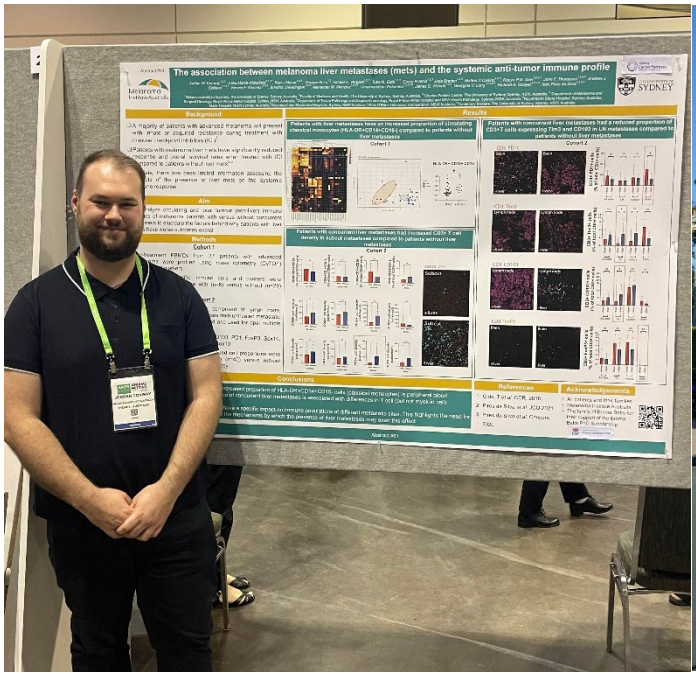
Name: Jordan Conway
Position & Affiliation: PhD Student, Melanoma Institute Australia, The University of Sydney.
Full Reference:The association between melanoma liver metastases (mets) and the systemic anti-tumor immune profile. **Jordan W. Conway[1,2,3]**, Felix Marsh-Wakefield[2,3,10], Kazi J Nahar[1,2,3], Serigne N.Lo[1,2], Ismael A. Vergara[1,2,3], Tuba N. Gide[1,2,3], Grace H.Attrill[1,2,3] Jorja Braden[1,2,3], Matteo S.Carlino[1,2,8], Robyn P.M. Saw[1,2,4,7], John F. Thompson[1,2,4,7], Andrew J. Spillane[1,2,6,7], Kerwin F. Shannon[1,4,9], Brindha Shivalingam[1,4,9], Alexander M. Menzies[1,2,6,7], Umaimainthan Palendira[1,2,3,10], James S. Wilmott[1,2,3], Georgina V. Long[1,2,3,6,7], Richard A. Scolyer[1,2,3,5], Inês Pires da Silva[1,2,3,8]
[1]Melanoma Institute Australia, The University of Sydney, Sydney, Australia, [2]Faculty of Medicine and Health, The University of Sydney, Sydney, Australia, [3] Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia, [4] Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Sydney, NSW, Australia, [5]Department of Tissue Pathology and diagnostic oncology, Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, NSW, Australia, [6]Royal North Shore Hospital, Sydney, Australia, [7]Mater Hospital, North Sydney, Australia,[8]Westmead and Blacktown Hospitals, Sydney, NSW Australia,[9]Chris O'Brien Lifehouse, Camperdown, NSW Australia,[10]Centenary Institute, The University of Sydney, Sydney, NSW, Australia
Conference/Meeting Name: American Association for Cancer Research (AACR) 2023 Annual meeting
Location: Orlando, Florida, USA
Dates: 14th-19th April 2023
Presentation Type: Poster




Picture 1: Presenting the poster at AACR. Picture 2: Visiting the Magic Kingdom at Disney World

The AACR annual meeting brings together cancer researchers, both clinicians and basic scientists of all levels and fields to present and discuss the latest in cancer research. It is the largest cancer conference in the world and this year there were approximately 21,000 attendees. There were a large range of interesting presentations throughout the conference. In the opening Plenary session Dr Deborah Schrag from MSKCC gave a very interesting talk on the early phase of a multi-cancer early detection test which may in the future be used as a non-invasive early screening method for detection of multiple cancers. Dr. David DeNardo from Washington University presented a very insightful overview on the current immunotherapies and successes and failures/challenges of

