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.”

**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
New high expression of FGFR1 or 4 and NSCLC genes had the poorest prognosis, while the group with high FGFR2 or 3 had the best prognosis. 

(FIGURE 1: A) AZD4634 treatment of low FGFR1/FGFR2-expressing models (violin plots) with selective FGFR4 inhibitors showed improved treatment efficacy in models with high FGFR3 expression; (B) Kaplan–Meier curves of overall survival (OS) showing high overall survival (Hazard Ratio of 0.89 [1.023-4.41], p = 0.039) compared to patients with low expression of both genes.

FIGURE 2 Updated efficacy outcome of the KEYNOTE-407 randomized clinical trial, showing an improvement in overall survival (OS) with pembrolizumab plus chemotherapy, compared to chemotherapy alone (HR: 0.7 [95% CI: 0.58-0.88]). In treatment-naïve patients with metastatic squamous non-small cell lung cancer (NSCLC).

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