Bavarian Nordic (BAVA DC/BVNRY)

Dendreon 2.0?

Ineffective Cancer Vaccine Masked by Misleading Data

Bavarian Nordic A/S (OMX: BAVA, OTC: BVNRY) is a $1.3B Danish vaccine-maker whose stock price has recently surged (up 63% YTD) thanks to excitement over its putative prostate-cancer treatment, Prostvac-VF, a therapeutic vaccine currently undergoing a Phase III clinical trial. Bavarian Nordic touts its earlier Phase II study of Prostvac as showing the "most pronounced survival to date in prostate cancer," with an 8.5-month improvement in median overall survival, handily outperforming blockbuster drugs like Zytiga and Xtandi. The announcement in March that Bristol-Myers Squibb was paying $60mm upfront for an exclusive option to license and commercialize the vaccine gave investors great confidence that, despite the uncertainty surrounding any clinical trial, Prostvac is likely to succeed.

This confidence is misplaced. The often cited 8.5-month improvement is an illusion: treatment-arm survival was unexceptional relative to the results of other trials in similar patient populations, while placebo-arm survival was anomalously poor. This strikingly bad placebo performance likely had several causes, but one important one was age: relative to men who received Prostvac, those who received a placebo were much older – indeed, older than any group we have come across in any prostate-cancer clinical trial. Researchers have clearly and consistently found – as common sense would suggest – that elderly men with prostate cancer, compared to their younger counterparts, do in fact live substantially less long. Comparing an unexceptional treatment group to an anomalously bad placebo group is a good way to show a strong benefit where none truly exists.

More recent efforts to demonstrate improved survival in patients receiving both Prostvac and the cancer drug Yervoy only further underscore Prostvac's inefficacy. In a 30-patient trial with no control group, across a range of Yervoy dose levels, median survival was 31.6 months – compared to the ~30-month survival seen over and over again in the control groups of other late-stage prostate-cancer studies, a negligible "improvement." Given that Yervoy itself clearly has some *standalone* anti-tumor activity and has been shown to extend survival by (a non–statistically significant) 1.2 months even in post-chemo prostate-cancer patients, Prostvac's combination-therapy data look even less impressive. The natural conclusion is that any apparent benefit comes from Yervoy; Prostvac itself accomplishes nothing.

This finding should come as no surprise: the history of therapeutic cancer vaccines is two decades of unmitigated failure. We expect nothing different from Bavarian Nordic.

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I. Investment Highlights

- **Prostvac's purported 8.5-month survival benefit is an artifact of a bad control**. In Prostvac's Phase II study, which began in late 2003, the Prostvac group lived for 25.1 months; the placebo group lived for 16.6 months. For the relevant subset of patients – men with metastatic, castration-resistant prostate cancer (mCRPC) who are minimally symptomatic or asymptomatic – 25.1 months is an unremarkable outcome. For instance, in the TAX-327 study, initiated back in March 2000, men with minimal symptoms had median survival of 25.6 months (1). More recent studies have yielded even better results: the *control groups* in trials for tasquinimod (2), abiraterone (3), enzalutamide (4), and orteronel (5), with enrollment start dates ranging from 2007 to 2010, survived 30.4, 30.3, 30.2, and 29.5 months in trials, respectively.

  Since there is nothing special about Prostvac's treatment-group performance, the purported benefit comes entirely from the anomalously bad performance of the placebo group. The original paper conceded that, applying a popular predictive model to a set of baseline prognostic factors, the treatment group had a 2.1-month survival "head start" (6), and an accompanying editorial (7) further noted (emphasis added):

  > [I]t is of concern that the control group had a median overall survival lower than that predicted by the Halabi et al. model (16.6 months actual compared with 20.4 months predicted). **The reasons for this discrepancy are not at all clear**, particularly given the eligibility criteria designed to select lower-risk patients.

  We hypothesize that an important source for this discrepancy is age: the median age in the Prostvac group was 71.5 years, while in the placebo group it was 79. We have found no group in any other prostate-cancer trial with an age distribution skewed so far to the right. The original paper's authors dismiss this massive imbalance (favoring the Prostvac group) with the claim that "age is not a significant prognostic factor in prostate cancer," citing the predictive model published in 2003 by Susan Halabi et al. (8), but this claim is wrong. Halabi's model was based on data from men with a relatively narrow range of ages, over which small differences may not matter.

  By contrast, a study focusing specifically on elderly mCRPC patients (aged 75 years and older) showed that those in relatively good condition experience median survival of 17.5 months (9) – very similar to the outcome for the Prostvac placebo group and approximately 10 months worse than that for younger men with similar disease characteristics (1) (10). Another publication showed that mCRPC patients aged 85 years or older have 5-year survival rates that are less than a third of those for younger men aged 65-74 (9), while a 2006 study by Halabi et al. noted that 60-to-69-year-olds experienced survival similar to that of 70-to-79-year-olds but lived almost twice as long

as 80-to-89-year-olds, who constituted roughly half of the Prostvac Phase II placebo group (10).

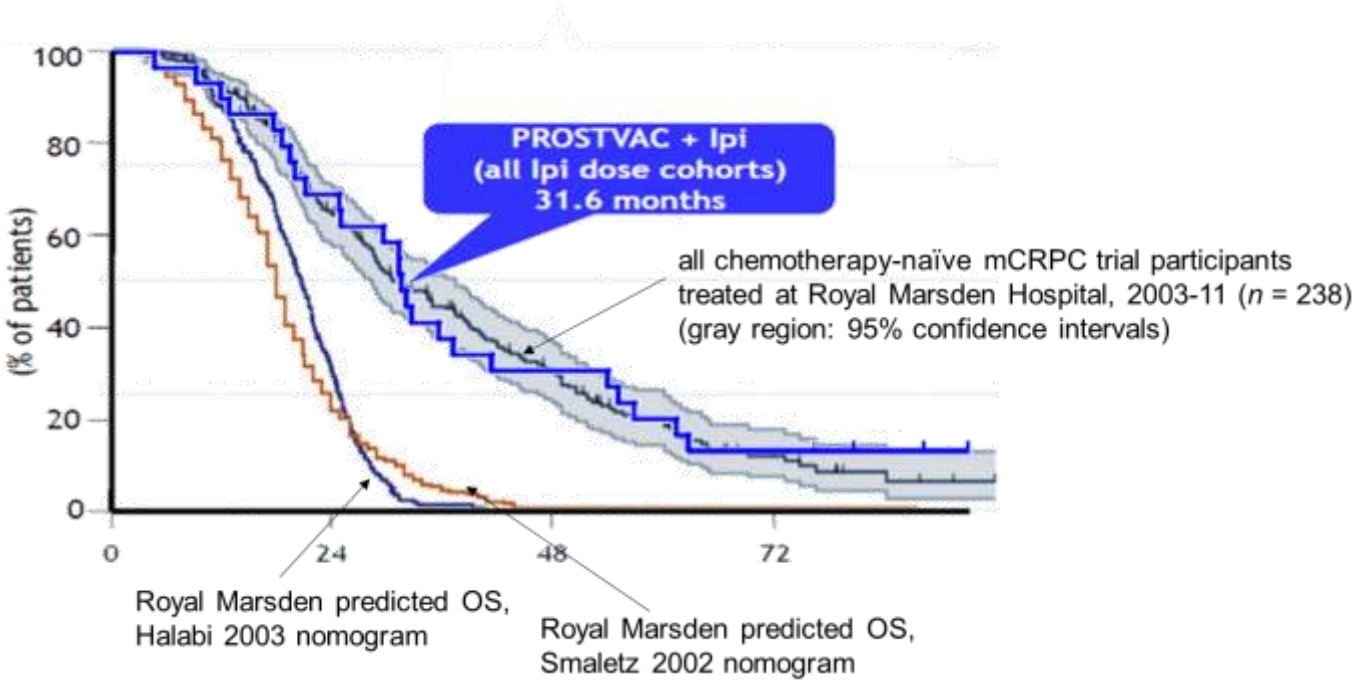
In short, age does affect overall survival even for men with late-stage prostate cancer, likely explaining, at least in part, the Prostvac placebo group's unusually bad performance. Regardless of the cause, though, there is no reason to expect such a bad control to recur in the larger Phase III study, set to finish in late 2016 or beyond; thus, there is no reason to expect Prostvac to show any benefit. The treatment will fail.

- **Early combination-therapy data confirm the absence of a meaningful survival benefit**. Although Prostvac's Phase II study is inarguably the centerpiece of Bavarian Nordic's case for the treatment's efficacy, the company has recently touted a second, more recent study as demonstrating even greater potential benefits. In this Phase I trial – which had no control group – patients received the same dose of Prostvac and a range of doses of Yervoy (ipilimumab), an immune checkpoint inhibitor produced by Bristol-Myers (11) (12). Across all doses, median overall survival was 31.6 months. Bavarian Nordic likes to portray this as a marked improvement over the Phase II trial's 25.1-month survival, but in reality all comparable mCRPC trials have produced similar results for many years, *even in placebo groups,* stemming from better overall medical care and the wide range of other life-extending drugs available to trial participants once their condition deteriorates. Bavarian Nordic also likes to benchmark this survival result to the aforementioned Halabi 2003 predictive model, but this model, drawing on 15-year-old data, is now badly out of line with current clinical outcomes; indeed, it has since been superseded by an updated version that gives more optimistic predictions (13).

  One striking illustration of both the inaccuracy of the Halabi 2003 predictive model and the mediocrity of the Prostvac/Yervoy data comes from a 2013 paper by Omlin et al. examining overall survival for all men with mCRPC participating in any clinical trial from 2003 to 2011 at one particular healthcare institution: the UK's Royal Marsden Hospital (14). Men with no prior history of chemotherapy (termed "chemotherapy-naïve") experienced median overall survival of 30.6 months, almost identical to the Prostvac/Yervoy result; meanwhile, the Halabi model predicted median survival of only 21 months, 31% worse than the actual outcome.

  Below we take a graph from the Omlin paper, plotting percentage survival against time from referral (measured in months) for chemo-naïve Royal Marsden mCRPC patients, and superimpose a graph from Bavarian Nordic, plotting the same metrics for Prostvac/Yervoy combination-therapy patients. The survival curves are stunningly similar, especially considering the small size of the combination trial. Thus, using the Royal Marsden data as a surrogate "control" shows that *the Prostvac recipients exhibit no advantage whatsoever.* Consistent with the Phase II trial when taking into account age and other prognostic factors, Prostvac, even in combination with Yervoy, appears to accomplish nothing. Moreover, as the dark blue curve toward the left shows, the Halabi 2003 model is simply not a relevant reference point anymore: it badly underestimates

expected survival, especially beyond the first year. It's ludicrous for Bavarian Nordic to congratulate itself for clearing such a low bar.



Source: Bavarian Nordic April 2015 investor presentation, Omlin et al. 2013 (14), Kerrisdale analysis

Another relevant point of comparison is tasquinimod, a drug previously under development for mCRPC by Active Biotech and Ipsen. In a 201-patient Phase II trial, median overall survival was 33.4 months in the treatment group and 30.4 months in the placebo group, a statistically significant difference (2). In April, however, tasquinimod development was suspended when a 1,200-patient Phase III trial failed to show any survival benefit over placebo. If tasquinimod, despite its track record of 33.4 months of expected survival, can't reliably outperform placebo, then Prostvac, with markedly less impressive results under its belt heading into Phase III, is bound to fail.

- **The Prostvac goalposts keep moving**. Back in 1999 when researchers conducted the first human trial of Prostvac, they highlighted that one of the six subjects saw his serum prostate-specific antigen (PSA), a widely used marker of prostate-cancer progression, plateau at a low level for months (15). In a 2000 follow-up, the highlight again was stable PSA levels and an apparent absence of disease progression in some patients (16). Thus the 125-patient Phase II trial had as its primary end point "progression-free survival," i.e. time elapsed without the cancer becoming significantly worse. But these observations of supposedly improved disease progression – made without reference to any control group – disappeared with larger sample size, and Prostvac failed to deliver the benefit it was supposed to. Overall, Prostvac has shown no ability to shrink tumors or prevent PSA increases. The strange theory that Prostvac improves *overall* survival but *not*

progression-free survival (or any other tangible measure of disease) was only cobbled together after the study was over.

Though some advocates suggest that an absence of progression benefit coupled with a real overall-survival benefit is typical of immunotherapy in general, this is false. The immune-checkpoint inhibitor ipilimumab, for instance – which failed to demonstrate a significant overall-survival increase in a large Phase III prostate-cancer study – *did* show a statistically significant 30% reduction in progression risk, and large PSA declines were 2.5x more frequent for ipilimumab patients than for placebo patients (17). To be sure, Dendreon's prostate-cancer vaccine Provenge has a profile similar to Prostvac's: a purported small survival benefit with no improvement in progression or other indicators of disease. But Provenge is not a happy precedent: despite its FDA approval in 2010, many clinicians harbored serious doubts about the evidence of its efficacy, and this pervasive skepticism (which continues to this day) was a key factor in Provenge's commercial failure and Dendreon's 2014 bankruptcy filing.

- **Therapeutic cancer vaccines have a long history of failure**. Harnessing the immune system to battle cancer is an exciting approach that, for certain patient populations, is finally starting to bear fruit. Sophisticated immunotherapies like checkpoint inhibitors and adoptive cell transfer have enjoyed some dramatic clinical successes. But simplistic therapeutic vaccines like Prostvac are another matter entirely; time and again, they have been tremendous disappointments. One review, published in 2004, compiled results from many different studies involving different cancers and different types of vaccines and concluded that "the overwhelming majority (>96%) of patients in the studies evaluated who received vaccine therapy for their underlying cancer did not exhibit objective evidence of cancer regression." An updated review, published in 2011 under the title, "Therapeutic Cancer Vaccines: Are We There Yet?" looked at studies released in the intervening years and found the same 96% failure rate (18). A review by different authors, published in 2014 and focusing specifically on prostate-cancer vaccines, compiled 41 studies performed from 2000 to 2012 using a wide range of vaccine approaches, from viral vectors to plasmids to peptides, and including 1,100 patients in the aggregate – of whom only *four* enjoyed any tangible improvement in tumor burden. The authors summarize: "Vaccinations yielded immunological responses, but no study showed evidence for clinically relevant therapeutic improvement" (19). (In the case of Prostvac, the data are even less impressive, since even the immunological responses have been modest and inconsistent (20).)

  Companies large and small have attempted to defy this track record of failure, only to fall flat on their faces:

  - In 2008, Cell Genesys had to terminate two Phase III trials for its GVAX prostate-cancer vaccine when it became clear that the treatment conferred no survival benefit; after its stock price collapsed, the company was forced to sell itself.

- In 2012, Oxford BioMedica abandoned its TroVax prostate-cancer vaccine as a result of several factors: difficulties enrolling trial participants; a vast increase in the number of life-extending treatment options (like enzalutamide, abiraterone, and radium-223) available to men with late-stage prostate cancer; and early results for TroVax that gave no sign of meaningful efficacy (21).
- In 2013, GlaxoSmithKline announced that its Phase III trial of a melanoma vaccine had failed to extend disease-free survival in its targeted patient population.
- In 2014:
    - Merck discontinued development of its non–small-cell lung-cancer vaccine tecemotide after it repeatedly failed to show any beneficial effect on overall survival or disease progression.
    - GlaxoSmithKline abandoned the Phase III trial of its non–small-cell lung-cancer vaccine after it failed to show any benefit.

While Bristol-Myers' willingness to pay $60mm upfront for an exclusive option on Prostvac was undoubtedly a vote of confidence – albeit on a very small scale, and with overall deal economics that imply a low probability of success – it would certainly not be the first time a large pharmaceutical company stumbled in this field. Moreover, the Bristol-Myers deal serves to cap any potential upside for Bavarian Nordic, since, in exchange for a series of additional payments that could total $915mm (but are likely to be substantially lower even if Prostvac succeeds), it has already traded away the vast majority of any future Prostvac revenue.

There is nothing special or innovative about Prostvac that would enable it to break the consistent pattern of failed cancer vaccines; to the contrary, the Prostvac concept is 20 years old. The entire approach of simply administering tumor-associated antigens and hoping for an effective immune response is a dead end.

- **The scientific literature furnishes a multitude of convincing explanations for the failure of cancer vaccines**. Why do therapeutic cancer vaccines fail to help patients even though they sometimes trigger a measurable immune response? One key factor is tolerance*:* the immune system has several mechanisms designed to *prevent* autoimmune attacks on self antigens like PSA, and the vast majority of nascent T cells targeting such antigens are killed before they ever exit the thymus. Another important factor is what scientists call the immunosuppressive tumor microenvironment. Tumors (and the immune system itself via negative-feedback mechanisms (22)) blunt incipient T-cell attacks in myriad ways. One paper provided the following head-spinning overview (23):

    > Multiple layers of immune suppression are operational in the tumor environment, including other co-inhibitory molecules expressed on T cells such as PD-1/PD-L1, Tim-3, and LAG-3, T_{reg}s, myeloid-derived suppressor cells, and soluble immunosuppressive mediators such as IDO (indoleamine 2,3-dioxygenase),

arginase, prostaglandin E2 (PGE2), IL-6, IL-10, VEGF, and other cytokines and chemokines.

