

Preliminary Findings on the Use of Targeted Therapy in Combination with Sodium Phenylbutyrate in Advanced Malignant Mesothelioma: A Strategy for Improved Survival

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Abstract

Advanced malignant mesothelioma (MM) is among the most aggressive and difficult-to-treat diseases. Industrialization and exposure to asbestos is the main causative factor for the dramatic increase in the incidence of MM, which carries a poor prognosis and a median survival of less than 12 months. Combination chemotherapy offers only palliative results; however, targeted therapy carries more promise for future successful treatment. This paper presents preliminary findings of improved overall survival (OS) using a combination of sodium phenylbutyrate (PB) with various chemotherapeutic and targeted agents in advanced MM. The data suggest using a strategy of simultaneous interruption of signal transduction involving RAS-MEK-ERK, PI3K-AKT, mTOR, Merlin, and angiogenesis pathways and interference in cell cycle and epigenetic processes. Complete response was determined in 15.4% and stable disease in 46.2% in the group of 13 evaluable patients. Median OS for MM was higher compared to other treatments (17 months compared to between 6 and 12.1 months). The longest surviving patient continues to be in complete response and in excellent condition for over 12.5 years from the treatment start. These findings are only preliminary and validation of the results using a well-designed phase I/II trial in advanced MM is proposed.

Keywords

Mesothelioma, Mesothelioma Survival, Personalized Targeted Therapy, Antineoplastons, Sodium Phenylbutyrate, Clinical Studies

1. Introduction

Advanced malignant mesothelioma (MM) is one of the most aggressive and difficult-to-treat neoplasms. It arises from the surface serosal cells of the pleura and peritoneum and in rare instances, the pericardium or gonads [1]. Exposure to asbestos fibers is the most common cause of MM. A very rare disease, industrialization and exposure to asbestos caused a dramatic increase in the incidence of MM once [2]. Further increase is expected, especially in developing nations [2]. The prognosis of MM is poor with the median survival from 9 to 12 months from diagnosis, despite advances in chemotherapy and use of targeted therapy [3]. Genetic analysis reveals involvement of a number of different signaling pathways and several important genetic alterations [1], which includes RAS-MEK-ERK, PI3K-AKT, m-TOR, Merlin, Hippo and angiogenesis pathways, interference in cell cycle and epigenetic changes. These mechanisms were described in detail in recent review articles [1] [4]-[7].

A combination of pemetrexed with cisplatin for unresectable pleural MM became the standard-of-care first-line chemotherapy [3]. Some targeted agents given as monotherapy or in combination, occasionally stabilize the disease, but none are recommended as standard first-line or second-line therapy [8].

For several years, our team has conducted research with antineoplastons (ANP), a group of anticancer agents consisting of peptides, amino acid derivatives, and carboxylic acids originally isolated from blood and urine of healthy subjects [9]-[11]. The anticancer activity of these compounds was confirmed in a number of preclinical and clinical studies [12]. After identification of the structure, numerous phase II studies were conducted with synthetic ANP A10 and ANP AS2-1 injections involving primary brain tumors and advanced colorectal cancer [13]-[18]. Further research revealed that some ingredients of ANP A10 and AS2-1, phenylacetylglutamate (PG) and phenylacetate (PN), are the same as metabolites of sodium phenylbutyrate (PB) a histone deacetylase (HDAC) inhibitor with multiple targets of activity, which is approved for urea cycle disorders and indicated for glioma and acute promyelocytic leukemia [13] [19] [20]. The study of PG and PN on the glioblastoma multiforme (GBM) genome has shown that they affect approximately 100 genes [21]. These data and molecular profiling led to the treatment of a number of patients at Burzynski Clinic (BC) with advanced malignancies, including GBM and pancreatic cancer using combinations of PB and targeted agents [22] [23].

This article provides a brief description of treatment results in patients with advanced malignant mesothelioma and suggests a rationale for conducting clinical trials with PB in combination with targeted agents.

2. Patients and Methods

Thirteen subjects were diagnosed with advanced malignant mesothelioma following pathology and radiologic evaluations performed by independent institutions. Thereafter, treatment was provided in the private practice of the BC in Houston, TX. The patients included consecutively admitted evaluable patients between November 9, 2000 and August 24, 2012.

Blood and urine tests were done by the BC laboratory and by outside clinical laboratories. Tests were undertaken that included standard blood and urine analysis and determination of genomic markers (when these were available). Tissue molecular profiling was performed by Caris Life Sciences in Phoenix, AZ. All patients were required to read, understand, and sign an informed consent document prior to treatment. Treatment plans were formulated based on molecular profiling when obtained and included PB given alone or in combination with targeted and chemotherapeutic agents. Therapy was undertaken on an outpatient basis. After an initial two to four weeks at BC, treatment continued under the care of a local oncologist. Prior to the treatment start, a computerized tomography (CT) scan with and without contrast and in some patients a positron emission tomography (PET) scan was performed. The product of two of the largest perpendicular diameters (LPD) of the largest measurable lesions were calculated and totaled providing a baseline evaluation for each study subject. This baseline provided the reference for determining response outcome to treatment. Additional pretreatment measurements included vital signs, clinical disease status, demographics, medical history, current medications, physical examination, electrocardiogram (EKG) and Karnofsky Performance Status (KPS). The evaluation of toxicity was performed according to the common terminology criteria for adverse events version 3 (CTCAEv.3). Possible responses to treatment were complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR required the disappearance of all lesions confirmed at the end of four weeks or a negative PET scan. PR required 50% or higher decrease of the LPD of measurable lesions confirmed at four weeks, PD was determined when new lesions appeared or when there was an increase over 25% in the existing lesions and SD represented the status of tumors classified as between PR and PD.

3. Results

3.1. Patient Demographics

The characteristics of the 13 patients studied are described in **Table 1**. All had involvement of the pleura, and seven patients had additional involvement of the peritoneum. Of all the patients, one had no prior treatment, whereas four patients had undergone surgery as their only treatment. The majority of patients had failed prior chemotherapy and one patient failed surgery and radiation therapy (RT). The data confirming diagnosis, recurrence, and response to treatment received are described in **Table 2(a)** and **Table 2(b)**.

3.2. Treatment

Details of medication dosing and treatment duration of patients who obtained CR and SD are described in **Table 3(a)** and **Table 3(b)**.

Five patients received treatment with the single agent PB. Five additional patients were treated with PB and erlotinib—Genentech/Astellas Pharma US/OSI Pharmaceuticals. In four of these, treatment was combined with multikinase inhibitors (sorafenib—Bayer and Onyx Pharmaceuticals, pazopanib—GlaxoSmithKline, or sunitinib—Pfizer). One of five patients that were treated with a combination that included erlotinib was also treated with bevacizumab (BVZ)—Genentech/Roche and chemotherapy consisting of pemetrexate—Eli Lilly and Company, and cisplatin—Bristol-Myers Squibb Company. Lastly, one patient who received erlotinib for a short period of time along with lapatinib—GlaxoSmithKline was also treated with the chemotherapy agent nab-paclitaxel—Abraxis BioScience/Celgene Corporation.

3.3. Responses and Survival

CR, SD and PD was achieved in 15.4% (N = 2), 46.2% (N = 6) and 38.4% (N = 5), respectively. Of the five patients who received treatment with PB as monotherapy, one obtained CR, two exhibited SD and two developed PD. Two patients are currently alive. One of these patients who were receiving PB monotherapy (Patient 1) experienced a remarkably prolonged OS in excess of 12.5 years after having failed three lines of chemotherapy.

