

Figure S1 Subclusters of macrophages, T cells, and endothelial cells subdivided according to their specific markers, respectively. (A) UMAP plot shows four main subtypes of macrophages: C1_Mac, C2_MMP9⁺ Mac, C3_CCL5⁺ Mac, and C4_SMIM25⁺ Mac. (B) Violin plots showing relevant marker genes in each macrophages subtypes. (C) UMAP plot shows main subtypes of T cells: C1_NKT cells, C2_T cells, and C3_CD8⁺ T cells. (D) Violin plots showing relevant marker genes in each T subtypes. (E) UMAP plot shows four main subtypes of endothelial cells: C1_ZFEP36⁺ ECs, C1_TMEM⁺ ECs, and C1_RACK1⁺ ECs. (F) Violin plots showing relevant marker genes in each subtypes of endothelial cells.

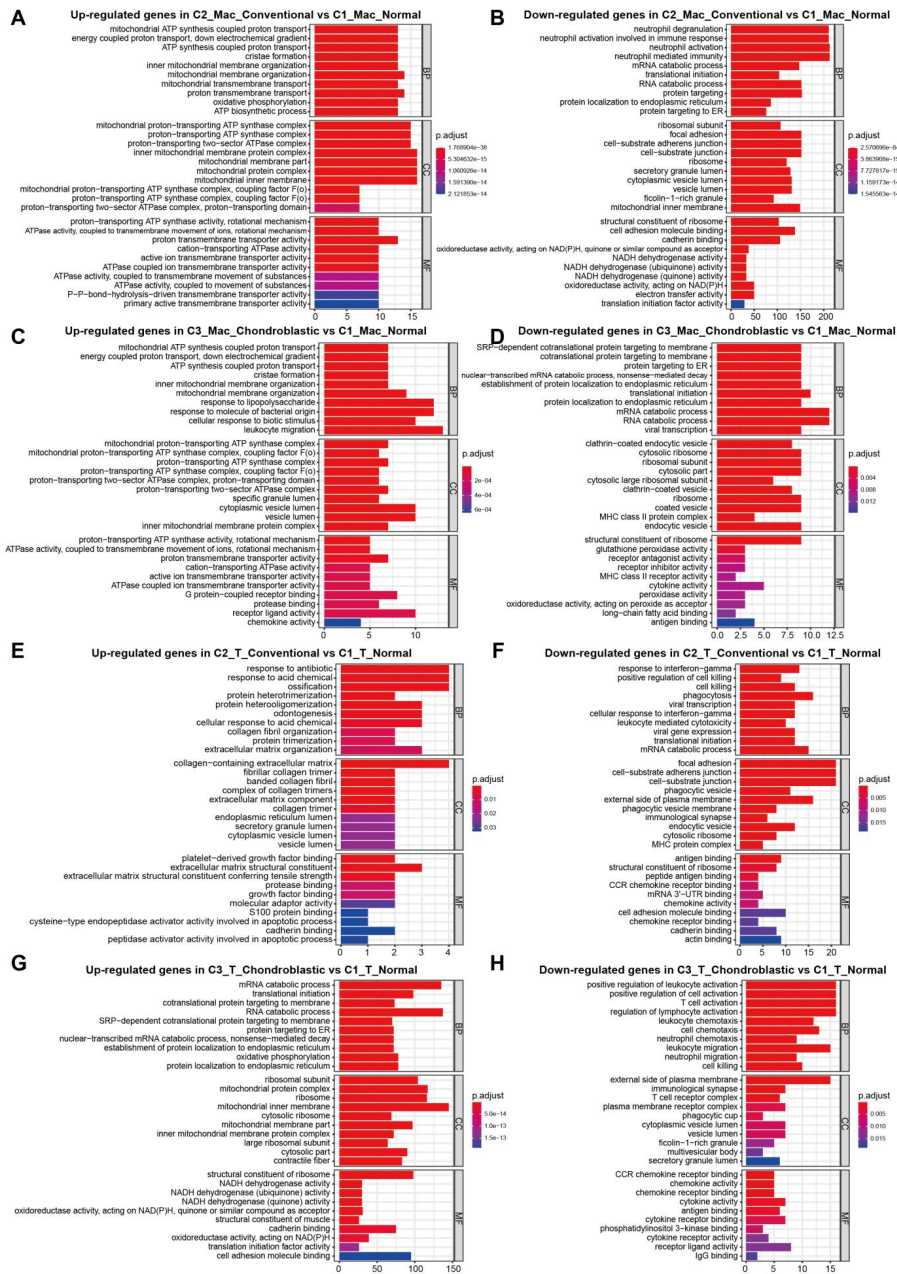