This list does not even include the possibility of "immune escape" as tumors evolve to downregulate the antigens that T cells have targeted. For example, even if Prostvac were to spark an initially effective immune response keyed on cells expressing PSA, the cancer might simply stop expressing PSA over time. This effect has been directly observed in a murine model of prostate cancer: researchers injected antigen-specific T cells into the mice and observed them killing off antigen-positive tumor cells, but this only led to the outgrowth of antigen-negative tumor cells and had no impact on the overall progression of the tumor (24).

Even the formidable challenges of immunosuppression and immune escape – which have foiled treatments far more robust than Prostvac – presuppose that T cells actually manage to traffic into the tumor, another major difficulty. They also presuppose that the immune system targets the desired recombinant antigen rather than simply focusing on the viral vector itself. Yet research suggests that T-cell responses to recombinant viral *vectors* – i.e. the viruses themselves, not their payload of foreign antigens (PSA in the case of Prostvac) – can be 20 to 30 times more intense than responses to the foreign antigens (25). This finding, an instance of the broader phenomenon of "immunodominance," is consistent with Prostvac data showing derisory PSA-specific T-cell responses in vaccinated patients (22); by contrast, typical responses to the vaccinia virus itself, one of the vectors for Prostvac, are an order of magnitude stronger. The immune system is fighting the vaccine far more diligently than it is attempting to fight the cancer.

Finally, since prostate cancer is primarily a disease of older men, Prostvac also faces the problem of "immunosenescence": immune responses across the board tend to deteriorate with age. Indeed, even conventional prophylactic vaccines like the flu vaccine are much less effective in elderly populations (26). Therapeutic cancer vaccines attempting to overcome strong barriers to autoimmunity and target "self" antigens like PSA are unlikely to fare any better.

In short, a wide array of mechanisms limits the potential effectiveness of therapeutic cancer vaccines, including tolerance, immunosuppression, immunodominance, and, for prostate cancer, immunosenescence. Prostvac is a weak agent that fails to address these daunting challenges, so it should be no surprise that it can't.

- **Bavarian Nordic's core business is at risk**. While market enthusiasm for Bavarian Nordic centers on Prostvac, the company's only material revenue source in the past several years has been the sale of Imvamune, a weaker form of the conventional smallpox vaccine intended for people with compromised immune systems, to the US government for its "strategic national stockpile." Notwithstanding the vaccine's high cost and unknown efficacy – the objects of criticism from some of the world's leading

smallpox experts, including the World Health Organization – the government appears committed to working with Bavarian Nordic to finalize a new, longer-lasting freeze-dried version. But given the likely dramatic increase in shelf life and thus dramatic decline in the need for future replenishment, revenue from the freeze-dried vaccine will effectively be non-recurring, putting this business's sustainability in doubt. Moreover, recently published research not only demonstrated the similarity of the liquid and freeze-dried formulations but also showed that, with a different route of administration (intradermal rather than subcutaneous), only 20% of the conventional dose could achieve the same level of protection, implying that the Strategic National Stockpile could purchase 5x less material from Bavarian Nordic yet cover the same target population (63). At best, this discovery will damage the company's bargaining position; at worst, it will decimate its future revenue.

Investors have come to view Bavarian Nordic as a de-risked bet on a very promising agent, with the purported 8.5-month survival improvement at the heart of the long thesis. One sell-side firm has gushed, "A significant Phase II survival benefit suggests PROSTVAC immunotherapy has the potential to revolutionise prostate cancer treatment." But Prostvac will revolutionize nothing. After taking into account the profound flaws of the Phase II trial as well as the weakness of the early combination-therapy results, it's clear that Prostvac is just as ineffective as every other failed cancer vaccine. Bavarian Nordic did not stumble onto the magical key to making this doomed approach work; it merely got lucky with a statistical fluke.

II. Company Overview

Bavarian Nordic: Capitalization and Financial Results

Capitalization

	DKK	USD
Share price	321.00	$ 47.53
Shares O/S (mm)	27.7	27.7
Market cap (mm)	8,902	$ 1,318

Financial results (USD)*

	2013	2014	2015†
Revenue	$ 216	$ 217	$ 142
EBIT	6	3	-
Cash/securities‡	98	159	213

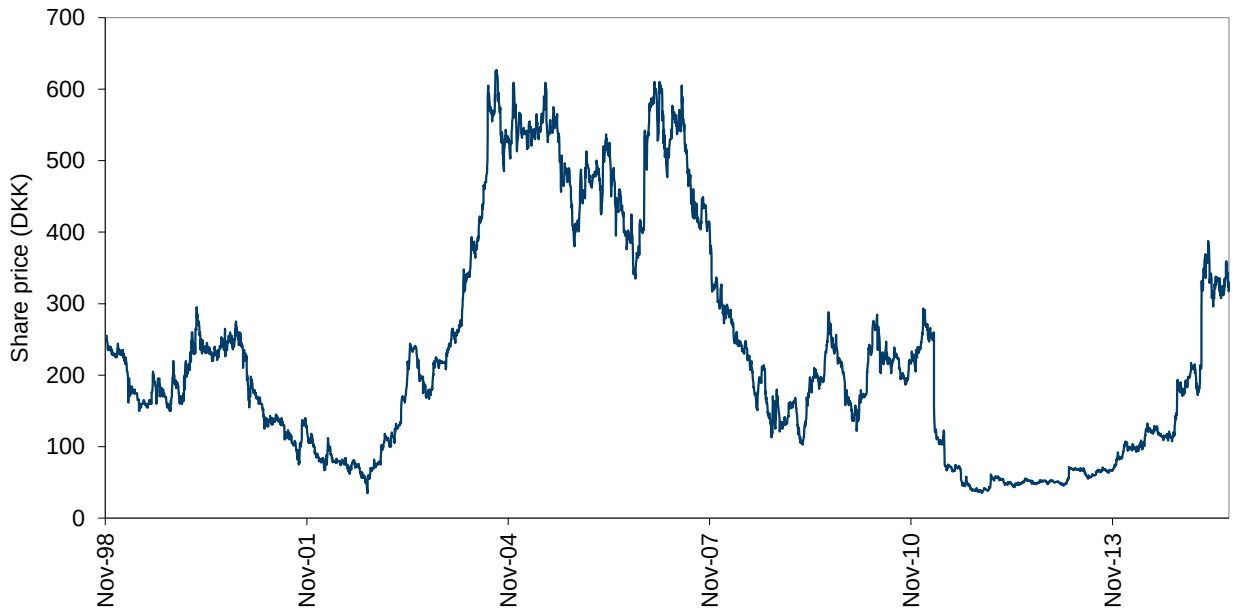
Source: company filings, Capital IQ, Kerrisdale analysis

* Revenue/EBIT converted from DKK at average exchange rates; cash converted at EOP rates.

† Revenue in dollars based on Needham presentation, 4/15/15.

‡ 2015 cash based on guided "cash preparedness" less DKK 11mm credit line (converted at spot FX rate).

Bavarian Nordic Share Price, 1998-2015



Source: Capital IQ, Kerrisdale analysis

Bavarian Nordic is a small vaccine manufacturer based in Kvistgård, Denmark. Founded in 1994 and taken public in 1998 at a price of DKK 235 per share, Bavarian Nordic was the second biotechnology company created by the Danish businessman Asger Aamund. (The first, NeuroSearch A/S, founded in 1989, never brought a single product to market, lost almost 100% of its equity value, and in 2012 commenced self-liquidation. Aamund has since called it "a smoking ruin.") Originally focused on using the attenuated viral strain called modified vaccinia Ankara (MVA) as a delivery vector in treatments for pancreatic cancer, melanoma, breast cancer, and HIV, Bavarian Nordic shifted its R&D in the wake of the September 11 attacks toward marketing MVA (under the name Imvamune) as a gentler version of the conventional

smallpox vaccine for emergency use by those with compromised immune systems. (Variola, the virus that causes smallpox, is not actually used in the modern smallpox vaccine; its less dangerous cousin vaccinia is. But even vaccinia can cause adverse reactions.) Ultimately the US government enlisted Bavarian Nordic to supply the Strategic National Stockpile with 28 million doses of Imvamune (a fraction of the Stockpile's holdings of the conventional smallpox vaccine) under a set of contracts that expired at the end of 2014. These contracts have been the company's only material source of revenue to date. (While Imvamune is Bavarian Nordic's sole commercial success, it may remain forever unknown if it's actually a clinical success; as the Centers for Disease Control explained in a recent set of guidelines "for smallpox vaccine use in a postevent vaccination program," "The efficacy of Imvamune against smallpox is unproven and cannot be tested clinically because of the global eradication of the disease in humans.")

Since inception, Bavarian Nordic had hoped to use its version of MVA as a vehicle for therapeutic cancer vaccines but made little progress on its own. In 2008, however, it announced a partnership with the US National Cancer Institute under which it acquired the rights to a prostate cancer vaccine candidate: Prostvac. In 2011, it also acquired a related experimental agent, CVAC-301 (previously known as Panvac). Both vaccines use regular vaccinia (along with fowlpox booster shots), not MVA, and trace their roots to Therion Biologics, a defunct Massachusetts-based firm that filed for Chapter 7 bankruptcy in 2006 after announcing two major failures back to back. First, Therion said, Prostvac "did not meet its primary efficacy endpoint of improving progression-free survival" in its Phase II trial; then, Panvac, in a Phase III trial for advanced pancreatic cancer, "did not meet its primary efficacy endpoint of improving overall survival compared with palliative chemotherapy or best supportive care." Therion put itself up for sale but found no buyers. In February 2007, the National Cancer Institute took back the rights to the vaccines before re-licensing Prostvac to Bavarian Nordic a year later.

Upon licensing Prostvac, BAVA quickly announced that, despite the vaccine's failure to meet its primary endpoint of progression-free survival, "mature" data showed "a statistically significant longer median overall survival," so it was moving forward to Phase III. In 2010, Bavarian Nordic indicated that it was in discussions to find a large partner to help fund the development of Prostvac, but in March 2011 management announced that it had judged all of its offers unattractive and would go it alone by raising additional capital. By the end of the year, the company's stock price had declined 85% from where it started. Danish newspapers frequently reported on the dire financial condition of Asger Aamund, the company's founder and chairman, especially when the leveraged investment vehicle through which he owned a large stake reported negative equity starting in 2011, surviving only via the forbearance of Aamund's bankers. (As the stock price recovered Aamund stepped down from the chairman role and, in January 2015 – *prior* to the Bristol-Myers announcement – his vehicle sold all of its shares.)

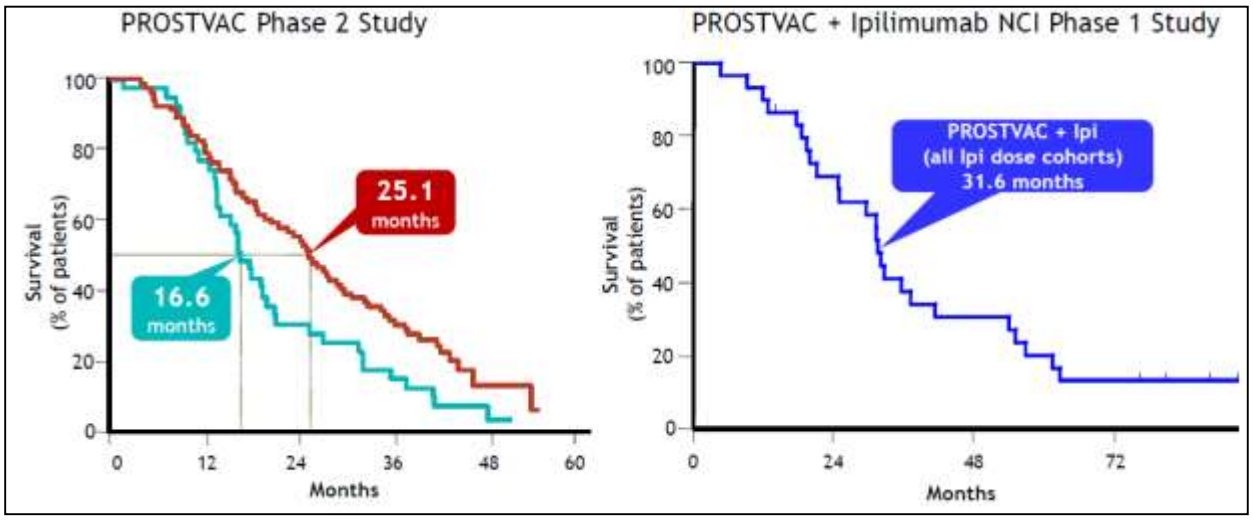
Despite this checkered history, Bavarian Nordic got a new lease on life in late 2014 when it announced a deal with Johnson & Johnson to supply an MVA-based boost to complement the experimental adenovirus-based Ebola vaccine that a J&J unit had been developing. The deal included $45mm in license and milestone payments, approximately $100mm in exchange for

millions of doses to be delivered in 2015, and a $43 million equity investment to replenish Bavarian Nordic's coffers. But while this Ebola transaction has helped keep Bavarian Nordic afloat despite the temporary lapsing of its crucial US smallpox contract in 2015 (since restored by a recently announced new order for deliveries in 2016-17), it is unlikely to contribute much to Bavarian Nordic's long-term value. After all, the West African Ebola outbreak, while not *completely* resolved, has already subsided dramatically, raising questions about whether ongoing Phase III trials of the two most promising vaccine candidates, which have substantial development head starts over J&J's candidate and do not require the complexities of a secondary boost, can even be completed. Moreover, Bavarian Nordic is not even the only small company offering MVA-based Ebola-vaccine boosts: Emergent BioSolutions is already working with GlaxoSmithKline on a similar project using its own version of MVA, which might be easier to manufacture than Bavarian Nordic's. Thus, the notion that Bavarian Nordic will get rich off of mass Ebola vaccinations is now looking less realistic than ever.

But before the Ebola hype could fizzle (though after Bavarian Nordic's founder, ex-chairman, and former largest shareholder sold a massive stake), Bavarian Nordic announced its partnership with Bristol-Myers Squibb, putting the spotlight squarely on the putative prostate-cancer treatment Prostvac. Shareholders have benefited from undiscriminating market enthusiasm for anything related to cancer immunotherapy. But "immunotherapy" is a broad term that encompasses both highly effective agents, like checkpoint inhibitors in melanoma, and totally ineffective agents, like simplistic therapeutic vaccines that have never had a meaningful clinical impact on any cancer over decades of research. Prostvac belongs to the latter category. As we will demonstrate, its vaunted Phase II survival benefit is meaningless, and other small-scale trials confirm Prostvac's inefficacy.

III. Prostvac's Clinical Trial Results Are Weak

Bavarian Nordic typically presents its Prostvac results to investors in the following way:



Source: Bavarian Nordic April 2015 presentation, slide 22

Both graphs plot overall survival against time: the percentage of patients still alive a given number of months after the commencement of the trial. In the graph on the left, the red line shows overall survival (OS) for the Prostvac treatment group, with a median OS of 25.1 months; the light blue line shows OS for the placebo group, which initially received "empty" (non-recombinant) vaccinia and fowlpox injections, with a median OS of 16.6 months. The difference in median OS, a standard measure of treatment efficacy, is 8.5 months, although the survival curves only begin to separate a year after randomization. The graph on the right, based on a more recent study, shows OS for patients who received both Prostvac and a range of doses of the checkpoint inhibitor ipilimumab; there was no control group, but the implied message is that the Prostvac/ipi combination is 6.5 months (31.6 – 25.1) better than Prostvac alone, which is itself supposedly 8.5 months better than placebo.

But there is less to these results than meets the eye. Compared to similar patients in a host of other prostate-cancer trials, neither the Prostvac group in the Phase II study nor the Prostvac/ipi recipients in the Phase I study survived particularly long. (Moreover, there was no sign of a clinical benefit other than the purported survival advantage.) The OS figures only look good in comparison to the Phase II placebo group, which was substantially sicker and older and sustained a surprisingly high death rate. Setting aside this uninformative and misleading benchmark, there is no evidence that Prostvac helps patients.

The Phase II Trial Was Flawed and Shows No Meaningful Benefit

The core idea of Prostvac is to expose the patient's immune system to prostate-specific antigen (PSA) – a protein almost exclusively expressed by prostate cells and used as a biomarker of prostate cancer – in conjunction with a mild viral infection. Initial efforts (15) involved only the vaccinia virus, engineered to carry the gene for PSA, but by the time of the Phase II trial researchers had made several additions:

- a series of follow-up boosts using a different recombinant virus, fowlpox, also engineered to express PSA;
- for both the vaccinia and fowlpox vectors, genes encoding a grab bag of proteins (dubbed "TRICOM") intended to further stimulate immune responses, including the CD28 (costimulatory) and CTLA-4 (co-inhibitory) ligand B7-1 and the adhesion molecules ICAM-1 and LFA-3; and
- an adjuvant, granulocyte macrophage colony–stimulating factor (GM-CSF), thought to provide yet more immune stimulation.

The hope is that these components will combine to generate an effective T-cell response aimed specifically at PSA-expressing tumor cells.* (With a treatment this complex – vaccinia-PSA-TRICOM + fowlpox-PSA-TRICOM + GM-CSF – the trial was bound to be difficult to interpret, since any effect identified might stem from PSA, TRICOM, GM-CSF, or any combination thereof, not just the preferred causal pathway of PSA.) A natural hypothesis is that the sought-after T-cell response, even if it fell short of eliminating tumors, might at least slow down the progression of the disease, and that is indeed what the Prostvac Phase II trial, initiated in 2003, was designed to assess (6):

> The planned primary end point was PFS [progression-free survival] defined as identification of two or more new sites of bone metastasis on the bone scan compared with the baseline scan, or an increase in the sum of measurable target lymph node metastasis on CT scan by >20% according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria compared with baseline. Patients who developed clinical signs or symptoms of progression but who did not meet the radiologic criteria were also considered to have progressed at the discretion of the investigator.

