The conference was held in Banff, Alberta on February 18 and 19, 2016. Speakers addressed a broad range of topics and issues in contemporary melanoma diagnosis and treatment. Part 1 of the report from the meeting includes extensive summaries of presentations by Axel Hauschild from University Hospital Schleswig-Holstein in Kiel, Germany, on adjuvant therapy and immunotherapy, as well as brief highlights from presentations by Dr. Vernon Sondak from the Moffitt Cancer Center; Dr. Antoni Ribas, Director of the Tumor Immunology Program at the Jonsson Comprehensive Cancer Center in Los Angeles; Dr. Keith Flaherty, Massachusetts General Hospital Cancer Center; and Teresa Petrella, Medical Oncologist, and Sten Myrehaug, Radiation Oncologist, from the Odette Cancer Centre at Sunnybrook Health Sciences Centre in Toronto.

**ADJUVANT THERAPY FOR MELANOMA**

Dr. Axel Hauschild addressed the meeting by videoconference from Germany. In this first presentation, he looked at current adjuvant treatment modalities and what we might expect from new and ongoing clinical trials.

**WHO NEEDS ADJUVANT TREATMENT?**

Dr. Hauschild said that in Germany there is a strong argument for adjuvant interferon treatment for Stage IIC and Stage IIIA, B, and C melanomas, and these groups are typically treated with it. In Stage IIA and IIB, the option of treatment is discussed with the patient, because low-dose interferon is approved in Europe for this indication from 1.5 mm onwards, even if the centre node is negative. He pointed to a wide diversity in European country recommendations for adjuvant interferon treatment. The majority of Europe is not using interferon widely. In Scandinavia and in the UK, regular use of interferon is not outlined in guidelines. In central Europe, low-dose interferon is used in some countries. Switzerland is the only country in Europe where pegylated interferon is approved (it was also approved in the US in 2011). There is no clear consensus in Europe, which, says Dr. Hauschild, explains the appeal of clinical trials for these patients.

He described a meta-analysis of all interferon trials showing an improvement of 14% for event-free survival (EFS) and a 10% improvement in overall survival (OS), however this includes 1 trial with very low-dose interferon where no benefit was seen at all for EFS and OS. If this trial is removed from the analysis, there is a 1.7% improvement in EFS. Dr. Hauschild states that while there have been many discussions around high-dose or low-dose interferon, there is now evidence showing that the outcome is almost the same.

**VACCINE THERAPY**

Dr. Hauschild presented data from the MAGE-A3 adjuvant-specific cancer immunotherapy (ASCI) vaccination trial. MAGE-A3 expression is found in about 50% of primary and metastatic melanomas. GlaxoSmithKline (GSK) tested the ASCI vaccine in 1,300 patients with metastatic melanoma and macrometastases of the lymph node. Results of the placebo-controlled double-blinded trial have not yet been published, but were presented in November 2015. Disease-free survival (DFS), the primary endpoint, was 11 months, and 11.2 months for placebo. It was thought that the predictive gene signature (PGS) would narrow down a group that might benefit, however, there was still no difference in DFS (9.9 months vs. 11.2 months with placebo), or OS (47% 1-year survival in both treatment and placebo arms) even in this group.