Figure S2 GO analysis of macrophages and T cells, respectively. (A-B) Bar chart showing the GO analyses of upregulated (left) and downregulated (right) DEGs in C2_Mac_Conventional vs. C1_Mac_Normal. (C-D) Bar chart showing the GO analyses of upregulated (left) and downregulated (right) DEGs of C3_Mac_Chondroblastic vs. C1_Mac_Normal. (E-F) Bar chart showing the GO analyses of upregulated (left) and downregulated (right) DEGs of C2_T_Conventional vs. C1_T_Normal. (G-H) Bar chart showing the GO analyses of upregulated (left) and downregulated (right) DEGs of C3_T_Chondroblastic vs. C1_T_Normal.

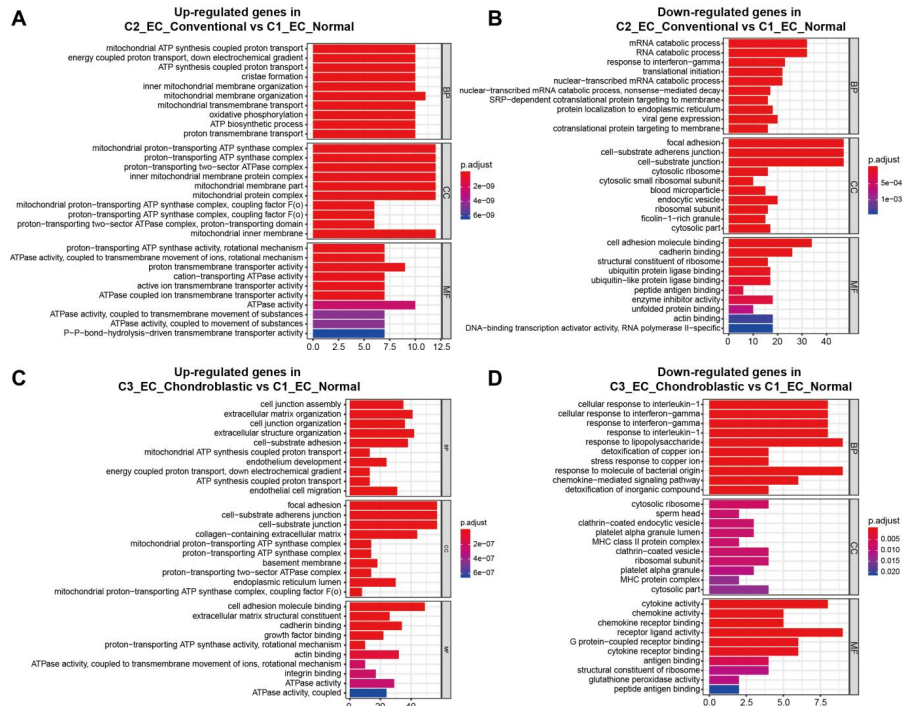


Figure S3 GO analysis of endothelial cells. (A-B) Bar chart showing the GO analyses of upregulated (left) and downregulated (right) DEGs in C2_EC_Conventional vs. C1_EC_Normal. (C-D) Bar chart showing the GO analyses of upregulated (left) and downregulated (right) DEGs of C3_EC_Chondroblastic vs. C1_EC_Normal.

