Mi experiencia en el tratamiento de LH en adultos mayores.

Abril 2025

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FUNDALEU

GATLA

Centro de Hematología
PAVLOVSKY
Atención médica y laboratorio de alta complejidad

LH en paciente adulto mayor

Quien es un adulto mayor en LH?

Por los riesgos asociados al tratamiento y su diferente pronóstico en LH, se considera adulto mayor al > 60 a.

LH en paciente adulto mayor

Como es el LH en adulto mayor?

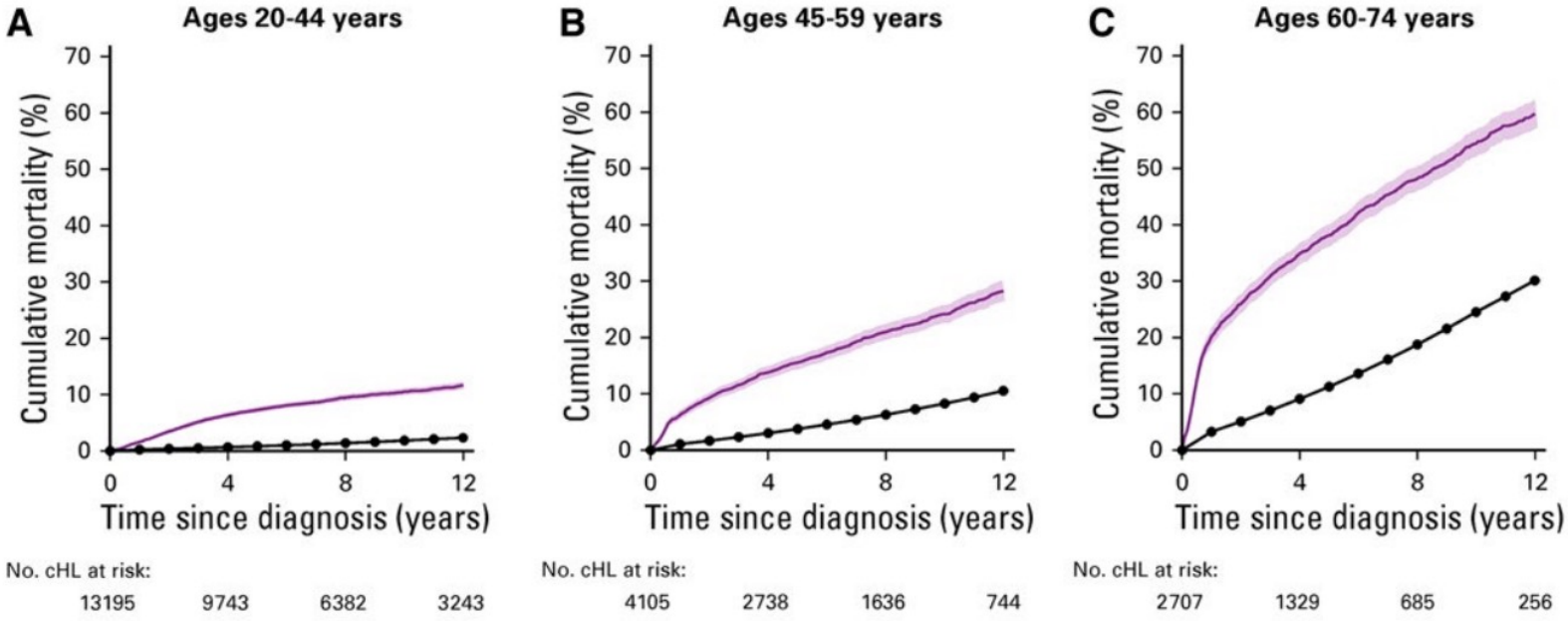
- Aumento de la incidencia de Celularidad Mixta.
- Aumento de la incidencia de localización infradiafragmatica.
- Mayor asociación con EBV.
- Predominio de estadíos avan y sint B.
- Peor pronóstico.

LH en paciente adulto mayor

Quien tiene más posibilidad de curarse?

Objetivo?

Sobrevida global en pts con LH



Dores GM et al. JCO 2020

Sobrevida global en pts con LH > 60 a.

Registro Noruego. 492 pts > 60 a. tratados 2000-2015- Mediana de edad 71 a.

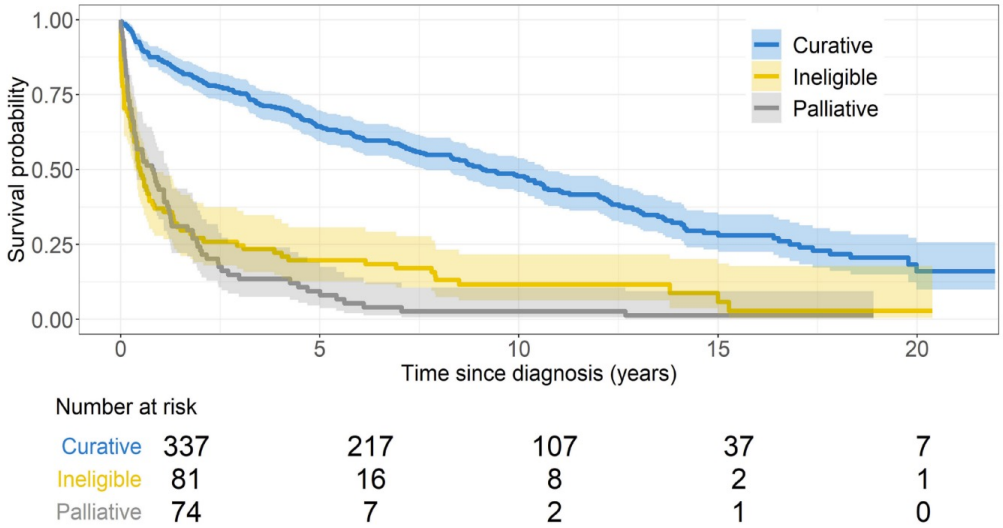


Figure 1. Overall survival according to treatment groups. Overall survival was analyzed by Kaplan-Meier statistics and groups compared using the log-rank test. Overall survival was significantly lower in the ineligible and palliative group compared to the curative group (*P*<0.001 for both comparisons).

Lia K et al., Haematologica 2024

Sobrevida global en pts con LH > 60 a.

Registro Noruego.

492 > pts 60 a.
tratados 2000-2015.

Tto de 1ra línea CHOP (74%), ABVD (30%)

Grupos	Sin tto	Tto paliativo	Tto curativo	Matched population
Mediana SG	6 meses	9 meses	9.1 a.	14 a.

Causas de muerte:
30% LH
8% TRM
44% otras causa

Lia K et al., Haematologica 2024

Porque le va peor al adulto mayor con LH?

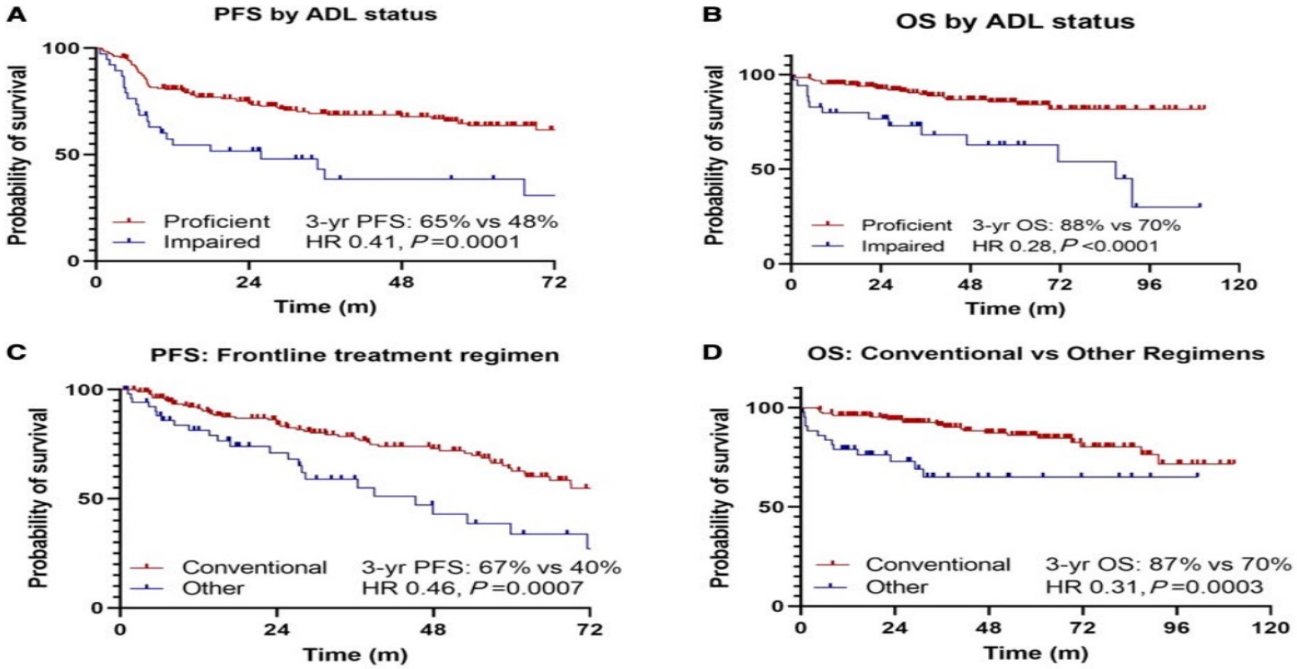
- Multifactorial:
  - Generalmente tienen co-morbilidades.
  - Peor PS.
  - Mas frecuentemente estadíos avanzados.
  - Inhabilidad para tolerar qt intensiva en dosis e intervalos correctos.
  - Menor numero de pacientes tratados en centros academicos, incluidos en protocolos de investigación o tratados con modalidad combinada.
  - Mortalidad relacionada al tratamiento.

