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DANIEL KEIZMAN *, Moshe Frenkel, Avivit Peer, Eli Rosenbaum, David Sarid, Ilan Leibovitch, Roy Mano, Ofer Yossepowitch, Ido Wolf, Ravit Geva, David Margel, Keren Rouvinov, Anat Stern, Hadas Dresler, Igal Kushnir, Isaac Eliaz

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Modified Citrus Pectin Treatment in Non-Metastatic Biochemically Relapsed Prostate Cancer: Long-Term Results of a Prospective Phase II Study

Daniel Keizman [1,*], Moshe Frenkel [2,*], Avivit Peer [2], Eli Rosenbaum [3], David Sarid [1], Ilan Leibovitch [4], Roy Mano [5], Ofer Yossepowitch [5], Ido Wolf [1], Ravit Geva [1], David Margel [6], Keren Rouvinov [7], Anat Stern [8], Hadas Dresler [9], Igal Kushnir [10,††] and Isaac Eliaz [8,††]

[1] Department of Oncology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[2] Department of Oncology, Rambam Medical Center, Haifa, Israel
[3] Department of Oncology, Rabin Medical Center, Petah-Tikva, Israel
[4] Department of Urology, Meir Medical Center, Kfar-Saba, Israel
[5] Department of Urology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
[6] Department of Urology, Rabin Medical Center, Petah-Tikva, Israel
[7] Department of Oncology, Soroka Medical Center, Beer – Sheva, Israel
[8] Amitabha Medical Clinic and Healing Center, Santa Rosa, CA, USA
[9] Department of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel
[10] Department of Oncology, Meir Medical Center, Kfar-Saba, Israel, affiliated to the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
*†† These authors contributed equally to this work.
* Correspondence: Daniel Keizman, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel; danielkeizman@gmail.com

Abstract: The optimal therapy for patients with non-metastatic biochemically relapsed prostate cancer (BRPC-M0) after local therapy is elusive. Thus, the evaluation of new non-toxic compounds in BRPC-M0 patients is warranted. PectaSol® modified citrus pectin (P-MCP) is a food supplement generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) and is a competitive inhibitor of galectin-3 protein, involved in cancer pathogenesis. P-MCP treatment of BRPC-M0 patients for 6 months led to a 75% prostate-specific antigen doubling time (PSADT) improvement. To determine the longer-term effects of P-MCP we investigated an additional 12 months of treatment (phase II) with oral P-MCP at 4.8 grams X 3/day in patients with no disease progression in the previous 6 months. Of the 46 patients that entered the second phase, 7 patients withdrew consent and continued therapy independently, and 39 received another 12 months of therapy. After a total of 18 months P-MCP treatment, 62% (n=24) had a decreased/stable PSA, 90% (n=35) had improved PSADT, and 85% (n=33) had a durable long-term response, with a decreased/stable PSA, and/or improvement of PSADT, and negative scans. No patient had grade 3/4 toxicity. In conclusion, P-MCP may have long term durable efficacy, and is safe, in BRPC-M0.

Keywords: modified citrus pectin; non-metastatic biochemically relapsed prostate cancer

1. Introduction

Globally, prostate cancer is the second most common solid tumor [1] and cause of cancer-related death in men from Westernized countries [2]. Though its etiology needs further elucidation [3], with an age-standardized incidence rate of 31 per 100,000 [1] and approximately 1.5 million new cases reported in 2020 [1,4], prostate cancer incidence is increasing worldwide [4,5] and presents a significant economic burden [6]. With the rapid evolution of treatment options [7], however, and with changes in screening protocols [8], prostate cancer-related mortality patterns have stabilized [5]. While primary treatments for localized prostate cancer, including radical prostatectomy and

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radiation therapy, and androgen suppression therapy (AST) for advanced cases [9], are often initially effective, subsequent cancers typically develop [2]. Within 10 years of treatment, approximately 20–50% of patients will experience biochemical relapse prostate cancer (BRPC) [9–11], diagnosed through rising prostate-specific antigen (PSA) [12], which is a glycoprotein found exclusively in healthy and neoplastic prostate cells [13]. While patients with BRPC often remain asymptomatic and free of clinical evidence of disease for years [14], BRPC and corresponding PSA doubling time (PSADT) [15] following localized treatment [10] can be predictive of future metastases and mortality [10,13,16]. The typically prolonged disease natural history of BRPC [17], however, means that elevating PSA or shortening PSADT do not indicate an imminent mortality risk [17]. With multiple definitions reported in the literature [18], including patients experiencing variable risk factors and treatment efficacies [19], definitive BRPC treatment remain poorly established [10,20], and is often reliant on intuitive care [21].

