Jeffrey S. Weber, MD, PhD: Hello and welcome to this educational activity, entitled *Optimizing Treatment Selection and Side Effect Management in* BRAF-*Mutant Melanoma*.

I'm Jeff Weber. I'm a medical oncologist and I'm Deputy Director at the Laura and Isaac Perlmutter Cancer Center at NYU Grossman School of Medicine in New York City.

We have a couple of disclaimers. This indicates that we may be discussing off-label use of approved agents or agents that are in development.

And here is my personal financial disclosure information.

And here are the learning objectives for today. Upon completion of this activity, our participants should be better able to assess the latest clinical data for doublet and triplet targeted therapy and immunotherapy combinations to optimize treatment selection for, and clinical management of, patients with *BRAF*-mutant melanoma.

Participants should be better able to integrate combination targeted therapy and immunotherapy approaches for the treatment of those patients with *BRAF*-mutant melanoma optimize outcomes.

And finally, they should be able to incorporate knowledge of safety profiles of combination BRAF/MEK inhibitors and immunotherapy to identify and manage treatment-related side effects in patients who have *BRAF*-mutant melanoma.

First, let's talk about combination approaches in advanced melanoma.

There are quite a few potential genetic targets in melanoma. In this analysis, which was published 3 or 4 years ago by Nick Hayward, *BRAF* is by and far the most common mutation in melanoma accounting for between 40% and 50% of all cases.

But there's also a fair number of patients who have *NRAS* mutations, maybe 10% or 15%, *NF1*, maybe another 10% and in mucosal melanomas we see kit exon 9 and 11 mutations. We see *GNA11* and *GNAQ* mutations in uveal melanoma.

There are very common deletions in *CDKN2A* and mutations in *CDK4*. So, there's quite a diverse genetic landscape in melanoma, many of which are potential driver mutations. But, of course, the most important ones, and the ones that we've heard the most about are *BRAF* mutations.

BRAF mutations, which tend to center around the 600 and 601 amino acids, are driver mutations. That is, when mutated they're able to drive the growth proliferation and metastasis with melanoma, along the now familiar, MAP kinase pathway, which goes from binding of some factor to a membrane-bound receptor, which then phosphorylates RAS, which then in turn phosphorylates RAF, which comes as ARAF, BRAF, and CRAF, which then phosphorylates MEK and ERK. And then makes its way to the nucleus to promote growth proliferation metastasis and activation of melanoma cells.

And you can intervene at various places along the pathway. Obviously, you can specifically block mutated *BRAF*. We have vemurafenib, dabrafenib, and encorafenib, the three approved drugs.

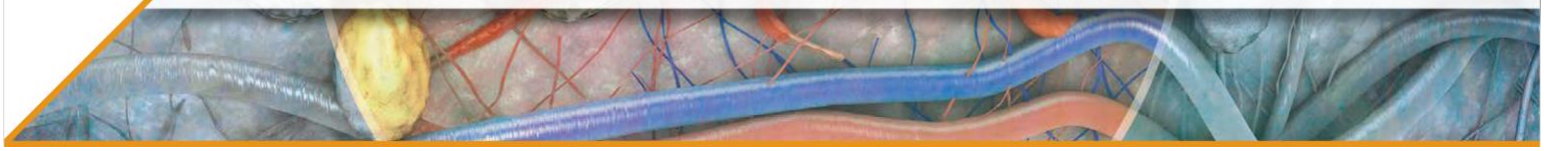
And then further down the pathway, you can block MEK and now this is not altered MEK, this is normal MEK. And we have drugs such as cobimetinib, trametinib, and binimetinib, that can block, not only at the mid-part of the pathway, but also further down the pathway to do a better job of suppressing proliferation, survival, invasion, and metastasis.

One of the first combination studies that tested a BRAF plus MEK combination was the coBRIM study. This was cobimetinib and vemurafenib. This was a 1:1 randomized study. Approximately 500 patients received either the combination of vemurafenib to BRAF inhibitor with cobimetinib, the MEK inhibitor, versus vemurafenib plus placebo, which was then the standard FDA-approved treatment for metastatic melanoma.

This was treatment until progression, unacceptable toxicity, or withdrawal. So, it was potentially a long treatment; progression-free survival assessed by the investigator was the primary endpoint.

The combination was clearly superior to single agent vemurafenib in terms of progression-free survival with that nice hazard ratio of 0.58 and overall survival with an almost as nice hazard ratio of 0.7, reflecting a 30% decrease in the risk of dying over time, which was maintained over the first couple of years of the study, which in part led to the approval of vemurafenib/cobimetinib as treatment for metastatic melanoma.

The long-term progression-free and overall survival data from the study indicate that over time, while the curves for the combo stay apart from the single agent, they tend to move together as time goes on toward 5 years, and only about 15% of patients are free



of progression at 5 years. Although the median progression-free survival clearly is superior at 12.6 to 7.2 months.

If you look at survival, the curves do a nice job of staying apart over time up to 5 years. And it looks like about 30%, 31% of patients will be alive and hopefully doing well 5 years from starting the BRAF plus MEK inhibitor combination of vemurafenib and cobimetinib.

It became clear early on that one of the most important factors associated with doing better or worse with combination BRAF/MEK therapy was disease burden as evidenced by lactate dehydrogenase (LDH) level. Having a normal LDH level means that at 5 years 43% of patients are alive, a very modest 16% if the LDH level is elevated, reflecting aggressiveness of tumor and tumor burden.

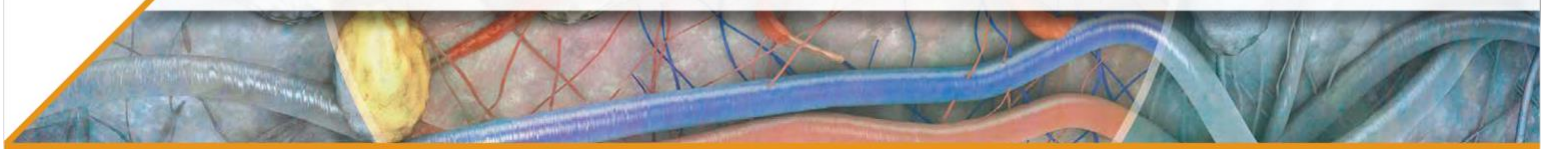
COMBI-d was another large, randomized study that screened more than 900 patients. This study included dabrafenib and trametinib, the BRAF/MEK drugs versus dabrafenib (FDA approved) alone. More than 400 patients were treated until disease progression, intolerability, or refusal.

