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Optimizing Diffuse Large B-Cell Lymphoma (DLBCL) Treatment: An Expert Roundtable on the Role of New and Emerging Targeted Therapies

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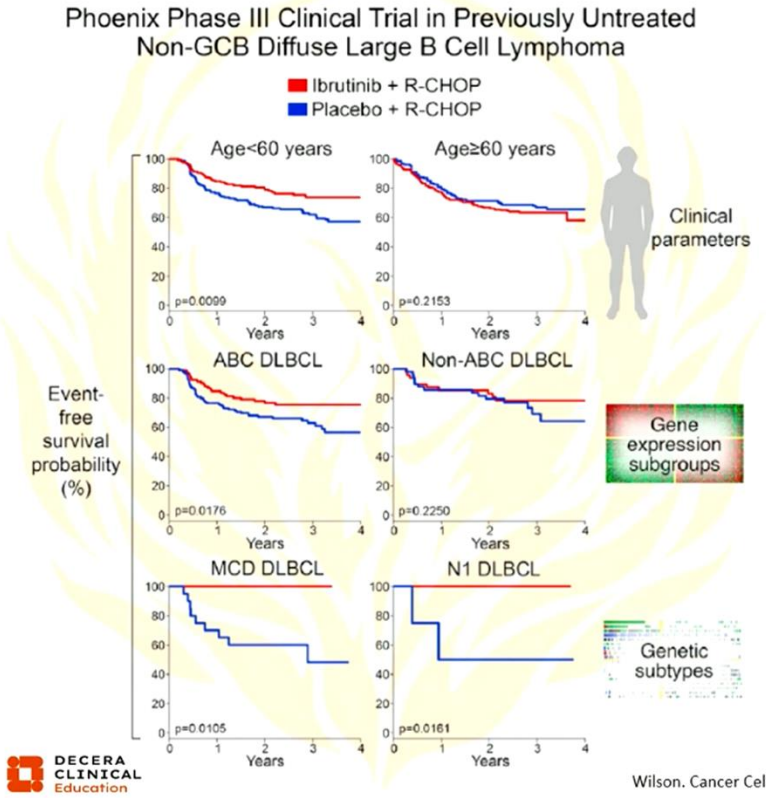
- **Medicina de Precisión e Inhibidores de BTK**
- **Biopsia Líquida y ADN Circulante (ctDNA)**
- **Alternativas terapéuticas en el campo del DLBCL R/R**

Optimizing Diffuse Large B-Cell Lymphoma (DLBCL) Treatment: An Expert Roundtable on the Role of New and Emerging Targeted Therapies

Medicina de Precisión e Inhibidores de BTK

Evidence Supporting R-CHOP + Ibrutinib in DLBCL Subsets



- Despite negative results from phase III Phoenix trial of R-CHOP ± ibrutinib, additional analyses support BTK inhibition in DLBCL patient subsets
  - Ibrutinib (BTKi) + R-CHOP is effective in younger patients with ABC DLBCL
  - DLBCL genetic subtypes differ in genotype, oncogenic mechanisms, and phenotype
  - Subtypes MCD and N1 acquire mutations that promote chronic active B-cell receptor signaling
  - Patients with subtypes MCD and N1 treated with ibrutinib + R-CHOP had 100% survival rates

Wilson. Cancer Cell. 2021;39:1643.

Slide credit: deceraclinical.com/education

Optimizing Diffuse Large B-Cell Lymphoma (DLBCL) Treatment: An Expert Roundtable on the Role of New and Emerging Targeted Therapies

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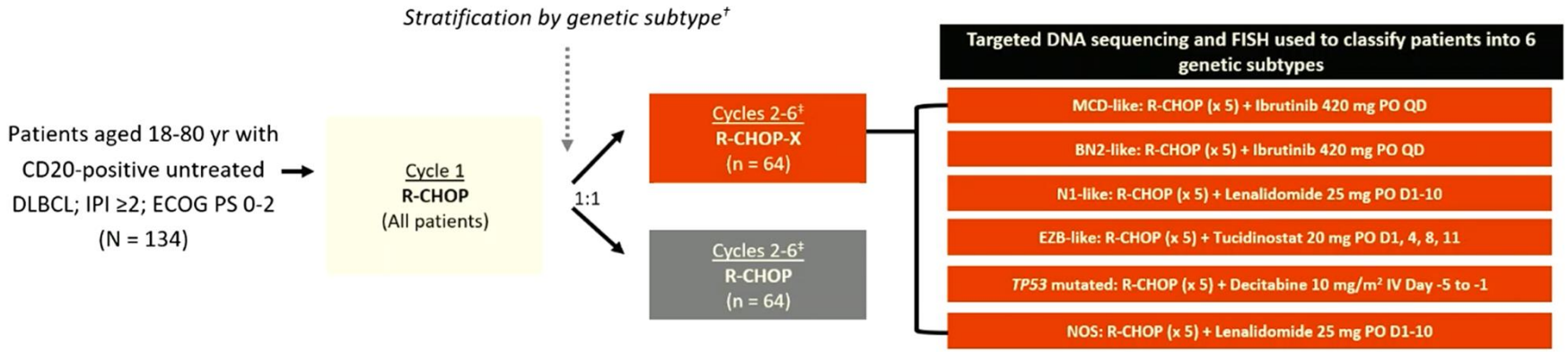
Medicina de Precisión e Inhibidores de BTK

GUIDANCE-01: R-CHOP vs R-CHOP-X* for Previously Untreated Intermediate- or High-risk DLBCL

- Biomarker-guided, randomized phase II study



*X = targeted tx. †By K-medoids algorithm (PAM)-simulated genetic subtyping using a targeted sequencing panel of 18 genes (*BTG1, CD70, CD79B, CREBBP, DTX1, EP300, EZH2, MPEG1, MTOR, MYD88, NOTCH1, NOTCH2, PIM1, STAT6, TBL1XR1, TNFAIP3, TNFRSF14,* and *TP53*). ‡G-CSF prophylaxis was given from cycle 2 of chemotherapy if grade ≥3 neutropenia present in cycle 1.

