The added value of joint modelling of progression free and overall survival in a restricted mean survival network meta-analysis

Jeremy Dietz[1], Lindsay Claxton[1], Nicky J. Welton[2,3]

1. National Institute of Health and Care Excellence (NICE)

2. Population Health Sciences, Bristol Medical School, University of Bristol

3. NICE Guidelines Technical Support Unit

NICE National Institute for Health and Care Excellence

University of BRISTOL Guidelines Technical Support Unit

Motivating Publication

Daly et al. Research Synthesis Methods.
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RESEARCH ARTICLE

Research Synthesis Methods WILEY

A non-parametric approach for jointly combining evidence on progression free and overall survival time in network meta-analysis

Caitlin H. Daly[1] | Ross Maconachie[2] | A. E. Ades[1] | Nicky J. Welton[1]

Objective: To develop an approach to jointly synthesise evidence from PFS and OS Kaplan-Meier curves, which

- Does not require any parametric assumptions
- Does not assume proportional hazards
- Conforms to the constraint that OS = PFS + PPS

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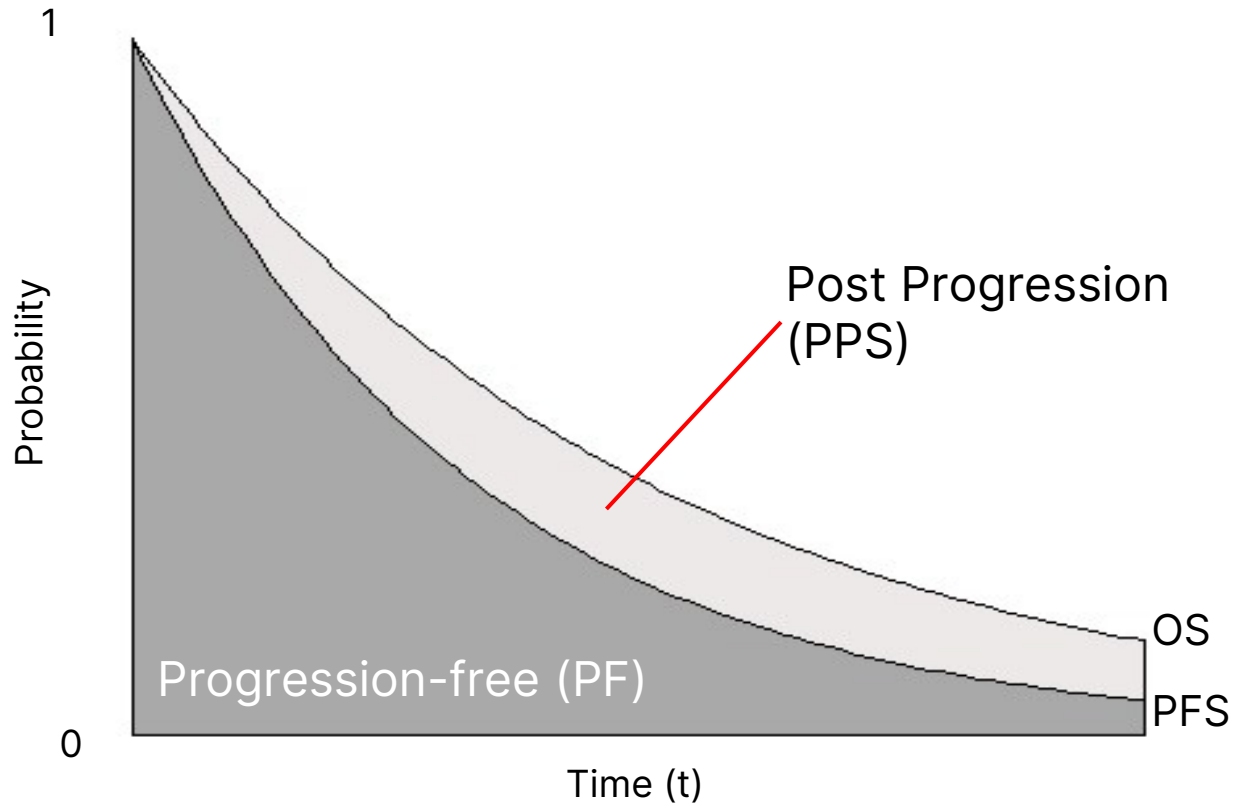
Joint Modelling of OS and PFS

Method pools areas under the curves

- PFS and OS are not independent
  - OS = PFS + PPS
- Should model these jointly, incorporating correlations

But does it matter if we model PFS and OS separately? What are the implications for:

- NMA estimates?
- Cost-utility estimates?



