Supplementary Figure legends.

Supplementary Figure S1 (A) RT-PCR with HPV16 L1 mRNA specific primers 773s and L1as on total RNA extracted from the C33A2 reporter cell line treated with 50- or 100-uM of melphalan for 22hrs (for location of primers see Fig. 1A). The bands were quantified, mean values and standard deviations determined and plotted in the graph to the right. The percentage spliced L1i and L1 mRNAs were calculated and indicated below the gel. Percentages refer to percent spliced L1i mRNAs of L1 and L1i mRNAs. This calculation is shown separately for C33A2 cells treated with 50uM melphalan and 100uM melphalan. **(B)** Schematic representation of ATRIP1 mRNA which encodes the DDR factor ATRIP1. Exons E3 and E12 that may be alternatively spliced are indicated. Arrows indicate RT-PCR primers that are used to discriminate between alternatively spliced ATRIP mRNAs. (**C)** RT-PCR with the indicated ATRIP primers on RNA extracted from DMSO- or melphalan- (100uM) treated C33A2 cells. RT-PCR over exons E2, E3 and E4 shows no indication of alternative splicing induced by melphalan, whereas RT-PCR over exons E11, E12 and E13 shows alternative splicing of exon E12 in the presence of melphalan. (**D)** RT-PCR with primers for the cellular PHB2 mRNA on total RNA extracted from the C33A2 reporter cell line treated with DMSO alone or 100-uM of melphalan for 22hrs. The two alternatively spliced PHB2 mRNAs are indicated. The results demonstrate alternative splicing of exon E-ALT (located between exons E4 and E5) in the presence of melphalan. RT-PCR reactions were performed in the absence (-) or presence (+) of RT-enzyme. Percent inclusion of the alternatively spliced exon is indicated below each gel.

Supplementary Figure S2 (A-E) Western blots with monospecific antibodies to various DNA damage response factors (ATM, Chk1, Chk2, BRCA1) or phosphorylated, activated forms of the same factors, and γH2AX, in C33A2 cells treated with DMSO or melphalan for the indicated time points. Densitrometric quantitations are shown below each gel. Fold difference of the phosphorylated form of the protein over total levels of the same protein in melphalan-treated cells over DMSO-treated cells (ATM (3hs, 6hrs, 22hrs) **(A)**, Chk1 (22hrs) (**B**-right panel), Chk2 (22hrs) (**C**-right panel) in which the phosphorylated form could be detected in DMSO treated cells, or as fold difference of the phosphorylated form of the protein over total levels of the same protein (Chk1 (3hs, 6hrs)(**B**-left panel), Chk2 (3hs, 6hrs)(**C**-left panel) in which the phosphorylated form could not be detected in DMSO treated cells. (**D**) Levels of phosphorylated BRCA1 at the various time points after addition of melphalan to C33A2 cells are normalized to actin. (**E**) Levels of γH2AX at the various time points after addition of melphalan are normalized to actin and expressed as fold over levels in DMSO-treated cells.

Supplementary Figure S3 (A) Western blotting with antibody to phosphorylated BRCA1 (p-BRCA1) on extracts from C33A2 cells treated with DMSO, 100uM melphalan or 100uM irinotecan. Quantitations of phosphorylated BCRA1 normalized to actin and to the levels of phosphorylated BRCA1 in DMSO treated cells. Ratios are shown below the gel. **(B)** Western blotting with antibodies to ATM or phosphorylated ATM (p-ATM) on extracts from C33A2 cells treated with DMSO, 100uM melphalan or 100uM irinotecan. Quantitations of phosphorylated ATM divided by total levels of ATM in DMSO treated cells. Ratios are shown below the gel. **(C)** Secreted luciferase enzyme activity (sLuc) in the cell culture medium of reporter cell line C33A2 treated with DMSO, 100uM melphalan or 100uM irinotecan. **(D)** RT-PCR with HPV16 L1 mRNA specific primers 773s and L1as on total RNA extracted from the C33A2 reporter cell line treated with DMSO, 100uM of melphalan or 100uM irinotecan (for location of primers see Fig. 1A). Quantified RT-PCR bands in melphalan- or irinotecan- treated cells were divided by L1 mRNA levels in DMSO treated cells. Ratios are shown below the gel.

Supplementary Figure S4 (A) C33A2 cells were incubated in DMSO or 100uM of melphalan for the indicated time periods. At each indicated time-point, cells were retrieved, counted and plotted against time in each substance. **(B)** C33A2 cells were incubated in DMSO or 100uM of melphalan for the indicated time periods. Cells were subjected to MTT assay at the indicated

time points to determine cell viability. MTT results were plotted against time. **(C)** Western blot analysis on extracts from C33A2 cells incubated in melphalan for the indicated time points with antibodies that detect PARP1 and the apoptosis-induced 89kDa cleavage product of PARP1 (left panel). Detection of cleaved PARP1 in control cells HN26 are shown (right panel). HN26 cells are HPV16-positive tonsillar cancer cells that will be described elsewhere. Quantitations were performed and are displayed as percentage PARP1 cleavage below the gels.

Supplementary Figure S5 sLuc activity in C33A2 cells treated with DMSO (-) or 100uM melphalan (+) in the absence (-) or presence (+) of MAPKp38 inhibitor SB203580 (left panel), or in the absence (-) or presence (+) of DNApk inhibitor NU7026 (right panel).

Supplementary Figure S6 (A) Schematic representation of the pBELsLuc reporter plasmid stably integrated in the genome of the C33A2 cells. Transcription of the HPV16 sequences in the pBELsLuc plasmid is driven by the human cytomegalovirus promoter (CMV). The sLuc gene inserted into the L1 region is indicated and is preceded by the poliovirus 2A internal ribosome entry site (IRES). Arrows represent ChIP PCR primers (See supplementary Table 1 for primer sequences). **(B)** Schematic representation of the pBELCAT reporter plasmid. Transcription of the HPV16 sequences in the pBELCAT plasmid is driven by the human cytomegalovirus promoter (CMV). The CAT gene inserted into the L1 region is indicated and is preceded by the poliovirus 2A internal ribosome entry site (IRES). **(C)** Schematic representation of the pBELsLuc reporter plasmid. The primers (CMVS and 757as) used for amplification of all mRNAs produced from pBELsLuc in the C33A2 cell line are indicated.

Supplementary Figure S7 (A) Western blots on acetylated histone H3 (H3Ac) or total levels of histone 3 (H3) in C33A2 cells treated with DMSO, HDAC inhibitor CUDC-907 or melphalan for the indicated time points. Quantitations below the gels show H3Ac normalized to H3 and divided by H3Ac levels in DMSO treated cells. **(B–C)** ChIP analysis on chromatin from C33A2 cells using antibodies to H3Ac or H4Ac and qPCR of the indicated HPV16 amplicons. The ChIP results obtained with antibodies to acetylated histones H3Ac and H4Ac, were all normalized to ChIP results of the same chromatin samples obtained with antibodies to unmodified histones H3 and H4, respectively. Mean values with standard deviations of the amount of immunoprecipitated DNA compared to input DNA are displayed. The q-PCR values obtained for each primer pair with DNA extracted from DMSO-treated C33A2 cells were set to 1 to correct for differences between different ChIP extracts. Chip extracts were prepared from C33A2 cells treated with melphalan for the indicated time-periods. All samples were analyzed in two independent ChIP assays and all qPCR reactions were performed in triplicates.

