

# DEBATE MM LEX 2024

## ¿CUADRUPLETES PARA TODOS EN PRIMERA LÍNEA?



¡¡¡SÍ!!!

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Hematólogo UC

13 Abril 2024

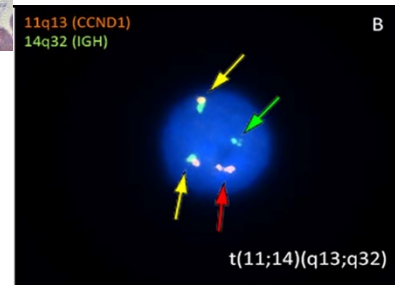
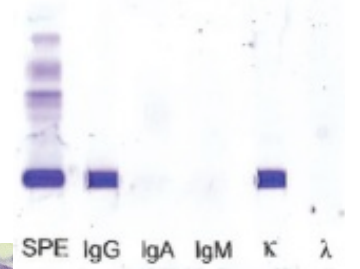
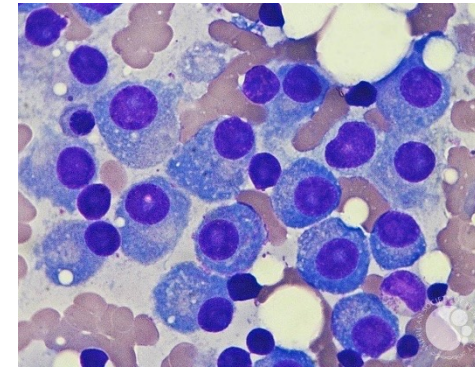
# CASO CLÍNICO



60 años



- Hb 9,5
- Normales:
  - Función renal
  - Ca
  - B2M/albúmina
  - LDH



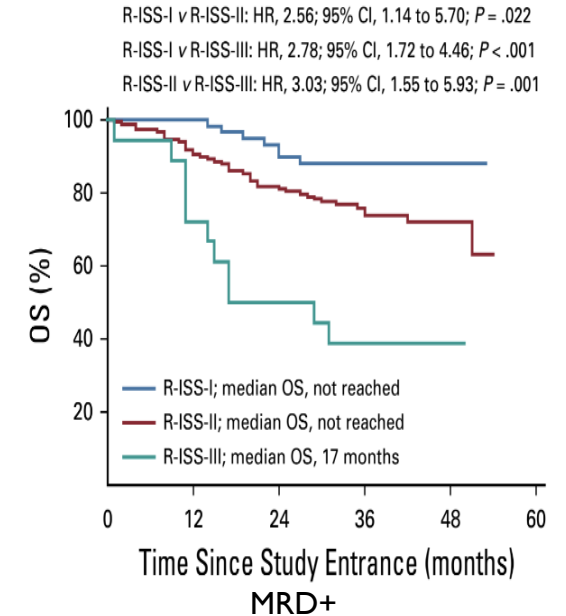
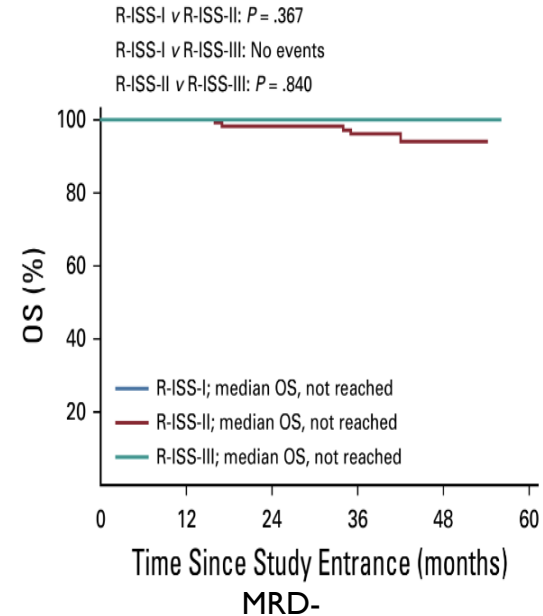
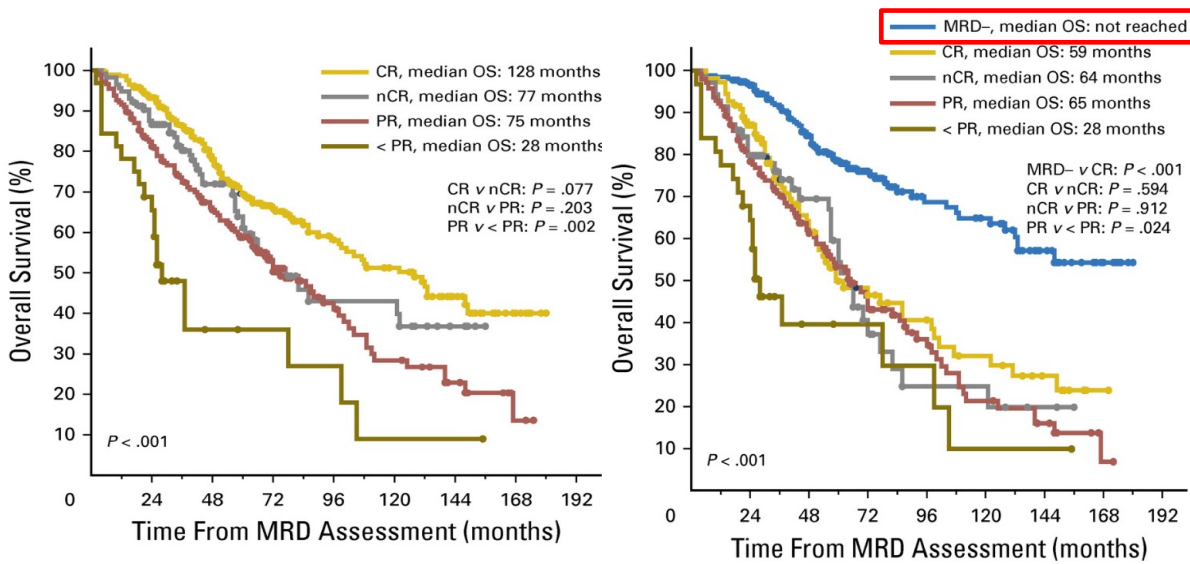
→ MM riesgo estándar (R-ISS I), candidata a TPH

# CONFLICTOS DE INTERÉS

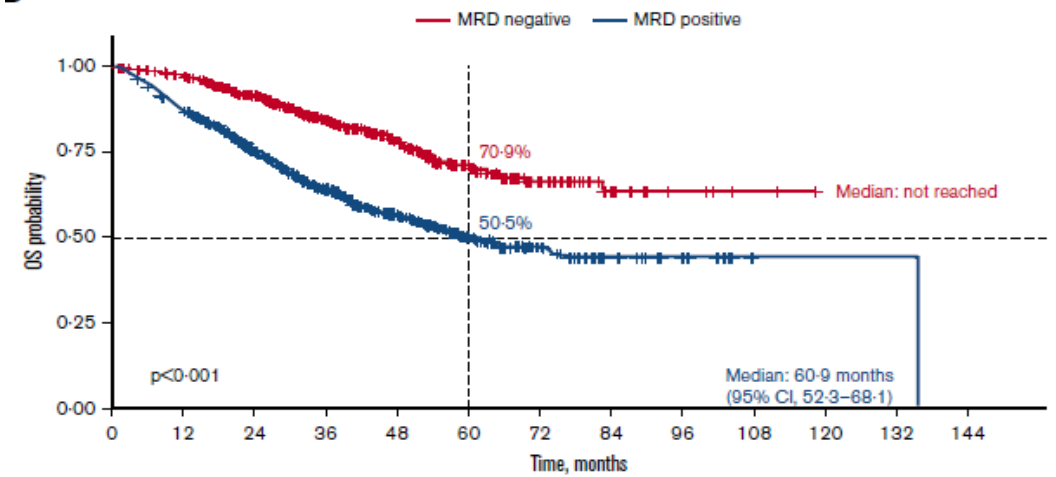
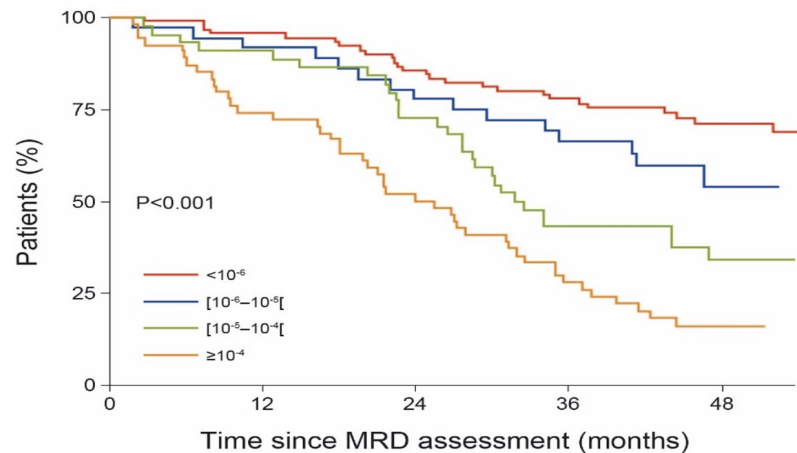
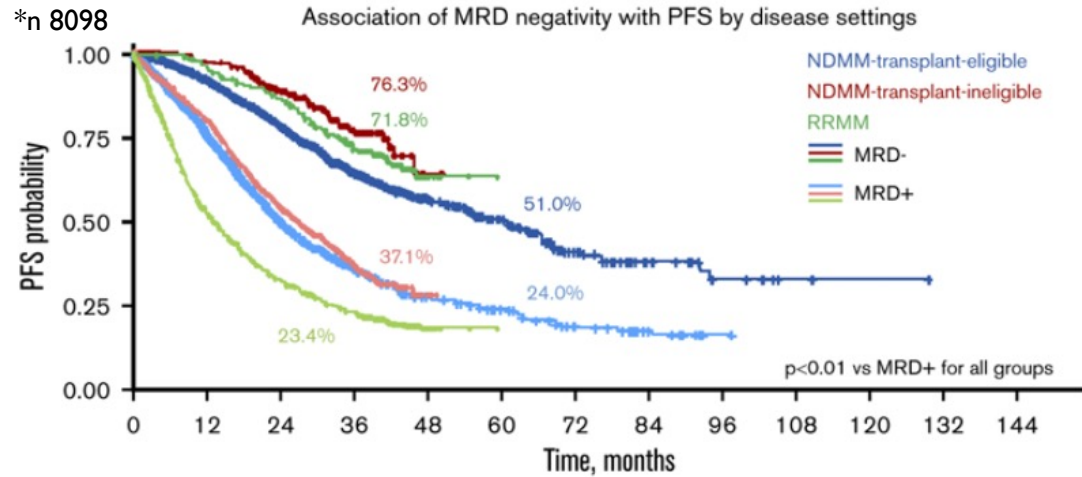
- **Nada que declarar**

# INTRODUCCIÓN

- Lograr respuestas profundas es clave



# INTRODUCCIÓN



	No. of patients	OS hazard ratio (95% CI)	p value
Disease setting	NDMM transplant eligible	2250	0.50 (0.42-0.59) <math>p < 0.001</math>
	NDMM transplant ineligible	1268	0.40 (0.31-0.51) <math>p < 0.001</math>
	RRMM	1026	0.28 (0.18-0.45) <math>p < 0.001</math>
MRD sensitivity threshold <sup>b</sup>	<math&gt;10^{-4}&lt; math&gt;<="" td=""> <td>1251</td> <td>0.50 (0.43-0.60) &lt;math&gt;p &lt; 0.001&lt;/math&gt;</td> </math&gt;10^{-4}&lt;>	1251	0.50 (0.43-0.60) <math>p < 0.001</math>
	<math&gt;10^{-5}&lt; math&gt;<="" td=""> <td>2630</td> <td>0.39 (0.31-0.49) &lt;math&gt;p &lt; 0.001&lt;/math&gt;</td> </math&gt;10^{-5}&lt;>	2630	0.39 (0.31-0.49) <math>p < 0.001</math>
	<math&gt;10^{-6}&lt; math&gt;<="" td=""> <td>596</td> <td>0.26 (0.13-0.51) &lt;math&gt;p &lt; 0.001&lt;/math&gt;</td> </math&gt;10^{-6}&lt;>	596	0.26 (0.13-0.51) <math>p < 0.001</math>
Cytogenetic risk	High-risk <sup>c</sup>	349	0.66 (0.46-0.94) 0.01
	Standard-risk <sup>d</sup>	293	0.65 (0.55-0.77) 0.001
Method of MRD assessment	MFC <sup>e</sup>	694	0.48 (0.31-0.73) <math>p < 0.001</math>
	NGS	2175	0.34 (0.26-0.45) <math>p < 0.001</math>
	PCR	163	0.47 (0.27-0.81) 0.01
Depth of clinical response at the time of MRD measurement	CR or better <sup>f</sup>	104	0.25 (0.10-0.60) <math>p < 0.001</math>
	VGPR or better <sup>g</sup>	490	0.41 (0.27-0.62) <math>p < 0.001</math>

# INTRODUCCIÓN

## Muchos pacientes reciben sólo una línea de terapia

**Table 4** Attrition rates by LOT

LOT	Frequency, N	Attrition, %	Deaths, n (%)	No subsequent treatment in follow-up, n (%)	Subsequent treatment, n (%)
Non-transplant					
1	22,062	–	2841 (12.9)	9716 (44.0)	9505 (43.1)
2	9505	56.9	1155 (12.2)	3168 (33.3)	5182 (54.5)
3	5182	45.5	636 (12.3)	1575 (30.3)	2971 (57.3)
4	2971	42.7	364 (12.3)	901 (30.3)	1706 (57.4)
5	1706	42.6	209 (12.3)	508 (29.8)	989 (58.0)
Transplant					
1	2763	–	36 (1.3)	543 (19.6)	2184 (79.0)
2	2184	21.0	60 (2.7)	613 (28.1)	1511 (69.2)
3	1511	30.8	63 (4.2)	494 (32.7)	954 (63.1)
4	954	36.9	60 (6.3)	276 (28.9)	618 (64.8)
5	618	35.2	49 (7.9)	180 (29.1)	389 (62.9)

LOT Line of therapy, SD Standard deviation

Tasas de desgaste:  
39-68%  
(optimistas: 7-19%)

## Análisis mundo real tratamientos con daratumumab (n 299)

	1 <sup>a</sup> L	2 <sup>a</sup> L	3 <sup>a</sup> +L
ORR	100%	78,8%	65,2%
VGPR+	73,1%	57,6%	40,7%
SLPIa	90%	75%	53%

