H12O-CNIO LUNG CANCER CLINICAL RESEARCH UNIT

Luis G. Paz-Ares
Clinical Research Unit Head

Staff Scientists
Teresa Argullo, Irene Ferrer, Rocio García, Eva M. Garrido, Santiago Ponce, M. Carmen Riesco

Clinical Investigator
M. Teresa Muñoz (since October)

Post-Doctoral Fellows
Pablo Gella (until May), María Pedraza (until April), Beatriz Soldevilla

Graduate Students
Carlos Carretero, Santiago García, Ángela Marrugal, Ángel Nuñez (since September), Laura Ojeda, Álvaro Quintanal (until February), Javier Ramos, Beatriz Rubio (since September), Patricia Yagüe

Technicians
M. Cristina Cirauqui (since July), Patricia Cozar, M. José Durán (until June), Aicha El Bakkali (until August), Mirella Gallego (since February), Laura García, Beatriz Gil, Rocío Suárez

Students in Practice
Ana González (until July), Alba Santos (since November)

OVERVIEW

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 that are closer to solving the problems of lung cancer patients. The two main research areas of our Unit involve: the identification of new molecular biomarkers that can be used in the clinic for diagnostic, prognostic and predictive purposes; and the development of novel treatment strategies that include 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. On the other hand, we have developed a patient-derived xenograft (PDX) platform of non-small-cell lung cancers to test new therapeutic strategies. Finally, our Unit has extensive experience in taking new drugs to the clinic (phase I trials), as well as in conducting practice-changing phase II/III trials in the fields of precision oncology and immuno-oncology.

"Our Unit has significantly contributed to the development of novel biomarkers that have impacted the currently availble selection of targeted therapies (e.g. EGFR mutation in the clinic) and novel inmunotherapeutics (e.g. tumour mutational burden). We have led randomised clinical trials with novel agents (e.g. erlotinib, afatinib, Nivolumab, M7824) as well as combinations of checkpoint inhibitors (e.g. Ipilimumab plus Nivolumab, chemotherapy plus Pembrolizumab, Durvalumab following chemoradiation) in lung cancer that have impacted clinical practice worldwide."

RESEARCH HIGHLIGHTS

Biomarker discovery and implementation

The Group has deciphered the biological role of FGFR1 and FGFR4 in non-small cell lung cancer (NSCLC) and has developed new biomarkers with a predictive role for anti-FGFR therapy in NSCLC. Currently, we are validating the results on a series of well characterised PDX models, generating a diagnostic kit and carrying out the technical validation of the biomarker, as well as planning a phase II trial proposal with an FGFR inhibitor in NSCLC patients with high expression of the novel biomarker.

The Group has also validated an NGS-based algorithm for the determination of genomic aberrations (in tumour tissue but also in cfDNA) that may guide treatment for clinical practice. More recently, we have led the first clinical validation of tumour mutational burden as a predictive biomarker for checkpoint inhibitors in lung cancer, and particularly, for Ipilimumab plus Nivolumab.

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 2018, we participated in more than 35 projects in this research area. Recently, our Group provided feasibility and encouraging initial data on the anti-tumour activity of M7824, a bifunctional fusion protein targeting PD-L1 and TGF-beta in pretreated NSCLC (response rate in PD-L1 expressing tumours in more than 50% of the cells: 71%). Encouraging tumour-agnostic data of Entrectinib in tumours driven by activated NTRK fusion proteins were presented at the ESMO 2018 Congress (response rate 57.4%; median progression-free survival of 11.4 moths).

Changing standard-of-care treatments in clinical practice

The Lung Cancer Clinical Research Unit has led phase III trials whose results have significantly impacted the clinical practice in the context of stage IV lung cancer with combinations of chemotherapy plus Pembrolizumab or Ipilimumab plus Nivolumab (Hellmann MD *et al.*, *NEJM* 2018; Paz-Ares L *et al.*, *NEJM* 2018). In addition, the Group has actively contributed to the results of a Phase III trial showing a significant improvement in survival for stage III NSCLC patients treated with the anti PD-L1 agent *Durvalumab* following chemoradiation (Antonia S *et al.*, *NEJM* 2018). ■

