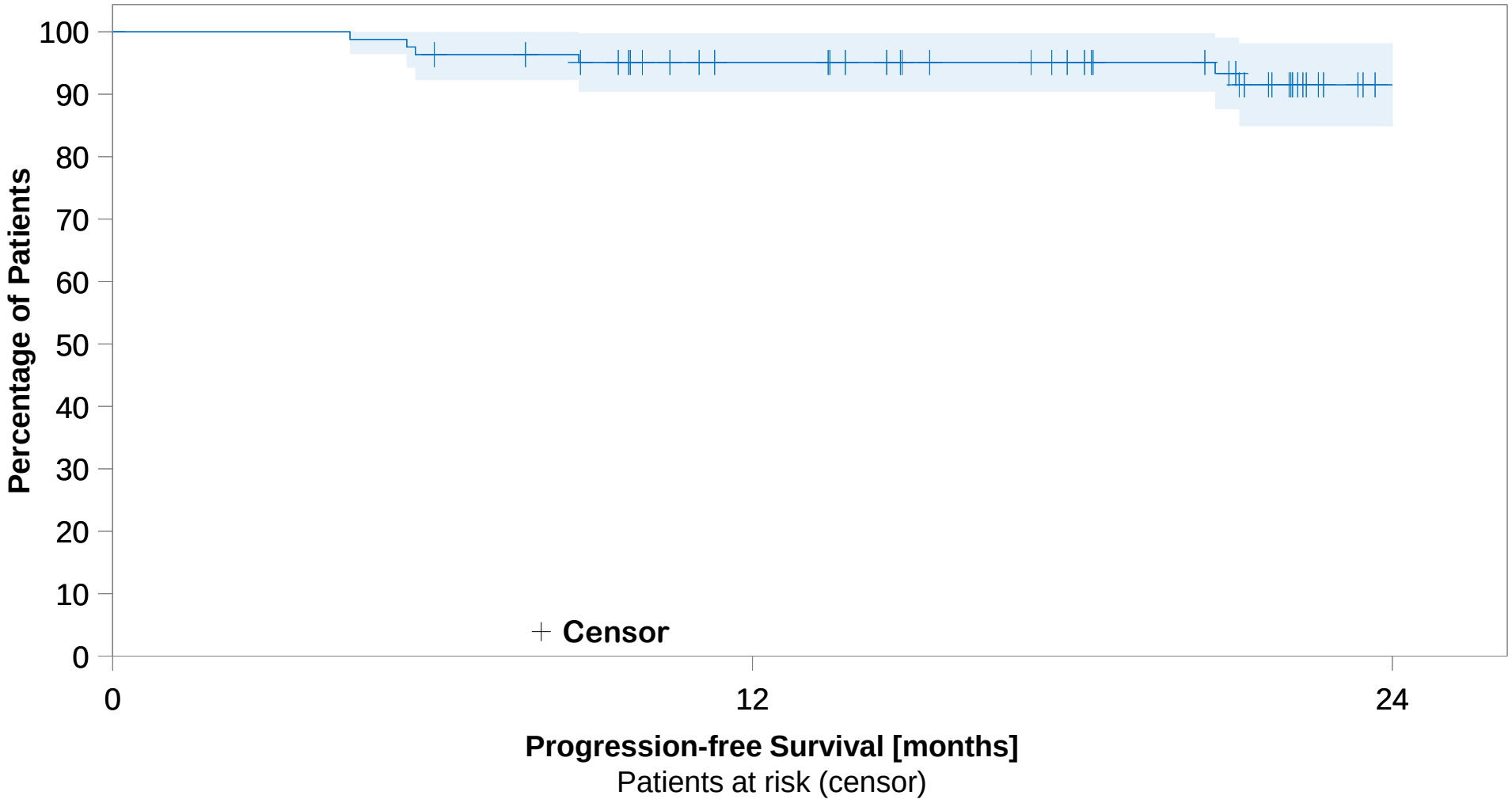
En pacientes de 60 a 70 años sin comorbilidad significativa, la terapia recomendada es ABVD +/- RT. Sin embargo, en estadios avanzados, sobre todo en pacientes mayores de 70 años y con comorbilidad, cabe plantearse otros esquemas terapéuticos, siempre que sea posible dentro de estudios controlados. Grado de recomendación D

Los pacientes que reciben bleomicina deben tener estrechamente monitorizada la función pulmonar. Grado de recomendación A

La utilización de esquemas de QT específicos para pacientes mayores, como VEPEMB o PVAG, están asociados a menor toxicidad, pero podrían ser menos efectivos en el control de la enfermedad. Solo deberían utilizarse en pacientes con contraindicación a recibir ABVD. Grado de recomendación C

Guías GELTAMO, 2023

BrECADD in Patients > 60 years. Progression-free survival. ITT population, mFU 23 months



Ferdinandus J et al, ISHL 2024

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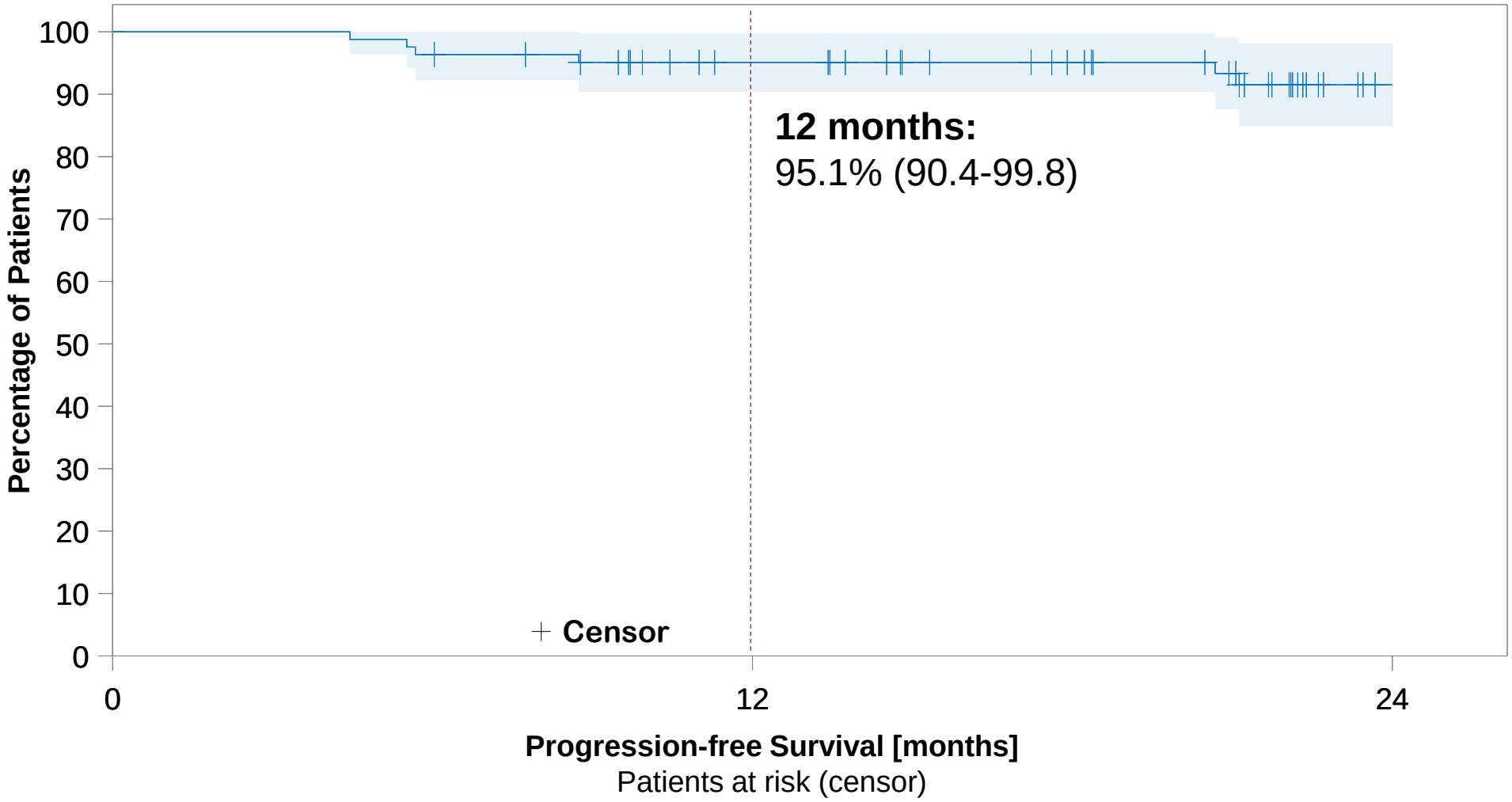

Patients at risk (censor)

83 (1) 68 (11) 35 (42)