Obtaining Area Under the Curve (AUC) Estimates from the Kaplan-Meier data

Synthetic individual patient data were reconstructed from Kaplan-Meier curves (Guyot et al (2012)

- Often in evidence synthesis don't have access to IPD

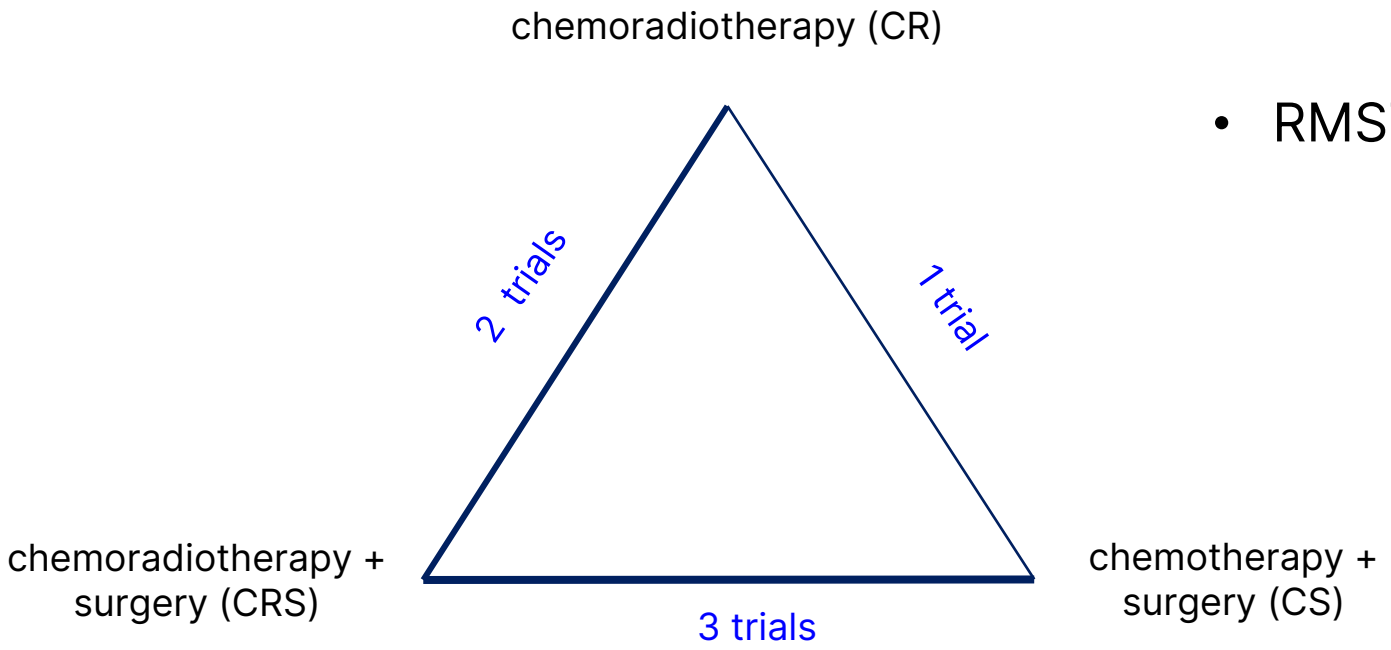
Estimates of AUC and variance for OS and PFS

- Uses a Reiman sum from Kaplan-Meier estimates (Klein and Moeschberger 2003) for each study, arm, and outcome

AUC must be greater for OS than PFS

- Bootstrap resampling discarding samples where $AUC_{PSF} > AUC_{OS}$
- Induces correlations between AUC_{PSF} and AUC_{OS}

Network Meta-Analysis for Treatments for Operable Stage IIIA-N2 Non-Small Cell Lung Cancer



- RMST at 5 years

National Institute for Health and Care Excellence, Lung cancer: diagnosis and management. 2019, National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng122, Evidence Review C

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Lung Cancer NMA Results: RMST at 5 years

