Journal of Cancer Therapy, 2014, 5, 1072-1091
Published Online October 2014 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2014.512113

Scientific Research

Preliminary Findings on the Use of Targeted Therapy in Combination with Sodium Phenylbutyrate in Recurrent Advanced Pancreatic Cancer—A Potential Strategy for Improved Survival

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Received 13 August 2014; revised 10 September 2014; accepted 5 October 2014

Abstract

Metastatic pancreatic cancer carries an estimated five-year survival rate of only 2%. Gemcitabine-based chemotherapy remains a first-line standard-of-care treatment for elderly patients with advanced pancreatic cancer. Combination chemotherapy FOLFIRINOX offers better results, but it is not recommended for the older patient population due to substantial toxicity. Standard-of-care second-line treatment is not yet established and is used in approximately 30% of patients since performance status is too low to consider further therapy. Targeted therapies with a single agent and in combinations have been tested in numerous clinical trials, but except for the combination of gemcitabine and erlotinib, have not yet proven efficacy. Here, we present preliminary findings of improved overall survival (OS) using a combination of sodium phenylbutyrate with various chemotherapeutic and targeted agents in stage IV A and B pancreatic cancer patients who failed at least one line of chemotherapy. The results suggest a strategy of simultaneous interruption of signal transmission involving multiple pathways in the second-line treatment that are believed to interfere with cell cycle, cancer cell metabolism, autophagy and maintenance of cancer stem cells and promote apoptosis. In this group of patients, median OS was higher compared to other second-line therapies (10.5 months compared to between 2.9 and 6.5 months in other studies, and in the best supportive care group, 2.3 months). Given the understanding that our findings are preliminary, we propose the validation of our initial results using a well-designed Phase I/II trial in recurrent advanced pancreatic cancer.

Keywords

Pancreatic Cancer, Pancreatic Cancer Survival, Personalized Targeted Therapy, Sodium

How to cite this paper: 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 of Cancer Therapy*, **5**, 1072-1091. http://dx.doi.org/10.4236/jct.2014.512113

Phenylbutyrate

1. Introduction

The American Cancer Society (ACS Cancer Statistics 2014) estimates that 39,590 patients will die from the pancreatic cancer and the number of new cases in the United States will increase to 46,420 [1]. Projected deaths from pancreatic cancer will surpass breast, prostate, and colorectal cancers and will become the second leading cause of cancer-related death by 2030 [2]. Furthermore, for patients with metastatic pancreatic cancer, the five-year survival rate is only 2% and is surpassed only by glioblastoma multiforme (GBM) [3]-[5]. Gemcitabine was introduced as a first-line standard-of-care therapy for advanced pancreatic cancer in 1997 [6]. Since, a number of phase II and III trials in advanced pancreatic cancer have been conducted, but significant improvement in survival has not been demonstrated, except for FOLFIRINOX and a combination of nab-paclitaxel with gemcitabine [7]-[27]. Despite these discouraging statistics, there is optimism with the rapid development of molecular targeted approaches for the treatment of this almost uniformly deadly disease [28] [29].

Standard-of-care second-line treatment in pancreatic cancer is not well-established and is only used in approximately 30% of patients, as positive treatment outcome in such patients is considered too low for further therapy [30].

Sodium phenylbutyrate (PB), the salt of an aromatic fatty acid is used to treat urea cycle disorders [31]. The drug, a histone deacetylase (HDAC) inhibitor is being explored in combination with cytotoxics and other novel drugs. Derived from its HDAC activity, PB is being investigated for use as a potential differentiation-inducing agent in malignant glioma, acute promyelocytic leukemia and many other disorders [32]-[34]. Bortezomib and the HDAC inhibitors vorinostat, valproic acid and PB showed synergistic cell killing activity of GBM stem-like cells [35]. In the liver, PB is metabolized to phenylacetylglutaminate (PG) and phenylacetate (PN). The data from the study of the effect of PG and PN on the GBM genome have shown that these compounds affect approximately 100 genes in the cancer genome [36].

This article provides a brief description of results of treatment of 14 cases of advanced pancreatic cancer patients who had failed first-line therapy and discusses a strategy for personalized targeted therapy for advanced recurrent pancreatic cancer.

2. Patients and Methods

Subjects were diagnosed with metastatic or locally advanced pancreatic ductal adenocarcinoma (PDA), and after recurrence received their treatment in private practice at Burzynski Clinic (BC) in Houston, TX. Fourteen patients were assessed who had failed at least one standard treatment modality, were diagnosed with Stage IVA or IVB pancreatic cancer and received treatment between November 28, 2007 and August 26, 2013. They all represent consecutively treated patients who could be evaluated for response.

Pathology and radiological evaluations prior to and during treatment were performed by institutions not associated with BC, whereas laboratory tests were performed by both outside laboratories and the laboratory at BC. Tests included standard blood and urine evaluations, as well as the determination of tumor and genomic markers. Molecular profiling on tumor tissue was performed by Caris Life Sciences, Phoenix, Arizona. Prior to treatment, all patients were provided details of the treatment and were required to sign an informed consent document. Treatment plans were formulated based on molecular profiling of patients and included the use of PB in combination with targeted and/or chemotherapeutic agents.