NO EXISTE UN TRATAMIENTO ESTANDAR PARA ESTOS PACIENTES.

Solo 25% reciben tto con intención curativa y 25% no recibe tratamiento.

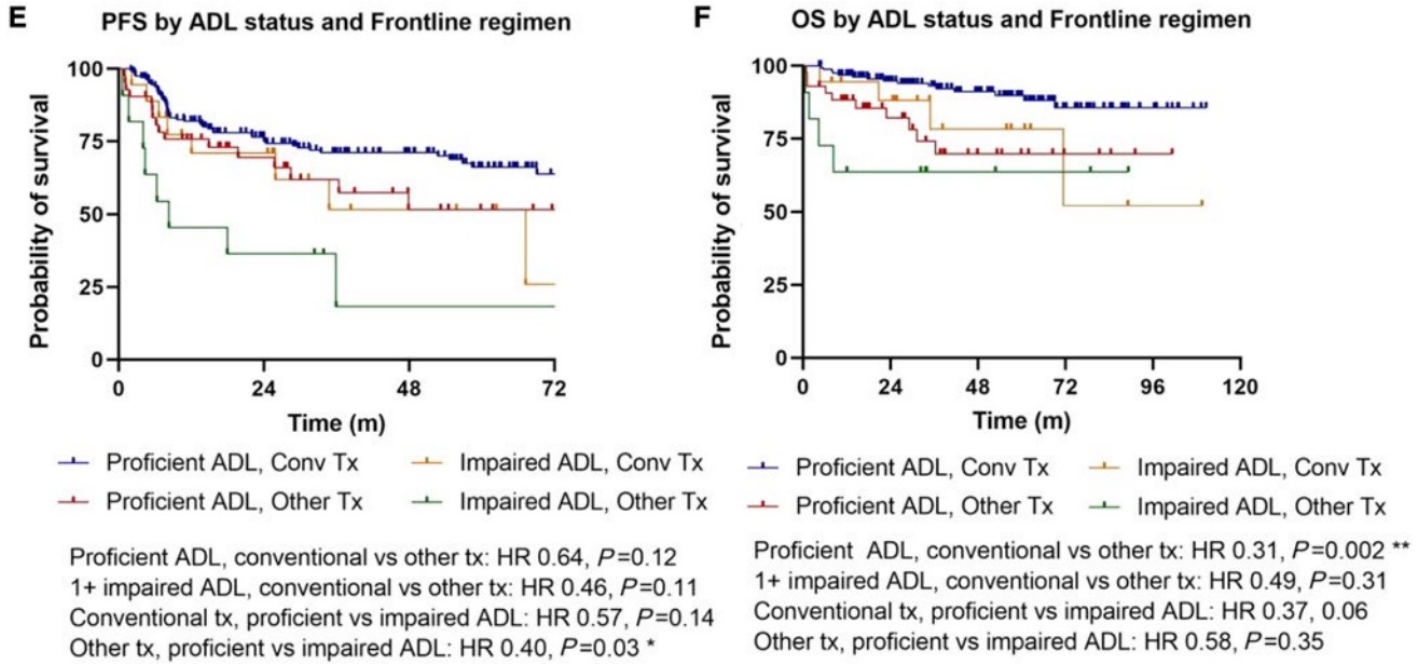
Roday, BJH 2020
Lia K et al., Haematologica 2024

Porque le va peor al adulto mayor con LH?



Orellana, Blood Adv. 2021

Porque le va peor al adulto mayor con LH?



Orellana, Blood Adv. 2021

LH en paciente

Quien tiene mas posibilidad de curarse?
El que recibe un tratamiento de intensidad con intension curativa.

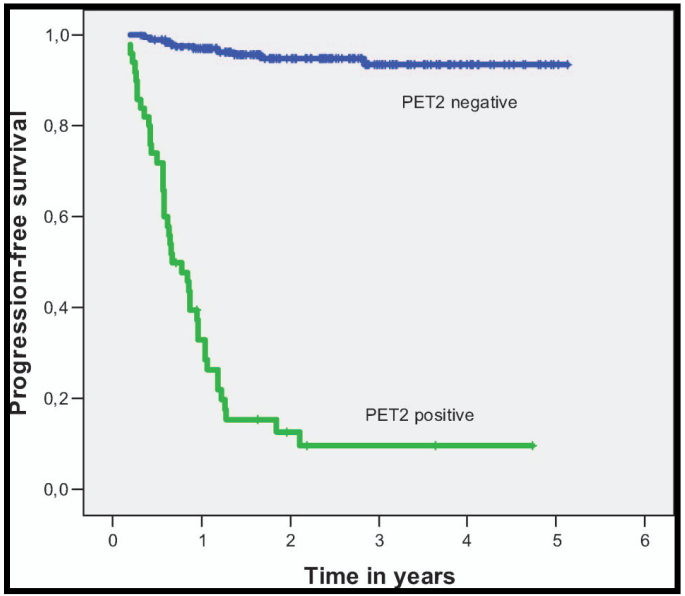
Objetivo? CURAR al paciente.

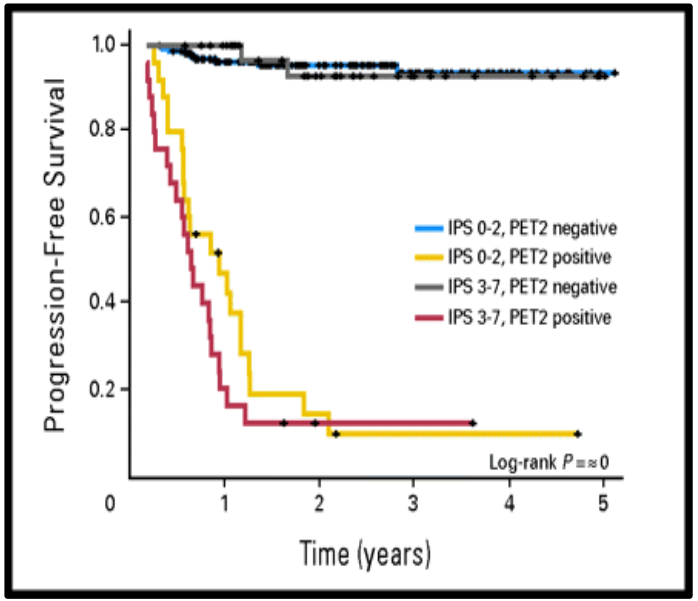
Un paciente > 60 a. *curado* de LH tiene SG similar a la población general.

Desafio: adaptar el mejor tratamiento
(el tto mas intensivo).

Famosas curvas en LH

FDG-PET scan was performed at baseline and after two courses of ABVD (PET-2). No treatment change was allowed on the basis of the PET-2 results.





Gallamini, BJH 2007

Análisis uni y multivariable SLE

Estadio AA	P= 0.004
Edad	0.58
Enf. Bulky	0.069
Comp Extranodal	0.010
PET/TC temprano	0.001

Estadio AA	0.001
PET /TC temprano	0.00007

Hutchings, Ann of Oncology, 2005.

Tratamiento de LH ha cambiado

ANTES	2025	CAMBIOS
Estatificación con TAC	**Estatificación con PET -TC**	**Up grade aprox 10%**
Est Loc: ABVD y RT **Est Avanz: ABVD-BEACOPP +- RT**	**Tratamiento adaptado a PETi**	**Menos quimio** **Menos RT**
Evaluación de la respuesta con TAC	**Evaluación de la respuesta con PET TC**	**Mayor % RC** **Menor falsos positivos** **Mejor pronostico en PET negativos.**
Solo qt en recaidos	**Nuevas drogas**	**Mejor pronostico**

Se curan mas pacientes con menos tratamiento

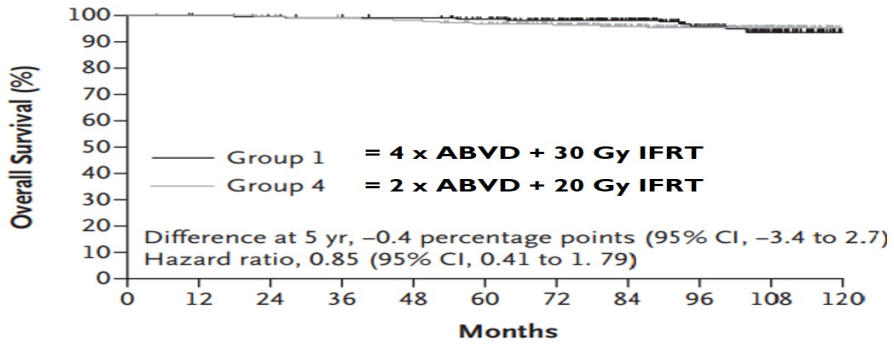
Puede mi paciente recibir ABVD?

GHSG: HD10 (ABVD x 2 +RT vs ABVD x 4 +RT)

1370 pts LH estadio localizado

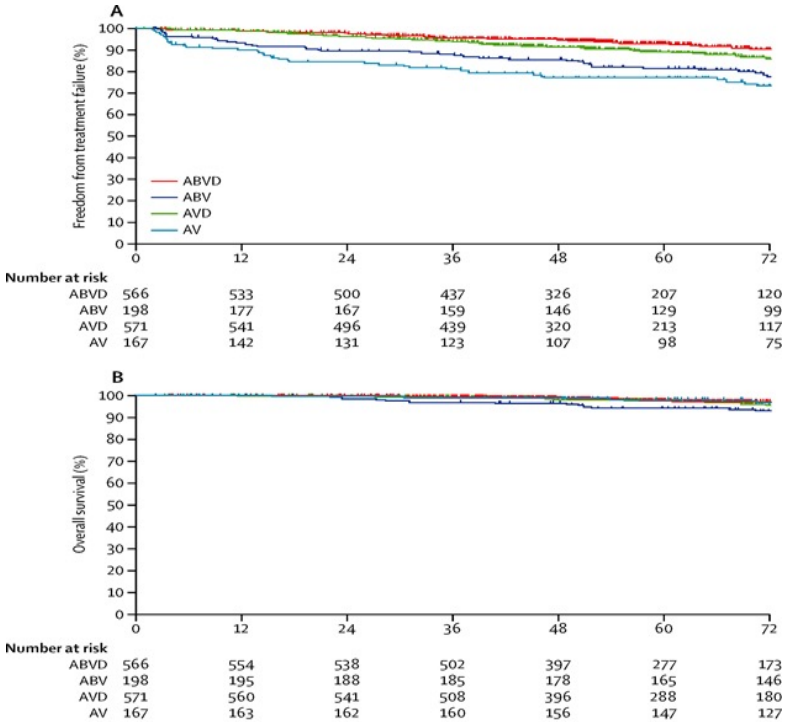
GHSG HD 10

- 2 x ABVD + 20 Gy IFRT (n=299)
  - 8-year FFTF 86%
  - 8-year OS 95%



Engert, NEJM , 2010

GHSG: HD13 ABVD es superior a 3 drogas.



