

P3.376: Reduced MTAP and CDKN2A mRNA Expression is Associated with Poor Outcome in Pleural Mesothelioma

Paolo Ambrosini¹, Ghazal Farhikhteh¹, Luca Invernizzi¹, Arianna Rigamonti¹, Daniele Lorenzini², Rebecca Romanò¹, Chiara Cavalli¹, Silvia Marchesi¹, Giulia Corrao¹, Laura Mazzeo¹, Teresa Beninato¹, Marta Brambilla¹, **Arsela Prelaj**¹, Claudia Proto¹, Filippo De Braud¹, Daniele Generali³, Giuseppe Lo Russo¹, Monica Ganzinelli¹, Mario Occhipinti¹

Affiliations: 1. Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy 2. Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy 3. Department of Medicine (DMED), University of Udine, Udine, Italy
Correspondence: paolo.ambrosini@istitutotumori.mi.it

INTRODUCTION

- ❑ **Pleural mesothelioma (PM)** is an aggressive malignancy with limited prognostic biomarkers.
- ❑ **9p21 deletion**, involving **CDKN2A** and frequently **MTAP**, is one of the most common molecular alterations in PM and is associated with aggressive behaviour.
- ❑ While these alterations are well characterized at the genomic level, their **mRNA expression and prognostic significance remain unclear**.

Aim

🎯 To assess the prognostic value of **MTAP** and **CDKN2A** mRNA expression in a real-world PM cohort and validate the findings in an independent **TCGA** dataset.

METHODS



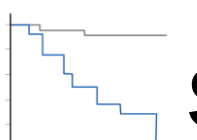
Cohort

- 150 patients, 125 with epithelioid ePM
- Median age: 72 years (IQR 65-77); male 74%
- Asbestos exp: yes (21.3%), no (22.0%), NA (56.7%)
- Immunotherapy: yes (16.0%), no (36.7%), NA 47.3%).



Transcriptomic profiling

- RNA extraction from FFPE samples
- 3' Digital Gene Expression Sequencing



Survival analysis

- Median-based stratification
- OS estimated by KM analysis
- Group comparisons performed with the log-rank test



External validation

- Independent validation using the TCGA PM cohort

RESULTS

MTAP

Low MTAP mRNA expression was significantly associated with shorter OS.

Overall PM cohort: log-rank $p=0.0027$; ePM subgroup: $p<0.0001$.

Validated in TCGA

Overall cohort: $p<0.0001$; ePM subgroup: $p=0.0007$.

Fig.1 OS by MTAP expression (overall cohort)