Table 1. Demographics of patients with advanced malignant mesothelioma.

Characteristic		N = 13	%
Age (year)		N	%
	Median	69	
	Range	41 - 79	
Sex			
	Male	9	69
	Female	4	31
KPS (Karnofsky performance status score)			
	90	4	31
	80	2	15
	70	3	23
	60	1	8
	50	3	23
Location			
	Pleura	6	46
	Pleura and peritoneum	7	54
Prior treatment			
	No prior treatment	1	8
	Surgery only	4	31
	Surgery and RT	1	8
	Chemotherapy only	2	15
	Surgery and chemotherapy	5	38

Table 2. (a) Confirmation of diagnosis, recurrence, treatment and response; (b) Confirmation of diagnosis, progression and response—mesothelioma, newly-diagnosed.

(a)

Confirmation of Diagnosis					Treatment	Confirmation of Recurrence		Confirmation of Response to PBT			Molecular Profiling	
Pathology		Radiology		Place and Date		Assessment	Place and Date	Assessment	OSD (Months)	OST (Months)		
Patient	Place and Date	Diagnosis	Place and Date									Diagnosis
RECURRENT (PERSISTENT) AFTER CHEMOTHERAPY AND RADIATION THERAPY												
1	University hospital August 16, 2001	Malignant mesothelioma right pleural effusion positive for malignancy	University hospital CT August 8, 2001	Omental nodularities, ascites, pleural effusion	Exploratory laparoscopy, partial omentectomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy August 10, 2001					157.3 +	150.2 +	
					Paclitaxel and carboplatin x3 August 21, 2001-October 3, 2001	Regional radiology CT November 7, 2001	Recurrence					
					Topotecan to February 29, 2002							
					Thalidomide to March 12, 2002	Regional radiology March 12, 2002	Persistent disease					
				Stage at admission to BC, Stage IV pleural and peritoneal malignant mesothelioma	BC. March 19, 2002. PB			Regional radiology PET December 6, 2002 and March 14, 2003	CR			
2	University hospital May 4, 2005	Malignant mesothelioma	Regional radiology CT April 18, 2005	Mass within the left lower lobe, mediastinal lymph nodes, left pleural effusion	Decortication and pleurodesis May 5, 2005. RT × 3 days	Regional radiology CT September 21, 2005	Recurrence			13.8	9.0	
				Stage at admission to BC: Stage IV, Pleural malignant mesothelioma	BC. September 29, 2005 PB, erlotinib, imatinib, sorafenib, methotrexate.			Regional radiology CT November 25, 2005	PD			VEGF and EGFR-elevated (blood)
3	University hospital July 6, 2006	Malignant mesothelioma	Regional medical center CT June 15, 2006	Very large left pleural effusion. Large mass involving the left lateral aspects of the arch of aorta.	Pemetrexed July 18, 2006	Regional radiology CT/PET August 1, 2006	Persistent disease			40.0	27.6	

Continued

			Stage at admission to BC. Stage IV pleural malignant mesothelioma	BC-July 28, 2006. PB, erlotinib, BVZ, cisplatin, pemetrexed		Regional radiology. PET December 5, 2006 and February 6, 2007	CR	VEGF and HER-2-elevated (blood)
4	Regional hospital February 22, 2006	Mesothelioma	Regional hospital CT February 18, 2006	Asbestosis in the lungs, plaques in the mesentery	Pemetrexed and cisplatin × 8 April 2006 to April 16, 2007	Regional radiology CT April 16, 2007	Recurrence	22.9 8.0
			Stage at admission to BC. Stage IV pleural and peritoneal malignant mesothelioma	BC. May 22, 2007. PB, BVZ, erlotinib, sunitinib		Regional radiology CT July 13, 2007	PD	VEGF-elevated (blood)
5	Regional hospital March 5, 2008	Malignant mesothelioma	University hospital Chest X-ray March 31, 2008	Diffuse pleural thickening of right hemithorax	Pemetrexed and gemcitabine April 2008	Regional radiology PET/CT May 19, 2008	Recurrence	17.4 17.1
			Stage at admission to BC. Stage IV pleural and peritoneal malignant mesothelioma	BC. May 16, 2008. PB, sorafenib, dasatinib		Regional radiology PET/CT September 4, 2008	SD	Negative (blood)
6	Regional hospital June 7, 2009	Malignant mesothelioma	Regional radiology CT April 17, 2009	Large ascites	Laparoscopy and omentectomy June 24, 2009. Laparotomy and partial excision of omentum. TAHBSO right diaphragm resection, appendectomy, cholecystectomy, colon and small bowel resection July 12, 2009, intraperitoneal doxorubicin and cisplatin	Regional radiology PET/CT July 19, 2011	Recurrence	63.0 37.8 + +
			Stage at admission to BC. Stage IV pleural and peritoneal malignant mesothelioma	BC. July 18, 2011. PB, erlotinib, sunitinib, sirolimus, vorinostat, trastuzumab, pazopanib, lapatinib		Regional radiology CT/PET December 14, 2011	SD	HER-2-elevated (blood). Tissue profiling-no targets

Continued

7	Regional hospital February 14, 2010	Malignant mesothelioma	Regional radiology CT January 21, 2010	Omental mass, Large ascites	Partial peritonectomy, omentectomy, tumor debulking April 21, 2010 Cisplatin IP April 22, 2010 Cisplatin and pemetrexed IV September 10, 2010 Cisplatin and pemetrexed IV August 9, 2011	Regional radiology CT July 27, 2011	Recurrence		27.8	9.0	
				Stage at admission to BC. Stage IV peritoneal and pleural malignant mesothelioma	BC. September 9, 2011 PB			Regional radiology CT/PET February 6, 2012	SD		Negative (blood)
											SPARC Monoclonal above threshold (Caris)
8	Regional hospital April 2007	Malignant mesothelioma	Regional hospital chest x-ray March 2007	Left pleural effusion	Carboplatin and methotrexate $\times 3$ April 2007 to June 2007 Left lung pneumonectomy July 2, 2007 Carboplatin and pemetrexed August 2007 to September 2007 $\times 2$ IMRT October 2007 to November 2007 54 Gy in 27 fractions Carboplatin, pemetrexed and BVZ $\times 6$ August 2008 to November 2008 Pemetrexed $\times 4$ January 2009 to April 2009 Pemetrexed and carboplatin $\times 4$ January 2011 to April 2011	Regional radiology CT August 2008	Recurrence		77.9	16.4	
	Cancer institute July 10, 2007	Malignant mesothelioma									

Continued

					Chemo embolization × 10 April 2011 to December 2011 with gemcitabine, cisplatin, and mitomycin				
					Restarted chemo embolization March 2012 to June 2012	Regional radiology CT March 2012	Recurrence		
					Pemetrexed and BVZ × 1 August 1, 2012	Regional radiology MRI June 28, 2012	Recurrence		
				Stage at admission to BC. Stage IV pleural malignant mesothelioma	BC. August 24, 2012 PB, pazopanib, everolimus	Regional PD radiology CT January 29, 2013		VEGF- elevated (blood), BRCA1, ERCC1, TS, RR1- low, MGMT- negative, SPARC mono clonal- positive (tissue, Caris)	

Abbreviations: BC—Burzynski clinic; BRCA1—breast cancer type 1 susceptibility gene; BVZ—bevacizumab; CT—computed tomography; EGFR—epidermal growth factor receptor; ERCC1—excision repair cross-complementation group 1 enzyme; HER2—human epidermal growth factor receptor 2; IMRT—intensity-modulated radiation therapy; MGMT—O-6-methylguanine-DNA methyltransferase; MRI—magnetic resonance imaging; OSD—overall survival from diagnosis; OST—overall diagnosis from treatment start; PB—sodium phenylbutyrate; PBT—PB and other drugs; PD—progressive disease; PET—positron emission tomography; RR1—ribonucleotide reductase; RT—radiation therapy; SD—stable disease; SPARC—secreted protein acidic and rich in cysteine; TAHBSO—total abdominal hysterectomy bilateral saphingo-oophorectomy; TS—thymidylate synthase enzyme; VEGF—vascular endothelial growth factor; +—patient is still alive.