But Prostvac did not meaningfully improve progression-free survival: median PFS in the treatment arm was 3.8 months, essentially identical to the placebo arm's 3.7 months, and by six months the percentage of the treatment arm that had progressed was actually slightly *higher* (worse) than that of the placebo arm. These results, analyzed under the aegis of Prostvac's "initial industrial sponsor" Therion, helped drive the company into bankruptcy, but, many months later, Prostvac rose from the ashes, as a 2008 newspaper article explained:

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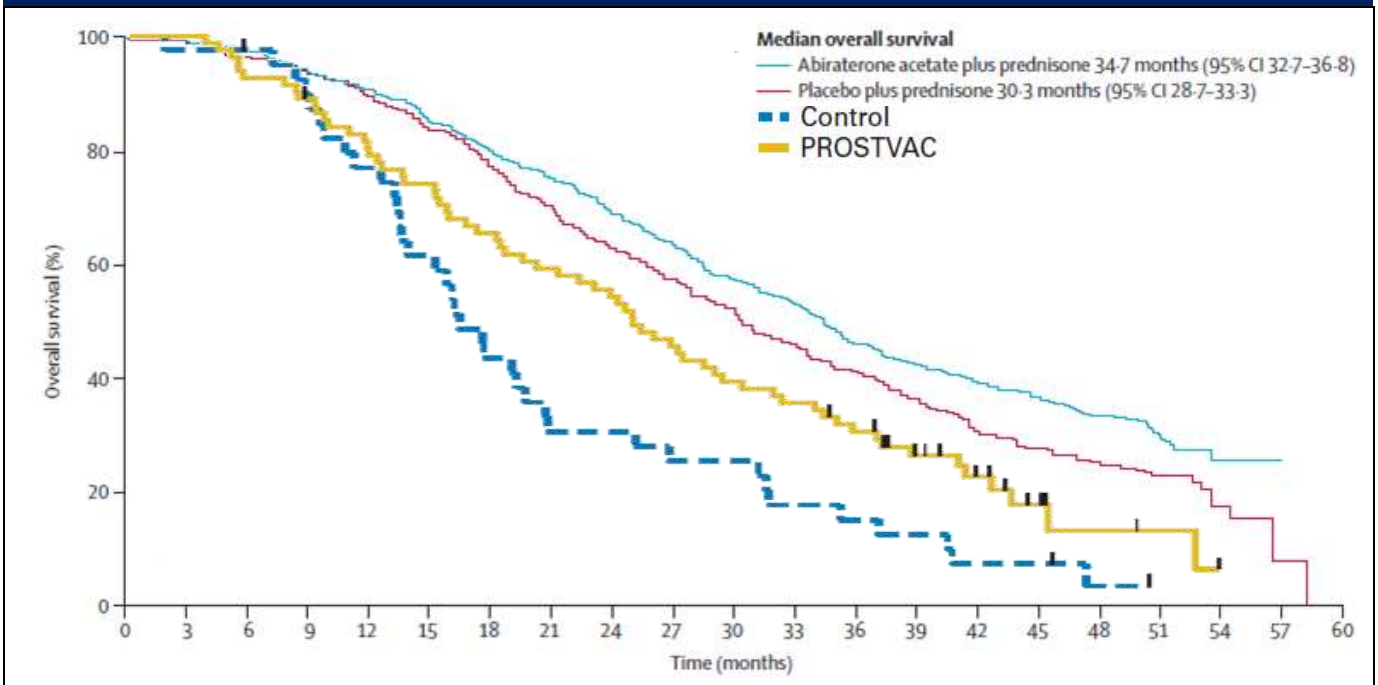
* There is an additional hope that initial success in killing PSA-expressing cells will lead to the release of other tumor-associated antigens that will in turn generate their own immune responses, leading to so-called antigen spread beyond PSA alone.

> Therion shut down in 2006 after disappointing clinical trial results from a cancer vaccine that didn't pass late-stage clinical trials.
>
> Investors pulled the plug. But Prostvac's Phase II trial results were still pending. Much of its technology was developed by both Therion and the National Cancer Institute, to which the Prostvac rights reverted after NCI sued Therion's investors. Danish company Bavarian Nordic got to claim all the glory instead. Financial details weren't disclosed, but Bavarian Nordic licensed the drug not too long ago from the National Cancer Institute.
>
> Bavarian Nordic took the initial study results and called patients from the trial to see who had survived over the past four years. That data follow-up led to the good news announced earlier this month.

As a result of the trial's disjointed management, researchers had no information about treatments received by the patients after they went "off study"; an imbalance in those treatments, like a greater fraction of Prostvac-group members than placebo-group members going on to take the life-extending chemotherapeutic agent docetaxel, could easily have distorted overall-survival comparisons. Moreover, once study participants saw their disease progress, they were unblinded with respect to group membership, after which 19 of the 40 patients in the placebo group opted to try Prostvac. Thus, while the original progression-free-survival criterion used a "clean" comparison of Prostvac to no Prostvac, the overall-survival analysis compared a treatment group, all of which received Prostvac, to a "placebo" group, half of which had also received the treatment. If Prostvac did indeed enhance survival, the anomalously bad survival of the placebo arm would be even more mysterious, since half of its members actually received the treatment only a few months later than their peers in the other arm.

In reality, though, Prostvac's OS results were not impressive. The trial only enrolled men with mCRPC who were minimally symptomatic or asymptomatic, meaning, among other things, that they had not previously received chemotherapy, had no visceral metastases, had Gleason scores (a histological measure of cancer severity) less than 8, and so on; in short, they were in relatively good condition. Below we take the survival results from another trial in a similar population – the Phase III, placebo-controlled study of abiraterone (Zytiga) in "asymptomatic or mildly symptomatic patients with chemotherapy-naive prostate cancer" (3) – and superimpose them over the OS graph from the Prostvac Phase II paper. Not only does the abiraterone arm, with median OS of 34.7 months, dramatically and consistently outperform the Prostvac arm; *so too does the abiraterone study's placebo arm,* with median OS of 30.3 months. Meanwhile, the Prostvac-trial placebo group looks terrible relative to the corresponding group in the abiraterone, dying off at a much higher rate.

Overall Survival: Abiraterone & Control vs. Prostvac & Control



Source: Ryan et al. 2015 (3), Kantoff et al. 2010 (6), Kerrisdale analysis

But it's not just abiraterone (and its placebo group) that makes Prostvac look bad. Below we compile survival data from a range of major studies involving minimally symptomatic, primarily chemotherapy-naïve men with mCRPC. The Prostvac treatment arm is clearly nothing special, even relative to older studies. For example, minimally symptomatic men enrolled in the TAX-327 study of docetaxel (initiated back in 2000) had median OS of 25.6 months, while even *placebo* groups in somewhat more recent studies of tasquinimod, orteronel, and enzalutamide had median OS of ~30 months. Without an anomalously bad control group to make it look better, Prostvac on its own would appear no better than a typical placebo (and perhaps slightly worse). Even worse, several of the treatments that *outperformed* Prostvac in comparable minimally symptomatic populations – GVAX, tasquinimod, and orteronel – failed to meet OS endpoints in Phase III trials, while Provenge is a controversial commercial flop. Prostvac's failure to outshine treatments that themselves have been abandoned as failures is obviously a bad omen for its own Phase III success.

With respect to Provenge, while the headline performance of the sipuleucel-T (Provenge) placebo group – median OS of 21.7 months – is somewhat worse than that of the Prostvac treatment group, the Provenge data are themselves still hotly debated, and some have argued that the "placebo" regimen (which entailed the removal of white blood cells from circulation) actually harmed patients, reducing their overall survival (27). If so, the Provenge "placebo" group would clearly be an inappropriate benchmark since it would be easy to beat. Even setting aside that hypothesis, the Provenge trial participants had worse baseline disease characteristics than the Prostvac trial participants. For instance, 18% had previously gone through chemotherapy (0% for Prostvac), implying a more advanced disease state, and 25% had

Gleason scores greater than 7 (0% for Prostvac), implying more aggressive tumors (27). Thus, the fact that the Prostvac treatment group's median OS was slightly higher than the Provenge placebo group's says very little, given that the former was clearly in better health to begin with.

Similarly, the headline results for GVAX showed 20.7 months of median OS for the treatment group and 21.7 months for the docetaxel control, worse than the results for the Prostvac treatment group. However, 47% of these patients had Gleason scores of 8 or higher, and 13% had visceral metastases, both of which predict poor survival. When researchers looked only at men with relatively good prognoses (predicted survival greater than 18 months based on the Halabi 2003 model), median OS for GVAX approached 30 months, and even the placebo group enjoyed median OS of 27.1 months. As with the Provenge data, while the headline figures for GVAX may appear to put Prostvac in a positive light, closer scrutiny and proper apples-to-apples comparisons reveal a consistent story: patients treated with Prostvac experience unremarkable outcomes, little different from similar patients treated with placebo.

Median Overall Survival in Men with Minimally Symptomatic mCRPC

Topic of study	Year initiated	Treatment group	Median OS	*n*	Ref
Prostvac	2003	Prostvac-VF + GM-CSF	25.1	82	6
		Vaccinia/fowlpox + saline	16.6	40	
Docetaxel (Taxotere)	2000	All minimally symptomatic men	25.6	110	1
		3-weekly docetaxel + pred.	28.4	29	
		Weekly docetaxel + pred.	25.9	33	
		Mitoxantrone + pred.	22.0	48	
Royal Marsden trial participants	2003	Various investigational agents	30.5	238	14
Sipuleucel-T (Provenge)	2003	Sipuleucel-T	25.8	341	28, 29
		Placebo	21.7	171	
		Sipuleucel-T + docetaxel	28.5	195	
		Placebo + docetaxel	27.1	86	
GVAX	2004	GVAX (predicted survival > 18mo)	29.7	~132	27
		Docetaxel + pred. (predicted survival > 18mo)	27.1	~132	
Queen Elizabeth Hospital, men with CRPC found upon diagnosis to have metastases	2006	Various (59% chemotherapy)	38.7	78	64
Tasquinimod	2007	Tasquinimod	33.4	134	2
		Placebo	30.4	67	
Abiraterone (Zytiga)	2009	Abiraterone acetate + pred.	34.7	546	3
		Placebo + pred.	30.3	542	
Orteronel	2010	Orteronel + pred.	31.4	781	5
		Placebo + pred.	29.5	779	
Enzalutamide (Xtandi)	2010	Enzalutamide	32.4	872	4
		Placebo	30.2	845	

Source: studies noted in "Ref" column, Kerrisdale analysis

The Halabi 2003 model, which incorporates performance status, Gleason score, lactate dehydrogenase levels, alkaline phosphatase levels, PSA levels, hemoglobin levels, and the presence of visceral disease, is an important part of how Bavarian Nordic presents the data on

Prostvac, and it can be a useful summary of key prognostic factors; patients with lower Halabi-predicted survival do in fact tend to die sooner. But it's a flawed and out-of-date benchmark, as its creators readily admit (13), and in real-world patient groups, survival typically exceeds what the model forecasts, sometimes by a large margin. Below we highlight the difference between forecasted and actual median OS in several mCRPC studies that provide these data:

Predicted and Actual Survival in mCRPC

	Prostvac		Sipuleucel-T		GVAX		Royal Marsden
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	
Median OS in months:							
Halabi-predicted	22.5	20.4	20.3	21.2	16.0	16.0	21.0
Actual	25.1	16.6	25.8	21.7	20.7	21.7	30.5
Difference	*2.6*	*(3.8)*	*5.5*	*0.5*	*4.7*	*5.7*	*9.5*

Source: Kantoff et al. 2010 (6), Kantoff et al. 2010 (28), Higano et al. 2009 (29), Omlin et al. 2013 (14), Kerrisdale analysis

For patients treated in clinical trials at the Royal Marsden Hospital, including many who received experimental agents that proved to be ineffective, median OS exceeded the Halabi 2003 forecast by 9.5 months. By contrast, the Prostvac treatment group only outperformed the model by 2.6 months – the worst of any treatment group. Both the GVAX treatment and placebo groups enjoyed substantially better relative performance compared to Prostvac – yet the GVAX trial was a complete failure.

What stands out from this table once more is the unusually bad outcome in the Prostvac placebo group – the only one that actually did worse than the otherwise overly conservative Halabi 2003 model predicted. Ordinarily, randomization alone is supposed to roughly equalize the baseline patient characteristics in a well-run clinical trial, leaving no important imbalances between arms. In the Prostvac trial, however, randomization apparently didn't do the trick, resulting in a "head start" for the treatment group, according to the Halabi 2003 model, of 2.1 months. However, this model understates the true magnitude of the "head start," because it neglects a key element: age.

Below we return to the same set of mCRPC studies already reviewed and compile median ages for the treatment and control groups. (When sub-group ages are not available, we show the figures for the overall populations.) Across all non-Prostvac studies, the median of the median ages is 71 years, right in line with the median age in the Prostvac treatment group. However, the Prostvac control group is a major outlier at 79 years old. No other group is anywhere close, and no other study has anything like the 7.5-year discrepancy in median age between treatment and control arms seen in the Prostvac study; the second-largest gap, in the sipuleucel-T trial, is only 2 years, and it favors the placebo arm, not the treatment arm. The opposite is true for Prostvac: younger patients disproportionately received the vaccine.

Median Overall Survival in Men with Minimally Symptomatic mCRPC

Topic of study	Treatment group	Median age (yrs)*	Ref
Prostvac	Prostvac-VF + GM-CSF	71.5	6
	Vaccinia/fowlpox + saline	79	
Docetaxel (Taxotere)	3-weekly docetaxel + pred.	68	30
	Weekly docetaxel + pred.	69	
	Mitoxantrone + pred.	68	
Royal Marsden trial participants	Various investigational agents	67.2	14
Sipuleucel-T (Provenge)	Sipuleucel-T	72	28
	Placebo	70	
GVAX	GVAX	71	31
	Docetaxel	71	
Queen Elizabeth Hospital	Various	67.8	64
Tasquinimod†	Tasquinimod	72.3	2
	Placebo	73.2	
Abiraterone (Zytiga)	Abiraterone acetate + pred.	71.0	32
	Placebo + pred.	70.0	
Orteronel	Orteronel + pred.	71.0	5
	Placebo + pred.	72.0	
Enzalutamide (Xtandi)	Enzalutamide	72.0	4
	Placebo	71.0	

* Number of decimal points shown based on presentation in original publication.

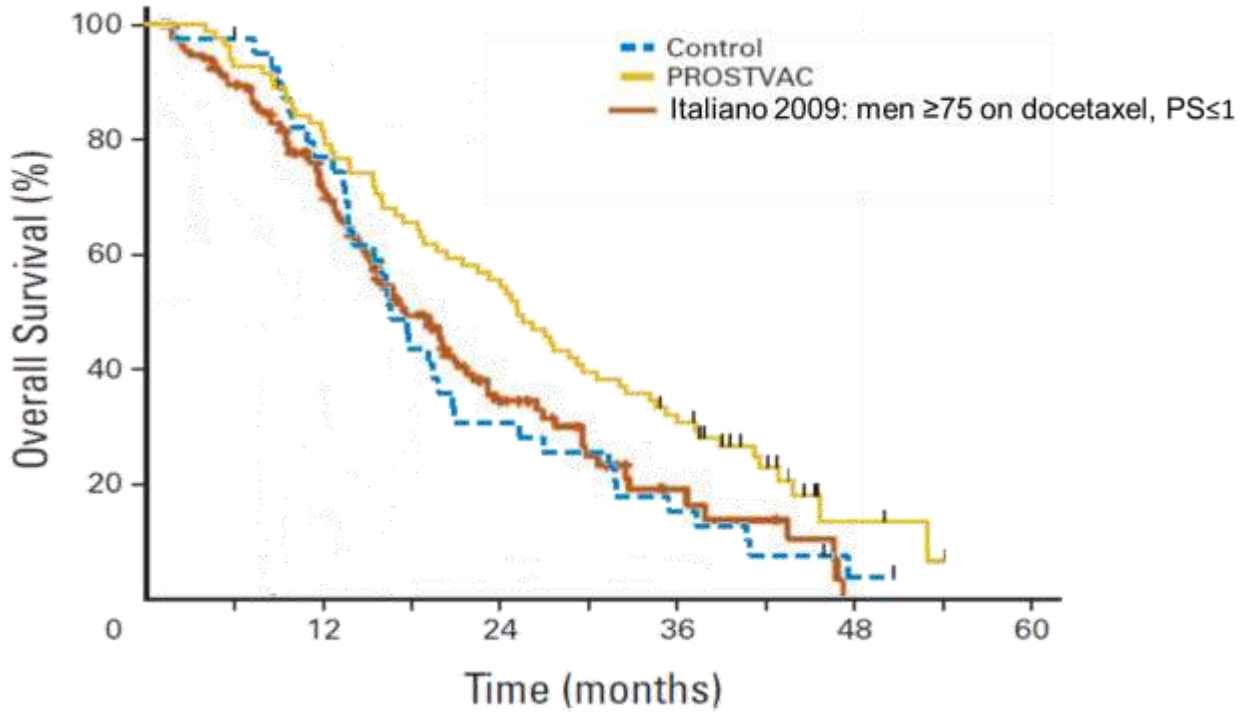
† Median not disclosed; age shown is mean.