After an initial two to four weeks of treatment performed on an outpatient basis under the authority of the BC, treatment was continued under the care of a local oncologist. Prior to treatment initiation, a computerized tomography (CT) scan with and without contrast and in some instances positron emission tomography (PET) scans were performed. The products of the two largest perpendicular diameters (LPD) of measurable lesions were calculated and totaled for each subject, which provided a baseline for determining response to treatment. Pretreatment evaluations also included Karnofsky Performance Status (KPS), vital signs, clinical disease status, demographics, medical history and current medications, physical examination, and electrocardiogram (EKG). Toxicity was evaluated according to the Common Toxicity Criteria for Adverse Events v.3 (CTCAEv.3). Poten-

tial responses to treatment included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR required the disappearance of all lesions confirmed at the end of four weeks, PR required 50% or higher decrease of the LPD of measurable lesions, PD was determined when there was over 25% increase of the lesions or new lesions, and SD was classified as the status between PR and PD. The duration of each response was measured from the date that the criteria of the outcome were first met and until the date that PD was first documented. In the case of SD, response duration was measured from the time that therapy commenced.

3. Patient Demographics

Patient characteristics are described in **Table 1**.

Among 14 pancreatic cancer patients, 12 cases were categorized as Stage IVB and two cases were Stage IVA. All patients had recurrent disease, with 50% failing one line of chemotherapy, 36% two lines, and 14% three or more lines of chemotherapy. The majority of patients (64.3%) had multiple liver metastases. Data confirming diagnosis, treatment, recurrence, and response to treatment received are shown in **Table 2**.

Table 1. Demographics of patients with recurrent adenocarcinoma of the pancreas, stage IVA and B.

Characteristic	N = 14	%
Age (year)		%
Median	54.5	
Range	40.5 - 84	
Sex		
Male	6	42.9
Female	8	57.1
KPS (Karnofsky performance status score)		
100	1	7.1
90	4	28.6
80	4	28.6
70	3	21.4
50	2	14.3
Pancreatic tumor location		
Head	5	35.7
Tail	3	21.4
Multicentric (head and body—4, head, body and tail—1, body and tail—1)	6	42.9
Level of CA 19-9		
Normal	2	14.3
Elevated	12	85.7
Metastatic sites in addition to the pancreas		
Lymph nodes	8	57.1
Liver	9	64.3
Lungs	4	28.6
Peritoneal	3	21.4
Spleen	1	7.1
Intestine	1	7.1
Ovary	1	7.1
Biliary stent	6	42.9
Whipple procedure	4	28.6
Chemotherapy		
1-line	7	50
2-line	5	35.7
3-line and more	2	14.3
Radiation therapy	2	14.3

Stage IVA—2 patients, IVB—12 patients.

Table 2. Confirmation of diagnosis, treatment, recurrence and response.

Patient	Confirmation of diagnosis: Pathology: Place and date	Pathology: Diagnosis	Radiology: Place and date	Radiology: Diagnosis	Treatment	Confirmation of recurrence: Place and date	Confirmation of recurrence: Assessment	Confirmation of response to PBT: Place and date	Assessment	OSD (days)	OST (days)	Molecular profiling
1	Regional medical center February 20, 2007	APMD	Regional radiology CT February 1, 2007	Large pancreatic mass (head and body)	Gemcitabine and oxaliplatin February-July 12, 2007	Regional medical center CT June 19, 2007	Recurrence					
				Multiple liver, spleen, and lymph nodes metastases	5-fluorouracil + leucovorin July 15-November 1, 2007	Regional medical center CT November 6, 2007	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. November 28, 2007. PB, erlotinib, capecitabine, BVZ			Regional radiology PET/CT February 19, 2008	SD	853	572	VEGF-elevated (blood)
2	Cancer institute October 29, 2008	APMD	Regional hospital CT September 5, 2008	Mass in pancreatic head	Whipple procedure September 9, 2008							
				Infiltration of portal and superior mesenteric vein. Multiple liver, lung, and lymph node metastases.	Gemcitabine x3 November-December 2009	Cancer institute CT February 22, 2009	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. March 12, 2009 PB, sorafenib, rapamycin, erlotinib, vorinostat, BVZ. Discontinued sorafenib, vorinostat, erlotinib, BVZ May 27, 2009 capecitabine, oxaliplatin			Regional radiology PET/CT June 8, 2009	PR	486	302	VEGF-elevated (blood)
3	Regional hospital May 13, 2008	APMD	Regional radiology CT March 26, 2008	Mass in body and tail of pancreas	Whipple procedure, splenectomy, wedge resections of the stomach May 9, 2008							

Continued

				Multiple liver and lymph node metastases.	RT and capecitabine June-August 2008	Regional radiology CT August 11, 2008	Recurrence					
					Gemcitabine x3 September 5, 2008-October 24, 2008	Regional radiology CT October 24, 2008	Recurrence					
					FOLFOX and hyperthermia January-July 2009	Regional radiology CT October 10, 2009	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. December 1, 2009 PB, sorafenib, riluzole, sirolimus, erlotinib to May 15, 2010. PB, sirolimus, riluzole, lapatinib to May 28, 2010			Regional radiology CT January 25, 2010	PD	775	204	Normal (blood)
4	Regional medical center October 5, 2009	APO	Regional medical center CT September 17, 2009	Mass in pancreatic tail. Multiple liver metastases	Gemcitabine and erlotinib October 20, 2009-December 29, 2009	Regional radiology CT January 26, 2010	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. January 25, 2010 PB, sorafenib, BVZ, capecitabine			Regional radiology CT April 16, 2010	PD	234	122	VEGF-elevated (blood)
5	Cancer institute May 6, 2008	APMD	Cancer institute CT May 2, 2008	Mass in the pancreatic head and body	Stent placement March 2008. Whipple procedure May 6, 2008							
	Cancer institute March 12, 2010	APO		Lung and lymph node metastases.	Gemcitabine and oxaliplatin x6 June 12, 2008-September 2, 2008							
					Gemcitabine and RT 99Gy September 15, 2008-October 28, 2008	Cancer institute CT November 9, 2009	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. April 15, 2010 PB, sorafenib, BVZ, trastuzumab, lapatinib			Regional radiology CT July 26, 2010	PD	1027	318	VEGF and HER-2-elevated (blood)
6	Cancer institute February 15, 2010	APO	Cancer institute CT May 2, 2009	Mass in the pancreatic head, body and tail	Stent placement May 2, 2009. Gemcitabine and TH302 (clinical trial) March 8, 2010-February 28, 2011	Regional radiology CT February 21, 2011	Recurrence					