ABVD vs ABV vs AVD vs AV
Todos los pts recibieron RT.

ABVD VS AVD
Solo 4 % diferencia en FFTF.
Recaídas tardias 3.5 %vs 6.5%.

- *Era pre PET*

Behringer K et al, Lancet 2015

Toxicidad pulmonary por Bleomicina (BLT) GHSG

- . Las tasas de eventos adversos de grado III-IV fueron similares en los pacientes que recibieron 2×AVD y 2×ABVD (40 % y 39 %, respectivamente), pero considerablemente más altas en aquellos que recibieron 4×ABVD (65 %).

- La BLT fue 1.5% en los pacientes que recibieron 2×ABVD, pero 10 % en pacientes 4×ABVD, con 3 eventos letales.

Boll et al, Blood 2016

Puede mi paciente recibir ABVD?

Aptos para Bleomicina? SI/NO

Factores de riesgo (???).

Dosis acumulada de Bleomicia.

Insuficiencia renal, ajustar dosis al clearance

Mayor edad.

Decidir usar Bleo en mayores de 60 a. de manera personalizada.
Pero:

- Con monitoreo continuo (Disminucion de DLCO >10% es predictiva).
- No mas de 2 ciclos.
- Evitar Filgrastrim (??).
- Evitar el uso de Bleomicina en mayores 70a.

BV monoterapia en pts > 60 a. BREVITY TRIAL

31 pts
25.8% RCM
Median PFS 7.3 meses

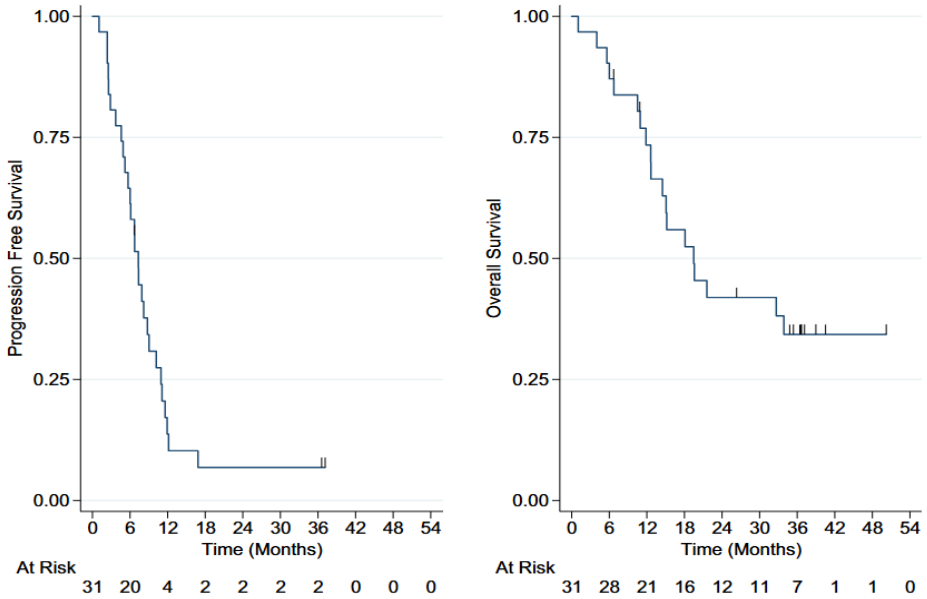
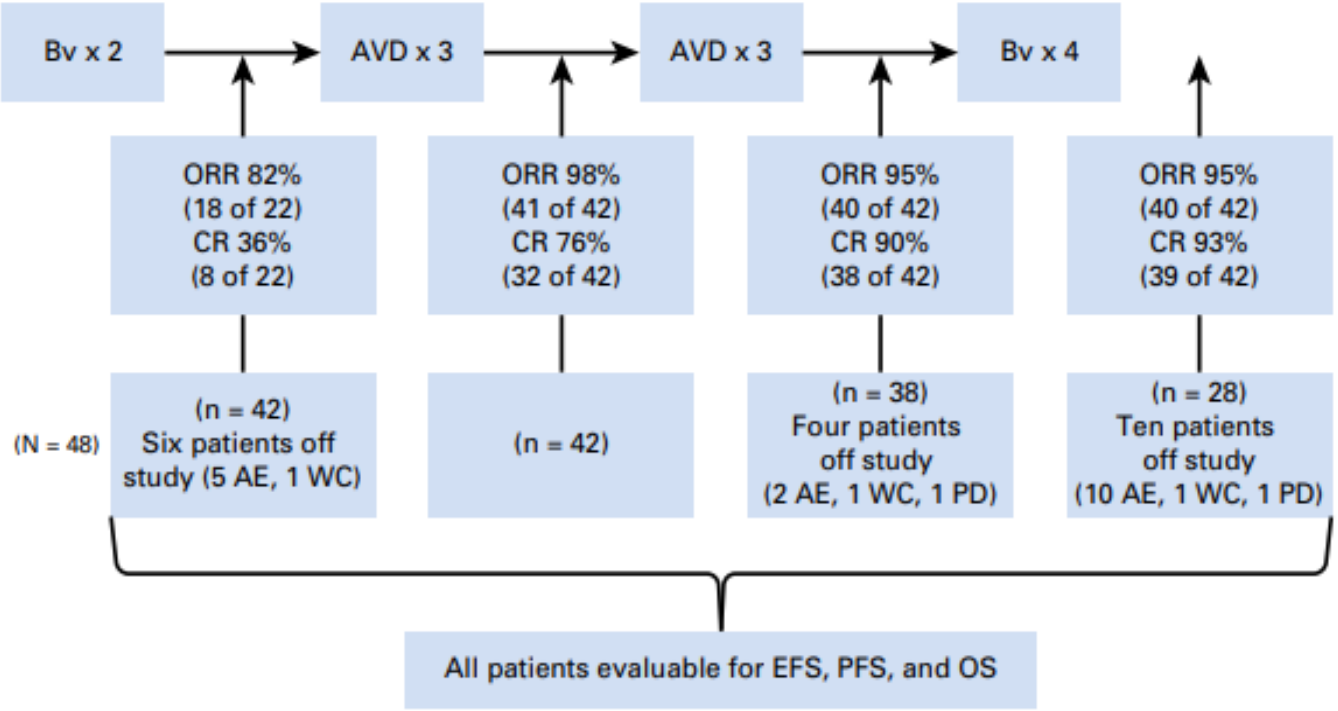


Fig 2. Kaplan–Meier progression-free (PFS) and overall survival (OS) curves. [Colour figure can be viewed at wileyonlinelibrary.com]

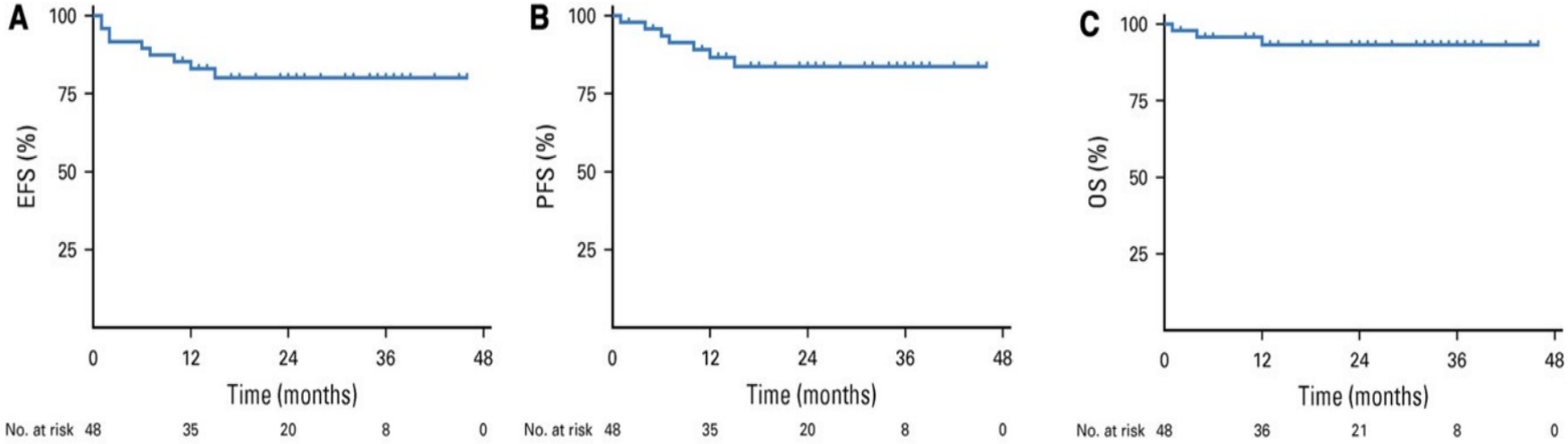
Gibb et al. BJH, 2020

Nuevas drogas en LH en paciente adulto mayor.