**BIOCHEMOTHERAPY: A NEW APPROACH FOR THE ADJUVANT TREATMENT OF MELANOMA?**

The European Organisation for Research and Treatment of Cancer (EORTC) conducted the ipilimumab trial that led to approval by the US Food and Drug Administration (FDA). Ipilimumab is an immune checkpoint inhibitor, a fully human, monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) to augment antitumour immunity. The treatment arm in this placebo-controlled trial in stage IV patients received a dose of 10 mg/kg (more than 3 times the currently-employed dose of 3 mg/kg) in 4 cycles for 3 months for 3 years. Results have been released, but OS data is still to come. Relapse-free survival (RFS) is the primary endpoint of the trial, an endpoint that was negotiated with agencies like the FDA. The difference in absolute terms was 9 months, or a 10% increase over placebo in DFS. After 3 years, DFS was 34.8% for those receiving ipilimumab, with a hazard ratio of 0.75. This is the only data currently available. High-dose ipilimumab associated with high rates of toxicity, including colitis and autoimmune hepatitis. Five patients died from ipilimumab in the treatment arm of the study: 3 from colitis, 1 from myocarditis, 1 with Guillain-Barré syndrome. Dr. Hauschild stated he is not, based on these results, very optimistic that ipilimumab would become the standard of care in the near future. It has been approved by the FDA, but not yet by the European Medicines Agency (EMA).
Dr. Hauschild considered the 2014 US Intergroup E1609 Phase III trial of ipilimumab, 10 mg/kg for 1 year vs high-dose interferon to be the most relevant adjuvant trial of ipilimumab. However, the Eastern Cooperative Oncology Group (ECOG) then opened a third study arm consisting of low-dose ipilimumab (3 mg/kg) for 1 year. The trial will show whether the efficacy outcome can be achieved in a regimen that is safer for patients.

**WHAT MIGHT CHANGE STANDARDS OF CARE BY 2018?**

Ongoing adjuvant melanoma trials include pegylated interferon, dabrafenib + trametinib, vemurafenib and pembrolizumab, and a nivolumab trial is planned for 2016. One-third of the patients have already been recruited for the pembrolizumab trial, which sets a new record for adjuvant trials. The ongoing European Organisation for Research and Treatment of Cancer (EORTC) randomized phase 3 trial of ulcerated primary melanoma involves 2 years of pegylated interferon vs observation in 1,000 patients. This trial is complicated by eligibility requirements that are difficult to meet in Western European countries, where the rate of ulcerated primaries is quite low, especially in patients younger than 70. As a result, recruitment is far behind the expected schedule.

Roche is conducting a trial called BRIM-8 with vemurafenib on 725 patients with stage IIIC to IIC melanoma against placebo for 1 year. The first results will be released in 2017. This trial opened at the same time as the GSK Combi AD trial by Novartis in stage IIIA to stage IIIC melanoma, using dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 1 year. In the metastatic setting, the combination of these 2 drugs was already known to have a better efficacy, with no increase in adverse events compared to dabrafenib alone. Dr. Hauschild expressed concern, however, that the proven benefits with BRAF/MEK inhibitors in stage IV melanoma will be eliminated or diminished if these treatments are given in the adjuvant setting due to the early development of resistance.

He described the adjuvant pembrolizumab trial as a first in melanoma to allow crossover. The trial has 2 parts. In Europe, MRC Technology, in collaboration with the EORTC, is comparing pembrolizumab vs observation, however, once disease progresses on placebo, patients are unblinded and can receive pembrolizumab for free. This is very attractive for the vast majority of patients at the moment, as in many European countries, pembrolizumab is approved but not reimbursed. In this study, patients have the opportunity to use a new drug that is affordable to many, even if they progress to stage IV disease. RFS is the primary endpoint, which makes sense in a crossover design where differences in OS are intentionally minimized. The second part is a US trial of pembrolizumab vs adjuvant interferon (typically high-dose) with OS as the endpoint. The 2 clinical trials are running in parallel on 2 continents, and the results will be of great interest.

**LOOKING AHEAD**

Dr. Hauschild expects to see a difference in DFS in the above-mentioned trials, though the balance between efficacy and tolerability will need to be assessed. Should the ongoing clinical trials show improved DFS and OS, Dr. Hauschild expects discussion about whether DFS is an appropriate endpoint to lessen. He says that each of the 7 new approvals in the past 6 years are contributing to prolonged OS, demonstrating that DFS might still be a good endpoint. He also favours the use of distant metastasis-free survival (DMFS) as an endpoint, but recognizes that it is harder to assess because of the timing of the scanning which is required.

He believes that new standards of care will come out of the current trials, but only if efficacy and tolerability are well balanced. Drug costing will also come into consideration. He related a term being used to describe the latest adversity in oncology: financial toxicity.

**IMMUNE CHECKPOINT INHIBITORS**

Dr. Axel Hauschild began his second talk by asking whether checkpoint inhibitors are truly revolutionary. Following a presentation in which he examines the benefits and drawbacks of different therapies, alone, in combination, and in sequence, his answer is a resounding “yes.”

