Lung cancer continues to be the most frequent cause of cancer-related deaths worldwide. Our Unit focuses on the study of lung cancer, from fundamental research proposals to other more clinically oriented ones, always aiming to solve the problems of lung cancer patients. We are particularly interested in two 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 to develop an extensive platform of patient-derived xenografts 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 II/III trials in the fields of personalised cancer care and immuno-oncology.

“Our Unit contributed remarkably to the development of predictive biomarkers that have impacted the currently available selection of targeted therapies (e.g., EGFR mutation, NTRK rearrangements) and novel immunotherapeutics (e.g., tumour mutational burden in the clinic). We have led controlled clinical trials with novel agents as well as combinations of targeted therapies (e.g., ramucirumab plus pembrolizumab) or checkpoint inhibitors (e.g., chemotherapy plus nivolumab plus ipilimumab) in lung cancer that have impacted clinical practice worldwide.”

RESEARCH HIGHLIGHTS

Biomarker discovery and implementation

We currently own an extensive patient-derived xenograft (PDX) platform that has led to the deciphering of the role of the tyrosine kinase receptors, FGFR1 and FGFR4, and the adhesion molecule N-cadherin in non-small cell lung cancer (NSCLC), and to develop new biomarkers with a predictive role for anti-FGFR therapy in NSCLC (Quintanal-Villalonga A et al., EBioMedicine 2020). In this study, only co-expression of FGFR1 and/or FGFR4 with N-cadherin in different lung cancer patient cohorts inferred a poorer outcome. Treatment of high FGFR1- and/or FGFR4-expressing lung cancer cell lines and PDXs with selective FGFR inhibitors showed high efficacy, but only in models with high FGFR1/4 and N-cadherin expression. We therefore provide in vitro and in vivo evidence showing that expression of the adhesion molecule N-cadherin is key for the oncogenic role of FGFR1/4 in NSCLC. In addition, our data show that the complementary determination of N-cadherin and FGFR1/4 expression may further optimise patient selection for anti-FGFR therapy efficacy. Moreover, our PDX platform has also contributed to discovering Notch as a novel therapeutic target in lung adenocarcinoma osimertinib-treated patients after disease progression (Bousquet Mur E et al., JCI 2020), as well as to test novel combination therapies, including a novel neutralising anti-HER3 antibody, to overcome resistance to EGFR targeted therapies (Romanello D. et al., Cancers (Basel) 2020).

In 2020, we performed a harmonisation study to determine the tumour mutational burden (TMB) in a clinically well-annotated cohort of 96 resected patients with NSCLC. We evaluated the TMB assessment concordance of 2 novel next generation sequencing (NGS) panels, TSO500 and Oncomine TML (OTML), compared to a reference assay...
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; in 2020, we participated in more than 45 projects in this research area, including 10 new projects. We reported data from novel combinations of first-line ramucirumab plus pembrolizumab (Herbst RS, et al., Lancet Oncol 2020) and second-line ramucirumab plus osimertinib (Yu Ha, et al., Lancet Cancer Res 2020). Recently, we tested the safety and efficacy of bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of the transforming growth factor-β receptor (TGF-βR) and LMP7, a transmembrane protease. In a phase III trial led by Luis Paz-Ares (Lancet Oncol 2020), in small cell lung cancer with encouraging activity on the second three-line setting (Trigo J, Paz-Ares L, Lancet 2020). At present, combination studies with immunotherapy and atezolizumab are ongoing. Bintrafusp and lurbinectin are now being tested in a phase IIA trial led by Luis Paz-Ares.

Changing standard-of-care treatments in clinical practice

The Lung Cancer Clinical Research Unit halted phase III trials whose results have significantly impacted clinical practice in the combination of pembrolizumab plus chemotherapy in NSCLC patients (Paz-Ares L, et al., JTO 2020). In the protocol-specified final analysis of KEYNOTE-407, this combination continued to exhibit a clinically meaningful improvement in overall survival (OS), progression-free survival (PFS), second PFS (PS2), overall response rate (ORR), and duration of response (DOR), compared with placebo plus carboplatin-paclitaxel/nab-paclitaxel in patients with previously untreated metastatic squamous NSCLC. In addition, the exploratory results of the PACIFIC trial of outcomes by tumour CT (programmed death-ligand 1 (PD-L1) expressing) showed that PFS benefit with durvalumab was observed across all subgroups, and OS benefit across all but TC <1%, for which limitations and wide HR CI preclude robust conclusions (Paz-Ares L, et al., Ann Oncol 2020). Finally, the WILA trial showed the superiority (including prolonged survival) of a short course of chemotherapy plus nivolumab and nivolumab, compared to chemotherapy alone in advanced NSCLC.

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**PUBLICATIONS**

- Vilarino J et al. (2020). Non-small cell lung cancer in the context of stage IV lung cancer, such as the combination of pembrolizumab plus chemotherapy in NSCLC patients (Paz-Ares L, et al., JTO 2020).
- 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; in 2020, we participated in more than 45 projects in this research area, including 10 new projects. We reported data from novel combinations of first-line ramucirumab plus pembrolizumab (Herbst RS, et al., Lancet Oncol 2020) and second-line ramucirumab plus osimertinib (Yu Ha, et al., Lancet Cancer Res 2020). Recently, we tested the safety and efficacy of bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of the transforming growth factor-β receptor (TGF-βR) and LMP7, a transmembrane protease. In a phase III trial led by Luis Paz-Ares (Lancet Oncol 2020), in small cell lung cancer with encouraging activity on the second three-line setting (Trigo J, Paz-Ares L, Lancet 2020). At present, combination studies with immunotherapy and atezolizumab are ongoing. Bintrafusp and lurbinectin are now being tested in a phase IIA trial led by Luis Paz-Ares.

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**CLINICAL RESEARCH PROGRAMME**

**NSCLC-1544 TRAILING LINE**

**FIGURE 1** (A) AZD4547 treatment of low (blue) and high (red) PD-L1 expressing NSCLC patients. (B) Kaplan-Meier curves showing high-FGFR1 and/or high-FGFR4-expressing PDXs with selective FGFR inhibitors showed high efficacy, but only high-FGFR1 inhibition achieved high overall survival (Hazard ratio of 0.89 [1.02-3.49], p = 0.039) compared to patients with elevated expression of both genes.

**FIGURE 2** Updated efficacy outcomes of the KEYNOTE-407 randomised clinical trial, showing an improvement in overall survival (OS) with pembrolizumab plus chemotherapy, compared to chemotherapy alone (HR 0.7; 95% CI 0.56-0.98); in treatment-naïve patients with metastatic squamous non-small cell lung cancer (NSCLC).

**SELECTED PUBLICATIONS AT OTHER INSTITUTIONS**