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Northwest Biotherapeutics (NWBO)

General information

Northwest Biotherapeutics, Inc.
https://www.nwbio.com
4800 Montgomery Lane, Suite 800
Bethesda, MD 20814
USA

Twitter
LinkedIn

Founded:	**1996**	Employees:	**19**

Pipeline:

Lead product candidate:	**DCVax-L**
Lead indication:	**GBM**
Clinical stage:	**Pre-BLA**

External perception (July 18, 2022):

Tweets per day:	**149.7**
Website traffic per month:	**2.868**
Avg. Stocktwits Volume:	**600**
Estimation:	**Very strong**

Stock information (July 18, 2022):

Ticker (Exchange):	**NWBO (OTC)**	Enterprise value:	**$704.50M**
Market cap:	**$677.85M**	52 Week Range:	**$0.39 – $2.05**
Avg. Vol (3 month):	**4.48M**	Avg. Vol. (10 day):	**1.83M**
Shares outstanding:	**984.25M**	Short Interest Ratio:	**13.54**
Insider Ownership:	**3.27 %**	Institutional Ownership:	**0.12 %**

Short summary

NWBO is a biotechnology company developing personalized immune therapies for cancer. The company develops the platform technology DCVax that uses activated dendritic cells to mobilize a patient's own immune system to attack cancer. NWBO's lead product, DCVax-L, recently has completed a Phase 3 clinical trial to treat Glioblastoma multiforme brain cancer. According to NWBO, the trial reached the primary endpoints, however, due to the study design results had to be compared to results of external trials. NWBO also develops DCVax-Direct to treat inoperable solid tumors.

Next catalysts

H2 2022	Publication of journal article of Phase 3 trial topline data for DCVax-L in GBM patients
Q4 2022	Pre-BLA meeting with the British MHRA
H1 2023	BLA filing for DCVax-L for the use in GBM patients

Pipeline

NWBO's product candidates are based on the DCVax technology, to address multiple different cancers and different patient situations.
Lead product candidate DCVax-L is made with cancer antigens from tumor lysate from the patient's own tumor tissue. As such, DCVax-L incorporates the full set of tumor antigens, making it difficult for tumors to find ways around it ("escape variants"). DCVax-L has been investigated in GBM brain cancer and ovarian cancer clinical trials, and a Phase 3 clinical trial in GBM patients has recently been finished. DCVax-L is expected to be used for any solid tumor cancers in situations in which the patient has their tumor surgically removed as part of standard of care.
DCVax-Direct is designed for situations in which the tumors are inoperable and thus it is not feasible or not desirable for patients to have their tumors surgically removed. DCVax-Direct incorporates the full set of tumor antigens in a way that the dendritic cells are partially matured in a special way to be ready to pick up antigens directly from tumor tissue in the patient's body. The partially matured dendritic cells are then injected directly into the patient's tumor(s). There, the dendritic cells pick up the antigens *in situ* and mobilize additional specialized cells of the immune system.

In this report, we will focus on the lead product candidate DCVax-L and the data and results published on it.

DCVax-L

Lead product of NWBO is DCVax-L. DCVax-L is a personalized immune therapy that uses a patient's own dendritic cells (DCs) as therapeutic agent. It is designed to cover all solid tumor cancers in which the tumors can be surgically removed. For DCVax-L, a patient's monocytes are obtained through leukapheresis. The monocytes are differentiated into DCs, matured, activated, and loaded with antigens from the patient's own tumor tissue. The activated, educated DCs are then isolated with very high purity and comprise the DCVax-L personalized vaccine. DCVax -L is administered to the patient through a simple intra-dermal injection in the upper arm, like a flu shot. The dendritic cells then convey the tumor biomarker information to the rest of the immune system agents (T cells, B cells and others), and the immune system agents then fan out through the body searching for anything with these biomarkers and attacking it. [1]

The scientific approach behind NWBO's DCVax-L can be summarized as follows:
Autologous DCs are collected from peripheral blood, primed by exposure to tumor antigens *ex vivo* and injected back into the patient.
DCs are well suited to activate a robust immune response: [2, 3, 4]

