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IDENTIFICATION AND PROGNOSTIC IMPACT OF *PBRM1* MUTATIONS IN BILIARY TRACT CANCERS: RESULTS OF A COMPREHENSIVE MOLECULAR PROFILING STUDY

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Background / Aim of the project

- Novel treatment strategies are needed to improve survival for biliary tract cancers (BTC) (1).
- Polybromo-1 (*PBRM1*) is a tumor suppressor gene that is involved in chromatin remodeling (2).
- Preclinical studies suggest induction of synthetic lethality by PARP inhibitors in *PBRM1*-mutated renal cell carcinoma (3).

Aim of the project:

- To describe the molecular and immunological landscape of PBRM1-mutated biliary tract cancers.

(1) Glimelius et al, Ann Oncol 1996; (2) Fountzilas et al, JNCI 2021 (3) Chabanon et al, AACR 2020

Patients and Methods

- 1,848 BTC samples were included in this study
- Specimens were analyzed centrally at Caris Life Sciences, Phoenix, AZ:
  - whole-exome-sequencing
  - whole-transcriptome sequencing
  - and immunohistochemistry
- Pathway gene set enrichment analyses were done using GSEA (1)
- Immune cell fraction was calculated using the QuantiSeq method (2)
- Survival was calculated from time of tissue collection to last contact using Kaplan-Meier estimates

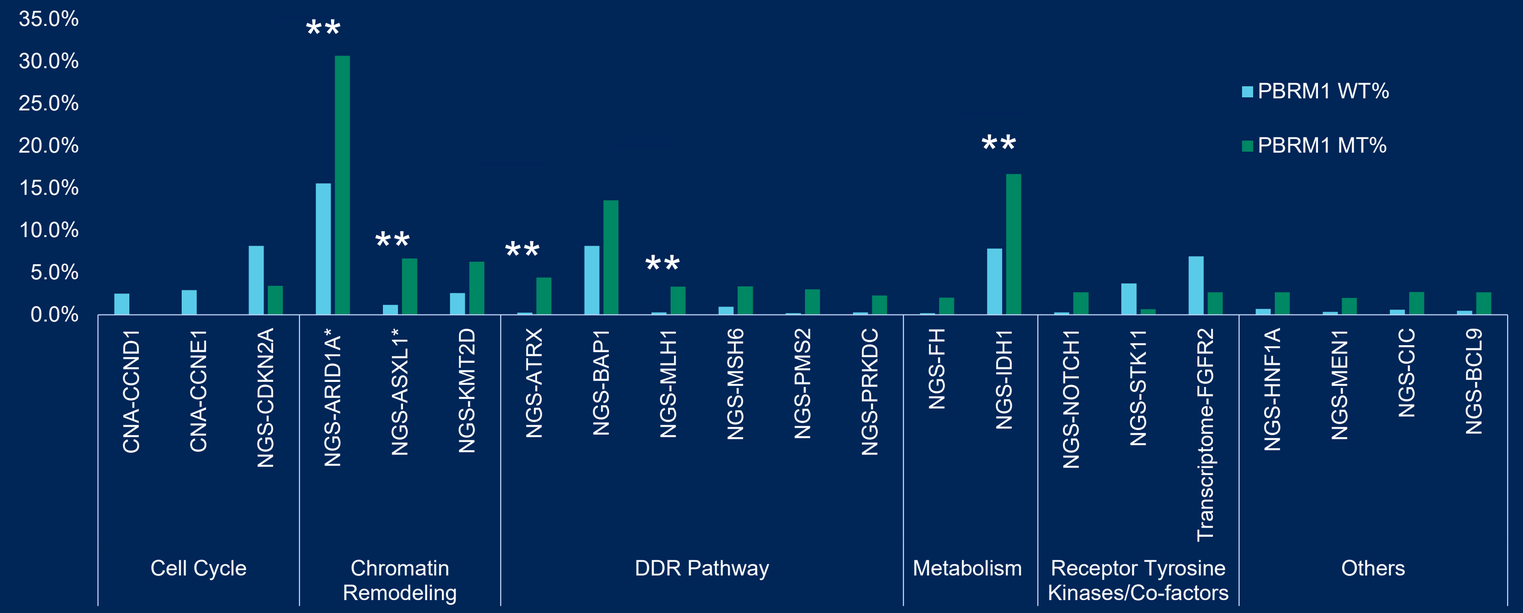
(1) Subramanian et al., Proc Natl Acad Sci U S A. 2005; (2) Finotello et al., Genome Med. 2019

