Editorial

Immunotherapy for small-cell lung cancer: rationale and clinical evidence

Niki Karachaliou[1], Aaron E. Sosa[1], Rafael Rosell[2,3]

[1]Institute of Oncology Rosell (IOR), University Hospital Sagrat Cor, Barcelona, Spain; [2]Germans Trias i Pujol Research Institute, Badalona, Spain; [3]Catalan Institute of Oncology, Germans Trias i Pujol University Hospital, Badalona, Spain

Correspondence to: Niki Karachaliou, MD, PhD. Medical Oncology Department, Institute of Oncology Rosell (IOR), C/Viladomat, 288, 08029 Barcelona, Spain. Email: nkarachaliou@oncorosell.com.

Comment on: Reck M, Luft A, Szczesna A, *et al*. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016. [Epub ahead of print].

Received: 22 October 2016; Accepted: 05 December 2016; Published: 21 January 2017.

doi: 10.21037/jxym.2017.01.03

View this article at: http://dx.doi.org/10.21037/jxym.2017.01.03

Recent advances in the molecular biology of small cell lung cancer (SCLC) translate into improved outcomes for patients (1-5). This includes rovalpituzumab tesirine (Rova-T), that targets delta-like protein 3 (DLL3). DLL3 is a ligand in the Notch signaling pathway, that is transcriptionally regulated by achaete-scute homolog-1 (ASCL1) and is overexpressed in SCLC (6). In neuroendocrine tumors, Notch action suppresses tumor growth, in contrast to other tumor types in which acts as an oncogenic stimulus. DLL3 is unable to activate the Notch signaling pathway (6). In an early phase clinical trial, patients whose tumors overexpressed DLL3 and received Rova-T as third-line treatment, tumor reduction was achieved in 50% of the patients and 92% experienced at least stabilization of disease (7). In addition, pharmacogenomics approaches to identify drug sensitivity in SCLC (8,9) have shown that DNA repair proteins are overexpressed in SCLC, including poly (ADP-ribose) polymerase 1 (PARP1) (9,10). PARP inhibitors are investigated in patients with SCLC in several clinical trials (11).

The immune system is crucial for the development of SCLC. Paraneoplastic syndromes, common in this disease, are a consequence of an immune imbalance between inhibitory and stimulating mechanisms (12). SCLC patients with paraneoplastic syndromes often have a better prognosis than those without, indicating that the immune system is able to induce an antitumor immune response (13). Immune checkpoint blockade (ICB), either alone or in combination with chemotherapy, represents a particularly promising approach to the treatment of this disease. The combination of ipilimumab, a fully human monoclonal antibody against-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), with etoposide was found to be synergistic in the M109 mouse model of lung cancer (14). Two phase II studies have shown that the combination of phased but not concurrent ipilimumab with paclitaxel and carboplatin improved immune-related progression-free survival (PFS) in chemotherapy-naive non-small cell lung cancer (NSCLC) (15) and extensive-stage disease SCLC (16) patients. However, no improvement in PFS or overall survival (OS) occurred in the SCLC study (16).

Based on the previous preclinical and clinical evidence, the phase III CA184-156 study attempted to evaluate the combination of ipilimumab with first line chemotherapy based on etoposide and platinum versus chemotherapy alone in extensive-stage disease SCLC (17). The study examined the efficacy of ipilimumab administered concurrently with etoposide and platinum versus etoposide and platinum alone. Specifically, patients with chemotherapy naive extensive-stage disease SCLC were randomized at a ratio of one to one to receive either a phased ipilimumab regimen (two doses of placebo/etoposide/platinum followed by two doses of ipilimumab/etoposide/platinum and two doses of ipilimumab alone) or a control regimen (four doses of etoposide/platinum followed by two doses of placebo) (17). The primary endpoint was OS. Secondary endpoint was PFS and exploratory endpoints included best overall response rate (ORR), duration of response, survival rate and safety. Median OS was 11.0 months

(95% CI, 10.45 to 11.33) in patients treated with chemotherapy plus ipilimumab versus 10.9 months (95% CI, 10.02 to 11.50) in those treated with chemotherapy plus placebo, with 1-year OS rates of 40% in both arms (17). Median PFS was 4.6 months (95% CI, 4.50 to 4.99) in patients treated with chemotherapy plus ipilimumab versus 4.4 months (95% CI, 4.37 to 4.63) in those treated with chemotherapy plus placebo (unstratified log-rank P=0.0161) between arms. Best ORRs were similar in the two arms. Immune-related adverse events were manageable with treatment guidelines (17). The investigators related the lack of benefit of the addition of ipilimumab to two factors: one is that ipilimumab requires a corresponding T-cell activation in the tumor microenvironment in order to have an effective antitumor response and the second is that chemotherapy-induced immunosuppression may be associated with limited T-cell activation and proliferation (17).

