Editorial Commentary

Checkpoint inhibitors first in patients with metastatic non-small cell lung cancer harboring *BRAF*^{V600E} mutation with PD-L1 90%—a debate in a niche population

Yusra F. Shao[1], **Ammar Sukari**[1], **Misako Nagasaka**[1,2]

[1]Department of Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; [2]Division of Neurology, Department of Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Correspondence to: Misako Nagasaka, MD. 4100 John R Detroit, MI 48201, USA. Email: nagasakm@karmanos.org.

Received: 11 October 2020. Accepted: 09 November 2020; Published: 30 December 2020.
doi: 10.21037/pcm-20-60
View this article at: http://dx.doi.org/10.21037/pcm-20-60

Lung cancer is the leading cause of cancer related death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and 55% of NSCLC is metastatic at the time of diagnosis (2). Fortunately, the advent of targeted therapy and immunotherapy has introduced a new era in the treatment of metastatic NSCLC (mNSCLC). In addition to epithelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), V600E mutant BRAF protein has emerged as a target of therapy in mNSCLC in combination with mitogen-activated protein kinase (MEK) inhibitors. In June 2017, the combination of dabrafenib and trametinib was approved for the treatment of *BRAF*^{V600E}-mutant mNSCLC (3). Similarly, great strides have been made at the immunotherapy front with the approval of immune checkpoint inhibitors (ICI) for the treatment of mNSCLC. In October 2016 and September 2019, pembrolizumab was approved as monotherapy for the first-line treatment of mNSCLC with programmed death ligand-1 (PD-L1) expression of greater than 50% and 1% respectively (4,5). Most recently, in May 2020, atezolizumab received approval for the first-line treatment of mNSCLC with high PD-L1 expression (6). Since BRAF/MEK inhibitors and ICI both appear to be effective in the first-line treatment of mNSCLC, debate has ensued on the best treatment approach for patients with *BRAF*^{V600E}-mutant mNSCLC and high PD-L1 status.

Here, we review the available evidence for anti-BRAF and ICI therapy in the assumed case of *BRAF*^{V600E}-mutant mNSCLC with PD-L1 status greater than 90%. We also conclude that ICIs represent a preferred course of first-line treatment in this niche population given comparable efficacy between anti-BRAF and ICI therapy and lesser adverse events with the latter.

BRAF inhibitors

BRAF is a serine/threonine kinase in the MAPK/ERK pathway (7). BRAF dimerization, induced by RAS, leads to the activation of MEK which subsequently activates the downstream target ERK (7). ERK, once activated on the cytoplasmic surface of the nuclear membrane, is internalized into the nucleus and triggers cell proliferation and differentiation (7). *BRAF*^{V600E} mutations constitutively lead to increased activation of the MEK/ERK pathway, evasion of senescence and apoptosis and subsequent cell proliferation, independent of KRAS signaling (7). *BRAF* gene mutations are detected in 2% of all NSCLC, half of which are V600E mutations which lead to glutamic acid substitution for valine at the 600th amino acid of BRAF protein (8). Patients with *BRAF*^{V600E} mutation are typically current or former smokers (9). This is unlike traditional markers of targeted therapy such as *EGFR* or *ALK* mutations which are common in nonsmokers or former light smokers (9).

BRAF/MEK inhibitor combination therapy works by inhibiting the upstream (BRAF) and downstream (MEK) activating signals of ERK (8). Dabrafenib is a tyrosine kinase inhibitor that inhibits the V600E mutant BRAF protein while the addition of trametinib, a MEK inhibitor, is shown to increase the efficacy of dabrafenib in pre-clinical and clinical studies (8). The combination of dabrafenib and trametinib has been used in the treatment of unresectable

Table 1 Summary of key clinical trials

	Dab plus tram, Planchard *et al.* (3)	Pembro (KEYNOTE-024), Reck *et al.* (4,11)	Pembro (KEYNOTE-042), TPS ≥50%, Mok *et al.* (5)	Atezo (IMPower110), Herbst *et al.* (6)		
				SP263 TC ≥50%	SP263 TPS ≥50%	SP142 TC3/IC3
Study design						
Arms	Single	Double	Double		Double	
Randomization	Non random	Random	Random		Random	
Phase	Phase 2	Phase 3	Phase 3		Phase 3	
Enrolled participants receiving treatment	36	154	299	150	134	107
Outcomes						
ORR	64%	46.1%	NA		NA	
Median PFS (month)	10.9	7.7	7.1	7.0	7.3	8.1
Median OS (month)	24.6	26.3	20.0	19.5	20.2	20.2

