

SUPPLEMENTARY TABLES

Supplementary Table 1: List of participant centers in the BIOSTORM study.

Principal Investigator	Center
Josep M Llovet	Principal investigator STORM and BIOSTORM
Jordi Bruix	Principal investigator STORM
Tadatoshi Takayama	Nihon University School of Medicine, Department of Digestive Surgery, Tokyo, Japan.
Gar-Yang Chau	Taipei Veterans General Hospital, Taipei, Taiwan.
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Sasan Roayaie	Mount Sinai Medical Center, New York, NY, U.S.
Kwan Sik Lee Lee	Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.
Norihiro Kokudo	University of Tokyo, Tokyo, Japan.
Ronnie Tung-Ping Poon	Queen Mary Hospital, Hong Kong, China.
Edward Gane	Auckland City Hospital, New Zealand.
Joong-Won Park	National Cancer Center, South Korea.
Chris Verslype	University Hospital Leuven, Department of Hepatology, Belgium.
Umberto Cillo	Azienda Ospedaliera Università di Padova, Unità Operativa di Chirurgia Epatobiliare e Trapianto Epatico, Italy.
Adina Emilia Croitoru	Institutul Clinic de Boli Digestive si Trasplant Hepatic Fundei, Departamentul de Oncologie Medicala, Romania.
Manuel de la Mata	Hospital Universitario Reina Sofia, Madrid, Spain.
Luigi Lupo	Sezione Chirurgia Generale e Trapianti di Fegato, Policlinico di Bari, Italia.
Simone Strasser	Royal Prince Alfred Hospital, Australia.

Supplementary Table 2: Predictive value of previously reported gene signatures. The association between the signatures and sorafenib treatment effect was evaluated using a Cox proportional hazards model with an interaction term (P value). In total, 140 HCC samples and 90 non-tumor adjacent tissues were analyzed. Signatures with a trend towards significance are displayed in bold. Signatures are referenced in Supplementary Table 11. N(%): number and percentage of patients positive for the signature. HR: Hazard ratio. CI: confidence interval.

Gene Signature	N (%)	Interaction with treatment		
		HR	95% CI	P value
CHIANG_SUBCLASS PROLIFERATION	53 (38)	2.111	0.627 - 7.114	0.228
CHIANG_SUBCLASS CTNNB1	28 (20)	1.674	0.385 - 7.274	0.492
CHIANG_SUBCLASS POLY7	16 (11)	0.336	0.032 - 3.509	0.362
CHIANG_SUBCLASS INF	19 (14)	0.543	0.061 - 4.849	0.585
HOSHIDA_SUBCLASS S1	59 (42)	1.076	0.332 - 3.482	0.903
HOSHIDA_SUBCLASS S2	17 (12)	1.335	0.201 - 8.888	0.765
HOSHIDA_SUBCLASS S3	47 (34)	0.999	0.273 - 3.659	0.999
BOYALT_SUBCLASS G3	43 (31)	1.647	0.499 - 5.437	0.413
CAIRO_HEPATOBLASTOMA	48 (34)	1.497	0.458 - 4.896	0.504
COULOUARN_TEMPORAL TGFB	22 (16)	1.398	0.369 - 5.289	0.622
KAPOSI_MET	18 (13)	0.893	0.226 - 3.523	0.871
LEE_SURVIVAL	37 (26)	0.674	0.199 - 2.287	0.527
RADAEVA_RESPONSE TO IFNA1	24 (17)	0.678	0.170 - 2.704	0.582
WOO_RECURRENCE	34 (24)	1.248	0.363 - 4.288	0.725
YAMASHITA_EPCAM	39 (28)	0.565	0.166 - 1.921	0.361
MINGUEZ_VASCULAR INVASION	22 (16)	7.593	0.823 - 70.055	0.074
TOVAR_IGF1R	43 (31)	2.239	0.618 - 8.108	0.220
TOVAR_SORAFENIB RESISTANCE	16 (11)	0.401	0.066 - 2.449	0.322
VILLANUEVA_CK19	54 (39)	1.187	0.357 - 3.944	0.779
VILLANUEVA_NOTCH	44 (31)	2.786	0.792 - 9.806	0.110
VILLANUEVA_pRPS6	63 (45)	1.318	0.401 - 4.330	0.649
HOSHIDA_SURVIVAL (adjacent tissue)	42 (47)	0.331	0.047 - 2.356	0.270

Supplementary Table 3: GSEA analysis of gene signatures associated with tumor patients displaying pERK positive hepatocytes. SIZE: number of genes in the gene set. NES: normalized enrichment score. Signatures are referenced in Supplementary Table 11.

