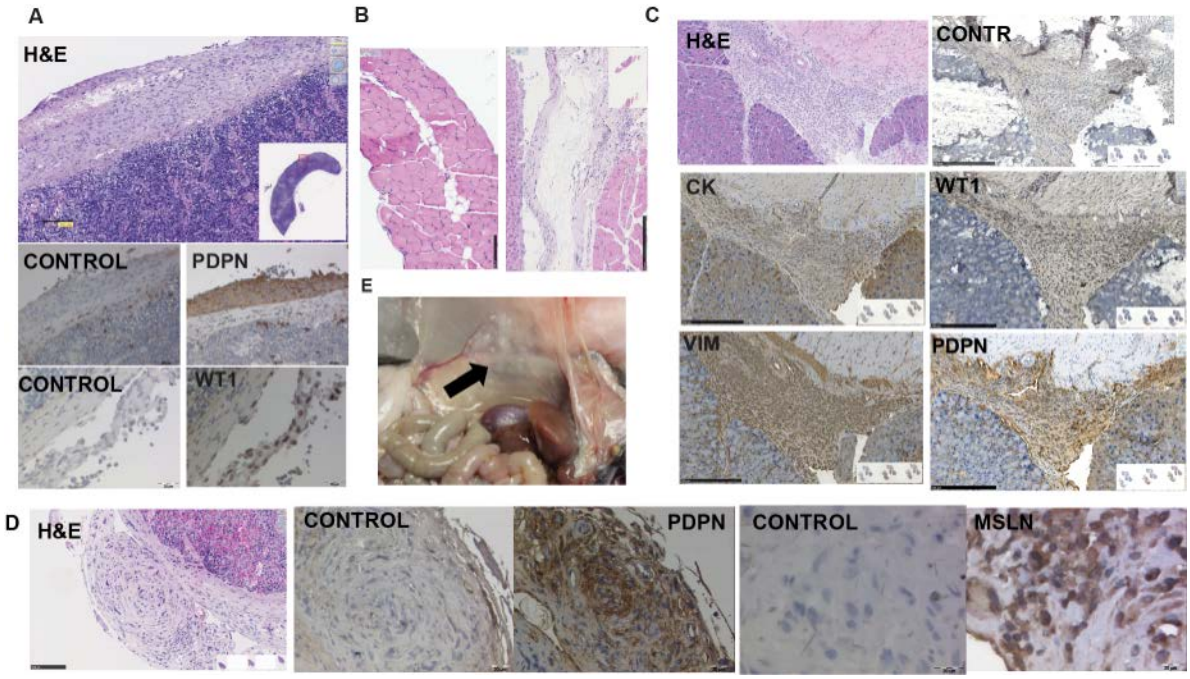
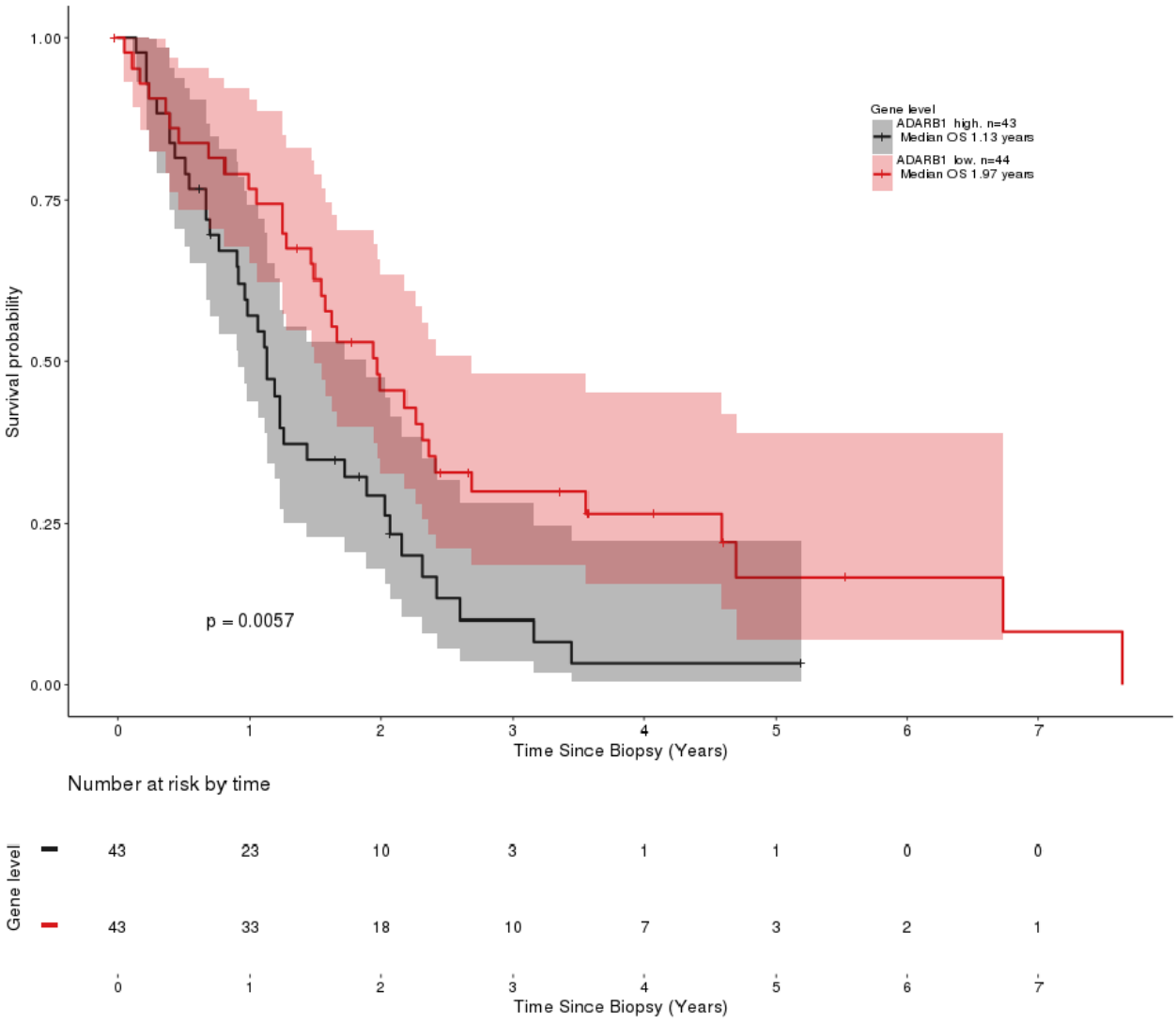
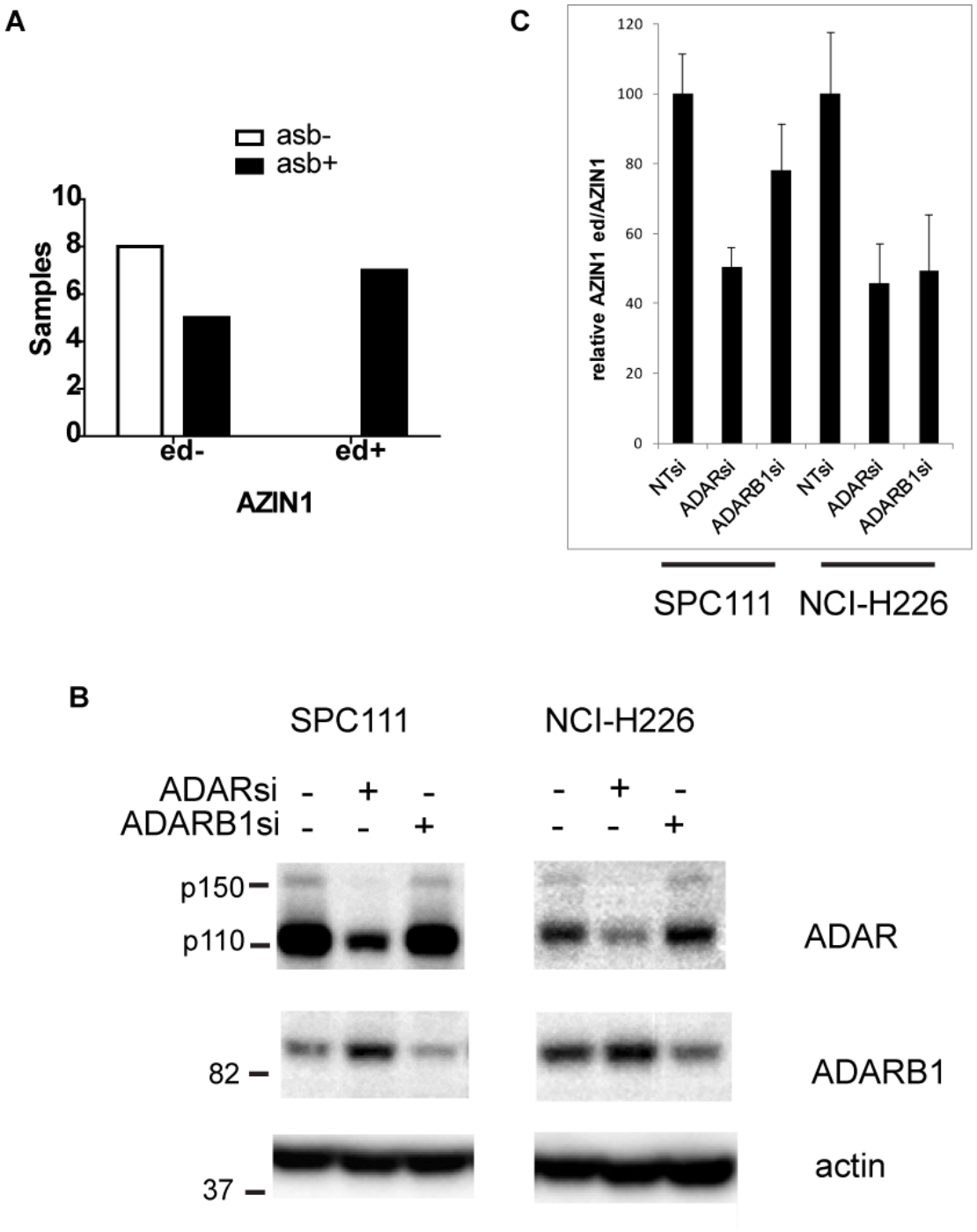


