EDITORIAL

Targeting DLL3: A New Weapon in Lung Neuroendocrine Tumors?

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Introduction

The latest 2021 WHO classification of lung neuroendocrine neoplasms (NENs) divides them into two main categories: low-grade and well-differentiated neuroendocrine tumors (NETs), including typical carcinoids (TCs, grade 1) and atypical carcinoids (ACs, grade 2); and high-grade and poorly differentiated neuroendocrine carcinomas (NECs), including SCLC and large cell NEC.[1]

TCs and ACs are distinguished on the basis of mitotic count and the presence or absence of necrosis, whereas the Ki-67 index is not considered a criterion; the WHO acknowledges that it might be useful for the differential diagnosis between well- or poorly differentiated NENs.[1]

Patients with lung carcinoids are generally younger, have a better prognosis, and do not have a strong association with smoking, as compared with SCLC and large cell NEC.[1] The incidence of lung carcinoids is very low, ranging from 0.2 to 2 of 100,000 persons per year in both the United States and Europe; they account for 20% to 25% of all NENs and 1% to 2% of all lung cancers.[2] Less than 20% of lung carcinoids are diagnosed at an advanced stage, with a prognosis mainly influenced by WHO pathology, with stage IV 10-year disease-specific survival moving from 59% to 18%, between TC and AC, respectively.[2]

Control of tumor growth and functioning syndromes is the goal of advanced lung carcinoids, with the objective of improving patients' quality of life and survival. The therapeutic arsenal of lung carcinoids relies on somatostatin analogs, targeted therapies, such as mTOR (proteine kinase mechanistic target of rapamycin) inhibitors and antiangiogenics, chemotherapy, and internal vectorized radiotherapy with peptide receptor radionuclide therapy. These agents may be associated with or succeed over time, considering the evolutionary slope of the disease, the existence of a secretory syndrome, the binding of somatostatin receptors in functional imaging, and the number and operability of metastases.[2]

Nevertheless, no specific phase 3 trials of lung carcinoids have been published thus far; evidence comes mostly from retrospective studies, less from phase 2 single-arm trials, and sporadically from randomized phase 2 or subgroups of phase 3 trials that enrolled most gastroenteropancreatic-NETs. Everolimus is the only treatment approved by the United States Food and Drug Association and the European Medicine Agency for lung carcinoids.[2]

In the search for alternative therapeutic blanks, delta-like ligand 3 (DLL3) has emerged as an attractive tumor-specific target because it is typically localized intracellularly in nontumoral cells but is overexpressed on the cell surface of NENs, with a range of DLL3-targeted therapeutics under development.[3]

The Present Clinical Case

Cooper et al.[4] presented a case of a 61-year-old nonsmoker woman with a challenging diagnosis of AC with an aggressive evolution and progressive disease with concomitant chemoradiotherapy and somatostatin analogs in less than 12-month intervals. Determination of DLL3 expression by immunohistochemistry was 100%, and tarlatamab was started with a sustained more than 12-week partial morpho-metabolic response.[4]

Tarlatamab (AMG 757) is a bispecific T-cell engager (TCE) that directs T cells to cancer cells expressing DLL3, independent of major histocompatibility complex

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class I. Tarlatamab binds to both DLL3 on cancer cells and CD3 on T cells, leading to T cell-mediated lysis of tumor cells.[5]

A phase 1 dose-exploration trial of tarlatamab in patients with previously treated SCLC reported encouraging antitumor activity, with a median duration of response of 12.3 months.[6] In the phase 2 DeLLphi-301 trial, tarlatamab administered as a 10-mg dose every two weeks, reported an objective response rate of 55% and a median progression-free survival of 4.9 months (95% confidence interval: 2.9–6.7). The most common adverse events were cytokine release syndrome (51%), decreased appetite (29%), and pyrexia (35%).[7]

Tarlatamab is also being evaluated in a few phase 3 studies comparing tarlatamab plus durvalumab to durvalumab alone, after platinum, etoposide, and durvalumab as first-line treatments for patients with extensive stage-SCLC (DeLLphi-30% trial), and tarlatamab versus second-line standard-of-care for refractory SCLC (DeLLphi-304). Moreover, some other bi- or trispecific TCE engagers (BI-764532, HPN328, RO7616789, QLS31904, and PT217) are under evaluation for refractory DLL3-expressing NENs in several phase 1 to 2 trials, with preliminary data showing a safe toxicity profile and promising efficacy.[5]

Future Perspectives

In addition to the standard histopathological classification of lung NENs, the introduction of molecular and sequencing techniques has led to new advances in the understanding of the biology of these diseases and may influence and subsequently improve their management.

Comprehensive genomic profiling suggests that NENs consist of heterogeneous tumors that can be further subdivided into molecular subtypes on the basis of genomic features, with carcinoids being characterized by mutations involving either *MEN1* or other genes encoding chromatin-remodeling–related genes.[8] A recent work using a multiomics data set revealed four distinct molecular groups of lung carcinoids, some of them showing high expression of ASCL1 and DLL3, suggesting that a subset of lung carcinoids might transform into high-grade neuroendocrine disease.[9] Moreover, single-cell RNA sequencing in one small study of lung carcinoid tumors, including both TC and AC, revealed an immunosuppressive microenvironment and a low tumor mutational burden (0.4 mutations per megabase).[2]

Data evaluating immune-checkpoint inhibitors (ICIs) in lung carcinoids have shown limited activity, with objective response rate between 0% and 16%, and exceptionally 33% in the phase 2 trial CA209-538 evaluating ipilimumab plus nivolumab; nevertheless, combination studies of ICIs with chemotherapy, targeted therapies, and radiotherapy are being investigated in NETs in several active trials.[2]