The combination of ICB with other conventional or targeted therapies requires deep understanding of the dual functions of interferon-related signaling on the immune system and its non-immune effects (18). During virus infection, virus derived nucleic acids are mainly sensed by certain pattern-recognition receptors (PRRs), such as retinoic acid-inducible gene 1 (RIG1). Binding of RIG1 to its ligand RNAs or short double-stranded RNAs, activates the signaling pathways dependent on the adaptor protein mitochondrial antiviral signaling proteins, leading to induction of the IFN-regulatory factor-3 (IRF-3) and NF-KB-dependent gene expression and the subsequent production of type I and type II IFNs and inflammatory cytokines (19,20). Chemotherapy and radiotherapy activate PRRs, which are critical for INF-I production, priming of T-cells and enhancement of ICB (18). Tumor material can act as damage-associated molecular patterns (DAMPs), that are engaged on dendritic cells and/or tumor-associated macrophages to finally augment IFN-I production and contribute to immune-mediated regression of irradiated or chemotherapy-treated tumors (18). However, when the INF-I signaling persists, it switches from immune stimulatory to immune suppressive. Persistent INFβ promotes expression of suppressive factors such as PD-L1. Interestingly, nivolumab [a fully human IgG4 programmed cell death protein 1 (PD-1) inhibitor antibody] monotherapy and nivolumab plus ipilimumab have shown antitumor activity with durable responses and manageable safety profiles in previously treated patients with SCLC (21). In a phase II study, the objective response was 55% for advanced non-squamous NSCLC patients treated with the combination of pembrolizumab (a humanized, monoclonal antibody against PD-1), carboplatin, and pemetrexed compared to 29% for those treated with chemotherapy alone (P=0.0016) (22). On the other hand, elevated expression of PRRs and INF-stimulated genes has also immune-independent effects and through stromal fibroblasts and cell exosomes leads to chemotherapy resistance (18).

The CA184-156 study is the largest phase III randomized trial conducted to date in a population of patients with extensive-stage disease SCLC (17). Currently many studies of immunotherapy are ongoing in SCLC (*Table 1*). The expression of PD-L1 on tumor cells, which is maybe until now the only predictive biomarker for ICB, is rarely found in SCLC cases, though PD-L1 can be expressed in tumor infiltrating macrophages. Stromal expression of PD-L1 can be a biomarker of response to immunotherapy (23). Unraveling the complexities of INF signaling with its immune-stimulatory and suppressive effects, and its immune-independent effects will pave the way for efficient ICB and chemotherapy combinations.

Table 1 Ongoing immunotherapy clinical trials in SCLC

Clinical trial identifier	Phase	Summary	Patient population	Primary outcome	Sponsor
PD-1 antibodies					
NCT02359019	II	Pembrolizumab after completion of platinum-based chemotherapy	ED-SCLC	PFS	Barbara Ann Karmanos Cancer Institute
NCT02481830	III	Nivolumab versus topotecan versus amrubicin (CheckMate 331)	Relapsed SCLC	OS	Bristol-Myers Squibb

Table 1 (*continued*)

Table 1 (*continued*)

Clinical trial identifier	Phase	Summary	Patient population	Primary outcome	Sponsor
NCT02551432	II	Pembrolizumab and paclitaxel	Refractory SCLC	RR	Seoul National University Hospital
NCT02402920	I	Pembrolizumab and chemoradiotherapy	LD-SCLC and ED-SCLC	MTD	M.D. Anderson Cancer Center
NCT02580994	II	Chemotherapy with or without pembrolizumab	ED-SCLC	PFS	EORTC
NCT02934503	II	Pembrolizumab and chemotherapy with or without radiotherapy	ED-SCLC	Dynamic changes in PD-L1 expression	New York University School of Medicine
ICB combinations					
NCT02538666	III	Nivolumab versus nivolumab plus ipilimumab versus placebo after completion of platinum-based chemotherapy (CheckMate 451)	ED-SCLC	OS, PFS	Bristol-Myers Squibb
NCT02046733	II	Nivolumab plus ipilimumab (STIMULI)	LD-SCLC	OS, PFS	ETOP
Other immunological agents					
NCT02200081	II	MGN1703 (TLR-9 antagonist), maintenance (IMPULSE)	ED-SCLC	OS	Mologen AG
NCT00483509	II	NGR-hTNF plus doxorubicin	Advanced or Metastatic SCLC	PFS	MolMed S.p.A