- **Primary endpoint:** CR rate
- **Secondary endpoints:** PFS, OS, ORR, safety

Optimizing Diffuse Large B-Cell Lymphoma (DLBCL) Treatment: An Expert Roundtable on the Role of New and Emerging Targeted Therapies

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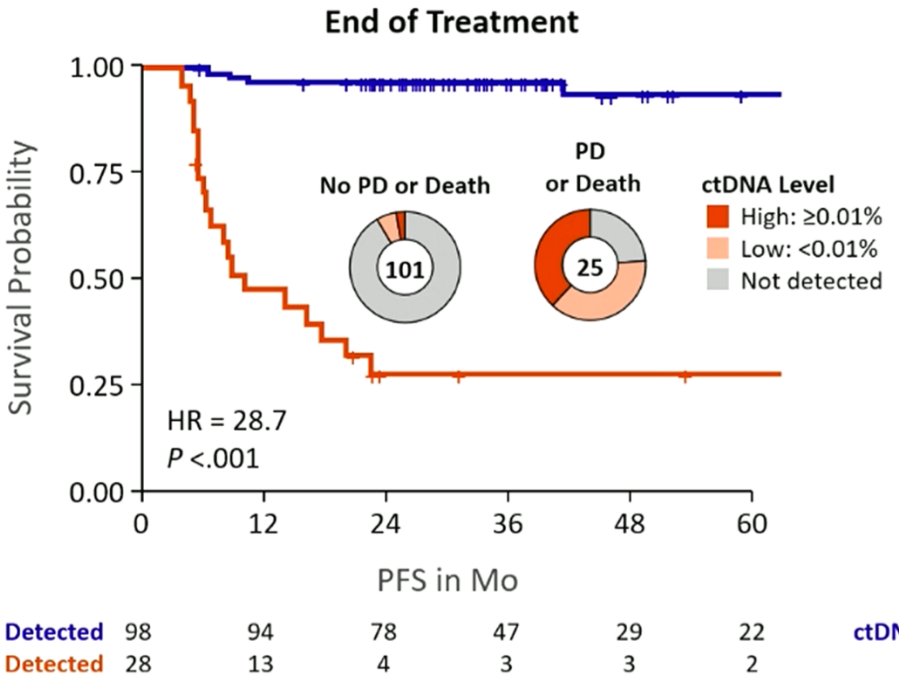
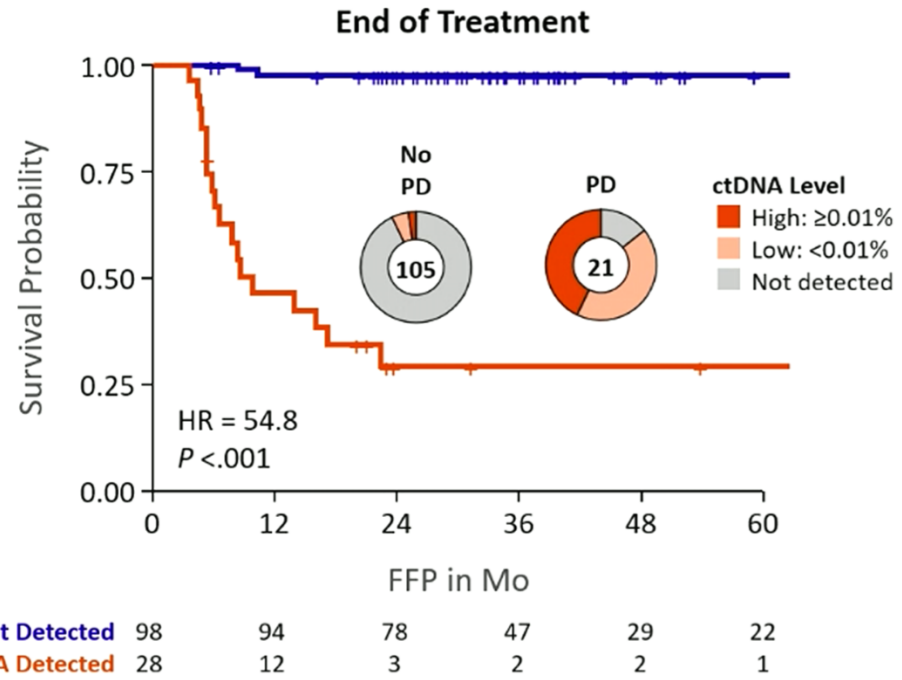
Biopsia Líquida y ADN Circulante (ctDNA)

ctDNA: Prognostic Utility

- ctDNA has greatest prognostic utility after therapy





Optimizing Diffuse Large B-Cell Lymphoma (DLBCL) Treatment: An Expert Roundtable on the Role of New and Emerging Targeted Therapies