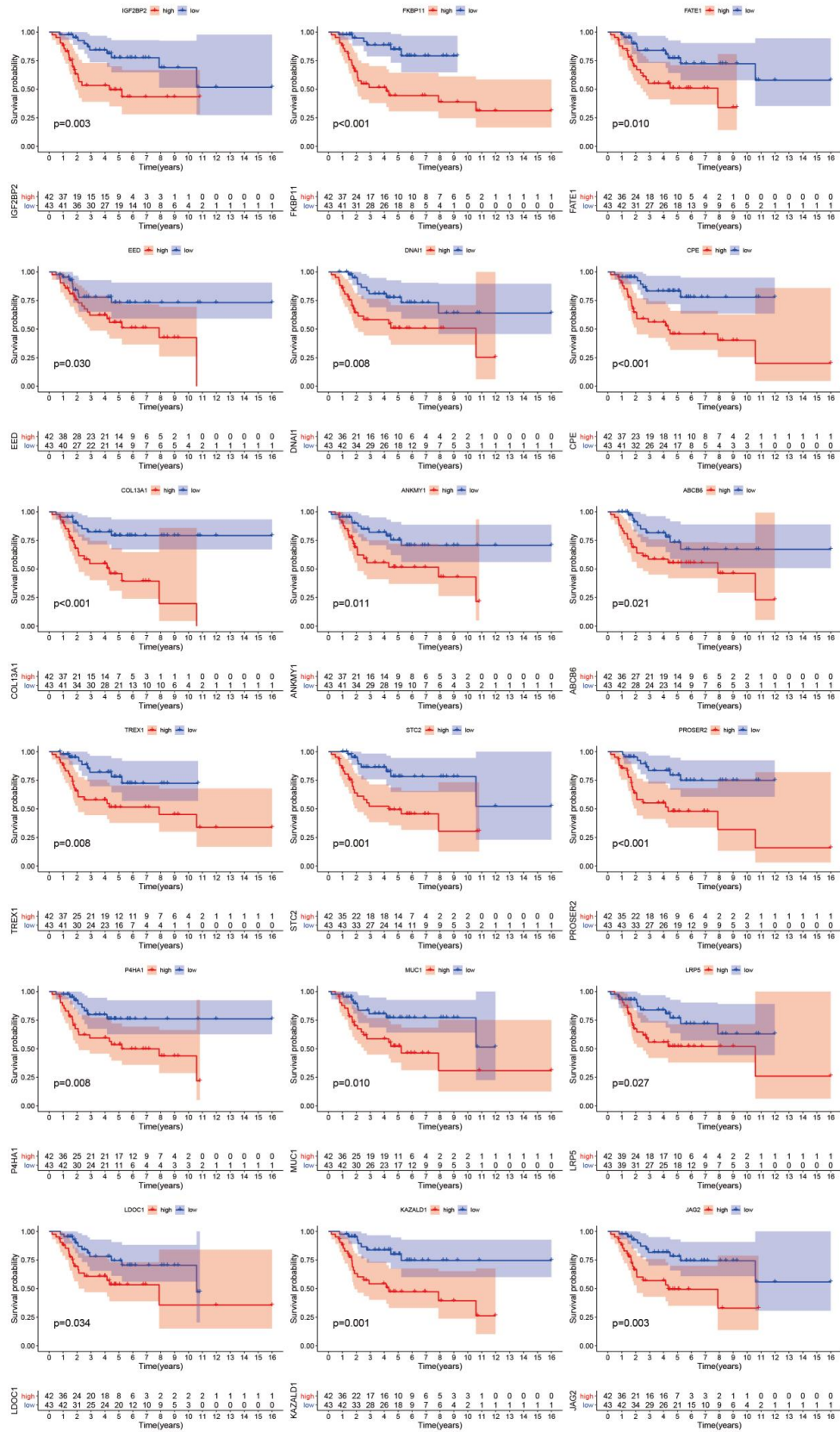


Figure S4 18 genes with poor prognosis obtained by survival analysis combined with TARGET-OS dataset.