The variation within the BRPC patient group, inconsistency in definitions within the literature and the protracted manifestation of the disease, present challenges to establishing effective patient management and salvage treatments [17]. While there are various localized therapy-specific protocols in place for BRPC [10,11], such as defined by The Phoenix Criteria [22], some treatment options are controversial [17,21]. Premature treatment with androgen deprivation treatment (ADT) in response to elevating PSA, for example, has uncertain benefits to survival potential though may negatively impact quality of life and increase the chances of comorbidities developing [10]. For example, ADT is associated with increased risk of cardiovascular (CV) adverse events [23,24], insulin resistance, dyslipidemia, obesity, and bone health disorders [14,25]. Characteristics of the BRPC patient population confound the identification of potential treatments [21]. BRPC's prolonged natural history [17] has led to a lack of validated endpoints that can be measured within conventional clinical trial time frames. Dynamic PSA measurements [26], including PSADT [27], have been proposed and used as surrogate endpoints, both as predictive and stratification factors for clinical disease progression [17,28] and an increasing PSADT is sought to determine the efficacy of active compounds in clinical studies [24,29,30].

There is an urgent need to discover and evaluate new treatments for effective BRPC management [2,10,11,31]. Natural compounds have been extensively explored for potential anti-prostate cancer activities e.g., [32–35] through selective targeting of key molecules or signaling pathways, such as androgen signaling [36] that might help reduce cancer as dysregulated cell proliferation [37]. Many such compounds modulate key signaling pathways affecting cell proliferation [33,38] and immune responses [39], and are plant-derived. The polyphenols curcumin, tannic acid and flavonoids [33,40], for example, have antioxidant and anti-inflammatory effects [41], and complex polysaccharides, like modified citrus pectin (MCP) [42], have anti-inflammatory, antitumor, and antimetastatic activities [42–44].

Pectins comprise carbohydrate-soluble fiber found in plant cell walls and are indigestible to humans in their unmodified form [43]. Modified citrus pectin (MCP), with a shorter polysaccharide units, are water soluble [43] and have demonstrated significant anticancer activity [42,43,45,46], potentially by disrupting tumor-promoting signaling by binding galactose-containing side chains to the carbohydrate recognition domains of galectins [42,47,48]. Galectins comprise an evolutionarily conserved family of endogenous glycan-binding proteins and they play multifunctional roles in tumor progression [42] through modulating and recalibrating inter and intracellular signaling [49]. Galectins affect cellular responses, including cell aggregation, growth, differentiation, apoptosis and proliferation [42,49,50] and may promote immune evasion of cancer cells [51]. Galectins, including Galectin1 (GAL1) and GAL3, have therefore been explored as potentially effective therapeutic targets for cancer patients [42,52,53].

PectaSol® Modified Citrus Pectin (P-MCP; EcoNugenics Inc, Santa Rosa, CA, USA) is a commercially available polysaccharide and is a Galectin-3 (Gal-3) inhibitor, binding to the Galectin-3 carbohydrate recognition domain [42,47]. Derived from the pith of citrus fruit peels and classified by the US-FDA as generally regarded as safe (GRAS), P-MCP is a food supplement with

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demonstrated cytotoxicity towards, and inhibition of, cancer cells [43,54], including prostate cancer cells [34,45,46] suggesting its viability in delaying disease progression [42].

In clinical trials, P-MCP delivered as oral therapy to BRPC patients has had a demonstrable effect on prostate-specific antigen (PSA) levels, leading to a lengthening of PSADT in the majority of participants and suggesting a reduction in tumor progression [34,45]. An increase in PSADT with P-MCP oral therapy at both six [34] and 12 [45] months, suggests the benefits may be perpetuated with extended treatment. Using the participant cohort of Keizman et al. 2021, which had demonstrated benefits from 6 months of P-MCP therapy, we herein report the influence of extending treatment to a total of 18 months treatment on BRPC indicators. We aim to establish whether the benefits of oral P-MCP therapy observed at 6 months [34] are sustained over a longer time period.

2. Methods and Materials

Study design: The eligibility criteria are described in our previous publication [34].