Ferdinandus J et al, ISHL 2024

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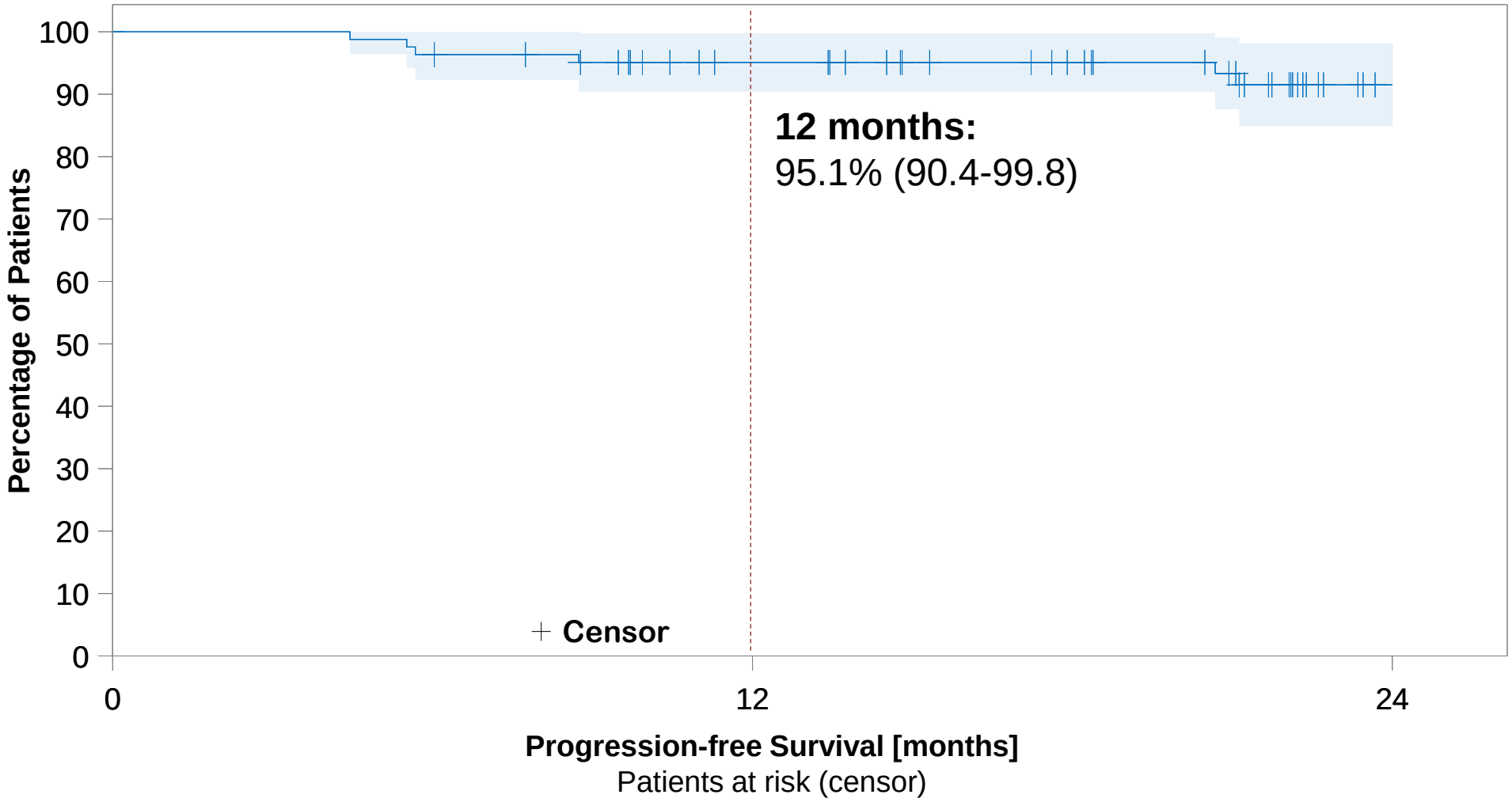

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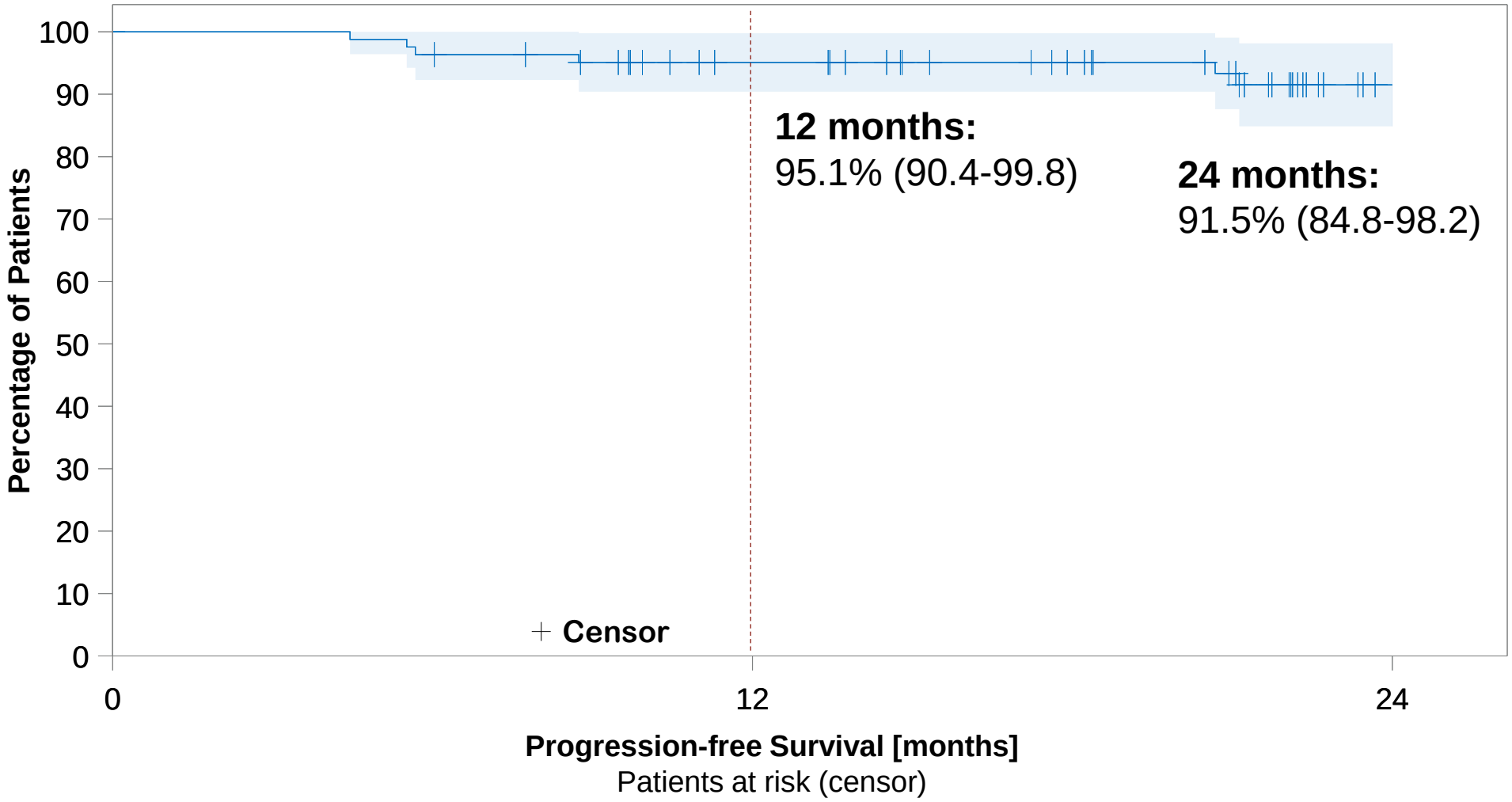

Patients at risk (censor)

0	12	24
83 (1)	68 (11)	35 (42)

Ferdinandus J et al, ISHL 2024

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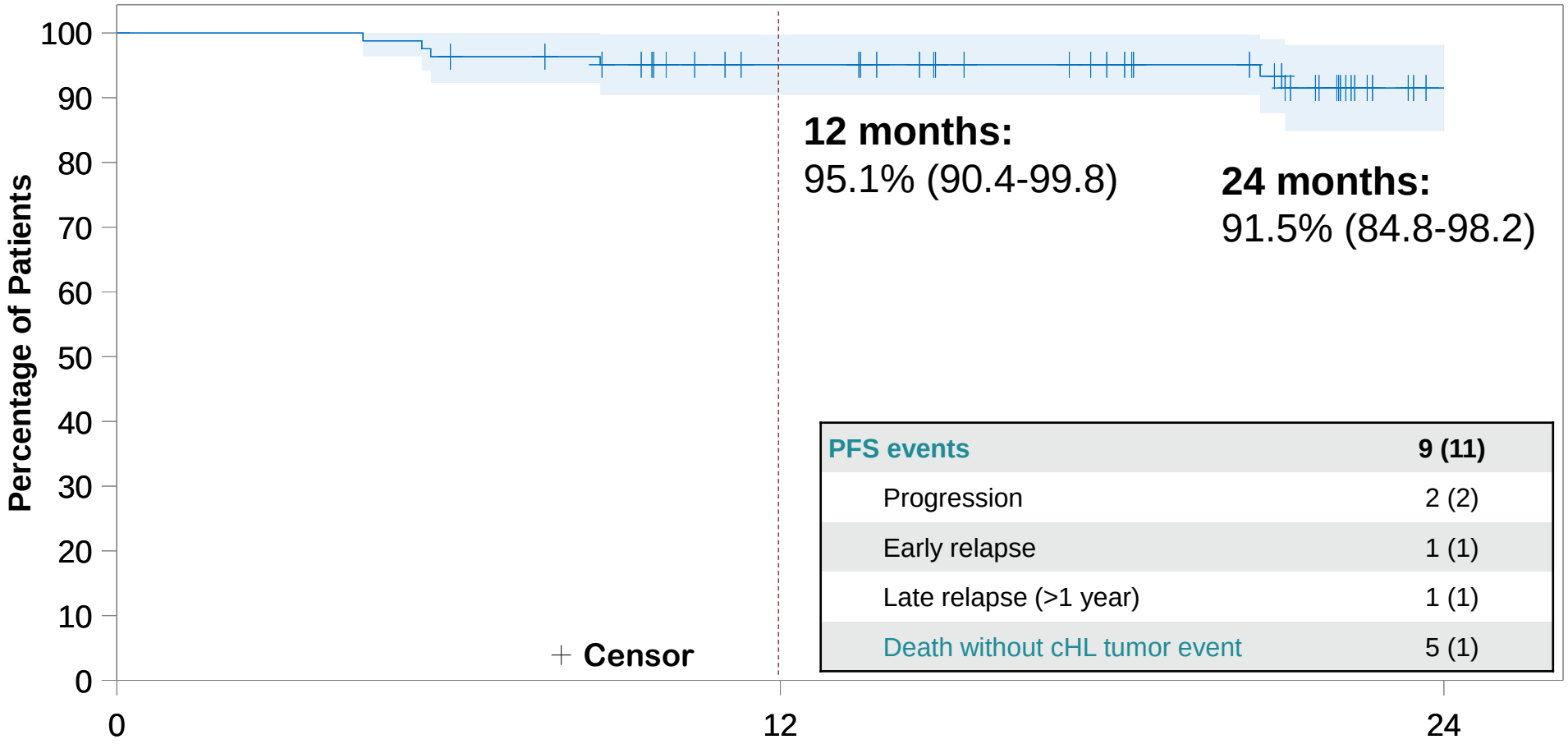