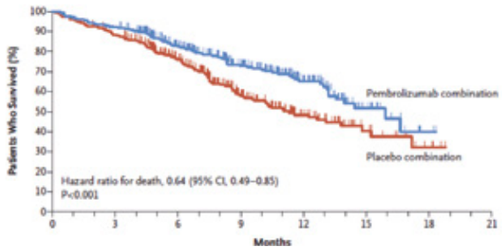

Figure 1 Results of the KeyNote 407 randomised clinical trial, showing an improvement in overall survival (OS) of chemotherapy plus Pembrolizumab, as compared to chemotherapy alone (HR 0.64; p<0.001) in stage IV Non-Small-Cell Lung Cancer (NSCLC) patients.

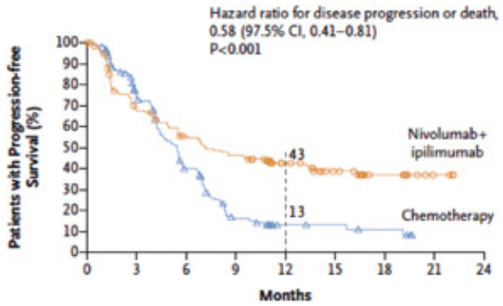

Figure 2 Results of the Checkmate 227 randomised clinical trial, showing the superiority in progression-free survival (PFS) for the Ipilimumab plus Nivolumab combination, as compared to platinum chemotherapy (HR 0.58; p<0.001) in stage IV NSCLC with high mutational burden (>10 mutations per MB).