- DCs are 'professional' antigen presenting cells (APCs), equipped with MHC class I and II molecules
- DCs express a vast array of costimulatory molecules – e.g., CD40, CD80, CD86 and OX40L
- DCs express the chemokine receptor CCR7, the ligands of which – CCL19 and CCL21 – are expressed constitutively at high levels in lymph nodes
- DCs migrate from the site of antigen capture to lymph nodes, where they may initiate a T-cell response

Thus, DCs are strong immune activators and are highly favorable for use in cancer immunotherapy. DC-based vaccines for brain/CNS tumors have been assessed in several clinical trials. In almost all trials, DC-based vaccines have been well tolerated by the patients, often fever was the most common adverse event. [5, 6]

Because of all these studies with predominantly positive results, it can certainly be confirmed that the scientific background on which DCVax-L is based is principally working.

[1] https://nwbio.com/dcvax-technology/
[2] https://pubmed.ncbi.nlm.nih.gov/22505809/
[3] https://pubmed.ncbi.nlm.nih.gov/16443510/
[4] https://pubmed.ncbi.nlm.nih.gov/23545055/
[5] https://pubmed.ncbi.nlm.nih.gov/23545055/
[6] https://pubmed.ncbi.nlm.nih.gov/25483653/

Clinical trials and clinical data

DCVax-L has been tested in a few clinical trials. Finding information on NWBO's earlier clinical trials of DCVax-L is proving difficult. This is probably mainly due to the length of time that has elapsed since then.
Most importantly, DCVax-L has been investigated in a large-scale Phase 3 trial in GBM patients. Data lock of this study was in October 2020, topline data have been presented on May 10, 2022.

Phase 1/2 trials

The following Phase 1 and Phase 2 clinical trials for DCVax-L can be found in the ClinicalTrials.gov database (search term: Northwest Biotherapeutics):

- A Phase 1 trial with DCVax-L in women with recurrent epithelial ovarian carcinoma or primary peritoneal cancer that was completed in December 2009 (NCT00683241)
- A Phase 1/2 trial with DCVax-L in patients with recurrent epithelial ovarian carcinoma or primary peritoneal cancer that was withdrawn (NCT00603460)
- A Phase 2 trial evaluating the combination therapy using DCVax-L and Nivolumab (an anti-PD-1 antibody) for patients with recurrent Glioblastoma Multiforme that was withdrawn (NCT03014804)

Thus, information on the predecessor studies performed on DCVax-L in GBM patients is not available in the ClinicalTrials.gov database.

In the press releases on NWBO's website, which go back to June 2010, there is no information on the GBM studies that were conducted. The press releases that can be viewed there deal exclusively with the Phase 2 trial at that time, which was later converted into the Phase 3 GBM trial.

A scientific overview titled “DCVax-L—Developed by Northwest Biotherapeutics” published by authors Stavros Polyzoidis and Keyoumars Ashkan in the journal *Human Vaccines & Immunotherapeutics* in 2014 describes Phase 1/2 trials with DCVax-L. [7] Both authors are (or were at time of publication) working at King’s College Hospital in London and Keyoumars Ashkan was leading investigator of the Phase 3 GBM trial in London enrolling patients into the trial. He even enrolled the greatest number of patients in the EU. [8] The authors write that two Phase 1/2 trials were carried out at the University of California, Los Angeles (UCLA) by Dr. Linda Liau and Dr. Robert Prins with 39 enrolled patients, 20 patients had newly diagnosed GBM and 19 patients had recurrent GBM and other gliomas. The cited sources are the NWBO website and a publication by Prins et al. published in *Predictive Biomarkers and Personalized Medicine* in 2010. [9]

[…] This version of the analysis does not provide the full text.