Several factors are thought to contribute to ICI resistance and immune escape in NENs, including downregulation of major histocompatibility complex molecules, failure of antigen presentation, and intratumorally heterogeneity.[5] One strategy to bypass the lack of canonical antigen presentation pathways is to target an alternative cell surface protein on cancer cells, such as DLL3, which can also be detected in low-grade, well-differentiated cases, such as TC (12.2%–32.8%) and AC (24.4%–37%) of the lung.[10,11]

DLL3 is an inhibitory ligand of the Notch 1 receptor in the Notch pathway, which is implicated in multiple oncogenic cellular processes such as cell proliferation, neuroendocrine cell plasticity, chemoresistance, and modulation of the immune microenvironment. By modulating Notch 1, DLL3 promotes migration and invasion in NENs.[3] The differential expression and localization profiles of DLL3 in normal and tumor cells render DLL3 an attractive, tumor-selective therapeutic target and several other DLL3-targeting approaches are being explored, including further TCE, antibody-drug conjugates, and chimeric antigen receptor T cells.[12]

In addition to its role in SCLC, tarlatamab engages and redirects T cells to kill DLL3-expressing in other NENs cells in vitro and induces antitumor activity in patient-derived xenografts and orthotopic NENs mouse models in vivo, making tarlatamab particularly relevant as a new treatment option in the management of different NENs.[5]

This clinical report exemplifies the wide spectrum of activity of tarlatamab in refractory advanced NENs with high expression of DLL3, reinforcing the need to make the DLL3 test a systematic reflex on diagnosis of advanced NENs, independent of their grade and differentiation.

In May 2024, the Food and Drug Association approved tarlatamab for refractory extended-SCLC treatment. In this sense, this case also highlights the urgent need for dedicated lung carcinoid clinical trials and the extension of breakthrough therapy approval to rarer subsets of cancers with limited therapeutic options.

Previous studies have shown that adjuvant chemotherapy worsens the 5-year survival rate of patients who undergo lobectomy for TCs with nodal metastases, with no randomized trial supporting the use of adjuvant chemotherapy for lung carcinoids after surgical resection. New therapies such as tarlatamab could also be explored in local disease settings.

The patient in this case presented good tolerance to the new TCE, with grade 1 typical adverse events and no evidence of cytokine release syndrome or neurologic

toxicity. Despite this example, it is also worth noting that despite the advanced stage of the disease, the better prognosis of lung carcinoids with a succession of numerous lines of therapy over time should particularly make clinicians more attentive to the toxicity profile of treatments.

In conclusion, NENs are a heterogeneous group of tumors most frequently located in the gastrointestinal tract, lungs, and pancreas. They are classified on the basis of histologic features and grade as well-differentiated NET or poorly differentiated NEC. Although targeted therapies, chemotherapy, and, to a lesser extent, immunotherapy offer some clinical benefit to patients with NENs, the need to identify new therapeutic options associated with more sustained responses and improved survival remains an ongoing challenge. New horizons are being explored with the recognition that DLL3 is enriched in NENs and with the advent of DLL3-targeted therapies, some of which have already reported clinical antitumor activity, thus bringing hope to the management of NENs.

CRediT Authorship Contribution Statement

Mariona Riudavets: Conceptualization, Data curation, Writing - original draft.

David Planchard: Validation, Project administration, Conceptualization, Data curation, Supervision, Validation, Writing - review & editing.

Disclosure

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References

1. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10:1243-1260.
2. Baudin E, Caplin M, Garcia-Carbonero R, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. *Ann Oncol*. 2021;32:439-451.
3. Rudin CM, Reck M, Johnson ML, et al. Emerging therapies targeting the delta-like ligand 3 (DLL3) in small cell lung cancer. *J Hematol Oncol*. 2023;16:66.
4. Cooper AJ, Rekhtman N, Baine MK, Thomas MC, Lynch AC, Gentzler RD. First report of response to tarlatamab in a patient with DLL3-positive pulmonary carcinoid: case report. *JTO Clin Res Rep*. 2024;5:100750.
5. Yao J, Bergsland E, Aggarwal R, et al. DLL3 as an emerging target for the treatment of neuroendocrine neoplasms. *Oncologist*. 2022;27:940-951.
6. Paz-Ares L, Champiat S, Lai WV, et al. Tarlatamab, a first-in-class DLL3-targeted bispecific T-cell engager, in recurrent small-cell lung cancer: an open-label, phase I study. *J Clin Oncol*. 2023;41:2893-2903.
7. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023;389:2063-2075.
8. Fernandez-Cuesta L, Foll M. Molecular studies of lung neuroendocrine neoplasms uncover new concepts and entities. *Transl Lung Cancer Res*. 2019;8(suppl 4):S430-S434.
9. Sen T, Dotsu Y, Corbett V, et al. Pulmonary neuroendocrine neoplasms: the molecular landscape, therapeutic challenges, and diagnosis and management strategies. *Lancet Oncol*. 2025;26:e13-e33.
10. Alì G, Di Stefano I, Poma AM, et al. Prevalence of delta-like Protein 3 in a consecutive series of surgically resected lung neuroendocrine neoplasms. *Front Oncol*. 2021;11:729765.
11. Xie H, Boland JM, Maleszewski JJ, et al. Expression of delta-like protein 3 is reproducibly present in a subset of small cell lung carcinomas and pulmonary carcinoid tumors. *Lung Cancer*. 2019;135:73-79.
12. Giffin MJ, Cooke K, Lobenhofer EK, et al. AMG 757, a half-life extended, DLL3-targeted bispecific T-cell engager, shows high potency and sensitivity in preclinical models of small-cell lung cancer. *Clin Cancer Res*. 2021;27:1526-1537.