2018 KCRNC-KCC-CUASF Research Grant: Update April 2019

Identifying prognostic and predictive biomarkers in metastatic renal-cell carcinoma:

An exploratory study of the International Metastatic renal-cell carcinoma Database Consortium (IMDC) tissue biorepository

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Supervisor: Dr. Daniel Heng, MD MPH FRCPC

Objective

- To evaluate novel prognostic and/or predictive biomarkers in mRCC using the IMDC database and tissue biorepository

- Specifically will study the addition of PBRM1, BAP1, SETD2, PD-L1 and p53 to the current IMDC criteria to improve their prognostic accuracy and/or predictive value in treatment selection
  - Update: Added EZH2 and H3K36me3 to biomarker panel

IMDC Risk Model

- Validated across multiple lines of therapy, clear-cell and non-clear cell histology, second-line immunotherapy

- Predictive effect (CheckMate 214 study)
  - Favourable-risk group – VEGF-TKI > IO
  - Intermediate/poor-risk group – IO > VEGF-TKI

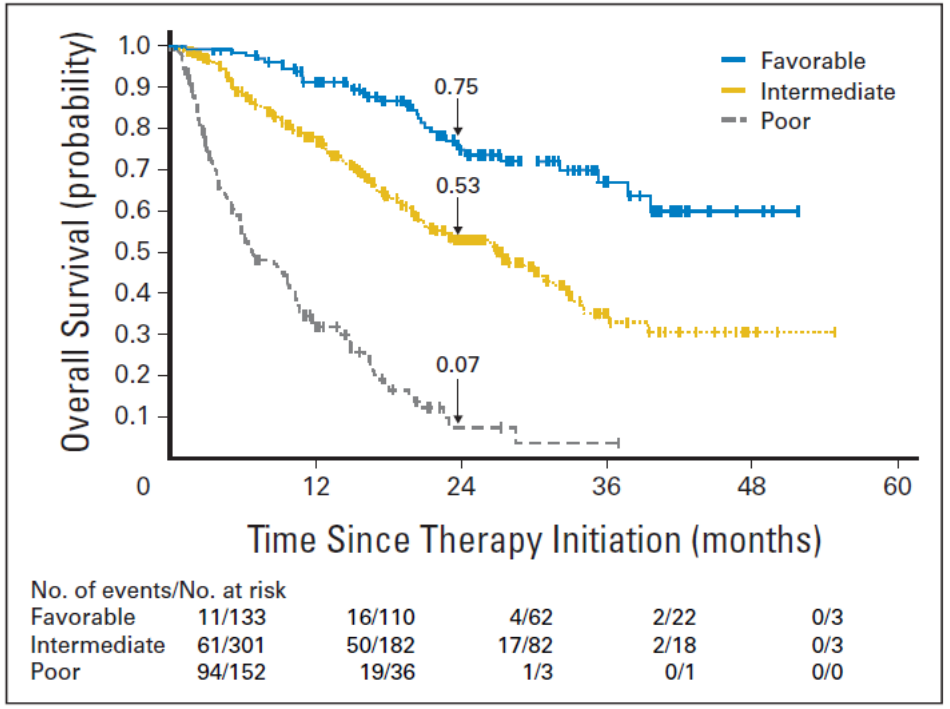

Fig 2. Overall survival probability according to time after therapy initiation and risk group.

Heng et al, JCO 2009; Heng et al, Lancet Onc 2013; Ko et al, Lancet Onc 2015; Wells et al, Eur Urol 2017; Kroeger et al, Cancer 2013; Yip et al, JCO 2017; Escudier et al, ESMO 2017

