HHS Public Access

Author manuscript

Expert Rev Anticancer Ther. Author manuscript; available in PMC 2020 August 05.

Published in final edited form as:

Expert Rev Anticancer Ther. 2020 February ; 20(2): 131–136. doi:10.1080/14737140.2020.1724097.

The potential for BRAF-targeted therapy combined with immunotherapy in melanoma

Sheida Naderi-Azad[1], **Ryan Sullivan**[2,*]

[1]University of Toronto Faculty of Medicine

[2]Center for Melanoma, Massachusetts General Hospital Cancer Center

1. Introduction

During the past decade, breakthroughs based on enhanced knowledge of oncogenic signaling and immunobiology have been made that have revolutionized the treatment of patients with melanoma. Specifically, two types of therapies, BRAF targeted therapy (TT), which target the constitutively active mitogen activated protein kinase (MAPK) pathway resulting from oncogenic *BRAF* mutations present in 40–50% of patients, and immunotherapy, which target the human immune system to enhance anti-tumor immunity, have been developed. A number of BRAF-targeted therapies have been approved by the United States Food and Drug Administration (FDA) and other regulatory authorities world-wide including BRAF inhibitor monotherapies (vemurafenib in 2011, dabrafenib in 2013), MEK inhibitor monotherapy (trametinib, 2013), and three combinations of BRAF and MEK inhibitors (dabrafenib and trametinib in 2014, vemurafenib plus the MEK inhibitor cobimetinib in 2015, and the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib in 2018) (1 – 7). In addition to targeted therapy, various immunotherapies have been FDA-approved including high-dose interleukin 2 (HD IL-2) in 1998, the anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) monoclonal antibody ipilimumab in 2011, and two anti-programmed death receptor 1 (PD-1) monoclonal antibodies, pembrolizumab and nivolumab in 2014, as well as the combination of ipilimumab and nivolumab in 2015 (8 – 11).

BRAF inhibitors have been shown in phase III clinical trials to be associated with significant response rates and improved survival, compared with chemotherapy, in patients with *BRAF* mutant melanoma (6, 12, 13). However, the current targeted therapy standard of care is the combination of BRAF and MEK inhibitors, which is based on the results of four randomized, Phase III trials, demonstrating improved survival with combined BRAF/MEK inhibitor therapy compared with single-agent BRAF inhibitor therapy (1 – 4). And yet, the efficacy of immunotherapy, specifically that of single-agent PD-1 inhibitors and the combination of ipilimumab plus nivolumab, has limited the use of front-line BRAF/MEK inhibitors in patients with advanced BRAF-mutant melanoma. While the choice of immunotherapy over BRAF-targeted therapy traditionally has been based on provider bias given the absence of level 1 evidence, the long-term follow-up data suggests that overall

*Corresponding Author: Ryan J. Sullivan, MD, MGH Cancer Center, 55 Fruit Street, Boston, MA 02114, rsullivan7@mgh.harvard.edu.

survival (OS) and progression free survival (PFS) may be better with front-line immunotherapy (nivolumab 4 year PFS and OS, 31% and 46%, respectively; ipilimumab plus nivolumab, 37% and 53%) versus BRAF targeted therapy (dabrafenib/trametinib 4 year PFS and OS, 21% and 37%, respectively); although to be fair, this conclusion is based on cross-trial comparison as there is no randomized prospective data available (1, 11). There are two large randomized trials (SECOMBIT, NCT02631447; DREAM-seq, NCT02224781) evaluating the optimal sequencing of BRAF-targeted therapy and immune checkpoint inhibitor therapy, although it likely will be some time before these results are available to help clinical decision-making (14, 15).