Evens AM et al, JCO 2018

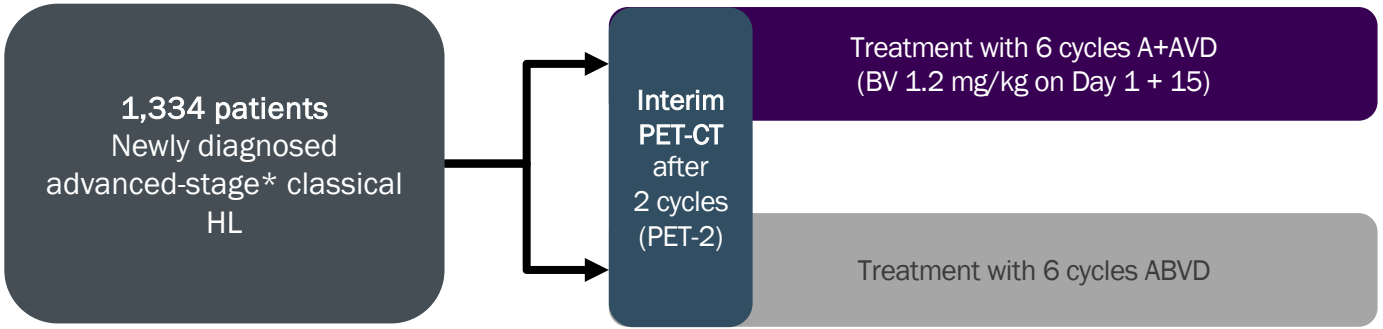
Nuevas drogas en LH en paciente adulto mayor.



Evens AM et al, JCO 2018

BV en 1L en LH estadios avanz.: ECHELON 1 trial

Phase III

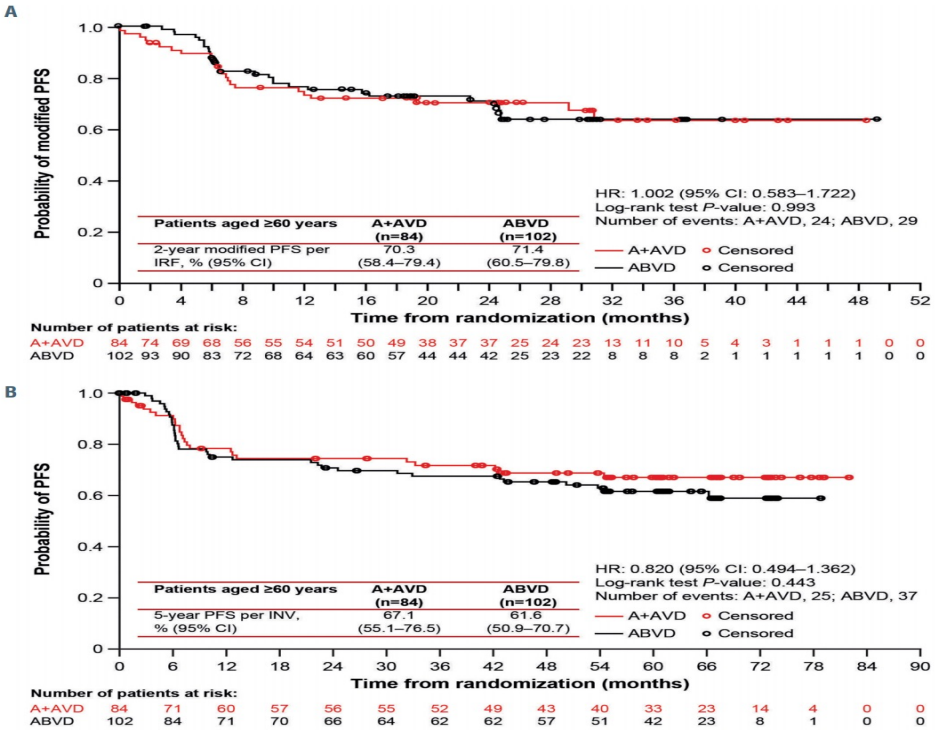


Primary endpoint: mPFS, time to progression, death or modified progression (evidence of non-complete response after completion of front-line therapy [by IRF] *and* use of subsequent anticancer therapy). Provides a superior assessment of treatment effectiveness

*Stage III–IV
†Results guided optional switch to alternative front-line therapy at physician's discretion for Deauville score of 5 (not considered a mPFS event)

Connors JM et al. *N Engl J Med* 2018;378:331–344.

ECHELON-1 en adultos mayores.



Evens et al, Haematologica, 2022

Pacientes que mas se beneficiarían con Bv + AVD

De acuerdo con la opinión del grupo de expertos, BV + AVD podría ser considerado como una nueva opción de tratamiento en los pacientes de mayor riesgo.

El análisis de subgrupos del estudio ECHELON-1, demostró que las ventajas más importantes del uso de BV + AVD vs. ABVD se dan en los pacientes con:

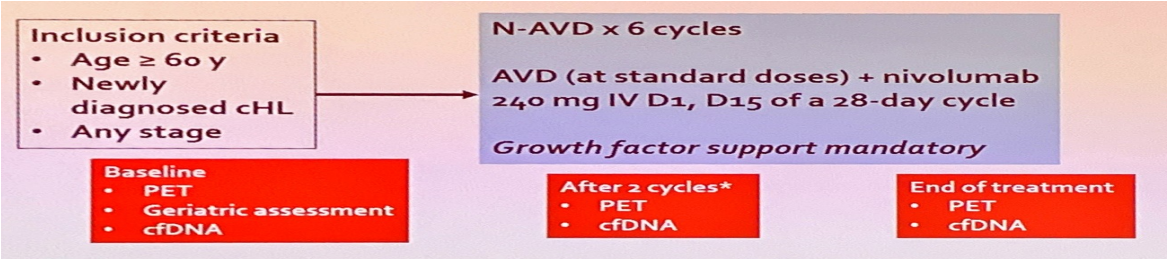
- **Estadio IV (HR: 0,48; IC95: 0,29 a 0,80),**
- **IPS 4-7 (HR: 0,48; IC95: 0,26 a 0,88),**
- **Compromiso de más de un sitio extranodal (HR: 0,30; IC95: 0,14 a 0,67).**
- **Menores 60 años**

Recomendación: consenso de expertos

Punto de buena práctica: la diferencia en la SG entre las terapias descritas en el estudio ECHELON-1, fue considerada por los expertos, tanto estadísticamente como clínicamente significativa.

Pavlovsky A, Altuve JIG, Cerutti A, Fiad L, Kurgansky N, Warley F, Negri Aranguren F., 2024. doi: 10.1016/j.htct.2024.07.007

Phase II trial Nivo-AVD

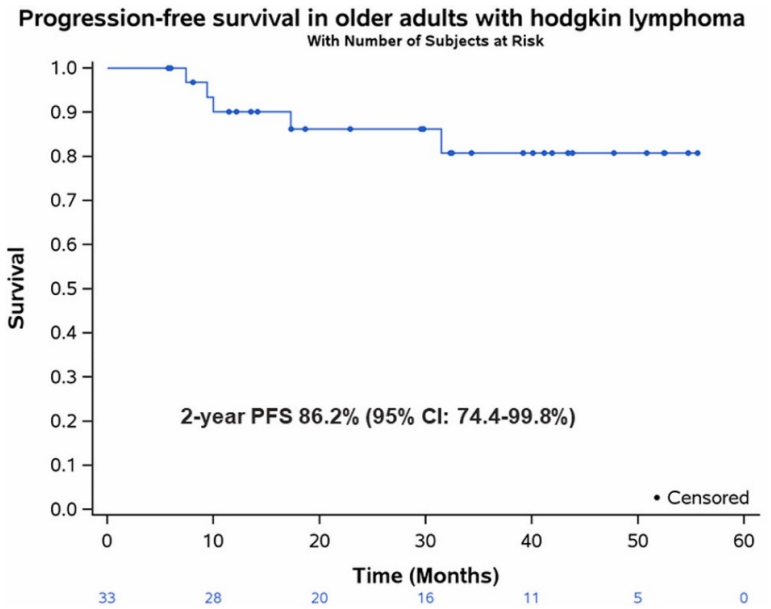


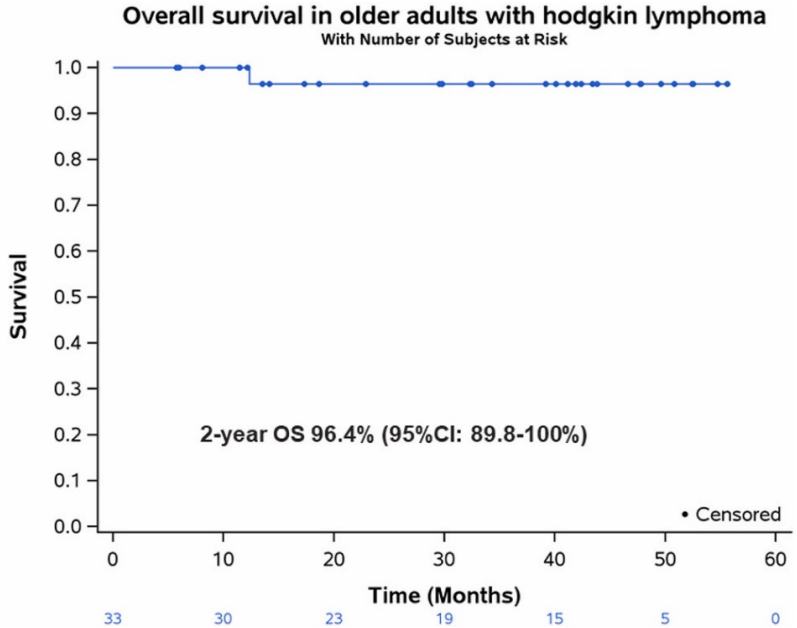
N= 40	n(%)
Median age (yrs; range)	66 (60-78)
Age ≥ 70	15 (38%)
Stage I/II III/IV	 9(22%) 31(78%)
IPSS 0-2 3-7	 13 (32%) 27 (68%)
B-symptoms	22 (55%)
Extranodal disease	17 (43%)

Response to therapy	End of treatment n (%)
ORR • CR • PR	33 (100) 32 (97) 1 (3)
SD	0
PD	0
NE	0
Duration of follow up (median)	37 months (5,7-55,6)

Torka P et al, ICML 2023

Phase II trial Nivo-AVD





Torka P et al, ICML 2023

ACCRU phase II trial Nivo+BV older or chemo-ineligible pts

Primary endpoint: ORR.
Secondary objectives: CMR response, progression-free survival, and overall survival.

