MelNet

Linking professionals in melanoma in New Zealand

Melanoma Research and Therapy Special Interest Group meeting

Highlights and recommendations

Background

This meeting of the Melanoma Research and Therapy Special Interest Group was held via Zoom on Friday 4 November 2022. Topics were:

- Improving access to clinical trials in New Zealand
- DNA and RNA signatures associated with melanoma resistance to Keytruda

Chaired by Dr Jody Jordan, the meeting was attended by 21 health professionals comprised of oncologists, researchers, nurses, surgeons, general practitioners and industry representatives.

Acknowledgements

MelNet would like to thank the presenters and all those who took the time out of their busy schedules to attend this meeting.

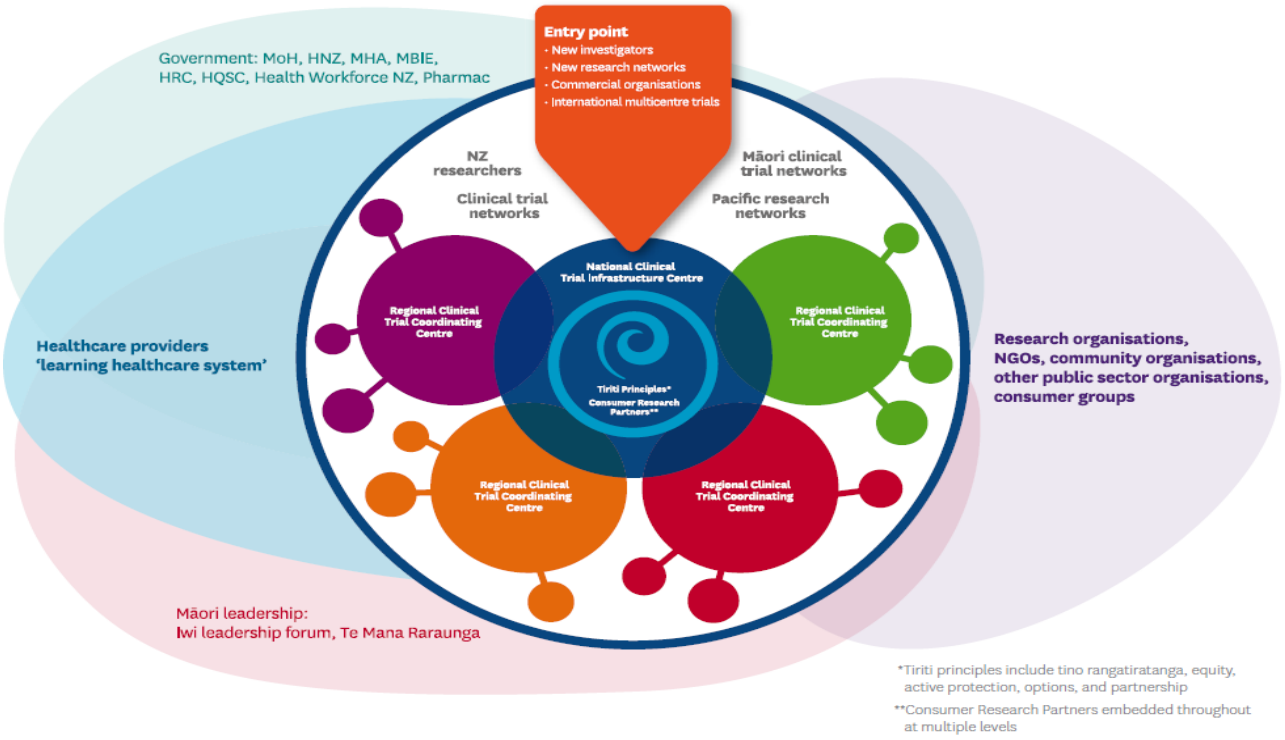
Topic 1: Improving access to clinical trials in New Zealand

Part A: Developing a national structure for clinical trials in NZ
Presentation from Michelle Ingram (Ministry of Health)

Presentation summary

- Responsibilities for research and innovation in the new health system (as approved by Ministers):
  - Ministry of Health sets strategic direction and commissions research to support policy
  - Te Aka Whai Ora provides co-governance with Ministry of Health to ensure that Te Tiriti is embedded in the strategic research agenda and priorities
  - Te Whatu Ora leads operations for conducting research in partnership with providers and communities
  - The Health Research Council is the lead funder of research and workforce capability and capacity.
- The 2017 Health Research Strategy is due to be refreshed – this review will be led by the Ministry of Health.
- From 1 July 2022, the Ministry of Health structure was extended to include a Research and Innovation Directorate with functions for analytics, research and evaluation, research and innovation system strategy, health surveys, and health economics.
- Research funded by MoH and Health Research Council in 2020 has provided evidence-based recommendations to inform the development of a sustainable and nationally coordinated approach to clinical trials in New Zealand. This comprehensive research project involved 58 focus groups, reviewed international clinical trial models, conducted a world café workshop to develop options and undertook a Delphi survey to identify critical priorities. Recommendations are centred on Te Tiriti principles and embedding research leadership and accountability in the system. (Report not yet publicly available).