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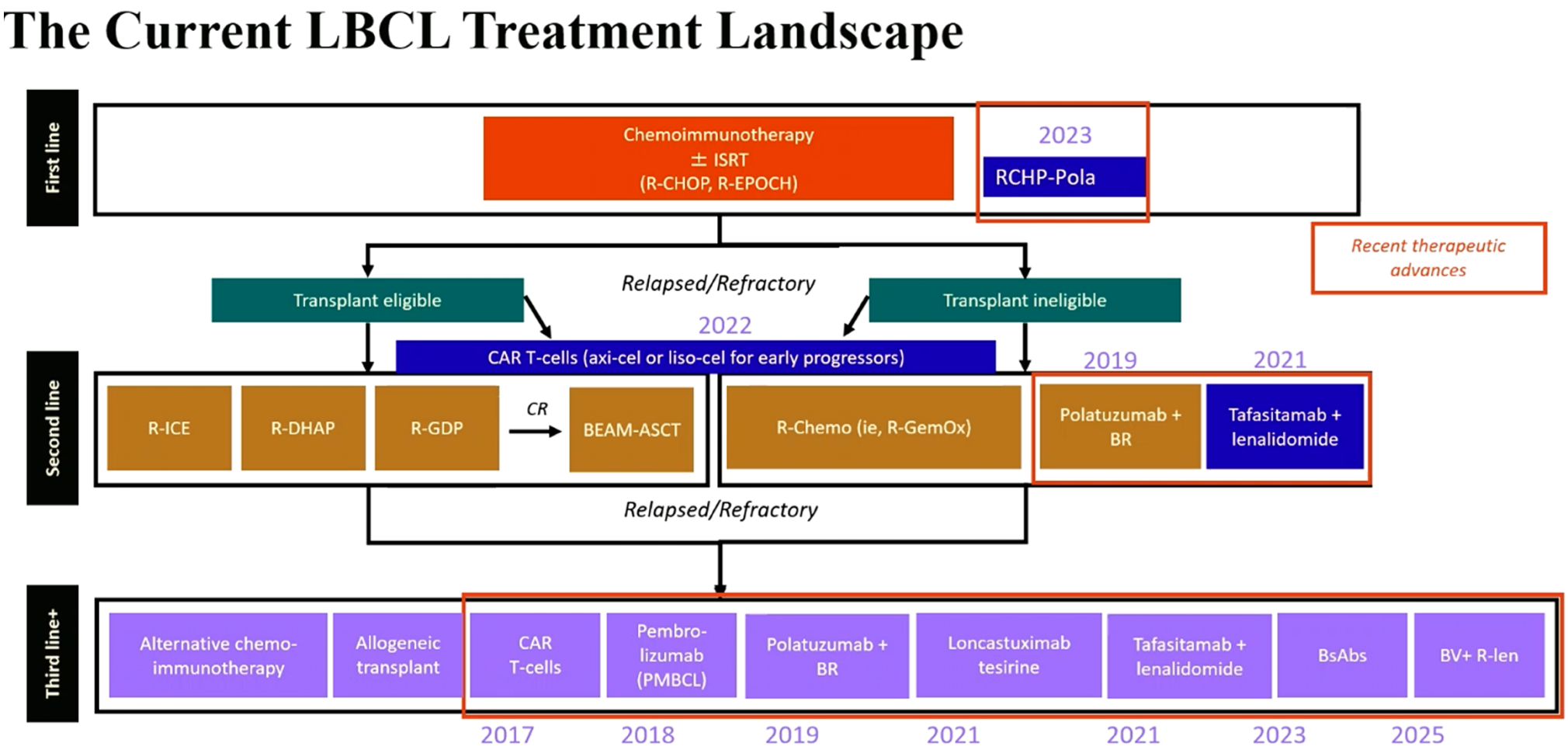
Alternativas terapéuticas en el campo del DLBCL R/R



Optimizing Diffuse Large B-Cell Lymphoma (DLBCL) Treatment: An Expert Roundtable on the Role of New and Emerging Targeted Therapies

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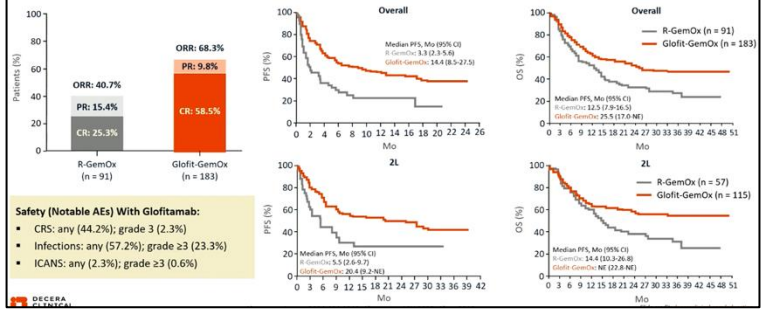
Multitud de alternativas terapéuticas en el campo del DLBCL R/R

STARGLO: Glofitamab + GemOx vs Rituximab-GemOx as Second-line Therapy for R/R DLBCL



SUNMO: Mosunetuzumab + Polatuzumab Vedotin vs R-GemOx for Transplant-Ineligible R/R DLBCL

- International, open-label, randomized phase III study

Stratified by prior lines of therapy (1 vs ≥2), relapsed vs refractory disease

Adults with CD20+ aggressive lymphoma*; ≥1 prior systemic therapy; ineligible for transplant; ECOG PS 0-2 (N = 208)

- **Mosunetuzumab** SC 5 mg on D1, 45 mg on D8, 15 of cycle 1, then 45 mg on D1 of cycles 2-8 + **Polatuzumab vedotin** 1.8 mg/kg IV on Day 1 of cycles 1-6 (21-day cycles) (n = 138) → *Follow-up after completion (24 wk) at 9 mo, 30 mo*
- **R-GemOx**† IV on Day 1 of cycles 1-8 (14-day cycles) (n = 70) → *Follow-up after completion (16 wk) at 24 wk, 9 mo, 30 mo*

*DLBCL NOS, HGBCL (NOS or double/triple hit), trFL, or FL grade 3b.

†Rituximab 375 mg/m² QD, gemcitabine 1000 mg/m² QD, oxaliplatin 100 mg/m² QD. Cycles could be extended to 21 days if needed because of hematologic toxicity.