NAME	SIZE	NES	P-value	FDR
CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_UP	168	2.171	0.000	0.001
BOYVAULT_LIVER_CANCER_SUBCLASS_G2	26	1.977	0.004	0.010
TOVAR_IGF1R_UP	150	1.756	0.000	0.053
VILLANUEVA_NOTCH_UP	220	1.732	0.000	0.053
VILLANUEVA_CK19_UP	151	1.676	0.015	0.073

Supplementary Table 4: List of genes evaluated by targeted exome sequencing and prevalence of identified and reported mutations. Predictive value (p of interaction) of HCC recurrence prevention with sorafenib in terms of RFS is shown for the most prevalent mutated genes.

	Targeted Gene	Prevalence in BIOSTORM	Reported prevalence ¹	p of interaction
Telomere maintenance	TERT promoter	87/163 (53)	54–60%	0.61
Cell cycle control	TP53	35/76 (46%)	27%	0.55
	ATM	3/76 (4%)	3.2%	ND
	RB1	0/76 (0%)	3%	ND
	CDKN2A	2/76 (3%)	1.4%	ND
Wnt-β catenin signaling	CTNNB1	16/76 (21%)	26.3%	0.47
	AXIN1	12/76 (16%)	4.8%	0.98
	APC	0/76 (0%)	1.6%	ND
Oxidative stress	KEAP1	1/76 (1%)	3.1%	ND
Epigenetic and chromatin remodeling	ARID1A	4/76 (5%)	5.8%	0.93
	ARID2	2/76 (3%)	6.7%	ND
	MLL / KMT2A	2/76 (3%)	2.9%	ND
	MLL3	5/76 (7%)	2%	0.99
PI3K-AKT-mTOR signaling	RPS6KA3	2/76 (3%)	3.2%	ND
	JAK1	2/76 (3%)	1.5%	ND
	PIK3CA	1/76 (1%)	1.5%	ND
	PDGFRA	0/76 (0%)	1%	ND
	PTEN	1/76 (1%)	1%	ND
Hepatic differentiation	HNF1A	1/76 (1%)	5%	ND

ND: not done because of small sample size.

Supplementary Table 5: 146 gene-expression based signature predictive of recurrence prevention on sorafenib. The genes and their calculated Cox score was associated with prognosis in terms of RFS in the set of 67 sorafenib-treated HCC patients and were not prognostic in the set of 73 placebo-treated HCC patients.

Poor Prognosis		
Gene Name	Statistic (Cox)	p value
GRAMD4	3.936	0.000
NCSTN	3.545	0.001
XRCC6	3.408	0.001
SPPL2A	3.408	0.001
EFNA2	3.376	0.001
HNRPR	3.335	0.001
SLC5A6	3.305	0.002
NME4	3.282	0.001
ZFP36L2	3.226	0.002
CAPZA2	3.212	0.001
CPS1	3.187	0.002
CPSF1	3.140	0.001
ACO2	3.103	0.002
ATP1B1	3.088	0.002
MRPS21	3.056	0.002
HGD	3.046	0.003
ARHGAP1	3.034	0.003
C1orf77	2.977	0.004
RAP1GAP	2.962	0.004
TACC1	2.952	0.005
CHERP	2.946	0.004
JSRP1	2.945	0.004
ATP5G2	2.921	0.004
ZRANB2	2.875	0.005
PBXIP1	2.863	0.004
RBPMS	2.848	0.007
ZCCHC2	2.826	0.005
MORC2	2.818	0.006
ATP2A2	2.811	0.006
IDH2	2.800	0.004
TOB1	2.771	0.008
DDX17	2.762	0.006
FTHL3	2.755	0.007
EIF4E2	2.748	0.006
MAPK14	2.747	0.007
SNORD4A	2.743	0.008
SNORD25	2.742	0.006
CAMK2N1	2.716	0.007
NUFIP2	2.710	0.007
NHP2L1	2.671	0.009
SNORD59A	2.669	0.010
PLXNB1	2.662	0.009
AGT	2.659	0.008