2. Rationale for combination BRAF-targeted therapy and immunotherapy

In addition to optimizing sequencing of therapy for *BRAF* mutant melanoma patients, a number of efforts have combined BRAF targeted therapy with immunotherapy. There is a fair amount of preliminary data that supports such an approach. Boni and colleagues initially examined the role of oncogenic BRAF in immune evasion by melanoma cells through suppression of melanocyte differentiation antigens (MDAs) (16). They showed that treatment with a MEK or BRAF inhibitor in *BRAF* mutant melanoma cell lines and tumor digests resulted in increased levels of MDAs, which was associated with improved recognition by antigen-specific T-lymphocytes (16). Building upon this, Frederick and colleagues, showed that treatment with BRAF inhibitor alone or in combination with MEK inhibition was associated with increased antigen expression and an CD8+ T-cell infiltration, when comparing pre- and early on-treatment patient tumor biopsies (17). In addition, there was a decrease in immunosuppressive cytokines like IL-6 and IL-8, an increase in CD-8 positive T-cells, and an increase in PD-1 ligand (PD-L1) expression (17). Furthermore, a number of investigators have shown that BRAF targeted therapy also is associated with increased expression of antigen presentation machinery, such as Class I major histocompatibility complex (MHC) expression; including one of these groups showing that the mechanism of this was reversal of oncogenic BRAF-mediated MHC-I internalization and sequestration. (18–20) These suggest that BRAF inhibition lead to favorable changes in the tumor microenvironment that providing support for BRAF/MEK combination therapy with immune checkpoint inhibitors.

Lymphocyte homing and function is another key aspect to improving the responsiveness of immunotherapy, and BRAF targeted therapy also may improve this as well. Specifically, reports have demonstrated an increased number of TILs in early tumor biopsies of patients treated with BRAF inhibitors, in particular $CD8^+$ (but not $CD4^+$) T cells (characterized by sequencing complementarity-determining region 3, CDR3, of T-cell receptor B chain-coding genes) (2, 17). However, upon disease progression with BRAF inhibitors, there appears to be a decrease in TILs, which was restored with the initiation of combined BRAF / MEK inhibition (21). In addition, vemurafenib combination with adoptive cell therapy (ACT) increased the function of T cells, likely through paradoxical activation of the MAPK pathway in T cells by vemurafenib (22). Furthermore, Cooper et al. performed a study combining a BRAF inhibitor with anti-PD-1 or anti-PD-L1 antibodies (23) in a syngeneic mouse model, and demonstrated that BRAF inhibitors led to a higher CD8:Treg ratio, suggesting a more favorable tumor microenvironment, as well as enhanced T-cell activity

with increased granzyme B, interferon-gamma, and TNF-α production (23). Similarly, Deken and colleagues examined the combination of BRAF and MEK inhibition with anti-PD-1 antibody in syngeneic models (24). The authors reported more volume reduction and increased proportion of animals achieving complete response with the combination and described that these benefits were through increased CD-8 T-cell populations (24). Thus, antigen expression and lymphocyte homing may contribute to the synergistic effects of combination therapies.

A number of studies have looked at the specific effects of BRAF and MEK inhibitors on immune function in melanoma patients. Chengwen and colleagues, for instance, have demonstrated that BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapies in mice (25). This study was performed on *BRAF*-mutated human melanoma tumor cell lines, and luciferase-expressing pmel-1 T-cells were produced to monitor T-cell migration *in vivo*. The increased T-cell infiltration purportedly was mediated by the BRAF inhibitor reduction of tumor cell vascular endothelial growth factor (VEGF) production, further supported by the downregulation of VEGF expression in tumor biopsies. A study by Wilmott and colleagues also supports marked T-cell infiltration with the use of selective BRAF inhibitors (26). The study was conducted on 37 tumor-biopsies from unresectable stage III or IV melanoma, and the results showed an increased tumor infiltration by CD4+ and CD8+ lymphocytes following BRAF inhibitor treatment ($p=0.015$ in both cases). The authors also showed a correlation between the degree of CD8+ infiltration and granzyme B-expressing lymphocytes in post-BRAF inhibitor-treated biopsies ($r=0.690$ and $p=0.013$) (23). In addition, intratumoral CD8+ expression was correlated with tumor reduction and necrosis in post-treatment biopsies. These two studies together support the addition of BRAF inhibitors to immunotherapy with regards to their impact on T-cell infiltration, tumor size reduction and necrosis. (25, 26)

Knight and colleagues have used two relatively resistant variants of $BRAF^{V600E}$-driven mouse melanoma cell lines (SM1 and SM1WT1) and melanoma-prone mice to similarly demonstrate the role that host immunity contributes to BRAF inhibitor activity (27). The authors discovered that treatment downregulated tumor *CCL2* gene expression and correspondingly CCL2 protein expression in both $BRAF^{V600E}$ mouse melanoma transplants and *de novo* melanomas. They also described that this CCL2 downregulation correlated with reduced tumor growth. Furthermore, analysis of SM1 tumor-infiltrating leukocytes in BRAF inhibitor treated tumors showed a robust increase in CD8+ T/FoxP3+CD4+ T cell ratio and Natural Killer cells. This data demonstrates the potential role of *CCL2* in BRAF inhibitor mechanism of action, and further supports the combination with immunotherapy.