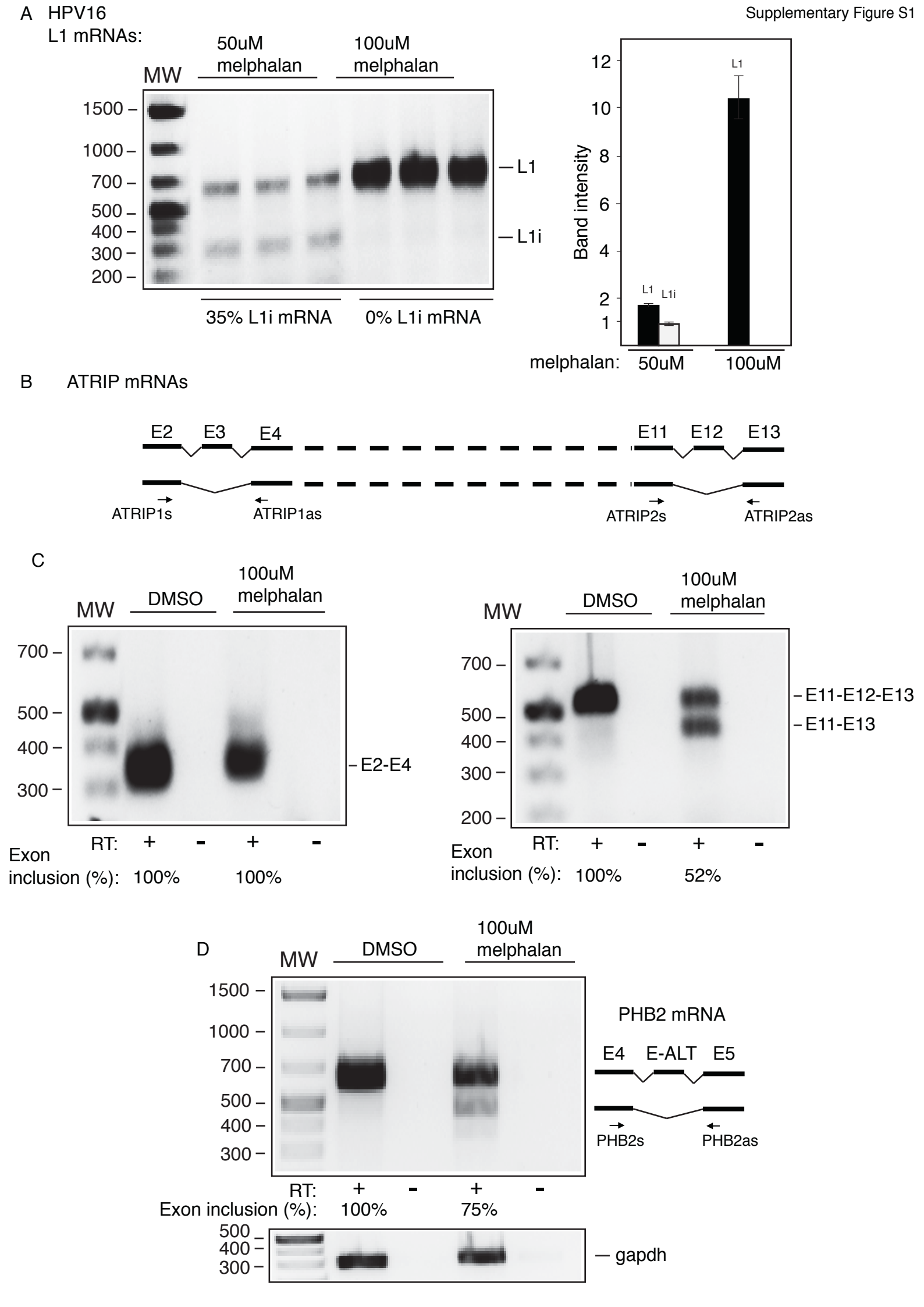
Supplementary Figure S8 (A) Western blot on phosphorylated SR proteins in C33A2 cells treated with DMSO (D) or with 100uM melphalan (M) for 6hrs, or with 25-, 50- or 100uM melphalan for 6hrs. **(B)** Quantitation of the Western blot shown in (A). Fold SR protein levels in cells treated with indicated concentrations of melphalan over SR protein levels in DMSO-treated cells are shown. **(C)** ChIP analyses on C33A2 cells using antibody to phosphorylated SR proteins and qPCR of the indicated HPV16 amplicons as described for Figure 7D. **(D)** C33A2 cells treated with DMSO or melphalan for the indicated time points were UV irradiated and subjected to CLIP assay as detailed in Materials and methods. The RNA-protein complexes were immunoprecipitated with antibodies to phosphorylated SR proteins, hnRNP G or HuR and the RNA extracted from the immunoprecipitated complexes were subjected to RT-PCR with primers that detect HPV16 E4 mRNAs spliced from SD880 to SA3358. The location in the HPV16 genome of the HPV16 RT-PCR primers is shown in Figure 1A, primer sequences are shown in Supplementary Table 3 and antibodies are listed in Supplementary Table 4.

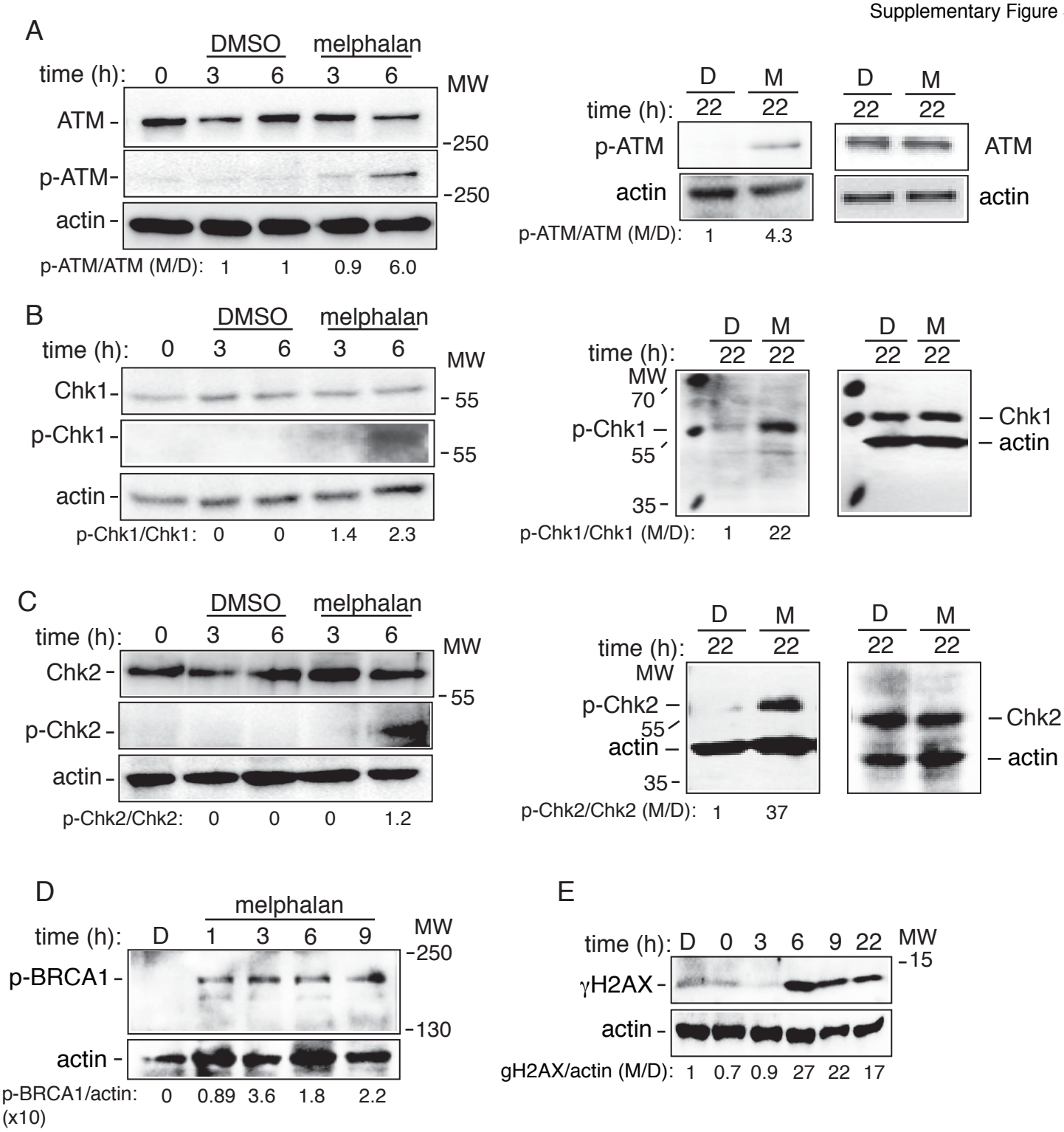
Supplementary Figure S9 (A) Schematic drawing of the HPV16 genome with a blow-up of the region around the E4 exon bordered by HPV16 splice sites SA3358 and SD3632. The 35-nucleotide biotinylated ssDNA oligos (overlapping by 5-nucleotides) used in pull down assays