## Las respuestas (y su duración) disminuyen progresivamente con cada línea

→ **Objetivo: lograr la mejor respuesta con la primera línea**

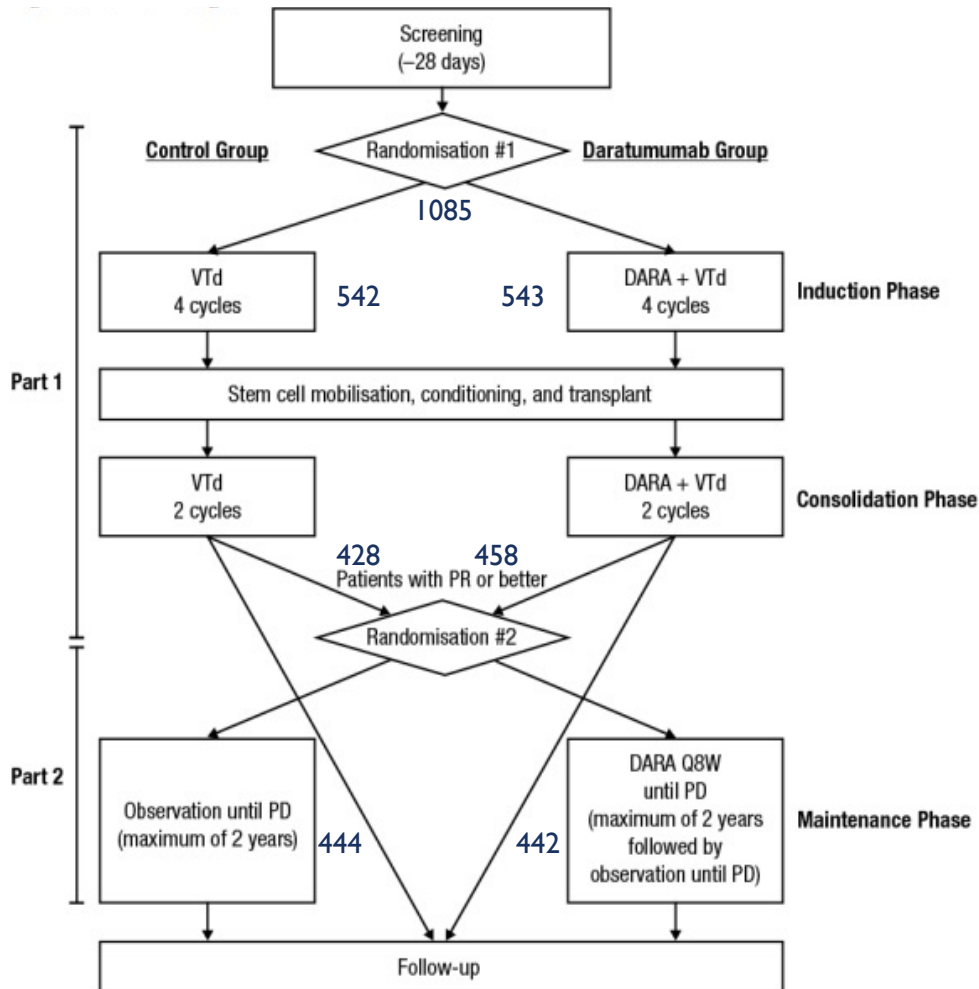


# ESTUDIOS MÁS RELEVANTES

CANDIDATOS A TPH



# CASSIOPEIA



- Fase 3. Mediana 59a; 15% ISS III; 15% citogenética alto R

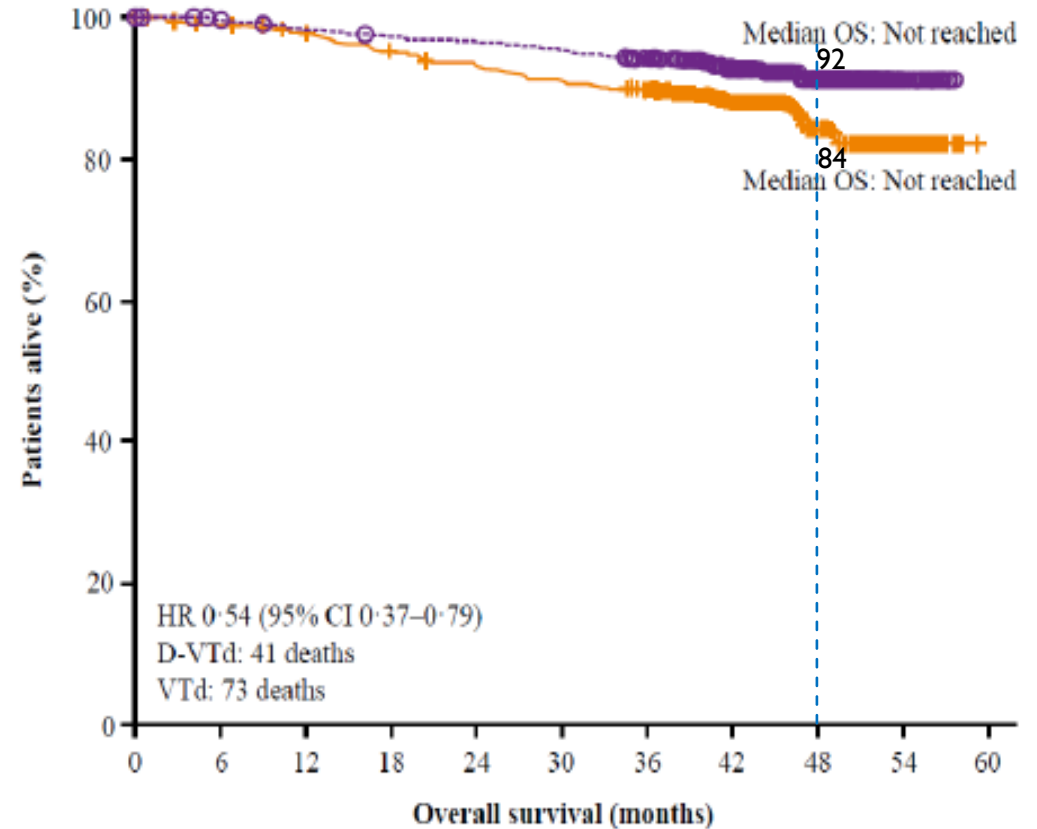
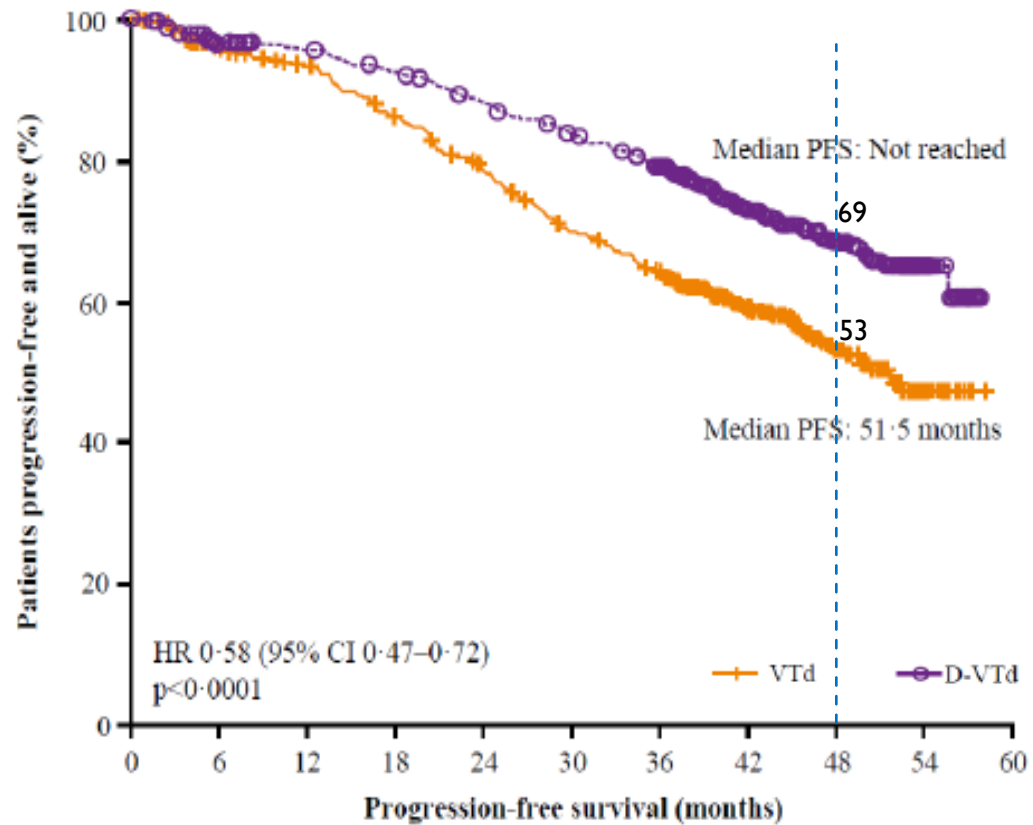
	D-VTd (n=543)	VTd (n=542)	p value*
<b>Overall response</b>			
Percentage (95% CI)	92.6% (90.1-94.7)	89.9% (87.0-92.3)	0.11
<b>Response</b>			
Stringent complete response	157 (29%)	110 (20%)	0.0010
Complete response or better	211 (39%)	141 (26%)	<0.0001
<b>MRD-negative status (10<sup>-3</sup>)†</b>			
MRD negative regardless of response	346 (64%)	236 (44%)	<0.0001

→ Todos subgrupos salvo:  
ISS III (29 vs 27%) y  
Alto R cit. (24 vs 28%)

Subgroup	VTd Minimal residual disease negative, n (%)	D-VTd	Odds Ratio (95% CI)
ISS disease stage			
I	103 (45.2)	137 (67.2)	2.48 (1.68-3.67)
II	96 (41.2)	155 (60.8)	2.21 (1.54-3.18)
III	37 (45.7)	54 (64.3)	2.14 (1.15-4.00)
Cytogenetic profile at trial entry			
High risk	38 (44.2)	49 (59.8)	1.88 (1.02-3.46)
Standard risk	197 (43.4)	296 (64.3)	2.35 (1.80-3.07)

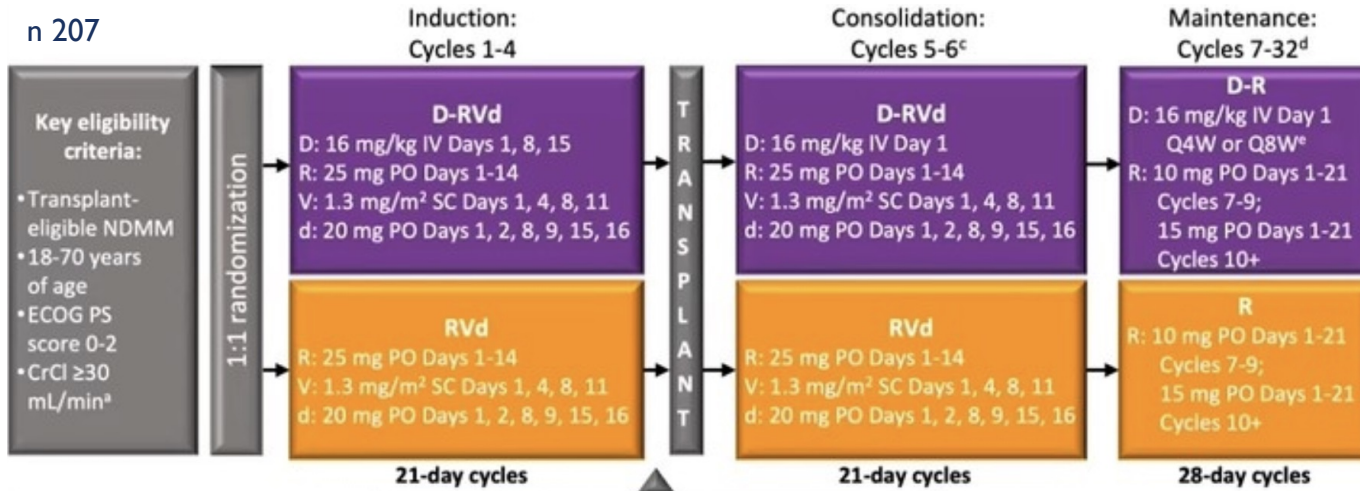
# CASSIOPEIA

FU 44,5m

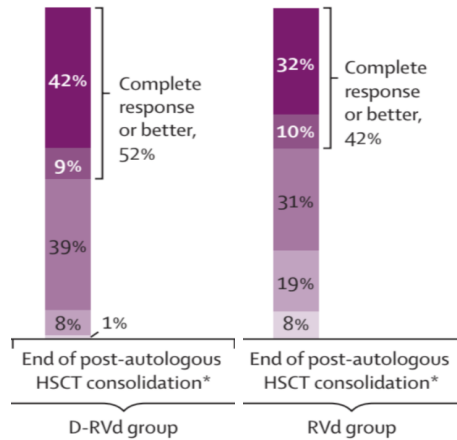


# GRIFFIN

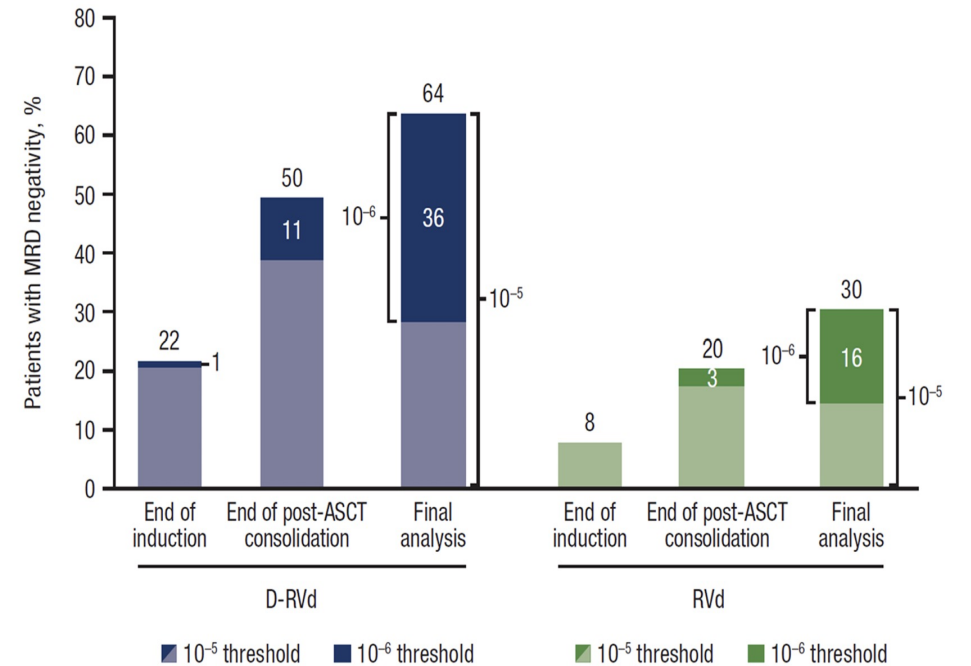
n 207



■ Stringent complete response   
 ■ Complete response   
 ■ Very good partial response  
■ Partial response   
 ■ Stable disease, progressive disease, or not evaluable