(b)

Confirmation of Diagnosis					Treatment	Confirmation of Progression	Confirmation of Response to PBT		Molecular Profiling	
Pathology		Radiology		Place and Date			Assessment	Place and Date		Assessment
Patient	Place and Date	Diagnosis	Place and Date							
NO PRIOR CHEMOTHERAPY OR RADIATION THERAPY										
9	University hospital January 20, 2000	Malignant mesothelioma	Regional radiology CT February 24, 2000	Right pleural thickening	Pleurodesis January 20, 2000			14.6	5.1	
					University hospital CT November 3, 2000	PD				
				Stage at admission to BC. Stage IV malignant pleural mesothelioma	BC. November 9, 2000. PB		University hospital January 8, 2001	PD	None	

Continued

10	Regional hospital November 28, 2001	Malignant mesothelioma	Regional hospital CT September 12, 2001	Extremely large pleural effusion. Lymph node enlargement in the right mammary lesion. Stage at admission to BC . Stage IV, malignant pleural mesothelioma	Exploratory thoracotomy November 20, 2001 BC . December 18, 2001. PB	Regional radiology CT November 16, 2001	PD	15.9	13.6	SD	None
11	Cancer institute January 2, 2002	Malignant mesothelioma	Regional radiology CT January 11, 2002	Multiple liver, peritoneal and lymph node metastases Stage at admission to BC . Stage IV malignant peritoneal and pleural mesothelioma	Laparotomy, TAH/BSO and appendectomy December 21, 2001 BC . January 23, 2002. PB	Regional radiology CT January 11, 2002	Persistent disease	141.4	140.8	PD	Negative (blood)
12	Regional hospital December 23, 2005	Malignant mesothelioma	Regional radiology CT November 2005	Large right pleural effusion. Pleural plaques Stage at admission to BC . Stage IV malignant pleural mesothelioma	None BC . January 13, 2006. PB, sunitinib, BVZ, and methotrexate	Regional radiology January 16, 2006	Persistent disease	45.2	42.9	SD	VEGF-elevated (blood)
13	Regional hospital March 21, 2011	Malignant mesothelioma	Regional radiology PET/CT December 10, 2010	Prominent right pleural effusion and ascites Stage at admission to BC . Stage IV malignant peritoneal and pleural mesothelioma	TAH/BSO, lymphadenectomy, and small bowel resection March 21, 2011 BC . May 10, 2011. PB, sorafenib, erlotinib, vorinostat, and BVZ	Regional radiology PET/CT May 11, 2011	Persistent disease	20.7	19.0	SD	VEGF-elevated (blood), KRAS—wild type, PTEN—above threshold, EGFR—not mutated

Abbreviations: **BC**—Burzynski clinic; **BVZ**—bevacizumab; **CT**—computed tomography; **EGFR**—epidermal growth factor receptor; **KRAS**—Kirsten rat sarcoma viral oncogene homolog; **MRI**—magnetic resonance imaging; **OSD**—overall survival from diagnosis; **OST**—overall diagnosis from treatment start; **PB**—sodium phenylbutyrate; **PBT**—PB and other drugs; **PD**—progressive disease; **PET**—positron emission tomography; **PTEN**—phosphatase and tensin homolog; **SD**—stable disease; **TAH/BSO**—total abdominal hysterectomy bilateral saphingo—oophorectomy; **VEGF**—vascular endothelial growth factor

Table 3. (a) Medication dose and duration of treatment until first response; (b) Medication dose and duration of treatment until first response.

(a)											
Patient	Targeted Drugs Daily Dose/Duration										
	PB	Erlotinib	Pazopanib	Sorafenib	Sunitinib	Sirolimus	Dasatinib	Vorinostat	Lapatinib	Bevacizumab	Trastuzumab
1	24 g/8.5 m										
3	15 g/4.5 m	100 mg/3 m								5 mg/kg × 6 10 mg/kg × 2	
5	12.5 g/4 m			400 mg/3.5 m			50 mg/3 m				
6	12 g/4.5 m	150 mg/0.5 m	200 mg/1 m		25 mg/4 m	1 mg/1 m		100 mg/1 m	750 mg/ 3.5 m		2 mg/kg × 2
7	12 g/5 m										
10	30 g/5 m										
12	18 g/3 m									10 mg/kg × 8	
13	12 g/3.5 m	150 mg/4 m		200 mg/7 m				100 mg/7 m		2.5 mg/kg × 6	

(b)			
Patient	Cytotoxic Chemotherapy Daily Dose/Duration		
	Pemetrexed	Cisplatin	Nab-paclitaxel
3	500 mg/m ² × 5	60 mg/m ² × 5	
6			100 mg/m ² × 2

Currently, she continues to be classified as CR and remains disease-free. The second patient who achieved CR (Patient 3) had received treatment with PB plus erlotinib, BVZ, pemetrexate, trastuzumab—Genentech, and cisplatin (cf. **Figure 1**). The remaining cases of SD were treated with a combination of PB plus erlotinib, multikinase inhibitors, and BVZ. One of these patients also received chemotherapy with nab-paclitaxel. The median OS in this evaluation was 17 months and is compared to the other studies, as described in **Table 4**. Survival was measured from the first day of administration of therapy at Burzynski Clinic until death from any cause, and time to treatment failure was likewise measured from the first day of the treatment until the date of first observation of progressive disease or death from any cause whichever came first. The distributions of survival and treatment failure were estimated by Kaplan-Meier analysis. OS compares favorably to the other studies with chemotherapy for advanced malignant mesothelioma. The Kaplan-Meier Survival Curves are presented in **Figure 2** and **Figure 3** (for all patients and for eight patients with recurrent MM, respectively). The Kaplan-Meier analysis was prepared by using the MedCalc Statistical Software version 13.3 (MedCalc Software bvba, Ostend, Belgium; 2014).

3.4. Safety and Adverse Events

Grades 3 and 4 adverse drug events (ADEs) described in **Table 5** were compared with results in other trials. The most common ADEs noted according to CTCAEv.3 were infections and diarrhea. Grade 2 ADEs are not included based upon a paucity of data in several of the comparator studies. Among the Grade 2 ADEs that were observed in this evaluation, most were nausea and vomiting, diarrhea, rash, fatigue and anorexia. These ADEs were readily reversible within a short time.

