

## MEETING REPORT

**Malignant Mesothelioma as both a challenge and an opportunity**Luciano Mutti\*<sup>1</sup> and V Courtney Broaddus<sup>2</sup><sup>1</sup>ASL 11, Laboratorio di Oncologia Clinica, Vercelli, Italy; <sup>2</sup>Lung Biology Center, Box 0854 UCSF, San Francisco General Hospital, University of California, San Francisco 94110, USA

**The International Mesothelioma Interest Group sponsored its 7th international meeting in Brescia, Italy from June 24–26, 2004. The meeting, entitled ‘How advanced technology and new drugs are changing the perspectives of patients with malignant mesothelioma’, was organized by Luciano Mutti (Vercelli, Italy) and GF Tassi (Brescia, Italy) and was attended by 350 participants. The general tone of the meeting was that real progress is now coming in the understanding of mesothelioma biology, progress that may soon translate into improved treatment options. The investigators and clinicians agreed on the importance of referring patients with mesothelioma to centers with expertise where patients can receive the best available treatments and can be offered entry into clinical trials of new and promising agents.**

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**Introduction**

Malignant mesothelioma (MM) is an aggressive cancer whose incidence is expected to rise dramatically over the next few decades. In the face of this frightening scenario, groups of scientists and clinicians from all over the world have been working from some years focusing on the biomolecular mechanisms underlying the development and progression of pleural and peritoneal MM. Recent translational advances are providing a rationale for novel therapeutic approaches to this tumour and will likely improve the prognosis of patients with mesothelioma in the near future.

These advances have been fostered by the International Mesothelioma Interest Group, established in 1991 to improve communication and collaboration among researchers and clinicians who are generally scattered all over the world in areas of asbestos concentration ([www.imig.org](http://www.imig.org)) see Appendix A. The VII IMIG meeting was held in cooperation with the Italian Group for the

Study and Therapy of MM (GIME: [www.gime.it](http://www.gime.it)) see Appendix A.

Most of groups and investigators working in this field attended the meeting and had the opportunity to present their new findings and exchange their points of view during very fruitful open discussions. The aim of this report is to summarize the most significant advances in the different disciplines applied to MM discussed in Brescia and how these advances will change the perspective of the patients with MM.

**Epidemiology***Asbestos*

Once more it was stressed that the dose of asbestos that triggers carcinogenesis may be small and that, for this reason, the role of environmental exposure (domestic and residential) should not be underestimated. In an ongoing study of a cohort of 1163 individuals exposed to crocidolite dust in the assembly of military gas masks, the risk of mesothelioma and other cancers is notable after exposure even briefly and at limited intensity to pure crocidolite fibre.

In another study, a prospective analysis revealed that the presence of benign pleural disease, especially on the lateral chest wall, increases the relative risk of mesothelioma and thus may serve as a factor to be considered in the follow-up of exposed subjects. Infection with HIV may also increase the risk or the rate of progression of mesothelioma. With a quarter of million of deaths expected in Western Europe among men occupationally exposed to asbestos, the complete ban on asbestos use is expected to decrease future mortality in the UK, US and The Netherlands after the peak due to the previous exposure. Unfortunately, in the Far East and Eastern European countries, asbestos use continues and the consumption of asbestos is even increasing in some countries such as China, Thailand and Indonesia. Moreover in other countries (e.g. Vietnam) the use of crocidolite is not restricted at all. Therefore, the concern about exposure to asbestos fibres is still a present one and, in some areas of the world areas with recent intense industrial development (e.g. China), there is a real risk of future mesothelioma epidemics.

*Simian virus 40 (SV40)*

In mesothelioma, more attention is being directed toward biomolecular markers, particularly in the design

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of epidemiologic studies. Using this approach, the contribution of additional risk factors for MM other than asbestos has been under investigation. One of the most controversial risk factors under discussion is SV40.

