H12O-CNIO LUNG CANCER CLINICAL RESEARCH UNIT

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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. ■

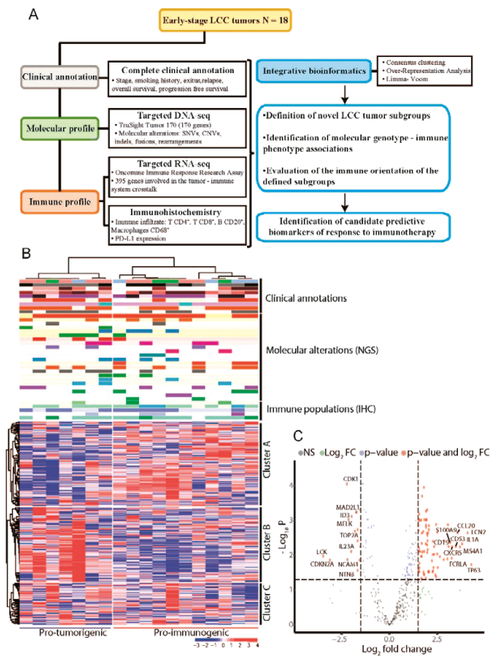

FIGURE 1 Immune profile of large cell carcinoma (LCC) of the lung. (**A**) Experimental design of the study. (**B**) Definition of novel LCC tumour subgroups. Heatmap of expression of genes involved in tumour-immune system communication. Groups of tumours are shown in the horizontal axis and clusters 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.

PUBLICATIONS

- O'Brien M, Paz-Ares L *et al.* (incl. EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators) (2022). Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 23, 1274-1286.
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- Monteiro C *et al.* (incl. Miarka L, Perea-García M, Priego N, García-Gómez P, Álvaro-Espinosa L, de Pablos-Aragoneses A, Yebra N, Retana D, Baena P, Fustero-Torre C, Graña-Castro O, Troulé K, Caleiras E, Ferrer I, Suárez R, Garrido-Martín EM, Paz-Ares L); RENACER, Valiente M (2022). Stratification of radiosensitive brain metastases based on an actionable S100A9/RAGE resistance mechanism. *Nat Med* 28, 752-765.
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- Garcia-Carbonero R *et al.* (incl. Riesco-Martinez MC, Del Pozo N, Martínez de Villarreal J, Real FX) (2022). Phase I, multicenter, open-label study of intravenous VCN-01 oncolytic adenovirus with or without nab-paclitaxel plus gemcitabine in patients with advanced solid tumors. *J Immunother Cancer* 10, e003255.
- Moutafi MK, Molero M, Martinez Morilla S, Baena J, Vathiotis IA, Gavrielatou N, Castro-Labrador L, de Garibay GR, Adradas V, Orive D, Valencia K, Calvo A, Montuenga LM, Ponce Aix S, Schalper KA, Herbst RS, Paz-Ares L, Rimm DL, Zugazagoitia J (2022). Spatially resolved proteomic profiling identifies tumor cell CD44 as a biomarker associated with sensitivity to PD-1 axis blockade in advanced non-small-cell lung cancer. *J Immunother Cancer* 10, e004757.
- Peters S, Paz-Ares L, Herbst RS, Reck M (2022). Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects. *J Immunother Cancer* 10, e004863.
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- Diaz-Cano I, Paz-Ares L, Otano I (2022). Adoptive tumor infiltrating lymphocyte transfer as personalized immunotherapy. *Int Rev Cell Mol Biol* 370, 163-192.
- Jimenez-Fonseca P *et al.* (incl. Riesco MDC, Garcia-Carbonero R) (2022). External validity of somatostatin analogs trials in advanced neuroendocrine neoplasms: the GETNE-TRASGU study. *Neuroendocrinology* 112, 88-100.
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- Paz-Ares L, Gondos A, Saldana D, Thomas M, Mascaux C, Bubendorf L, Barlesi F (2022). Genomic testing among patients with newly diagnosed advanced non-small cell lung cancer in the United States: a contemporary clinical practice patterns study. *Lung Cancer* 167, 41-48.
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- Tsuboi M, Goldman JW, Wu YL, Johnson ML, Paz-Ares L, Yang JC, Besse B, Su W, Chao BH, Drilon A (2022). LIBRETTO-432, a phase III study of adjuvant selpercatinib or placebo in stage IB-IIIA RET fusion-positive non-small-cell lung cancer. *Future Oncol* 18, 3133-3141.

Selected publications at other institutions

- Paz-Ares LG *et al.* (2022). Safety of first-line nivolumab plus ipilimumab in patients with metastatic non-small cell lung cancer: a pooled analysis of CheckMate 227, CheckMate 568, and CheckMate 817. *J Thorac Oncol* 18, 79-92.
- Vidal J *et al.* (incl. Garcia-Carbonero R) (2022). Liquid biopsy detects early molecular response and predicts benefit to first-line chemotherapy plus cetuximab in metastatic colorectal cancer: PLATFORM-B study. *Clin Cancer Res* 29, 379-388.
- Levy B, Barlesi F, Paz-Ares L *et al.* (2022). Phase II study of afatinib plus pembrolizumab in patients with squamous cell carcinoma of the lung following progression during or after first-line chemotherapy (LUX-Lung-IO). *Lung Cancer* 166, 107-113.
- Paredes-Ruiz D *et al.* (incl. Paz-Ares L) (2022). Incidence of venous thromboembolism in patients with non-hematological cancer admitted for COVID-19 at a third-level hospital in Madrid. *J Thromb Thrombolysis* 53, 471-478.
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- Chen Y, Paz-Ares L *et al.* (2022). Impact of brain metastases on treatment patterns and outcomes with first-line durvalumab plus platinum-etoposide in extensive-stage SCLC (CASPIAN): a brief report. *JTO Clin Res Rep* 3, 100330.

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.

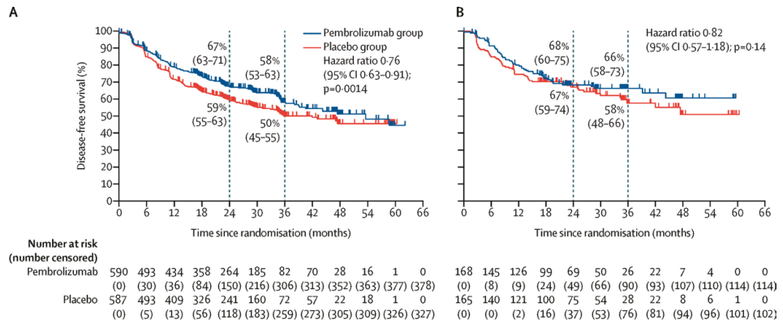

FIGURE 2 PEARL phase 3 trial evaluating adjuvant pembrolizumab versus placebo in patients with resected early-stage NSCLC. Kaplan-Meier estimates of disease-free survival assessed per RECIST version 1.1 for (**A**) the overall population and (**B**) the PD-L1 Tumour Proportion Score (TPS) of 50% or greater 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).