4. Discussion

For over ten years, standard first-line therapy for advanced MM includes combination chemotherapy with pemetrexate and cisplatin [3]. Additional chemotherapy regimens have been proposed including mitomycin-C plus vinblastine and cisplatin, and cisplatin plus gemcitabine, but the response rate and OS was lower compared to

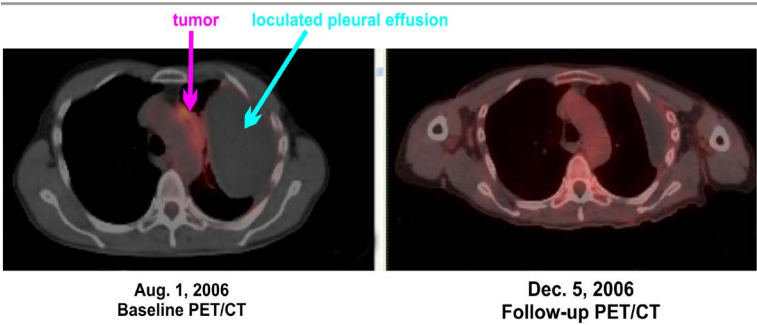


Figure 1. A complete response of pleural malignant mesothelioma; patient 3 PET/CT scan indicating a complete resolution of the tumor.

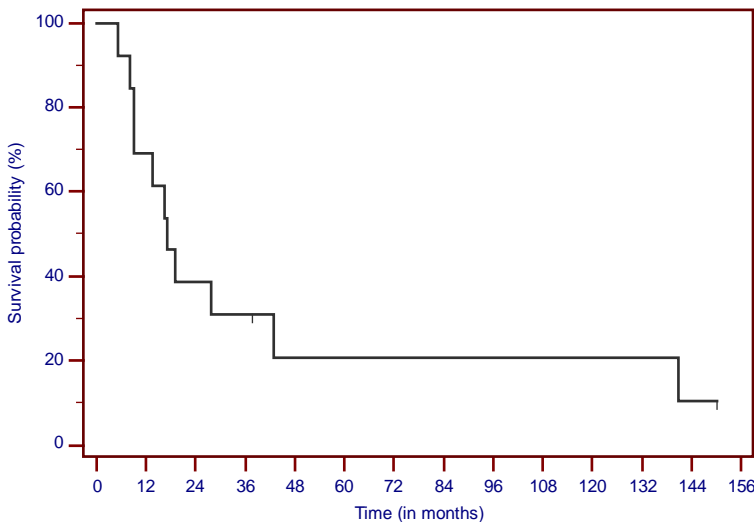


Figure 2. The Kaplan-Meier survival curve. Overall survival from the treatment start for all patients.

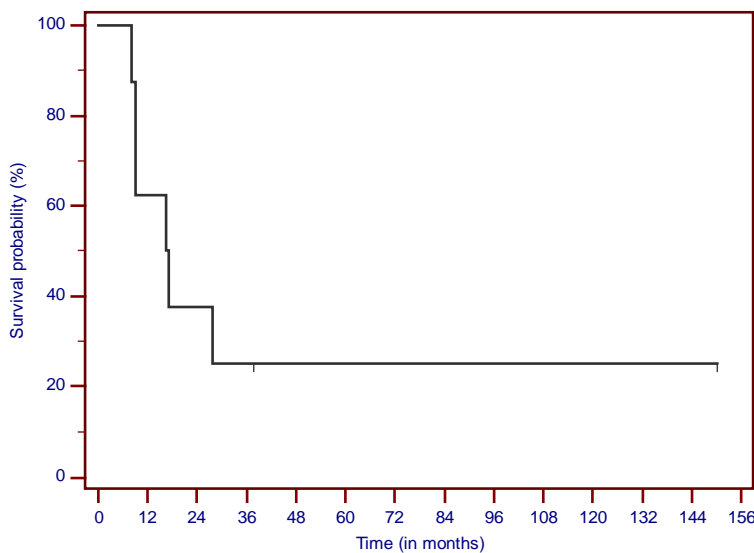


Figure 3. The Kaplan-Meier survival curve. Overall survival from the treatment start for patients with recurrent MM.

Table 4. Selected clinical studies in advanced malignant mesothelioma.

Reference	Treatment	Number of patients	Median OS (months)
Middleton <i>et al.</i> 1998 ²⁴	Mitomycin-C, vinblastine + cisplatin	39	6
Nowak <i>et al.</i> 2008 ²⁵	Cisplatin + gemcitabine	53	11.2
Vogelzang <i>et al.</i> 2003 ³	Pemetrexed + cisplatin	226	12.1
Vogelzang <i>et al.</i> 2003 ³	Cisplatin	222	9.3
Burzynski <i>et al.</i> 2014	PB + targeted combination	13	17

Abbreviations: OS—overall survival; PB—sodium phenylbutyrate.

Table 5. Incidence of adverse drug events (ADEs), grades 3 and 4 in second-line therapy of patients with advanced mesothelioma.

ADE (incidence %)		REFERENCES							
		Middleton <i>et al.</i> 1998 ²⁴		Nowak <i>et al.</i> 2008 ²⁵		Vogelzang <i>et al.</i> 2003 ³ Pemetrexed + Cisplatin 226	Vogelzang <i>et al.</i> 2003 ³ Cisplatin	Burzynski <i>et al.</i> 2014	
		Grades		Grades		Grades	Grades	Grades	
		3	4	3	4	3/4	3/4	3	4
General									
	Fatigue					10.2	8.6	7.7	
	Fever					1.3			
	Infection	5.4	-	4	-	1.3	0.5	15.4	
Hematologic									
	Hemoglobin	2.7	-	7	-	4.8			
	Leukopenia	10.8	2.7	30	6	17.7	0.9	7.7	
	Lymphopenia								
	Neutropenia			32	24	27.9	2.3	7.7	
	Thrombocytopenia	2.7	-	17	32	5.8			7.7
Gastrointestinal									
	Anorexia					2.2	0.5	7.7	
	Constipation	2.7	-						
	Diarrhea	-	-	2	-	4.4		15.4	
	Dyspepsia								
	Dehydration					4.0	0.5		
	Mucositis	-	-					7.7	
	Nausea/vomiting	8.1	-	20/17	-	14.6/13.3	6.3/3.6	-/7.7	
	Stomatitis			-	-	4			
Cardiovascular									
	Hypertension							7.7	
	Chest pain							7.7	
Neurologic									
	Paresthesia							7.7	
	Other			13	-				
Dermatologic									
	Rash					1.3			
Metabolic									
	Hypokalemia							7.7	

Toxicity criteria: WHO-Middleton; CTCAE v.2-Nowak; CTCAE V.3-Burzynski.

the pemetrexate-cisplatin combination [24] [25]. Unfortunately, after failure of first-line chemotherapy, the standard therapy has yet to be recommended [26]. Numerous targeted therapy regimens have been studied and results summarized in recent reviews [8].

After some success in treating non-small-cell carcinoma of the lung with tyrosine kinase inhibitors (TKI) gefitinib and erlotinib, use of these agents in MM appeared reasonable. Most MM tumors (68%) expressed epidermal growth factor receptor (EGFR), but contrary to lung cancer, the activating mutations of EGFR are rare in MM [27] [28]. This may explain the failure of erlotinib in phase II trials in MM used as a single agent or in combination with BVZ [29] [30]. Platelet derived growth factor (PDGF) plays an important part in MM pathogenesis, but the PDGF inhibitor imatinib failed to produce objective responses in phase II trials [31] [32]. PR was shown in 2% of SRC and PDGF inhibitor dasatinib patients, but patients developed serious toxicity [33]. Inhibition of angiogenesis was another important aspect of the activity of MM. Monoclonal antibody against vascular endothelial growth factor type 2 (VEGF2) and BVZ in combination with cisplatin and pemetrexate, used as a first-line regimen, produced a 43% response rate [34]. Multitargeted TKIs, both sunitinib and sorafenib, produced responses and a median OS of 6.7 and 10.7 months, respectively and pazopanib is currently under investigation [35] [36]. Histone deacetylase inhibitors have also been tested in clinical studies in MM. Vorinostat is most advanced of these studies and has shown PRs in an early phase I trial. Based upon these results, a phase III trial has been initiated, but was not successful [37].