- **Coprimary endpoints:** ORR, PFS
- **Key secondary endpoints:** OS, CR, DOCR

ECHELON-3 Study of Brentuximab Vedotin Plus Lenalidomide and Rituximab (R^2) vs R^2 Plus Placebo

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

Stratified by CD30 status (≥1% vs <1%), cell of origin (GCB vs non-GCB), prior CAR T-cell therapy (yes vs no), prior SCT (yes vs no)

Patients with R/R DLBCL* after ≥2 lines of systematic therapy (no prior BV or lenalidomide), ineligible for/PD after HSCT or CAR T-cell tx, ECOG PS ≤2, FDG-avid measurable disease, and no active cerebral/meningeal disease or grade ≥2 peripheral neuropathy (N = 230)

- **BV** 1.2 mg/kg Q3W + **rituximab** 375 mg/m² IV Q3W + **lenalidomide** 20 mg PO QD (n = 112)
- **Placebo** + **rituximab** 375 mg/m² IV Q3W + **lenalidomide** 20 mg PO QD (n = 118)

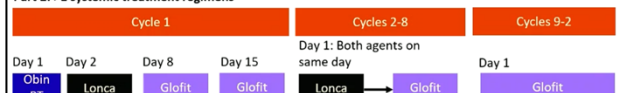
*Including but not limited to transformed DLBCL, high-grade DH/TH lymphoma, DLBCL-NOS.

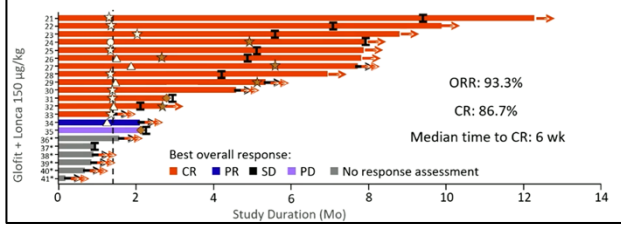
- **Primary endpoint:** OS in ITT population
- **Key secondary endpoints:** PFS and ORR by investigator in ITT population, CR and DoR by investigator, OS in patients with CD30+ disease, safety/tolerability

Loncastuximab Tesirine + Glofitamab in R/R DLBCL

- International, open-label, multiarm phase Ib study after 3L+ R/R B-NHL (part 1) and 2L+ R/R LBCL (part 2)

Part 2: >1 systemic treatment regimens





Glofitamab + Loncastuximab (n = 21)

Notable AEs,	n (%)
Any CRS	5 (23.8)
• Grade ≥3	0
Any ICANS	1 (4.8)
• Grade ≥3	0

- Current phase II expansion enrolling up to N = 100
- Potential to be best in class in 2L setting

Following the red thread in multiple myeloma (MM): aligning innovation with clinical practice

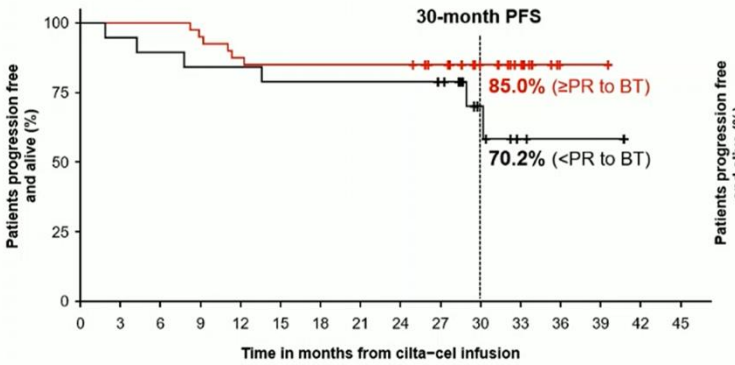
- **Maximizar el "Tumor Debulking“ con Terapia Puente: Supervivencia y tolerancia**
- **Manejo de las toxicidades neurológicas NO-ICANS de Cilta-Cel**
- **Consolidación de los BiEspecíficos como alternativa en líneas tempranas (Teclistamab, Elranatamab, Linvoseltamab)**

Following the red thread in multiple myeloma (MM): aligning innovation with clinical practice

Maximizar el "Tumor Debulking“ con Terapia Puente: Supervivencia y reducción de toxicidad

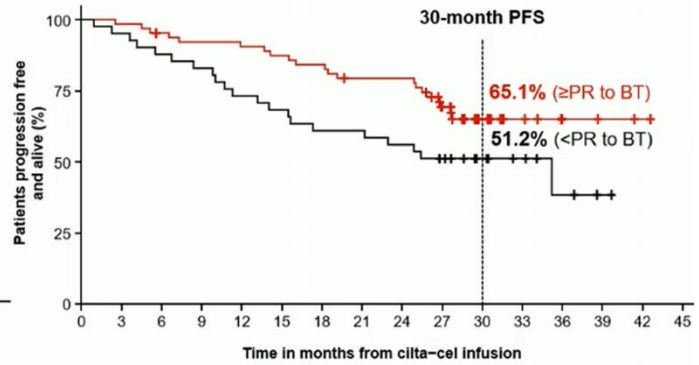
Choosing an effective bridging therapy can help to optimise efficacy and tolerability[1–3]

CARTITUDE-4 PFS: standard-risk by response to BT[1]



OS at 30 months: **92.5% if ≥PR to BT** vs 76.6% if <PR to BT[1]

CARITUDE-4 PFS: high-risk by response to BT[1]



OS at 30 months: **87.2% if ≥PR to BT** vs 75.6% if <PR to BT[1]

- Patients with ≥PR to BT had no cases of IEC-EC, fewer fatal infections and lower rates of NRM vs patients with <PR to BT[1]
- In two RW studies, patients with decreased disease during BT had lower rates of CRS, ICANS, parkinsonism and NRM than those with stable/increased disease[2,3]

Following the red thread in multiple myeloma (MM): aligning innovation with clinical practice

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Manejo de las toxicidades neurológicas NO-ICANS de Cilta-Cel

Non-ICANS neurological events are infrequent, manageable, and largely reversible with prompt recognition[1–6]

Non-ICANS neurological events usually occur in the sub-acute to late-onset setting (≥3–4 weeks after infusion)[1]

Prevention[1–4]

- **Using an effective bridging therapy and intensive CRS management** to reduce disease burden before CAR-T cell infusion may help mitigate neurological events
- **ALC ≥3000/µL on Days 7–14 may serve as a potential threshold** for identifying patients with RRMM at elevated risk warranting close monitoring

Monitoring and awareness[1,2]

