Science and biology drives the immune system to cure lung cancer patients: a revolution but not without challenges

Niki Karachaliou and Rafael Rosell

Keywords: anti-PD-1/PD-L1, biomarkers, combinations, immunotherapy, lung cancer

Introduction
In 2002, the immune checkpoint programmed death ligand-1 (PD-L1), also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1), was for the first time described as a mechanism of immune escape for tumor cells.1,2 Injection with an anti-PD-1 monoclonal antibody, subsequently developed by Bristol-Myers Squibb as nivolumab, inhibited the hematogenous dissemination of various tumor cells in mice models.1 Now in 2017, several drugs that release the constraints of immune checkpoints offer unique therapeutic opportunities in several type of tumor. Immunotherapy has redefined standard-of-care treatment of non-small cell lung cancer (NSCLC) patients in the first- and second-line setting. There is also enthusiasm about its potential in small-cell lung cancer.3,4 In this Special Collection for Therapeutic Advances in Medical Oncology, entitled ‘Immunotherapy for Lung Cancer: Progress, Opportunities and Challenges’, many prestigious investigators will express their opinion and describe their own experience on the progress of immunotherapy for lung cancer patients, including the benefits and the challenges that this novel therapeutic approach has posed in our daily clinical practice.

NSCLC patients who receive nivolumab as second-line therapy have a 28% lower risk of death in comparison with those receiving standard chemotherapy.5-7 Another anti-PD-1 monoclonal antibody, pembrolizumab, prolongs overall survival of previously treated metastatic NSCLC patients but only if at least 1% of tumor cells express PD-L1.8 In two clinical trials, the anti-PD-L1 antibody atezolizumab benefited the survival of previously treated NSCLC patients compared with docetaxel, independent of PD-L1 status.9,10 The safety and antitumor activity of the anti-PD-L1 inhibitor avelumab has been reported in patients with progressive or platinum-resistant metastatic or recurrent NSCLC, irrespective of PD-L1 expression.11 Finally the anti-PD-L1 inhibitor durvalumab achieved durable responses in heavily-pretreated PD-L1-positive metastatic NSCLC patients.12 Nivolumab, pembrolizumab and atezolizumab are approved for the management of previously treated patients with advanced NSCLC, with pembrolizumab being restricted to tumors expressing PD-L1.

Single-agent pembrolizumab provides a clear progression-free survival and overall survival benefit for previously-untreated NSCLC patients with PD-L1 expression on at least 50% of tumor cells.13 In the CheckMate-026 study, nivolumab was not able to demonstrate similar clinical benefit in the first-line setting for NSCLC patients with PD-L1 expression on at least 5% of tumor cells, when compared with platinum-based chemotherapy.14 Single anti-PD-L1 monotherapies with atezolizumab or avelumab are currently being evaluated for the first-line treatment of PD-L1-positive NSCLC patients, in the phase III clinical trials IMpower 110 [Clinical Trials.gov identifier: NCT02409342] and JAVELIN Lung 100 [ClinicalTrials.gov identifier: NCT02576574], respectively. Clinical activity was seen with durvalumab as first-line therapy in NSCLC patients with more than 25% PD-L1 positive tumor cells,15 data that are further being evaluated in the ongoing PEARL phase III clinical trial.16
Very importantly, adjuvant durvalumab after chemoradiotherapy prolonged progression-free survival compared with placebo for patients with locally advanced unresectable NSCLC. The results of the PACIFIC study undeniably point to implementing immunotherapy after chemoradiotherapy in patients with stage III NSCLC. Doubts may be raised on the efficacy of immune checkpoint blockade as adjuvant therapy for resectable NSCLC. For instance, in breast cancer, neoadjuvant immunotherapy eradicated distant metastases more efficiently than adjuvant immunotherapy. This may be due to the fact that lymph node dissection reduces the antitumor activity of the immune system.