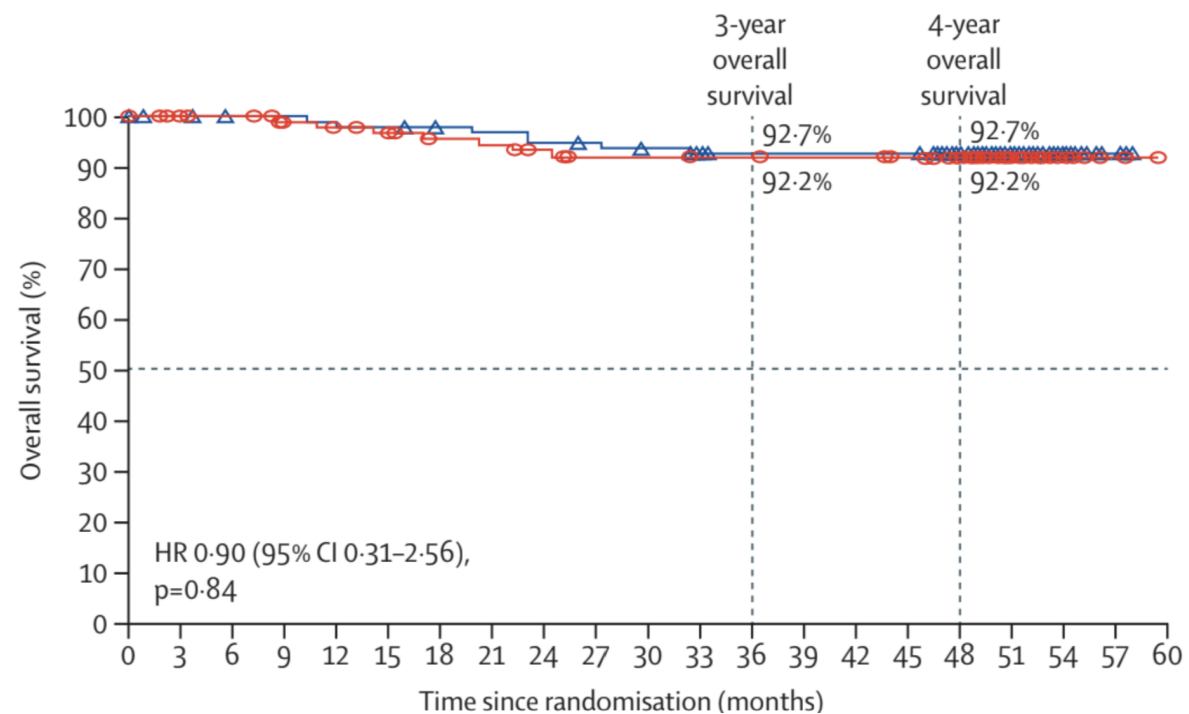
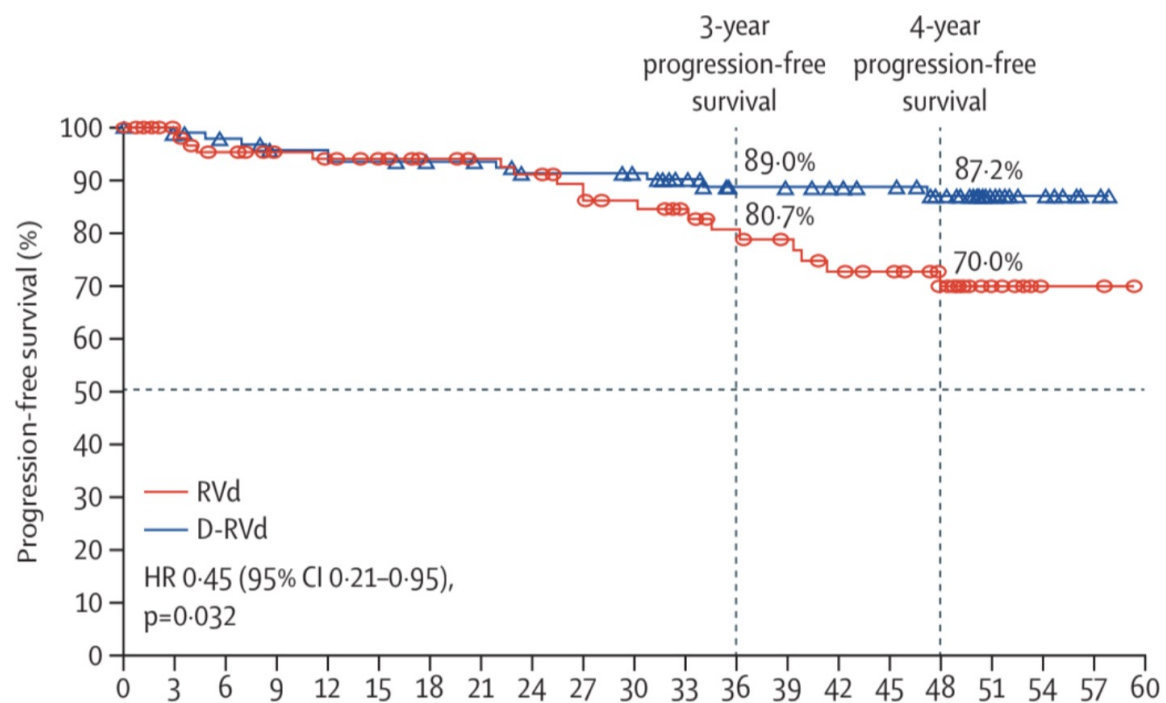


## ■ Fase 2. Mediana 60a (14% ISS III, 15% alto R)

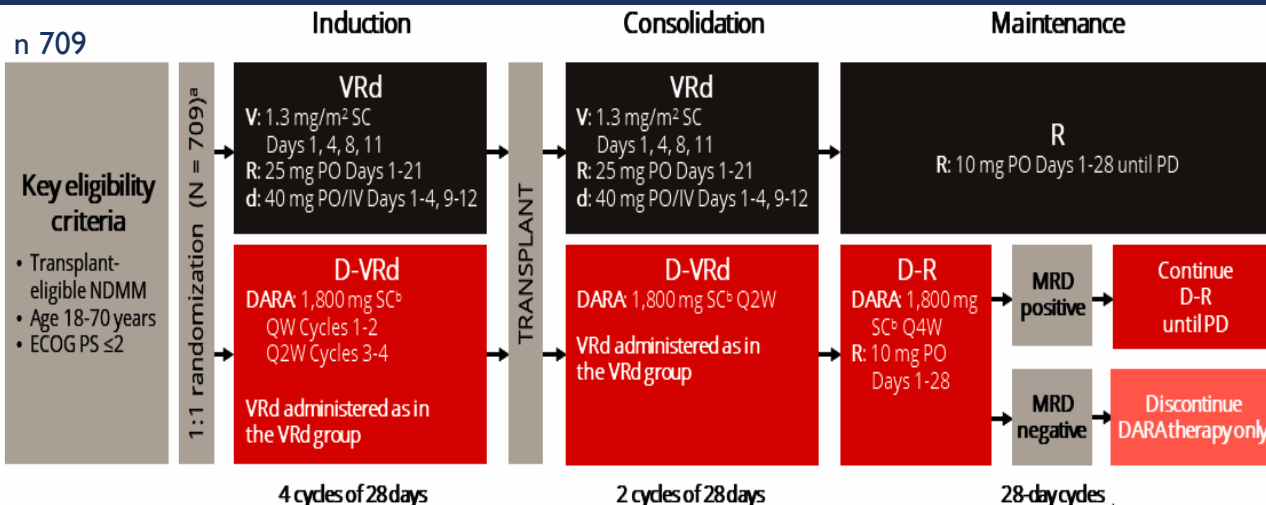


# GRIFFIN

FU 49,6m

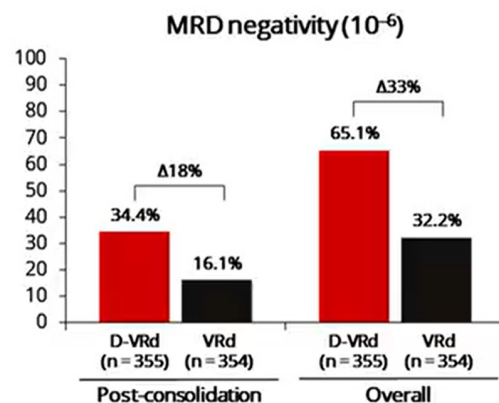
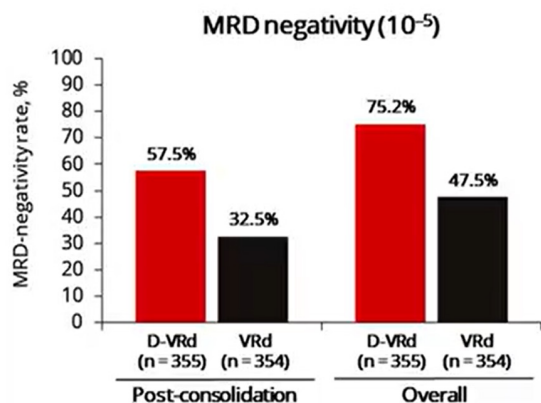


# PERSEUS



- Fase 3. Mediana 65a (15% ISS III, 22% alto R)

Variable	D-VRd (N=355)	VRd (N=354)	P Value*
Overall response — no. (% [95% CI])	343 (96.6 [94.2–98.2])	332 (93.8 [90.7–96.1])	—
Response — no. (%)			
Stringent complete response	246 (69.3)	158 (44.6)	—
Complete response or better — no. (%)	312 (87.9)	248 (70.1)	<0.001



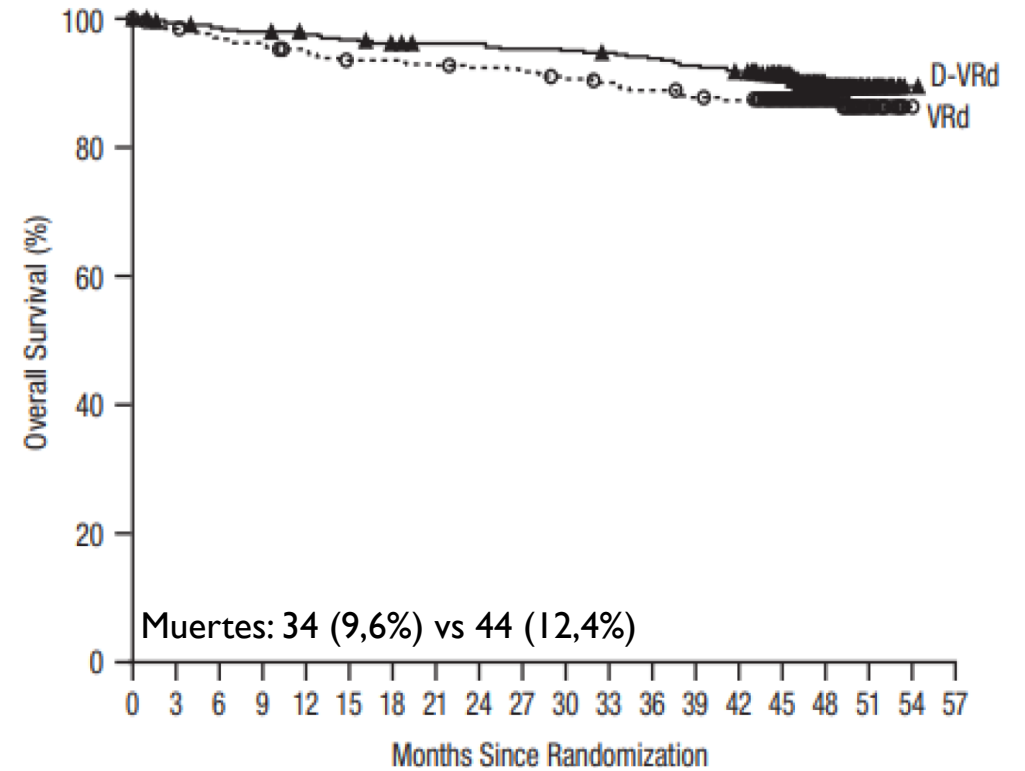
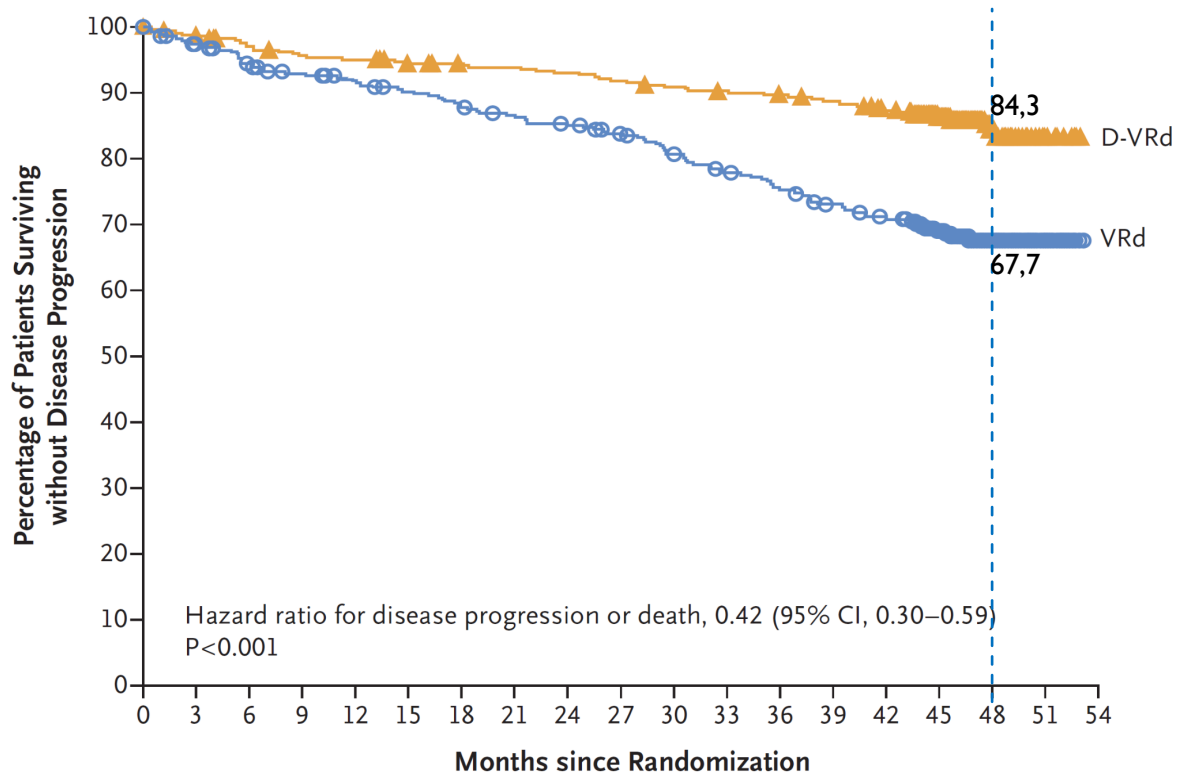
Subgroup	VRd no. of patients with minimal residual disease negativity/total no. (%)	D-VRd no. of patients with minimal residual disease negativity/total no. (%)	Odds Ratio (95% CI)*
ISS staging			
I	88/178 (49.4)	146/186 (78.5)	3.73 (2.36–5.89)
II	58/125 (46.4)	84/114 (73.7)	3.23 (1.87–5.58)
III	21/50 (42.0)	37/55 (67.3)	2.84 (1.28–6.29)
Cytogenetic risk			
Standard risk	128/266 (48.1)	204/264 (77.3)	3.67 (2.52–5.33)
High risk	37/78 (47.4)	52/76 (68.4)	2.40 (1.24–4.63)
Indeterminate	3/10 (30.0)	11/15 (73.3)	6.42 (1.09–37.73)