The data for overall survival, which was the endpoint of the study, looked very favorable. with relatively early follow-up at 2 years, there was a very significant difference in survival with a nice hazard ratio of 0.75. Meaning the combination is better than single agent, with a 25% reduction in the risk for death.

On the heels of that study came a larger randomized phase 3 study of more than 700 patients, who got dabrafenib and trametinib (COMBI-v). At that time, the first FDA-approved drug was vemurafenib. So, that was the standard. This was a 1:1 randomization with survival as the primary endpoint.

At the second interim analysis of survival, this was clearly called a positive study. There’s no question that there was improvement in overall and progression-free survival times.

If you look at all patients, pooled together, with dabrafenib and trametinib, looking at progression-free survival, you do a little better than what we saw in that prior study, but it’s only about 19% at 5 years.



And again, if you look at progression-free survival according to LDH level, if you have LDH at or below the upper limit of normal, you're at 25%, but it drops to 8% progression-free survival with an abnormal LDH level.

Looking at overall survival, you can do fairly well with, again, about one-third of the patients alive at 5 years in both COMBI-d and COMBI-v. However, if you have a normal LDH level, you're going to do better than if you have an elevated LDH, and if you look at the patients who have a normal LDH and few, meaning fewer than three disease sites, more than half of them are alive at 5 years. This is a reflection of tumor burden, which determines the outcome significantly with almost all BRAF/MEK combinations.

If you think about who gets the most benefit, if you look at the patients with LDH levels twice the upper limit of normal or more, those patients do very poorly with progression-free survival (PFS) at 5 months.

But the patients who have a normal LDH and less than three affected organ sites—24-month median PFS with a response rate of 83% and a complete response (CR) rate of 42%. Those are the best actors; those are the patients who are going to do the best with almost any BRAF/MEK combination. Although, these are data specifically for the pooled, combination from COMBI-d and COMBI-v.

The third combination that came along was encorafenib and binimetinib in the COLUMBUS study, which initially assessed the progression-free and overall survival for encorafenib plus binimetinib versus just encorafenib versus the then standard of care, vemurafenib.

If you look at the initial data with modest follow-up in the range of 2 years, published back in 2018, looking at PFS or overall survival, there is la clear, nice difference with a hazard ratio for overall survival of 0.61, a 39% reduction in the risk of dying, if you get encorafenib plus binimetinib, the combination versus the then standard vemurafenib alone, with a *P* of .0001.

In the long-term follow-up with that COLUMBUS study of encorafenib and binimetinib, interestingly, although the combo clearly starts out higher, in terms of survival, the curves of encorafenib/binimetinib or encorafenib alone will come together to some degree. Although there was the potential for crossover versus just vemurafenib alone, either is grossly superior, without question, you'd rather be taking the combination than vemurafenib or encorafenib alone.

If you compile all of the data from phase 3 trials of BRAF/MEK combinations, look at the hazard ratios for progression-free survival, they're amazingly consistent. They go from 0.67 to 0.56 to 0.58 to 0.51. Very impressive, consistent data for a superiority of PFS for the combination of BRAF/MEK versus BRAF alone, usually vemurafenib.

Overall survival also had amazingly consistent hazard ratios of 0.71, 0.69, 0.7, and for encorafenib/binimetinib, 0.61 actually is somewhat the best survival, although that was the most recently done study.

If you think about the doublets, how do you choose among them? Dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib are all attractive combination regimens. They differ by the number of pills. Dabrafenib/trametinib, the fewest number at 5. Encorafenib/binimetinib is 12 pills a day.

There's inflexibility regarding meals with dabrafenib/trametinib, a little bit less inflexibility with vemurafenib/cobimetinib, and great flexibility for encorafenib/binimetinib.

So, it is a bit rigid with respect to taking the drugs before or after food for dabrafenib/trametinib, a little less rigid for some of the others, and no rules for encorafenib/binimetinib.

And there's flexibility with dose reductions for encorafenib and binimetinib because you have so many pills, less flexibility for dabrafenib and trametinib, you just have fewer pills.

In looking at an idea that arose in mice, which is that you could give intermittent BRAF/MEK inhibition, which in a very nice article in *Nature,* back in 2017 or 2018, it was suggested that if you gave a mouse intermittent BRAF/MEK inhibition, it worked much better than just continuous BRAF/MEK inhibition.

This was tested in a cooperative group study. Alan Algazi was the principal investigator. This was published in *Nature Medicine*, and unfortunately, giving intermittent BRAF/MEK starting with your survival from 8 weeks into treatment versus giving discontinuous BRAF/MEK, there was no difference in survival, with a median of 29.2 months for each.

The most overlapping survival curves I've ever seen, albeit in a small study, only a couple hundred patients, but it did not appear that the superiority of intermittent BRAF/MEK applies to humans.

A lot of attention has been paid to the activity of BRAF/MEK combinations in brain metastases, which have a pretty impressive response rate. And here we see the use of vemurafenib in treatment-naïve and refractory brain met patients. You clearly get a higher response rate in patients who are not previously treated with what looks like a response rate in the range of 50% in the brain. Very impressive.

Less response rate in those previously treated, but still pretty significant. And again, if you look at the progression-free and overall survival rates, though, it is not as good as with those without brain metastases.

Your median PFS, whichever way you do it, whether it's previously treated or not previously treated, it's only about 4 months. Very unimpressive.

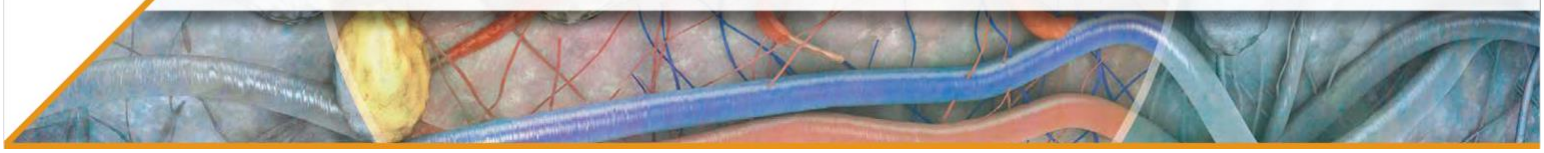
If you look at the overall survival, instead of the median survival of 22 to 32 months, seen with BRAF/MEK combinations in extracranial disease, your median is only about 9 months, whether you're previously treated or not with BRAF/MEK combinations. So, again, not that impressive.