Continued

				Stage at admission to BC: IVA, recurrent	BC. March 24, 2011 PB, pazopanib, everolimus, vorinostat, BVZ			Regional radiology PET/CT July 22, 2011	PD	819	417	VEGF-elevated (blood)
7	Regional medical center May 11, 2011	APO	Regional medical center CT May 6, 2011	Mass in pancreatic tail, metastatic disease to the liver	Gemcitabine May 19, 2011	Regional radiology PET/CT July 20, 2011	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. July 20, 2011 PB, erlotinib, pazopanib, trastuzumab, everolimus, nab-paclitaxel			Regional radiology CT October 17, 2011	SD	258	186	EGFR1, HER-2, and VEGF elevated (blood)
												PDGFRA /B-over-expressed (tissue-Caris)
8	Regional medical center September 22, 2010	APPD	Regional radiology CT September 9, 2010	Mass in the head and body of the pancreas	Subtotal distal pancreatectomy and splenectomy September 16, 2010							
				Metastases to the peritoneum, ovary, fallopian tube, bowel and lymph nodes. Multiple liver metastases.	Gemcitabine October 2010 to March 2011 x15							
					Gemcitabine and capecitabine to April 2011	Regional radiology CT April 2011	Recurrence					
					Laparotomy, omentectomy, resection of small intestine tumor, left salpingo-oophorectomy April 28, 2011	Regional radiology CT May 26, 2011	Recurrence					
					FOLFOX x3 May 2011 to July 2011	Regional radiology CT July 13, 2011	Recurrence					

Continued

				Stage at admission to BC: IVB, recurrent	BC. July 29, 2011 PB, sunitinib, dasatinib, irinotecan			Regional radiology CT December 17, 2011	PD	503	187	VEGF-elevated (blood), EPHA2, c-Kit, PDGFRA /B-over-expressed (tissue-Caris)
9	Regional hospital June 20, 2011	APO	Regional medical center CT March 7, 2011	Tumor in the uncinate process of the pancreas	Stent placement November 30, 2010							
					Sphincterotomy and papillotomy March 2, 2011							
			Regional medical center CT May 5, 2011	Liver and lymph node metastases.	Gemcitabine April to May 2011	Regional radiology CT September 2, 2011	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. August 30, 2011 PB, erlotinib, oxaliplatin, capecitabine			Regional radiology CT January 9, 2012	SD	509	333	Negative (blood and tissue-Caris)
10	Regional hospital June 21, 2011	APMD	Regional hospital CT June 7, 2011	Mass in the pancreatic head and body, multiple metastases to the lungs and lymph nodes	Phase I study: gemcitabine and SOM230 June-August 2011	Regional radiology PET/CT August 30, 2011	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. August 27, 2011 PB, pazopanib, erlotinib, dasatinib, gemcitabine			Regional radiology CT December 5, 2011	SD	492	425	VEGF-elevated (blood) Negative, (tissue-Caris)
11	Regional hospital May 31, 2011	APMD	Regional radiology CT June 6, 2011	Mass in the pancreatic head	Stent placement March 18, 2011							
					Aborted Whipple procedure. Palliative bypass April 28, 2011							
					FOLFIRINOX x3 June 20, 2011- September 27, 2011	Regional radiology CT September 27, 2011	Persistent disease					

Continued

				Stage at admission to BC: IVA, persistent	BC. October 7, 2011 PB, gemcitabine			Regional radiology CT January 5, 2012	SD	431	228	Non-conclusive (tissue-Caris)
12	Regional hospital February 1, 2010	APMD	Regional radiology CT January 2010	Mass in the pancreatic head	Stent placement January 18, 2010, Whipple procedure February 1, 2010							
				Lung, lymph node, and mesenteric metastases	Clinical trial gemcitabine plus vaccination	Regional radiology CT May 13, 2011	Recurrence					
					RT August 2010							
					RT and capecitabine to September 2011	Regional radiology PET/CT November 2, 2011	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. November 4, 2011 PB, nab-paclitaxel x5 gemcitabine x1			Regional radiology PET/CT January 25, 2012	SD	872	231	Negative (blood and tissue-Caris)
13	Regional hospital September 27, 2011	APMD	Regional radiology CT September 25, 2011	Mass in the pancreatic head	Stent placement September 25, 2011, FOLFIRINOX x3 October 9, 2011-November 20, 2011							
				Liver and peritoneal metastases		Regional radiology CT December 13, 2011	Recurrence					
					Stent placement Capecitabine December 11, 2011							
					Gemcitabine and docetaxel, capecitabine January 2, 2012-January 18, 2012	Regional radiology CT March 4, 2012	Recurrence					
				Stage at admission to BC: IVB, recurrent	BC. February 29, 2012 PB, pazopanib-discontinued (financial concerns, duration-1 day). Everolimus-discontinued (duration-2 days), erlotinib, gemcitabine, nab-paclitaxel			Regional radiology CT July 3, 2012	PD	304	148	Negative (blood), RRM1, SPARC, Poly-clonal-Negative Monoclonal above the threshold (tissue-Caris)

