Supplementary Materials for

Biological signatures of International Prognostic Index in diffuse large B-cell lymphoma

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Supplementary Table S1A. Frequency of oncogenic mutations related to different IPI risk groups (n = 1233).

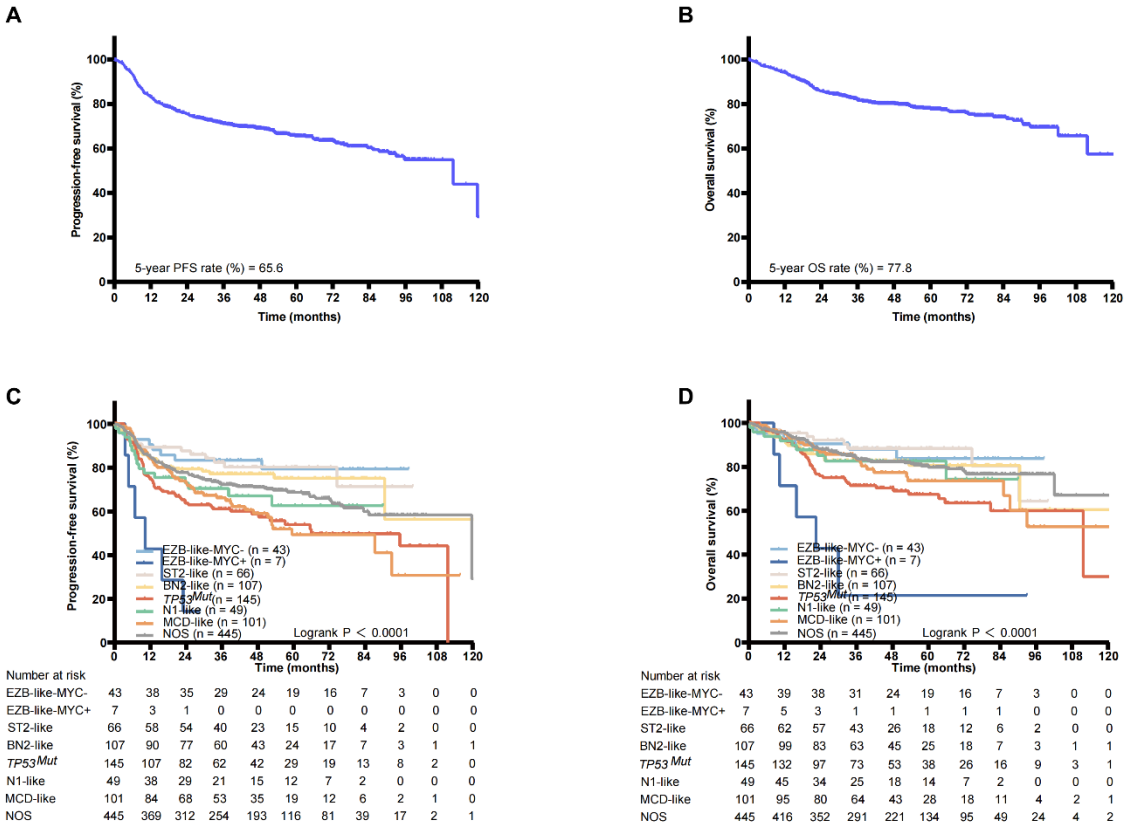
	IPI 0-1 (%)	IPI 2 (%)	IPI 3 (%)	IPI 4-5 (%)	P
CARD11	6.8	10.0	11.7	11.2	0.015
CD79A	1.4	2.2	3.3	3.7	0.026
CD79B	11.0	10.0	13.8	23.5	＜0.0001
CREBBP	8.9	10.8	8.3	16.0	0.037
FAS	6.3	6.9	6.3	11.8	0.049
FBWX7	1.0	2.2	3.3	2.7	0.040
MYC	6.1	8.2	7.9	10.7	0.044
MYD88	17.9	19.0	19.2	30.5	0.002
PIM1	23.3	20.8	22.9	33.2	0.036
PRDM1	5.9	9.1	11.7	10.7	0.005
TBL1XR1	7.1	7.8	5.8	13.9	0.042
SGK1	10.6	3.9	5.8	6.4	0.014
$MYD88^{L265P}$	12.2	11.7	13.8	22.5	0.002
$MYD88^{L265P}$/*CD79B* double mutation	3.8	3.0	5.4	10.7	0.001

Supplementary Table S1B. Frequency of oncogenic mutations related to risk factors within IPI (n = 1233).