Source: studies noted in "Ref" column, Kerrisdale analysis

The Prostvac Phase II paper acknowledges the age imbalance but dismisses its importance with a brief phrase – "age is not a significant prognostic factor in prostate cancer" – and a citation to the Halabi 2003 model. To be sure, this model does not make use of age in order to predict survival. However, as we have already seen, the Halabi 2003 model is outdated, drawing on clinical trials conducted between 1992 and 1998, and, like any model, it does not capture all the relevant factors. Furthermore, the learning sample used to construct the model suffers from a fairly narrow age range, with an interquartile range (IQR) of 65 to 75. This is similar to (albeit younger than) the Prostvac treatment group's IQR of 67 to 79 but looks quite different from the control group's IQR of 72 to 83, with a 7-to-8-year shift in the elderly direction. In other words, the data on which the Halabi 2003 model was built come from a substantially younger population than the Prostvac control group, making it hazardous to extrapolate from one to the other.

Although there aren't many studies that specifically examine the relationship between age and survival in mCRPC, the available evidence makes it clear that, as common sense would dictate, elderly men with mCRPC tend to have fewer years ahead of them than their younger counterparts. One of the most direct illustrations comes from a retrospective study reviewing "the clinical files of 175 patients aged ≥ 75 yr with CRPC treated with first-line docetaxel in nine French tertiary care cancer centres from 2000 to 2007" (30). Median age was 78 years; notably, then, a study specifically focused on "elderly patients" actually had a median age one year *younger* than that of the Prostvac control group. Median OS among these elderly patients on docetaxel was 15 months – very different from the ~25 to 30 months seen in mainstream studies but similar to the 16.6 months seen in the Prostvac control group. Better still, when researchers disaggregated survival based on "performance status" – a simple measure of patient health in which 0 means "fully active," 1 indicates restrictions on "physically strenuous" activity only, 2 and 3 indicate wider-ranging restrictions, and 4 means death – they found that elderly patients with performance statuses of 0 or 1 had median OS of 17.5 months, slightly *higher* than the Prostvac control group, 100% of which had a performance status of 0 or 1. Similarly, elderly patients without visceral disease had median OS of 16.4 months, almost identical to the Prostvac control group, 100% of which likewise lacked visceral disease. Below we combine the survival curve from the Prostvac control group (in blue) with the survival curve from the retrospective French study for men 75 and older with performance status of 0 or 1 (in red-orange). The curves are effectively indistinguishable.

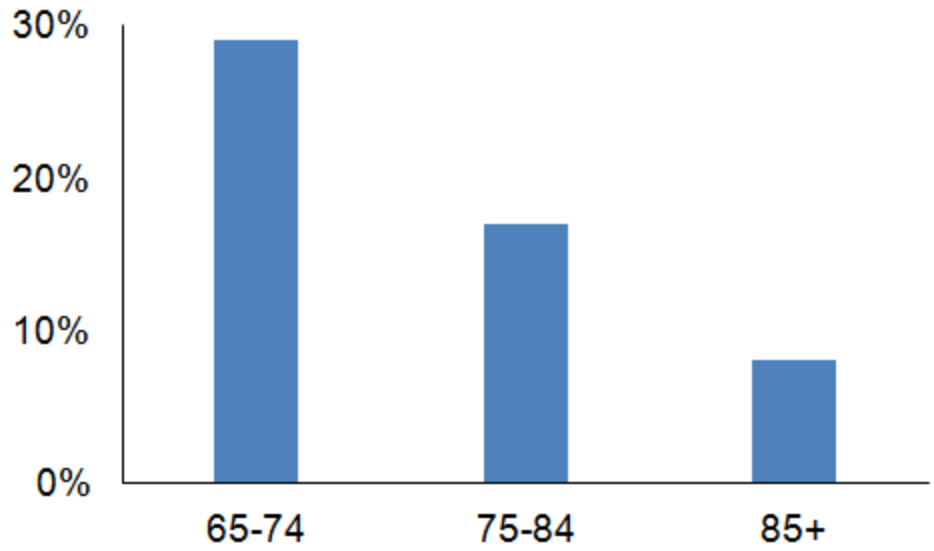
Median Overall Survival: Prostvac Phase II Study vs. Elderly Patients on Docetaxel



Source: Kantoff et al. 2010 (6), Italiano et al. 2009 (30), Kerrisdale analysis

These data are consistent with other lines of evidence clearly demonstrating that age is, in fact, a prognostic factor in mCRPC. One recent publication, based on detailed registry data from 2000 to 2009, showed that survival rates for men with metastatic prostate cancer clearly *do* differ by age; for instance, comparing men 85 or older with those aged 65-74 and looking out five years from diagnosis, the older men are *less than a third* as likely to still be alive (9).

Metastatic Prostate Cancer: 5-Year Survival Probability by Age Group



Source: Howlader 2014 (9), Kerrisdale analysis

A 2006 study by Halabi *et al.* came to a similar conclusion (10), noting that "[t]he results of this analysis support the hypothesis that older men [with mCRPC] have a worse prognosis than their younger counterparts," with 60-to-69-year-olds enjoying similar survival to 70-79-year-olds – likely accounting for the misperception in other studies that age doesn't matter – but surviving almost *twice as long* as 80-89-year-olds (who constituted roughly half of the Prostvac Phase II placebo group). Below we summarize additional data points on median OS among elderly men with mCRPC. While each study has its limitations, together they paint a fairly consistent picture, especially the older studies: median OS in the mid-teens, with a potential improvement indicated in the large-scale abiraterone trial.

Median Overall Survival in Elderly Men with mCRPC

Population	Age cutoff	Median age	Year initiated	Treatment	Median OS	*n*	Ref
9 French tertiary-care cancer centres	≥75	78	2000	Docetaxel	15	175	30
TAX-327 clinical trial	≥75	not stated	2000	3-weekly docetaxel	18.9	68	67
				Weekly docetaxel	16.1	71	
				Mitoxantrone	12.5	68	
5 Japanese hospitals	≥75	77	2005	Docetaxel	15.5	20	65
3 Australian hospitals	≥80	83	2006	Docetaxel	13.4	20	66
COU-AA-302 clinical trial	≥75	79	2009	Abiraterone	28.6	185	68
		79		Placebo (initially)	25.6	165	

Source: studies noted in "Ref" column, Kerrisdale analysis

In sum, the results of the Prostvac Phase II study are badly confounded by age differences, and the likely magnitude of the age impact could well be so large as to eliminate any apparent benefit of Prostvac over placebo. Rather than measure the efficacy of Prostvac, the study actually measured the survival advantage of being younger rather than older. In the COU-AA-302 trial for abiraterone, for instance, younger (<75 years old) men on abiraterone experienced median OS 6.7 months higher than their older counterparts, while men on placebo saw a 5.3-month benefit from age alone. Alternatively, consider again the results of the subgroup analysis from the main Provenge Phase III study, initiated around the same time as the Prostvac Phase II study: placebo recipients who went on take docetaxel had median OS of 27.1 months. Meanwhile, based on the French study, *elderly* men in good condition taking docetaxel have median OS of only 17.5 months. **This implies an almost 10-month advantage in median overall survival based purely on an age difference comparable to that observed in the Prostvac Phase II study.** Thus Prostvac's apparent 8.5-month survival benefit plausibly stems *entirely* from the age imbalance, with no room left over for Prostvac itself to have any benefit.

While this age-based hypothesis is compelling and makes sense of the otherwise bizarre underperformance of the Prostvac control group, the explanation for this underperformance is less important than the indisputable fact that the control group represents an uninformative benchmark. Beating such an anomalously bad result is not much of an achievement. If the treatment group's overall survival were itself more impressive, standing out relative to other comparable studies, then the weakness of the control group might not matter; in reality, though, the treatment group shows no meaningful advantage over other studies' *placebo* arms, let alone patients who received clearly beneficial drugs like abiraterone and enzalutamide. There is simply nothing there to see. Prostvac does not enhance survival.

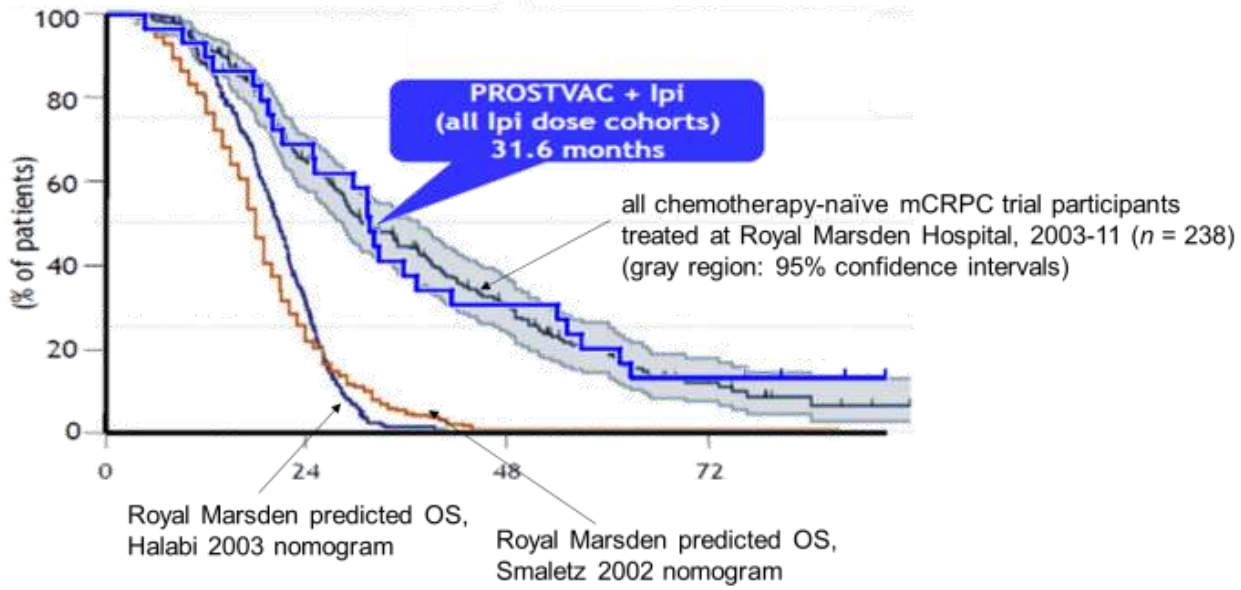
Early-Stage Combination-Therapy Data Further Demonstrate Prostvac's Inefficacy

Though Prostvac's Phase III results will only be available in late 2016 or 2017, we already have additional confirmation of its inefficacy via the very combination study that Bavarian Nordic touts

as demonstrating its promise. In that study, 30 patients received both Prostvac and the checkpoint inhibitor ipilimumab (Yervoy), with different sub-groups receiving 1, 3, 5, and 10 mg/kg doses of ipilimumab. There was no placebo or other comparison group, and, given the small sample size, "[t]here was no significant difference in overall survival on the basis of dose" (13), although Bavarian Nordic likes to ignore such statistical niceties and highlight the 37.2-month median OS in the 15-person cohort receiving the highest ipilimumab dose. Across all doses, however, the median OS was only 31.6 months, a result that, while superior to the Prostvac-only Phase II study, looks pedestrian relative to the other large mCRPC trials already reviewed and is worse, for example, than what tasquinimod achieved in a much larger Phase II study. (Tasquinimod's developer has since announced that the drug failed to outperform placebo in an even larger Phase III.)

Below we superimpose the survival curve from the Prostvac/ipilimumab trial over the data generated by all clinical-trial participants at the UK's Royal Marsden Hospital from 2003 to 2011. Relative to this historical control, the Prostvac combination data have nothing to recommend them. Moreover, the graph again underscores the irrelevance of the Halabi 2003 model as a baseline for expected survival since it badly underestimates real-world outcomes.

Prostvac/Ipilimumab Survival Data Compared to Royal Marsden Historical Control



Source: Bavarian Nordic April 2015 investor presentation, Omlin et al. 2013 (14), Kerrisdale analysis

Even if the combination trial had produced better results, the obvious question would be to what degree those results were attributable to Prostvac or to ipilimumab. While ipilimumab has so far produced disappointing survival outcomes in post-chemotherapy mCRPC (19), the drug is indisputably biologically active (leading to immune-related adverse effects) and has well-established efficacy in melanoma; many prostate-cancer researchers and clinicians continue to

hold out hope that it will prove to increase survival in the right patient subset, such as men with earlier-stage disease or no visceral metastases. (Among those with "favourable prognostic features" in the post-chemotherapy ipilimumab-monotherapy trial, median OS for the treatment group exceeded that for the placebo group by 6.9 months.) Thus Prostvac/ipilimumab combination therapy might ultimately work simply because ipilimumab might work in prostate cancer, not because Prostvac itself has any effect. Indeed, not only was median OS unimpressive; the combination therapy also failed to elicit a meaningful immune response to Prostvac's targeted antigen, PSA. Of nine evaluable patients, only two demonstrated *any* detectable increase in their T-cell immune response to PSA, of which one was close to the lower bound of detectability. In fact, one patient who showed a T-cell response to PSA *prior* to vaccination saw a *decline* in the magnitude of his response after vaccination (13). As we will detail further, numerous other Prostvac studies reveal the same type of negligible and inconsistent immune response to PSA, calling into question Prostvac's entire raison d'être. Even if Prostvac performed as intended, it would likely still fail to help patients, but it appears to fall short of even that low standard.

Interestingly, there is a clear precedent for the failure of a vaccine to add any value in combination with a checkpoint inhibitor: the Phase III trial of ipilimumab for melanoma (32). That study contained three arms: 1) ipilimumab plus gp100, a peptide vaccine targeted at a melanoma-associated glycoprotein; 2) ipilimumab alone; and 3) gp100 alone. While vaccine-only patients experienced median OS of 6.4 months, ipilimumab-only patients saw 10.1 months, while ipilimumab/vaccine combination patients saw an almost identical 10.0 months. In short, the vaccine contributed nothing whatsoever to the efficacy of ipilimumab in melanoma, just as Prostvac appears to contribute nothing in prostate cancer.

Prostvac Does Not Slow Disease Progression or Elicit Significant Immune Responses

Since the purpose of Prostvac is to trigger an immune response to the patient's cancer, centered (at least initially) on the tumor-associated antigen PSA, it would seem logical to expect the treatment to slow down disease progression. However, as previously discussed, the Phase II study failed to show any improvement in progression-free survival. A smaller Phase II study, pairing Prostvac with docetaxel, produced similar results: the 14 patients in the Prostvac-only group saw median time to progression of 1.8 months, while the 14 patients in the Prostvac/docetaxel combination group saw median time to progression of 3.2 months, almost identical to the 3.7 months experienced by a historical control *using docetaxel only* on the same dose and schedule and in a similar patient population at the same institution where the trial was conducted (33). In other words, Prostvac plus docetaxel led to the same time to progression as would be expected for docetaxel alone, consistent with Prostvac's failure to improve progression-free survival in the larger Phase II study. Moreover, in a 2011 review of several different prostate-cancer treatments that analyzed changes in the growth rate of circulating PSA levels, under the theory that effective treatments would tend to cause PSA measurements to

increase more slowly (even if they didn't cause PSA to actually decline), researchers found that Prostvac again failed to have any measurable impact (34) (bold added):

> Thus, the data...show that successive *chemotherapy regimens* have achieved greater efficacy as evidenced by both greater reductions in *g* [PSA growth rate], and a greater number of patients achieving a complete PSA response**. Such an effect, however, was not observed with the PSA-TRICOM vaccine where on-study *g* values were not statistically different (*t*-test, *P* = 0.46), from pre-enrollment *g* values for patients receiving vaccine.**

Not only was the change in PSA growth rate induced by Prostvac not *statistically* significant; it was indistinguishable from zero, with the log daily growth rate going from -2.0 to -2.1. While the authors, taking Prostvac's putative 8.5-month survival benefit at face value, cast about for some plausible explanation of the inconsistency between, on the one hand, the vaccine's strange inability to at least slow down increases in PSA levels and, on the other hand, its apparent clinical efficacy, Occam's razor dictates a simpler conclusion: Prostvac is ineffective across the board. It doesn't slow down PSA growth, just like it doesn't slow down other measures of disease progression, just like it doesn't actually enhance overall survival outside of one distorted and misleading Phase II study.

Furthermore, notwithstanding strained rhetoric to the contrary, Prostvac barely elicits any measurable immune responses. This runs counter to its entire proposed mechanism of action: in the words of one study, Prostvac "is a novel vector-based vaccine designed to generate a robust immune response against prostate-specific antigen (PSA)-expressing tumor cells" (22). Prostvac advocates readily admit that the vaccine does not induce a *humoral* immune response to PSA, with almost no patients generating anti-PSA antibodies. (This is itself somewhat peculiar: even Provenge, a dendritic-cell vaccine that targets prostatic acid phosphatase (PAP), not PSA, has been shown to cause a two-fold or greater increase in PSA-specific antibodies in 39% of patients (35).) However, they argue that there is "clear evidence of immune responses to PSA in the majority of patients post-vaccination" – specifically, T-cell responses.

