Time-dependent prediction of development of melanoma brain metastases (MBM) from the start of BRAF/MEK inhibitors (BRAF/MEKi) or anti-PD-1(PD1)-based immunotherapy (IO)

Inês Pires da Silva[1,2,3], Ismael Vergara[1,2], Isabel Li[1], Serigne Lo[1,2], Matteo S. Carlino[1,2,3], Alexander M. Menzies[1,2,4], Richard A. Scolyer[1,2,5], Georgina V. Long[1,2,4]

1. Melanoma Institute Australia, Sydney, Australia; 2. The University of Sydney, Sydney, Australia; 3. Westmead and Blacktown Hospitals, Sydney, Australia; 4. Royal North Shore and Mater Hospitals, Sydney, Australia; 5. Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, Australia.

BACKGROUND

- Melanoma brain metastases (MBM) are associated with a poor prognosis[1,2].
- Advances in systemic therapies and increased surveillance have decreased the number of patients presenting with MBM at stage IV diagnosis, reduced the development of MBM and improved survival of those with MBM[3,4,5].
- Nevertheless, MBM still occur during therapy, even in those with extracranial disease control.
- Data regarding the risk of MBM in patients commencing systemic therapy are required to inform surveillance approaches.

OBJECTIVES

We aimed to predict the likelihood of metastatic patients developing melanoma brain metastases at the start of BRAF/MEKi or PD1-based immunotherapy, and at 3, 6, 9 and 12 months thereafter.

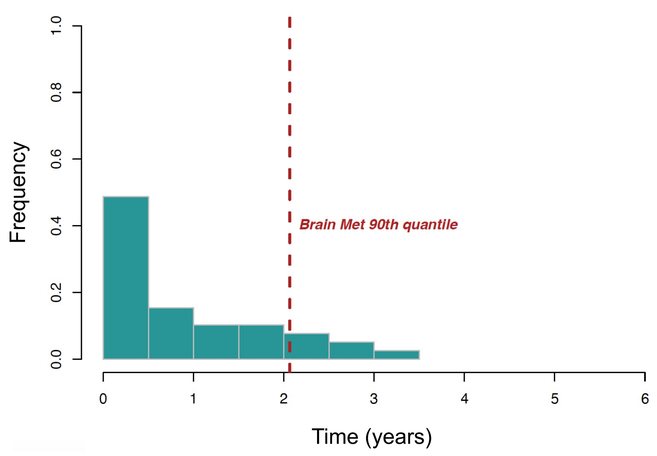
METHODS

- Patients with stage IV melanoma with no MBM at the time of 1st line treatment with PD1-based immunotherapy (n=331) or BRAF+/-MEKi (n=186) were included.
- Demographics (age, gender) and disease characteristics (primary site, ECOG PS, LDH, site and number of metastases) were collected at baseline and landmark time points.
- Statistical Analysis:
  - *Dynamic Prediction using Landmark Models with Competing Risks:* At each selected landmark time point (at the start of immunotherapy or of BRAF/MEKi, and 3, 6, 9, 12 months thereafter), patients without MBM were included in a predictive model for survival incorporating disease status at that time point.
  - *Survival Model:* Fine-Gray subdistribution hazard model was used to predict the risk of interest (MBM) with the presence of the competing risk (death).
  - *Model Selection:* Backward stepwise elimination was used to select variables for each landmark analysis.

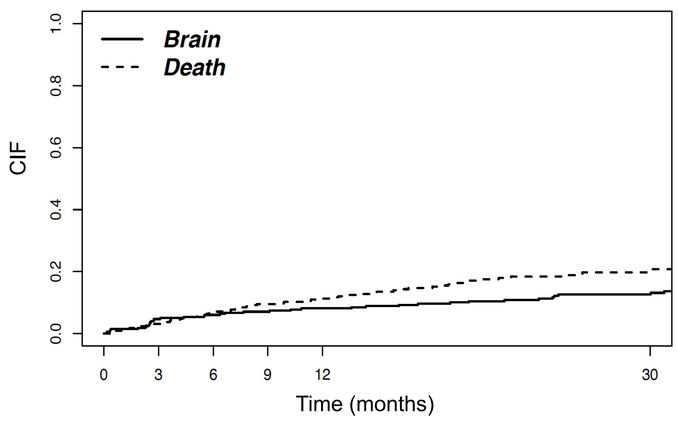
RESULTS

Figure 1. Time-dependent prediction of development of MBM from the start of PD-1-based immunotherapy (IO)