On the “hit list” of genetic alterations in hematologic malignancies and solid tumours published in *Nature* in 2013, melanoma ranks highest, with an average of 30,000 mutations per tumour, followed by lung and bladder cancer. These diseases are the focus of the developments in immunotherapy, and programmed cell death protein 1 (PD-1) in particular. Dr. Hauschild emphasized the importance, when looking at checkpoint blockade, of differentiating between 2 groups of molecules affecting T-cells. With inhibitory receptors, of which the best examples are CTLA-4 and PD-1 (although there are also other ones of interest, like TIM-3 and LAG-3), the interest is in blocking the inhibition, whereas with activating receptors, such as OX40 and CD28, the aim is to turn up the activation. In this presentation, he examined developments over the past few years that have led to new standards of care, and questions that may be answered in ongoing trials.

**IPILIMUMAB**

Ipilimumab was the first inhibition blocker approved in metastatic melanoma. Dr. Hauschild recalled the first results, published by Steven Rosenberg’s group, which

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In Germany, most dermatologists, at least in the hospital setting, are deeply involved in the treatment of metastatic melanoma. This is because our medical oncologists gave up on melanoma 30 years ago: they essentially believed it was an untreatable disease. But now they have found an interest again.

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described a patient who showed good response to ipilimumab but also developed colitis. Two other early trials in melanoma demonstrated OS benefits. Dr. Hauschild said these showed some long-term responders and some complete responses, but low response rates, PFS and OS; however, they were a door-opener for immunotherapy in metastatic melanoma. In Canada, Dr. Hauschild remembers, the main concern was the price of the drug; today, he says, this debate is just as common in Germany.

More recent studies have shown 5-year survival for ipilimumab of 20% in meta-analysis, with some patients going beyond 5 years. Dr. Hauschild cautions that these results reflect not just ipilimumab, but also potentially first, second, and third-fourth-line treatments, as a number of new drugs became available during the study time frame. Overall survival, and long-term survival in particular, is affected by every line of treatment. He also mentions a trial comparing dacarbazine chemotherapy to dacarbazine plus ipilimumab for 5-year survival, which showed that long-term survival is doubled by the addition of ipilimumab.

**PD-1 Antibodies**
The Keynote-006 pembrolizumab trial was the first to use a newly approved agent, namely ipilimumab, in the comparator arm, rather than chemotherapy, and showed a response rate to pembrolizumab in the range of 34% and an OS improvement. This study made it clear that ipilimumab was no longer the standard of care as first-line treatment for metastatic melanoma and was replaced immediately by the PD-1 antibodies, pembrolizumab and nivolumab. Dr. Hauschild has no doubt that these 2 drugs have absolutely no difference in terms of efficacy and tolerability. The only data on 4-year survival available at the moment comes from a presentation on the nivolumab phase 1 trial in 2014, which traced survival at 1 year (63%), 2 years (48%), 3 years (42%), and 4 years (32%) in first- and second-line patients. A nivolumab versus dacarbazine trial in 418 metastatic melanoma patients showed a response rate of 40% with nivolumab and led to its approval in first- and second-line settings. Dr. Hauschild described as nonsense Canadian restrictions on the use of PD-1 antibodies based on mutational status and line of treatment. What excites him most about the nivolumab vs dacarbazine trial, and the pembrolizumab trial, are the very low numbers of patients discontinuing treatment due to toxicities. The rate of grade 3-4 adverse events for nivolumab was 12%, compared to 18% for dacarbazine. Dr. Hauschild pointed to very consistent data showing these agents are well tolerated.

**Determinants of Response**
Early dogma stipulated that immunotherapy had good results in patients with low tumour load, but that patients with high tumour load were unlikely to respond. However, a 2013 presentation on pembrolizumab showed a patient who received 3 lines of some sort of immunotherapy and still responded well. Keynote-001 involved 655 stage IV patients in a dose escalation phase 1 study; 75% of patients were BRAF wild-type. The trial achieved a 33% response rate in first and second line, with 8% complete responses. The most interesting finding, in Dr. Hauschild’s view, was that patients with BRAF wild-type and patients with BRAF mutant melanoma had the same response rate to the PD-1 antibody. “With pembrolizumab or nivolumab, it doesn’t matter,” he concludes. “Selection criteria for BRAF inhibition or PD-1 cannot be driven by BRAF status, because both have a reasonable response rate, in the range of 45%.”

