CASE REPORT

An unusual neck tumor in a young pregnant woman: challenge diagnosis and response to treatment

Juan F. Arango[1],*, Juan C. López[2], Virginia Arrazubi[1], Silvia Cisneros[3], Angel Rodríguez[4], Aitor Zabala[5] and Purificación Martinez del Prado[1]

[1]Department of Medical Oncology, Hospital Universitario Basurto, Bilbao, Spain, [2]Department of Pathology, Hospital Universitario Basurto, Bilbao, Spain, [3]Department of Radiology, Hospital Universitario Basurto, Bilbao, Spain, [4]Department of Radiation Oncology, Hospital Universitario Basurto, Bilbao, Spain, and [5]Department of Otolaryngology, Hospital Universitario Basurto, Bilbao, Spain

*Correspondence address. Department of Medical Oncology, Hospital Universitario Basurto, Avenida Montevideo 18, 48013. Bilbao, Vizcaya, Spain. Tel: +34-944006000; Fax: +34-944006397; E-mail: jarango980@gmail.com

Abstract

We report the case of a 19-year-old woman 33 weeks pregnant who presented a painful mass of progressive growth in the neck, having also dysphonia and dyspnea. Physical examination revealed a primary laryngeal tumor. A neuroendocrine small-cell carcinoma was diagnosed after histopathology, immunohistochemistry and genetic studies. Chemo-radiotherapy with a cisplatin-etoposide schedule was administered. Despite obtaining a complete response, the patient relapsed and finally survived 35 months with successive cisplatin-based treatments. Small-cell neuroendocrine carcinoma of the larynx is an uncommon entity, differential diagnosis can be problematic and treatment is challenging.

INTRODUCTION

Neuroendocrine neoplasms, including small-cell neuroendocrine carcinoma, account for <1% of all laryngeal neoplasms [1]. The diagnosis of this rare entity is challenging and many differential diagnoses should be considered. After diagnosis, the evidence for treatment is scarce and it has a poor prognosis.

CASE REPORT

A non-smoker, 19-year-old woman, 33 weeks of pregnancy, came to our emergency department on 7 January 2011 because she had been suffering from a week long period of progressive dyspnea. In the last 3 months, she had had an 8-cm large painful mass of progressive growth on the left side of her neck and dysphonia. An indirect laryngoscopy found a left hemilaryngeal tumor with a reduction of >50% of the glottic lumen, with left vocal cord fixation and displacement of the right vocal cord. An urgent tracheotomy was done. Induction of the childbirth was carried out successfully. A gross needle biopsy of the cervical lymphadenopathy and a biopsy of the laryngeal tumor were performed. Both biopsies showed identical histology: the tumor was composed of a high density of cell proliferation, with uniform, laminar and invasive growth, without evidence of fibrillary material between the elements. Cells showed nuclear hyperchromasia, nuclear molding, scant cytoplasm, high nuclear/cytoplasmic ratio, necrosis and a high-mitotic rate. The lining epithelium of the larynx did not show dysplasia (Fig. 1).

In immunohistochemistry tumor cells showed strong and diffuse immunoreactivity for p63, synaptophysin, CD56, CD57 and p16 and were negative for CD45 (leukocyte common antigen), chromogranin, TTF-1, desmin, myogenin, p40, CK 5/6, CK20, TdT

and S-100 protein. The cells showed focal staining for vimentin and CD99, the latter only as focal and weak nuclear or citoplasmatic pattern. AE1/AE3, CK7 and CK8/18 were negative in the first biopsy but stained for AE1/AE3 focally in the lung biopsy (see below). Ki-67 evaluation was 100%. Figures 2 and 3 show the main immunohistochemistry stainings. An analysis for the NUT gene rearrangement was performed with a negative result. A fluorescence *in situ* hybridization (FISH) technique was done to detect EWS gene rearrangements involved in the EWS-FLI1/ERG fusions of the Ewing tumor with an inconclusive result.

Computed tomography (CT) scan showed a mass of 3.5 cm at its largest diameter on the left side of the glottic and supraglottic space, occupying the vallecula and left pyriform sinus and extended to the epiglottis with the thickening of the vocal cords, and a soft tissue mass occupying the anterior commissure and pronounced displacing and decreasing of the airway lumen (Fig. 4); an adenopathic conglomerate (7.2 × 3.5 cm) was found in the left cervical level II. Neither the thoraco-abdominal CT nor the bronchoscopy showed any other dissemination of the disease.