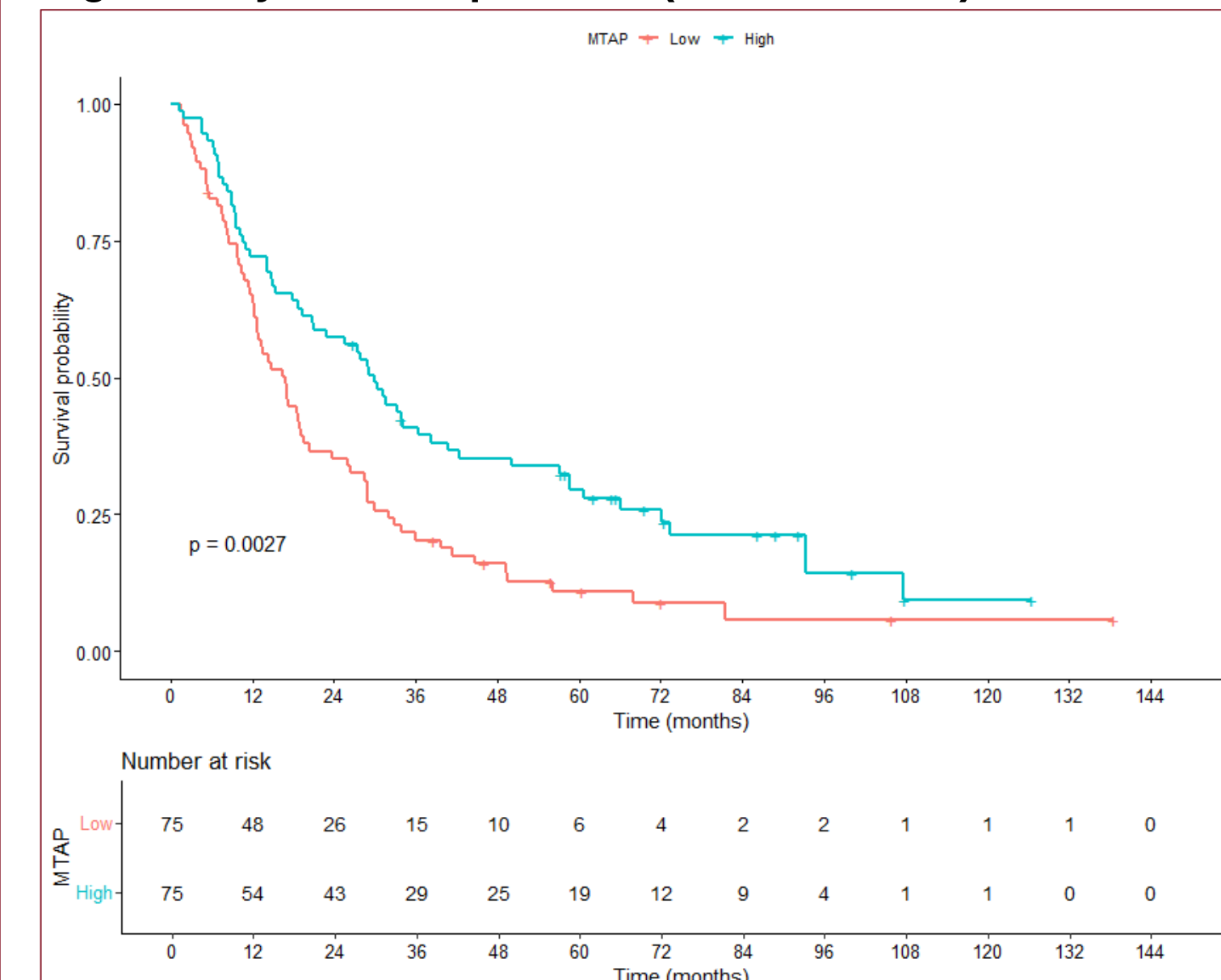


Fig.2 OS by MTAP expression (ePM cohort)

