Immunotherapy Benefit in a Patient With Non-Small Cell Lung Cancer and a Rare BRAF Mutation

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Abstract
Immunotherapy is less effective in non-small cell lung cancer (NSCLC) with driver mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) and some may extrapolate this trend to other driver mutations. Up to 4% of NSCLC cases contain a BRAF mutation. Most BRAF mutations are V600E, and little is known about the impact of treatment in rare BRAF G469A mutations. We present a case of a patient found to have BRAF G469A mutated NSCLC. She was diagnosed with Stage IIIB NSCLC and treated with concurrent chemotherapy and radiation. Post-treatment imaging demonstrated disease progression and she was started on nivolumab, resulting in a dramatic and prolonged response which is ongoing after 76 cycles. Her substantial response and prolonged benefit suggest that BRAF–mutated NSCLC may respond better than EGFR- or ALK-driven disease to immunotherapy. Due to the rarity of specific mutations, this case adds to the limited current published literature on NSCLC harbouring a BRAF G469A mutation and suggests that immunotherapy is a reasonable treatment option.

Introduction
The therapeutic approach to non-small cell lung cancer (NSCLC) has dramatically shifted with identification of targetable driver mutations and the introduction of immune-checkpoint inhibitors (ICI) [1]. Treatment algorithms for tumors possessing epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations involve targeted tyrosine kinase inhibitors then cytotoxic chemotherapy, before considering ICI monotherapy due to concerns about poor efficacy of ICI in the driver mutation-activated population [2]. Other activating mutations have been identified, including the BRAF gene, representing potential sites for direct acting or downstream therapeutic targets where the impact of ICI is not known [3].

Case Presentation
Here we present a case of a 61-year-old female, previous smoker, diagnosed with Stage IIIB NSCLC, adenocarcinoma subtype, programmed death-ligand 1 (PD-L1) >50%, ALK translocation, EGFR mutation, and KRAS mutation-negative and de novo BRAF G469A mutated. She was originally treated on a clinical trial with radical radiation (66 Gray in 33 fractions) and concurrent chemotherapy (cisplatin and etoposide), randomized to receive metformin in combination. Post-treatment computed tomography (CT) demonstrated improvement of her right hilar mass, but new 6.0 x 4.4 cm left adrenal mass and 3.1 x 2.5 cm right adrenal mass (Figure 1). She started nivolumab alone, with near-complete response after 33 cycles. She has received 76 cycles of nivolumab with ongoing disease control more than four years later. Her treatment has been complicated with Grade 1 diverticulitis and recurrent Grade 1 pneumonitis which has required steroid treatment.

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Discussion

Somatic activating BRAF mutations were first described in 2002 and are best recognised in melanoma, identified in up to 66% of patients [4,5]. BRAF mutations are also found in several other malignancies including 100% of classic hairy cell leukemia, 50% of papillary thyroid cancer, and 15% of colon cancers [4,6]. NSCLC genomic studies have found that 1–4% of all NSCLC, predominantly adenocarcinoma, harbor a BRAF mutation and have similar survival as patients with wild type BRAF [7-10]. ALK-positive and EGFR mutant NSCLC are found more frequently in non-smokers and within the Asian population, while BRAF mutations appear to be more common in current or past smokers and the Caucasian population [5,7,8,10]. Over half of NSCLC BRAF mutations are V600E (exon 15), the remainder being non-V600E (exon 11 or 15). G469A accounts for approximately 23% of NSCLC BRAF mutations, however very little is published on patients whose cancer carries this mutation [10].

Dual BRAF inhibition with dabrafenib and vemurafenib significantly improves overall survival in advanced melanoma [5]. In BRAF V600E mutant metastatic NSCLC, an objective response rate (ORR) of 33–42% is seen in response to the same treatment, without a similar response observed in non-V600E BRAF carriers [11-13]. Dual BRAF and mitogen-activating protein kinase pathway inhibition, using a combination of dabrafenib and trametinib, respectively, has also been employed in BRAF V600E mutant metastatic NSCLC and found to have a 61–65% ORR. Unfortunately, BRAF non-V600E mutations were excluded from the trial [14]. With these results the Food and Drug Administration (FDA) approved dabrafenib plus trametinib for BRAF V600E mutant metastatic NSCLC [15]. Although these treatment options are promising, they cannot be applied to patients with BRAF G469A mutations. ICI therapies have now proven to be an effective option for many cancers [16]. However, only a portion of patients respond and experience the benefits of long-term disease control. In patients with NSCLC, the likelihood of response can be partially predicted by the level of PD-L1 expression on cancer cells, but this biomarker has proven far less useful in other malignancies [17,18].

EGFR- or ALK-mutation-positive NSCLCs typically have shorter and less complete response to ICI, compared to NSCLC without these oncogenic drivers, even with high PD-L1 expression [2]. This reduction in benefit results in ICI monotherapy being left until late in the treatment algorithm for NSCLC with EGFR- or ALK-driven NSCLC and some would extrapolate this concern to other driver mutations. Multiple hypotheses on this diminished response have been proposed, including lower tumor mutation burden or tumor-infiltrating lymphocytes, microenvironment differences, and an alternate escape pathway that is not associated with PD-1/PD-L1 [17]. Most current ICI clinical trials exclude patients with EGFR-mutant- or ALK-positive NSCLCs and most new data is achieved through small subgroup analysis and real-world data. Whether BRAF-mutant NSCLCs also have a similar response to ICI remains unclear. Guisier et al. recently considered the efficacy of ICI in Stage IV NSCLC harboring BRAF, HER2, MET mutation, or RET translocation. Twenty-six patients with BRAF V600E mutations demonstrated a 26% ORR with a median overall survival of 22.5 months. Comparatively, 18 patients had BRAF non-V600E mutations demonstrating a 55% ORR and 12.0 months median overall survival with ICI, but the specific G469A subgroup was not reported. Patients were predominantly treated with nivolumab; PD-L1 expression was ≥50% in 11% of patients and unknown for 56% [9]. Our BRAF G469A mutant NSCLC index case experienced a deep and durable response. Given that BRAF mutant NSCLC is found more commonly in current or past smokers, and is associated with high tumor mutation burden, strong response to ICI might be reasonable to expect [1].

Conclusions
Research is evolving in the evaluation of rare oncogenic drivers. Due to the rarity of specific mutations, accrual of patients in clinical trials is challenging. This profound and prolonged response to an ICI adds to the limited current literature on NSCLC harbouring a BRAF G469A mutation and further suggests that ICI may be of benefit and a reasonable treatment option.

**Additional Information**

**Disclosures**

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