Canadian Melanoma Conference

The Canadian Melanoma Conference was held in Whistler from February 19 to 22, 2015. The conference dealt with the basic science, pathology and epidemiology of melanoma; surgery and dermatology; and immunology and systemic therapy. This summary is not an exhaustive account of the meeting but presents key points made in a number of presentations. Videos of the conference sessions are available at www.oncologyeducation.com for those who are interested in finding out more.

A TAXONOMIC FRAMEWORK
Towards an integrated taxonomy of melanocytic neoplasms

Dr. Boris Bastian, Professor of Dermatology and Pathology, University of California at San Francisco, reviewed current knowledge of the pathogenesis and clinical, histologic and genetic features of primary melanocytic neoplasms, and integrated them into a taxonomic framework. He examined the presentation of benign melanocytic nevi and the genetic alterations that enable progression to malignant tumours. In non-epithelium-associated melanoma, GNAQ and GNA11 mutations are found in almost half of cases where uveal nevus progresses to uveal melanoma, while NRAS mutations appear in almost all progression from congenital nevus of the skin to melanoma. Epithelium-associated melanoma in a low-ultraviolet (UV) context progressing from acquired nevus involves BRAF about 75% of the time, while fusions are the most important contributor in progression from Spitz nevus to spitzoid melanoma. In a high-UV context, BRAF, NRAS and Kit mutations may each account for a fraction of chronically sun-damaged (CSD) melanoma development. Half of all melanoma-initiating oncogenes and BRAF mutations occur primarily in melanoma with an intermediate mutation burden. There are two main melanoma classes on sun-exposed skin: BRAFV600E-dependent in younger individuals, and BRAFV600E-independent in older individuals.

Melanomas comprise multiple biologically distinct categories that differ in cell of origin, age of onset, clinical and histologic presentation, pattern of metastasis, ethnic distribution, causative role of UV radiation, predisposing germline alterations, mutational processes and patterns of somatic mutations.

This work has been pivotal to the increased understanding of the molecular aberrations associated with various melanoma phenotypes and to the development of more effective treatment strategies. Targeted agents that exploit the presence of these mutations have been utilized and have led to improved clinical outcomes.

MOLECULAR PHENOTYPING
Identifying T cell-mediated inflammation in tissue by molecular phenotyping: lessons from kidney transplantation

Dr. Philip Halloran, Director of the Alberta Transplant Applied Genomics Centre presented work underway at the University of Alberta in T cell-mediated rejection (TCMR) of kidney transplants that has potential relevance to current developments in melanoma immunotherapy, where the challenge is predicting and monitoring the effects of treat-
The hypothesis is that potential responsiveness to immunotherapy has a signal like TCMR. Dr. Halloran described the approach to molecular phenotyping of biopsies post kidney transplant, and stressed that there may not be perfect agreement between the histology phenotype determined by lesions and the molecular phenotype derived from data and metadata. The molecular microarray approach uses a trademarked Molecular Microscope Diagnostic System (MMdx)™ to measure transcript changes in a biopsy, compare these to a reference set and generate an automated report of classifiers, including a TCMR score. The reference set was compiled from 703 kidney biopsies, 3 days to 35 years post transplant, with full characterization of histology, clinical presentation and outcomes. The molecular phenotype is discovered through associations with conventional findings (histology, outcome, response to therapy) by t-tests.

The value of this work for melanoma comes from the prominence in TCMR of proteins being targeted by antibody drugs in melanoma, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed death ligand 1 (PD-L1/CD274), tumour necrosis factor superfamily, member 9 (TNFS9/CD137), and indoleamine 2,3-deoxygenase (IDO); and results with the B7 blocker belatacept in kidney transplants that indicate possible accidental removal of an inhibitory effect of CTLA4. Dr. Halloran sees an opportunity to use the MMDx system to detect TCMR-like reactions that can predict and/or monitor responses to immunotherapy in melanoma. He proposes a research agenda to develop a reference set, optimize conventional phenotype classification and engineer a reporting system for centralized testing.

**MISSED MELANOMA IN SLNB**

The rate of missed melanoma in sentinel node-negative patients: the Ottawa experience

Dr. Chloé Ward, from the Ottawa Regional Cancer Centre, presented research undertaken to ascertain whether recurrence rates of melanoma in patients with negative sentinel lymph node biopsy (SLNB) could be attributed in part to pathology technique. SLNB is a major independent prognostic factor for survival. However, the literature shows that between 6% and 23% of negative SLNB patients have metastases (compared to 50% to 60% of positive SLNB patients). The Ottawa team conducted a retrospective chart review of 140 patients diagnosed with single primary cutaneous melanoma between 1999 and 2004 who were followed at the Ottawa Regional Cancer Centre. The rate of metastatic melanoma after negative SLNB was 28.6% and the 5-year mortality from melanoma in this group was 19%.

