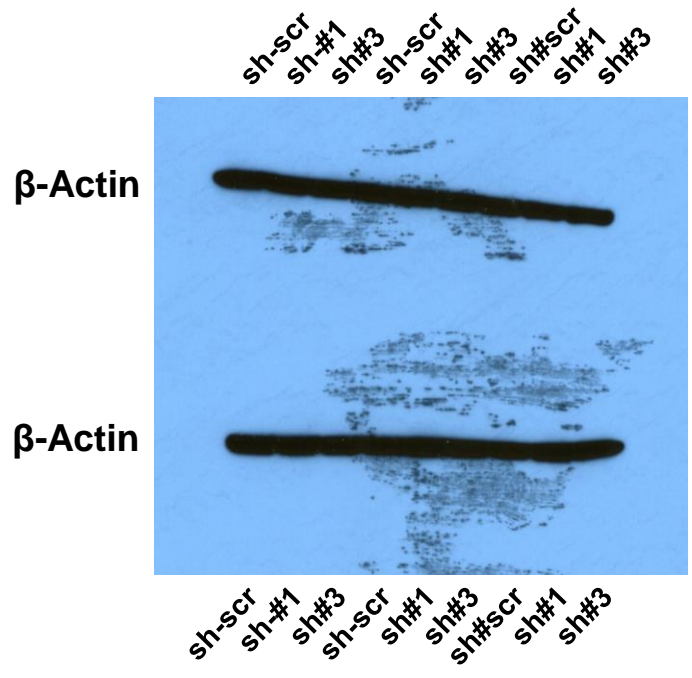
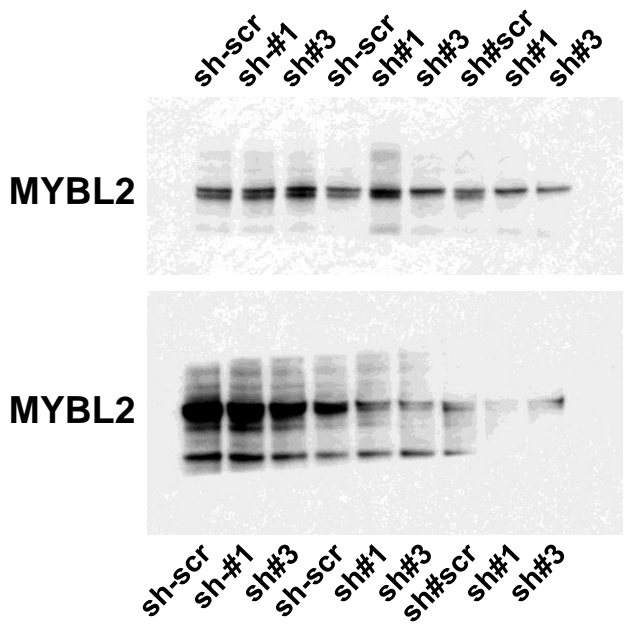