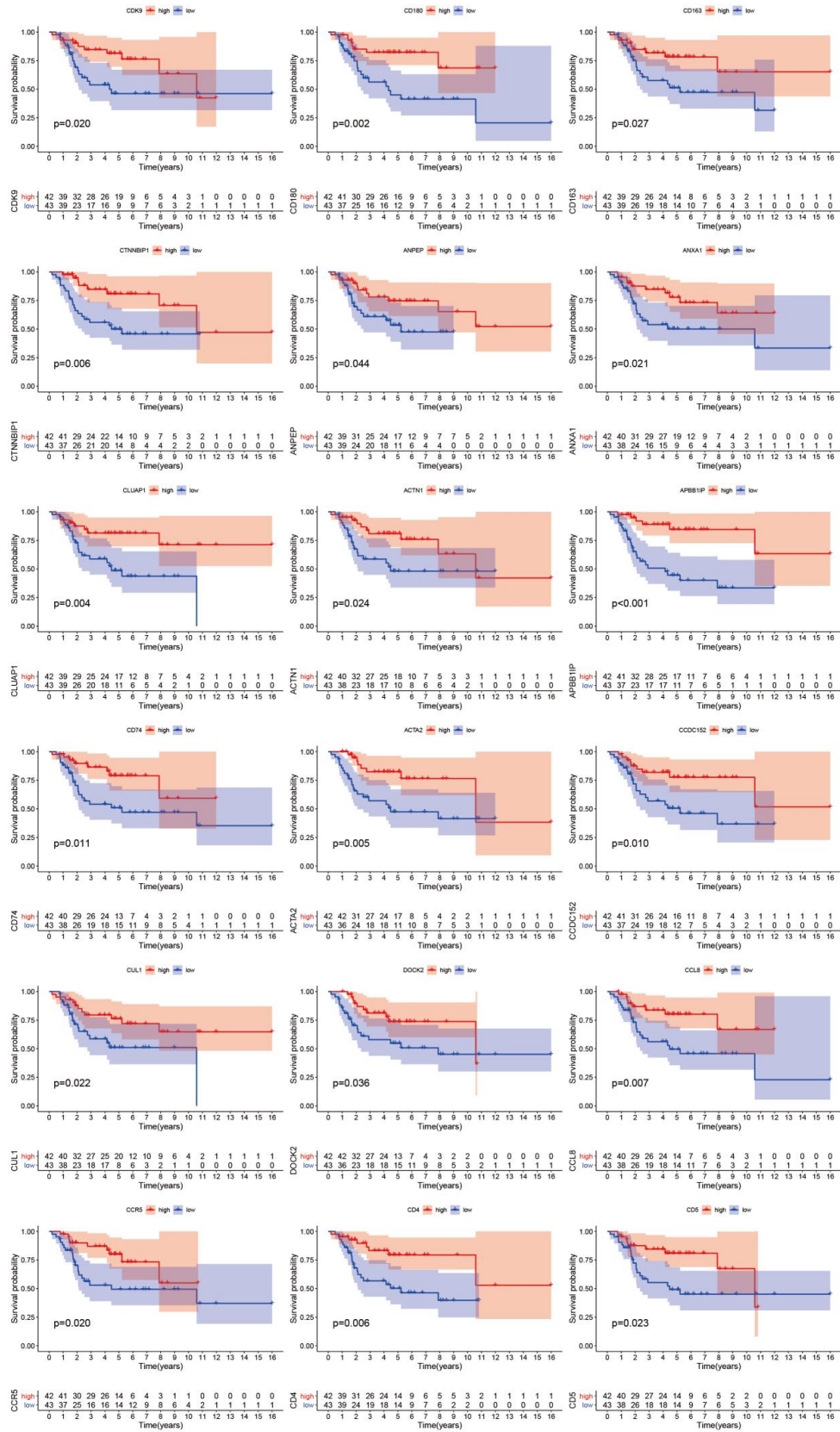


Figure S5_1 The first eighteen of 49 genes with good prognosis obtained by survival analysis combined with TARGET-OS dataset.

