Predictive Biomarkers and Personalized Medicine

Serum Soluble Mesothelin Concentrations in Malignant Pleural Mesothelioma: Relationship to Tumor Volume, Clinical Stage and Changes in Tumor Burden

Jenette Creaney1,2, Roslyn J. Francis1,3, Ian M. Dick1, Arthur W. Musk1,6, Bruce W. S. Robinson1,2,4, Michael J. Byrne1,5, and Anna K. Nowak1,5

Abstract

Purpose: To examine the clinical utility of soluble mesothelin in patients with malignant pleural mesothelioma.

Experimental Design: A total of 97 patients (female: 11; male: 86) were prospectively enrolled, longitudinal serum samples collected, and mesothelin concentrations determined. Baseline mesothelin levels were analyzed relative to tumor stage, presence of metastatic disease, the positron emission tomography (PET) parameters maximum standardized uptake value, tumor volume, total glycolytic volume, and survival. Changes in mesothelin level were correlated to objective response to chemotherapy, as assessed radiologically and by PET imaging, and with patient survival.

Results: Baseline mesothelin levels greater than 5 nmol/L were a significant negative prognostic indicator (HR = 2.25; 95% CI, 1.20–4.21) and correlated with tumor stage and volume. In 55 patients who received chemotherapy, change in mesothelin correlated with radiological response ($r^2 = 11.32; P = 0.023$) and change in metabolically active tumor volume ($r = 0.58; P < 0.01$). Median survival for patients with a reduction in mesothelin following chemotherapy (19 months) was significantly longer than for patients with increased mesothelin (5 months; $P < 0.001$).

Conclusion: These findings show the potential value of changes in mesothelin levels for prognostication and monitoring of treatment response in mesothelioma.

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Introduction

Malignant mesothelioma is an aggressive, asbestos-induced tumor of serosal surfaces (1, 2). Palliative use of first-line chemotherapy for advanced pleural mesothelioma is widely accepted (3) and, although controversial, some patients also receive surgical interventions (4–6). Early-phase clinical trials commonly use radiological endpoints such as objective response rate, time to progression, and 6-month progression-free survival to assess the efficacy of novel therapies. The utility of early-phase clinical trials in predicting the outcomes of subsequent randomized phase III investigations depends on these radiological endpoints being robust, reproducible, and clearly related to overall survival and patient benefit. Unfortunately, these conditions do not conform to assessment of response in malignant pleural mesothelioma (7, 8). The unique morphology of mesothelioma presents some difficulties for quantitative radiological measures. The tumor tends to grow as a *“rind” around the pleural surface, rather than as a spherical mass.

Although a modification of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (9) has in part addressed the specific application of RECIST to the anatomic distribution of mesothelioma (10), these measurements are still difficult to reproduce, vary between observers, and the relationship of the modified RECIST measurements to tumor volume is unclear (11, 12).

Previously, we and others have shown that serial FDG-PET (Fludeoxyglucose positron emission tomography) scanning can predict response to chemotherapy and patient survival (13–15). Nevertheless, change in FDG uptake can be difficult to interpret in the setting of surgery or previous pleurodesis, due to false-positive uptake in inflammatory tissue (16). Pleurodesis is a common procedure in patients with mesothelioma, and limits the proportion of patients who can be monitored this way.

Tumor markers offer an attractive means of monitoring tumor response in patients, being less expensive and less invasive for repeated use. Indeed, it is in such a setting that markers are most clinically useful in other forms of cancer (17–22). For mesothelioma patients, tumor markers could offer a quantitative measure of tumor response and a
were approached to participate. Eligibility criteria included referred to a tertiary outpatient oncology service between 2003 until 2007. All eligible consecutive patients were included in the study. The study was approved by the institutional human research ethics committee, and all patients provided informed written consent. CT imaging

Each patient had a contrast-enhanced thoracic and upper abdominal helical computed tomography (CT) scan with 5-mm slices. For patients receiving chemotherapy, a CT scan was done up to 4 weeks before the first cycle and following the first and third or fourth cycle, with an additional CT scan to confirm response when appropriate. Radiological response to therapy was assessed using the modified RECIST criteria for mesothelioma (10). CT scans were assessed by a thoracic radiologist, experienced in mesothelioma measurement and unaware of patient outcome. Radiological complete response was defined as the disappearance of all target lesions with no evidence of tumor elsewhere, and radiological partial response (PR) was defined as at least a 30% reduction in the summed unidimensional tumor measurement. A confirmed response required a repeat observation on 2 occasions at least 4 weeks apart. Radiological progressive disease (PD) was defined as an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new lesions. Patients with stable disease were those who fulfilled the criteria for neither PR nor PD.

