# CLINICAL RESEARCH PROGRAMME

**MIGUEL QUINTELA-FANDINO** Acting Programme Director



The Clinical Research Programme (CRP) has 2 main goals: 1) to translate preclinical research into novel clinical care standards; and 2) to address novel clinical oncology challenges with preclinical research. The specific areas of work include: 1) the development of novel agents; 2) the study of mechanisms of action of novel compounds and tackling drug resistance; and 3) moving forward in the field of biomarkers, functional taxonomy, and precision medicine. Currently, 2 functional objectives summarise the new operating model: a) generating synergies with ongoing research lines in the basic research programmes; and b) constituting a bi-directional bridge to facilitate interaction between the CNIO and tertiary cancer hospitals. The clinical activity of the CRP's Clinical Units takes place through agreements with tertiary hospitals (*Hospital 12 de Octubre*, *Hospital La Paz*, and *Hospital de Fuenlabrada*). These agreements foster the interaction between clinicians and scientists and enable scientists from all CNIO Programmes to participate in translational research studies. The ongoing collaborations between CRP Units and CNIO Groups from other Programmes now represent 18 projects and 4 coordinated grants, which account for the CNIO's high translational research activity. During 2022, 9 medical oncology residents from different Spanish hospitals completed their optional training visits (3-month stays) at the CNIO.

Although clinical activity was hampered considerably in 2022 due to COVID-19, the clinical groups have managed to produce highly impactful research. The Breast Cancer Clinical Research Unit, led by Miguel Quintela-Fandino, found the first specific, predictive, and explainable predictive factors for paclitaxel. The Lung Cancer Clinical Research Unit, led by Luis Paz-Ares, contributed to several immunotherapy registration trials for new standards of care in lung cancer. The Haematological Malignancies Clinical Research Unit, headed by Joaquín Martínez López, developed a CAR-T therapy against multiple myeloma, a highly unmet clinical need. The Molecular Diagnostics Unit, headed by Luis Lombardía, continues to provide support to hospitals in the diagnosis of different malignancies, performing >1000 diagnosis this year. Also in 2022, the Junior Prostate Cancer Clinical Research Unit ended its stay with us because of the completion of the Junior Group Leader's career development plan at the CNIO, and we started a process of recruiting additional Groups for the Clinical Research Programme. The selection process is now complete and we are excited to announce the incorporation of 2 new Senior Groups: the *Hospital 12 de Octubre*-CNIO Cancer Immunotherapy Clinical Research Unit, led by Dr Luis Álvarez-Vallina; and the *Hospital La Paz*-CNIO Paediatric Cancer Clinical Research Unit, headed by Dr Antonio Pérez-Martínez. These groups will cover 2 unmet needs at the CNIO: the development of novel cancer immunotherapy agents, as well as research in childhood cancer. ■

**"The Clinical Research Programme aims to improve cancer care by developing novel agents and personalising therapeutic approaches on the basis of novel biomarkers."**

# BREAST CANCER CLINICAL RESEARCH UNIT

Miguel Quintela-Fandino
Clinical Research Unit Head

Research Scientists
María José Bueno, Silvana A. Mouron

Post-Doctoral Fellows
Rebeca G. Jimeno, Ana M. Roncero



Gradutate Student
José Luis Ruiz

Technicians
Verónica Jiménez, Manuel Muñoz

Student in Practice
Naomí Patricia (March-August) (*Universidad Alfonso X El Sabio*, Madrid, Spain)

Visiting Scientists
Ana Garrido (until October) (*Hospital Universitario de la Princesa*, Madrid, Spain), Elisa I. Gómez (until September) (*Hospital Universitario de Fuenlabrada*, Madrid, Spain),

Cristina Merino (until July) (*Hospital Universitario 12 de Octubre*, Madrid, Spain), Rocío Moreno (*Hospital Universitario 12 de Octubre*, Madrid, Spain), Berta Nassarre (Peaches Biotech, Madrid, Spain)

## OVERVIEW

The Breast Cancer Clinical Research Unit (BCCRU) focuses on the translational interface of therapeutic development. Breast cancer is a heterogeneous disease and, thus, there are large inter-patient variations in terms of disease course, prognosis, relapse, and resistance to conventional or targeted therapeutics. Our activities are directed towards personalised treatment and range from preclinical models to correlative studies and clinical trials.

**"At the Breast Cancer Clinical Research Unit, we are focused on individualising therapy for advanced breast cancer."**

Our current research areas aim to:

- → Study the implications of hypoxia for immunotherapies.
- → Understand the individual factors regulating the response to immunotherapy in breast cancer, taking advantage of an advanced, personalised "tumouroid" platform.
- → Tackle the mechanisms of resistance against novel therapies in advanced breast cancer.
- → Incorporate our findings into concept-driven clinical trials.