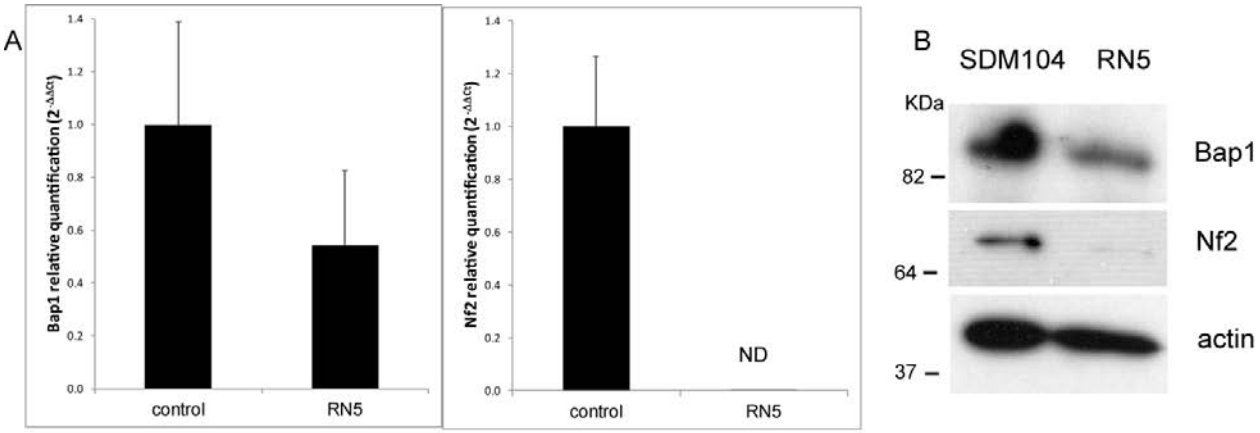
Supplementary Figure 1 Histopathology of Nf2 (+/-) mice following repeated i.p. injections of crocidolite fibers A. A localized malignant mesothelioma on the surface of the spleen was stained with H&E, podoplanin (PDPN) and WT-1. **B**. Morphology of the diaphragm shows inflammatory cell infiltrates and reactive mesothelium after crocidolite exposure (right panel) compared to the normal single-layer mesothelium in sham-exposed mice (left panel). **C**. Benign mesothelial cell growth on the serosal surface of organs showing co-expression of for vimentin (vim), cytokeratin (CK), WT-1 and PDPN **D**. Benign growth on serosal surfaces and in spheroids implanted on the visceral organs showing immunoreactivity for PDPN and mesothelin (Msln). **E**. Nodules growing after crocidolite exposure on the parietal mesothelium, which was scraped for obtaining tissue for gene expression analysis.