But on closer inspection, those responses amount to very little. Below we show the key table from a recent review paper summarizing T-cell responses to Prostvac across a number of different small studies (22).

Table 1. PSA-specific T cells induced after vaccination with poxviral vaccines encoding PSA

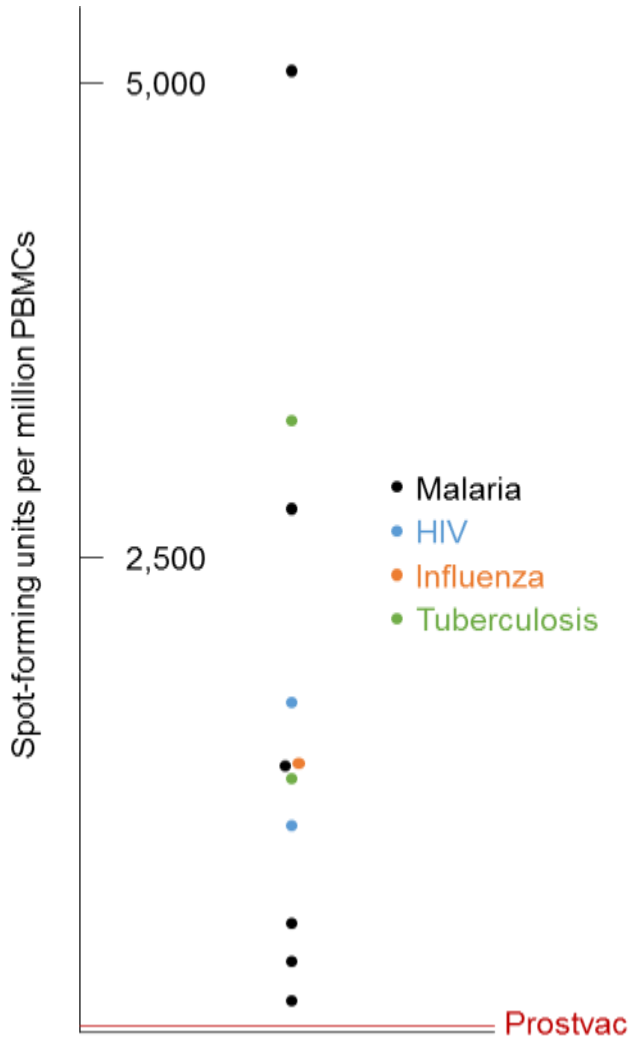
Disease state	Percentage of patients with PSA+ ELISPOT (≥2-fold increase)	Trial (NCT #; ref)
Localized	72.0% (18/25)	NCT00005916 (11, 15)
bCRPC	62.5% (5/8)	NCT00020254 (14)
bCRPC	25.0% (1/4)	NCT00450463 (17)
mCRPC	48.6% (17/35)	NCT00060528 (9)
mCRPC	11.1% (1/9)	NCT00113984 (13)
mCRPC	73.9% (17/23)	NCT00045227 (16)
Total	**56.7% (59/104)**	
	Median	**Min.–Max.**
Baseline PSA-specific T cells[a]	5.00	5.00–20.00
Maximum post-vaccine PSA-specific T cells[a]	30.00	10.00–202.51
Fold increase in PSA-specific T cells post-vaccine	5.00	2.00–19.33
Flu-specific T cells[a]	33.33	6.67–343.29

NOTE: Levels of circulating PSA-specific T cells in patients whose PSA-specific T cells increased 2-fold or more following vaccine (57% or 59/104 evaluated patients), and comparison with baseline levels of circulating influenza matrix protein-specific T cells in these same patients. Of 193 post-vaccine ELISPOTs, 60% (115/193) had a 2-fold increase in PSA-specific T cells compared with baseline, with 31 of 59 patients having more than 1 post-vaccine ELISPOT.
Abbreviations: Localized, localized prostate cancer; bCRPC, biochemically progressive (nonmetastatic) castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.
[a]Spots per million.

First, consider the "percentage of patients with PSA+ ELISPOT," which refers to the fraction of evaluated patients who demonstrate a meaningful level of PSA-specific T cells post-vaccination. (Requiring at least a 2-fold increase in the ELISPOT assay is fairly conventional, although some researchers argue for stricter and more rigorous rules (36) (37).) Across six different patient groups, the fraction of individuals who experienced *any* PSA-specific T-cell response ranged from 11% to 74%, averaging just 57% in aggregate; equivalently, 43% experienced no change in PSA-specific T-cell levels. By the standards of ordinary prophylactic vaccines, this is a stunningly weak result.

Even for the patients who did record an increase in PSA-specific T cells, the absolute magnitude of the response was tiny. While the table draws attention to the five-fold median increase in PSA-specific T cells (among the slender majority of patients experiencing an increase), which might sound impressive, it is a large increase off of a very low baseline. The median level of post-vaccine PSA-specific T cells is only 30 per million PBMCs (peripheral blood mononuclear cells). For reference, the following chart depicts the T-cell responses that were obtained by *unsuccessful* viral-vector vaccines for several major infectious diseases (38). The figures range from a low of 195 per million to a high of 5,090 per million, *one to two orders of magnitude higher than the PSA-specific response elicited by Prostvac* (in the fraction of patients who experienced any meaningful response at all).

Immunogenicity of Prostvac vs. Other T-Cell-Inducing Vaccines



Source: Gilbert 2011 (38), Kerrisdale analysis
Includes all viral-vector vaccines from Gilbert 2011 Table 1 (and thus excludes DNA and BCG vaccines and sip-T).

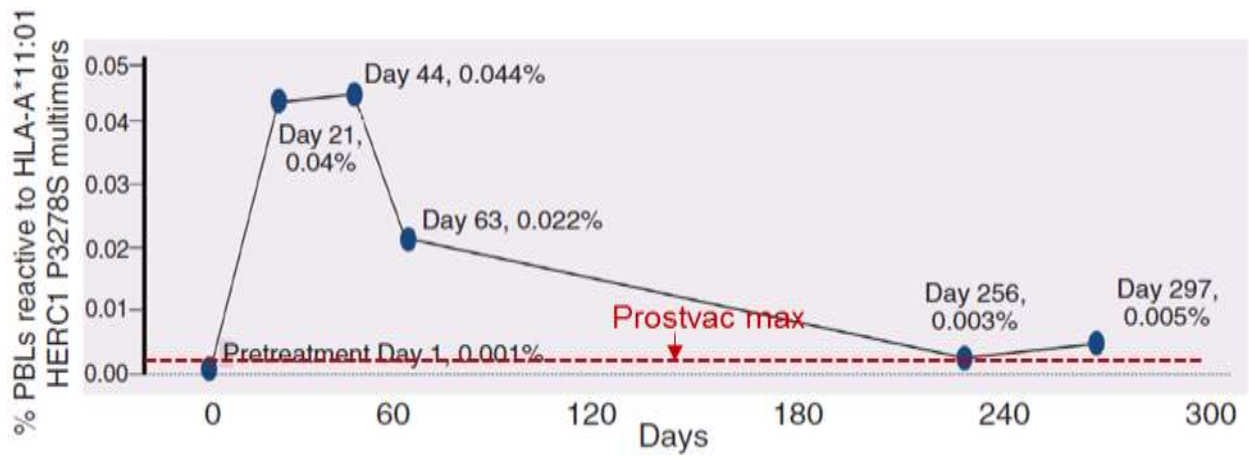
Indeed, analysts looking at ELISPOT results to assess T-cell-based treatments typically expect hundreds or thousands of spots per million PBMCs, not the minuscule 30 seen with Prostvac; in fact, some researchers regard 25 per million as the lower limit of detection, and others require more than 50 or 55 spots before regarding responses as meaningful (36) (37). When used as a smallpox vaccine, vaccinia virus itself – the vector for the Prostvac prime injection – causes a median specific T-cell response of ~300 per million PBMCs (39). Thus, the typical vaccinia-specific T-cell response is at least 10x larger than the typical PSA-specific T-cell response caused by Prostvac. It is counterintuitive, to say the least, to suggest that such a tiny immune response, 10 or 100 times weaker than what typical vaccines produce, could overcome the manifold immunosuppressive mechanisms associated with cancer and confer any clinical benefit.

This phenomenon has not escaped the notice of other researchers. A recent review paper on cancer vaccines made the same point using a slightly different metric, explicitly calling out Prostvac along the way and dubbing results of its ilk "disheartening" (emphasis added) (69):

> Two of the most effective human viral vaccines, YF-vax for yellow fever and Dryvax for small pox induce a CD8 T-cell population of **around 5-30% of the entire CD8 population** in the peripheral blood....In comparison to these viral vaccine regimes in healthy hosts, current cancer vaccines only induce around a 2-fold to 10-fold increase in antigen specific T-cells. Prostvac...increased the number of PSA specific T-cells in patients by on average 5-fold to produce 30 vaccine specific cells per million PBMCs. **This number is around 0.03% of the total CD8 T-cell population.**

Consider another data point from a recent study published in *Science*: a single non–small-cell–lung-cancer (NSCLC) patient who enjoyed an "exceptional response" to pembrolizumab, an anti-PD-1 checkpoint inhibitor. Trying to determine what drove this response, researchers discovered a large increase in $CD8^+$ T cells targeting a particular patient-specific mutation in the *HERC1* gene. After administration of pembrolizumab, these mutation-targeting T cells expanded to 400-440 per million PBMCs within the first several weeks of treatment – 13 to 15 times higher than the maximum PSA-specific immune response generated by Prostvac. 256 days after treatment, the researchers wrote, "this T cell response returned to levels just above background" (40). But the *minimum* magnitude of this T-cell response, characterized as "just above background," was equal to the maximum T-cell response seen with Prostvac (30 per million). This case study reveals the hollowness of some of the excuses made for Prostvac's derisory immunogenicity, like the notion that perhaps the sought-after PSA-specific T cells migrate into tumors and thus evade detection in the peripheral blood. This NSCLC patient clearly benefited from pembrolizumab and clearly mounted a tumor-specific T-cell response, and this response was fully detectable in multiple blood samples.

Specific T-Cell Response in NSCLC Patient Benefiting from Pembrolizumab



Source: Rizvi 2015 (40), Kerrisdale analysis

All of this evidence is consistent:

- Prostvac does not improve progression-free survival.
- Prostvac does not cause PSA levels to decline.
- Prostvac does not reduce the rate of increase in PSA levels.
- Prostvac does not trigger the production of PSA-specific antibodies.
- Prostvac fails to elicit any measurable PSA-specific T-cell response in a large fraction of patients and only elicits a minuscule immune response in the others.
- Prostvac does not produce noticeably better overall survival than what's seen with placebo in numerous other mCRPC trials.
- Prostvac only *appears* to enhance overall survival when compared with an anomalously poor placebo group, likely because of imbalances in age and other prognostic factors.

In short, Prostvac is ineffective across the board. It's worthless.

There's nothing remarkable about this conclusion: time after time, similar approaches to therapeutic vaccines for cancer have failed. Simply loading up a viral vector with a tumor-associated antigen – in particular, a normal self-antigen that the immune system has spent decades "learning" to tolerate, unlike the mutated, often patient-specific tumor *neo*antigens to which checkpoint inhibitors appear to unleash responses – has never worked, and scientists now understand the many reasons why such approaches cannot succeed. There is no good reason to believe that Prostvac will be an exception to this pattern.

IV. Therapeutic Cancer Vaccines Have a Long History of Failure

Eleven years ago, Steven A. Rosenberg and two co-authors took stock of cancer immunotherapy research and noted that the vaccine approach, which had initially generated a lot of excitement, did not seem to be panning out (41):

> Great progress has been made in the field of tumor immunology in the past decade, but optimism about the clinical application of currently available cancer vaccine approaches is based more on surrogate endpoints than on clinical tumor regression. In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others.
>
> ... In the field of cancer immunotherapy, most enthusiasm has been directed at the use of cancer vaccines—active immunizations designed to treat growing tumors. A recent review of dendritic cell vaccines mentioned 98 published studies involving over 1,000 patients. A tabulation in 2003 listed 216 ongoing vaccine clinical trials in cancer patients. These studies were conducted, and others are underway, despite the absence of convincing animal data that cancer vaccines used alone can affect invasive, vascularized tumors.
>
> ...[I]nvestigators have been enthusiastic about the use of active immunization for patients with solid tumors because of an over-reliance on surrogate and subjective endpoints, such as histologic evidence of tumor necrosis or lymphocyte infiltration, rather than objective cancer regressions. Thus, despite the absence of any significant proportion of patients who achieved clinical responses, many cancer vaccine trials have been optimistically reported because surrogate or subjective endpoints were achieved.
>
> In light of these very large numbers of patients treated with vaccines and the exceedingly low objective response rates reported for the cancer types included in Table 5, a reevaluation of future directions for cancer immunotherapy trials would be valuable.

Rosenberg is today regarded as one of the great pioneers of effective cancer immunotherapy, and he and his collaborators have achieved stunning clinical results, including apparent cures, using non-vaccine immunotherapies like adoptive cell transfers. In stark contrast, the vaccine approach has continued to flounder. In 2011, Rosenberg's group reviewed post-2004 vaccine data and again found them lacking. Below we reproduce a key table showing the paucity of objective responses (i.e. tumor shrinkage or elimination) across a wide array of vaccine types (peptide, dendritic cell, virus, protein, tumor cell, and plasmid DNA) and a wide range of cancer types (melanoma, prostate, kidney, lung, breast, brain, esophagus, urothelial, gynecologic, thyroid, prostate, colorectal, mesothelioma, and head and neck):

Table 1. Results of selected early phase therapeutic vaccine trials in patients with metastatic solid cancers since 2004

Vaccine type	Reference	Cancer type	Vaccine	Total patients	Patients responding
Peptide	Fourcade et al. (155)	Melanoma	NY-ESO-1 + CpG	8	0
	*Slingluff Jr et al. (156)	Melanoma	Multi-epitope vaccine alone	17	2 (PR)
	Celis (157)	Melanoma	gp100 + IFA ± GM-CSF	28	0
	Khong et al. (158)	Melanoma	NY-ESO-1 + IFA	37	1 (PR)
	Suekane et al. (159)	Kidney	Multi-epitope vaccine + IFA	10	0
	Uemura et al. (160)	Kidney	CA9 multi-epitope vaccine + IFA	23	3 (PR)
	Barve et al. (161)	Lung	Multi-epitope vaccine + IFA	63	1 (CR)/1 (PR)
	Bolonaki et al. (162)	Lung	Telomerase peptides + IFA	22	0
	Tsuruma et al. (163)	Breast	Survivin peptide ± IFA	17	0
	Izumoto et al. (164)	Brain	WT1 + IFA	21	2 (PR)
	Aoki et al. (165)	Esophagus	CHP-NY-ESO-1 and CHP-Her2 peptides + OK-432	8	0
	Kono et al. (166)	Esophagus	Multi-epitope vaccine + IFA	10	1 (CR)
	Honma et al. (167)	Urothelial	Survivin peptide + IFA	9	0
	Ohno et al. (168)	Gynecologic	WT1 peptide + IFA	12	0
	Kaumaya et al. (169)	Multiple	Chimeric Her2 peptide + ISA 720	24	1 (PR)
	Kitano et al. (170)	Multiple	CHP-Her2 ± GM-CSF or OK-432	9	0
	Morita et al. (171)	Multiple	WT1 + IFA	10	1 (PR)
	Mavroudis et al. (172)	Multiple	Telomerase peptides + IFA	19	0
Response rate					13/347 (3.7%)
Dendritic cell	Butterfield et al. (173)	Melanoma	Transduced with MART-1	17	0
	Von Euw et al. (174)	Melanoma	Pulsed with allogeneic tumor lysate	7	0
	Palucka et al. (175)	Melanoma	Pulsed with allogeneic tumor lysate	20	1 (CR)/1 (PR)
	O'Rourke et al. (176)	Melanoma	Pulsed with autologous tumor lysate	46	3 (CR)/3 (PR)
	Kyte et al. (177)	Melanoma	Transfected with RNA	20	0
	Lesimple et al. (178)	Melanoma	Pulsed with peptides	12	0
	Berntsen et al. (179)	Kidney	Pulsed with peptides	30	0
	Avigan et al. (180)	Kidney	Allogeneic DC fused with autologous tumor	20	2 (PR)
	Svane et al. (181)	Breast	Pulsed with peptides	26	0
	Bachleitner-Hofmann et al. (182)	Thyroid	Pulsed with allogeneic tumor lysate	10	0
	Babatz et al. (183)	Multiple	Pulsed with CEA peptide	9	0
	Loveland et al. (184)	Multiple	Pulsed with mannan-MUC1 fusion protein	10	0
	Morse et al. (185)	Multiple	Modified with pox-virus encoding CEA + TRICOM	13	0
Response rate					10/240 (4.2%)
Virus	Lindsey et al. (186)	Melanoma	Heterologous prime-boost poxvirus-tyrosinase	13	0
	Amato et al. (187)	Kidney	Poxvirus-encoded 5T4	13	0
	Arlen et al. (188)	Prostate	Heterologous prime-boost poxvirus-PSA + TRICOM	7	0
	Harrop et al. (189)	Colorectal	Poxvirus-encoded 5T4	17	0
	Marshall et al. (65)	Multiple	Poxvirus-encoded CEA + TRICOM	58	1
Response rate					1/108 (0.9%)
Protein	Nicholaou et al. (190)	Melanoma	NY-ESO-1 protein + ISCOMATRIX	27	0
PBMC	Motohashi et al. (191)	Lung	αGalCer-pulsed PBMC cultured with IL-2 + GM-CSF	17	0
Ganglioside	Osorio et al. (192)	Melanoma	Ganglioside + IFA	22	1 (PR)
Endothelial cell	Okaji et al. (193)	Multiple	Fixed human umbilical vein endothelial cells	9	1 (CR)/2 (PR)
RNA	Weide et al. (194)	Melanoma	Autologous tumor mRNA	8	0
Response rate					4/83 (4.8%)
Tumor cells	Nemunaitis et al. (195)	Lung	Allogeneic tumor line transduced with anti-sense TGF-β_2	21	0
	Nemunaitis et al. (196)	Lung	Autologous tumor mixed with allogeneic GM-CSF transduced tumor	49	0
	Powell et al. (197)	Mesothelioma	Autologous tumor + GM-CSF	22	0
	Fakhrai et al. (198)	Brain	Autologous tumor transduced with anti-sense TGF-β_2	6	2 (PR)
Response rate					2/98 (2.0%)
Plasmid DNA	Weber et al. (199)	Melanoma	MART-1 and Tyrosinase	19	0
	Cassaday et al. (200)	Melanoma	gp100 ± GM-CSF	8	0
	Victora et al. (201)	Head and neck	Hsp65	21	4 (PR)
	*Ginjatic et al. (202)	Multiple	NY-ESO-1	12	0
Response rate					4/60 (6.7%)
Overall response rate					34/936 (3.6%)

GM-CSF, granulocyte-macrophage colony-stimulating factor; IFA, incomplete Freund's adjuvant.
*Some trials contain fewer reported total numbers of patients than in the primary report as only patients with evaluable disease at the time of enrollment are included on this table.