0.1 1 10  
 ← VRd Better | D-VRd Better →

Sostenida >12m: 64,8 vs 29,7%

# PERSEUS

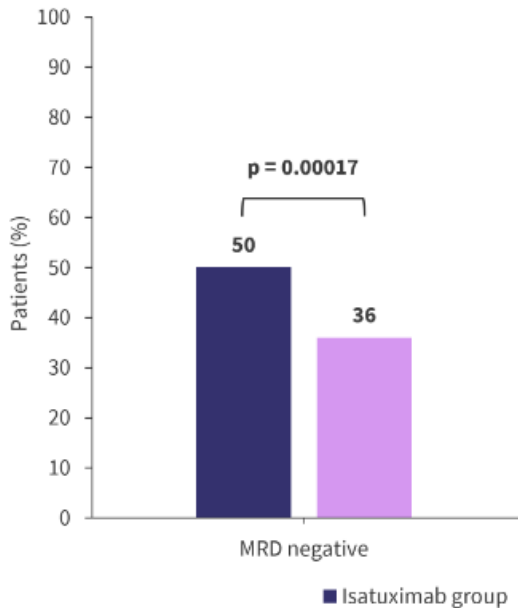
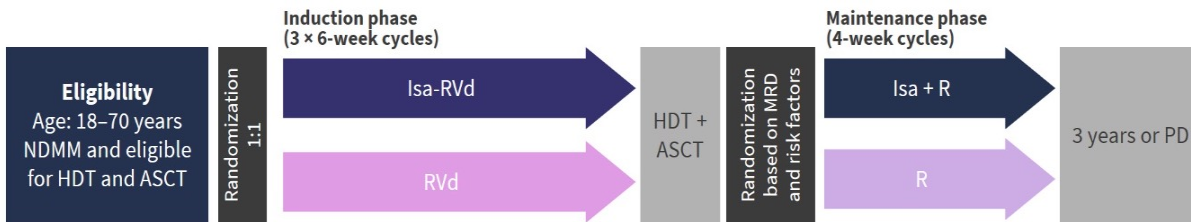
FU 47,5m



\*Rama mantenimiento DR → 64,3% han suspendido D

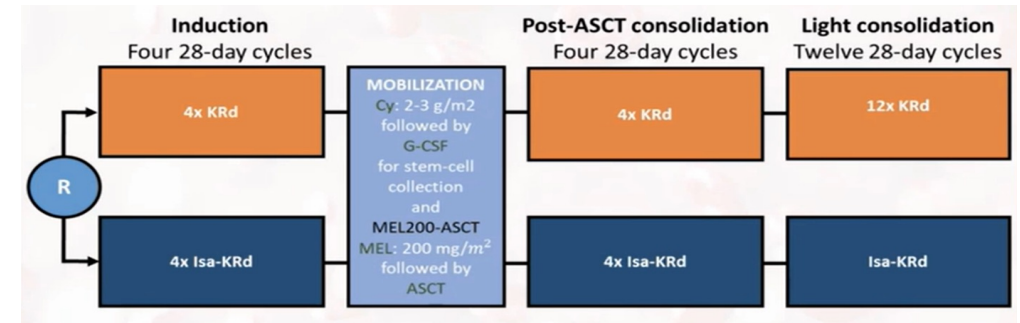
# OTROS RANDOMIZADOS EN CANDIDATOS A TPH

## ■ GMMG-HD7 (fase 3). n 660, 59a; 19% alto R

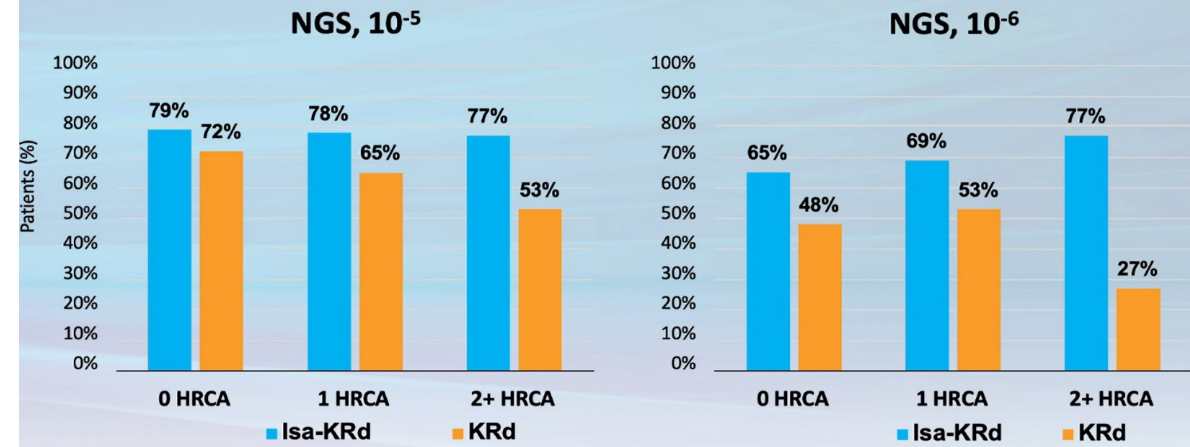


- Post inducción
- VGPR+ 77 vs 61%
- VGPR+EMR-: 47 vs 32%

## ■ ISKIA (fase 3). n 302, 61a; 19% alto R



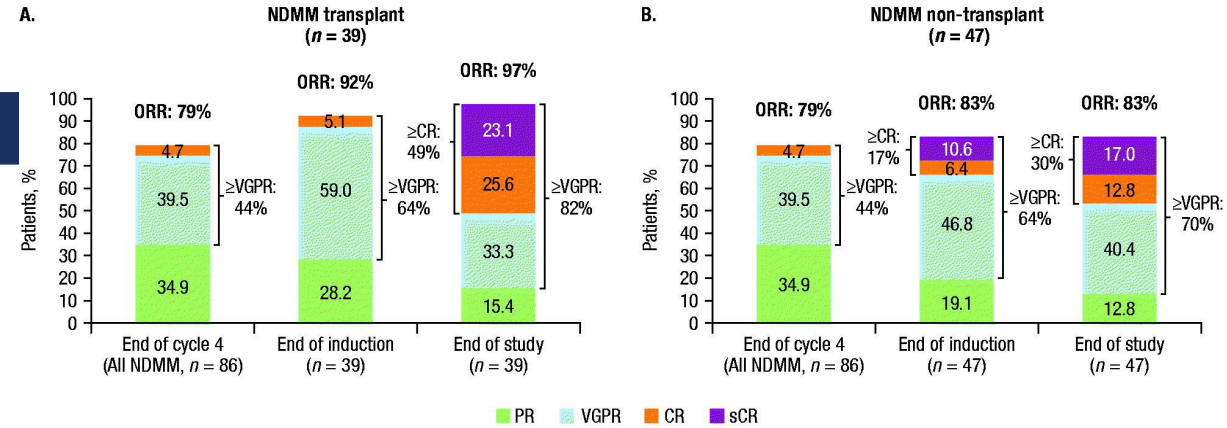
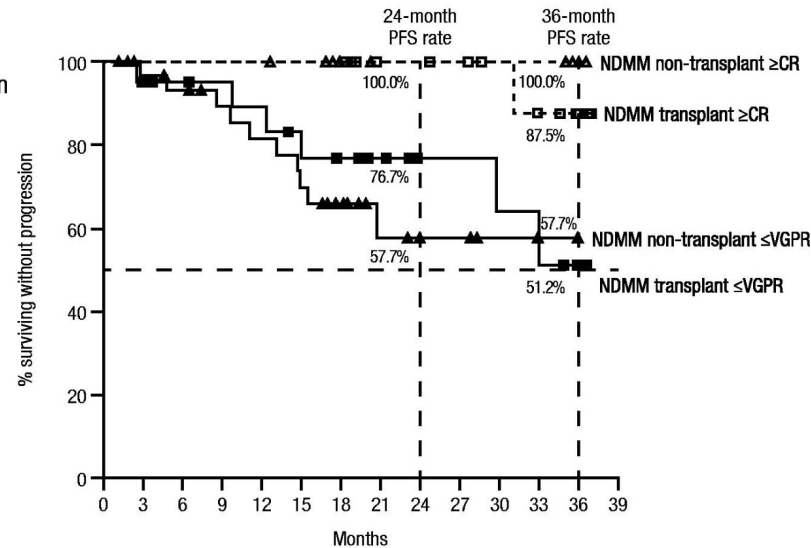
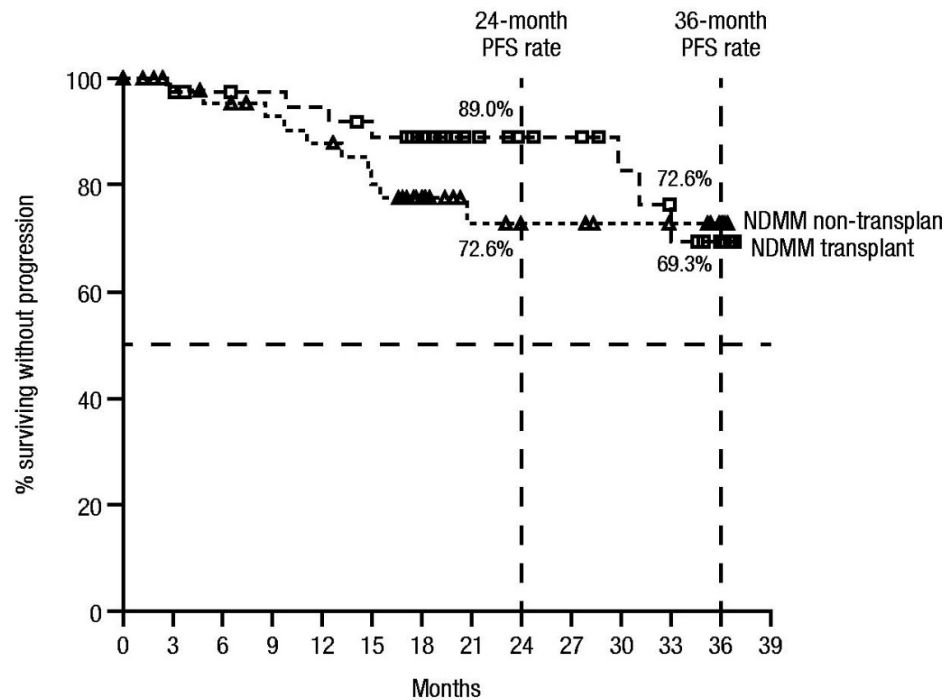
### Post-consolidation MRD negativity by NGS Subgroup analysis by cytogenetic risk



# DARATUMUMAB + CYBORD (EN MM)

■ LYRA (fase 2 una rama); FU 35,7m

■ N 101 **39 NDMM TE** **48 NDMM NTE** **14 RRMM**



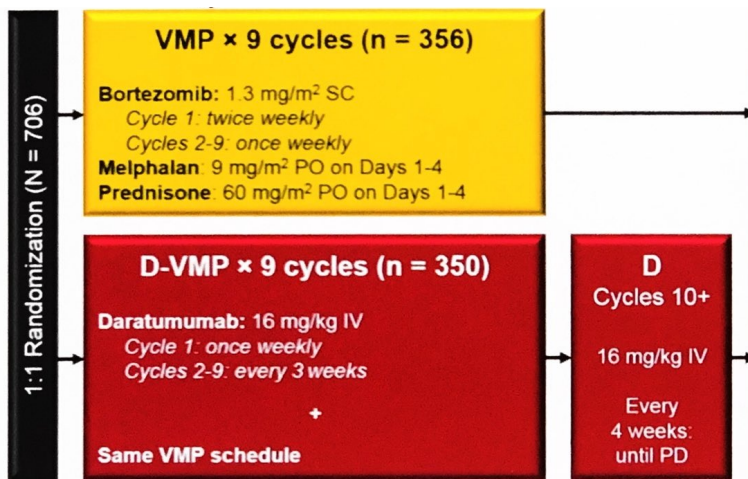


# ESTUDIOS MÁS RELEVANTES

NO CANDIDATOS A TPH (INCLUSIÓN ANTI-CD38 EN 1<sup>a</sup>)



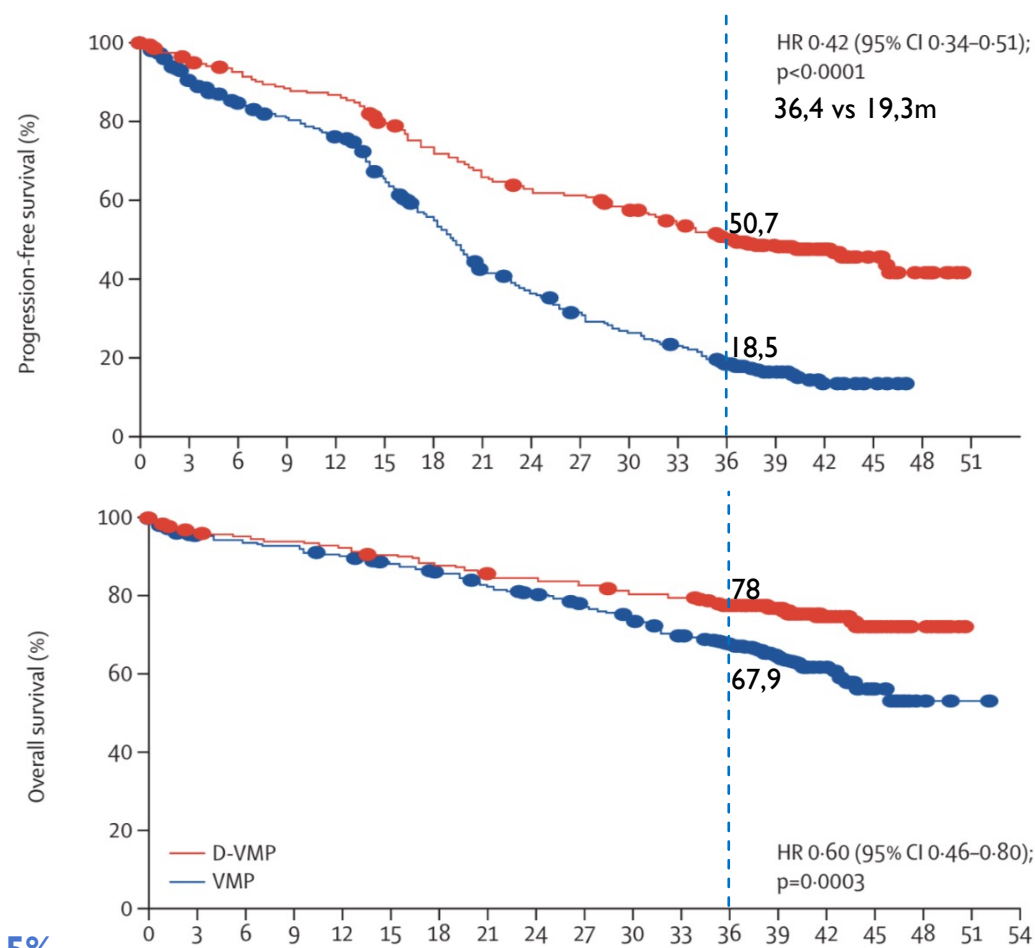
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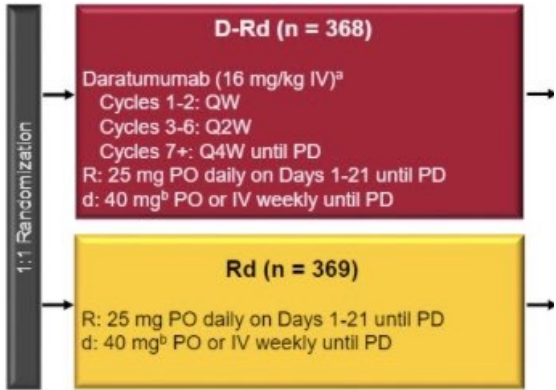
- Fase 3
- 7Ia (40-93)
- FU 40,1m