immunotherapy including targeting diverse tumour microenvironments. Dr DeNardo discussed the large diverse range of immunotherapy options not only specific for immune checkpoint inhibitors but other approaches. He further highlights the need to move away from only targeting T cell immunity but also a larger range of immune cells including macrophages, NK cells and dendritic cells and targeting these cell types in anti-cancer treatments whilst considering the entire systemic immune response. Dr Tomi Akinyemiju another invited plenary session speaker also discussed the impact of social factors on cancer risk and survival particularly focusing on cancer disparities in under represented communities. This year there was no one single overly focused area but rather a handful of areas with particular focus. There was an emphasis on understudied cell types away from T cells including B cells/tertiary lymphoid structures, particularly the ability of B cells to modulate cancer growth attributed to cytokine release, antigen presentation and antibody production. There was also a focus on neutrophils and their role in progression and immunotherapy resistance including their ability to regulate CD8+ t cells with some studies looking to deplete specific neutrophil populations in an attempt to try and increase response in mice models. This year there was a lot of work and advances in 3D-organoids and functional techniques which was also presented on by Corning themselves unveiling new and future reagents under development to aid in this space. Specifically, there was a lot of focus on using these techniques to provide novel prediction tools for personalised drug screening assays. Another area that was featured heavily throughout the conference was CAR-T cells and forms of immunotherapy other than immune checkpoint inhibitors. Particular focus was on implementation of CAR-T cell technologies in solid cancers, a treatment which previously only showed promising results in blood-based cancers. Researchers are now looking to increase the activity of these therapies in solid tumour cancers one such way being to target the chemokine axis to aid in trafficking of developed T cells into solid tumours as well as co-targeted approaches. The above research was extremely informative for myself and I learnt a lot in areas that I typically do not research which will help me broaden my approach in my work. I was also able to meet Dr Erik Sahai from the Francis Crick Institute in the UK who is working in a similar field to myself focused on site specific responses to immunotherapies and overcoming resistance of liver metastases. My discussion with Dr. Sahai about his work was extremely informative and may also help me in my future planned work. I was able to take an enormous amount of new learnings from this conference. To date a lot of my work has been very descriptive and broad and the knowledge I have gained at AACR as I move forward with my research will allow me to approach my work with more depth and more functional plans that will help progress my research greatly. I intend to take what I have learnt and functionally test hypothesised resistant mechanisms in functional models of liver metastases and I aim to find new targets that can possibly be exploited to overcome this resistance. This work is also highly translational and relevant to Sydney Cancer Partners being that immunotherapy resistance, particularly in patients with liver metastases, is an extremely pertinent clinical issue that patients face not only in melanoma but in other cancers. I hope to take what I have learnt and continue towards a goal of generating good quality and in depth data that may be used to improve patient response and survival. Overall AACR 2023 was an amazing experience. Being my first large scale conference, it was extremely engaging, informative and re-invigorated my drive to progress my research and help advanced melanoma patients and patients with other advanced cancers. I also had such an amazing experience outside of the conference in Orlando attending a local social salsa night hosted by Akoya Biosciences which included salsa dancing and was not only a great social event but further expanded my networking connections. I was also lucky enough to be able to visit Disney World and Universal Studios which has been a life long dream of mine rounding off what was an amazing experience from start to finish. I am very grateful to Sydney Cancer Partners for their support without which I would not have been able to attend the conference or have the experience that I did.

The association between melanoma liver metastases (mets) and the systemic anti-tumor immune profile

Jordan W. Conway[1,2,3], Felix Marsh-Wakefield[2,3,10], Kazi J Nahar[1,2,3], Serigne N.Lo[1,2], Ismael A. Vergara[1,2,3], Tuba N. Gide[1,2,3], Grace H.Attrill[1,2,3] Jorja Braden[1,2,3], Matteo S.Carlino[1,2,8], Robyn P.M. Saw[1,2,4,7], John F. Thompson[1,2,4,7], Andrew J. Spillane[1,2,6,7], Kerwin F. Shannon[1,4,9], Brindha Shivalingam[1,4,9], Alexander M. Menzies[1,2,6,7], Umaimainthan Palendira[1,2,3,10], James S. Wilmott[1,2,3], Georgina V. Long[1,2,3,6,7], Richard A. Scolyer[1,2,3,5], Inês Pires da Silva[1,2,3,8]