	Age＞60 (%)	**Age ≤ 60 (%)**	**P**
BTG1	12.9	9.2	0.04
CD79B	16.9	10.0	< 0.0001
DTX1	13.6	10.0	0.049
FAS	8.9	5.8	0.033
MYD88	25.0	16.4	< 0.0001
TBL1XR1	9.9	6.5	0.036
TET2	16.2	9.9	0.001
$MYD88^{L265P}$	17.5	10.9	0.001
$MYD88^{L265P}$/*CD79B* double mutation	7.2	3.2	0.001
	Ann Arbor stage III-IV (%)	**Ann Arbor stage I-II (%)**	
CARD11	10.9	7.3	0.028
CD58	7.2	4.3	0.027
CREBBP	12.7	7.9	0.005
FBXW7	2.8	1.1	0.028
MYC	9.2	6.0	0.034
PRDM1	10.0	6.8	0.04
SGK1	5.5	9.9	0.004
	Extra-nodal involvement ≥ 2 (%)	**Extra-nodal involvement 0-1 (%)**	
CD79A	3.6	1.7	0.046
CD79B	17.6	11.4	0.003
FBXW7	3.6	1.3	0.007
MYC	10.2	6.4	0.023
MYD88	23.7	18.9	0.010
$MYD88^{L265P}$	17.9	12.3	0.010
$MYD88^{L265P}$/*CD79B* double mutation	7.4	4.0	0.012
	LDH ratio＞1*ULN (%)	**LDH ratio normal (%)**	
BTG1	13.5	8.4	0.004
CD79B	16.3	10.2	0.001
MYC	9.5	5.6	0.011
MYD88	22.8	17.7	0.026
NOTCH2	8.6	5.0	0.011
PRDM1	10.0	6.8	0.044
TP53	18.8	11.8	0.001
SGK1	9.7	5.9	0.013

MYD88^{L265P}/*CD79B* double mutation	6.5	3.5	0.017
	ECOG PS ≧ 2 (%)	**ECOG PS 0-1 (%)**	
CD79B	18.8	12.5	0.039
HIST1H1C	11.6	5.8	0.010
TMSB4X	13.8	8.2	0.031

Supplementary Figure S1. (A) PFS of patients with available genetic subtypes (n = 963). (B) OS of patients with available genetic subtypes (n = 963). (C) Kaplan-Meier models of PFS according to genetic subtypes. (D) Kaplan-Meier models of OS according to genetic subtypes.



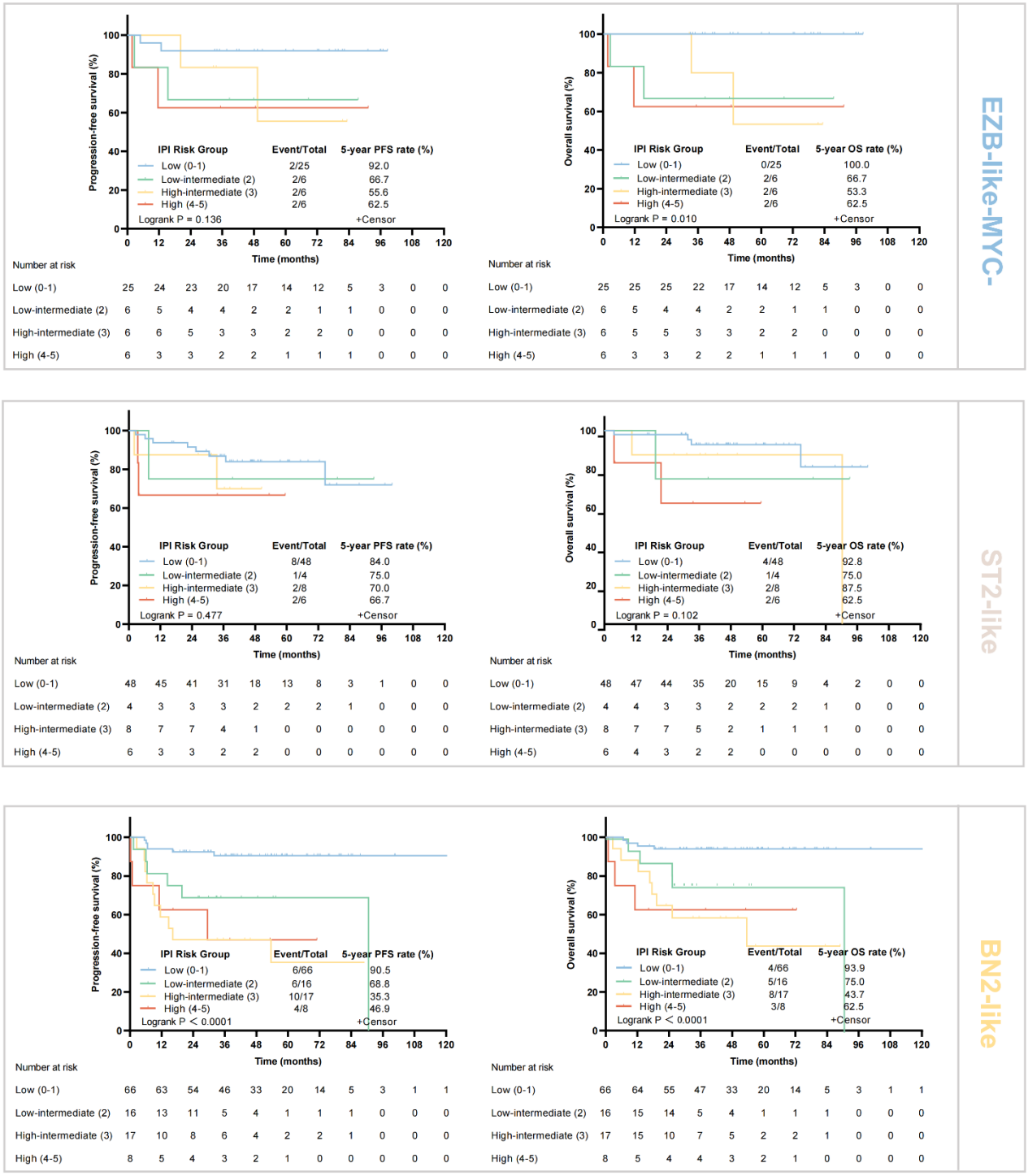
Supplementary Table S2. Stratified models for progression-free survival and overall survival of IPI risk groups and genetic subtypes in BCC cohort (n = 296).