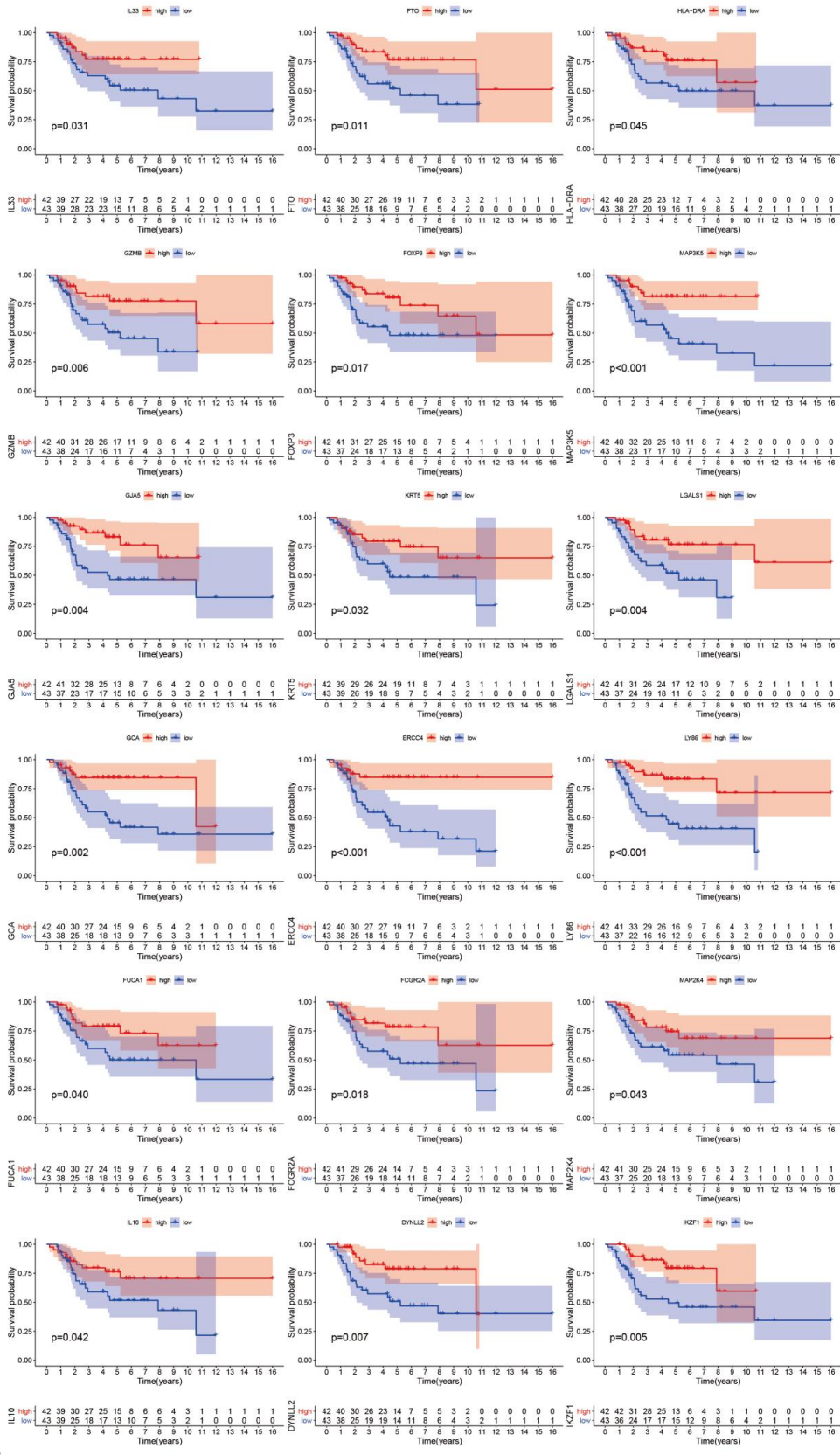


Figure S5_2 The second eighteen of 49 genes with good prognosis obtained by survival analysis combined with TARGET-OS dataset.