Continued

14	Regional hospital January 15, 2013	APO	Regional radiology January 21, 2013	Mass in the pancreatic tail	FOLFIRINOX x12 February 8, 2013-August 4, 2013									
				Liver metastases		Regional radiology CT August 6, 2013	Recurrence							
				Stage at admission to BC: IVB, recurrent	BC. August 26, 2013 PB, sirolimus, sorafenib, BVZ			Regional radiology CT February 4, 2014	PR	445	216	Negative (blood), PTEN-negative, PIK3CA-wild type (tissue-Caris)		

Abbreviations: **APMD**—adenocarcinoma of the pancreas moderately differentiated; **APO**—adenocarcinoma of pancreatic origin; **APPD**—adenocarcinoma of the pancreas poorly differentiated; **BC**—Burzynski Clinic; **BVZ**—bevacizumab; **c-Kit**—type of receptor tyrosine kinase and a type of tumor marker (CD117 and stem cell factor receptor); **CT**—computed tomography; **EGFR**—epidermal growth factor receptor; **EPHA2**—ephrin type-A receptor 2 (protein-coding gene); **HER-2**—human epidermal growth factor receptor 2; **OSD**—overall survival from diagnosis; **OST**—overall diagnosis from treatment start, **PB**-sodium phenylbutyrate; **PBT**—PB and other drugs; **PD**—progressive disease; **PDGFRA**—alpha-type platelet-derived growth factor receptor; **PDGFRB**—beta-type platelet-derived growth factor receptor; **PET**—positron emission tomography; **PIK3CA**—phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha gene; **PTEN**—phosphatase and tensin homolog; **RRM1**—ribonucleotide reductase M1; **RT**—radiation therapy; **SD**—stable disease; **SPARC**—secreted protein, acidic, cysteine-rich (osteonectin); **VEGF**—vascular endothelial growth factor.

4. Treatment

Details of dosing and duration of drug administration for patients treated with combinations containing PB and erlotinib are described in **Table 3(a)** and **Table 3(b)**.

Seven patients received combination treatment with PB, erlotinib, and additional chemotherapeutic and targeted agents. Two patients received treatment with the single agent PB, without any additional targeted agents, whereas one patient each was given capecitabine and oxaliplatin in addition to PB and erlotinib. Patient 11 who received monotherapy with PB returned to the UK, where he was treated with gemcitabine and radiation therapy under the care of a British physician. Patient 12 was treated with PB, gemcitabine and nab-paclitaxel (**Table 3(a)** and **Table 3(b)**). Three out of seven patients with PB + erlotinib received additionally pazopanib, and another two patients were given sorafenib and sirolimus. One other patient received PB and pazopanib with everolimus, vorinostat, BVZ, and capecitabine. The single patient treated with PB and sorafenib was also given bevacizumab and vorinostat and another patient had riluzole added to the treatment. Among those patients treated with pazopanib, one received additional trastuzumab and another dasatinib and gemcitabine. In the group of patients who did not receive erlotinib, two were treated with sorafenib and bevacizumab; one was given additional capecitabine and another trastuzumab and lapatinib. A further patient was treated with PB, pazopanib, everolimus, bevacizumab, and vorinostat, while another with PB, sunitinib, dasatinib and irinotecan. Patients treated with pazopanib, sorafenib, sunitinib, dasatinib, and vorinostat received doses that were 50% - 80% lower as compared to their respective maximum recommended dose, thereby minimizing possible combined toxicity of these drugs.

5. Responses and Survival

PR (14.3%) was observed in two patients, SD (42.9%) was determined in six patients, whereas six patients developed PD. PR and SD were observed in five patients who were treated with combinations containing PB and erlotinib, two patients who were treated with PB and chemotherapy (gemcitabine or gemcitabine/nab-paclitaxel) and one patient who was given PB, sorafenib, sirolimus and BVZ. However, one patient treated with PB, erlotinib, gemcitabine, and nab-paclitaxel and another patient treated with a combination of PB, erlotinib, sorafenib, and sirolimus developed PD. The data are not sufficient to draw definite conclusions, but the results suggest that a successful treatment combination could consist of PB, erlotinib, pazopanib, or sorafenib in combination with a mammalian target of rapamycin (mTOR) inhibitor (sirolimus or everolimus), SRC inhibitor (dasatinib) or human epidermal growth factor receptor 2 (HER-2) inhibitor (trastuzumab) for patients with amplification of

Table 3. Medication dose and duration of treatment of targeted drugs until first response.

(a)

Patient	Targeted Drugs Daily Dose/Duration								
	PB	Erlotinib	Pazopanib	Sorafenib	Sirolimus	Everolimus	Vorinostat	Bevacizumab	Trastuzumab
1	18 g/2.5m	150 mg/2.5m						5mg/kg q2w/2.5m	
2	12 g/3m	75 mg/3m		200 mg/3m	1 mg/2m		100 mg/3m	5 mg/kg q2w/2m	
7	12 g/3m	150 mg/3m	400 mg /3m			10 mg/2m			2 mg/kg/w/3m
9	12 g/4m	150 mg/1m							
10	9 g/3m	150 mg/1.5m	200 mg/2.5m						
11	8 g/5m								
12	12 g/3m								
14	12 g/2.5m			200 mg/0.5m	1 mg/2.5m			10 mg/kg q2w/5m	

Abbreviations: m—month(s), **w**—week(s).