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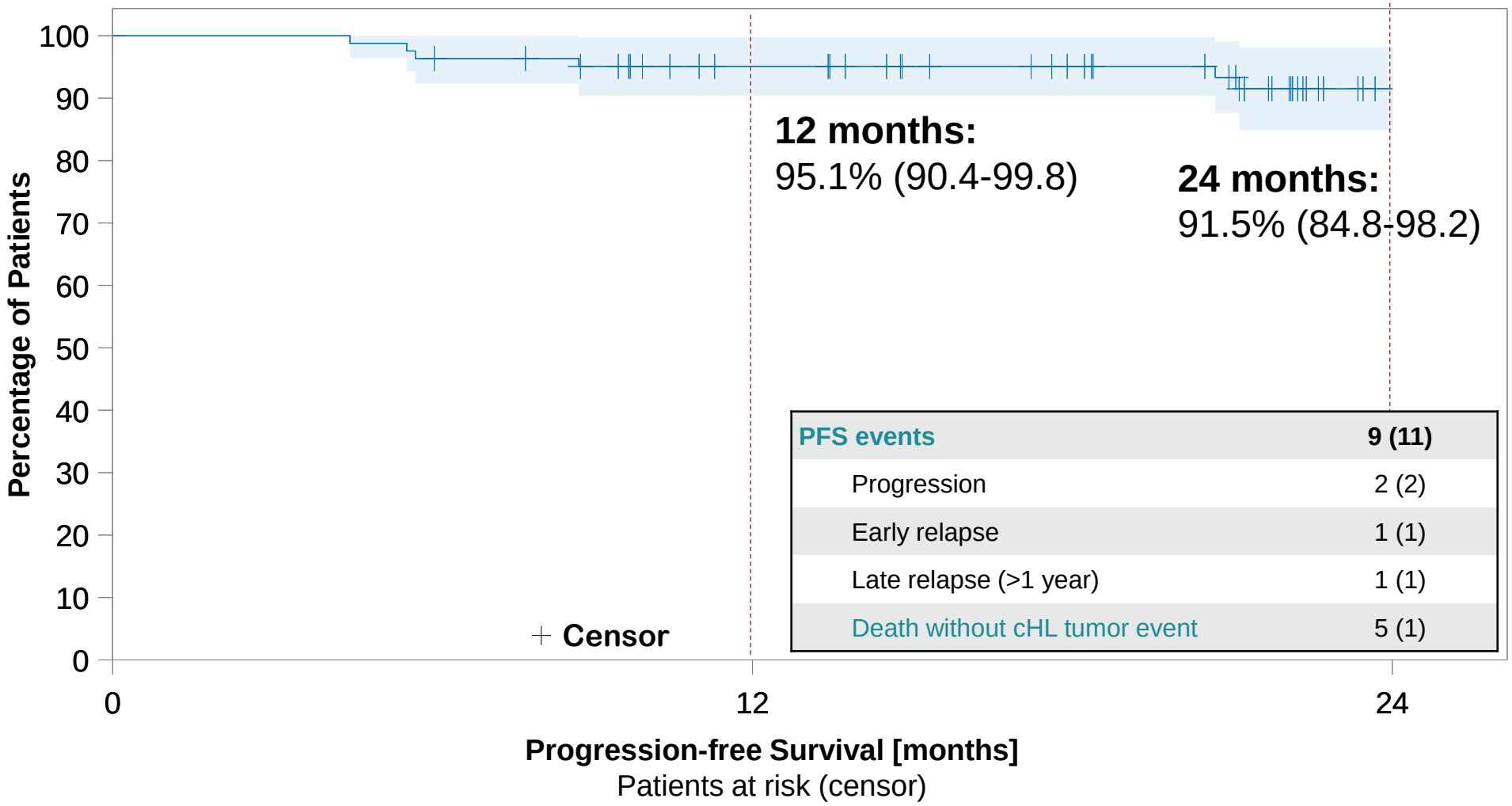


Ferdinandus J et al, ISHL 2024

Nivolumab + AVD vs Brentuximab Vedotin + AVD in Newly Diagnosed Advanced Stage cHL (SWOG S1826 – Older Patients)

Older patient sub-analysis population

Patients enrolled in SWOG S1826 aged ≥60 years with Stage 3–4 HL (n=99)

- **Median age: 66 years** (range: 60–83)
- Male: 63%
- White: 85%
- Stage IV disease: 60%
- IPS 4–7: 44%

Safety results:

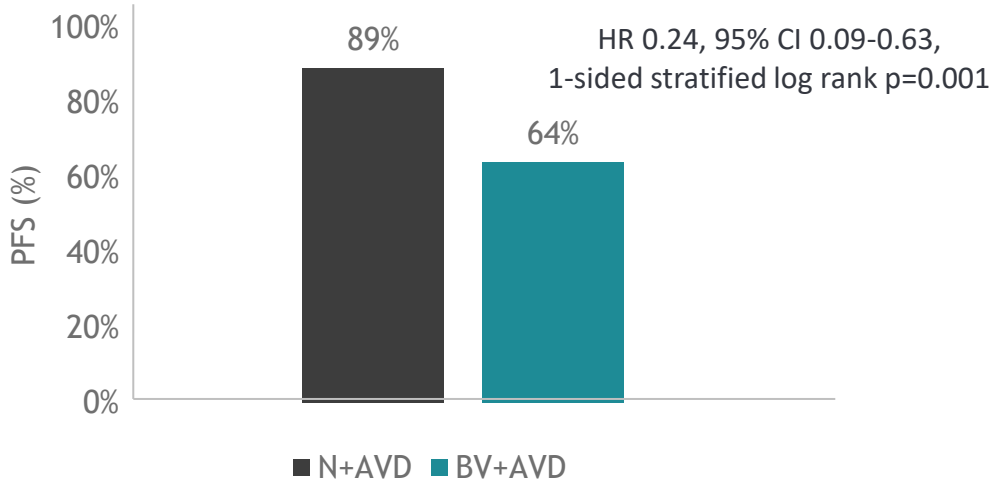
Median follow-up: 2.1 years

SAFETY, n (%)	N + AVD (N=50)	BV + AVD (N=49)
All treatment discontinuation	5 (10)	16 (33)
Discontinuation due to AEs	2 (4)	7 (14)
N or BV discontinuation	7 (14)	25 (51)

- Three deaths in N + AVD (2 infection/sepsis, 1 hepatic failure) vs 10 in BV + AVD (5 infection/sepsis, 2 lymphoma, 1 cardiac arrest, 1 pneumonitis, 1 second malignancy)
- Four progressions/relapses in N + AVD vs 9 in BV + AVD
- AE more frequent with N + AVD vs BV + AVD: neutropenia, hypothyroidism, rash
- AEs more frequent with BV + AVD vs N + AVD: febrile neutropenia, sepsis, infections, peripheral neuropathy

Efficacy results: PFS for patients aged ≥60 years

Median follow-up: 2.1 years



2-year OS
96 % with N + AVD vs
85 % with BV + AVD
HR 0.16, 95% CI 0.03-0.75
Stratified 1-sided logrank p=0.005

AE, adverse event; BV+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; CI, confidence interval; EFS, event free survival; HL, Hodgkin lymphoma; HR, hazard ratio; IPS, International Prognostic Score; N+AVD, nivolumab, doxorubicin, vinblastine, dacarbazine; OS; overall survival; PFS, progression-free survival

Rutherford SC, et al. ISHL 2024 [abstract #T077]: see the abstract

Agenda

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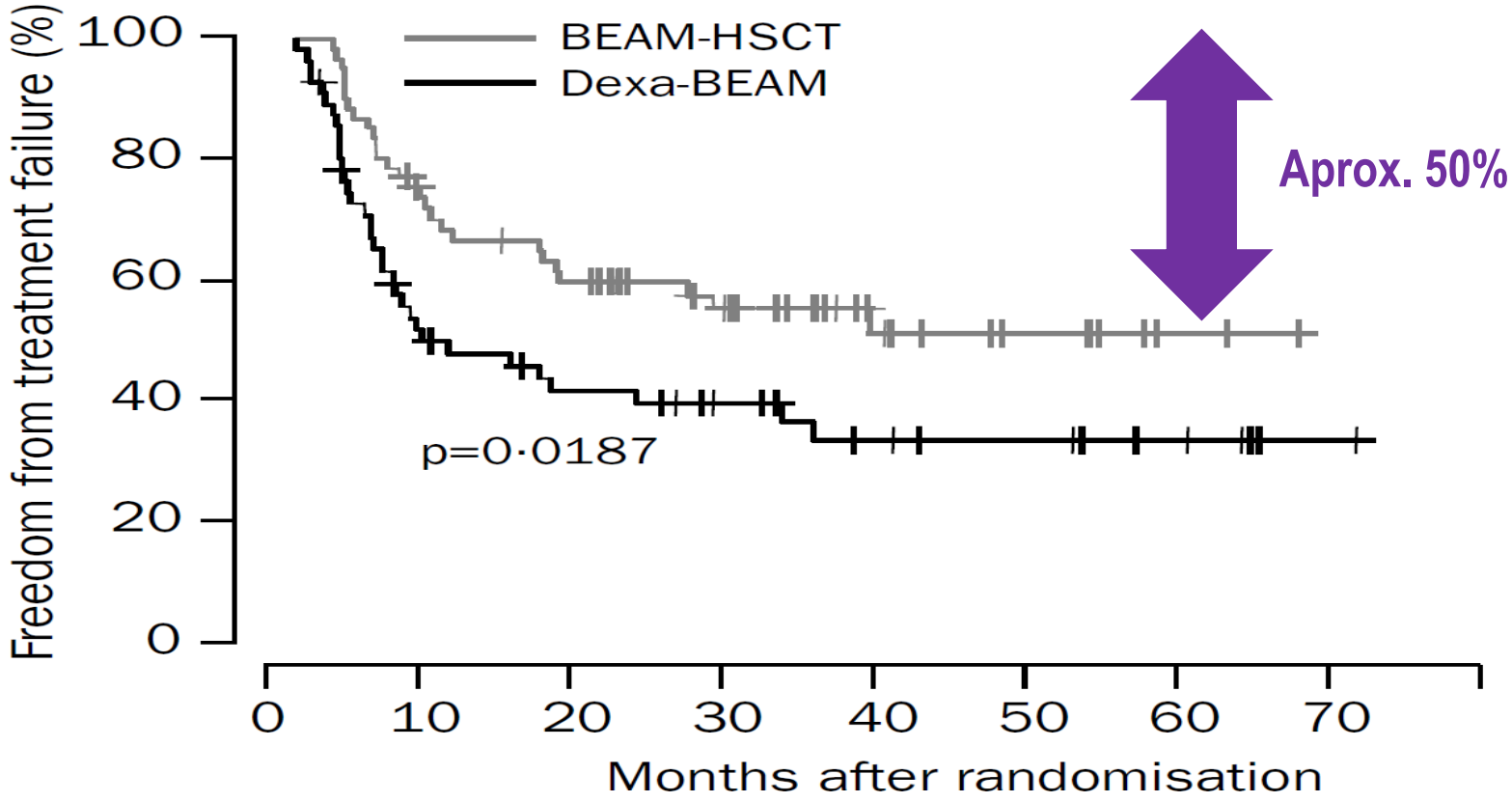
Auto-HCT is the standard therapy for HL Relapsing after 1st Line Chemotherapy. HDR1 Trial (GHSG/EBMT) Dexa-BEAM + Auto-HCT *vs* Dexa-BEAM



