Editorial

Double trouble: combined large-cell neuroendocrine and small-cell lung carcinoma

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Lung cancer has seen spectacular progress during the past 10 years. The widespread use of targeted drugs and immune checkpoint inhibitors for metastatic disease, as guided by DNA and RNA next-generation sequencing (NGS) (1), has significantly prolonged survival and facilitated long-term disease control for approximately 30% of patients (2). Nevertheless, certain constellations remain very problematic, among which high-grade neuroendocrine tumors are arguably the most challenging.

In the current issue of *Translational Cancer Research*, Ai *et al.* offer insight into today's worst case scenario: the co-existence of large-cell neuroendocrine (LCNEC) and small-cell lung carcinoma (SCLC) (3), two tumors types with dismal prognosis and a median overall survival (OS) not exceeding 1 year (4,5). One first challenge for combined LCNEC/SCLC is accurate diagnosis, especially in the setting of metastatic disease, because of the limited material available through small biopsies. This is aggravated by the low frequency of LCNEC and SCLC, 15% and 3% among pulmonary malignancies, respectively, while their coexistence is very rare, <1% of lung cancers and only 1/4 of LCNEC (6). Both are characterized by neuroendocrine differentiation, i.e., immunohistochemical expression of CD56, chromogranin A, or synaptophysin, and a high proliferation rate >10 mitoses/2 mm^2, so that despite divergent aspects, i.e., large cell size >3 resting lymphocytes, peripheral palisading, rosettes, organoid nesting and trabeculae for LCNEC *vs.* the typical oat-cell pattern of SCLC (6), their morphologic distinction remains problematic. Several studies have reported considerable interobserver variability with a potential for misclassification in >20% of diagnoses based on small biopsies (7). However, for the patient reported by Ai *et al.* (3), the diagnosis fulfilled all formal pathologic criteria and can be considered certain, since initial detection of LCNEC was based on ample surgical material obtained through video-assisted thoracoscopy (VATS), while the SCLC component and mixed character of the tumor were confirmed in two different subsequent rebiopsies from the lung and supraclavicular lymph nodes. The mere performance of three longitudinal tissue biopsies during the relatively short disease course of the reported patient is a remarkable feat of the authors, which not only ensured accuracy of a very difficult and infrequent diagnosis, but also reflects extraordinary quality of medical care, because the practicability of repeat biopsies for metastatic lung cancer is only 50% in academic centers, as demonstrated prospectively (8).

A second major problem with high-grade neuroendocrine lung tumors is the paucity of therapeutic options. Actionable mutations, like *EGFR* mutations or *ALK* fusions, are exceedingly rare, with a frequency <5% in LCNEC (9)

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and even lower in SCLC (10). Therefore, routine molecular workup with NGS is not mandatory for these histologies, but should be considered in the special case of a never-, long-time ex-, or light-smoker with <15 pack-years (11), because patients with *EGFR*, *ALK*, *RET* or other druggable alterations can gain many months of survival under tyrosine kinase inhibitors (TKIs), according to several case reports and small retrospective series (4,10,12). Due to his 40-year-long smoking history, the patient reported by Ai *et al.* definitely did not qualify for this exception and was therefore not tested (3), however, it should be noted that extremely rare cases of oncogene-driven LCNEC and SCLC in smokers do exist in the scientific literature (10,12).

Beyond the perspective of TKI administration, NGS is also important for the molecular typing of LCNEC, which can have therapeutic relevance, as well. Pivotal studies during the last years have shown that LCNEC comprises two different molecular subsets at the genetic level: "NSCLC-like" (aka "type 1") LCNEC with bi-allelic *TP53* and *STK11/KEAP1* or *KRAS* alterations, *vs.* "SCLC-like" (aka "type 2") LCNEC enriched for inactivation of *TP53* and *RB1* (9,13). In addition, it has been reported that "NSCLC-like" LCNEC respond better to platinum-taxane or platinum-gemcitabine doublets compared to the platinum-etoposide chemotherapy usually employed for SCLC (14). In the particular case reported by Ai *et al.*, these considerations are probably not relevant, because the LCNEC component of a combined LCNEC/SCLC tumor is expected to be "SCLC-like" too, as also demonstrated by the only two such cases with published genetic workup (15,16) (*Table 1*), and "SCLC-like" LCNEC derives similar benefit from all aforementioned regimens (14). Another interesting aspect is that pemetrexed, which was administered in the first line by Ai *et al.*, has shown inferior efficacy than other platinum partners in LCNEC (18), but in retrospect this probably did not impact the clinical course of the index patient, either, because he anyway did not response to subsequent taxane-, etoposide- and irinotecan-based combinations, as well (3). Of note, only 3 additional cases of metastatic combined LCNEC/SCLC have been reported in the literature so far (*Table 1*) (15-17), which underlines the importance of the report by Ai *et al.* as precious evidence about a particularly rare and unfavorable tumor type: based on all 4 published cases, primary resistance to routinely available therapies and very short OS emerge as cardinal features of metastatic combined LCNEC/SCLC. Along the same lines, these tumors have a very poor prognosis also in operable stages, for example the OS for patients with resected mixed SCLC tumors was 3 times shorter if the secondary component was LCNEC compared to non-LCNEC alternatives, mainly adenocarcinoma, squamous or adenosquamous tumors, in a large retrospective analysis (19).