The authors then set out to determine, through histological reexamination, the number of missed melanoma micrometastases in “negative” SLNB patients who developed metastatic melanoma at 5-year followup. Samples from an equal number of patients who did not develop metastases were also reexamined as controls. The researchers found missed melanoma in 11% of patients who developed metastases (0% in controls). Factors that may have contributed to missed melanoma on SLNB included variability in SLNB technique, variability in pathology, variability in the mechanism of spread, and aggressive tumours. The authors conclude that only a small proportion of SLN metastases are missed on histology and that clinicians should be guarded about long-term prognosis, given that nearly one-third of patients develop metastatic melanoma at 5-year followup despite negative SLNB.

**MELANOMA DETECTION**

Diagnostic advances in melanoma detection

Dr. Jason Rivers, Clinical Professor at the University of British Columbia, presented the wide and growing array of diagnostic technologies for melanoma, from traditional dermoscopy to digital dermoscopy and total body photography, multispectral imaging devices, spectrophotometric intracutaneous analysis, electrical bioimpedance spectroscopy, and laser Raman spectroscopy. Other technologies have been developed to assess gene expression consistent with melanoma (the Pigmented Lesion Assay and Noninvasive Genomic Detection or EGIR®, which has shown over 90% sensitivity and specificity). Teledermatology is being combined with different technologies to increase access to dermatologic expertise, and patients are being empowered to interact directly with experts using devices such as the Molescope® and other smartphone applications.

**PULMONARY METASTATECTOMY**

Clinical outcomes following pulmonary metastatectomy for melanoma: a population-based study

Dr. Carl Chauvin from Queen’s University is working to fill the gap in population-based studies of management, outcomes and prognostic factors for pulmonary melanoma metastasis resection, which is becoming favoured as a first-line treatment despite a paucity of information about its safety and effectiveness or even how widely the procedure is used. Recent studies have identified a number of predictors of survival among metastasectomy patients, including the number of pulmonary metastases, the presence of extrathoracic metastasis, the patient’s disease-free interval between primary and metastatic diagnosis, and the doubling time of the tumour. Pulmonary lesion size is quite understudied in the present literature.

The aim of the retrospective study Dr. Chauvin presented was to identify predictors of survival. It looked at lung resection procedure codes and pathology reports from all cases in Ontario between 2004 and 2012, compiling the study database by combining data from the Canadian Institute for Health Information database with pathology reports from the Ontario Cancer Registry and data from the Provincial Death Registry. A total of 99 patients were included. The most common procedure performed was a wedge resection; most patients had only one lesion resected, the
majority had lesions less than 2 cm in size, and most had negative margins. Metastatic lesion size and number of pulmonary lesions were most strongly associated with reduced survival, although only lesion size met statistical significance in the models employed.

Dr. Chauvin’s group found that pulmonary metastasectomy appears safe and effective in this population-based sample. There was no observed 60-day postoperative mortality. Furthermore, resection was associated with long-term overall survival (OS) for approximately 20% of the study population. Additionally, the authors found that pulmonary lesion size is an important predictor of survival for potential surgical candidates with pulmonary metastatic melanoma, and that size and margin status are strongly correlated.

Dr. Axel Hauschild, Professor of Dermatology at the University of Kiel, Germany, focused on patients with high-risk melanoma who are known to have higher recurrence rates and relatively poor survival. Dr. Hauschild reviewed the treatments and trials that have shaped today’s standard of care and looked ahead to what the future may hold. German recommendations in 2014 for stage II >2.0 mm tumour thickness and negative sentinel nodes involves discussion of low-dose interferon (IFN) alpha, 3 MIU thrice weekly for 18 months. Recommendations for stage IIc and III include either high- or low-dose IFN alpha. Pegylated IFN is not approved in Europe. He regards the best alternative at present as referral to clinical trials.

Dr. Hauschild then reviewed recent trials involving patients with intermediate and high-risk melanoma. The study ECOG 1697 compared adjuvant IFN alfa-2b post-surgery to observation. No significant different in 5-year OS was found. The AVAST-M trial compared bevacizumab to observation and again found no OS benefit. The immune checkpoint inhibitor ipilimumab 10 mg/kg was studied against placebo in a similar population in EORTC 18071/CA184-029, and recurrence-free survival (RFS) was found to be longer in the treatment group (46.5 vs 34.8 months); however, 5.5% of patients on ipilimumab experienced grade 4 adverse events, including 5 deaths (1.1%), and 90.4% experienced adverse events of any grade. Ipilimumab is also being studied in the US Intergroup E1609 phase III trial, which completed accrual in summer 2014, at both the 10 mg/kg dose and at a lower 3 mg/kg dose. The phase III DERMA study is investigating adjuvant immunotherapy with MAGE-A3 in patients with lymph node involvement. Recruitment was completed in 2011, and unpublished data showed a failure to improve RFS in the first analysis of the primary endpoint.