If you look at dabrafenib and trametinib, this was the COMBI-MB study in those with brain metastases with multiple cohorts, either no symptoms, without prior therapy, asymptomatic with prior therapy, so those were the first two cohorts.

All of which was in patients with a V600E mutation. Or patients who had other mutations, who were asymptomatic or patients who were symptomatic and generally required steroids.

You figure that last group would probably do the worse, but in fact, with the use of dabrafenib and trametinib, if you look at the waterfall plots, the cohort A is the most common one, which is asymptomatic, no prior local treatment. They had a very nice response rate with that outstanding waterfall plot.

There were good responses, even in those who were symptomatic and were on steroids, which was cohort D and even in cohort C with non-V600E disease. Very impressive.



The response rates across the board are actually pretty good. They're anywhere between 44% and 65%. The biggest cohort, of course, was cohort A with asymptomatic patients, no local treatment. Very nice, 58% response rate. Disease control, again, very impressive, 79%.

And you saw some CRs, but mostly partial responses and duration of response, the median was about 6 months, 12 months for those who were not necessarily, were previously treated, and were still asymptomatic.

And again, fairly impressive data suggesting that there was clear benefit to those with brain metastases who received dabrafenib and trametinib.

However, the PFS is not as good as in those who had extracranial disease only who were seen in the COMBI-d and COMBI-v trials.

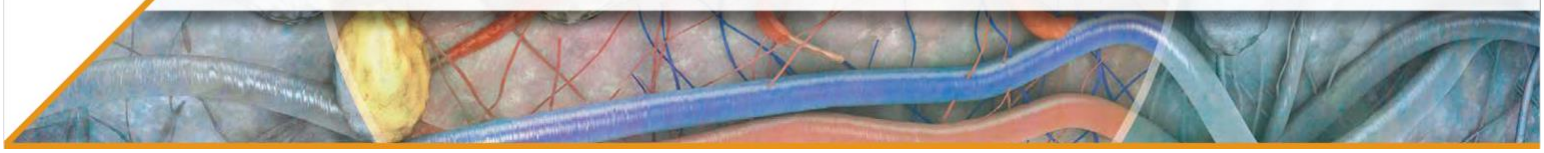
If you look at the biggest cohort, cohort A, the median PFS is only 5.6 months, which is quite modest. As opposed to 10 or 11 months, which is what you'd see with extracranial disease. And even though you had a higher response rate, at 58%, median survival is nowhere near what you'd see with extracranial disease. As opposed to 25.6 months, it's only 10.8 months for those who are asymptomatic in the largest cohort, A.

So you can see regression, but you do not do as well as if you have extracranial disease.

The real-world experience with dabrafenib and trametinib in those with brain metastases who were not on a clinical trial included a multi-centered trial that collected data from non-protocol patients, if you look at the survival, the median is about 9 months, which is not that much different than what you saw in large trials. And the median PFS is a little better, interestingly, at 5.3 months, but again, most patients eventually experience disease progression.

The combination of encorafenib and binimetinib has not been subjected to a large study in brain metastases, but it had a small study in approximately 30 patients. And it suggests that if you had prior BRAF/MEK inhibitor or not, you could still have a finite response rate in the 30% range in the CNS in patients who are asymptomatic.

If we are successful in the metastatic mode, we always think, 'could you apply this to an earlier stage of disease and would it be more impressive and more effective?'



And, of course, the combination of dabrafenib and trametinib has been in a randomized, adjuvant study. It was a very well-done study called COMBI-AD, 870 patients were randomly allocated, who had stage IIIA, B, and C disease by the AJCC 7 criteria, to get either dabrafenib and trametinib at standard doses for 1 year, versus two matched placebos, and the primary endpoint was relapse-free survival.

And this study was clearly, positive, in looking at 3-year, 4-year, 5-year, relapse-free survival. Very impressive. It looks like there's a plateau at about 50% just past 5 years. So, the median regression-free survival is going to be beyond 5 years.

These are very impressive data with clear superiority to placebo. A 16-percentage point absolute difference at 5 years, with a curve that splits at the first evaluation and stays significantly apart all the way though. With a hazard ratio of 0.51, a 49% reduction in the risk of relapsing.

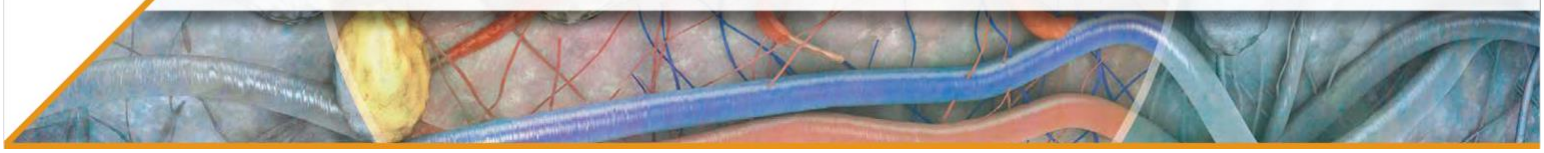
And if you look at distant metastasis-free survival, which many folks think is a surrogate for overall survival, again, very impressive benefit to dabrafenib/trametinib versus placebo at 5 years, and 11% absolute percentage point difference. There's a similar hazard ratio for relapse-free survival of 0.55, reflecting a 45% reduction in the risk for distant metastasis-free survival with dabrafenib/trametinib versus placebo in resected stage III melanoma.

At the first interim analysis, the relatively immature survival data also suggests a difference with a *P* of .006 and a hazard ratio of 0.57 for survival. Although these data are much earlier, they are impressive. The data I showed you just now, prior to this for relapse-free survival, and distant metastasis-free survival, are mature at 5 years.

We've talked through adjuvant therapy, what about adding immunotherapy to targeted therapy. If targeted therapy works, if immunotherapy works, to prolong survival and PFS and they both work as adjuvant therapy, would it be better to add them together?

That's a legitimate question. And it has a background justification, suggesting that when patients get BRAF/MEK inhibition over a relatively brief time, say 6 to 8 weeks, you can actually upregulate expression of melanosomal antigens like MART-1. You decrease cytokines such as IL-6, IL-8, and IL-10, which are immunosuppressive cytokines.

You increase the infiltration of T cells. Look at the immunohistochemistry—pre, very few CD8 T cells; post, lots of T cells after BRAF inhibition.