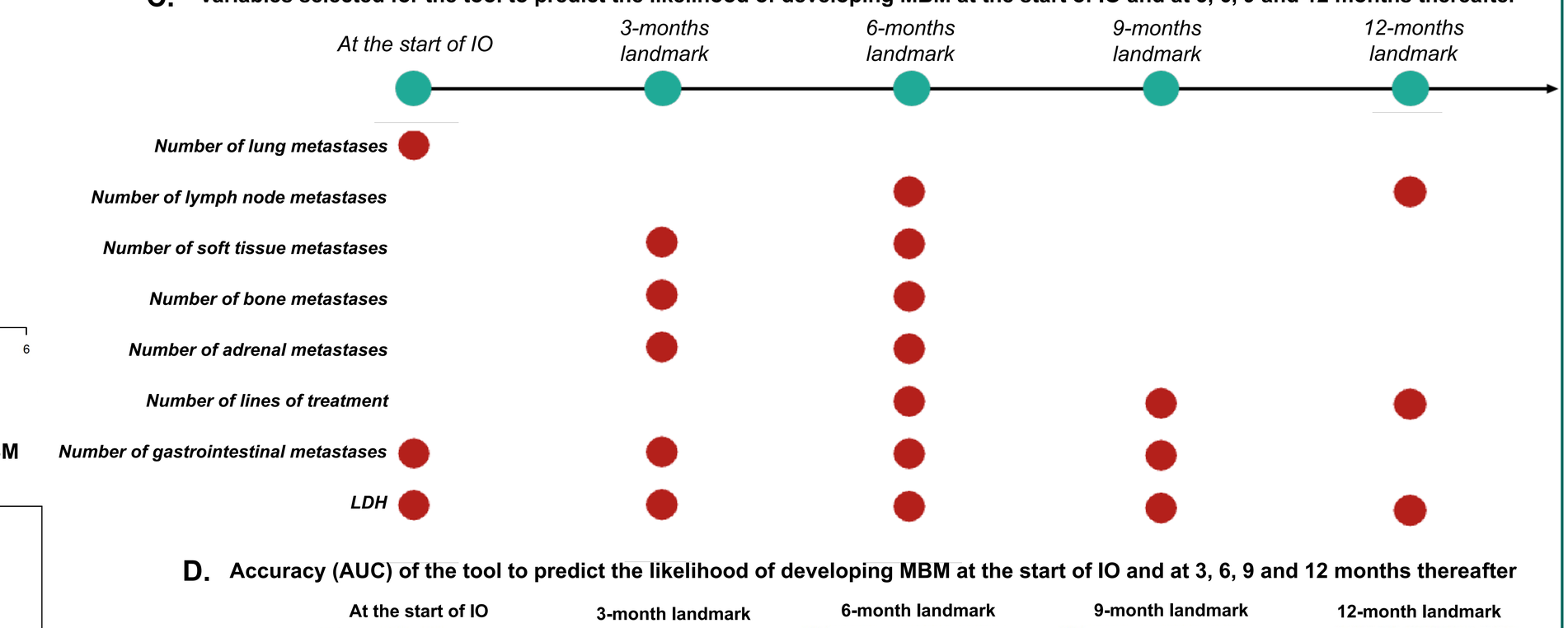
A. Frequency of MBM since the start of IO



B. Cumulative Incidence Function (CIF) of MBM since the start of IO



C. Variables selected for the tool to predict the likelihood of developing MBM at the start of IO and at 3, 6, 9 and 12 months thereafter



D. Accuracy (AUC) of the tool to predict the likelihood of developing MBM at the start of IO and at 3, 6, 9 and 12 months thereafter

