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Inmunoterapia y Hemopatías

Aplicación de terapias avanzadas en patología linfoide: células CAR-T y anticuerpos biespecíficos

DEBATE

Células CART vs Ac biespecíficos en linfomas indolentes

A favor de los Ac biespecíficos

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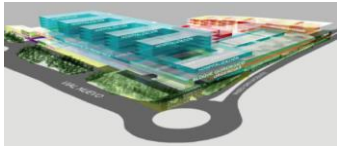

Hematología

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IBSAL

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Speaker's Disclosures in the last 2 years

- Honoraria and or consulting fees: Abbvie, AstraZeneca, BMS, Genmab, Gilead / Kite, GSK, Ideogen, Incyte, Janssen, Kyowa Kirin, Lilly, Miltenyi, Regeneron, Roche, Sobi, Takeda, BeiGene
- Research support: Gilead / Kite

Bispecific antibodies in 3L+ R/R FL

Therapy Key phase 2 study	Structure	Formulation	Treatment schedule	EMA approval
Mosunetuzumab GO29781[1,2]	Full-length, humanized IgG1 **CD20:CD3** 1:1[3]	**IV** or SC[1,4]	**Fixed duration**: Q3W* for up to 17 cycles[1]	**3L+**
Epcoritamab EPCORE NHL-1[5]	Full-length, human IgG1 **CD20:CD3** 1:1[6]	**SC**[7]	QW*, C1–3; Q2W C4–9; Q4W **until progression**[5]	**3L+**
Odronextamab ELM-2[8]	Hinge-stabilized, fully human IgG4 **CD20:CD3** 1:1[9,10]	**IV** or SC[10]	QW*, for four cycles; Q2W **until progression**[8]	**3L+**

*Following step-up dosing

1. Budde LE, et al. Lancet Oncol 2022; 2. Sehn L et al. Blood 2024; 3.Sun LL, et al. Sci Transl Med 2015; 4. Bartlett NL, et al. ASH 2021, #P3573; 5. Linton KM et al. Lancet Haematol 2024; 6. Engelberts PJ, et al. eBioMed 2020; 7. Hutchings M, et al. Lancet 2021; 8. Kim TM et al. Ann Oncol 2024; 9. Smith EJ, et al. Sci Rep 2015; 10. Bannerji R, et al. Lancet Haematol 2022

Phase II GO29781 study of mosunetuzumab in R/R FL

Key inclusion criteria[1]

- FL (Grade 1–3a)
- ECOG PS 0 or 1
- ≥2 prior regimens, including an anti-CD20 antibody and an alkylator

Endpoints[1]

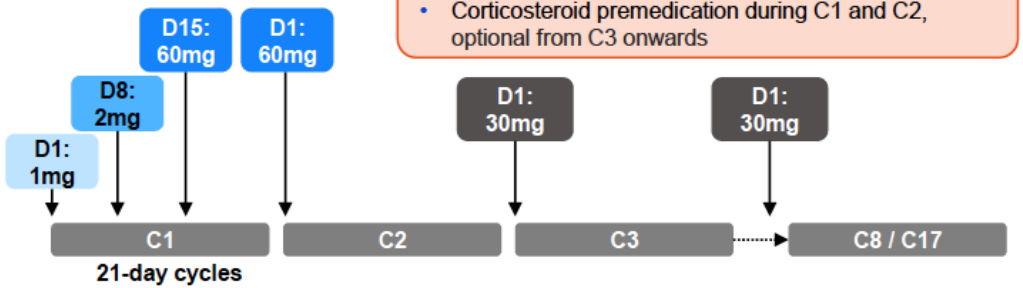
- Primary: CR (best response) rate by independent review*
- Secondary: ORR, DOR, PFS, safety and tolerability

Mosunetuzumab administration[1]

- Q3W intravenous administration
- **Fixed-duration treatment**
  - Eight cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**
- Retreatment permitted at relapse for patients who achieved a CR

CRS mitigation

- Step-up dosing during C1
- Corticosteroid premedication during C1 and C2, optional from C3 onwards

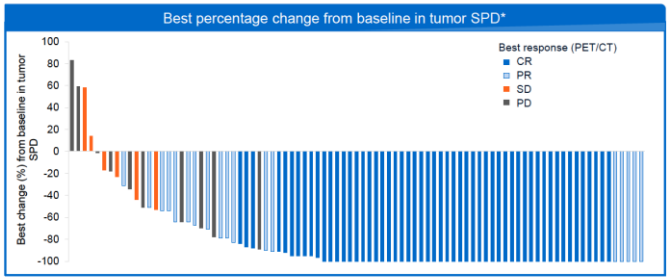


*Assessed by CT and PET-CT using Cheson 2007 criteria and versus 14% historical control CR rate.[2,3]
CRS, cytokine release syndrome; CT, computed tomography; D, day; DOR, duration of response; ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; SD, stable disease.