18F-FDG PET

Whole body FDG-PET imaging was done on a germanium oxyorthosilicate Phillips Allegro PET scanner.
Patients fasted for 6 hours and were imaged 90 minutes following 215MBq/m2 FDG administration. Scans were done at baseline, repeated before commencing chemotherapy, if the patient had undergone a period of observation before starting treatment, and then repeated after the first and fourth cycle of chemotherapy. In view of the potential confounding effect of talc pleurodesis, only patients without talc pleurodesis in the previous 6 months were included in the PET scan–related analyses. Each FDG-PET scan was staged by two experienced PET physicians, using UICC TNM staging criteria (28), with consensus reporting used to attain agreement. The PET physicians were blinded to CT stage and patient outcome, but were permitted to utilize the CT scan for anatomic correlation.

Semi quantitative analysis of PET scans was done using a previously described 3-dimensional (3D) iterative region growing algorithm to define tumor volumes of interest (VOI) and derive a TGV and maximum standardized uptake value (SUV_{max} refs. 13, 29). All SUV measurements were calculated using body weight. The region growing software was implemented in Interactive Data Language version 6.1 on a Windows platform. The growing function of the algorithm uses an adaptive threshold to delineate —3D tumor boundaries. The threshold, which is reapplied at each iteration, is determined by the current mean, the activity in neighboring pixels and the maximum normal background activity in liver (29). Contiguous 3D VOI are generated, and the operator is required to reseed on non-contiguous tumor elements. TGV and SUV_{max} were then determined from the tumor VOI, with TGV being a composite measure of metabolic activity and volume of the whole tumor mass whereas SUV_{max} represents the maximum SUV value in the tumor VOI.

Mesothelin
Mesothelin concentrations were determined following the manufacturer’s instructions using the MESOMARK assay (Fujirebio Diagnostics). All assays were done on coded samples by investigators who were unaware of the patient’s clinical characteristics.

Statistical analysis
The work reported in this article was performed as a substudy of a study powered to answer imaging questions; hence the sample size was determined independently of this pilot substudy.

Measurements between groups were compared using the nonparametric Mann–Whitney U test. Correlations between measurements were analyzed using the nonparametric Spearman’s test. The association of mesothelin concentration with survival was analyzed by entering it into a Cox proportional hazards regression model as either a continuous or as a grouped variable, both with and without covariates. A P value of less than 0.05 was considered significant. The statistical analysis was done using the PASW version 18 statistics package (SPSS Inc.).

Results

Patients
A total of 97 patients were prospectively recruited over 5 years. Two patients were ineligible because of concomitant nonmesothelioma tumors detected on FDG-PET scan. Almost one quarter of the patients received best supportive care, 61 received first-line chemotherapy, 7 underwent trimodality therapy, and 2 received radiotherapy (Fig. 1). The demographic characteristics of the patients and the histologic characterization of their tumors are shown in Table 1. As the study addressed multiple independent questions, some patients were assessable for different aspects of the study. For example, those patients who were not eligible for FDG-PET scanning due to previous talc pleurodesis or surgery remained eligible for aspects assessing the relationship between radiological tumor response and mesothelin levels. At the time of censoring, 10 patients were alive; median survival for the overall group of 95 patients was 15 months.

Prognostic significance of baseline mesothelin

Serum for baseline mesothelin measurement was collected as close as possible to the time of diagnosis of mesothelioma, with a median (range) time difference of 2 (3 to 33) weeks from the date of diagnosis. For this study, soluble mesothelin levels at baseline ranged from undetectable to 103 nmol/L, with a median concentration of 2.16 nmol/L. When patients were grouped into tertiles by baseline serum mesothelin level, the median survival from the time of diagnosis for patients with the lowest tertile of mesothelin level (<1 nmol/L) was 20 (0–57) months, significantly longer than those in the highest tertile of mesothelin level (>5 nmol/L; 12.5 (1–44) months; P = 0.012; Fig. 2A). Univariate analysis of mesothelin levels entered as a continuous variable indicated that baseline mesothelin was not a significant predictor of survival; however, a mesothelin level greater than 5 nmol/L was associated with decreased survival compared with a mesothelin level of less than 1 nmol/L (Table 2). Univariate analysis indicated that sarcomatoid histology, CT stage IV disease, and high baseline PET volume and TGV were associated with decreased survival (Table 2). After adjustment for age, gender, serum creatinine levels, histology, and treatment in a Cox regression model (Table 2; Model A), baseline mesothelin entered into the model as a continuous variable was a significant predictor of survival (P = 0.038). However, when the Cox regression model was adjusted for PET measures (Table 2; Model B) mesothelin measurements were not a significant prognostic predictor of patient survival. Adjustment of the model for CT staging resulted in neither mesothelin measures nor CT staging being significant prognostic predictors of survival (data not shown).