PBRM1 mutations are frequent in intrahepatic BTC

Patient characteristics

Cancer Types/Gender	PBRM1 WT	PBRM1 MT	Total	%
EHBC	233	11	244	4.5%
Gallbladder Cancer	455	29	484	6.0%
IHBC	942	103	1045	9.9%
Unclear	68	7	75	9.3%
Female	948	95	1043	9.1%
Male	750	55	805	6.8%
All Cholangiocarcinoma	**1698**	**150**	**1848**	**8.1%**

Molecular Profile of *PBRM1* mutated BTCs



**q<0.05

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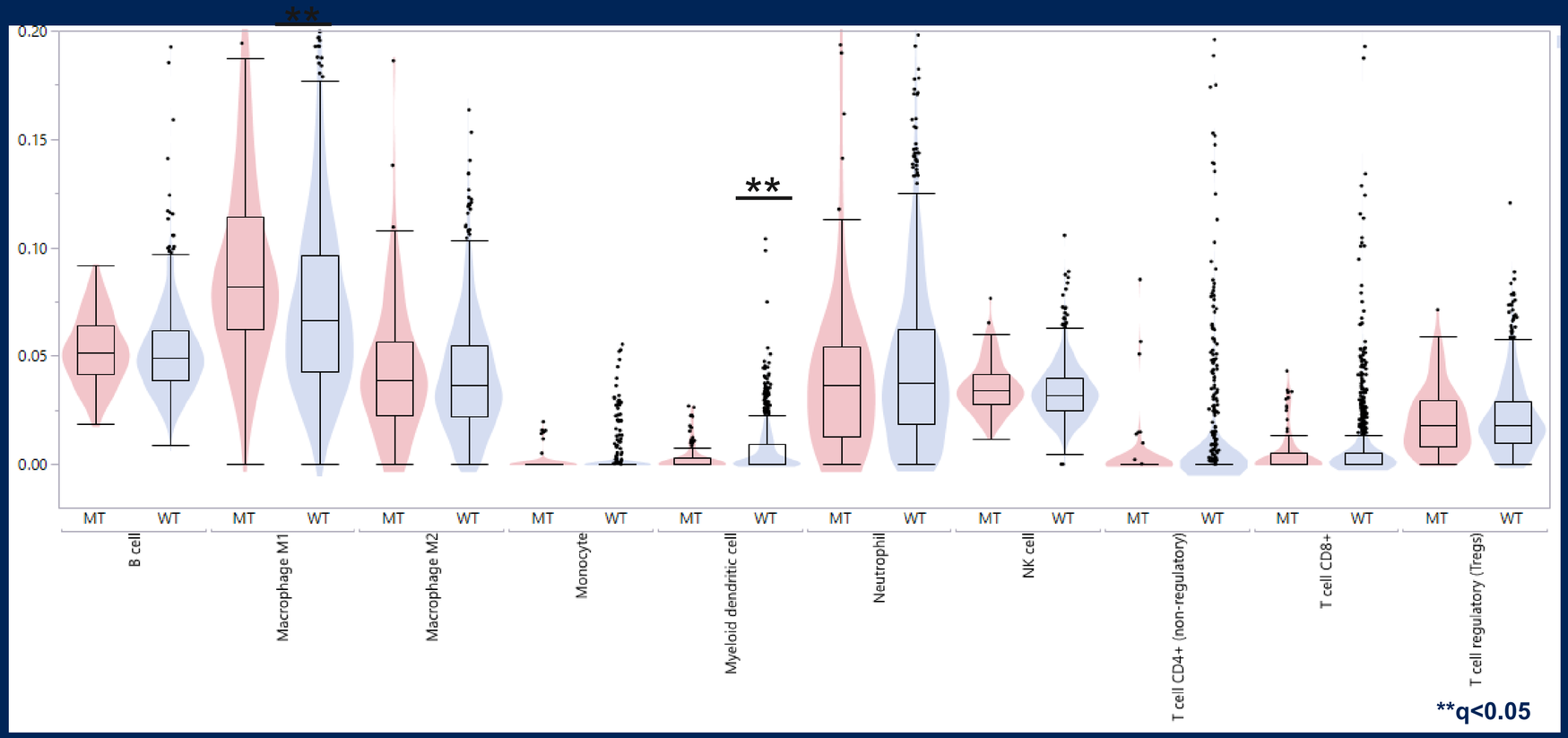
PBRM1 mutations are associated with a pro-inflammatory phenotype

