predicts prognosis in lung neuroendocrine neoplasms. *Cancers (Basel)*. 2021;13:4875.
14. Volante M, Mete O, Pelosi G, Roden AC, Speel EJM, Uccella S. Molecular pathology of well-differentiated pulmonary and thymic neuroendocrine tumors: what do pathologists need to know? *Endocr Pathol*. 2021;32:154–168.
15. Detterbeck FC, Gibson CJ. Turning gray: the natural history of lung cancer over time. *J Thorac Oncol*. 2008;3:781–792.

Molecular Knowledge and Clinical Relevance - Stepping Stones in Improving Classification of Lung Neuroendocrine Neoplasms

To the Editor:

As a response to our review,[1] Pelosi wrote a letter entitled "The natural history in lung neuroendocrine neoplasms: The stone guest who matters."[2] As a respected clinician and researcher in the neuroendocrine tumor field, his commentary adds to the relevant discussion on how to best classify neuroendocrine lung neoplasms (NENs). From his more biologically oriented point of view, also risk factors acting on individual variables (e.g., stochastic gene alterations, sex, age, life environment, and lifestyle) should be considered when diagnosing lung NENs. He elaborates on three groups of lung NENs, that is, (1) primary high-grade neuroendocrine carcinoma (p-HGNEC), originating from primary carcinogenic events leading to a *RB1* and *TP53* mutant subtype (e.g., classical SCLC), (2) secondary HGNEC (s-HGNEC), potentially arising from secondary events in NSCLC and carcinoid and resulting in subtypes including SCLC-like ($RB1^{-/-}$ and $TP53^{-/-}$) and NSCLC-like ($RB1^{+/-}$ and *KRAS* or *STK11* or *KEAP* mutated) and the highly proliferative carcinoid, and (3) indolent NEN, originating from epigenomic events leading to primary carcinoid with a slow-growing behavior. Indeed, current literature seems to provide a rational for this conceptualization of lung NEN classification as also hinted on in our review. Nevertheless, whether or not the natural history is the crucial factor here can be debated. Discussion points regarding the proposed classification model of Pelosi are as follows:

First, investigations into the molecular biology of tumors and related risk factors provide insight into the origin of a disease and may inform us on how it develops and evolves. Nevertheless, these investigations only become relevant when they lead to the recognition of clinically identifiable subcategories with potential consequences for prevention, treatment or related prognosis. In case of NECs (i.e., SCLC or large cell NEC [LCNEC]), smoking is the main risk factor. In rare cases (1%–2%), such tumors occur in never smokers potentially associated with radon exposure. Comparison of SCLC from never-smoker and (former) smoking patients has revealed some different features (e.g., more female, higher age, less *TP53* and *RB1* mutations), but importantly, their prognosis is comparable.[3,4] In addition, in patients with germline mutations potentially causal to SCLC development, no difference in overall survival was observed compared with patients without such mutations.[5] Thus, the studies investigating associated risk factors in SCLC (and LCNEC), although limited in size, thus far have not emphasized the clinical importance of the so-called natural history.

Second, considering the proposed p-HGNEC classification, recent studies reveal that classic SCLC can be subdivided into several subtypes on the basis of transcriptomic analyses and that this in part may reflect the cell of origin.[6] For transformation of NSCLC toward SCLC and/or LCNEC, a preexisting genetic context of (subclonal) *RB1* and *TP53* inactivation may facilitate neuroendocrine plasticity although transformation itself seems particularly driven by transcriptomic changes and not on the basis of sequential mutational events.[7,8] Yet, these transcriptomic changes are not adequately reflected in the p-HGNEC/s-HGNEC classification model proposed by Pelosi, which is especially driven on mutational events. Nature thus proves to be complex and requires more molecular events to be caught in a schematic pulmonary NEN classification model.

Third, when we consider p-HGNEC (e.g., classical SCLC) treatment, this currently seems not to be meaningfully different from that of s-HGNEC (LCNEC) with SCLC-like subtype, because both subtypes are amendable for etoposide-platinum chemotherapy combined with immunotherapy. Furthermore, in patients with *EGFR*-mutated NSCLC transformed into histologic SCLC (defined as s-HGNEC by Pelosi), treatment with platinum-etoposide chemotherapy has similar outcome as in patients with classical SCLC (p-HGNEC).[9] We agree that s-HGNEC (LCNEC) with NSCLC-like subtype may be

Address for correspondence: Jules L. Derks, MD, PhD, Department of Pulmonary Diseases, GROW School for Oncology & Developmental Biology, Maastricht University Medical Center, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: j.derks@maastrichtuniversity.nl.