Correlation of baseline serum mesothelin levels with tumor stage
Baseline serum mesothelin concentrations were obtained within a mean ±SD of 0.1 ± 3.5 weeks of CT.
imaging, and correlated with tumor stage. There was a modest significant increase in serum mesothelin with more advanced radiological stage (Fig. 2B). The median (range) mesothelin level was 0.88 (0.34–2.71) nmol/L for the stage I group and 2.5 (0.38–103.17) nmol/L for stage IV ($P = 0.008$). Nevertheless, some individuals with stage IV disease had low serum mesothelin. There was no significant difference in mesothelin levels between patients with ($n = 16$) or without ($n = 70$) CT evidence of metastatic disease ($P = 0.118$; data not shown).

In the 55 eligible patients, there was no significant increase in mesothelin concentrations with increasing stage as assessed by FDG-PET scan (Fig. 2C). FDG-PET identified unrecognized metastatic disease in 4 patients; mesothelin levels did not differ between those patients with and without PET-identified metastases (data not shown).

**Correlation of mesothelin concentration with tumor burden**

Staging represents the anatomic extent of tumor involvement, and may not always correspond to tumor burden in this disease. Correlation of metabolically active tumor volume with serum mesothelin levels was examined in 52 patients with serum mesothelin concentrations available within 4 weeks of the FDG-PET scan. Patients who did not have an FDG-PET scan for any reason, those with pleurodesis within 6 months of the scan, and 3 patients who had minimal $^{18}$F-FDG avid disease that was unable to be quantified were excluded. Mesothelin levels correlated significantly with metabolically active tumor volume as measured by FDG-PET TGV (Spearman’s $r = 0.419$; $P = 0.002$). Mesothelin levels also correlated with tumor volume ($r = 0.409$; $P < 0.001$) and with the intensity measure, $SUV_{max}$ ($r = 0.291$; $P < 0.05$; Fig. 2).

**Change in mesothelin concentration following therapy**

Six patients underwent extrapleural pneumonectomy with macroscopic clearance of tumor but positive histologic margins. Five patients had samples taken between 2 months and 24 hours preoperatively and within 24 to 72 hours postoperatively; in these patients, mesothelin levels decreased to a mean of 54% of the baseline level (range, 27%–83% of baseline). It is unclear whether subsequent more profound declines would have occurred, as further postoperative mesothelin levels were not available on any of these patients, 3 of whom died before additional testing. In the sixth patient, a postoperative mesothelin level was not taken until 5 months following surgery and approximately 9 months before recurrence, and at that time it was 50% of the initial baseline measurement. The half-life of the protein and the trajectory of decline following
Macroscopic resection are unknown and should be explored by serial measurements over the immediate postoperative period to examine the nadir reached after macroscopic complete resection and the relationship of this nadir to subsequent clinical outcomes.

Of the patients receiving chemotherapy in this study, 55 were analyzable for changes in mesothelin levels: 39 received gemcitabine and a platinum agent, 16 received pemetrexed combined with cisplatin. The number of treatment cycles ranged from 1 to 6.

Changes were assessed by comparing an individual patient’s prechemotherapy mesothelin level with the lowest level achieved during treatment. Following chemotherapy, serum mesothelin decreased by 25% or more of the baseline levels in 24 of 55 patients (decreased group); remained within 25% above, or below, the baseline in 23 patients (stable group), and increased by more than 25% of baseline in 8 patients (increased group). There was a significant correlation ($\chi^2 = 11.32, P = 0.023$) between radiological response as determined by the modified RECIST criteria and changes in serum mesothelin (Table 3). Of the 17 patients with a PR to chemotherapy, a reduction in mesothelin levels was seen in 12; none had increased mesothelin levels.

Of the 55 patients, 28 had concurrent assessment of tumor changes by FDG-PET. There was a significant correlation ($r = 0.58; P < 0.001$) and volume ($r = 0.61; P < 0.001$; Fig. 3). Mesothelin concentrations over time and PET and CT scans pre- and postchemotherapy are shown for a representative patient in Figure 3.