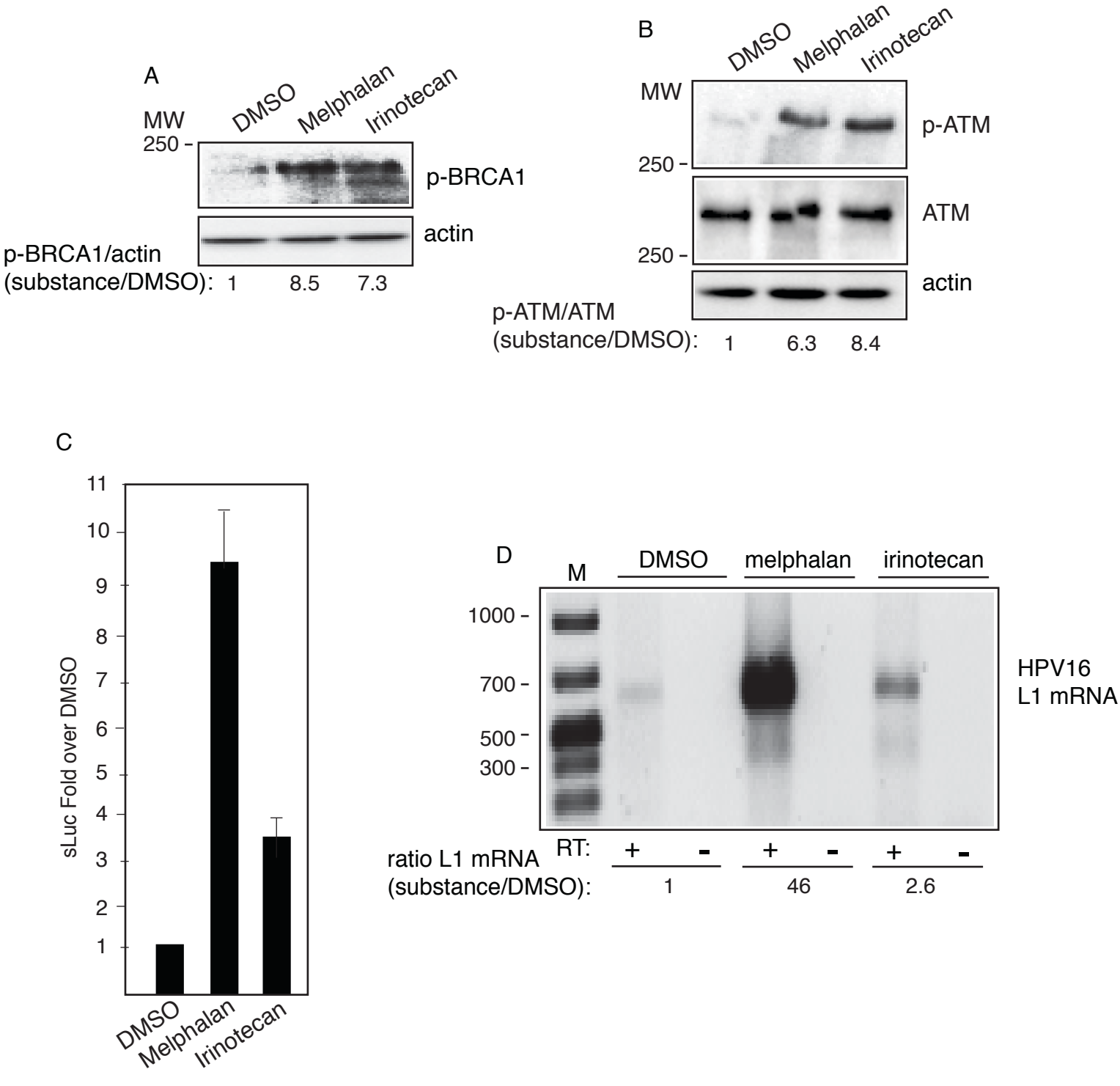
are indicated. **(B)** Western blot with antibody to U2AF65 on proteins pulled down with the indicated biotinylated oligos using cellular extracts prepared from C33A2 cells treated with DMSO (-) or melphalan (+) for 6hrs. Ratios of quantified levels of U2AF65 in melphalan treated cells (+) over levels of pulled down U2AF65 in DMSO-treated cells (-) are shown below the gel. (**C**) As an additional control for specificity, pull downs of U2AF65 or hnRNP C with oligo 8 from extracts of C33A2 cells treated for various time periods with melphalan are shown. While hnRNP C is readily observed after pull down, U2AF65 is undetectable. **(D)** Western blot on U2AF65 on pull-downs with biotinylated HPV16 ssDNA oligo #1 (wt), or antisense version of oligo #1 (mut) to show sequence-specific pull down of U2AF65. Ratio of quantified levels of U2AF65 pulled down by wild-type (wt)-oligo over antisense oligo (mutant) is shown below the gel. **(E)** Western blot with antibody to U2AF65 on proteins pulled down with the indicated biotinylated oligos using cellular extracts prepared from C33A2 cells treated with DMSO (-) or melphalan (+) for the indicated time periods. **(F)** Western blot on pull-downs with biotinylated RNA oligos.

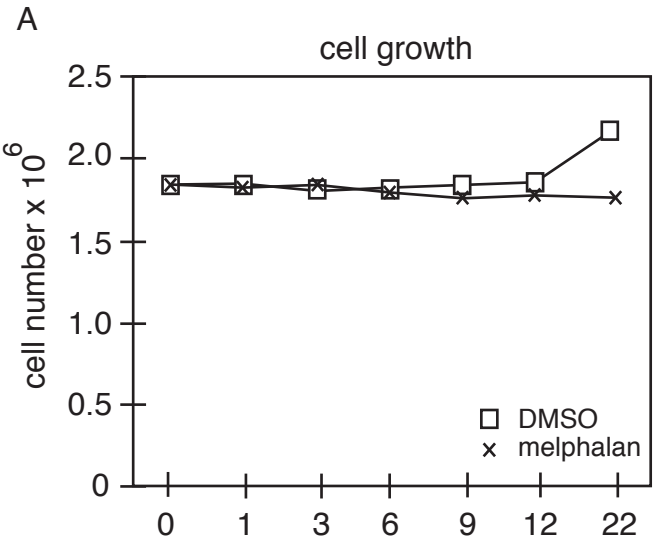
Supplementary Figure S10 Western blot on the indicated polyadenylation factors in C33A2 cells or C33A2 cells treated with DMSO or 100uM melphalan for the indicated time points. Bands were quantified and normalized to actin then divided by the levels of each protein in DMSO-treated cells. Ratios are shown below each gel.

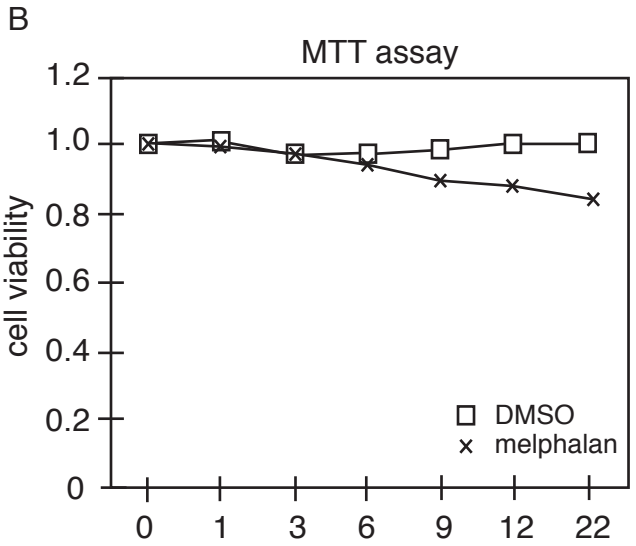
Supplementary Figure S11 (A) C33A2 cells treated with DMSO or 100uM melphalan for the indicated time points were subjected to UV radiation to cross-link RNA and protein prior to cell lysis. Cells were lysed in total cell lysis-buffer (Materials and Methods) and 5% of the cell extract was saved and subjected to Western blotting with monoclonal antibodies to hnRNP C and U2AF65 (input) (**A**). The remaining cell extracts were mixed with oligodT-magnetic beads to extract polyA mRNAs and proteins cross linked to these mRNAs. Following multiple washes in RIPA buffer, the proteins were eluted by RNase treatment of the beads, and subjected Western blotting with monoclonal antibodies to hnRNP C and U2AF65 (pull-down) (**B**). The bands in each lane were quantified and rations of protein levels in melphalan (M) treated cell over DMSO (D) treated cells were determined. The ratios are shown below each gel. **(C)** Ratios of hnRNP C or U2AF65 levels in melphalan versus DMSO in pulled down samples were divided with ratios of hnRNP C or U2AF65 levels in melphalan versus DMSO in input samples. These ratios are displayed and show that at least after 3hrs of melphalan treatment, the increases in RNA binding of hnRNP C and U2AF65 is bigger than the increase in levels of these proteins in the cells.

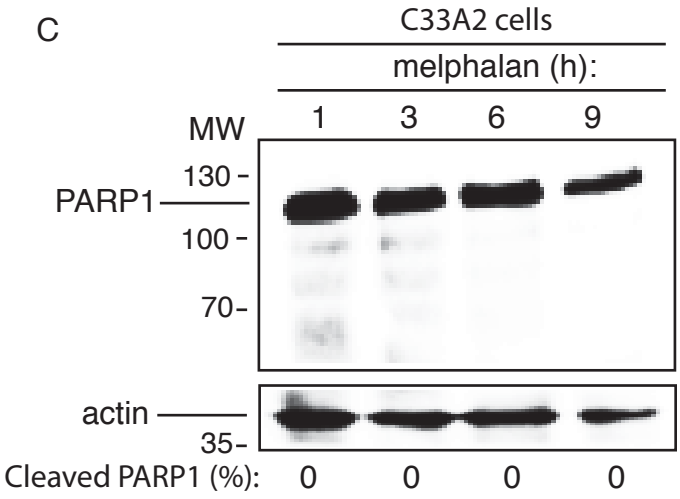

A HPV16
L1 mRNAs:
50uM melphalan
100uM melphalan
MW
1500
1000
700
500
400
300
200
L1
L1i
35% L1i mRNA
0% L1i mRNA
Band intensity
12
10
8
6
4
2
1
L1
L1i
melphalan: 50uM 100uM
B ATRIP mRNAs
E2 E3 E4 E11 E12 E13
ATRIP1s
ATRIP1as
ATRIP2s
ATRIP2as
C
MW
DMSO
100uM melphalan
700
500
400
300
E2-E4
RT: + - + -
Exon inclusion (%): 100% 100%
MW
DMSO
100uM melphalan
700
500
400
300
200
E11-E12-E13
E11-E13
RT: + - + -
Exon inclusion (%): 100% 52%
D
MW
DMSO
100uM melphalan
1500
1000
700
500
400
300
PHB2 mRNA
E4 E-ALT E5
PHB2s
PHB2as
RT: + - + -
Exon inclusion (%): 100% 75%
500
400
300
gapdh