The findings reported in this paper are derived from the treatment of consecutively admitted evaluable MM patients in private practice at BC. The majority of these cases had already failed standard treatment and were given little, if any, hope by their prior treating physicians. The choice of targeted agents and molecular profiling was very limited when the initial patients began treatment and for this reason, they were treated only with the HDAC inhibitor, PB.

As indicated by our studies on the effect of PB metabolites on the neoplastic genome, the PB treatment may affect over 100 genes instrumental in the promotion of malignant growth [38]. Knowing that the effect of PB is not very strong, we were surprised when one out of five patients on PB monotherapy responded with a long period of complete response and survival in excess of 12.5 years. Also of note is that this patient had disease recurrence after three lines of chemotherapy prior to PB. Another patient who obtained a CR was previously treated with pemetrexate, which was continued under our care in combination with PB, erlotinib, BVZ, and cisplatin. Two additional patients obtained SD on PB monotherapy and two other patients obtained SD as the result of a combination of PB, erlotinib plus the multikinase inhibitor, sorafenib or pazopanib. One additional patient had SD after treatment with the combination of PB, sorafenib, and dasatinib. Following is a discussion of the emerging strategy for the successful treatment of advanced malignant mesothelioma.

Carcinogenesis induced by asbestos fibers in MM is discussed in numerous articles [4]-[7]. Through a number of different mechanisms, asbestos fibers induce genetic damage and activate signaling networks in mesothelial and stromal cells and macrophages that support transformation and maintenance of the neoplastic process. RAF-MEK-ERK and PI3K-AKT pathway activation plays an important part in this process and can be triggered upstream by several RTK's including EGFR, PDGF, and metastatic oncogene receptor, (MET) [27] [28] [39]. One of the downstream targets of PI3K-AKT pathways is mammalian target of rapamycin (mTOR). Simultaneous activation of PI3K-AKT and mTOR signaling was associated with reduced survival in MM [40]. Overactive SRC kinases can also play an important part in progression of MM indicating the therapeutic application of dasatinib [41]. As described earlier, angiogenesis is an important mechanism in MM, which suggests the potential therapeutic use of BVZ and multitargeted TK's, pazopanib, or sorafenib [34]-[36]. Among the most frequently inactivated tumor suppressor genes in MM is cyclin-dependent kinase inhibitor 2A/alternative reading frame inactivation (*CDKN2A/ARF*). Loss of activity of this gene inactivates tumor suppressing pathways of *p53* and retinoblastoma. PB activates *p53* and retinoblastoma pathways through inhibition of cyclin-dependent kinases 2 and 4 (*CDK2/4*) and cyclins E and D3 [38].

MM cells frequently carry mutations of the neurofibromatosis type 2 (*NF2*) gene [42] [43]. The *NF2* product, merlin, down-regulates mTOR component 1 (mTORC1) [44] [45]. This indicates the therapeutic use of mTOR inhibitors sirolimus and everolimus [44]. In addition to genetic changes, epigenetic alterations are involved in the progression of MM [46] [47]. PB and vorinostat can address these abnormalities when added to therapeutic combinations [37] [38].

Results with personalized targeted therapy in patients treated for MM and data emanating from research on molecular mechanisms in this cancer permitted us to propose the following strategy for improving survival of

patients suffering from advanced MM (Figure 4 and Figure 5). Interruption of two crucial signaling pathways: RAF-MEK-ERK and PI3K-AKT plays a very important part in the successful treatment in MM. This can be accomplished through the combination of erlotinib, pazopanib, BVZ, dasatinib, and PB. Alternatively, pazopanib, lapatinib or trastuzumab can be used in patients with amplification of *HER-2*. Sorafenib can replace pazopanib and PB may be substituted by ANP. Another important aspect is mTOR and mTOR negative feedback loop signaling. Merlin, a product of oncogene *NF2*, plays an important part in down-regulation of mTOR, but abnormal integrin $\alpha5/\beta1$ and CD44 and mutation on *NF2* negate this action. This can be overcome by everolimus or sirolimus. Increased signaling through the pathways leads to dysregulated cell cycle, cancerous cell metabolism, inhibition of apoptosis, and maintenance and functions of CSC. These complex mechanisms can be controlled by PB, everolimus, and vorinostat or alternatively by ANP, sirolimus, and bortezomib (Figure 5).

The combination therapy with PB, selected targeted agents and/or chemotherapy appears to provide another option for improved survival in patients with advanced MM. The dose reduction of these medications in combination can help avoid serious adverse drug experiences. We are reporting the results of the treatment of a small series of patients who were consecutively admitted for the treatment at BC over the last few years. The strategy was to construct a treatment plan based on molecular profiling when this was obtainable. This resulted in some patients being treated with PB as monotherapy, which in one case contributed to excellent control of the disease (Patient 1). Results obtained in the retrospective evaluation indicate that it was possible to obtain a complete response, stabilization of the disease, and longer median OS compared to other treatment modalities for such patients. We recognize that our findings are preliminary and should be confirmed by well-designed clinical trials.

5. Conclusion

Combination chemotherapy with pemetrexed and cisplatin has become the standard-of-care for advanced and

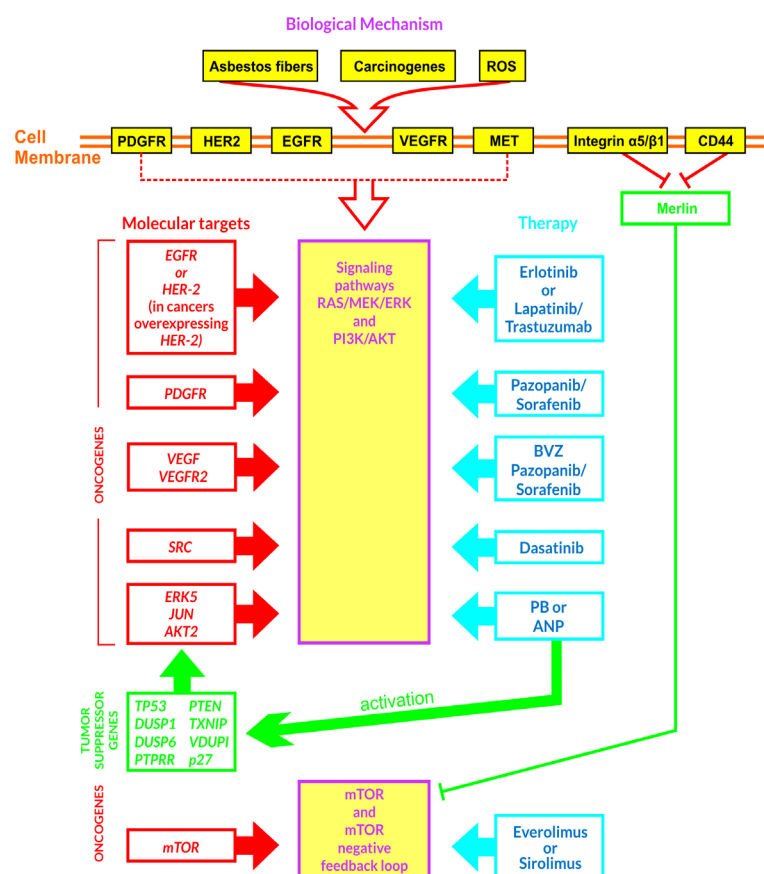


Figure 4. Interruption of signal transduction pathways by PB and targeted agents.