	Joint Modelling	Separate NMAs	Percent difference
Mean PFS			
Chemoradiotherapy	1.461	1.525	4.29%
Chemotherapy + surgery	1.43	1.491	4.18%
Chemoradiotherapy + surgery	1.755	1.824	3.86%
Mean PPS			
Chemoradiotherapy	0.5421	0.704	25.99%
Chemotherapy + surgery	0.4782	0.64	28.94%
Chemoradiotherapy + surgery	0.3337	0.487	37.36%
Mean OS			
Chemoradiotherapy	2.0031	2.229	10.68%
Chemotherapy + surgery	1.9082	2.131	11.03%
Chemoradiotherapy + surgery	2.0887	2.311	10.11%

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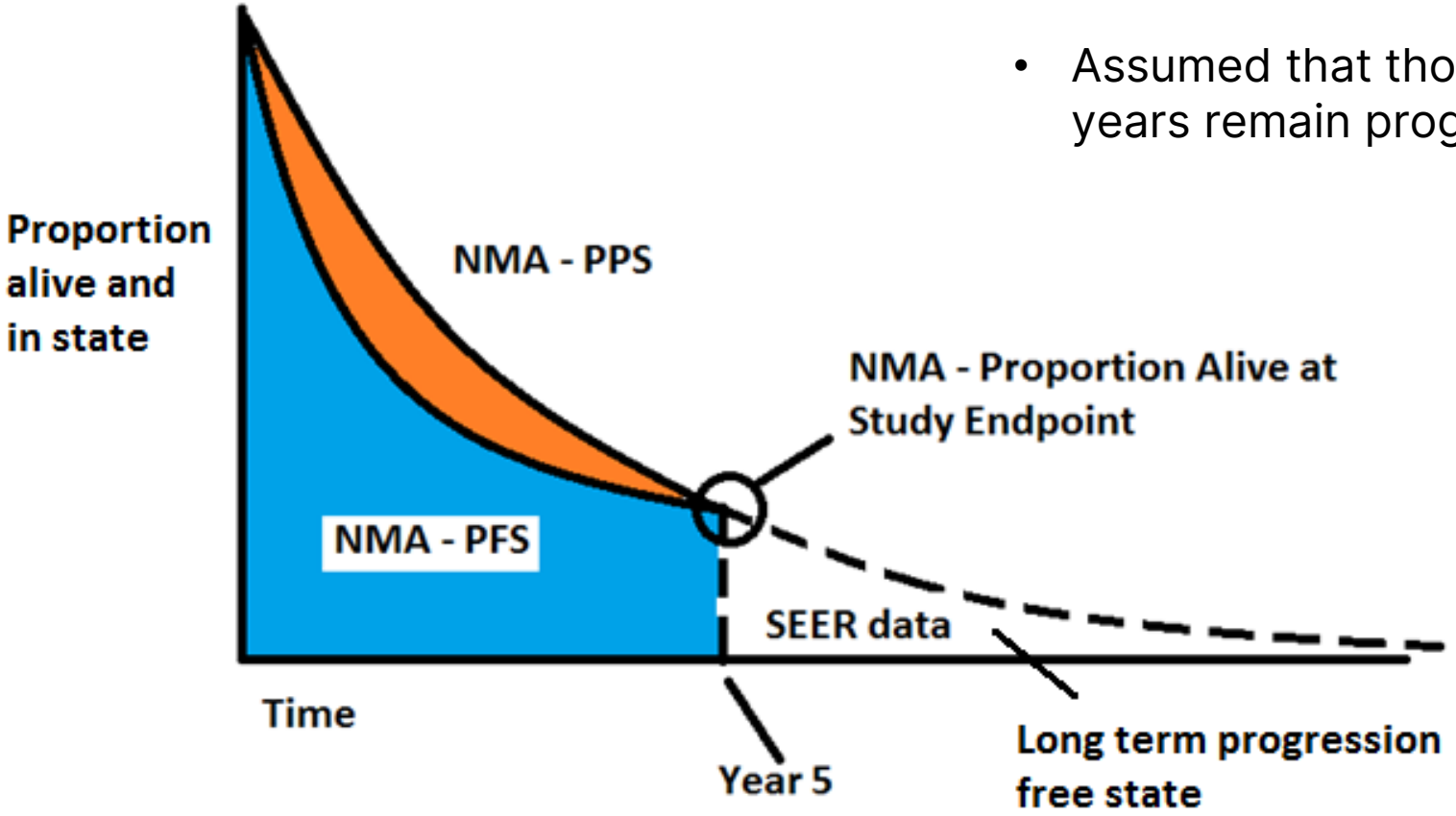
Lung Cancer Cost-utility Model