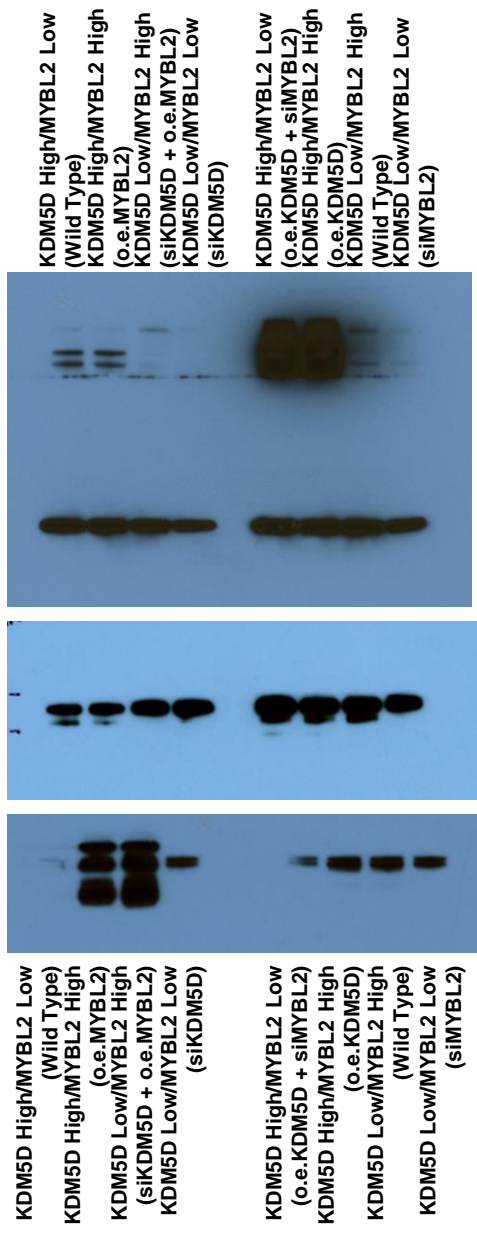
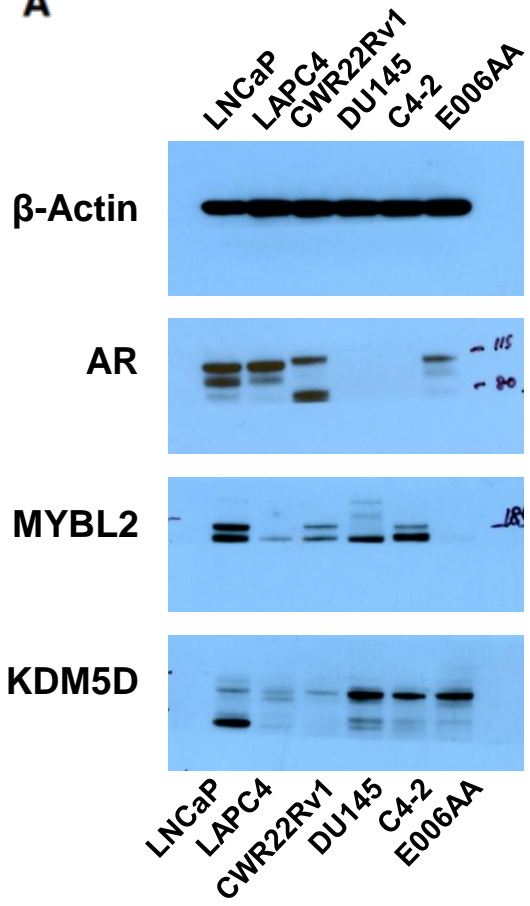
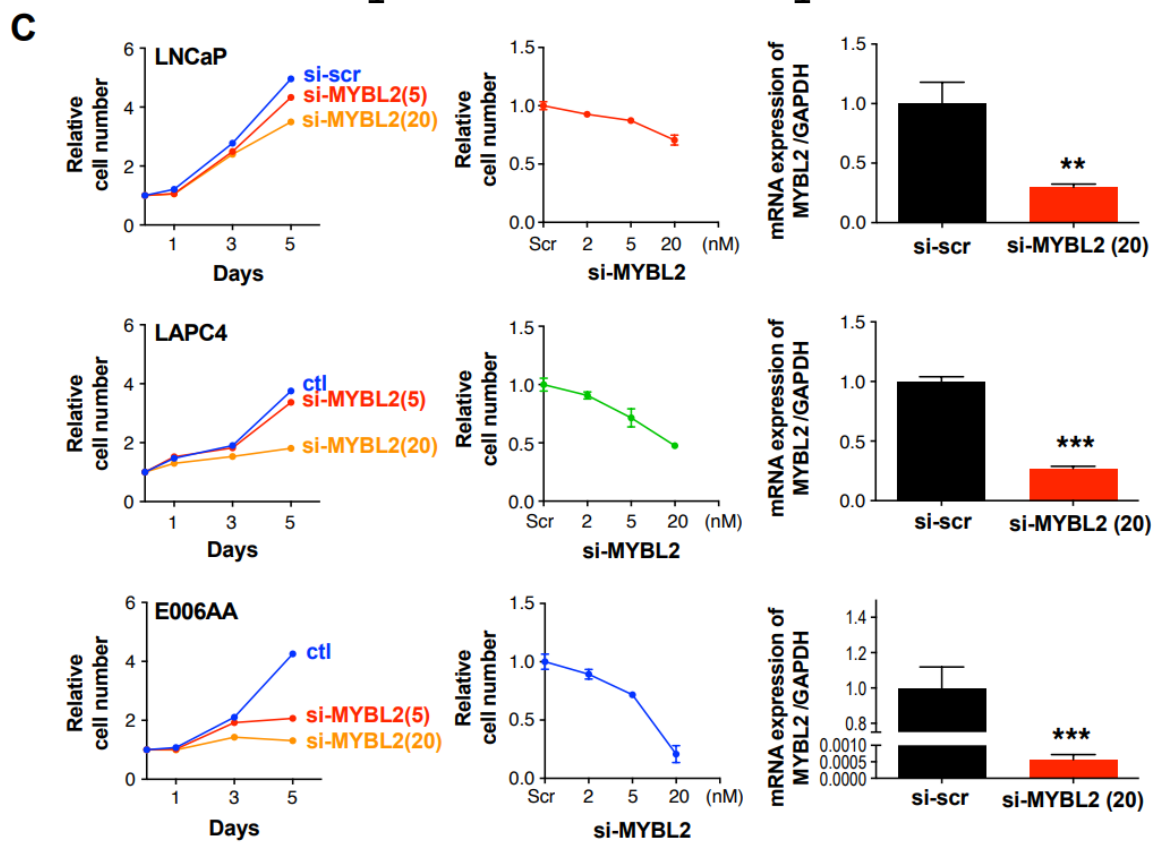