## RESEARCH HIGHLIGHTS

We have established a collection of 35 patient-derived *tumoroids* from breast cancer patients. We call a *tumoroid* a mix of a patient-derived organoid (a well-established model for cancer research, which perpetuates the tumour material from a given patient, preserving its mutations and general features, and is highly reliable for drug screening and predictive purposes) and the patient's cells derived from the immune system. This sophisticated model allows us not only to screen conventional drugs, but also to understand their impact on the ability of the immune system to reject the tumour, a feature that is absent in common patient-derived mouse models of cancer. Tumoroids enable us to improve our understanding of immunotherapy and to better understand the impact of other drugs on the immune system, allowing for personalised synergistic treatment combinations. This collection is expanding, and we plan this to be the core of our research in the coming years.

A critical problem in hormone-positive breast cancer is the development of clonal heterogeneity. Tumours, after progression on aromatase plus CDK4/6 inhibitors, develop many different mutations to circumvent drug exposure, impacting the duration of response to subsequent treatment lines. Our preliminary data suggest that different tumour sub-compartments harbour different sets of mutations, and even selecting a "right" therapeutic choice is insufficient for eradicating a whole tumour. We are now undertaking an approach based on mutational signatures that are pervasive across different clones and that may allow for selecting therapies that kill broader tumour compartments than therapies selected according to traditional point mutations. This is being tested in patient tumoroids.

We finalised our work regarding predictive factors of sensitivity to paclitaxel in early breast cancer from the perspective of phosphorproteomics. A CDK4-Filamin A axis that converges in the regulatory machinery of tubulin acetylation is responsible for turning cancer cells sensitive to this drug. This pair of markers is highly accurate in predicting sensitivity in the clinical setting. ■

### PUBLICATIONS


- S. Mouron, M. J. Bueno, A. Lluch, L. Manso, I. Calvo, J. Cortes, J. A. Garcia-Saenz, M. Gil-Gil, N. Martinez-Janez, J. V. Apala, E. Caleiras, Pilar Ximénez-Embún, J. Muñoz, L. Gonzalez-Cortijo, R. Murillo, R. Sánchez-Bayona, J. M. Cejalvo, G. Gómez-López, C. Fustero-Torre, S. Sabroso-Lasa, N. Malats, M. Martinez, A. Moreno, D. Megias, M. Malumbres, R. Colomer, M. Quintela-Fandino (2022). Phosphoproteomic analysis of neoadjuvant breast cancer suggests that increased sensitivity to paclitaxel is driven by CDK4 and filamin A. *Nat Commun* 13, 7529.
- Choudhury AD, Higano CS, de Bono JS, Cook N, Rathkopf DE, Wisinski KB, Martin-Liberal J, Linch M, Heath EI, Baird RD, García-Carbacho J, Quintela-Fandino M, Barry ST, de Bruin EC, Colebrook S, Hawkins G, Klinowska T, Maroj B, Moorthy G, Mortimer PG, Moschetta M, Nikolaou M, Sainsbury L, Shapiro GI, Siu LL, Hansen AR (2022). A Phase I study investigating AZD8186, a potent and selective inhibitor of PI3Kβ/δ, in patients with advanced solid tumors. *Clin Cancer Res* 28, 2257-69.
- Zhu L, Retana D, García-Gómez P, Álvaro-Espinosa L, Priego N, Masmudi-Martín M, Yebra N, Miarka L, Hernández-Encinas E, Blanco-Aparicio C, Martínez S, Sobrino C, Ajenjo N, Artiga MJ, Ortega-Paino E, Torres-Ruiz R, Rodríguez-Perales S; RENACER, Soffietti R, Bertero L, Cassoni P, Weiss T, Muñoz J, Sepúlveda JM, González-León P, Jiménez-Roldán L, Moreno LM, Esteban O, Pérez-Núñez Á, Hernández-Laín A, Toldos O, Ruano Y, Alcázar L, Blasco G, Fernández-Alén J, Caleiras E, Lafarga M, Megías D, Graña-Castro O, Nör C, Taylor MD, Young LS, Varešlija D, Cosgrove N, Couch FJ, Cussó L, Desco M, Mouron S, Quintela-Fandino M, Weller M, Pastor J, Valiente M (2022). A clinically compatible drug-screening platform based on organotypic cultures identifies vulnerabilities to prevent and treat brain metastases. *EMBO Mol Med* 14, e14552.
- Hühn D, Martí-Rodrigo P, Mouron S, Hansel C, Tschapalda K, Porebski B, Häggblad M, Lidemalm L, Quintela-Fandino M, Carreras-Puigvert J, Fernandez-Capetillo O (2022). Prolonged estrogen deprivation triggers a broad immunosuppressive phenotype in breast cancer cells. *Mol Oncol* 16, 148-165.