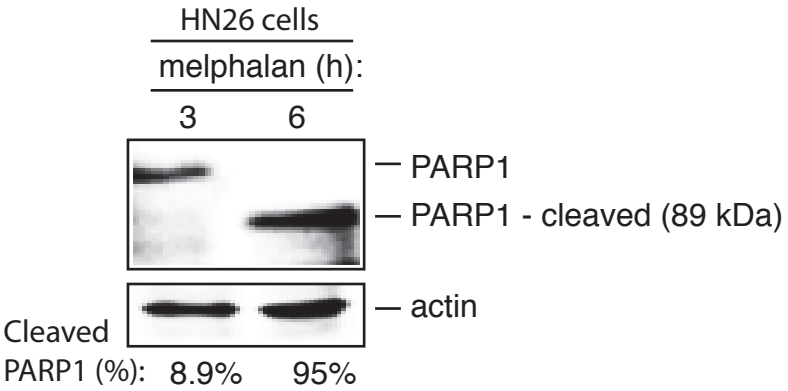

A
DMSO
melphalan
time (h): 0 3 6 3 6
MW
ATM
p-ATM
actin
250
250
p-ATM/ATM (M/D): 1 1 0.9 6.0
D M D M
time (h): 22 22 22 22
p-ATM
actin
ATM
actin
p-ATM/ATM (M/D): 1 4.3
B
DMSO
melphalan
time (h): 0 3 6 3 6
MW
Chk1
p-Chk1
actin
55
55
p-Chk1/Chk1: 0 0 1.4 2.3
D M D M
time (h): 22 22 22 22
MW
70
p-Chk1
55
35
Chk1
actin
p-Chk1/Chk1 (M/D): 1 22
C
DMSO
melphalan
time (h): 0 3 6 3 6
MW
Chk2
p-Chk2
actin
55
p-Chk2/Chk2: 0 0 0 1.2
D M D M
time (h): 22 22 22 22
MW
p-Chk2
55
actin
35
Chk2
actin
p-Chk2/Chk2 (M/D): 1 37
D
melphalan
time (h): D 1 3 6 9
MW
p-BRCA1
actin
250
130
p-BRCA1/actin: 0 0.89 3.6 1.8 2.2
(x10)
E
time (h): D 0 3 6 9 22
MW
γH2AX
actin
15
gH2AX/actin (M/D): 1 0.7 0.9 27 22 17

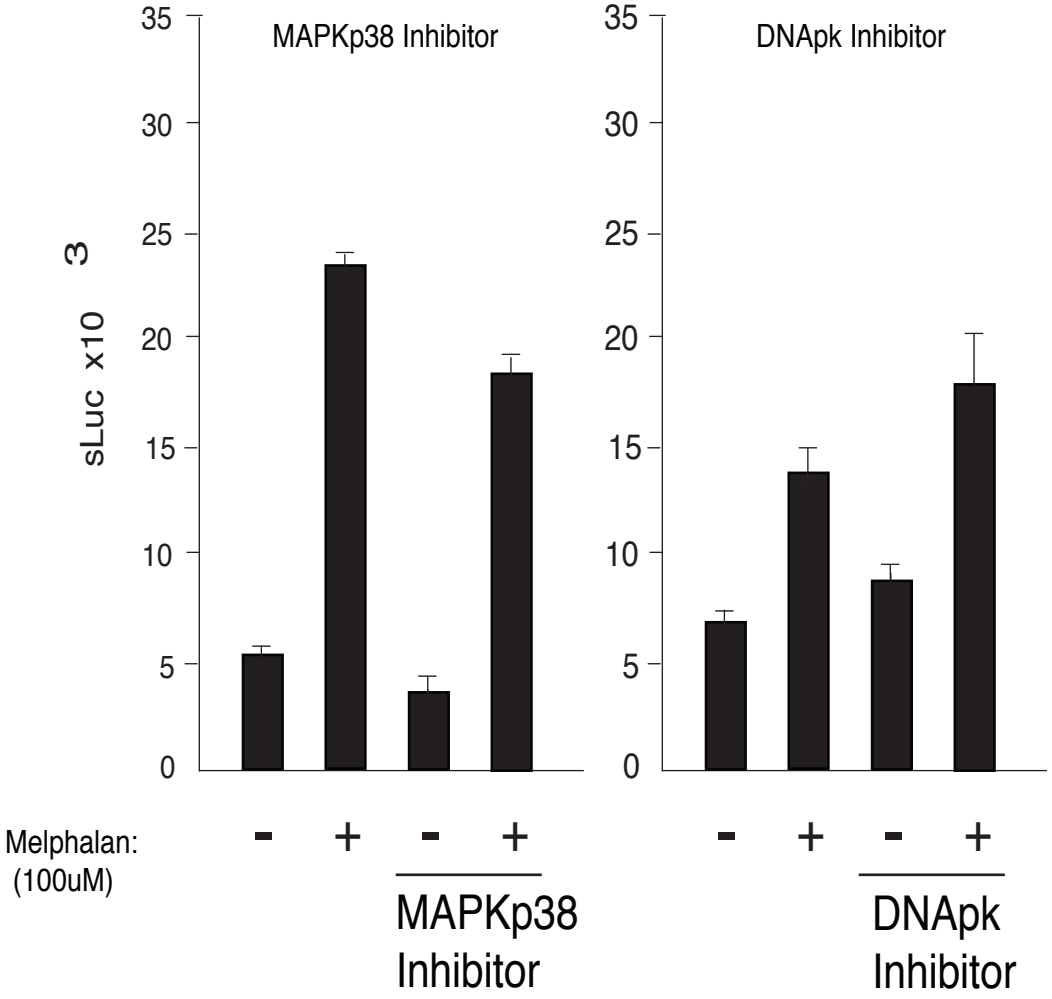

A
MW
DMSO
Melphalan
Irinotecan
250
p-BRCA1
actin
p-BRCA1/actin
(substance/DMSO): 1 8.5 7.3
B
DMSO
Melphalan
Irinotecan
MW
250
p-ATM
ATM
250
actin
p-ATM/ATM
(substance/DMSO): 1 6.3 8.4
C
sLuc Fold over DMSO
11
10
9
8
7
6
5
4
3
2
1
DMSO
Melphalan
Irinotecan
D
M
DMSO
melphalan
irinotecan
1000
700
500
300
HPV16
L1 mRNA
RT: + - + - + -
ratio L1 mRNA
(substance/DMSO): 1 46 2.6