Summary and Inconsistencies:
Both sources, the review by Stavros Polyzoidis and Keyoumars Ashkan, and the NWBO website, write of two Phase1/2 studies conducted. There are no entries in the ClinicalTrials.gov database, nor are there adequate results in the press releases after June 2010.
Stavros Polyzoidis and Keyoumars Ashkan cite the NWBO website and a scientific publication for their statements, but this publication describes a Phase 1 trial only. Assuming the published results of the Phase 1 study by Prins et al. belonged to a Phase 1/2 study, why was this not mentioned in the publication? Furthermore, Prins et al. did not investigate the effect of DCVax-L alone, but in combination with a TLR agonist. If one would nevertheless assume that the Prins et al. study is one of the two Phase 1/2 studies mentioned, does the second study only account for 16 additional patients? This would be a very small number as the NWBO website mentions 39 patients in total.
It is necessary to say herewith that the conducted Phase 1/2 studies cannot be traced. The publication of the results took place exclusively on the NWBO website, without insight into the more detailed data and without publication in a scientific journal.

[7] https://pubmed.ncbi.nlm.nih.gov/25483653/
[8] https://pubmed.ncbi.nlm.nih.gov/29843811/
[9] https://pubmed.ncbi.nlm.nih.gov/21135147/

Leaving aside the manner of data publication, the results described on the NWBO website look excellent. DCVax-L appears to significantly prolong survival in GBM patients, particularly in patients with newly diagnosed GBM.

	SOC	Prins et al., 2010		NWBO website	
Phase	-	Phase 1		2 x Phase 1/2	
GBM	-	ND-GBM	r-GBM	ND-GBM	r-GBM
Patients	-	15	8	20	19
Tumor recurrence	6.9 months	?	?	24 months	?
Median OS	14.6 months	35.9 months	17.9 months	36.0 months	?

GBM = glioblastoma multiforme; ND-GBM = newly diagnosed GBM; r-GBM = recurrent GBM; OS = overall survival

Phase 3 trial

In January 2011, NWBO announced that the Company is resuming enrollment of additional new patients into its ongoing **240-patient**, double blind, randomized, placebo-controlled **Phase 2** clinical trial of DCVax-L for Glioblastoma multiforme brain cancer.
"To date [24. Jan 2011], this trial has been conducted at 13 clinical sites across the U.S., with **33 patients already having been enrolled**. These patients have continued to be treated with the DCVax regimen and follow-up during the last two years. The only aspect of the trial that stopped for a period of time was the enrollment of additional new patients beyond the 33 patients who were already enrolled and receiving ongoing treatment. The Company is now resuming the process of accepting additional new patients to complete the trial." [10]
There is no information available, why NWBO stopped enrollment in the Phase 2 trial before January 2011.

[…] This version of the analysis does not provide the full text.

When NWBO announced in May 2012 the transition of the Phase 2 trial to a Phase 3 trial, interim analyses of the trial were also announced. The planned interim analyses are triggered by events defined as either a tumor recurrence or a death. The pre-specified trigger number for this first interim analysis is 66 such events, comprising 60% of the 110 events required to reach the primary endpoint of the Phase 3 trial. Another interim analysis will occur when 88 events, comprising 80% of the total 110 events, have been reached. [11] Without giving clear information about the required number of events, the authors Stavros Polyzoidis and Keyoumars Ashkan write that three interim analyses have been scheduled to take place for data evaluation while the Phase 3 trial is ongoing, citing the NWBO website. [12]
On December 10, 2013, NWBO announced that the required number of events have been reached to conduct the first interim analysis meaning 66 events. On March 7, 2014, NWBO announced that the Data Safety Monitoring Board (DSMB) has made an unblinded review of the safety data for the Company's ongoing international Phase 3 GBM trial and has recommended that the trial **continues as planned**. [13] Although NWBO stated that the DSMB's review of the efficacy data is still pending, **interim results of efficacy data have never been published**.

[…] This version of the analysis does not provide the full text.