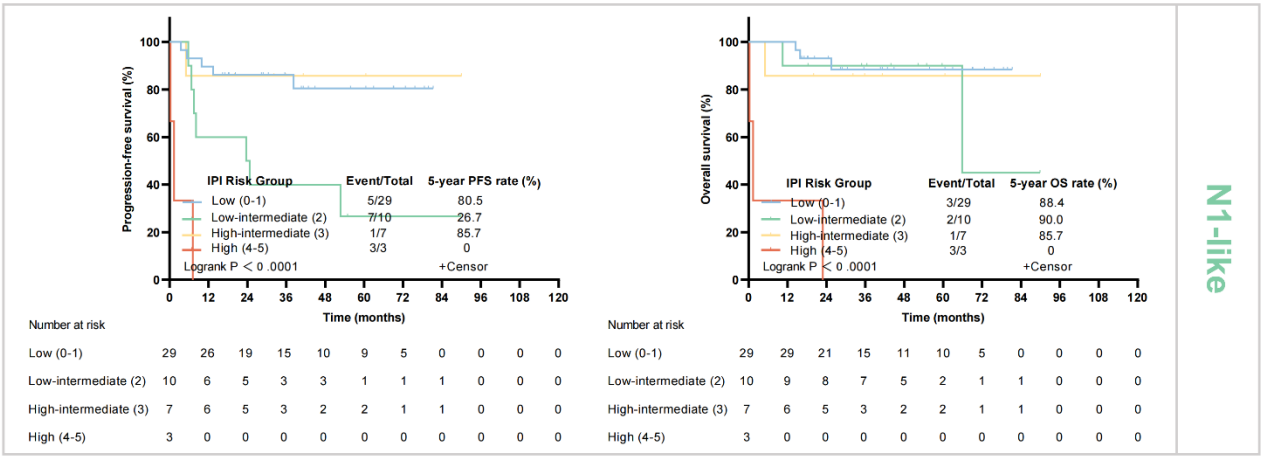
Risk factor	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
IPI risk groups								
IPI 0-1	reference		reference		reference		reference	
IPI 2	1.770 (1.097-2.856)	0.019	1.844 (1.134-3.000)	0.014	1.723 (1.018-2.915)	0.043	1.800 (1.055-3.070)	0.031
IPI 3	3.063 (1.865-5.031)	＜0.0001	2.800 (1.671-4.692)	＜0.0001	3.234 (1.897-5.514)	＜0.0001	2.977 (1.707-5.192)	＜0.0001
IPI 4-5	4.590 (2.851-7.387)	＜0.0001	4.561 (2.814-7.394)	＜0.0001	5.515 (3.331-9.131)	＜0.0001	5.622 (3.372-9.373)	＜0.0001
Genetic subtypes								
NOS	-	-	reference	-	-	-	reference	-
EZB-like-MYC-	0.498 (0.304-0.817)	0.006	0.609 (0.328-1.130)	0.116	0.432 (0.248-0.754)	0.003	0.557 (0.283-1.094)	0.089
EZB-like-MYC+	0.909 (0.401-2.062)	0.820	0.963 (0.389-2.380)	0.934	0.873 (0.357-2.138)	0.767	0.962 (0.361-2.565)	0.938
ST2-like	0.686 (0.395-1.191)	0.180	1.025 (0.528-1.992)	0.941	0.711 (0.400-1.261)	0.243	1.112 (0.557-2.220)	0.764
BN2-like	1.138 (0.630-2.057)	0.667	1.268 (0.632-2.544)	0.504	1.212 (0.653-2.250)	0.542	1.418 (0.685-2.933)	0.347
$TP53^{Mut}$	1.615 (1.135-2.299)	0.008	1.641 (0.995-2.705)	0.052	1.668 (1.150-2.419)	0.007	1.768 (1.047-2.986)	0.033
N1-like	1.752 (0.648-4.741)	0.269	1.512 (0.511-4.478)	0.455	2.072 (0.764-5.618)	0.152	1.832 (0.614-5.466)	0.278
MCD-like	1.909 (1.210-3.012)	0.005	1.754 (0.976-3.153)	0.060	1.778 (1.103-2.864)	0.018	1.689 (0.915-3.116)	0.094