Cross trial comparison must be taken with caution. Dab, dabrafenib; Tram, trametinib; Pembro, pembrolizumab; Atezo, atezolizumab; ORR, overall response rate; PFS, progression free survival; OS, overall survival.

and metastatic $BRAF^{V600E}$-mutant melanoma (10). This combination was approved for the first-line treatment of mNSCLC based on the results of a phase 2 study of patients with $BRAF^{V600E}$-mutant mNSCLC previously untreated for their metastatic disease (*Table 1*) (3). This non randomized, open label, multicenter study enrolled 36 patients with $BRAF^{V600E}$-mutant mNSCLC. Patients received oral dabrafenib 150 mg two times daily and oral trametinib 2 mg daily. Scans were followed every 6 weeks. The primary endpoint was overall response rate (ORR) and secondary endpoints were progression free survival (PFS), duration of response (DOR) and overall survival (OS). At a median follow up of 15.9 months, investigators reported an ORR of 64% (complete response- 6%, partial response 58%), median PFS of 10.9 months, DOR of 10.4 months and median OS of 24.6 months. Although this is not a head-to-head study comparing outcomes of BRAF/MEK directed therapy to standard of care, the efficacy exceeds what is expected from standard chemotherapy.

Immune checkpoint inhibitors

Similar to the increased efficacy of BRAF/MEK inhibitors, ICIs have shown promising results in the treatment of mNSCLC. ICIs bind to PD-1 on T lymphocytes or PD-L1 on tumor cells (TC) (12). PD-L1 is expressed on normal cells that, upon binding PD-1 on T-lymphocytes, inhibits their cytotoxic function (12). PD-L1 is overexpressed on malignant cells allowing them to evade cytotoxic T-lymphocytes (12). Pembrolizumab is a PD-1 inhibitor while atezolizumab is a PD-L1 inhibitor, both inhibiting the ability of malignant cells to evade cytotoxic T-lymphocytes (12).

Pembrolizumab was approved for the first-line treatment of mNSCLC with high PD-L1 expression (≥50%) based on the results of KEYNOTE-024 study (*Table 1*) (4). This randomized, open label study compared single agent pembrolizumab with standard platinum-based chemotherapy for previously untreated mNSCLC with PD-L1 expression ≥50%. Three hundred and five patients were enrolled. One hundred and fifty-four patients received pembrolizumab 200 mg every 3 weeks while 151 patients received platinum-based doublet chemotherapy. Investigators demonstrated a median PFS of 10.3 months and ORR of 44.8% in the pembrolizumab arm compared to 6 months and 27.8% in the chemotherapy arm (PFS HR 0.50, 95% CI, 0.37–0.68) (4). A long-term follow-up demonstrated a median OS of 26.3 months and 13.4 months in the pembrolizumab and chemotherapy arms respectively (HR 0.63, 95% CI, 0.47–0.86) (13). Subsequently, in KEYNOTE-042, pembrolizumab was compared to platinum-based chemotherapy in patients with previously untreated, locally advanced or metastatic NSCLC with PDL1 expression ≥1% (5). The primary endpoint of

the study was PFS in the subgroup with PD-L1 ≥50% while the secondary outcome was PFS and OS in PD-L1 ≥1% and PD-L1 ≥50% subgroups. Analysis of the PD-L1 ≥50% subgroup showed a PFS of 7.1 *vs.* 6.4 months and OS of 20.0 *vs.* 12.2 months in the pembrolizumab and chemotherapy arms respectively (PFS HR 0.81, 95% CI, 0.67–0.99; OS HR 0.69, 95% CI, 0.56–0.85). This study confirmed the efficacy of pembrolizumab compared to chemotherapy as first-line treatment for mNSCLC with high PD-L1 expression. It also allowed for an expanded approval of pembrolizumab for treatment of locally advanced NSCLC with high PD-L1 expression and as single agent therapy for mNSCLC with PD-L1 status ≥1%.