Good Prognosis		
Gene Name	Statistic (Cox)	p value
SYAP1	2.916	0.006
LOC392395	2.818	0.006
DOCK1	2.805	0.007
ZNF430	2.747	0.007
LOC642947	2.742	0.006
FLJ44124	2.732	0.006
GJC1	2.716	0.007
FAM40B	2.707	0.008
FBP2	2.682	0.008
OR8S1	2.672	0.009
SLC16A12	2.616	0.008
NUBPL	2.569	0.012
TNFRSF8	2.564	0.014
LOC729603	2.561	0.009
SLC5A8	2.557	0.010
LOC100134868	2.516	0.012
LOC646996	2.511	0.015
MIR146B	2.469	0.016
TDRD1	2.463	0.017
NLRP8	2.460	0.012
OR1J1	2.455	0.015
EDG7	2.454	0.018
SMCR5	2.424	0.017
COL4A3	2.423	0.020
FLJ45256	2.419	0.018
KRT16	2.390	0.018
LILRB3	2.386	0.017
ORC6L	2.385	0.017
ZNF652	2.382	0.019
IMAA	2.368	0.018
GSDM1	2.360	0.023
OR4F29	2.355	0.019
LRRN4CL	2.354	0.028
ATG9B	2.331	0.023
MIR1913	2.328	0.022
C2orf69	2.314	0.022
C18orf10	2.314	0.023
PLA2G2D	2.307	0.023
FLJ25996	2.305	0.024
LOC348174	2.296	0.023
C9orf80	2.295	0.022
LOC641522	2.292	0.030
ANKFN1	2.287	0.025

BAT3	2.653	0.009
C22orf13	2.640	0.009
ISCU	2.640	0.008
C5	2.634	0.009
DHX8	2.633	0.009
FNDC3B	2.612	0.009
DDIT4	2.608	0.012
SNORD21	2.607	0.010
C8G	2.602	0.011
ERAP2	2.598	0.009
OXA1L	2.596	0.011
CSRP1	2.579	0.013
BRI3BP	2.564	0.009
TMED9	2.548	0.012
FLAD1	2.542	0.012
CLCN5	2.529	0.011
SLC39A1	2.518	0.010
SNORD48	2.503	0.013
FTCD	2.490	0.013
C5orf32	2.479	0.014
MGC71993	2.471	0.013
ADAR	2.469	0.012
RAB7A	2.465	0.014
LRP3	2.462	0.017
TFR2	2.457	0.015
SNORD95	2.445	0.014
GIT2	2.428	0.014
SRP72	2.423	0.016
DDX39	2.408	0.016
SCNN1D	2.398	0.016
LPCAT3	2.388	0.019
CTBP1	2.377	0.016
SEPT9	2.368	0.018
MTSS1L	2.349	0.019
SNORD56	2.315	0.020
CDC42EP1	2.303	0.021
PPIG	2.288	0.021
DDT	2.287	0.020
NEU4	2.281	0.023
TNFAIP2	2.274	0.023
PCNX	2.261	0.024
PSMA1	2.257	0.021
RRP7A	2.246	0.024
CNN2	2.223	0.027

ZNF674	2.286	0.024
MGC16703	2.275	0.028
GSDMB	2.252	0.025
COX16	2.251	0.024
OR1M1	2.238	0.028
DCDC5	2.236	0.030
ZC3H12D	2.230	0.028
IL9R	2.225	0.029
REC8	2.212	0.031
STAP2	2.201	0.032
MIR575	2.193	0.031
KHDRBS3	2.183	0.033
KIAA0895L	2.179	0.031
OR2AE1	2.162	0.033
POU4F1	2.155	0.031
EOMES	2.134	0.038

Supplementary Table 9: Characteristics of patients as per their response to sorafenib according to the gene set signature.