In a recent epidemiologic study, the risk or hazard ratio of developing MM due to asbestos exposure alone or SV40 infection alone was compared with the hazard ratio due to asbestos exposure plus SV40 infection. Asbestos exposure alone was associated with MM and SV40 alone was not; however, the combination of SV40 infection plus asbestos exposure was associated with a 27-fold higher risk for MM than asbestos exposure alone. Therefore, this study gives some epidemiological support for a possible co-carcinogenic effect between SV40 and asbestos exposure in MM.

### Carcinogenic mechanisms of asbestos fibres

Although new findings clearly suggest a cooperation with other causative agents, asbestos fibres exposure will always play the most important role in MM carcinogenesis. For this reason, the evaluation of the fibres lung burden remains important for knowing the actual type and dose of toxic fibres. The continued reliance on these *in vivo* fibre analyses is necessary because of a substantial discrepancy between '*in vitro*' and '*in vivo*' models of asbestos carcinogenesis and the need to reveal previously unsuspected pathogenic mineral particles and/or the exact amount of fibres that patients have actually retained in their lungs. Especially in case of potentially new occupational hazards, the lung fibres burden analysis will be more relevant than environmental dust studies.

#### *Apoptotic signalling*

Asbestos can also exert a toxic effect on human mesothelial cells (HMC) and a progressive resistance to this cytotoxic effect is closely linked to the transformation process. Certain signalling pathways may be important in asbestos-induced transformation. Tyrosine kinase receptor-dependent (TKr) PI3K/Akt and MAP-K (ERK 1–2) signalling pathways and Hepatocyte Growth Factor (HGF) provide significant cytotoxic resistance of the human mesothelial cell (HMC) to amphibole fibres. Via activation of these resistance pathways, resistant mesothelial cells may then emerge and go toward a progressive transformation. This progressive resistance, although in the context of a more complex multistep/oncogenic recessive process, remains functionally relevant in MM cells and suggests therapeutic options. Furthermore, MM cells are characterized by a resistance to most of the apoptotic stimuli which may explain why this tumour is highly refractory to chemotherapy.

Nonetheless, activation of both intrinsic (mitochondrial-dependent) and extrinsic (death receptor-dependent) apoptotic pathways can induce a synergistic apoptosis. In contrast to non malignant HMC, MM cells were particularly sensitive to activation of intrinsic

pathways by DNA-damaging chemotherapeutic drugs and of extrinsic pathways by TNF-related apoptosis-inducing ligand (TRAIL). Such approaches may interfere with MM development and progression.

Most of these findings suggest several targets for normalizing the cell machinery with 'smart' drugs, some of which are already in early clinical testing.

#### *Chrysotile as a carcinogenic fibre*

As opposed to crocidolite and other amphibole asbestos fibres, all well-acknowledged genotoxic agents, chrysotile fibre-dependent genotoxicity remains a subject of vigorous debate. New advances provide further demonstration that, in addition to the highly tumorigenic amphibole fibres, chrysotile fibres can also be tumorigenic to epithelial and mesothelial cells in '*in vitro*' and '*in vivo*' models. These findings implicate p21cip and Integrin Receptor Associated Gene Big-H3 downregulation in chrysotile-dependent tumours.

#### *Asbestos, genetics and MM*

The importance of the loss of tumour suppressive genes (TSG) has been well demonstrated now in animal models. For example, experiments clearly show that p53/Rb knockout mice are more sensitive to the carcinogenic effect of these fibres than are wild-type mice. Thus, the mechanism of asbestos transformation may involve both an oncogenic recessive process whereby proteins controlling cell growth such as p16, p15, p14 and Rb are lost and key steps in extrinsic and intrinsic apoptosis are inactivated or perhaps inhibited by overactive survival pathways such as PI3K/Akt or MAPK. The role of the loss of tumour-suppressive proteins p16 and p14 was underscored during this meeting but also new findings on the role of the NF2 gene were widely discussed. Merlin, the protein encoded by the NF2 gene, was reported to act as an oncosuppressive protein by inhibiting the cell cycle via decreased expression of cyclin D1. The loss of merlin protein predisposes to the carcinogenic effect of the asbestos fibres and allows the activation of signalling pathways involved in cell proliferation and motility (Rac and Pak). Therefore, it has been also hypothesized that targeted drugs favouring merlin signalling could induce a depressant effect on cell proliferation and motility of MM cells.