1. Budde EL, et al. Lancet Oncol 2022;23:1055–65;
2. Cheson BD, et al. J Clin Oncol 2007;25:579–86;
3. Dreyling M, et al. J Clin Oncol 2017;35:3898–905.

Mosunetuzumab in 3L+ FL: Pivotal phase 2 (GO29781)

Anti-tumor efficacy

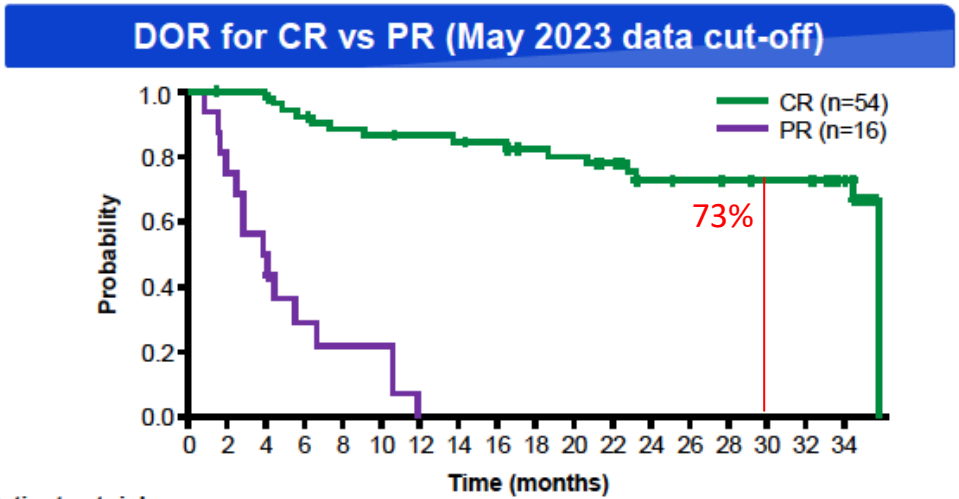


*in all patients with a baseline and ≥1 post-baseline SPD available; PD, progressive disease; SPD, sum of product diameters

Efficacy endpoint[1]	IRF N (%) [95% CI]
CR	**54 (60%)** [49%, 70%]
ORR	**72 (80%)** [70%, 88%]

IRF, independent review facility

N = 90, Median age 60 (29-90) y.
Median 3 (2-10) prior lines, 52% POD24
69% refractory to last therapy, 53% double refractory



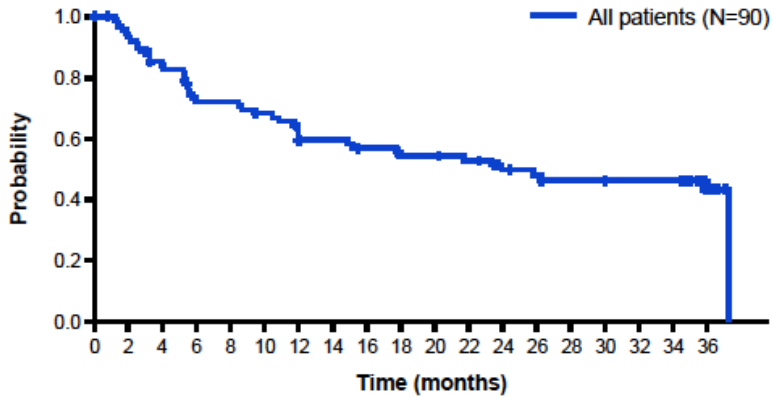
Median DOR in patients with CR, months (95% CI); n=54*	35.9 (NE–NE)
Median DOR in patients with PR, months (95% CI); n=16*	4.0 (2.5–6.7)

Budde LE, et al. ASH 2021, #127; Lancet Oncol 2022; Bartlett NL, et al. ASH 2022, #610; Schuster SJ et al, ASH 2023, #603

Mosunetuzumab in 3L+ FL: Pivotal phase 2 (GO29781)