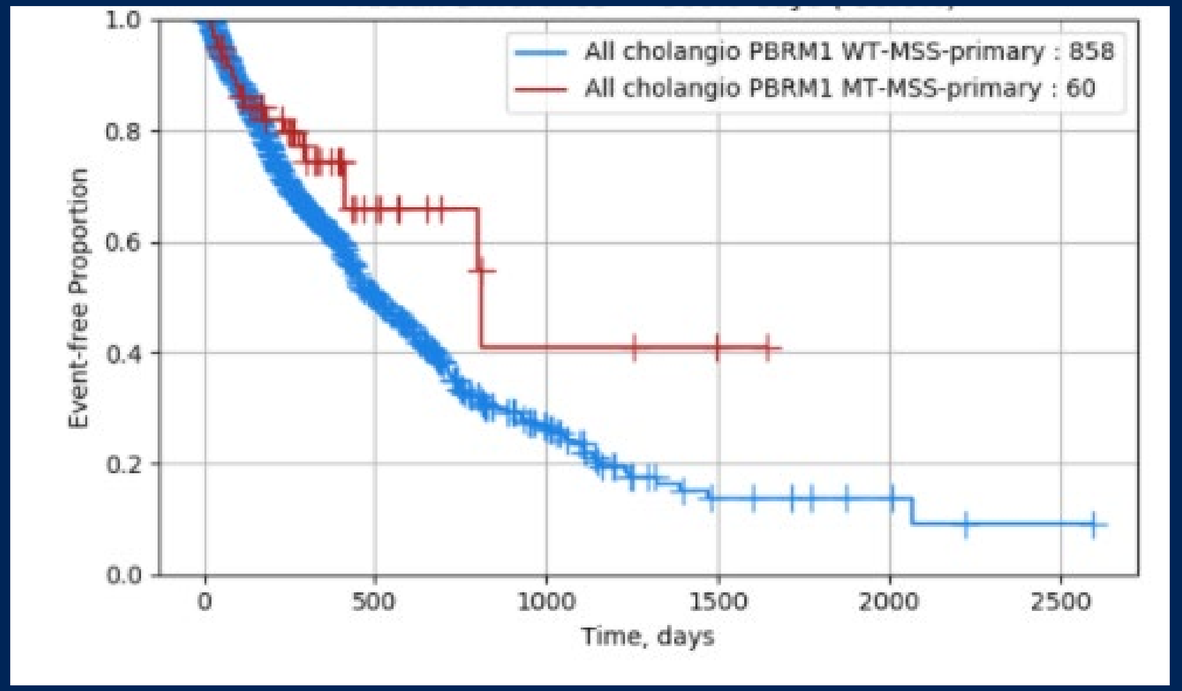
Analysis of the Tumor Microenvironment using QuantiSeq (1)



(1) Finotello et al. Genome Med. 2019

PBRM1 mutations are associated with a favorable overall survival

Overall survival was better in PBRM1 mutated patients



HR 1.667 (95% CI 1.026-2.71), p = 0.037

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Conclusion

- **This is the first study describing the genetic and immunological landscape of *PBRM1*-mutated BTCs.**
- **Co-mutations in chromatin-remodelling and DNA damage repair genes might set the stage for testing of PARP inhibitors in *PBRM1*-mutated BTC.**
- **A distinct TME characterized by high M1 macrophages infiltration and an enrichment of inflammatory genes suggest a potential benefit of immunotherapy.**