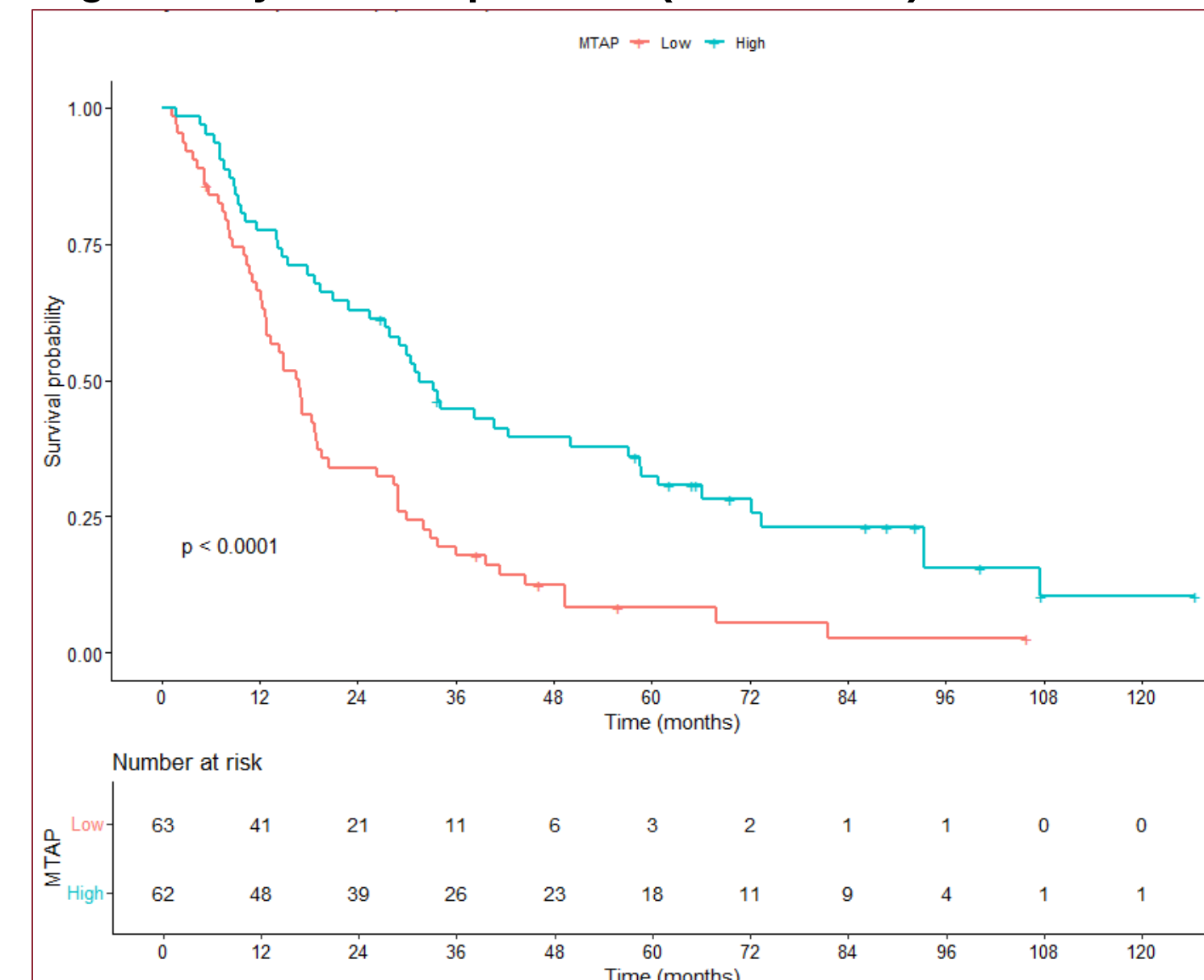


Fig.3 OS by MTAP expression (TCGA full cohort)