In May 2018, **interim results based on a full data collection in March 2017** were published. Interim blinded survival data from the Phase 3 GBM trial were collected by the independent contract research organization managing the trial, tabulated by an independent statistical firm, and published with 69 co-authors in the peer reviewed *Journal of Translational Medicine (JTM)*. The interim data set are blinded aggregate data, which include patients from both arms of the trial combined (2/3 of the patients, who received standard of care plus DCVax-L, and 1/3 of the patients, who received standard of care plus a placebo). Due to the crossover design, **nearly 90% of the total 331 patients in the trial have received DCVax-L** treatment. For the total 331 patients the **median survival as of this analysis was 23.1 months** from surgery. With the standard of care (surgery, radiation, and chemotherapy), median survival for newly diagnosed Glioblastoma was at this time 15-17 months.

[10] https://nwbio.com/northwest-biotherapeutics-resuming-enrollment-in-promising-240-patient-clinical-trial-of-dcvax-for-brain-cancer-2/
[11] https://nwbio.com/first-interim-analysis-of-nw-bios-phase-iii-gbm-trial-triggered-by-reaching-required-number-of-events/
[12] https://pubmed.ncbi.nlm.nih.gov/25483653/
[13] https://nwbio.com/nw-bio-receives-recommendation-to-continue-with-phase-iii-gbm-brain-cancer-trial/

The top 100 patients (30%) of the total 331 patients in the trial showed particularly extended survival, with **median survival of 40.5 months from surgery** (95% CI 35.5 – 46.5 months). This extended survival was not fully explained by known prognostic factors such as age younger than 50 years, methylated MGMT gene status and complete resection (surgical removal) of all the tumor. Only 8% of these 100 patients had the favorable status on all 3 of these prognostic factors.
Only **7 of the 331 patients (2.1%) have experienced a serious adverse event** that was deemed at least possibly related to the treatment. The rate of total adverse events (including non-serious events) was comparable to the rate of adverse events with standard of care alone. [14, 15]

An update on these interim results was published in November 2018 based on data collection from October 2018. Median OS of the top 100 patients was 58.4 months with a 95% confidence interval ranging from 45.9 to 94.5 months. Median OS of the ITT population remained 23.1 months. [16]

	SOC	Prins et al., 2010	NWBO website	Full data interim analysis
Phase	-	Phase 1	Phase 1/2	Phase 3
GBM	-	ND-GBM	ND-GBM	ND-GBM
Patients	-	15	20	331
Median OS	15-17 months	35.9 months	36.0 months	23.1 months
mOS 1 year	~58% [17]	91%	?	89.3%
mOS 2 years	25%	55%	?	46.4%
mOS 3 years	?	47%	?	28.2%

GBM = glioblastoma multiforme; ND-GBM = newly diagnosed GBM; OS = overall survival; mOS = median OS
Note: Prins et al. calculate mOS from the time of initial diagnosis. NWBO's Phase 3 trial calculates mOS from time-point of randomization, which happens approximately three months after initial surgery.

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On May 10, 2022, NWBO presented the topline data of the Phase 3 trial at the scientific symposium *Frontiers in Cancer Immunotherapy 2022*. [18, 19] The presentation was held by Dr. Paul Mulholland. According to the presentation, the Phase 3 trial met the primary endpoint mOS, which was changed from PFS due to the impossibility to differentiate between progression and pseudoprogression in the GBM patients.

[…] This version of the analysis does not provide the full text.

Conclusion

The scientific approach of DCVax-L is convincing and good data from Phase 1 studies exist. The Phase 3 trial ran for a very long time and the publication of the topline data was delayed for more than one and a half years after data lock. The mOS results of the Phase 3 trial are not bad, but not outstanding either. Major shortcoming of the trial is that the study design prevents comparison to an internal control group, leaving only comparison to external studies. This type of comparison has not yet been established and must be included in the statistical analysis plan, if at all, before a clinical trial begins - this is not the case with NWBO. It is not known whether the external studies were selected in consultation with regulatory authorities. Particularly in the case of rGBM patients, the mOS values of the studies used differed considerably, which poses major uncertainties.
An approval process based on these Phase 3 data and the selected comparative studies will be difficult and lengthy because the data are good but not convincing and because it will be a precedent-setting case.