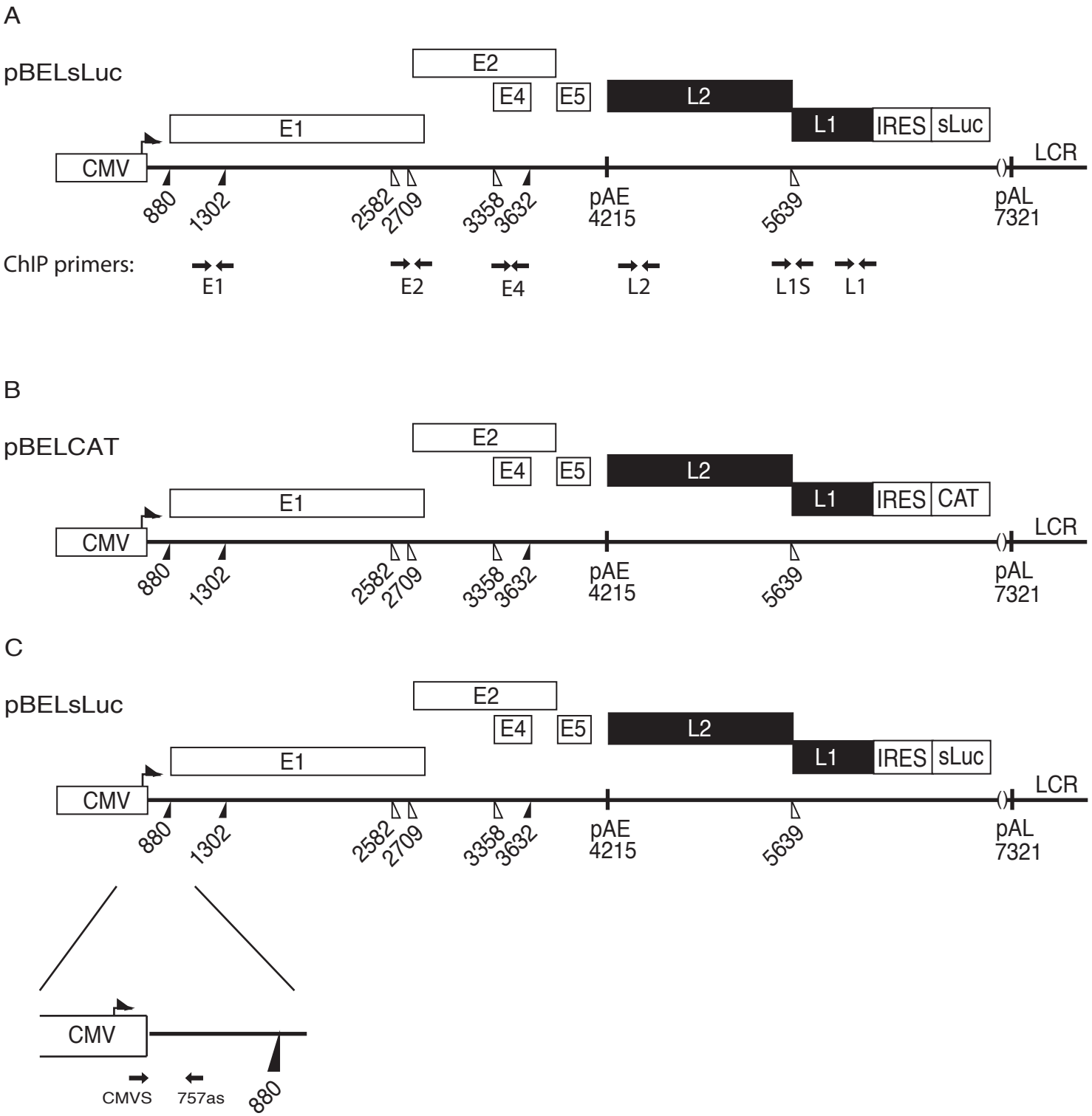

A
cell growth
cell number x 10^6
2.5
2.0
1.5
1.0
0.5
0
0 1 3 6 9 12 22
DMSO
melphalan


B
MTT assay
cell viability
1.2
1.0
0.8
0.6
0.4
0.2
0
0 1 3 6 9 12 22
DMSO
melphalan


C
C33A2 cells
melphalan (h):
1 3 6 9
MW
130
PARP1
100
70
actin
35
Cleaved PARP1 (%): 0 0 0 0


HN26 cells
melphalan (h):
3 6
PARP1
PARP1 - cleaved (89 kDa)
actin
Cleaved
PARP1 (%): 8.9% 95%


MAPKp38 Inhibitor
DNApk Inhibitor
sLuc x10 3
35
30
25
20
15
10
5
0
Melphalan:
(100uM)
-
+
-
+
MAPKp38
Inhibitor
DNApk
Inhibitor


A
pBELsLuc
E2
E4
E5
L2
E1
L1
IRES
sLuc
CMV
LCR
880
1302
2582
2709
3358
3632
pAE
4215
5639
pAL
7321
ChIP primers:
E1
E2
E4
L2
L1S
L1
B
pBELCAT
E2
E4
E5
L2
E1
L1
IRES
CAT
CMV
LCR
880
1302
2582
2709
3358
3632
pAE
4215
5639
pAL
7321
C
pBELsLuc
E2
E4
E5
L2
E1
L1
IRES
sLuc
CMV
LCR
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3632
pAE
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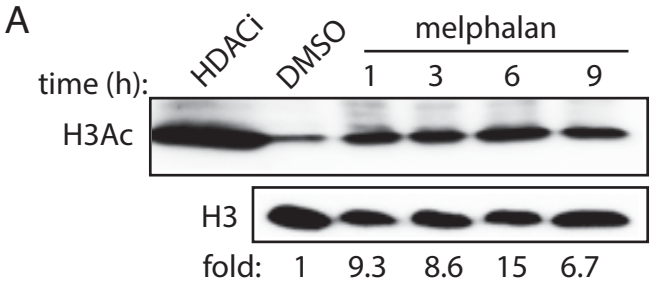
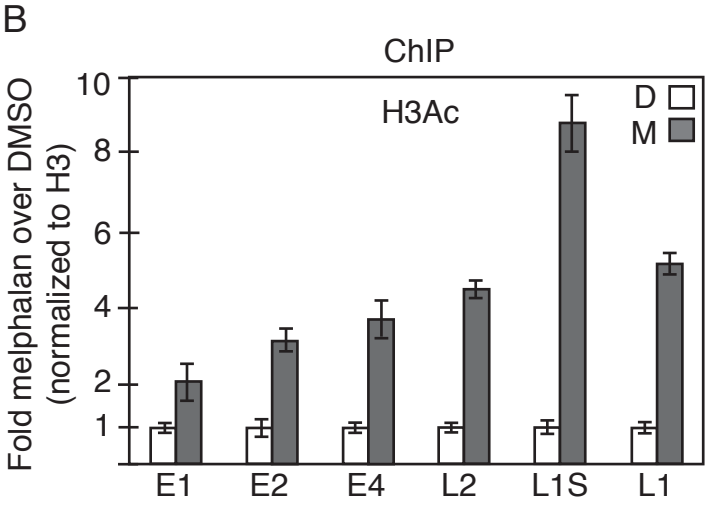
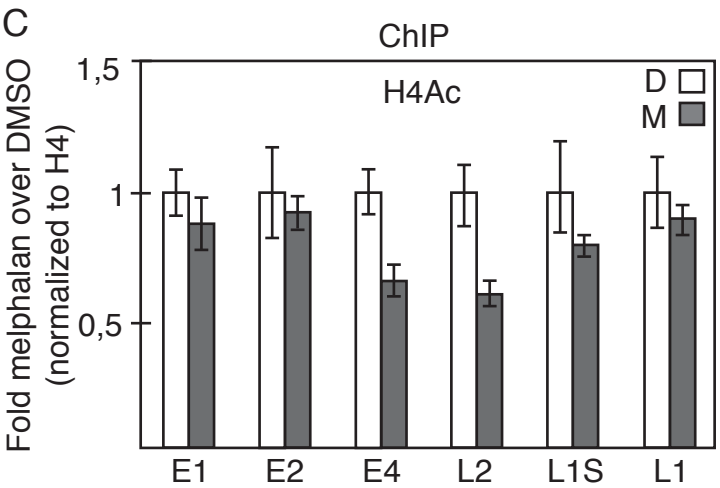
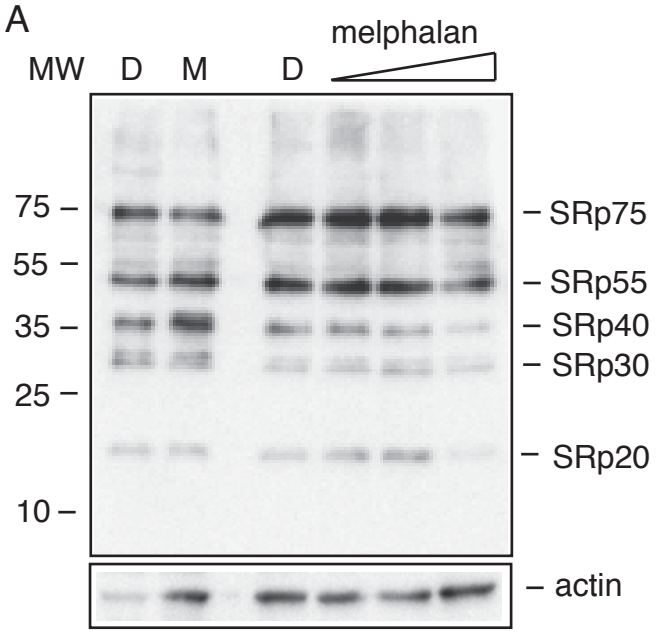
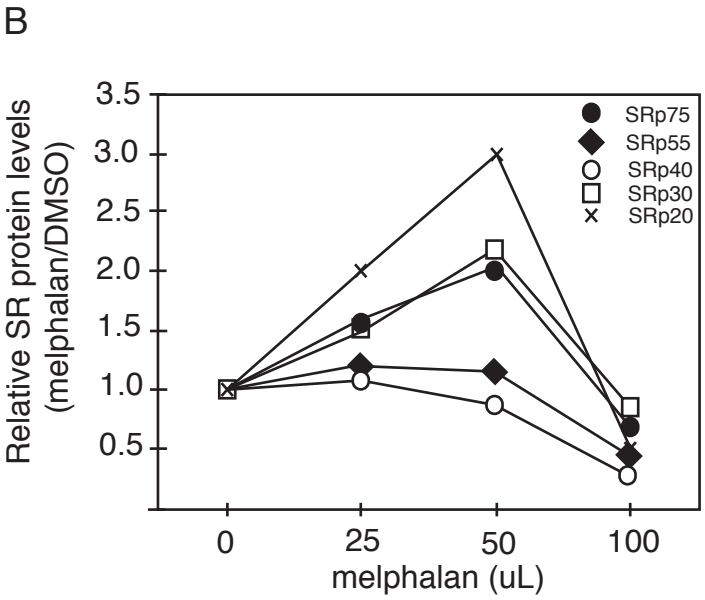
5639
pAL
7321
CMV
CMVS
757as
880

