**OVERVIEW**

Lung cancer remains 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 specifically focus on 2 research areas: the identification of novel 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 evaluate emerging therapeutic strategies. Finally, our Unit has extensive experience in taking new drugs (pemetrexed, erlotinib, nivolumab, tarlatamab and many others) to the clinic, as well as in conducting practice-changing trials in the fields of personalised cancer care and immuno-oncology.

“We have provided proof of concept that T cell engagers (TCEs) provide an efficacious strategy, at the cost of reasonable side effects, in cold solid tumours such as SCLC, including those lacking canonical T cell activation through antigen presentation (JCO 2023; NEJM 2023).”
Tarlatamab showed promising antitumour activity in patients with small cell lung cancer (SCLC)

Two early trials led by our group demonstrated the efficacy of tarlatamab, a bispecific T-cell engager targeting DLL3 and NCAM1, in patients with SCLC. In the first-in-human (FIH) clinical trial, 107 patients treated with tarlatamab revealed a 23.4% objective response rate, a median response duration of 12.3 months and median survival of 13.2 months, with encouraging safety outcomes, despite treatment-related adverse events in 67.0%, mainly cytokine-release syndrome (32%). In the second phase 2 clinical trial, involving 220 patients with previously treated SCLC, the administration of tarlatamab at dosages of 10 mg or 100 mg every 2 weeks demonstrated antitumour activity with durable responses, showing 40% and 32% objective response rates, respectively. Median progression-free survival was 4.9 months and 3.9 months, with estimated 9-month overall survival rates of 68% and 66%, respectively. Cytokine-release syndrome was the most common adverse event, but a low percentage of patients discontinued treatment due to adverse events in both arms. These findings underscore tarlatamab’s potential in pretreated SCLC, warranting further evaluation.

Efficacy of sotorasib compared to docetaxel for the treatment of non-small-cell lung cancer (NSCLC)

In this clinical trial, we evaluated the efficacy and safety of sotorasib compared to docetaxel in the treatment of NSCLC with KRASG12C mutations. Patients treated with sotorasib showed significant improvement in progression-free survival (HR 0.65) and overall response rate compared to patients receiving docetaxel, in addition, sotorasib-treated patients presented better toxicity profiles, providing better quality of life. As a result of this investigation, the EMA recently approved the therapeutic use of tarlatamab in pretreated patients with NSCLC having underlying KRASG12C mutations.

ONCOS-102 combined with pemetrexed and platinum chemotherapy for the treatment of malignant pleural mesothelioma (MPM)

In this early clinical trial, we showed the synergistic effect of combining a new immunotherapy agent, ONCOS-102 (an oncolytic adenovirus), with the conventional standard plus platinum chemotherapy regimen for the treatment of MPM. We evaluated both the clinical outcome of patients plus the impact of the novel strategy on the tumour microenvironment. The treatment resulted in a relevant median overall survival (up to 30 months), and the results were particularly promising in chemotherapy-naive patients. We observed increased T-cell infiltration in patients with KRASG12C-treated patients, differences in the transcriptome of several genes, including those associated with complement activation, humoral immune response, and regulation of acute inflammatory response. The results might shed light on new ways to tackle this very challenging disease.

• PUBLICATIONS
  • Paz-Ares L et al. (2023). Tarlatamab, a bispecific antibody against DLL3 and NCAM1, for the treatment of non-small-cell lung cancer (NR-012): a single-arm, open-label, phase 2b trial. Eur J Cancer. PMID: 37786770.

• RESOURCES

- The Kaplan-Meier curve of progression-free survival among patients in the sorafenib group and patients in the placebo group could be assessed for a response according to blinded, independent central review.

- The panel shows the time to response, the duration of response, and patient status as of the data cut-off date for all the patients who were assessed as having an objective response (complete or partial response; primary end point) at 10 mg or 100 mg of tarlatamab.