The molecular study of HMC transformation and of MM cell biology is consistent with this concept of MM as a multistep recessive 'genetic' disease similar to other human tumours. In the case of MM, a further question arises about a genetic susceptibility to develop the tumour because only a small percentage of individuals exposed to asbestos develop MM.

The 'Turkish' experience has revealed a possible autosomal dominant transmission of susceptibility to MM. In Cappadocia, Turkey, mesothelioma develops at a strikingly high rate in only certain families among a population with equivalent exposure to erionite, an extremely potent carcinogenic, asbestos-like fibre

belonging to the zeolite family. None of the specimens from this area show infection with SV40 so the research is focusing on a possible interaction between erionite and the genome. Another study reported the appearance of MM in five sisters from the same family. These findings have encouraged many groups to investigate potential gene(s) predisposing to MM and many studies designed to identify any familial susceptibility for MM and to identify the gene(s) responsible are currently ongoing (see below).

#### *Genetic models of disease*

Exciting new animal models of disease were presented with many novel features including mesothelin-targeted expression of SV40, conditional cre-lox knockouts targeted to the pleura with intrapleural adeno-Cre, and combinatorial knockouts of genes of interest. In addition to the p53/Rb knockouts described above, this next generation of animal models will refine our understanding of the role of various genes in mesothelioma development and progression.

### **The role of SV40 and other advances in MM pathogenesis**

#### *SV40: controversy or consensus?*

Over the last few years, many studies have attempted to identify the role of SV40 as an adjunctive causative factor for MM and to clarify the entire multistep process leading to MM. SV40 viral sequences are detectable by PCR in a significant portion of MM specimens from all over the world, as was confirmed again at this meeting. SV40 can affect the normal HMC machinery by affecting several pathways and functions. This virus interferes with the two main control points of the cell by binding to and inactivating the tumour suppressors, p53 and retinoblastoma protein (Rb). In addition, SV40 can activate release of growth factors such as IGF-1, VEGF, HGF (with subsequent specific tyrosine kinase receptors activation) and to activate other oncogenes such as NOTCH. More recently, SV40 has been demonstrated to exert another type of carcinogenic effect, the methylation of tumour suppressor genes. Via methylation, SV40 can further silence TSG function affecting not only the development of MM but even worsening the prognosis of patients with MM. In association with SV40 infection, methylation of particular tumour suppressors, DCR1, RRAD, RASSF1A, HIL-1, CRBP1, TMS1 and HPP1, was reported. Moreover, methylation of TMS1 and HIL1 correlated with poor survival, a finding with possible clinical implications.

Another relevant SV40-dependent mechanism already mentioned above is the activation of the PI3K/Akt signalling that contributes to HMC neoplastic transformation and to MM growth and progression. SV40 can activate this pathway in HMC via induction of HGF release and met activation and confer a high resistance to asbestos-induced DNA damage. In MM cells (mostly in SV40-positive MM cells), PI3K/Akt activation has

also been detected and contributes to the tumour cell resistance to genotoxic agents.

These data offer the rationale for the use of drugs aimed at inhibiting the signalling either by interfering with TKr activation (already on the market) or directly 'switching' the signalling off (in course of clinical testing). SV40-dependent PI3K/Akt activation can also downregulate the sensitivity of the Fas receptor involved in the extrinsic pathway of apoptosis. Therefore, combined therapy for MM with kinase inhibitors and chemotherapy could possibly overwhelm the characteristic chemoresistance of this cancer.