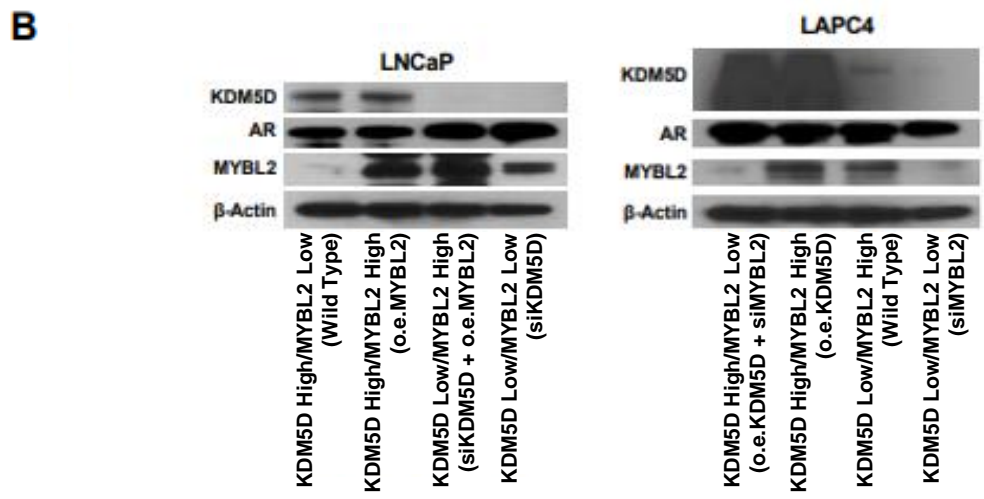
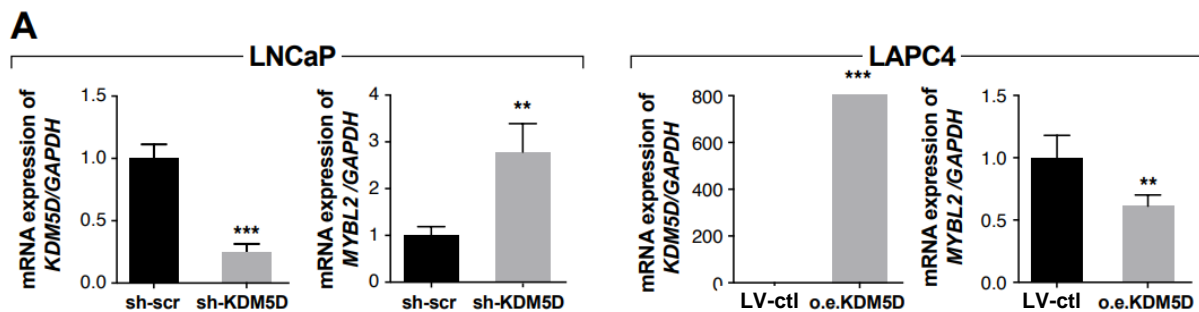


