Editorial Commentary



# BRAF$^{V600E}$ mutant, PD-L1 TPS 90% NSCLC: 1st line treatment with targeted therapy

**Edwin H. Yau**

Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA

*Correspondence to:* Edwin H. Yau. Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA.
Email: Edwin.Yau@RoswellPark.org.

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## Introduction

Over the last decade, we have witnessed significant advances in the treatment of advanced non-small cell lung cancer (NSCLC) through the joint revolutions of targeted genomic therapy and immunotherapy. We now have multiple effective therapeutics for metastatic NSCLC patients in the front-line setting that offer proven and durable clinical benefit compared to platinum doublet chemotherapy. As our tool set of therapeutics expand, so has the development of predictive and prognostic biomarkers. These biomarkers have been crucial in better defining subsets of NSCLC and directing optimal therapeutics in these more defined subsets. Currently, the main biomarkers in NSCLC that predict therapeutic efficacy include driver oncogene alterations detected by next-generation sequencing (NGS), such as ALK, ROS1, and NTRK fusions, sensitizing EGFR mutations, RET rearrangements, MET exon 14 skipping mutations, and BRAF$^{V600E}$ mutations, and immune profiling with immunohistochemistry for Programmed death ligand-1 (PD-L1) expression level.

For NSCLC patients with sensitizing driver mutations in oncogenes detected by NGS, matched kinase inhibitors offer excellent response rates and often with minimal toxicity. For NSCLC patients without driver mutations, immunotherapy with immune checkpoint inhibitors (ICI) targeting programmed death-1 (PD-1) or its ligand (PD-L1) offer improved overall survival, especially in patients with high PD-L1 expression, driven by the subset of patients that achieve remarkable durable responses. Despite our significant advancements, many questions remain, and among them being the optimal combination and sequencing of efficacious therapies.

## BRAF$^{V600E}$ targeted therapy in NSCLC

Mutations in BRAF, an oncogene in the RAF kinase family that is part of the canonical MAPK signaling cascade (downstream of RAS and upstream of MEK) involved in cell growth and proliferation (1), are detected in 2–4% of NSCLC patients. The most common BRAF mutation in NSCLC and other cancers is the V600E mutation in exon 15 representing approximately 50% of BRAF mutations in NSCLC and in general mutually exclusive with other NSCLC driver oncogene mutations such as EGFR, KRAS, ALK, ROS1, MET, and RET alterations (2). Unlike EGFR, ALK, ROS1, and RET alterations which are generally found in non-smokers, BRAF$^{V600E}$ mutations can be found in both smokers and non-smokers with conflicting findings from retrospective series, but on the whole favoring a slight enrichment of former and current smokers and a slight female predominance (2).

The BRAF$^{V600E}$ mutation leads to constitutive activation of the kinase and the promotion of cell proliferation mediated by downstream signaling through MEK and ERK. Multiple potent BRAF inhibitors (BRAFi), such as vemurafenib, dabrafenib, and encorafenib, have been developed against activated BRAF$^{V600E}$ and extensively studied in melanoma, where activating BRAF$^{V600E}$ mutations represent the majority (~70–80%) of BRAF mutations found in approximately 40% of metastatic melanoma patients. Monotherapy with first and second generation selective BRAFi demonstrated clinical response in BRAF$^{V600E}$ mutated metastatic melanoma, but had somewhat limited efficacy due to acquired resistance as well as adverse events, particularly the development of secondary malignancies due to paradoxical MAPK activation through upstream RAS (3).

The combination of MEK inhibitors (MEKi), such as trametinib, binimetinib, and cobimetinib, with BRAFi can delay the emergence of resistance and decrease adverse events due to paradoxical MAPK activation, and multiple phase III clinical trials have demonstrated combination BRAFi and MEKi as significantly more efficacious than single agent BRAFi in $BRAF^{V600E}$ mutant metastatic melanoma patients with overall response rates (ORR) of 64–68%, median progression free survival (PFS) of 11.1–14.9 months, and median overall survival (OS) of 22.3–33.6 months (4). The combination of BRAFi with MEKi is now established as the standard of care targeted therapy regimen in $BRAF^{V600E}$ mutated metastatic melanoma.