A large number of patients had a significant increase in T-cell infiltration with BRAF inhibition, at week 6 to 8. The clonality of T cells goes up and interestingly, PD-L1 goes up, which might bode well for the immunogenicity of the tumor.

This set the stage for the conduct of a number of trials of BRAF/MEK plus PD-1 blockade; for example, the KEYNOTE-022 study combined dabrafenib and trametinib with pembrolizumab, a PD-1 blocking antibody.

Initial data suggested there wasn't a statistically significant difference that broached a barrier that needed a *P* of less than .01. The *P* is borderline at .42 even though the hazard ratio is good.

The data are not reliable. With more follow-up, interestingly, the data looked better with a median of 16 versus 10 months, for dabrafenib/trametinib plus pembrolizumab versus dabrafenib/trametinib alone, with a very nice hazard ratio. Although the decision was made not to pursue this based on the initial PFS data.

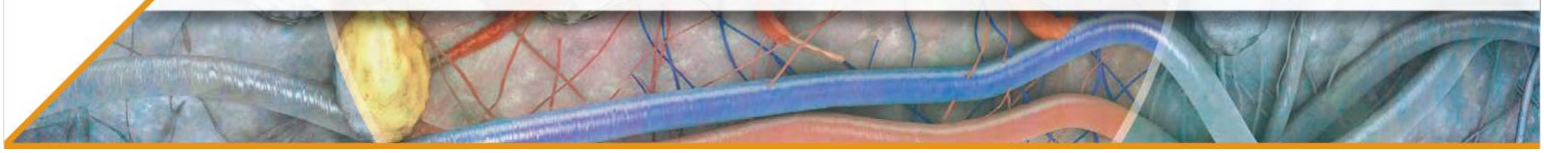
Vemurafenib and cobimetinib have been combined with atezolizumab, the PD-L1 blocking antibody in a trial called IMspire150. This was a relatively large, well-powered study. If you look at the data from IMspire150 in terms of investigator-called PFS, you see an interesting late break at about 7 or 8 months. Then the PFS curves stay apart with a *P* of .02.

And if you look at survival, again, a very late break, beyond 12 months, but survival curves begin to break apart with a 7-percentage point absolute difference and a three-month difference in median survival, with some additivity of side effects.

In terms of other PD-1 antibodies, spartalizumab is another PD-1 antibody that has been combined with dabrafenib and trametinib. This was a randomized phase 2 study of spartalizumab/dabrafenib and trametinib versus dabrafenib and trametinib alone.

The PFS rates are different with the triple combination, better than the doublet, but the *P* value is borderline, and it did not meet the threshold required for success (.042). It's just not quite good enough.

And if you look at the overall survival, the curves at 2 years are very close. Only a few percentage points apart. So, it was not clear that the addition of spartalizumab really added anything in terms of efficacy to dabrafenib and trametinib.



Currently, there's a STARBOARD trial going on evaluating encorafenib and binimetinib with pembrolizumab. After an open-label safety lead in and phase 2 study at two dose levels of encorafenib/binimetinib with pembrolizumab, there will be a randomized double-blind placebo-controlled phase 3 study. It'll be encorafenib and binimetinib plus pembrolizumab versus placebo plus pembrolizumab.

This is now not being compared to BRAF/MEK, it's being compared to pembrolizumab. Which frankly on average will have a 36-month median survival, whereas the best BRAF/MEK median survivals are anywhere between 25 and 32 months.

So, I think the safest or the best comparison is to pembrolizumab. And I like that.

Now, what considerations do we have for selecting patients to be able to sequence their therapy?

If you look at the NCCN Guidelines, the top categories go to single agent PD-1 blockade, ipilimumab/nivolumab or a BRAF/MEK-targeted therapy.

Down the list are the category 2B recommendations, and that's where you get vemurafenib and cobimetinib with atezolizumab from IMpower150 and dabrafenib/trametinib with pembrolizumab, so still hanging in there.

In terms of second-line therapy, it's very similar, but you begin to expand your repertoire. If you look at ipilimumab with T-VEC; cytotoxic agents; larotrectinib, if there is a *NTRK* fusion; binimetinib for *NRAS*-mutated melanoma.

Then the question becomes, you have all of these potential options, what should you start first? Should you start BRAF/MEK inhibition first? Or should you start ipilimumab/nivolumab first?

Well, if you look at some of the data that have been published, Doug Johnson, this is now a couple of years ago, if you look at anti–PD-1 alone, BRAF inhibitor, not a lot of difference in terms of overall survival. But, if you look at the triple combination, it looks fairly impressive.

Again, that's BRAF inhibitor plus anti–PD-1. And that's BRAF then anti–PD-1. If you look at anti–PD-1, then BRAF, it actually looks like it's a worse outcome. Again, that's an open question, which will be answered in a randomized trial, which is a phase 3 study of dabrafenib/trametinib and then if there's progression you get

ipilimumab/nivolumab, versus ipilimumab/nivolumab and then you get dabrafenib/trametinib if there is progression.

A press release came out suggesting that the trial has been stopped prematurely before even accruing all of its patients because patients were better off getting ipilimumab/nivolumab first and then getting dabrafenib/trametinib second, rather than the other way around.

And that's been pretty much confirmed in the updated data from the SECOMBIT trial, which stands for sequential combo immune and targeted therapy. Again, that's encorafenib/binimetinib versus ipilimumab/nivolumab.

And again, there's also been another sequencing study that included cobimetinib/vemurafenib. Then you go to atezolizumab versus atezolizumab then you go to cobimetinib/vemurafenib.

Not all those trials have matured. The SECOMBIT trial, which was the second trial that I described, shows that in terms of PFS, things are very close, but we think that arm C looks rather encouraging.

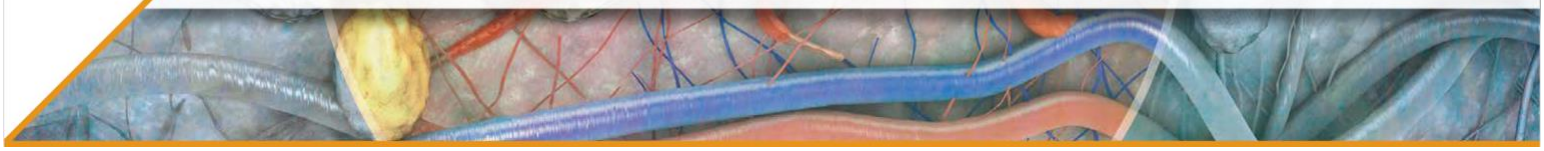
If you look at the updated data, the best data will end up coming from arm A. So, the initial data are shown with less than 2 years of follow-up. There's been more than 3.5 years of follow-up and those data were presented at ESMO showing that arm A is superior—which means you go first ipilimumab/nivolumab then BRAF/MEK.