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2021.11.014

a unique biological entity requiring different treatment, including NSCLC-based chemotherapy and occasionally targeted treatment.[1] Prospective studies that strengthen the retrospective observations, however, are still lacking in the literature. From these points, an important conclusion on HGNEC classification could thus be that for most p-HGNEC/s-HGNEC, the natural history does not seem to be relevant. Rather, we would recommend to identify molecular vulnerabilities amendable for tumor-specific treatment, preferably detectable as easily applicable (transcriptomic) biomarkers.

Fourth, when considering the classification of lung carcinoid and the potential existence of carcinoid with increased proliferation, we agree with Pelosi that the natural history may be relevant. Nevertheless, the conceptualization of one indolent NEN group and a subtype of s-HGNEC originating from carcinoid with increased proliferation seems reductive and does not appreciate the different subtypes of carcinoid recognized.[10,11] On the basis of recent genomic data, at least three subtypes of carcinoids have been identified, including a "supra" carcinoid group revealing neuroendocrine carcinoma like on top of dedifferentiated carcinoid features.[11] If this is the consequence of dedifferentiation from indolent carcinoid toward an aggressive carcinoma, histologically mimicking SCLC or LCNEC is still a subject of debate. Indeed, very few cases have been described mimicking such a behavior and being classified as neuroendocrine carcinoma while their molecular profile may better reflect carcinoid.[12,13] In these cases, the natural history of disease could be informative (e.g., endobronchial localization, younger age, and *MEN1* mutated), but we lack large studies that enable us to associate clinical features with these molecular-identified subtypes.[10] Recent genomic analysis suggests that there is a very long preclinical phase for the larger part of (nonsmoking) patients with lung carcinoid.[14] Unfortunately, in-depth multiregional and temporal molecular analysis of lung NEN tumors is still lacking, although some studies are in progress (e.g., TRACERx study). Again, further studies are required to prove whether the identified molecular carcinoid subtypes indeed have biologically different behavior and associate with unique clinical features and/or different outcomes after systemic therapy (e.g., SSRT2a analogues, mTOR inhibition, and different chemotherapy agents).

In conclusion, we strongly believe that the time is now to extensively correlate clinically relevant outcomes with identified molecular subtypes of lung NEN (including those conceptualized by Pelosi) in both retrospective and prospective studies. These evaluations will provide us the stepping stones to further improve the classification of lung NENs.

CRediT Authorship Contribution Statement

Jules L. Derks: Conceptualization, Methodology, Writing—original draft preparation.

Anne-Marie C. Dingemans, Ernst-Jan M. Speel: Writing—review and editing, Manuscript finalization.

Compliance With Ethical Standards

This is response to a letter to the editor; thus, no approval by Internal Review Board was required.

Jules L. Derks, MD, PhD
Department of Pulmonary Diseases
GROW School for Oncology & Developmental Biology
Maastricht University Medical Centre
Maastricht, The Netherlands

Anne-Marie C. Dingemans, MD, PhD
Department of Respiratory Medicine
Erasmus MC Cancer Institute
Erasmus University Medical Center
Rotterdam, The Netherlands

Ernst-Jan M. Speel, PhD
Department of Pathology
GROW School for Oncology & Developmental Biology
Maastricht University Medical Centre
Maastricht, The Netherlands

References

1. Derks JL, Rijnsburger N, Hermans BCM, et al. Clinical-pathologic challenges in the classification of pulmonary neuroendocrine neoplasms and targets on the horizon for future clinical practice. *J Thorac Oncol*. 2021;16:1632–1646.
2. Pelosi G. The natural history in lung neuroendocrine neoplasms: the stone guest who matters'. *J Thorac Oncol*. 2022;17:e5-e8.
3. Torres-Durán M, Ruano-Ravina A, Kelsey KT, et al. Small cell lung cancer in never-smokers. *Eur Respir J*. 2016;47:947–953.
4. Thomas A, Mian I, Tlemsani C, et al. Clinical and genomic characteristics of small cell lung cancer in never smokers: results from a retrospective multicenter cohort study. *Chest*. 2020;158:1723–1733.
5. Tlemsani C, Takahashi N, Pongor L, et al. Whole-exome sequencing reveals germline-mutated small cell lung cancer subtype with favorable response to DNA repair-targeted therapies. *Sci Transl Med*. 2021;13:eabc7488.
6. Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer*. 2019;19:289–297.
7. Quintanal-Villalonga A, Taniguchi H, Zhan YA, et al. Multiomic analysis of lung tumors defines pathways activated in neuroendocrine transformation [e-pub ahead of print]. *Cancer Discov*. https://doi.org/10.1158/2159-8290.CD-20-1863. Accessed November 24, 2021.