Briefly, patients with BRPC-M0, rising PSA post-primary therapy (surgery and/or radiation) and negative scans were included. All patients had a normal level of serum testosterone > 150 ng/ml, and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at study entry. All participating patients signed an Institutional Review Board (IRB)-approved consent form. Study participants were recruited between 2013 to 2019 from 5 medical centers in Israel (Meir, Rabin, Rambam, Soroka, and Tel-Aviv Sourasky). Patients were given 4.8 grams of P-MCP to take orally, times 3 per day for the duration of the study. The P-MCP was provided by PectaSol-C ®, EcoNugenics, Santa Rosa, CA, USA, in packs of 270 capsules. Patients without evidence of disease progression or dose-limiting toxicity after 6 months of therapy (n=46), entered the second long term phase of the study, and were given an additional 12 months of treatment. A total of 39 patients completed the full 18 months of treatment. The study design is described in Figure 1.

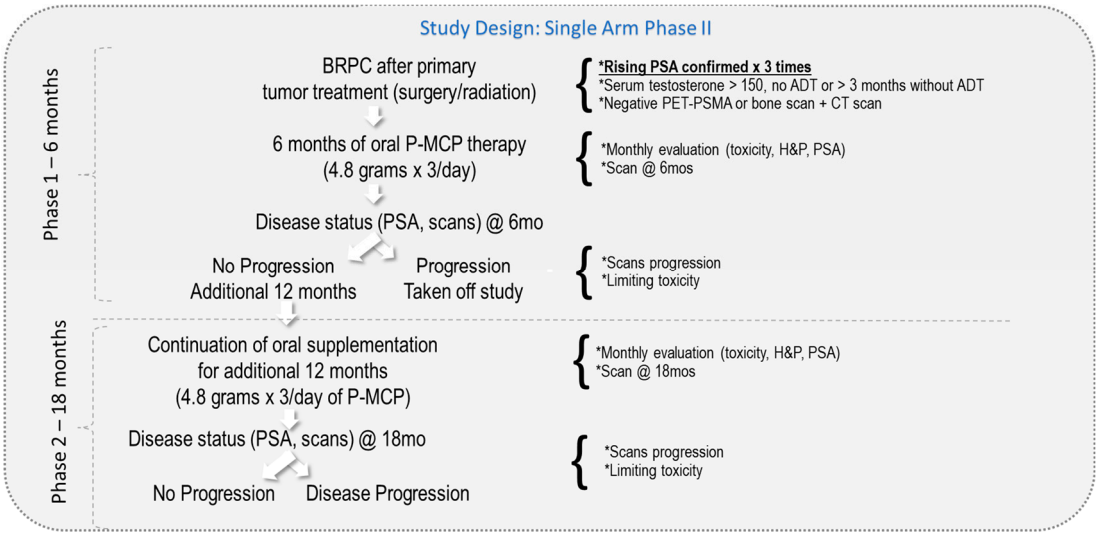

Figure 1. Study design.

Evaluation of disease status: Patients underwent monthly visits for toxicities, physical examinations, and serum PSA, with baseline measurements taken prior to starting the P-MCP treatment protocol. A positron emission tomography (PET) - prostate-specific membrane antigen (PSMA) scan was conducted after 6 and 18 months in patients without clinical or PSA progression, or earlier upon clinical or PSA progression. The primary efficacy endpoint was the rate of patients without PSA progression (defined as an increase of ≥ 25% from baseline) and/or patients with improvement (lengthening) of PSADT versus baseline. The post-baseline PSADT was calculated using baseline PSA measurements obtained at the start of the study and every month during treatment. Secondary endpoints included the rate of patients without radiologic progression and

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toxicity, and with treatment benefits according to the PSADT risk grouping (e.g., poor < 3 months, intermediate 3-8.99 months, and good ≥9 months) [34].

Duration of treatment: Treatment as per the protocol continued for 12 additional months or until biochemical or clinical disease progression or dose-limiting toxicity. Disease progression was defined as biochemical progression, and/or new radiological evidence of metastases.

Safety evaluation of toxicity: Toxicity was defined according to the National Cancer Institute (NCI) Common Toxicity Criteria with treatments terminated at grades 3/4 and patients monitored weekly until ≤ grade 1 before restarting therapy. Treatment would be discontinued upon the recurrence of a same grade 3/4 event, and for any toxicity requiring longer than 4 weeks to recover to ≤ grade 1.

