



LETTERS TO THE EDITOR

Long duration of immunotherapy in a *STK11* mutated/*KRAS* wild-type non-small cell lung cancer patient



Serine/threonine kinase 11 gene (*STK11*) codes a kinase involved in the regulation of cell growth, polarity and motility, through phosphorylation of adenosine monophosphate-activated protein kinase (AMPK). Somatic mutations have been reported in up to 30% of Caucasian non-squamous non-small cell lung cancer (NSCLC) patients. *STK11* mutations may assume oncogenic functions, associated to reduced survival in lung adenocarcinoma.¹ We present a case of a *STK11* mutated lung adenocarcinoma presenting a good outcome with immunotherapy.

A 51-year-old female patient, light smoker, diagnosed in May/2015 with two synchronic tumours: lung adenocarcinoma cT2aN2M1c (one cerebellar asymptomatic lesion; *EGFR* wild-type, *ALK/ROS1*-, *KRAS*-, *HER2*-, PD-L1 < 1% by 22C3 assay); and breast invasive ductal carcinoma grade 3, cT2N0M0, hormonal receptors positive (ER 100%, PR 45%), *HER2*- and Ki-6740%. Whole exome sequencing of lung tumour showed a somatic S69* variant in *STK11* gene (*STK11* c.208C>A) at 27% allelic frequency, without additional tar-

getable mutations, and a tumour mutational burden (TMB) of 4.9 mutations/megabase (<10 mutations/megabase).

She started chemoradiotherapy for lung cancer and stereotactic radiosurgery of cerebellar metastasis, as an oligometastatic NSCLC. After 2 months, disease progression (DP) was observed with new adrenal lesions.

Second line docetaxel was started, presenting DP of NSCLC after one month, but with breast cancer reduction.

In September/2015, the patient started a third line with nivolumab. Partial response was observed at two months and patient continued with the immunotherapy. After fifteen months lung and breast tumours increased, and local therapy was performed (stereotactic radiotherapy for lung, followed by breast lumpectomy, pT1cN0M0). Post-lumpectomy RT was considered to have no further benefit. She started adjuvant therapy with letrozole.

In March/2018, after thirty months, lung tumour had a second DP under immunotherapy, and underwent a new biopsy. At this point, this lung biopsy along the primary breast tumour were analysed through the VHIO-300 panel (450 genes) revealing presence of the *STK11* mutation in lung at DP (52.4% mutant fraction) and complete absence of the variant in breast.