Finally, preclinical experiments by a number of groups demonstrated improved outcomes with combined BRAF and/or MEK inhibition with anti-PD1/PD-L1 compared to BRAF, MEK, or PD-1/PD-L1 inhibition. For example, the combination of dabrafenib, trametinib and a mouse anti-PD-1 antibody lead to improved tumor responses compared with either monotherapy (21, 28) in syngeneic mouse models of melanoma. Moreno and colleagues also showed that the addition of one of these antibodies to make a four-drug regimen was superior to the three-drug regimen after testing additional immune-stimulating antibodies to CD137 and CD134 (28).

3. Early clinical trials with cytokine-based therapies:

One of the first combination BRAF inhibitor plus immunotherapy studies was a pilot trial of vemurafenib with adoptive cell therapy (ACT) in patients with advanced, *BRAF* mutant melanoma. This regimen was well-tolerated overall, with similar toxicity to that seen with vemurafenib or standard TIL therapy alone (29). The authors reported that all patients had at least one transient and reversible grade 3 toxicity including hyperbilirubinemia (n=1), hypocalcemia (n=1), hypermagnesemia (n=1), hypophosphatemia (n=1), hypokalemia (n=1), hyperkalemia (n=1), prolonged QTc interval (n=1), hypoxia (n=1), altered partial thromboplastin time (n=1), oliguria (n=1), rash (n=1), thrombus (n=1), dyspnea (n=1), pericoronitis (n=1), cellulitis (n=1), increased creatinine (n=2), febrile neutropenia (n=4), infection (n=5) and anemia (n=7). Furthermore, two patients had reversible grade 4 toxicities, increased creatinine (n=1) and dyspnea (n=1). Interestingly, proliferation and viability of infusion bag TIL and peripheral blood T cells were inhibited *in vitro* by vemurafenib at concentrations approaching serum Cmax of 125 micromolar. Nine out of 15 patients experienced an objective clinical response (60%) and 3 had complete response (20%). Furthermore, there was no difference observed in anti-tumor response with the addition of vemurafenib to ACT (p=1.0; Fisher's exact test). Thus, the results showed the combination trials had similar efficacy and toxicity profiles as the monotherapies.

In addition to these findings, there have been two studies evaluating the combination of vemurafenib and high-dose IL-2 (30, 31). The largest, a multi-center phase II study of 53 patients, showed that vemurafenib given in sequence with high-dose IL-2 did not change the known toxicity profile for either drug (30). In cohort 1, previously untreated patients with advanced *BRAF*-mutant melanoma received vemurafenib 960mg BID for 6wk prior to IL-2, while patients in cohort 2 received vemurafenib anywhere from 7 to 18 week prior to enrollment. The overall response rate at 10 weeks +/−3 was 10% (95%CI 3–24) for both cohorts combined, and 27% (95%CI 8–55) at 26 weeks +/− 3. In a second study, Mooradian and colleagues reported that combined vemurafenib/HD IL-2 therapy is well-tolerated and associated with treatment responses (31). Specifically, responses were seen in 5 of the 6 enrolled patients, however none were durable off therapy, as all patients ultimately progressed. Additionally, this trial, which originally was planned to enroll over 40 patients, was closed early as enrollment was reported to have been poor due to the emergence of BRAF/MEK inhibitor combinations and anti-PD-1 therapy. Together, both studies show that combination vemurafenib and IL-2 therapy is feasible, reasonably well-tolerated, and efficacious in some patients, but did not lead to a marked improvement in patient outcomes over either single-agent therapies. (30, 31)

4. Combinations with ipilimumab

With the approval of ipilimumab and vemurafenib in 2011, it was clear that a trial combining those two agents was going to happen no matter the preclinical justification. In the phase I trial that assessed the safety of the combination of vemurafenib and ipilimumab in patients with metastatic *BRAF*-mutation melanoma, vemurafenib was given as a single agent for 1 month followed by 3 mg/kg ipilimumab intravenous infusion every 3 weeks for a planned four doses with continued concurrent vemurafenib (32). This trial was terminated

due to the high frequency of hepatotoxicity. Specifically, 6 of the 10 patients who received the combination developed grade 3 transaminitis, with most requiring glucocorticoids to manage the toxicity.