### PATENT


- Quintela Fandiño MA. P27 single-nucleotide polymorphism as a predictor of benefit of hormonal therapy alone or in combination with CDK inhibitors in breast cancer. PCT application (2022). *PCT/EP2022/051700. WO2022161984A1.*


### INTELLECTUAL PROPERTY REGISTRATION

- Luis Manso Sanchez, Miguel Quintela-Fandino (2022). LUMICA V. 1.0. Algorithm – a proprietary algorithm for precision nutrition allocation for cancer patients. Registered with Safe Creative with registration code *2210252495358*.

### AWARDS AND RECOGNITION

- Panel Member, *Proyectos de Investigación en Salud, Instituto de Salud Carlos III* (*ISCIII*), Spain.





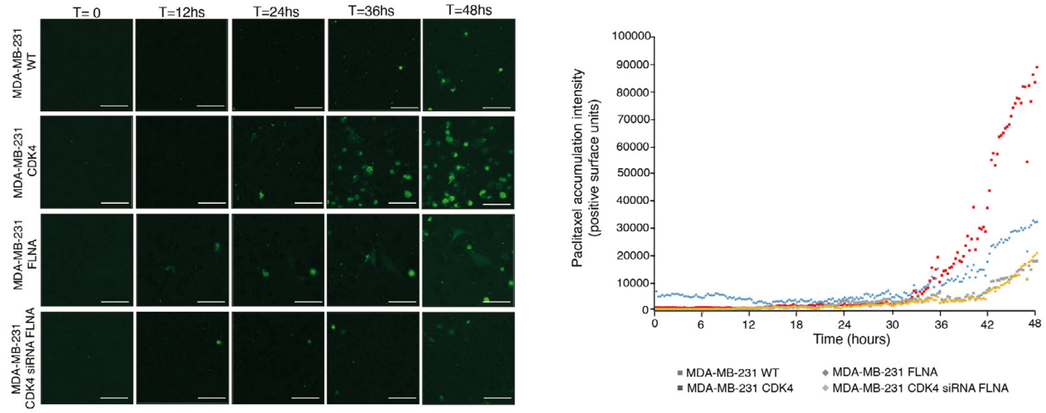


**FIGURE 1** Fluorescently labelled paclitaxel was added to live cultures of MDA-MB-231 WT, CDK4 or FLNA cells. MDA-MB-231 CDK4 cells with filamin A knockdown were added to the experiment as well. The greater the green signal, the higher the amount of paclitaxel bound to microtubules. One can appreciate how both CDK4- and filamin A-overexpressing cell lines display both earlier and higher paclitaxel binding. Scale bar: 75 micrometres. The chart on the right-hand side depicts the signal (in fluorescent surface units) tracing paclitaxel accumulation over a 48-hour time interval, displaying a clear increase in the 2 overexpressing transfectants (CDK4 and FLNA) compared to the parental cell line, and a reversion of the phenotype by filamin A knockdown in MDA-MB-231 CDK4 cells. General methodology for patient-derived organoid generation.

# MOLECULAR DIAGNOSTICS UNIT

Luis Lombardía
Unit Head

Technician
Diana Romero

Students in Practice
Paula Broncano and Giselle Coronel (March-June) (*Centro Educación Mª Inmaculada - Ríos Rosas*, Madrid, Spain), Silvia Novo (September-October) (*Universidad Autónoma de Madrid*, Spain)

Visiting Scientist
Ana Jambrina (*Hospital General Universitario Gregorio Marañón*, Madrid, Spain)

## OVERVIEW

The Molecular Diagnostics Unit (MDU) is primarily engaged in providing support to oncologists, haematologists and pathologists of our National Health System, by offering quality molecular tests for cancer patients. In this regard, the Unit has developed a catalogue with a broad variety of sensitive and specific assays to determine changes in sequences or expression levels of crucial genes that are involved in cancer, and that help to monitor minimal residual disease in patients showing clinical remission as well as to follow-up on their response to therapy. Consequently, MDU is also committed to implementing novel diagnostic solutions, not only to improve clinical practice but also to resolve periodic inquiries from CNIO's Research Units and Groups. MDU also forms part of several international and national groups aimed at normalising and improving molecular tests in cancer. Finally, an essential part of our mission is to contribute to academic programmes by hosting clinical post-residents and pre/post graduate students.

**"The ongoing accumulation and combination of actionable biomarkers included in molecular diagnostics tests is bringing us closer to precision medicine, especially for haematological tumours."**





## CORE UNIT HIGHLIGHTS

During 2022, our catalogue grew with the addition of a new assay, which will enable the detection, through bi-directional Sanger sequencing, of structural alterations in exon 3 of the β-catenin gene, *CTNNB1*. High frequencies of CTNNB1 activating mutations and in-frame deletions have been spotted in 3% of all cancers, including melanoma, lung, endometrium, colon, kidney, and ovarian tumours. Since they have been associated with altered sensitivity to specific drugs, their analysis can be useful as a predictive marker by suggesting different therapy options.