Now what about non-V600 mutations. I told you the vast majority of mutations in *BRAF* molecule were at the 600 or 601 amino acids. Well, there are other mutations. There's *K601E*, there's *L597Q*, there's *G469A*, there are *BRAF* fusions, there's V600R/D/M/G. And it's predicted that they might be susceptible to BRAF/MEK inhibition, and very few people have actually tested that.

And that was tested in a study that was published a couple of years back in the *Journal of Clinical Oncology* and it was over 100 patients who had non-V600 E or K mutations, which are the most common ones. And it had actually a modest number of non-V600, and the majority were V600 K/D/R.

You also have kinase-activating mutations—that's *L597* and *K601*. Then there are these so-called kinase-dead mutations or kinase-impaired mutations, and that's *A598*, *D594*, and *G593*, as you can tell all in the same area.

Optimizing Treatment Selection and Side Effect Management in *BRAF*-Mutant Melanoma



In looking at BRAF/MEK activity, there's very little activity in these nontraditional *BRAF*-mutated patients to just single agent BRAF. Single-agent MEK inhibitor is modest, but BRAF-MEK does have activity in the non-traditional mutated *BRAF*, K/D/R, and *L597*.

When it comes to the fusion *BRAF* that's probably only going to be MEK inhibition. BRAF inhibition probably won't touch that.

And again, *BRAF*/MEK fusions are very interesting. It's a surprisingly common phenomenon that fuses the kinase domain of *BRAF* with the 5' end of another gene. And again, the kinase becomes constitutively activated and the expression is "controlled" by the promoter of the fusion partner. And again, not uncommon, and there's evidence that MEK inhibition should have some impact on this.

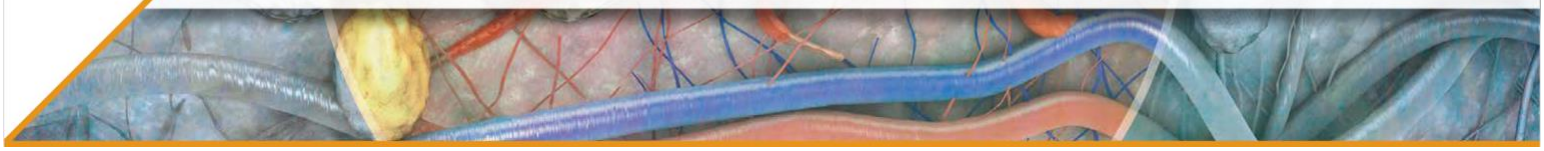
This is preclinical work and now it's been subjected to anecdotal clinical attempts. This is an anecdotal case published from Australia, by Alex Menzies. It shows a patient with previously treated melanoma who had a *BRAF* fusion and again a fusion was in *BRAF* Intron 10, and the patient got trametinib MEK inhibitor and they actually did very well. Real shrinkage of disease by week 6.

Now an important topic, of course, is identifying, assessing and managing adverse events from these targeted therapies. We've heard a lot about immune-related adverse events from checkpoint inhibitors. But the targeted therapies have their own spectrum of side effects.

If you put COMBI, COMBI-d, and COMBI-v together, the three studies with the longest follow-up and the largest number of patients, you see that photosensitivity is a big deal with vemurafenib/cobimetinib, but pyrexia, chills, is much more of a deal with dabrafenib and trametinib. And if you look at increased alanine aminotransferase, it probably is a little higher with vemurafenib.

There are a number of other issues such as headache, nausea, vomiting, diarrhea, alopecia, hyperkeratosis. And then, the cutaneous squamous cell cancers or keratoacanthomas which are probably not uncommon in either dabrafenib, trametinib or vemurafenib and cobimetinib. But would be much more common than single agent BRAF inhibitor.

As you might expect, the cutaneous toxicity of these drugs can be pretty profound. The cutaneous toxicities of the BRAF inhibitor are often a cutaneous maculopapular rash.



You can definitely get photosensitivity and having practiced in Florida, I can assure you, that's a big deal.

You get palmar-plantar erythrodysesthesia, which you see with some chemotherapy drugs. And these little keratoacanthomas, which are these annoying little things that appear on the sun-damaged areas of the face and upper body and arms. And they look like little volcanos but those are early squamous cancers. And you can see squamous cancers too.

You can also, with the MEK inhibitors, see this classic acneiform/pustular rash. You can see fissures on the palms and soles, which are really painful, and paronychia and nail dystrophy. And again, that's extremely annoying.

The management of these side effects, well, if you have hand-foot syndrome and you use keratolytic agents, that's very time honored, or thick moisturizers like petroleum jelly. For the photosensitivity, you have to protect yourself and use broad-spectrum sunscreens. For the rashes, we usually use topical or oral steroids and oral antihistamines.

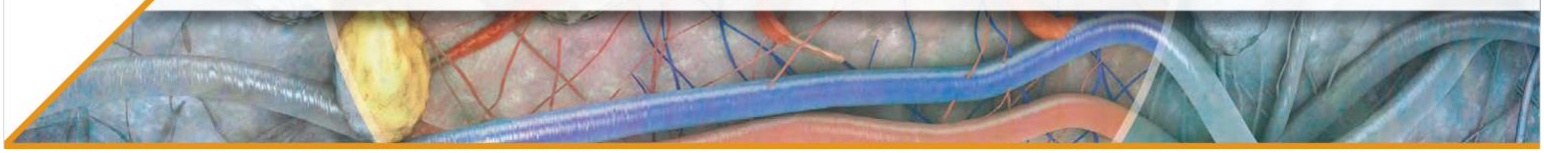
For MEK, it's either steroids or the use of topical antibiotics, if it's that acneiform rash. And lastly you could use isotretinoin.

A MEK-associated toxicity that can be extremely disturbing to patients is the retinal disturbances. This includes serous retinopathy, which can certainly occur with BRAF/MEK combinations due to the MEK drug. If you look at the ultrasound, you can see how the retina is lifted off its normal layers.

Then you stop the treatment and this just goes away, and patients go back to normal.

