

## H12O-CNIO HAEMATOLOGICAL MALIGNANCIES CLINICAL RESEARCH UNIT



**Joaquín Martínez-López**  
Clinical Research Unit Head

Research Scientists  
Santiago Barrio, Lucia V. Fernández, Miguel Gallardo, María Linares

Clinical Investigators  
Rosa Ayala, María Calbacho, Gonzalo Carreño, Pilar Carreras, Teresa Cedena, Francisco Javier de La Serna, Ana Jiménez, Pilar Martínez, Inmaculada Rapado,

Antonia Rodríguez, Ricardo Sánchez

Post-Doctoral Fellows  
Almudena García, Larissa A Haertle (since Feb.), Alejandra Leivas, Yanira Ruiz-Heredia, Antonio Valeri, María Velasco-Estévez (MSCA fellow)\*

\* Marie Skłodowska-Curie Actions (MSCA).

Graduate Students  
Pedro Aguilar, Noemí Álvarez, Eva Castellano, Laura Córdoba, Jessica Encinas, Roberto García, Marta Ibáñez, Elena Maroto, Michael Ochieng, Alejandra Ortíz, Álvaro Otero (since Feb.), Alba Rodríguez, Laura Sánchez

Technicians  
Raquel Ancos, Andrés Arroyo (since Feb.), Irene Bragado (since Feb.)

Natalia S. Buenache, Sara Dorado, Adrián Fernández, Alicia Giménez, Laura Moreno, Miguel A. Navarro, Juan M. Rosa, Laura Rufián, Daniel Valdés (until Jul.)

Visiting Scientists  
María Hernández-Sánchez (Jul.-Dec.) (IBSAL, Salamanca, Spain), Alfonso Navarro (FIBHULP, Madrid, Spain)

Student in Practice  
Carmen Cano (Jan.-June) (Bachelor's Degree Final Project) and Andrea Sánchez de La Cruz (until June) (Master's Thesis) (Univ. Autónoma de Madrid, Spain)

### OVERVIEW

Haematological clinical research has traditionally focused on haematological malignancies, aplasia and syndromes. Now, with advances in immunotherapy, haematologists play a key role in research on novel immunotherapeutic approaches, the role of the immune response to tumours, or the role of infection and inflammation in cancer.

In the Haematological Malignancies Clinical Research Unit at CNIO we investigate:

- Traditional haematological neoplasms (leukaemia, myeloma, lymphoma): new diagnostic approaches, biomarkers, and treatments.
- Aplastic haematological malignancies such as bone marrow failures: new drivers and molecular mechanisms.
- Novel diagnosis and tumour burden monitoring: liquid biopsy and minimal residual disease.
- Role of inflammation and infection in haematological neoplasms.
- Novel immunotherapeutic approaches in haematological malignancies: NK-CARs, BITES.
- Traditional immunotherapeutic approaches in haematological malignancies and paediatric cancers: T-CARs and immune checkpoints inhibitors.

**“Teclistamab, a bispecific anti-CD3 and anti-BCMA monoclonal antibody, marker of myeloma cells, has demonstrated a high rate of deep and durable response in relapsed multiple myeloma patients.”**

## RESEARCH HIGHLIGHTS

**Teclistamab in relapsed or refractory multiple myeloma**

Teclistamab is a bispecific anti-CD3 and anti-BCMA monoclonal antibody. We recently published, in collaboration with other groups in the consortium, a novel clinical trial in multiple myeloma-relapsed patients. Our results showed a high rate of durable and deep response in the patients studied, with toxicity (grade 1 and 2) consistent with T-cell redirection.

