Talimogene Immunotherapy—Clinical Data In Local, Regional, and Distantly Metastatic Melanoma

In Zurich, Dr. Andtbacka reported that analysis of biomarkers in the phase 1b/2 trial showed increases from baseline after treatment with T-VEC and further increases after ipilimumab treatment in total and activated CD8 T cells in peripheral blood. Increases in CD4 T cells expressing inducible T-cell costimulatory molecule also followed ipilimumab treatment, indicating upregulated CTLA-4 blockade. Importantly, patients with disease control after T-VEC had more than 1.4 times as many activated CD8 T cells, while four out of five patients with tumor growth did not.

The objective overall response rate for T-VEC in CHNM was 47.5% versus 7.7% for GM-CSF (P = 0.0004). Complete and partial response rates with T-VEC were 29.5% and 18.0% versus 0.0% and 7.7% with GM-CSF, respectively.

“In patients with cutaneous head or neck melanoma, T-VEC as a monotherapy or likely in a combination will be an important treatment modality,” Dr. Andtbacka concluded. “If you have head or neck melanoma and you had a durable response to TVEC, you were likely to have a very long-lasting response.”

In earlier phase 1 reporting (American Society of Clinical Oncology, 2014) of the phase 1b/2 trial of T-VEC plus ipilimumab versus T-VEC alone in 18 patients with previously untreated or unresected advanced melanoma, there were no dose-limiting toxicities and a 56% response rate with complete responses (CRs) in 33%—results Dr. Andtbacka called “very encouraging.” Because T-VEC promotes the release and presentation of tumor-derived antigens and ipilimumab, an immune checkpoint inhibitor, improves T-cell responses, there is potential for enhanced efficacy beyond that of either therapy alone, he said.

Dr. Ross elaborated on the rationale for combining systemic immunotherapies with ablative intralesional treatments in an interview. “I am actually very enthusiastic about the combination of these oncolytic immunotherapies with the other targeted immunotherapies like the anti-CTLA-4 or anti-PD-1 agents,” he said. The anti-PD-1 and anti-CTLA-4 agents affect precise targets: for example, blocking a specific receptor to activate T cells and make the immune system function, he said. They differ from “classic” immunotherapies that elicit very specific T-cell responses through antigen presentation.

The oncolytic immunotherapies, including an oncolytic virus such as T-VEC or the chemical ablator PV-10, rupture the tumor to express antigens in a way that is useful to the immune system.” So the type of oncolysis may be very relevant. The tumor ablative agents could be synergistic with ipilimumab. It would make sense because they act at different places in the immune system.”

In treatments with T-VEC or GM-CSF, patients who had a durable response to T-VEC had a very long-lasting response. T-VEC treatment alone, he said.

Robert Andtbacka, Associate Professor, University of Utah School of Medicine; and Merrick Ross, MD, Professor, University of Texas MD Anderson Cancer Center, Houston, Texas

In a subanalysis of results among patients with advanced unresected cutaneous head and neck melanoma (CHNM) in the OPTiM trial and in a phase 1b/2 multicenter, open-label trial in previously untreated advanced melanoma patients, talimogene laherparepvec (T-VEC) demonstrated significant benefits. T-VEC is a herpes simplex virus-1–derived oncolytic immunotherapy.

Compared with other tumor locations, Dr. Andtbacka said, CHNM has a higher risk for recurrence, a worse prognosis, and limited treatment options. “The in-transit and nodal recurrences and visceral disease can be very challenging to treat. Lesions can become symptomatic and cosmetically disfiguring,” he said.

The OPTiM trial included 436 patients with injectable, unresectable stage IIIB–IV melanoma who were randomized 2:1 to T-VEC or granulocyte-macrophage colony-stimulating factor (GM-CSF). Dr. Andtbacka reported on 61 of 295 patients (20.7%) in the T-VEC arm and 26 of 141 patients (18.4%) in the GM-CSF arm with CHNM.