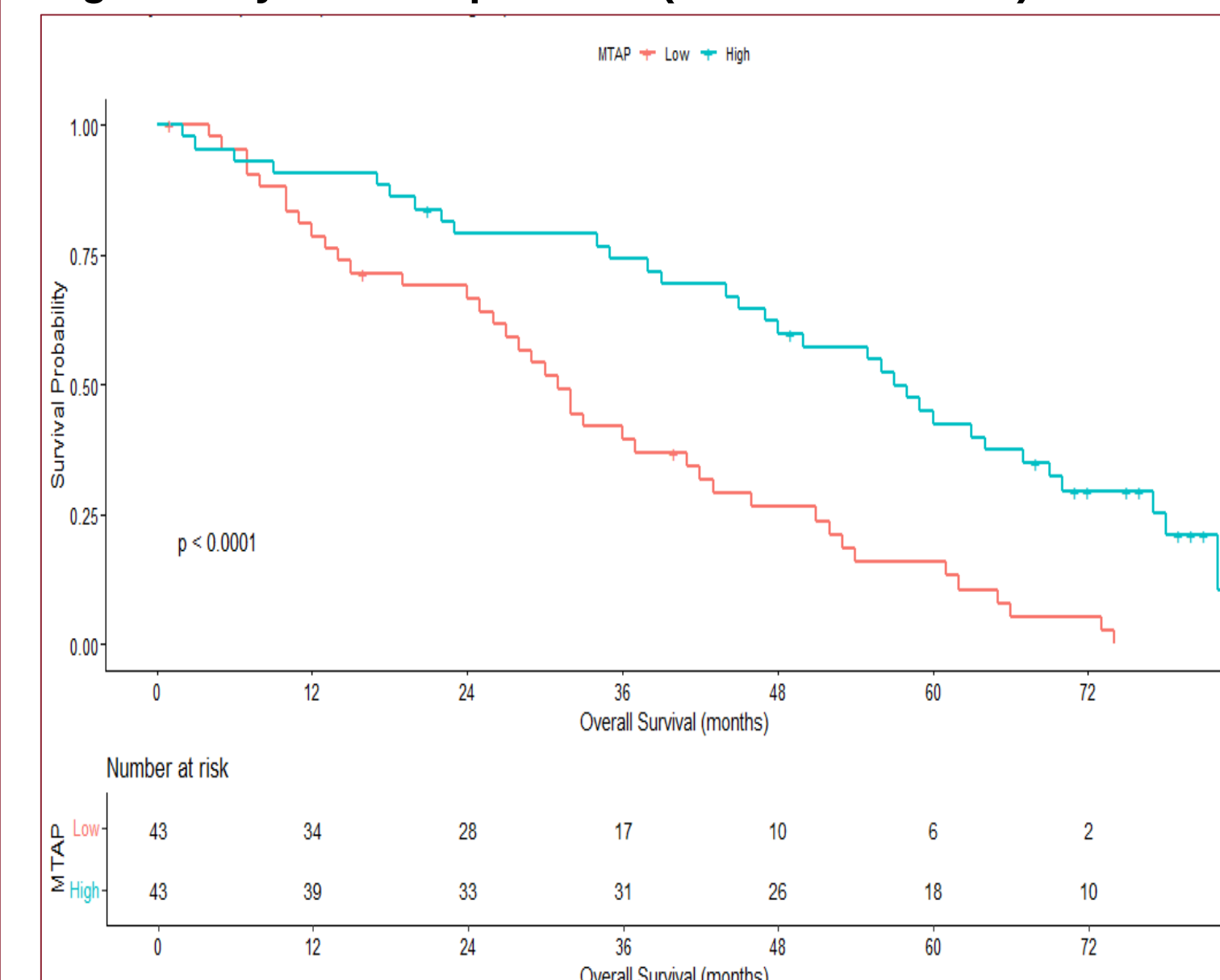
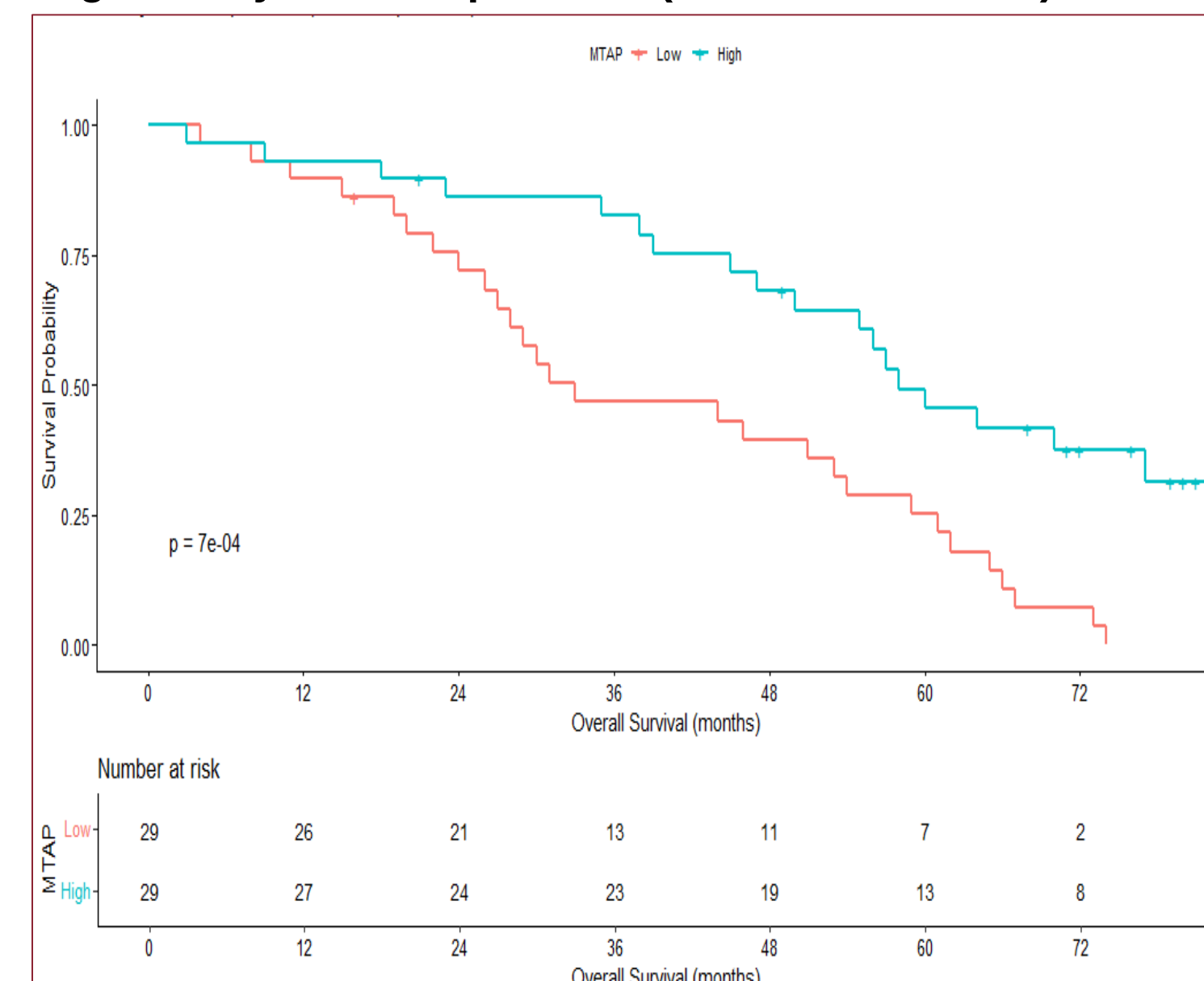