	Total (n=46)
Cycle 8 metabolic rate	61% (45–75)
Complete metabolic response	22 (48%)
Partial metabolic response	6 (13%)
Progressive Metabolic Disease	7 (15%)
Off before cycle 8	11 (24%)
Best overall response rate (all cycles)	91% (79–98)
Complete metabolic response	30 (65%)
Partial metabolic response	12 (26%)
No metabolic response	1 (2%)
Progressive metabolic disease	1 (2%)
Not evaluated	2 (4%)
Median duration of response	NR (11·1–NR)
Median overall survival	NR (NR–NR)
Median progression-free survival (months)	18·3 (12·7 to NR)

Data are median or % (95% CI) or n (%), unless otherwise specified. NR=not reached.

Table 2: **Patient outcomes and response to therapy**

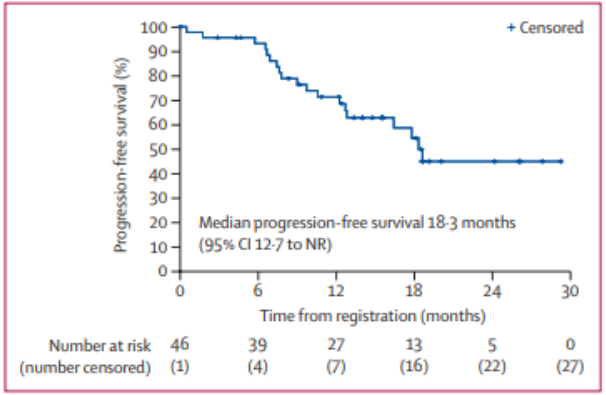
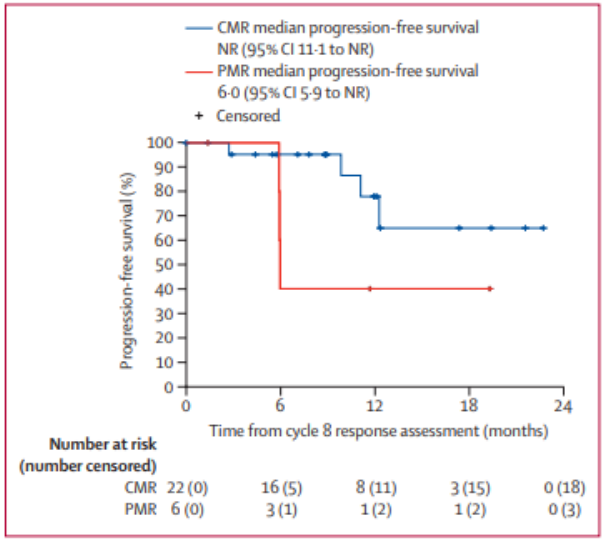


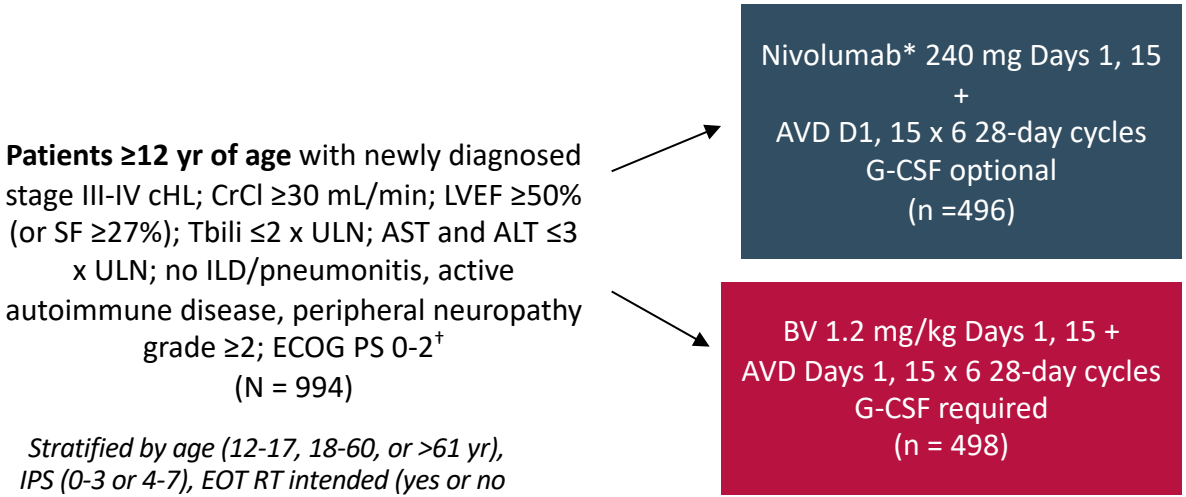
Figure 2: **Progression-free survival**
NR=not reached.



Cheson BD et al, Lancet hematol , 2020

SWOG S1826: Diseño de estudio

- International, randomized, open-label phase III trial

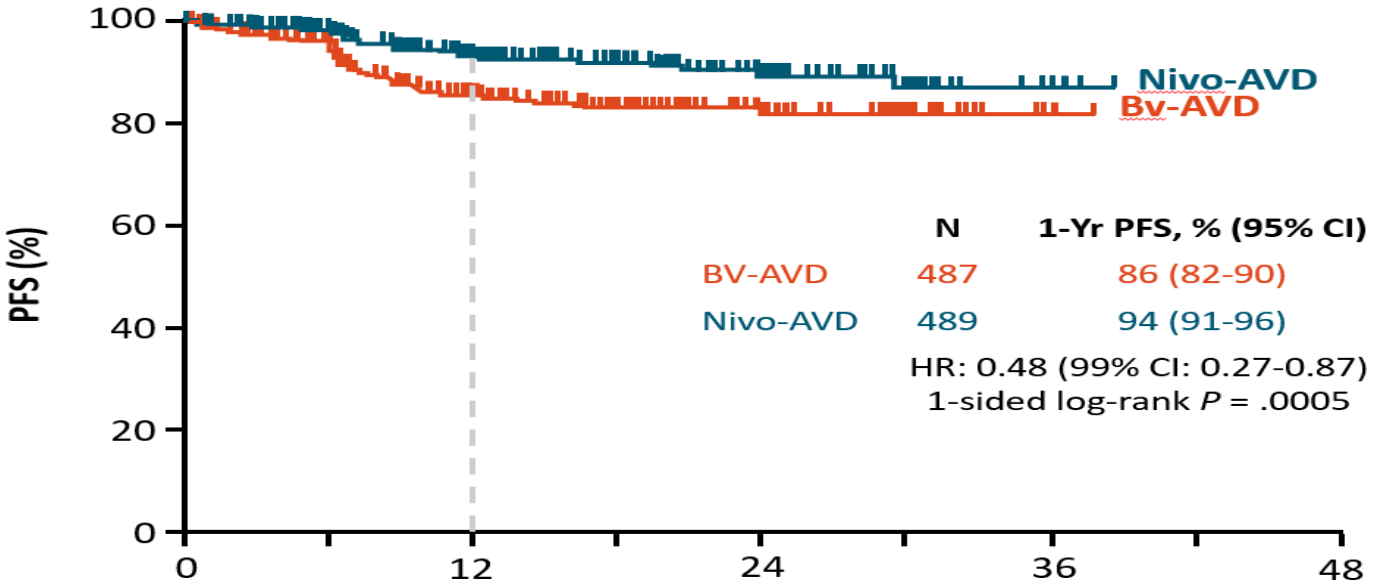


- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, EFS, safety

†Pediatric: Lansky score vs ECOG; CrCl/GFR ≥70 mL/min or SCr ≤1.5 ULN.

Herrera. ISHL 2024.

SWOG: 1826 SLP

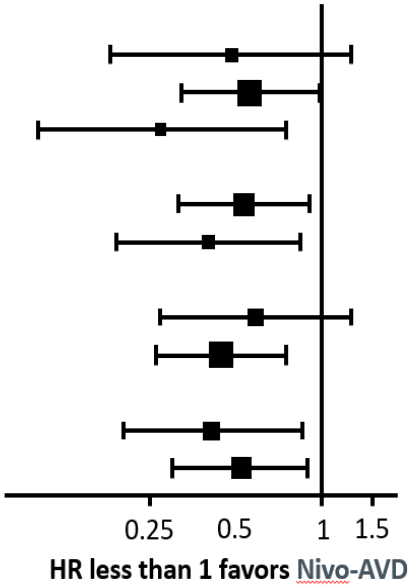


: 12.1 mo

Herrera. ISHL 2024 .