Durable responses were defined as a complete or partial response that began at any point within 12 months of initiation of therapy and lasted continuously for six months or longer. T-VEC durable response rates were higher in the CHNM patients than in the OPTiM general population (36.1% compared with 16%). The durable response rate for GM-CSF in CHNM patients was 3.9% (P = 0.003 versus T-VEC in CHNM). Among responders, Dr. Andtbacka emphasized, 73% had responses lasting 15 months or longer.

The overall objective response rate for T-VEC in CHNM was 47.5% versus 7.7% for GM-CSF (P = 0.0004). Complete
not have such increases. The phase 2 study comparing T-VEC plus ipilimumab to T-VEC is going forward and adding patients based on these findings.

Combined BRAF/MEK Inhibitor Therapy in BRAF-Mutant Melanoma

- Keith Flaherty, MD, Director of the Henri and Belinda Termeer Center for Targeted Therapies, Massachusetts General Hospital Cancer Center

The call to explore two-pathway solutions went out even before phase 3 data were available on BRAF monotherapy inhibition, Dr. Flaherty said in an interview. “When translational research suggested reactivation of the MAP kinase pathway for BRAF and MEK, that immediately pointed to the concept of BRAF/MEK combination therapy as a strategy, given the ready availability of numerous MEK inhibitors that were already reasonably far along in clinical development.”

Recent clinical trial data showing unequivocal improvements in overall survival (OS) for regimens joining BRAF and MEK inhibition in BRAF-mutant melanoma effectively “close the book” on defining clinical benefit, Dr. Flaherty said in his presentation. Increases in CR rates suggest that with longer-term follow-up, increases in durable responses will be demonstrated as well.

Preclinical evidence suggested that BRAF/MEK inhibition could be safe and better tolerated than either monotherapy—taking advantage of the fact that BRAF inhibitors have a very different effect on signaling in the MAP kinase pathway in tumor tissue versus normal tissue that lacks BRAF mutations. This separates the BRAF/MEK combination, Dr. Flaherty said, from other two-drug pairings in other cancers.

Combined BRAF/MEK inhibition improved response rates, progression-free survival (PFS), and OS, based on data accrued in the last year and presented at the European Society of Medical Oncology. In the phase 3 BRIM trial of vemurafenib (n = 336) versus DTIC (n = 336), the hazard ratio for OS favoring vemurafenib was 0.37 (95% confidence interval [CI], 0.26–0.55; P < 0.001). It is the OS finding that “closes the book,” Dr. Flaherty said.

Dr. Flaherty’s research comparing BRAF/MEK to single-agent BRAF inhibition (dabrafenib) showed delayed resistance for the combination, with respective PFS of 9.4 months and 5.9 months (hazard ratio [HR], 0.39; P < 0.001). With dabrafenib monotherapy, rates of cutaneous squamous-cell carcinoma, skin papilloma, and hyperkeratosis were 19%, 15%, and 30% versus 7%, 4%, and 9%, respectively, for patients receiving dabrafenib/trametinib.

Dr. Flaherty added that in a recent study by Long et al\(^2\) in stage IIIIC or IV BRAF-mutant melanoma, six-month HRs for PFS and OS in those treated with dabrafenib/trametinib versus dabrafenib were significantly superior. Similarly, in a dabrafenib/trametinib combination trial by Robert et al\(^3\), vemurafenib was the comparator, HRs favored the combination for PFS and OS.

In a BRAF/MEK inhibition trial by Larkin et al\(^4\) favoring the combination of vemurafenib/cobimetinib versus vemurafenib, the HRs were 0.51 for PFS (95% CI, 0.39–0.68; P < 0.0001) and 0.65 for OS (95% CI, 0.42–1.00; P = 0.046).