**Change in mesothelin concentration following chemotherapy and survival**

When examined as a continuous variable, Cox regression analysis showed that percentage change in mesothelin level in the 55 patients available for analysis following chemotherapy was predictive of patient survival ($HR = 1.05; 95\% CI, 1.02–1.07; P < 0.001$, per 10% change in mesothelin level). When categorized on the percentage change in mesothelin levels into 3 groups. Both the stable mesothelin group (HR = 2.02; 95\% CI, 1.10–3.13; $P < 0.001$) and the increased mesothelin group (HR = 23.03; 95\% CI, 7.47–70.92; $P < 0.001$) had an increased risk compared with the decreased mesothelin group. Kaplan-Meier analysis (Fig. 4) illustrates the significant relationship between percent change in mesothelin levels following chemotherapy and survival.

**Discussion**

In this study, we showed that change from baseline mesothelin level in response to chemotherapy reflects patient prognosis, suggesting a possible role for mesothelin in monitoring response to treatment. This study confirmed and extended upon recent findings that showed a correlation between change in mesothelin levels and radiological response (26). Tumor markers are widely used in ovarian cancer, breast cancer, colorectal cancer, and prostate cancer both in clinical trials and in routine clinical practice. In some cases measurement of CA 15-3 is used as an adjunct to monitoring response clinically and by imaging, and to decrease the requirement for additional investigations or increase the duration between tests, despite baseline levels not being prognostic or predictive (30).

Our data show a modest correlation between baseline mesothelin level and tumor stage, and no value of baseline mesothelin in differentiating between patients with or without metastatic disease. However, mesothelin levels were more strongly correlated with tumor burden and metabolically active tumor volume as measured by FDG-PET. This disconnect between stage and tumor burden is not unexpected, as tumor stage is determined by anatomic site and extent of tumor involvement and not necessarily related to tumor bulk. We have previously shown that tumor volume on FDG-PET is strongly associated with

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>No chemotherapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>95</td>
<td>28</td>
<td>67</td>
</tr>
<tr>
<td>Median age (range), y</td>
<td>66 (41–94)</td>
<td>72 (47–94)</td>
<td>66 (41–80)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Male</td>
<td>84</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>68</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>Biphasic</td>
<td>18</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Median survival* (range), mo</td>
<td>15 (1–66)</td>
<td>7 (1–44)</td>
<td>15 (1–66)</td>
</tr>
</tbody>
</table>

*From diagnosis.
survival on univariate analysis \((P = 0.008; \text{ref. 15})\). Here, the correlation between tumor volume and mesothelin level is also reflected in the observation that patients with high baseline mesothelin levels have a significantly reduced survival. This finding that high baseline mesothelin correlates with poor survival has been previously shown by others \((25, 31, 32)\). In our study, this was independent of age, sex, histology, and treatment. The addition of histologic type to the analysis increased the significance of mesothelin examined as a trend variable, because it adjusted the analysis for the decreased survival time of the sarcomatoid histology type, which had lower mesothelin levels than the epithelioid and biphasic types. The addition of either tumor volume or TGV removed the significance of mesothelin, examined as either a trend or grouped variable, as a predictor of survival, which suggests that mesothelin does not have any significant predictive value for survival beyond its relation with tumor size, as measured by PET analysis. Indeed, from the data presented here, the prognostic information provided by baseline mesothelin is mainly associated with its relationship to tumor volume; therefore, the blood-based assay could be used as a surrogate for tumor volume as determined by FDG-PET.

Changes in serum mesothelin levels reflected changes in tumor burden. Despite the small patient numbers exam-
ined, mesothelin levels invariably decreased in response to debulking surgery, suggesting a clear relationship between decrease in volume of viable tumor and levels of the tumor marker. This relationship is strengthened by our observation that mesothelin levels changed in concert with observations of objective radiological response, and with FDG-PET–quantified tumor volume and metabolically active tumor volume. Similar findings have recently been reported in a smaller patient group but without assessment of metabolic tumor volume (26).

Radiological response as assessed by the modified RECIST criteria uses unidimensional measurements and does not provide a quantitative evaluation of change in tumor burden. It has been shown to correlate with important endpoints such as survival, and pulmonary function (10). Similarly, we have shown the relationship between change in mesothelin levels on therapy, and overall survival.

Limitations to this study include the small patient numbers and heterogeneous clinical treatment received. Some patients had mesothelin levels below the limits of detection reducing the number with quantifiable results. Furthermore, the study was primarily designed and powered to answer another primary study question. Nevertheless, a comprehensive imaging study including both CT and FDG-PET techniques is an ideal setting in which to explore the role of a serum biomarker.