PFS and OS; median follow-up >36 months

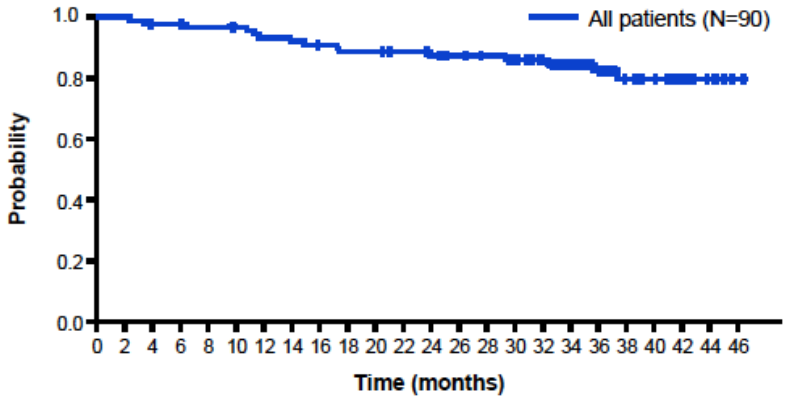
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
36-month PFS, months (95% CI)	**43.2%** (31.3–55.2)

OS



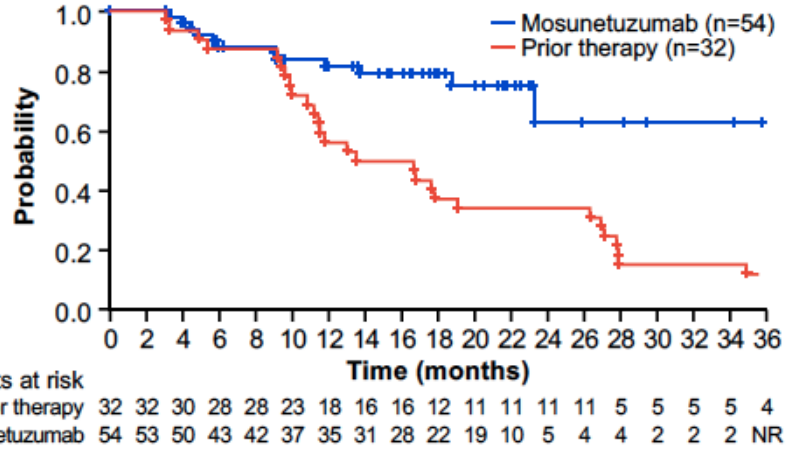
Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, months (95% CI)	**82.4%** (73.8–91.0)

Schuster SJ et al, ASH 2023, #603

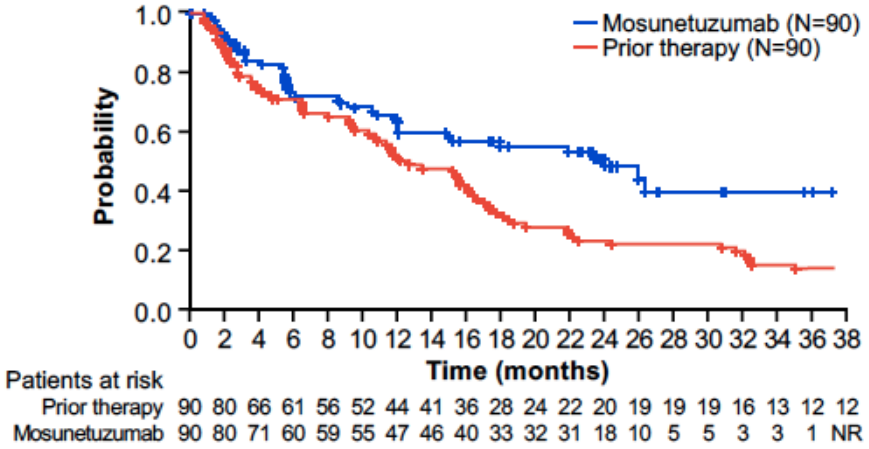
DOCR and PFS with mosunetuzumab versus last prior therapy

DOCR



	Mosunetuzumab (n=54)	Last prior therapy (n=32)
Median DOCR, months (95% CI)	**NR** (23–NR)	**15** (11–26)