[14] https://pubmed.ncbi.nlm.nih.gov/29843811/
[15] https://nwbio.com/nwbio-announces-scientific-publication-interim-survival-data-phase-3-trial-dcvax-l-glioblastoma-brain-cancer/
[16] https://nwbio.com/updated-interim-data-from-phase-3-trial-of-dcvax-l-for-glioblastoma/
[17] https://pubmed.ncbi.nlm.nih.gov/21984115/
[18] https://nwbio.com/presentation-about-phase-3-trial-of-dcvax-l-for-glioblastoma/
[19] https://virtualtrials.org/dcvax.cfm

Competitive situation

There are several approaches to develop new cancer therapies and thus therapies to cure GBM. In addition to cancer vaccines, to which DCVax-L belongs, there are other strategies including CAR T cells, oncolytic viruses, and checkpoint blockade inhibitors that have been recently investigated in GBM. [20] Some of these approaches resulted in approved drugs used for the treatment of brain cancer, including Avastin® (Roche Holding AG), Gliadel® (Eisai Co. Ltd.), and Temodar® (Merck & Co., Inc.), as well as the Optune electro-therapy device (Novocure). [21] Many therapies are currently still being tested and clinical trials are ongoing. However, many trials are still in Phase 1 or 2, only a few therapies have been or are being tested in Phase 3 trials. Of these, some Phase 3 trials have already failed meaning that current explorations in CAR T cells, oncolytic viruses, vaccines, and immune checkpoint inhibitors have yet to show improvements in survival outcomes. [22] Only three vaccination agents have reached Phase 3 clinical trial: Rindopepimut, DCVax-L, and PPV. In a Phase 3 clinical trial investigating rindopepimut in GBM patients with minimal residual disease, there was no significant difference in overall survival between the rindopeptimut and control group (median 20.1 months in the rindopepimut group versus 20.0 months in the control group; HR 1.01, 95% CI .79–1.30; P = 0.93). [23] The results of a Phase 3 trial investigating PPV (personalized peptide vaccine) were unfavorable as well. The primary endpoint of OS was not met in this clinical trial. Median OS was 8.4 months with PPV and 8 months with best supportive care. [24]
While this is disastrous news for patients and once again highlights that the development of new GBM therapies is top of mind, it is beneficial for NWBO. The Phase 3 results show a slight but important survival benefit, at least compared to the selected external control studies. DCVax-L is thus ahead of other therapies that are only in Phase 1 or 2 trials in terms of time due to the completed Phase 3 trial and is also gaining ground against direct competitors due to the positive results.

Market size

Originally, the Phase 3 trial investigated differences in PFS between patients treated with DCVax-L and patients treated with placebo. As a result, despite the crossover design, results would have been determined exclusively for newly diagnosed GBM patients. Due to the change of the primary endpoint to mOS in newly diagnosed and recurrent GBM patients, results are available for both patient groups. [25]
According to Les Goldman, a BLA filing for DCVax-L will cover both newly diagnosed GBM and recurrent GBM. [26]

Market size is estimated based on the number of total GBM patients. The Phase 3 trial (NCT00045968) inclusion and exclusion criteria contain only age as a relevant limiting factor so that DCVax-L can in principle be prescribed to all GBM patients between 18 and 70 years. [27]

Incidence:

Annual patients (ages 18 - 70) with newly diagnosed GBM in the USA: [28]	9,500 patients
Annual patients (ages 18 - 70) with newly diagnosed GBM in the EU: [29, 30]	12,800 patients
Annual patients (ages 18 - 70) with newly diagnosed GBM in the UK: [31]	1,500 patients

