



## THE CANADIAN MELANOMA CONFERENCE

February 22 to 24, 2018, Banff, Alberta

## THE SAN ANTONIO BREAST CANCER SYMPOSIUM

December 5 to 9, 2017, San Antonio, Texas

## THE CANADIAN ASSOCIATION OF MEDICAL ONCOLOGY ANNUAL MEETING

April 26, 2018, Toronto

### Report from the Canadian Melanoma Conference

The 12<sup>th</sup> annual Canadian Melanoma Conference was held in Banff Alberta at the end of February, chaired by Dr. Scott Ernst, Professor at the University of Western Ontario. Videos from many of the conference presentations are now available on the Oncology Education website at: [www.oncologyeducation.com](http://www.oncologyeducation.com).

Below, we present summaries of some of the outstanding presentations that describe the evolving understanding of cutaneous melanoma and its treatment.

## Adjuvant therapy in high-risk melanoma

**Dr. Jason Luke, MD, FACP**, Assistant Professor of Medicine, University of Chicago Medicine & Biological Sciences, Chicago, Illinois

At the Canadian Melanoma Conference, Dr. Luke reviewed melanoma diagnosis and staging, discussed evolving paradigms in risk stratification, and outlined historical, current and future treatment approaches for adjuvant and neoadjuvant therapy.

Melanoma incidence continues to rise, but mortality associated with the disease is going down. In the US, deaths from cutaneous melanoma have fallen below 10,000 a year.<sup>1</sup>

### DEFINING MELANOMA: THE STAGING DILEMMA

The current 8<sup>th</sup> edition of American Joint Committee on Cancer (AJCC) staging<sup>2</sup> highlights the difference in outcomes expected in patients with stage IIIa and IIIb melanoma. Patients with stage IIIa do about as well as patients with stage IIa and IIb melanoma, and there is an active debate in the field about whether to treat these patients with adjuvant therapy. “Some people in our field advocate quite strongly that these patients have a very low risk of recurrence, and that we might be overtreating them,” Dr. Luke pointed out, cautioning that it was still too early to know with certainty. The significant change from the 7<sup>th</sup> to the 8<sup>th</sup> edition of AJCC has generated some controversy, as ground-breaking clinical trials were based on the 7<sup>th</sup> edi-

tion, and the change makes it more difficult to see how those trials apply to the new patient classification.

Another change has been shifting views toward a standard of care involving sentinel lymph node biopsy, which might have some therapeutic effect, but away from completion lymph node dissection, which does not appear to have a substantial impact on patient survival.<sup>3,4</sup> There is some difficulty in determining who might benefit from completion dissection, and surgeons are likely to continue with completion in patients with multiple nodes positive on sentinel node biopsy, but this change is likely to further complicate the staging system. Dr. Luke noted, “So we’re not even going to really get the information (required for staging) in the first place, because we’re not going to be doing completion dissection in most of these patients... The majority of stage III patients who come into a practice now are going to be stage IIIa.”

Alongside the staging classification changes, advances in molecular classification are also changing diagnostics and helping to determine which patients are likely to experience melanoma recurrence. A new test, Decision-DX (not Food and Drug Administration [FDA]-approved yet), is clinically available in the US and is starting to develop a fairly robust dataset. A recent presentation on its use in an older, stage I population found that the test performed better than senti-

nel lymph node biopsy at differentiating who was likely to have a recurrence. In the future, as further prospective data are available, clinicians may start incorporating gene expression into diagnosis and staging.

**ADJUVANT TREATMENT**

Dr. Luke then reviewed adjuvant trials leading to regulatory approval in the US up to 2017. Mocellin et al<sup>5</sup> looked at all interferon studies and concluded there was a survival benefit, but that it was slight and must be considered in the context of interferon’s toxicity. “I don’t think there’s any role for interferon anymore in the management of melanoma,” said Dr. Luke.

Ipilimumab was a leap forward, “although with some caveats,” Dr. Luke pointed out, “notably the toxicity associated with the 10 mg/kg dose.” The study by Eggermont et al<sup>6</sup> showed about an absolute 10% improvement on relapse-free survival and overall survival (OS) at 5 years. This was useful in patients with stage IIIc melanoma. However, treatment-related adverse events (AEs) occurred in about 45% of patients; many were immune-related. Other studies<sup>7</sup> raised questions about dosing, with 3 mg/kg appearing to provide relapse-free survival equal to the 10 mg/kg dose, with fewer adverse events. “The issue has become less important with the availability of nivolumab,” Dr. Luke emphasized.