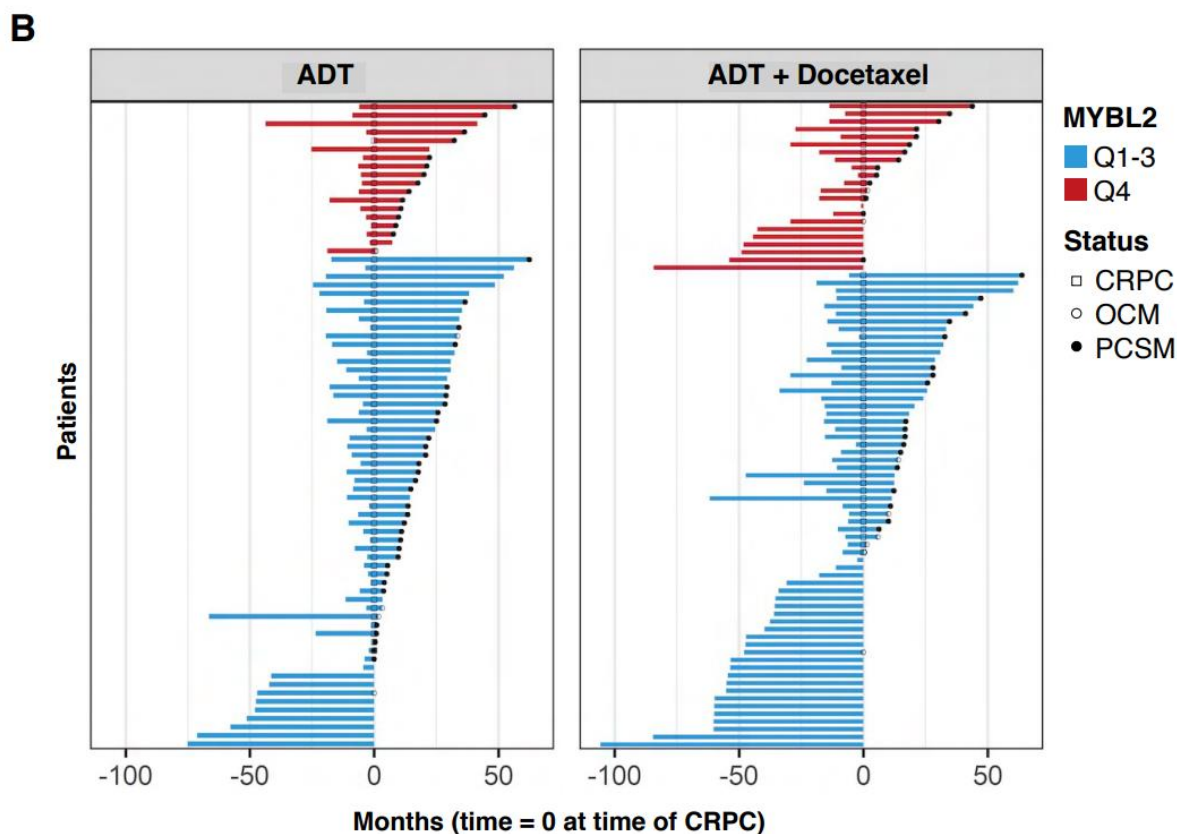
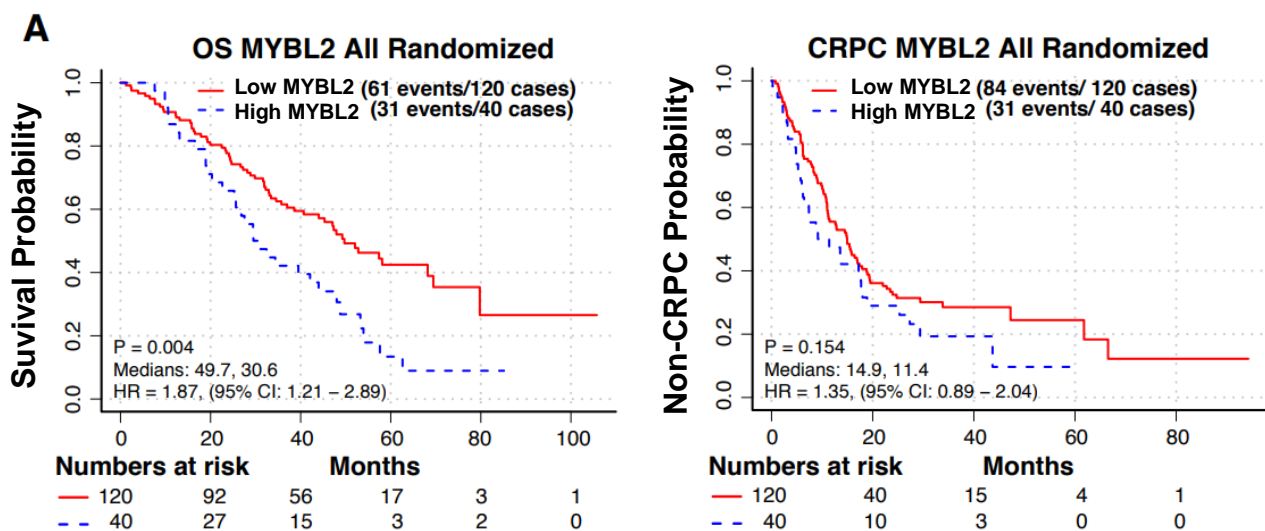
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