**Sequencing Treatment**
A trial comparing nivolumab (3mg/kg, q2w x 6) followed 2 weeks later by ipilimumab (3mg/kg, q3w x 4) against ipilimumab followed 3 weeks later by nivolumab (2mg/kg, q2w x 6) found that the response rate in the nivolumab-first group (41%) was double that seen in the ipilimumab-first group (20%), providing very clear guidance that nivolumab-first makes sense. Important differences were also seen in tolerability, with almost no grade 3-4 toxicity (7%) in the nivolumab-first group vs 24% in the ipilimumab-first group. When ipilimumab is given alongside nivolumab as second-line treatment, the grade 3-4 toxicity rate climbs to 52%. Dr. Hauschild considers it clear that all the adverse events are driven by ipilimumab and not by the PD-1 antibody.

**Combinations**
Dr. Hauschild regards the phase 2 CA209-069 trial as most significant in leading to approval in the US. It compared combination nivolumab and ipilimumab to ipilimumab alone and showed a 59% response with the combination vs 11% for ipilimumab alone. PFS was impressively different between the 2 arms, with the distinct advantage to the combination. There is no doubt, he feels, that ipilimumab is toxic, as anyone who has treated patients knows, and as seen in the 30% discontinuation rates in the clinical trials. However, what was interesting to Dr. Hauschild in the combination trial is that 67.5% of patients (81/120) who discontinued the nivolumab plus ipilimumab combination due to serious treatment-related adverse events also developed a lasting response. He considers that this brings a completely new question into discussion: if there is a chance for ipilimumab plus nivolumab to become the new standard of care, is it really necessary to treat until disease progression? He suggests the possibility of treating patients for a limited time and managing toxicity well. There may be something for dermatologists and medical oncologists to learn from the discussions hematologists have with leukemia patients contemplating stem cell transplantation, which entails serious toxicities, but also offers a chance of cure.

Dr. Hauschild also addresses questions around concurrent or sequential use of targeted therapies and immunotherapies, pointing to preliminary results from a trial combining BRAF inhibitors, MEK inhibitors, and anti-PD-1. He looked to Dr. Antoni Ribas’s work at UCLA with a mouse model that showed best efficacy with dabrafenib, trametinib and a PD-1 antibody, whereas other combination approaches eventually led to steep increases in tumour volume. Dr. Hauschild believes there is a theoretical basis,
at least, to test this in clinical trials. Data presented at ASCO, ESMO, SMR and other conferences demonstrates consistently that combining targeted therapies with PD-1 antibodies are tolerable, while combining targeted therapies with ipilimumab is not. The ongoing Keynote-22 study on the safety and efficacy of pembrolizumab in combination with trametinib and dabrafenib in advanced melanoma is a good design. Dr. Hauschild considers, as it compares the triple regimen to the new standard of care involving combined dabrafenib and trametinib. “There is no space,” he says, “in the year 2016 for single-agent BRAF inhibitors.”

GUIDELINE CHANGES FOR ADVANCED OR METASTATIC MELANOMA

Dr. Hauschild gave a preview of new German guidelines expected in Spring 2016. They update 2014 guidelines that distinguished between BRAF wild-type and BRAF mutated patients, but also between high vs low tumour load and rapidly vs slowly progressive disease. As they investigated all available literature, Dr. Hauschild says, his team could not find an OS difference between these groups for BRAF plus MEK inhibition: the median is 25 months. The OS for PD-1 antibody alone is also 25 months. Overall survival for BRAF plus MEK and PD-1 antibody is the same. The guideline leaves open the determination of first- and second-line treatment.