On the whole, although not able to provide an irrefutable demonstration, these experimental approaches aimed at clarifying the role of SV40 in MM clearly strengthen the hypothesis that SV40 can collaborate with asbestos in causing this tumour. Only prospective long-term studies of molecular epidemiology aimed at assessing the effects of SV40 on the incidence rate of MM in subjects exposed to asbestos can actually settle this lively controversy.

### **MM diagnosis. Some steps forward**

#### *Immunohistochemistry*

For clinical advances to proceed, early detection, reliable diagnosis, staging and post-treatment monitoring are essential. Immunohistochemistry (IHC) for MM diagnosis is now a well standardized procedure that, through a panel of antibodies, can establish the diagnosis of MM with great accuracy. The main conditions to be respected are the use of the appropriate panel on the appropriate material derived exclusively from thoracoscopy or thoracotomy. IHC can also be of help to determine the expression of certain prognostic factors, for example, p27, a positive prognostic factor, or carbonic anhydrase IX or COX-2, negative prognostic factors.

#### *Imaging*

Developments in imaging techniques for MM were discussed during the meeting. Monitoring of MM for determining tumour responses has been troublesome, due to the pattern of tumour spread and its irregular shape. Computer-assisted analysis of CT scan imaging may provide more consistent and accurate measurements of tumour size than the usual manual methods.

Whereas CT and MRI together can improve pre-surgical staging, PET is more accurate in the N2 (mediastinal nodal) disease whose detection represents a poor prognostic group and thus highly influences the therapeutic approach. Therefore, PET was recommended for helping to select patients for either surgical or medical approaches, and for assisting in prognosis. A standardized uptake value (SUV) higher than 4 was reported to be negative prognostic factor. Interestingly, a high SUV together with a mixed histology was associated with the poorest prognosis in this report.

Low-dose spiral computerized tomography (LDCT) has also been tested to screen the early stages of asbestos-related lung cancer or MM in asbestos-exposed subjects. One study demonstrated that this method was able to detect patients with early stages of resectable lung cancer and many patients with benign pleural thickening. These latter will be enrolled for strict radiological monitoring by annual LDCT and, in case of changes, by high-resolution computerized tomography (HRCT) and/or invasive procedures in order to detect also the early stages of MM. To date, this study has not shown that screening is effective in detecting early stage mesothelioma. Computerized tomography may however be useful for discriminating patients with peritoneal MM who can be selected for treatment with surgery plus intraperitoneal chemotherapy.

### *Biological markers*

New biological markers aimed at screening, early detection and monitoring of MM are progressively entering clinical practice. One of the most intriguing biologic markers is serum mesothelin-related protein (SMRP), measured in serum or in pleural fluid by ELISA. Circulating SMRP were reported to be elevated in 84% of patients with MM, but in only 2% of cases of lung cancer or other thoracic malignant and benign diseases. When analysed in concert with serum CA125, the diagnostic value of SMRP was improved further. The SMRP levels also correlated with tumour size, with the response to therapy and with recurrence. In studies in which banked samples were tested, elevated levels of SMRP were found up to 4 years prior to the clinical diagnosis of MM, suggesting a potentially important role of this marker in the screening of subjects exposed to asbestos. Considering the characteristic long latency period of MM development from exposure, the use of such a test could represent a terrific step forward in the early detection of MM among people with past exposure to asbestos fibres.

### **Genomics and proteomics of MM**

Many groups reported that gene expression profiling with microarrays can assist in determining the diagnosis and prognosis of MM. For example, clustering of gene expression data has demonstrated an epithelial-related genomic profile and has the potential to identify unsuspected mesothelioma subgroups.

In using array data for diagnosis, determining 'gene expression ratios' between genes with high and low expression was reported as a valuable analytical approach because does not require a control set and should be independent of the particular microarray platform. Therefore, there is promise that the gene ratios may be applicable across many institutions. Some informative gene ratios were shown that predicted a diagnosis of mesothelioma while other gene ratios correlated with prognosis, with a high accuracy in predicting the clinical outcome of patients with MM

following surgical resection. Further studies will determine the minimal sample size needed for analysis.