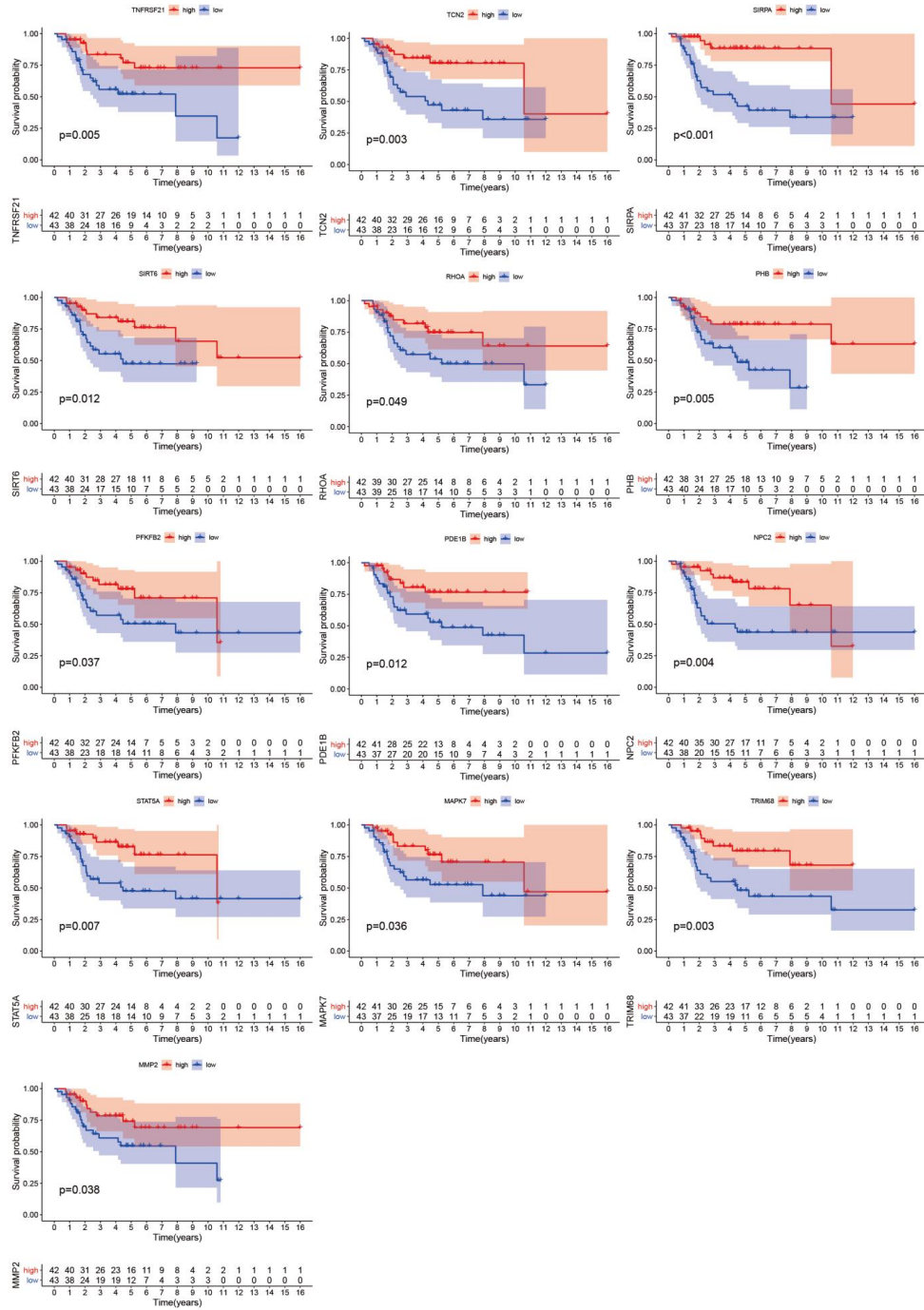


Figure S5_3 The last thirteen of 49 genes with good prognosis obtained by survival analysis combined with TARGET-OS dataset.

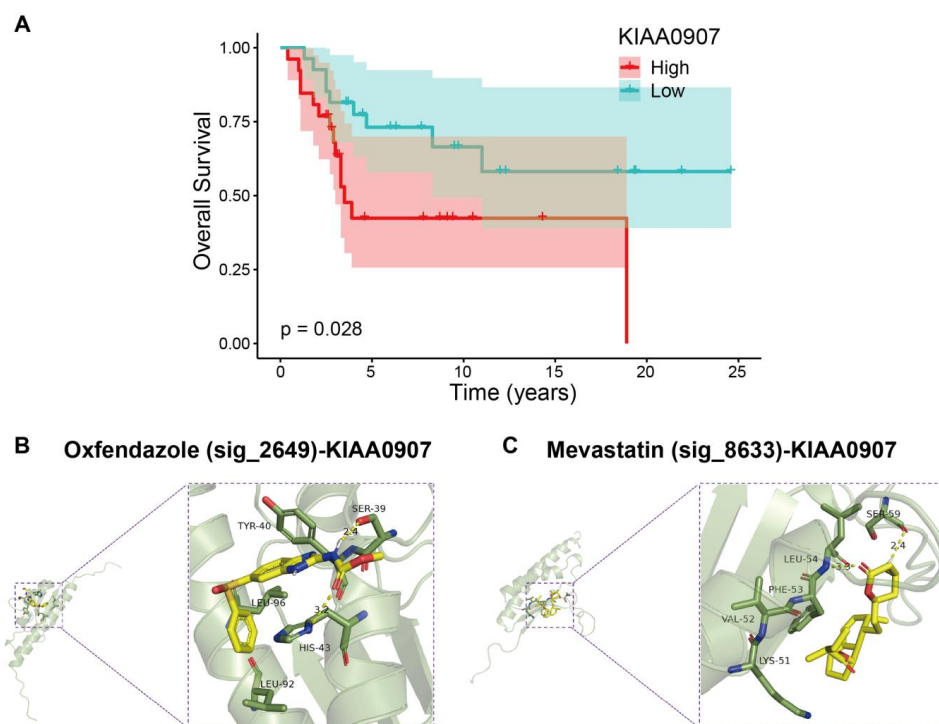


Figure S6 Interaction diagram of drugs with their respective therapeutic targets identified using the Beyondcell analysis. (A) Kaplan-Meier survival curve of KIAA0907. Predicted binding conformations of (B) oxfendazole (sig_2649)-KIAA0907, and (C) mevastatin (sig_8633)-KIAA0907 visualized via PyMol.

Supplementary table 1 The canonical markers of cell types.

