Editorial

Could WNT inhibitors really knock on the treatment door of small cell lung cancer?

Laura Esteller[1], Susana Hernández[2], Fernando Lopez-Rios[2], Jordi Remon[1]

[1]Medical Oncology Department, Centro Integral Oncología Clara Campal Barcelona, HM-Delfos, Barcelona, Spain; [2]Patología y Laboratorio de Dianas Terapéuticas HM Hospitales, Barcelona y Madrid, Spain

Correspondence to: Jordi Remon, MD. CIOCC Barcelona, HM Delfos, Avinguda Vallcarca, 151, 08023 Barcelona, Spain. Email: jordi.remon@delfos.cat.

Provenance: This is an invited Editorial commissioned by the Section Editor Long Jiang (Department of Thoracic Oncology, Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Wagner AH, Devarakonda S, Skidmore ZL, *et al*. Recurrent WNT pathway alterations are frequent in relapsed small cell lung cancer. Nat Commun 2018;9:3787.

Submitted Oct 27, 2018. Accepted for publication Dec 06, 2018.
doi: 10.21037/jtd.2018.12.46
View this article at: http://dx.doi.org/10.21037/jtd.2018.12.46

Small cell lung cancer (SCLC) is an exceptionally lethal cancer for which new therapeutic approaches are needed. Despite over 30 years of clinical research, little progress has been made in the management of SCLC, and outcomes remain poor with median overall survival (OS) of 29 months with chemo-radiotherapy and prophylactic cranial irradiation in limited stage SCLC, and of 9–11 months in the metastatic setting with platinum-etoposide, even in the most recent randomized clinical trials with chemotherapy alone (1,2). Owing to the short-term clinical benefit of chemotherapy in SCLC, an understanding of the molecular basis of the onset of chemotherapy resistance in this population is easily awaited, as this could trigger the development of new treatment strategies, and help to identify potential druggable genomic alterations. Over the past few years several research teams have applied various profiling approaches to characterize the SCLC genome, epigenome, and transcriptome. The findings suggest the presence of biologically different subsets of disease, so we can no longer consider SCLC to be a homogenous entity (3,4). These comprehensive analyses of SCLC have shown inactivation of *TP53*, *RB1* or *NOTCH*, and amplification of *MYC*, *FGFR1* and *SOX2*, among other genes (5), leading to the identification of new potential predictive biomarkers for conventional chemotherapy, targeted therapies based on different aspects of SCLC biology, as well as immunotherapies (6,7).

Wagner *et al*. (8) have recently reported the results of whole exome sequencing (WES) of 30 SCLC tumor samples at the time of chemotherapy resistance (15 samples from limited and 15 from extensive-stage SCLC patients, including 12 tumor paired samples at baseline and at the time of progression), to understand the mechanisms of acquired resistance. The authors reported WNT pathway mutation and activation as a mechanism of chemo-resistance in SCLC samples. This observation was, validated *in vitro* by the authors in chemosensitive human SCLC cell lines through APC knockdown, as a model for WNT activation, and cells were re-sensitized to chemotherapy following overexpression of a wild-type APC. The scarcity of tissue biopsy at baseline and at the time of progression is a major issue in SCLC limiting exploration of the dynamic biology of this disease. For this reason, the initiative by Wagner *et al.* (8) is remarkable, as it is the first study reporting a potential mechanism of chemo-resistance in humans based on paired tumor samples, and also provides a rationale for testing WNT inhibitors as a therapeutic strategy to overcome this resistance, which could result in a substantially improvement in the orphan SCLC treatment landscape.

WNT-signaling as a potential chemo-resistance mechanism in SCLC is an interesting hypothesis. In fact, WNT signaling confers resistance to a variety of tumors, mostly by DNA repair or metabolic adaption (9), exemplifying the links between deregulated WNT signaling, stemness, and chemoresistance (10). However, in the study published by Wagner *et al.* (8), considerations