	D-VMP group (n=350)	VMP group (n=356)	p value
Overall response (%; 95% CI)	318 (90.9%; 87.3-93.7)	263 (73.9%; 69.0-78.4)	<0.0001
Complete response or better	160 (46%)	90 (25%)	<0.0001
Stringent complete response	81 (23%)	28 (8%)	..
Negative status for minimal residual disease	99 (28%)	25 (7%)	<0.0001

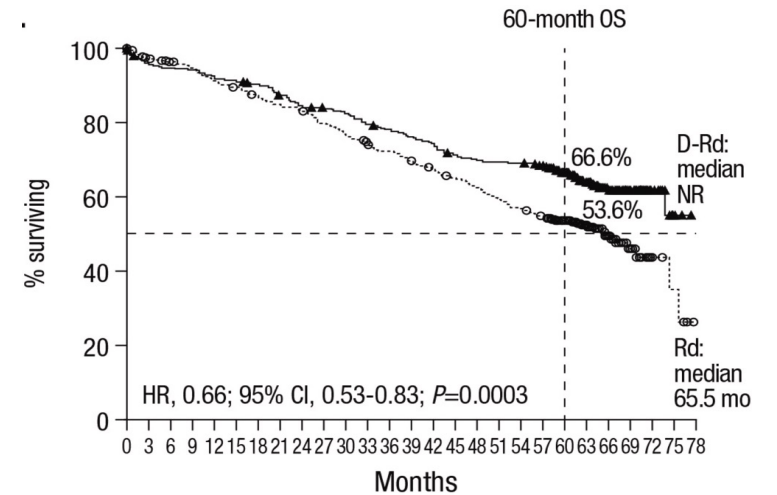
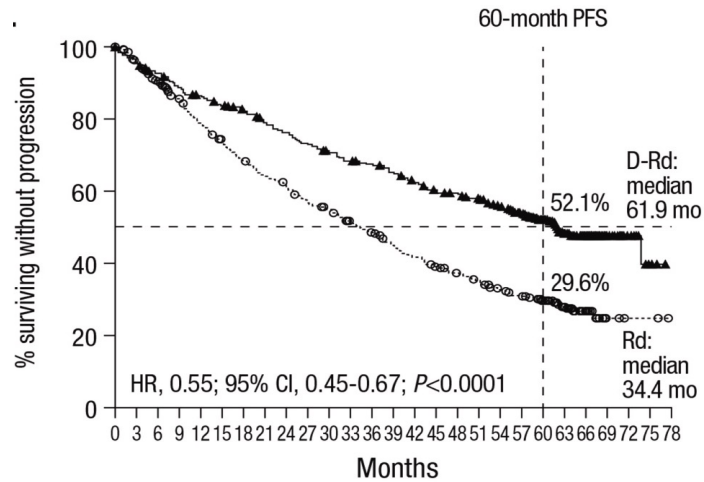
**\*No frágiles: SLP 45,7 vs 19,1m / SG 83,6% vs 74,5%**  
**\*Frágiles: SLP 32,9 vs 19,5m / SG 71,4% vs 59%**



# MAIA



- Fase 3
- 73a
- FU 64,5m



**\*No fráguiles: SLP HR 0,48**  
**\*Fráguiles: SLP HR 0,62**

	D-Rd	Rd		HR (95% CI)
	Median PFS (mo)	Median PFS (mo)		
Age ≥75 years	54.3	31.4		0.59 (0.44-0.79)
ISS stage III	42.4	24.2		0.61 (0.43-0.86)
Renal insufficiency (CrCl ≤60 mL/min)	56.7	29.7		0.55 (0.41-0.75)
High cytogenetic risk <sup>a</sup>	45.3	29.6		0.57 (0.34-0.96)

0.1      0.5      1.0  
 ← Favours D-Rd      Favours Rd →

	Daratumumab plus lenalidomide and dexamethasone group (n=368)	Lenalidomide and dexamethasone group (n=369)	p value
Overall response	342 (92.9%; 89.8-95.3)	301 (81.6%; 77.2-85.4)	<0.0001
Complete response or better	188 (51%)	111 (30%)	<0.0001
Stringent complete response	130 (35%)	56 (15%)	<0.0001
Negative status for minimal residual disease* <sup>13</sup>	114 (31%)	38 (10%)	<0.0001

Lancet Oncol 2021;22(11):1582-1596  
 Blood 2022;140(Suppl 1): 7297-7300  
 Leukemia 2022;36(4):1066-1077  
 Hemasphere 2023;7(Suppl): 14-15  
 Blood 2022;140(Suppl 1): 10150-3

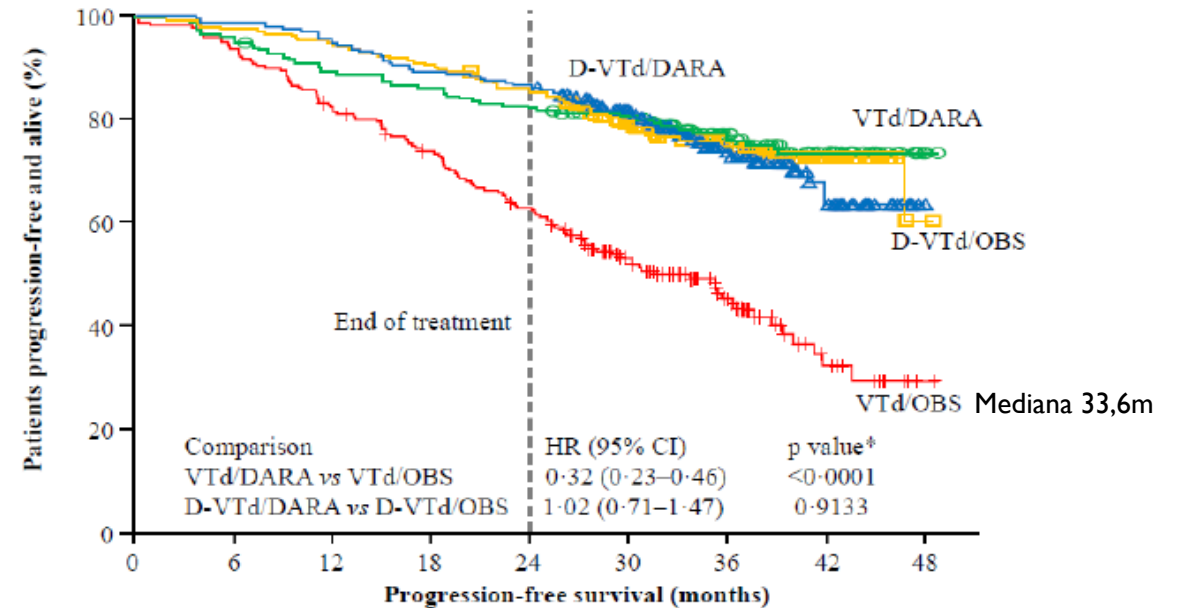
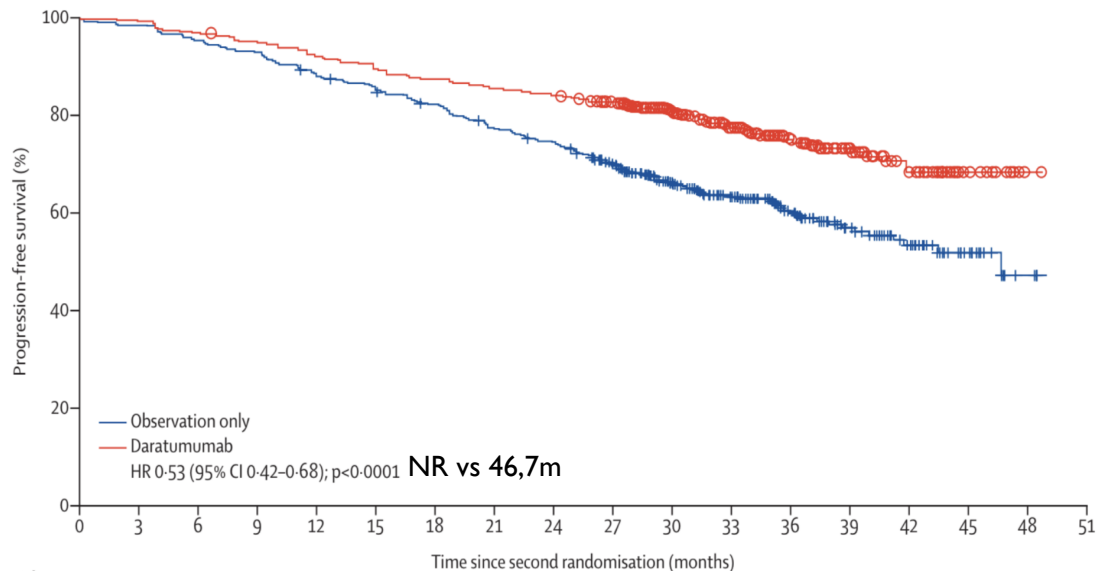


# DURACIÓN DEL ANTI-CD38



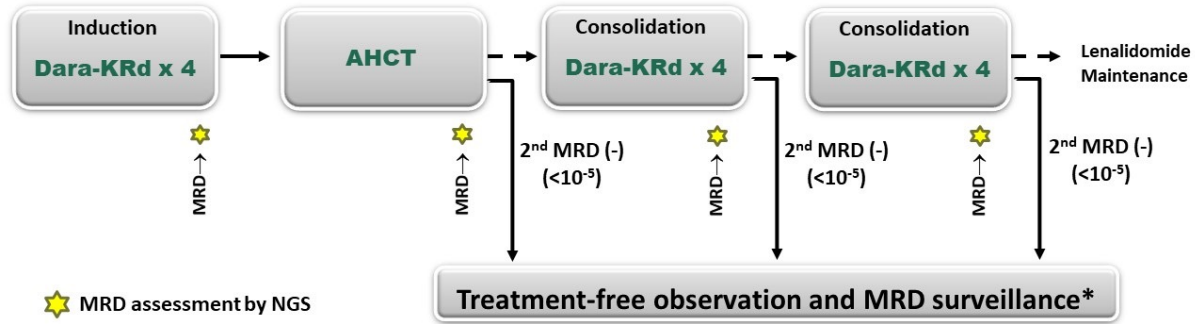
# CASSIOPEIA, SEGUNDA RANDOMIZACIÓN

FU 35,4m desde segunda R

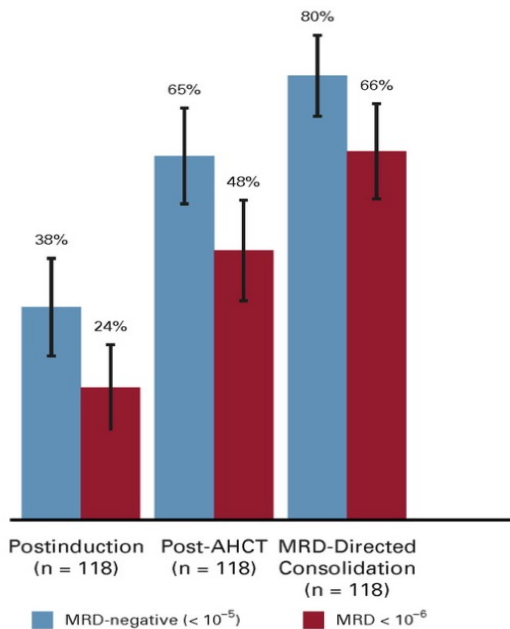


→ Si usamos daratumumab en inducción, no se observa beneficio de mantenimiento  
...Por lo tanto, su uso podría ser breve

# MASTER



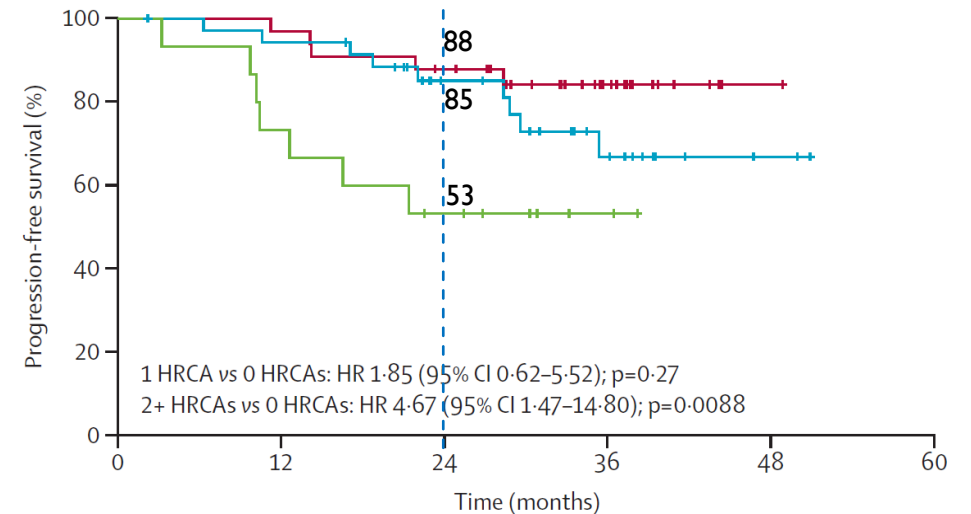
★ MRD assessment by NGS



	SLP3a	SG3a
0 HRCA	88%	94%
1 HRCA	80%	94%
2 HRCA	50%	75%

→71% entraron a observación sin tratamiento (66/82/63%)

- Fase 2; N 118
- 43% 0 HRCA, 37% 1 HRCA, 20% 2+ HRCA
- FU 42,2m (32,7m desde inicio observación)



... desde suspensión (SG2a 97/93/100%)