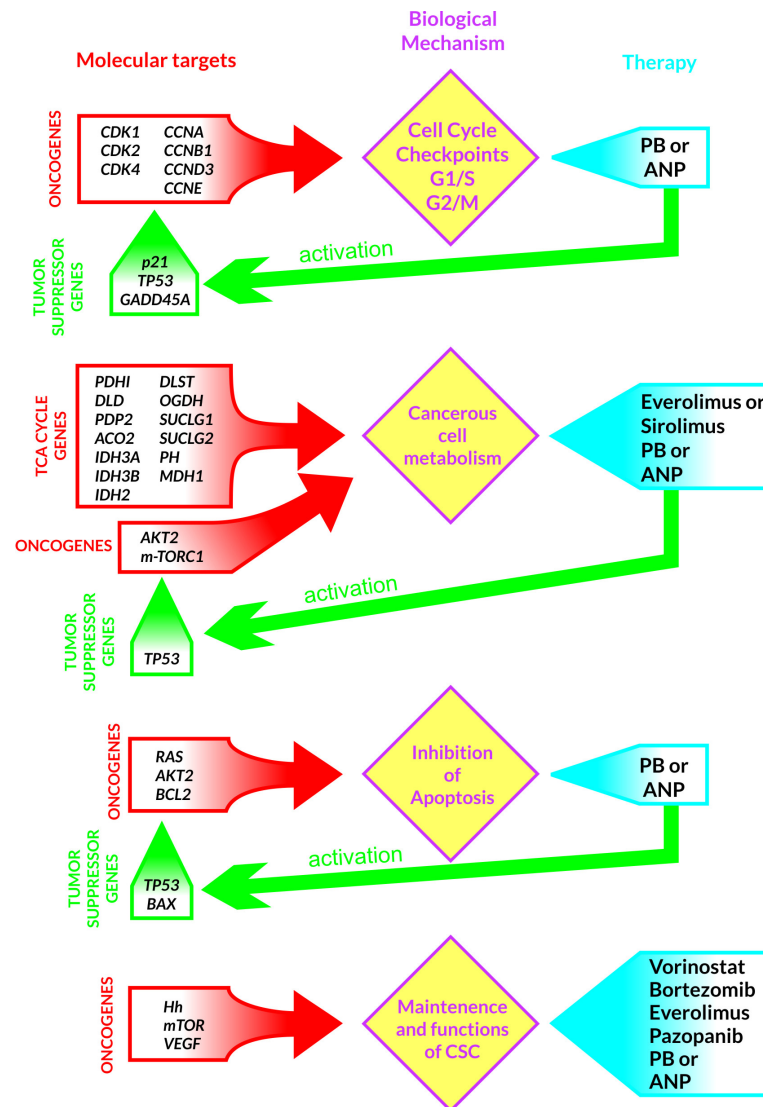


Figure 5. Inhibition of cell cycle, metabolism, maintenance and function of CSCs and promotion of apoptosis by PB and targeted agents.

unresectable pleural MM. Targeted therapy carries more promise, but only occasionally stabilizes the disease and is not yet recommended as standard treatment. This retrospective evaluation shows substantial increase of OS and tolerable toxicity compared to other available treatments. Median OS is substantially higher compared to other treatment regimens. The authors realize that these are initial findings and should be validated by a well-designed phase I/II clinical trial with PB or ANP in combination with targeted agents. We advise caution in the use of these combinations, since clinical trials have not yet been conducted to validate this approach. We anticipate that future clinical trials based on molecular profiling will help select a subgroup of cases of advanced MM and correlate the treatment response with genomic changes.

Competing Interests

All authors are employed by Burzynski Clinic. Dr. Stanislaw R. Burzynski and Dr. Gregory S. Burzynski are shareholders and directors, and Dr. Tomasz J. Janicki is the vice-president of Burzynski Research Institute, Inc. Dr. Stanislaw R. Burzynski is president of Burzynski Research Institute, Inc. Dr. Gregory S. Burzynski is vice-president of Burzynski Clinic and Dr. Sheldon Brookman is director of Pharmaceutical Development of Burzynski Clinic.

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References

- [1] Sekido, Y. (2013) Molecular Pathogenesis of Malignant Mesothelioma. *Carcinogenesis*, **34**, 1413-1419. <http://dx.doi.org/10.1093/carcin/bgt166>
- [2] Robinson, B.W.S. and Lake, R.A. (2005) Advances in Malignant Mesothelioma. *New England Journal of Medicine*, **353**, 1591-1603. <http://dx.doi.org/10.1056/NEJMra050152>
- [3] Vogelzang, N.J., Rusthoven, J.J., Symanowski, J., Denham, C., Kaukel, E., *et al.* (2003) Phase III Study of Pemetrexed in Combination with Cisplatin versus Cisplatin Alone in Patients with Malignant Pleural Mesothelioma. *Journal of Clinical Oncology*, **21**, 2636-2644. <http://dx.doi.org/10.1200/JCO.2003.11.136>
- [4] Sekido, Y. (2011) Inactivation of Merlin in Malignant Mesothelioma Cells and the Hippo Signaling Cascade Dysregulation. *Pathology International* **61**, 331-344. <http://dx.doi.org/10.1111/j.1440-1827.2011.02666.x>
- [5] Zucali, P.A., Ceresoli, G.L., De Vincenzo, F., Simonelli, M., Lorenzi, E., *et al.* (2011) Advances in the Biology of Malignant Pleural Mesothelioma. *Cancer Treatment Reviews*, **37**, 543-558. <http://dx.doi.org/10.1016/j.ctrv.2011.01.001>
- [6] Jean, D., Daubriac, J., Le Pimpec-Barthes, F., Galateau-Salle, F. and Jaurand, M.-C. (2012) Molecular Changes in Mesothelioma with an Impact on Prognosis and Treatment. *Archives of Pathology & Laboratory Medicine*, **136**, 277-293. <http://dx.doi.org/10.5858/arpa.2011-0215-RA>
- [7] Mossman, B.T., Shukla, A., Heintz, N.H., Verschraegen, C.F., Thomas, A. and Hassan, R. (2013) New Insights into Understanding the Mechanisms, Pathogenesis, and Management of Malignant Mesotheliomas. *American Journal of Pathology*, **182**, 1065-1077. <http://dx.doi.org/10.1016/j.ajpath.2012.12.028>
- [8] Greillier, L., Marco, S. and Barlesi, F. (2011) Targeted Therapies in Malignant Pleural Mesothelioma: A Review of Clinical Studies. *Anti-Cancer Drugs*, **22**, 199-205. <http://dx.doi.org/10.1097/CAD.0b013e328341ccdd>
- [9] Burzynski, S.R. (1969) Investigations on Unknown Ninhydrin-Reacting Substances in Human Blood Serum. I. Attempts at Identification of Three Such Substances. *Experientia*, **25**, 490-491. <http://dx.doi.org/10.1007/BF01900774>
- [10] Burzynski, S.R. (1976) Antineoplastons: Biochemical Defense against Cancer. *Physiological Chemistry and Physics*, **8**, 275-279.
- [11] Burzynski, S.R. (1986) Antineoplastons—History of the Research (I). *Drugs under Experimental and Clinical Research*, **12**, 1-9.
- [12] Burzynski, S.R. (1986) Synthetic Antineoplastons and Analogs. *Drugs of the Future*, **11**, 679-688.
- [13] Burzynski, S.R. (2004) The Present State of Antineoplaston Research (1). *Integrative Cancer Therapies*, **3**, 47-58. <http://dx.doi.org/10.1177/1534735403261964>
- [14] Burzynski, S.R. (2006) Treatments for Astrocytic Tumors in Children: Current and Emerging Strategies. *Pediatric Drugs*, **8**, 167-168. <http://dx.doi.org/10.2165/00148581-200608030-00003>
- [15] Burzynski, S.R., Janicki, T.J., Burzynski, G.S. and Marszalek, A. (2014) The Response and Survival of Children with Recurrent Diffuse Intrinsic Pontine Glioma Based on Phase II Study of Antineoplaston A10 and AS2-1 in Patients with Brainstem Glioma. *Childs Nervous System*, Published Online. <http://dx.doi.org/10.1007/s00381-014-2401-z>
- [16] Burzynski, S.R., Janicki, T.J., Burzynski, G.S. and Marszalek, A. (2014) A Phase II Study of Antineoplastons A10 and AS2-1 in Children with High-Grade Glioma. Final Report and Review of Recent Trials. *Journal of Cancer Therapy*, **5**, 565-577. <http://dx.doi.org/10.4236/jct.2014.56065>
- [17] Burzynski, S.R., Janicki, T.J. and Burzynski, G.S. (2014) A Phase II Study of Antineoplastons A10 and AS2-1 in Adult Patients with Recurrent Glioblastoma Multiforme. Final Report (Protocol BT-21). *Journal of Cancer Therapy*, **5**, 946-956. <http://dx.doi.org/10.4236/jct.2014.510100>
- [18] Burzynski, S.R., Janicki, T.J., Burzynski, G.S., Marszalek, A. and Brookman, S. (2014) A Phase II Study of Antineoplastons A10 and AS2-1 in Children with Recurrent, Refractory or Progressive Primary Brain Tumors. Final Report (Protocol BT-22). *Journal of Cancer Therapy*, **5**, 977-988. <http://dx.doi.org/10.4236/jct.2014.510102>
- [19] Brusilow, S.W., Danney, M., Waber, L.J., Batshaw, M., Burton, B., *et al.* (1984) Treatment of Episodic Hyperammonemia in Children with Inborn Errors of Urea Synthesis. *New England Journal of Medicine*, **310**, 1630-1634. <http://dx.doi.org/10.1056/NEJM198406213102503>
- [20] Phuphanich, S., Baker, S.D., Grossman, S.A., Carson, K.A., Gilbert, M.R., *et al.* (2005) Oral Sodium Phenylbutyrate in Patients with Recurrent Malignant Gliomas: A Dose Escalation and Pharmacologic Study. *Neuro-Oncology*, **7**, 177-