The best evidence for BRAF/MEK synergy, aside from these findings, Dr. Flaherty said, is the near-doubling of CR rates. In the phase 2 trial that supported the Food and Drug Administration’s accelerated approval of dabrafenib/trametinib in BRAF-mutant unresectable or metastatic melanoma, the respective CR rates for dabrafenib/trametinib and dabrafenib monotherapy were 9% and 4%. In Roberts et al, the CR rates with dabrafenib/trametinib and vemurafenib were 13% and 8%, respectively.

As a counter-argument to skeptics who suggest that combination therapy may merely be a “temporizing strategy” that fails to create more durable responses, Dr. Flaherty said, “We know that complete responders to BRAF-inhibitor monotherapy have the most durable responses. So it’s reasonable to expect, based on dabrafenib/trametinib data showing that complete responders shine through as the patients not only who maintain response the longest, but clearly also who survive the longest, that another year of follow-up data will likely assure this concern.”

Long-term Survival of Ipilimumab-Naïve Patients With Advanced Melanoma Treated With Nivolumab

- F. Stephen Hodi, Director of the Melanoma Center and the Center for Immuno-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts.

Long-term survival in previously treated patients with advanced melanoma receiving single-agent nivolumab (a PD-1 inhibitor) in the phase 1 CA209-003 study was comparable to that seen with current standard-of-care agents. Responses occurred early and were durable.

The 107 advanced melanoma patients enrolled had received between one and five prior lines of systemic therapy. Their mean age was 61 years (range, 29–58); 67% were male. Most patients (62%) had received two or more systemic regimens, of which 65% were immunotherapies (but not CTLA-4 or PD-1 inhibitors). At baseline, visceral metastases were present in 78% of patients, and elevated lactate dehydrogenase levels were found in 36%. Dr. Hodi emphasized that the median follow-up of 55 months in this study is longer than that of any other study of an anti-PD-1 agent.

Patients received up to 96 weeks of nivolumab at doses between 0.1 mg/kg and 10 mg/kg intravenously every two weeks. While safety and tolerability were the study’s primary objectives, preliminary efficacy was a secondary objective, and the protocol was amended to collect OS and retreatment outcomes data as well, Dr. Hodi said.

The overall response rate for all doses was 32% (34 of 107), with a median response duration of 23 months (range, 4–32). For the 3-mg/kg dose ultimately selected for phase 3 studies, the overall response rate was 41% (7 of 17), and the median duration of response was 22 months (range, 9–27). Among responding patients, 44% (15 of 34) showed a response at the week 8 first tumor assessment. In addition, among responders who discontinued for reasons other than disease progression, responses lasted for 16 months or longer in 21 patients. Responses are ongoing in 14 patients.

OS rates with the 3-mg/kg dose (n = 17) in years 1 to 4 are...
MEETING HIGHLIGHTS: American Heart Association Scientific Sessions

65%, 47%, 41%, and 35%, respectively, and for all the cohorts are 63%, 48%, 42%, and 32%, respectively. Dr. Hodi noted, “There is a suggestion of a plateau in the curve at this point … but further confirmation will obviously be needed in continued follow-up.”

For all cohorts, median OS was 17.3 months (95% CI, 12.5–37.8). For the 3-mg/kg dose, it was 20.3 months (7.2, NE). Median PFS was longest in the 3-mg/kg group (10 months; CI, 2–16). Median OS in this cohort was 20 months (CI, 7, NE).

Investigators also conducted an exploratory analysis of patients who entered the follow-up period with ongoing disease control (CR, partial response, or stable disease). Treatment was permitted in these patients after confirmed disease progression at the same dose assigned for up to a total of three years. Prolonged response or stabilization of disease was observed among five patients who were retreated; an increased adrenal mass was successfully excised in one patient. “We need prospective analyses to evaluate the efficacy and safety of nivolumab retreatment,” Dr. Hodi said.