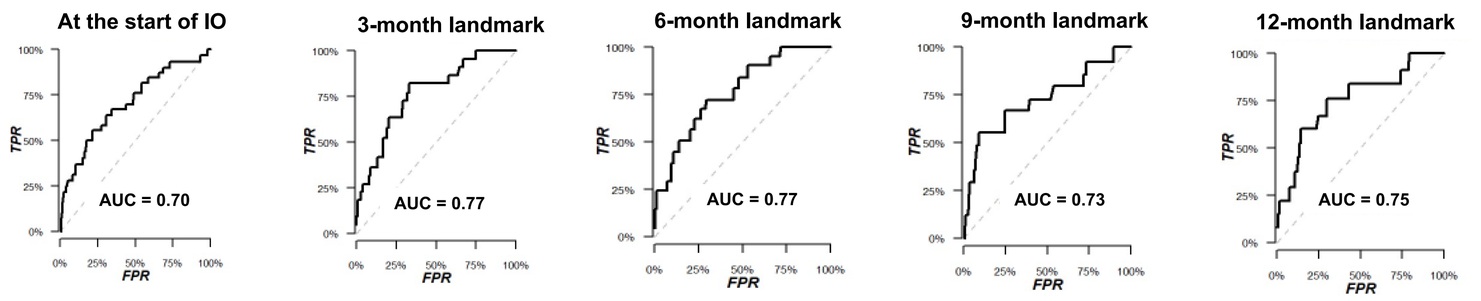
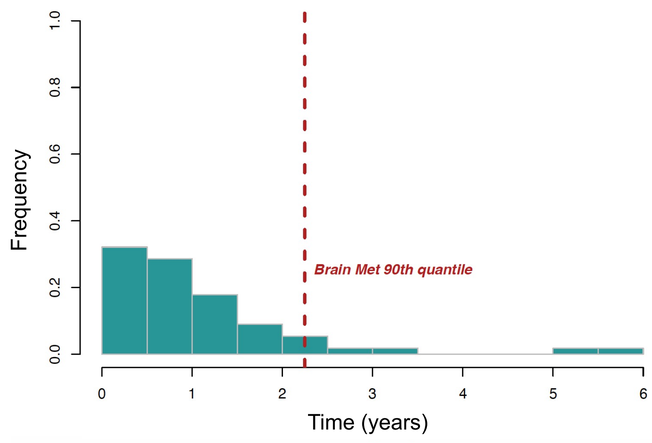
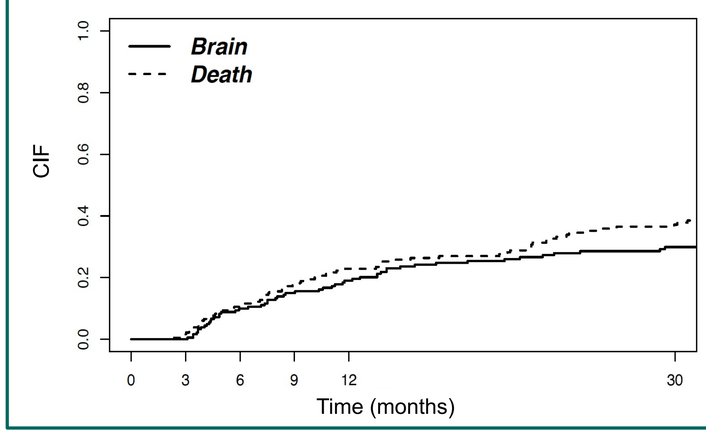


Figure 2. Time-dependent prediction of development of MBM from the start of BRAF/MEK inhibitors (targeted therapy – TT)