182. <http://dx.doi.org/10.1215/S1152851704000183>
- [21] Burzynski, S.R. and Patil, S. (2014) The Effect of Antineoplastons A10 and AS2-1 and Metabolites of Sodium Phenylbutyrate on Gene Expression in Glioblastoma Multiforme. *Journal of Cancer Therapy*, **5**, 929-945. <http://dx.doi.org/10.4236/jct.2014.510099>
- [22] Burzynski, S.R., Burzynski, G.S. and Janicki, T.J. (2014) Recurrent Glioblastoma Multiforme, a Strategy for Long-Term Survival. *Journal Cancer Therapy*, **5**, 957-976. <http://dx.doi.org/10.4236/jct.2014.510101>
- [23] Burzynski, S.R., Janicki, T.J., Burzynski, G.S. and Brookman, S. (2014) Preliminary Findings on the Use of Targeted Therapy in Combination with Sodium Phenylbutyrate in Recurrent Advanced Pancreatic Cancer—A Potential Strategy for Improved Survival. *Journal Cancer Therapy*, in Press.
- [24] Middleton, G.W., Smith, I.E., O'Brien, M.E.R., Norton, A., Hickish, T., Priest, K., *et al.* (1998) Good Symptom Relief with Palliative MVP (Mitomycin-C, Vinblastine and Cisplatin) Chemotherapy in Malignant Mesothelioma. *Annals of Oncology*, **9**, 269-273. <http://dx.doi.org/10.1023/A:1008236010868>
- [25] Nowak, A.K., Byrne, M.J., Williamson, R., Ryan, G., Segal, A., Fielding, D., *et al.* (2002) A Multicentre Phase II Study of Cisplatin and Gemcitabine for Malignant Mesothelioma. *British Journal of Cancer*, **87**, 491-496. <http://dx.doi.org/10.1023/A:1008236010868>
- [26] Scherpereel, A., Astoul, P., Baas, P., Berghmans, T., Clayson, H., De Vuyst, P., *et al.* (2010) Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the Management of Malignant Pleural Mesothelioma. *European Respiratory Journal*, **35**, 479-495. <http://dx.doi.org/10.1183/09031936.00063109>
- [27] Dazzi, H., Hasleton, P.S., Thatcher, N., Wilkes, S., Swindell, R. and Chatterjee, A.K. (1990) Malignant Pleural Mesothelioma and Epidermal Growth Factor Receptor (EGFR). Relationship of EGFR with Histology and Survival Using Fixed Paraffin Embedded Tissue and the F4, Monoclonal Antibody. *British Journal of Cancer*, **61**, 924-926. <http://dx.doi.org/10.1038/bjc.1990.207>
- [28] Cortese, J.F., Gowda, A.L., Wali, A., Eliason, J.F., Pass, H.I. and Everson, R.B. (2006) Common EGFR Mutations Conferring Sensitivity to Gefitinib in Lung Adenocarcinoma Are Not Prevalent in Human Malignant Mesothelioma. *International Journal of Cancer*, **118**, 521-522.
- [29] Garland, L.L., Rankin, C., Gandara, D.R., Rivkin, S.E., Scott, K.M., Nagle, R.B., *et al.* (2007) Phase II Study of Erlotinib in Patients with Malignant Pleural Mesothelioma: A Southwest Oncology Group Study. *Journal of Clinical Oncology*, **25**, 2406-2413. <http://dx.doi.org/10.1200/JCO.2006.09.7634>
- [30] Jackman, D.M., Kindler, H.L., Yeap, B.Y., Fidias, P., Salgia, R., Lucca, J., *et al.* (2008) Erlotinib plus Bevacizumab in Previously Treated Patients with Malignant Pleural Mesothelioma. *Cancer*, **113**, 808-814. <http://dx.doi.org/10.1002/cncr.23617>
- [31] Mathy, A., Baas, P., Dalesio, O. and Van Zandwijk, N. (2005) Limited Efficacy of Imatinib Mesylate in Malignant Mesothelioma: A Phase II Trial. *Lung Cancer*, **50**, 83-86. <http://dx.doi.org/10.1016/j.lungcan.2005.04.010>
- [32] Porta, C., Mutti, L. and Tassi, G. (2007) Negative Results of an Italian Group for Mesothelioma (g.I.Me.) Pilot Study of Single-Agent Imatinib Mesylate in Malignant Pleural Mesothelioma. *Cancer Chemotherapy and Pharmacology*, **59**, 149-150. <http://dx.doi.org/10.1007/s00280-006-0243-4>
- [33] Dudek, A., Pang, H., Kratzke, R.A., Otterson, G.A., Vokes, E.E. and Kindler, H.L. (2010) CALGB 30601: A Phase II Study of Dasatinib (D) in Patients (pts) with Previously Treated Malignant Mesothelioma (MM) (Abstract 7037). *Journal of Clinical Oncology*, **28**.
- [34] Dowell, J.E., Lan, C., Gerber, D., Hughes, R., Yan, J., Xie, Y., *et al.* (2009) Pemetrexed, Cisplatin and Bevacizumab in Patients with Advanced Malignant Mesothelioma: A Multi-Center Phase II Trial (Abstract b1.2). *Journal of Thoracic Oncology*, **4**, S319.
- [35] Nowak, A.K., Millward, M., Francis, R.J., Hasani, A., Van Der Schaaf, A.A., Seguard, T., *et al.* (2010) Final Results of a Phase II Study of Sunitinib as Second-Line Therapy in Malignant Pleural Mesothelioma (MPM) (Abstract 7036). *Journal of Clinical Oncology*, **28**.
- [36] Janne, P.A., Wang, X.F., Krug, L.M., Hodgson, L., Vokes, E.E. and Kindler, H.L. (2007) Sorafenib in Malignant Mesothelioma (MM): A Phase II Trial of the Cancer and Leukemia Group B (CALGB 30307) (Abstract 7707). *Journal of Clinical Oncology*, **25**.
- [37] Kelly, W.K., O'Connor, O.A., Krug, L.M., Chiao, J.H., Heaney, M., Curley, T., *et al.* (2005) Phase I Study of an Oral Histone Deacetylase Inhibitor, Suberoylanilide Hydroxamic Acid, in Patients with Advanced Cancer. *Journal of Clinical Oncology*, **23**, 3923-3931. <http://dx.doi.org/10.1200/JCO.2005.14.167>
- [38] Burzynski, S.R., Burzynski, M.D. and Patil, S. (2014) The Effect of Antineoplastons A10 and AS2-1 and Metabolites of Sodium Phenylbutyrate on Gene Expression in Glioblastoma Multiforme. *Journal of Cancer Therapy*, **5**, 929-945. <http://dx.doi.org/10.4236/jct.2014.510099>

