Is Keytruda for advanced melanoma cost-effective? Applying the BODE3 rapid cost effectiveness calculator

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Keytruda, or pembrolizumab, is a new immune inhibitor drug that appears to have pronounced effectiveness in slowing – even reversing – disease progression in patients with advanced melanoma. It has received much media attention in recent months, and even calls from politicians to over-rule the PHARMAC process (currently PHARMAC do not recommend funding). In this blog I apply our BODE^3 rapid cost-effectiveness calculator, and find that Keytruda may well be (just) cost-effective – but with huge uncertainty, and variably by age. This blog closely reflects a Radio New Zealand interview with Wallace Chapman last Sunday.

Keytruda, or pembrolizumab, is a new immune inhibitor that appears to have pronounced effectiveness in slowing – even reversing – disease progression in patients with advanced melanoma. The evidence base consists of trials published in the major journals: NEJM, Lancet and Lancet Oncology. Briefly, pembrolizumab appears to delay (substantially) disease progression in about a third of patients. There is also about a third lower mortality rate. And the adverse effect profile is better than Ipilimumab – the current 'best' treatment (that is not funded in NZ either). The evidence on the effectiveness of pembrolizumab (Keytruda) is mostly for patients either failing on ipilimumab, or compared to ipilimumab – which does make an analysis of likely cost-effectiveness in the NZ setting a bit tricky, as our comparator would be yet another drug: dacarbazine.

PHARMAC have considered pembrolizumab most recently in November 2015. Whilst noting the promise of the drug, they considered the uncertainty too great for a strong recommendation to fund. In particular, some of the data from earlier trials (where long-term follow-up should be done) has not been provided, and in the more recent trials that long-term data on survival is simply not there yet. But, most importantly, pembrolizumab is expensive (maybe about NZ$200,000 per course). And there are other similar drugs coming on tap soon that may be cheaper.

So what might the cost-effectiveness be? In our BODE^3 Programme, we have harnessed the high quality linked health data in NZ to create some online calculators. One allows rapid cost-effectiveness analyses of a treatment for a cancer with pre-populated data (from us) on survival, costs etc – but is not specific to cancer stage. Here we want to look at advanced, or 'distant stage', melanoma. So we use a more generic calculator, which still has expected population (i.e. non-diseased) mortality and morbidity, and health system costs, 'behind the scenes', but requires us to input the cancer and treatment specific data. Namely:

- The calculator works through changes in mortality or survival. So we first input that advanced melanoma has a five-year relative survival of about 15%.
- We then input health system costs for advanced melanoma (ignoring pembrolizumab for now). Previous work we have done suggests about $10,000 in the first year of diagnosis (if not within a year of death; this may be an underestimate for advanced cancer if major surgery is required – but does not make too much difference for our analyses); about $2000 a year if in remission (and not in the first year of diagnosis, or last year of life); and about $40,000 if in the last year of life and dying of melanoma.
- Next, select the type of person – in this case I chose a 65 year old female with advanced melanoma to start with.
- Finally – and by far most importantly – input the treatment cost ($200,000) and treatment effect. Regarding effect, the trials report about a 30% reduction in mortality rate with pembrolizumab – or a rate ratio of 0.7.

So what result does our online calculator spit out? That the cost-effectiveness is about $108,000 – call it $100,000 – per quality-adjusted life-year (QALY) gained. That is, $100,000 that we – the tax-payer – spend to gain a full healthy life year. Is this "cost-effective"? Should we fund it? This all depends on how much funding is available to reallocate in a given year, and other considerations (e.g. equity, is the disease rare, etc). However, for now let's focus on just cost-effectiveness. As a very rough rule of thumb, a society might use its GDP per capita as a threshold for funding – if it costs more than $45,000 per QALY gained, then we in NZ may decide not to fund it. So at this point, pembrolizumab would get the thumbs down.

However, the above evidence on effectiveness was for a trial comparing Pembrolizumab with Ipilimumab; Ipilimumab is not current or funded practice in NZ, and the health gains for pembrolizumab versus dacarbazine (current practice in NZ) would therefore probably be somewhat greater – let's assume a 40% reduction in mortality rate (which appears about the same as used by a group in the UK City of Sheffield in a study addressing the pembrolizumab versus dacarbazine or best supportive care comparator). Second, PHARMAC is incredibly good at hard bargaining to obtain discounted prices from the pharmaceutical industry, so let's assume the pembrolizumab price for a course is $130,000.

What happens now? The cost effectiveness using our calculator is $54,000 per QALY gained for a 65 year old woman (see the screenshot of the calculator below). At this point, one has to say that more modelling – purpose built – is required. And we really need the data from long-term follow-up of the trials. That is, this is a hard place for PHARMAC to be in!

Baseline Parameters	
5 yr RSR	15%
Disease Cost	
First year of diagnosis	$ 10,000
Last year of life	$ 40,000
Remission	$ 2,000
Disutilities	
First year of diagnosis	0.1
Last year of life	0.4
Remission	0.01

Heterogeneity	
Sex	Female
Age	65

Model Structure	
Discount rate	3%
Annual decline in BMR	2%
CE Threshold	$ 45,000

Intervention	
Effect size (HR)	0.6
Intervention Cost	
First year	$ 130,000
Second year	$ 5,000

RESULTS

	QALYs	Costs	Incr QALY	Incr Costs	ICER
Comparator	2.7	$ 52,369	**0.00**	**0**	**0**
Intervention	5.0	$ 174,438	**2.27**	**$ 122,069**	**$ 53,794**

The above scenario is the major focus of an interview between Wallace Chapman and myself on Radio NZ. Just before leaving the calculator, it is important to note that cost-effectiveness can vary enormously by age, as older people have less to gain because of higher competing mortality risk. Jimmy Carter, past president of the USA, has recently just received pembrolizumab – and has benefited with receding brain metastases. However, before giving the treatment, and if he lived in NZ, we could use the above calculator and input 85 year old male – the cost effectiveness is $120,000 per QALY gained. Age matters.

So what should NZ do? It is interesting to note that Minister of Health Jonathan Coleman just last week admitted that a previous government had got it wrong with the drug Herceptin, and should not have intervened seven years ago to over-rule PHARMAC. I agree. PHARMAC has a thorough and rational process for prioritising its limited funds. Nevertheless, it is proper and right to challenge PHARMAC when appropriate, and for the analyses to be updated as new data are released. But in general, to not respect the PHARMAC process is probably unwise. Clearly new data on melanoma treatments will soon become available in coming months to years – and PHARMAC should closely look at this issue again. When it does, it would be great if it also made comparisons with the cost-effectiveness of primary prevention such as promoting hat use and sun-block in school children.

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