

Supplementary Table 2A. TCGA-LIHC PDE4DIP expression in primary tumors and solid tissue normal samples

TCGA sample-type code 01 was classified as primary tumor and code 11 as solid tissue normal. The matched analysis used 50 patient-matched tumor-normal pairs.

Analysis	Assay	Expression scale	Tumor n	Normal n	Tumor median	Normal median	P value
Unpaired primary tumor vs solid tissue normal	tpm_unstrand	log2(TPM + 1)	371	50	2.770	2.319	5.992E-07
Matched paired tumor vs solid tissue normal	tpm_unstrand	log2(TPM + 1)	50	50	3.045	2.319	9.246E-05

For the matched analysis, group medians are descriptive summaries, whereas statistical significance was assessed using the paired Wilcoxon signed-rank test on within-patient tumor-normal differences. TCGA solid tissue normal samples are not equivalent to healthy-volunteer liver controls.

Supplementary Table 2B. PDE4DIP expression by clinicopathological group

Expression values are log2(TPM + 1) derived from tpm_unstrand. P values are global tests across all levels of each variable.

Clinical variable	Group	n	Median expression	Mean expression	Test	P value
AJCC pathological stage	I	171	2.67	2.67	Kruskal-Wallis	0.475
AJCC pathological stage	II	86	2.75	2.82		
AJCC pathological stage	III	85	2.90	2.79		
AJCC pathological stage	IV	5	2.53	2.59		
Tumor grade	G1	55	2.71	2.70	Kruskal-Wallis	0.305
Tumor grade	G2	177	2.85	2.80		
Tumor grade	G3	122	2.74	2.73		
Tumor grade	G4	12	2.35	2.41		
Ishak fibrosis group	0	74	2.94	2.88	Kruskal-Wallis	0.366
Ishak fibrosis group	1-2	31	2.86	2.80		
Ishak fibrosis group	3-4	28	2.69	2.58		
Ishak fibrosis group	5-6	79	2.77	2.85		

Sparse categories (e.g., stage IV) are reported descriptively and should not be overinterpreted.

Supplementary Table 2C. Overall survival analyses

Kaplan-Meier, univariate Cox, multivariable Cox, and fibrosis-adjusted sensitivity analyses using PDE4DIP log2(TPM + 1).

Kaplan-Meier and univariate Cox analyses

Analysis	Group / variable	n	Events	Median OS (days)	HR	95% CI lower	95% CI upper	P value
Kaplan-Meier median split	PDE4DIP-low	183	60	1852				
Kaplan-Meier median split	PDE4DIP-high	183	70	1560				
Log-rank test	High vs low	366	130					0.123
Continuous univariate Cox	PDE4DIP expression (per 1-unit increase)	366	130		1.131	0.913	1.400	0.260

Main multivariable Cox model

Variable (reference)	HR	95% CI lower	95% CI upper	P value	n	Events
PDE4DIP expression (per 1-unit increase)	1.046	0.843	1.298	0.684	340	114
Age (per year)	1.011	0.996	1.026	0.143	340	114
Male vs female	0.912	0.615	1.353	0.648	340	114
AJCC stage II vs I	1.429	0.860	2.374	0.168	340	114
AJCC stage III vs I	2.850	1.847	4.398	2.230E-06	340	114
AJCC stage IV vs I	5.360	1.593	18.037	0.007	340	114
Grade G2 vs G1	1.133	0.622	2.064	0.684	340	114
Grade G3 vs G1	1.291	0.696	2.397	0.417	340	114
Grade G4 vs G1	2.535	0.889	7.229	0.082	340	114

Exploratory fibrosis-adjusted Cox sensitivity model

Variable (reference)	HR	95% CI lower	95% CI upper	P value	n	Events
PDE4DIP expression (per 1-unit increase)	0.988	0.710	1.375	0.944	199	60
Age (per year)	1.038	1.013	1.064	0.003	199	60
Male vs female	1.274	0.671	2.419	0.459	199	60
AJCC stage II vs I	1.135	0.583	2.209	0.709	199	60
AJCC stage III vs I	2.273	1.167	4.430	0.016	199	60
AJCC stage IV vs I	8.348	2.217	31.433	0.002	199	60
Grade G2 vs G1	1.869	0.637	5.483	0.255	199	60
Grade G3 vs G1	2.865	0.951	8.631	0.061	199	60
Grade G4 vs G1	9.951	2.076	47.692	0.004	199	60
Ishak 1-2 vs 0	0.793	0.320	1.964	0.616	199	60
Ishak 3-4 vs 0	0.730	0.272	1.963	0.533	199	60
Ishak 5-6 vs 0	1.040	0.515	2.100	0.913	199	60

The median cutoff was log2(TPM + 1) = 2.773025. Reference groups were female, AJCC stage I, tumor grade G1, and Ishak fibrosis group 0. PDE4DIP HRs are per 1-unit increase in log2(TPM + 1).