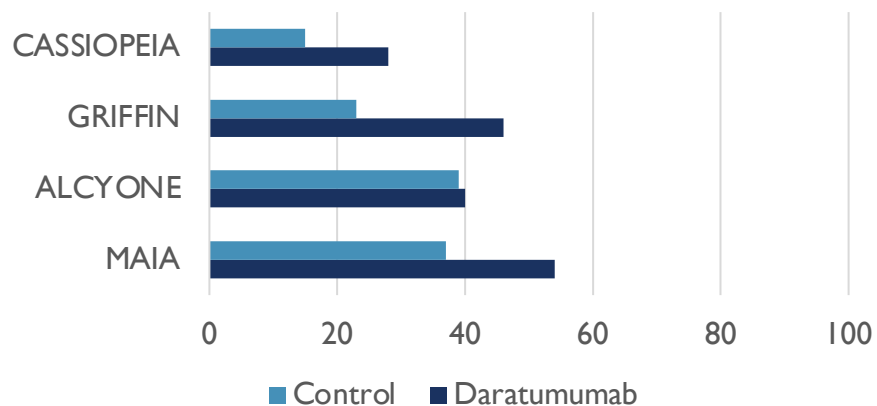


OTROS ANÁLISIS CLAVE PARA DECIDIR

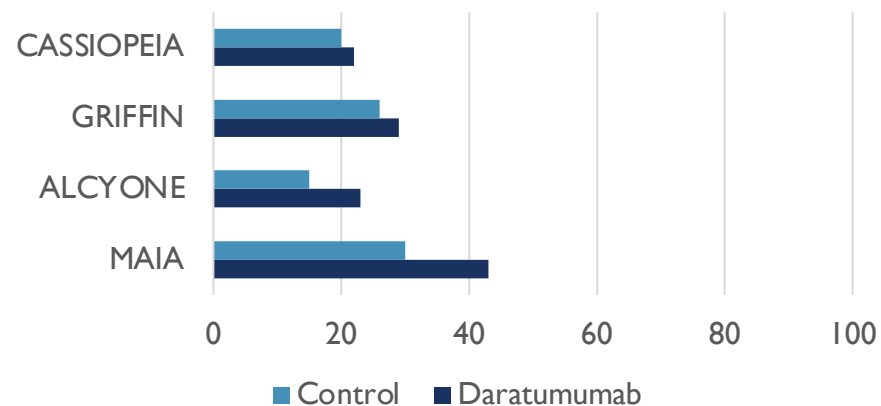


# EVENTOS ADVERSOS

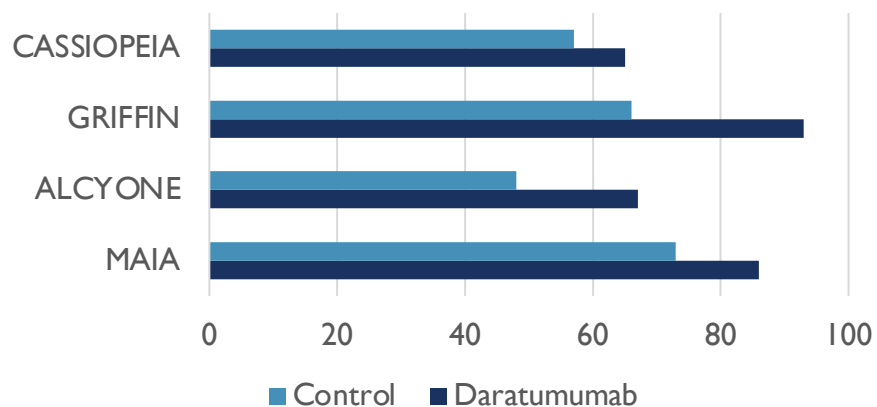
## Neutropenia G3+



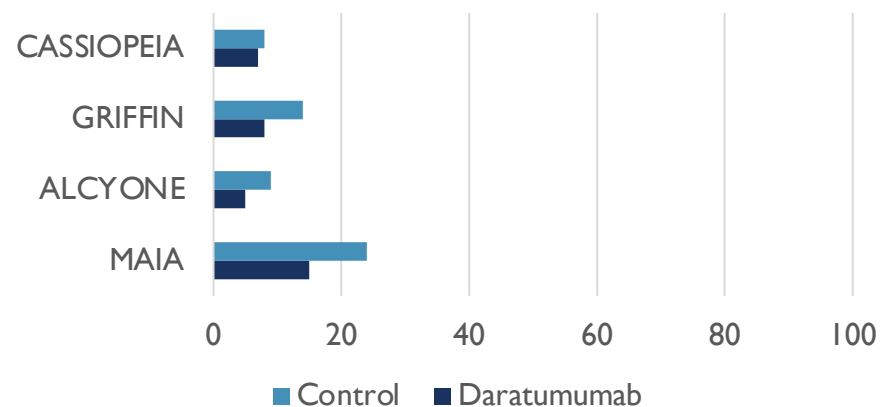
## Infecciones G3+



## Infecciones cualquier grado



## Descontinuación por EA



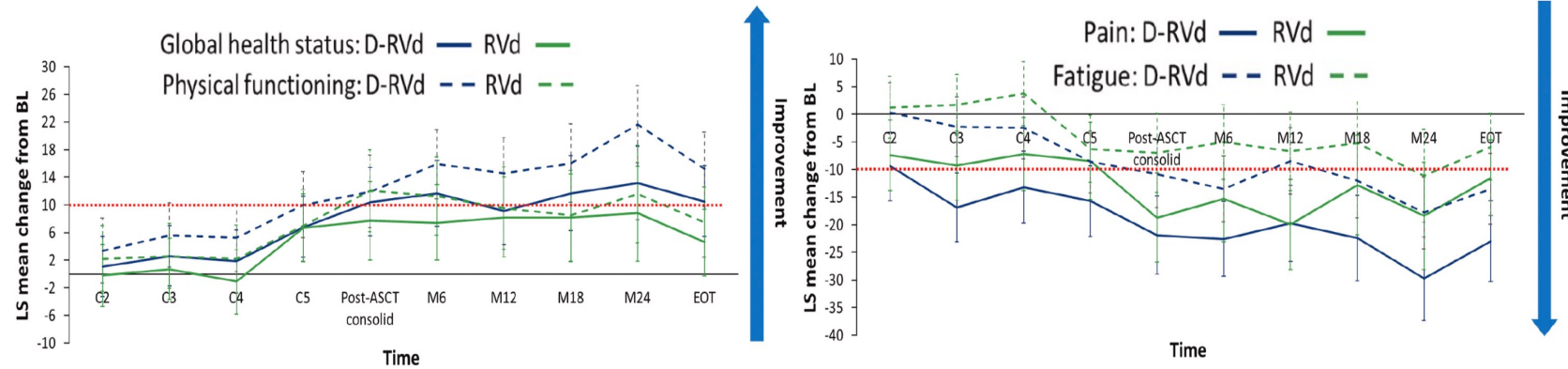
# CALIDAD DE VIDA

## CASSIOPEIA

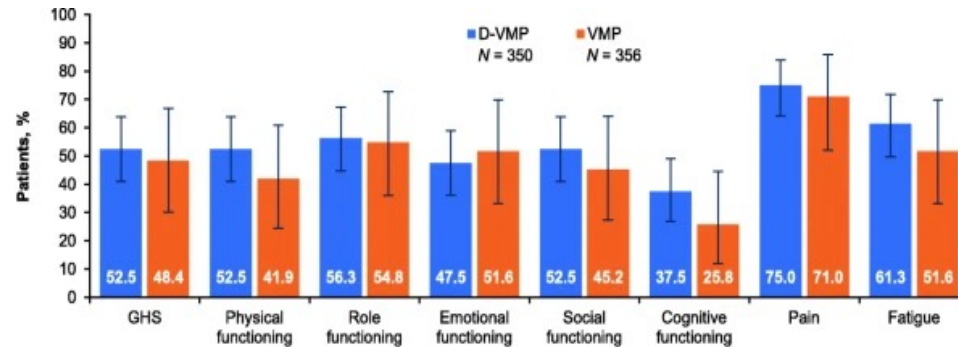
	Post-consolidation scores		p value*
	D-VTd group	VTd group	
<b>EORTC QLQ-C30</b>			
Global health status	9.7 (7.4 to 11.9)†	8.7 (6.5 to 11.0)†	0.45
Emotional	13.0 (10.4 to 15.5)†	9.5 (6.9 to 12.1)	0.013
Cognitive	-5.0 (-7.6 to -2.4)	-7.9 (-10.6 to -5.3)	0.036
Pain	-23.3 (-26.6 to -20.0)†	-19.7 (-23.0 to -16.3)†	0.042
Constipation	-3.2 (-7.3 to 0.9)	1.8 (-2.4 to 6.0)	0.025

Table 2: Change from baseline in patient-reported outcome instrument scores

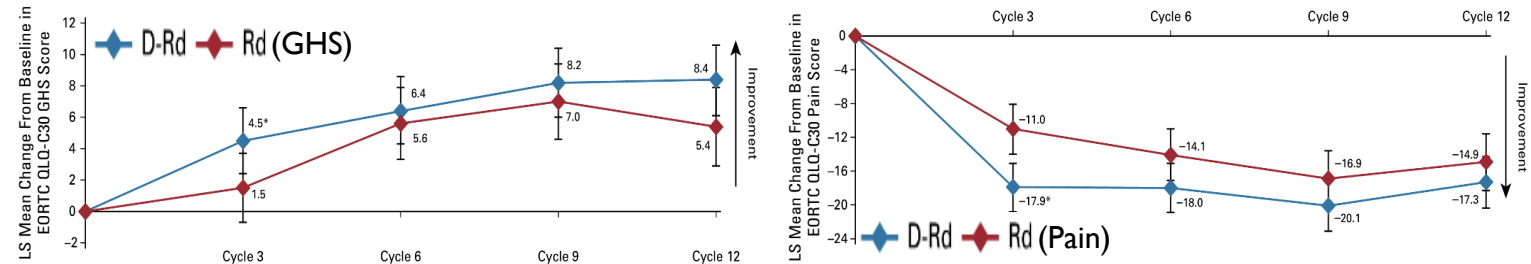
## GRIFFIN



## ALCYONE

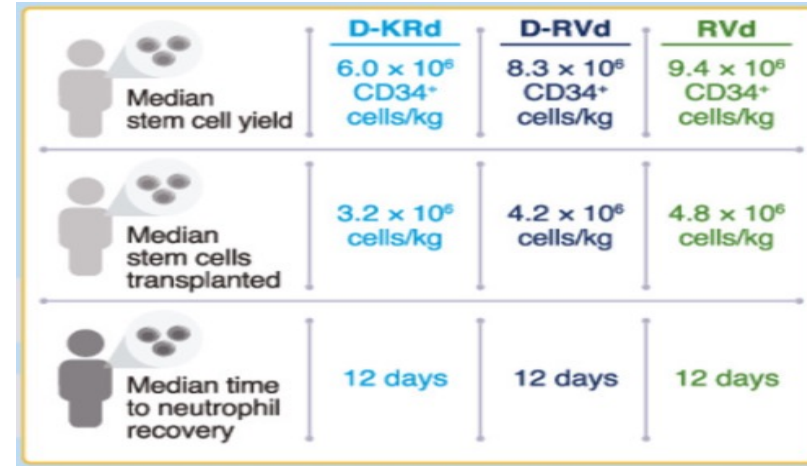
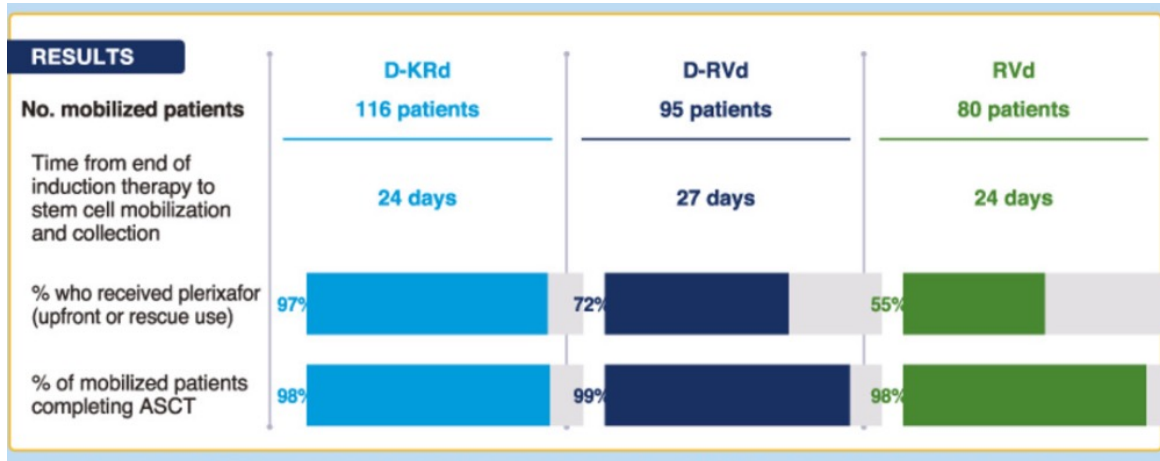


## MAIA

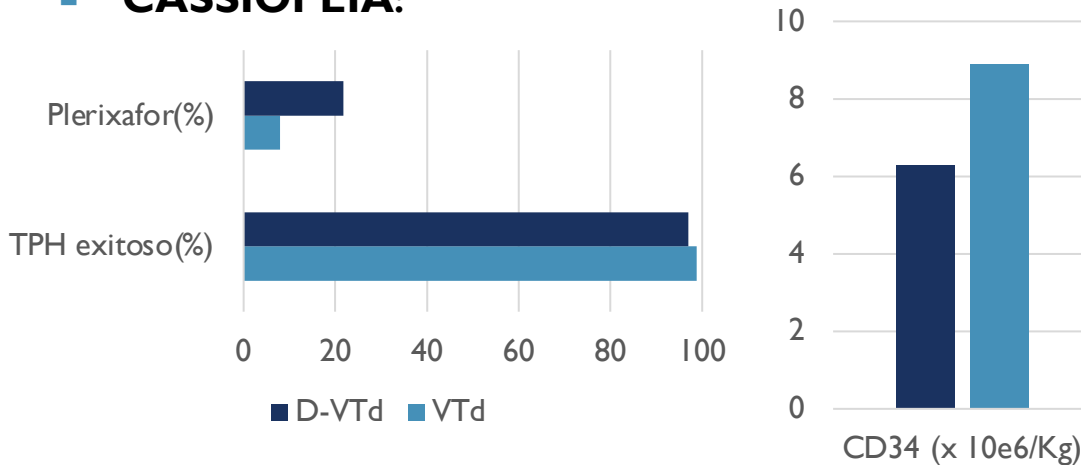


Lancet Haematol 2020;7(12):e874-e883  
 Blood. 2022;140(suppl\_1):1146-1149  
 BMC Cancer 2021;21(1):659  
 J Clin Oncol 2021;39(3):227-237