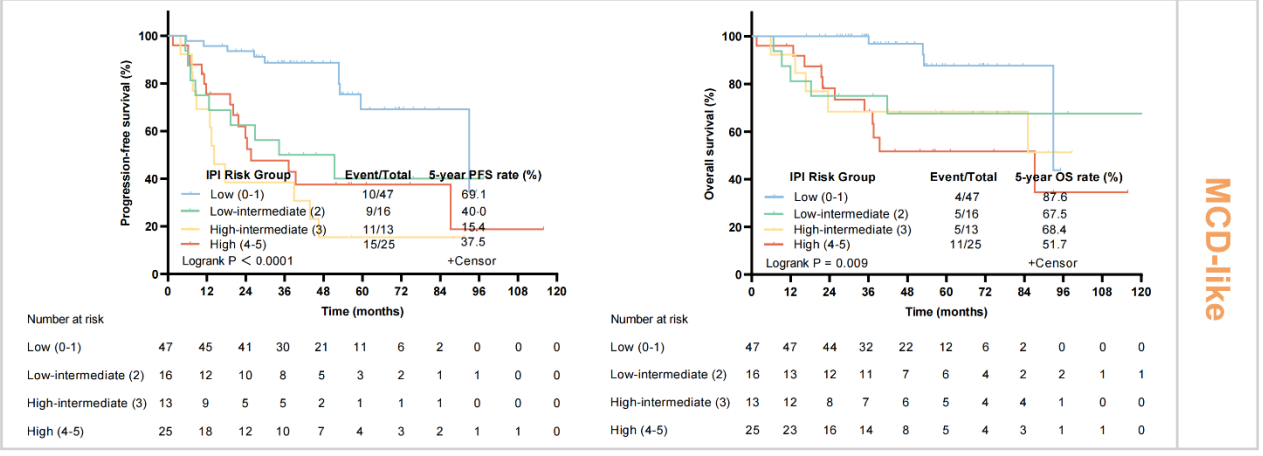
Supplementary Table S3. Stratified models for progression-free survival and overall survival of individual IPI risk factors and genetic subtypes in Ruijin cohort (n = 963).

Risk factor	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
Age ＞60	1.966 (1.573-2.457)	＜0. 0001	1.632 (1.297-2.054)	＜0. 0001	2.740 (2.058-3.648)	＜0. 0001	2.457 (1.830-3.300)	＜0. 0001
Ann Arbor stage III-Ⅳ	3.702 (2.926-4.685)	＜0. 0001	2.324 (1.749-3.086)	＜0. 0001	4.209 (3.097-5.720)	＜0. 0001	2.450 (1.705-3.520)	＜0. 0001
Multiple ENI	2.323 (1.851-2.915)	＜0. 0001	1.023 (0.787-1.330)	0.866	2.230 (1.680-2.961)	＜0. 0001	0.967 (0.703-1.328)	0.835
LDH ratio > 1*ULN	3.727 (2.944-4.718)	＜0. 0001	2.266 (1.737-2.957)	＜0. 0001	4.415 (3.244-6.010)	＜0. 0001	2.603 (1.840-3.681)	＜0. 0001
ECOG ＞1	3.157 (2.341-4.258)	＜0. 0001	1.633 (1.197-2.229)	0.002	3.266 (2.290-4.658)	＜0. 0001	1.700 (1.179-2.453)	0.005
EZB-like-MYC-	0.478 (0.237-0.966)	0.04	0.537 (0.264-1.092)	0.086	0.592 (0.263-1.334)	0.206	0.730 (0.321-1.660)	0.452
EZB-like-MYC+	5.353 (2.378-12.048)	＜0. 0001	6.643 (2.917-15.126)	＜0. 0001	4.984 (2.047-12.136)	＜0. 0001	4.756 (1.921-11.776)	0.001
ST2-like	0.562 (0.323-0.980)	0.042	0.709 (0.403-1.246)	0.232	0.626 (0.321-1.223)	0.17	0.761 (0.385-1.504)	0.432
BN2-like	0.697 (0.467-1.042)	0.078	-	-	0.908 (0.572-1.442)	0.683	-	-
TP53Mut	1.575 (1.195-2.076)	0.001	1.498 (1.119-2.007)	0.007	1.791 (1.288-2.490)	0.001	1.699 (1.196-2.414)	0.003
N1-like	1.105 (0.668-1.827)	0.698	-	-	0.979 (0.501-1.911)	0.95	-	-
MCD-like	1.435 (1.047-1.968)	0.025	1.130 (0.809-1.580)	0.474	1.145 (0.753-1.741)	0.528	0.841 (0.540-1.311)	0.444

Supplementary Figure S2. Survival analysis of IPI risk groups under different genetic subtypes.