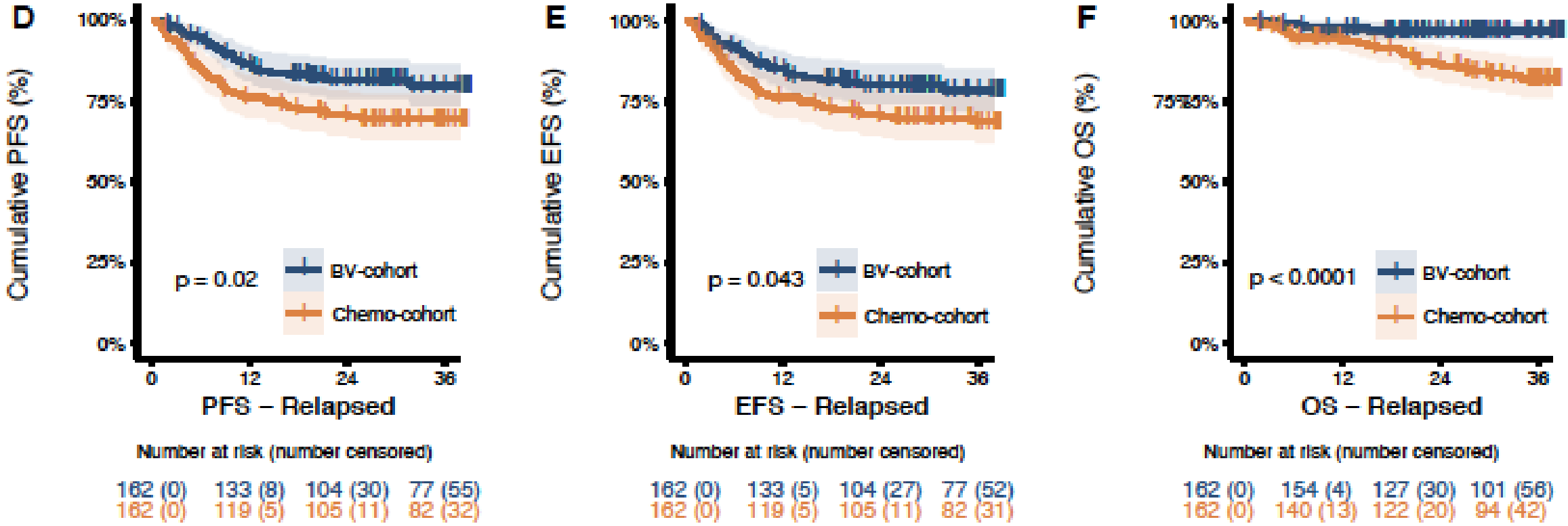
Number of patients

BEAM-HSCT	61	43	34	25	13	8	7	0
Dexa-BEAM	56	27	20	15	10	8	5	1

Figure 3: **Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin's disease**

Schmitz N et al, Lancet 2002

BV + Chemotherapy vs Chemotherapy Alone as 1st Line Salvage Strategy in RR cHL. Relapsed Patients



Driessen J et al, Blood Adv 2024

Study Design, Objectives, Consort Diagram

Primary refractory/relapsed cHL (N=160) 18–65 years

n = 9 screening failures

Randomization 1:1 (n = 151)

ESHAP (× 3 cycles) (n = 75)

BV-ESHAP (× 3 cycles) (n = 76)

PET CT after 3rd cycle

Not Centrally Reviewed for Decision Making

mCR (DS 1–2)

No mCR (DS 3–5)

Amendment 3/2022 - mCR (1–3)

Amendment 3/2022 - mCR (4–5)

BV consolidation (up to 16 cycles in total)

Out of study survival follow-up

Key exclusion criteria:

- Lymphocyte predominant nodular HL
- Prior therapy with BV
- History of PN ≥2
- Prior malignancies

Key inclusion criteria:

- Adult patients (>18 years up to 65 years)
- Diagnosis of cHL
- Primary refractory or 1st relapse (early or late relapse)
- Measurable disease at the time of enrollment
- ECOG 0–2
- Adequate 'standard' laboratory values
- Written informed consent

Primary objective:

- mCR rate after 3 cycles of ESHAP vs BV-ESHAP
- Feasibility of BV consolidation after attaining mCR with second-line therapy

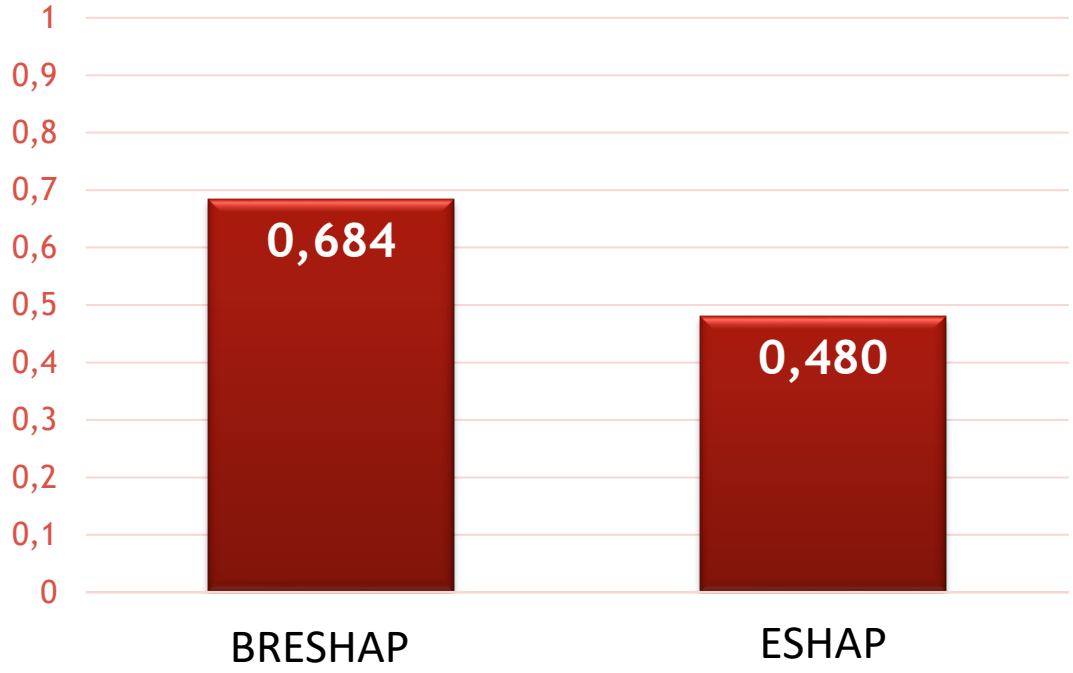
Secondary objectives:

- 2-yr PFS, OS, DOR, TTP
- Hematological and extra-hematological toxicities
- Stem cell collection yield
- QoL

BRESELIBET (ClinicalTrials.gov ID: NCT04378647)

Sureda A et al, ISHL13

Primary Endpoint & Stem Cell Collection



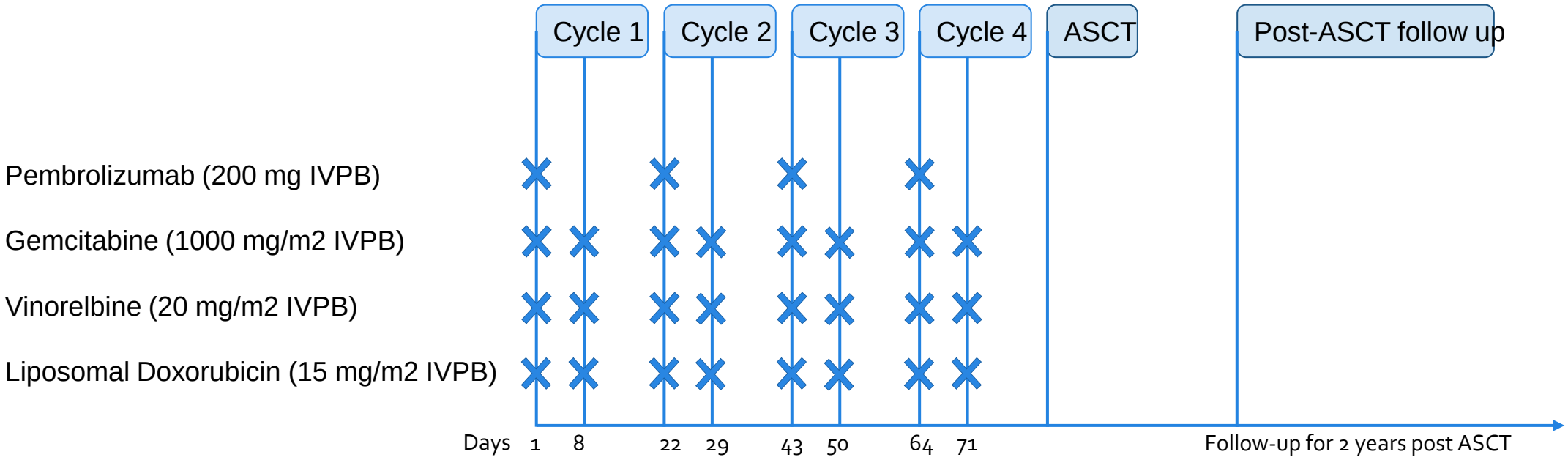
	BRESHAP (n = 76)	ESHAP (n = 75)	P value
mCR (DS 1-3)	52 (68.4%)	36 (48%)	0.011
No mCR (DS 4–5)	24 (31.6%)	39 (52%)	