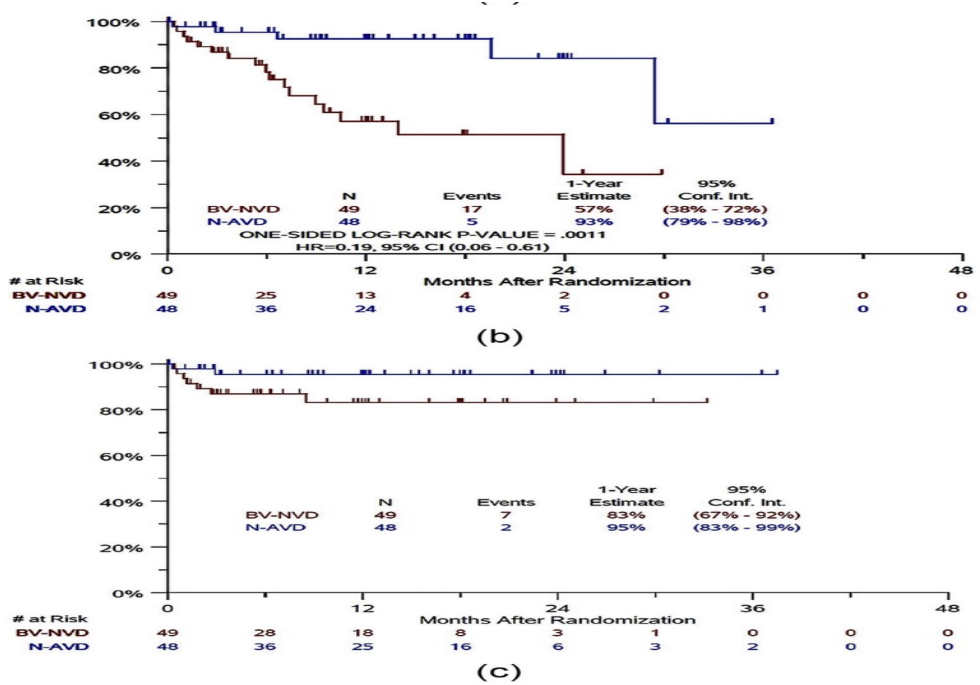
SWOG: 1826 SLP Análisis de subgrupos

Subgroup	Nivo + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	*P*-Value
Age				
12-17 yr	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18-60 yr	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
>60 yr	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0-3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4-7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Herrera. ISHL 2024.

SWOG: 1826 Pts > 60 años cohorte - EFS, SG



Evens A. ISHL 2024

Nuevas opciones en el tratamiento de primera línea del linfoma de Hodgkin

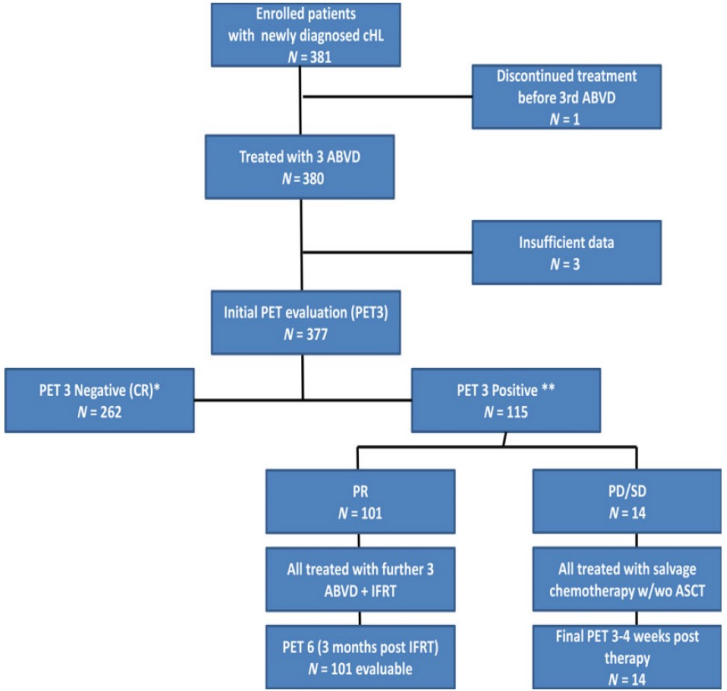
- **SWOG study :**

- Se incluyeron 97 pacientes > 60 años
- Seguridad y mayor PFS con N-AVD vs. BV-AVD
- Reducción de la radioterapia (< 1%)
- Análisis de ctDNA y TMTV en curso
- ¿Necesitamos un seguimiento a largo plazo? Toxicidad a largo plazo.
- Esta combinación de tratamiento aún no ha sido aprobada.

PET-adapted therapy after three cycles of ABVD for all stagesof Hodgkin lymphoma: GATLA LH-05 trial

Table I. Clinical characteristics of evaluable patients.

Characteristic	All evaluable patients (n = 377)
Median age (range), years	31 (18–89)
Male sex, n (%)	173 (46)
Performance status, n (%)	
0–1	362 (95)
2	6 (2)
≥3	3 (1)
Not available	6 (2)
Ann Arbor stage, n (%)	
Early (I to II non-bulky)	239 (63)
Advanced (II, bulky-III-IV)	138 (37)
Bulky disease, n (%)	66 (17)



Pavlovsky A et al, BJH, 2019

SAFETY AND EFFICACY ANALYSIS IN OLDER PATIENTS TREATED WITHIN THE GATLA LH-05 PROTOCOL: PET-ADAPTED THERAPY AFTER 3 CYCLES OF ABVD FOR ALL STAGES OF HODGKIN LYMPHOMA. P1082

L. FIAD, MV. PRATES, I. FERNANDEZ, N. KURGANSKY, A. CERUTTI, F. NEGRI ARENGUREN, L. GUANCHIALE, F. SACKMAN, J. MARADEI, A. ENRICO, P. NEGRI ARANGUREN and A. PAVLOVSKY. On behalf of GATLA, Argentina.

INTRODUCTION

Treatment for classic Hodgkin lymphoma (cHL) in older age population continues to be a challenge. Comorbidity prevalence, increase toxicity to the standard treatments and the lack of inclusion in clinical trials all contribute to this phenomenon. The obtained results are inferior in comparison to young adults and there is shortage of evidence regarding effective therapeutic strategies. Recently, GATLA has analyzed the long-term follow-up of the results of the PET/CT adapted strategy after 3 cycles of ABVD, regardless of the stage at diagnosis with no upper age limit.

OBJECTIVE

To assess the effectiveness and safety of this PET/CT adapted treatment in patients older than 60 years.

METHODS

- A retrospective analysis of the LH-05 database was performed. Patients were included ≥ aged 60 with recent diagnosis of cHL stage I-IV and HIV negative.
- All patients received 3 cycles of ABVD and were evaluated with PET-TC (PET3).
- Those patients with negative PET (Deauville score 1 and 2) were considered to be in complete remission (CR) and they finalized the treatment.
- Patients with DS 3 and 4 completed 6 ABVD cycles and involved-field radiotherapy in hypermetabolic areas in interim PET3.
- Patients with DS 5 were considered to have progressive disease.
- Progression-free survival (PFS) and overall survival (OS) were evaluated.
- Kaplan-Meier method and Log-rank test were used for survival analysis.

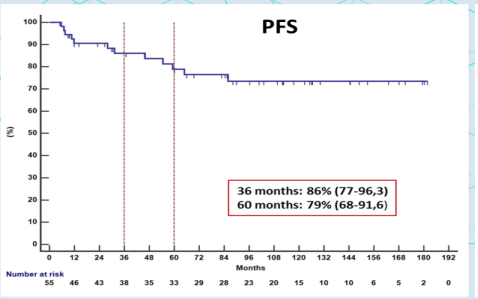
RESULTS

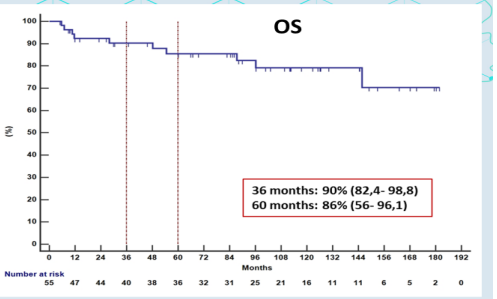
Of a total of 490 patients included in the GATLA LH-05 protocol, 59 were 60 or older. Of this cohort, the mean age was of 66 years (range: 60-89), and 75% presented in localized stage (I-II), 90% presented a PS <2. The most frequent histological subtype was Nodular Sclerosis (54%).

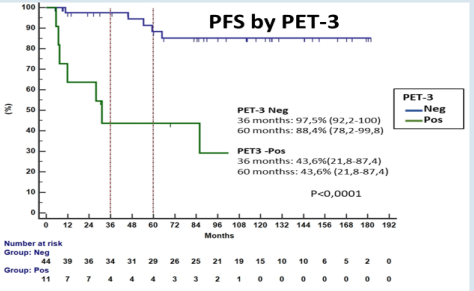
All patients received initial treatment with 3 cycles of ABVD and were evaluated by PET: 81% presented negative PET3 and 19% were PET 3 positive. No GIII-IV toxicity or treatment-related deaths were recorded.
With a median follow-up of 10 years, median PFS and OS were not reached. At 36 and 60 months, PFS was 86% and 78,9%, and OS was 90% and 85.5%, respectively.
Negative PET3 patients had a PFS of 85.4%, while positive PET3 patients had a PFS of 43% (p=0,0001).

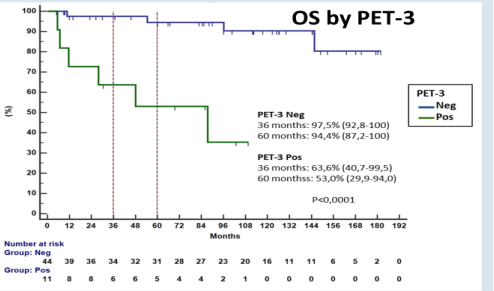
In the multivariable analysis that included age (>60 vs <60), stage (localized vs. advanced), IPS (<2 vs. >2), extranodal areas, bulky disease and PET3 result, **only age and PET3 result had significant impact in PFS (p=0.046 and p=0,001 respectively).** PFS of PET/TC- positive patients was significantly lower than in the cohort of patients younger than 60.

OS at 36 and 60 months in PET negative patients was 97.5% and 94.5% respectively, versus 63.6% and 53% in PET/TC positive patients.