[1]Melanoma Institute Australia, The University of Sydney, Sydney, Australia, [2]Faculty of Medicine and Health, The University of Sydney, Sydney, Australia, [3] Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia, [4] Department of Melanoma and Surgical Oncology, Royal Prince Alfred Hospital, Sydney, NSW, Australia, [5]Department of Tissue Pathology and diagnostic oncology, Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, NSW, Australia, [6]Royal North Shore Hospital, Sydney, Australia, [7]Mater Hospital, North Sydney, Australia,[8]Westmead and Blacktown Hospitals, Sydney, NSW Australia,[9]Chris O'Brien Lifehouse, Camperdown, NSW Australia,[10]Centenary Institute, The University of Sydney, Sydney, NSW, Australia

Background

- A majority of patients with advanced melanoma will present with innate or acquired resistance during treatment with immune checkpoint inhibitors (ICI)[1]
- Patients with melanoma liver mets have significantly reduced response and overall survival rates when treated with ICI compared to patients without liver mets[2,3]
- To date, there has been limited information assessing the impacts of the presence of liver mets on the systemic immune response

Aim

- To analyze circulating and local tumour (non-liver) immune profiles of melanoma patients with versus without concurrent liver mets to elucidate the factors behind why patients with liver mets have worse outcomes overall

Methods

Cohort 1

- Pre-treatment PBMCs from 37 patients with advanced melanoma were profiled using mass cytometry (CyTOF) spanning 46 markers.
- Expression of specific immune cells and clusters were compared between those with (n=8) versus without (n=29) liver mets

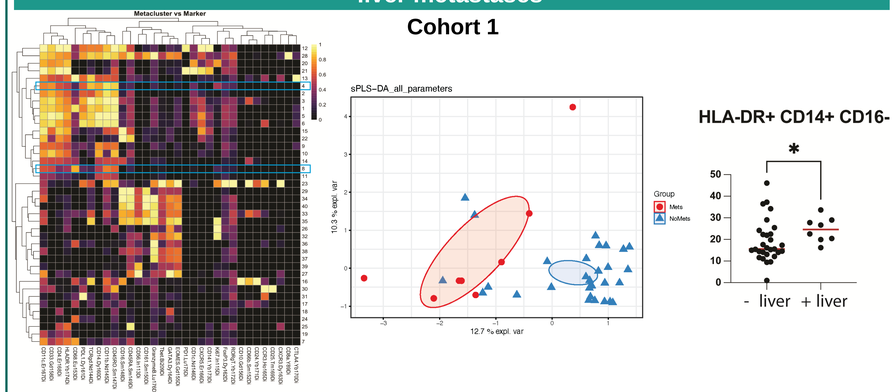
Cohort 2

- 93 FFPE melanoma biopsies comprised of lymph node, subcutaneous and brain metastases from untreated metastatic melanoma patients were identified and used for opal multiple IHC (mIHC):
  - *mIHC panels:* (1) CD3, Tim3, CD103, PD1, FoxP3, Sox10; (2) CD68, CD14, CD16, PD-L1, Sox10
  - *Analysis:* Immune cell densities and cell proportions were compared between patients with (n=40) versus without (n=53) liver mets at the time of biopsy

Results

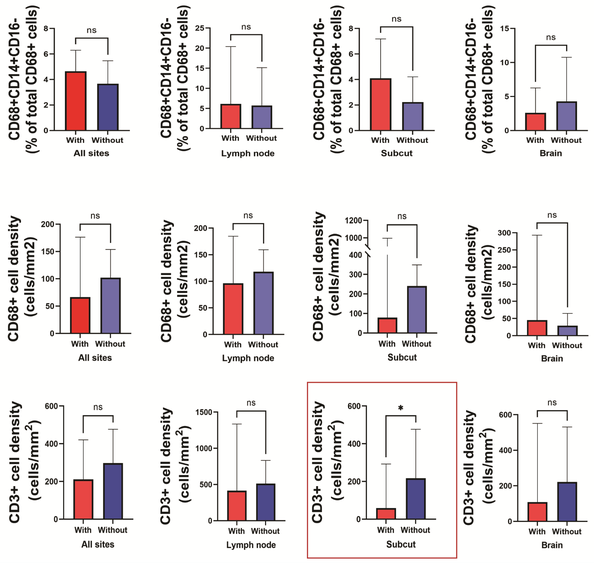
Patients with liver metastases have an increased proportion of circulating classical monocytes (HLA-DR+CD14+CD16-) compared to patients without liver metastases