Following this first study, a phase I trial of dabrafenib with or without trametinib in combination with ipilimumab showed no grade 3/4 ALT elevations or dose-limiting toxicities (33). Puzanov and colleagues also cite various other studies that corroborate their results, thus concluding that the combinations of dabrafenib / ipilimumab, as well as dabrafenib / ipilimumab / trametinib were not associated with significant hepatotoxicity (33). Minor and colleagues more thoroughly described the toxicity with the dabrafenib / trametinib / ipilimumab combination in metastatic melanoma patients (34). The triplet therapy included a run-in period of 14 days of targeted therapy with dabrafenib and trametinib followed by 3 mg/kg ipilimumab given via intravenous infusion every three weeks for up to four doses. Overall, 2 out of 7 patients that received the three-drug regimen developed colitis with intestinal perforation, and this arm was closed. The authors noted that in the combination arm that included only the doublet, dabrafenib and ipilimumab, just 1 out of 25 patients experienced colitis (which was without perforation), thus implicating the interaction of trametinib with ipilimumab as the cause of increased risk of colitis and perforation.

5. Combinations with anti-PD-1/anti-PD-L1 therapy

KEYNOTE-022 is a multi-arm trial which included a dose escalation cohort of the triple combination of dabrafenib and trametinib with pembrolizumab (35). The dose escalation part of this trial enrolled 15 patients with BRAFV600-mutated metastatic melanoma (35). Eleven patients (73%) experienced grades 3/4 adverse events, the most common of which was elevation of liver function tests and pyrexia. Furthermore, 11 patients (73%, 95% CI: 45–92%) had an objective response, and 6 (40%; 95% CI: 16–68%) continued in response at a median follow-up of 27 months for all patients. While the numbers of patients evaluated is too few to appreciate if there are benefits of triple-combined therapy in a subset of metastatic melanoma patients who otherwise would not have had benefit with either BRAF targeted therapy or anti-PD-1 therapy, it is clear that the combination was generally safe although associated with an increased frequency of grade 3 and 4 toxicity.

The KEYNOTE-022 trial also included a Phase II cohort that randomized 120 patients with previously untreated advanced, *BRAF*-mutant melanoma to either dabrafenib, trametinib, pembrolizumab or dabrafenib, trametinib, placebo (36). While the triplet numerically improved the progression-free survival (16.0 months compared to 10.3 months in doublet group; hazard ratio 0.66; one-sided $p = 0.043$), the initial analysis of this trial, after a median follow up of 9.6 months, did not reach the expected benefit for a statistically significant improvement in PFS. The median duration of response was 18.7 months (95% CI: 10.1–22.1) for triple therapy and 12.5 months (95% CI: 6.0–14.1) for doublet treatment. Lastly, grade 3–5 adverse events occurred in 58.3 and 26.7% of patients treated with triplet and doublet therapy, respectively. The results thus show a trend towards improved progression-free survival, improved response duration, as well as increased adverse events with triplet therapy. An update from this trial presented in late 2019 with an additional 14+ months of

follow up showed a marked difference in median and two-year PFS, 16.9 vs 10.7 months and 41% vs 16%, respectively, with a hazard ratio of 0.53 (95% CI, 0.34 – 0.83). (37) Duration of response remained better with triplet therapy, and although there was no statistically significant difference in overall survival, there was a trend in favor of triplet therapy (hazard ratio 0.64, 95% CI 0.38 – 1.06).