Source: Klebanoff 2011 (20)

Evidence of improvement in overall survival was also difficult to find, with no results in melanoma, kidney, or lung cancer and questionable results in prostate cancer:

Table 2. Overall survival results of randomized controlled trials of therapeutic cancer vaccines in patients with advanced solid cancers

Cancer type	Phase	Total patients	Trial design	Clinical setting	Survival	Reference
Melanoma	3	322	Hsp-96 versus physician's choice	Stage IV	No improvement in overall survival ($P = 0.32$)	Testori et al. (203)
Melanoma	3	185	gp100:209-217(210M) peptide + high dose IL-2 versus high dose IL-2	Stage IV	No improvement in overall survival ($P = 0.11$)	Schwartzentruber et al. (29)
Kidney	3	733	Poxvirus-encoded 5T4 + SOC versus SOC only	Stage III/IV	No improvement in overall survival ($P = 0.55$)	Amato et al. (204)
Lung	3	515	Bec2/BCG versus observation	Limited-stage SCLC after major response to chemo-radiation induction therapy	No improvement in overall survival ($P = 0.28$)	Giaccone et al. (205)
Lung	2	171	Liposomal BLP25 + Cyclophosphamide + BSC versus BSC alone	Stage IIIB/IV NSCLC	No improvement in overall survival ($P = 0.11$)	Butts et al. (206)
Lung	2	80	EGF protein + IFA + cyclophosphamide versus BSC	Stage IIIB/IV NSCLC	No improvement in overall survival ($P = 0.10$)	Neninger et al. (207)
Prostate	3	512	Sipuleucel-T versus placebo	Asymptomatic or minimally symptomatic metastatic CRPC, any Gleason score	4.1-month improvement in median overall survival ($P = 0.02$)	Kantoff et al. (28)
Prostate	3	127	Sipuleucel-T versus placebo	Asymptomatic metastatic CRPC, any Gleason score	4.5-month improvement in median overall survival ($P = 0.01$)	Small et al. (49)
Prostate	3	98	Sipuleucel-T versus placebo	Asymptomatic metastatic CRPC, any Gleason score	No improvement in overall survival ($P = 0.33$)	Higano et al. (51)
Prostate	3	621	Prostate GVAX versus docetaxel + prednisone	Asymptomatic or minimally symptomatic metastatic CRPC, chemotherapy naïve, any Gleason score	No improvement in overall survival ($P = 0.78$)	Higano et al. (208)
Prostate	3	114	Prostate GVAX + docetaxel + prednisone versus docetaxel + prednisone	Metastatic CRPC, chemotherapy naïve, any Gleason score	Study terminated early due to excessive deaths in vaccine arm ($P = 0.01$)	Small et al. (209)
Prostate	2	125	Heterologous prime-boost poxvirus-PSA + TRICOM versus control vector	Asymptomatic or minimally symptomatic metastatic CRPC, Gleason score ≤7	8.5-month improvement in median overall survival ($P = 0.001$)	Kantoff et al. (50)

SOC, standard of care; BSC, best supportive care; CRPC, castration-resistant prostate cancer; IFA, incomplete Freund's adjuvant.

Source: Klebanoff 2011 (20)

As the authors argue, the apparent success of sipuleucel-T (Provenge) may be illusory:

> This pattern of increased survival in the absence of objective responses or a delay in time to progression runs counter to previous experience with conventional cytotoxic chemotherapies where either disease regression or stabilization of disease was correlated with improvements in overall survival. As such, these findings have been met with caution and reserve among some investigators.

They point out that sipuleucel-T patients tended to receive docetaxel earlier and more frequently than placebo patients and that, relative to the TAX-327 median OS for minimally symptomatic men of 25.6 months, the 25.8 months achieved by sipuleucel-T does not look like an improvement. They go on to criticize the Prostvac trial on similar grounds:

> In a separate prostate cancer vaccine trial using a heterologous prime-boost regimen with recombinant pox-viruses encoding PSA, a significant improvement in overall survival was also observed, although the study's primary end-point of improved time to progression was not met. However, several confounding factors with this trial have been brought to attention. Specifically, there were apparent imbalances between the two groups such that survival in the control arm was far less than would be predicted based on established nomograms. Additionally, no information regarding subsequent therapies such as docetaxel was reported, limiting the ability to determine the extent to which differences in outcome may be attributed to the effects of the experimental vaccines versus those of established therapies.

This skepticism toward simplistic therapeutic cancer vaccines like Prostvac is not some fringe viewpoint; it's widely shared. In a recent review entitled "Vaccines and Melanoma," the authors summarize the history of the field with the phrase, "Previous vaccine approaches in melanoma: some promise, but limited clinical activity," noting that "vaccines have resulted in the induction of immune responses, although clinical benefit has not been clearly documented" (42). In another influential publication, entitled "Oncology Meets Immunology: The Cancer-Immunity Cycle," the authors write (59):

> Attempts to activate or introduce cancer antigen-specific T cells, as well as stimulate the proliferation of these cells over the last 20 years, have led to mostly no, minimal or modest appreciable anticancer immune responses. The majority of these efforts involved the use of therapeutic vaccines...[T]he prospects for vaccine-based approaches used alone are likely to be limited.

The authors held out hope for new data, noting that "[a] large, monovalent antigen trial (using the C-T antigen MAGE-A3) is currently under way, yet it is not clear that any one candidate will necessarily generate robust T cell responses in all patients." This caution was justified: that MAGE-A3 trial, conducted by GlaxoSmithKline, was ultimately ended in 2014 when it became clear that the vaccine didn't outperform placebo on any of three co-primary endpoints.

The failure of vaccines has extended to prostate cancer just as it has to other cancer types. A 2014 review entitled "Inefficacy of Therapeutic Cancer Vaccines and Proposed Improvements: Casus of Prostate Cancer" explained that, in the aggregate, "therapeutic vaccines trigger anticancer immune response" (although Prostvac is an outlier in that regard) yet "therapeutic vaccination yields no clinically relevant anticancer effect" (21). Below we reproduce the authors' summary of the therapeutic results from a host of different prostate-cancer vaccines targeting a number of different antigens; in short, there were almost no objective responses, consistent with the results in other cancers.

Table II. *Summarized therapeutic results from studies employing different vaccination strategies.*

Principle	Number of Studies (*)	Number of Patients	Response, n (%) CR	Response, n (%) PR	Reference
hTERT vaccination	1 (–)	18	-	-	(116)
PSMA	2 (1)	43	-	-	(117, 118)
Peptide vaccination	4 (–)	110	-	1 (0.9%)	(119-122)
Carbohydrate	1 (–)	25	-	-	(123)
DNA vaccine	2 (–)	42	-	-	(119)
Viral prostate Ag	3 (–)	161	-	-	(124, 125)
BRM	2 (–)	54	-	-	(126, 127)
APC8015	7 (3)	182	1 (0.5%)	-	(24, 25, 27, 128-130)
GM-CSF	5 (1)	116	-	1 (0.9%)	(28, 131-134)
MVA-MUC-IL2	4 (–)	98	-	-	(135-138)
All vaccine only	31 (5)	849	1 (0.1%)	2 (0.2%)	All the above
Co-stimulation	11 (5)	251	-	1 (0.4%)	(8, 26, 132, 134, 139-144)

*Number of studies with metastasized disease. CR: Complete response; PR: partial response; hTERT: human Telomerase reverse transcriptase; PSMA: prostate-specific membrane antigen; Ag: antigen; BRM: biological response modifiers; APC8015: Sipuleucel-T (trade name Provenge); GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor; MVA-MUC-IL2: modified vaccinia virus Ankara (MVA) strain encoding human mucin 1 (MUC1) and interleukin-2 (IL-2).

Source: Jacobs 2014 (21)

Against this highly consistent backdrop of failure, the inefficacy of Prostvac makes perfect sense; after all, the treatment dates back to at least 1995 and in no way improves on the highly similar failed approaches reviewed above. It was part of the same wave of (in retrospect) unjustified enthusiasm that Rosenberg *et al.* were sharply and publicly criticizing by 2004. Indeed, Therion Biologics, the company driven into bankruptcy by the failure of Prostvac and its sister therapy Panvac, initially planned to treat a wide range of cancers. In 1998 it announced a partnership with the large vaccine-maker Pasteur Mérieux Connaught (now part of Sanofi) "to develop and market vaccines for colorectal [and] lung cancers and melanoma"; Therion also worked on a prophylactic HIV vaccine. None of these lines of research yielded anything valuable. Similarly, Bavarian Nordic's cancer immunotherapy work beginning in the late 1990s initially focused on using the MVA vector in vaccines for melanoma and breast cancer; again, these efforts never bore fruit. Bavarian Nordic and Therion never had any special insight into prostate cancer that would logically allow Prostvac to succeed where so many other vaccines failed; to the contrary, prostate cancer was just one of several cancers they hoped to address with the same basic, misguided strategy.

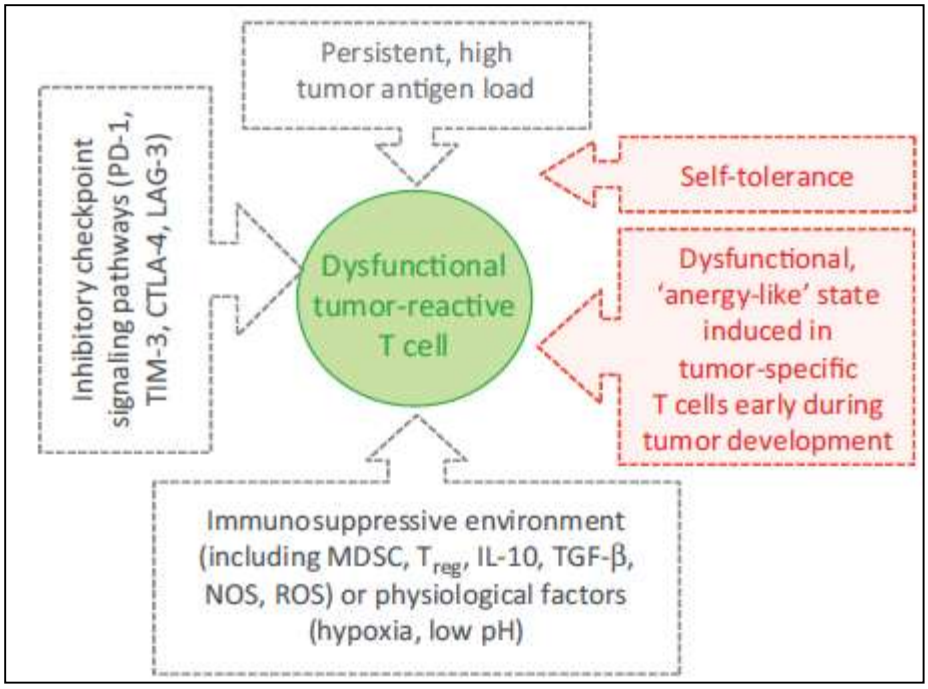
Tolerance and Immunosuppression Impede Vaccine Efficacy

Why have vaccines failed to live up to '90s-era expectations? As researchers now understand in ever greater detail, the ability of cancer to outmaneuver the immune system is not incidental; indeed, "evading immune destruction" is now regarded as an "emerging hallmark of cancer" (43). A popular immunology textbook gives a useful basic overview (44):

> ***Immune responses frequently fail to prevent the growth of tumors.*** There may be several reasons that anti-tumor immunity is unable to eradicate transformed cells. First, many tumors have specialized mechanisms for evading host immune responses. ... Second, tumor cells are derived from host cells and resemble normal cells in many respects. Therefore, many tumors tend to be weakly immunogenic. ... Many spontaneous tumors induce weak or even undetectable immunity. This may be because the tumors that grow have undergone mutations that reduce their ability to stimulate strong immune responses. ... Third, the rapid growth and spread of a tumor may overwhelm the capacity of the immune system to effectively control the tumor, which requires that all the malignant cells be eliminated.

In the case of Prostvac, tolerance to PSA is likely a major hurdle. The immune system has several mechanisms to prevent potentially dangerous self-reactive T cells from proliferating, including central deletion within the thymus and peripheral policing via regulatory T cells (T_{reg}s). Furthermore, any surviving PSA-specific T cells presented with PSA by dendritic cells prior to vaccination likely received no co-stimulation, potentially putting them into the unresponsive, non-functional state of anergy. This tolerizing process, playing out over a period of decades, is unlikely to be reversed in a period of weeks by a small injection of PSA-expressing poxvirus.

Even if Prostvac did elicit a strong response from functional T cells – which the data do not suggest it does – it would have to contend with the formidable challenges of the immunosuppressive tumor microenvironment. The diagram below, taken from a review of the "mechanisms of T cell dysfunction" in chronic infections and cancer summarizes some of the key barriers to successful T-cell responses, including myeloid-derived suppressor cells, T_{reg}s, inhibitory cytokines like interleukin-10 and TGF-β, unusual physiological conditions like hypoxia and low pH, and immunosuppressive signaling pathways involving inhibitory receptors like PD-1, TIM-3, CTLA-4, and LAG-3 (45). Furthermore, recent research suggests that at least some of these immunosuppressive mechanisms are themselves driven by the influx of T cells into the tumor as part of a self-regulatory negative feedback loop (24). Prostvac has no means of overcoming all of these problems, which have bested far more robust therapies, including far more immunogenic vaccines. In the words of the title of one 2005 paper by Rosenberg *et al.,* "Tumor progression can occur despite the induction of very high levels of self/tumor antigen-specific $CD8^+$ T cells in patients with melanoma" (46). Prostvac does not even induce high levels of antigen-specific T cells, so its ability to positively impact tumor progression is even more dubious.



Source: Schietinger and Greenberg 2014 (45)

Even if Prostvac were to trigger PSA-targeted tumor-cell killing, it would likely still fail to have a major clinical benefit. Such killing would in effect be "artificial selection" for tumor cells expressing little or no PSA, as well as tumor cells downregulating the MHC class I molecules that serve to present intracellular antigens to T cells. For Prostvac, this "antigen drift" – i.e. tumor evolution toward reduced presentation of specific antigens targeted by T cells, enabling malignant cells to "hide" from the immune system – would be an especially attractive evolutionary strategy since PSA, the antigen in question, is not functionally important to tumor growth; indeed, some evidence suggests that PSA expression is *lower* in more aggressive tumors compared to less aggressive ones (70). However, since Prostvac has no impact on circulating PSA levels, it appears that the treatment never gets to the point of causing the death of enough PSA-expressing tumor cells to promote the outgrowth of non-PSA-expressing mutants, so this potential barrier to Prostvac's efficacy is likely purely hypothetical. The treatment is so weak that it fails at a much earlier stage.

Checkpoint Inhibitors Will Not Be Prostvac's Salvation

Perhaps tacitly recognizing the inefficacy of Prostvac as a standalone agent, Bavarian Nordic and its supporters talk up the potential of pairing Prostvac with checkpoint inhibitors like ipilimumab. While the metaphor of checkpoint inhibitors "taking your foot off the brake" and vaccines like Prostvac "putting your foot on the gas" is intuitively appealing, an accumulating body of evidence strongly suggests that these approaches have no real synergies. (Recall the ipilimumab melanoma trial, in which ipilimumab coupled with a peptide vaccine performed

identically to ipilimumab alone.) Indeed, as already discussed, the survival data from the Prostvac/ipilimumab Phase I study show no clear benefit.