Fig.4 OS by MTAP expression (TCGA ePM cohort)



CDKN2A

Low CDKN2A mRNA expression was significantly associated with shorter OS.

Overall PM cohort: $p=0.02$; ePM subgroup: $p=0.0013$.

Validated in TCGA

Overall cohort: $p<0.0001$; ePM subgroup: $p<0.0001$.

Fig.5 OS by CDKN2A expression (overall cohort)

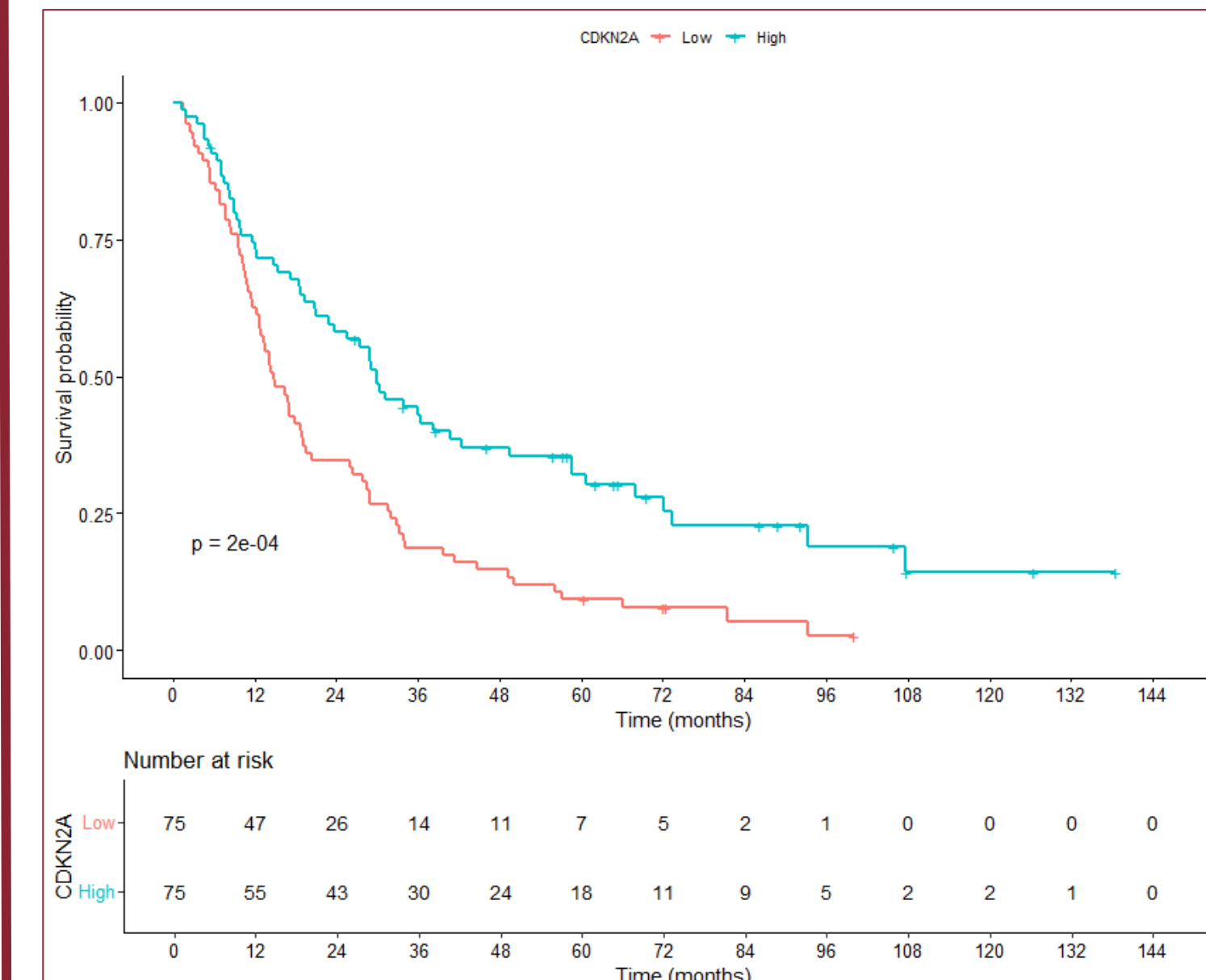


Fig.6 OS by CDKN2A expression (ePM cohort)

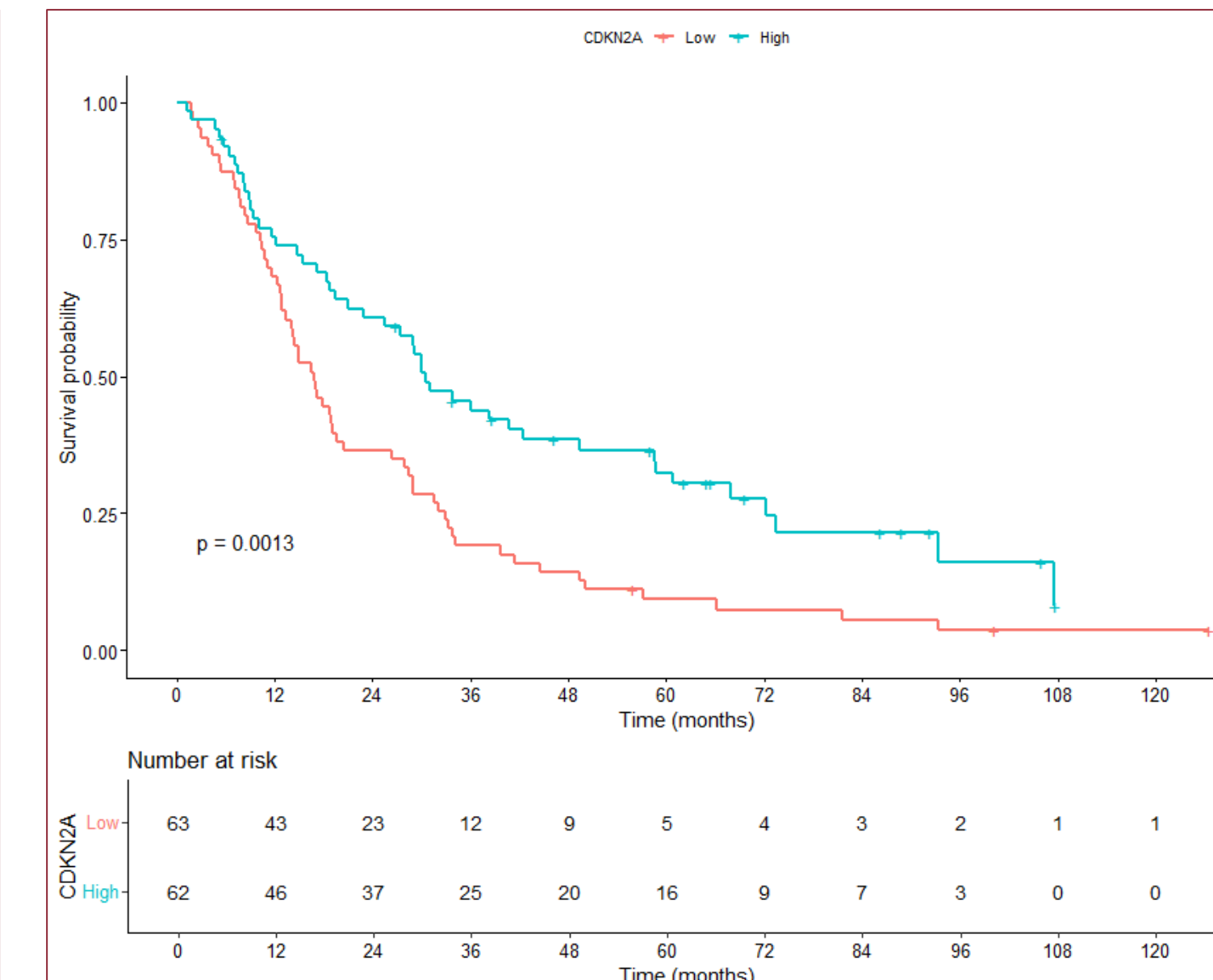


Fig.7 OS by CDKN2A expression (TCGA full cohort)