PUBLICATIONS

- Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Faivre-Finn C, Reck M, Vansteenkiste J, Spigel DR, Wadsworth C, Melillo G, Taboada M, Dennis PA, Özgüroğlu M; PACIFIC Investigators (2018). Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 379, 2342-2350.
- Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, Minenza E, Linardou H, Burgers S, Salman P, Borghaei H, Ramalingam SS, Brahmer J, Reck M, O'Byrne KJ, Geese WJ, Green G, Chang H, Szustakowski J, Bhagavatheeswaran P, Healey D, Fu Y, Nathan F, Paz-Ares L (2018). Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 378, 2093-2104.
- Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B, Kowalski DM; KEYNOTE-407 Investigators (2018). Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 379, 2040-2051.
- Bonomi PD, Gandara D, Hirsch FR, Kerr KM, Obasaju C, Paz-Ares L, Bellomo C, Bradley JD, Bunn PA Jr, Culligan M, Jett JR, Kim ES, Langer CJ, Natale RB, Novello S, Pérol M, Ramalingam SS, Reck M, Reynolds CH, Smit EF, Socinski MA, Spigel DR, Vansteenkiste JF, Wakelee H, Thatcher N (2018). Predictive biomarkers for response to EGFR-directed monoclonal antibodies for advanced squamous cell lung cancer. *Ann Oncol* 29, 1701-1709.
- Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L (2018). Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol* 29(suppl_1), i10-i19.
- Siena S *et al.* (2018). Dynamic molecular analysis and clinical correlates of tumor evolution within a phase II trial of panitumumab-based therapy in metastatic colorectal cancer. *Ann Oncol* 29, 119-126.
- Tabernero J *et al.* (2018). Analysis of angiogenesis biomarkers for ramucirumab efficacy in patients with metastatic colorectal cancer from RAISE, a global, randomized, double-blind, phase III study. *Ann Oncol* 29, 602-609.
- Zugazagoitia J *et al.* (incl. Paz-Ares L, Manzano A) (2018). Incidence, predictors and prognostic significance of thromboembolic disease in patients with advanced ALK-rearranged non-small cell lung cancer. *Eur Respir J* 51, 1702431.
- Kim ES, Kelly K, Paz-Ares LG, Garrido P, Jalal S, Mahadevan D, Gutierrez M, Provencio M, Schaefer E, Shaheen M, Johnston EL, Turner PK, Kambhampati SRP, Beckmann R, Hossain A, John WJ, Goldman JW (2018). Abemaciclib in combination with single-agent options in patients with stage IV non-small cell lung cancer: a phase Ib study. *Clin Cancer Res* 24, 5543-5551.
- Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn PA Jr, Kim ES, Langer CJ, Natale RB, Novello S, Paz-Ares L, Pérol M, Reck M, Ramalingam SS, Reynolds CH, Spigel DR, Wakelee H, Thatcher N (2018). Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol* 13, 165-183.
- Barriuso J, Custodio A, Afonso R, Alonso V, Astudillo A, Capdevila J, García-Carbonero R, Grande E, Jimenez-Fonseca P, Marazuela M, Rodríguez-Antona C, Aller J (2018). Prognostic and predictive biomarkers for somatostatin analogs, peptide receptor radionuclide therapy and serotonin pathway targets in neuroendocrine tumours. *Cancer Treat Rev* 70, 209-222.
- Block MS *et al.* (incl. Paz-Ares L) (2018). MyD88 and TLR4 expression in epithelial ovarian cancer. *Mayo Clin Proc* 93, 307-320.
- Ferrer I, Quintanal-Villalonga Á, Molina-Pinelo S, Garcia-Heredia JM, Perez M, Suárez R, Ponce-Aix S, Paz-Ares L, Carnero A (2018). MAP17 predicts sensitivity to platinum-based therapy, EGFR inhibitors and the proteasome inhibitor bortezomib in lung adenocarcinoma. *J Exp Clin Cancer Res* 37, 195.
- Nuñez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, Capdevila J, Castaño-Pascual Á, Benavent M, Pi Barrio JJ, Teule A, Alonso V, Custodio A, Marazuela M, Segura Á, Beguiristain A, Llanos M, Martinez Del Prado MP, Diaz-Perez JA, Castellano D, Sevilla I, Lopez C, Alonso T, Garcia-Carbonero R (2018). Neuroendocrine tumor heterogeneity adds uncertainty to the World Health Organization 2010 classification: real-world data from the Spanish tumor registry (R-GETNE). *Oncologist* 23, 422-432.
- Quintanal-Villalonga Á, Mediano M, Ferrer I, Meléndez R, Carranza-Carranza A, Suárez R, Carnero A, Molina-Pinelo S, Paz-Ares L (2018). Histology-dependent prognostic role of pERK and p53 protein levels in early-stage non-small cell lung cancer. *Oncotarget* 9, 19945-19960.
- Sorbye H, Baudin E, Borbath I, Caplin M, Chen J, Cwikla J, Frilling A, Grossman A, Kaltsas G, Scarpa A, Welin S, Garcia-Carbonero R, ENETS 2016 Munich Advisory Board Participants (2018). Unmet needs in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). *Neuroendocrinology*. PMID: 30153658.