With dabrafenib/trametinib, you get this classic pyrexia fatigue syndrome and that can be very annoying. It can be morbid. It usually occurs in the first 1 to 2 months of therapy. It can last 9 days in the beginning and 4 to 5 days subsequently. There's no association with clinical benefit, despite the urban legend that you've heard about. And you might get symptoms of fatigue with no fever. You might get fever with fatigue.

And the way you handle it is you withhold the drugs. If the pyrexia is uncomplicated without symptoms, you don't need to perform a full fever workup. And you stop the drug, sometimes you give them oral methylprednisolone, sometimes you don't.



But you restart drugs without dose modification and sometimes you give 5 mg or 10 mg of steroids, hopefully every other day as prophylaxis and that allows patients to get through the regimen.

You may have symptoms without fever. It may just present as fatigue. But usually, fever is the sine qua non.

In terms of surveillance recommendations for BRAF/MEK combinations, cardiomyopathy is a potential toxicity. You should probably do an ultrasound at baseline, and I repeat one at 2 to 3 months. I don't keep repeating them. I get an ECG at baseline, 2 weeks later, and then 8 to 12 weeks later.

For creatine kinase elevations, we monitor creatine phosphokinase. For dermatologic toxicity, I have all of my patients see a dermatologist at least every 3 to 6 months. And you have to be on the lookout for the squamous cancers and the keratoacanthomas and they should be removed.

And finally, you need to have your favorite ophthalmologist deal with retinal vein occlusion, uveitis, and central serous retinopathy.

The special considerations really relate to increased toxicity, which in my view is additive for the triplet, which combines combination targeted therapy and immunotherapy. Just compared to the doublet.

What are the key takeaways? BRAF/MEK drugs can achieve long-term survival plateaus in patients with metastatic melanoma. Triple therapy has superior PFS versus the doublet. Atezolizumab/vemurafenib/cobimetinib compared to vemurafenib/cobimetinib alone looks better. Pembrolizumab/dabrafenib/trametinib compared to dabrafenib/trametinib was clearly better, although it had a very high bar to meet and didn't meet it. The side effects of BRAF/MEK combinations are complex to manage but unlikely to have a permanent impact on patients' health and well-being.

Now, let's talk about a virtual case from our virtual case clinic.

A 70-year-old woman had a primary melanoma of the right arm diagnosed 2 years ago, Clark's level IV, 4.2 mm Breslow depth, ulcerated with six mitoses per mm^2.

After a wide local excision, and a surprising negative sentinel lymph node biopsy from the right axilla, the patient declined going on a clinical trial and was simply observed. In the past month, the patient began to feel a mass in the right axilla.

She was referred by her primary care doctor to a surgeon who palpated a 5-cm right axillary mass. A fine needle aspirate was positive for S100 positive Melan-A positive, SOX10-positive melanoma.

The patient had PET/CT scans that suggested that there were multiple right axillary and subpectoral nodes that were enlarged and also had an abnormal standardized uptake value (SUV).

Molecular testing showed that the patient's tumor had the *BRAF* V600K mutation.

What would you advise in this case? Surgery, neoadjuvant dabrafenib and trametinib, neoadjuvant pembrolizumab, neoadjuvant ipilimumab/nivolumab?

The surgeon initially thought that the tumor would potentially be resectable with surgery, but there were concerns about the extent of the adenopathy in the chest wall.

The patient was then referred to a medical oncologist, who proposed neoadjuvant ipilimumab/nivolumab to facilitate subsequent surgery and provide prognostic data—this is because the level of pathologic remission in the treated specimen would inform the prognosis.

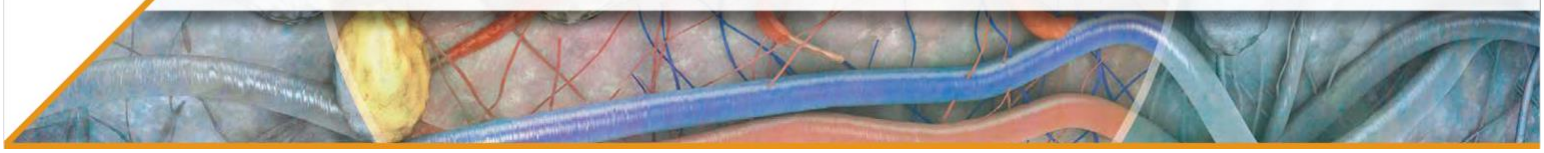
The patient was started on intravenous nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks for two cycles.

After 2 weeks, the patient complained of an itchy rash on the abdomen and thighs.

The rash was treated with topical steroids and diphenhydramine at night to allow sleep, and the ipilimumab/nivolumab was continued for a second cycle with a clear-cut reduction in the size of the mass by week 4.

At week 5 after two cycles of treatment, the patient complained of a fever (101.4°F) and fatigue.

After speaking to the oncologist, the patient was seen that day in the clinic. Her exam was unrevealing with no evidence of infection.



Blood cultures were taken, CBC count, chem panel, results were normal, and the patient was tachycardic and hyper-reflexic. The TSH was 0.04, T4 was 13 mcg/dL.

The fever was thought to be due to hyperthyroidism, which is what these values are consistent with. A 0.04 TSH is very low and a T4 of 13 is clearly abnormal.

The patient was placed on nonsteroidal agents twice daily and a beta blocker and there was resolution of fever after 24 hours.

The patient felt much better and did well for another 2 weeks and then had repeat thyroid function tests showing that the T4 had dropped to 0.4 and the TSH was now elevated.

What do you do now?

The patient felt quite weak even though she was afebrile and was told to stop taking the beta blocker that she had been given for her hyperthyroidism. An ACTH and cortisol were drawn that afternoon and the cortisol returned as normal; this gave the investigator the chance to start levothyroxine at 75 mcg daily, orally.

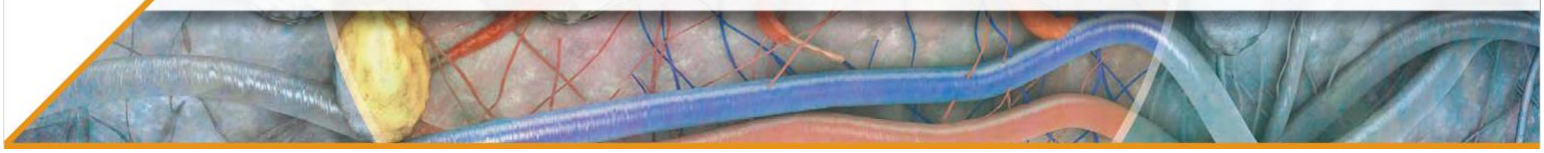
You generally don’t want to give levothyroxine to someone whose ACTH and cortisol levels are unknown because you might have panhypopituitarism and you might give levothyroxine and precipitate an adenosine crisis.

