Melanoma Research and Therapy Special Interest Group meeting

Highlights and recommendations

Background

The fourth meeting of the Melanoma Research and Therapy Special Interest Group was held at Ko Awatea, Middlemore Hospital on Friday 14 June 2019. Topics were:

- **Clinical trials in New Zealand:** How can we improve the number of trials in New Zealand and the access to those trials?
- **Audit of immune checkpoint inhibitor data:** How does New Zealand coordinate auditing and standardisation of outcomes across DHBs? How can we draw DHBs together to reach similar outcomes and what audit resources could be used to support this work?

The meeting was co-chaired by Professor Mike Eccles and Dr Jody Jordan.

Summary of actions and recommendations

The following will be recommended to the MelNet Executive Committee to consider:

1. Continue discussions with Ministry of Health about consistency between ethics committees (led by NZHR)
2. Implement a Memorandum of Understanding between NZHR and MelNet, identifying opportunities to collaborate on advocacy and lobbying initiatives.
3. Liaise with Melanoma Institute of Australia to understand more about their clinical database.
4. Facilitate a support structure (including a database of specialists) for those working with immunotherapy treatments and toxicities.
5. A follow up meeting should be held in approximately six months-time to report on progress and agree next steps.

Acknowledgements

MelNet would like to thank the three presenters and all those who took the time out of their busy schedules to attend this meeting. We would also like to acknowledge MSD NZ Ltd for their support of this meeting and their ongoing support of MelNet.

Topic 1: Clinical trials in New Zealand

Presentation from Chris Higgins, Chief Executive New Zealanders for Health Research. This covered:

a. New Zealanders for Health Research (NZHR) role and objectives

New Zealanders for Health Research is a public education and advocacy alliance committed to making health research a higher priority in New Zealand.

b. Clinical trial milestones

- *Health Committee review of clinical trials 2011*
- *Health Research Strategy 2017*
- *Government R&D Investment Strategy 2018*
- *Therapeutic Products Legislation*

c. New Zealand clinical trials trends 2008 - 2021

- Data from "Clinical Trials Landscape in New Zealand 2006 – 2015" projected the number of clinical trials in NZ to increase until 2021, while HDEC data projected a plateau.
- Industry funded/sponsored trials are projected to increase (based on data from "Clinical Trials Landscape in New Zealand 2006 – 2015" and HDEC).
- Drug trials are expected to plateau (based on HDEC and SCOTT data).
- International pharma funded trials are projected to decline (based on international Pharma data obtained from US Trial registry, European registry and NZCTR).
- The New Zealand percentage of New Zealand and Australia total industry funded trials is expected to plateau.
- Hospital sponsored trials are expected to decline (based on HDEC and ANZCT registry data).
- Ringfenced Government investment in health research is projected to remain static until 2031.

d. Feedback from Roy Morgan Research NZHR annual public opinion poll

This poll collates the responses of 500 New Zealanders who make up a representative cross-section of the country by geography, age, gender and ethnicity. The margin of error is 3.5%. It is unknown whether respondents have medical conditions.

Responses from 2018 and 2019 poll relevant to clinical trials	2018 (%)	2019 (%)
Asked to participate in trials	14	11
Ever participated in trials	8	7
Currently participating in trials	2	0
Important to be able to participate	79	81
Ability to participate as important as giving blood	62	67
More opportunities to participate	66	71
Willing to participate in a trial if had a condition it might be able to treat	83	87

e. NZHR lobbying and advocacy

- Full implementation of the recommendations from the 2011 Health Committee CT enquiry.
- Health research as a key enabler of health outcomes in the design/redesign of New Zealand's health and disability system.
- Full resourcing of the implementation of New Zealand Health Research Strategy.
- The Ministry of Health through its contracting and commissioning processes mandates health and medical research as a core requirement of all publicly funded health service providers.

- Government ringfenced investment in health research be increased by 18.6% per year through to 2027.
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- Supporting New Zealand's health outcomes objectives, innovation and investment in health research and development of new therapies and interventions should be additional objectives for the proposed therapeutic products regime.
- Barriers to clinical trials should not be introduced into new therapeutic products legislation.
- R&D tax incentive increased from 15% to 35% of eligible expenditure.
- Discussion about clinical trials being a routine aspect of patient care as part of the informed consent process
- ACC coverage to be extended to harm resulting from commercially funded clinical trials

Mike Eccles shared a list of current melanoma trials in New Zealand.

Discussion

The group discussed:

- the need for standardisation between ethics committees or a multi-site or national ethics approval process. It was noted that:
    - different boards have different approaches and feedback differs between Committees
    - there are significant time delays in approval processes
    - there is often a lesser outcome if the primary investigator is unavailable in person or by phone.
- equitability of patient access to trials – both location and ethnicity. It was noted that:
    - in Hawke's Bay patients must travel to Palmerston North (Mid Central DHB) to participate in trials or may not be eligible because they aren't based in Palmerston North
    - rural patients do not have the same opportunities and often do not receive support for travel costs
    - in Christchurch some trials allow drugs to be couriered to rural patients
    - tele-trials are being used in Australia (NSW and Victoria) in order to increase spread
    - a national standard would make expanding to rural locations easier
    - MSD will fund travel across DHBs for trials.
- adequacy of communications to patients about the availability of and access to trials
    - Cancer Trials NZ provided results from their "Insight Study" which looked at recruitment barriers for cancer patients. Results showed:
        - 10% thought a clinical trial was a last resort
        - 44% were interested in being on a trial where they would have to travel
        - 11% would consider relocating for a trial
        - 19% had been on a clinical trial
        - 86% would consider going on a trial
- the level of paperwork involved in trials in order to satisfy sponsor requirements. It was noted that:
    - other countries have more routine employment of research fellows. Having fixed research fellow positions in DHBs would make a difference and stop investigator burnout
    - the Auckland Phase I trials unit and Auckland trials unit have their own resources to assist with paperwork however there is a high "burnout" of these staff also.
- opportunities for collaboration between NZHR and MelNet.