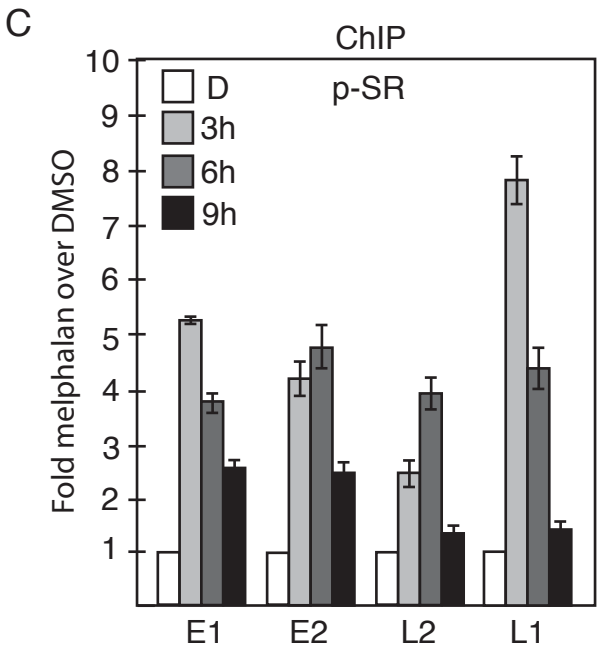

A
HDACi
DMSO
melphalan
time (h):
1
3
6
9
H3Ac
H3
fold:
1
9.3
8.6
15
6.7

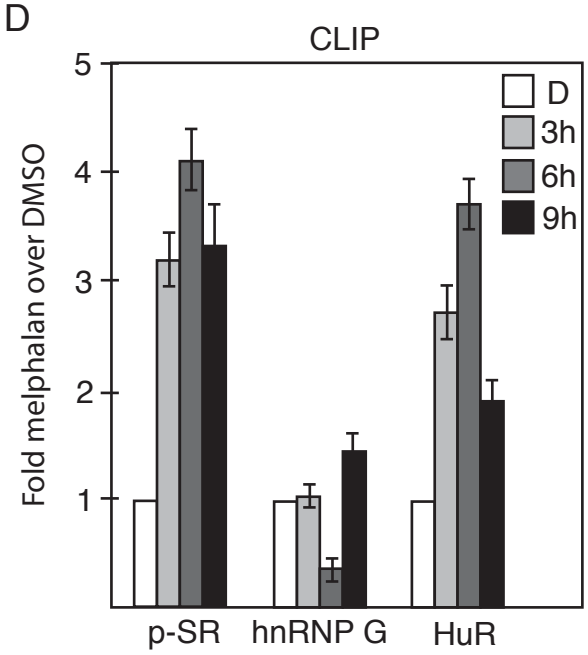

B
ChIP
H3Ac
D
M
Fold melphalan over DMSO
(normalized to H3)
10
8
6
4
2
1
E1
E2
E4
L2
L1S
L1

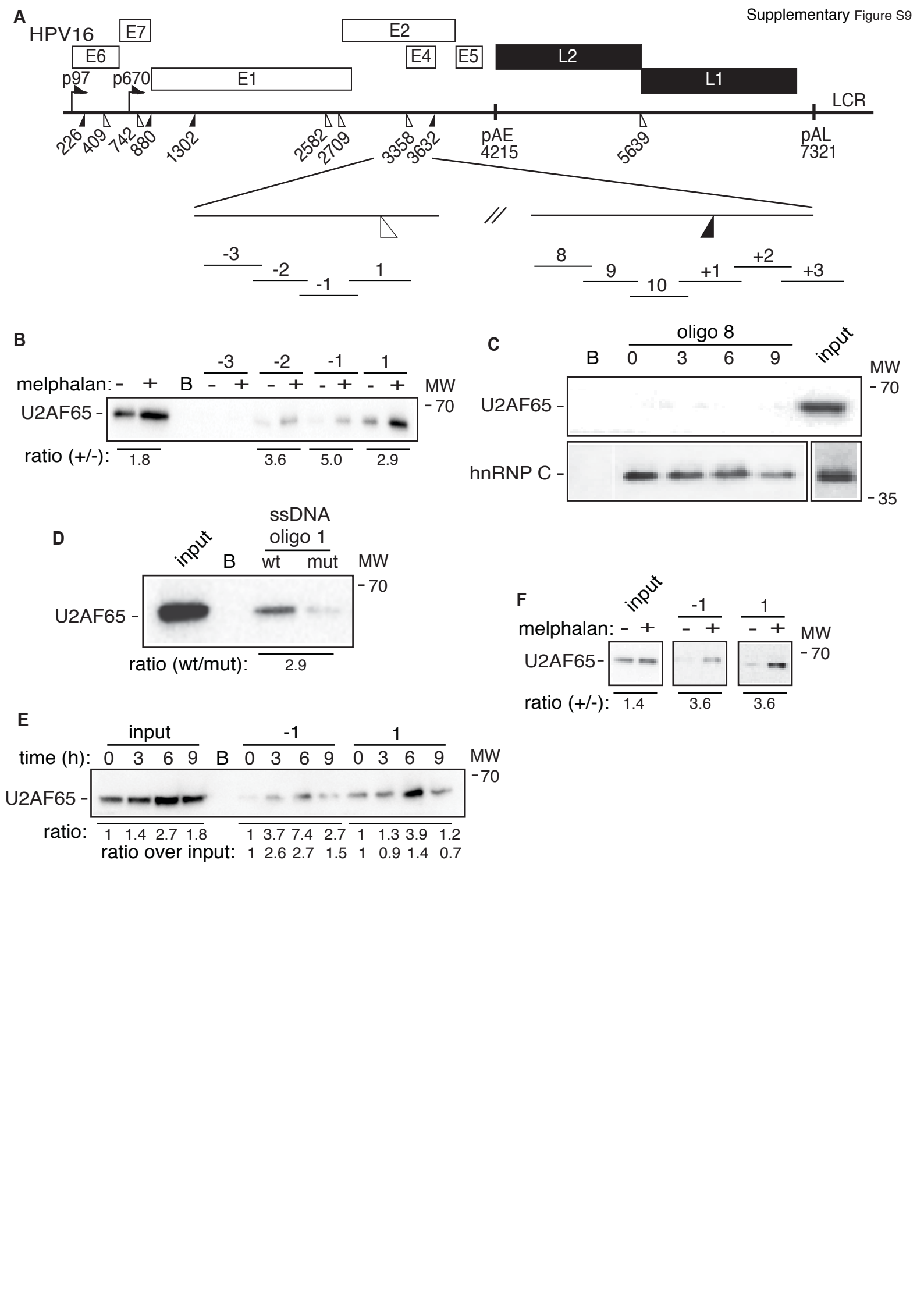

C
ChIP
H4Ac
D
M
Fold melphalan over DMSO
(normalized to H4)
1,5
1
0,5
E1
E2
E4
L2
L1S
L1

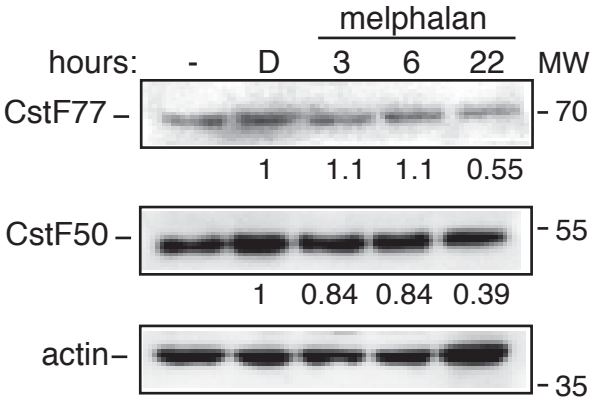

A
melphalan
MW
D
M
D
75 –
55 –
35 –
25 –
10 –
– SRp75
– SRp55
– SRp40
– SRp30
– SRp20
– actin

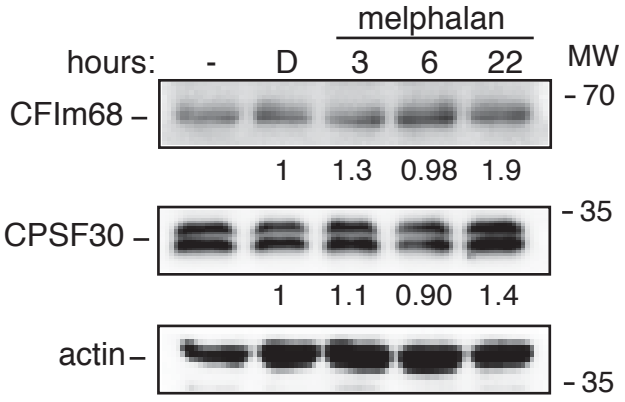

B
Relative SR protein levels (melphalan/DMSO)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
SRp75
SRp55
SRp40
SRp30
SRp20
0
25
50
100
melphalan (uL)