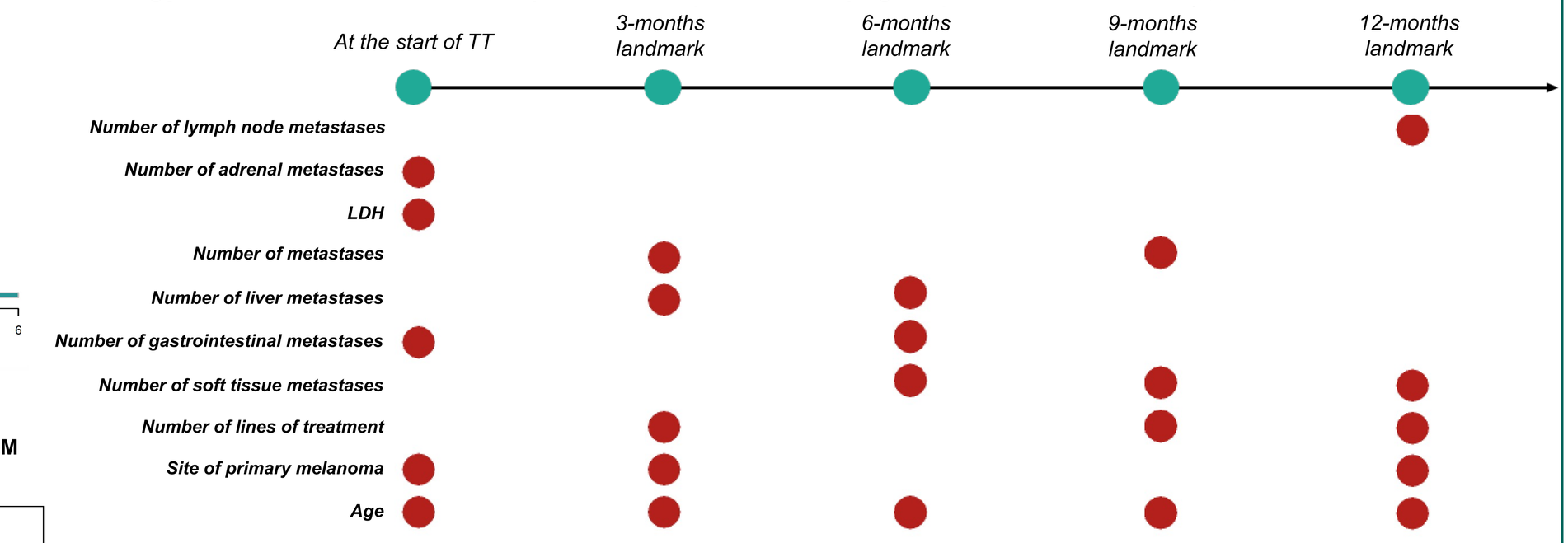
A. Frequency of MBM since the start of TT



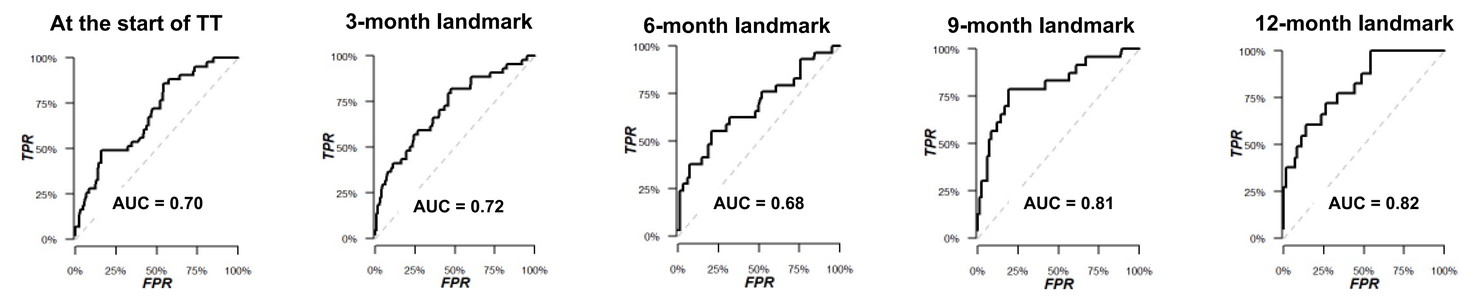
B. Cumulative Incidence Function (CIF) of MBM since the start of TT



C. Variables selected for the tool to predict the likelihood of developing MBM at the start of TT and at 3, 6, 9 and 12 months thereafter



D. Accuracy (AUC) of the tool to predict the likelihood of developing MBM at the start of TT and at 3, 6, 9 and 12 months thereafter



CONCLUSIONS

- This tool to predict the development of melanoma brain metastases at different time points from the start of drug therapy will help guide discussions with patients and may define appropriate surveillance.
- While this model requires validation, this approach can be applied to predict the likelihood of developing other sites of metastases.

REFERENCES

1. Davies MA *et al*. Cancer 2011
2. Pires da Silva *et al*. JCO 2021
3. Davies MA *et al*. Lancet Oncol 2017
4. Long GV *et al*. Lancet Oncol 2018
5. Tawbi HA *et al*. NEJM 2018

ACKNOWLEDGEMENTS

- All patients and their families
- Melanoma Institute Australia