should be given to the small sample size of SCLC patients with paired tumor samples (N=12, 8 from patients with limited and 4 from patients with extensive-disease) calling into question the reproducibility of the results. Moreover, previous chest radiotherapy may also have had an impact on the development of this mechanism of acquired resistance. Indeed, in the whole cohort, more than 90% of tissue samples at the time of chemo-resistance were performed after more than one previous platinum chemotherapy line. This could introduce some kind of bias in the final conclusions regarding whether this is a mechanism of platinum-resistance or whether it is independent of the chemotherapy subtype. This is an important issue as platinum-sensitivity in SCLC clearly correlates with the prognosis of the disease. The authors (8) reported WNT activation as a mechanism of resistance in 80% of the whole population and in 50% of patients with paired tumor samples. However, Wagner *et al.* (8), did not report the clinical characteristics and outcome of patients with or without WNT pathway activation to define the potential prognostic value of this mechanism of resistance. Also, it merits further clinical evaluation to discern whether WNT pathway activation is an early event of resistance that may preclude a platinum-refractory disease; or whether it correlates with a different metastatic pattern at progression. However, only two out of 30 patients had only received platinum-based chemotherapy at the time of chemo-resistance but neither of both had paired tissue biopsies, so it could not be established whether, WNT pathway mutation correlates with an increased risk of developing a platinum-refractory disease. Finally, tumor heterogeneity in WNT pathway activation cannot be ruled out; as tumor paired samples were not carried out in the same site at baseline and at the time of resistance.

Based on the potential role of WNT pathway in chemo-resistance, authors hypothesized that the use of WNT signaling inhibitors may delay the time until chemo-resistance. Several pharmacological agents with broad biological effects, such as thalidomide, can also impact WNT signaling. In a randomized phase III clinical trial in extensive SCLC patients, the addition of thalidomide to chemotherapy after two cycles of induction chemotherapy did not significantly improve progression free survival and OS compared to placebo (11), not clinically supporting the current evidence that blocking WNT pathway may delay the chemo-resistance onset. However, lack of progression free survival benefit with thalidomide could also be explained by the poor safety profile of thalidomide, which resulted in a high rate of dose reduction and short-term duration of treatment. Likewise, patients enrolled in this trial were not selected according to WNT pathway status, and it remains unknown whether thalidomide is the most appropriate WNT-inhibitor. For instance, no specific anti-WNT treatment has been approved. However, *in vitro* the combination of cisplatin and XAV939 (a small molecule inhibitor of WNT signaling pathway) has reported synergistic efficacy in the cell inhibition rate in a dose- and time-dependent manner (12), suggesting that combination strategies could delay the onset of platinum-resistant disease. However, the potential synergistic efficacy of a combination treatment must be balanced with an optimal toxicity profile. Recently the combination of veliparib (a PARP inhibitor, as PARP1 is overexpressed in SCLC tumors and PARP inhibitors have shown activity in SCLC cell lines and animal models) and platinum chemotherapy in extensive-disease SCLC patients reported efficacy with an increase in hematological toxicity (13).

Immune checkpoint inhibitors (ICI) have irrupted in the treatment landscape of thoracic malignancies, including SCLC. Contrary to non-small cell lung cancer (NSCLC), only 30% of SCLCs express programmed death-ligand 1 (PD-L1) (14) and one third of SCLC patients have a high tumor mutational burden (TMB) due to the strong association between SCLC and long-term exposure to the carcinogens present in cigarette smoke (15). Interestingly, Wagner *et al.* (8), have reported a lack of TMB dynamic increase between treatment-naïve and relapsed SCLC samples, as well as, a lack of TMB spatial-heterogeneity at different metastatic sites. In SCLC, TMB is proposed as a potential predictive biomarker of nivolumab efficacy either in monotherapy or in combination with ipilimumab, but it is not clear the predictive role of TMB for the combination of chemotherapy and ICI (15,16). Recently, the addition of atezolizumab to carboplatin and etoposide in first-line extensive-disease SCLC patients, resulted in significantly longer progression free survival and OS compared to chemotherapy alone (16); and this combination may become a potential standard of care in advanced first-line setting. Indeed, the Food and Drug Administration (FDA) approved nivolumab as third-line treatment in unselected SCLC patients owing to the durable response rate achieved in the CheckMate-032 (NCT01928394) regardless of PD-L1 expression (17). However, in a recent press release, in the phase III CheckMate 331 trial (NCT 02481830), nivolumab did not improve the OS compared with topotecan or amrubicin in this population, suggesting a potential over

selection of the patients enrolled in the previous CheckMate 032 trial. Despite the evidence of ICI efficacy in SCLC in the first-line setting, there is increasing evidence to suggest that aberrant WNT signaling promotes immunoevasion and resistance to different ICIs (9), suggesting that ICI could be less effective in platinum pretreated SCLC patients with WNT signaling. However, the specific weight of the immunosuppressive effect and resistance to ICI therapies in the case of WNT pathway activation among SCLC tumors with high TMB is still unknown. Also, as WNT signaling is an acquired mechanism of resistance, it should not decrease the efficacy of upfront chemotherapy in combination with ICI in the SCLC population. Evidence exists to suggest that the therapeutic activity of WNT inhibitors stems from the re-establishment of anticancer immunity (9) suggesting a potential immunomodulatory effect of WNT inhibitors. The ongoing clinical trials (NCT02675946, NCT02013154) with WNT pathway inhibitors in combination with ICI in solid tumors may elucidate whether this strategy could impact the outcome. Nevertheless, patients enrolled in these trials are not selected according to WNT-status.