The patient did well for the next week after starting levothyroxine at 75 mcg per daily per day. She had a re-evaluation set of scans at week 7.

The mass was slightly decreased in size on scanning with some heterogeneity in the contrast uptake.

A PET/CT scan showed some resolution of abnormal uptake in the subpectoral nodes but continued uptake in the right axillary mass.

The patient was subsequently referred to surgery for right axillary and subpectoral node dissection. At surgery there were enlarged nodes noted with pigment present in the low axilla/subpectoral region and one predominant mass of matted nodes of 4 cm in the axilla.



Pathology ultimately showed less than 50% regression in the resected axillary lymph node and in the subpectoral nodes 90% necrosis was seen with lots of pigment-laden macrophages.

So, the question is, what do you do now? Continue the PD-1 blockade alone, give dabrafenib/trametinib for an additional 44 weeks, give ipilimumab/nivolumab every 3 weeks for 1 year, give pembrolizumab alone for an additional 44 weeks?

Keep in mind that you had a very modest level of necrosis.

The medical oncologist elected to place this patient on 44 additional weeks of dabrafenib and trametinib to complete 1 year of treatment, given the lack of sufficient pathologic response in the axilla to immunotherapy.

The patient really didn't have much of a response. So, continuing with immunotherapy would not have been sensible and I applaud the decision to go with dabrafenib and trametinib adjuvant therapy.

At week 8 of the 44 planned weeks, the patient had a temp of 104°F. The patient was then started on methylprednisolone with resolution of the fevers by 48 hours. But after restarting the medicines, the fevers and the fatigue again returned as the methylprednisolone was finished.

The patient had the medicines withheld, prednisone was started at 10 mg every other day, and the fevers abated within 1 week and dabrafenib and trametinib were restarted with continuation of the every-other-day prednisone.

The patient managed to finish the additional 44 weeks of BRAF/MEK drugs and PET/CT scans done every 3 months during therapy showed no evidence of disease.

Two years and three months after finishing therapy, while on an every-6-month follow-up, the patient complained of a growing mass on the scalp and results of this fine needle aspirate of the mass were positive for metastatic melanoma.

An MRI of the brain and PET/CT scan showed uptake in the scalp lesion with an SUV of 18 and multiple liver metastases. A biopsy of a liver lesion was positive for melanoma.

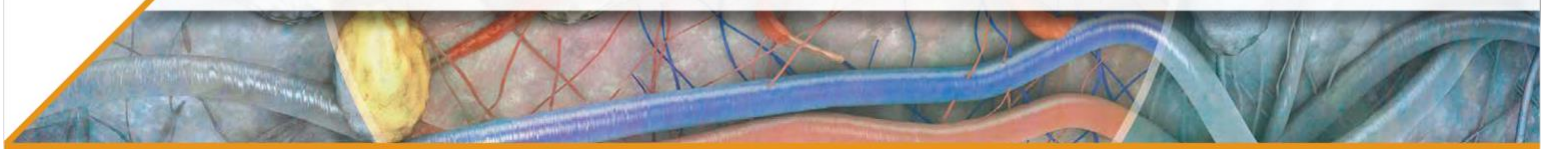
What would you do now? Restart ipilimumab/nivolumab at full doses, restart dabrafenib only because of the fevers, start pembrolizumab, restart dabrafenib/trametinib for four to seven days and then advance as tolerated.

The liver biopsy specimen had the *BRAF* V600K mutation. And the patient was eventually restarted on dabrafenib/trametinib for 4 of 7 days due to her previous fevers.

At week 4, the patient was without fevers and was advanced to a 7-day week regimen.

At 8 weeks, there was significant regression. The patient had a near CR at week 16, continues on treatment, and has a performance status 0.

That's the end of our case, and I just want to thank you and thank you all for participating in this activity, which was, again, *Optimizing Treatment Selection and Side Effect Management in* BRAF-*Mutant Melanoma*. Thank you very much.



References

Algazi AP, Othus M, Daud AI, et al. Continuous versus intermittent BRAF and MEK inhibition in patients with BRAF-mutated melanoma: a randomized phase 2 trial. *Nat Med*. 2020;26(10):1564-1568.

Anforth R, Liu M, Nguyen B, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. *Australas J Dermatol* 2014;55(4):250-254.

Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17(9):1248-1260.

Ascierto PA, Dreno B, Larkin J, et al. 5-year survival update of cobimetinib plus vemurafenib BRAF V600 mutation-positive advanced melanoma: final analysis of the coBRIM study. *Clin Cancer Res*. 2021;27(19):5225-5235.

Ascierto PA, Dummer R, Gogas HJ, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. *Eur J Cancer* 2020;126:33-44.

Ascierto PA, Ferrucci PF, Fisher R, *et al.* Dabrafenib, trametinib and pembrolizumab or placebo in *BRAF*-mutant melanoma. *Nat Med.* 2019;25(6):941-946.

Ascierto PA, Mandala M, Ferrucci PF, et al. First report of efficacy and safety from the phase II study SECOMBIT (SEquential COMBo Immuno and Targeted therapy study). *Ann Oncol*. 2020;31(suppl 4):S1142-S1215.

Balagula Y, Barth K, Busam KJ, et al. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). *Invest New Drugs* 2011;29(5):1114-1121.

Botton T, Talevich E, Mishra VK, et al. Genetic heterogeneity of BRAF fusion kinases in melanoma affects drug responses. *Cell Reports* 2019;29:573-588.

Carlino MS, Long GV, Kefford RF, Rizos H. Targeting oncogenic BRAF and aberrant MAPK activation in the treatment of cutaneous melanoma. *Crit Rev Oncol Hematol*. 2015;96(3):385-398.

Carlos G, Anforth R, Clements A, et al. Cutaneous Toxic Effects of BRAF Inhibitors Alone and in Combination With MEK Inhibitors for Metastatic Melanoma. *JAMA Dermatol*. 2015;151(10):1103-1109.

Corcoran RB, Settleman J, Engelman JA. Potential therapeutic strategies to overcome acquired resistance to BRAF or MEK inhibitors in BRAF mutant cancers. *Oncotarget* 2011;2:336-346.

