MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: John M. Kirkwood, MD

In the Pipeline: Encorafenib and Binimetinib in *BRAF*-Mutated Melanoma

Keith Flaherty, MD
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

H&O What makes the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib a good combination for use in *BRAF*-mutated melanoma?

KF Like other combinations of BRAF and MEK inhibitors, encorafenib/binimetinib has been demonstrated to be superior to monotherapy with a BRAF inhibitor for patients who have *BRAF*-mutated melanoma. The phase 3 COLUMBUS trial (Study Comparing Combination of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in BRAF Mutant Melanoma) showed better progression-free survival (PFS) and overall response rates (ORRs) with encorafenib/binimetinib than with the BRAF inhibitor vemurafenib (Zelboraf, Genentech/Daiichi Sankyo).

Follow-up in this trial has not been long enough to determine whether encorafenib/binimetinib improves overall survival (OS). However, trials of the 2 BRAF/MEK inhibitor combinations approved by the US Food and Drug Administration (FDA)—dabrafenib (Tafinlar, Novartis) plus trametinib (Mekinist, Novartis) and vemurafenib plus cobimetinib (Cotellic, Genentech)—have shown consistent improvements in OS.

Another benefit of encorafenib/binimetinib combination therapy is that it appears to be better tolerated than BRAF inhibitor monotherapy. This is particularly important because patients take this therapy for many months.

The FDA is currently reviewing the use of encorafenib/binimetinib in patients with *BRAF*-mutant locally advanced, unresectable, or metastatic melanoma; Array BioPharma submitted the application in June 2017 on the basis of the results of COLUMBUS. Nothing further will be known until the FDA has completed its standard review.

H&O Could you talk more about the design and results of COLUMBUS?

KF COLUMBUS, which I presented at the Society for Melanoma Research 2016 Congress in November of that year, was designed to demonstrate the superiority of encorafenib/binimetinib over encorafenib alone or vemurafenib (Table). It included 921 patients who had locally advanced, unresectable, or metastatic melanoma with a *BRAF* V600 mutation. The primary endpoint was PFS; OS and ORRs were secondary endpoints.

In the blinded independent central review, we found that the median PFS was significantly better for patients treated with encorafenib/binimetinib (14.9 months) than for those treated with vemurafenib (7.3 months). There was also a trend toward better PFS with encorafenib/binimetinib (14.9 months) than with encorafenib alone (9.6 months). In addition, the median PFS was significantly better with encorafenib alone (9.6 months) than with vemurafenib (7.3 months). The ORR was significantly better with encorafenib/binimetinib (63%) than with vemurafenib (40%).

Table. Progression-Free Survival in COLUMBUS

Comparison	mPFS, Blinded Independent Central Review		mPFS, Local Review	
Enco/Bini vs vemurafenib	Enco/Bini	Vemurafenib	Enco/Bini	Vemurafenib
	14.9 mo	7.3 mo	14.8 mo	7.3 mo
	HR, 0.54; 95% CI, 0.41-0.71; *P*<.001		HR, 0.49; 95% CI, 0.37-0.64; *P*<0.001	
Enco/Bini vs Enco	Enco/Bini	Enco	Enco/Bini	Enco
	14.9 mo	9.6 mo	14.8 mo	9.2 mo
	HR, 0.75; 95% CI, 0.56-1.00; *P*=.051		HR, 0.68; 95% CI, 0.52-0.90; *P*=.006	
Enco vs vemurafenib	Enco	Vemurafenib	Enco	Vemurafenib
	9.6 mo	7.3 mo	9.2 mo	7.3 mo
	HR, 0.68; 95% CI, 0.52-0.90; *P*=.007		HR, 0.70; 95% CI, 0.54-0.91; *P*=.008	

Bini, binimetinib; Enco, encorafenib; HR, hazard ratio; mo, months; mPFS, median progression-free survival.

Source: Dummer R et al. Presented at: Society for Melanoma Research Thirteenth International Congress; November 6-9, 2016; Boston, Massachusetts.

H&O Why was vemurafenib used as a control treatment in COLUMBUS?

KF Encorafenib is still an investigational therapy, of course, so if COLUMBUS had simply demonstrated superior efficacy for encorafenib/binimetinib vs encorafenib alone, the question of whether encorafenib was as effective as vemurafenib and dabrafenib would have remained open.

Regarding vemurafenib vs dabrafenib, both of those were considered standard treatment at the time that COLUMBUS was initiated, so either could have been used to create a standard-of-care control arm. Vemurafenib was chosen in part because it was the first BRAF inhibitor to receive FDA approval. A study by Chapman and colleagues also had demonstrated better OS with vemurafenib than with dacarbazine. Furthermore, vemurafenib had been used as the control treatment in the phase 3 trial of dabrafenib/trametinib that was published by Robert and colleagues. And of course, vemurafenib was the control arm in the phase 3 study of vemurafenib/cobimetinib that was published by Larkin and colleagues. So, using vemurafenib as the control arm in this study provided the opportunity to have a common comparator across all 3 BRAF/MEK inhibitor combination trials.