We also improved the clinical utility of *KRAS* gene testing by supplementing the detection of the recurrent mutations already implemented in exons 2 and 3 to exon 4. The extended assay is intended to enable clinicians to manage their patients with colorectal, pancreatic, or lung adenocarcinomas, since somatic mutations in exon 4 have been linked to a better prognosis, and they can also be used as an inclusion criterion to enrol patients in active or forthcoming clinical trials.

Additionally, in the context of our partnership with *GBMH* (*Grupo de Biología Molecular y Hematología*), we are participating in the development of comprehensive national guidelines for the management of patients with different haematological cancers. Our initial contribution was to complete a list of diagnostic, prognostic, and predictive markers that should be systematically analysed using Next Gene Sequencing (NGS) in order to manage patients with acute myeloid leukaemia (AML). To evaluate the clinical and analytical utility of this diagnostic tool, the next step will be to design a panel containing at least the markers required for the analysis, and then to establish the feasibility of using RNAseq technology to be able to analyse simultaneously both single and fusion genes (FIGURE 1).

Finally, during 2022, in the framework of our training policy, we hosted a medical resident, an undergraduate student, and 2 future technicians in anatomical pathology. ■

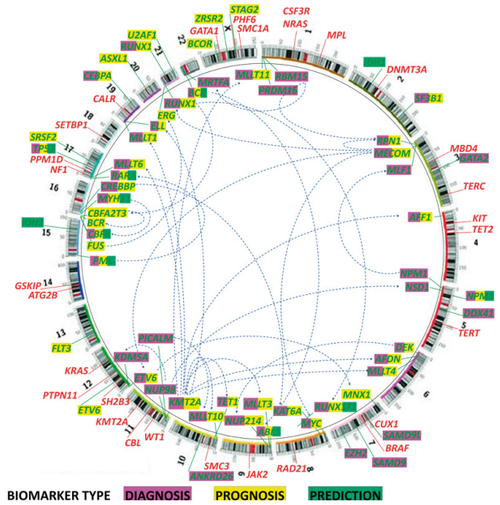


**FIGURE 1** The comprehensive massive sequencing of validated markers (green) would directly contribute to improved diagnosis, prognosis, and treatment of patients with AML. Other markers (red), yet to be validated, are expected to complete the whole panel required for full precision medicine of AMLs.

# H12O-CNIO HAEMATOLOGICAL MALIGNANCIES CLINICAL RESEARCH UNIT

Joaquín Martínez-López
Clinical Research Unit Head

Research Scientists
Santiago Barrio, Lucía 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 Rodríquez, Ricardo Sánchez

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

** Marie Sklodowska-Curie Actions* (MSCA).

Gradutate 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.)

Studenst 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)

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

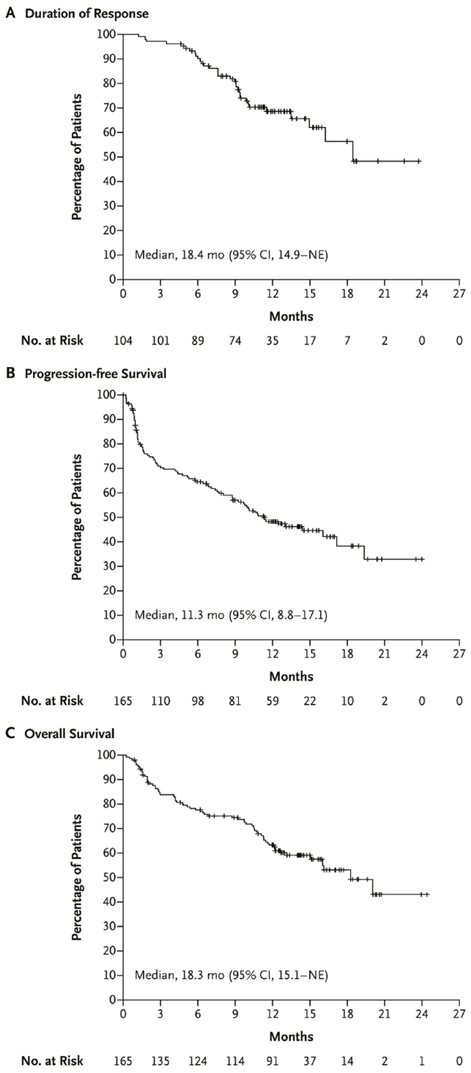


**FIGURE 1** Teclistamab trial in multiple myeloma. Kaplan–Meier analysis of response duration and of progression-free and overall survival.