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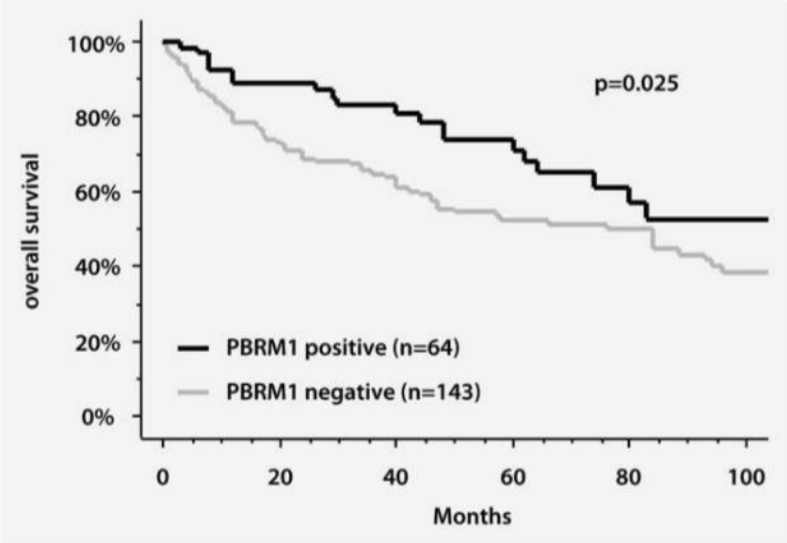
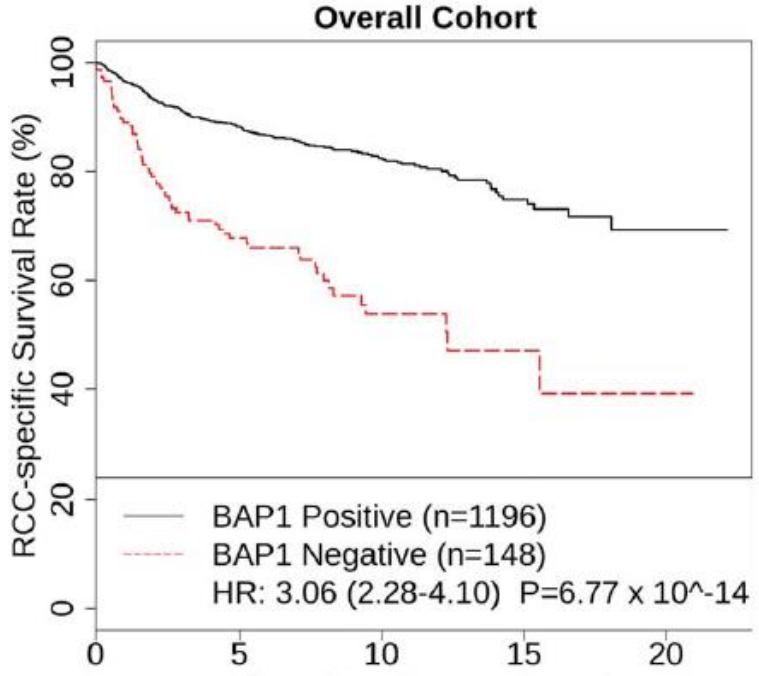
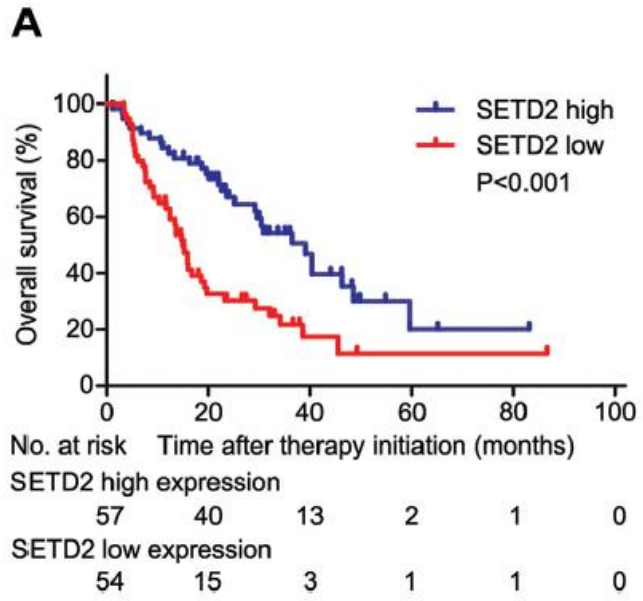
PBRM1



BAP1



SETD2



Pawlowski et al, Int Journal Can 2013; Joseph et al, Cancer 2014; Wang et al, J Urol 2016