CONCLUSIONS

With the PET/TC adapted treatment after 3 cycles of ABVD in 59 patients > 60 years old, 81% of patients achieved negative PET and therefore received no further treatment. These patients had an excellent result with a PFS of 85.4% at 3 years, similar to the younger patient population. However, a significant reduction in PFS was observed in PET3 positive patients > 60 years old compared to younger ones. Implementation of this PET/TC guided strategy, regardless of stage at diagnosis, resulted in reduced exposure to chemotherapy and radiotherapy, contributing to the absence of severe treatment-related morbidity and mortality.

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1. PET-adapted therapy after three cycles of ABVD for all stages of Hodgkin lymphoma: results of the GATLA LH-05 trial. Pavlovsky A. et al, Br J Haematol. 2019;185(5):865–73. 2. Risk-adapted therapy with three or six cycles of oxorubicin/bleomycin/vinblastine/dacarbazine plus involved-field radiation therapy in Hodgkin lymphoma, based on prognosis at diagnosis and early response: Results from the GATLA study. Pavlovsky S. et al, Clin Lymphoma, Myeloma Leuk. 2010;10(3):181–5.

CONTACT INFORMATION

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GATLA LH05 EN MAYORES DE 60 a.

Characteristics : n: 59	n (%)
Median Age (Range) **≥70 ys**	66 (60-89)/ 20 (34%)
PS 0 1 ≥2	 41 (69) 12 (20) 6 (11)
B symptoms Yes No	 36 (61) 23 (39)
Stage I-II III-IV	 44 (75) 15 (25)

Characteristics	n (%)
Bulky Yes No	 5 (9) 54 (91)
Extranodal Yes No	 7 (12) 52 (88)
Histopathologic Subtypes Nodular sclerosis Mixed cellularity Lymphocyte-rich Lymphocyte-depleted	 34 (58) 19 (32) 6 (10) 0

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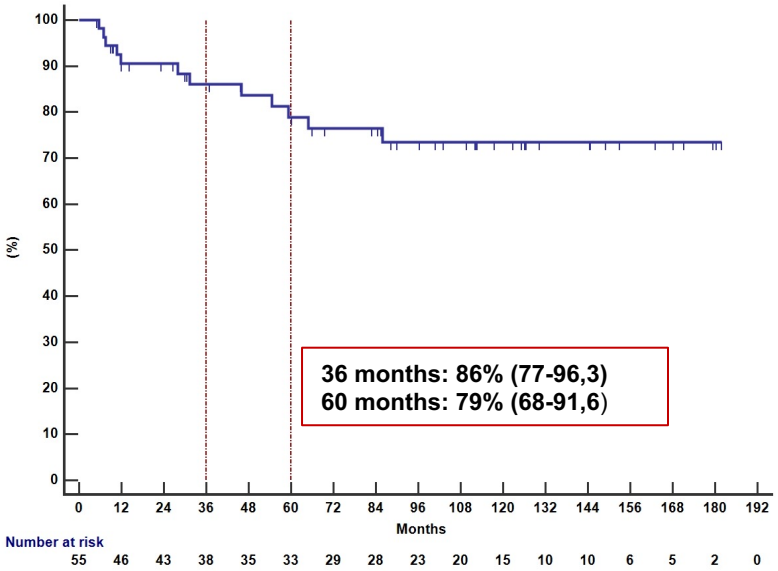
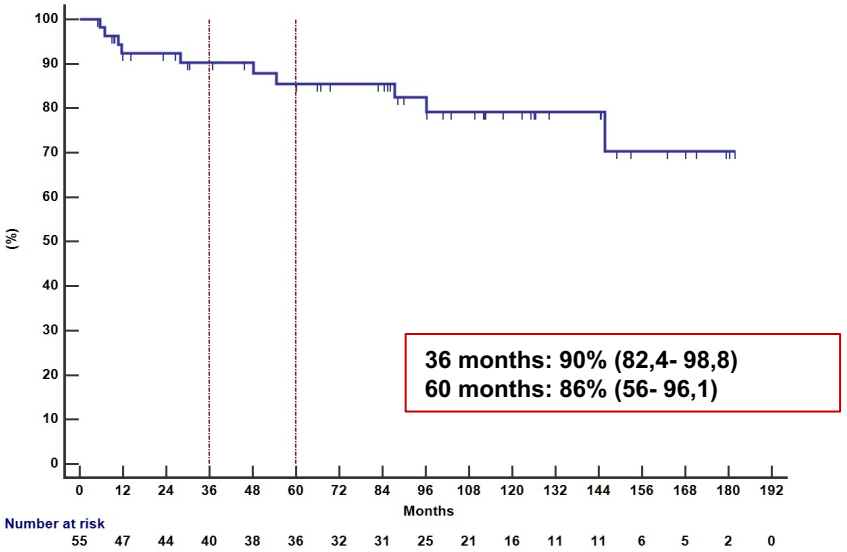
GATLA LH05 EN MAYORES DE 60 a.

PFS



OS



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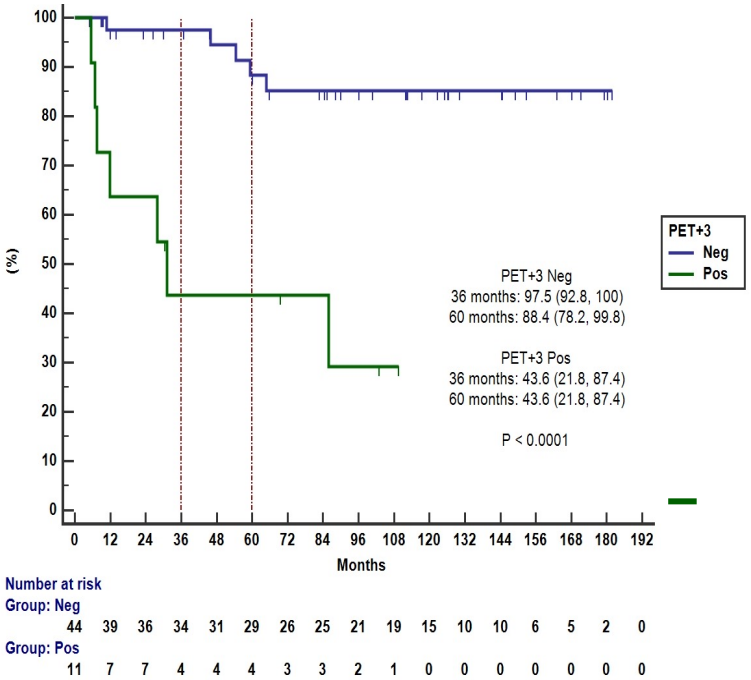
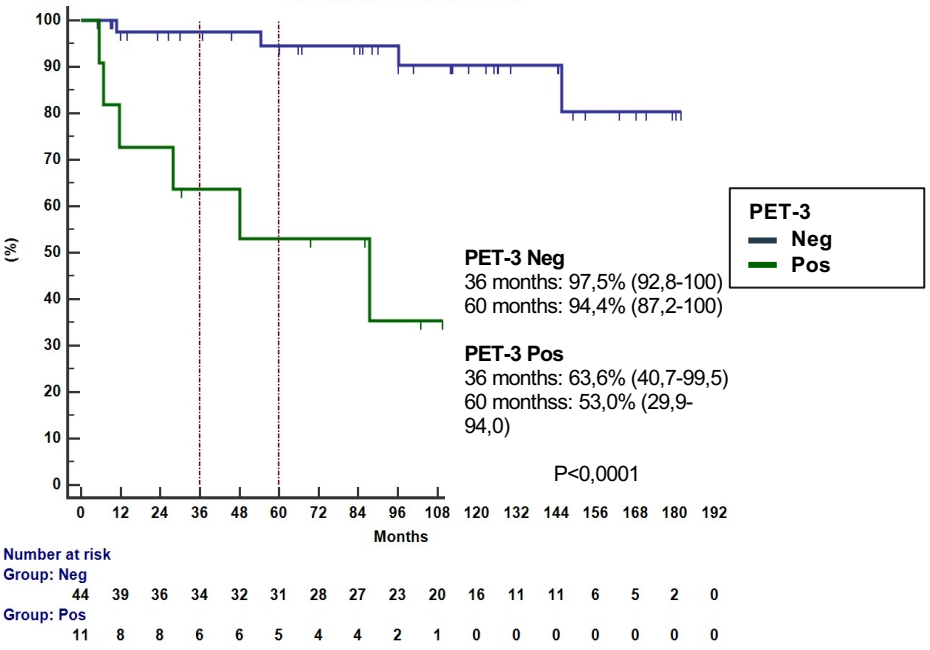
GATLA LH05 EN MAYORES DE 60 a.