Extending the clinical use of targeted therapies against $BRAF^{V600E}$ mutations from melanoma to NSCLC, a retrospective study of 35 European BRAF-mutant (>80% V600E) NSCLC treated with BRAFi monotherapy showed an ORR of 53%, PFS of 5.0 months, and median OS of 10.8 months suggesting clinical benefit of $BRAF^{V600E}$ targeted therapy in NSCLC (5). A basket trial evaluating monotherapy with vemurafenib in a variety of $BRAF^{V600}$ mutated cancers demonstrated a 42% ORR and PFS of 7.3 months in 19 $BRAF^{V600}$ mutant NSCLC patients (6). A recent French study of vemurafenib monotherapy in NSCLC showed similar results in 96 $BRAF^{V600E}$ mutant NSCLC patients with an ORR of 44.8%, median PFS of 5.2 months, and median OS of 10 months (7).

The prospective evaluation of dabrafenib monotherapy in $BRAF^{V600E}$ mutant NSCLC in an open-label, multicenter, phase 2 trial also demonstrated some clinical activity with ORR of 33% and a median PFS of 5.5 months, and OS of 12.7 months in 78 previously treated patients (8). Two additional cohorts in this phase 2 dabrafenib trial evaluated the BRAFI and MEKi combination of dabrafenib and trametinib in previously treated and in untreated NSCLC patients, and showed a more substantial and durable responses that lead to the FDA approval in 2017 of the combination of dabrafenib and trametinib for NSCLC patients with $BRAF^{V600E}$ mutations. In the previously treated cohort of 57 $BRAF^{V600E}$ mutant NSCLC patients, dabrafenib plus trametinib treatment demonstrated a 63% ORR, PFS of 9.7 months, and OS of 18.2 months (9). In the front-line cohort of 36 $BRAF^{V600E}$ mutant NSCLC patients, combination dabrafenib plus trametinib treatment demonstrated a similar ORR of 64% with longer PFS of 10.9 months and a remarkable median OS of 24.6 months (10). Treatment was tolerated in both previously treated and untreated cohorts, with a 12–22% rate of adverse events that lead to discontinuation. Similar open-label phase 2 studies are currently evaluating the combination of encorafenib with binimetinib in $BRAF^{V600E}$ mutant NSCLC in front-line and second-line settings. Currently, the NCCN panel recommends the dabrafenib and trametinib combination as the preferred first-line systemic option in metastatic NSCLC with $BRAF^{V600E}$ mutations.

## Immunotherapy in PD-L1 high NSCLC and $BRAF^{V600E}$ NSCLC

The development of ICI targeting PD-(L)1 has revolutionized the treatment of metastatic NSCLC and ICI have quickly emerged as a near universal component in front-line treatment of metastatic NSCLC without driver oncogene mutations. The phase III open-label KEYNOTE-024 demonstrated the use of PD-L1 expression levels as a biomarker to select for patients who can be treated successfully with front-line ICI monotherapy. In metastatic NSCLC patients with high PD-L1 expression (tumor proportion score, TPS ≥50%) without EGFR sensitizing mutations or ALK fusions, pembrolizumab monotherapy demonstrated superior median OS of 30.0 months compared to 14.2 months with platinum doublet chemotherapy (11). NSCLC patients with high levels of PD-L1 expression also derived significant benefit of the addition of ICI to chemotherapy, with the PD-L1 high subset in the phase 3 randomized KEYNOTE-189 trial demonstrating an ORR of 62.1% to combination chemotherapy with ICI and a 51.9% 24-month survival (12).

Efforts to extend the benefit of these remarkable durable responses from ICI treatment to genomic subsets of NSCLC has not been straightforward, especially in the largest genomic subset of sensitizing EGFR mutant NSCLC. Meta-analysis of second-line ICI in NSCLC trials did not show a survival benefit of ICI compared to chemotherapy in EGFR mutant NSCLC (13). The prospective ATLANTIC trial evaluating durvalumab in the third-line setting showed lower response rates in the combined EGFR and ALK mutant cohort compared to cohorts lacking EGFR and ALK mutations (14). Similarly, the phase II trial of pembrolizumab in PD-L1 positive, EGFR mutated NSCLC was terminated early due to lack of response in the initial 11 patients (15). These findings resulted in the exclusion of EGFR and ALK patients from many front-line ICI clinical trials. Whether these findings in EGFR mutant NSCLC extend to other oncogene driver subsets in NSCLC such as $BRAF^{V600E}$ remains unknown.

 

Also unknown is whether the benefit of ICI in front-line extends to genomic subsets given the lack of selection or stratification for other oncogene drivers in the large, pivotal ICI trials in NSCLC. Given the 1–2% prevalence of $BRAF^{V600E}$ in NSCLC, only a handful of patients were likely enrolled in each of the front-line ICI studies, limiting our interpretation of the effectiveness of front-line ICI in $BRAF^{V600E}$ mutant NSCLC.

