**Supplementary Materials and Methods:**

**Patient samples**

In total 182 MPM patients were analyzed. The Austrian cohort consisted of 29 retrospectively included patients (diagnosed between 1994 and 2009) (1) and 54 prospectively collected cases (diagnosed between 2010 and 2016) (2) from the Department of Thoracic Surgery, Medical University of Vienna. The retrospectively collected Slovenian cohort contained 76 patients diagnosed between 2007 and 2012 at the Department for Pulmonology, University Clinic Golnik and was part of a previous study (1). The Croatian cohort was based on an earlier prospective study (3) and included 23 patients who were treated at the Department for Respiratory Diseases Jordanovac, University of Zagreb, between 2013 and 2014. The study was approved by the Ethics Committees at the Medical University of Vienna (#904/2009) and at the University Hospital Center Zagreb (#02/21AG). All prospectively included patients gave informed written consent. The Institutional Review Board of the University Clinic Golnik granted a waiver for the retrospective analyses.

**Array CGH**

Array CGH data were visualized and evaluated using the Agilent Genomic Workbench software (version7). The ADM-1 algorithm and a threshold of 6 were applied. Borders for aberrations were set to +/-0.25 with a minimum number of 3 probes per region (default settings). The number of aberrations (gains and losses) of each sample was calculated from the “interval based text report”. “% genome affected” was calculated as percentage of altered probes in relation to the 43096 probes of the 44K oligonucleotide genome array that were considered as 100%. For definition of “gain”, “loss”, or “deletion” of those selected genes that are represented by more than 1 oligonucleotide on the microarray, the mean log2 ratio of the signals of the respective oligonucleotides was calculated. A deletion was defined if either the mean or at least one probe reached a log2 ratio below -2.

**Quantitative reverse transcription PCR (qRT-PCR) for *TERT* mRNA determination**

qRT-PCR for *TERT* mRNA expression in MPM cell models was performed as published recently (4).

The following primers were used: *TERT* fw (5ʹ-CCAAGTTCCTGCACTGG-3ʹ) and *TERT* rev (5ʹ-TTCCCGATGCTGCCTGAC-3ʹ); *RPL41* fw (5ʹ-CAAGTGGAGGAAGAAGC-3ʹ) and *RPL41* rev (5ʹ-TTACTTGGACCTCTGCCT-3ʹ). *RPL41* was used as housekeeping gene and for normalization. All reactions were performed in triplicates at least twice. For calculation of 1/∆Ct, ∆Ct values were calculated (Ct value of *TERT* minus Ct value of *RPL41*) and de-logarithmized (base 2). Then the reciprocal value was calculated, multplied with 100, and logarithmized (base 2) again.

**PCR for analysis of genomic status of *GSTT1* and *RBFOX1***

For confirmation of *GSTT1* and *RBFOX1* deletions detected by array CGH and NGS in mesothelioma cell lines and analysis in the corresponding tumor/healthy tissues, genomic DNA from patient blood, frozen tumor tissues, and mesothelioma cell models was isolated using the QIAmp DNA Blood Mini Kit (Qiagen). Detection of *GSTT1* gene deletions in healthy tissues was performed using primers and PCR conditions as published (5). For analysis of *RBFOX1* deletion status, two primer pairs flanking the DNA regions found deleted by array CGH and NGS were designed: *RBFOX1*\_cov1-fw 5` GAGATGCCCTTCAGGTACGG 3` and *RBFOX1*\_cov1-rev 5` TGCAGAAGCTGCCTGGTCTC 3` and *RBFOX1*\_cov2-fw 5` TGCAAACACCGCAGTATG 3` and *RBFOX1*\_cov2-rev 5` CCTGGGTTCAATTCACAGAG 3`. PCR conditions for analysis of *RBFOX1* were identical as decribed for *GSTT1*. For all PCR analyses performed with genomic DNA, *GAPDH* was used as a housekeeping gene for internal control (*GAPDH* genomic fw 5` AGGTGGAGCGAGGCTAGC 3`and *GAPDH* genomic rev 5` TTTTGCGGTGGAAATGTCCT 3`).