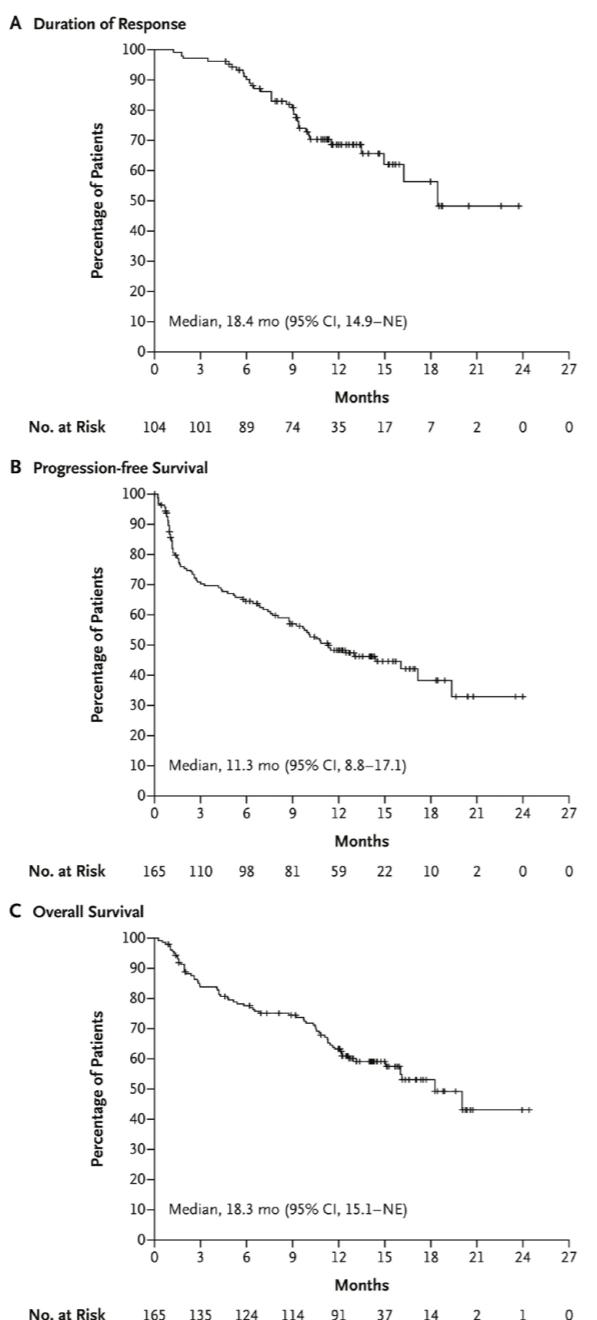
**Tisagenlecleucel trials in B-cell lymphomas**

Tisagenlecleucel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for different B-cell lymphomas. In 2022 we published, in collaboration with other groups in the consortium, an article in the *New England Journal of Medicine* describing the results of second-line tisagenlecleucel in aggressive B-cell lymphoma. Our results showed that tisagenlecleucel was not superior to standard salvage therapy in this trial.

However, in another clinical trial, the ELARA phase 2 multinational trial against follicular lymphoma, we reported its safety and effectiveness in high-risk patients with relapsed follicular lymphoma. This work was recently published in *Nature Medicine*.

**Infection prediction in multiple myeloma**

Infections are among the most common complications in multiple myeloma, in association with morbidity and mortality. We analysed the clinical variables of 4 clinical trials of the Spanish Myeloma Group with n=1,347 patients. We discovered that an increased risk of severe infection correlates with serum albumin, ECOG, gender, and non-IgA type multiple myeloma. These simple variables led to the stratification into low, intermediate, and high risk of severe infection. Patients with intermediate and high risk could be candidates for prophylactic antibiotic therapy. This work was published in *Blood Cancer Journal*. ■