Statistical analysis: Comparisons between pre- and post-treatment endpoint parameters, and within groups were analyzed using the Wilcoxon Signed Rank test for abnormally distributed data, or the two-tailed Student t-test for normally distributed data, with results reported as number, percentage, mean or median, and standard deviation (SD). A p-value ≤ 0.05 was considered statistically significant.

Regulatory Considerations: The research was conducted in accordance with the approval by the IRB committee of our institution. The study was registered at clinicaltrials.gov (NCT01681823).

3. Results

Patients: Of the 46 patients that displayed a benefit from the initial 6 months of therapy (in terms of stabilization/decrease of PSA, and/or improvement of PSADT, and with negative scans), and that were eligible the second phase of additional 12 months therapy (to a total of 18 months of treatment), 7 patients withdrew consent during the first month of the additional year of therapy, and chose to continue the effective therapy independently due to the travel distance to monthly medical visits. Thus, 39 patients were treated as per the protocol for a total of 18 months of treatment. Patient pre-treatment characteristics are summarized in Table 1.

Table 1. Pre-treatment (baseline) patient characteristics.

Parameter	n = 39
Age (years): Median (range)	75 (52 - 88)
Gleason: % (n)	
6	41% (n=16)
7	38% (n=15)
8-10	21% (n=8)
Local therapy: % (n)	
Radical prostatectomy	18% (n=7)
Radiation therapy	54% (n=21)
Surgery+RT	28% (n=11)
Prior ADT	38% (n=15)
PSA (ng/ml): Median (range)	4.1 (0.28-30)
PSADT (months) risk grouping: % (n)	
Poor <3	8% (n=3)
Intermediate 3-8.99	33% (n=13)
Good ≥9	59% (n=23)
PSADT (months): Median (range)	
Whole cohort	10.3 (1.4 – 55)
Poor PSADT risk	1.6 (1.4 – 1.8)
Intermediate risk	5.12 (3.5 – 8.2)
Good risk	14.74 (9.10 – 54.6)

Long-term outcome as determined by PSA level, PSADT, and disease progression: After the 39 patients had received 18 months of treatment, 85% (n=33) demonstrated a decreased or stable PSA (Figure 2) and/or improvement of PSADT (54%, n = 21) and negative scans (90%, n = 35). Median PSADT improved significantly compared to baseline (p = 0.003), from a median pre-treatment PSADT of 10.3 (median range = 1.4 – 54.6) months to a median post-treatment PSADT of 43.5 (median range = 3.5 – 981.0) months (Tables 1 and 2).

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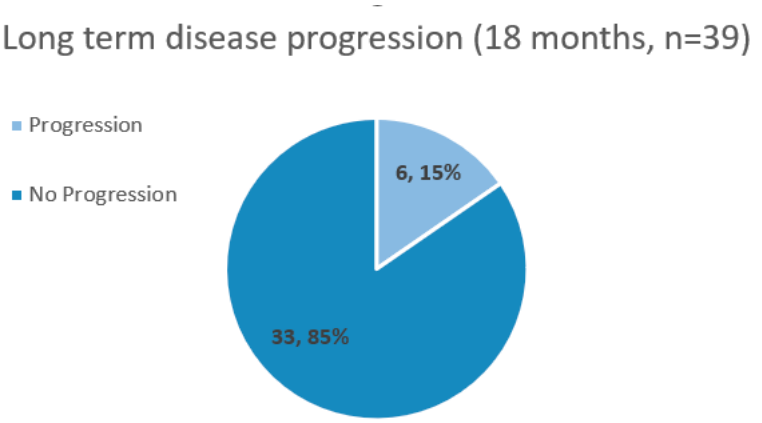

Figure 2. Disease progression status after 18 months of PectaSol® Modified Citrus Pectin (P-MCP) therapy.

Table 2. Treatment characteristics and responses after 18 months of PectaSol® Modified Citrus Pectin (P-MCP) therapy.