**Analysis of telomerase activity** **by Telomerase Repeat Amplification Protocol (TRAP-assay)**

TRAP-Assay was performed as recently published (6) using the TRAPEZE® Telomerase Detection Kit from Chemicon (Millipore, Billerica, MA, USA) based on the method described by Kim et al. (7). In brief, 106 cells were lysed in 200µl 1XChaps Lysis Buffer containing 100 units/ml RNAse Inhibitor, incubated on ice for 30 min and centrifuged at 12000xg for 20 min at 4°C. The supernatant was rapidly frozen on dry ice and stored at -80°C. The concentration of protein was measured with the Micro BCA Protein Assay Kit (Thermo Fisher Scientific Inc, Rockford, IL, USA). The further procedure followed the instructions of the manufacturer. A duplicate of each sample was incubated at 85°C for 10 min prior to the TRAP-assay to inactivate telomerase, representing the heat-inactivated control. Telomerase-negative brain tissue received from epilepsy surgery was utilized as another negative control and the primer-dimer/PCR contamination control was performed using Chaps Lysis Buffer only instead of protein extract. Telomerase-positive cell extract obtained from the human glioma cell line CRL1690 was included as a positive control in every reaction set-up. Each extract (500ng protein) was assayed in a 25µl reaction mixture containing 2.5 µl 10x TRAP Reaction Buffer, 0.5 µl 50x dNTPs, 0.5 µl TS Primer, 0.5 µl Primer Mix and 1 unit iTaq DNA Polymerase (BioRad). After 30 min incubation at 30°C for telomerase extension, the reaction mixture was subjected to PCR amplification in a thermal cycler for 33 cycles (94°C for 30 s, 59°C for 30 s, 72°C for 30 s) and a final elongation step at 72°C for 10 min. Then, 12µl of PCR products were separated by 12% polyacrylamidgel electrophoresis, stained with ethidiumbromide and visualized under UV illumination (ChemiDoc; BioRad). Product ladder bands were quantified by Quantity One Quantitation software (BioRad) and calculated relatively to the DNA ladder of 0.1 atto-mol Telomerase Quantitation Control Template TSR8 following the manufacturer’s instructions. All results were confirmed in at least two independent experiments.

**Telomere length measurement by qPCR**

Relative telomere length was determined as published (6,8). In brief, DNA of all mesothelioma cell models was isolated with the QIAmp DNA Blood Mini Kit (Qiagen). All samples were analyzed in duplicates on the Rotor-Gene Q (Qiagen). Each reaction was composed of: 20ng DNA, 1x Maxima SYBR Green/ROX qPCR Master Mix (Fermentas), 100nM telomere forward primer (CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT), 100nM telomere reverse primer (GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT) (9,10). A single copy gene, 36B4, (fw 5`-CAGCAAGTGGGAAGGTGTAATCC-3`, rev 5`-CCCATTCTATCATCAACGGGTACAA-3`, also 100nM each per reaction), which encodes the acidic ribosomal phosphoprotein P0, was used as amplification control for every sample performed (10). Cycling conditions for both products were: 10 min at 95°C, followed by 40 cycles at 95°C for 15s and 60°C for 1min. Finally, melting curve analysis was performed. A standard curve was generated to measure the content of telomeric sequences (kb) for each sample using known quantities of a synthesized 84mer oligonucleotide being composed of 14 TTAGGG repeats (8). DNA from two osteosarcoma cell lines (SA-OS and U2-OS), both positive for the alternative lengthening of telomere (ALT) mechanism, were used as long telomere controls (11). The data of total telomeric length in kb per human diploid genome per sample were calculated relatively to the SA-OS cells set arbitrarily as 1.

**Whole exome sequencing**

Exome sequencing for all MPM cell models was performed with the Nextera DNA Exome Kit from Illumina (TruSeq Rapid Capture Exome 45Mb, 6 samples per lane HiSeq 4000 2x75 bp paired-end) by the Medical University of Vienna Biomedical Sequencing Facility following the instructions. Sequencing depth was >100x; after removal of duplicates, the achieved mean coverage per base within the target region was 106-fold (range: 98-115). Next generation sequencing (NGS) reads were aligned to the b37 reference genome with BWA MEM (12). We then applied GATK (13) base quality score recalibration, indel realignment, duplicate removal, and performed SNP and INDEL discovery and genotyping across all samples simultaneously using standard hard filtering parameters or variant quality score recalibration according to GATK Best Practices recommendations (14,15).