MANAGEMENT OF BRAIN METASTASES

Medical oncologist Teresa Petrella and radiation oncologist Sten Myrehaug, from the Odette Cancer Centre at Sunnybrook Health Sciences Centre, looked at the evolution of radiation and systemic therapies in the management of brain metastases.

Brain metastases (mets) are very common in stage IV melanoma, with incidence ranging from 10% to 40% in clinical studies. Autopsy studies reveal that 55% to 75% of patients who die from metastatic melanoma have central nervous system (CNS) involvement. At first diagnosis, 20% of patients will present with CNS mets, and 60% will develop them at some point in the course of the disease. The risk is higher in patients who have a BRAF or NRAS mutation.

Prognosis is grim, with less than 5% of patients surviving 1 year, even with treatment. Factors related to poor prognosis in patients with brain mets are the presence of neurologic symptoms, the number (>3) and size of brain mets, extracranial mets, and pretreatment lactate dehydrogenase (LDH) levels. Untreated patients have an average survival of about 6 weeks. Whole-body radiation therapy (WBRT) offers a 2- to 5-month survival; surgical resection or stereotactic radiosurgery (SRS) offers 8- to 11-month survival, and patients with a single lesion treated with surgery and radiation have an average survival of 13 to 14 months.

Standard therapies for brain metastases include surgery, WBRT, SRS and systemic therapies. Surgery is preferred for solitary metastasis and when the mass compromises neurologic function. For decades, WBRT has been the standard of care for patients post resection and for those with multiple brain metastases, but it brings only modest benefit. Technologic advances in imaging, and especially magnetic resonance imaging (MRI), along with radiation planning and delivery, has allowed for the development of radiosurgery techniques. Delivery to a small volume allows for extreme dose escalation, which may overcome the tumour’s radioresistance. The intent of treatment is not simply to control the tumour, but to destroy it. The precision of targeting allows normal brain parenchyma to be spared.

Adding SRS to WBRT has been found to produce better survival in patients with solitary metastases and better local control.20 Meta-analysis of studies comparing SRS alone or in combination with WBRT found a benefit with the combined treatment.21 However, WBRT increases the risk of neurocognitive toxicity. Using a validated neurocognitive tool (the HVLT-R), Chang et al22 found that 4-month total recall deteriorated in 20% of patients receiving SRS alone vs 64% of patients receiving SRS plus WBRT, with the difference persisting to 6 months. This was the first trial to show an improvement in survival in SRS alone23 and was met with skepticism. The Alliance phase 3 randomized controlled trial (NCCTG N0574), presented in 2015,24 confirmed these findings in patients with 1 to 3 brain metastases, with median OS of 10.7 months with SRS alone vs 7.5 months with SRS + WBRT. Deterioration in immediate recall, delayed recall and verbal fluency were considerably more frequent with combined treatment. Recent studies of SRS alone have shown results in local control in 49% to 75% of patients.24

NOVEL THERAPIES

Three drugs have demonstrated activity in brain metastases. In the CA184-042 study, ipilimumab with steroids showed overall response rates (ORR) of 9.8% and brain response rates of 15.7%. In a subpopulation of patients with asymptomatic brain metastases, ORR at 1 year reached 20%.25 Dabrafenib, in a phase 2 study of patients with asymptomatic brain metastases and BRAF mutation, produced an ORR of 38% in reducing intracranial target lesions and a median OS of 31.4 to 33.1 weeks.24 Vemurafenib was tested in 24 patients with unresectable brain metastases who had failed at least 1 treatment and required corticosteroids for symptom control, achieving a median OS of 5.3 months.25

COMBINATIONS

Combined modality therapy has been tested in only a few studies. In a retrospective study of patients receiving SRS and nivolumab,26 the local failure rate was 11% and median OS from date of SRS was 11.8 months. Another study of BRAF inhibitor and SRS27 found that median OS increased from 6.7 months with SRS alone to 11.2 months with SRS and BRAF inhibitor; 12-month survival in BRAF-mutated disease with SRS and BRAF inhibition was 41%. Other studies are showing promising results with combined systemic and SRS treatment, up to 75% 1-year local control with SRS and vemurafenib.28

As Dr. Petrella concluded, there has been much progress made, with 6 drugs now approved that have efficacy in the
brain, and general acceptance of SRS over WBRT as the standard of care. For solitary metastases, or those causing significant neurologic compromise, surgical resection is the most appropriate therapy. The challenge now is to determine the best sequence or combination of treatment modalities to improve survival and quality of life.

