

Supplementary Material 1: Univariate Cox regression for MCC-specific survival in the full population, with adjusted p-values after the Benjamini-Hochberg method.

Gene	HR (95% CI)	<i>p</i> -value	Adjusted <i>p</i> -value
<i>PIK3CA</i>	3.07 (1.74 – 5.41)	< 0.001	0.003
<i>SETBP1</i>	3.18 (1.74 – 5.82)	< 0.001	0.002
<i>KDR</i>	2.78 (1.59 – 4.86)	< 0.001	0.028
<i>RET</i>	2.1 (1.25 – 3.53)	0.005	0.033
<i>NF1</i>	2.07 (1.13 – 2.79)	0.018	0.09
<i>ASXL1</i>	2.14 (1.11 – 4.13)	0.023	0.1
<i>RB1</i>	1.68 (1.02 – 2.79)	0.042	0.15
<i>ARID1B</i>	1.88 (1.01 – 3.50)	0.046	0.14
<i>KMT2D</i>	1.73 (1.00 – 3.00)	0.052	0.14
<i>CREBBP</i>	1.84 (0.95 – 3.54)	0.070	0.17
<i>ARID1a</i>	1.75 (0.94 – 3.23)	0.076	0.17
<i>NOTCH2</i>	1.64 (0.88 – 3.05)	0.12	0.25
<i>TP53</i>	1.46 (0.88 – 2.43)	0.14	0.27
<i>KMT2A</i>	1.50 (0.84 – 2.67)	0.17	0.30
<i>PIK3CB</i>	1.38 (0.68 – 2.82)	0.38	0.63
<i>ROS1</i>	1.30 (0.67 – 2.52)	0.43	0.68
<i>MTOR</i>	0.76 (0.38 – 1.55)	0.46	0.67
<i>ERBB4</i>	1.29 (0.63 – 2.62)	0.49	0.68
<i>APC</i>	1.24 (0.68 – 2.26)	0.49	0.64
<i>BRCA2</i>	1.23 (0.68 – 2.21)	0.49	0.61
<i>SMARCA4</i>	0.85 (0.42 – 1.72)	0.65	0.77
<i>FAT1</i>	0.87 (0.41 – 1.83)	0.71	0.81
<i>CUX1</i>	1.11 (0.56 – 2.20)	0.76	0.83
<i>NOTCH1</i>	1.09 (0.63 – 1.87)	0.77	0.8
<i>GLI2</i>	0.97 (0.41 – 2.25)	0.94	0.94

Supplementary Material 2: Multivariable Cox regression model for *PIK3CA* and MCC-specific survival, performed separately for each selected gene and adjusted variables.

Variable	HR (95% CI)	<i>p</i>
<i>PIK3CA</i>	2.07 (1.10 – 3.88)	0.024
Age	1.03 (1.00 – 1.05)	0.043
TMB	1.00 (0.99 – 1.02)	0.64
Stage III	2.05 (0.87 – 4.82)	0.10
Stage IV	7.50 (3.04 – 18.50)	< 0.001
Immunotherapy	1.91 (1.02 – 3.55)	0.042

Supplementary Material 3: Multivariable Cox regression model for *SETBP1* and MCC-specific survival, performed separately for each selected gene and adjusted variables.

Variable	HR (95% CI)	<i>p</i>
<i>SETBP1</i>	1.28 (0.63 – 2.60)	0.50
Age	1.02 (0.99 – 1.05)	0.19
TMB	1.01 (1.00 – 1.02)	0.27
Stage III	1.81 (0.77 – 4.24)	0.17
Stage IV	6.37 (2.57 – 15.76)	< 0.001
Immunotherapy	2.12 (1.15 – 3.92)	0.017

Supplementary Material 4: Multivariable Cox regression model for KDR and MCC-specific survival, performed separately for each selected gene and adjusted variables.

Variable	HR (95% CI)	<i>p</i>
<i>KDR</i>	1.37 (0.69 – 2.71)	0.37
Age	1.02 (0.99 – 1.05)	0.17
TMB	1.01 (0.99 – 1.02)	0.39
Stage III	1.91 (0.81 – 4.49)	0.14
Stage IV	6.37 (2.60 – 15.65)	< 0.001
Immunotherapy	2.13 (1.16 – 3.93)	0.015

Supplementary Material 5: Multivariable Cox regression model for RET and MCC-specific survival, performed separately for each selected gene and adjusted variables.

Variable	HR (95% CI)	<i>p</i>
<i>RET</i>	1.61 (0.94 – 2.74)	0.08
Age	1.02 (1.00 – 1.05)	0.07
TMB	1.01 (0.99 – 1.02)	0.38
Stage III	1.86 (0.79 – 4.37)	0.15
Stage IV	6.85 (2.81 – 16.71)	< 0.001
Immunotherapy	2.11 (1.16 – 3.83)	0.014

Supplementary Material 6: Baseline clinicopathologic and treatment characteristics according to *PIK3CA* mutation status. Normally distributed continuous variables were tested with two-tailed Student's t-test and non-normally distributed continuous variables were tested with Wilcoxon test. Categorical variables were tested with chi-square/Fisher exact test.

Variable		<i>PIK3CA</i> mutated	<i>PIK3CA</i> wild type	<i>p</i>
n		22 (27.5%)	58 (72.5%)	
Age	Mean (SD)	72.6 (16.3)	74.3 (9.6)	0.64
Male Sex	n (%)	12 (54.5%)	42 (72.4%)	0.21
Stage	I/II	6 (27.3%)	14 (24.1%)	0.62
	III	10 (45.5%)	33 (56.9%)	
	IV	6 (27.3%)	11 (19.0%)	
TMB	Median (IQR)	36.1 (18.0 – 44.8)	25.3 (13.5 – 31.0)	0.04
Immunotherapy	n (%)	14 (63.6%)	22 (37.9%)	0.07

Supplementary Material 7. Prognostic impact of *PIK3CA* status across different clinical contexts. Hazard ratios (HR), 95% confidence intervals (CI), and p-values derived from multivariable Cox regression models and sensitivity analyses. The primary multivariable model was adjusted for age, stage, immunotherapy use, and tumor mutational burden (TMB). Sensitivity analyses include: (1) high-TMB subgroup; (2) model excluding immunotherapy; (3) stage I–III restricted cohort; and (4) Fine-Gray subdistribution hazard model for competing risks.

Sensitivity Analysis	HR (95% CI)	<i>p</i>
Multivariable Cox Regression	2.07 (1.10 – 3.88)	0.024
High TMB Population	2.52 (1.20 – 5.27)	0.014
Excluding Immunotherapy variable	2.43 (1.31 – 4.54)	0.005
Excluding Stage IV patients	3.03 (1.22 – 7.51)	0.017
Competing Risks	2.12 (1.06 – 4.26)	0.035