Daud A and Tsai K. Management of treatment-related adverse events with agents targeting the MAPK pathway in patients with metastatic melanoma. *Oncologist* 2017;22(7):823-833.

Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:863-873.

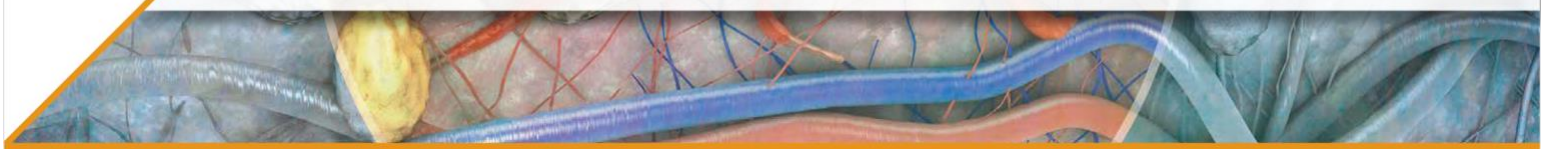
Drago JZ, Lawrence D, Livingstone E, et al. Clinical experience with combination BRAF/MEK inhibitors for melanoma with brain metastases: a real-life multicenter study. *Melanoma Res*. 2019;29(10:65-69.

Dummer R, Asceierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF*-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.

Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(10):1315-1327.

Ferrucci PF, Di Giacomo AM, Del Vecchio M, et al. KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in BRAF-mutant melanoma. *J Immunother Cancer* 2020;8:e001806. doi:10.1136/jitc-2020-001806.

Francis JH, Habib LA, Abramson DH, et al. Clinical and morphologic characteristics of MEK inhibitor-associated retinopathy: differences from central serous chorioretinopathy. *Ophthalmology* 2017;124(12):1788-1798.



Frederick DT, Prris 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. *Clin Cancer Res*. 2013;19(5):1225-1231.

Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected *BRAF* V600–mutant stage III melanoma. *J Clin Oncol*. 2018;4:1382-1388.

Hauschild A, Dummer R, Santinami M, et al. Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III *BRAF* V600–mutant melanoma: five-year analysis of COMBI-AD. *J Clin Oncol*. 2020;38(15):10001.

Hayward NK, Wilmott JS, Mann GJ. Whole-genome landscapes of major melanoma subtypes. *Nature* 2017;545:175-180.

Holbrook K, Lutzky J, Davies MA, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: a case series. *Cancer* 2020;126(3):523-530.

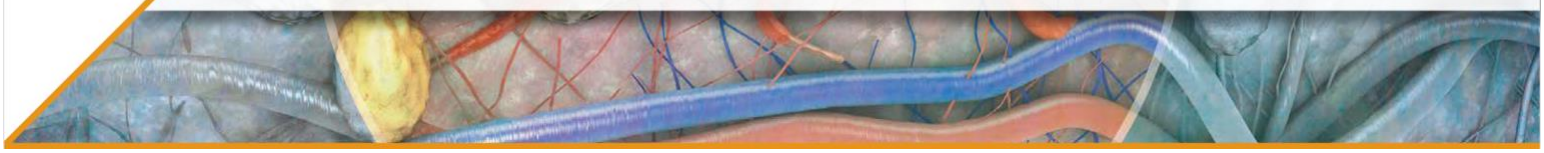
Johnson DB, Pectasides E, Feld E, et al. Sequencing treatment in BRAFV600 mutant melanoma: anti-PD-1 before and after BRAF inhibition**.** *J Immunother.* 2017;40(1):31-35.

Lacourture ME, Duvic M, Hauschild A, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. *Oncologist* 2013;18(3):314-322.

Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in *BRAF*-mutated melanoma. *N Engl J Med.* 2014;371:1867-1876.

Long GV, Stroyakovskiy D, Gogas H. et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015;386:444-451.

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(7):1631-1639.



Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III *BRAF*-mutated melanoma. *N Engl J Med*. 2017;377:1813-1823.

McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. *Ann Oncol*. 2017;28:634-641.

McArthur GA, Stroyakovskiy D, Gogas H, et al. Evaluation of atezolizumab, cobimetinib, and vemurafenib in previously untreated patients with BRAF V600 mutation-positive advanced melanoma: Primary results from the phase 3 IMspire150 trial. *Cancer Res*. 2020;80(suppl 16):CT012.

Menzer C, Menzies AM, Carlino MS, et al. Targeted therapy in advanced melanoma with rare *BRAF* mutations. *J Clin Oncol*. 2019;37(33):3142-3151.

Menzies AM, Yeh I, Botton T, et al. Clinical activity of the MEK inhibitor trametinib in metastatic melanoma containing BRAF kinase fusion. *Pigment Cell Melanoma Res*. 2015;28(5):607-610.

Nathan P, Dummer R, Long GV, et al. Spartalizumab plus dabrafenib and trametinib (Sparta-DabTram) in patients (pts) with previously untreated BRAF V600–mutant unresectable or metastatic melanoma: Results from the randomized part 3 of the phase III COMBI-i trial. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215.

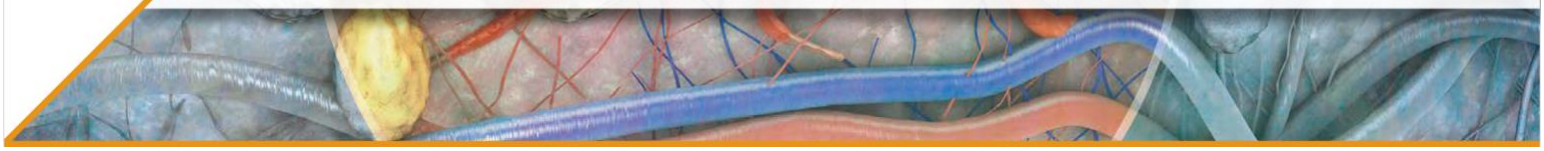
Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372:30-39.

Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381:626-636.

Ross JS, Wang K, Chmielecki J, et al. The distribution of *BRAF* gene fusions in solid tumors and response to targeted therapy. *Int J Cancer* 2016;138(4):881-890.

Schadendorf D, Long GV, Stroiakovski D, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. *Eur J Cancer* 2017;82:45-55.

Swetter SM, Thompson JA, Albertini MR, et al. NCCN Clinical Practice Guidelines in Oncology. Melanoma: Cutaneous. V 2.2021. ©2021 National Comprehensive Cancer



Network, Inc. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.

Wan PTC, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* 2004;116(6):855-867.