N1-like
Progression-free survival (%)
IPI Risk Group
Event/Total
5-year PFS rate (%)
Low (0-1) 5/29 80.5
Low-intermediate (2) 7/10 26.7
High-intermediate (3) 1/7 85.7
High (4-5) 3/3 0
Logrank P < 0.0001
+Censor
Time (months)
Number at risk
Low (0-1) 29 26 19 15 10 9 5 0 0 0 0
Low-intermediate (2) 10 6 5 3 3 1 1 1 0 0 0
High-intermediate (3) 7 6 5 3 2 2 1 1 0 0 0
High (4-5) 3 0 0 0 0 0 0 0 0 0 0
Overall survival (%)
IPI Risk Group
Event/Total
5-year OS rate (%)
Low (0-1) 3/29 88.4
Low-intermediate (2) 2/10 90.0
High-intermediate (3) 1/7 85.7
High (4-5) 3/3 0
Logrank P < 0.0001
+Censor
Time (months)
Number at risk
Low (0-1) 29 29 21 15 11 10 5 0 0 0 0
Low-intermediate (2) 10 9 8 7 5 2 1 1 0 0 0
High-intermediate (3) 7 6 5 3 2 2 1 1 0 0 0
High (4-5) 3 0 0 0 0 0 0 0 0 0 0


MCD-like
Progression-free survival (%)
IPI Risk Group
Event/Total
5-year PFS rate (%)
Low (0-1) 10/47 69.1
Low-intermediate (2) 9/16 40.0
High-intermediate (3) 11/13 15.4
High (4-5) 15/25 37.5
Logrank P < 0.0001
+Censor
Time (months)
Number at risk
Low (0-1) 47 45 41 30 21 11 6 2 0 0 0
Low-intermediate (2) 16 12 10 8 5 3 2 1 1 0 0
High-intermediate (3) 13 9 5 5 2 1 1 1 0 0 0
High (4-5) 25 18 12 10 7 4 3 2 1 1 0
Overall survival (%)
IPI Risk Group
Event/Total
5-year OS rate (%)
Low (0-1) 4/47 87.6
Low-intermediate (2) 5/16 67.5
High-intermediate (3) 5/13 68.4
High (4-5) 11/25 51.7
Logrank P = 0.009
+Censor
Time (months)
Number at risk
Low (0-1) 47 47 44 32 22 12 6 2 0 0 0
Low-intermediate (2) 16 13 12 11 7 6 4 2 2 1 1
High-intermediate (3) 13 12 8 7 6 5 4 4 1 0 0
High (4-5) 25 23 16 14 8 5 4 3 1 1 0

Supplementary Table S4. Multivariable Cox PH Regression With Internal Validation Parameters (A) and Molecularly-enhanced IPI Model Definition (B) (n = 963).

(A) Factors	Hazard ratio (95%CI) for PFS	z-Score	Ratioa	Weight	P
TP53Mut	1.548 (1.173-2.044)	3.084	1.000	1	0.002
IPI					
IPI 0-1	1.000	-	-		
IPI 2	3.748 (2.734-5.137)	8.210	2.662	3	< 0.0001
IPI 3	4.615 (3.409-6.249)	9.893	3.208	3	< 0.0001
IPI 4-5	7.223 (5.277-9.885)	12.350	4.005	4	< 0.0001

(B) Molecularly-enhanced IPI	n (%)	Hazard ratio (95%CI) for PFS	P for PFS	Hazard ratio (95%CI) for OS	P for OS
Risk groups (score)					
Low (0-1)	540 (56.1)	1.000		1.000	
Low-intermediate (3)	252 (26.2)	3.920 (2.967-5.178)	< 0.0001	4.469 (3.080-6.484)	< 0.0001
High-intermediate (4)	154 (16.0)	6.120 (4.552-8.228)	< 0.0001	7.935 (5.416-11.625)	< 0.0001
High (5)	17 (1.8)	14.796 (8.627-25.376)	< 0.0001	19.980 (10.476-38.104)	< 0.0001

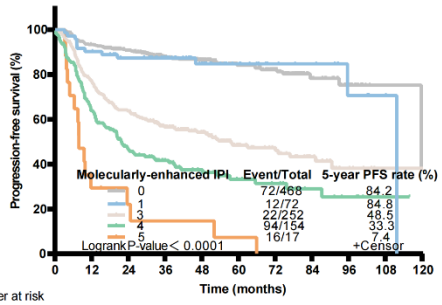
The weights were obtained rounding the ratio. Score: sum of weights.

Abbreviations: HR, hazard ratio; IPI, International Prognostic Index; OS, overall survival; PH, proportional hazard.

[a] The z-score for any factor was divided by the minimum z-score observed (*TP53*^{Mut}, considered as reference) to obtain the ratio.

Supplementary Figure S3. (A) Progression-free survival (PFS) by five levels of risk stratified by Molecularly-enhanced IPI in training cohort. **(B)** Overall survival (OS) by five levels of risk stratified by Molecularly-enhanced IPI in training cohort. **(C)** OS into four main risk groups stratified by Molecularly-enhanced IPI in training cohort. **(D)** OS for IPI risk groups in training cohort. **(E)** PFS into four main risk groups stratified by Molecularly-enhanced IPI in validation cohort. **(F)** OS into four main risk groups stratified by Molecularly-enhanced IPI in validation cohort. **(G)** PFS for IPI risk groups in validation cohort. **(H)** OS for IPI risk groups in validation cohort.