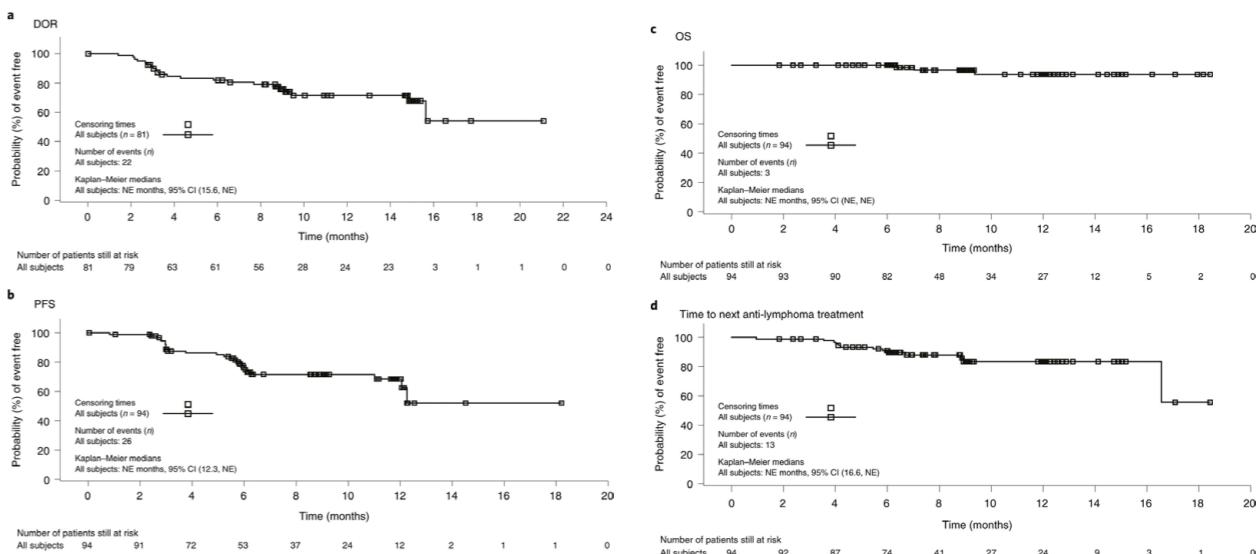


**FIGURE 1** Teclistamab trial in multiple myeloma. Kaplan-Meier analysis of response duration and of progression-free and overall survival.

**PUBLICATIONS**

- ▶ **Teclistamab in relapsed or refractory multiple myeloma.** *N Engl J Med* 386, 629–639.
- ▶ **Fowler NH et al.** (incl. Martinez-López J) (2022). Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med* 28, 325–332.
- ▶ **Termini R et al.** (incl. Martinez-López J; PETHEMA/GEM and iMMunocell Cooperative Groups) (2022). Circulating tumor and immune cells for minimally invasive
- ▶ **Bishop MR et al.** (incl. Martinez-López J) (2022). Second-line tisagenlecleucel or standard care in aggressive B-cell lym-

- ▶ phoma. *N Engl J Med* 386, 629–639.
- ▶ **Moreau P et al.** (incl. Martinez-López J) (2022). Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 387, 495–505.
- ▶ **Haertle L, Barria S, Munawar U, Han S, Zhou X, Simicek M, Vogt C, Trugen M, Fernandez RA, Steinhardt M, Weingart J, Snaurova R, Nerrerter S, Teufel E, Gartano-Trojola A, Da Vila M, Ruiz-Heredia Y, Rosenwald A, Bolli N, Hajek R, Raab P, Raab MS, Weinhold N, Haferlach C, Haaf T, Martinez-López J, Einsele H, Rasche L, Kortüm KM** (2022). Single nucleotide variants and epimutations induce proteasome inhibitor resistance in multiple myeloma. *Clin Cancer Res.* PMID: 36282272.
- ▶ **Valeri A, García-Ortiz A, Castellano E, Córdoba L, Maroto-Martín E, Encinas J, Leivas A, Rio P, Martínez-López J** (2022).



**FIGURE 2** Kaplan-Meier curves for patients with relapsed or refractory (r/r) follicular lymphoma who received tisagenlecleucel infusion.