Why don't checkpoint inhibitors gain strength from simple vaccines? The reason appears to be that the T-cell responses unleashed by these drugs target unusual "neoantigens" – proteins expressed by tumor cells but not by normal cells, resulting from mutations within the tumor that are often unique to individual patients; they do not target antigens like PSA, which may be specific to a certain cell type but are normal, non-mutated proteins to which the immune system has built up a strong tolerance. Indeed, patients whose tumors bear higher mutational loads tend to respond better to checkpoint inhibitors than those with less mutated tumors, and researchers have developed advanced techniques for predicting the mutant proteins mostly likely to trigger robust T-cell responses (47) (48) (49) (50) (51). A therapeutic vaccine based on particular patient-specific neoantigens (ideally multiple in order to make it more difficult for the tumor to "escape" by evolving lower expression or presentation of a single targeted antigen) could perhaps work well with checkpoint inhibitors; future research will shed light on this possibility. But given the increasingly clear-cut evidence that checkpoint inhibitors achieve their effects by easing the restraints on T cells targeting unique, mutated neoantigens – not normal, non-mutated antigens like PSA, viewed by the immune system as "self" and protected from attack by multiple tolerance mechanisms – there is no reason to expect that a first-generation vaccine like Prostvac will add value to the likes of Yervoy or Keytruda. Putting your foot on the gas in a parked car doesn't get you anywhere.

Vector Immunodominance Likely Contributes to Prostvac's Weak Immunogenicity

As previously noted, while tolerance and various forms of immunosuppression would badly blunt the impact of even a more successful version of Prostvac, Prostvac actually induces a detectable T-cell response in only about half of patients. And when a response is induced, it's, charitably speaking, modest. We suspect that one reason for this feeble and inconsistent response is immunodominance, a phenomenon in which the immune system selectively focuses its anti-pathogen efforts on a very narrow subset of possible antigens (and possible epitopes of those antigens). When Prostvac's recombinant poxviruses infect patients' antigen-presenting cells, those cells will process and display many different *viral* antigens, not just the PSA that the vaccine is intended to elicit a response to. The immune system may likely end up targeting vaccinia or fowlpox components to the exclusion or near exclusion of PSA.

Since available data on Prostvac don't compare responses to PSA with responses to the viral vectors themselves, we don't know to what degree vector immunodominance affects vaccine efficacy in this instance. But the literature furnishes a number of informative precedents. In one study using a mouse model, researchers modified the vaccinia virus to express a particular foreign gene, then quantified the immune responses to the virus relative to the protein encoded by the inserted gene. As the authors wrote, "The total number of CD8 T cells responding to [the foreign protein] were approximately 20- to 30-fold lower than the number responding to the [vaccinia virus] vector. … These data bring to light the impressive magnitude of the specific

immune response elicited by the [recombinant vaccinia] backbone compared to that directed against the inserted gene" (Harrington, 2002). A human study using modified vaccinia Ankara (MVA), a weakened form of vaccinia, came to a similar conclusion, finding that "the vaccine-driven CTL [cytotoxic T lymphocyte] hierarchy is dominated by poxviral-specific responses" – that is, responses to the poxvirus vector, *not* to the products of the inserted foreign gene that the vaccine was *intended* to mobilize the immune system against. "Ultimately," conclude the researchers, "the efficiency with which vaccinia and other large viruses (such as adenoviruses) generate CTL responses" – i.e. responses to the viruses themselves – "may limit their success as backbone delivery vectors in recombinant vaccine strategies" (Smith, 2005). Summarizing these and other results, a 2014 paper explains (Bell, 2014):

> Live virus vaccines have proven to be effective for driving CD8 + T-cell responses for therapy to treat a variety of diseases, making them appealing as vectors for antigen-specific immunotherapy. One of the major limitations to their efficacy, however, is the induction of immunity to vector antigens rather than recombinant target antigens. Competition between embedded and endogenous virus antigens limits the effectiveness of the vaccine response, decreasing their potential as antigen-specific therapy.

For many patients, therefore, Prostvac likely functions more as an accidental smallpox vaccine than a prostate-cancer vaccine, inducing immunity to endogenous vaccinia and fowlpox antigens, not PSA. It has no way of circumventing the challenge of immunodominance.

Age Degrades the Capabilities of the Immune System

The immunosuppressive tumor microenvironment poses a major challenge to any therapeutic cancer vaccine, while immunodominance affects those that employ viral vectors. But prostate cancer is a disease of older men (the average age at diagnosis is 66), which brings an additional problem to bear: immunosenescence. Simply put, the elderly tend to have less functional immune systems than the young. In particular, as one review notes, "In the older adult, the benefits of vaccination to prevent infectious diseases are limited, because of the adaptive immune system's inability to generate protective immunity" (28). Aging is associated with a higher threshold for T-cell responsiveness, greater expression of inhibitory T-cell receptors, lower expression of co-stimulatory molecules, and reduced antigen presentation and T-cell proliferation; as one consequence, according to another review, "Even in years in which the influenza vaccine is well matched and efficacious in young people, efficacy in the elderly can be <20%" (54). Meanwhile, key populations of regulatory T cells, which suppress immune responses to their specific antigen targets, accumulate with age (55).

Given all the deficits of immune-system functionality that build up with age, a therapeutic cancer vaccine aimed at older men automatically faces an unusually slim chance of success. Such vaccines already struggle to induce clinically beneficial T-cell responses; more T_{reg}s, stronger negative feedback loops, and reduced proliferative capacity can't help.

Prostvac's Numerous Flaws Easily Explain Its Weak Clinical Results

In multiple ways, Prostvac is a profoundly suboptimal candidate for a therapeutic cancer vaccine:

- It targets a normal, non-mutated "self" antigen, continuously secreted into the circulation for decades of patients' lives, and thus can't have an impact unless it breaks pre-existing tolerance;
- It uses large, complex viruses as vectors, raising the likelihood that the immune response elicited focuses on components of the viruses and largely ignores the inserted antigen; and
- It aims to treat older men, whose immune systems tend to be compromised in ways that specifically reduce the probability of a meaningful T-cell response to a "self" antigen (likely subject to protection from regulatory T cells).

Given the abysmal track record of therapeutic cancer vaccines that *didn't* suffer from all of these disadvantages, it should be no surprise whatsoever that the available data on Prostvac, when interpreted rationally rather than optimistically, indicate no clinical benefit. While Bristol-Myers Squibb's apparent support for Prostvac may seem to validate its approach, this would hardly be the first time in recent history that a large pharmaceutical company failed to beat the odds in the field of cancer vaccines. As an April 2015 review on "T cell exclusion, immune privilege, and the tumor microenvironment" gently points out, GlaxoSmithKline should have known better than to expect success from its lung-cancer vaccine program (56):

> Unambiguous evidence for the inability in humans of a systemic immune response to eliminate immunogenic cancer cells was provided by Boon's studies [published in 1991]…of the antigens that elicit specific CD8+ T cell responses in melanoma patients. Cloned CD8+ T cells from a melanoma patient were used to identify the antigen expressed by that patient's cancer: MAGE-A1. The explicit demonstration of the coexistence of a progressing melanoma with melanoma-specific T cells in this patient implicitly raised the question of why the T cells did not control the growth of the cancer. Immunoediting, or the elimination of immunogenic cancer cells, could be excluded, which left the possibility of immune suppression by the tumor microenvironment (TME). Despite this evidence that the presence of antigen-specific CD8+ T cells alone may not be sufficient for the control of cancer, a major pharmaceutical company recently conducted phase III trials in patients with non–small cell lung cancer (NSCLC) of the clinical efficacy of vaccination with the MAGE-A3 antigen (MAGRIT, NCT00480025). The study did not meet its primary end point of extending disease-free survival and was discontinued in 2014.

We expect the same failure and disappointment from Prostvac.

V. Even If Prostvac Succeeds, It Has Limited Commercial Potential

While the scientific evidence and clinical data strongly establish Prostvac's inefficacy, it's worth noting that the deal with Bristol-Myers Squibb has already removed much of the possible upside for Bavarian Nordic even if Prostvac were to succeed. The product on the market most similar to Prostvac – a therapeutic vaccine targeting a prostate cancer-associated antigen – is Provenge, owned by Dendreon prior to its bankruptcy and now owned by Valeant. Since receiving FDA approval in 2010, Provenge peaked at $325mm of revenue in 2012 and now generates approximately $300mm:

Provenge Sales, 2010-2015

	2010	2011	2012	2013	2014*	2015**
Dendreon product revenue	$ 48	$ 214	$ 325	$ 284	$ 304	$ 296

*Estimated based on growth rate in first nine months of 2014.

**2015 Q2 Provenge sales reported by Valeant, annualized.

Source: company filings, Kerrisdale analysis

To be sure, Provenge had problems that Prostvac doesn't share, in particular the need for the complex and costly leukapheresis required to create each "personalized" dose. But Prostvac has its own logistical headache: its use of live viral vectors could be difficult to manage at oncology clinics treating old and immunosuppressed patients (like those on chemotherapy). Furthermore, Provenge's practical shortcomings are just one factor behind its disappointing sales; many doctors also simply doubted whether the concept of a treatment that modestly extended overall survival without having any other tangible effect on conventional markers of disease really made sense. Prostvac would suffer from the exact same problem. In light of the availability of proven, effective oral drugs like Zytiga and Xtandi, which both prolong survival *and* clearly impact disease progression, Prostvac has little appeal. Thus, while a single dose of Prostvac would certainly be cheaper than one of Provenge, Prostvac's revenue in the aggregate should at best be similar to Provenge's.

Under the Bristol-Myers deal, however, Bavarian Nordic will only receive "double-digit" percentage royalties on future Prostvac sales, typically estimated at 15-25%. The deal also includes a complex set of contingent milestone payments, with a headline maximum value of $975mm. However, the *likely* payout even if Prostvac succeeds is far lower, as the company and sell-side analysts acknowledge. The $975mm figure includes $60 upfront, $80mm upon Bristol-Myers' exercise of its licensing option, $50mm for positive Phase III data, an additional variable payment based on the Phase III survival results ($180mm if they replicate the Phase II 8.5-month median-OS difference), up to $110mm based on regulatory approvals across multiple jurisdictions, and up to $495mm in sales-based milestones based on a series of revenue

targets. But even most Prostvac believers don't expect Phase III results as (superficially) good as the Phase II results, so the actual data-driven payment would be less than $180mm. Similarly, while Bavarian Nordic hasn't disclosed what is required to achieve the maximum $495mm sales-based milestone payment, similar licensing deals reserve these maximum payments for blockbuster outcomes that, again, even company supporters don't expect. Approval-driven milestones may also fall short of the maximum depending on the pace at which foreign regulators move and the possibility that a full payout would require label expansion beyond mCRPC.

As a result, and in line with standard sell-side estimates, we assume realistic milestone totals of $400 to $500mm conditional on Prostvac success. In total, using generous price-to-peak-sales multiples of 5-7x, we find that the value of Prostvac *even if it succeeds* cannot justify Bavarian Nordic's current market cap, much less offer meaningful upside:

Illustrative Analysis of Prostvac Value to Bavarian Nordic Conditional on Success

	Low	High
(*$mm*)		
Prostvac peak sales	$ 300	$ 500
BN share (%)	15%	25%
BN share ($)	$ 45	$ 125
Value to peak sales	5x	7x
Value of peak sales	$ 225	$ 875
Value of milestones	400	500
Total value	$ 625	$ 1,375
Note: BN market cap	*$ 1,318*	*$ 1,318*

Source: Kerrisdale analysis

From Bristol-Myers's perspective, the company is paying $60mm upfront; if Prostvac succeeds, it will (based on the arithmetic above) acquire an asset worth $1.1 to $3.0B (75%-85% of peak sales of $300-500mm capitalized at sales multiples of 5-7x) less $400-500mm of milestone payments owed to Bavarian Nordic. For that net value, conditional on success, of $0.7B to $2.5B – obviously a wide range – Bristol-Myers has paid just $60mm. This "option premium" in effect implies a break-even probability of success of just 2-8%. Applying those same success probabilities to *Bavarian Nordic* would result in expected Prostvac values of at most $110mm – a factor of 12 less than the company's current market cap.

Illustrative Analysis of Prostvac's Value to Bristol-Myers Squibb

	Low	High
Conditional on success:		
(*$mm*)		
Prostvac peak sales	$ 300	$ 500
BMS share (%)	75%	85%
BMS share ($)	$ 225	$ 425
Value to peak sales	5x	7x
Value of peak sales	$ 1,125	$ 2,975
Less: milestones	400	500
Net value to BMS	$ 725	$ 2,475
BMS option premium	$ 60	$ 60
Implied P(success)	8%	2%

Source: Kerrisdale analysis

In today's crowded, highly competitive prostate-cancer market, even a successful version of Prostvac would struggle to gain traction, and the Bristol-Myers deal has already capped the upside for Bavarian Nordic at or substantially below its current market cap. In reality, the situation is even worse: Prostvac is not a mildly effective treatment that will face stiff competition but an ineffective treatment that likely won't make it past Phase III.

VI. Bavarian Nordic's Core Smallpox-Vaccine Business Is at Risk

Although the exuberance surrounding Bavarian Nordic clearly centers on Prostvac, the company's core business – selling its form of modified vaccinia Ankara as a smallpox vaccine for immunocompromised populations to the US's Strategic National Stockpile – has served as a key source of cash and perceived value floor. Today, Bavarian Nordic's long-term contract with the US government has lapsed, but the company recently received a $133mm order that could serve as the first step toward a new contract for a freeze-dried (lyophilized) version of the same vaccine with an extended shelf life of ~10 or more years, far higher than the ~2-year shelf life of the existing ~20-million dose stockpile. This extension in shelf life, though necessary for Bavarian Nordic to keep the overseers of the Strategic National Stockpile happy, would obviously have a major negative effect on the value of this contract and makes the resulting revenue far less "recurring." Furthermore, while some analysts dream of higher prices and more doses under a new contract, a recent Department of Health and Human Services budget document indicates that the government is only planning to spend $132mm per year on 3 to 5 million doses of freeze-dried vaccine going forward, no better than historical levels and consistent with the size of the new order, and there is no indication of any interest in a larger stockpile. Below we show an illustrative analysis of the vaccine's overall value based on the following simple assumptions:

- A 20-million dose stockpile maintained via five-year cycles of four million doses per year, with the first cycle starting in 2016, then next in 2026, etc., out to 2100;
- 3% annual inflation in the price per dose;
- A 35% EBIT margin, equal to Bavarian Nordic's 2014 EBIT margin excluding the drag from the money-losing Cancer Immunotherapy segment;
- A 22% Danish corporate tax rate; and
- An 8% discount rate.

Under these assumptions, the value of Imvamune is only $397mm, just 30% of Bavarian Nordic's market cap. Thus, while Imvamune does arguably establish a floor for Bavarian Nordic's value, it is 70% below the current stock price.

Illustrative Analysis of Imvamune (Smallpox Vaccine) Value

	2016	2017	2018	2019	2020	2021	…	2100
Doses (mm)	4	4	4	4	4	-		4
Price per dose	$ 33	$ 34	$ 35	$ 36	$ 37	$ 38		$ 395
Revenue ($mm)	$ 132	$ 136	$ 140	$ 144	$ 149	$ -		$ 1,581
EBIT margin	35%	35%	35%	35%	35%	35%		35%
EBIT ($mm)	$ 46	$ 48	$ 49	$ 50	$ 52	$ -		$ 553
Tax rate	22%	22%	22%	22%	22%	22%		22%
Net income	$ 36	$ 37	$ 38	$ 39	$ 41	$ -		$ 432
NPV of net income	$ 33	$ 32	$ 30	$ 29	$ 28	$ -		$ 1
Discount rate	8%							
Net present value ($mm)	$ 397							

Source: Kerrisdale analysis

In addition, while Bavarian Nordic appears to be entrenched as an alternative smallpox-vaccine provider today, Imvamune is in fact a controversial product in the biosecurity community. In 2014, two highly respected authorities on smallpox who had served as directors of the World Health Organization Global Smallpox Eradication Program wrote critically of the wastefulness and riskiness of Imvamune (57) (emphasis added):

> Which vaccines should be available for emergency use? The WHO Scientific Advisory Group of Experts (SAGE) met in November 2013 to provide advice to member countries as to which smallpox vaccines should be included in a stockpile and how they should be used in case of an outbreak. SAGE recommended that the vaccines should be lyophilized (to maximize shelf-life of stockpiles), they should be capable of being administered by bifurcated needles (to allow reduction of the dose needed for traditional scratch vaccination), and they should produce a visible major cutaneous reaction as a correlate of protection. Only the 2 licensed vaccines, ACAM2000 and LC16m8, meet these stipulations. SAGE recommended that if neither of these vaccines was available, countries should use locally produced vaccines like those used during eradication, which met WHO standards of potency, purity, and stability.
>
> **SAGE observed, in passing, that a recently developed vaccine, Imvamune (known as Imvanex in Europe), is not recommended until more information is available regarding its efficacy and safety and until it is produced as a lyophilized product.**
>
> ...[Imvamune] is substantially more expensive and requires the administration of 2 doses of vaccine by syringe and needle. Full protection is not obtained until 14 days after the second dose. The vaccine is stable for only 2 years at –20°C. More concerning is the fact that fewer than 7,000 people have been vaccinated. Reported adverse reactions are few, but, even so, incomplete studies indicate possible risks of myocardial effects. There is no apparent programmatic use for the vaccine at this time.