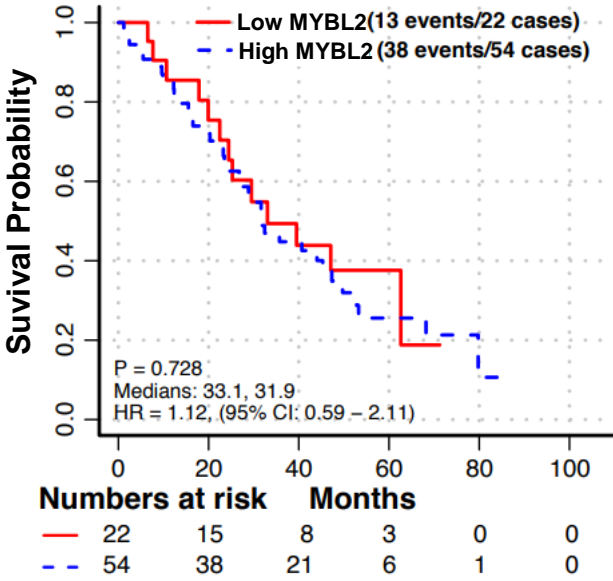
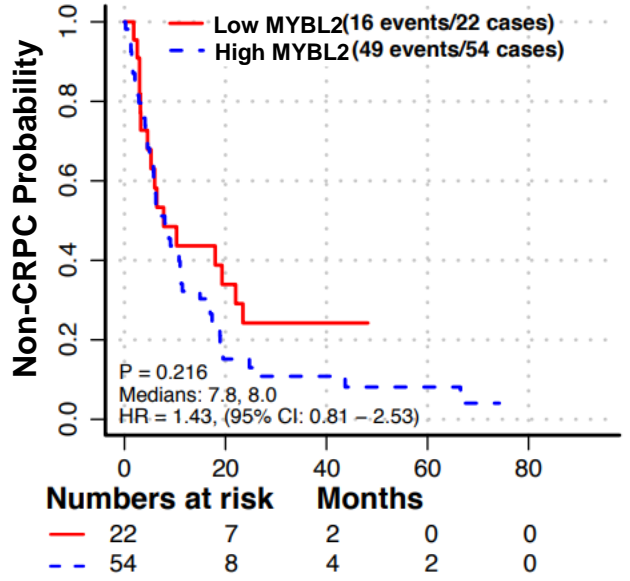
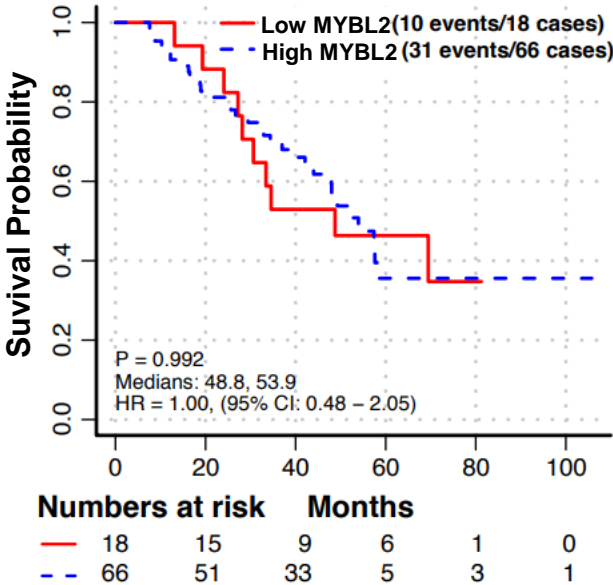
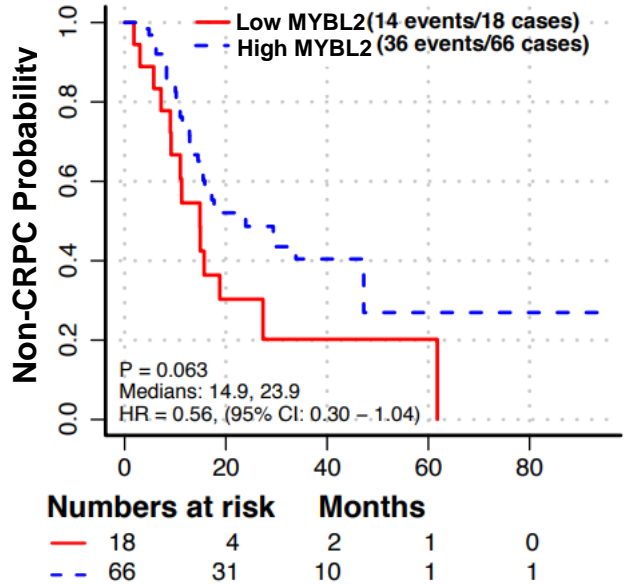