Treatment-related immune-mediated adverse events were reported in 58% of patients, with 5% of grade 3 or 4. They included skin (38%), gastrointestinal (19%), endocrine (14%), and infusion reactions (6%). Dr. Hodi noted that immune-mediated adverse events with potential immunological etiologies require more frequent monitoring and/or unique interventions. In general, Dr. Hodi said, nivolumab treatment was well tolerated, with no new safety signals after a year of follow-up.

Three ongoing phase 3 trials are evaluating nivolumab 3 mg/kg in patients with advanced melanoma.

American Heart Association Scientific Sessions

This year’s American Heart Association (AHA) Scientific Sessions drew an estimated 17,835 cardiologists, researchers, and other health care professionals to Chicago from November 15 to 19, with 6,421 international visitors among them. Sessions of particular interest covered the thorny issue of duration of anticoagulation therapy during procedures, a novel alternative to statins, and the risks of endocarditis when dental antibiotic prophylaxis is dropped.

ODYSSEY ALTERNATIVE: Efficacy and Safety of Alirocumab Versus Ezetimibe, in Patients With Statin Intolerance Defined by Placebo Run-In And Statin Rechallenge Arm

• Patrick M. Moriarty, MD, Director of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, Kansas

In clinical practice, statin intolerance limits the ability of about 10% to 25% of patients to meet goals for low-density lipoprotein cholesterol (LDL-C). Myalgia is the most common complaint among these patients. While alternative statin-lowering drugs are available, large-scale, well-controlled randomized trials with those drugs are lacking, Dr. Moriarty said at an AHA press conference.

Ezetimibe is a recommended option for statin-intolerant patients. ODYSSEY ALTERNATIVE, a multinational study, compared the efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, to that of ezetimibe in patients with statin intolerance.

Patients with coronary heart disease or other cardiovascular risk factors were first given a four-week placebo challenge and excluded if they experienced muscle-related adverse events. Continuing patients were randomized 2:2:1 to alirocumab 75 mg self-administered via a 1-mL prefilled pen every two weeks (n = 126), ezetimibe 10 mg/day (n = 122), or atorvastatin 20 mg/day for 24 weeks (n = 63, safety analysis only). Their mean age was approximately 63 years; about 55% were male. The alirocumab dose was increased to 150 mg at week 12 depending on cardiovascular risk and week 8 LDL-C levels. The primary endpoint was the percent change in LDL-C from baseline to week 24. Patients could enter an open-label extension and receive alirocumab 75 mg or 150 mg every two weeks.

Mean LDL-C was 191.1 mg/dL in the alirocumab group, 193.5 mg/dL in the ezetimibe group, and 187.3 mg/dL in the atorvastatin group. After the placebo run-in, 6.9% of patients discontinued because of muscle-related adverse events.

At 24 weeks, the mean LDL-C level was 108.5 mg/dL in the alirocumab group, with about 42% of alirocumab patients achieving their LDL-C goals compared with 4% in the ezetimibe group (P < 0.001). Alirocumab reduced LDL-C from baseline by 45.0%, compared with a 14.6% reduction with ezetimibe (P < 0.0001). About half of the alirocumab patients who had received at least one injection by week 12 did not need dose increases.

Myalgia was reported in 24.6%, 23.4%, and 27.0% of patients receiving alirocumab, ezetimibe, and atorvastatin, respectively, while discontinuations for adverse events occurred at rates of 23.8%, 33.6%, and 33.3%, respectively. Only two patients discontinued because of myalgia among the 89.5% of patients who entered the open-label extension.

Dr. Moriarty concluded, “Alirocumab may be considered a good alternative therapy in patients with a history of statin intolerance.”

Is 6 Months DAPT Post-Coronary Stenting Non-Inferior to 24 months? The Italics/Italic+ Randomized Trial: Results of the One-Year Primary Endpoint

• Martine Gilard, MD, University of Brest, Brest Cedex, France

Currently, the recommended duration of dual antiplatelet therapy (DAPT) for reducing the risk of late stent thrombosis in drug-eluting stent recipients is 12 months, especially in those with acute coronary syndromes. However, DAPT is associated with increased bleeding that may affect outcomes, especially in patients who have comorbidities or require surgical treatment.