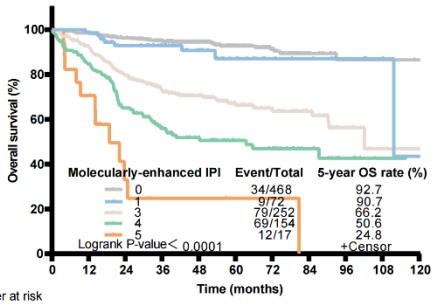
A



Number at risk

0	468	435	388	316	235	147	99	37	19	2	1
1	72	65	57	44	29	19	12	10	5	2	0
3	252	188	150	112	78	48	36	23	6	1	1
4	154	94	59	45	31	19	15	8	5	1	0
5	17	5	3	2	2	1	0	0	0	0	0

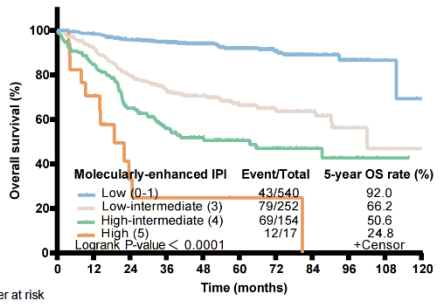
B



Number at risk

0	468	459	412	341	255	161	110	44	21	3	2
1	72	71	61	48	32	20	12	10	6	3	1
3	252	226	184	141	99	66	47	33	13	3	2
4	154	125	83	59	43	29	23	12	5	1	0
5	17	12	4	2	2	1	1	0	0	0	0

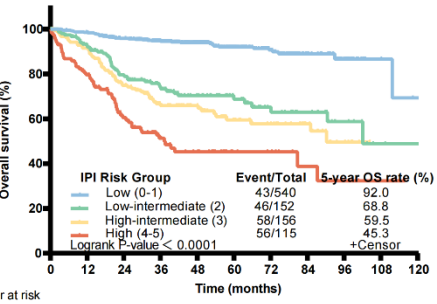
C



Number at risk

0-1	540	530	473	389	287	181	122	54	27	6	3
3	252	226	184	141	99	66	47	33	13	3	2
4	154	125	83	59	43	29	23	12	5	1	0
5	17	12	4	2	2	1	1	0	0	0	0

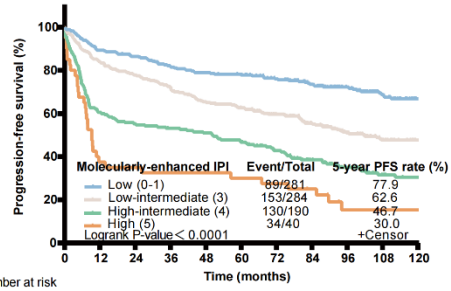
D



Number at risk

0-1	540	530	473	389	287	181	122	54	27	6	3
2	152	136	108	86	60	43	29	20	9	3	2
3	156	139	108	78	58	40	31	19	7	0	0
4-5	115	88	55	38	26	13	11	6	2	1	0

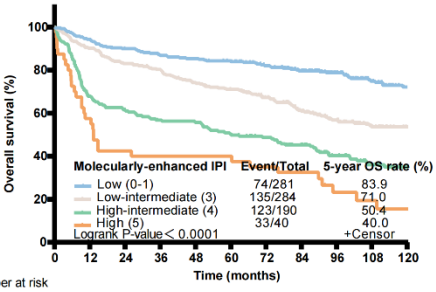
E



Number at risk

0-1	281	251	241	228	220	215	199	175	139	106	82
3	284	238	221	205	184	173	156	129	103	82	68
4	190	115	105	99	95	87	74	57	43	32	26
5	40	15	14	13	13	12	11	9	4	4	4

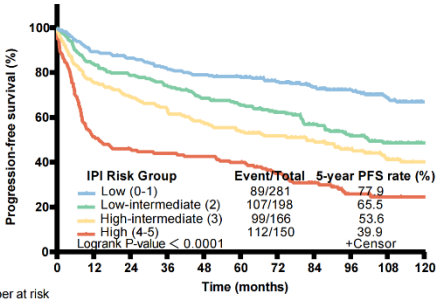
F



Number at risk

0-1	281	265	251	242	238	231	215	194	156	117	95
3	284	256	236	227	208	196	177	146	120	93	80
4	190	129	116	106	104	94	84	71	53	38	31
5	40	23	18	16	16	16	14	11	6	5	4

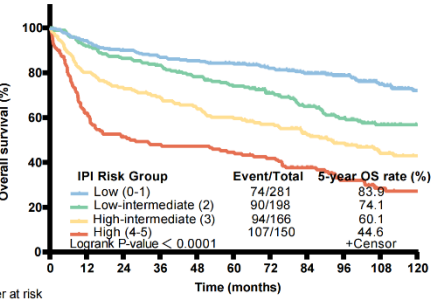
G



Number at risk

0-1	281	251	241	228	220	215	199	175	139	106	82
2	198	166	156	146	133	124	110	91	73	59	46
3	166	125	115	106	96	89	81	69	54	43	37
4-5	150	77	68	65	63	59	50	35	23	16	15

H



Number at risk

0-1	281	265	251	242	238	231	215	194	156	117	95
2	198	182	171	164	152	141	126	107	88	70	57
3	166	133	122	114	106	99	89	74	60	45	39
4-5	150	93	76	71	70	66	60	47	31	21	19

Supplementary Table S5. Stratified models for PFS and OS in training cohort (n = 963).