- Patients, their caregivers and CAR-T cell treatment centres should be **educated on the incidence, signs and symptoms** of delayed neurological events
- **Prompt neurological assessment** should be initiated **following identification of signs and symptoms**

Treatment[5]

- **Guillain–Barré syndrome:** consider IV corticosteroids and IVIG
- **Cranial nerve palsies:** consider a short course of oral corticosteroids
- **MNT:** consider early use of systemic steroids as 1L treatment, with escalation to high-dose IV cyclophosphamide if symptoms worsen

PÓSTER

Real-world outcomes and subsequent treatment utilization following anti–B-cell maturation antigen antibody–drug conjugate exposure in patients with multiple myeloma

Meletios-Athanasios Dimopoulos,[1] Jorge Monge,[2] Efstathios Kastritis,[1] Xavier Leleu,[3] David S. Siegel,[4] Enrique M. Ocio,[5] Madhu Nagaraj,[6] Rafla Hassan,[6] Sundar Jagannath,[7] Katja C. Weisel,[8] Nicolle Bonar,[9] Mostafa Shokoohi,[9] Christian Hampp,[10] Jeannette Green,[10] Olivier Humblet,[10] Alexander Breskin,[10] Glenn S. Kroog,[10] Qiufei Ma,[10] Shaji Kumar[6]

TAKEAWAYS

POSTER PF839

- Most patients with heavily pretreated, anti-BCMA ADC-exposed MM were re-treated with similar therapy classes used prior to anti-BCMA ADC
- IMF IMWG academic sites used novel therapies (i.e., CAR T therapy and bispecific antibodies) more often, and their patients had longer survival and TTNT than those predominately from community sites (COTA/GRN)
- Patients treated after anti-BCMA ADC exposure continued to experience suboptimal clinical outcomes, underscoring the need for more effective and accessible treatment options

BACKGROUND AND OBJECTIVE

- The anti–B-cell maturation antigen (BCMA) antibody–drug conjugate (ADC) belantamab mafodotin was first granted accelerated US Food and Drug Administration (FDA) approval in 2020 for heavily pretreated relapsed/refractory multiple myeloma (RRMM), but approval was withdrawn in 2023 after the DREAMM-3 trial failed to confirm clinical benefit[1]
- In 2025, the FDA and European Medicines Agency (EMA) approved belantamab mafodotin in combination with bortezomib and dexamethasone for RRMM[2,3]
- Given the recent re-approval of belantamab mafodotin, there is renewed clinical interest in understanding outcomes for MM patients post anti-BCMA ADC exposure
- Outcomes following anti-BCMA ADC exposure have been evaluated in clinical trial populations.[4–7] However, real-world evidence describing outcomes associated with subsequent lines of therapy (LOTs) after anti-BCMA ADC exposure remains limited[8–9]
- **Objective:** To characterize real-world treatment patterns following anti-BCMA ADC exposure and associated clinical outcomes in patients with RRMM

METHODS

- Adult patients (aged ≥18 years) with triple class exposed MM who received an anti-BCMA ADC between August 7, 2018 and December 21, 2022 and initiated ≥1 subsequent LOT were included
  - Patients treated with bispecific antibodies and chimeric antigen receptor T-cell (CAR T) therapies prior to anti-BCMA ADC exposure were excluded
- The index date was the day the first post–anti-BCMA ADC LOT was initiated
- Real-world cohorts were derived from two separate data sources: chart reviews conducted at International Myeloma Foundation International Myeloma Working Group (IMF IMWG) academic sites, and US electronic health records (COTA and Guardian Research Network [GRN]) which consisted of data primarily from community sites
- Outcomes included distribution of treatment regimens, overall survival (OS), and time to next treatment (TTNT)
  - Time to event outcomes were estimated with the Kaplan–Meier (KM) estimator

DISCUSSION

- As this patient population predates the approval of belantamab mafodotin plus bortezomib and dexamethasone, the impact on bispecific antibody and CAR T uptake following failure of this regimen remains unknown. Ongoing evaluation will be important as the adoption of newer MM therapies continues to evolve in community practice
- This analysis is descriptive in nature, providing an overview of observed treatment patterns without formal statistical comparisons

Multiple myeloma

Scan the QR code for a copy of the poster

Poster

RESULTS

- Baseline characteristics for the IMF IMWG and COTA/GRN groups including demographic, clinical, treatment and disease characteristics (**Table 1**)

TABLE 1. Baseline characteristics

		IMF IMWG (n=40)	COTA/GRN (n=39)
Age at index date (years), mean (SD)		70.8 (8.2)	67.5 (9.0)
Sex, n (%)	Female	22 (55.0)	19 (48.7)
	Male	18 (45.0)	20 (51.3)
Race, n (%)	Asian	1 (2.5)	2 (5.1)
	Black or African American	1 (2.5)	7 (17.9)
	White	35 (87.5)	28 (71.8)
	Unknown/not stated	3 (7.5)	2 (5.1)
BMI classification, n (%)	Underweight	2 (5.0)	1 (2.6)
	Normal	16 (40.0)	11 (28.2)
	Overweight/obese	21 (52.5)	17 (43.6)
	Missing	1 (2.5)	10 (25.6)
ECOG PS score, n (%)	0	10 (25.0)	7 (17.9)
	1	26 (65.0)	10 (25.6)
	2	2 (5.0)	3 (7.7)
	Missing	2 (5.0)	19 (48.7)
MM subtype, n (%)	IgA	6 (15.0)	7 (17.9)
	IgG	22 (55.0)	19 (48.7)
	Light chain	10 (25.0)	9 (23.1)
	Non-secretory	1 (2.5)	1 (2.6)
	Missing	1 (2.5)	3 (7.7)
Cytogenetic risk, n (%)	High	4 (10.0)	9 (23.1)
	Standard	17 (42.5)	24 (61.5)
	Missing	19 (47.5)	6 (15.4)
Anti-BCMA ADC LOT number, n (%)	≤2	0	0
	3	2 (5.0)	1 (2.6)
	4	4 (10.0)	3 (7.7)
	5	8 (20.0)	2 (5.1)
	6	3 (7.5)	4 (10.3)
	≥7	23 (57.5)	29 (74.4)
Anti-BCMA ADC LOT number, mean (SD)		7.5 (3.4)	7.9 (2.5)
Prior HSCT, n (%)	Yes	26 (65.0)	32 (82.1)
	No	14 (35.0)	0
	Missing	0	7 (17.9)
R-ISS at index date, n (%)	I	1 (2.5)	0
	II	6 (15.0)	6 (15.4)
	III	2 (5.0)	7 (17.9)
	Missing	31 (77.5)	26 (66.7)
Time from MM diagnosis to start of first treatment following anti-BCMA ADC therapy (year), mean (SD)		8.6 (3.5)	6.5 (3.5)
Penta-class exposed, n (%)		13 (32.5)	21 (53.8)