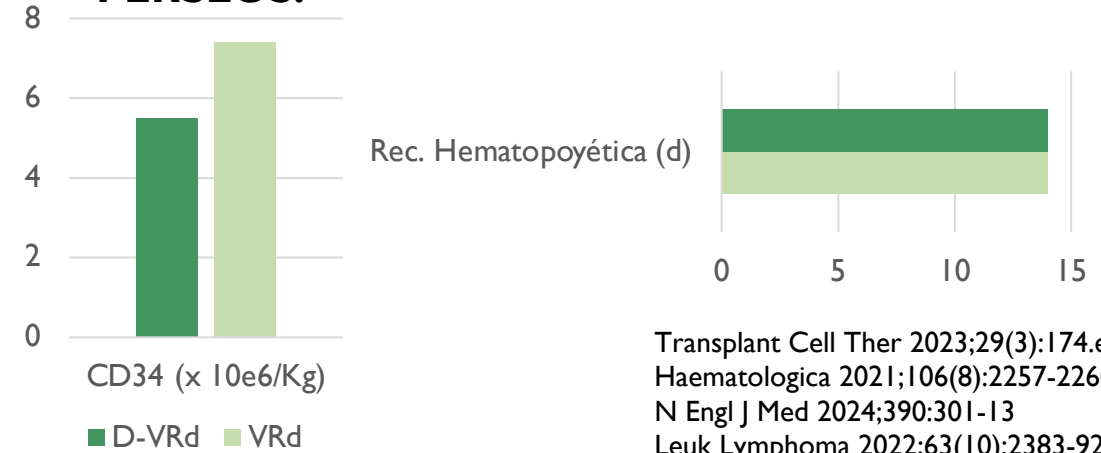
# IMPACTO DE DARATUMUMAB EN TPH



## ■ CASSIOPEIA:



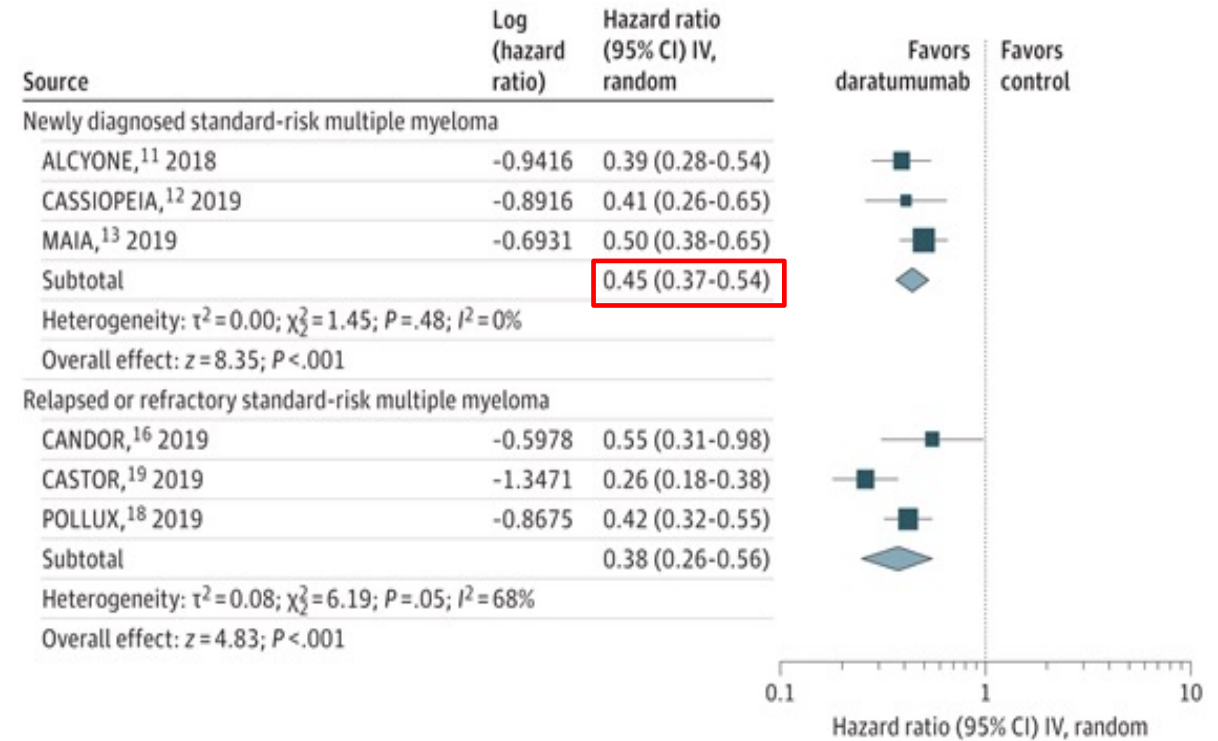
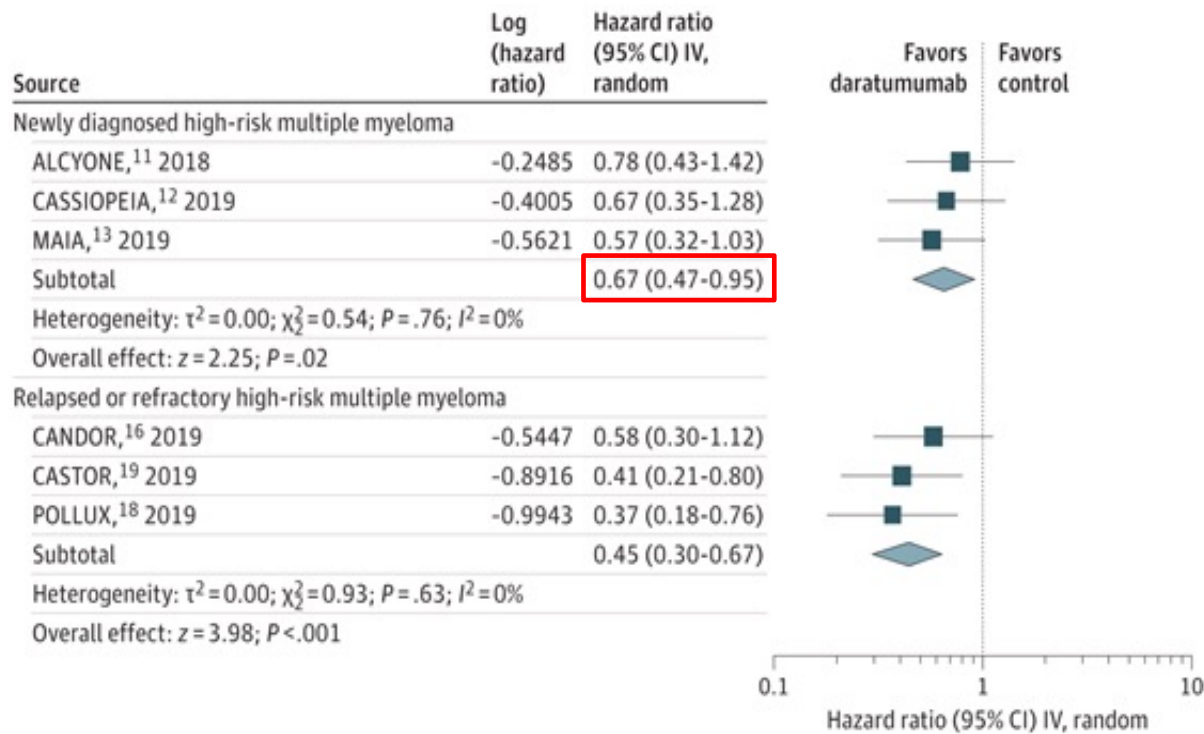
## ■ PERSEUS:



Transplant Cell Ther 2023;29(3):174.e1-10  
 Haematologica 2021;106(8):2257-2260  
 N Engl J Med 2024;390:301-13  
 Leuk Lymphoma 2022;63(10):2383-92

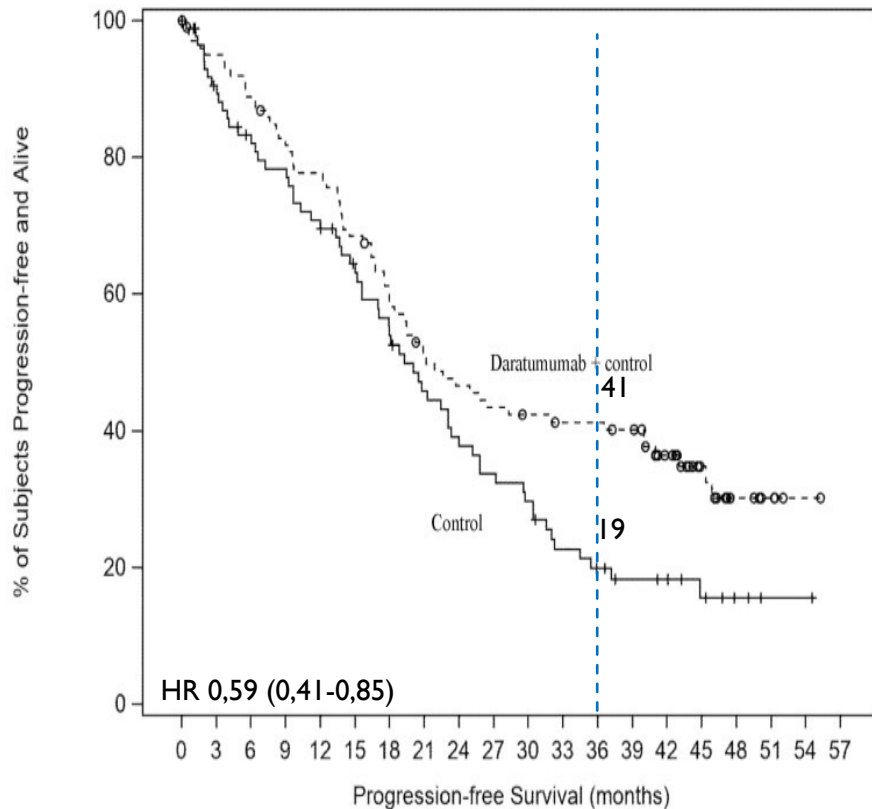
# ¿Y SIRVE EN ALTO RIESGO?

- Metanálisis más actualizado

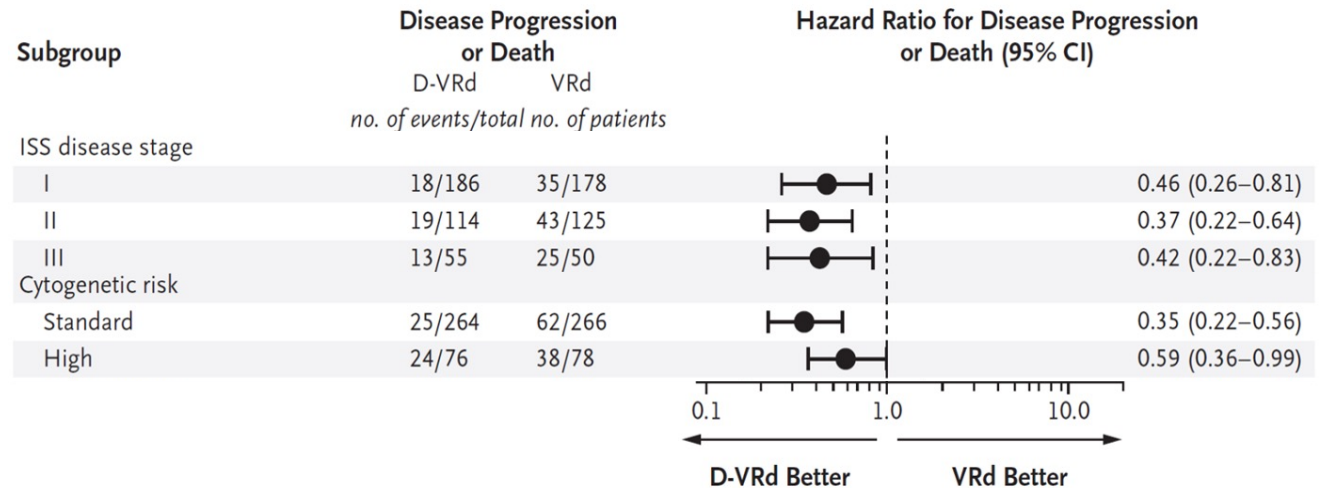


# ¿Y SIRVE EN ALTO RIESGO?

## ■ MAIA+ALCYONE

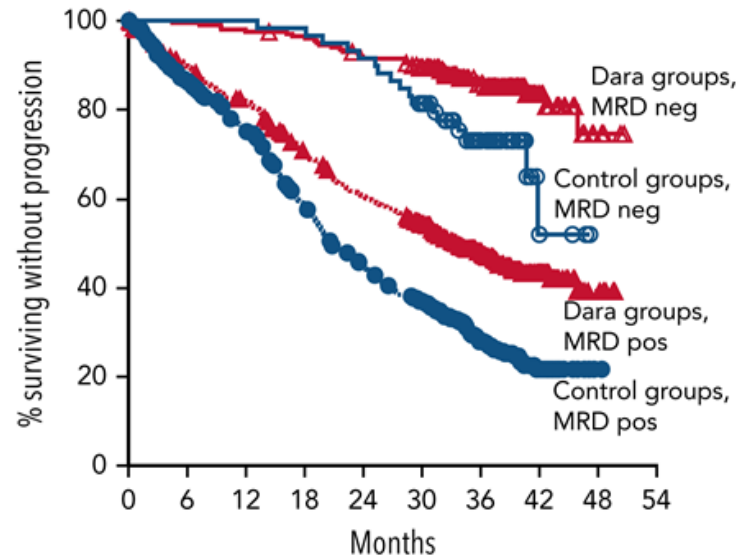
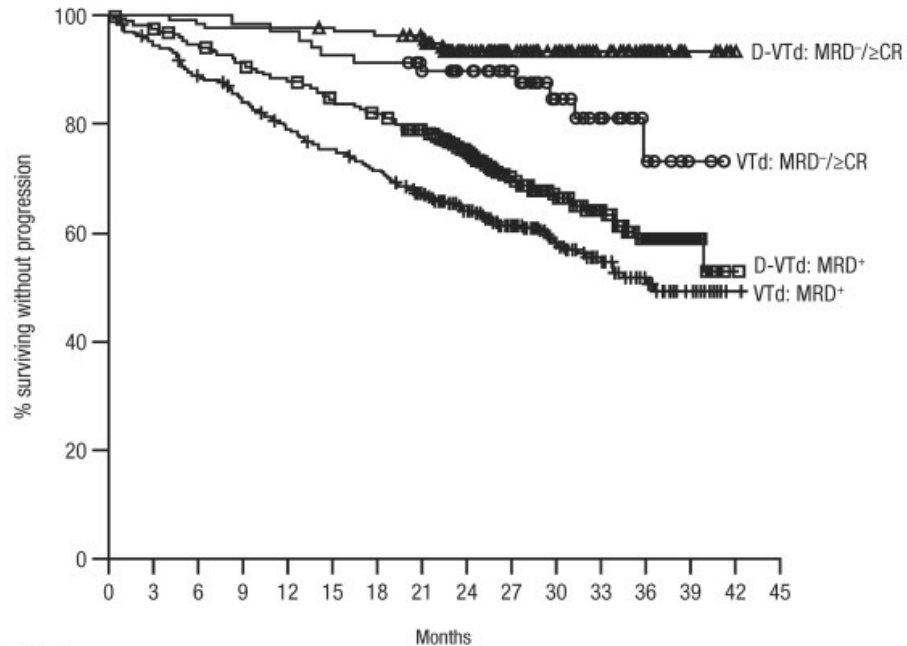


## ■ PERSEUS



# SI LO IMPORTANTE ES LOGRAR EMR-... ¿IMPORTA CON QUÉ LO LOGRO?

Figure: Landmark PFS analysis of pts progression-free at 1 year post-induction for pts who achieved 1 year sustained MRD negativity and pts who did not by treatment group