- Hirsch FR, Kerr KM, Bunn PA Jr, Kim ES, Obasaju C, Pérol M, Bonomi P, Bradley JD, Gandara D, Jett JR, Langer CJ, Natale RB, Novello S, Paz-Ares L, Ramalingam SS, Reck M, Reynolds CH, Smit EF, Socinski MA, Spigel DR, Stinchcombe TE, Vansteenkiste JF, Wakelee H, Thatcher N (2018). Molecular and immune biomarker testing in squamous-cell lung cancer: effect of current and future therapies and technologies. *Clin Lung Cancer* 19, 331-339.
- Wu YL, Sequist LV, Tan EH, Geater SL, Orlov S, Zhang L, Lee KH, Tsai CM, Kato T, Barrios CH, Schuler M, Hirsh V, Yamamoto N, O'Byrne K, Boyer M, Mok T, Peil B, Märten A, Chih-Hsin Yang J, Paz-Ares L, Park K (2018). Afatinib as first-line treatment of older patients with EGFR mutation-positive non-small-cell lung cancer: subgroup analyses of the LUX-lung 3, LUX-lung 6, and LUX-lung 7 trials. *Clin Lung Cancer* 19, e465-e479.
- Gridelli C, Baas P, Barlesi F, Ciardiello F, Crinò L, Felip E, Gadgeel S, Papadimitrakopoulou V, Paz-Ares L, Planchard D, Perol M, Hanna N, Sgambato A, Casaluce F, de Marinis F (2018). Second-line treatment options in non-small-cell lung cancer: report from an international experts panel meeting of the Italian association of thoracic oncology. *Clin Lung Cancer* 19, 301-314.
- Reck M, Garon EB, Paz-Ares L, Ponce S, Jaime JC, Juan O, Nadal E, Kiura K, Widau RC, He S, Dalal R, Lee P, Nakagawa K (2018). Randomized, double-blind phase Ib/III study of erlotinib with ramucirumab or placebo in previously untreated EGFR-mutant metastatic non-small-cell lung cancer (RELAY): phase Ib results. *Clin Lung Cancer* 19, 213-220.
- Pavel M, Gross DJ, Benavent M, Perros P, Srirajaskanthan R, Warner RRP, Kulke MH, Anthony LB, Kunz PL, Hörsch D, Weickert MO, Lapuerta P, Jiang W, Kassler-Taub K, Wason S, Fleming R, Fleming D, Garcia-Carbonero R (2018). Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Relat Cancer* 25, 309-322.
- Ciuleanu T, Socinski MA, Obasaju C, Luft AV, Szczesna A, Szafrański W, Ramlau R, Bálint B, Molinier O, Depenbrock H, Nanda S, Paz-Ares L, Thatcher N (2018). Efficacy and safety of necitumumab continuation therapy in the Phase III SQUIRE study of patients with stage IV squamous non-small-cell lung cancer. *Clin Lung Cancer* 19, 130-138.
- Zugazagoitia J, Rueda D, Carrizo N, Enguita AB, Gómez-Sánchez D, Díaz-Serrano A, Jiménez E, Mérida A, Calero R, Lujan R, De Miguel E, Gámez P, Díaz-Hellín V, Nuñez JA, Iglesias L, Ferrer I, Paz-Ares L, Ponce-Aix S (2018). Prospective clinical integration of an amplicon-based next-generation sequencing method to select advanced non-small-cell lung cancer patients for genotype-tailored treatments. *Clin Lung Cancer* 19, 65-73.e7.
- Quintanal-Villalonga Á, Ojeda-Márquez L, Marrugal Á, Yagüe P, Ponce-Aix S, Salinas A, Carnero A, Ferrer I, Molina-Pinelo S, Paz-Ares L (2018). The FGFR4-388Arg variant promotes lung cancer progression by N-cadherin induction. *Sci Rep* 8, 2394.
- Ferrer I, Zugazagoitia J, Herbertz S, John W, Paz-Ares L, Schmid-Bindert G (2018). KRAS-mutant non-small cell lung cancer: from biology to therapy. *Lung Cancer* 124, 53-64.
- Young K, Paz-Ares L, Thatcher N, Spigel DR, Shahidi J, Soldatenkova V, Grau G, Kurek R, Shepherd FA (2018). Venous thromboembolism with EGFR monoclonal antibody necitumumab in stage IV non-small cell lung cancer: a retrospective cohort analysis. *Thromb Res* 167, 50-56.
- Almendros I *et al.* (2018). Early career members at the ERS lung science conference: cell-matrix interactions in lung disease and regeneration: early career forum. *Breathe (Sheff)* 14, e78-e83.

Selected publications at other insitutions

- Fehrenbacher L *et al.* (2018). Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. *J Thorac Oncol* 13, 1156-1170.
- Salazar R, Garcia-Carbonero R *et al.* (2018). Phase II study of BEZ235 versus everolimus in patients with mammalian target of rapamycin inhibitor-naïve advanced pancreatic neuroendocrine tumors. *Oncologist* 23, 766-e90.
- Van Cutsem E *et al.* (2018). Regorafenib for patients with metastatic colorectal cancer who progressed after standard therapy: results of the large, single-arm, open-label phase IIIb CONSIGN study. *Oncologist*. PMID: 30190299.
- Martinez-Perez J, Riesco-Martinez MC, Garcia-Carbonero R (2018). The safety of trifluridine and tipiracil for the treatment of metastatic colorectal cancer. *Expert Opin Drug Saf* 17, 643-650.

AWARDS AND RECOGNITION

- *Premio* 'Best in Class (BIC)' 2018 *en Investigación en Oncología*, Spain.