*Annotation of multi-sample vcf files*

Multi-sample variant call files (.vcf) were filtered using VCFtools (*vcftools.sourceforge.net*), merged using BCFtools (*samtools.github.io/bcftools*), and finally annotated with ANNOVAR (version 2017jul16, *annovar.openbioinformatics.org*) (16). COSMIC data files were downloaded from *https://cancer.sanger.ac.uk/cosmic/download* (v83). Final annotated lists were exported to Excel spreadsheets for data analysis. Curated information on cancer genes from COSMIC Cancer Gene Census (v85, released 08-May-18) was incorporated using Excel functions. A maximum minor allele frequency of 1:2000 (ExAc 0.3) was used as a threshold for interpreting mutations (because matched normal samples were not available).

*Analysis of read coverage to capture copy number changes*

Read coverage was calculated using the 'samtools view' (*github.com/samtools/samtools*) command on .bam files and an interval description that was prepared based on protein coding transcript annotations from the Ensembl GRCh37 release 75 (*ensembl.org*). Sample-wise relative read depth was calculated from median normalized coverage in Excel.

**Targeted Ion Torrent Sequencing**

DNA from mesothelioma tumor tissues was isolated with the QIAmp DNA Mini Kit. DNA libraries were generated by multiplex polymerase chain reaction (PCR) with the Oncomine Comprehensive Assay v3 (Thermo Fisher, Waltham, MA), which covers mutation hotspots of 161 genes, mostly oncogenes and tumor suppressor genes that are frequently mutated in tumors. The template preparation for next-generation-sequencing utilised an IonChefTM instrument (Thermo Fisher). Sequencing was performed with an Ion S5 system (Thermo Fisher). The sequencing data were analysed with Torrent Suite and Ion Reporter software (Thermo Fisher) and an in-house developed variant annotation tool. For variant calls a coverage threshold of at least 250x was used.

**Protein isolation and Western blot**

Analysis of total protein extracts of MPM cell models was performed as described (17). Primary antibodies were BAP1 monoclonal mouse (1:500; C-4; Santa Cruz Biotechnology) and β-actin monoclonal mouse AC-15 (1:2000; Sigma, Vienna, Austria). Peroxidase-labelled anti-mouse secondary antibody (Santa Cruz Biotechnology) was used in a 1:10 000 working dilution.

**BAP1 immunohistochemistry**

Immunohistochemistry from formalin-fixed, paraffin-embedded MPM tissue specimens of 75 patients was performed as described previously (17,18). After deparaffinization and rehydration, 4 µm tissue sections were heated for 10 min in 10 mM citrate buffer (pH 6.0), then incubated for 1 h at room temperature with primary antibody (BAP-1, Clone C-4, sc-28383, Santa Cruz; dilution 1:200). Antibody binding was detected using the UltraVision LP detection system (Lab Vision Corporation, Fremont, CA). BAP1 immunostaining was independently evaluated by two involved pathologists (FO, LB). Both nuclear and cytoplasmic BAP1 staining was evaluated specifically in tumor cells. Lymphocyte and stromal cell positivity was used as internal positive control in each specimen. Cases with no tumor cell staining or with cytoplasm-only staining were considered BAP1 negative MPM as described (19).

**Statistics**

Survival was analyzed by Kaplan-Meier method and log rank (Mantel-Cox) test. For uni- and multivariate survival analyses Cox proportional hazardous regression models were applied to calculate hazard ratios (HR) and corresponding CIs. Association of *TERT* promoter mutations and clinicopathological parameters was calculated by Fisher`s exact test. Overall survival data in MPM subgroups were compared by Kaplan Meier curves using log-rank (Mantel-Cox) test. For determination of the impact of *TERT* promoter status, MPM histology, and tumor stage at time of cell culture establishment on cell line formation Fisher`s exact test was performed. Differences in *TERT* promoter activity (luciferase assays) were calculated by two-tailed Student`s *t* test. Differences in *TERT* mRNA expression, telomerase activity (TPG units), and telomere lengths between *TERT* promoter mutated and wild-type models as well as differences in the number of gained and lost array CGH probes were calculated by two-tailed Student`s *t*-test with Welch`s correction. Differences between the percentages of cell models harboring mutations/deletions of the genes indicated in Fig. 4 were calculated by Chi-square test.

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