Looking ahead to possible standards of care in 2018, Dr. Hauschild presented currently activated and ongoing trials of adjuvant treatment for high-risk melanoma. Pegylated IFN is being assessed in ulcerated primary melanoma. The phase III trial of combined dabrafenib and trametinib in BRAF V600-positive melanoma patients was stopped early after showing an OS benefit compared to vemurafenib. Two adjuvant studies of pembrolizumab vs IFN alpha in stage Iib-c and vs observation in stage Ia-c melanoma are currently underway, and a nivolumab trial is planned for 2015. Prolongation of disease-free survival (DFS) and OS are the aims of almost all adjuvant trials at the moment. For the moment, outside of clinical trials, Dr. Hauschild recommended discussing with patients existing treatment options (low-dose and high-dose interferon) and a “wait and see” approach with regular follow-ups.

**ADVANCED MELANOMA**

The role of neoadjuvant therapy in resectable advanced melanoma

Dr. Merrick Ross, Professor of Surgical Oncology at the University of Texas MD Anderson Cancer Center in Houston, provided a talk on the new landscape of advanced melanoma, with recent approval of BRAF and MEK inhibitors and checkpoint blockade for unresectable stage III and stage IV disease, as well as the recently reported randomized trial of oncolytic immunotherapy (T-VEC). The spectrum of advanced disease includes nodal disease (stage IIIb/c), limited local/satellite/in-transit metastases, and resectable stage IV disease. Dr. Ross specified that the definition of unresectable can include cases where resection is technically impossible, but also cases where it is feasible but offers no meaningful benefit in long-term survival and regional disease control.

He described the goals of management as durable local and regional control to maximize long-term survival, provide palliation and minimize morbidity, as well as reduce the risk for distant failure, and emphasized the need to assess the risks and benefits of the various modalities in this context.

Despite 6 new pharmacologic therapies approved in the last 2 years, none has yet shown response rates that are both high and durable. Dr. Merrick saw a continued role for surgery, noting that long-term survival after complete surgical resection has been observed: SWOG S9430 showed 31% OS at 4 years in patients who were completely resected. He also pointed to the therapeutic polyvalent melanoma vaccine Canvaxin, which showed 40% 5-year survival in patients with 2 sites, 5 nodules, complete resection and no brain metastases within 6 months of surgery.

Important prognostic factors in the stage IV population include the number of sites and nodules, the tumour doubling time and the disease-free interval. The standard of care for stage III and IV melanoma is therefore upfront surgery, selective use of adjuvant nodal basin irradiation, and adjuvant interferon or clinical trial. However, questions persist on a number of fronts, including the definition of resectability and the appropriate time to start BRAF inhibitors, ipilimumab or anti-PD-1 therapy.

Dr. Ross noted limitations of current adjuvant approaches: only a relatively small fraction of patients benefit and there
is significant toxicity, and no good pretherapy markers of response for BRAF wild-type are available. As well, he stressed that phase III randomized trials are too long and expensive, and involve a patient population that is too heterogeneous, resulting in doubts that a negative result actually means the therapy is ineffective.

He presented an alternative approach that would see neoadjuvant systemic therapy provided first, and surgery performed in patients whose disease is stable, responsive to therapy, or even locally progressive without distant metastases. The advantage would be to have an in situ marker for response and greater likelihood of surgery being effective when tumours respond to systemic therapy. It would also allow tissue samples to be studied pre and post treatment to identify predictors of response and resistance, and biologic correlates and response rates could then serve as endpoints for shorter and smaller randomized phase II and single-arm biomarker trials.

Dr. Ross discussed new and upcoming trials designed on this model: the randomized phase II study of dabrafenib/trametinib vs standard of care (surgery + adjuvant); the ipilimumab + nivolumab vs nivolumab alone trial, which has been approved and funded will open by the end of year; the pembrolizumab + pegylated IFN vs pembrolizumab alone trial, which is in development; and the neoadjuvant T-VEC trial, which will open soon. He considered that combinatorial strategies are rational and offer the promise of future advancement.

He emphasized the necessity of multidisciplinary input, and identified essential participants in a multidisciplinary conference as the pathologist, diagnostic radiologist, medical, surgical, radiation and dermatologic oncologists, and clinical trial research staff. He also stressed the importance of introducing summaries of pertinent patient data.

WHO GETS IMMUNOTHERAPY?
Immunotherapy in stage III melanoma: a population-based analysis of demographic and health system factors using the National Cancer Registry database

Dr. Dayna Miyashiro, from the Creighton University School of Medicine, presented this analysis of access to immunotherapy in the US. Adjuvant immunotherapy with IFN is the only approved treatment option for stage III melanoma. Relapse-free survival benefit and minimal OS benefit are supported by various trials, meta-analyses and guidelines.