Stem cells were collected in 124 patients (82.2%); collection was successful (> 2.0 x 10^6 $CD34^+$ cells / kg) in 93.5% of the patients. No differences between BRESHAP and ESHAP treated patients

Sureda A et al, ISHL13

Pembro-GVD as Salvage Strategy in Transplant Candidates

- **Eligibility**: relapsed or refractory cHL following 1-line of therapy
- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles



Memorial Sloan Kettering Cancer Center

Moskowitz A et al, ISHL2022 (with permission)

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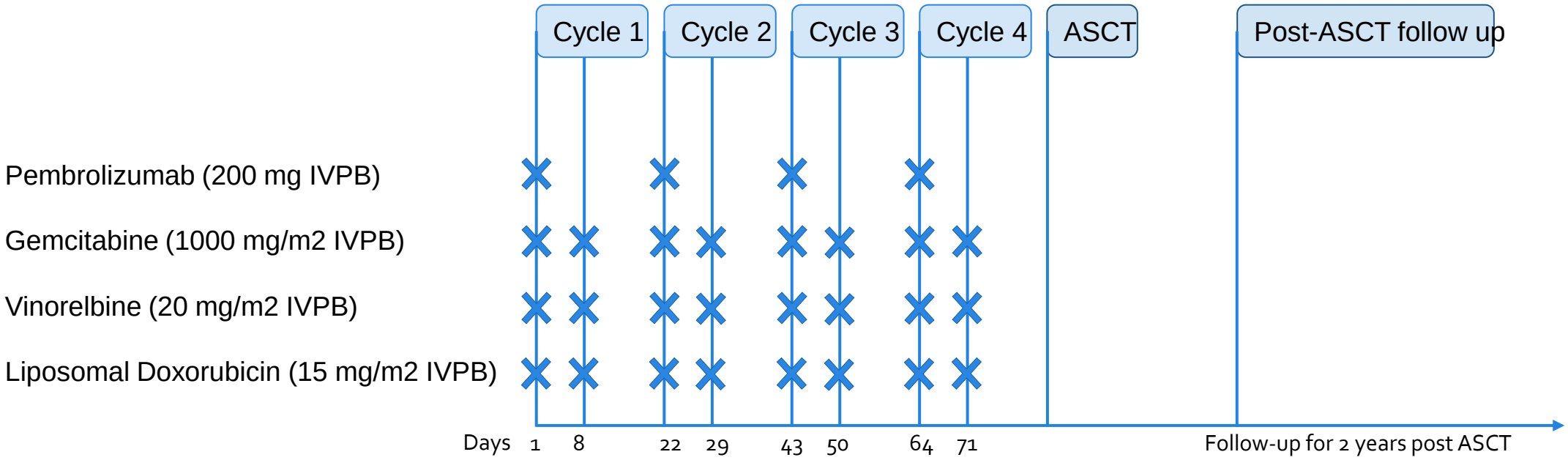

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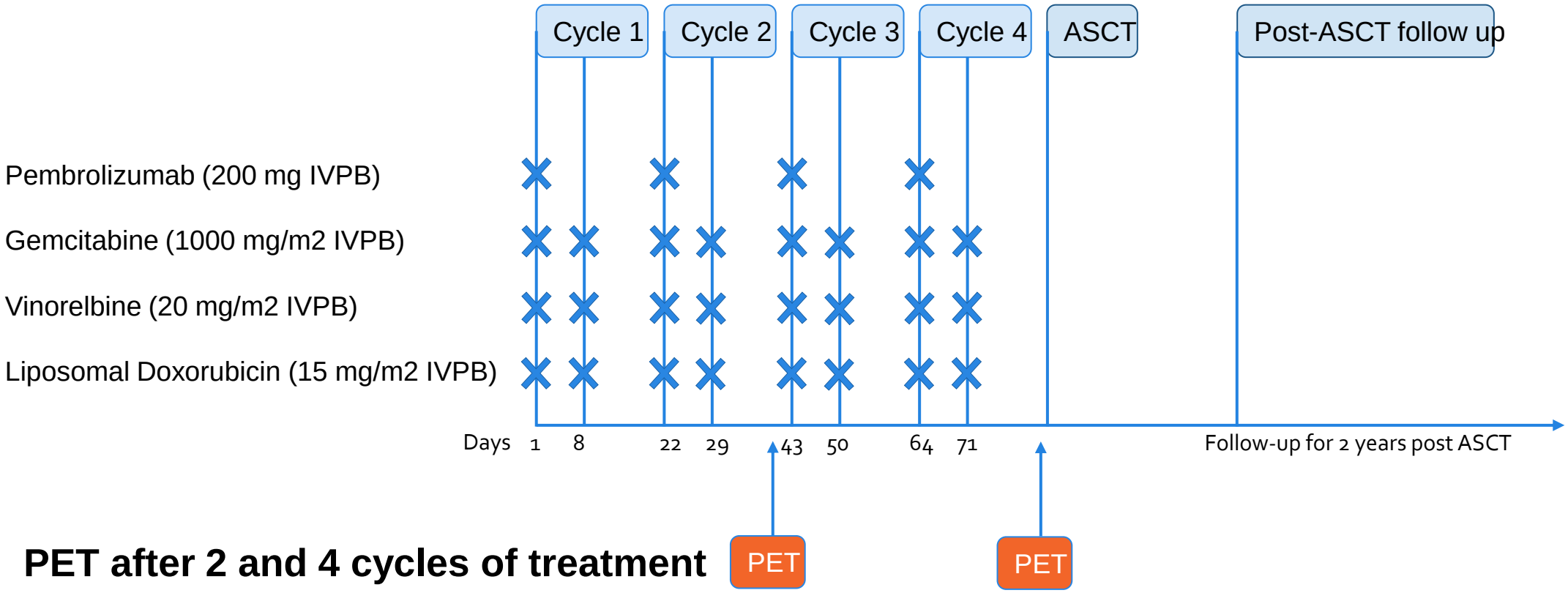

PET after 2 and 4 cycles of treatment

Memorial Sloan Kettering Cancer Center

Moskowitz A et al, ISHL2022 (with permission)

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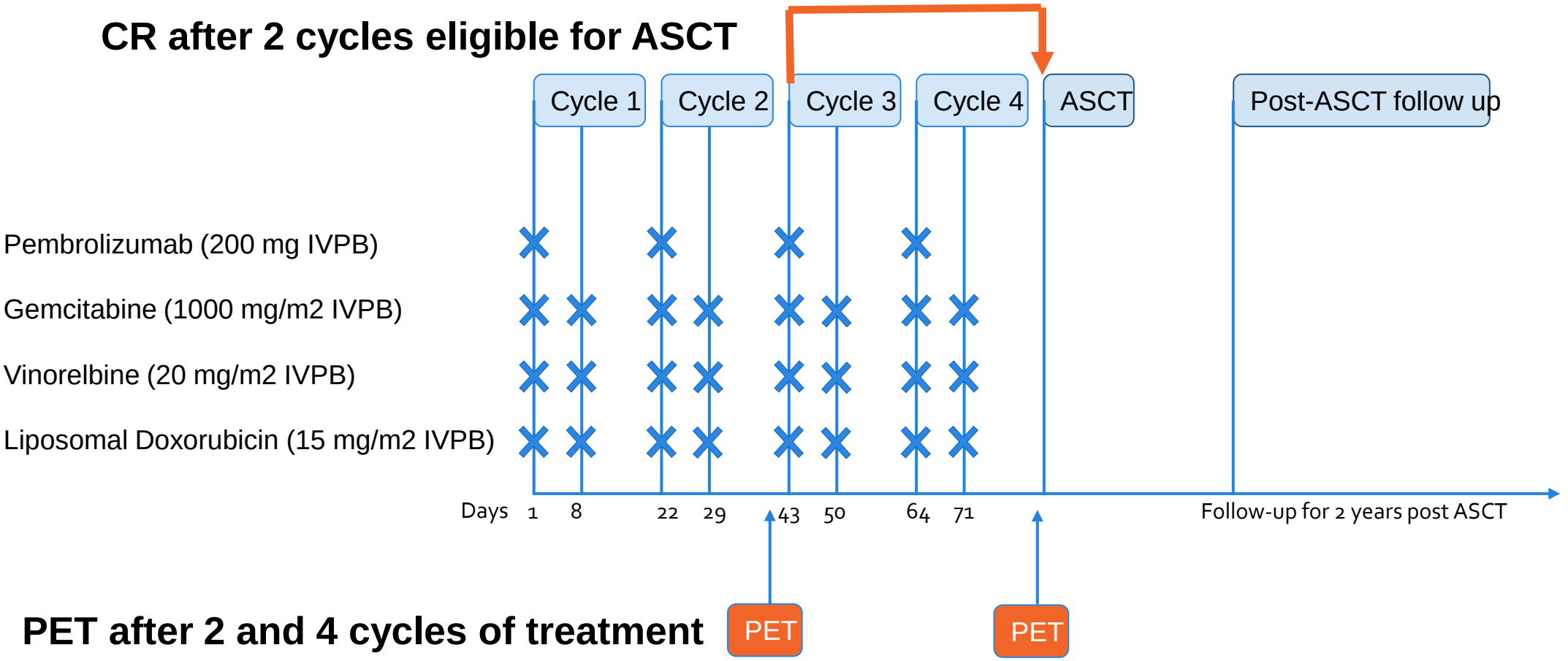
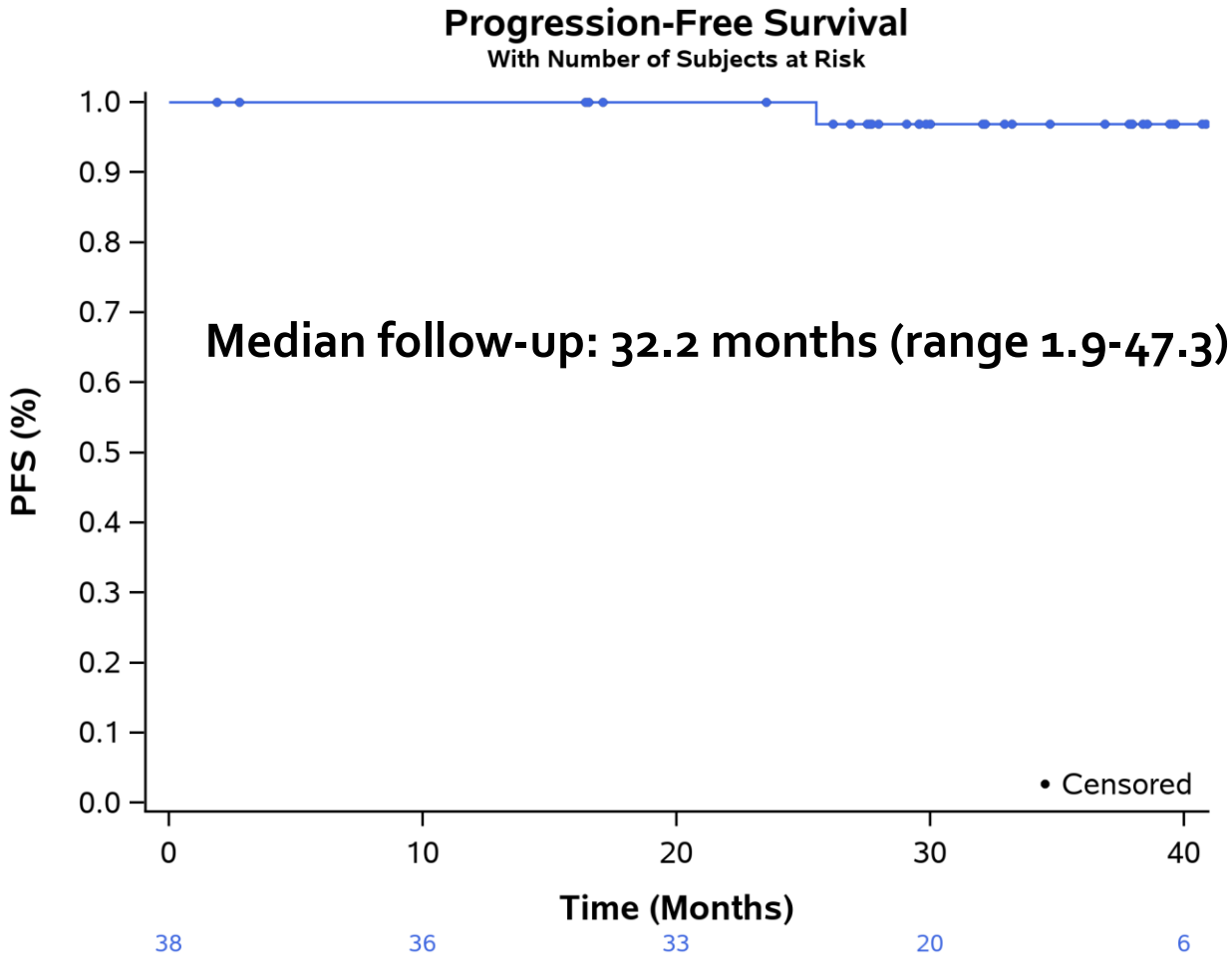