Compared to the situation in 2011, when the only options for metastatic disease were chemotherapy and interleukin-2 (and the latter only for fit patients), there is now a “smorgasbord” of agents to try (see **Table 1**). “We don’t really know which is best to do first, second and third,” states Dr. Luke, “and for some contemporary populations with metastatic disease the median survival rate right now is really unknown.” In each of the trials in metastatic disease, the OS was somewhere around 2 years, but there is little evidence about the additive impact of multiple therapies.

Dr. Luke then discussed the possibility of incorporating these agents from the metastatic setting into the adjuvant setting.

**Targeted therapies**

Combining BRAF and MEK inhibitors has been shown to be more effective and less toxic than monotherapy in metastatic disease, making it reasonable, according to Dr. Luke, to wonder whether it could work in the adjuvant setting to potentially cure more patients. He points out that the history of using targeted therapy in the adjuvant setting is not that great in other tumours, and cancer often recurred as soon as the drug was stopped. The COMBI-AD study randomized patients with stage IIIa–c disease to get either dabrafenib and trametinib or 2 matched placebos. Relapse-free survival was impressive with the combination, with 1-year survival of 88% vs 56% for placebo.<sup>8</sup> Of note, the benefit for stage IIIa patients was quite robust (whereas this group was not included in the nivolumab trial), and all disease stage subgroups benefited. Distant metastasis-free survival results also showed benefit from the combination. “...This data does reassure that we’re making a difference

**TABLE 1. Therapies for metastatic disease available in 2018**

<b>Targeted therapy</b>
- BRAF: dabrafenib + trametinib or vemurafenib + cobimetinib
- KIT: imatinib
- GNAQ/11, NRAS, NFI, MEK1: MEK inhibitor?
<b>Immunotherapy</b>
- ipilimumab (anti-CTLA-4 antibody)
- pembrolizumab (anti-PD-1 antibody)
- nivolumab (anti-PD-1 antibody)
- ipilimumab + nivolumab
<b>Virotherapy</b>
- talimogene laherparepvec (T-VEC; oncolytic modified herpesvirus)

CTLA-4: cytotoxic T-lymphocyte associated protein 4; PD-1: programmed cell death protein 1.

in terms of recurrences that would lead to the patient’s demise,” said Dr. Luke.

OS was a secondary endpoint in the study, and more time is needed to see the complete picture, but in the stage III population, there does appear to be a survival advantage with the BRAF and MEK inhibitor combination. The advantage increases over time: by 3 years, OS in the group receiving combination therapy was 86% vs 77% for those on placebo. Dr. Luke then looked at the types of treatment patients who experienced recurrence received after adjuvant combination therapy. He noted the greater use of radiotherapy in the population of patients who had been on the dabrafenib and trametinib combination, and considered that, if these patients had an isolated site of recurrence that was irradiated, they might regain long-term disease control or even cure. In terms of side effects, patients receiving the combination had considerable more grade 3 or 4 AEs (41% vs 14% in the placebo group) and 26% discontinued therapy due to AEs. Fever is the most frequent AE with the combination.

**Immunotherapy**

Our thinking around the mechanism by which immunotherapy works may need to be revisited, Dr. Luke believes. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) blockade is thought to have activity on mediating the activation step of the immune response, so it might enable global immunity that then could be active even in the context of micrometastatic disease. Alternatively, anti-programmed cell death protein 1 (PD-1) antibodies are thought to act in the tumour microenvironment, which might suggest a lower likelihood of activity in the adjuvant setting, given the lack of a visible tumour. “... So do they work by a different mechanism, or is it the case that this tumour microenvironmental niche does actually exist, even in the context of patients in the adjuvant setting?” asked Dr. Luke. In a trial of patients with high-risk resected stage IV disease and some stage III patients,<sup>9</sup> treatment with anti-PD-1 and nivolumab resulted in relapse-free survival and OS rates over 80%, with low toxicity. It suggested that anti-PD-1 could be effective in this role.

The Checkmate 209-238 Study<sup>10</sup> was a randomized phase 3 trial comparing nivolumab vs ipilimumab in patients with stage IIIB, IIIC or resected stage IV melanoma who were randomized 1:1 to either get nivolumab 3 mg/kg with ipilimumab placebo, or ipilimumab 10 mg/kg with nivolumab placebo, for a maximum treatment duration of 1 year. Recurrence-free survival showed a benefit at 12 months for nivolumab compared with ipilimumab, with a relapse-free survival rate of 71% vs 61%, and that has carried that out over time. “This data was pretty impressive for many of us in the field,” stated Dr. Luke. The benefit for adjuvant anti-PD-1 relative to CTLA-4 blockade was quite consistent between PD-L1-positive and -negative tumour types, emphasizing the need to look more closely at the tumour microenvironment. One-year OS in the PD-L1-positive population was 82% with nivolumab vs 74% with ipilimumab, and in the PD-L1-negative group, it was 64% with nivolumab against 54% with ipilimumab. Nivolumab also provided benefit across BRAF subgroups. Finally, safety results were better with nivolumab than ipilimumab.