[20] https://cogentoa.tandfonline.com/doi/full/10.1080/21645515.2022.2055417
[21] https://www.sec.gov/ix?doc=/Archives/edgar/data/1072379/000141057822000244/nwbo-20211231x10k.htm, page 6
[22] https://cogentoa.tandfonline.com/doi/full/10.1080/21645515.2022.2055417
[23] https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30517-X/fulltext
[24] https://academic.oup.com/neuro-oncology/article/21/3/348/5219198
[25] https://virtualtrials.org/dcvax.cfm
[26] Personal phone call between Les Goldman, NWBO, and Prof. Dr. Christian Schleuning, BiotechProfSchleuning, on May 24, 2022
[27] https://clinicaltrials.gov/ct2/show/NCT00045968
[28] https://academic.oup.com/neuro-oncology/article/23/Supplement_3/iii1/6381476?login=true#305518768
[29] https://ecis.jrc.ec.europa.eu/explorer.php?$0-0$1-AE27$4-1,2$3-All$6-20,69$5-2020,2020$7-7$2-All$CEstByCancer$X0_8-3$CEstRelativeCanc$X1_8-3$X1_9-AE27$CEstBySexByCancer$X2_8-3$X2_-1-1
[30] https://gbmresearch.org/blog/glioblastoma-survival-rate
[31] https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours#heading-Zero

NWBO is expected to submit the first application for approval of DCVax-L in the UK. Here, about 1,500 patients with newly diagnosed GBM could be treated annually; if approvals in the EU and the USA are added, this number will grow by about 12,800 and 9,500 patients, respectively.
The recurrence rate of GBM is close to 100%. [32], [33] To date, no precise data have been published from the Phase 3 DCVax-L trial on the number of patients treated with DCVax-L who experienced tumor recurrence. Based on survival and recurrence rate, we can roughly expect 50% recurrent GBM patients. Thus, in addition to the above patient numbers, this adds up to 750 patients for the UK, 6,400 for the EU, and 4,700 for the US annually.

Manufacturing

NWBO uses a batch manufacturing technology for its DCVax products, and when a batch of DCVax product has been made, it is cryopreserved. Personalized batch manufacturing for each patient and cryopreservation are essential elements of NWBO's manufacturing model and product economics. The manufacturing process is rapid: about eight days for DCVax-L, and seven days for DCVax-Direct, followed by quality control and release testing (including a sterility test that may take a couple of weeks).
NWBO developed a manufacturing facility in Sawston, U.K. The Sawston facility contains a total of 88,345 square feet on two floors. The initial production capacity comprises two manufacturing suites, occupying approximately 4,400 square feet on the ground floor. These two suites, together with some additional support and storage space, have anticipated potential capacity to produce dendritic cell vaccines for about 40 to 45 patients per month, or approximately 450 to 500 patients annually. The buildout of Phase 1A of the facility was completed in Q4 2020.
The facility received a Human Tissue Authority (HTA) license in October 2021 and the MHRA license was issued in December 2021. Following some required validation work after the licenses were issued, production of DCVax-L began in February 2022. [34, 35] In July 2022, NWBO announced that application for license of the manufacturing facility in Sawston for commercial manufacturing of cellular therapies has been submitted to the MHRA. [36]
On December 31, 2021, NWBO entered a sub-lease for a small portion of the space to contract manufacturer, Advent BioServices. The subleased space may enable some production of third-party cell therapy products. According to NWBO, such production of other products will fulfill the loan-related commitment to the Cambridge authority, will help support the capital-intensive Sawston facility costs and, considering the growing demand for cell therapy manufacturing capacity, could substantially increase the asset value of the Sawston facility. All development activities for the Sawston facility have been carried out or managed by Advent BioServices, who is also the contract operator of the facility. [37]

Management

NWBO's management team excels with years of experience and expertise. The core team has been employed by NWBO for at least 10 years. In particular, the scientific team consisting of Chief Technical Officer Dr. Marnix Bosch and Chief Scientific Officer Dr. Alton L. Boyton impresses with years of accumulated knowledge.

[…] This version of the analysis does not provide the full text.