- Assumed that those progression free at 5 years remain progression free

Probabilistic cost-utility results

Intervention	Incremental		
	Costs	QALYs	ICER
Joint Modelling			
Chemoradiotherapy	-	-	Ref.
Chemotherapy and Surgery	£3,248	0.042	£77,698
Chemoradiotherapy and Surgery	£3,896	0.205	£19,017
Separate Modelling			
Chemoradiotherapy	-	-	Ref.
Chemotherapy and Surgery	£3,281	0.042	£78,721
Chemoradiotherapy and Surgery	£3,717	0.205	£18,114

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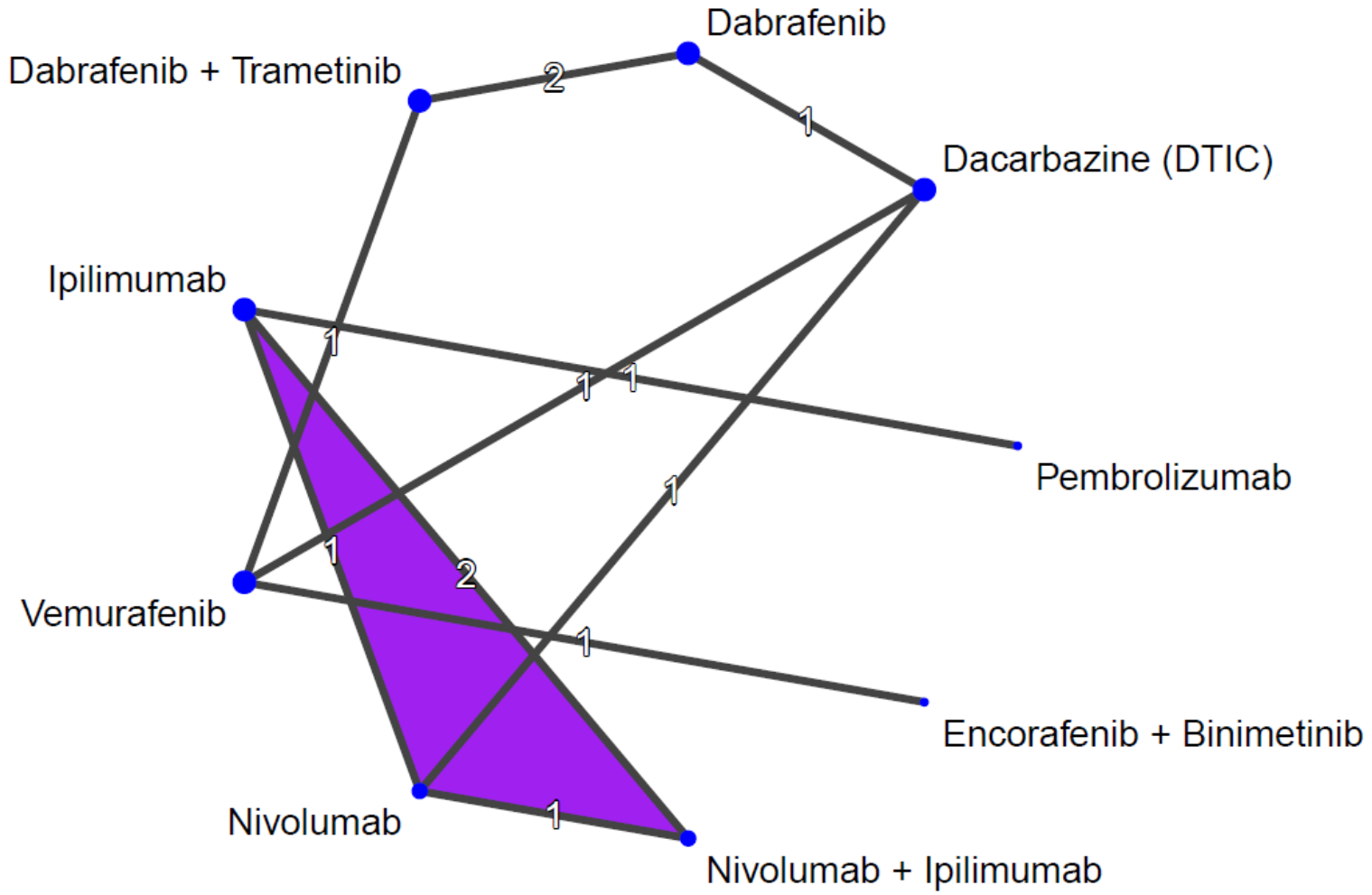
Network Meta-Analysis for Treatments for Advanced Melanoma