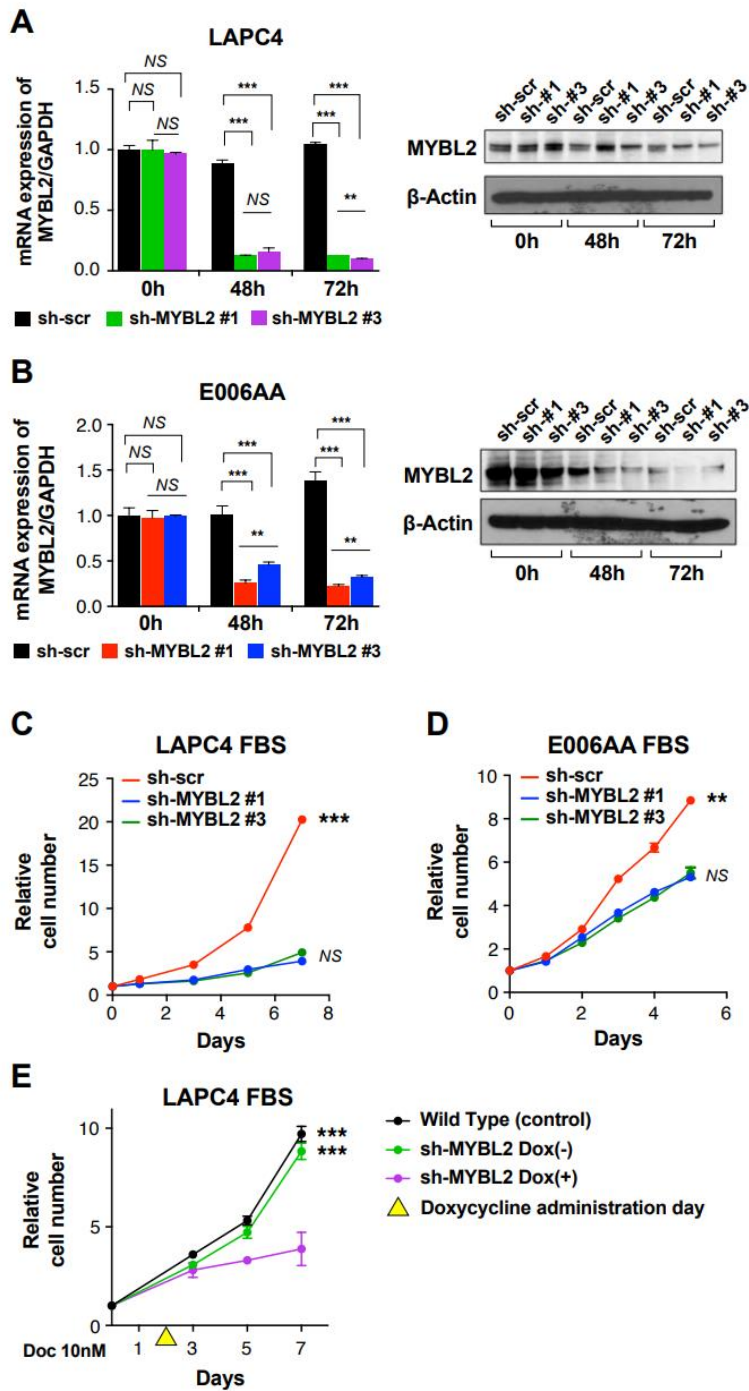
Supplementary Figure 1

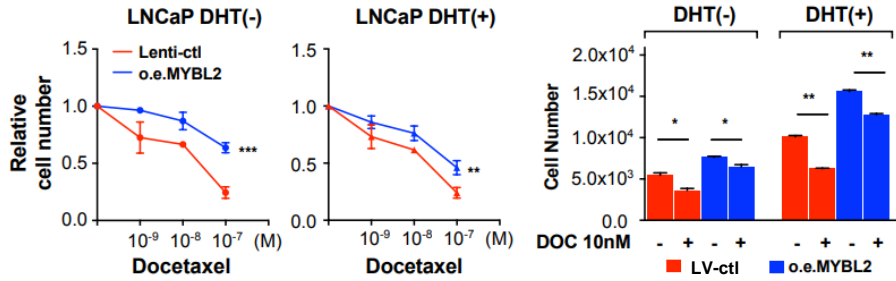
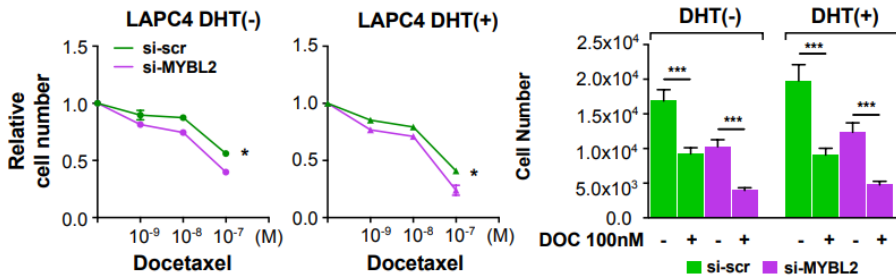
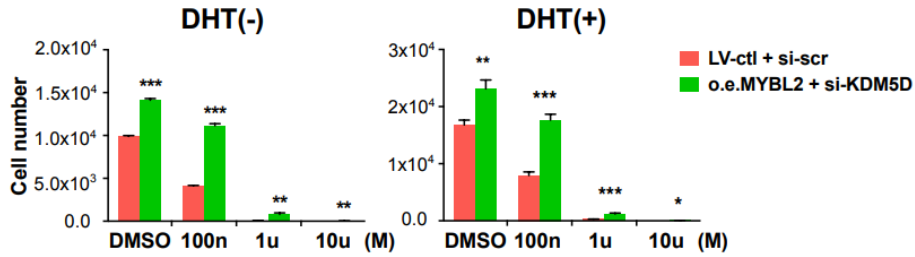
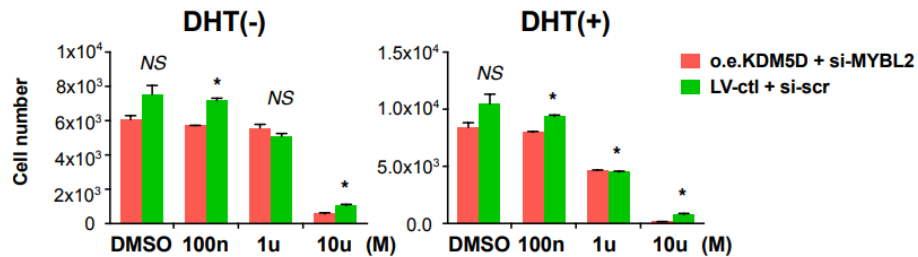


Supplementary Figure 2



A**OS KDM5D ADT****CRPC KDM5D ADT****B****OS KDM5D ADT + Docetaxel****CRPC KDM5D ADT + Docetaxel**



A**LNCaP Docetaxel 3 Days****B****LAPC4 Docetaxel 3 Days****C****LNCaP VE-822****D****LAPC4 VE-822**

Supporting Information section

Supplementary Figure Legends

Supplementary Figure 1: Western blot sheet

(A) Western blot sheet

Upper left; The protein expression levels of KDM5D, β -Actin, AR, and MYBL2 in LNCaP, LAPC4, CWR22Rv1, DU145, C4-2, and E006AA cell lines.