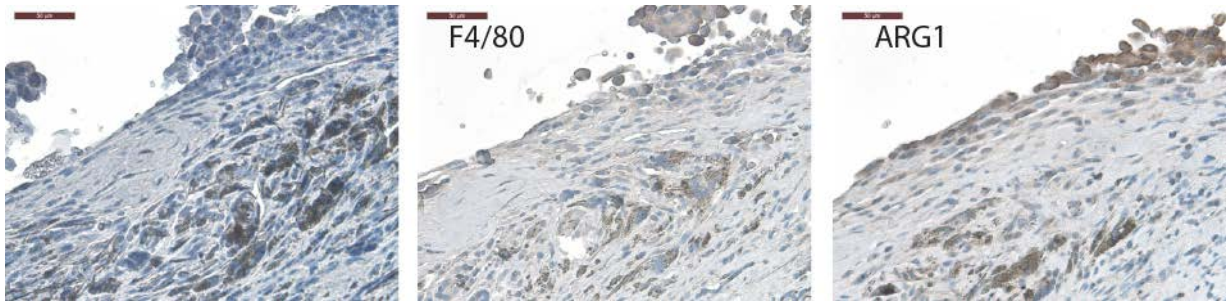
Supplementary Figure 2 High ADARB1 expression is associated with decreased overall survival in mesothelioma patients. Kaplan-Meyer overall survival data were obtained using TCGA browser (http://tcgabrowser.ethz.ch:3838/PROD/).