Gene	Marker of	Reference
CD3D	C1_T cells	1, 2
CD3E	C1_T cells	1, 2
CD3G	C1_T cells	2
SOX9	C2_Malignant cells	3
ALPL	C2_Malignant cells	4
RUNX2	C2_Malignant cells	4
CD14	C3_Monocytes	5
VCAN	C3_Monocytes	2
FCN1	C3_Monocytes	2
SFTPC	C4_Alveolar cells	6
SLPI	C4_Alveolar cells	7
CD163	C5_Osteoclasts	8
ACP5	C5_Osteoclasts	4, 8
ATP6V0D2	C5_Osteoclasts	9
CTSK	C5_Osteoclasts	4, 8
PECAM1	C6_Endothelial cells	3, 10
EGFL7	C6_Endothelial cells	11
PLVAP	C6_Endothelial cells	12
KIT	C7_Mast cells	13
HPGDS	C7_Mast cells	14
TPSB2	C7_Mast cells	15
MKI67	C8_Proliferative cells	3, 15
CDK1	C8_Proliferative cells	2, 15, 16
TOP2A	C8_Proliferative cells	3
CD163	C9_Macrophages	3
MRC1	C9_Macrophages	3
MSR1	C9_Macrophages	17, 18
APOE	C9_Macrophages	19
CD5L	C9_Macrophages	20
VCAN	C10_Fibroblasts	15
PDGFRA	C10_Fibroblasts	10
FAP	C10_Fibroblasts	21
CLEC9A	C11_Dendritic cells	15
XCR1	C11_Dendritic cells	15
CD1C	C11_Dendritic cells	15
CLEC10A	C11_Dendritic cells	15
CD19	C12_B cells	10, 19
CD79A	C12_B cells	19
MS4A1	C12_B cells	19
ACTA2	C13_Muscle cells	15
TAGLN	C13_Muscle cells	15

MUC5AC	C14_Secretory cells	22, 23
MUC5B	C14_Secretory cells	23
SCGB1A1	C14_Secretory cells	24
EPCAM	C15_Ciliated cells	15
PIFO	C15_Ciliated cells	15
FOXJ1	C15_Ciliated cells	15
XBP1	C17_Plasma cells	15
JCHAIN	C17_Plasma cells	15

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Supplementary table 2 Genes previously reported to be associated with survival of osteosarcoma.

Genes	References
ABCB1	1-4
ABCB6	5
ABCC3	1, 3
ABCC5	6
ABCG2	7, 8
AEG-1	9
AKT1	10
ALDOA	11
ALOX5AP	12
Angptl2	13
ANKMY1	14
ANPEP	15
ANXA1	16
APBB1IP	17, 18
APEX1	19
ARHGAP25	17
ARHGAP35	20
ASPA	21
ASPM	22
ATF5	23
ATF6alpha	24
ARID1A	25
B7-H4	26
BACE2	27
Bax	28
Bcl-2	28, 29
BHMT2	30
Birc2 (cIAP1)	31
Birc3 (cIAP2)	31
BMP8A	32
BMPR2	33
BNIP3	17
BRAF	32
BZW1	14
C12orf75	22
C3AR1	34
CNN3	35
caprin1	36
CARD11	34
CASP3	6
CBLN4	14

CBX3	37
CBX4	38
CCDC152	39
CCL2	34
CCL5	40
CCL8	34, 40
CCN3	41
CCR4	40
CCR5	40
CD133	8, 42, 43
CD14	34
CD163	44
CD180	45
CD209	34
CD4	46
CD44	47
CD44V6	48
CD5	49
CD68	46
CD74	12
CD79A	50
CD8	51
CDC2	52
CDC20	53
CDCA4	54
CDK11	55
CDK9	56
CDR3	57
CGREF1	17
CHCHD8	23
CHIC2	39
CK1 α	58
CLDN7	14
CLUAP1	59
c-MYC	29
COCH	60
COL13A1	17, 59
CORO6	17
CORT	17, 32
CPA6	21
CPE	61
CSE1L	62
CSF1R	46
CSF3R	34, 50

CTNNBIP1	59
CTTN	63
Cullin-1 (CUL1)	64
CXCL14	65
CXCR4	66, 67
Cyclin E1	68
CYP3A4	6
DCN	69
DeltaNp63	70
DLG4	17
DNAI1	45
DNALI1	30
DOCK2	30
DRP5	71
DSCR8	72
DYNLL2	73
EGFR	74
EHHADH	75
ENOPH1	23
EPB41	76
Eps15	77
ERCC1	78-85
ERCC2	79-81, 84-87
ERCC4	59, 85, 88
ERCC5	85
ESR1	89
EVI2A	90
EZH2	91
Ezrin	92-97
FAM83H	98
FANCF	88
FasL	6
FATE1	17, 45
FCER1G	34
FCGR2A	12
FCGR2B	34
FKBP11	18
FKBP14	99
FLNA	15
FOXM1	100
FOXP3	51
FPR1	34
FTL	101
FTO	102, 103