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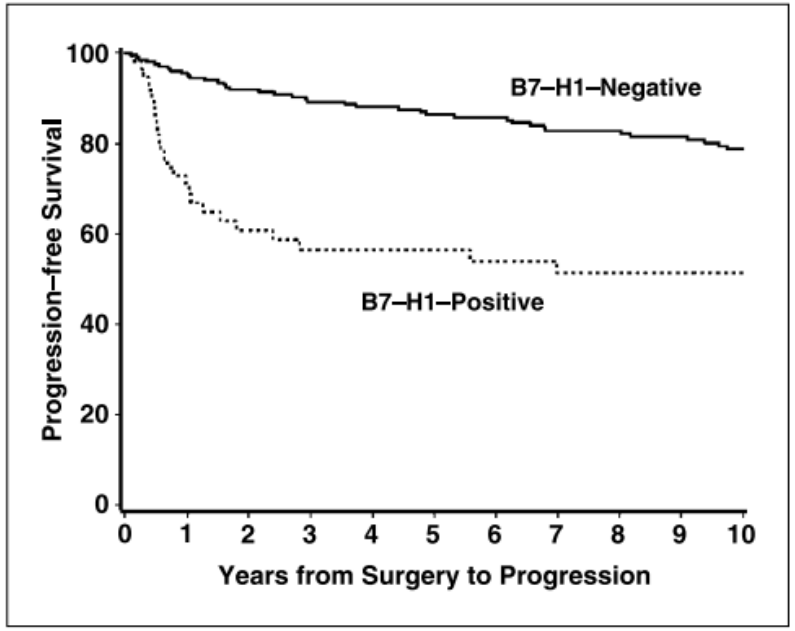
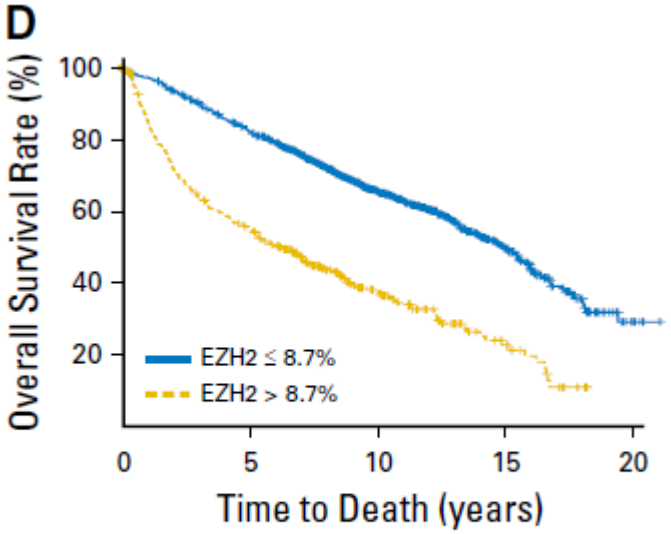
PD-L1

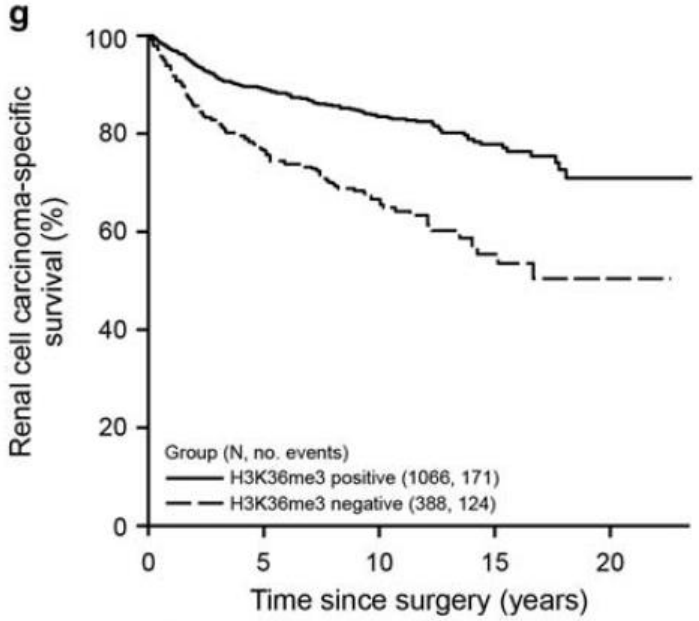


EZH2



No. at risk:				
EZH2 ≤ 8.0%	989	781	390	109
EZH2 > 8.0%	349	186	68	17

H3K36me



No. at risk				
1066	806	405	123	18
388	246	113	30	6

Thompson et al, Cancer Res 2006; Ho et al, JCO 2017; Ho et al, Modern Pathology 2016

Hypothesis

- Altered expression of PBRM1, BAP1, SETD2, PD-L1, p53, EZH2 and/or H3K36me may be independently predictive of outcome (prognostic biomarker) and/or predictive of response to therapy (predictive biomarker) in clear-cell mRCC

- The integration of these biomarkers into the current IMDC model may improve it's prognostic accuracy and/or predictive value

Design & Methodology

- Will evaluate the prognostic/predictive features of biomarker panel through the IMDC database and tissue biorepository

- IMDC Tissue Biorepository
  - Biobank of archival tissue from patients in the IMDC
    - Fully annotated via IMDC database
  - Includes 1200+ FFPE tissues worldwide
    - ~450 patients in Alberta

Update

- 25k received in August 2018
- Identified and requested 587 specimens from 440 patients across Alberta
  - Plan to create TMAs with 2 cores per specimen
- 6 IHC antibodies identified and acquired (PD-L1 to be performed in Edmonton)
- First TMA with 147 specimens from 122 patients from Calgary made and stained
  - 242 further cases received (coring), 198 outstanding

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Update

Next Steps

- Create TMAs after receiving and coring outstanding specimens
- Perform IHC staining and scoring
- Assessing prognostic value:
  - Univariate and multivariate analyses to assess independent effect of each biomarker on OS, while adjusting for known IMDC risk factors
- Assessing predictive value:
  - Assess for interaction between altered expression of each biomarker with treatment-specific outcomes of interest such as RR, TTF, TNT in second-line therapy (VEGF vs. IO vs. mTOR)

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