The IMMUNOTARGET retrospective study of 551 NSCLC patients with known oncogenic driver alterations treated with single-agent ICI demonstrated a range of response rates and PFS in different oncogene alterations with 0% and 12% ORR in ALK and EGFR mutant subsets respectively compared to 26% ORR in KRAS mutant subsets (16). This perhaps speaks to the different clinical pathologic characteristics of different mutation subsets. The BRAF mutant subset, which included n=17 V600E mutants and n=18 non-V600E mutants, demonstrated a 24% ORR comparing similarly to the KRAS mutant subset. On univariate analysis in BRAF mutants, the V600E subset trended towards a lower PFS (1.8 months) compared to non-V600E BRAF mutants (4.1 months), no difference in PFS between number of previous lines of treatment, and a significantly higher PFS was noted in smokers compared to never smokers (4.1 *vs.* 1.9 months, P=0.03) (16).

Another small retrospective study by Dudnik *et al.* evaluated PD-L1 status and response to ICI in a cohort of 39 BRAF mutant NSLC patients (n=21 with V600E mutations and n=18 with non-V600E mutations) treated with ICI (17). In this cohort, non-V600E BRAF mutant patients were significantly enriched for smokers (78% smokers) compared to $BRAF^{V600E}$ mutant patients (43% smokers). Of the 39 patients, 29 were tested for PD-L1 expression and higher rates of high PD-L1 expression (TPS ≥50%) were found in BRAF mutants compared to the expected 30% prevalence in unselected NSCLC, with 42% of $BRAF^{V600E}$ mutants with high PD-L1 expression and 50% of $BRAF^{non\text{-}V600E}$ mutants with high PD-L1 expression. However, given the limited number of patients, and some evidence that PD-L1 expression in oncogene-mutated NSCLC may be more reflective of aberrant oncogene signaling rather than predictive of immune engagement, it remains to be seen if PD-L1 expression is predictive of ICI response in $BRAF^{V600E}$ mutant NSCLC. Response rates to ICI in this cohort were similar to the IMMUNOTARGET cohort with 25% ORR in $BRAF^{V600E}$ mutant patients and 33% ORR in $BRAF^{nonV600E}$ mutant patients.

These two retrospective studies do suggest that at least some $BRAF^{V600E}$ mutant NSCLC respond to ICI treatment, with the subset (especially in smokers) perhaps more similar to KRAS mutant subset than EGFR/ALK subset in terms of ICI response and the response rates of 24–25% compares favorably to second line ICI trials in unselected NSCLC. Given the decrease in efficacy of ICI in non-smokers compared to smokers, it seems likely that driver mutation subsets that are enriched for non-smokers would have lower rates of response to ICI, while subsets such as KRAS and BRAF mutant NSCLC that harbor significant amount of smokers may contain more patients that are sensitive to ICI.

## Sequencing of targeted therapy and immunotherapy in $BRAF^{V600E}$ NSCLC

In a metastatic $BRAF^{V600E}$ mutant NSCLC patient with PD-L1 >90% TPS, front line combination BRAFi and MEKi treatment with dabrafenib and trametinib, ICI monotherapy, or ICI combined with chemotherapy would all be appropriate FDA approved front-line treatment options, with no prospective head to head clinical trials to help choose the best front-line option. Given the similarities with available treatment options in $BRAF^{V600E}$ mutated melanoma, it seems reasonable to gain insight from the debate in melanoma over the optimal sequencing of targeted therapy compared to ICI, while acknowledging that there are significant differences between melanoma compared to NSCLC both in tumor biology (with different distributions of BRAF mutations and where PD-L1 as a biomarker seems to have important clinical differences) as well as therapy options (where CTLA-4 blockade has been more commonly incorporated in melanoma compared to NSCLC therapy which includes chemotherapy combinations with ICI).

Initial retrospective studies of CTLA-4 blockade with ipilimumab in advanced melanoma patients with $BRAF^{V600}$ mutations seemed to favor front line treatment with anti-CTLA4 prior to targeted therapy as response and outcomes to ipilimumab were better before targeted therapy compared to after targeted therapy (18). However, retrospective analysis of trials incorporating PD-(L)1 targeted therapies, which are perhaps more relevant to the NSCLC debate, suggest a more complicated picture. Given the different mechanisms of action of CTLA-4 blockade, which is postulated to act more centrally, compared to PD-1/PD-L1 blockade and BRAF/MEK inhibition both acting more directly intratumorally and in the tumor microenvironment, it should not be surprising to find differences with prior ipilimumab data. And since both

 

PD-(L)1 blockade and BRAF/MEK inhibition both affect tumor signaling and the tumor microenvironment, there is a concern for overlapping toxicities as well as common mechanisms of resistance.