[32] https://www.cancertherapyadvisor.com/home/tools/fact-sheets/cancer-recurrence-statistics/
[33] https://pubmed.ncbi.nlm.nih.gov/33152694/
[34] https://www.sec.gov/ix?doc=/Archives/edgar/data/1072379/000141057822000244/nwbo-20211231x10k.htm, pages 4 - 5
[35] https://nwbio.com/northwest-biotherapeutics-announces-commencement-of-cancer-vaccine-production-at-its-sawston-uk-facility/
[36] https://nwbio.com/northwest-biotherapeutics-announces-filing-of-application-for-license-for-commercial-manufacturing-at-sawston-uk-facility/
[37] https://www.sec.gov/ix?doc=/Archives/edgar/data/1072379/000141057822000244/nwbo-20211231x10k.htm, page 5

Financial overview

According to the Quarterly Report from May 2022, NWBO had cash and cash equivalents of $6.96 million as of March 31, 2022, compared to $15.17 million as of December 31, 2021. [38] NWBO had a net loss of $14.2 million and $4.1 million for the three months ended March 31, 2022 and 2021, respectively.

Cash Flow Statement								
	06/30/20	09/30/20	12/31/20	03/31/21	06/30/21	09/30/21	12/31/21	03/31/22
Net Income	-58.05	-194.10	-280.30	-4.12	-4.41	45.52	133.32	-14.21
Total Depreciation & Amortization	0.09	0.10	-0.20	0.16	0.13	0.15	-0.12	0.16
Cash from Operations	-6.33	-8.02	-10.20	-13.25	-6.79	-7.01	-11.25	-12.97
Cash from Investing	-1.24	-3.80	-3.03	-0.26	-1.51	-2.69	-1.55	-0.06
Cash from Financing	13.17	16.68	15.82	10.76	4.78	8.92	23.67	3.92
Net Change in Cash	5.19	3.30	0.73	-2.52	-3.71	0.08	11.33	-8.21
Free Cash Flow	-7.57	-10.26	-13.26	-13.51	-8.30	-9.70	-12.80	-13.03

Based on the last eight quarters, NWBO has spent an average of $9.48 million per quarter, ranging between $6.33 and $13.25 million. In the 3 months ended on March 31, 2022, NWBO reported a 13% increase in the cash used in operations from $11.25 million in the 3 months ended in December 2022 to then $12.97 million. It shows the company used up approximately $4 million every month. The Phase 3 trial is finished and a BLA filing for DCVax-L is planned, so spending of around $10 million can be expected for the coming quarters until the end of 2022 and maybe even into 2023.
Based on these assumptions and information, NWBO's existing cash for end of June 2022 can be calculated approximately as follows:

	$6.96 million	(March 31, 2022)
–	$10.0 million	(Cash burn Q2 2022)
–	**$3.04 million**	

In a personal phone call, Senior Vice President Les Goldman asserted that the company has sufficient cash through 2023 due to warrants and options. [39] Expenditures can be expected to increase due to the upcoming BLA filing towards the end of 2022, but at the latest in H1 2023.

[…] This version of the analysis does not provide the full text.

Intellectual property

In its 2021 Annual report, ATNM states that as of December 31, 2021, the company has 204 issued patents and 59 pending patent applications worldwide, grouped into 11 patent families. Of these, 200 issued patents and 47 pending patent applications directly relate to the DCVax products. In the United States and Europe, some of these patents and applications relate to compositions and the use of products, while other patents and applications relate to other aspects such as manufacturing and quality control. NWBO has U.S. and European patents and applications that cover, among other things, quality control for DCVax and an automated system, which will help enable the scale-up of production for large numbers of patients on a cost-effective basis.
With the acquisition of Flaskworks, NWBO gained ownership of a portfolio of patents and patent applications, which include those held by Flaskworks as well as patents and patent applications exclusively licensed by Flaskworks from Northeastern University. The portfolio includes a total of thirteen patent families, with issued patents and pending applications worldwide. Collectively these patents and patent applications cover key aspects of the design and function of automated cell culture systems.