The authors conclude that, given the availability of "2 excellent replicating strains of freeze-dried vaccine virus that are highly protective, whose shelf life is 10 years or more, and whose cost is

about $3 per dose" – one of which, produced by the Japanese firm Kaketsuken, is a "gentler" attenuated version likely suitable for immunocompromised patients (58) – there is no reason to fund less proven, more speculative products like Bavarian Nordic's Imvamune.

Not only is Kaketsuken's attenuated strain, which is ~10 times cheaper than Bavarian Nordic's, a threat to Imvamune's long-term role in the Strategic National Stockpile; so too is the MVA variant produced by Emergent BioSolutions, a company with strong relationships in biodefense and large existing contracts for stockpiled anthrax countermeasures. Earlier in the year, Emergent announced an agreement to use its strain of MVA as an experimental boost for GlaxoSmithKline's candidate Ebola vaccine. While Emergent had previously hoped to use MVA as a vector for a tuberculosis vaccine (which failed), there is no reason why it can't respond to any future government RFPs for attenuated smallpox vaccines, threatening Bavarian Nordic's franchise.

Finally, based on a recently published paper (whose authors include Bavarian Nordic's CEO) – the same paper used to demonstrate the equivalence of the freeze-dried and liquid formulations – the Strategic National Stockpile already possesses far more effective doses than ever envisioned, because it turns out that *intradermal* administration requires at most one-fifth the quantity of virus as *subcutaneous* administration to induce the same immune response (63). The paper's abstract makes the point very clearly: "ID [intradermal] vaccination could be used, increasing the number of available doses in the SNS 5-fold (i.e., from 20 million to 100 million doses)." The logical conclusion is that, if the government previously believed 20 million "doses" were adequate, it can now achieve the same desired population coverage at one-fifth the price. It will be difficult for Bavarian Nordic to sustain its revenue in light of this new information; if one discovered that one-fifth the usual amount of sunscreen conferred the same degree of protection, one would not keep buying the same volume of sunscreen.

Overall, Imvamune has only modest value and faces economic risks from shelf-life extension and reduced order sizes and competitive risks from comparable or superior alternative vaccines. Bavarian Nordic's only successful product in its 20-year history is low in innovation, high in cost, unknown in efficacy, and unlikely ever to be used in real life.

VII. Conclusion

Bavarian Nordic's stock price has appreciated dramatically thanks to widespread excitement about cancer immunotherapy compounded by a succession of thrilling headlines following the Bristol-Myers Squibb announcement. But Prostvac is a failed, 20-year-old product that has only managed to look promising thanks to a misleading statistical fluke in its Phase II data coupled with the absence of any meaningful point of reference in its combination trial with ipilimumab. An abundance of scientific literature clearly shows that treatments like Prostvac have never worked, and Prostvac itself is an unusually ineffective agent even within the profoundly futile category of therapeutic cancer vaccines. It will join the likes of GVAX, Stimuvax, and MAGE-A3 in the annals of predictable clinical disappointment. Meanwhile, Bavarian Nordic's smallpox vaccine can justify only a small fraction of the company's current valuation, and BAVA has no track record of productive R&D to fall back on. Current shareholders will come to envy Bavarian Nordic's founder and former chairman, who sold out before the current hype had a chance to evaporate.

VIII. References

1. *Treatment of Hormone-Refractory Prostate Cancer with Docetaxel or Mitoxantrone: Relationships between Prostate-Specific Antigen, Pain, and Quality of Life Response and Survival in the TAX-327 Study.* **Berthold, Dominik R.** 2008, Clinical Cancer Research, pp. 2763-2767.
2. *Long-term Survival and Biomarker Correlates of Tasquinimod Efficacy in a Multicenter Randomized Study of Men with Minimally Symptomatic Metastatic Castration-Resistant Prostate Cancer.* **Armstrong, A.J.** 2013, Clinical Cancer Research, Vol. 19, p. 6891.
3. *Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study.* **Ryan, CJ.** 2, 2015, Lancet Oncology, Vol. 16, pp. 152-60.
4. *Enzalutamide in Metastatic Prostate Cancer before Chemotherapy.* **Beer, Tomasz M.** 2014, New England Journal of Medicine, Vol. 371, pp. 424-433.
5. *Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial.* **Saad, Fred.** 3, 2015, The Lancet Oncology, Vol. 16, pp. 338-348.
6. *Overall Survival Analysis of a Phase II Randomized.* **Kantoff, Philip W.** 7, 2010, Journal of Clinical Oncology, Vol. 28, pp. 1099-1105.
7. *Developing Immunotherapy As Legitimate Therapy.* **Small, Eric J. and Fong, Lawrence.** 7, 2010, Journal of Clinical Oncology, Vol. 28, pp. 1085-1087.
8. *Prognostic Model for Predicting Survival in Men With Hormone-Refractory Metastatic Prostate Cancer.* **Halabi, Susan.** 7, April 1, 2003, Journal of Clinical Oncology, Vol. 21, pp. 1232-1237.
9. *Docetaxel-Based Chemotherapy in Elderly Patients (Age 75 and Older) with Castration-Resistant Prostate Cancer.* **Italiano, Antoine.** European Urology, Vol. 55, pp. 1368-1376.
10. **FDA Division of Clinical Evaluation and Pharmacology/Toxicology.** *BLA 125197, Sipuleucel-T: .* 2010.
11. *Providing Clinicians and Patients With Actual Prognosis: Cancer.* **Howlader, Nadia, et al., et al.** 2014, Journal of the National Cancer Institute Monographs, Vol. 49, pp. 255-264.
12. *Clinical Outcomes by Age in Men With Hormone Refractory Prostate Cancer: A Pooled Analysis of 8 Cancer and Leukemia Group B (CALGB) Studies.* **Halabi, Susan, et al., et al.** 1, July 2006, The Journal of Urology, Vol. 176, pp. 81-86.
13. *Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial.* **Madan, Ravi A.** 2012, The Lancet Oncology, Vol. 13, pp. 501-508.
14. *A combination trial of vaccine plus ipilimumab in metastatic castration-resistant prostate cancer patients: immune correlates.* **Jochems, Caroline.** 2014, Cancer Immunology, Immunotherapy, Vol. 63, pp. 407-418.
15. *Updated Prognostic Model for Predicting Overall Survival in First-Line Chemotherapy for Patients with Metastatic Castration-Resistant Prostate Cancer.* **Halabi, Susan.** March 1, 2014, Journal of Clinical Oncology, Vol. 32, pp. 671-677.

16. *Improved Survival in a Cohort of Trial Participants with Metastatic Castration-resistant Prostate Cancer Demonstrates the Need for Updated Prognostic Nomograms.* **Omlin, Aurelius.** 300-306, 2013, European Urology, Vol. 64.
17. *Recombinant vaccinia-PSA (PROSTVAC) can induce a prostate-specific immune response in androgen-modulated human prostate cancer.* **Sanda, M.G.** 1999, Urology, Vol. 53, pp. 260-266.
18. *A Phase I Trial of a Recombinant Vaccinia Virus Expressing Prostate-specific Antigen in Advanced Prostate Cancer.* **Eder, Joseph Paul.** 2000, Vol. 6.
19. *Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial.* **Kwon, Eugene D.** 7, 2014, Vol. 15, pp. 700-712.
20. *Therapeutic cancer vaccines: are we there yet?* **Klebanoff, Christopher A.** 1, January 2011, Immunological Reviews, Vol. 239, pp. 27-44.
21. *Inefficacy of Therapeutic Cancer Vaccines and Proposed Improvements. Casus of Prostate Cancer.* **Jacobs, John J.L.** 2014, Anticancer Research, Vol. 34, pp. 2689-2700.
22. *Immune impact induced by PROSTVAC (PSA-TRICOM), a therapeutic vaccine for prostate cancer.* **Gulley, JL.** 2, February 2014, Cancer Immunology Research, Vol. 2, pp. 133-141.
23. *Clinical Efficacy of TroVax in the Treatment of Progressive Castration-resistant Prostate Cancer.* **Amato, Robert J. and Stepankiw, Mika.** 2012, Clinical Medicine Insights: Oncology, Vol. 6, pp. 67-73.
24. *Up-Regulation of PD-L1, IDO, and Tregs in the Melanoma Tumor Microenvironment Is Driven by CD8+ T Cells.* **Spranger, Stefani.** 200, August 2013, Science Translational Medicine, Vol. 5, p. 200ra116.
25. *CTLA-4 and PD-1/PD-L1 Blockade: New Immunotherapeutic Modalities with Durable Clinical Benefit in Melanoma Patients.* **Ott, Patrick A.** October 2013, Clinical Cancer Research, Vol. 19, pp. 5300-5309.
26. *CD8+ T-cell Responses Rapidly Select for Antigen-Negative Tumor Cells in the Prostate.* **Bak, S. Peter.** September 2013, Cancer Immunology Research, Vol. 1, pp. 393-401.
27. *Recombinant vaccinia virus-induced T-cell immunity: quantitation of the response to the virus vector and the foreign epitope.* **Harrington, LE.** 7, April 2002, Journal of Virology, Vol. 76, pp. 3329-3337.
28. *Understanding immunosenescence to improve responses to vaccines.* **Goronzy, Jörg J and Weyand, Cornelia M.** 2013, Nature Immunology, Vol. 14, pp. 428-436.
29. *Interdisciplinary Critique of Sipuleucel-T as Immunotherapy in Castration-Resistant Prostate Cancer.* **Huber, Marie L.** 2012, Journal of the National Cancer Institute, Vol. 104, pp. 273-279.
30. *Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer.* **Kantoff, Philip W.** 5, 2010, New England Journal of Medicine, Vol. 363, pp. 411-422.
31. *A phase III trial of GVAX immunotherapy for prostate cancer versus docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer (CRPC).* **Higano, C.** Orlando, FL : s.n., 2009. 2009 Genitourinary Cancers Symposium.
32. *Improved Survival with Ipilimumab in Patients with Metastatic Melanoma.* **Hodi, F. Stephen.** August 19, 2010, New England Journal of Medicine, Vol. 363, pp. 711-723.

33. *A Randomized Phase II Study of Concurrent Docetaxel Plus Vaccine Versus Vaccine Alone in Metastatic Androgen-Independent Prostate Cancer.* **Arlen, Philip M.** 4, 2006, Clinical Cancer Research, Vol. 12, pp. 1260-1269.
34. *Tumor Regression and Growth Rates Determined in Five Intramural NCI Prostate Cancer Trials: The Growth Rate Constant as an Indicator of Therapeutic Efficacy.* **Stein, Wilfred D.** 2011, Clinical Cancer Research, Vol. 17, pp. 907-917.
35. *Humoral Immune Response against Non-Targeted Tumor Antigens after Treatment with Sipuleucel-T and Its Association with Improved Clinical Outcome.* **GuhaThakurta, Debraj.** 2015, Clinical Cancer Research.
36. *Response definition criteria for ELISPOT assays revisited.* **Moodie, Z.** 10, 2010, Cancer Immunology, Immunotherapy, Vol. 59, pp. 1489-1501.
37. *ELISpot for measuring human immune responses to vaccines.* **Slota, Meredith.** 3, 2011, Expert Rev Vaccines, Vol. 10, pp. 299-306.
38. *T-cell-inducing vaccines – what's the future.* **Gilbert, Sarah C.** 2011, Immunology, Vol. 135, pp. 19-26.
39. *Comparison of the safety and immunogenicity of ACAM1000, ACAM2000 and Dryvax® in healthy vaccinia-naive adults.* **Frey, Sharon E.** 2009, Vaccine, Vol. 27, pp. 1637-1644.
40. *Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.* **Rizvi, Naiyer A.** 6230, April 2015, Science, Vol. 348, pp. 124-128.
41. *Cancer immunotherapy: moving beyond current vaccines.* **Rosenberg, Steven A.** 9, 2004, Vol. 10, pp. 909-915.
42. *Vaccines and Melanoma.* **Ott, Patrick A.** 2014, Hematol Oncol Clin N Am.
43. *Hallmarks of Cancer: The Next Generation.* **Hanahan, Douglas and Weinberg, Robert A.** 5, March 4, 2011, Cell, Vol. 144, pp. 646-674.
44. **Abbas, Abul K., Lichtman, Andrew H. and Pillai, Shiv.** *Cellular and Molecular Immunology.* 8th. Philadelphia : Elsevier Saunders, 2015.
45. *Tolerance and exhaustion: defining mechanisms of T cell dysfunction.* **Schietinger, Andrea and Greenberg, Philip D.** 2, February 2014, Trends in Immunology, Vol. 35, pp. 51-60.
46. *Tumor Progression Can Occur despite the Induction of Very High Levels of Self/Tumor Antigen-Specific CD8+ T Cells in Patients with Melanoma.* **Rosenberg, Steven A.** 9, November 1, 2005, Journal of Immunology, Vol. 175, pp. 6169-6176.
47. *High-throughput epitope discovery reveals frequent recognition of neo-antigens by CD4+ T cells in human melanoma.* **Linnemann, Carsten.** 2015, Nature Medicine, Vol. 21, pp. 81-85.
48. *A vaccine targeting mutant IDH1 induces antitumour immunity.* **Schumacher, Theresa.** 7514, 2014, Nature, Vol. 512, pp. 324-327.
49. *Mutant MHC class II epitopes drive therapeutic immune responses to cancer.* **Kreiter, Sebastian.** 2015, Nature, Vol. 520.
50. *Tumor Exome Analysis Reveals Neoantigen-Specific T-Cell Reactivity in an Ipilimumab-Responsive Melanoma.* **van Rooij, Nienke.** 32, 2013, Journal of Clinical Oncology, Vol. 31.
51. *Neoantigens in cancer immunotherapy.* **Schumacher, Ton N. and Schreiber, Robert D.** 6230, 2015, Science, Vol. 348, pp. 69-74.
52. *Immunodominance of poxviral-specific CTL in a human trial of recombinant-modified vaccinia Ankara.* **Smith, CL.** 12, 2005, Journal of Immunology, Vol. 175, pp. 8431-8437.

53. *A CD8 T-Cell Epitope Variant Enhances Immune Targeting to a Recombinant Picornavirus Vaccine Antigen.* **Bell, Michael P.** 7, 2014, Viral Immunology, Vol. 27, pp. 361-366.
54. *Immunosenescence and novel vaccination strategies for the elderly.* **Dorrington, Michael G and Bowdish, Dawn M.E.** June 2013, Frontiers in Immunology, Vol. 4, pp. 1-10.
55. *Regulatory T Cells and the Immune Aging Process: A Mini-Review .* **Jagger, Ann, et al., et al.** 2014, Gerontology, Vol. 60, pp. 130–137.
56. *T cell exclusion, immune privilege, and the tumor microenvironment.* **Joyce, Johanna A. and Fearon, Douglas T.** 6230, April 2015, Science, Vol. 348.
57. *The Smallpox Threat: A Time to Reconsider Global Policy.* **Henderson, D.A. and Arita, Isao.** 3, 2014, Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science, Vol. 12.
58. *Safety of attenuated smallpox vaccine LC16m8 in immunodeficient mice.* **Yokote, Hiroyuki.** 2014, Clinical Vaccine Immunology.
59. *Oncology Meets Immunology: The Cancer-Immunity Cycle.* **Chen, Daniel S. and Mellman, Ira.** July 25, 2013, Immunity, Vol. 39, pp. 1-10.
60. *Docetaxel plus Prednisone or Mitoxatrone plus Prednisone for Advanced Prostate Cancer.* **Tannock, Ian F.** 2004, New England Journal of Medicine, Vol. 351, pp. 1502-1512.
61. *A Phase 3 Trial of GVAX Immunotherapy for Prostate Cancer vs. Docetaxel plus Prednisone in Asymptomatic, Castration-Resistant Prostate Cancer (CRPC).* **Higano, C.**
62. *Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy.* **Ryan, Charles J.** 2013, New England Journal of Medicine, Vol. 368, pp. 138-148.
63. *Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects.* **Frey, Sharon E., et al.** 2015, Vaccine (in press).
64. *Shifting paradigms in the estimation of survival for castration-resistant prostate cancer: A tertiary academic center experience.* **Afshar, Mehran, et al.** 2015, Urologic Oncology, Vol. 33.
65. *Feasibility of Tri-Weekly Docetaxel-Based Chemotherapy for Elderly Patients (Age 75 and Older) with Castration-Resistant Prostate Cancer.* **Takaha, Natsuki, et al.** 2011, Urologia Internationalis, Vol. 87, pp. 263-269.
66. *Docetaxel in very elderly men with metastatic castration-resistant prostate cancer.* **Wong, Hui-li, et al.** 2015, Prostate International.
67. *Tolerability and efficacy of docetaxel in older men with metastatic castrate-resistant prostate cancer (mCRPC) in the TAX 327 trial.* **Horgan, Anne M., et al.** April 2014, Vol. 5, pp. 119-126.
68. *Efficacy and Safety of Abiraterone Acetate in Elderly (≥75 Years) Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer.* **Smith, Matthew R., et al.** 2015, Journal of Urology.
69. *The role of active vaccination in cancer immunotherapy: lessons from clinical trials.* **Kissick, Haydn T, and Sanda, Martin G.** 2015, Current Opinion in Immunology, Vol. 35, pp. 15-22.
70. *Immunophenotypic Characterization of 225 Prostate Adenocarcinomas with Intermediate or High Gleason Scores.* **Goldstein, Neal S.** 2002, American Journal of Clinical Pathology, Vol. 117, pp. 471-477.

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