PFS by PET-3



OS by PET-3



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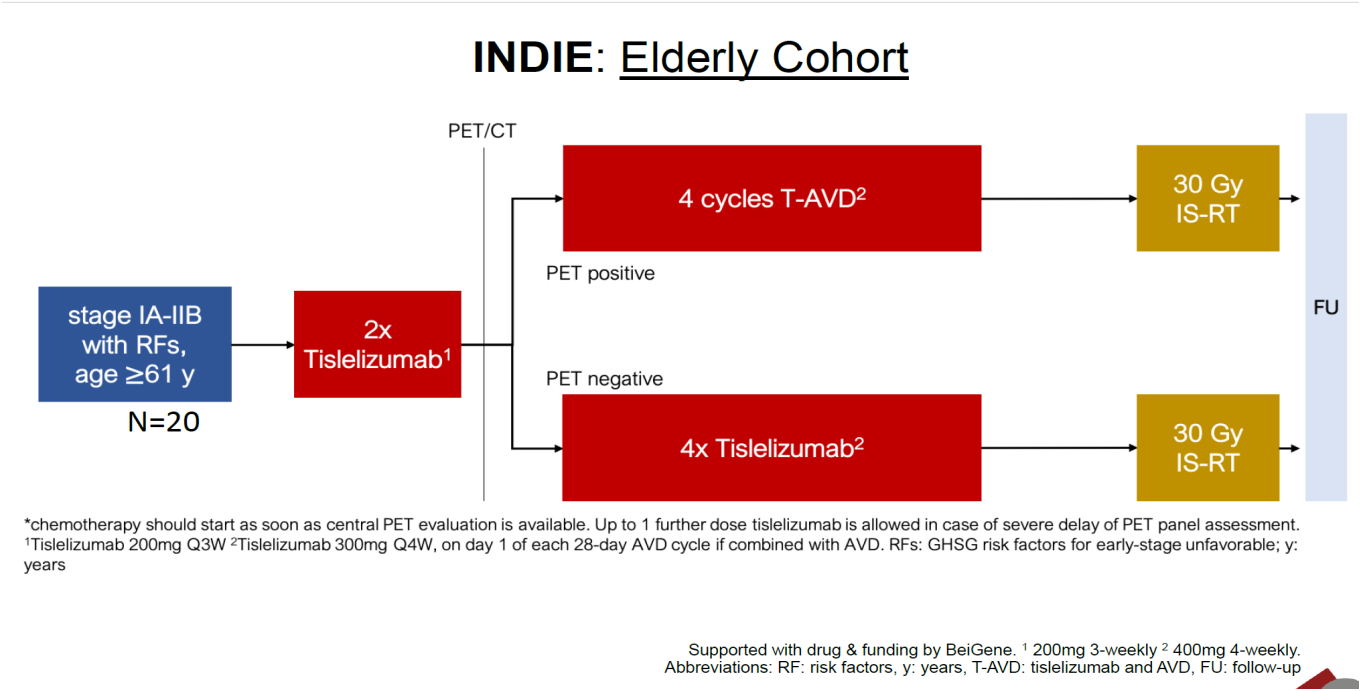
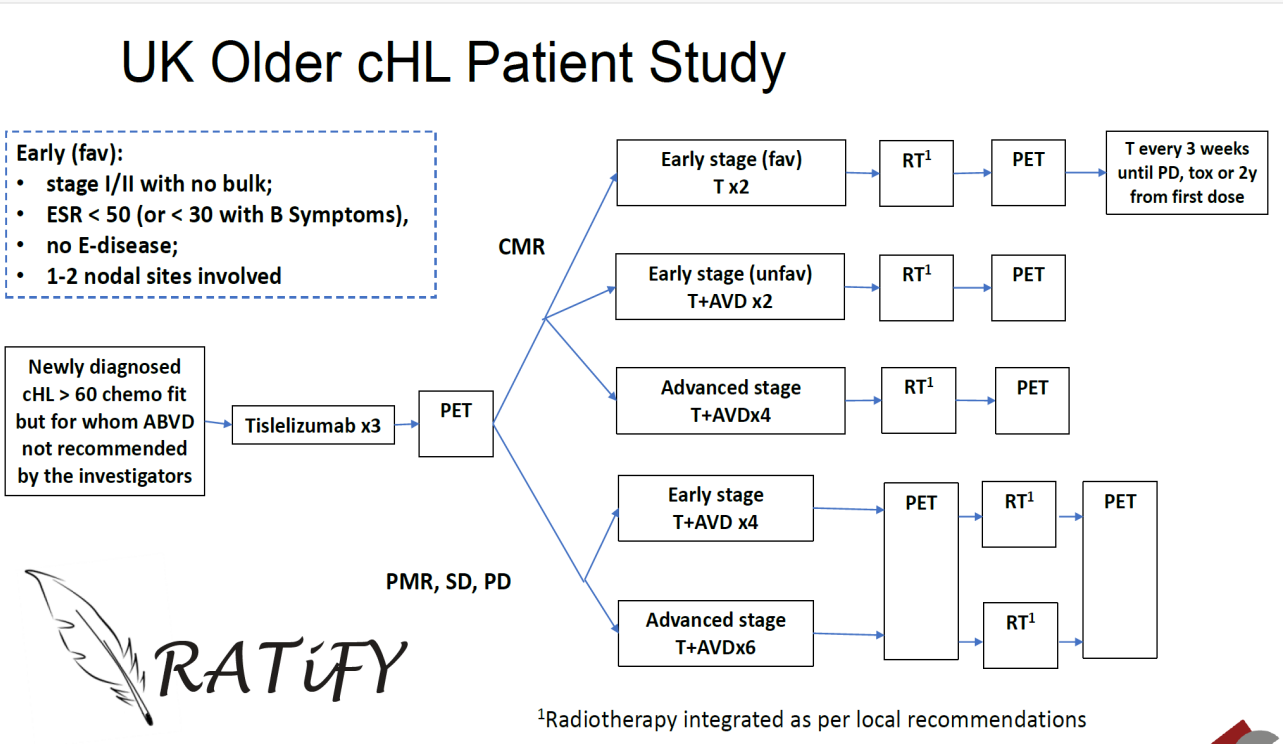
Tislelizumab en LH en adultos mayores



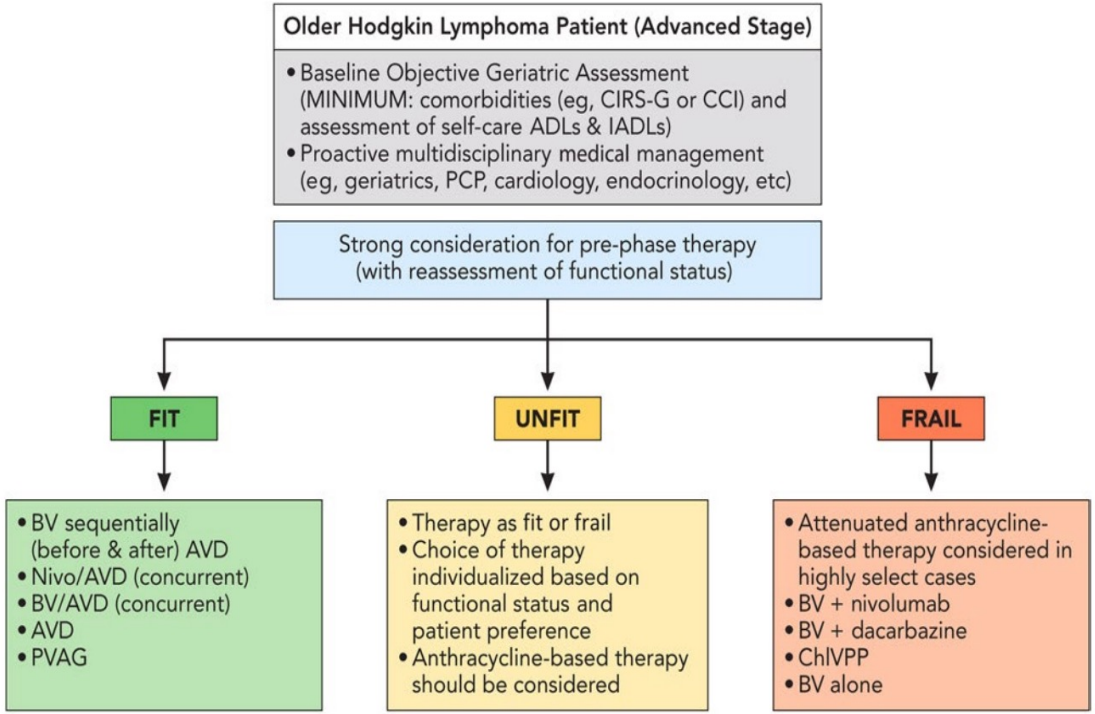
Supported with drug & funding by BeiGene. [1] 200mg 3-weekly [2] 400mg 4-weekly.
Abbreviations: RF: risk factors, y: years, T-AVD: tislelizumab and AVD, FU: follow-up

Tislelizumab en LH en adultos mayores



Collins G. 2024

El gran desafío:
Caminar por la cuerda floja entre eficacia y toxicidad.



Criteria	Fit	Unfit	Frail
ADL	6	5	≤4
IADL	8	6-7	≤5
CIRS-G	0 score of 3-4 and <5 of score 2	0 score of 3-4 and 5-8 of score 2	≥1 score of 3-4 and/or >8 of score 2
Age	<80 years	≥80 years FIT	≥80 years UNFIT

Evens A, ASH Educ, 2023

Como trato yo pacientes con LH adultos mayores

- **Estadios localizados y avanzados**:
  - Catergorizacion del pte segun CIRS y ADL.

  - Intento pensar en poder dar ABVD adaptado al resultado del PET.
    - Considero acortar el numero de ciclos de qt. No mas de 2-3 ciclos de Bleo.
    - Si Bleo esta contraindicada y sin posibilidad de BV, AVD y evaluar la factibilidad de RT.

    - No apto para ABVD:
    - CHOP? Resutados inferiores

    - En caso de contraindicacion a antraciclicos:
    - Considerar Adria Liposomal.
    - Omitir Adria.

Como *trataría* yo pacientes con LH adultos mayores

- A la espera de la aprobacion de N-AVD ….

- Con la esperanza de la aprobación de N-AVD y resultados semejantes en la vida real.

LH recaído refractario en adultos mayores.

- No hay protocolos especificos para este grupo de pacientes.
- La incorporación de BV e iCP han mejorado el pronóstico.
- Es probable que el uso secuencial de nuevas drogas y qt adaptado al resultado del PET, sea la opción mas atractiva.

El arte del equilibrio en pts > 60 a con LH.

- El manejo del linfoma de Hodgkin en adultos mayores requiere un ***equilibrio*** entre eficacia y tolerabilidad.

- Adaptar el tratamiento según la funcionalidad del paciente (usar scores!), utilizar esquemas ajustados a la respuesta y flexibilizar el numero de ciclos y las dosis son claves para optimizar los resultados.

- A medida que avanzamos en la integración de nuevos agentes, podemos reducir la toxicidad sin comprometer la eficacia.

El arte del equilibrio en pts > 60 a con LH.

- El pronóstico de un paciente adulto mayor con LH es desfavorable con respecto al resto de los grupos etarios.

- Estudios recientes muestran protocolos con resultados superadores.

MUCHAS GRACIAS.

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