Memorial Sloan Kettering Cancer Center

Moskowitz A et al, ISHL2022 (with permission)

Results of long-term follow up in the ITT cohort

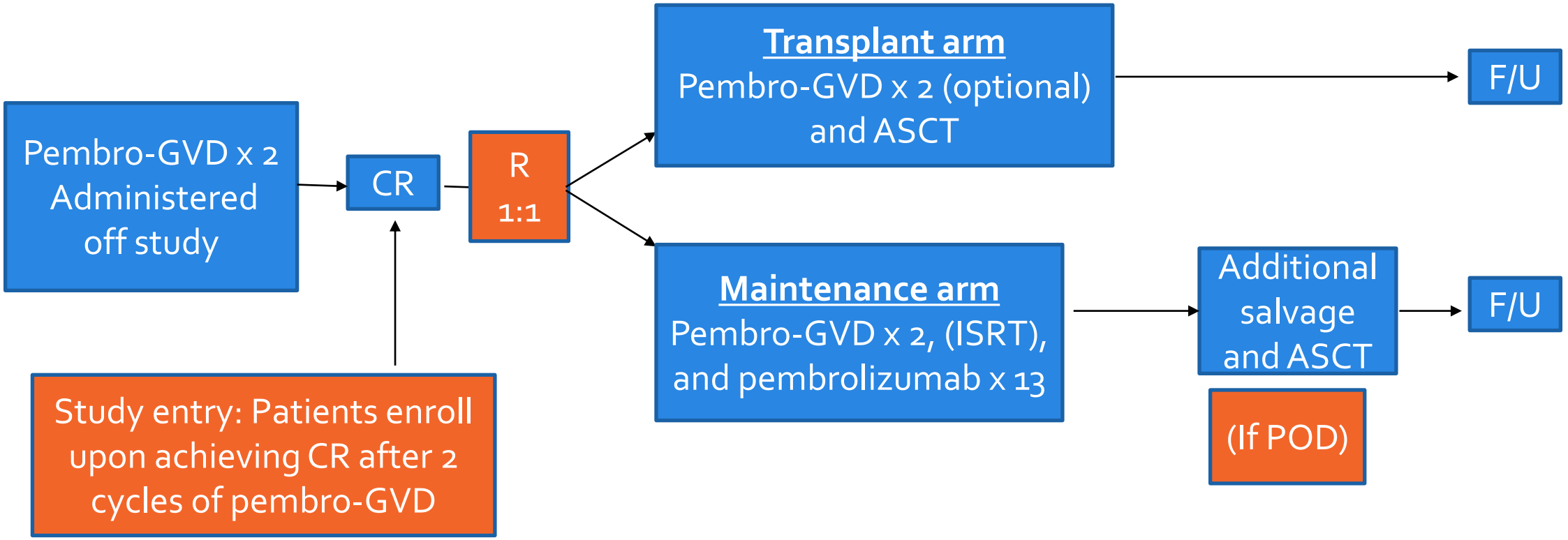
- 38 evaluable patients
- ORR: 100%
- CR: 95% (92% after 2 cycles)
- 36 pts proceeded to ASCT
- 1 relapse, 1 death (unrelated)
- 30 month PFS: 96%



Moskowitz A et al, ISHL2022 (with permission)

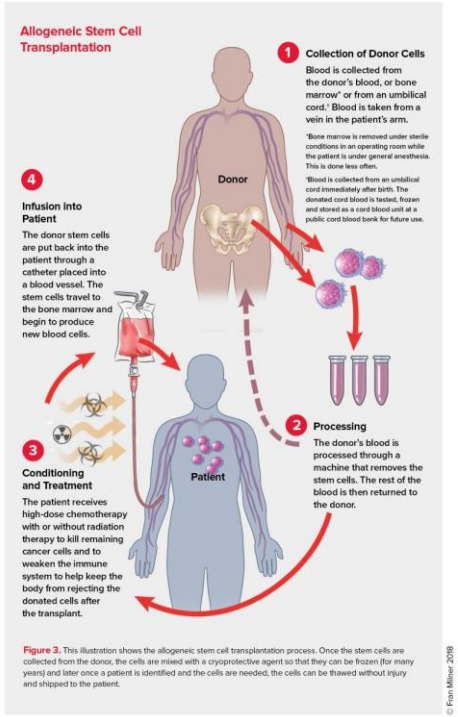
Data cut off: 10/6/2022

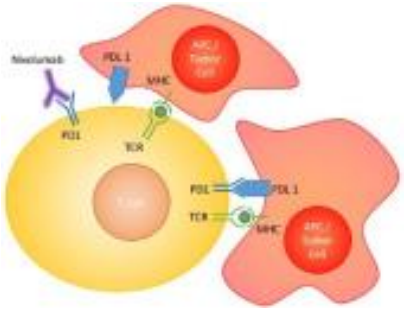
Phase II randomized, non-inferiority study evaluating immediate vs delayed transplant for stage I-III rel/ref HL

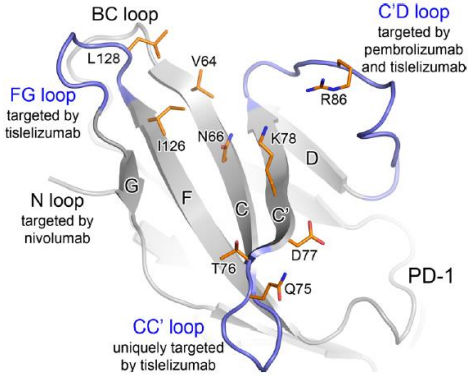


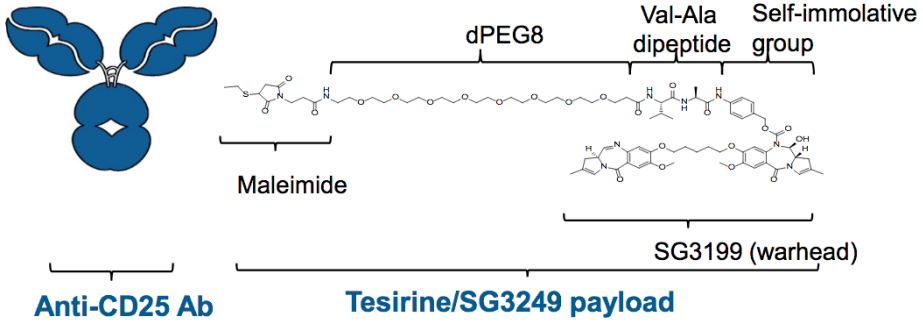
Primary endpoint: Freedom from disease at 5 years post-randomization
Patients to be stratified according to use of front-line PD-1 blockade
n=178

