The BRAF-Positive Patient: How Should a Clinician Decide?

• Michael B. Atkins, MD, Deputy Director, Georgetown- Lombardi Comprehensive Cancer Center, Washington, D.C.

Presenting the cases for either immunotherapy or molecularly targeted therapy as frontline treatment for advanced BRAF-mutant melanoma, Dr. Atkins said that survival curves for the two options cross over at a little past two years. While BRAF inhibitor survival is superior at first, later CTLA-4 inhibition with ipilimumab is better, reaching a steady plateau sustained past five years.

In the column favoring immunotherapies is their ability to produce treatment-free tumor responses. BRAF inhibitors don’t share that capacity. A study by Schadendorf et al. showed a 21% three-year overall survival (OS) for ipilimumab, which compared favorably with Dr. Atkins’ trial of high-dose interleukin-2 (IL-2) with an OS of 11% at more than five years, and median OS with BRAF inhibition of approximately 26 months (median progression-free survival [PFS], approximately 10–13 months). While combined BRAF/MEK inhibition has produced the best outcomes in normal lactate dehydrogenase (LDH) patients, the benefit is strongest in patients with elevated LDH, more advanced disease (M1c versus IIIC/M1a/M1b) and greater tumor burden (three or more disease sites). Immunotherapy, however, works as well against BRAF V600 mutant melanoma as it does against wild-type tumors. Other confirmatory studies demonstrated survival benefit regardless of NRAS mutation status. 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Dr. Andtbacka concluded that “the future of oncolytic immunotherapy is in combination with other therapies,” based on his comparison of response rates in advanced unresectable stage III/IV melanoma between monotherapies (ipilimumab, 6–15%; pembrolizumab, 27–38%; nivolumab, 34–40%; T-VEC, 26%) and combination therapies (nivolumab plus ipilimumab, 52%; T-VEC plus ipilimumab, 50%; T-VEC plus pembrolizumab, 56%).

Conference Chairman and Moderator Sanjiv Agarwala, MD, wrapped up the debate stating, “Intralesional therapy is here to stay.” In the course of taking polar positions on intralesional monotherapy, the debaters effectively affirmed their own and Dr. Agarwala’s position.

Debate on Combination Checkpoint Blockade

Combination Checkpoint Blockade: The New Standard For All Patients

• Steven O’Day, MD, Professor of Medical Oncology, the John Wayne Cancer Institute, Santa Monica, California

Dr. O’Day began by listing factors supporting combinations of checkpoint blockade immunotherapy as the standard in metastatic melanoma, such as high disease control rates; rapid deep responses; improved response rates; longer progression-free survival (PFS); and good estimated overall survival (OS), approaching 70% at three years.

By comparison, the traditional cell-directed therapies are characterized by short responses with little impact on survival. The new therapies produce durable tumor responses with early disease control and symptom management, and offer patients time without symptoms or treatment and often long-term survival.

Response rates with ipilimumab, the CTLA-4 blockade agent that was the first agent in decades to show an OS benefit in advanced melanoma, have been far surpassed by nivolumab and pembrolizumab, the new programmed death-1 (PD-1) blockade agents. In the phase 3 CheckMate 067 trial, objective response rates (ORRs) were 19% for ipilimumab, 44% for nivolumab, and 58% for the combination of nivolumab and ipilimumab. Complete responses were reported in 2.2% for ipilimumab, 8.9% for nivolumab, and 11.5% for the nivolumab/ipilimumab combination. Similarly, median PFS was 2.9 months for ipilimumab, 6.9 months for nivolumab, and 11.5 months for the combination.

The combination, however, had increased grade 3–4 adverse events at 53.0%, compared with 27.3% and 16.3%, respectively, for ipilimumab and nivolumab. No treatment-related deaths were reported in the nivolumab/ipilimumab arm (0.3% each for the ivolumab and ipilimumab arms).