The most important challenge for lung cancer immunotherapy is that these treatments have demonstrated efficacy in a minority of patients. Until now, the identification of biomarkers that can help us to select patients for cancer immunotherapy has been a very difficult process. Immunohistochemistry assays that evaluate the proportion of tumor cells expressing PD-L1 are the ones that have been prospectively evaluated in clinical trials and are most commonly used in daily clinical practice. However, there are concerns regarding how a test using a fixed percentage of PD-L1-positive tumor cells can determine the appropriate patients for treatment. No single biomarker can discriminate responders from non-responders in PD-1/PD-L1 blockade therapy, and this point will be extensively discussed in the current Special Collection of Therapeutics Advances in Medical Oncology.

PD-L1 expression is induced by interferon gamma (IFN-γ), or by oncogenic signaling pathways. Smoking status and high tumor-mutation burden have been associated with clinical efficacy of immune checkpoint blockade in lung cancer. In contrast, response rates to immune checkpoint blockade of only 3–4% have been reported for lung cancer patients who are never or light smokers, or their tumor is driven by epidermal growth factor receptor (EGFR) mutations or echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangements. The association of tumor-mutation burden with response to immune checkpoint blockade is higher when clonality or neoantigen heterogeneity is simultaneously assessed. Tumor-mutation burden can be assessed in the blood, and recently a blood-tumor mutation burden of more than 16 was retrospectively found to be predictive of outcome to atezolizumab. Currently, the blood-tumor mutation burden has been incorporated as a noninvasive companion diagnostic assay of response to first-line atezolizumab in advanced NSCLC patients in the randomized phase III Blood First Assay Screening Trial (BFAST). The recent finding that both the tumor genome and the features of the microenvironment evolve in response to anti-PD-1/PD-L1 therapy has added to the complexity of the mechanisms of action of immune checkpoint blockade. Mutational contraction, defined as a decrease of the initial high frequency of tumor clonal and single nucleotide variations after therapy with nivolumab, is observed in good responders. In contrast, a high frequency of novel single nucleotide variations during nivolumab therapy (mutational persistence) was observed in nonresponders to PD-1 blockade. Therefore, more than a clinical assessment of response, a molecular phenotype of response (tumor genomic contraction/persistence) at an early time point of treatment could more adequately represent the underlying biological changes and predict the outcome to immune checkpoint blockade.

Another point that will be highlighted in the Special Collection is combinational immunotherapy strategies. Apart from the inhibitory receptors PD-1 and PD-L1, there are several other T-cell activating or inhibitory receptors that control immune responses and immune tolerance. The combination of anti-PD-1 and anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) antibodies has been approved for melanoma patients and is being clinically tested in other type of tumors, including lung cancer. The safety and promising efficacy of the anti-CD137 (or anti-41BB) monoclonal antibody utolimumab combined with pembrolizumab was recently demonstrated. Several clinical trials combining immune checkpoint inhibitors, chemotherapy and targeted therapies are underway. Finally, immune checkpoint blockade alone and even more in combinatorial therapeutic approaches have generated a new type of adverse events, the immune-related adverse events (IrAEs). IrAEs can be potentially fatal and require early identification and management, and the optimal management of IrAEs will also be discussed in the collection.

The Special Collection is composed of original research studies, reviews and editorials that highlight advances in the field of lung cancer
immunotherapy but also decipher critical points, such as: ‘Why do only some patients respond to anti-PD-1/PD-L1 therapies?’, ‘Which can be the best biomarkers to discriminate responders from nonresponders?’, ‘Which are the best partners to be combined with anti-PD-1/PD-L1 antibodies for lung cancer patients’? We hope that this collection will be of great interest to researchers in a diverse range of fields.

Funding
Work in Dr. Rosell’s laboratory is partially supported by a grant from La Caixa Foundation, by a European Grant (ELBA No 765492) and an Instituto de Salud Carlos III grant (RESPONSE, PIE16/00011).

Conflict of interest statement
The authors declare that there is no conflict of interest.