**PUBLICATIONS**

- Moreau P *et al.* (incl. Martínez-López J) (2022). Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 387, 495-505.
- Bishop MR *et al.* (incl. Martinez-Lopez J) (2022). Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. *N Engl J Med* 386, 629-639.
- Fowler NH *et al.* (incl. Martinez-Lopez 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-Lopez J; PETHEMA/GEM and iMMunocell Cooperative Groups) (2022). Circulating tumor and immune cells for minimally invasive risk stratification of smoldering multiple myeloma. *Clin Cancer Res* 28, 4771-4781.
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- Valeri A, García-Ortiz A, Castellano E, Córdoba L, Maroto-Martín E, Encinas J, Leivas A, Río P, Martínez-López J (2022). 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, Ruíz-Heredia Y, Martín-Muñoz A, Rosa-Rosa JM, Ribera J, García O, Jimenez-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, Serí C, Anguita E, Barragán E, Sargas C, Ferrer-Marín F, Sánchez-Calero J, Sevilla J, Ruíz E, Villalón L, Del Mar Herráez 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). Detection of kinase domain mutations 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.
- Kayser S, Martínez-Cuadrón D, Hanoun M, Stölzel F, Gil C, Reinhardt HC, Aguiar E, Schäfer-Eckart K, Burgues JMB, Steffen B, Bernal T, Krause SW, Riaza R, Schliemann C, Cervera J, Kaufmann M, Torres-Miñana L, Hänel M, Acuña-Cruz E, Jost E, Algarra JL, Crysandt M, Fransecky L, Cornago-Navascues J, Kraus S, Martin-Lopez J, Einsele H, Niemann D, Neubauer A, Seggewiß-Bernhardt R, Scholl S, Klein SA, Schmid C, Schaich M, Schmidt-Hieber M, Zukunft S, Ho AD, Platzbecker U, Baldus CD, Müller-Tidow C, Thiede C, Bornhäuser M, Serve H, Levis M, Montesinos P, Röllig C, Schlenk RF (2022). Characteristics and outcome of patients with acute myeloid leukemia and trisomy 4. *Haematologica*. PMID: 35678031.
- Garcés JJ *et al.* (incl. Martinez-Lopez 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. Martinez Lopez J, PETHEMA/GEM Cooperative Group) (2022). Unsupervised machine learning improves risk stratification in newly diagnosed multiple myeloma: an analysis of the Spanish Myeloma Group. *Blood Cancer J* 12, 76.
- 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, Bigot-Corbel E, Hermouet S, Martínez-López J (2022). Efficacy of antiviral treatment in hepatitis C virus (HCV)-driven monoclonal gammopathies including myeloma. *Front Immunol* 12, 797209.
- Zozaya N *et al.* (incl. García-Sanz R, Martínez-López J) (2022). A strategic reflection for the management and implementation of CAR-T therapy in Spain: an expert consensus paper. *Clin Transl Oncol* 24, 968-980.






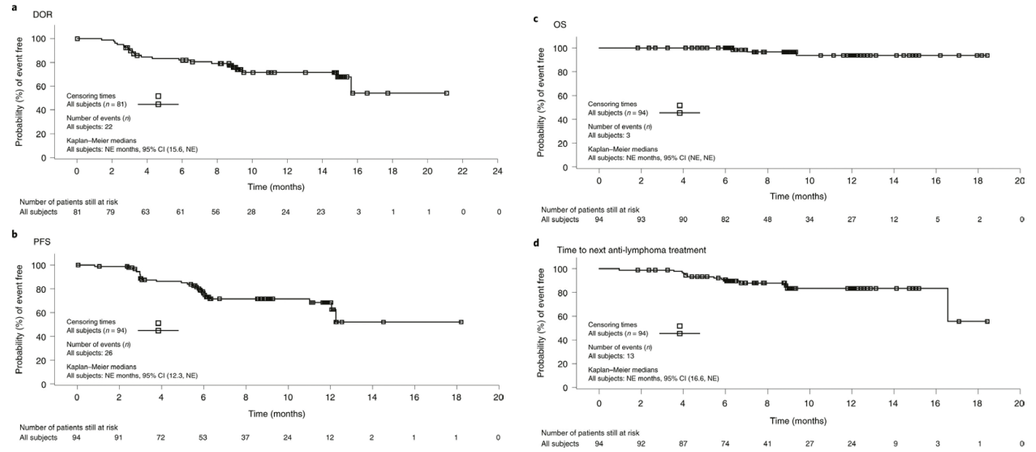


**FIGURE 2** Kaplan–Meier curves for patients with relapsed or refractory (r/r) follicular lymphoma who received tisagenlecleucel infusion.