The National Cancer Registry was established in 1989 and serves as a comprehensive clinical surveillance resource for cancer care in the US. It includes data from more than 1,500 cancer programs, representing about 70% of all newly diagnosed cancer cases. This study included all cases of stage III melanoma diagnosed between 2000 and 2011 (n=38,287), including 9,029 patients who received immunotherapy. The team evaluated patient demographics and clinical characteristics and found that age, race, gender, annual household income, insurance type and Charlson comorbidity score all affected the delivery of immunotherapy.

While 44% of patients under 20 years of age received immunotherapy, this dropped to 22.31% in patients aged 60 to 69 and just 8.82% in patients aged 70 to 79. With regards to insurance type, while only 9.8% of patients covered by Medicare received immunotherapy, the figure was 29.22% for patients on Medicaid and 31.94% for patients with private insurance. Only 11.3% of those with 2 or more comorbidities received immunotherapy vs 25.33% of those with none. The researchers concluded that in patients with stage III melanoma diagnosed between 2000 and 2011, demographic and health system factors played a key role in the likelihood of receiving adjuvant immunotherapy. They advised that better measures be taken to provide more access to treatment for these groups and more studies are required to assess the impact of these combinations of factors on patient survival and outcomes.

TARGETED THERAPY
A genetic approach to melanoma: targeted therapy for the non-BRAF V600 mutant melanoma patient

Dr. Jeff Sosman, Director, Melanoma & Tumor Immunotherapy Program, Vanderbilt-Ingram Cancer Center in Nashville, stressed that melanoma is a genetically heterogeneous disease and oncogenic driver mutations are present in most tumours. These mutations have clinical implications. Dr. Sosman touched on the rapid evolution in understanding the molecular biology of melanoma, from the identification of BRAF mutations in 2002, to whole-genome sequencing in 2012 and melanoma being added to the Cancer Genome Project (TCGA) in 2013. The most common mutations to date are BRAF and NRAS; where these are wild-type, mutations in MAPK genes and cell cycle regulators are frequently observed. As new mutations are identified, research is needed to determine their prognostic and therapeutic significance. In cutaneous melanoma there is a high prevalence of MAPK pathway mutations and concurrent activation of multiple pathways in a subset of patients.

Dr. Sosman is investigating sensitivity to MEK inhibition in the non-BRAF V600 mutations. He described the design of a phase II 2-arm study designed to determine the activity and safety of the MEK inhibitor trametinib in subjects with melanoma harbouring mutations in BRAF at locations other than codon 600, or BRAF fusions. Another ongoing phase Ib/II study of LEE011 (an oral selective inhibitor of CDK4/6) in combination with binimetinib (an oral selective MEK1/2 inhibitor) in patients with advanced NRAS-mutant melanoma showed early encouraging clinical activity. A third phase I/II study is beginning as a dose escalation monotherapy study of trametinib and palbociclib, after which the effect of the combination of these drugs on tumour biomarkers, safety and anticancer activity will be evaluated in subjects with BRAF V600 wild-type and NRAS wild-type or mutant melanoma. A randomized phase II study will then look at the relative contribution of palbociclib to the combination in subjects with BRAF V600 wild-type.
The conference also included 3 sponsored symposia. At a symposium sponsored by Merck, Dr. Marcus Butler, medical oncologist at the Princess Margaret Cancer Centre, presented on how the new anti-PD-1/PD-L1 class of agents is likely to be integrated into clinical practice. He discussed the role of PD-1 signalling pathway inhibitors in cancer treatment and the breakthrough efficacy of this new class of agents relative to existing therapies. A Bristol-Myers Squibb sponsored symposium had Dr. David Hogg from the University of Toronto and Dr. Xinni Song from the University of Ottawa discuss the appropriate sequencing of immunotherapies and targeted treatments in metastatic melanoma and revisit the optimal management of toxicities seen with immunooncology agents. A session sponsored by Hoffman-La Roche on the evaluation of treatment for advanced melanoma underscored the importance of early detection and patient stratification through molecular profiling. The importance of multidisciplinary teams in the management of difficult skin cancers was emphasized in another session, at which Dr. Merrick Ross from the MD Anderson Cancer Center stressed the following points:

- Multidisciplinary input is critical.
- Initial therapy should not be recommended in isolation, but as part of a comprehensive plan.
- Reaching a consensus is the goal — patients should know that everyone is on the same page.
- The multidisciplinary conference is a good forum for trainee education and enables differences to be resolved respectfully. It also provides an opportunity to establish evidence based treatment guidelines.

These are optimistic times in melanoma and we look forward to mature data from these important trials over the next 2 years.

References

The World Congress of Dermatology is being held in Vancouver, June 8–13, 2015.