- The proposed model has a nationally coordinated structure with regional centres which bring together different types of expertise and integrate with local communities:



- This will require strong joint leadership and significant financing for set up and ongoing costs.
- Ministry of Health, Te Whatu Ora and Te Aka Whai Ora are discussing how to jointly progress the development of this network within the health system. Te Aho o Te Kahu will input into the development process.

Questions and discussion

- **How will this system support commercial studies?**
  The Ministry is looking at overseas models to identify possible ways for industry to engage effectively with the health system.
- **Will clinical trials be available to everyone in this national based system?**
  Yes – this will take time but the intention is to enable those in areas without infrastructure and expertise to be able to access that.
- **Clinicians are currently set up to deliver services but little time, resource and priority is given to clinical trials. How will this be addressed?**
  The vision is for trials to become part of care provision, whereby patient and research data is integrated in the same system. The intention is to first strengthen the environment for what exists then look to address these types of barriers. Solutions to these tensions need to be developed collaboratively with clinicians.

Part B: Supporting equitable access to cancer trials in NZ
Presentation from Nisha Nair (Te Aho o Te Kahu)

Presentation summary

- Role of Te Aho o Te Kahu: Te Aho o Te Kahu provides national leadership and coordination across the cancer continuum with the purpose of delivering better cancer outcomes for New Zealanders. They are a standalone departmental agency reporting directly to the Minister of Health and are accountable for demonstrating

progress towards the goals in the Cancer Action Plan. They do not have any regulatory or commissioning powers.

- The challenges that contribute to low and inequitable access to cancer clinical trials are well-known. Part of the role of Te Aho o Te Kahu in the reformed health system is to support the Ministry of Health in developing national equitable clinical trials infrastructure by providing a cancer perspective to the work.
- Te Aho o Te Kahu is also funding the development of core infrastructure to support teletrials in New Zealand. This will be another way to address the problem of inequitable access to clinical trials, giving patients living outside major centres the chance to participate without having to travel. These have been successfully implemented in Australia.
- Other initiatives include using the Quality Performance Indicators programme to start signalling clinical trial participation as a core part of cancer care.
- Te Aho o Te Kahu also has longer-term plans for a cancer health informatics platform that aims to allow timely sharing of relevant and accurate cancer data. (https://teaho.govt.nz/reports/canshare). Over time, this would provide opportunities to better identify patients that are eligible for active clinical trials.

[Unfortunately due to external environmental factors Nisha was unable to complete her presentation. Some of these notes have been provided by Nisha post-meeting]

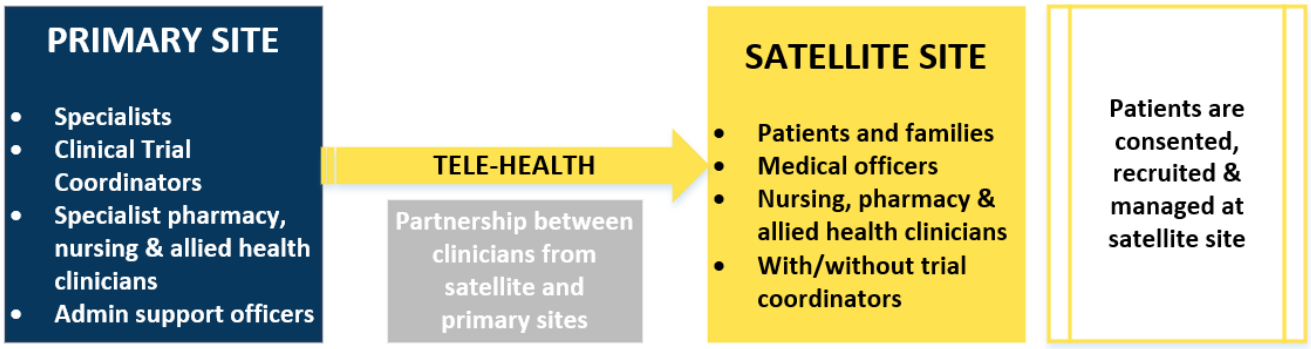
Part C: Bringing more melanoma clinical trials to NZ

Presentation from Gabrielle Byars (MASC Trials)