In the US, anti-PD-1 is now approved, and BRAF/MEK inhibitors are likely to be approved very quickly. The National Comprehensive Cancer Network (NCCN) updated its guidelines very quickly after the European Society for Medical Oncology (ESMO) to say either of these approaches is reasonable. “The FDA approved nivolumab for all stage III melanoma, despite not having treated any stage IIIa patients in the relevant study,” Dr. Luke pointed out. “I presume that’s because they see where the field is going, and it’s just going to be impossible to sort out the stage III population adequately to know where to apply the drug.”

## THE FUTURE

Dr. Luke anticipates that all the agents that have been approved for metastatic disease will now move forward to also be used as adjuvant, neoadjuvant and potentially primary therapy in stage III melanoma. Studies are underway with various combinations and hope to answer new questions about the potential of treating in this way prior to surgery: “Could we eradicate the disease, or at least the metastatic disease, such that when we resect a tumour, the patient truly is cured?” asks Dr. Luke.

New agents are also on the horizon, and Dr. Luke highlighted inhibitors of indoleamine dioxygenase-1 (IDO-1), another interferon gamma-linked molecule (like PD-L1) in the tumour microenvironment currently in phase 3 clinical trials. IDO inhibitors may be appropriate in the adjuvant setting to improve cure rates without increasing toxicity.

## NEOADJUVANT THERAPY

### Early trials

Dr. Luke pointed to 4 small studies underway comparing neoadjuvant treatment prior to surgery to postsurgical adjuvant treatment in unresectable or resectable stage III/IV melanoma: the REDUCTOR study<sup>11</sup> of 8 weeks of neo-

adjuvant treatment with dabrafenib and trametinib in unresectable stage III and stage IV melanoma; the MD Anderson Combi-Neo study<sup>12</sup> of the same combination in resectable stage III/IV, comparing presurgical to postsurgical treatment; the MIA Neo-Combi trial<sup>13</sup> of neoadjuvant plus adjuvant treatment with dabrafenib and trametinib in resectable stage IIIB and IIIC melanoma; and the OpACIN trial of ipilimumab and nivolumab in palpable stage III melanoma<sup>14</sup>, comparing surgery plus adjuvant therapy to 6 weeks of neoadjuvant therapy prior to surgery plus 6 weeks of adjuvant therapy afterwards. Toxicity is considerable, with 90% of patients in the OpACIN trial experiencing grade 3 or 4 adverse events with neoadjuvant therapy, though all were able to undergo surgery. While the numbers are small, the approach appears promising for achieving pathologic complete response.

## New agents

Talimogene laherparepvec (T-VEC) is a modified oncolytic herpesvirus that’s been attenuated so it can be injected directly into the tumour to drive local infiltration by T cells, followed by initiation of pembrolizumab. Data published by Antoni Ribas in Cell<sup>15</sup> showed that a subset of patients with advanced cancer had a baseline level of T cell infiltrate, and that T-VEC followed by pembrolizumab produced a massive influx of T cells. “In the adjuvant setting, that could really be a powerful way to eradicate both the local tumour and potentially activate a systemic immune response, hopefully to cure patients over a long period of time,” said Dr. Luke.

Dr. Luke is working on a phase 3 study of anti-PD-1 vs placebo in the stage II population (KEYNOTE-716), where patients would receive treatment for 1 year. One rationale for the study, despite concerns about costs of expanding use of these therapies to earlier-stage patients, is that this population faces much higher recurrence and death rates than might be expected. “The vast majority of stage IIb and IIc disease have somewhere between a 20% and 50% risk of recurrence,” noted Dr. Luke. “I really do think if a therapy is not toxic, we have an obligation to investigate it.”

In conclusion, as melanoma incidence continues to rise, it highlights the need for risk factor modification, heightened dermatologic screening, and identifying who is likely to have recurrence. In terms of surgical paradigms, the current 8<sup>th</sup> edition of the AJCC has changed melanoma diagnostic staging and risk stratification. Adjuvant therapy is now BRAF-MEK or PD-1 in stage III disease in the US at least, maybe soon here in Canada and elsewhere. Dr. Luke argues there is really no future for adjuvant ipilimumab, or at least not as monotherapy. Finally, major advances in metastatic melanoma are coming to the adjuvant and neoadjuvant paradigms. Dr. Luke concludes, “By this I mean the next few years, not a decade from now.”

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