The fibrosis-adjusted model is exploratory (n = 199, 60 deaths); sparse categories, particularly stage IV and grade G4, yield imprecise estimates and should not be emphasized.

Supplementary Table 2D. Tumor purity analyses

Association between PDE4DIP expression and ABSOLUTE tumor purity, followed by a purity-adjusted overall-survival model.

Correlation between PDE4DIP expression and ABSOLUTE tumor purity

Analysis	n	Correlation coefficient	P value
Spearman correlation	354	0.211	6.536E-05
Pearson correlation	354	0.203	1.240E-04

ABSOLUTE-purity-adjusted Cox regression for overall survival

Variable (reference)	HR	95% CI lower	95% CI upper	P value	n	Events
PDE4DIP expression (per 1-unit increase)	1.061	0.850	1.324	0.602	324	110
Age (per year)	1.013	0.998	1.029	0.096	324	110
Male vs female	0.924	0.617	1.382	0.699	324	110
AJCC stage II vs I	1.505	0.905	2.503	0.115	324	110
AJCC stage III vs I	2.712	1.737	4.234	1.140E-05	324	110
AJCC stage IV vs I	5.498	1.630	18.549	0.006	324	110
Grade G2 vs G1	1.187	0.640	2.201	0.586	324	110
Grade G3 vs G1	1.372	0.724	2.602	0.332	324	110
Grade G4 vs G1	2.590	0.897	7.484	0.079	324	110
ABSOLUTE tumor purity (per 1.0 unit)	1.015	0.371	2.775	0.976	324	110

The observed correlations were weak and positive. The complete-case Cox model included n = 324 and 110 deaths. Reference groups were female, AJCC stage I, and tumor grade G1.

ABSOLUTE purity ranges from 0 to 1; its HR is shown per 1.0-unit increase, not per 1% increase.

Supplementary Table 2E. Analysis notes and interpretation boundaries

These notes define the analytical scope and prevent overinterpretation of gene-level PDE4DIP results as MMG8 isoform-specific clinical evidence.

Item	Description
Scope	This supplementary table summarizes TCGA-LIHC gene-level PDE4DIP analyses of tumor-versus-normal expression, clinicopathological variables, tumor purity, overall survival, and recurrence-data availability.
Expression definition	Tumor-versus-normal, clinicopathological association, purity-correlation, Kaplan-Meier, and Cox analyses used PDE4DIP log2(TPM + 1) values derived from tpm_unstrand. The separate DESeq2/GSEA workflow is not covered by this statement.
Variable availability	Age and gender were available for multivariable modeling. AJCC stage was valid for 347/371 tumors, tumor grade for 366/371, Ishak fibrosis group for 212/371, and ABSOLUTE purity for 354/371. HBV/HCV status, etiology, and alcohol history were unavailable in the clinical annotation used.
OS cohort	The overall-survival cohort included 366 patients and 130 deaths after excluding one case with missing survival time and four cases with non-positive survival time.
Cox effect scale	PDE4DIP HRs are reported per 1-unit increase in log2(TPM + 1); age HRs are per year. ABSOLUTE-purity HR is per 1.0-unit increase on the 0-1 scale.
Reference groups	Female, AJCC stage I, tumor grade G1, and Ishak fibrosis group 0 were reference categories where applicable.
Model sample sizes	Main multivariable Cox: n = 340, 114 deaths. Exploratory fibrosis-adjusted model: n = 199, 60 deaths. Purity-adjusted model: n = 324, 110 deaths.
Proportional-hazards checks	No evidence of proportional-hazards violation was detected: univariate global P = 0.86; main multivariable P = 0.69; fibrosis-adjusted P = 0.24; purity-adjusted P = 0.83.
Tumor-normal comparison	Unpaired comparisons used the Wilcoxon rank-sum test. The 50 matched tumor-normal pairs were analyzed using the paired Wilcoxon signed-rank test; group medians are descriptive summaries and are not themselves the paired effect estimate.
Recurrence endpoint	No valid recurrence-time values were available in the clinical annotation file used; recurrence-free survival was not modeled.
Purity source	TCGA PanCanAtlas ABSOLUTE purity estimates: https://gdc.cancer.gov/about-data/publications/pancanatlas
Purity matching	ABSOLUTE purity estimates and RNA-expression records were restricted to primary solid tumor samples and matched at the participant level using the first 12 characters of the TCGA barcode. When multiple eligible records were available for a participant, the first record after alphanumeric sorting of the sample barcode was retained.
Overall interpretation	Gene-level PDE4DIP expression was higher in TCGA-LIHC tumors and weakly correlated with ABSOLUTE purity, but the TPM-based survival analyses did not support PDE4DIP as an independent overall-survival prognostic factor.