Pooled data from 4 clinical trials encompassing 106 $BRAF^{V600}$ mutant melanoma patients showed similar response rates to nivolumab before (33.1%) and after (24.5%) BRAF inhibitor therapy (19). A larger pooled analysis of 3 pembrolizumab clinical trials encompassing 434 $BRAF^{V600}$ mutant melanoma patients showed better response rates and better PFS to pembrolizumab in BRAFi naïve patients (ORR 44.2%, 4-year PFS 27.8%) compared to patients who received prior BRAFi with or without MEKi (ORR 28.4%, 4-year PFS 15.2) (20). Patients who received prior BRAF targeted treatment were patients with generally poorer prognosis with worse performance status, more PD-L1 negative tumors, more with prior ipilimumab treatment, higher LDH levels, and who had received more lines of treatment. While multivariate analysis still identified prior BRAF targeted therapy as associated with poorer response to pembrolizumab, there is no analysis of how patients do with BRAF targeted salvage therapy after pembrolizumab treatment in this study, and this poorer response may simply reflect patients with aggressive disease who share common mechanisms of resistance and who will respond poorly to both classes of therapy.

Indeed, a 2017 retrospective study of 114 $BRAF^{V600}$ melanoma patients demonstrated that both PD-1 and BRAF targeted therapies were efficacious in the treatment naïve setting with similar OS and PFS, but both showed poorer efficacy as the salvage treatment, with ICI showing modest activity after prior BRAFi (25% ORR after BRAFi *vs.* 40% ORR in treatment naïve), but salvage BRAFi therapy after prior ICI showing the worst outcomes (21). It seems that there may be overlap in patients who benefit from both BRAFi and ICI or in patients with intrinsically aggressive disease who are resistant to both treatments, as patients who benefited from BRAFi therapy for more than 6 months had a higher ORR to subsequent ICI of 34% compared to 15% ORR to subsequent ICI in patients who had less than 6 months of benefit from BRAFi treatment (21). Another study looking at the combined analysis of survival curves grouped by type of systemic therapy in melanoma trials showed a superiority of combined BRAFi with MEKi compared to ICI in the first 6 months and then a gradual crossing of the curves perhaps speaking to the development of resistance and the more durable response of patients who respond to ICI (22). Given these two analyses, it seems a strategy of upfront BRAFi therapy followed by a switch to ICI may be a viable sequence, or a combination approach if toxicity can be managed. Two recent melanoma trials have demonstrated promise in combining BRAFi and MEKi with ICI with PD-(L)1 inhibitors (23). The phase 2 KEYNOTE-022 trial combining the triplet combination of pembrolizumab with full doses of dabrafenib and trametinib lead to significantly longer median PFS of 16.0 months compared to PFS of 10.3 months with doublet BRAFi/MEKi treatment at the cost of increased side effects with 25% discontinuation rate in the triplet therapy compared to 15% in the doublet. The phase 3 IMspire150 trial evaluated the addition of the PD-L1 inhibitor atezolizumab to BRAFi vemurafenib and MEKi cobimetinib using a modified dosing schedule that allowed for 28-day run-in of BRAFi and MEKi first prior to the addition of atezolizumab with a dose reduction in vemurafenib in the triplet combination arm. This study met its endpoint of improved PFS in the triplet atezolizumab combination of 15.1 months compared to 10.6 months with doublet BRAFi/MEKi with similar response rates and low rates of discontinuation due to adverse events (13% in triplet with reduced dose vemurafenib and 16% in doublet with full dose BRAFi/MEKi). Similar to the retrospective analysis of survival curves in Ugurul *et al.*, in both KEYNOTE-022 and IMspire150 trials, the improvement in PFS curves also did not become evident until 7 months into treatment. We await the results of many prospective phase III trials in melanoma that are randomizing between different sequences and combinations of BRAFi/MEKi and ICI in the hopes of more definitive answers in optimal use of these agents.

In addition to concerns of similar mechanisms of resistance, there is also concern for increased toxicity in sequencing some kinase inhibitor therapies after PD-(L)1 therapy. Sequencing PD-(L)1 blockade prior to kinase inhibitor therapy with osimertinib in EGFR mutant NSCLC led to a high rate of severe immune mediated adverse events that was not seen with osimertinib treatment prior to ICI therapy (24). A retrospective study evaluating BRAFi/MEKi in melanoma patients previously treated with PD-1 based therapy also showed concerning rates of adverse events, with dose modifications seen in 84% of patients compared to the dose modification rates in ICI naïve settings which ranged from 33–61% (25).