Parameter	Whole cohort (n=39)	According to Pre-study PSADT (months) risk grouping		
		Poor < 3.00 (n=3)	Intermediate 3.00-8.99 (n=13)	Good ≥ 9.00 (n=23)
Overall response to therapy (decrease or stabilization of PSA, and/or lengthening of PSADT, with negative scans)	85% (n=33)	66% (n=2)	77% (n=10)	91% (n=21)
PSA response				
Stable/decreased	54% (n=21)	67% (n=2)	23% (n=3)	70% (n=16)
Progression	46% (n=18)	33% (n=1)	77% (n=10)	30% (n=7)
PSADT (months): Median (range)	43.5 (3.5-981)	9.8 (6-200)	18.3 (6.7-500)	47.7 (3.5-981)
PSADT (months) risk grouping: % (n)		0% (n=0)	13% (n=5)	87% (n=34
PSADT lengthening	90% (n=35)	100% (n=3)	92% (n=12)	87% (n=20)
Change to a better PSADT risk grouping	36% (n=14)	100% (n=3)	85% (n=11)	not applicable
Radiologic response	90% (n=35)			
Negative scans	10% (n = 4)	67% (n=2)	75% (n=11)	96% (n=22)
Disease progression		33% (n=1)	15% (n=2)	4% (n=1)

The benefits of 18 months of therapy in terms of PSA stabilization or decrease, and/or PSADT lengthening were seen in all PSADT risk groups (Table 2). There was also an improvement in PSADT risk grouping after 18 months of treatment (Table 2, Figure 3). After 18 months of P-MCP therapy, all patients with a pre-treatment PSADT risk grouping of poor (<3 months), improved their PSADT to

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intermediate-good risk, and most patients (77%) with a pre-treatment risk PSADT of intermediate improved their PSADT risk to good (Table 2, Figure 3). In patients with a pre-treatment PSADT risk of good, 91% retained their risk grouping and 87% of which had an improved PSADT. After 18 months of therapy, no patients remained in the poor PSADT risk group, and the proportion of patients with a PSADT risk of good (≥ 9.00) increased from 59% (n=23) at baseline to 87% (n=34) after 18 months of therapy (Figure 3). The pre-treatment (baseline) distribution of PSADT risk groupings improved after 18 months of P-MCP therapy, with the proportion of patients in the PSADT poor risk group reducing from 8% to 0. Similarly, the proportion of patients in the intermediate PSADT risk group reduced from 33% to 13% and the good risk group saw an increase from 59% to 87% (Tables 1 and 2). There was a significant change in the median PSADT after 18 months of P-MCP therapy (Table 2) as compared to baseline (Table 2), for patients with a pre-treatment PSADT good risk (45.9 versus 14.7 months, p=0.027) and intermediate risk (22.75 versus 5.1 months, p=0.0015). Disease progression during the 18 months of therapy was observed in 18% (n=7) of patients, 8% (n=3) of which had PSA progression only (without radiological progression) and 10% (n=4) presented with both PSA and radiologic progression.

Toxicity and compliance: None of the patients had grade 3/4 toxicity during the 18 months of therapy. Grade 1 toxicity was observed as transient and reversible bloating *that did not require treatment discontinuation.* This grade 1 toxicity was noted in 20% (n=12) of patients during the first six months of therapy, and in 23% (n=9) during the additional 12 months of treatment.

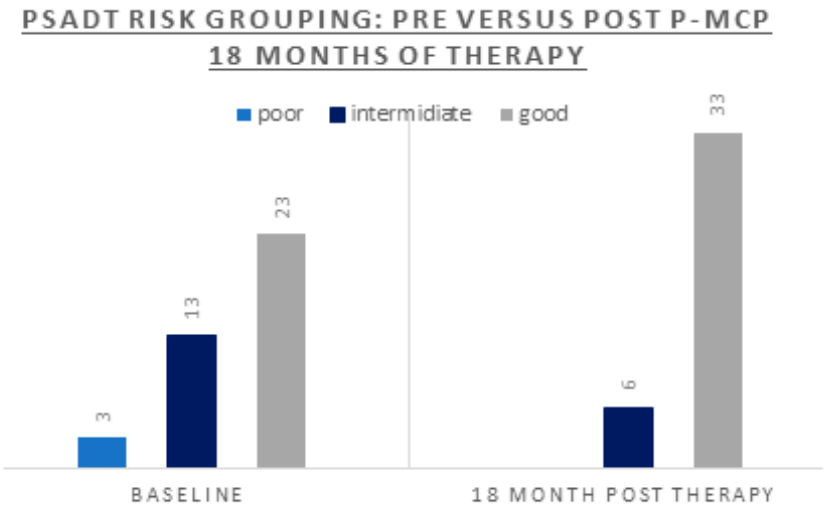

Figure 3. The number of patients in each PSADT risk group at baseline and after 18 months of PectaSol® Modified Citrus Pectin (P-MCP) therapy.