	BIOSTORM (n=140)	
	Sorafenib RFS Responders (n=42)	Non-responders (n=98)
Age (years), median (range)	60 (41 - 75)	63 (26 - 82)
≥65 years, n (%)	14 (33.3)	45 (45.9)
Sex, n (%)		
Males	39 (92.9)	84 (85.7)
Females	3 (7.1)	14 (14.3)
Race, n (%)		
Asian*	26 (61.9)	79 (80.6)
White*	16 (38.1)	16 (16.3)
Other	0 (0)	3 (3.1)
Region, n (%)		
Americas (North, South)	4 (9.5)	6 (6.1)
Asia-Pacific (inc. Australia, New Zeland)	26 (61.9)	73 (74.5)
Europe	12 (28.6)	19 (19.4)
Etiology, n (%)		
Hepatitis B only*	28 (66.7)	41 (41.8)
Hepatitis C only*	4 (9.5)	41 (41.8)
Alcohol only	4 (9.5)	4 (4.1)
Unknown	4 (9.5)	11 (11.2)
Other	2 (4.8)	1 (1.0)
BCLC stage, n (%)		
Very early stage (0)	4 (9.5)	6 (6.1)
Early stage (A)	38 (91.5)	92 (93.9)
Number of lesions, n (%)		
1	39 (92.9)	87 (88.8)
2	3 (7.1)	9 (9.2)
≥ 3	0 (0)	2 (2.0)
Maximum tumor size (mm), median (range)	40 (15 - 117)	32.5 (12 - 175)
Microscopic vascular invasion, n (%) ¹		
No	28 (66.7)	46 (47.4)
Yes*	14 (33.3)	51 (52.6)
Tumor satellites, n (%) ¹		
No	40 (95.2)	91 (93.8)
Yes	2 (4.8)	6 (6.2)
Histological grade, n (%)		
1	9 (21.4)	11 (11.2)
2	26 (61.9)	65 (66.3)
3	7 (16.7)	22 (22.4)
Risk of recurrence, n (%) ¹		
Intermediate	21 (50.0)	33 (34.0)
High	21 (50.0)	64 (66.0)
Months resection to random, median (range)	1.8 (1.4 - 3.5)	1.7 (1.4 - 7.1)
Liver cirrhosis present, n (%)	29 (69.0)	57 (58.2)
Child Pugh, n (%)		
5	31 (73.8)	82 (83.7)
6	11 (26.2)	15 (15.3)
7	0 (0)	1 (1.0)
Albumin (g/dl), median (range)	4.1 (3.2 - 4.8)	4.0 (2.8 - 5.1)
Total Bilirubin (mg/dl), median (range)	0.6 (0.2 - 1.8)	0.6 (0.2 - 1.4)
AFP (ng/ml), median (range)	4.6 (1.3 - 60.8)	6.1 (2.0 - 239.7)

Footnote: ¹ Not available in 1 patient. * p-value < 0.05 for comparisons between patients in 'sorafenib RFS responders' and 'non-responders'.

Supplementary Table 10: HCC signatures tested for prognosis in terms of RFS in the BIOSTORM cohort. Signatures significantly associated with outcome are highlighted. N(%): number and percentage of patients positive for the signature. HR: Hazard ratio. CI: confidence interval. Signatures are referenced in Supplementary Table 10. Signatures recognizing less than 10% of the patients in the cohort are not displayed.