PFS

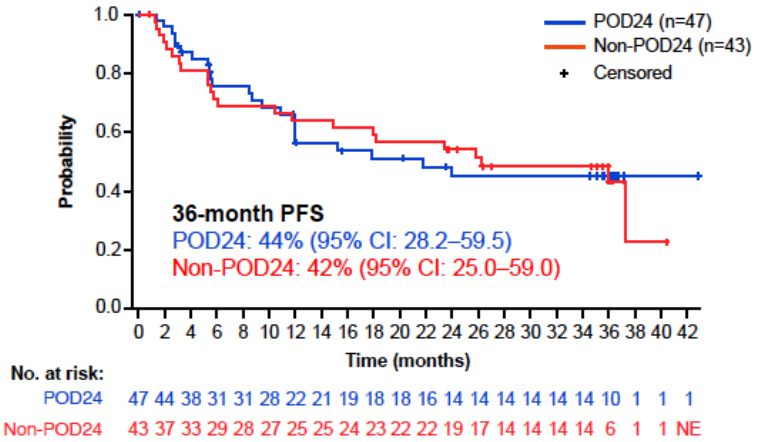


	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	**24** (12–NR)	**12** (10–16)

Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

GO29781: mosunetuzumab efficacy – POD24 status

PFS in non-POD24 versus POD24



Efficacy endpoints*	Overall population (N=90)	POD24 status	
		Non-POD24 (n=43)	POD24 (n=47)
ORR, n (%) [95% CI]	70 (78) [67.8–85.9]	32 (74) [58.8–86.5]	38 (81) [66.7–90.9]
CR rate, n (%) [95% CI]	54 (60) [49.1–70.2]	26 (61) [44.4–75.0]	28 (60) [44.3–73.6]
Median DOCR, months [95% CI]	NR [33.0–NE]	NR [31.5–NE]	NR [18.7–NE]
30-month DOCR, % [95% CI]	71 [58.2–84.0]	75 [56.5–92.6]	67 [48.8–86.1]

After extended follow-up of over 3 years, mosunetuzumab achieved durable remissions regardless of POD24 status

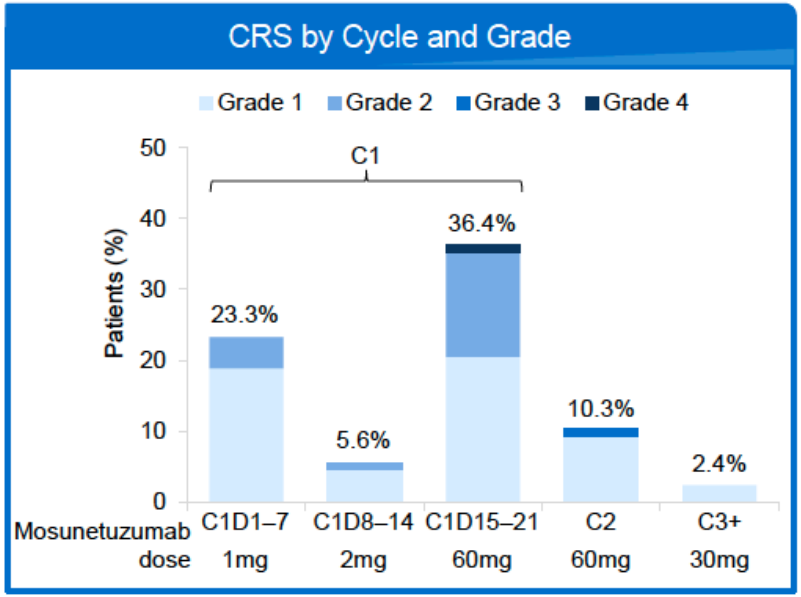
*By investigator assessment.
DOCR, duration of complete response; NR, not reached.

Assouline S, et al. EHA 2024; Oral presentation (abstract #S233).

Mosunetuzumab in 3L+ FL: Pivotal phase 2 (GO29781)

Cytokine release syndrome

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)



- **CRS was predominately low Grade and in Cycle 1. All events resolved.**

*assessed using ASTCT criteria[1]; †patient with leukemic phase FL

1. Lee et al. Biol Blood Marrow Transplant 20192019;25:625–38

Budde LE, et al. ASH 2021, #127; Lancet Oncol 2022

Bispecific antibodies in 3L+ R/R FL

	GO29781[1] Mosunetuzumab (N=90)	EPCORE NHL-1[2] Epcoritamab (N=128)	ELM-2[3] Odronextamab (N=128)
Prior lines, median (range)	3 (2 – 10)	3 (IQR 2 – 4)	3 (2 – 13)
POD-24, %	52	52	49
Refractory to last therapy, %	69	69	72
Double refractory, %	53	70	41
ORR (CR), %	78 (60)	82 (62.5)	80 (73)
Follow-up, median, months	36	17	20
DOR (DOCR), median, months	36 (NR)	NR (NR)	23 (25)
PFS, median, months	24	15	21
OS, median, months	NR	NR	NR