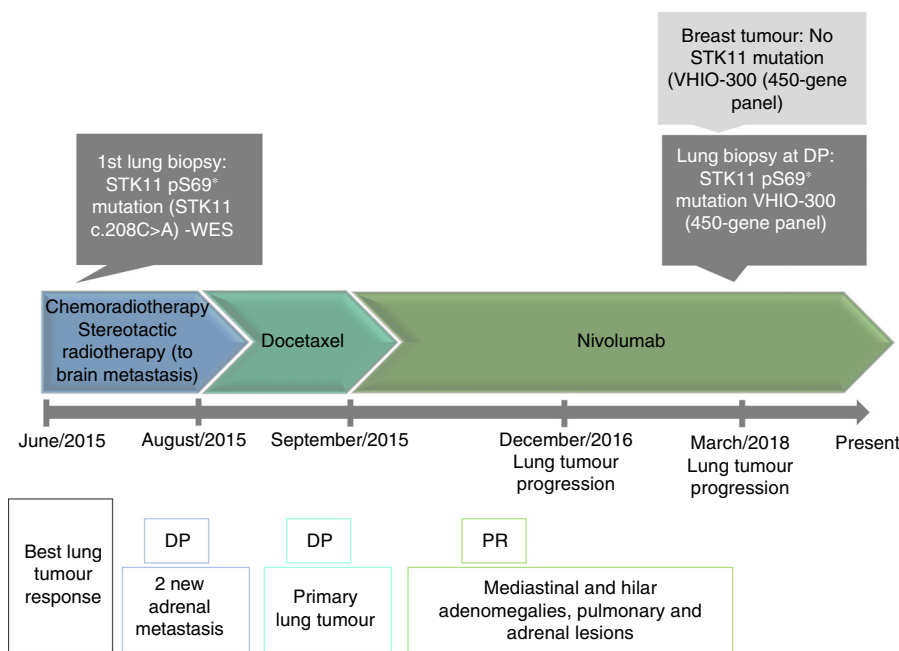


Figure 1 Sequence of treatments and outcomes. DP: disease progression. PR: partial response. *STK11*: serine/threonine kinase 11 gene. VHIO: Vall d'Hebron Institute of Oncology. WES: whole exome sequencing.

Despite DP, she remained asymptomatic, with good tolerance to nivolumab and letrozole. Immunotherapy proceeded until present (thirty-nine months), given the clinical benefit (Fig. 1).

In synchronous tumours, the most advanced assumes a prognostic importance. Although lung and breast tumours are common in females, their synchronous diagnosis is infrequent.² The patient's tumours didn't present a common mutational background.

Molecular classification of NSCLC has a direct impact on prognosis and treatment choices. *STK11* is thought to have a role on pulmonary tumorigenesis, often associated with *KRAS*.^{3,4} The reported *STK11* pS69* mutation results in a premature stop codon within its kinase domain, associated to more aggressive tumours, shorter progression-free survival and overall survival.^{1,3} Additionally, this mutation has been associated with significantly shorter time on PD-1/PD-L1 blockade therapy in NSCLC (or even resistance),³ possibly by reducing density of tumour infiltrating cytotoxic CD8+T lymphocytes.⁵ Despite the *STK11* mutation, our patient presented a long survival and a clinical benefit from immunotherapy, as well as from thoracic radiotherapy and its possible abscopal effect.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Conflicts of interest

The authors have no conflicts of interest to declare.

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 Available online 7 August 2019
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 2531-0437/
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Mutational profile of non-small cell lung cancer patients: Use of next-generation sequencing



Lung cancer has the highest incidence and mortality worldwide.¹ Nowadays target therapy is the first line therapy in metastatic non-small cell lung cancer (NSCLC) in patients with target mutations.^{2,3} Next-generation sequencing (NGS) permits simultaneous reading of DNA sequences, with deep sequencing, allowing for the detection of genetic variants that occur at low percentages,⁴ in a short period of time and with relatively low cost.⁵

The aim of this study was to evaluate the mutational profile in patients with NSCLC, diagnosed in a Tertiary Hospital, which performed molecular testing by NGS.

We carried out a retrospective review of 204 patients with NSCLC who performed NGS in the Thoracic Tumors

Multidisciplinary Unit of Vila Nova de Gaia-Espinho Hospital Center between April 2016 and May 2018. We included in our study only patients with at least one mutation identified by NGS. Sociodemographic and clinical data were retrospectively reviewed from clinical files. Descriptive statistics were used to analyze patient's characteristics.

Our NGS technique include the "Oncomine Solid Tumor DNA" and the "Oncomine Solid Tumor Fusion Transcript" panels that allow for the identification of variants in the genes *EGFR*, *KRAS*, *NRAS*, *BRAF*, *MET*, *ERBB4* (*HER4*), *ERBB2* (*HER2*), *ALK*, *PI3KCA* and *PTEN* and gene rearrangements in *ALK*, *ROS1* and *RET*. This NGS technique, developed and validated by IPATIMUP Diagnostics, allowed us, with a sensibility >99%, to detect nucleotide substitutions with allelic fraction >5% and rearrangements in 1% of the RNA, in samples with more than 20% of neoplastic cells.

As a result, of the 204 patients with NSCLC who performed NGS 121 (59%) had some mutation and therefore