While adverse events led to discontinuation of therapy in 29.4% of patients receiving the ipilimumab/nivolumab combination, the ORR among discontinuing patients was nearly 70%. “Those responses are still durable, so with coming off therapy, while it shortens treatment, the opportunity for long-term survival is still there,” Dr. O’Day said. “If patients are educated and prepared for side effects and communicate about them rapidly, early intervention reverses almost all of them,” he added.
Resolved: Ipilimumab Plus Nivolumab
Not Suitable for All Metastatic Melanoma Patients

• Jeffrey Weber, MD, PhD, Perlmutter Cancer Center, NYU Langone Medical Center, New York, New York

Toxicities with checkpoint inhibitor combinations were at the center of Dr. Weber’s position. “You can talk about a zero death rate in a very tightly controlled, well-put-together randomized phase 3 trial, but when it comes to treatment in the community, where physicians have less experience, it’s going to be a different scenario.”

“The toxicity of combination therapy suggests that those over 75 to 80 years of age or with significant comorbidities should be treated with single-agent PD-1 [programmed death-1] or a PD-1 combination other than ipilimumab,” he said. Among patient populations unlikely to tolerate combination (but appropriate for single-agent nivolumab or pembrolizumab) are patients with prior grade 3–4 ipilimumab therapy-related adverse events and patients with prior allografts or a history of hepatitis or controlled human immunodeficiency virus infection, he added.

Other candidates for checkpoint monotherapy other than ipilimumab include the roughly 40% of melanoma patients with “hot” programmed death ligand 1 (PD-L1)-positive tumors with an “inflammatory signature” who are likely to benefit from PD-1 abrogation. Also, BRAF-mutated melanoma patients with low to normal lactate dehydrogenase (LDH) will likely respond as well to targeted BRAF plus MEK inhibitors like dabrafenib and trametinib that have demonstrated a 30% overall survival plateau as they will to ipilimumab plus nivolumab. The BRAF plus MEK combination, importantly, is much less toxic. For high LDH BRAF-mutated patients, a brief induction with BRAF plus MEK followed by ipilimumab plus nivolumab might be preferred because the BRAF plus MEK combination induces a T-cell influx into tumors and converts a “cold” tumor to a responsive “warm” tumor, Dr. Weber said.

Dr. Weber noted a promising future combination—pembrolizumab with an indoleamine 2,3-dioxygenase (IDO) inhibitor—that has demonstrated a 53% objective response rate, similar to ipilimumab/nivolumab but with significantly less toxicity. “Therefore, ipilimumab plus nivolumab combination therapy is not indicated for all metastatic melanoma patients,” he concluded.

Dr. O’Day, in a post-debate interview, pointed out that combinations of a PD-1 agent with ipilimumab at lower doses, or with a third intralesional therapy such as T-VEC or PV-10, may also prove successful.

He emphasized, too, that among ipilimumab side effects, while the pituitary cases (hypophysitis) generally require lifelong replacement therapy, a “hassle” factor for the patient, the more important colitis and liver toxicities are generally reversible. “I completely agree with Dr. Weber,” he said, “that the combinations with ipilimumab should be given through experienced hands. There needs to be a big commitment from the patient and the family to communicate information about side effects.”

The Heart Outcomes Prevention Evaluation (HOPE)-3 Trial

• Eva Lonn, MD; Jackie Bosch, MD; and Salim Yusuf, MD, Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

HOPE-3 evaluated blood pressure (BP) lowering with candesartan 16 mg daily added to hydrochlorothiazide (HCTZ) 12.5 mg daily combined with cholesterol lowering with rosvuastatin 10 mg daily in an intermediate-risk population (N = 12,705). The trial assessed the effects of this regimen and of the BP-lowering and cholesterol-lowering components separately on cardiovascular events in patients without cardiovascular disease.

Dr. Lonn said that the lack of strict BP or hypertension history or low-density lipoprotein-cholesterol (LDL-C) criteria for trial entry along with the ethnically diverse population made this global trial unique. Mean age was 66 years (46% female), with mean BP of 138/82 mm Hg and mean LDL-C of 128 mg/dL. Waist-to-hip ratio was elevated in 87% of subjects.