Given the experience with other oncogene driver subsets in NSCLC that have favored the paradigm of targeted therapy first prior to ICI, especially with the increased risk of potential toxicities of BRAF targeted therapies

 

after ICI, combined with the small amount of $BRAF^{V600E}$ mutant patients in front-line ICI studies compared to the larger prospective trial demonstrating durable efficacy of dabrafenib and trametinib combination in $BRAF^{V600E}$ mutated NSCLC, and the retrospective studies suggesting good response rates of second line and beyond ICI in $BRAF^{V600E}$ mutant NSCLC, it seems that even in the setting of high PD-L1 expression, the preferred initial treatment for a $BRAF^{V600E}$ mutant NSCLC should be targeted therapy.

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## References

1. Downward J. targeting RAS signaling pathways in cancer therapy. Nat Rev Cancer 2003;3:11-22.
2. Nguyen-Ngoc T, Bouchaab H, Adjei AA, et al. BRAF Alterations as Therapeutic Targets in Non-Small-Cell Lung Cancer. J Thorac Oncol 2015;10:1396-403.
3. Gibney GT, Messina JL, Fedorenko IV, et al. Paradoxical oncogenesis—the long-term effects of BRAF inhibition in melanoma. Nat Rev Clin Oncol 2013;10:390-9.
4. Schummer P, Schilling B, and Gesierich A. Long-Term Outcomes in BRAF-Mutated Melanoma Treated with Combined Targeted Therapy or Immune Checkpoint Blockade: Are We Approaching a Ture Cure? Am J Clin Dermatol 2020;21:493-504.
5. Gautschi O, Milia J, Cabarrou B, et al. Targeted Therapy for patients with BRAF-mutant lung cancer: Results from the European EURAF cohort. J Thorac Oncol 2015;10:1451-7.
6. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med 2015;373:726-36.
7. Mazieres J, Cropet C, Montané L, et al. Vemurafenib in non-small-cell lung cancer patients with BRAFV600 and BRAFnonV600 mutations. Ann Oncol 2020;31:289-94.
8. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in BRAF V600E-Mutant Advanced Non-Small Cell Lung Cancer: an Open-label, Single arm, Multicenter, Phase 2 Trial. Lancet Oncol 2016;17:642-50.
9. Planchard D, Besse B, Growen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol 2016;17:984-93.
10. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017;18:1307-16.
11. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019;37:537-46.
12. Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2020;38:1505-17.
13. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer – a

 

meta-analysis. J Thorac Oncol 2017;12:403-7.
14. Garassino MC, Cho BC, Kim JH, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018;19:521-36.
15. Lisberg A, Cummings A, Goldman JW, et al. A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC. J Thorac Oncol 2018;13:1138-45.
16. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol 2019;30:1321-8.
17. Dudnik E, Peled N, Nechushtan H, et al. BRAF Mutant Lung Cancer: Programmed Death Ligand 1 Expression, Tumor Mutational Burden, Microsatellite Instability Status, and Response to Immune Check-Point Inhibitors. J Thorac Oncol 2018;13:1128-37.
18. Ascierto PA, Simeone E, Sileni VC, et al. Sequential treatment with ipilimumab and BRAF inhibitors in patients with metastatic melanoma: data from the Italian cohort of the ipilimumab expanded access program. Cancer Invest 2014;32:144-9.
19. Larkin J, Lao CD, Urba WJ, et al. Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma: A Pooled Analysis of 4 Clinical Trials. JAMA Oncol 2015;1:433-40.
20. Puzanov I, Ribas A, Robert C, et al. Association of BRAF V600E/K Mutation Status and Prior BRAF/MEK Inhibition With Pembrolizumab Outcomes in Advanced Melanoma: Pooled Analysis of 3 Clinical Trials. JAMA Oncol 2020;6:1256-64.
21. Johnson DB, Pectasides E, Feld E, et al. Sequencing Treatment in BRAFV600 Mutant Melanoma: Anti-PD-1 Before and After BRAF Inhibition. J Immunother 2017;40:31-5.
22. Ugurel S, Rohmel J, Ascierto PA, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247-57.
23. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;395:1835-44.
24. Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and Osimertinib. Ann Oncol 2019;30:839-44.
25. Saab KR, Mooradian MJ, Wang DY, et al. Tolerance and Efficacy of BRAF Plus MEK Inhibition in Patients with Melanoma Who Previously Have Received Programmed Cell Death Protein 1-Based Therapy. Cancer 2019;125:884-91.

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