A new study has been conducted with the anti-PD1 antibody spartalizumab in combination with dabrafenib and trametinib in advanced *BRAF* v600-mutant melanoma patients (38). Remarkably, more than 40% (15 of 36) patients treated with spartalizumab + dabrafenib + trametinib had a confirmed complete response. Furthermore, the median PFS was 23.7 months (95% CI, 12mo-NE) overall and 10.7 months (95% CI, 4.6 mo-NE) in patients with elevated baseline LDH levels. Similar to the KEYNOTE-022 cohorts, grade 3 toxicities were common, 78%, and dose adjustment or interruption was required for every patient. These findings demonstrate the potential efficacy of combination therapy with anti-PD1 antibodies, which will be further corroborated by the ongoing global, placebo-controlled, randomized part 3 of COMBI-i trial (NCT02967692).

Finally, the combination of the anti-PD-L1 monoclonal antibody atezolizumab has been evaluated in combination with vemurafenib (VA) as well as vemurafenib and cobimetinib (VCA) (39). In this phase I trial of patients with metastatic *BRAF* mutant melanomas, 17 patients were treated with VA and 39 with VCA. Based on toxicity and feasibility, a 28 day-lead in of targeted therapy was settled on prior to triplet therapy. Toxicity was commonly seen, with grade 3–4 treatment-related adverse effects seen in 88% (15 of 17) and 67% (26 of 39), respectively with VA and VCA. Complete responses were seen in 3 patients with VA and 8 (20.5%) patients with VCA. Additionally, 14 patients treated with VCA either had a complete response and/or a 100% reduction in target lesion tumor volume (35). The triplet combination is being investigated in a randomized, phase 3 trial (TRILOGY) compared with vemurafenib, cobimetinib, and placebo (NCT02908672).

6. Conclusion

The combination of BRAF targeted therapy with immunotherapy has demonstrated exciting data regarding depth and duration of response in patients with advanced, *BRAF*-mutant melanoma. The mechanisms behind the potential synergistic effects of combination therapy include increased antigen presentation, as well as improved lymphocyte homing and function, although none of these potential mechanisms have been validated in any clinical trials to date. Importantly, adverse effects with these combinations appear to be higher and may interfere with the anti-tumor effects. While randomized data showing better efficacy will be necessary to translate these regimens into the clinic, alternative dose approaches may be required to optimize the benefits of these combinations.

7. Expert Opinion:

Since the earliest days of modern oncology, combinations of antineoplastic therapies have been sought to maximize benefit. A hallmark of these efforts was inhibiting multiple targets that were critical for tumor survival, in the early days various components of cell division,

with agents that ideally had non-overlapping toxicity. As a result, treatment regimens were design, tested, and adopted as standard practice for a number of malignant conditions including lymphoma, leukemia, testicular cancer, and over time just about every condition for which cytotoxic chemotherapy has shown any utility. With the development of newer drugs that target oncogenic mutations and/or their downstream signaling, as well as inhibitors of immune checkpoints, it is logical that combinatorial regimens including these newer agents will be brought forward.

The earliest efforts with these approaches in melanoma have been supported by preclinical data suggesting that BRAF targeted therapy sets up the tumor immune microenvironment to be more sensitive to immunotherapy. The first of these efforts explored combinations with the earliest immunotherapies, high-dose IL2 and adoptive cell therapy, and were associated with, if anything, a modest improvement in efficacy yet not dramatically more than would be expected by either therapy alone. Logically, combinations with immune checkpoint inhibitors have also moved forward and have demonstrated substantial toxicity, particularly with regimens that include ipilimumab. More recently, the first reports of BRAF/MEK therapy with anti-PD1/PDL1 inhibition have been published and indicate, again, higher than anticipated toxicity without definitive benefit beyond BRAF targeted therapy or anti-PD1/PDL1 therapy. Included among these is the first randomized trial comparing triplet therapy, in this case dabrafenib, trametinib, and pembrolizumab versus a BRAF targeted therapy doublet (dabrafenib and trametinib). Here the results are even mixed as the toxicity and durable response was higher with triplet, the response rate higher with the doublet, and the progression free survival no different amongst the two arms. Yet, the overall survival curves appear to be separating at the tail, albeit not statistically significantly so; a finding if confirmed that bodes well for the two randomized trials of doublet versus triplet that are awaiting read-out (TRILOGY, COMBI-i). So, how can this be?