Data in the table are sourced from different studies; the limitations of cross-study comparisons apply

1. Sehn L et al. Blood 2024; 2. Linton KM et al. Lancet Haematol 2024; 3. Kim TM et al. Ann Oncol 2024

Table 3. Safety of bispecific antibodies in phase II trials for treatment of patients with relapsed/refractory follicular lymphoma

Agent	Trial	N	Rate of CRS: any grade (grade ≥3)	CRS: Rates of tocilizumab use	Rate of ICANS: any grade (grade ≥3)	Rate of neutropenia: any grade (grade ≥3)	Rate of infections: any grade (grade ≥3)	Treatment discontinuation rate due to adverse events
Mosunetuzumab[17]	GO29781 (NCT02500407)	90	44% (2%)	8%	5% (0%)	29% (27%)	51% (17%)	4%
Epcoritamab[15]	EPCORE NHL-1: pivotal cohort	128	66% (2%)	24%	6% (0%)	29% (26%)	NA	19%
Epcoritamab[15]	EPCORE NHL-1: optimization cohort	86	49% (0%)	12%	0% (0%)	20% (19%)	NA	3%
Odronextamab[14]	ELM-2 (NCT03888105)	128	56% (4%)	17%	1% (0%)	40% (32%)	80% (36%)	16%

Therapy	CRS mitigation
Mosunetuzumab GO29781	Step-up on C1 (1, 2, 60 mg) C2D1 60 mg, C3D1 30 mg **Steroids (C1D1, 8, 15 & C2D1)**
Epcoritamab EPCORE NHL-1, pivotal cohort	Step-up on C1 (0.16, 0.8, 48 mg) **Steroids (daily C1 on days 1-4, 8-11, 15-18, 22-25)**
Epcoritamab EPCORE NHL-1, optimization cohort	Step-up on C1 (0.16, 0.8, 3, 48 mg) **Steroids (daily C1 on days 1-4, 8-11, 15-18, 22-25)**
Odronextamab ELM-2	Step-up: Split dosing on days 1, 2, 8, 9, 15, 16 **Steroids on C1D1&2, 8&9, 15&16, C2D1, and 12-24h predose C1**

Imran A. Nizamuddin and Nancy L. Bartlett, Haematologica 2024

Table 4. Grade 5 (fatal) toxicities on BsAb trials.

Agent	Trial	N	Median follow-up (mo)	Number of grade 5 toxicities	Number of grade 5 toxicities considered treatment-related	Causes of Deaths
Mosunetuzumab[37]	GO29781	90	18.3	8	1	Progressive FL (6), pneumonia (1), pulmonary hemorrhage (1)
Epcoritamab[15]	EPCORE NHL-1	128	17.4	13	0	COVID-19 infection (6), sepsis (1), lymphoma transformation (1), pre-existing MDS (1), interstitial lung disease (1), organizing pneumonia (1), cardiorespiratory failure (1)
Odronextamab[14]	ELM-2	128	20.1	18	4	COVID-19 infection (8), other infection (7), progressive multifocal leukoencephalopathy (1), others not reported (2). Non-COVID–19 infections included pneumonia (3), sepsis (1), systemic mycosis (1), progressive multifocal leukoencephalopathy (1), pseudomonal pneumonia (1), and Escherichia sepsis (1). Treatment-related deaths: pneumonia (1), progressive multifocal leukoencephalopathy (1), Pseudomonal pneumonia (1), and COVID-19 pneumonia + systemic mycosis (1)

Imran A. Nizamuddin and Nancy L. Bartlett, Haematologica 2024

Considerations in choosing between biespecifis and CART in FL

Biespecifics	CAR T-cells
Excellent efficacy, with shorter follow up	Excellent efficacy, with longer follow up
Off the shelf	Requires 3-4 weeks of manufacturing
Logistically less complex	Logistically more complex
8-17 cycles (mosun) or until progression (epco, odro)	“One and done”
No lymphodepleting chemo	Needs lymphodepleting chemo
Lower risk of CRS, neurotoxicity, and cytopenias	Higher risk of CRS and neurotoxicity (axi > tisa and liso), and cytopenias
Usually outpatient	Usually inpatient

Slide courtesy of Jeremy Abramson, ASH 2023 (modified)