8. Hermans BCM, Derks JL, Hillen LM, et al. In-depth molecular analysis of combined and co-primary pulmonary large cell neuroendocrine carcinoma and adenocarcinoma. *Int J Cancer*. 2022;150:802–815.
9. Ferrer L, Giaj Levra M, Brevet M, et al. A brief report of transformation from NSCLC to SCLC: molecular and therapeutic characteristics. *J Thorac Oncol*. 2019;14:130–134.
10. Laddha SV, da Silva EM, Robzyk K, et al. Integrative genomic characterization identifies molecular subtypes of lung carcinoids. *Cancer Res*. 2019;79:4339–4347.
11. Alcala N, Leblay N, Gabriel AAG, et al. Integrative and comparative genomic analyses identify clinically relevant pulmonary carcinoid groups and unveil the supra-carcinoids. *Nat Commun*. 2019;10:3407.
12. Rekhtman N, Desmeules P, Litvak AM, et al. Stage IV lung carcinoids: spectrum and evolution of proliferation rate, focusing on variants with elevated proliferation indices. *Mod Pathol*. 2019;32:1106–1122.
13. Sazonova O, Manem V, Orain M, et al. Transcriptomic data helps refining classification of pulmonary carcinoid tumors with increased mitotic counts. *Mod Pathol*. 2020;33:1712–1721.
14. Zhang T, Joubert P, Ansari-Pour N, et al. Genomic and evolutionary classification of lung cancer in never smokers. *Nat Genet*. 2021;53:1348–1359.

Comparing Addition of Radiotherapy in EGFR- and ALK-Positive NSCLC With Brain Metastases: Are We Evaluating the Optimal End Point?

To the Editor:

We read with great interest the article of Thomas et al.[1] recently published in the *Journal of Thoracic Oncology*.

The authors have performed a multicentric retrospective evaluation of 147 patients with EGFR- and ALK-positive NSCLC with brain metastases (BMs), divided into two cohorts (tyrosine kinase inhibitor [TKI] alone versus TKI + BM radiotherapy [RT]). They found no substantial differences between the two cohorts in terms of time to progression, time to intracranial progression, or time to treatment failure and concluded that new-generation TKIs may enable deferral central nervous system (CNS)-RT in appropriately selected patients.

The article is extremely interesting, as in this context, no clear guidelines have been defined and the treatment choice remains empirical and often related to the experience and personal beliefs of the different clinicians.

The first enthusiastic results concerning the favorable impact of TKIs in EGFR-positive patients with NSCLC bearing BMs both on the clinical course (relief of symptoms, if present) and objective response rates[2] have therefore induced in an exceedingly confident attitude within the oncological community, that is, neglecting in-depth imaging investigation of the brain, such as magnetic resonance imaging, instead of the routine total-body contrast computed tomography, and addressing the subject of possibly further improving outcomes with RT. The presence of multiple small-sized BMs at the clinical onset of EGFR-positive NSCLC should not be overlooked, even if of apparently limited impact on immediate therapeutic decisions. The paucity of related data both from specifically addressed clinical trials and retrospective studies grounds the opportunity for prospectively improving the knowledge of this kind of presentation both in terms of the natural history of the disease and long-term response to therapy.

Conversely, CNS-RT has extremely evolved in the past decades, with different approaches (whole-brain irradiation [WBI], hippocampal-sparing WBI, stereotactic RT [SRT]) on the basis of the number of metastases, the prognosis of the patient, and the experience of the clinicians,[3–6] with different side effects, especially in terms of cognitive impairment. More recently, Sperduto et al.[7] revised their original diagnosis-specific graded prognostic assessment scale to include genetic and molecular data, called Lung-mol-GPA, where the number of BM remains a prognostic factor.

As for the possible prognostic advantage of an upfront RT treatment, preceding TKI therapy, some relevant information is available.[8] Similarly, Thomas et al.[1] discuss that outcomes between the two cohorts did not differ despite the imbalances favoring the TKI-alone cohort (larger size of BMs, symptomatic disease, steroid use), so that early CNS-RT may have provided additive disease control.

In light of the above-mentioned findings, we strongly believe that the evaluation of adding CNS-RT in this particular setting is extremely complex and must take into consideration also other variables, such as the

Address correspondence to: Valerio Nardone, MD, Department of Precision Oncology, University Hospital of Campania "L. Vanvitelli," Naples, Italy. E-mail: Valerio.nardone@unicampania.it.

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.09.019