Presentation summary

- MASC Trials work collaboratively with over 2000 researchers across 11 countries to deliver clinical trials and related research that improve melanoma and skin cancer outcomes. They are funded by Cancer Australia (which gives access to additional services) with top up funding from industry.
- Membership is free and open to anyone with an interest in melanoma and skin cancer clinical research – visit www.masc.org.au/membership for more information.
- MASC Trials governance is supported by nine discipline-specific advisories. These advisories are forums for researchers, clinicians and consumers to share ideas, review research and offer feedback. New Zealand members are encouraged to join these advisories, and there is opportunity to extend representation of NZ patients with lived experience of melanoma and skin cancer.
- MASC Trials services include concept development, peer review, consumer review, budget build, grant development and trial management.
- Current recruiting trials include:
    - MelMarT-11 – this trial looks at survival for 1cm v 2cm excision margins for stage II melanoma with the aim of setting worldwide guidelines.
    - IMAGE – a randomized control trial looking at the effectiveness of surveillance photography for early detection. Recruitment for this trial is nearly complete.
    - GoTHAM and I-MAT – both look at treatment strategies to complement radiotherapy and surgery for Merkel Cell Carcinoma
    - Uveal registry – a global effort to collect data on the clinical features and history of uveal melanoma
- Start up trials include:
    - SOCRATES – this trial will analyse the increased risk to heart health in patients being treated with checkpoint inhibitors.
    - SiroSkin – this trial will look at chemoprevention treatment for facial squamous cell carcinoma in transplant recipients.
    - BETTER – this trial will look at immune checkpoint inhibitors with radiotherapy for the treatment of melanoma brain metastases.

- Clinical Oncology Society of Australia have developed a model for successfully delivering teletrials to regional, rural and remote patients.



Sabesan & Zalcberg, EJCC 2016

- The primary site can support a number of satellite sites. Staffing and services may vary at satellite sites. This has been effective in Australia, particularly Queensland who can set up satellite sites quickly.
- There is interest to extend trials to New Zealand sites.

Part D: Getting a melanoma combination therapy clinical trial up and running
Presentation from Professor Peter Shepherd (University of Auckland)

Presentation summary

- BRAF inhibitors work well but resistance arises quickly and they don't work in wild type which makes up 60% of tumours. BRAF + MEK inhibitors are the standard of care overseas but this treatment type is not accessible in NZ.
- In colorectal cancer BRAF + Pyrvinium (threadworm medicine) displayed the same effect as BRAF + MEK combination therapies.
- Using a panel of 100 early passage melanoma cell lines (developed in Auckland), this research tests the effect of BRAF + VEGFR axitinib inhibitors on mutant melanoma. Axitinib was chosen as VEGFR as it is potent and used in clinic already so side effect profile already known.
- Results showed a stronger effect and more efficacy than BRAF inhibitors alone. The combination has also been totally effective in cells resistant to BRAF.
- When tested on BRAF wildtypes, results show the same effect. This suggests that this combination may be useful in all melanoma.
- When tested with other BRAF and VEGFR inhibitors, results show the same effect indicating that any combination of BRAFi/VEGFRi may work.
- Tests in mouse models showed sustained long terms survival advantage for combination.
- These findings show the efficacy of BRAF inhibitors could be significantly increased and resistance mechanism overcome by horizontal combination treatments with VEGFR inhibitors. A clinical trial in New Zealand could benefit patients, and since these drugs are coming off patent soon this would provide cost effective improvements in treatment outcomes.
- The researchers are working with Auckland oncologists to set up a trial but are having difficulties finding a funding mechanism. Costs were estimated at $1 - $2 million.

Questions and discussion

- Phase 1 v Phase 2

- A randomised phase 2 trial may be the best way to proceed.
- Researchers are confident that VEGFR inhibitors don't need to be dosed high. There have been no toxicity issues in mice.
- A trial management group is being set up to consider Phase 1B or Phase 2 pathways.

Topic 2: DNA and RNA signatures associated with melanoma resistance to Keytruda

Presentation from Professor Mike Eccles (University of Otago)

Presentation summary

- Immune checkpoint inhibitor therapies are the current first-line treatment strategy for unresectable stage IV metastatic melanoma however most patients do not respond to this therapy. No biomarkers are currently used to predict response to these therapies as those available are very inaccurate.
- This research is investigating whether DNA methylation or gene expression can help explain why some patients don't respond to immune-checkpoint inhibitor therapies.
- Melanoma tissues from 40 patients were used. All patients had received anti-PD1 monotherapy as a firstline treatment – 19 had exhibited a complete response, partial response or stable disease for longer than 6 months (classified as responders) and 21 had progressive disease (classified as non-responders).
- Using next generation sequencing, high mutation burden in responders was compared with non-responders. Responders showed a relatively higher tumour mutation load than non-responders which may suggest that these mutations can help to stimulate the immune system to recognize the tumour. However, no mutation was able to discriminate responders from non-responders.
- Differential DNA methylation analysis identified 43 genes that were commonly altered in both methylation and gene expression. This analysis shows that specific DNA methylation marks correlate with immune checkpoint inhibitor response and there may be potential functional relationships between the methylation changes and the gene expression changes.
- RNA-Seq analysis showed significant differential expression for up to 315 genes, and that phenotype switching of melanomas results in a neural crest or undifferentiated gene expression signature. This signature characterizes a set of invasive melanomas with low immune scores, lower tumour mutation burdens and less neoantigen expression, all of which are associated with non-activation of the adaptive T-cell immune responses. These melanomas also have poor anti-tumour immunity and have aggressive resident macrophage populations, and they are immunologically cold. Overall, this process is associated with non-response to immune checkpoint inhibitor therapy.

Next meeting

- The group agreed to next meet in May/June 2023.