**Publications at other institutions**

- Ribera JM, García-Calduch O, Ribera J, Montesinos P, Cano-Ferri I, Martínez P, Esteve J, Esteban D, García-Fortes M, Alonso N, González-Campos J, Bermúdez A, Torrent A, Genescà E, Mercadal S, Martínez-Lopez J, García-Sanz R (2022). Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood Adv* 6, 5395-5402.
- Dimopoulos MA, Moreau P, Augustson B, Castro N, Pika T, Delimpasi S, De la Rubia J, Maiolino A, Reiman T, Martinez-Lopez J, Martin T, Mikhael J, Yong K, Risse ML, Asset G, Marion S, Hajek R (2022). Isatuximab plus carfilzomib and dexamethasone in patients with relapsed multiple myeloma based on prior lines of treatment and refractory status: IKEMA subgroup analysis. *Am J Hematol* 98, E15-E19.
- Guerrero C, Puig N, Cedena MT, Goicoechea I, Perez C, Garcés JJ, Botta C, Calasanz MJ, Gutierrez NC, Martin-Ramos ML, Oriol A, Rios R, Hernandez MT, Martinez-Martinez R, Bargay J, de Arriba F, Palomera L, Gonzalez-Rodriguez AP, Mosquera-Orgueira A, Gonzalez-Perez MS, Martinez-Lopez J, Lahuerta JJ, Rosiñol L, Blade J, Mateos MV, San-Miguel JF, Paiva B (2022). A machine learning model based on tumor and immune biomarkers to predict undetectable MRD and survival outcomes in multiple myeloma. *Clin Cancer Res* 28, 2598-2609.


**PATENT**

- Martinez 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.

# H12O-CNIO LUNG CANCER CLINICAL RESEARCH UNIT

Luis G. Paz-Ares
Clinical Research Unit Head

Research Scientists
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Clinical Investigators
Rocio García-Carbonero, José Luis Solórzano, Jon Zugazagoitia

Post-Doctoral Fellows
M. Magdalena Abraham, M. Cristina Cirauqui, Juan Manuel Coya, Gorka Ruiz de Garibay

Gradutate Students
Carlos Carretero, M. Inés Díaz, M. Carmen Fernández, Santiago García, David Gómez, María Gutiérrez, Alberto Lens, Ángel Núñez, Javier Ramos, Beatriz Rubio, Joan Salvador Russo (since Sep.), Alba Santos, Patricia Yagüe

Technicians
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Students in Practice
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*Titulado Superior* (Advanced Degree)

## OVERVIEW

Lung cancer continues to be the most frequent cause of cancer-related deaths worldwide. Our Unit focuses on the study of lung cancer, with a pragmatic orientation, always aiming to solve the problems of lung cancer patients. We are particularly interested in 2 research areas: the identification of new molecular biomarkers for diagnostic, prognostic, and predictive purposes; and the development of novel treatment strategies, including targeted therapies and immunotherapeutics. For example, we have contributed to elucidating the molecular determinants of EGFR or FGFR oncogenicity and have discovered biomarkers that may guide the efficacy of inhibitors of those receptors in lung cancer. We have continued developing an extensive platform of patient-derived xenografts (PDXs) and organoids (PDOs) of non-small-cell and small cell lung cancers to test new therapeutic strategies. Finally, our Unit has extensive experience in taking new drugs to the clinic, as well as in conducting practice-changing phase 2/3 trials in the fields of personalised cancer care and immuno-oncology.

**"Our Unit has significantly contributed to the development of novel biomarkers that have impacted the currently available selection of targeted therapies (e.g., EGFR mutation in the clinic) and novel immunotherapeutics (e.g., tumour mutational burden). We have led randomised clinical trials with novel immunotherapies and other agents as monotherapies or in combination (e.g., chemotherapy plus durvalumab in SCLC or chemotherapy plus nivolumab and ipilimumab in NSCLC) in lung cancer that have impacted clinical practice worldwide."**

## RESEARCH HIGHLIGHTS

**Biomarker discovery and implementation**

We own an extensive patient-derived xenograft (PDX) platform of 50 non-small cell lung cancer (NSCLC) and 7 small cell lung cancer (SCLC) models that are comprehensively characterised at the histological, genomic, transcriptomic, and proteomic levels, and that have contributed to the discovery of relevant findings. For example, 2 NSCLC PDX models with high and low expression levels of EGFR contributed to demonstrate that cetuximab-functionalised gold nanoparticles can be used for selective drug delivery in mitochondria-targeted cancer therapy (González-Rubio S *et al.*, *Nanoscale*, 2022). In addition, SCLC PDXs were used to confirm YES1 as a new druggable oncogenic target in SCLC. Pharmacologic blockade with the novel YES1 inhibitor CH6953755 or dasatinib induced marked antitumour activity in organoid models and cell- and patient-derived xenografts (Redin E *et al.*, *J Thorac Oncol*, 2022). Our platforms are expanding in numbers and histologies (NSCLC, SCLC and mesothelioma as well), cell source (tumours but also circulating tumour cells), and include PDX and patient-derived organoids. We have also successfully developed a number of huPDx models.

We have comprehensively characterised the molecular and immune features of a cohort of 18 early-stage, clinically annotated, large cell carcinoma (LCC) cases by genomic and immune-targeted sequencing panels, along with immunohistochemistry of immune cell populations (FIGURE 1). Unbiased clustering defined 2 novel subgroups of LCC that allowed us to identify a set of biomarkers that could potentially predict response to immunotherapy in the least studied form of NSCLC (Ramos-Paradas J,...., Paz-Ares L, *J Clin Med*, 2022). In addition, we performed a multiparametric characterisation of a cohort composed of 120 resected tumour samples from limited-stage

SCLC patients. Samples were described by immunohistochemistry, RNA-seq targeted panel of immune related-genes, exome sequencing, and spatial transcriptomics. We found a novel classification of early-stage SCLC with potential clinical impact in both prognosis and immunotherapy response (manuscript in preparation).