HCC GENE SIGNATURES		N (%)	All patients			Placebo			Sorafenib		
			HR	95%CI	P value	HR	95%CI	P value	HR	95% CI	P value
1	CHIANG_SUBCLASS PROLIFERATION	53 (38)	1.180	0.680-2.047	0.556	1.036	0.502-2.138	0.924	1.457	0.606-3.504	0.401
	CHIANG_SUBCLASS CTNNB1	28 (20)	0.892	0.448-1.777	0.746	0.647	0.250-1.677	0.370	1.437	0.521-3.959	0.483
	CHIANG_SUBCLASS POLY7	16 (11)	0.534	0.193-1.480	0.228	0.778	0.237-2.553	0.679	0.260	0.035-1.942	0.189
	CHIANG_SUBCLASS INF	19 (14)	1.324	0.646-2.713	0.444	1.539	0.692-3.419	0.290	0.676	0.090-5.071	0.704
2	HOSHIDA_SUBCLASS S1	59 (42)	1.670	0.973-2.865	0.063	1.741	0.878-3.452	0.112	1.541	0.640-3.708	0.335
	HOSHIDA_SUBCLASS S2	17 (12)	0.786	0.336-1.838	0.578	0.802	0.282-2.287	0.681	0.812	0.188-3.509	0.780
	HOSHIDA_SUBCLASS S3	47 (34)	1.042	0.585-1.855	0.890	0.907	0.431-1.909	0.798	1.197	0.475-3.022	0.703
3	BOYAUULT_SUBCLASS G3	43 (31)	1.734	1.002-3.001	0.049	1.563	0.763-3.202	0.223	2.088	0.866-5.031	0.101
4	CAIRO_HEPATOBLASTOMA	48 (34)	1.519	0.882-2.617	0.132	1.409	0.699-2.841	0.338	1.750	0.727-4.213	0.212
5	COULOUARN_TEMPORAL TGFB	22 (16)	1.788	0.935-3.419	0.079	1.588	0.646-3.900	0.314	2.148	0.824-5.596	0.118
6	KAPOSI_MET	18 (13)	2.278	1.160-4.474	0.017	2.481	0.994-6.193	0.051	2.154	0.781-5.937	0.138
7	LEE_SURVIVAL	37 (26)	1.522	0.860-2.694	0.149	1.964	0.939-4.109	0.073	1.159	0.461-2.915	0.754
8	RADAEVA_RESPONSE TO IFNA1	24 (17)	2.093	1.131-3.873	0.019	2.371	1.079-5.213	0.032	1.705	0.618-4.701	0.302
9	WOO_RECURRENCE	34 (24)	1.536	0.852-2.772	0.154	1.466	0.655-3.280	0.352	1.763	0.720-4.320	0.215
10	YAMASHITA_EPCAM	39 (28)	1.521	0.872-2.655	0.140	1.954	0.971-3.931	0.060	1.042	0.399-2.722	0.933
11	MINGUEZ_VASCULAR INVASION	22 (16)	1.159	0.545-2.464	0.701	0.572	0.137-2.392	0.444	1.923	0.736-5.029	0.182
12	TOVAR_IGF1R	43 (31)	1.227	0.689-2.186	0.487	1.070	0.482-2.375	0.868	1.505	0.623-3.636	0.363
13	TOVAR_SORAFENIB RESISTANCE	16 (11)	1.238	0.558-2.743	0.599	1.976	0.762-5.121	0.161	0.603	0.140-2.601	0.497
14	VILLANUEVA_CK19	54 (39)	0.875	0.499-1.535	0.642	0.888	0.430-1.833	0.747	0.865	0.354-2.118	0.752
15	VILLANUEVA_NOTCH	44 (31)	1.007	0.565-1.793	0.982	0.680	0.295-1.567	0.365	1.694	0.704-4.075	0.240
16	VILLANUEVA_pRPS6	63 (45)	1.318	0.769-2.260	0.316	1.305	0.657-2.593	0.447	1.401	0.580-3.384	0.454
17	HOSHIDA_SURVIVAL (adjacent tissue)	42 (47)	0.631	0.289-1.379	0.249	1.071	0.429-2.676	0.883	0.289	0.058-1.443	0.130

Supplementary Table 11: Publicly available gene signatures used in the study.

Name used to refer to the signature	Supplementary Reference
BOYAULT_LIVER_CANCER_SUBCLASS_G2	2
BOYAULT_SUBCLASS G3	
G3 (present vs absent)	
G56 Class	
CAIRO_HEPATOBLASTOMA	3
CHIANG_SUBCLASS CTNNB1	4
CHIANG_SUBCLASS INF	
CHIANG_SUBCLASS POLY7	
CHIANG_SUBCLASS PROLIFERATION	
Proliferation Class	
CTNNB1 Class	5
COULOUARN_TEMPORAL TGFB	
HOSHIDA_SUBCLASS S1	6
HOSHIDA_SUBCLASS S2	
HOSHIDA_SUBCLASS S3	
S1 Class	
S3 Class	
HOSHIDA_SURVIVAL	7
KAPOSI_MET	8
MET (present vs absent)	
LEE_SURVIVAL	9
MINGUEZ_VASCULAR INVASION	10
RADAEVA_RESPONSE TO IFNA1	11
response to IFN α 1 (present vs absent)	
TOVAR_IGF1R	12
TOVAR_SORAFENIB RESISTANCE	13
VILLANUEVA_CK19	14
VILLANUEVA_NOTCH	15
VILLANUEVA_pRPS6	16
WOO_RECURRENCE	17
YAMASHITA_EPCAM	18
Wnt-TGFb	19
HCC Immune Class	20
T Cell Exhaustion signature	21
PD-1 signature	
Stromal141_UP	22
Immune141_UP	
Immunophenoscore	23
Activated CD8+ T cells	
Activated CD4+ T cells	
Effector Memory CD8+ T cells	
Effector Memory CD4+ T cells	
MHC	
Macrophages	
Mast cells	
TH1 cells	
TH2 cells	

B.P. metagene	24
T.NK. metagene	
Expanded IFN signature	25
6-gene IFN signature	
CD8+ T cells	26
Central Memory CD8+ T cells	
B cells	
TFH cells	
NK ^{CD56dim} cells	
Neutrophils	
Eosinophils	
TLS	20

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