Patients with anti-BCMA ADC exposure and a subsequent LOT. ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; GRN, Guardian Research Network; HSCT, hematopoietic stem cell transplant; Ig, immunoglobulin; IMF IMWG, International Myeloma Foundation International Myeloma Working Group; LOT, line of therapy; MM, multiple myeloma; R-ISS, Revised International Staging System; SD, standard deviation.

- Among anti-BCMA ADC-treated patients initiating a subsequent LOT, proportions of anti-BCMA ADC monotherapy were higher in the IMF IMWG cohort versus COTA/GRN (85% vs 56%, respectively), whereas combination therapy was more common in COTA/GRN versus the IMF cohort (44% vs 15%, respectively)
  - Belantamab mafodotin comprised 100% of anti-BCMA ADC monotherapy use in the COTA/GRN cohort and 82% in the IMF IMWG cohort
- The IMF IMWG and COTA/GRN cohorts included 29 and 32 unique post–anti-BCMA ADC index regimens, respectively, defined as specific drug combinations
- In contrast, **Table 2** presents grouped treatment categories of similar regimens
  - Selinexor-based regimens were most commonly used (27.5% and 23.1%), with higher use of bispecific antibodies in IMF IMWG cohort (15.0%) and venetoclax-based regimens in COTA/GRN cohort (17.9%) (**Table 2**)

TABLE 2. Distribution of the first treatment regimen after anti-BCMA ADC exposure

Distribution of treatment regimens*, n (%)	IMF IMWG (n=40)	COTA/GRN (n=39)
Selinexor-containing regimens	11 (27.5)	9 (23.1)
Selinexor	2 (5.0)	0
Selinexor + dexamethasone	2 (5.0)	1 (2.6)
Selinexor + PI + corticosteroid	6 (15.0)	5 (12.8)
Other	1 (2.5)	3 (7.7)
Bispecific antibodies	6 (15.0)	0
Anti-BCMA	5 (12.5)	0
Non–anti-BCMA (cevostamab)	1 (2.5)	0
PI + alkylating agent + corticosteroid	4 (10.0)	2 (5.1)
PI + pomalidomide + dexamethasone	3 (7.5)	0
Alkylating agent with/without dexamethasone	2 (5.0)	6 (15.4)
Alkylating agent	1 (2.5)	4 (10.3)
Alkylating agent + dexamethasone	1 (2.5)	2 (5.1)
CAR T therapy	2 (5.0)	1 (2.6)
Idecabtagene vicleucel	2 (5.0)	0
Not specified (with alkylating agent)	0	1 (2.6)
Venetoclax-containing regimen	0	7 (17.9)
Chemotherapy regimens containing cyclophosphamide and etoposide	1 (2.5)	3 (7.7)
Elotuzumab containing regimen	2 (5.0)	1 (2.6)
Other	9 (22.5)	10 (25.6)

*The most common treatment categories for the IMF and COTA/GRN cohorts (used in ≥3 LOT) received across all eligible LOTs after receiving an anti-BCMA ADC treatment.
ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T-cell; GRN, Guardian Research Network; IMF IMWG, International Myeloma Foundation International Myeloma Working Group; LOT, line of therapy; PI, proteasome inhibitor.

- Re-treatment with a pre-ADC drug class (proteasome inhibitor, immunomodulatory drug or anti-cluster of differentiation 38 therapy) occurred in 60.0% of patients in the IMF IMWG cohort and 53.8% of patients in the COTA/GRN cohort (**Table 3**)

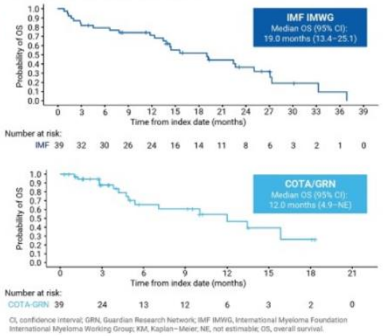
TABLE 3. Triple-class therapies received before and after anti-BCMA ADC exposure

Received a similar class of therapy before and after ADC exposure, n (%)	IMF IMWG (n=40)	COTA/GRN (n=39)
PI	21 (52.5)	17 (43.6)
IMiD	7 (17.5)	4 (10.3)
Anti-CD38	4 (10.0)	3* (7.7)
At least one similar class of therapy	**24 (60.0)**	**21 (53.8)**

*One patient who received daratumumab before, and both daratumumab and isatuximab after, an anti-BCMA ADC therapy was counted once.
ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; CD, cluster of differentiation; GRN, Guardian Research Network; IMF IMWG, International Myeloma Foundation International Myeloma Working Group; IMiD, immunomodulatory drug; PI, proteasome inhibitor.