H&O How does encorafenib/binimetinib compare with dabrafenib/trametinib and vemurafenib/cobimetinib for *BRAF*-mutated melanoma?

KF It is always somewhat hazardous to perform cross-trial comparisons. Having said that, encorafenib/binimetinib appears to be very comparable with dabrafenib/trametinib and vemurafenib/cobimetinib. The improvements seen in PFS and ORR are very similar to those seen with vemurafenib. The median PFS for encorafenib/binimetinib—14.9 months—is the longest we have seen in any of the BRAF/MEK inhibitor phase 3 trials. Whether this finding reflects a somewhat more favorable population of patients or a truly superior regimen is difficult to say. It does, however, appear that the tolerability of encorafenib/binimetinib may be superior to that of either of the FDA-approved BRAF/MEK inhibitor combinations. Specifically, encorafenib/binimetinib is not associated with an appreciable rate of fever or photosensitivity. Other class effect BRAF/MEK inhibitor toxicities have been observed with encorafenib/binimetinib, but at rates similar to those seen with the approved regimens.

H&O What are the side effects of encorafenib/binimetinib, and how do these compare with the side effects of other treatments?

KF The most common side effects of encorafenib/binimetinib are fatigue, rash, arthralgia, and diarrhea. These are generally mild to moderate and can be managed easily with dose interruptions. For patients who have persistent or escalating toxicities, dose reductions can be effective and allow people to remain on therapy. The side effects seen and the management strategies used are very similar to those for the 2 FDA-approved BRAF/MEK inhibitor combination regimens. The side effects are quite different from those of immunotherapy, which carries a risk for autoimmune toxicity. Another difference is that BRAF/MEK inhibitor therapy is administered as a daily

oral regimen, which allows alterations in treatment—interruptions and dose reductions—to be made readily. Treatment modifications are more challenging with the currently available immunotherapies; these are long-lived antibodies that take several weeks to leave the body following each administration. The toxicities associated with encorafenib/binimetinib typically decrease within a few days of dose interruption.

H&O How does encorafenib/binimetinib compare with immunotherapy for *BRAF*-mutated melanoma?

KF Encorafenib/binimetinib and the other BRAF/MEK inhibitor combinations have not been directly compared with immunotherapy in randomized trials. Encorafenib/binimetinib, like other BRAF/MEK inhibitor combinations, has a very high response rate—even higher than the response rates seen with the programmed death 1 (PD-1)/cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) combination regimens. The most commonly used immunotherapy strategy is PD-1 antibody monotherapy, which has a 40% response rate in treatment-naive patients. Encorafenib/binimetinib, on the other hand, has a 70% response rate. This is important when treatment options are considered for patients with symptoms, or other features suggestive of aggressive disease, at presentation.

PFS at 6 and 12 months is superior for encorafenib/binimetinib when comparisons are made across clinical trials. The follow-up time of the encorafenib/binimetinib phase 3 trial, however, is too short for it to be possible to comment on comparable efficacy at 2 years and beyond. Long-term efficacy will become important as this clinical trial cohort is followed over time. In the melanoma field, substantial advances have been made with regard to improvements in short- to intermediate-term outcomes. Now our focus has shifted to improving long-term survival.

H&O How many studies across the country are examining the use of BRAF and MEK inhibitors, and how quickly are they accruing patients?

KF Many ongoing trials are employing a BRAF/MEK combination backbone. This backbone is combined with either an immune checkpoint antibody or a third targeted therapy in an effort to overcome mechanisms of resistance to BRAF/MEK inhibition. The immunotherapy combination approach has moved into phase 3 trials, whereas the approach of triple targeted therapy remains in phase 1 and 2 trials.

H&O Why did Array withdraw binimetinib from FDA consideration for *NRAS*-mutant melanoma in March 2017?

KF Although the phase 3 NEMO (Binimetinib Versus Dacarbazine in Patients With Advanced NRAS-Mutant Melanoma) trial met its primary endpoint of improvement in PFS for binimetinib over dacarbazine, most patients in the trial had not received one of the immunotherapy regimens that are now standard before study participation. This makes it difficult to interpret the efficacy of binimetinib in the context of current clinical practice. In addition, the effect of the treatment across the entire population was modest in absolute terms.

The results observed in the NEMO trial endorse the idea that MEK inhibitor therapy confers a benefit for some patients with *NRAS* mutations. Following the emergence of immunotherapy for this population, it is now important to determine if this benefit exists in patients whose disease has failed to respond to immunotherapy or if MEK inhibitor therapy can be added to immunotherapy to further improve outcomes in treatment-naive patients.

Disclosure

Dr. Flaherty is a consultant for Roche, Novartis, and Array BioPharma.

Suggested Readings

Array BioPharma provides NEMO update [press release]. Array BioPharma. http://investor.arraybiopharma.com/phoenix.zhtml?c=123810&p=irol-newsArticle&ID=2255017. March 19, 2017. Accessed August 25, 2017.

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