In another study using genetic profile analysis, the downregulation of 16 genes was correlated with poor outcome. These predictor genes were found to be located on only four chromosomes, in six chromosomal bands, suggesting that loss of these specific regions of chromosomes, and their tumour suppressor gene loci, are important in development or progression of mesothelioma. The study suggests the use of these genes as novel markers of mesothelioma prognosis.

Microarrays are also being used to investigate possible human susceptibility genes. In one study, such genetic susceptibility is being evaluated via analysis of single-nucleotide polymorphisms (SNP) in patients' circulating lymphocytes. This report of 91 patients with mesothelioma, 105 patients with lung cancer and 73 healthy controls were studied for polymorphisms in 49 metabolism and DNA repair genes. There were significant differences among the groups between mesothelioma and the controls. The higher the number of SNP in these genes, the higher the risk of having mesothelioma; when there were as many as nine SNP differences, the odds ratio for mesothelioma was approximately 100-fold.

In early studies of the proteomic profile of pleural effusions, certain protein peaks were found that associated with mesothelioma. If any proteins prove useful in differentiating mesothelioma from other cancers, these could be useful for diagnosis. In addition, such proteins, if linked to the MM cells and found to have a functional role, could provide possible targets by tailoring specific drugs to interfere with their function and possibly tumour growth.

### **'Standard' therapies for MM: now more useful than before?**

#### *Background*

Chemotherapy, radiotherapy and surgery (in early stage mesothelioma) have been the cardinal approaches to patients with MM. While these treatments often failed to improve survival, it was hoped that they at least improved the quality of life of patients with mesothelioma. The tumour has thus been considered incurable. However, an increasing number of clinical trials incorporating standard chemotherapy as well as new agents have now been reported. The findings of these studies renewed interest in possible targets for therapy and are changing the previously defeatist attitude towards treating mesothelioma into a more optimistic attitude.

#### *Chemotherapy*

One report examining the value of standard platinum-based chemotherapy focused on patients with mesothelioma, in whom the symptoms were stable for at least 4 weeks prior to the study. In these patients, early therapy

may have provided a longer time until symptom progression compared to late therapy (25 weeks compared to 11 weeks) and a survival advantage (14 months compared to 10 months).

In regard to newer chemotherapeutic agents, wide consensus has been reached for combining an antifolate such as pemetrexed or raltitrexed with cisplatin as the current frontline chemotherapy for mesothelioma. Other phase II clinical trials aimed at assessing the efficacy of pemetrexed with gemcitabine are currently ongoing.

Moreover, in the next years, innovative trials with neo-adjuvant chemotherapy may provide new strategies against MM. In these trials, patients who respond to chemotherapy will then undergo extrapleural pneumonectomy (EPP) and radiotherapy.

### *The 'combined' approach*

With the use of surgery, chemotherapy and radiotherapy as 'multimodality' treatment, a gain of survival has been reported in the patients eligible for this therapy (in patients in Stage I/II up to 79 and 38% of survival after 2 and 5 years, respectively). Prognosis depended on surgical findings with positive prognostic factors including negative resection margins, the absence of extrapleural-positive nodes and the epithelial subtype. Also, women generally had a better prognosis than did men. Interestingly, there was still discussion about the proper staging system, an issue that is still in debate. Indeed, there was also discussion about the role and the value of surgery itself. One report argued that patient outcome was better predicted by Karnovsky scores than by either the stage of disease or surgical results, highlighting the problems in determining the survival impact of resection without randomized trials.