Actions and recommendations

1. Continue discussions with Ministry of Health about consistency of ethics committees (led by NZHR).
2. Progress the development of a Memorandum of Understanding between NZHR and MelNet, identifying opportunities for collaboration on advocacy and lobbying initiatives.

Topic 2: Immune checkpoint inhibitors

Presentations from Mike McCrystal, Medical Oncologist Auckland DHB and Jody Jordan, Medical Oncologist HBDHB. These two presentations covered:

a. Background to immunotherapy treatment for melanoma in New Zealand

- Immunotherapy drugs were made available under set criteria from Pharmac in 2016. The criteria required patients to have:
  - metastatic stage III or IV melanoma
  - measurable disease defined by at least on CT or MRI lesion
  - not received prior anti PD-1 therapy
  - an ECOG status of 0 – 2.
- Around 30% of patients are intrinsically resistant to immunotherapy. Some patients have a small response and some have an incredibly positive response.
- There is an improved survival rate of 42% at four years.

b. **The Auckland/Bay of Plenty and Hawke's Bay experiences: retrospective review of patients diagnosed with metastatic melanoma and treated with at least one cycle of immunotherapy**

Auckland/Bay of plenty – patients between 1 July 2016 and 30 June 2017. Data provided by Dr Alistair Wickham. Hawke's Bay – patients between 1 July 2016 and 31 December 2018. Data collated by Toni Nieuwland.

Statistics

	Auckland/BoP	Hawke's Bay
Total patients	102	35
Age range	19 – 86 (median 68)	Age range: 22 - 88
Sex	67% male	63% male
BRAF mutation	41%	6 out of 9 patients tested
Brain metastases	23%	11.4%
Performance status		
0 – 1	75%	51%
2	21%	9%
3 – 4	5%	6%
0 – 1 and no BM	58%	Not recorded
Not recorded	-	34%

Outcomes

Results from both studies were similar to overseas literature and clinical trial data. They showed:

- Pembrolizumab and nivolumab had similar efficacy (Auckland study).
- Immunotherapy treatment is more effective when patients are well and ambulant.
- Responses were durable.
- Sometimes positive responses can take 6 – 12 weeks to show.

- Those with performance status >1 or brain metastases are less likely to derive benefit but responses, when obtained, are just as durable.
- Patients with underlying autoimmune disorders had poor response and high toxicity
- Ocular melanoma did not respond well to treatment.

Toxicity and deaths

- Toxicity is greater than expected – approximately 15% will get significant side effects.
- Very few have fatal complications, but toxicity can be derailing.
- Sometimes side effects can be treated easily and early with steroids.
- Toxicity can occur after the discontinuation of drugs

	Auckland/Bay of Plenty	Hawke's Bay
Discontinued early due to toxicity	7 Skin: 2 Colitis: 2 Transverse myelitis: 1 Pneumonitis: 1 Arthritis: 1	Not reported
Toxicity that required intervention	Not reported	17 (48%) Rash: 9 Hypothyroidism 2 Diarrhoea: 5 Arthralgia 4
Deaths	0	18 Progressive disease: 12 ▪ 4 patients died after one dose Toxicity: 3 ▪ Liver haemorrhage ▪ Diarrhoea ▪ Sepsis Other: 3 ▪ Incarcerated inguinal hernia + progressive disease ▪ Septic foot after MVA ▪ Progression of CLL

Discussion

The group discussed:

- an audit of New Zealand data and the development of a central registry for side effects. It was noted that:
  - results are similar to literature so this may not be useful
  - Melanoma Institute of Australia has developed a clinical database for this purpose
  - any database would need to be automated, pulling data through the health system
  - Pharmac had been contacted to discuss this, but to date had not expressed an interest.
- MelNet facilitating the development of support structure for toxicities:

    - Attendees agreed a national database/network of specialists who can be contacted for advice when treating various side effects would be incredibly useful. These specialists would be those seeing immunotherapy side effects often and would need to be comfortable giving advice on what to do and when. The group noted that this would be particularly helpful for smaller centres who are not seeing the same number of immunotherapy cases as centres such as Auckland.
    - The group also discussed an online forum for case discussion, website resources and utilisation of existing meetings to create opportunities discussion.
- "Chemo holidays" – under Pharmac criteria you would not be funded to restart treatment if you choose to stop. Many patients are choosing to continue treatment after two years when they may not need to.

Actions and recommendations

1. Liaise with Melanoma Institute of Australia to understand more about their clinical database.
2. Establish a database of specialists for toxicities.
3. Investigate other possibilities to facilitate discussion about immunotherapy treatment and toxicities.