One hope for these patients today is immunotherapy with PD-(L)1 inhibitors, which have demonstrated efficacy and are routinely available after approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for both metastatic SCLC and LCNEC. Upfront administration of atezolizumab or durvalumab in combination with platinum-etoposide could prolong the OS of patients with extensive SCLC by approximately 8–10 weeks in two randomized phase 3 trials (5), while an even larger gain of several months has been observed in retrospective series of patients with metastatic LCNEC receiving PD-(L)1 inhibitors alone or in combination with chemotherapy (4,20). The biological rationale for immunotherapy in LCNEC is multifaceted and includes not only the high mutational burden of these tumors, uniquely >10 mut/Mb in median, which is more that of all other lung cancer subtypes (9), but also the tissue upregulation of immune-related pathways and the high blood T-cell reactivity with readily detectable T-cell receptor repertoire alterations in many patients (13,21). An open question is whether administration of nivolumab or any other immune checkpoint inhibitor available in China in 2020 by Ai *et al.* might have favorably influenced the clinical course of their patient. That being said, the only published combined LCNEC/SCLC under immunotherapy was refractory to atezolizumab, nivolumab and ipilimumab (#3 in *Table 1*) (16), which demonstrates the current therapeutic cul-de-sac for these tumors and the pressing need for next-generation immunotherapeutics, such as multi-specific antibodies (22) and cell therapies (23).

The OS of the patient diagnosed by Ai *et al.* with lung, lymph node and bone metastases was very short, measuring 7 months only, despite administration of 4 different therapy lines (3). This stands in good agreement with the findings of a recent large real-world analysis in 191 metastatic LCNEC patients, which showed shorter OS for *de novo* compared to secondary stage IV tumors, 8.7 *vs.* 12.6 months in median respectively, and an even worse outcome in case of multiple metastatic sites (4). Of note, patient attrition between successive treatment lines was approximately 50% in this study and underlines the paramount engagement of Ai *et al.*, who managed to administer 4 different chemotherapy lines despite the very aggressive disease course (#4

Table 1 Published case reports of metastatic combined LCNEC/SCLC in the literature

#	Stage	Genetic alterations	Surgery	RT	Chemotherapy	Best response (stage IV)	OS from stage IV	Ref.
1	II →	*TP53, RB1*	Y	N	Carbo/pemetrexed (adj)			(15)
	IV (relapse)	*SLC17A6*[1]	N	N	Carbo/etoposide	PD	<3 months	
2	IIIb →	n/a	N	CRT	Cis/etoposide (CRT)			(17)
	IIIB →		N	CRT	Cis/paclitaxel (CRT)			
	IV (relapse)		N	N	Tem/cap	PR	≈6 months	
					Pemetrexed	PD		
					Cis/irinotecan	PD		
					Etoposide	PD		
3	IV	*TP53, RB1*[2]	N	Y	Carbo/etoposide/atezo	PD	>11 months (ongoing[4])	(16)
					Irinotecan	PD		
					Nivolumab/ipilimumab	PD		
		CDK12 p.spl[3]			Olaparib/paclitaxel (off-label)	PR		
4	IV (current case)	n/a	N	N	Carbo/pemetrexed/beva	PD	7 months	(3)
					Carbo/docetaxel	PD		
					Carbo/etoposide	PD		
					Carbo/irinotecan	PD		

[1], whole exome sequencing: *TP53* p.R273H, *SLC17A6* p.W505L, *RB1* p.L267X; also *MYH8* p.Q1814K and *PTPN5* p.M40I mutations of unknown significance. [2], Tempus xT assay; *TP53* p.M246V, *RB1* copy-number loss; also copy-number gain of *MYCL*, and *ATP7B* germline mutation. [3], Guardant360 CDx ctDNA assay; *CDK12* c.2109-1G>A; also *TP53* p.M246V, *PIK3CA* amplification, *BRAF* amplification, and *CCNE1* amplification. [4], this patient was primary refractory to multiple chemotherapies and immunotherapies, but was still alive at 11 months due to an exceptional response to off-label olaparib/paclitaxel, presumably facilitated by the presence of a CDK12 splice site mutation (16). Nonetheless, at the time of last follow-up at 11 months the response was already mixed and some lesions had started growing. LCNEC, large-cell neuroendocrine; SCLC, smallcell lung carcinoma; Y, yes; N, no; RT, radiotherapy; cis, cisplatin; carbo, carboplatin; tem/cap, temozolomide/capecitabine; atezo, atezolizumab; beva, bevacizumab; adj, adjuvant chemotherapy; CRT, chemoradiotherapy; PR, partial remission; PD, progressive disease; OS, overall survival; Ref., reference; n/a, not available.