Two main patterns of multimodality therapies were also presented: surgery plus radiotherapy or surgery plus both chemotherapy and radiotherapy. Radiotherapy has often been integrated with surgical resection to improve local control of disease. Intensity modulated radiation therapy (IMRT) is a new technique of radiotherapy delivery that allows highly conformal dose distribution with customized intensity patterns. By more accurately focusing the dose to areas of disease, this modality of delivery can render high doses of radiotherapy more tolerable. Reports on IMRT following EPP describe excellent local control; failure mostly is due to distant metastatic spread of disease. In patients with more advanced stages of disease (mediastinal spread of disease or metastatic spread), induction chemotherapy is being combined with surgery in those who respond to the therapy. With induction platinum/gemcitabine, followed by EPP and high dose of radiotherapy, favorable survival is suggested in patients rendered resectable following induction therapy. Another multimodal approach under investigation involves EPP combined with intraoperative, intrathoracic hyperthermic cisplatin (with amifostine protection) followed by adjuvant chemotherapy (cisplatin/gemcitabine) and radiotherapy within 8 weeks. To

summarize, by their newer combinations, the 'old' therapies may be more effective now than before, with clinical trials ongoing. Incorporating new biological approaches offers promise for increasing effectiveness further.

### **Experimental 'translational' therapies for MM: is this the future?**

#### *Background*

In the future, cancer treatment will increasingly move beyond chemotherapy. The huge and growing body of knowledge about the molecular biology of tumour cells will surely be exploited in the next few years to furnish more specific 'biologic' therapies. One can predict that these new approaches will be combined with and progressively replace chemotherapy. During the meeting, many groups presented results of preclinical and clinical studies and reported early findings on 'biological' drugs and approaches for the treatment of MM.

#### *Immunotherapy*

Enhancing the immune response against MM cells holds great promise as a way to control early disease or residual disease postresection. The use of immunomodulatory cytokines and costimulatory proteins are aimed at giving the MM cells the capability to present the tumour antigens to the immunoeffector cells. Indeed, in animal models, there are strong '*in vivo*' data that mesothelioma can be treated effectively using IL2, IL4, IL12, GM-CSF, or B7-1/2 as an adjuvant immunotherapy. Several related approaches were presented including the development of autologous tumour vaccines, modulation of immunosuppressive cytokines such as TGF beta and intrapleural gene therapy with immunostimulatory interferons.

Immunotherapeutical strategies can be aimed at targeting the antigens on the MM cell known to elicit an immune response. Cancer testis antigens (CTA), previously described as antigens on melanoma cells, were reported to be significantly expressed on MM cells too, suggesting the use of CTA as a new vaccine therapy in the treatment of this neoplasm. Furthermore, demethylating agents have been shown to augment CTA suggesting value from combined therapy with vaccination and demethylating agents. Other groups showed intriguing '*in vitro*' and '*in vivo*' findings that MM cells may possess antigens able to elicit an effective immune response. In a murine study, vaccination with autologous dendritic cells (DC) pulsed with lysate from apoptotic MM cells elicited an effective cytotoxic T-lymphocyte response (CTL) able to prolong the survival of mice injected with lethal doses of tumour cells.

'*In vitro*' models furnished the evidence that DC pulsed with apoptotic MM cells generated a CTL response against both MM and melanoma cells reinforcing the view that antigens are shared between these two tumours. The MM cells most effective at eliciting the

CTL response had been heat-shocked and expressed the heat-shock protein hsp70.

The capability of MM cells to evade the immune response through TGF beta release was also underscored in studies addressing new potential therapeutic strategies aimed at TGF beta blockade by specific antagonist molecules. Benefits of immune responses had been suggested by analysis of an earlier, unrelated gene therapy trial. Intrapleural adenoviral delivery of the Herpes simplex virus thymidine kinase followed by treatment with ganciclovir demonstrated adenoviral immune responses and some long-term survivors. The relative low transfection efficiency of the therapeutic gene in these responders and the slow time of tumour regression suggested that the clinical responses could be due to a vector-dependent immune response. Thus, in a Phase I clinical trial, intrapleural adenoviral delivery of the immunostimulant cytokine INF-beta has begun with early encouraging results in a few patients. Moreover, preclinical data suggest that a combination of this immunostimulant therapy with chemotherapy, COX-2 inhibition and surgical debulking may be effective and will be incorporated in future trials.