Model	PFS			OS		
	Hazard ratio (95%CI)	C-index	AIC	Hazard ratio (95%CI)	C-index	AIC
Molecularly-enhanced IPI						
Low (0-1)	1.000			1.000		
Low-intermediate (3)	3.920 (2.967-5.178)	0.711 (0.684-0.739)	3898.918	4.469 (3.080-6.484)	0.743 (0.711-0.775)	2462.153
High-intermediate (4)	6.120 (4.552-8.228)			7.935 (5.416-11.625)		
High (5)	14.796 (8.627-25.376)			19.980 (10.476-38.104)		
IPI						
Low (0-1)	1.000			1.000		
Low-intermediate (2)	3.772 (2.752-5.171)	0.711 (0.683-0.739)	3914.485	4.210 (2.771-6.395)	0.742 (0.709-0.775)	2472.199
High-intermediate (3)	4.717 (3.486-6.384)			5.643 (3.801-8.378)		
High (4-5)	7.104 (5.193-9.719)			9.631 (6.460-14.359)		

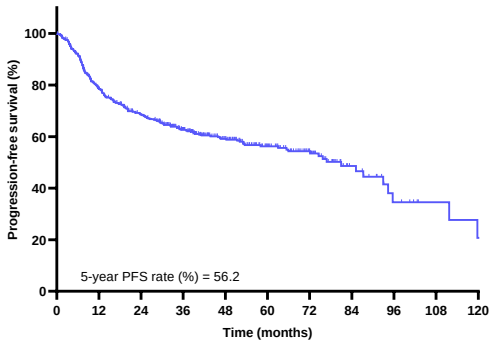
*The AIC provided a relative measure of model quality; smaller values correspond with a better fitting model. Differences in AIC＜2 between models indicate no improvement in fit, differences＞2 but＜10 indicate increasing improvement in fit, and differences≥10 indicate substantial improvement in the fit of the model.

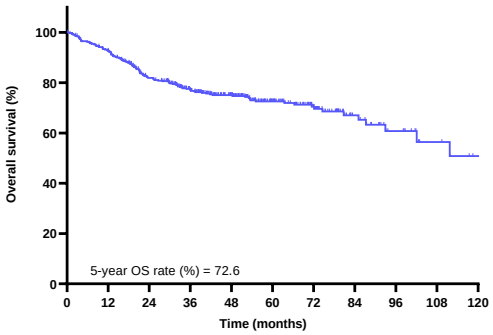
†The C-index provided a measure of predictive ability of the model, defined as the probability of concordance between predicted and observed survival. The C-index corresponds to the area under the receiver operating characteristics curve for censored data. C-index values of 0.5, 0.7, and 1.0 indicate that the model has completely random, acceptable, or perfect discrimination, respectively, between short and long survival times.

Supplementary Table S6. Stratified models for PFS and OS in validation cohort (n = 795).