in *Table 1*) (3). The lack of any response to routinely available therapies in this and the three other published patients (*Table 1*) additionally highlights the need for novel therapeutic strategies in order to improve clinical outcome (24). For example, a refractory patient with inactivating CDK12 mutation (#3 in *Table 1*) could achieve an exceptional response lasting over 5 months under off-label olaparib/paclitaxel (16). Unfortunately, due to the low frequency of metastatic LCNEC, very few clinical trials are dedicated to this entity (25), which perpetuates lack of evidence, because LCNEC patients are then severely underrepresented in trials of unselected NSCLC. A list of currently active studies explicitly addressing metastatic LCNEC is given in *Table 2*, of which most would accept patients with combined LCNEC/SCLC tumors, as well. Among the trials of *Table 2*, there is only one really novel drug, namely HPN328, which is an anti-CD3/anti-DLL3-directed bispecific antibody (22).

In summary, high-grade neuroendocrine lung tumors represent an unmet need in modern thoracic oncology with almost no benefit from the spectacular advances of the last decade. In particular, the rare coexistence of LCNEC with SCLC is an extremely unfavorable constellation, characterized by primary resistance to routinely available drugs and very short survival, whose management requires expedient combination of clinical skills, advanced molecular

Table 2 Active clinical trials specifically addressing metastatic LCNEC. Most allow for enrollment of patients with combined LCNEC/SCLC, as well, as shown in the rightmost column, while the only trial testing a novel drug is in italic

Clinical trial ID	Phase	Status	Setting	Regimen	Primary endpoint	LCNEC/SCLC eligible (Y/N)
NCT03728361	II	Active, not recruiting	R/R NEC (incl. SCLC, LCNEC)	Nivolumab + Temozolomide	ORR	Y
NCT05126433 (EMERGE-201)	II	Recruiting	R/R LCNEC (and other tumors)	Lurbinectedin	ORR	Y (no explicit exclusion)
NCT05262985	II	Recruiting	advanced LCNEC (1L)	Durvalumab + platinum/ etoposide	PFS	Y (no explicit exclusion)
NCT05470595 (ALPINE)	II	Recruiting	Advanced LCNEC	Atezolizumab + platinum/ etoposide	OS	Y (if LCNEC ≥50%)
NCT04471727	*I/II*	*Recruiting*	*R/R SCLC or any tumor with high DLL3 expression*[1]	*HPN328 (aDLL3/aCD3 bispecific Ab)*	*MTD, PK*	*Y*
NCT04079712	II	Active, not recruiting	R/R NEC (incl. LCNEC)	Cabozantinib +Nivo/ Ipilimumab	ORR	N (exclusion)
NCT03976518 (CHANCE)	II	Recruiting	R/R NSCLC with rare histology (incl. LCNEC)	Atezolizumab	DCR	Y (no explicit exclusion)
EudraCT 2020-005942-41	II	Recruiting	R/R LCNEC	Durvalumab + platinum/ etoposide	OS	Y (no explicit exclusion)

[1], LCNEC is also characterized by DLL3 expression in the majority (>70%) of cases. Advanced disease: stage IV or stage III not amenable to definitive chemoradiation; LCNEC, large-cell neuroendocrine; SCLC, smallcell lung carcinoma; NEC, neuroendocrine cancer; R/R, relapsed/refractory; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; 1L, first line; Ab, antibody; MTD, maximum tolerated dose; PK, pharmacokinetics; OS, overall survival; Nivo, nivolumab; Y/N, yes/no.

profiling, and access to experimental therapeutics.