Blood Pressure–Lowering Component

After a median follow-up (99.1%) of 5.6 years, the mean change in systolic blood pressure was –6.0 mm Hg (–3.0 mm Hg for placebo). The composite primary outcomes (first, cardiovascular death, myocardial infarction [MI], or stroke; and second, the same plus resuscitated cardiac arrest, heart failure, or revascularizations) were reported at similar rates between the candesartan plus HCTZ and placebo arms (coprimary 1: 4.1% candesartan plus HCTZ versus 4.4% placebo, P = 0.40; coprimary 2: 4.9% candesartan plus HCTZ versus 5.2% placebo, P = 0.51). Rates for individual components were all similar.

A prespecified analysis of the coprimary outcomes with stratification according to thirds of BP found a significant benefit for candesartan plus HCTZ versus placebo among subjects with BP above 143.5 mm Hg (mean, 154 mm Hg) for both the first coprimary outcome (95% confidence interval [CI], 0.56–0.94; hazard ratio [HR] = 0.73) and the second coprimary outcome (95% CI, 0.60–0.96; HR = 0.76). For patients in the middle third, results were neutral. There was a suggestion of possible harm with the candesartan plus HCTZ combination in patients without very high BP at baseline (131.5 mm Hg or lower systolic blood pressure; CI, 0.92–1.70; HR = 1.25), Dr. Lonn said.

Although treatment discontinuation rates were similar between the treatment arms, lightheadedness was significantly more common in the combination group (3.4% versus 2.0% placebo; P < 0.001).

“The overall main message is treat blood pressure when it’s elevated; don’t treat when there’s no increase,” Dr. Lonn said.
said. She noted that the Eighth Joint National Committee Guidelines for the Management of Hypertension in Adults and the European guidelines still debate the precise entry level for uncomplicated mild hypertension. “Our trial helps define the thresholds at which patients should be treated.”

American College of Cardiology (ACC) discussant Valentin Fuster, MD, Director of Mount Sinai Heart in New York, pointed out that the patients in SPRINT, a trial with results seeming to indicate “treat blood pressure to the lowest level you can,” included patients at significantly higher risk. “You have to individualize,” he said.

**Cholesterol-Lowering Arm Results**

HOPE-3 studied moderate-risk primary prevention in diverse ethnic groups, Dr. Bosch said. There were no lipid-level entry criteria and no routine monitoring. While the fixed dose of 10 mg daily is low, she commented, rosuvastatin is a potent statin. The mean reduction in LDL-C from baseline was 34.5 mg/dL as compared with placebo at the study end ($P < 0.001$). Reductions in apolipoprotein B100 (mean $\Delta 0.23 g/L$) and C-reactive protein (CRP) (log mean $\Delta 0.19 mg/L$) compared with placebo were also observed.

Outcomes analysis revealed significant reductions with rosuvastatin for the two coprimary endpoints (24% and 25%; $P = 0.002$ and $P = 0.0004$) and for myocardial infarction (35%; $P = 0.02$), stroke (30%; $P = 0.02$), and cardiovascular hospitalizations (25%; $P = 0.0003$). The 11% reduction in cardiovascular death, however, was not statistically significant ($P = 0.51$).

Regarding the reduction in the second coprimary outcome (cardiovascular death, MI, stroke, cardiac arrest, revascularization, heart failure), Dr. Bosch noted that the rosuvastatin and placebo curves start to diverge at about one year and continue separating out to 5.6 years and beyond. A pattern of somewhat later but consistently diverging curves in favor of rosuvastatin over placebo was apparent for coronary heart disease and stroke.

While trends favoring better outcomes with rosuvastatin in subjects with LDL-C 112 mg/dL or lower, INTERHEART Risk Score tertile 1 less than or equal to 12, systolic BP 131.5 mm Hg or lower, and European descent were noted, interactions between events and subgroup categories overall were nonsignificant.

Permanent discontinuations were more common in the placebo group (23.7% rosuvastatin versus 26.2% placebo; $P = 0.001$), but muscle pain/weakness (5.8% rosuvastatin versus 4.7% placebo; $P = 0.005$) and the need for cataract surgery (3.3% rosuvastatin versus 2.6% placebo; $P = 0.02$) were higher for rosuvastatin. Dr. Bosch emphasized that muscle pain/weakness was generally reversible with temporary discontinuations. “There were no increases in serious adverse events such as rhabdomyolysis or new diabetes,” she said.