Most recently, atezolizumab gained approval for the first-line treatment of mNSCLC with high PD-L1 expression tested via Ventana SP142 assay (6). PD-L1 high expression is defined by Ventana SP142 assay as TC with PD-L1 expression ≥50% or PD-L1 stained immune infiltrating cells (IC) covering more than 10% of tumor area (6). This approval was based on the IMpower110 study of atezolizumab compared to platinum-based chemotherapy for the first-line treatment of mNSCLC (6). Subgroup analysis was based on three different assays of PD-L1 testing. Difference in PFS and OS was significant favoring atezolizumab in the subgroup with PD-L1 expression ≥50% by 22C3 assay (PFS HR 0.61, 95% CI, 0.46–0.82; OS HR 0.6, 95% CI, 0.41–0.86). Difference in PFS and OS was also significant in the SP142 assay subgroup with TC ≥50% or IC ≥10% (PFS HR 0.59, 95% CI, 0.43–0.82; OS HR 0.59, 95% CI, 0.40–0.89). Subgroup with PDL1 ≥50% by SP263 assay showed a statistically significant difference in PFS and a trend towards OS favoring atezolizumab (PFS HR 0.67, 95% CI, 0.51–0.89; OS HR 0.71, 95% CI, 0.5–1.0). This study led to the approval of atezolizumab as first-line therapy for mNSCLC in PD-L1 high subgroup and for the approval of Ventana SP142 assay as a companion diagnostic test for selection of mNSCLC with high PD-L1 expression. Of note, patients with *ALK* and *EGFR* mutations were excluded from KEYNOTE-024, KEYNOTE-042 and Impower110 studies. While *BRAF* mutated patients were not excluded, it is unclear how many patients in these trials were *BRAF* mutated.

The efficacy of immune checkpoint inhibitors appears related to the degree of PD-L1 expression on TC. A retrospective study of 187 patients who received first-line pembrolizumab for *EGFR*-negative, *ALK*-negative, PD-L1 ≥50% mNSCLC showed an ORR of 32.7% *vs.* 60% for PD-L1 50–89% *vs.* ≥90% (14). Similarly, IMpower110 study showed a median OS of 19.5–20.2 *vs.* 12.9–16.5 months for PD-L1 high (≥50% by 22C3 assay, PD-L1 ≥50% by SP263, TC3 or IC3-WT by SP142 assay) and PD-L1 low (1–49% by 22C3 assay, 1–49% by SP263, TC1/2 or IC1/2-WT by SP142 assay) subgroups respectively (6). Based on these results, a patient with high PD-L1 expression would be expected to have a greater benefit from ICIs when compared to patients with low PD-L1 expression.

Comparing therapies

Though the efficacy of BRAF inhibitors and ICIs appears comparable, their side effects differ drastically. *Table 2* summarizes the most common side effects of dabrafenib/trametinib and pembrolizumab (3,5,11). All patients receiving dabrafenib/trametinib experienced some adverse event (AE) while 63–75% of patients receiving pembrolizumab experienced AEs (3,5,11). Furthermore, grade 3–4 AEs occurred in 69% of patients treated with dabrafenib/trametinib while they were only seen in 16–31% of patients receiving pembrolizumab (3,5,11). However, it must be noted that 1.3–2% of patients receiving pembrolizumab experienced an AE that lead to death while no death occurred due to AEs in patients receiving dabrafenib/trametinib (3,5,11). This observation points to the rare yet potentially life threatening immune related adverse events (IRAEs) that may occur with ICIs (5,11). The most common AE experienced by patients receiving dabrafenib/ trametinib was pyrexia (53%) which only occurred in 0-11.7% of patients on pembrolizumab (3,5,11). Most common AE with pembrolizumab was diarrhea (16.2%, grade 3–4 3.9%) in the KEYNOTE-024 study and hypothyroidism (11%, grade 3–4 <1%) in the KEYNOTE-042 study (5,11). Hypothyroidism, along with pneumonitis, hepatitis, colitis, adrenal insufficiency and hypophysitis are unique IRAEs caused by ICIs that have not been observed in patients receiving dabrafenib/ trametinib (3,5,11). Despite the unique AEs of pembrolizumab, it appears that it is better tolerated than dabrafenib/trametinib with lesser overall AEs. This greater tolerance is reflected in KEYNOTE-024 study where, at the end of follow up (median follow up 11.2 months), 48% of patients receiving pembrolizumab remained on treatment while 13.6% had discontinued treatment due to AEs (11). On the contrary, 31% of patients receiving dabrafenib/ trametinib remained

Table 2 Summary of common adverse events

Adverse events (AE)	Dabrafenib + Trametinib, Planchard *et al.* (3)	Pembrolizumab (KEYNOTE-024), Reck *et al.* (4,11)	Pembrolizumab (KEYNOTE-042), Mok *et al.* (5)
Any AE	100%	75%	63%
Grade 3–4 AE	69%	31%	16%
Leading to death	Not reported	1.3%	2%
AE Grade 3–4 >10%			
Pyrexia	11%	0%	0%
Alanine aminotransferase increase	11%	0%	1%
Hypertension	11%	0%	0%
Any AE >30%			
Pyrexia	53%	11.7%	0%
Nausea	56%	9.7%	5%
Diarrhea	33%	16.2%	5%
Fatigue	36%	0%	8%
Peripheral edema	36%	0%	0%
Dry skin/pruritus	33%	11.7%	7%
Decreased appetite	33%	9.7%	6%

Cross trial comparison must be taken with caution.

on treatment at the end of follow up (median follow up 15.9 months) while 69% discontinued treatment due to AEs. KEYNOTE-042 study notes a median follow up of 12.8 months where 14% of patients receiving pembrolizumab remained on treatment at the end of follow up (5). However, treatment related AEs as a cause of treatment discontinuation was not specified. No head-to-head study of pembrolizumab and dabrafenib/ trametinib has been done in $BRAF^{V600E}$-mutant NSCLC and efficacy and safety data derived from independent studies of these two treatments should be compared with caution.