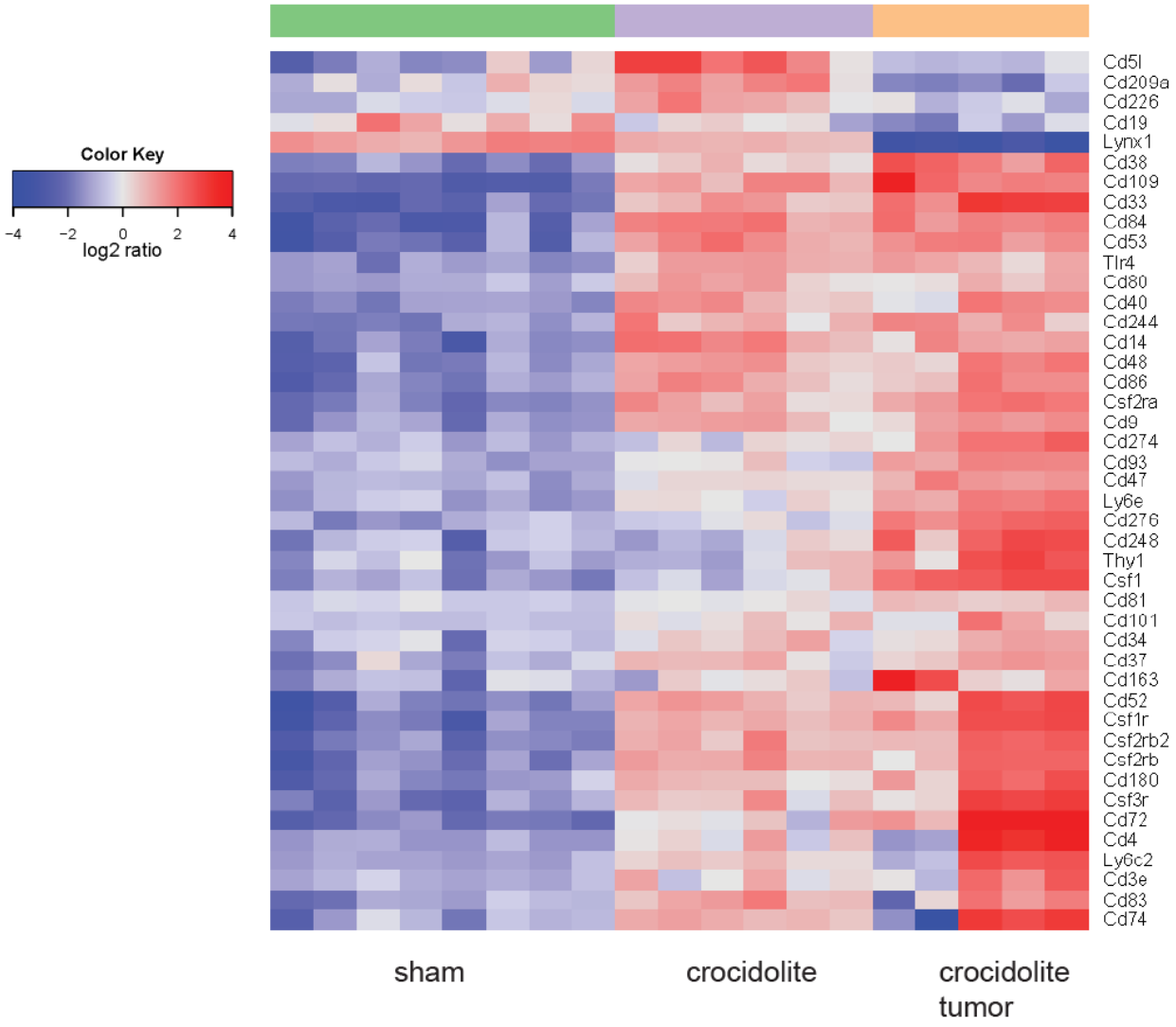
Supplementary Figure 3 ADAR-family substrate AZIN1 is edited in tissues from asbestos exposed mice and mesothelioma cells. A. RNA editing of AZIN1 (ed+) is present in tissues from asbestos exposed mice (asb+) compared to sham mice (asb-). Both ADAR and ADARB1 are expressed in mesothelioma cells and their silencing (B, representative of three independent experiments) results in decreased AZIN1 editing (C, Mean ±SD, representative of two independent experiments). NT: non-targeting.