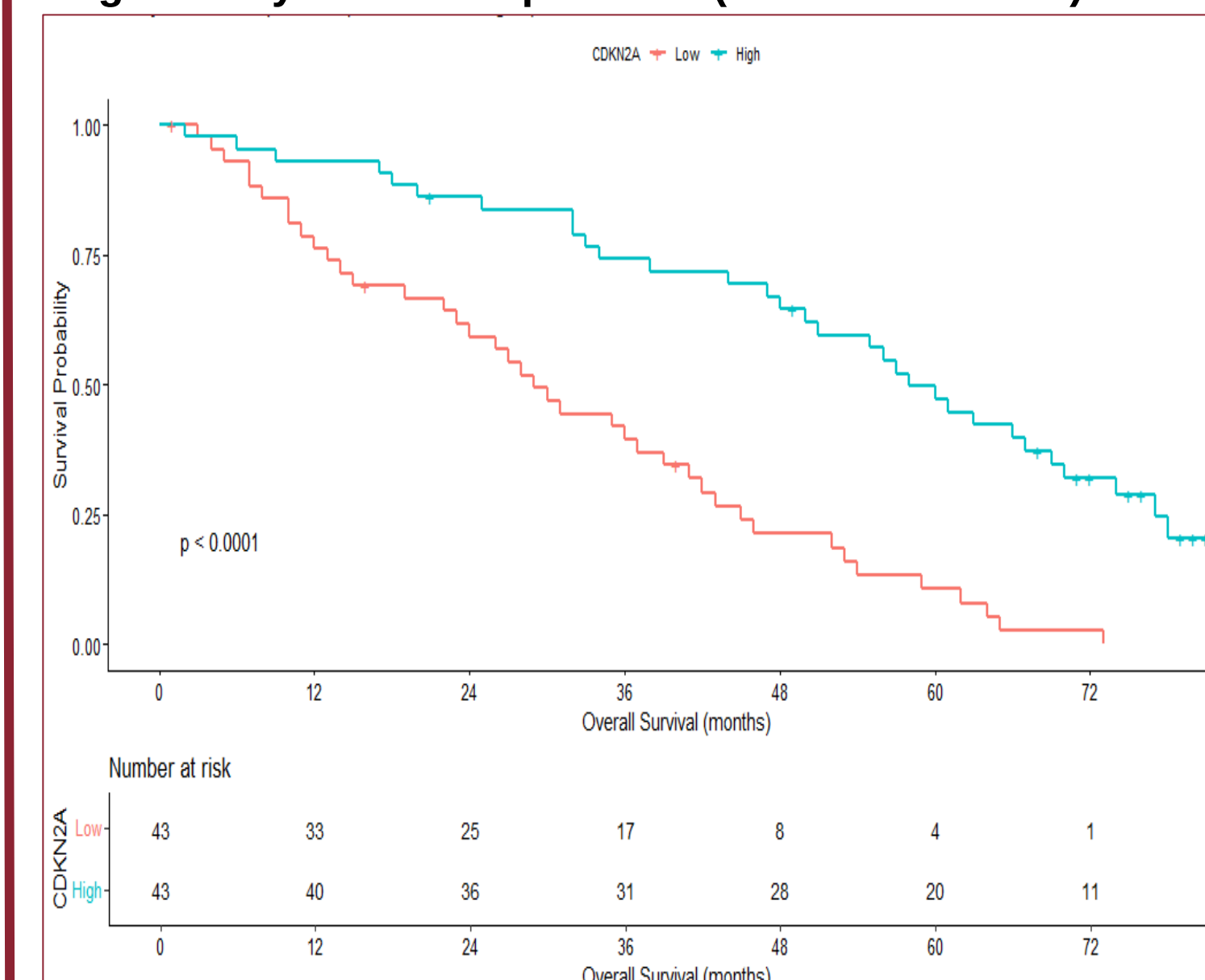
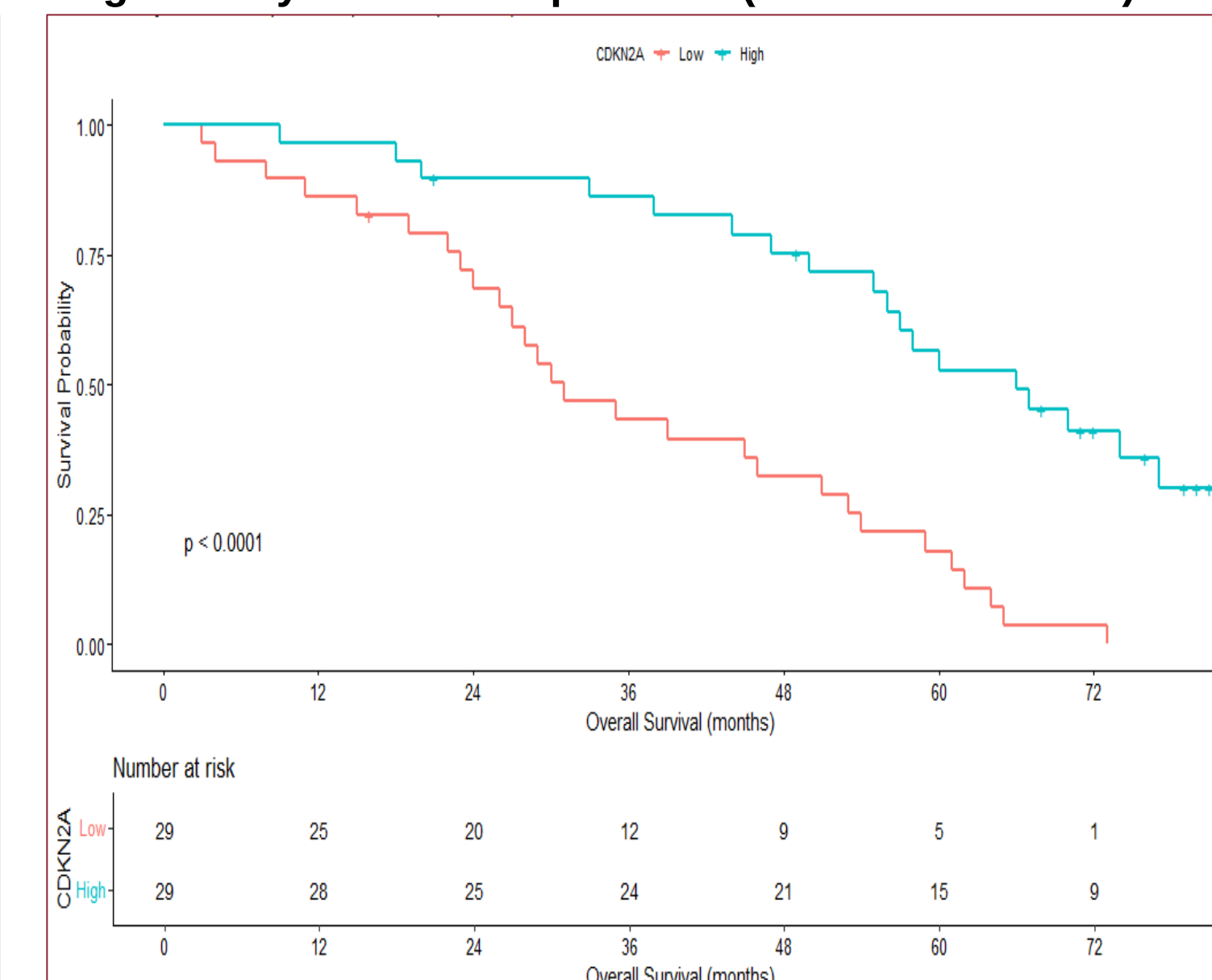


Fig.8 OS by CDKN2A expression (TCGA ePM cohort)



CONCLUSION

Low MTAP and CDKN2A expression are associated with poor survival in PM and may serve as prognostic biomarkers, particularly in ePM. Furthermore, MTAP loss may identify a therapeutically actionable subgroup, supporting biomarker-driven treatment approaches.