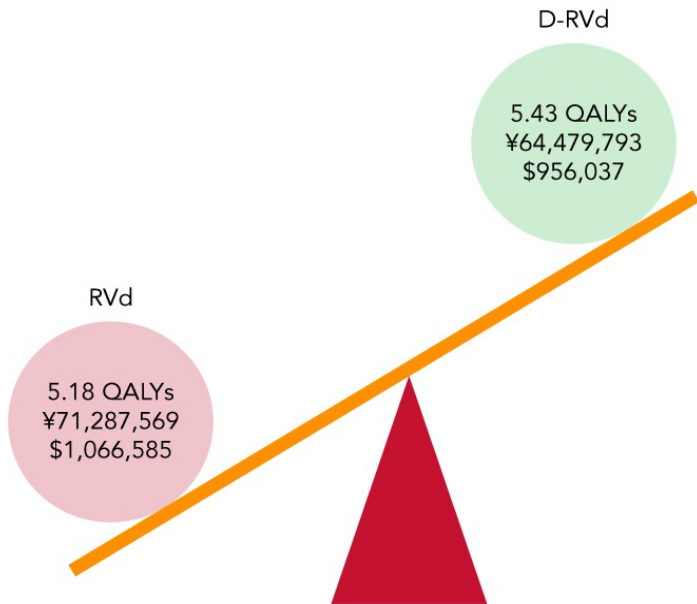
Groups	HR (95% CI)	P
Dara groups, MRD neg vs Control groups, MRD neg	0.51 (0.28-0.92)	.0253
Dara groups, MRD neg vs Dara groups, MRD pos	0.21 (0.14-0.30)	<.0001
Dara groups, MRD neg vs Control groups, MRD pos	0.12 (0.09-0.18)	<.0001

- CASSIOPEIA
- EMR- sostenida 1a : 50,1% vs 30,1%

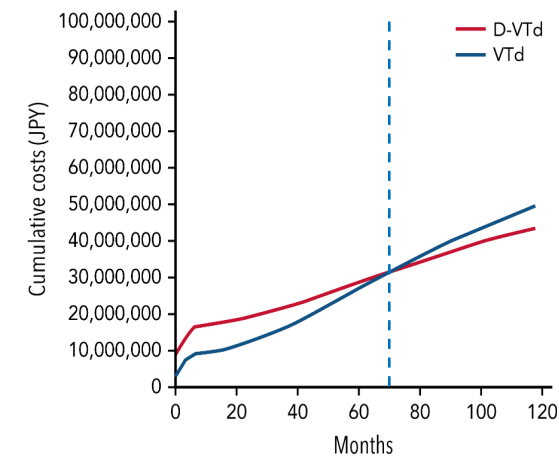
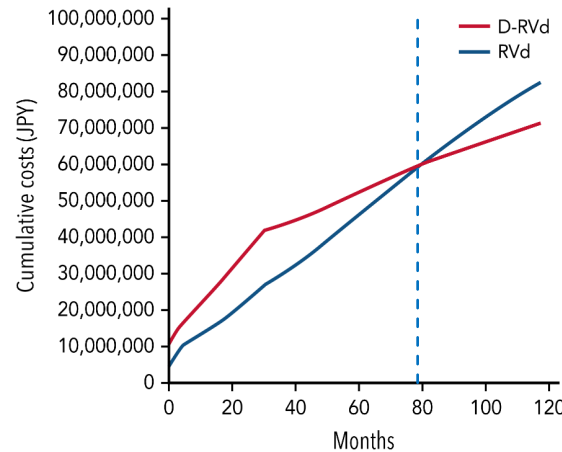
- Combinado MAIA/ALCYONE
- EMR-: 27,9% vs 8,1%
- Sostenida 1a: 12,4% vs 2,6%

# ¿Y SI GUARDAMOS DARATUMUMAB PARA DESPUÉS?

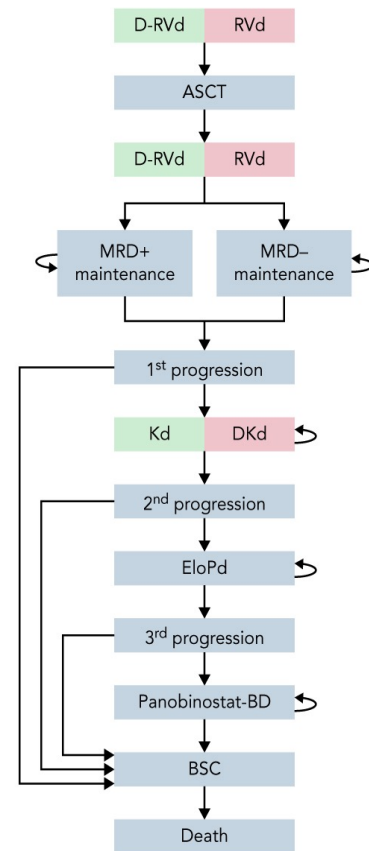
- Análisis costo-efectividad, horizonte 10 años
- Modelo Markov usando EMR para predecir SLP
- Basado en CASSIOPEIA y GRIFFIN



para D-VTd vs VTd:  
5,67 vs 5,42 QALY  
\$673919 vs 746903

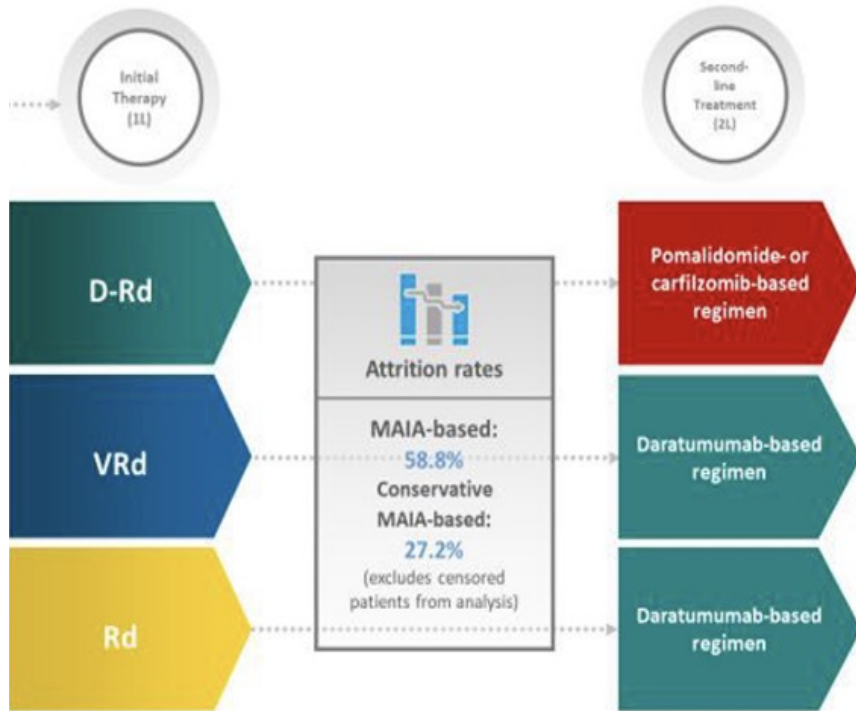


For transplant-eligible NDMM patients, first-line daratumumab dominates second-line daratumumab with lower costs and higher QALYs over 10 years.

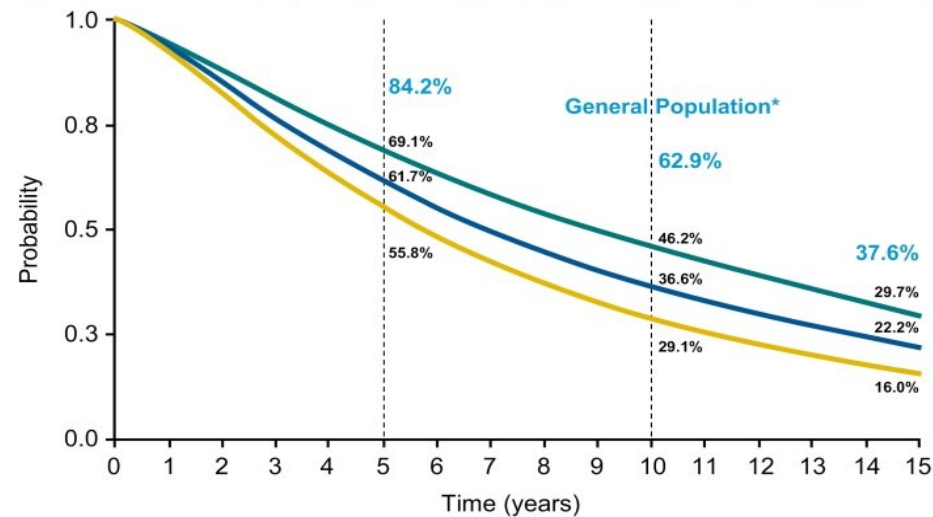


# ¿Y SI GUARDAMOS DARATUMUMAB PARA DESPUÉS?

- Modelo en no candidatos considerando tasas de desgaste



	Base Case (58.8% attrition rate)			Sensitivity Analysis (27.2% attrition rate)		
	D-Rd in 1L, POM-/CAR- in 2L	VRd in 1L, DARA- in 2L	Rd in 1L, DARA- in 2L	D-Rd in 1L, POM-/CAR- in 2L	VRd in 1L, DARA- in 2L	Rd in 1L, DARA- in 2L
OS, years	7.6 (6.75–8.83)	5.1 (4.42–6.33)	4.1 (3.33–5.33)	9.1 (8.00–10.50)	6.7 (5.92–7.92)	5.7 (4.83–7.00)
Incremental (D-Rd vs VRd or Rd), years	--	2.5 (1.00–3.75)	3.5 (1.92–4.92)	--	2.4 (0.75–4.00)	3.4 (1.67–5.08)
5-year survival rate, %	62.6 (56.7–73.3)	51.0 (47.3–60.2)	44.1 (40.1–53.2)	69.9 (62.8–80.1)	60.7 (55.5–70.3)	54.9 (49.4–65.3)
10-year survival rate, %	41.8 (39.8–45.0)	29.6 (27.3–33.0)	22.8 (20.5–26.2)	46.7 (43.1–52.3)	35.4 (31.5–40.6)	28.6 (24.4–34.1)



— Rd in 1L, DARA- in 2L — VRd in 1L, DARA- in 2L — D-Rd in 1L, POM-/CAR- in 2L

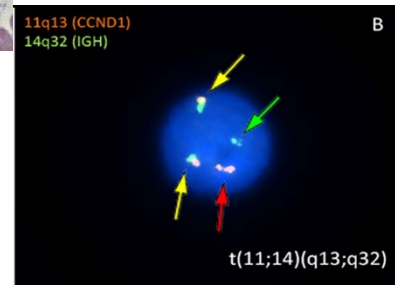
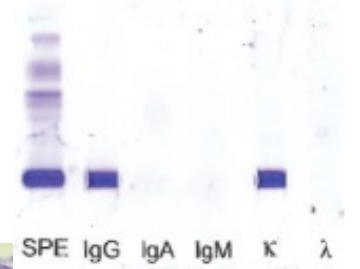
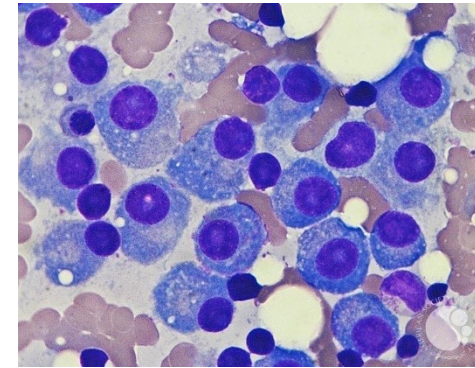
# CASO CLÍNICO



60 años

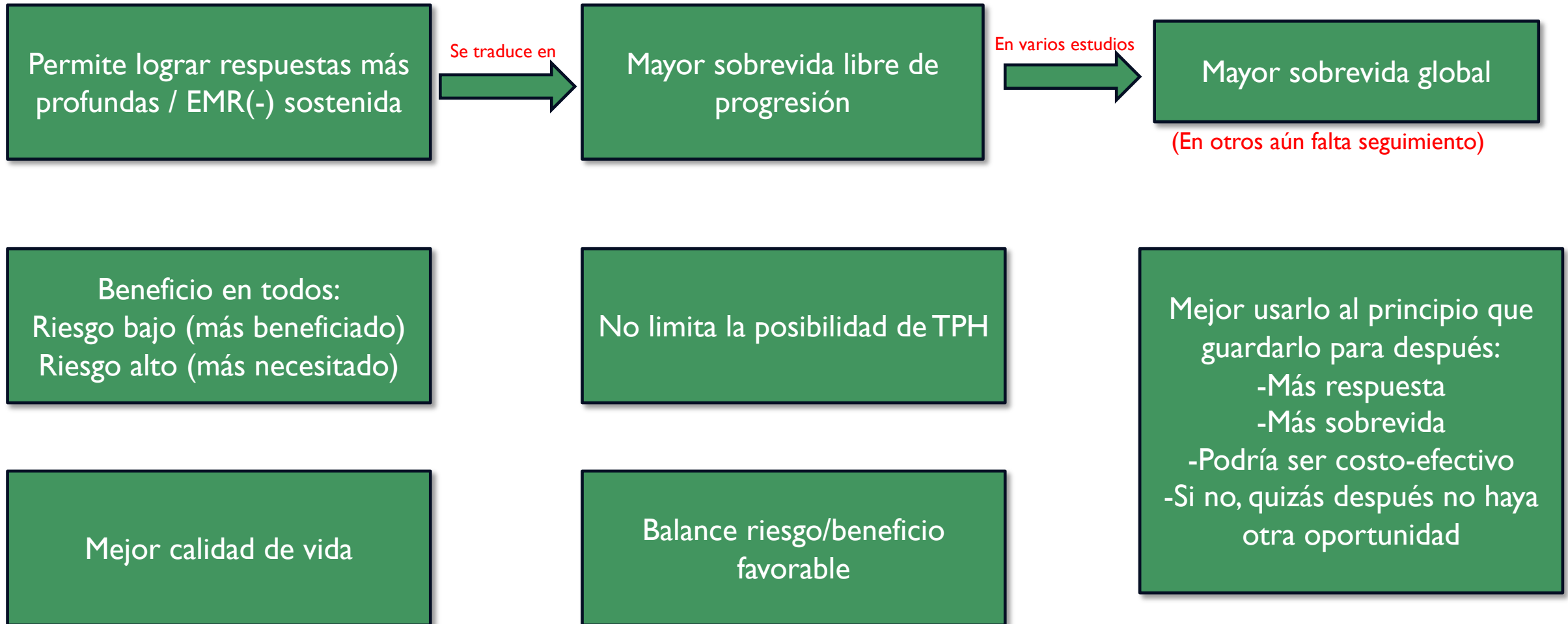


- Hb 9,5
- Función renal N
- Ca N
- B2M/albúmina N
- LDH N



→ MM riesgo estándar (R-ISS I), candidata a TPH

# DEBERÍAMOS USAR CUADRULETE / INCLUIR ANTI-CD38 EN PRIMERA LÍNEA PORQUE:



## AL USAR ANTI-CD38 EN PRIMERA LÍNEA:

**Duración breve, no en mantenimiento**

- Contiene costos; opción reutilizar

**Profilaxis infecciones**

**Acceso a EECC**

- Para los pocos pacientes que fallen