[38] https://www.sec.gov/ix?doc=/Archives/edgar/data/1072379/000141057822001218/nwbo-20220331x10q.htm, page 3
[39] Personal phone call between Les Goldman, NWBO, and Prof. Dr. Christian Schleuning, BiotechProfSchleuning, on May 24, 2022

The expiration dates of the issued U.S. patents involved in NWBO's current business range from 2022 to 2036, and pending applications may involve longer time periods. The expiration dates of the issued European patents involved in NWBO's current business range from 2022 to 2024, and pending applications may involve longer time periods. For some of the earlier dates, NWBO plans to seek extensions of the patent life. [40]

Timeline

NWBO's Phase 3 trial has ended, and results were first presented on May 10, 2022. [41, 42] The next steps are therefore to hold a pre-BLA meeting with the regulatory authorities - in the case of NWBO, presumably the UK MHRA - and then to submit a BLA for approval of DCVax-L. In addition, the Phase 3 results are expected to be published soon in a scientific journal; Les Goldman told us by phone in late May that the manuscript has already been submitted to a high-class journal. [43]
DCVax-L was granted orphan drug designation in both the U.S. and Europe for GBM and other glioma brain cancers. [44] This designation provides a drug developer with certain benefits and incentives, including a period of marketing exclusivity if regulatory approval is ultimately received for the designated indication; potential tax credits on U.S. clinical trials; eligibility for orphan drug grants; and waiver of certain administrative fees. [45] However, NWBO has not yet received a designation from the FDA or any other regulatory authority for DCVax-L that would allow for an accelerated priority review process of the BLA. Therefore, it can be assumed that an approval decision by regulatory authorities after submission of the BLA will take a total of 12 months and will therefore not occur before 2024.

Timeframe by NWBO	Catalyst	Estimated timeframe
H2 2022	Publication of journal article	September 2022
H2 2022	Pre-BLA meeting with the British MHRA	Q4 2022
H1 2023	BLA filing for DCVax-L	Q2 2023

There are several catalysts coming up in the next six months with the publication of the article and preparations for the BLA. However, it cannot be said with certainty whether NWBO will keep to the schedule described here. It may be several months, if not years, before final approval of DCVax-L.

Summary

NWBO scores high on the fact that DCVax is a platform technology that could be made applicable to many different solid tumors. The use of dendritic cells as a vaccine to generate a broad immune response has long been explored and there are many positive examples that the technology principally works.
DCVax-L has tremendous advantages as a personalized cancer therapy based on patient tumor lysate over standard T cell therapies or mRNA or protein vaccination. By using the whole tumor lysate to activate dendritic cells, the possibility of patient escape variants is minimized.
The previous clinical trials with DCVax-L have shown convincing good results. The Phase 3 trial also shows good, but not superior results. Due to the unfortunate study design, there is a need for comparison to external control studies. The comparison to the internal control arm is missing and NWBO has not yet published a comparison to the 35 placebo patients. Some data on the rGBM patients are also missing. For a final evaluation of the Phase 3 results, we have to wait for the publication of the data in a peer-reviewed article.

[40] https://www.sec.gov/ix?doc=/Archives/edgar/data/1072379/000141057822000244/nwbo-20211231x10k.htm, page 5
[41] https://nwbio.com/presentation-about-phase-3-trial-of-dcvax-l-for-glioblastoma/
[42] https://virtualtrials.org/dcvax.cfm
[43] Personal phone call between Les Goldman, NWBO, and Prof. Dr. Christian Schleuning, BiotechProfSchleuning, on May 24, 2022
[44] https://nwbio.com/nw-bio-responds-to-shareholder-inquiries-following-immune-therapy-sectors-recent-market-decline/
[45] https://ir.actiniumpharma.com/press-releases/detail/161

The next catalysts are clear, but their time frame can only be estimated. Overall, due to the first-time situation of retrospective use of external control studies, the potential approval of DCVax-L may still drag on for several months or even years.

All in all, NWBO convinces with its DCVax platform technology, but less with its outstanding data. A final evaluation of the Phase 3 results can only be made after publication in a scientific journal. The approval of DCVax-L based on these Phase 3 results and the use of external control studies cannot be ruled out but is at least extremely risky and promises to be a lengthy process.

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