SCLC, small cell lung cancer; ED-SCLC, extensive-stage disease SCLC; LD-SCLC, limited-stage disease SCLC; PFS, progression-free survival; OS or overall survival; EORTC, European Organization for Research and Treatment of Cancer; ETOP, European Thoracic Oncology Platform; NGR-hTNF, asparagine-glycine-arginine-human tumor necrosis factor.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Min Li, MD, MD (Department of Respiratory Medicine, Xiangya Hospital, Central South University, Key Cite of National Clinical Research Center for Respiratory Disease, Changsha, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2017.01.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bunn PA Jr, Minna JD, Augustyn A, et al. Small Cell Lung Cancer: Can Recent Advances in Biology and Molecular Biology Be Translated into Improved Outcomes? J Thorac Oncol 2016;11:453-74.
2. Karachaliou N, Pilotto S, Lazzari C, et al. Cellular and

molecular biology of small cell lung cancer: an overview. Transl Lung Cancer Res 2016;5:2-15.
3. Karachaliou N, Sosa AE, Rosell R. Unraveling the genomic complexity of small cell lung cancer. Transl Lung Cancer Res 2016;5:363-6.
4. Santarpia M, Daffinà MG, Karachaliou N, et al. Targeted drugs in small-cell lung cancer. Transl Lung Cancer Res 2016;5:51-70.
5. Karachaliou N, Rosell R. Small-cell lung cancer: where are we now and what can we expect for the future? Future Oncol 2013;9:1065-8.
6. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med 2015;7:302ra136.
7. Rudin CM, Pietanza MC, Bauer T, et al. Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC). J Clin Oncol 2016;34:abstr LBA8505.
8. Karachaliou N, Papadaki C, Lagoudaki E, et al. Predictive value of BRCA1, ERCC1, ATP7B, PKM2, TOPOI, TOPO-IIA, TOPOIIB and C-MYC genes in patients with small cell lung cancer (SCLC) who received first line therapy with cisplatin and etoposide. PLoS One 2013;8:e74611.
9. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798-811.
10. Rosell R, Wannesson L. A genetic snapshot of small cell lung cancer. Cancer Discov 2012;2:769-71.
11. Thomas A, Pommier Y. Small cell lung cancer: Time to revisit DNA-damaging chemotherapy. Sci Transl Med 2016;8:346fs12.
12. Darnell RB. Onconeural antigens and the paraneoplastic neurologic disorders: at the intersection of cancer, immunity, and the brain. Proc Natl Acad Sci U S A 1996;93:4529-36.
13. Maddison P, Newsom-Davis J, Mills KR, et al. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. Lancet 1999;353:117-8.
14. Jure-Kunkel M, Masters G, Girit E, et al. Synergy between chemotherapeutic agents and CTLA-4 blockade in preclinical tumor models. Cancer Immunol Immunother 2013;62:1533-45.
15. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.
16. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75-83.
17. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016. [Epub ahead of print].
18. Minn AJ, Wherry EJ. Combination Cancer Therapies with Immune Checkpoint Blockade: Convergence on Interferon Signaling. Cell 2016;165:272-5.
19. Dear AE. Epigenetic Modulators and the New Immunotherapies. N Engl J Med 2016;374:684-6.
20. Sato S, Li K, Kameyama T, et al. The RNA sensor RIG-I dually functions as an innate sensor and direct antiviral factor for hepatitis B virus. Immunity 2015;42:123-32.
21. Antonia SJ, López-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;17:883-95.
22. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.
23. Schultheis AM, Scheel AH, Ozretić L, et al. PD-L1 expression in small cell neuroendocrine carcinomas. Eur J Cancer 2015;51:421-6.

doi: 10.21037/jxym.2017.01.03
Cite this article as: Karachaliou N, Sosa AE, Rosell R. Immunotherapy for small-cell lung cancer: rationale and clinical evidence. J Xiangya Med 2017;2:3.