The patient was diagnosed with laryngeal neuroendocrine small-cell carcinoma cT3N3M0, Stage IV B.

The patient began radical treatment on 27 January 2011, following a treatment of cisplatin 80 mg/m^2 Day 1, etoposide 100 mg/m^2 Days 1, 2 and 3 every 21 days (total 4 cycles) and concomitant radiotherapy during second and third cycles, reaching 70 Gy after volumetric reduction at 50 Gy (2 Gy/fraction, 5 fractions/week). After the fourth cycle (5 May 2011) a control CT scan showed a significant reduction of the supraglottic mass size and a 13 mm persistent adenopathy in the left cervical level IIA (Fig. 5). An indirect laryngoscopy demonstrated left vocal cord

Figure 1: (A) Hematoxylin and eosin staining of laryngeal tumor: low-power field (40×) in the main image and high-power field (100×) in the detail. Description in the text. **(B)** Larynx lining epithelium.

fibrosis and a lack of tumor in the pyriform sinus and subglottic space. Both the laryngeal function and mobility were recovered.

Considered as a complete local response and likely nodal persistence, a dissection of the left cervical lymph node was performed. No residual tumor was demonstrated on pathological examination. The patient remained illness-free during 5 months with a subsequent pulmonary relapse in the lower right lobe. A bronchoscopy biopsy confirmed recurrence of the same tumor. She was re-treated with the same chemotherapy regimen with a new complete response after 5 cycles, which was maintained for 8 months. A second relapse in the tracheal lumen and right basal pyramid was histologically confirmed in December 2012. She received 3 cycles with the same previous regimen with partial response. However, due to treatment toxicity, a dose reduction was necessary in the last two cycles and, finally, treatment was suspended. Following the partial response evaluation, sequential radiotherapy treatment was proposed. She received a radiotherapy-based scheme of up to 60 Gy (200 cGy per fraction) between 11 March 2013 and 23 April 2013. Nevertheless, illness progression was demonstrated with both hepatic and pulmonary metastatic spread. Finally, the patient died 7 months later in December, 2013, with an overall survival of 2 years and 11 months.

DISCUSSION

Neuroendocrine neoplasms, account for <1% of all laryngeal neoplasms [1, 2]. The current classification of neuroendocrine carcinomas of the larynx was established in 2005 by the World Health Organization. This classification includes five histological subtypes: (i) Typical carcinoid tumor, (ii) Atypical carcinoid tumor, (iii) Small-cell neuroendocrine carcinoma, (iv) Combined small-cell and non-small-cell carcinoma and (v) Paraganglioma [3].

In the particular case of small-cell neuroendocrine carcinoma, clusters of small cells with hyperchromatic nuclei and scant cytoplasm can be found in the histology. Cell necrosis and high-mitotic activity are common. The tumors may stain for synaptophysin (100%), cytokeratin (96%), chromogranin-A (94%), calcitonin (80%), carcinoembrionary antigen (75%), somatostatin (50%), serotonin (21%) and adrenocorticotropic hormone (17%). Some may also express TTF-1 [4].

The differential diagnosis is made with the large group of small round blue cell tumors. In this way, a metastatic small-
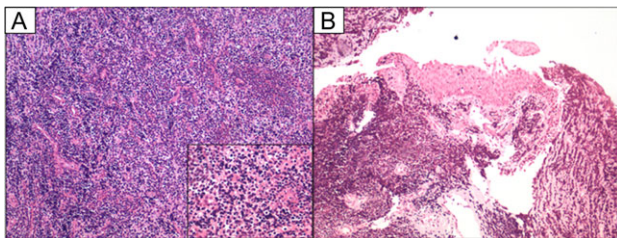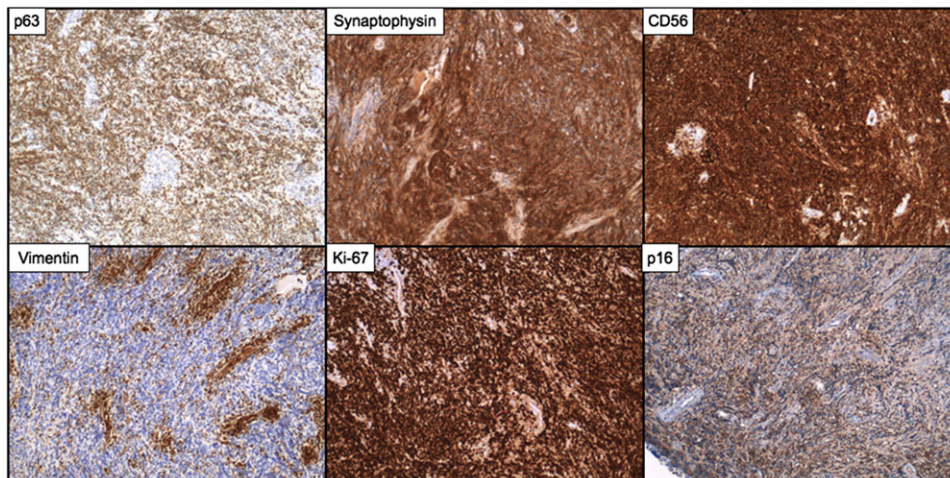