**COMBINATION THERAPIES: WHAT MAKES SENSE AND WHAT’S TO COME?**

Dr. Keith Flaherty, from Massachusetts General Hospital Cancer Center, discussed current evidence and future prospects for combination therapies.

A meta-analysis of phase 2 and 3 trials of BRAF inhibition alone and in combination with MEK inhibition showed an advantage with the latter in terms of OS, and another study showed PFS of 11 months with a combination of dabrafenib and trametinib vs 8.8 months for dabrafenib alone. Looking at long-term survival, the combination of nivolumab and ipilimumab shows a higher rate of PFS until about 17 months, after which it falls to below the rate achieved with nivolumab alone. The side-effect burden was much greater with the combination therapy (55% grade 3–4 vs 16% in nivolumab monotherapy).

Dr. Flaherty, looking at principles of combining targeted therapy and immunotherapy, considered that synergistic effects would justify widespread use, and that even additive effects would justify use in higher-burden patients. “These combinations are too important to give up after a single approach,” he stated. The evidence supporting combinations to overcome de novo, adaptive and acquired resistance continues to grow. He regards prioritization and personalization as key challenges and believes a focus on early surrogate markers may help triage combinations and improve patient selection.

**RESPONSE AND RESISTANCE TO PD-1 BLOCKADE**

Dr. Antoni Ribas, Director of the Tumor Immunology Program at the Jonsson Comprehensive Cancer Center in Los Angeles, described the challenge of selecting patients who would respond to PD-1/PD-L1 blockade.

Dr. Ribas looked at preexisting T-cell infiltration that triggers adaptive PD-1 ligand 1 (PD-L1) expression, mutational load, interferon signature by expression profiling, PD-L1, PD-L2, and JAK2 (PDJ) amplon, and T-cell receptor (TCR) clonality as factors in response. He then described the process of adaptive immune resistance-mediated PD-1/PD-L1 interactions, where adaptive immune resistance can be inhibited through PD-1 blockade. In his view, management of cancer in the post-anti-PD-1/PD-L1 era involves overcoming this resistance, bringing T cells into tumours, and generating T cells using vaccines.

Dr. Ribas predicts that patients with advanced cancers will be selected to get anti-PD1/L1 therapy by assessing them for preexisting presence of T cells turned off by PD-1/PD-L1 interactions. If this is not found, then combinations will be designed to bring T cells to cancers with CTLA-4 blockade, with BRAF and MEK inhibitors being rational choices. He considers that “true” PD-L1 negativity is rare, and that it is inducible by interferon stimulation in 95% of melanoma cell lines. Interferon signalling defects were identified among cell lines with no response to interferons. He also notes that JAK1 loss-of-function mutations have been identified in biopsies from patients with melanoma or colon cancer with high mutational load who did not respond to anti-PD1 therapy.

**SURGERY IN THE IMMUNOTHERAPY ERA**

Dr. Vernon Sondak from the Moffitt Cancer Centre Center discussed the potential benefits of combining surgery with systemic therapy.

The standard approach to stage IIIC-IV melanoma at the Moffitt Cancer Center, said Dr. Sondak, involves resection of all disease (if possible) and consideration of an adjuvant therapy clinical trial. Patients who are not resectable can be treated with anti-PD-1 antibody therapy with or without ipilimumab. BRAF with or without MEK inhibitors can be provided to patients with BRAF V600 mutant melanoma and high disease burden, or after anti-PD-1 failure. The future standard of care may see surgery offered as “consolidation” for residual disease following targeted immunotherapy. At Moffitt, a phase 1 trial is underway using adjuvant nivolumab in stage IIIC-IV resected melanoma, and OS has been extended out to 48 months. Dr. Sondak concludes that surgery is certainly not obsolete, and that combining it with neoadjuvant treatment with new agents holds considerable promise.

**References**