- Overcoming tumor resistance mechanisms in CAR-NK cell therapy. *Front Immunol* 13, 953849.
- ▶ Salles GA et al. (incl. Jiménez-Ubieto A, Martínez-López J) (2022). Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma. *Blood Adv* 6, 5835–5843.
- ▶ Sánchez R, Dorado S, Ruiz-Heredia Y, Martín-Muñoz A, Rosa-Rosa JM, Ribera J, García O, Jiménez-Ubieto A, Carreño-Tarragona G, Linares M, Rufián L, Juárez A, Carrillo J, Espino MJ, Cáceres M, Expósito S, Cuevas B, Vanegas R, Casado LF, Torrent A, Zamora L, Mercadal S, Coll R, Cervera M, Morgades M, Hernández-Rivas JÁ, Bravo P, Seri C, Anguita E, Barragán E, Sargas C, Ferrer-Marín F, Sánchez-Calero J, Sevilla J, Ruiz E, Villalón L, Del Mar Herrázquez M, Riaza R, Magro E, Steegman JL, Wang C, de Toledo P, García-Gutiérrez V, Ayala R, Ribera JM, Barrio S, Martínez-López J (2022). Characteristics and outcome of patients with acute myeloid leukemia and trisomy 4. *Haematologica*. PMID: 35678031.
- ▶ Garcés JJ et al. (incl. Martínez-López J) (2022). Circulating tumor cells for the staging of patients with newly diagnosed transplant-eligible multiple myeloma. *J Clin Oncol* 40, 3151–3161.
- ▶ Mosquera Orgueira A et al. (incl. Martínez-López J, PETHEMA/GEM Cooperative Group) (2022). Unsupervised machine learning improves risk stratification in BCR:ABL1 leukemia by ultra-deep sequencing of genomic DNA. *Sci Rep* 12, 13057.
- ▶ Sanz A, Ayala R, Hernández G, Lopez N, Gil-Alos D, Gil R, Colmenares R, Carreño-Tarragona G, Sánchez-Pina J, Alonso RA, García-Barrio N, Pérez-Rey D, Meloni L, Calbacho M, Cruz-Rojo J, Pedrera-Jiménez M, Serrano-Balazote P, de la Cruz J, Martínez-López J (2022). Outcomes and patterns of treatment in chronic myeloid leukemia, a global perspective based on a real-world data global network. *Blood Cancer J* 12, 94.
- ▶ Rojas EA et al. (incl. Martínez-López J) (2022). Expression of p53 protein isoforms predicts survival in patients with multiple myeloma. *Am J Hematol* 97, 700–710.
- ▶ Puig N et al. (incl. Martínez-López J) (2022). Mass spectrometry vs immunofixation for treatment monitoring in multiple myeloma. *Blood Adv* 6, 3234–3239.
- ▶ Rodríguez-García A, Linares M, Morales ML, Allain-Maillet S, Mennesson N, Sanchez R, Alonso R, Leivas A, Pérez-Rivilla A, Martínez-López J, Lahuer JJ, Rosiñol L, Blade J, Mateos MV, San-Miguel JF, Paiva B (2022). A machine learning mod-

el based on tumor and immune biomarkers to predict undetectable MRD and survival outcomes in multiple myeloma. *Clin Cancer Res* 28, 2598–2609.

**PATENT**

- ▶ Martínez Lopez J, Valeri Lozano A, García Ortiz A, Gallardo Delgado M, Encinas Mayoral J, Maroto Martín E, Castellano Esparza E. Combination of CAR-NK cells with NKG2A blocking agents, pharmaceutical composition comprising the same and use thereof. PCT application (2022). *PCT/EP2022/060537, WO2022223684A1*.

**AWARDS AND RECOGNITION**

- ▶ María Velasco-Estevez: CRIS Cancer Foundation Post-Doc Talent Award, Spain.
- ▶ María Linares: Health Research Project (ISCIII); I+D+I RETOS Colaboración Project (MCI), Spain.
- ▶ Larissa Haertle: DFG Walter Benjamin Programme Fellowship (German Research Foundation); Poster prize, DGHO congress (German Society for Hematology and Medical Oncology); UNA4CAREER Award, Spain.
- ▶ Pedro Aguilar: Young EHA PhD Research Student Award from the European Hematology Association (EHA); FEHH Fellowship from the Spanish Foundation for Hematology and Hemotherapy (FEHH).
- ▶ Álvaro Otero: Predoctoral Health Research Training (PFIS) Contract (MCI), Spain.
- ▶ Alba Rodríguez: FEHH Fellowship, The Spanish Foundation for Hematology and Hemotherapy.
- ▶ Pedro Aguilar and Roberto García: Presidential Symposium of the European Hematology Association.