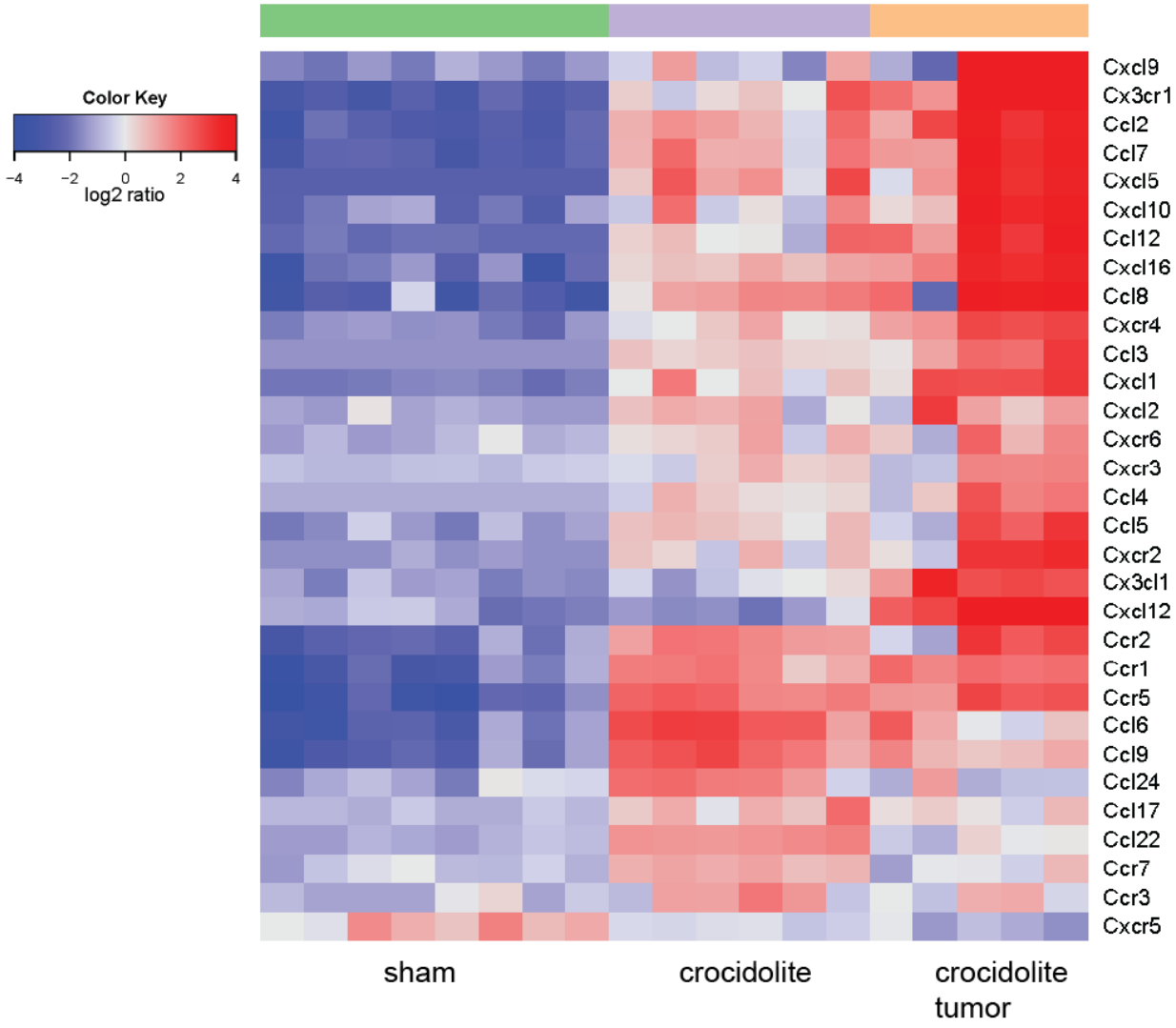
Supplementary Figure 4 Bap1 and Nf2 copy number variation and protein levels in a cell line derived from an asbestos-induced tumor A. Relative quantification of *Bap1* and *Nf2* in genomic DNA from RN5 cells *vs.* DNA extracted from normal tissue. , Mean ±SD. ND: not detected. **B.** Western blot analysis of Bap1 and Nf2 in RN5 cells or mesothelial cells SDM104 (Echeverry et al, 2015).