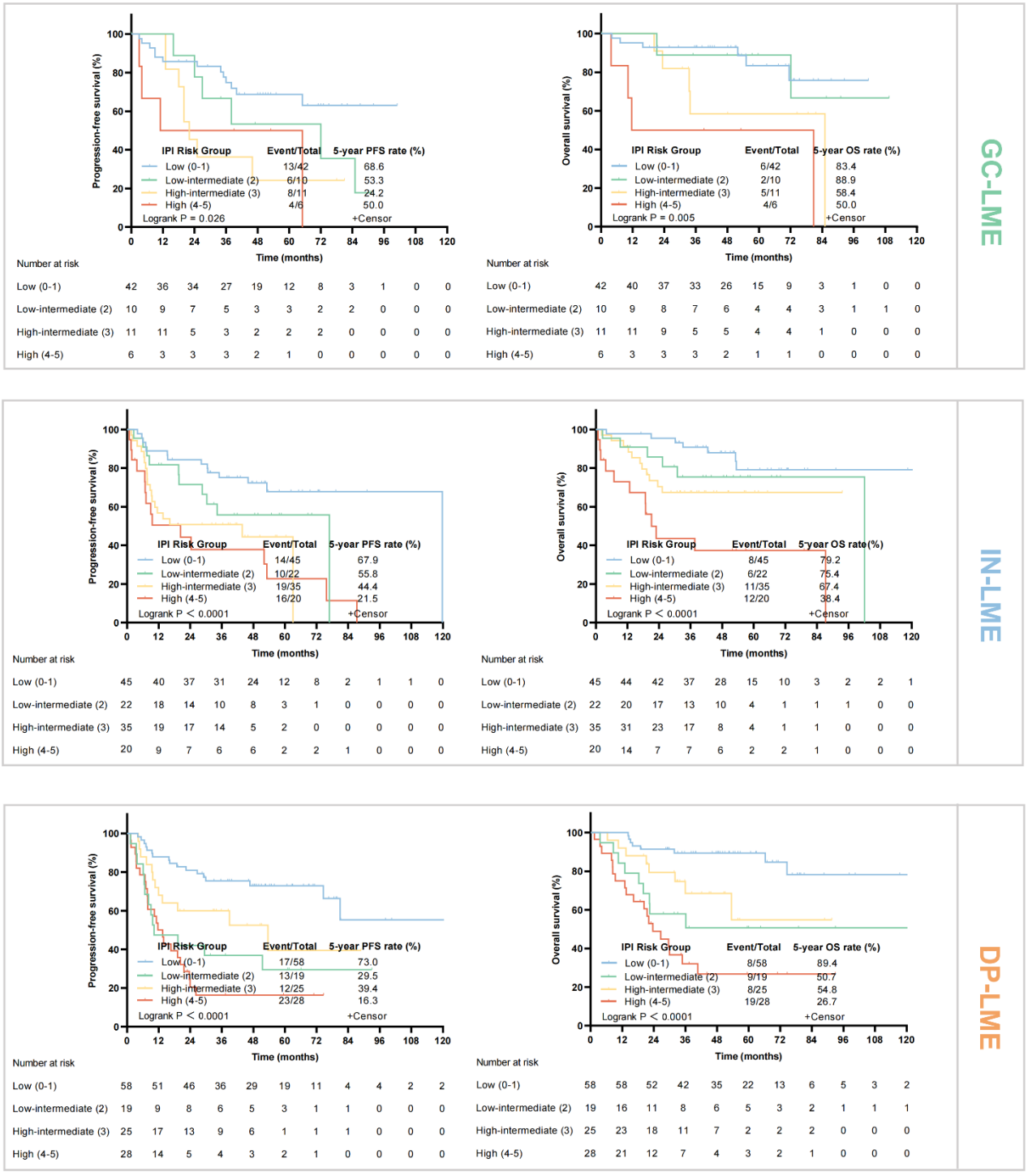
Model	PFS			OS		
	Hazard ratio (95%CI)	**C-index**	**AIC**	**Hazard ratio (95%CI)**	**C-index**	**AIC**
Molecularly-enhanced IPI						
Low (0-1)	1.000			1.000		
Low-intermediate (3)	1.934 (1.489-2.512)	0.643 (0.616-0.670)	4955.806	2.026 (1.526-2.691)	0.655 (0.627-0.683)	4442.604
High-intermediate (4)	3.294 (2.514-4.315)			3.670 (2.748-4.901)		
High (5)	5.465 (3.673-8.131)			6.076 (4.024-9.175)		
IPI						
Low (0-1)	1.000			1.000		
Low-intermediate (2)	1.921 (1.450-2.545)	0.644 (0.617-0.671)	4962.667	1.884 (1.385-2.563)	0.661 (0.633-0.690)	4443.204
High-intermediate (3)	2.343 (1.759-3.121)			2.710 (1.998-3.676)		
High (4-5)	4.128 (3.119-5.463)			4.628 (3.436-6.235)		

Supplementary Figure S4. Survival analysis of patients with available LME categories (n = 487).





Supplementary Table S7. Stratified models for progression-free survival and overall survival of individual IPI risk factors and LME categories (N = 487).

Risk factor	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
Age ＞60	1.543 (1.177-2.024)	0.002	1.241 (0.940-1.638)	0.128	2.256 (1.589-3.203)	＜0.0001	2.001 (1.399-2.862)	＜0.0001
Ann Arbor stage Ⅲ-Ⅳ	3.218 (2.391-4.332)	＜0.0001	2.299 (1.614-3.276)	＜0.0001	3.326 (2.265-4.883)	＜0.0001	1.979 (1.264-3.099)	0.003
Multiple ENI	2.169 (1.643-2.862)	＜0.0001	1.004 (0.729-1.385)	0.979	2.199 (1.552-3.116)	＜0.0001	1.063 (0.719-1.572)	0.760
LDH ratio＞ 1*ULN	2.940 (2.178-3.970)	＜0.0001	1.992 (1.435-2.766)	＜0.0001	3.653 (2.439-5.471)	＜0.0001	2.461 (1.580-3.834)	＜0.0001
ECOG ＞1	3.003 (2.092-4.312)	＜0.0001	1.996 (1.374-2.899)	＜0.0001	3.062 (1.988-4.717)	＜0.0001	2.070 (1.329-3.223)	0.001
GC-LME	0.956 (0.652-1.400)	0.816	-	-	0.838 (0.503-1.396)	0.497	-	-
MS-LME	0.625 (0.460-0.849)	0.003	0.616 (0.452-0.840)	0.002	0.644 (0.438-0.947)	0.025	0.641 (0.434-0.948)	0.026
IN-LME	1.299 (0.961-1.756)	0.089	-	-	1.258 (0.861-1.840)	0.236	-	-
DP-LME	1.330 (0.993-1.783)	0.056	-	-	1.409 (0.981-2.023)	0.063	-	-

Supplementary Figure S5. Survival analysis of IPI risk groups under different LME categories.