Dr. Bosch concluded that rosuvastatin 10 mg/day reduced cardiovascular disease by 25% and that benefits were consistent regardless of LDL-C levels, systolic BP, overall risk, CRP, or ethnicity.

**Combined Blood-Pressure and Cholesterol Lowering Versus Double Placebo**

Dr. Yusuf, at an ACC press briefing, pointed out that HOPE-3 was the first formal testing of clinical events with the “polypill” concept. While patients in HOPE-3 did not actually receive a polypill, the combined regimen did test the concept.

Among the 6,356 patients receiving the candesartan 16 mg plus HCTZ 12.5 mg regimen versus double placebo ($n = 6,349$), the mean reductions in systolic BP were $\Delta 6.2$ mm Hg and those in LDL-C were 33.7 mg/dL.

The coprimary endpoint rate for the double-active-agent arm was 3.6%, a significant reduction (95% CI 0.56–0.90; $HR = 0.71$; $P = 0.0054$) from the 5.0% rate in the double-placebo arm. For the second coprimary endpoint, the finding was similar at 4.3% for candesartan plus HCTZ and 5.9% for double placebo (95% CI 0.57–0.89; $HR = 0.72$; $P = 0.0030$). Rates for MI, stroke, and cardiovascular hospitalization also favored the double-active group ($P = 0.026/0.009/0.0046$, respectively) compared with double placebo. The reduction in cardiovascular death (2.4% candesartan plus HCTZ versus 2.9% double placebo) did not reach statistical significance ($P = 0.19$).

The prespecified evaluation of the combination versus double placebo relative risk reduction (RRR) by systolic BP tertiles showed no benefit in the lower two tertiles of systolic BP patients for the triple combination of rosvastatin plus HCTZ and candesartan (20%) versus rosuvastatin alone (31%) or candesartan plus HCTZ (-7%). In the highest systolic BP tertile, however, the RRR for the combination was 39%, compared with 18% for rosvastatin alone and 21% for the dual antihypertensive arm.

Dr. Yusuf also noted, “These trials of five or six years tend to underestimate the benefit.” He pointed out that in the curves for stroke and coronary heart disease (fatal/nonfatal MI, coronary revascularization) benefit, the second three years showed greater statin/antihypertensive benefit than the first three years, with the curve separation widening over time.

Dr. Fuster reiterated that over time, the benefits of combination therapy in primary prevention will accumulate.

Safety was nearly identical between the combination and double-placebo arms, with increase in lightheadedness (with antihypertensives only) and more muscle pain/weakness for the combination (6.2% versus 4.1%). Permanent discontinuations were similar (21.9% combination versus 23.9% double placebo).

Dr. Yusuf concluded, “Overall, it seems that most of the benefits from the combination come through statins—but that hides the fact that in those with elevated blood pressure about half of the 40% reduction in major vascular events comes from blood pressure lowering.”

“An important implication,” Dr. Yusuf said, “is that you don’t need to measure lipids or certainly not frequently. Also, you don’t need to bring people back for intensive monitoring to titrate drugs. When you reduce visits like this, you save money both at the health care level and for individuals … you can avoid many indirect costs.”

Dr. Fuster commented, “The future of prevention, no question, is simplicity.” He also cautioned that emphasizing a relative risk reduction of 30%, when the absolute reduction is 1.5% to 2%, is misleading to many. Still, he added, over time that absolute reduction “means a lot.”
The Effect of Community Pharmacist Prescribing And Care on Cardiovascular Risk Reduction: The RxEACH Multicenter Randomized Controlled Trial

Dr. Tsuyuki said that while cardiovascular diseases are among the leading causes of death, most cardiovascular deaths are caused by modifiable risk factors. “Yet their identification and control are still suboptimal. Pharmacists, though, are accessible, front-line primary health care providers who frequently see patients with or at risk for cardiovascular events,” he said.