Another approach based on the immune response is a method using a recombinant immunotoxin. Mesothelin is a good target for cancer treatment given its limited expression on normal tissues and high expression on certain cancers including MM. Thus, a phase I clinical trial with the anti-mesothelin Fv (obtained by phage display) linked to a mutated *Pseudomonas* exotoxin (PE38) that mediates cell killing has been used for peritoneal and pleural MM with good preliminary results. In general, the immunotherapy was seen to have a future role in MM, in the early stages or in later stages combined with either surgical debulking or tumour chemotherapy/apoptosis induction.

#### *Preclinical and clinical findings based on the novel agents affecting proliferative and antiapoptotic signalling of MM cells*

Survival pathways may include several key cytokines. NFkB activation appears to be a feature of MM cells and new therapeutic agents as the proteasome inhibitor PS341 (Velcade®) can block this activation by interfering with IκB. The proteasome inhibitor PS341 appears capable of inducing apoptosis of MM cells *in vitro* and *in vivo* suggesting that this compound, already on the market, could be fruitfully utilized for MM therapy. Interfering with the HGF autocrine loop and the subsequent met receptor activation by a specific met receptor signalling inhibitor (PHA-665752) has also been shown to inhibit MM cell proliferation rate and motility and sensitize these cells to cisplatin. These findings provide the rationale for a clinical trial with this inhibitor used in a combined approach with chemotherapy. Finally, an inhibitor of the PDGF and cKit tyrosine kinase receptor (STI571, Gleeve®) has been demonstrated to be active against MM cells and to enhance their sensitivity to gemcitabine. A Phase I trial with this combination is currently to start.

Another field of interest discussed has been the use of antiangiogenic agents for MM therapy. VEGF may be of particular interest because VEGF is an autocrine growth factor for MM cells and VEGF blockade inhibits MM growth. Early data from clinical trials of SU5416, bevacizumab, thalidomide and tetrathiomolybdate, a copper chelator, appear promising. A new generation of clinical trials in mesothelioma will clarify the role of angiogenesis inhibitors in the chemo-naive, refractory and adjuvant settings and studies in combination with other agents are also planned.

## Conclusions

Knowledge of MM biology is rapidly expanding and the meeting offered a precious opportunity to understand how these findings may translate to the clinical arena in the near future. New diagnostic and prognostic methods made available by genomics and proteomics will improve selection of patients and there is increasing confidence that new biological therapies will be effectively combined with surgery, chemo- or radiotherapy to improve the effectiveness of therapy for this refractory disease.

## Epilogue

'I just turned to wood.

The doctor said 'You've got mesothelioma' and I can't remember anything after that.'

Patient's wife: 'She said 'It's mesothelioma, it's malignant, it's terminal and there's no treatment'

Mr Y, ex-railway maintenance engineer

We hope that these efforts will change the perspective of patients with MM who ask us to do something to make them live longer and better than we have in the past.

'If you always do  
what you always did,  
you always get  
what you always got'

Mark Twain

## Appendix A

International Mesothelioma Interest Group (IMIG) Executive Committee: DH Sterman (President, Philadelphia, USA), SE Mutsaers (Secretary, Perth, Australia), P Baas (Treasurer, Amsterdam, The Netherlands); SM Albelda (Philadelphia, USA), VC Broaddus (San Francisco, USA), MC Jaurand (Creteil, France), H Kindler (Chicago, USA), S Knuutila (Helsinki, Finland), D Mattson (Helsinki, Finland), L Mutti (Vercelli, Italy), T Nakano (Nishinomiya, Japan), H Pass (Detroit, USA), BWS Robinson (Perth, Australia).

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