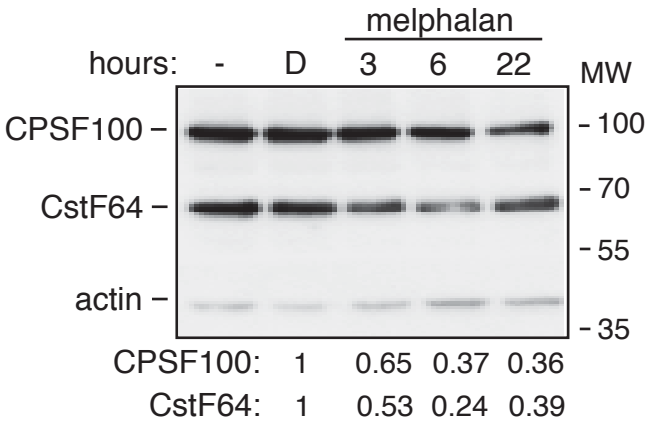

C
ChIP
p-SR
D
3h
6h
9h
Fold melphalan over DMSO
10
9
8
7
6
5
4
3
2
1
E1
E2
L2
L1

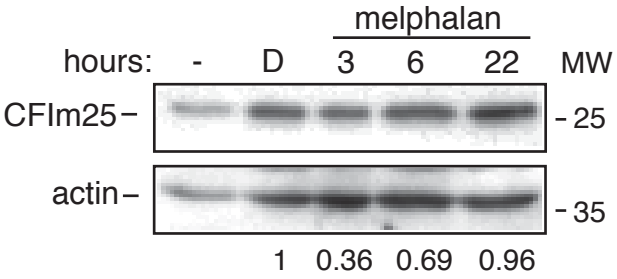

D
CLIP
D
3h
6h
9h
Fold melphalan over DMSO
5
4
3
2
1
p-SR
hnRNP G
HuR


A
HPV16
E7
E6
E2
E4
E5
L2
L1
p97
p670
E1
LCR
226
409
742
880
1302
2582
2709
3358
3632
pAE
4215
5639
pAL
7321
-3
-2
-1
1
8
9
10
+1
+2
+3
B
melphalan:
B
MW
70
U2AF65
ratio (+/-):
1.8
3.6
5.0
2.9
C
oligo 8
B
0
3
6
9
input
MW
70
U2AF65
hnRNP C
35
D
ssDNA
oligo 1
input
B
wt
mut
MW
70
U2AF65
ratio (wt/mut):
2.9
E
input
-1
1
time (h):
0
3
6
9
B
MW
70
U2AF65
ratio:
1
1.4
2.7
1.8
1
3.7
7.4
2.7
1
1.3
3.9
1.2
ratio over input:
1
2.6
2.7
1.5
1
0.9
1.4
0.7
F
input
-1
1
melphalan:
MW
70
U2AF65
ratio (+/-):
1.4
3.6
3.6

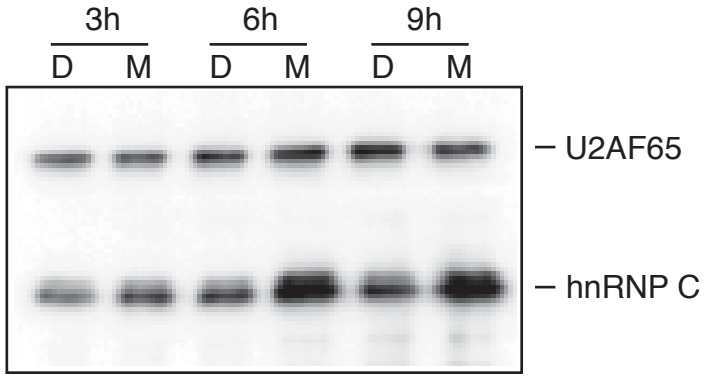

melphalan
hours: - D 3 6 22 MW
CstF77 –
70
1 1.1 1.1 0.55
CstF50 –
55
1 0.84 0.84 0.39
actin –
35


melphalan
hours: - D 3 6 22 MW
CFIm68 –
70
1 1.3 0.98 1.9
CPSF30 –
35
1 1.1 0.90 1.4
actin –
35


melphalan
hours: - D 3 6 22 MW
CPSF100 –
100
CstF64 –
70
55
actin –
35
CPSF100: 1 0.65 0.37 0.36
CstF64: 1 0.53 0.24 0.39


melphalan
hours: - D 3 6 22 MW
CFIm25 –
25
actin –
35
1 0.36 0.69 0.96

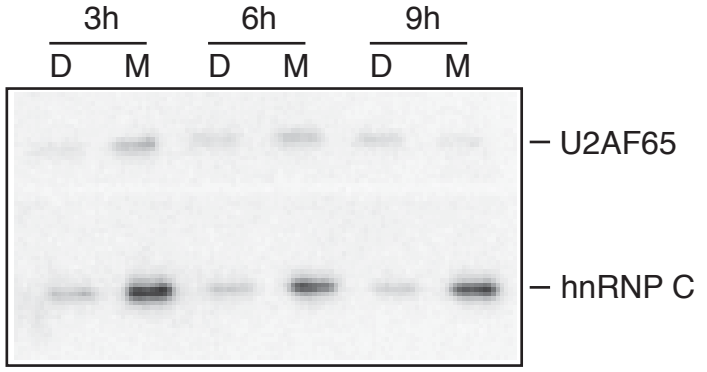
A



input:

	3h	6h	9h
U2AF65 (M/D):	0.95	1.3	0.78
hnRNP C (M/D):	1.4	2.1	1.8

B



pull down:

	3h	6h	9h
U2AF65 (M/D):	2.7	1.5	0.45
hnRNP C (M/D):	4.0	3.1	5.0

C

	3h	6h	9h
pull down (M/D)/input (M/D) (U2AF65):	2.8	0.77	0.58
pull down (M/D)/input (M/D) (hnRNP C):	2.9	1.5	2.8

Supplementary Table 1. Cancer drugs that activate HPV16 late gene expression.

Function	Substance
Akt kinase inhibitor	GC0068
Kinase inhibitor	Lapatinib
DNA alkylation	Uracil mustard
DNA alkylation	Melphalan hydrochloride
DNA alkylation	Triethylenemelamine
Topoisomerase inhibitor	Topotecan hydrochloride
Topoisomerase inhibitor	Irinotecan hydrochloride
Topoisomerase inhibitor	Teniposide
DNA breakage	Bleomycin sulfate
Microtubule disruptive	Vinblastine sulfate
Microtubule disruptive	Cabazitaxel
DNA synthesis inhibitor	Nelarabine
Hormone receptor agonist	Megestrol acetate

Supplementary Table 2.

NCS ID	Common nan	sLuciferase Fold over DMSO			
Plate 1		6hrs mean	6hrs STDEV.	22hrs mean	22hrs STDEV.
32065	Hydroxyurea	1,051	0,238	0,841	0,393
1390	Allopurinol	1,071	0,172	0,902	0,316
19893	Flurouracil	1,239	0,45	1,118	0,647
752	Thioguanine	0,728	0,096	0,715	0,082
755	Mercaptopurir	0,899	0,085	0,87	0,069
762	Mechlorethan	0,91	0,38	0,793	0,481
6396	Thiotepa	0,511	0,326	0,438	0,256
18509	Aminolevulinic	0,895	0,356	0,962	0,321
45388	Dacarbazine	0,871	0,077	0,851	0,08
92859	Arsenic trioxic	0,998	0,254	0,899	0,291
362856	Temozolomid	0,911	0,022	0,985	0,082
750	Busulfan	0,804	0,208	0,6	0,044
13875	Altretamine	1,047	0,118	0,859	0,08
27640	Floxuridine	1,166	0,504	1,124	0,54
45923	Methoxsalen	1,049	0,317	0,935	0,379
79037	Lomustine	1,044	0,309	1,165	0,321
102816	Azacitidine	0,944	0,14	0,536	0,49
127716	Decitabine	1,2	0,43	1,124	0,523
409962	Carmustine	0,703	0,053	0,985	0,346
26271	Cyclophospha	1,04	0,277	1,431	0,81
34462	Uracil mustrac	2,738	0,255	5,448	4,215
63878	Cytarabine hy	1,128	0,427	1,812	0,607
66847	Thalidomine	1,047	0,288	1,182	0,209
77213	Procarbazine	1,047	0,288	1,734	0,102
85998	Streptozocin	1,032	0,269	0,83	0,326
105014	Cladribine	1,318	0,379	1,673	0,32
109724	Ifosfamide	0,987	0,236	0,9	0,382
119875	Cisplatin	1,036	0,125	0,857	0,238
122758	Tretinoin	0,829	0,224	0,843	0,063
169780	Dexrazoxane	1,037	0,126	1,035	0,368
218321	Pentostatine	1,144	0,286	0,921	0,464
613327	Gemcitabine	1,051	0,143	0,734	0,344
686673	Nelarabine	1,034	0,004	2,845	1,399
701852	Vorinostat	1,107	0,33	1,442	0,332
713563	Exemestane	1,277	0,301	1,1683	0,045
719344	Anastrozole	1,3	0,335	1,188	0,599
719345	Letrozole	1,156	0,259	1,128	0,191
747972	Lenalidomide	1,067	0,211	1,214	0,029
3088	Chlorambucil	1,177	0,343	1,516	0,006
26980	Mitomycin	1,272	0,49	1,569	0,454
38721	Mitotane	1,017	0,164	0,786	0,347
606869	Clofarabine	1,086	0,209	1,185	0,343
25154	Pipobroman	1,131	0,215	1,076	0,226
71423	Megestrol ace	1,585	0,667	2,314	0,384
138783	Bendamustin	1,298	0,527	1,833	0,69