(b)

Patient	Cytotoxic Chemotherapy Daily Dose/Duration			
	Capecitabine	Gemcitabine	Oxaliplatin	Nab-paclitaxel
2	1000 mg/2w		100 mg/m^2/ × 2	
7				100 mg/m^2, 3 weeks on, 1 week off /2m
9	3000 mg/1m		130 mg/m^2 × 2	
10		700 mg/m^2/ × 3		
11		Standard Regimen		
12		800 mg/m^2/ × 1		100 mg/m^2/ × 3

Abbreviations: m—month(s), **w**—week(s).

HER-2. The selection of the targeted and chemotherapy agents was supported by molecular profiling based on increased levels of extracellular domains of HER-2, vascular endothelial growth factor (VEGF), and epidermal growth factor receptor (EGFR) and tissue profiling performed by Caris Life Sciences (through increased expression of platelet derived growth factor receptor type A or B (PDGFRA/B) and negative phosphatase and tensin homolog (PTEN). Conversely to not impressive response data, the OS compares favorably to selected clinical studies in advanced pancreatic cancer treated with second-line therapy (**Table 4**) [37]-[43].

Median OS of 10.5 months appears significantly higher than in other studies (**Figure 1**).

6. Safety and Adverse Events

Grade 2 and 3 adverse drug events (ADEs) are described in **Table 5** and are compared with other clinical trials. The most common ADEs observed were hematologic toxicities that included leukopenia and thrombocytopenia, and gastrointestinal effects that involved nausea, vomiting, dyspepsia, and diarrhea. Hypertension, Grade 2 occurred in 7% of patients and increased transaminases and alkaline phosphatase each in 7% of patients. ADEs were easily reversible within a short time.

7. Discussion

This paper describes an emerging strategy for more successful treatment of advanced pancreatic cancer. The development of PDA depends on sequential involvement of numerous signaling pathways comparable to normal development. The pattern of mutations is complex and may involve as many as 12 different signaling pathways [44]. Most PDAs are associated with somatic mutations of Kirsten rat sarcoma viral oncogene homolog (*KRAS*), cyclin-dependent kinase inhibitor (*INK4A*), tumor suppressor gene p53 (*TP53*), and Smoothened (*SMO*) and *MAD* protein family member 4 (*SMAD4*) [45]-[49]. The most common is, however, the *KRAS* mutation found in over 95% of cases. It results in the synthesis of protein that is continuously active and transduces signal to downstream effectors [50]. Differing to findings with colon or lung cancers in which activation of EGFR receptors is mutually exclusive with *KRAS* mutation, EGFR signaling is essential for *KRAS* driven pancreatic cancer [51]. The EGFR inhibitor, erlotinib, is approved for treatment of metastatic pancreatic cancer [15]. The overex-

Table 4. Selected clinical studies in advanced pancreatic cancer with second-line therapy.

Reference	Treatment	Number of patients	OS median (months)
Milella *et al.* 2004[37]	5-FU + celecoxib	17	3.5
Cantore *et al.* 2004[38]	Irinotecan + oxaliplatin	30	5.9
Androulakis *et al.* 2005[39]	Oxaliplatin	18	3.5
Demols *et al.* 2006[40]	Gemcitabine + oxaliplatin	33	6.0
Ignatiadis *et al.* 2006[41]	Docetaxel + gefitinib	26	2.9
Boeck *et al.* 2007[42]	Pemetrexed	52	4.6
Kulke *et al.* 2007[16]	Capecitabine + erlotinib	30	6.5
Xiong *et al.* 2008[18]	Oxaliplatin + capecitabine	39	5.7
Wolpin *et al.* 2009[43]	Everolimus	33	4.5
Pelzer *et al.* 2011[30]	Oxaliplatin, folinic acid + 5-FU	23	4.8
Pelzer *et al.* 2011[30]	BSC	23	2.3
Burzynski *et al.* 2014	PB + a targeted combination	14	10.5

Abbreviations: BSC—best supportive care, **FU**—fluorouracil, **OS**—overall survival, **PB**—sodium phenylbutyrate.

Table 5. Incidence of adverse drug events (ADEs), grades 2, 3 and 4 in second-line therapies for patients with advanced pancreatic cancer.

ADE (incidence %)	References														
	Cantore[38]			Ignatiadis[41]			Boeck[42]			Kulke[16]		Pelzer[30]		Burzynski	
	Grades			Grades			Grades			Grades		Grades		Grades	
	2	3	4	2	3	4	2	3	4	2	3	2	3	2	3
General															
Fatigue	10			19	4		4			37	3				
Fever	13			4											
Infection							6	6							
Hematologic															
Hemoglobin	23			11			10	2	2	13		48			
Leukopenia	10	3	3				11	10	6	3				7	14
Neutropenia	3	3		11	19	15	4	13	4	3	7				7
Thrombocytopenia	3	3					6	4	2			9		7	14
Gastrointestinal															
Abdominal pain							6	4							
Anorexia										17					
Constipation										3					
Diarrhea	37	3		8	8		10	4		37	17	4	9	7	
Dysgeusia										7					
Dyspepsia														7	
Mucositis							4			20	10				
Nausea/vomiting	47			4			6			13	10	17	4	21	
Cardiovascular															
Hypertension														7	
Edema										3					
Neurologic															
Paresthesia	6	6										4			
Pruritus										7					
Dermatologic															
Hand-foot syndrome										17	13				
Rash				11			4	2		17	13				

Continued

	Alopecia	3					
Metabolic							
	AP				3		7
	ALT				3	7	
	AST			3			7
	GGT						7
	Bilirubin			7	3		
	Creatinine		2				
	Hypokalemia		2				

Toxicity criteria: WHO-Cantore; NCI-Ignatiadis; CTC-Boeck; CTCAE v.3-Kulke; CTCAE V.2-Pelzer.