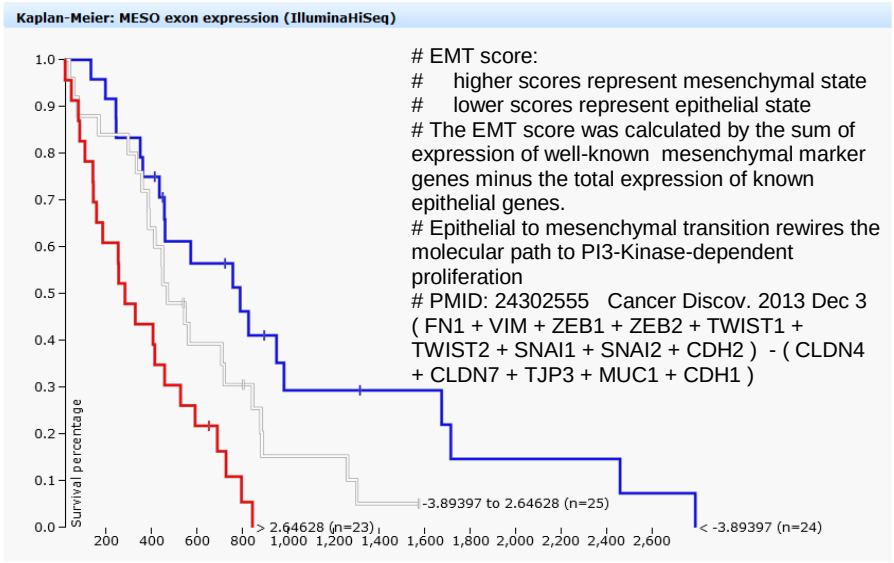
Supplementary Figure 5 Arginase1 immunoreactivity in reactive mesothelium. The expression of Arginase 1 was detected in some reactive mesothelial cells, which were not stained with macrophage marker F4/80 in crocidolite-exposed inflamed mesothelium.



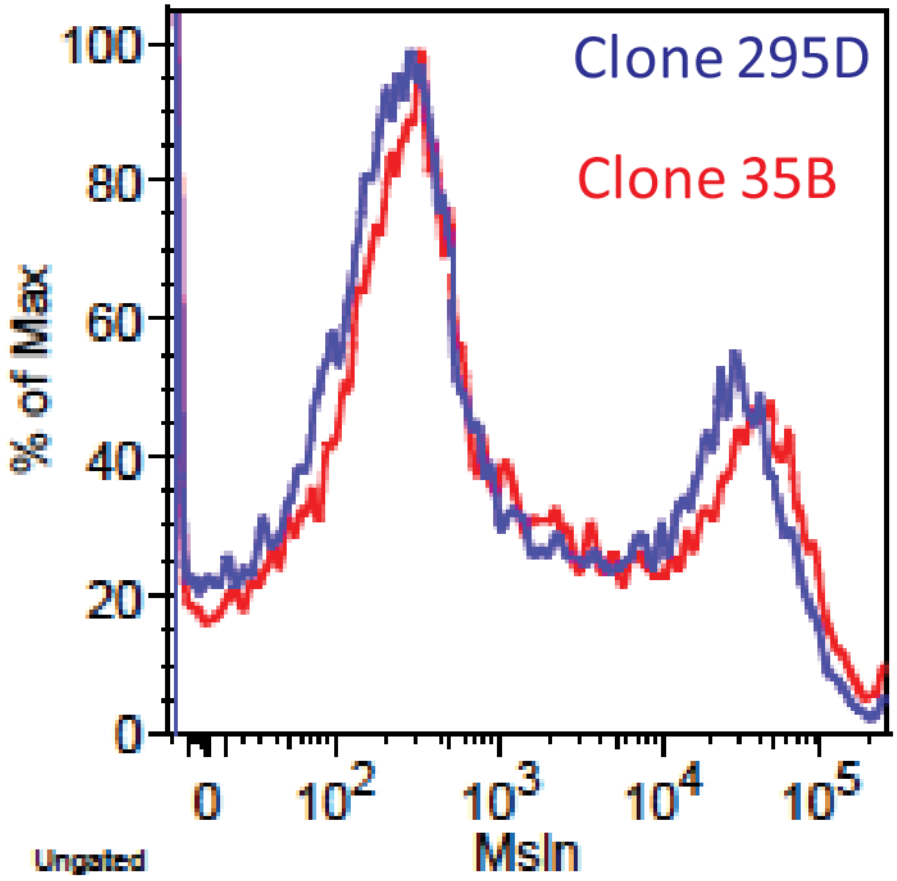
Supplementary Figure 6 Variation of the expression of selected surface markers and their ligands after exposure to crocidolite. Curated heatmap was generated for gene set belonging cell surface receptors and some ligands. Molecules associated with M2 –macrophages such as *Csf1*, *Csfr1* and *Cd163* were upregulated during mesothelioma development. *CD90 (Thy-1)* and *CD34* were also upregulated.