## Early clinical trials

Our Group has significantly expanded its activities regarding the testing of new molecules and combinations in solid tumours, particularly in the field of immune-based approaches and targeted therapies; in 2022, we participated in more than 150 projects in this research area, including 85 new trials. We reported data from a multicenter, international, phase 2 study in which trastuzumab deruxtecan was administered to patients who had metastatic HER2-mutant NSCLC that was refractory to standard treatment. Trastuzumab deruxtecan showed durable anticancer activity, and the observed toxic effects were generally consistent with those in previously reported studies (Li BT,..., Paz-Ares L,..., *N Engl J Med*, 2022). We also evaluated the efficacy and safety of pralsetinib in patients with RET fusion-positive solid tumours. Our pan-cancer phase 1/2 clinical trial showed pralsetinib as a potential well-tolerated treatment option with rapid, robust and durable anti-tumour activity in these patients (Subbiah V,..., Paz-Ares L,..., *Nat Med*, 2022).

## Changing standard-of-care treatments in clinical practice

The Lung Cancer Clinical Research Unit has led phase 3 trials whose results have significantly impacted clinical practice in the context of stage IV lung cancer, such as the combination of first-line nivolumab plus ipilimumab in advanced NSCLC (Paz-Ares L *et al.*, *J Thorac Oncol*, 2022). With the updated results from the randomised, open-label, phase 3 CheckMate 227 Part 1 trial, we showed that at more than 4 years' minimum follow-up, with all the patients off immunotherapy treatment for at least 2 years, first-line nivolumab plus ipilimumab continued to demonstrate durable long-term efficacy. We also assessed pembrolizumab as adjuvant therapy for completely resected stage IB-IIIA NSCLC (O'Brien M, Paz-Ares L, *et al.*, *Lancet Oncol*, 2022). In this randomised, triple-blind, phase 3 trial we found that pembrolizumab significantly improved disease-free survival compared with placebo and was not associated with new safety signals (FIGURE 2). Pembrolizumab is potentially a new treatment option for stage IB-IIIA NSCLC after complete resection and, when recommended, adjuvant chemotherapy, regardless of PD-L1 expression. ■

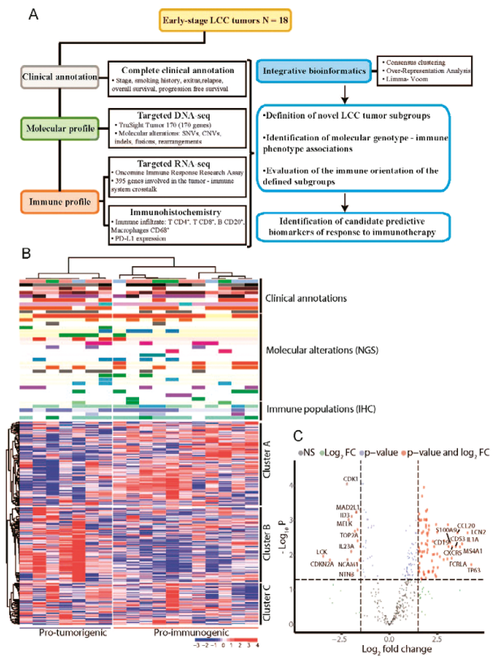


**FIGURE 1** Immune profile of large cell carcinoma (LCC) of the lung. (**A**) Experimental design of the study. (**B**) Definition of novel LCC tumour subgroups. Heatmap of expression of genes involved in tumour-immune system communication. Groups of tumours are shown in the horizontal axis and clusters of genes in the vertical axis as defined by consensus clustering. Molecular, immune and clinical annotations are shown above the heatmap. (**C**) Volcano plot of differentially expressed genes between the pro-immunogenic group and the pro-tumorigenic group of LCC tumours. A false discovery rate (FDR) ≤ 0.05 and log2 fold change ≥ 1l1 were required to reach statistical significance.

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### AWARDS AND RECOGNITION

- International accreditation within the Quality Oncology Practice Initiative (QOPI): to the Medical Oncology Service of the University Hospital *12 de Octubre* for achieving quality standard as defined by the American Society of Clinical Oncology (ASCO), in recognition of excellence in patient assistance.
- *José Baselga* Prize for Translational Innovation in Oncology, 10th annual edition of the Foundation for Excellence and Quality in Oncology (ECO Foundation) - ECO Awards 2022.