FUCA1	15, 17
GAGE1	72
GAL	32
GCA	59
GJA5	18
GLDC	104
GLS1	105
GNRH1	32
GNRH2	106
GPR110	107
GPR142	39
GRF-1	108
GRN	32, 34
GSTP1	2, 4, 87, 109-111
GZMB	14
HCK	34
HER-2	112
HIPK2	49
HLA-DMA	22
HLA-DRA	22
HMBOX1	113
HMOX1	34
HOXC8	114
HSP90B1	115
HSPD1	65
IFNgamma	116
IGF2BP2	103
IGHG2	34
IGHG3	34
IGLC2	34
IKZF1	115
IL10	34, 117
IL12	118
IL2RA	34
IL2RG	34
IL33	119-121
IL-6	122
ING2	27
ING4	123
JAG2	59
JAK2	124
KAZALD1	59
KCNJ15	21
Keap1	125

Ki-67	126
KIF25	17
KRT5	49
KRTCAP3	14
KRTDAP	14
LAMA3	15
LAMP3	127
LANCL3	21
LCP2	34
LDOC1	128
LEPRE1	129
LGALS1	15
LILRB3	34
LOC286367	23
LRH-1	130
LRRC15	131
LY86	61
LY9	14
LYL1	39
LYZ	22
MACC1	132
MAP2K4	133
MAP3K5	49
MAPK7	133, 134
MATN2	22
MATN3	15
MCM2	135
MCM3	135
MDM2	106, 136
Med19	137
MELK	138
METTL3	102
mGluR1	139
mGluR4	139
mGluR5	139
MIG-7	140
MMP13	31, 141
MMP2	142, 143
MMP27	39
MMP9	67
MMS19L	144, 145
MCT4	146
MSH2	6
MSH6	62, 88

MSR1	34, 147
MT2A	148
MTAP	149
MTNR1B	50
MUC1	59
MYC	17, 39, 45
MYL1	72
MYOM2	60
Nestin	8
NF-kappaB	150
NKD1	151
Notch3	152
NPC2	18
NPPC	50
NPRL2	153
Nrf2	125
NSD2	154
NUBP1	17
NUPR1	22
ONZIN	155
OPG	156
p14ARF	89
p27	157
P4HA1	5, 69
p53	28, 29, 156, 158, 159
p62	160
PCK2	161
PDE1B	60
PDGFRA	162
PDK1	34
PD-L1	163
PEA15	22
PEF1	17
PFKFB2	14
PHC3	164
pIgR	165
PIK3R5	34
PIKFYVE	73
PKR	166
PLA2G16	167
PLEKHG1	72
PLK2	168
PLOD1	169
PML	76

Polo-like kinase (Plk) 1	170
PPARG	34
PQBP1	161
PRC1	171
PRC2	171
PRF1	34
PCNA	172
PROSER2	45
PSAT1	16
PSMD10	32
PTEN	150, 173, 174
PTPN22	14
PTPRC	34
QKI2	175
RAB40C	59
RAD23A	17
RB1	176
REM1	21
RHBDL2	17
RIPK3	30
RPL34	177
Runx2	178
S100A13	17
S100A4	179
SAXO2	72
SCARA5	21
SCN1A	72
SCUBE3	65
SDC3	32
SETD2	154
SGCG	15
SIRPA	59
SIRT6	180
SLC11A1	34
SLC19A1	181
SLC24A4	21
SLC38A5	17
SMAR1	182
SNP309	136
SPAG5	183
STAT3	124, 184, 185
STAT5A	186
STC2	5, 17, 187
SULT1A3	11

survivin	188
SUZ12	115
TCN2	59
Tim-3	189
TLR1	34
TLR2	34
TLR7	34, 147
TLR8	34
TMEM125	72
Tmem41b	141
TNFRSF11B	32
TNFRSF21	32
TNFSF8	34
TP53	190
TRA	57
Transferrin receptor-1	191
TREX1	192
TRH	21
TRIM10	193
TRIM66	194
TRIM68	73
Trps1	195
TSSC3	196, 197
Twist-1	198
UGT3A2	72
URG4	199
USP11	17, 59
VAV1	32, 34
VEGF	191, 200-203
VEGFA	15, 32
VEGFR	204
VEGFR2	205
vitamin D receptor (VDR)	206
VM	207
WNT5A	15
WNT6	208
XBP1	209
XPD	210
XPG	144, 145
XRCC3	211
XRCC6	212
YTHDC1	102

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