- [39] Brevet, M., Shimizu, S., Bott, M.J., Shukla, N., Zhou, Q., Olshen, A.B., *et al.* (2011) Coactivation of Receptor Tyrosine Kinases in Malignant Mesothelioma as a Rationale for Combination Targeted Therapy. *Journal of Thoracic Oncology*, **6**, 864-874. <http://dx.doi.org/10.1097/JTO.0b013e318215a07d>
- [40] Varghese, S., Chen, Z., Bartlett, D.L., Pingpank, J.F., Libutti, S.K., Steinberg, S.M., *et al.* (2011) Activation of the Phosphoinositide-3-Kinase and Mammalian Target of Rapamycin Signaling Pathways Are Associated with Shortened Survival in Patients with Malignant Peritoneal Mesothelioma. *Cancer*, **117**, 361-371. <http://dx.doi.org/10.1002/cncr.25555>
- [41] Menges, C.W., Chen, Y., Mossman, B.T., Chernoff, J., Yeung, A.T. and Testa, J.R. (2010) A Phosphotyrosine Proteomic Screen Identifies Multiple Tyrosine Kinase Signaling Pathways Aberrantly Activated in Malignant Mesothelioma. *Genes and Cancer*, **1**, 493-505. <http://dx.doi.org/10.1177/1947601910375273>
- [42] Thurneysen, C., Opitz, I., Kurtz, S., Weder, W., Stahel, R.A. and Felley-Bosco, E. (2009) Functional Inactivation of NF2/Merlin in Human Mesothelioma. *Lung Cancer*, **64**, 140-147. <http://dx.doi.org/10.1016/j.lungcan.2008.08.014>
- [43] Stamenkovic, I. and Yu, Q. (2010) Merlin, a “Magic” Linker between the Extracellular Cues and Intracellular Signaling Pathways That Regulate Cell Motility, Proliferation and Survival. *Current Protein and Peptide Science*, **11**, 471-484. <http://dx.doi.org/10.2174/138920310791824011>
- [44] Lopez-Lago, M.A., Okada, T., Murillo, M.M., Socci, N. and Giancotti, F.G. (2009) Loss of the Tumor Suppressor Gene *NF2*, Encoding Merlin, Constitutively Activates Integrin-Dependent mTORC1 Signaling. *Molecular and Cellular Biology*, **29**, 4235-4249. <http://dx.doi.org/10.1128/MCB.01578-08>
- [45] James, M.F., Han, S., Polizzano, C., Plotkin, S.R., Manning, B.D., Stemmer-Rachamimov, A.O., *et al.* (2009) NF2/Merlin Is a Novel Negative Regulator of mTOR Complex 1 and Activation of mTORC1 Is Associated with Meningioma and Schwannoma Growth. *Molecular and Cellular Biology*, **29**, 4250-4261. <http://dx.doi.org/10.1128/MCB.01581-08>
- [46] Christensen, B.C., Houseman, E.A., Godleski, J.J., Marsit, C.J., Longacker, J.L., Roelofs, C.R., *et al.* (2009) Epigenetic Profiles Distinguish Pleural Mesothelioma from Normal Pleura and Predict Lung Asbestos Burden and Clinical Outcome. *Cancer Research*, **69**, 227-234. <http://dx.doi.org/10.1158/0008-5472.CAN-08-2586>
- [47] Goto, Y., Shinjo, K., Kondo, Y., Shen, L., Toyota, M., Suzuki, H., *et al.* (2009) Epigenetic Profiles Distinguish Malignant Pleural Mesothelioma from Lung Adenocarcinoma. *Cancer Research*, **69**, 9073-9082. <http://dx.doi.org/10.1158/0008-5472.CAN-09-1595>

Abbreviations

ADEs—adverse drug events
ANP—antineoplastons
BC—Burzynski Clinic
BRCA1—breast cancer type 1 susceptibility gene
BVZ—bevacizumab
CDK2/4—cyclin-dependent kinases 2 and 4
CDKN2A/ARF—cyclin-dependent kinase inhibitor 2A/alternative reading frame inactivation
CR—complete response
CT—computerized tomography
CTCAEv.3—common toxicity criteria for adverse events version 3
EGFR—epidermal growth factor receptor
EKG—electrocardiogram
ERCC1—excision repair cross-complementation group 1 enzyme
GBM—glioblastoma multiforme
HDAC—histone deacetylase
HER2—human epidermal growth factor receptor 2
IMRT—intensity-modulated radiation therapy
KPS—Karnofsky performance status
KRAS—Kirsten rat sarcoma viral oncogene homolog
LPD—largest perpendicular diameters
m—month(s)
MET—metastatic oncogene receptor
MGMT—O-6-methylguanine-DNA methyltransferase
MM—malignant mesothelioma
MRI—magnetic resonance imaging
mTOR—mammalian target of rapamycin
NF2—neurofibromatosis type 2
OS—overall survival
OSD—overall survival from diagnosis
OST—overall survival from treatment start
PB—sodium phenylbutyrate
PBT—PB and other drugs
PD—progressive disease
PDGF—platelet derived growth factor
PET—positron emission tomography
PG—phenylacetylglutamine
PN—phenylacetate
PR—partial response
PTEN—phosphatase and tensin homolog
RR1—ribonucleotide reductase
RT—radiation therapy
SD—stable disease
SPARC—secreted protein acidic and rich in cysteine
TAH/BSO—total abdominal hysterectomy bilateral saphingo-oophorectomy
TKI—tyrosine kinase inhibitors
TS—thymidylate synthase enzyme
VEGF—vascular endothelial growth factor
VEGF2—vascular endothelial growth factor type 2
+—patient is still alive

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