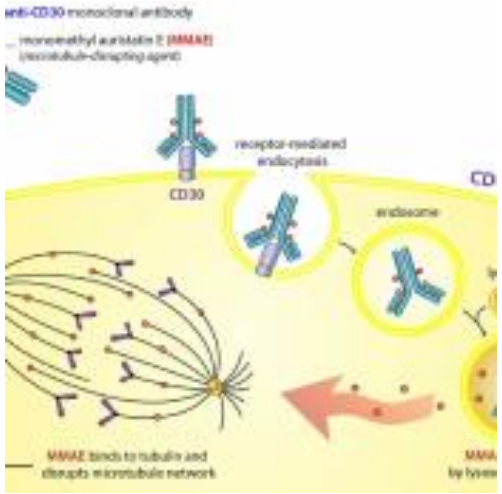
The Future is Bright for RR HL

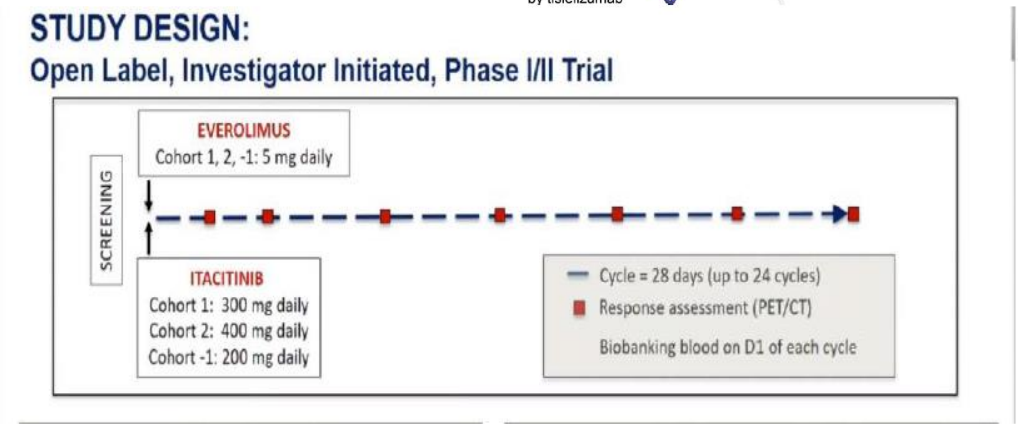


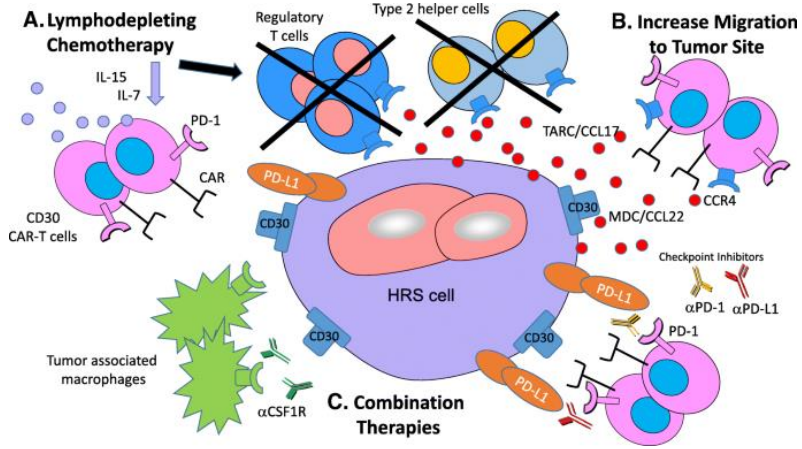












Allotransplants after CPIs

N = 209
- 87 Haplo/PtCy
- 25 non-Haplo/PtCy
- 91 non-Haplo/non-PtCy
- 6 PtCy + ATG

Median age: 31.5 yrs

Male patients - 60%

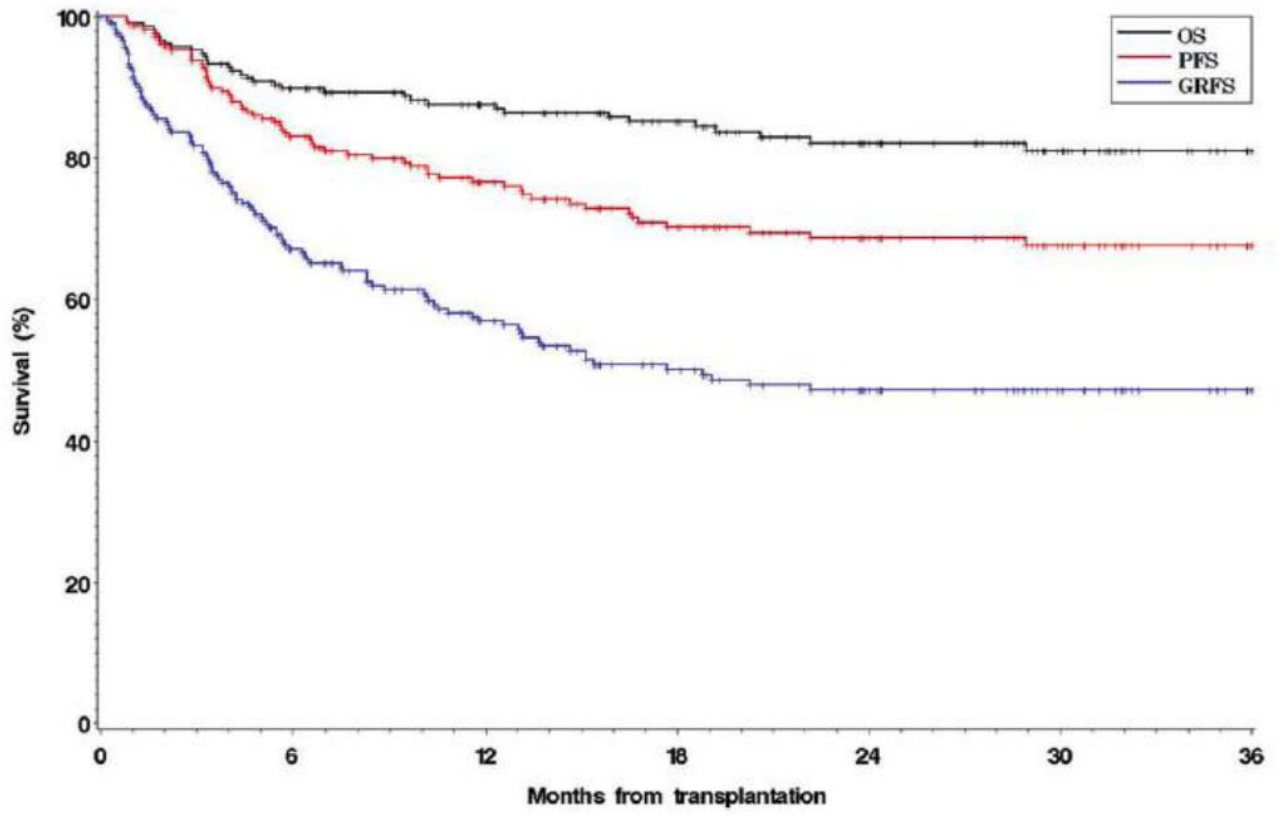
HCT-CI
- 0-2 - 129
- ≥ 3 – 66

Median number of tx: 4 (2-11)

Best response to CPIs CR – 39%

Median time from last dose CPIs to Allo-HCT, 81 days

CR before allo-HCT – 58%



Merryman RW et al, Leuk 2021

Five Year FU of CHECKMATE-205. Nivolumab Monotherapy in RR cHL

Key inclusion criteria
- R/R cHL after auto-HCT
- Age ≥18 years
- ECOG ≤1
- Measurable disease

Cohort A:
BV naïve (n=63)

Cohort B:
BV after auto-HCT (n=80)

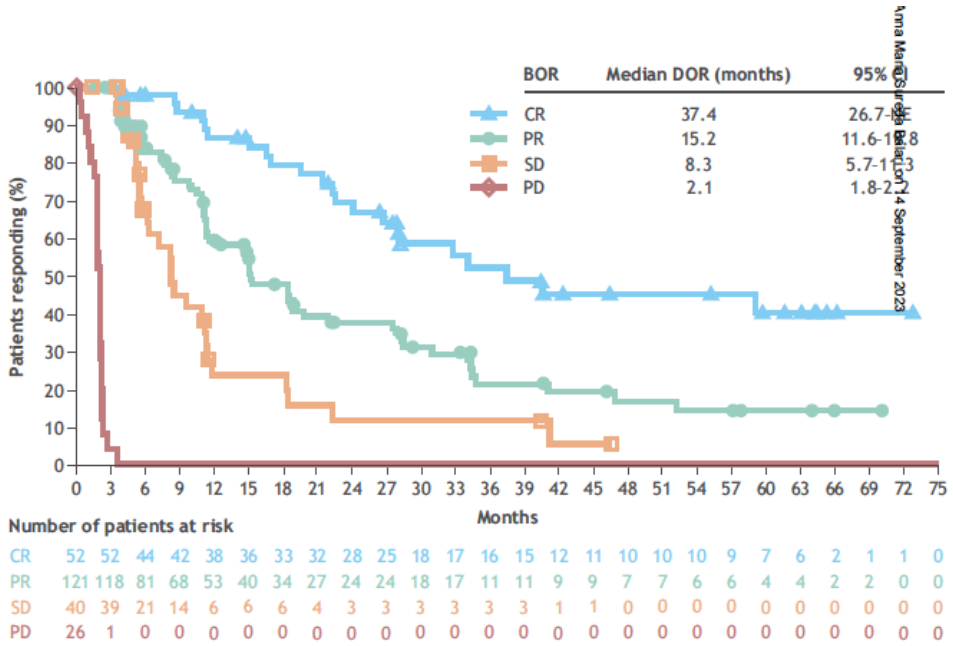
Cohort C:
BV before and/or after auto-HCT (n=100)

Nivolumab
3 mg/kg IV Q2W
Treatment until disease progression or unacceptable toxicity*
OR
Cohort C:
Patients in CR ≥1 year discontinue per protocol