The likeliest results of these trials is that the triplet therapy will be too toxic for some and thereby limit the effectiveness for these patients, not effective enough for others and thus not add much for these patients beyond sequencing these types of treatments, but for a select group of patients, the combination will provide synergistic benefit while both improving the initial portion as well as the tail on the survival curve. Whether that last group of patients will be large enough to cause the above-mentioned trials to be “positive” is unknown but predicted here to be so. The reason for this optimism indeed is in the early analysis of an immature overall survival curve from the randomized portion of Keynote 022 and the fact that a large percentage of patients across multiple Phase I/II trials have either complete responses or profound responses (e.g. 100% decrease in tumor volume but not a CR). While the ultimate answer will likely be a few years away, it is expected that the next issues to tackle will be identifying for which patients triplet therapy is most useful and whether alternative regimens such as intermittent targeted therapy will be implemented to allow for those who otherwise would not tolerate full dose to reap the benefits of the combination.

References:

1. Robert C, Grob JJ, Stroyakovskiy D et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019 [Available from: https://www.ncbi.nlm.nih.gov/pubmed/31166680].

2. Long GV, Wilmott JS, Haydu LE, et al. Effects of BRAF inhibitors on human melanoma tissue before treatment, early during treatment, and on progression Pigment Cell Melanoma Res 26: 499–508,2013. [PubMed: 23557327]

3. Ascierto PA, McArthur GA, Dreno B, et al. Cometinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double blind, phase 3 trial. The Lancet Oncology 2016;17(9):1248–1260. [Available from: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30122-X/fulltext]. [PubMed: 27480103]

4. Dummer R, Ascierto PA, Gogas HJ et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multi-centre, open-label, randomised phase 3 trial. The Lancet Oncology 2018;19(5):P603–615. [Available from: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30142-6/fulltext].

5. McArthur GA, Chapman PB, Robert C et al. Safety and efficacy of vemurafenib in BRAFv600 and BRAFv600k mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014; 15: 323–332. [PubMed: 24508103]

6. Hauschild A, Grob JJ, Demidov LV et al. Dabrafenib in BRAF-mutation metastatic melanoma: a multi-centre, open-label phase 3 randomized controlled trial. Lancel Oncol 2012; 380 (9839): 358–65.

7. Schadendorf D, Hauschild A, Santinami M et al. Patient-reported outcomes in patients with resected, high-risk melanoma with BRAFv600E or BRAFv600K mutations treated with adjuvant dabrafenib plus trametinib (COMBI-AD): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20(5):701–710. [Available from: https://www.ncbi.nlm.nih.gov/pubmed/30928620]. [PubMed: 30928620]

8. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine 2010;363(8):711–23. [Available from: https://www.ncbi.nlm.nih.gov/pubmed/20525992]. [PubMed: 20525992]

9. Sharp M and Dohme Corp. Study to evaluate the safety and efficacy of two different dosing schedules of pembrolizumab (MK-3475) compared to ipilimumab in participants with advanced melanoma (MK-3475–006/KEYNOTE-006). Clinical Trials 2013 [Available from: https://clinicaltrials.gov/ct2/show/NCT01866319].

10. Squibb BM. Study of nivolumab (BMS-936558) compared with dacarbazine in untreated, unresectable, or metastatic melanoma (CheckMate 066). Clinical Trials 2012 [Available from: https://clinicaltrials.gov/ct2/show/NCT01721772].

11. Hodi FS, Chiarion-Sileni V, Gonzalez R et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;(11):1480–1492. [Available from: https://www.ncbi.nlm.nih.gov/pubmed/30361170]. [PubMed: 30361170]

12. Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation N Engl J Med 2011;364: (2507–2516). [PubMed: 21639808]

13. Flaherty KT, Robert C, Hersey P et al. Improved survival with MEK inhibition in BRAF-mutated melanoma N Engl J Med 2012; 367: 107–114. [PubMed: 22663011]

14. Fondazione Melanoma Onlus. Sequential combo immuno and target therapy (SECOMBIT) study. Clinical Trials 2019. NCT02631447.

15. National Cancer Institute. DREAMSeq (double, randomized, evaluation in advanced melanoma sequencing) a Phase III trial. Clinical Trials 2014. NCT02224781.