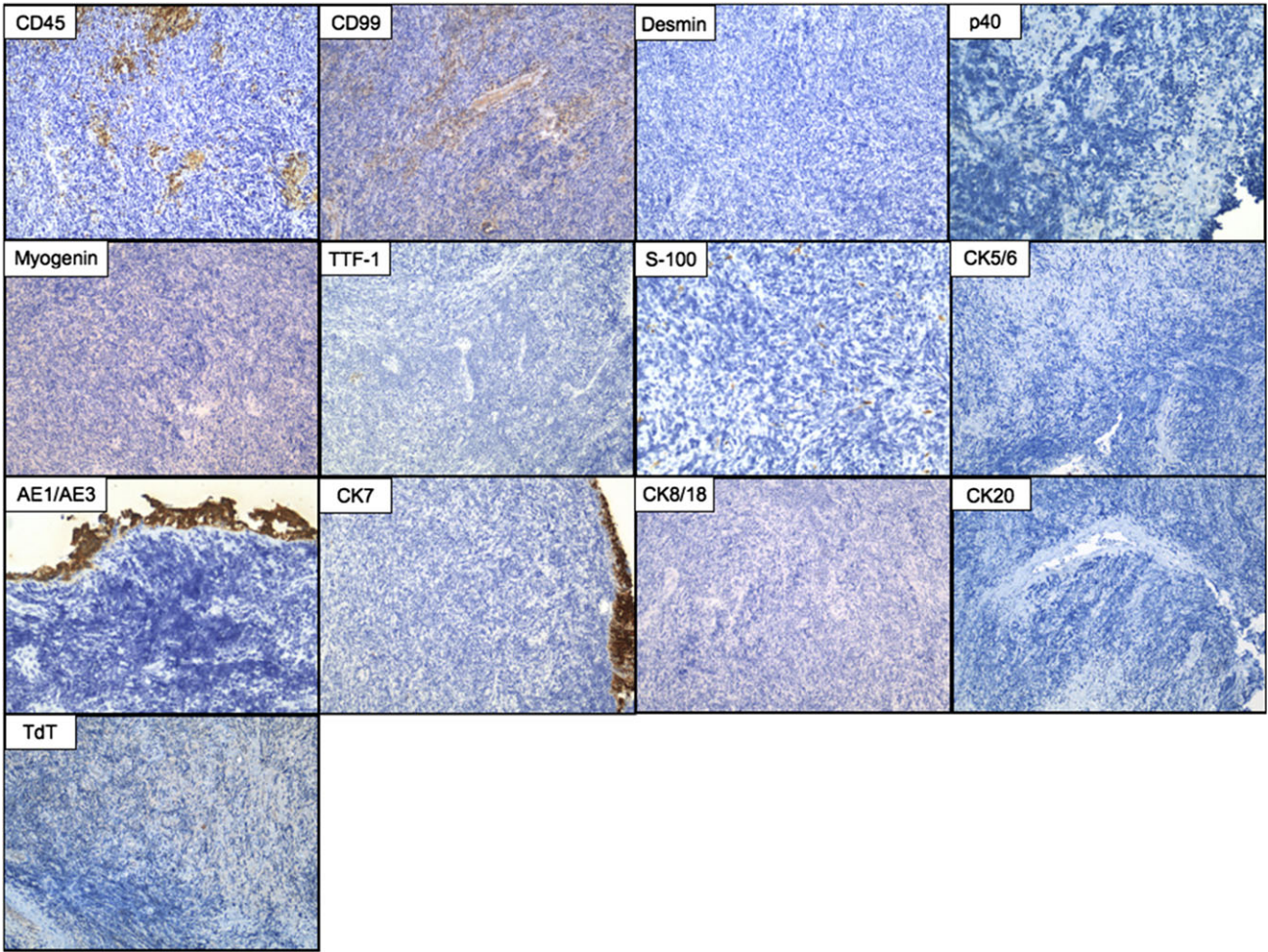**Figure 2:** Positive immuno-stainings. Description in the text.