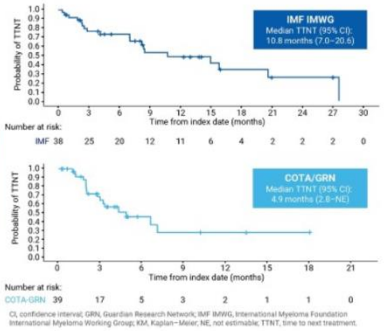
- For the first treatment after anti-BCMA exposure, the median follow-up duration was 26.0 months (95% confidence interval [CI] 15.9–Not estimable [NE]) in the IMF IMWG cohort and 9.2 months (95% CI 3.5–13.5) in the COTA/GRN cohort
  - The median OS was 19.0 and 12.0 months, respectively (**Figure 1**)
  - The median TTNT was 10.8 and 4.9 months, respectively (**Figure 2**)

FIGURE 1. KM curves for OS



CI, confidence interval; GRN, Guardian Research Network; IMF IMWG, International Myeloma Foundation International Myeloma Working Group; KM, Kaplan–Meier; NE, not estimable; OS, overall survival.

FIGURE 2. KM curves for TTNT



CI, confidence interval; GRN, Guardian Research Network; IMF IMWG, International Myeloma Foundation International Myeloma Working Group; KM, Kaplan–Meier; NE, not estimable; TTNT, time to next treatment.

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OUTCOMES AFTER FRONTLINE QUADRUPLET FAILURE IN TRANSPLANT-ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA

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GEMMAC — GRUP PER L'ESTUDI DEL MIELOMA MÚLTIPLE I L'AMILOIDOSI DE CATALUNYA

INTRODUCTION

Quadruplet (quad) regimens incorporating anti-CD38 MoAb are now standard **frontline therapy for transplant-eligible (TE) newly-diagnosed multiple myeloma (NDMM).**

Data on **response depth, MRD kinetics, long-term survival projections, and outcomes after 2L therapy** following quad failure remain **scarce.**

OBJECTIVE

- To describe **response rates, MRD dynamics, PFS and OS.**
- Including **parametric long-term projections** and **relative survival.**
- Characterize **baseline predictors of relapse and 2L outcomes.**
- **Population: TE-NDMM** patients receiving **frontline quad regimens.**

METHODS

- **Retrospective multicenter study** — GEMMAC (4 centers in Catalonia, Barcelona)
- **N = 98 TE-NDMM** patients receiving **frontline quad regimens** (01/2019–05/2025)
- **Median follow-up: 21.8 months** (95% CI 17.8–26.7)
- **~41% received 1L therapy within a clinical trial**
- Responses assessed per IMWG criteria; **MRD by NGF**
- Survival analyses: Kaplan-Meier, Cox regression (uni- and multivariable)
- **Parametric extrapolation per NICE TSD14** (7 distributions, AIC-based selection)
- **Relative survival** vs. Spanish general population (Ederer II method, HMD 2023)
- Cutoff date: 31 December 2025

RESULTS

Table 1. Selected Basal Characteristics (N=98)

Variable	N (%) or median (IQR)
Median age, years (range)	61 (36–78)
Male sex	52 (53%)
ECOG PS ≥2	18 (18.4%)
ISS III	22 (22.4%)
R-ISS III	13 (13.3%)
LDH >ULN	9 (9.2%)
BM plasma cells, %	37 (24–57)
Serum M-protein, g/L	28.8 (9.7–43.6)
High-risk cytogenetics (IMWG)	21 (21.4%)
IgG / IgA / BJP	62 (63%) / 23 (23%) / 8 (8%)
Extramedullary disease	7 (7.1%)
Enrolled in clinical trial	40 (40.8%)

BM, bone marrow; BJP, Bence Jones protein; ECOG PS, Eastern Cooperative Oncology Group performance status; HRC, high-risk cytogenetics; IQR, interquartile range; ISS, International Staging System; LDH, lactate dehydrogenase; R-ISS, Revised ISS; ULN, upper limit of normal. High-risk cytogenetics defined per IMWG 2025 criteria: del(17p), gain/amp(1q), del(1p), t(4;14), t(14;16), t(14;20).

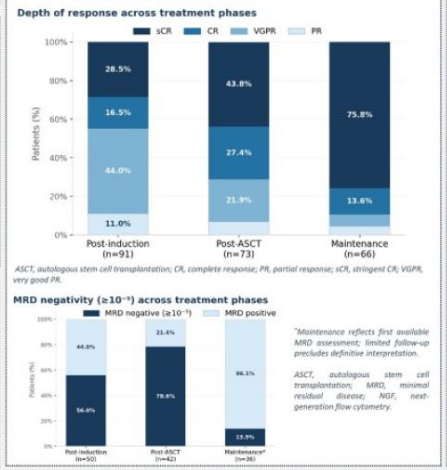
RESULTS

Table 2. Treatment Exposure

Variable	N (%) or median (IQR)
DVRd / DVTD / IsaVRd / Other	68 (69%) / 17 (17%) / 10 (10%) / 3 (3%)
Median induction cycles (IQR)	6 (4–6)
Upfront ASCT performed	80 (82%)
— Single auto / Tandem auto-auto / Tandem auto-allo	54 (71%) / 21 (28%) / 1 (1%)
Consolidation	36 (37%)
Maintenance (N=76)	
— Lenalidomide	41 (54%)
— Anti-CD38 + IMiD (len/iber)	24 (32%)
— Bortezomib + lenalidomide	8 (10%)
— Elranatamab	3 (4%)

allo, allogeneic; anti-CD38, anti-CD38 monoclonal antibody; ASCT, autologous stem cell transplantation; auto, autologous; DVRd, daratumumab-bortezomib-lenalidomide-dexamethasone; DVTD, daratumumab-bortezomib-thalidomide-dexamethasone; iber, ibersmide; IMiD, immunomodulatory drug; IQR, interquartile range; IsaVRd, isatuximab-bortezomib-lenalidomide-dexamethasone; len, lenalidomide.

Figure 1. Responses & MRD



ASCT, autologous stem cell transplantation; CR, complete response; PR, partial response; sCR, stringent CR; VGPR, very good PR.