- RMST at 18 months



National Institute for Health and Care Excellence, Melanoma: assessment and management. 2022, National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng14/evidence/network-metaanalysis-report-for-evidence-review-f-pdf-11186433037, Network meta-analysis report

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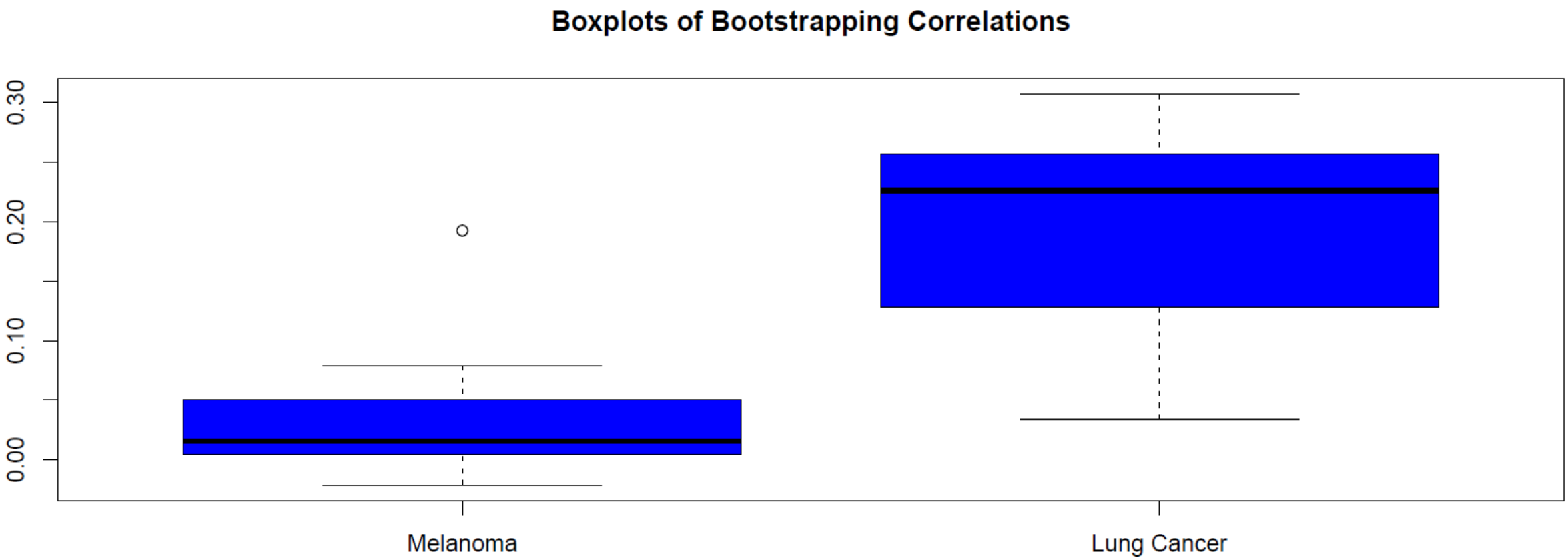
Melanoma NMA results: RMST at 18 months

	Percent difference PFS	Percent difference PPS	Percent difference OS
Dacarbazine	0.19%	0.03%	0.05%
Dabrafenib	0.09%	0.08%	0.03%
Dabrafenib + Trametinib	0.00%	0.58%	0.15%
Ipilimumab	0.82%	0.39%	0.14%
Vemurafenib	0.08%	0.56%	0.17%
Nivolumab	0.32%	0.23%	0.12%
Nivolumab + Ipilimumab	0.26%	0.24%	0.13%
Encorafenib + Binimetinib	0.00%	1.08%	0.26%
Pembrolizumab	0.58%	0.45%	0.19%

Bootstrapping correlations



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Discussion

NMA results

- Lung Cancer
  - Correlations are high – NMA results for joint modelling vs separate NMAs can vary substantially
    - Suggests if we know correlations are high, joint modelling ought to be done, otherwise you risk getting results that are biased
- Melanoma
  - Correlations are low – NMA results for joint modelling vs separate NMAs do not vary much
    - Suggests if we know correlations are low, it is good enough to model separately as impacts are negligible

Cost utility results

- Lung Cancer
  - Impact on cost-utility results is small and doesn't affect decision making
    - NMA results only affect 5 years of the model, so it not surprising the model is not as sensitive to this input

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Thank you