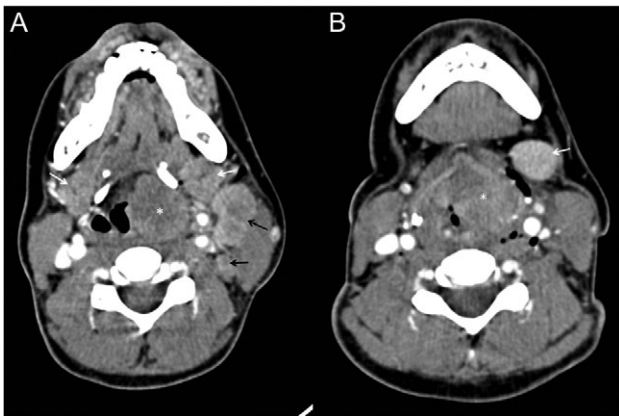**Figure 3:** Negative immuno-stainings. Description in the text.

Figure 4: Post-contrast cervical CT at diagnosis: (**A**) Cranial slice and (**B**) Caudal slice. The image shows a mass (*), adenopathic conglomerate (black arrows) and submandibular glands (white arrows).
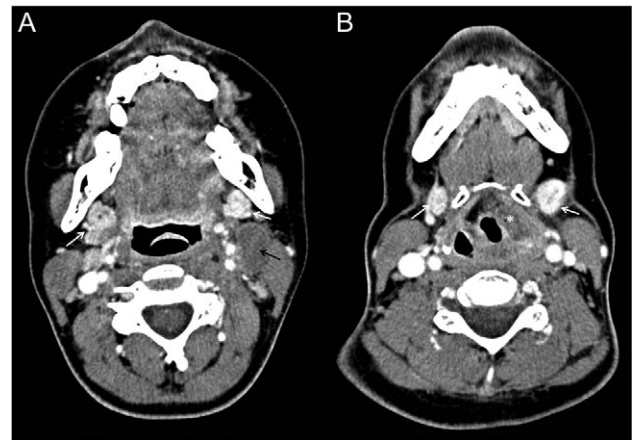

Figure 5: Post-contrast cervical CT after first radical chemo-radiotherapy treatment: the image shows (**A**) Decreased size of the larger adenopathy at level IIa, which has become necrotic (black arrow) and disappearance of smaller one. (**B**) The mass has been replaced by increased density paraglottic fat (*). Submandibular glands indicated by white arrows.

cell lung carcinoma must be considered. However, in our case an exhaustive review of the lungs was negative. Merkel cell carcinoma, a type of small-cell carcinoma that grow mainly in the skin with some few cases reported in the head and neck area, mostly in the parotid gland [5], should also be considered, but negative CK20 and TdT staining did not favor that possibility. Melanoma can also resemble a neuroendocrine tumor, especially if it is of an amelanotic form. However, the S-100 stain

was negative and the melanoma was excluded. In the specific case of our patient, the immunophenotype of the initial biopsy and the absence of lymphoid and muscle markers seemed to favor the possibility that it was an extraskeletal Ewing group sarcoma/primitive neuroectodermal tumor. It also proposed as a second diagnostic possibility a 'NUT midline carcinoma', taking into account the clinical and radiological characteristics and the expression of p63. The analysis for the NUT gene rearrangement was negative. A FISH technique was performed to detect EWS gene rearrangements involved in the EWS-FLI1/ERG fusions of the Ewing tumor. Unfortunately this study was inconclusive, but immunohistochemical analyses of the sample study were consistent with the diagnosis of small-cell neuroendocrine carcinoma. The expression of p63 also suggested the possibility of the presence of a squamous component in the tumor; in fact, there are reported few cases of primary laryngeal combined squamous cell carcinoma and small-cell carcinoma [6], but in our case p40 and CK 5/6 negativity did not reflect this extremely rare condition.