Furthermore, some limitations of studies of dabrafenib/ trametinib and pembrolizumab should be noted. Firstly, dabrafenib/trametinib has only been studied in phase 2 trials with a small number of patients (3). Therefore, results related to survival must be interpreted with caution. Pembrolizumab and atezolizumab, contrarily, have shown PFS and OS benefit in randomized, phase 3 studies (5,6,11). Therefore, survival benefit with these therapies in mNSCLC with high PD-L1 expression appears unequivocal when compared to standard chemotherapy. Secondly, it is unclear how many patients in the pembrolizumab and atezolizumab studies carried a $BRAF^{V600E}$-mutation (4-6). Although we know that single agent ICIs typically have lower efficacy in *ALK* and *EGFR* mutated NSCLC, this may not be necessarily true for *BRAF* mutated NSCLC. For example, a retrospective study of 58 patients showed that the ORR with ICIs was 3.6% *vs.* 23.3% in patients who were *EGFR* and/or *ALK*-positive *vs. EGFR* and *ALK*-negative respectively with PD-L1 status ≥1% (15). However, median PFS was similar in both groups with 2.07 *vs.* 2.58 months respectively. Similarly, another retrospective study of 551 patients treated with ICIs showed an ORR of 0% and 12% for *ALK*-positive and *EGFR*-positive patients (9). Median PFS was similar to the prior study with 2.5 months and 2.1 and median OS of 17 months and 10 months for *ALK*-positive and *EGFR*-positive groups respectively (9). This study showed a higher ORR in the *BRAF* mutated group at 28% compared to *ALK* and *EGFR* mutated groups with median PFS of 3.1 months and median OS of 13 months (9). However, the PFS and OS were lower than what were observed in phase 3 studies of pembrolizumab and atezolizumab in treatment of patients unselected for *BRAF* mutation and PD-L1 high status (PFS 5.4–5.8 months, OS

16.7–17 months) (5,6,13).

Lastly, the safety of sequential use of ICI with BRAF/MEK inhibitors must be taken into consideration. A retrospective analysis of 41 *EGFR*-positive patients sequentially treated with EGFR inhibitors and ICI showed an increased risk of grade 3–4 pneumonitis (4/41) in patient who received ICI prior to receiving EGFR inhibitor while no IRAEs were observed in the group receiving EGFR inhibitors first (16). Therefore, in *EGFR*-positive patients, the preferred course of treatment is to use EGFR inhibitors as first-line treatment even if PD-L1 expression is high. Furthermore, a phase 1/2 study of nivolumab plus crizotinib demonstrated an increased risk of grade 3–4 immune meditated hepatitis (5/13) in *ALK*-positive patients requiring the study to be terminated (17). Therefore, the combination of ICIs with ALK inhibitors is generally discouraged. In contrast to the observed increase in IRAEs with ICI and EGFR and ALK inhibitors, the use of BRAF/MEK inhibitors with ICI appears feasible. The tolerability of vemurafenib and cobimetinib in combination with atezolizumab was demonstrated in the IMspire150 study of unresectable or metastatic melanoma (18). The study compared BRAF/MEK inhibitors in combination with atezolizumab or placebo. The combination arm showed better PFS (15.1 *vs.* 10.6 months, HR 0.78, 95% CI, 0.63–0.97) without significant increase in IRAEs and led to the FDA approval of atezolizumab in combination with vemurafenib and cobimetinib in this population. Both groups experienced grade 3–4 adverse events of 73–79% while the combination group experienced a slightly increased risk of elevated aminotransferase levels (8% *vs.* 4%). Though this study was conducted in patients with melanoma, it signifies the tolerability of combined and/or sequential use of BRAF/MEK inhibitors with ICI. Furthermore, other smaller retrospective studies have also demonstrated the safety and efficacy of ICI in mNSCLC patients harboring *BRAF* mutation (19,20). Therefore, in the case of very high PD-L1 status mNSCLC, it may be reasonable to start treatment with ICI and switch treatment to BRAF/MEK inhibitors at progression of disease. Studies of trametinib in combination with pembrolizumab are ongoing (NCT03299088 and NCT03225664) in patients with *KRAS* mutated NSCLC in metastatic and recurrent disease.

