Systemic Treatment Options for Metastatic Melanoma in New Zealand in 2015

In 2015, the only currently funded therapy in New Zealand for advanced melanoma is the cytotoxic agent dacarbazine, which is cheap and well-tolerated but melanoma experts consider this treatment to be futile and obsolete. It has been replaced in standard treatment algorithms by the BRAF and MEK targeted agents and the immunotherapy treatments pembrolizumab, nivolumab and ipilimumab, typically given sequentially. The view of international experts attending the Melanoma Summit in November was that if only a single drug were to be funded in New Zealand, they would recommend pembrolizumab (KEYTRUDA), which has the highest response rate of the currently available agents (and is possibly a cure for some patients) with acceptable toxicity.

A further disadvantage for New Zealand patients with metastatic melanoma is a paucity of clinical trials, which in other countries provides an important access route to effective therapies.

The following data are provided to support these conclusions:

- Dacarbazine chemotherapy
  - 3-weekly IV 30 min infusion. Funded. Cheap. Generally easy to give and tolerate but poor response rates (10-15%). Palliative. No survival benefit.
- Other chemotherapy drugs (e.g., carboplatin and paclitaxel) can be used but more toxic and no more effective than single agent dacarbazine
- Interferon
  - Marginally better response rates than chemotherapy but toxic with lots of side effects. Funded but rarely used in NZ
- Targeted therapy with BRAF and MEK inhibitors
  - Oral agents. Work best when given in combination (but can be used as single agents)
  - Only helpful in melanoma that expresses the BRAF mutation (approximately 30-40% of melanoma cases in NZ)
  - Work quickly with good response rates (approximately 60-70%) but duration of response generally less than one year. BRAF monotherapy and combination BRAF and MEK inhibitor therapy improves overall survival for advanced melanoma patients in numerous phase IIII clinical trials, but remains palliative in nature. These treatments are considered standard of care internationally.
  - Previously available on compassionate access, until July 2015
  - Now registered but not PHARMAC funded; therefore all new patients must receive this in the private setting so all need to pay private overheads.
  - Cost approximately $20,000 per month
- Immunotherapy with checkpoint inhibitors:
  - Ipilimumab (anti-CTLA-4 antibody). Unfunded, therefore can't be administered in a public hospital so also need to pay private overheads. Given IV over 90 minutes every 3 weeks. Costs approximately $40,000 per

dose with a recommended course being 4 doses. A minority of patients develop significant immune-related toxicity. Response rates approximately 20% but duration of response and overall survival data measures in these patients is very impressive, and likely represent a cure for the minority.

- Anti-PD-1 antibodies: pembrolizumab and nivolumab. These are showing dramatic results. Appear to be more effective than ipilimumab with response rates approximately 30-40% with less toxicity. More importantly they are also demonstrating significant survival benefit in patients with metastatic melanoma, with the latest phase 3 data for pembrolizumab showing an unprecedented one-year overall survival rate of 74%.
- Both are given IV over approximately 30 minutes (pembrolizumab every 3 weeks and nivolumab every 2 weeks).
- Pembrolizumab is now registered (since Sept 2015) but not funded by PHARMAC. Costs approximately $20,000 per dose (including private overheads). Recommended treatment course is for 2 years (as long as tolerated and is working) so even with a cost-share scheme (that the drug company currently offers) still easily over $100,000 per year.
- Nivolumab not registered in NZ. There is a compassionate access programme BUT requires patients to have received ipilimumab first which is not funded
- International practice is already moving toward combination ipilimumab and PD-1 inhibitor treatment.

- Clinical trials (available Wellington Blood and Cancer Centre) and some other centres in New Zealand)
  - MELVAC phase II vaccine study (collaboration with Malaghan institute. For patients with high-risk resected melanoma. Immune rather than clinical endpoints.
  - BGB phase I study. For solid tumours (not just melanoma) expressing BRAF mutation. Testing a novel 2nd generation BRAF/EGFR inhibitor (oral medication). Other recruiting sites include oncology centres in Melbourne.
  - Adjuvant pembrolizumab versus placebo phase III international study in patients with resected stage III melanoma. Five centres in New Zealand are part of this.

25 November 2015