Small-cell neuroendocrine carcinoma of the larynx is a biologically aggressive malignancy with 90% of patients that eventually develop systemic metastatic disease. In the literature, consulted <200 cases have been published [7]. Most patients are men aged between 50 and 70 years, with a background of smoking. The fact that the patient was a young non-smoker woman was striking and assess the hypothesis of causal role other-than tobacco was necessary; high-grade neuroendocrine carcinomas (HGNECs) of the head and neck, included small-cell carcinoma, could be histologically similar to human papillomavirus (HPV)-associated non-keratinizing squamous cell carcinomas. As in our case, a recent cases series [5] showed a high rate of strong and diffuse p16 expression (a recognized surrogate marker of HPV-infection in oropharyngeal non-keratinizing squamous cell carcinoma) in HGNECs of the head and neck but in none of these cases HPV DNA was detected and this overexpression was attributed to p16/Rb/cyclin D1 pathway dysregulation and not related to HPV-infection.

Presenting symptoms and clinical signs that vary, but about half of patients present a palpable neck mass. The prognosis of this tumor is very poor, being the most lethal tumor of the larynx. According to various case reviews, the median survival time is 9.8 months (1–26 months) [1]. Survival rates at 2 and 5 years are 16% and 5%, respectively [8]. Tumor stage on presentation seems to be a strong predictor of 5-year disease-specific survival (8.5% for Stage IV vs 25.9–45.8% for Stages I–III) [5].

Regarding the clinical course of the patient under study, the fact is noteworthy that she had two complete responses to cisplatin-based treatment regimens received during the evolution, with long progression-free intervals, living for 35 months despite having been diagnosed at an advanced stage.

The evidence for treatment of the small-cell neuroendocrine carcinoma of the larynx is scarce. There is a general consensus that surgery alone or in combination with radiotherapy does not improve local tumor control and is not the initial treatment of choice [7, 9, 10]. The preferred treatment, in the absence of specific trials, is extrapolated to that used in small-cell neuroendocrine lung carcinoma (SCLC): concurrent or sequential chemo-radiotherapy and platinum-based chemotherapy is the regimen more widely extended [11]. The combination of carboplatin, cisplatin and etoposide is commonly used in this setting. Cases series have been recently published. Deep *et al.* [2] published a series with eight patients (three of whom had a small-cell carcinoma) with different stage of presentation and treated with multimodality therapy (surgery, chemotherapy

and radiotherapy) or single therapy. In this series, a trend toward improved survival is noted when patients were presented with early stage disease and were treated with multimodality therapy. Iqbal *et al.* [12] published a series with nine patients with small-cell neuroendocrine carcinoma of the larynx. The treatment modality was primarily a combination of platin-based chemotherapy and radiotherapy. Nevertheless, outcomes remained poor, consistent with other previous publications [12].

Successive lines of treatment after relapse are also extrapolated from the treatment of SCLC, according to the progression-free interval, toxicity and general condition of the patient. Plausible alternatives are retreatment with platinum-based chemotherapy or the use of other agents like topotecan, vincristine, doxorubicin and cyclophosphamide [12].

Multiple targets are been identified in SCLC to test new therapies against [13]. This is the case of MYC gene family of transcriptions factors [14] or the epigenetic processes [15]. However, genomic profiling seems to be different between small-cell neuroendocrine carcinomas arising in different sites [16]. That suggests that an in-depth analysis of site-specific alterations and targeteable mutations will be desirable in the specific case of the small-cell neuroendocrine of the larynx.

CONFLICT OF INTEREST STATEMENT

None declared.

ETHICAL APPROVAL AND CONSENT TO PUBLISH

Because the patient was dead at moment of the case report drafting and as it was not possible to contact with her immediate relatives, we obtained an authorization issued by our institutional review board (Ethics and Clinical Research Committee) to publish the case in accordance with institutional and state legal rules and regulations. A copy of this approval is available in an attached file. Anyway, this case report does not contain either personal data or identifying images.

GUARANTOR

Dr. Juan Fernando Arango Arteaga and Dr. Virginia Arrazubi Arrula are guarantors of the manuscript.