Dr. Tsuyuki’s trial assessed a province-wide program in Alberta, Canada, where pharmacists presently can independently prescribe and order laboratory tests. The primary objective was to evaluate the effects of community pharmacy-based case finding and intervention in patients at high risk for cardiovascular events. Researchers looked specifically at reductions in estimated major cardiovascular event risk among patients using 56 community pharmacies across Alberta.

Adults at high risk for cardiovascular events because of diabetes, chronic kidney disease (CKD), established atherosclerotic vascular disease, or multiple risk factors and Framingham risk scores above 20% were eligible, as well as those with at least one uncontrolled risk factor (blood pressure [BP], low-density lipoprotein-cholesterol [LDL-C], elevated hemoglobin A1c [HbA1c], current smoking). All had a standard medication therapy management consultation including the following: 1) patient assessment (BP, waist circumference, weight, and height); 2) lab assessment of HbA1c, lipids, and kidney function; 3) individualized cardiovascular disease risk calculation and education about this risk; 4) treatment recommendations, prescription adaptation, and prescribing as appropriate to meet treatment targets as per the latest Canadian practice guidelines; 5) follow-up every three to four weeks for three months.

Patients were randomized to RxEACH advanced care or to usual pharmacy/physician care with no specific interventions or follow-up. After three months, patients in the usual care group crossed over to the RxEACH intervention.

The primary outcome was the difference from baseline in estimated risk for future cardiovascular events based on validated risk engines (United Kingdom Prospective Diabetes Study, International, Framingham).

Dr. Tsuyuki noted that 79% of subjects at baseline had uncontrolled HbA1c, 72% had uncontrolled BP, 58% had uncontrolled LDL-C, and 27% were current smokers. Mean age was 62 years (58% male). Of 720 enrolled patients, 41% had CKD, 81% had diabetes, 85% had hypertension (uncontrolled in 72%), and 32% had atherosclerotic vascular disease. At baseline in the initial intervention group, mean HbA1c was 8.6% (uncontrolled in 79%); mean glucose was 9.2 mmol/L, and mean estimated glomerular filtration rate was 78.7 mL/min/1.73m². Mean BP was 137/81 mm Hg. Twenty-six percent were current smokers. At baseline, the most common medications were metformin (57.0%), insulin (28.9%), diuretics (34.6%), angiotensin-converting enzyme inhibitors (39.5%), angiotensin II receptor blockers (28.7%), calcium-channel blockers (29.2%), beta blockers (25.4%), and statins (60.5%).

As a result of assessment in the intervention group, medication changes (dosage change, cessation, or new drug started) were ordered for hypoglycemics in 39.1%, for antihypertensives in 28.7%, and for antidyssrhythmics in 18.6%.

Dr. Tsuyuki reported that guideline targets were achieved more commonly in the intervention group. LDL-C targets were met in 55.5% and 45.6% in the intervention and usual care groups, respectively. BP targets were met in 50.9% and 27.8%, and HbA1c in 42.2% and 24.6% respectively. Current smoking was lower, as well (19.7% versus 26.6%, a 20.2% drop; P < 0.001). The relative reduction for estimated cardiovascular risk (RRR) from baseline in the intervention group was 21% (absolute RR, −5.37; 95% CI −6.56 to −4.17; P < 0.001). Risk remained constant in the usual care group. BP changes in the intervention group were −9.37 mm Hg/−2.92 mm Hg (P < 0.001); LDL-C was lowered by 0.2 mmol/L (P = 0.001) and HbA1c was reduced by 0.92% (P < 0.001). Dr. Tsuyuki concluded, “A community pharmacist case-finding and intervention program reduced the estimated risk for cardiovascular events by 21% in only three months through improvements in all major risk factors. This provides a new paradigm for community-based cardiovascular risk reduction that is complementary to and in collaboration with physician care.”

Dr. Tsuyuki cited a few comments from pharmacists on their reactions to participating in the study. One wrote: “It was very interesting and exciting to be part of a study where you can feel like you’re making a difference for your patients.”

REFERENCES