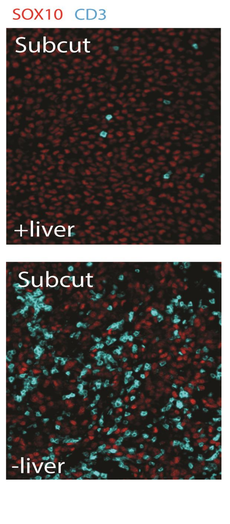
Cohort 1



Patients with concurrent liver metastases had reduced CD3+ T cell density in subcut metastases compared to patients without liver metastases

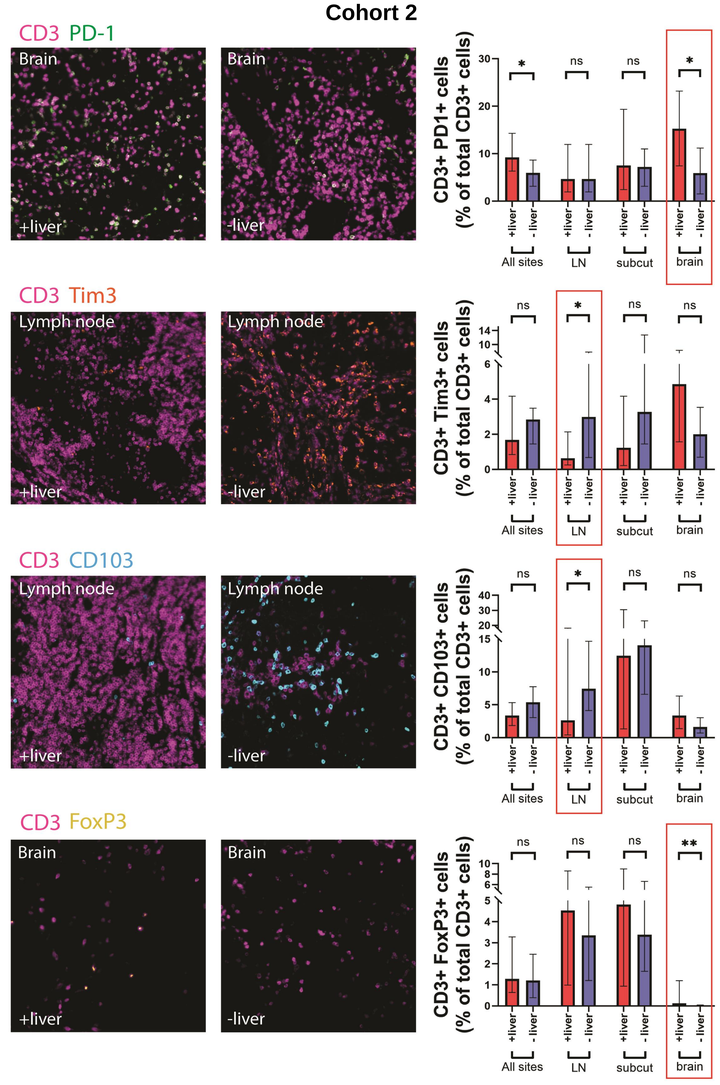
Cohort 2





Patients with concurrent liver metastases had a reduced proportion of CD3+T cells expressing Tim3 and CD103 in LN metastases compared to patients without liver metastases

Cohort 2



Conclusions

- Patient with liver metastases have an increased proportion of HLA-DR+CD14+CD16- cells (classical monocytes) in peripheral blood
- In non-liver tumor biopsies, the presence of concurrent liver metastases is associated with differences in T cell (but not myeloid cell) populations
- The presence of liver metastases may have a specific impact on immune populations at different metastatic sites. This highlights the need for further validation and investigation into the mechanisms by which the presence of liver metastases may exert this effect

References

1. Gide, T *et al.* CCR, 2018
2. Pires da Silva *et al.* JCO 2021
3. Pires da Silva *et al.* Cancers, 2020

Acknowledgements

- All patients and their families
- Melanoma Institute Australia
- The family of Emma Betts for their support of the Emma Betts PhD Scholarship

Proudly supported by Cancer Institute NSW