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References

1. Volckmar AL, Leichsenring J, Kirchner M, et al.

Combined targeted DNA and RNA sequencing of advanced NSCLC in routine molecular diagnostics: Analysis of the first 3,000 Heidelberg cases. Int J Cancer 2019;145:649-61.
2. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol 2021;39:2339-49.
3. Ai L, Li J, Ye T, et al. Progressive neuroendocrine tumor of lung with combined categories in metastatic site: a case report. Transl Cancer Res 2022;11:2438-42.
4. Fisch D, Bozorgmehr F, Kazdal D, et al. Comprehensive Dissection of Treatment Patterns and Outcome for Patients With Metastatic Large-Cell Neuroendocrine Lung Carcinoma. Front Oncol 2021;11:673901.
5. Dumoulin DW, Dingemans AC, Aerts JGJV, et al. Immunotherapy in small cell lung cancer: one step at a time: a narrative review. Transl Lung Cancer Res 2021;10:2970-87.
6. WHO Classification of Tumors Editorial Board, editor. WHO classification of tumours; 5th Edition; Thoracic Tumors. Lyon: International Agency for Research on Cancer, 2021.
7. den Bakker MA, Willemsen S, Grünberg K, et al. Small cell carcinoma of the lung and large cell neuroendocrine carcinoma interobserver variability. Histopathology 2010;56:356-63.
8. Wessels S, Muley T, Christopoulos P, et al. Comprehensive serial biobanking in advanced NSCLC: feasibility, challenges and perspectives. Transl Lung Cancer Res 2020;9:1000-14.
9. Rekhtman N, Pietanza MC, Hellmann MD, et al. Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma-like and Non-Small Cell Carcinoma-like Subsets. Clin Cancer Res 2016;22:3618-29.
10. Shiao TH, Chang YL, Yu CJ, et al. Epidermal growth factor receptor mutations in small cell lung cancer: a brief report. J Thorac Oncol 2011;6:195-8.
11. Planchard D, Popat S, Kerr K, et al. ESMO Clinical Practice Living Guidelines - Metastatic Non-Small-Cell Lung Cancer. 2021. Available online: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer, accessed 18 Apr 2021.
12. Wiedemann C, Kunz J, Kirchner M, et al. A Rare Case of Large-Cell Neuroendocrine Lung Carcinoma Sensitive to ALK Inhibitors. Oncol Res Treat 2019;42 Suppl 4:1-336.
13. George J, Walter V, Peifer M, et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. Nat Commun 2018;9:1048.
14. Derks JL, Leblay N, Thunnissen E, et al. Molecular Subtypes of Pulmonary Large-cell Neuroendocrine Carcinoma Predict Chemotherapy Treatment Outcome. Clin Cancer Res 2018;24:33-42.
15. Zhu Y, Zhang F, Yu D, et al. Genomic Feature of a Rare Case of Mix Small-Cell and Large-Cell Neuroendocrine Lung Carcinoma: A Case Report. Front Oncol 2022;11:794744.
16. Bae WH, Hwang JY, Hur WK, et al. Metastatic CDK12-Mutated Neuroendocrine Tumor of Lung Showed an Exceptional Response to Olaparib and Paclitaxel. JCO Precis Oncol 2021;5:751-5.
17. Zhang B, Wang D, Zhang X, et al. Temozolomide Combined With Capecitabine In The Treatment Of Mixed Neuroendocrine Carcinoma Of The Lung With Poor Tolerance After Repeated Radiochemotherapy: A Case Report And Literature Review. Onco Targets Ther 2019;12:9663-8.
18. Derks JL, van Suylen RJ, Thunnissen E, et al. Chemotherapy for pulmonary large cell neuroendocrine carcinomas: does the regimen matter? Eur Respir J 2017;49:1601838.
19. Zhang C, Yang H, Zhao H, et al. Clinical outcomes of surgically resected combined small cell lung cancer: a two-institutional experience. J Thorac Dis 2017;9:151-8.
20. Dudnik E, Kareff S, Moskovitz M, et al. Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung. J Immunother Cancer 2021;9:e001999.
21. Christopoulos P, Schneider MA, Bozorgmehr F, et al. Large cell neuroendocrine lung carcinoma induces peripheral T-cell repertoire alterations with predictive and prognostic significance. Lung Cancer 2018;119:48-55.
22. Elshiaty M, Schindler H, Christopoulos P. Principles and Current Clinical Landscape of Multispecific Antibodies against Cancer. Int J Mol Sci 2021;22:5632.
23. Gaissmaier L, Elshiaty M, Christopoulos P. Breaking Bottlenecks for the TCR Therapy of Cancer. Cells 2020;9:2095.
24. Gaissmaier L, Christopoulos P. Immune Modulation in Lung Cancer: Current Concepts and Future

Strategies. Respiration 2020. [Epub ahead of print]. doi: 10.1159/000510385.
25. Christopoulos P, Engel-Riedel W, Grohé C, et al. Everolimus with paclitaxel and carboplatin as first-line treatment for metastatic large-cell neuroendocrine lung carcinoma: a multicenter phase II trial. Ann Oncol 2017;28:1898-902.

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