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.

**RESEARCHER 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 Y851 as a new druggable oncogenic target in SCLC. Pharmacologic blockade with the novel Y851 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 (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
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 with metastatic HER2-mutant NSCLC that was refractory to standard-of-care therapy. Trastuzumab deruxtecan showed durable antitumor activity, and the observed toxicity effects were generally consistent with those in previously reported studies (Li RT, Paz-Ares L, Nat Eng J Med. 2022).

We also evaluated the efficacy and safety of pralsetinib in patients with RET fusion-positive solid tumours. Our pan RET phase I/II clinical trial showed pralsetinib as a potential well-tolerated treatment option with robust, rapid and durable antitumor activity in these patients (Subbhi 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 in recent years. In 2022, we participated in more than 23 phase 3 trials. The Lung Cancer Clinical Research Unit has led phase 3 trials in various fields, including immune-based approaches and targeted therapies; in 2022, we participated in more than 30 phase 3 trials.