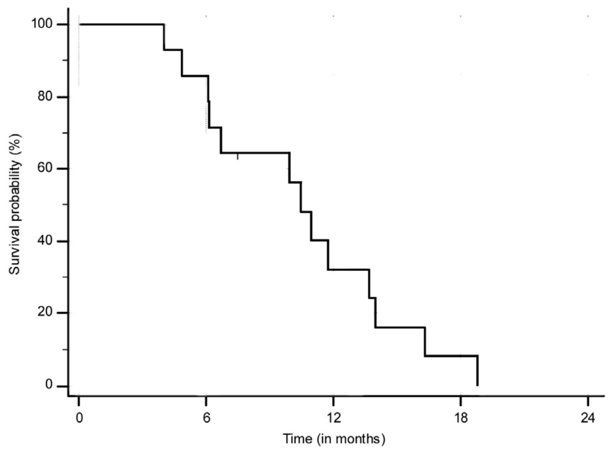

Figure 1. The Kaplan-Meier survival curve. Overall survival from the treatment start.

pression of the HER-2 receptor contributes to the worst prognosis of pancreatic cancer [52]. This finding was further explored in experiments with pancreatic cancer xenografts, where treatment with monoclonal antibodies against EGFR and HER-2, cetuximab and trastuzumab exhibited antitumor effects [53]. Direct inhibition of *KRAS* has failed to produce responses in pancreatic cancer thus far, and for this reason, attention has shifted to the interruption of signal transduction in RAF-MEK-ERK, and PI3K-AKT pathways [54]. *RAF* inhibition antagonizes the inhibition of *MEK* and should be avoided. On the other hand, *MEK* inhibition leads to the activation of *AKT* and for this reason, both of these should be inhibited simultaneously [55]. *mTOR* inhibitors, sirolimus and everolimus, activate phosphorylation of AKT [55]. Erlotinib and dasatinib can help to down-regulate phosphorylation of AKT [56]. Sorafenib plus lapatinib and trastuzumab decrease phosphorylation of AKT in cancers expressing *HER-2* [57]. Dasatinib also decreases phosphorylation of ERK and mitogen-activated protein kinase (MAPK) [56]. Genomic studies of PDA revealed that frequently there is simultaneous activation of KRAS-RAF-MEK-ERK and PI3K-AKT pathways [58]. In preclinical studies, combination treatment of dual *PI*3*K-mTOR* inhibitor, NVP-BEZ235, and HDAC inhibitor, panobinostat, effectively blocked the growth of PDA by interfering with signaling of both pathways [59].

Angiogenesis plays a critical role in tumor growth and promotion of metastasis of pancreatic cancer. High expression of VEGF is associated with poor prognosis and liver metastasis in pancreatic cancer which provides rationale for therapeutic use of monoclonal antibodies and tyrosine kinase inhibitors (TKI) against VEGF [60].

In cells of PDA, there is frequent deregulation of embryonic signaling pathways, Hedgehog (Hh) and Wnt-β-catenin [61]. According to recent studies, Hh signaling is activated in the microenvironment through the autocrine mechanism, but alone is not sufficient to drive the development of PDA [62] [63]. This may explain the failure of the *Smo* inhibitor vismodegib in clinical trials in pancreatic cancer [64]. On the other hand, *Smo* activates Hh targeted genes and its inhibition by vismodegib was instrumental in the successful treatment of medulloblastoma [65]. Contrary to medulloblastoma and colon cancer in which upregulated Hh or Wnt can provide the

starting event, abnormal Hh or Wnt signaling alone is not sufficient to trigger the development of PDA [65]. Increased activity of *KRAS* differentiates acinar pancreatic cells into ductal epithelial neoplastic cells. Hh and Wnt signaling, which was initially at a low level, is then reactivated and helps PDA maintenance [61]. The other signal transduction pathways, Notch and TGFβ, modulate Wnt-β-catenin signaling [66] [67]. Hh signaling also supports the maintenance of cancerous stem cells (CSC), which is helped by autocrine VEGF and integrin signaling [68] [69]. Pazopanib and sorafenib block signaling of vascular endothelial growth factor receptor 2 (VEGFR2) and metastasis oncogene (*MET*) and affect the maintenance of CSCs [70].

Additional approaches to control PDA may include interference in cell cycle, cancer cell metabolism, angiogenesis and autophagy, and inhibition of apoptosis. We effectively explored these mechanisms in the treatment of recurrent GBM by using PB in combination with targeted agents [4].

Based on research on molecular mechanisms in PDA and our experience with personalized targeted therapy, we propose the following strategy for improving survival of patients with advanced pancreatic cancer who failed standard chemotherapy including gemcitabine, 5-fluorouracil, oxaliplatin, irinotecan, docetaxel, and nab-paclitaxel. This strategy is illustrated in **Figure 2** and **Figure 3** and consists of simultaneous interference in signal transmission in multiple pathways: 1) KRAS-MEK-ERK, 2) PI3K-AKT, 3) angiogenesis, and 4) mTOR and mTOR negative feedback loop. It is also necessary to interfere in cell cycle, cancer cell metabolism, autophagy, and to promote apoptosis, and block maintenance and function of CSCs.

KRAS-MEK-ERK and PI3K-AKT signaling can be disrupted with a combination of erlotinib, everolimus, vorinostat and PB. *MEK* inhibitors, including trametinib can be considered instead of vorinostat. In cases that overexpress HER-2, trastuzumab or lapatinib can be considered instead of erlotinib. Dasatinib can be also be used in patients who do not tolerate erlotinib.