Upper right; The protein expression levels of KDM5D, β -Actin, AR, and MYBL2 in LNCaP and LAPC4 (each cells shows High/ Low KDM5D and High/ Low MYBL2) cell lines.

Under left; The protein expression levels of MYBL2 in sh-MYBL2 in LNCaP and E006AA.

Under right; The protein expression levels of β -Actin in sh-MYBL2 in LNCaP and E006AA.

Supplementary Figure 2: Cell lines phenotype silencing MYBL2

(A) mRNA expression level of KDM5D and MYBL2 in LNCaP (sh-control and sh-KDM5D) and LAPC4 (sh-control and over expression KDM5D) with FBS media. Error bars indicate standard deviation. (t-test; ** indicates $p < 0.01$; ***, $p < 0.001$).

(B) Western blot analysis of KDM5D, AR and MYBL2 levels corresponding to the RNA manipulations for Fig 2B after overexpressing or silencing KDM5D and/or MYBL2 as indicated

(C) Cell proliferation silencing MYBL2 (si-control, si-MYBL2 (5nM, 20nM)) with FBS media in three kind of cell lines. Cell proliferation after 3 days induced si-MYBL2 dose dependent (si-control(20nM), si-MYBL2 (2nM, 5nM, 20nM)) in three kind of cell lines. mRNA expression levels of MYBL2 by silencing MYBL2. Error bars indicate standard deviation. (t-test; ** indicates $p < 0.01$; ***, $p < 0.001$).

Supplementary Figure 3: Clinical outcomes in CHAARTED

(A) Clinical outcomes time to CRPC and OS related with MYBL2 expression level in all treatment from CHAARTED. (High = upper quartile)

(B) Time to CRPC and time from CRPC to death by treatment arm and MYBL2 status.

Abbreviations: CRPC, castration resistant prostate cancer; OCM, other cause mortality; PCSM, prostate cancer specific mortality; Q1, lowest quartile; Q2-3, middle quartiles; Q4, highest quartile.

Supplementary Figure 4: Impact of KDM5D and MYBL2 on time to CRPC and OS in CHAARTED

(A) Clinical outcomes time to CRPC from CHAARTED by KDM5D levels (Low = lower quartile).

(B) Clinical outcomes time to OS from CHAARTED by KDM5D levels (Low = lower quartile).

Supplementary Figure 5: Doxycycline induced sh-MYBL2

Error bars indicate standard deviation. (t-test; ** indicates $p < 0.01$; ***, $p < 0.001$).

(A) The time course of mRNA expression levels of MYBL2 in LAPC4 sh-control, sh-MYBL2#1, and sh-MYBL2#3 after administrated doxycycline 0 hour, 48 hours, and 72 hours.

(B) The time course of mRNA expression levels of MYBL2 in E006AA sh-control, sh-MYBL2#1, and sh-MYBL2#3 after administrated doxycycline 0 hour, 48 hours, and 72 hours.

(C) Cell proliferation assay of indicated cell lines in FBS media. LAPC4 sh-control vs sh-MYBL2#1 and #3.

(D) Cell proliferation assay of indicated cell lines in FBS media. E006AA sh-control vs sh-MYBL2#1 and #3.

(E) Cell proliferation assay of indicated cell lines with doxycycline inducible MYBL2 in FBS media. LAPC4 sh-control vs sh-MYBL2#1 and #3 with doxycycline treatment.

Supplementary Figure 6: Impact of KDM5D and MYBL2 on Sensitivity to drugs in HSPC

Error bars indicate standard deviation. (t-test; * indicates $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

(A) Docetaxel sensitivity Lenti-control ($=KDM5D^{Hi} / MYBL2^{Lo}$) vs overexpression MYBL2 ($=KDM5D^{Hi} / MYBL2^{Hi}$) in LNCaP with CSS plus DHT without DHT.

(B) Docetaxel sensitivity si-control ($=KDM5D^{Lo} / MYBL2^{Hi}$) vs si-MYBL2 ($=KDM5D^{Lo} / MYBL2^{Lo}$) in LAPC4 with CSS plus DHT without DHT.

(C) Drug sensitivity of VE-822 (ATR-inhibitor) Lenti-control plus si-control ($=KDM5D^{Hi} / MYBL2^{Lo}$) vs overexpression MYBL2 plus si-KDM5D ($=KDM5D^{Lo} / MYBL2^{Hi}$) in LNCaP with CSS plus DHT without DHT.