**Maintenance reflects first available MRD assessment; limited follow-up precludes definitive interpretation.*

ASCT, autologous stem cell transplantation; MRD, minimal residual disease; NGF, next-generation flow cytometry.

Figure 2. PFS and OS

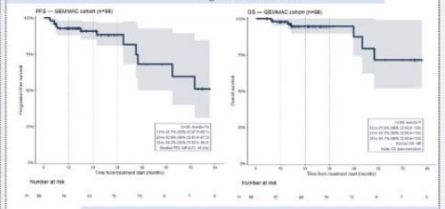
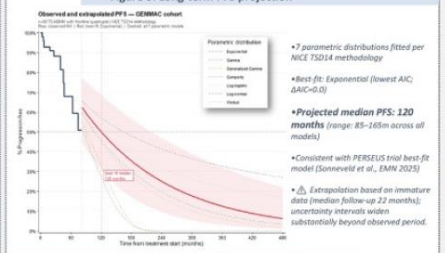
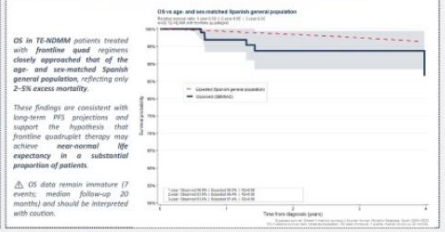


Figure 3. Long-term PFS projection



- *7 parametric distributions fitted per NICE TSD14 methodology
- *Best-fit: Exponential (lowest AIC; ΔAIC=0.0)
- **Projected median PFS: 120 months** *(range: 85–165m across all models)*
- *Consistent with PERSEUS trial best-fit model (Sonneveld et al., EMN 2025)
- ⚠ *Extrapolation based on immature data (median follow-up 22 months); uncertainty intervals widen substantially beyond observed period.*

Figure 4. Relative Survival vs. Spanish General Population



OS in TE-NDMM** patients treated with **frontline quad regimens** **closely approached that of the age- and sex-matched Spanish general population**, reflecting only **2–5% excess mortality.

*These findings are consistent with long-term PFS projections and support the hypothesis that frontline quadruplet therapy may achieve **near-normal life expectancy in a substantial proportion of patients.***

⚠ *OS data remain immature (7 events; median follow-up 20 months) and should be interpreted with caution.*

Table 3. Safety & Tolerability

Variable	N (%)	Variable	N (%)
Any AE reported	66 (67.3%)	**Dose reductions**	**35 (35.7%)**
Grade ≥3 AEs	**19 (19.4%)**	— IMiD and/or PI	29 (29.6%)
— Hematologic	17 (17.3%)	— Dex only	4 (4.1%)
— Infectious	8 (8.2%)	**Permanent discontinuation**	**12 (12.2%)**
— Neurologic	5 (5.1%)	— Bortezomib	6 (6.1%)
— Hepatic	4 (4.1%)	— IMiD	5 (5.1%)
— Cutaneous	4 (4.1%)	— Bortezomib + IMiD	1 (1.0%)

AE, adverse event; IMiD, immunomodulatory drug; PI, proteasome inhibitor. Grade ≥3 AEs by category are not mutually exclusive. AE collection was non-systematic in this real-world cohort.

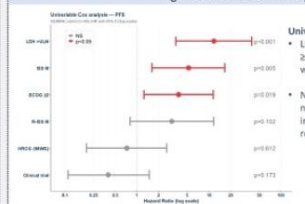
Table 4. Relapse & 2L Outcomes

- 14/98 patients (**14.3%**) experienced **disease progression**
- **Early relapse (≤18m):** 7/14 (**50%**); all during induction, prior to ASCT
- 4/5 early-relapsing patients failed to proceed to ASCT after 2L salvage
- **2L regimens heterogeneous; carfilzomib-based most common (43%)**
- **No patient received bispecific antibodies or CAR-T in 2L**

	Early relapse (≤18m)	Late relapse (>18m)
N	7	7
Timing (median)	5 months (IQR 3-6)	45 months (IQR 26-63)
ORR to 2L	43% (3/7)	50% (2/4)*
Median PFS2	4.3 months	10.1 months
Proceeded to ASCT after 2L	3/7 (43%)	N/A

**Response data available in 4/7 late-relapsing patients. ASCT, autologous stem cell transplantation; ORR, overall response rate; PFS2, progression-free survival after 2nd-line therapy. ⚠ Analyses limited by small sample size (n=11 with available PFS2 data).*

Figure 5. Predictors of Relapse



Univariable analysis (Cox-PFS):

- LDH >ULN, ISS III and ECOG PS ≥2 independently associated with shorter PFS.
- No patient achieving MRD negativity or ≥CR post-induction experienced early relapse.

Multivariable Cox model — Independent predictors of PFS

Variable	Adjusted HR	95% CI	p
LDH >ULN	12.35	3.56–42.77	<0.001
ECOG PS ≥2	4.35	1.34–14.11	0.014

Concordance = 0.80. Model selected by AIC (LDH+ECOG vs LDH alone). 1-in-10 rule applied (14 events, max 2 covariates). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal.

CONCLUSIONS

- Frontline **quad regimens** achieve **deep and sustained responses** in TE-NDMM in a RW multicenter setting, with PFS rates of 90.9% at 24 months.
- Sequential MRD deepening across treatment phases confirms the critical role of transplant in consolidating response.
- **Long-term PFS projections** (best-fit exponential; projected median **120 months**) and near-normal relative survival (RS ratio 0.95–0.98 at 3 years) support the hypothesis of functional cure in a substantial proportion of patients.
- **LDH >ULN and ECOG PS ≥2 are independent baseline predictors of shorter PFS.**
- Outcomes after quad failure remain suboptimal, particularly in **early relapses (median PFS2 4m),** with no access to novel immunotherapies in 2L in this cohort.
- These findings highlight an **unmet need for improved risk stratification and more effective salvage strategies** — including bispecific antibodies and CAR-T — following frontline quad failure.

CONTACT INFORMATION

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