Angiogenesis can be blocked through application of pazopanib or bevacizumab. PB and other agents can interfere in cell cycle, cancer cell metabolism, and autophagy and can promote apoptosis, whose mechanism is explained in a recent publication [4]. Treatment can be wide-ranging and may include a combination of as many as five or six medications. Based on our experience, this would necessitate a reduction of doses by 50% to 75%, as described in **Table 3(a)** and **Table 3(b)**. With appropriate dose reduction, treatment appears reasonably well-tolerated. Additional targeted agents may replace some medications based on molecular profiling.

After reduction of the bulk of the disease, the emphasis may be switched to the destruction of CSCs. Hh, mTOR, and VEGF inhibitors can be considered for this purpose, which would include vismodegib, everolimus, pazopanib, vorinostat, bortezomib, and PB [35].

Treatment with PB in combination with targeted agents and chemotherapy appears to provide another option for improved outcomes in patients who failed first-line chemotherapy for advanced pancreatic cancer. With proper dosage reduction, the treatment appears tolerable and provides a longer OS than other available treatments. With the accessibility of new targeted drugs and with advanced genomic analyses, options for more successful treatment outcomes are a distinct possibility. Though the findings with PB in combination with targeted agents and/or chemotherapy are preliminary, we suggest the validation of our initial findings using a well-designed Phase I/II trial in recurrent advanced pancreatic cancer. We further propose using this principle in a Phase I/II trial for the treatment of PDA in patients who have failed first-line therapy with antineoplastons (ANP), which share ingredients with metabolites of PB and that have shown promise in the treatment of various brain tumors, including recurrent GBM [4] [36] [71]-[77]. ANP can offer the advantage of higher anticancer activity since they are available in intravenous dosage form [36].

8. Conclusion

An established standard-of-care for recurrent, advanced pancreatic cancer is not yet available. Despite numerous clinical trials, progress in this area has been very modest. The use of targeted agents as a single treatment or in combination with chemotherapy did not provide substantial survival benefit. The results reported by us are based on a small series of patients who were consecutively admitted for treatment at BC during the last few years. This is a retrospective evaluation that shows substantial increase of OS and tolerable toxicity compared to the other available treatments. The choice of targeted agents was very limited when this treatment began. Molecular profiling was in its infancy, providing only limited data that were helpful for the design of treatment plans. This group included only evaluable patients, which is typical for a retrospective assessment, but the results of some other studies reported in **Table 4** were also limited to evaluable patients. The authors realize that these are

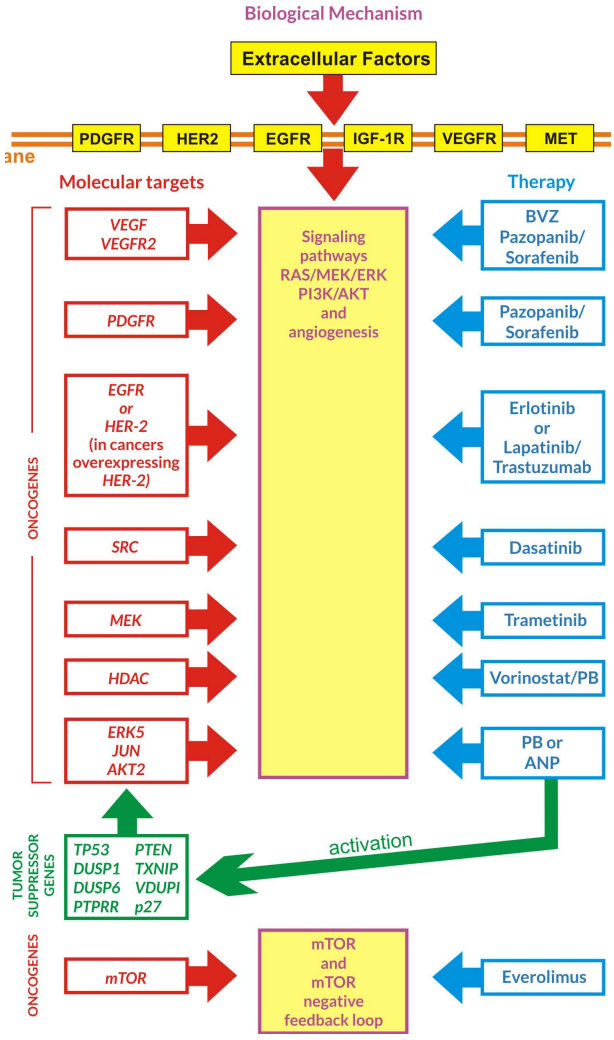

Figure 2. Interruption of signal transduction by PB and targeted agents. Abbreviations: AKT—protein kinase B; AKT2—protein kinase B 2; ANP—antineoplastons; BVZ—bevacizumab; DUSP1—dual specificity protein phosphatase 1; DUSP6—dual specificity protein phosphatase 6; EGFR—epidermal growth factor receptor; ERK—extracellular signal regulated kinase; ERK5—extracellular-signal-regulated kinase 5; HDAC—histone deacetylase; HER-2—human epidermal growth factor receptor 2; IGF-1R—insulin-like growth factor 1 receptor; JUN—proto-oncogene; MEK—MAP kinase; MET—mesenchymal epithelial transition factor; mTOR—mammalian targets of rapamycin; p27-kinase inhibitor protein p27, PB—sodium phenylbutyrate; PDGFR—platelet derived growth factor receptor; PI3K—phosphoinositide 3 kinase; PTEN—phosphatase and tensin homolog; PTPRR—protein phosphatase R; RAS—rat sarcoma gene protein family; SRC—Rous sarcoma inducing oncogene; TP53—tumor protein p53; TXNIP—thioredoxin-interacting protein; VDUP1—vitamin D3 up-regulated protein; VEGF—vascular endothelial growth factor; VEGFR—vascular endothelial growth factor receptor; VEGFR2—vascular endothelial growth factor receptor 2.

preliminary results and should be validated by well-designed phase I/II clinical trials with ANP or PB in combination with targeted agents. Caution should be exercised when combining these agents, since no clinical trials have been conducted yet with such combinations. We propose that future clinical trials should include molecular profiling to help select the subgroups of cases of pancreatic cancer and correlate genomic changes with responses.