References
1. Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA* 2002; 99: 12293–12297.
2. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; 8: 793–800.
3. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016; 17: 883–895.
4. Hellmann M, Antonia S, Ponce S, et al. MA09.05 Nivolumab alone or with ipilimumab in recurrent Small Cell Lung Cancer (SCLC): 2-year survival and updated analyses from the CheckMate 032 trial. *J Thorac Oncol* 2017; 12: S393–S394.
5. Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017; 35: 3924–3933.
6. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; 373: 1627–1639.
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; 373: 123–135.
8. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387: 1540–1550.
9. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; 387: 1837–1846.
10. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389: 255–265.
11. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2017; 18: 599–610.
12. Garassino M, Vansteenkiste J, Kim J-H, et al. PL04a.03: Durvalumab in ≥3rd-Line locally advanced or metastatic, EGFR/ALK wild-type NSCLC: results from the phase 2 ATLANTIC study. *J Thorac Oncol* 2017; 12: S10–S11.
13. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; 375: 1823–1833.
14. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 2017; 376: 2415–2426.
15. Antonia SJ, Brahmer JR, Balmanoukian AS, et al. Safety and clinical activity of first-line durvalumab in advanced NSCLC: updated results from a phase 1/2 study. *J Clin Oncol* 2017; 35: e20504.
16. Wu YL, Lu S, Clarke S, et al. 1378TiP A phase 3 study of first-line durvalumab vs platinum-based chemotherapy in patients with advanced NSCLC and high PD-L1 expression: PEARL. *Ann Oncol* 2017; 28: mdx380.079.
17. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III
18. Venkatesan P. Durvalumab lengthens survival in patients with NSCLC. *Lancet Respir Med* 2017; 5: 850.

19. Liu J, Blake SJ, Yong MC, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov* 2016; 6: 1382–1399.

20. Chamoto K, Chowdhury PS, Kumar A, et al. Mitochondrial activation chemicals synergize with surface receptor PD-1 blockade for T cell-dependent antitumor activity. *Proc Natl Acad Sci USA* 2017; 114: E761–E770.

21. Melero I, Berraondo P, Rodriguez-Ruiz ME, et al. Making the most of cancer surgery with neoadjuvant immunotherapy. *Cancer Discov* 2016; 6: 1312–1314.

22. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med* 2016; 375: 1767–1778.

23. Kataoka K, Shiraishi Y, Takeda Y, et al. Aberrant PD-L1 expression through 3′-UTR disruption in multiple cancers. *Nature* 2016; 534: 402–406.

24. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; 348: 124–128.

25. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. *Clin Cancer Res* 2016; 22: 4585–4593.

26. McGranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 2016; 351: 1463–1469.

27. Gandara DR, Kowanetz M, Mok TSK, et al. 1295O Blood-based biomarkers for cancer immunotherapy: tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L+ NSCLC (POPLAR and OAK). *Ann Oncol* 2017; 28: mdx380.

28. Riaz N, Havel JJ, Makarov V, et al. Tumor and microenvironment evolution during immunotherapy with nivolumab. *Cell* 2017; 171: 934–949.

29. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013; 369: 122–133.

30. Tolcher AW, Szolov M, Hu-Lieskovan S, et al. Phase Ib study of utomilumab (PF-05082566), a 4–1BB/CD137 agonist, in combination with pembrolizumab (MK-3475) in patients with advanced solid tumors. *Clin Cancer Res* 2017; 23: 5349–5357.

31. Perez-Ruiz E, Etxeberria I, Rodriguez-Ruiz ME, et al. Anti-CD137 and PD-1/PD-L1 antibodies en route toward clinical synergy. *Clin Cancer Res* 2017; 23: 5326–5328.

32. Iwai Y, Hamanishi J, Chamoto K, et al. Cancer immunotherapies targeting the PD-1 signaling pathway. *J Biomed Sci* 2017; 24: 26.

33. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016; 375: 1749–1755.

34. Kumar V, Chaudhary N, Garg M, et al. Current diagnosis and management of immune related adverse vents (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol* 2017; 8: 49.

35. Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28(Suppl. 4): iv119–iv142.

36. Day D and Hansen AR. Immune-related adverse events associated with immune checkpoint inhibitors. *BioDrugs* 2016; 30: 571–584.