Wagner *et al.* (8) tested WNT pathway status by WES. This comprehensive approach, very useful in the first phases of molecular studies to identify all candidates, has very limited use in daily clinical practice. Targeted next generation sequencing (NGS) panels in tissue or in blood (liquid biopsies) could be a more pragmatic approach for testing the WNT-pathway status, alongside other potentially useful biomarkers in SCLCs (18).

Overall, the mechanism of acquired resistance reported by Wagner *et al.* (8) is an important and noticeable first-step for understanding the biological basis of chemotherapy resistance in SCLC and to define future treatment strategies. WNT pathway merits further evaluation in larger cohorts to elucidate the real prognostic and predictive value of this pathway in SCLC. Whether WNT inhibitors will knock on the treatment door of SCLC or whether WNT pathway status will impact treatment decisions for patients who are going to be treated with ICI are important questions that await urgent answers.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Levy A, Le Péchoux C, Mistry H, et al. Prophylactic Cranial Irradiation for Limited-Stage Small-Cell Lung Cancer Patients: Secondary Findings From the Prospective Randomized Phase 3 CONVERT Trial. J Thorac Oncol 2019;14:294-7.
2. 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;34:3740-8.
3. Poirier JT, Gardner EE, Connis N, et al. DNA methylation in small cell lung cancer defines distinct disease subtypes and correlates with high expression of EZH2. Oncogene 2015;34:5869-78.
4. Borromeo MD, Savage TK, Kollipara RK, et al. ASCL1 and NEUROD1 Reveal Heterogeneity in Pulmonary Neuroendocrine Tumors and Regulate Distinct Genetic Programs. Cell Rep 2016;16:1259-72.
5. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53.
6. Cardnell RJ, Li L, Sen T, et al. Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies. Oncotarget 2017;8:73419-32.
7. Sabari JK, Lok BH, Laird JH, et al. Unravelling the biology of SCLC: implications for therapy. Nat Rev Clin Oncol 2017;14:549-61.
8. Wagner AH, Devarakonda S, Skidmore ZL, et al. Recurrent WNT pathway alterations are frequent in relapsed small cell lung cancer. Nat Commun 2018;9:3787.
9. Galluzzi L, Spranger S, Fuchs E, et al. WNT Signaling in Cancer Immunosurveillance. Trends Cell Biol 2019;29:44-65.
10. Cai J, Fang L, Huang Y, et al. Simultaneous overactivation of Wnt/β-catenin and TGFβ signalling by miR-128-3p confers chemoresistance-associated metastasis in NSCLC. Nat Commun 2017;8:15870.
11. Pujol JL, Breton JL, Gervais R, et al. Phase III double-blind, placebo-controlled study of thalidomide in extensive-disease small-cell lung cancer after response to chemotherapy: an intergroup study FNCLCC cleo04 IFCT 00-01. J Clin Oncol 2007;25:3945-51.
12. Pan F, Shen F, Yang L, et al. Inhibitory effects of XAV939 on the proliferation of small-cell lung cancer H446 cells

and Wnt/β-catenin signaling pathway in vitro. Oncol Lett 2018;16:1953-8.
13. Atrafi F, Groen HJ, Byers LA, et al. A Phase I Dose-Escalation Study of Veliparib Combined with Carboplatin and Etoposide in Patients with Extensive-Stage Small Cell Lung Cancer and Other Solid Tumors. Clin Cancer Res 2019;25:496-505.
14. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol 2017;35:3823-9.
15. Hellmann MD, Callahan MK, Awad MM, et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. Cancer Cell 2018;33:853-61.e4.
16. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
17. Hellmann MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032. J Clin Oncol 2017;35:8503.
18. Blackhall F, Frese KK, Simpson K, et al. Will liquid biopsies improve outcomes for patients with small-cell lung cancer? Lancet Oncol 2018;19:e470-81.

Cite this article as: Esteller L, Hernández S, Lopez-Rios F, Remon J. Could WNT inhibitors really knock on the treatment door of small cell lung cancer? J Thorac Dis 2019;11(Suppl 3):S381-S384. doi: 10.21037/jtd.2018.12.46