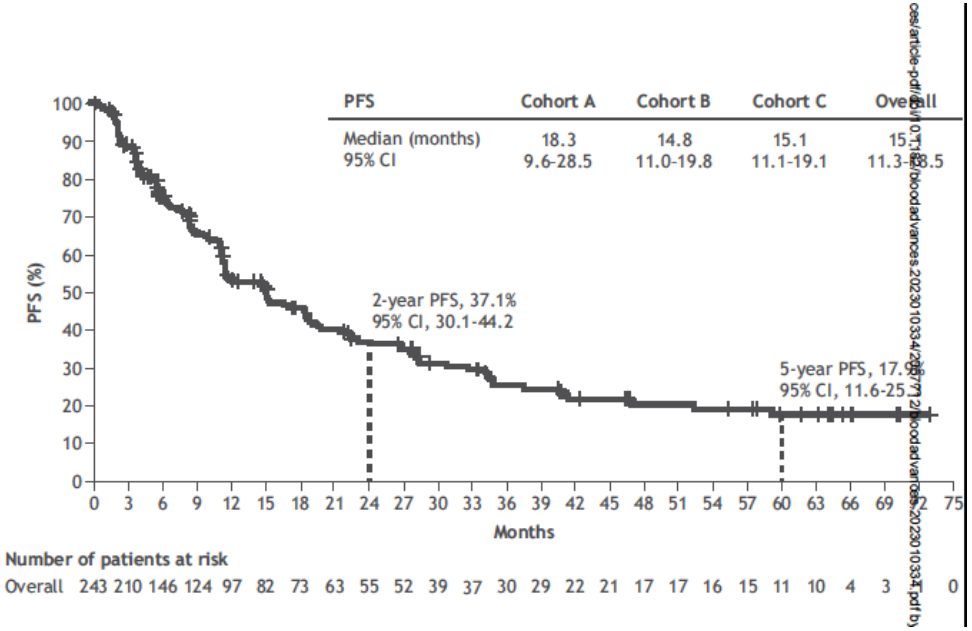
Cohort C

Re-treatment
if relapse ≤2 years

C



B



Ansell S et al, Blood Adv 2023

Five Year Follow Up of KEYNOTE-087. Pembrolizumab Monotherapy in RR cHL

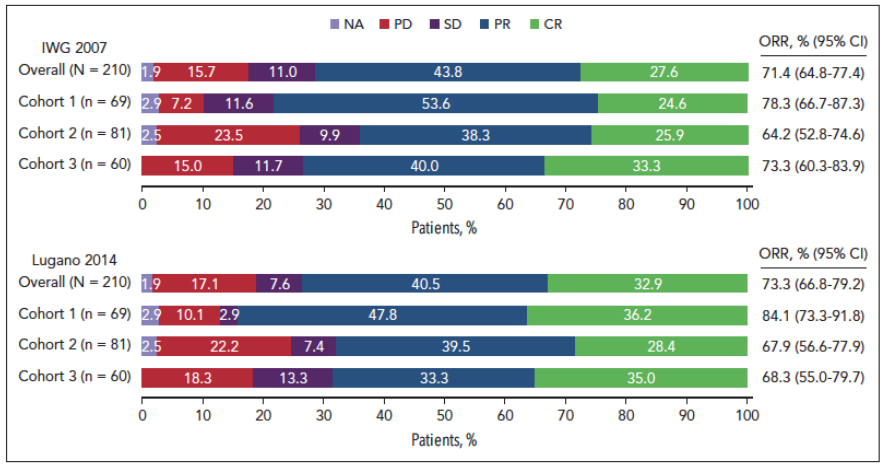
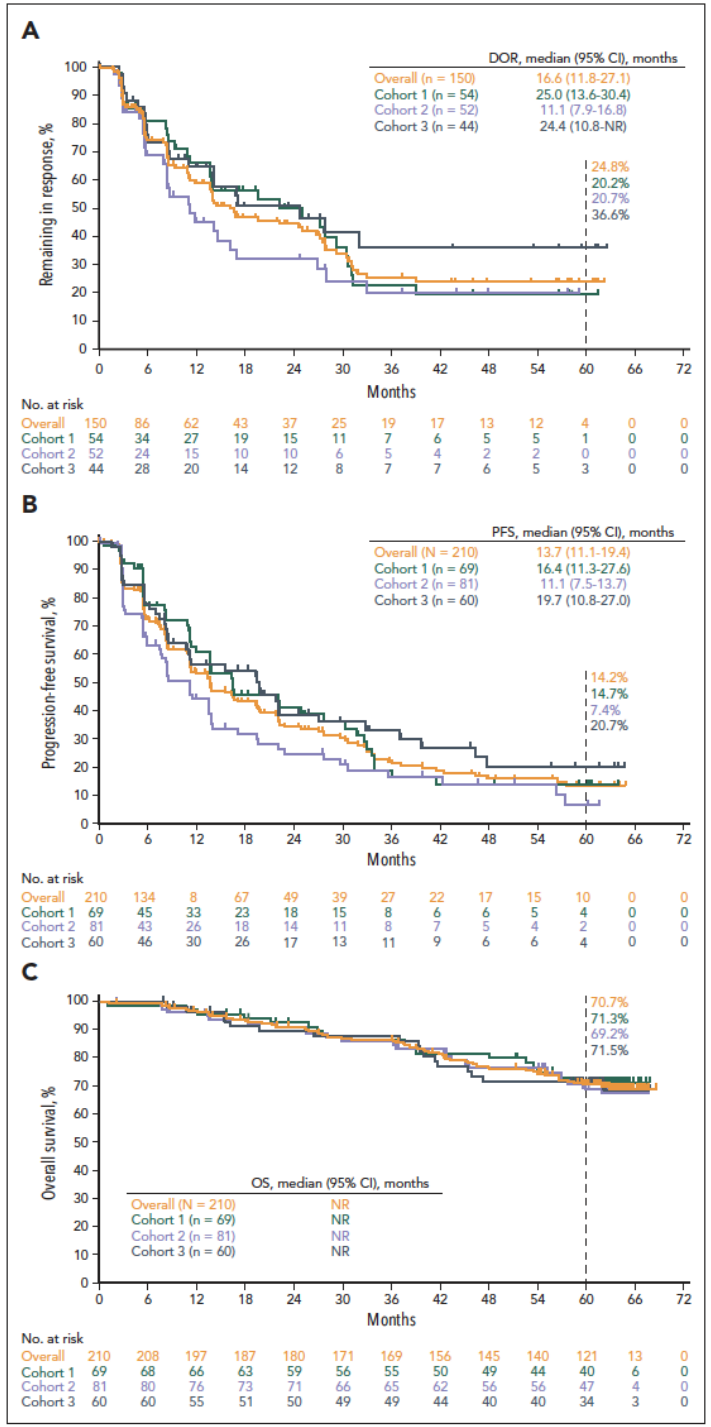
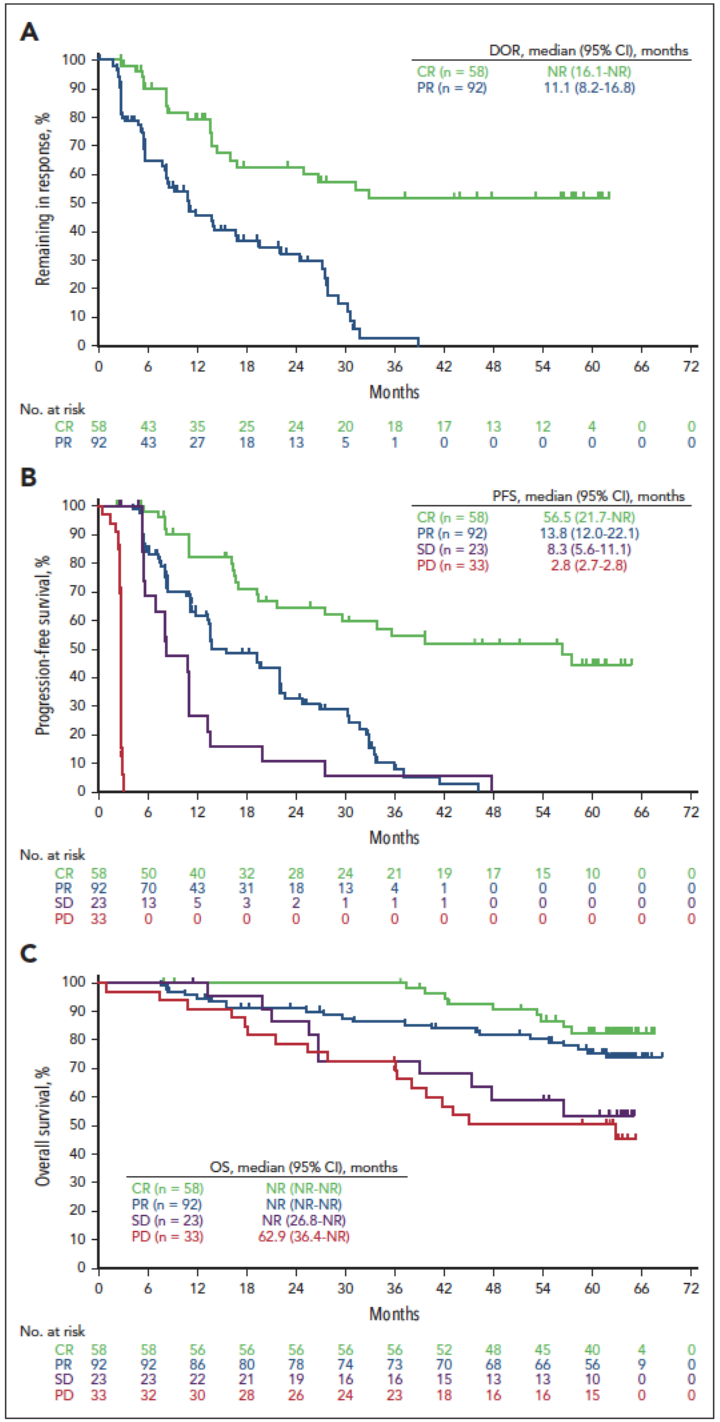


Figure 1. ORR per IWG 2007 and Lugano 2014 criteria for the overall population and by cohort. NA, not assessed; SD, stable disease.

Armand P et al. Blood 2023





Which Is the Best Sequence?

Brentuximab Vedotin → Check Point Inhibitor (NIVO, PEMBRO) → Allogeneic Stem Cell Transplantation

Curative Potential (?)

Better short-term toxicity profile

Mature Results

Known Curative Potential

Significant morbi-mortality

Long-term Follow Up

Well identified risk-adapted patient's profile

Conclusions

- Impact of targeted therapy in first line treatment strategies (early and advanced stages)
  - Significant decrease in the use of involved field radiotherapy
- New options for the elderly population of patients
- Auto-HCT continues to be the standard of care for patients with relapsed/refractory disease. Results have improved with the introduction of new drugs
- Allo-HCT, to be considered in the triple refractory population of patients