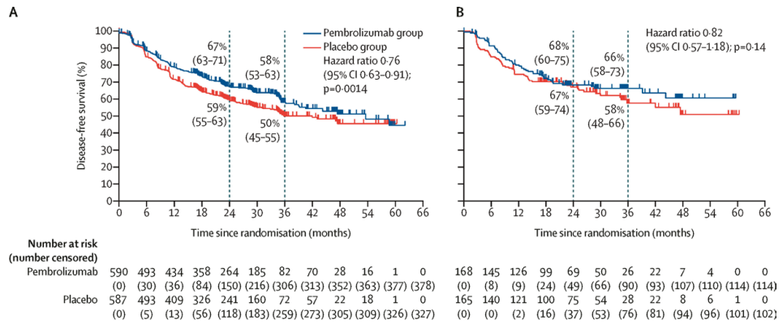


**FIGURE 2** PEARL phase 3 trial evaluating adjuvant pembrolizumab versus placebo in patients with resected early-stage NSCLC. Kaplan-Meier estimates of disease-free survival assessed per RECIST version 1.1 for (**A**) the overall population and (**B**) the PD-L1 Tumour Proportion Score (TPS) of 50% or greater population, showing a sustained benefit in the pembrolizumab group (53.6 months) versus the placebo group (42.0 months) (HR 0·76 [95% CI 0·63–0·91], p=0·0014).

# H12O-CNIO CANCER IMMUNOTHERAPY CLINICAL RESEARCH UNIT

Luis Álvarez-Vallina
(since November)
Clinical Research Unit Head

Research Scientists
Belén Blanco, Anáis Jiménez

Post-Doctoral Fellows
Rodrigo Lázaro, Ángel Ramírez, Antonio Tapia, Ivana Zagorac

Gradutate Students
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Technician
María de La Yedra Pacheco

## OVERVIEW

Our Unit focuses on understanding the molecular and cellular mechanisms of cancer immune escape in order to design next-generation cancer immunotherapies. For example, we have developed a novel strategy based on the secretion of bispecific T cell-engaging antibodies by engineered human T (STAb-T) cells, which has been shown to be effective in solid and haematological malignancies and is currently being tested in clinical trials. The Cancer Immunotherapy Clinical Research Unit has several research areas of interest: 1) reactivation of tumour-specific endogenous T cells; 2) development of tumour-reactive "artificial" T cells; and 3) development of multi-targeting approaches recognising extra- and intracellular tumour antigens. Our group also has a strong interest in the generation of multi-specific antibodies and the use of engineered mRNA-based delivery systems. Finally, our Unit is firmly committed to introducing new immuno-oncology drugs and adoptive cell therapies in the clinic, to provide high-quality personalised treatments.





## RESEARCH HIGHLIGHTS

The year 2022 saw the consolidation of the "STAb-T" cancer immunotherapy strategy as a viable therapeutic option for many cancer patients. The "STAb-T strategy" is a novel adoptive cell therapy (ACT) designed by our Unit, based on the endogenous Secretion of T-cell engaging (TCE) Antibodies (STAb) by T cells (FIGURE 1). The secreted TCE antibodies recruit and activate T cells against cancer cells expressing a predefined tumour antigen. STAb-T cells offer several potential advantages over current T redirection strategies (FIGURE 1). First, *in vivo* secretion might result in effective concentrations of TCEs. Second, *in vivo* secretion can remove potential concerns regarding the formulation and long-term storage of TCEs in a manner that prevents aggregation and deterioration. Third, in STAb-T strategy, T cell recruitment is not restricted to engineered T cells, as in the case of CAR-T cell approaches. The polyclonal recruitment by TCEs of both engineered and unmodified bystander T cells, present at the tumour site, might lead to a significant boost in antitumour T cell responses (FIGURE 1). During 2022, we demonstrated the remarkable therapeutic impact in preclinical models of haematological cancers (B cell leukaemia, T cell leukaemia and multiple myeloma), with a cell product (STAb-T19) currently in a phase I, first-in-human clinical trial in patients with B cell malignancies. Throughout this period, the implementation of this strategy in solid tumours, as well as the design of dual targeting strategies, has been considerably improved. ■

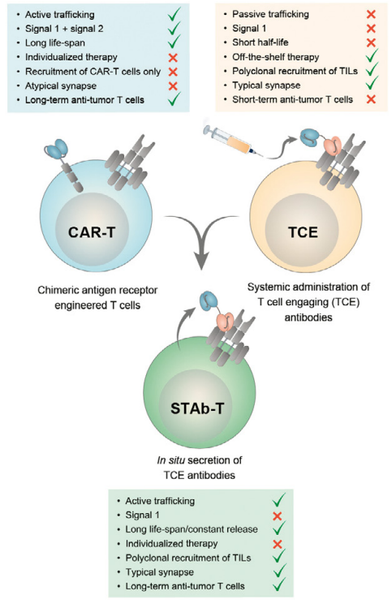


**FIGURE 1** Schematic diagram summarising the advantages (green tick) and limitations (red cross) of T cell-redirecting strategies.

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