Supplementary Figure 7 Variation of the expression of chemokines signaling after exposure to crocidolite. Curated heatmap was generated for gene set belonging to chemokines and their receptors. Upregulation of *Ccr1* and its ligands *Ccl6, Ccl3, Ccl8* and *Ccl9, Ccr3* and its ligand *ccl24, Ccr5* with its ligands *ccl5* and *ccl4* and *Cxcr3* with its ligands *cxcl9,10, Cxcr4* with its ligand *cxcl12, Cxcr6* with its ligand *Cxcl16, Cx3cr1* and its ligand *Cx3cl1* were observed.



Supplementary Figure 8 EMT signature is associated with decreased overall survival in mesothelioma patients. Kaplan-Meyer plot was generated using TCGA mesothelioma data with UCSC Cancer Browser. Red indicates high EMT signature.



Supplementary Figure 9 Similar mesothelin immunoreactivity of peritoneal lavage lavage cells obtained with two different anti-mesothelin antibodies. Mesothelin immunophenotyping of peritoneal lavage cells after i.p. injection of RN5 cells was similar using two different antibodies derived using as antigen oncostatin-dependent intraembryonic aorta-gonad-mesonephros region-derived LO cells.

Supplementary Table 1. **The list of genes significantly upregulated in crocidolite-exposed inflamed tissue compared to sham was analyzed using gene set enrichment analysis to extract biological knowledge.**

Gene Set Name	# Genes in Gene Set (K)	Description	# Genes in Overlap (k)	k/K	p-value	FDR q-value
HALLMARK_INTERFERON_GAMMA_RESPONSE	200	Genes up-regulated in response to IFNG [GeneID=3458]	99	0.495	3.89E-79	1.95E-77
HALLMARK_INFLAMMATORY_RESPONSE	200	Genes defining inflammatory response.	95	0.475	8.43E-74	2.11E-72
HALLMARK_ALLOGRAFT_REJECTION	200	Genes up-regulated during transplant rejection.	88	0.44	8.32E-65	1.39E-63
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	200	Genes defining epithelial-mesenchymal transition, as in wound healing, fibrosis and metastasis.	77	0.385	1.44E-51	1.8E-50
SNF5_DN.V1_UP	177	Genes up-regulated in MEF cells (embryonic fibroblasts) with knockout of SNF5 [Gene ID=6598] gene.	69	0.390	9.14E-47	8.63E-45
RB_P107_DN.V1_UP	140	Genes up-regulated in primary keratinocytes from RB1 and RBL1 [Gene ID=5925, 5933] skin specific knockout mice.	54	0.386	1.33E-36	8.41E-35

Supplementary Table 2. **The list of genes significantly upregulated in tumors compared to crocidolite-exposed inflamed tissue was analyzed using gene set enrichment analysis to extract biological knowledge.**

Gene Set Name	# Genes in Gene Set (K)	Description	# Genes in Overlap (k)	k/K	p-value	FDR q-value
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	200	Genes defining epithelial-mesenchymal transition, as in wound healing, fibrosis and metastasis.	113	0.565	8.92E-81	4.46E-79
RB_P107_DN.V1_UP	140	Genes up-regulated in primary keratinocytes from RB1 and RBL1 [Gene ID=5925, 5933] skin specific knockout mice.	66	0.4714	4.77E-41	4.51E-39
HALLMARK_MITOTIC_SPINDLE	200	Genes important for mitotic spindle assembly.	75	0.375	6.11E-38	1.53E-36
MEL18_DN.V1_UP	141	Genes up-regulated in DAOY cells (medulloblastoma) upon knockdown of PCGF2 [Gene ID=7703] gene by RNAi.	72	0.4397	2.04E-36	7.71E-35
BMI1_DN.V1_UP	147	Genes up-regulated in DAOY cells (medulloblastoma) upon knockdown of BMI1 [Gene ID=648] gene by RNAi.	61	0.415	4.34E-34	1.17E-32
CORDENONSI_YAP_CONSERVED_SIGNATURE	57	YAP conserved signature.	33	0.5789	5.21E-25	6.16E-24