241240	Carboplatin	1,043	0,325	1,045	0,272
266046	Oxaliplatin	1,02	0,293	0,94	0,314
312887	Fluarabine ph	1,056	0,345	1,083	0,397
681239	Bortezomib	0,944	0,154	0,835	0,272
712807	Capecitabine	1,284	0,613	1,297	0,607
719627	Celecoxib	0,935	0,309	0,957	0,269
750690	Sunitinib	0,485	0,131	0,304	0,291
757441	Axitinib	1,032	0,502	0,794	0,682
279836	Mitoxantrone	0,507	0,172	0,34	0,322
698037	Pemetrexed	0,765	0,619	1,209	0,261
715055	Gefitinib	0,686	0,481	0,905	0,614
755986	Vismodegib	1,059	0,121	0,829	0,24
756645	Crizotinib	0,674	0,078	0,348	0,291
740	Methotrexate	1,072	0,346	0,794	0,555
14229	14229	0,686	0,381	0,097	0,251
609699	Topotecan hy	0,511	0,35	5,157	1,293
732517	Dasatinib	0,712	0,099	0,447	0,262
737754	Pazopanib hy	0,776	0,167	0,801	0,721
743414	Imatinib	0,804	0,209	0,55	0,425
747971	Sorafenib	0,96	0,159	0,449	0,321
747974	Raloxifene	0,697	0,097	0,691	0,227
754230	Pralatrexate	0,967	0,054	0,597	0,364
760766	Vandetanib	0,68	0,034	0,443	0,263
761431	Vemurafenib	0,871	0,173	0,641	0,348
747973	Ixabepilone	0,809	0,245	1,442	0,31
754143	Romidepsin	0,77	0,177	1,402	0,378
82151	Daunorubicin	0,673	0,029	0,99	0,273
123127	Doxorubicin h	0,565	0,103	0,286	0,278
141540	Etoposide	0,991	0,388	1,312	0,866
180973	Tamoxifen cit	0,681	0,005	0,369	0,309
745750	Lapatinib	0,665	0,141	5,854	2,764
616348	Irinotecan hyd	2,392	1,002	3,514	0,546
719276	Fulvestrant	0,82	0,37	0,915	0,441
122819	Teniposide	0,616	0,16	2,796	0,435
246131	Valrubicin	0,661	0,137	0,552	0,281
Plate 2					
628503	Docetaxel	0,775	0,219	0,84	0,206
761432	Cabazitaxel	0,991	0,099	2,784	0,418
125973	Paclitaxel	0,707	0,082	0,607	0,063
49842	Vinblastine su	1,01	0,167	2,241	0,144
67574	Vincristine sul	1,156	0,184	1,563	0,212
226080	Sirolimus	0,971	0,137	1,253	0,552
733504	Everolimus	0,705	0,06	0,282	0,026
3053	Dactinomycin	0,429	0,035	0,192	0,006
24559	Plicamycin	1,03	0,041	1,676	0,57
125066	Bleomycin sul	1,013	0,068	2,934	0,287
608210	Vinorelbine ta	0,816	0,003	0,845	0,241
758252	Carfilzomib	0,859	0,195	1,604	0,434

369100	Imiquimod	1,023	0,097	1,114	0,191
9706	Triethyleneme	1,276	0,033	2,716	0,045
718781	Erlotinib hydr	0,884	0,011	0,907	0,242
296961	Amifostine	0,915	0,055	0,977	0,197
721517	Zoledronic a	0,927	0,234	0,847	0,132
749226	Abiraterone	0,731	0,09	0,702	0,279
8806	Melphalan hy	5,994	0,37	38,191	10,783
747599	Nilotinib	1,156	0,112	1,973	0,439
702294	Estramustine	1,135	0,248	1,258	0,066

STDEV= standard deviation from the mean

Supplementary Table 3. PCR primers.

RT-PCR primer name	**Amplified region**	**Sequence 5'-3'**
773s	E4,L1,E2	GCACACACGTAGACATTCGTACTTTG
E4as	E4	TGCTGCCTAATAGTTTCAGGAGAGG
E2as	E2	CCTGACCACCCGCATGAACTTCC
1302s	E2	CATAGAGATGCAGTACAGGTTCT
F-set3	L2	GCACCCCCTTTAACAGTAGATCC
R-set3	L2	TACAGATGGGTCAGTGAAAGTG
L1as	L1	GCAACATATTCATCCGTGCTTACAACC
E4sVar	E4	CCTCTCCTGAAATTATTAGGCAGCG
P3-17dT	3'-RACE	GACTCGAGTCGACATCGATTTTTTTTTTTTTTTT
68	3'-RACE-pAL	CAGGTGGACAGATGCGCCAGCTG
F-set2	3'-RACE-pAE	TTGATACTGCATCCACAACATT
atrip1s	ATRIP	TCGAATTAGAGGTACTTCAGGCACA
atrip1as	ATRIP	TGGAGTTCAGACTGCAATGATTGGA
atrip2s	ATRIP	CTGTACATGTACATCACATCACGG
atrip2as	ATRIP	TCACATCAGGAAGCCCTCGGAT
PHB2S	PHB2	GTCAACGAGGTGCTCAAGAGTG
PHB2as	PHB2	CAAGGTTGTCAGCTGTGAGATAGATA
F-GAPDH	GAPDH	ACCCAGAAGACTGTGGATGG
R-GAPDH	GAPDH	TTCTAGACGGCAGGTCAGGT
CMVS	All mRNAs	CGCAAATGGGCGGTAGGCGTG
757as	All mRNAs	CGTGTGTGCTTTGTACGCACAACCG
ChIP and DIP PCR and qPCR primers	**Amplified region**	**Sequence 5'-3'**
E1F	E1	AGTAGAGCTGCAAAAAGGAGATTA
E1R	E1	CTGACTACATGGTGTTTCAGTCTC
E2F	E2	CTGGAAATCCTTTTTCTCAAGG
E2R	E2	CATTTTCATAATGTGTTAGTATTTTGTC
E4F	E4	ATCTGTGTTTAGCAGCAACGAA
E4R	E4	TGGAGCACTGTCCACTGAGTCT
L2F	L2	GACCCTGCTTTTGTAACCACTC
L2R	L2	ATGCTGGCCTATGTAAAGCAAC
L1SF	L1S	CCTTTAGTATCAGGTCCTGATATACCC
L1SR	L1S	GCAACATATTCATCCGTGCTTACAACC
L1F	L1	TTAGGTGTGGGCATTAGTGG
L1R	L1	TCCCCTATAGGTGGTTTGCA

Supplementary Table 4. Antibodies.

Antigen	Vendor	Cat #
ATM	Abcam	ab32420
p-ATM	Santa Cruz Biotech	b81292
ATR	Abcam	ab2905
BRCA1	Santa Cruz Biotech	SC-642
p-BRCA1	Santa Cruz Biotech	SC-101647
Chk2	Santa Cruz Biotech	SC-9064
p-Chk2	Santa Cruz Biotech	SC-16297-R
Chk1	Santa Cruz Biotech	SC-8408
p-Chk1	Santa Cruz Biotech	SC-17922
gH2AX	Abcam	ab2893
pan-H3Ac	Abcam	ab47915
pan-H4Ac	Active Motif	39243
Histone H3	Cell signalling	D2B12-4620S
Histone H4	Abcam	Ab10158
BARD1	Bethyl laboratories	A300-263A
U2AF65	Santa Cruz Biotech	SC-53942
SF3B	Bethyl laboratories	A300-996A
BCLAF1	Santa Cruz Biotech	SC-79204
TRAP150	Santa Cruz Biotech	SC-133250
p-SR	Millipore	MABE50
hnRNP C	Santa Cruz Biotech	SC-32308
hnRNP G	Abcam	ab118688
hnRNP H	Abcam	ab10374
HuR	Santa Cruz Biotech	SC-5261
TIAR	Bethyl laboratories	A303-613A-T
CPSF100	Sigma	HPA024238
CPSF30	Bethyl laboratories	A301-584A-M
CstF64	Bethyl laboratories	A301-092A-M
CstF77	Bethyl laboratories	A301-094A-T
CstF50	Bethyl laboratories	A301-094A-T
CFIm68	Bethyl laboratories	A301-357A-T
CFIm25	Abcam	ab183660
Fip1	Santa Cruz Biotech	SC-398392
actin	Santa Cruz Biotech	SC-1616
melphalan	Abcam	ab97554
IgG Rabbit	Cell Signaling	2729P
Anti mouse IgG (HRP)	Sigma	A9044
Anti rabbit IgG (HRP)	Sigma	A4914
Anti goat IgG (HRP)	Sigma	A8919
Ms Kappa light chain (HRP)	Abcam	ab99632
Rb IgG light chain	Abcam	ab99697
Anti FLAG tag	Sigma	F1804