16. Boni A, Cogdill AP, Dang P, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. Cancer Res. 2010 7 1;70(13):5213–9. doi: 10.1158/0008-5472.CAN-10-0118. [Available from: https://www.ncbi.nlm.nih.gov/pubmed/20551059.] [PubMed: 20551059]

17. Frederick D, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clinical Cancer Research. 2013;19(5):1225–1231. [Available from: http://clincancerres.aacrjournals.org/content/19/5/1225.full-text.pdf.] [PubMed: 23307859] This, along with Wilmott et al CCR 2016 (ref 26), were the first report of the effects of BRAF targeted therapy on the tumor microenvironment in tumors obtained from serial biopsies in patients with BRAF

mutant melanoma treated with either single-agent BRAF or combined BRAF/MEK inhibition. The findings in this paper of increased antigen expression, decreased immunosuppressive cytokines, increased T cell infiltration and PD-L1 expression served as the justification to combined BRAF targeted therapy with anti-PD-1/PD-L1 therapies.

18. Bradley SD, Chen Z, Melendez B, et al. BRAFV600E Co-opts a Conserved MHC Class I Internalization Pathway to Diminish Antigen Presentation and CD8+ T-cell Recognition of Melanoma. Cancer Immunol Res. 2015;3(6):602–609. doi:10.1158/2326-6066.CIR-15-0030 [PubMed: 25795007]
19. Sabbatino F, Wang Y, Scognamiglio G, et al. Antitumor Activity of BRAF Inhibitor and IFNα Combination in BRAF-Mutant Melanoma. J Natl Cancer Inst. 2016 2 5;108(7). doi: 10.1093/jnci/djv435. Print 2016 Jul.
20. Kakavand H, Rawson RV, Pupo GM, et al. PD-L1 Expression and Immune Escape in Melanoma Resistance to MAPK Inhibitors. Clin Cancer Res. 2017 10 15;23(20):6054–6061. doi: 10.1158/1078-0432.CCR-16-1688. Epub 2017 Jul 19. [PubMed: 28724663]
21. Hu-Lieskovan S, Robert L, Moreno BM, and Ribas A. Combining targeted therapy with immunotherapy in BRAF-mutant melanoma: promise and challenges. Journal of Clinical Oncology 2014; 32(21): 2248–2254. [Available from: https://ascopubs.org/doi/10.1200/JCO.2013.52.1377?fbclid=IwAR0KhkWdCfsmielnoVy6wguEJpN65dI-N7TVvnNF8TsrQvJ-qARev2jBb5s&.] [PubMed: 24958825]
22. Koya RC, Mok S, Otte N, et al. BRAF inhibitor vemurafenib improves the antitumor activity of adoptive cell immunotherapy Cancer Res 72: 3928–3937,2012. [PubMed: 22693252]
23. Cooper ZA, Frederick DT, Ahmed Z, et al. Combining checkpoint inhibitors and BRAF-targeted agents against metastatic melanoma Oncoimmunology 2: e24320,2013. [PubMed: 23762807]
24. Deken MA, Gadiot J, Jordanova ES, et al. Targeting the MAPK and PI3K pathways in combination with PD1 blockade in melanoma. Oncoimmunology 2016; 5: e1238557. [PubMed: 28123875]
25. Chengwen L, Peng W, Xu C et al. BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice. Clinical Cancer Research 2013; 19(2): 393–404. [Available from: http://clincancerres.aacrjournals.org/content/19/2/393.full-text.pdf]. [PubMed: 23204132]
26. Wilmott JS, Long GV, Howle JR et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clinical Cancer Research 2012; 18(5): 1366–1395. [Available from: http://clincancerres.aacrjournals.org/content/18/5/1386.full-text.pdf].
27. Knight DA, Ngiow SF, Li M et al. Host immunity contributes to the anti-melanoma activity of BRAF inhibitors. Journal of Clinical Investigation 2013; 123(3):1371–1381. [Available from: https://www.jci.org/articles/view/66236]. [PubMed: 23454771]
28. Moreno BH, Mok S, Comin-Anduix B et al. Combined treatment with dabrafenib and trametinib with immune-stimulating antibodies for BRAF Mutant Melanoma. Oncoimmunology 2015; 5(7): 00–00.
29. Deniger DW, Kwong ML, Pasetto A, et al. A pilot trial of the combination of vemurafenib with adoptive cell therapy in patients with metastatic melanoma. Clin Cancer Research. 2018;23(2):351–362. [Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5245178/].
30. Clark J, Ernstoff MS, Milhem MM et al. A multi-center phase II study of high dose IL-2 (HD IL-2) sequenced with vemurafenib in patients with BRAF-V600E mutation positive advanced melanoma. Journal of Immunotherapy of Cancer 2018; 6: 76 [Available from: 10.1186/s40425-018-0387-x].
31. Mooradian MJ, Reuben A, Prieto PA et al. A phase II study of combined therapy with a BRAF inhibitor (vemurafenib) and interleukin-2 (aldesleukin) in patients with metastatic melanoma. Oncoimmunology 2018; 7(5): e1423172 [Available from: https://www.ncbi.nlm.nih.gov/pubmed/29721378]. [PubMed: 29721378]
32. Ribas A, Hodi FS, Callahan M, et al. Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 2013; 368: 1365–1366. [PubMed: 23550685]
33. Puzanov I, Callahan MK, Linette GP, et al. Phase 1 study of the BRAF inhibitor dabrafenib with or without the MEK inhibitor trametinib in combinatino with ipilimumab for V600E/K mutation – positive unresectable or metastatic melanoma. Journal of Clinical Oncology 2014 32:15_suppl,