Supplementary Table 3. p53 target genes (Bieging et al., 2014) or associated with replicative stress (Kotov et al., 2014) or associated with deregulated NF2/Hippo pathway (Stein et al., 2015, Zhao et al., 2011, Zanconato et al., 2015, Ren et al., 2011) upregulated more than 2-fold (p<0.01) 33 wks after first exposure to crocidolite. (*Ren et al., 2011 and Bardet and Schübeler, personal communication.)

	crocidolite	common	tumor
p53	Adora2b, Gpx1, Irf5, Ncf2, Ptprv, Tlr2, Tlr4	Apaf1, Ccl2, Cx3cl1, Dram1, Icam1, Isg15, Pm1, Rrm2, Tlr1, Tlr3, Tlr6, Tlr7, Tlr8, Ulbp1	Ddit4, Fancc, Tlr5, Tlr9
Replicative stress	Brip1, Chek1	Asf1b, Ccne1, Cdc7, Cdk1, Cdkn2a, Dclre1c, Fancd2, Mms22l, Myc, Plk2	Atad5, Obfc1, Topbp1, Wee1, Wrn
Deregulated NF2/Hippo	Casc5, Cdc6, Cdca4 Cenpf, Cenpl, Gltp Itgb2, Kif20b, Mybl1 Nuf2, Plau, Psrc1 Ptger2, Rbl1, Tll1 Trim14	Anxa3, Arsj, Atad2, Axl Basp1, Birc5, Bub1b Ccna2, Ccnd1, Cdca5 Cdca8, Cdk6, Cep55 Ckap2l, Cmip, Col12a1 Coro1c, Diaph3, Dusp4 Efnb2, Enc1, Ercc6l Fam46b, Fzd1, Gja1 Hyi, Iqgap3, Kif14 Kif23, Kif2c, Kntc1 Layn, Lima1, Mamdc2 Mcm3, Mest, Msln* Myc, Pawr, Rab11fip1 Rnd3, Rpl3, Rrm2 Serpine1, Sgol1, Soat1, Tbc1d2, Top2a, Wtip, Zwilch	Adamts16, Adamts5, Adamts6 Ajuba, Akap12, Amotl2 Ankrd1, Arntl2, Asap1 Bcat1, Bmp4, Cep57 Crim1, Ctgf, Cyr61 Dlc1, Edn1, Eif5a2 Ets1, F3, Fam57a Fgf2, Fjx1, Fosl1 Foxf2, Frmd6, Fst Has2, Ick, Igfbp3 Inhba, Lats2, Lhx4 Lrig3, Lrrc8c, Maff Magohb, Map3k1, Matn2 Mcm7, Mta2, Mutyh Neil2, Nup188, Phactr1 Pkn3, Plekha7, Prickle1 Ptx3, Rad18, Ralgps2 Rrp1b, Sart3, Sertad4 Sf3b3, Snai2, Srbd1 Tead2, Tead3, Timeless Tk1, Tmem200b, Tram2 Trip6, Troap, Ube2e2 Uck2, Usp43, Utp15 Wwc1, Wwc2, Xpo5

Supplementary Table 4. Primers used for q-PCR confirmation of RNA-seq data

gene name	forward primer	reverse primer
mGrem1	AACAGCCGCACTATCATCAA	GCAGAAGGAGCAAGACTGAA
mArg1	GTCCCTAATGACAGCTCCTTTC	CCACACTGACTCTTCCATTCTT
mNF2	GCGACTTTCCATGGAGATAGAG	GTCTCCCGCTCTTTGAGTTT
mBAP1	TCAAGGAGGAGGTGGAGAAA	CCAGCATGGATATGAAGGTACAG
mSpp1	CTTTCACTCCAATCGTCCCTAC	CAGAAACCTGGAAACTCCTAGAC
mMsln	ATGGACCTTGTGAACGAGATT	TGGATCAGGGACTCAGGATAG
mCTGF	ACTATGATGCGAGCCAACTG	CTCCAGTCTGCAGAAGGTATTG

Supplementary Table 5. Primers used for the relative quantification of copy number variation

gene name	forward primer	reverse primer
mSox2	GCGCCCTGCAGTACAACTC	GCTGGCCTCGGACTTGAC
mNF2	CCTCCTAGACACTGGTTCTTTG	GGTGAACTCCTTCATGCTTAGA
mBAP1	TCAAGGAGGAGGTGGAGAAA	CCAGCATGGATATGAAGGTACAG