4. Discussion

Prostate cancer is a leading cause of death in men worldwide [1], with tumor progression after primary treatment presenting a persistent therapeutic challenge [10,20]. As such, determining effective treatment for the slow, and often cryptic, progression of biochemical relapse prostate cancer (BRPC) [14] has proven problematic [2,10,11,20]. The anticancer properties of natural products [32–35] offer important investigative potential for cancer therapies, including in relation to long-term BRPC treatment [34,45]. Building on the promising results of Keizman et al.'s (2021) 6-month clinical study into the efficacy of PectaSol® Modified Citrus Pectin (P-MCP; EcoNugenics Inc, Santa Rosa, CA, USA) [34], we document a lengthening of PSADT within the same participant cohort after sustained P-MCP treatment for 18 months.

Consistent with investigations of other natural products [30,35], treatment with P-MCP for a total of 18 months led to an increase in PSADT for 90% of the participants, as compared to pre-treatment baseline. In the preceding 6-months of P-MCP therapy, three quarters of the participant cohort demonstrated a lengthening of PSADT, suggesting that the additional 12-months of treatment

increased the likelihood of efficacy. PSADT is an important measure of BRCP-M0 progression and predictor of future metastases [10,13,15,16,25] and, while a shortening of PSADT is not necessarily indicative of imminent risk [17], a lengthening of PSADT can be used to indicate effective therapeutic management [27]. Findings therefore suggest that oral therapy with P-MCP three times daily is potentially effective in managing BRPC-M0 patients over a sustained period.

BRPC-M0 patients within the study were categorized into one of the three PSADT risk groupings [16,20], with risk staying stable or improving with P-MCP treatment for all but 5% of participants. In the absence of placebo control group, the proportion of participants that may have been stable, improved or reduced their PSADT risk grouping of over an 18-month period without P-MCP therapy is unknown. The improvement of all participants in the poor risk category at baseline, however, suggests that P-MCP is beneficial for BRPC-M0 patients at highest risk of metastasis. Such findings should be further validated with a higher sample size for the poor risk category. Additionally, as with the previous study, no long-term or significant toxic effects were recorded, suggesting P-MCP can be safely taken over a prolonged period.

A major limitation of the study is the lack of placebo (control) arm, which would have have provided confirmation that the recorded PSADT lengthening was a consequence of P-MCP therapy. Using only the patient cohort from Keizman et al. (2021) that demonstrated beneficial responses P-MCP by 6 months of therapy may have provided a skewed sample population by eliminating participants who were unresponsive to treatment. It is therefore possible that the 90% benefit rate observed in this study will be higher than that for a randomly selected cohort of BRCP-M0 patients. Additionally, the low sample size within the PSADT poor risk grouping (n = 3) means that benefits of P-MCP for this cohort need further validation. Furthermore, although retrospective studies have shown that PSADT is a strong predictor of metastasis-free survival, overall survival [11,13] or both [28,30], further validation is required to establish whether change in PSADT is an acceptable endpoint for clinical trials in this patient population. Investigating the mechanisms of PSADT lengthening in BRPC patients, such as by galectin inhibition [42], was beyond the scope of the study but is a key avenue for future research.

Overall, we demonstrated a sustained benefit of P-MCP therapy for the majority of our study cohort, without toxicity, over an 18-month period. This indicates that P-MCP treatment should be continued for the long-term to ensure maximum benefit and BRPC-M0 management. Further double-blind placebo controlled clinical studies are planned to optimize the therapeutic use of P-MCP in this patient population.

Author Contributions: DK: MF, AP, IK, ER, DS, IL, RM, OY, DM, KR, AS, HD and IE contributed equally to this work. DK and IE devised the concept and designed the study. DK, MF, AP, IK, ER, DS, IL, RM, OY, DM, KR and HD conducted the most experiments. DK and IE contributed to the manuscript writing. All authors reviewed the manuscript and signed-off on its accuracy.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Meir Medical Center (Protocol 019-2-12 MMC. Current ongoing approval date 23/08/2019). The study was registered at clinicaltrials.gov (NCT01681823).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in the study are available with the investigator Dr. Daniel Keizman.

Conflicts of Interest: IE discloses being the developer of the sponsoring dietary supplement company but holds no ownership in the company. The other authors declare no potential conflicts of interest.

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