### Table 2. Cox regression model of mortality from the time of measurement of baseline mesothelin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Mesothelin (per 5 nmol/L increase)</td>
<td>1.04 (0.96–1.11)</td>
<td>NS</td>
<td>1.09 (1.00–1.19)</td>
</tr>
<tr>
<td>Mesothelin grouped (cf. &lt;1 nmol/L) (1–5 nmol/L)</td>
<td>1.35 (0.80–3.31)</td>
<td>NS</td>
<td>1.48 (0.79–2.78)</td>
</tr>
<tr>
<td>Mesothelin grouped (cf. &lt;1 nmol/L) (&gt;5 nmol/L)</td>
<td>2.25 (1.20–4.21)</td>
<td>0.011</td>
<td>2.31 (1.11–4.81)</td>
</tr>
<tr>
<td>S creatinine (per unit increase)</td>
<td>0.99 (0.97–1.00)</td>
<td>0.066</td>
<td>0.98 (0.96–0.99)</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.02 (1.00–1.04)</td>
<td>NS</td>
<td>1.04 (1.01–1.19)</td>
</tr>
<tr>
<td>Gender (females cf. males)</td>
<td>0.47 (0.38–1.47)</td>
<td>NS</td>
<td>0.58 (0.27–1.24)</td>
</tr>
<tr>
<td>Treatment (cf. none)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>0.87 (0.41–1.77)</td>
<td>NS</td>
<td>1.25 (0.58–2.68)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.96 (0.54–1.72)</td>
<td>NS</td>
<td>0.74 (0.41–1.32)</td>
</tr>
<tr>
<td>Histology (cf. epitheloid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic</td>
<td>1.11 (0.60–2.04)</td>
<td>NS</td>
<td>1.19 (0.73–2.54)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>3.65 (1.61–8.29)</td>
<td>0.002</td>
<td>4.41 (1.89–10.29)</td>
</tr>
<tr>
<td>Pleurodesis (cf. not done)</td>
<td>0.87 (0.52–1.46)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CT stage (cf. stage I)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stage II</td>
<td>1.21 (0.40–3.65)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>1.61 (0.75–3.48)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.21 (1.04–4.68)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>PET measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (per 1,000 unit increase)</td>
<td>1.50 (1.15–1.95)</td>
<td>0.003</td>
<td>1.77 (1.23–2.54)</td>
</tr>
<tr>
<td>TGV (per 1,000 unit increase)</td>
<td>1.08 (1.02–1.13)</td>
<td>0.003</td>
<td>1.11 (1.03–1.19)</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

*Mesothelin, measured at the time of diagnosis, was entered into the model as a categorical or as a trend variable. Survival was measured from the time of diagnosis.

*Mesothelin, measured at the time of the PET scan, was entered into the model as a categorical or as a trend variable. Either TGV or volume was entered into the model. Adjusted mesothelin result shown is after adjustment for PET volume. A similar result for mesothelin after adjustment for the TGV was observed.

### Table 3. Correlation of change in mesothelin concentration with radiological response

<table>
<thead>
<tr>
<th>Mesothelin*</th>
<th>Response (CT modified RECIST)</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>12 (7)</td>
<td>10 (11)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>5 (7)</td>
<td>12 (11)</td>
<td>6 (5)</td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>0 (2)</td>
<td>4 (4)</td>
<td>4 (2)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Results are number of patients observed (expected number of patients); \( \chi^2 = 11.32; \ P = 0.023 \). Abbreviation: SD, stable disease.

*Decrease: levels reduced by 25% or greater of baseline values; Stable: levels within 25% of the baseline value; Increase: levels increased by 25% or greater of baseline values.
Although none of the currently available tools for monitoring response in patients with mesothelioma represents a “gold standard,” additional information is needed clinically. Serial monitoring of radiological response is difficult to assess in this disease. Formal measurement of response is time consuming and readily confounded by the presence of pleural effusion and atelectasis. The measurement of soluble serum mesothelin may represent a cheaper, less invasive technique that can provide support for clinical judgment and potentially decrease the frequency of radiological monitoring in routine clinical practice, particularly with regards to monitoring the efficacy of therapy. Mesothelin may also prove an informative surrogate endpoint in clinical trials. Further, prospective, multicenter validation studies are necessary before these findings can enter routine clinical practice, and ongoing Australian clinical trials in mesothelioma are currently collecting serial mesothelin measurements to contribute to this validation process.

These data suggest that in the clinical context of the management of an individual patient an elevated level of serum mesothelin may provide useful guidance for the clinician. Higher baseline levels suggest larger tumor volume, more advanced tumor stage and bode a poorer prognosis. A fall in the level following chemotherapy increases the likelihood that the tumor is responding to therapy, may encourage continuation of treatment and increases the likelihood of a longer patient survival.

**Disclosure of Potential Conflict of Interest**

No potential conflicts of interest were disclosed.

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