A meta-analysis of extended DAPT after percutaneous coronary intervention (PCI) by Cassese et al., Dr. Gilard noted at an AHA late-breaking clinical trial press conference, showed lower cerebrovascular accident and Thrombolysis in Myocardial Infarction (TIMI) major bleeding rates for controls than for extended DAPT. The ITALIC trial hypothesized that antiplatelet treatment with aspirin alone six months after drug-eluting stent implantation may be noninferior to DAPT in patients who are not resistant to aspirin.
ITALIC was conducted at 55 sites in Europe and the Middle East among 2,031 patients eligible for PCI who received at least one Xience V drug-eluting stent. All patients were pretreated with aspirin plus clopidogrel, prasugrel, or ticagrelor. Individuals pretreated with abciximab and those receiving primary PCI for acute myocardial infarction or treatment of the left main artery were excluded.

The actual randomization occurred among the 1,850 patients who experienced no events during the first six months after PCI. Their mean age was 61.6 years; about 80% were male. About 15% had prior myocardial infarction. Half received aspirin alone and half received another 18 months of DAPT, followed subsequently by aspirin alone. The primary endpoint was the composite of death, myocardial infarction, emergency target-vessel revascularization, stroke, or major bleeding (TIMI criteria) within 12 months.

Rates of the primary endpoint and all death favored 24-month DAPT in the subgroup of patients with acute coronary syndromes (ACSs) (HRs, 1.773 and 4.041, respectively). In the non-ACS group, the primary endpoint, all death, and cardiac death favored six-month DAPT (HRs, 0.79, 0.660, and 0.661), and myocardial infarction and minor bleeding favored 24-month DAPT (HRs, 1.990 and 3.981). Analysis, Dr. Gilard said, confirmed the overall noninferiority of six-month DAPT (P = 0.0002).

“I think this is very important because this trial showed that with six months of DAPT there is no problem at all,” Dr. Gilard commented. “In our daily practice with the new generation of drug-eluting stents we can shorten the duration of DAPT and give aspirin alone.” While he concluded that six-month DAPT was noninferior to 24-month DAPT in patients who responded well to aspirin, he added that confirming optimal DAPT duration for ACS patients will require further trials.

Increased Risk of Ischemic Events Upon Discontinuation of Prasugrel After 12 or 30 Months of Therapy Following Placement of the Taxus Liberté Paclitaxel-Eluting Coronary Stent

- Kirk N Garratt, MD, Associate Chair of Research & Quality, Interventional Cardiology, Lenox Hill Heart and Vascular Institute, New York, New York

Patients undergoing drug-eluting stent procedures face late risks of both ischemia and bleeding. The optimal prolonged antiplatelet therapy balancing these risks is unknown, Dr. Garratt said at an AHA press conference.

The TAXUS Liberté Post-Approval Study was an international, randomized, double-blind, placebo-controlled trial comparing 30 versus 12 months of dual antiplatelet therapy (DAPT) with a thienopyridine (prasugrel) plus aspirin for 30 months. It was a broadly inclusive trial powered for stent thrombosis, cardiovascular events, and bleeding. The coprimary effectiveness endpoints were stent thrombosis and major adverse cardiac and cerebrovascular events (MACCE) over the 12 to 30 months after the index procedure. The primary safety endpoint was the incidence of major bleeding (moderate or severe GUSTO, or Global Utilization of Streptokinase and TPA for Occluded Arteries). Subjects with very low body mass or advanced age were excluded from the study.

In the randomized population of 2,191 patients receiving drug-eluting stents (out of 25,682 in the larger DAPT study), 51% had at least one risk factor for stent thrombosis at the index procedure (26% with ACSs, 11% with acute ST elevation myocardial infarction, and 12% with a thrombus-containing lesion).