9. Competing Interests

All authors are employed by Burzynski Clinic. BC was established in 1977 to treat advanced cases of cancer in a private practice setting and to conduct clinical trials. Between November 2007 and August 2013, BC employed

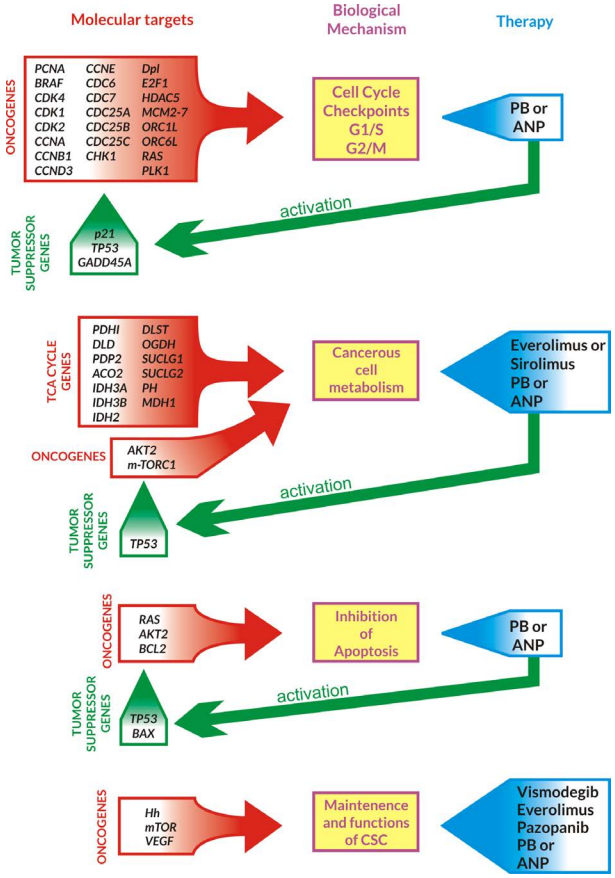

Figure 3. Inhibition of cell cycle, metabolism, maintenance and function of CSC and promotion apoptosis by PB and targeted agents. Abbreviations: ACO2—aconitase; AKT2—protein kinase B 2; ANP—antineoplastons; BAX—BCL-2 associated X protein; BCL2—B cell lymphoma 2; BRAF—serine/threonine protein kinase B-raf; CCNA—cyclin A; CCNB1—G2/mitotic-specific cyclin B1 protein-coding gene; CCND3—gene for cyclin D3; CCNE—G1/S-specific cyclin E1 gene; CDC6—cell division control protein 6; CDC7—cell division cycle 7-related protein kinase; CDC25A—M-phase inducer phosphatase 1; CDC25B—M-phase inducer phosphatase 2; CDC25C—M-phase inducer phosphatase 3; CDK1—cyclin-dependent kinase 1; CDK2—cyclin-dependent kinase 2; CDK4—cyclin-dependent kinase 4; CHK1—checkpoint kinase 1; CSC—cancerous stem cells; DLD—dihydrolipoamide dehydrogenase; DLST—dihydrolipoamide S-succinyl-transferase; Dpl—transcription factor Dpl; E2F1—E2F family transcription factor 1; GADD45A—DNA-damage-inducible protein; HDAC5—histone deacetylase 5; Hh—Hedgehog gene; IDH2—isocitrate dehydrogenases 2; IDH3A—isocitrate dehydrogenases 3 alpha; IDH3B—isocitrate dehydrogenases 3 beta; MCM2-7—mini-chromosome maintenance 2-7 helicase complex; MDH1—malate dehydrogenate; mTOR—mammalian targets of rapamycin; m-TORC1—mammalian target of rapamycin complex 1; OGDH—oxoglutarate (alpha-ketoglutarate) dehydrogenase; ORC1L—origin recognition complex subunit 1-like; ORC6L—origin recognition complex subunit 6-like; p21—p21 ras protein; PB—sodium phenylbutyrate; PCNA—proliferating cell nuclear antigen; PDHI—pyruvate dehydrogenase 1; PDP2—pyruvate dehydrogenase phosphatase catalytic subunit 2; PH—gene controlling acidity; PLK1—polo-like kinase; RAS—Rous sarcoma gene protein family; SUCLG1—succinyl-CoA ligase 1; SUCLG2—succinyl-CoA ligase 2; TP53—tumor protein p53; VEGF—vascular endothelial growth factor.

three oncologists/hematologists, three internists, and a family practitioner in addition to medical support staff. 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.

Acknowledgements

The authors express their appreciation to the additional physicians involved in the care of the patients: Drs.

Zanhua Yi, Alejandro Marquis, Robert Weaver, Sheryl Acelar, Lourdes De Leon, and Mohammad Khan. Preparation of the manuscript was provided by Carolyn Powers and Maria Corzo. Biostatistical analysis was provided by Rho, Inc.

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