(D) Drug sensitivity of VE-822 (ATR-inhibitor) Lenti-control plus si-control ($=KDM5D^{Lo} / MYBL2^{Hi}$) vs overexpression KDM5D plus si-MYBL2 ($=KDM5D^{Hi} / MYBL2^{Lo}$) in LAPC4 with CSS plus DHT without DHT.

Supplementary Table 1: Materials

Protein	Antibody	Vendor	Catalog Number
Androgen Receptor	Rabbit	Cell Signaling Technology	#5153
KDM5D / Jarid1D	Rabbit	Abcam	ab227728
B-Myb	Rabbit	Novus Biologicals	NBP2-33930
β -Actin	Mouse	Santa Cruz Biotechnology	sc-47778
PARP	Rabbit	Cell Signaling Technology	#9542
CyclinA	Mouse	Santa Cruz Biotechnology	sc-271682
p27 Kip1	Rabbit	Cell Signaling Technology	#2552
RNA(Primer)	Target		Catalog Number
MYBL2	Human	Hs00942540_m1	4331182
MYBL2	Human	Hs00942547_m1	4351372
MYBL2	Human	Hs00942552_m1	4351372
MYBL2	Human	Hs00942541_m1	4351372
MYBL2	Human	Hs00942551_m1	4351372
MYBL2	Human	Hs00942549_m1	4351372
KDM5D	Human	Hs00190491_m1	4331182
KDM5D	Human	Hs05049162_s1	4351372
KDM5D	Human	Hs01104401_g1	4351372
KDM5D	Human	Hs01104405_gH	4351372
KDM5D	Human	Hs01104389_g1	4351372
KDM5D	Human	Hs01104397_gH	4331182
GAPDH	Human	Hs99999905_m1	4331182
siRNA	Target	Vendor	Catalog Number
si-MYBL2	Human	Dharmacon	L-010444-00-0005
si-KDM5D	Human	Dharmacon	L-010820-00-0005
Overexpression			
B-MYB		Origene	RC203540L3V
KDM5D		Dharmacon	MHS6278-213246113

shRNAs

sh-scramble (control)

Forward:

CCGGTTTCTCCGAACGTGTCACGTCTCGAGACGTGACACGTTCCGAGAATTTTTG

Reverse:

AATTCAAAAATTCTCCGAACGTGTCACGTCTCGAGACGTGACACGTTCCGAGAAA

sh-KDM5D

Forward:

CCGGTGTAACACACACCCGTTTGACACTCGAGTGTCAAACGGGTGTGTGTTACTTTTTG

Reverse:

AATTCAAAAAGTAACACACACCCGTTTGACACTCGAGTGTCAAACGGGTGTGTGTTACA

sh-MYBL2 #1

Forward:

CCGGTGCTTCTTGAGCGAGTCCAAAGCTCGAGCTTTGGACTCGCTCAAGAAGCTTTTTG

Reverse:

AATTCAAAAAGCTTCTTGAGCGAGTCCAAAGCTCGAGCTTTGGACTCGCTCAAGAAGCA

sh-MYBL2 #3

Forward:

CCGGTGACACAGGAGGCTTCTTGAGCCTCGAGGCTCAAGAAGCCTCCTGTGTCTTTTTG

Reverse:

AATTCAAAAAGACACAGGAGGCTTCTTGAGCCTCGAGGCTCAAGAAGCCTCCTGTGTCA

Drug	Vendor	Catalog Number
Docetaxel	Selleckchem	S1148
Cabazitaxel	Selleckchem	S3022
VE-822	Selleckchem	S7102
Ribociclib	Selleckchem	S7440
Abiraterone	Selleckchem	S1123

Supplementary Table 2: quantitative analysis of cell cycle profiles

LNCaP Wild Type			
	G0 / G1 phase	S phase	G2/M phase
%Gated	66.7	9.0	22.9
Mean	1501.3	2103.6	2827.9

LNCaP LV-control + si-scramble			
	G0 / G1 phase	S phase	G2/M phase
%Gated	64.9	13.4	18.2
Mean	1406.4	2102.6	2773.2

LNCaP o.e.MYBL2 + si-KDM5D			
	G0 / G1 phase	S phase	G2/M phase
%Gated	64.5	12.2	20.1
Mean	1385.4	2150.3	2734.8

LAPC4 Wild Type			
	G0 / G1 phase	S phase	G2/M phase
%Gated	58.5	14.7	25.5
Mean	1226.3	1757.5	2311.5

LAPC4 LV-control + si-scramble			
	G0 / G1 phase	S phase	G2/M phase
%Gated	59.4	14.6	24.9
Mean	1252.3	1753.4	2303.1

LAPC4 o.e.KDM5D + si-MYBL2			
	G0 / G1 phase	S phase	G2/M phase
%Gated	40.5	12.7	45.7
Mean	1150.1	1769.5	2242.7