Conclusions

BRAF/MEK inhibitors and ICIs have high efficacy in $BRAF^{V600E}$-mutant mNSCLC with positive PD-L1 status (≥1%). However, the first-line use of ICIs may be preferred in $BRAF^{V600E}$-mutant mNSCLC with very high PD-L1 status (≥90%) for several reasons. ICIs appear to have less frequent toxicities than BRAF/MEK inhibitors requiring infrequent discontinuation of treatment due to side effects. Secondly, though BRAF/MEK inhibitors have shown promising PFS benefit, these were single arm open labeled phase 2 studies. On the contrary, the OS benefit with ICIs is clear in randomized phase 3 trials comparing them to standard of care chemotherapy. Additionally, this survival benefit, appears to be more pronounced with higher PD-L1 status making ICIs an attractive choice in patients with PD-L1 very high status. Lastly, sequential or combined use of ICIs with BRAF/MEK inhibitors appears well tolerated. Therefore, a $BRAF^{V600E}$-mutant mNSCLC patient with very high PD-L1 status may reasonably be treated with first-line ICIs while keeping BRAF/MEK inhibitors as a viable option for second-line treatment.

Acknowledgments

Funding: No direct funding has been made available for this study. Outside of this study, MN has been awarded the 2020 Karmanos Cancer Institute Cancer Immunology and Immunotherapy Pilot Award (P30 CA022453).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor Grace K. Dy for the series "Evidence and Controversies in the treatment of metastatic NSCLC" published in *Precision Cancer Medicine*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure forms (available at: http://dx.doi.org/10.21037/pcm-20-60). The series "Evidence and Controversies in the treatment of metastatic NSCLC" was commissioned by the editorial office without any funding or sponsorship. AS serves on the advisory board for Merck and Eisai. He has received study funding from Eisai. MN serves on the advisory board for AstraZeneca, Caris Life Sciences, Daiichi-Sankyo, Takeda, Novartis, EMD Serono, Blueprint Medicines and has received study funding from Tempus. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. WHO. Cancer. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Available online: https://seer.cancer.gov/csr/1975_2014/
3. 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.
4. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
5. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.
6. Herbst RS, De Marinis F, Giaccone G, et al. Clinical efficacy of atezolizumab in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry assays and by blood tumor mutational burden: results from the IMpower110 study. Ann Oncol 2019;30:xi62-3.
7. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26:3291-310.
8. Leonetti A, Facchinetti F, Rossi G, et al. BRAF in non-small cell lung cancer (NSCLC): Pickaxing another brick in the wall. Cancer Treat Rev 2018;66:82-94.
9. 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.
10. Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 2017;28:1631-9.
11. Reck M, Rodríguez-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. Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov 2018;8:1069-86.
13. Brahmer JR, Rodriguez-Abreu D, Robinson AG, et al. KEYNOTE-024 5-year OS update: first-line pembrolizumab vs. platinum-based chemotherapy in patients with metastatic non-small cell lung cancer and PD-L1 tumor proportion score ≥50%. Ann Oncol 2020;31:S1142-215.
14. Aguilar EJ, Ricciuti B, Gainor JF, et al. Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression. Ann Oncol 2019;30:1653-9.
15. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: A retrospective analysis. Clin Cancer Res 2016;22:4585-93.
16. 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.
17. Spigel DR, Reynolds C, Waterhouse D, et al. Phase 1/2 Study of the Safety and Tolerability of Nivolumab Plus Crizotinib for the First-Line Treatment of Anaplastic Lymphoma Kinase Translocation - Positive Advanced Non-Small Cell Lung Cancer (CheckMate 370). J Thorac Oncol 2018;13:682-8.
18. 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 randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;395:1835-44.

19. Guisier F, Dubos-Arvis C, Viñas F, et al. Efficacy and Safety of Anti-PD-1 Immunotherapy in Patients With Advanced NSCLC With BRAF, HER2, or MET Mutations or RET Translocation: GFPC 01-2018. J Thorac Oncol 2020;15:628-36.
20. 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.

doi: 10.21037/pcm-20-60
Cite this article as: Shao YF, Sukari A, Nagasaka M. Checkpoint inhibitors first in patients with metastatic non-small cell lung cancer harboring *BRAF*^{V600E} mutation with PD-L1 90%—a debate in a niche population. Precis Cancer Med 2020;3:35.