The rate of MACCE at 540 days for patients receiving 12 months of prasugrel plus aspirin was 8.8%, significantly higher (P < 0.001) than that for those receiving prasugrel and aspirin for 30 months (3.7%; HR = 0.407; 95% CI, 0.261–0.589). The MACCE difference was driven entirely by a higher rate of ARC (Academic Research Consortium) myocardial infarction in the 12-month group (7.1% versus 1.9%; HR, 0.255; 95% CI, 0.156–0.417; P < 0.001).

The 12-month prasugrel coprimary endpoint rate for definite or probable stent thrombosis at 540 days was again significantly higher (2.9% versus 0.2%; HR, 0.063; CI, 0.015–0.264; P = 0.001) than the 30-month rate. GUSTO moderate or severe bleeding was higher in the 30-month prasugrel group (2.4% versus 1.7%), but not significantly so (P = 0.234).

The Data Monitoring Committee, Dr. Garratt noted, recommended discussion of continuing open-label prasugrel based on the early increase in ischemic events following withdrawal of active prasugrel therapy in both groups.

“Whether the reduction in late ischemic events demonstrated with prasugrel plus aspirin and the TAXUS Liberté paclitaxel-eluting coronary stent would be observed with other dual antiplatelet regimens and/or other drug-eluting stents will require further study including insights from the larger DAPT Study,” Dr. Garratt said.


- Mark J. Dayer, Consultant Cardiologist, Taunton and Somerset NHS Trust, Taunton, United Kingdom (UK)

The fact that invasive dental procedures can result in viridans streptococci being released into the circulation has been known for many years, Dr. Dayer said in an AHA press conference. “It is believed,” he added, “that infective endocarditis can develop as a consequence of this in susceptible individuals.”

Since the National Institute for Health and Care Excellence (NICE) in England withdrew its recommendation for antibiotic prophylaxis before invasive dental procedures, there has been a documented rise in endocarditis cases. There has been no change in current practice recommendations, but after Dr. Dayer’s analysis, NICE will review its guidance.

Subsequent to issuance of the first AHA guidelines on anti-biotic prophylaxis in 1955, guideline-recommended antibiotic doses have progressively become lower with shorter duration of administration and fewer patients indicated as being at risk. However, NICE surprised the health community in March 2008, Dr. Dayer said, when it recommended a cessation of antibiotic prophylaxis in the UK due to the lack of supportive evidence for efficacy. It specifically listed individuals undergoing dental, gastrointestinal, genitourinary, and respiratory tract procedures as being exempt from prophylaxis.
To evaluate the effects of the guideline change, Dr. Dayer and colleagues reviewed all single-dose prescriptions for amoxicillin 3 g or clindamycin 600 mg between January 2004 and March 2013; they reviewed 19,804 cases in the UK with primary diagnoses of infective endocarditis in the same period.

The 2008 guideline change did indeed have an effect, based on a 90% decline in prescriptions. By March 2013, the number of infective endocarditis cases per month had risen by 25% (from 140 to 175) more than would have been expected. Increases were in both the highest and lowest risk groups, but were nearly doubled in the latter. The change was observed to begin just three months after the new guideline was introduced. However, a slight upward shift in death rates in the infective endocarditis population since the guideline change is not significant, Dr. Dayer said.

“We want to emphasize that although we have demonstrated a temporal association, we have not demonstrated a cause–effect relationship, and other explanations for the change are possible,” Dr. Dayer said. A prospective, randomized controlled trial is necessary to determine whether or not the association is in fact causal, he added.

The AHA discussant, Dhruv S. Kazi, MD, of the University of California at San Francisco, concurred: “As presented, these data are inadequate to alter the weight of evidence on which the prophylaxis guidelines are based, and should not prompt changes in prescribing practice at this time.”

Dr. Dayer’s study was published concurrently in The Lancet.

REFERENCES