REFERENCES

1. Ferlito A, Silver CE, Bradford CR, Rinaldo A. Neuroendocrine neoplasms of the larynx: an overview. *Head Neck* 2009;**31**: 1634–46. doi:10.1002/hed.21162.
2. Deep NL, Ekbom DC, Hinni ML, Zarka MA, Patel SH. High-grade neuroendocrine carcinoma of the Larynx: the mayo clinic experience. *Ann Otol Rhinol Laryngol* 2016;**125**:464–9. doi:10.1177/0003489415619179.

3. Barnes L. Neuroendocrine tumours. In: Barnes L, Eveson J, Reichart P, Sidransky D, eds. *Pathology and Genetics of Head and Neck Tumours. World Health Organization Classification of Tumours. Lyon.* Lyon: IARC Press, 2005,135–9.

4. Woodruff JM, Senie RT. Atypical carcinoid tumor of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec* 1991;**53**:194–209.

5. Alos L, Hakim S, Larque AB, De la Oliva J, Rodriguez-Carunchio L, Caballero M, *et al.* p16 overexpression in high-grade neuroendocrine carcinomas pf the head and neck: potential diagnostic pitfall with HPV-related carcinomas. *Virchows Arch* 2016;**469**:277–84. doi:10.1007/s00428-016-1982-1.

6. Nakano T, Motoshita J, Tanaka R, Okabe M, Tamae A, Shiratsuchi H, *et al.* Primary combined small cell carcinoma of the oropharynx with special reference to EGFR status of small cell carcinoma component: case report and review of the literature. *Auris Nasus Larynx* 2016. doi:10.1016/j.anl.2016.07.011. pii: S0385-8146(16)30217-6.

7. Van der Laan TP, Plaat BE, van der Laan BF, Halmos GB. Clinical recommendations on the treatment of neuroendocrine carcinoma of the larynx: a meta-analysis of 436 reported cases. *Head Neck* 2015;**37**:707–15. doi:10.1002/hed.23666.

8. Ferlito A, Devaney KO, Rinaldo A. Neuroendocrine neoplasms of the larynx: Advances in identification, understanding, and management. *Oral Oncol* 2006;**42**:770–88.

9. Devaney KO, Ferlito A, Rinaldo A. Neuroendocrine carcinomas of the larynx: what do the different histologic types really mean? *Eur Arch Otorhinolaryngol* 2010;**267**:1323–5. doi:10.1007/s00405-010-1318-8.

10. Lambea Sorrosal JJ, Tres Sánchez A. Tumores dentarios. Ameloblastoma. Tumores neuroendocrinos de cabeza y cuello. In: Escobar Alvarez Y., ed. *Tumores poco frecuentes de cabeza y cuello. Papel del oncólogo médico.* Madrid: Luzán, 2010,107–26.

11. Ferlito A, Rinaldo A. Primary and secondary small cell neuroendocrine carcinoma of the larynx: a review. *Head Neck* 2008;**30**:518–24. doi:10.1002/hed.20797.

12. Iqbal MS, Paleri V, Moor J, Dobrowsky W, Kelly C, Kovarik J. Small cell neuroendocrine carcinoma of larynx: case series and literature review. *J Laryngol Otol* 2015;**129**:910–5. doi:10.1017/S0022215115001668.

13. George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, *et al.* Comprehensive genomic profiles of small cell lung cancer. *Nature* 2015;**524**:47–53. doi:10.1038/nature14664.

14. Hwang DH, Sun H, Rodig SJ, Hornick JL, Sholl LM. Myc protein expression correlates with MYC amplification in small-cell lung carcinoma. *Histopathology* 2015;**67**:81–9. doi:10.1111/his.12622.

15. Luchenko VL, Salcido CD, Zhang Y, Agama K, Komlodi-Pasztor E, Murphy RF, *et al.* Schedule-dependent synergy of histone deacetylase inhibitors with DNA damaging agents in small cell lung cancer. *Cell Cycle* 2011;**10**:3119–28. Epub 2011 Sep 15.

16. Bergsland EK, Roy R, Stephens P, Ross JS, Bailey M, Olshen A. Genomic profiling to distinguish poorly differentiated neuroendocrine carcinomas arising in differents sites. *J Clin Oncol* 2016;**34** (suppl; abstract 4020).