2511–2511. [Available from: https://ascopubs.org/action/showCitFormats?doi=10.1200/jco.2014.32.15_suppl.2511].

34. Minor D, Puzanov IJ, Callahan MK et al. Severe gastrointestinal toxicity with administration of trametinib in combination with dabrafenib and ipilimumab. Pigment Cell Melanoma Res. 2015;28:611–2. [Available from: https://www.semanticscholar.org/paper/Severe-gastrointestinal-toxicity-with-of-trametinib-Minor-Puzanov/7ec67f4b56a6a8309c6f71e3b322b9cd5820a8a1#citing-papers]. [PubMed: 25996827] This report of the phase I combination of dabrafenib, trametinib and ipilimumab describes a very high rate of colonic perforation with the triple combination by not seen with dabrafenib plus ipilimumab. The results from this study led to a paradigm shift of avoiding MEK inhibitors with CTLA-4 blockade.
35. Ribas A, Lawrence D, Atikinson V et al. Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in BRAF-mutant melanoma. Nature Medicine 2019; 25:930–940.
36. Ascierto PA, Ferrucci PF, Fisher R et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nature Medicine 2019; 25: 942–946.This is the first randomized data with triplet therapy versus BRAF/MEK combination therapy. The results show a trend towards improved PFS with triplet therapy (later confirmed with longer follow up; ref 37), although a numerically lower response rate and a higher rate of grade 3 and 4 toxicities. The improved durability of response, and based on the update (ref 37), trend towards improved overall survival are encouraging and suggest that triplet therapy may provide value to a subset of patients.
37. Ferrucci PF, Ascierto PA, Maio M, et al. Updated Survival In Patients With BRAF-mutant Melanoma Administered Pembrolizumab, Dabrafenib And Trametinib. Society of Melanoma Research Annual Congress, 2019.
38. Long GV, Lebbe C, Atkinson V et al. The anti-PD1 antibody spartalizumab in combination with dabrafenib and trametinib in previously untreated patients with advanced BRAF V600-mutant melanoma: updated efficacy and safety from parts 1 and 2 of COMBI-i. American Society of Clinical Oncology Annual Meeting 2019.
39. Sullivan RJ, Hamid O, Gonzalez R et al. Atezolizumab plus cobimetinib and vemurafenib in BRAF-mutated melanoma patients. Nat Med 2019; 25(6): 929–925. [Available from: https://www.ncbi.nlm.nih.gov/pubmed/31171876]. [PubMed: 31171876]

Article Highlights:

- Early preclinical data showed that BRAF and MEK inhibitors lead to changes in tumor cells and in tumor immune microenvironments including increased melanocytic antigen expression (cell lines, tumors), increased PD-L1 expression (tumors), increased T cell infiltration (tumors), and increased HLA-expression (cell lines and tumors).
- Combined BRAF targeted therapy and immunotherapy has shown mixed results in the initial clinical trials reported.
- There is strong preliminary clinical trial data supporting combined BRAF targeted therapy plus anti-PD-1/PD-L1 therapy and the likeliest outcome is that these approaches will help, at least, a significant minority of patients with BRAF mutant melanoma.