Austrian milestone

Phase 1 trial ready to start shortly

ExpreS2ion Biotechnologies has received final approval by the Austrian Agency for Health and Food Safety, BASG, to start a first-in-human, phase 1 trial with ES2B-C001, the most advanced vaccine candidate in the ExpreS2ion pipeline.

This decision follows a clinical trial application which was submitted by the company in August. The trial will be conducted at the Oncology department of Medical University of Vienna.

HER2 positive cancer patients to be included

Participants are diagnosed with metastatic or locally advanced HER2 positive breast cancer and will receive five doses of ES2B-C001, either adjuvanted by Montanide or unadjuvanted. Participants are no longer responding to Herceptin, the standard anti-HER2 treatment in breast cancer.

Depending on the final number of patients, we expect enrollment to be ongoing during the course of 2025 and a topline result ready by the first half of 2026. The primary endpoint will be safety and tolerability, but signs of clinical activity in the participants will also be measured.

The promise of a vaccine immunotherapy

ES2B-C001 will be studied as a therapeutical agent, not in the preventive setting generally assigned to vaccines. The vaccine antigen is designed to overcome treatment resistance that limits the current monoclonal standard treatments by producing polyclonal antibodies binding to the entire HER2 protein instead of a single epitope.

ES2B-C001 may also show a longer protection to relapsed disease, which needs to be studied over a longer time span. If these properties can be proven in a phase 3 study by a future partner, we expect sales of ES2B-C001 to surpass USD 3bn.

Fair value at SEK 91 offers substantial upside

The recent slump in the share price of ExpreS2ion Biotechnologies makes the outcome of the TO10 less impressive, adding gross proceeds of SEK 10m. We expect the company to enter next year with a cash position of SEK 70m, which should extend beyond the TO11.

Our assumption in ES2B-C001 is 11 percent likelihood of approval, reflecting a better chance of approval than the average oncology drug initiating a phase 1 study. Fair value is trimmed at 91 SEK (96), offering a substantial upside once the phase 1 study starts to generate a positive news flow.

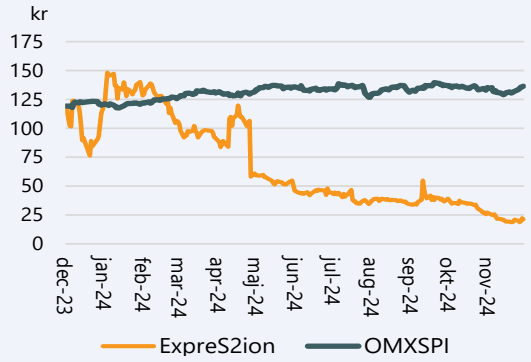
ExpreS2ion Biotech

Date	9 december 2024
Analyst	Sten Westerberg

Facts

Industry	Vaccine Development
Chairman of the Board	Martin Roland Jensen
CEO	Bent U. Frandsen
Year of Listing	2016
Stock List	First North Growth Market
Ticker	EXPRS2
Share price, SEK	22
No. of shares, mln.	2,66
Market cap, SEKm	58
Cash, SEKm	70
Fair value, SEK	**91**
Web site	www.expres2ionbio.com

Kursutveckling senaste året



Source: Refinitiv

Forecasts & Key ratios, SEKm

	2023	2024p	2025p	2026p
Revenues, risk-adjust.	9	7	9	14
R&D expenses	-51	-39	-57	-62
EBIT	-106	-65	-79	-81
Earnings per share	-50,0 kr	-30,8 kr	-37,4 kr	-38,4 kr
Revenue growth	43%	-18%	22%	56%
Cash	58	70	7	33
New share issue	58	42	15	108

Source: Company, Analysguiden forecasts

Design of immunotherapy study

According to the CTIS study protocol patients to be included in the trial are diagnosed with metastatic or locally advanced HER2 positive breast cancer, a cancer susceptible to HER2 protein. At this stage patients are no longer eligible to resection by surgery. The trial will also have the option to include patients with low levels of HER2.

Included participants will have relapsed under maintenance therapy, either with Herceptin or Perjeta, two monoclonal antibodies which have shown improved progression-free survival in HER2+ breast cancer but with a growing risk of developing tumor resistance and progression.

The vaccine candidate ES2B-C001, combined with the adjuvant Montanide, will be added to the standard treatment and tested in three different levels up to 400 mg unless dose-limiting toxicity occurs at a lower dose.

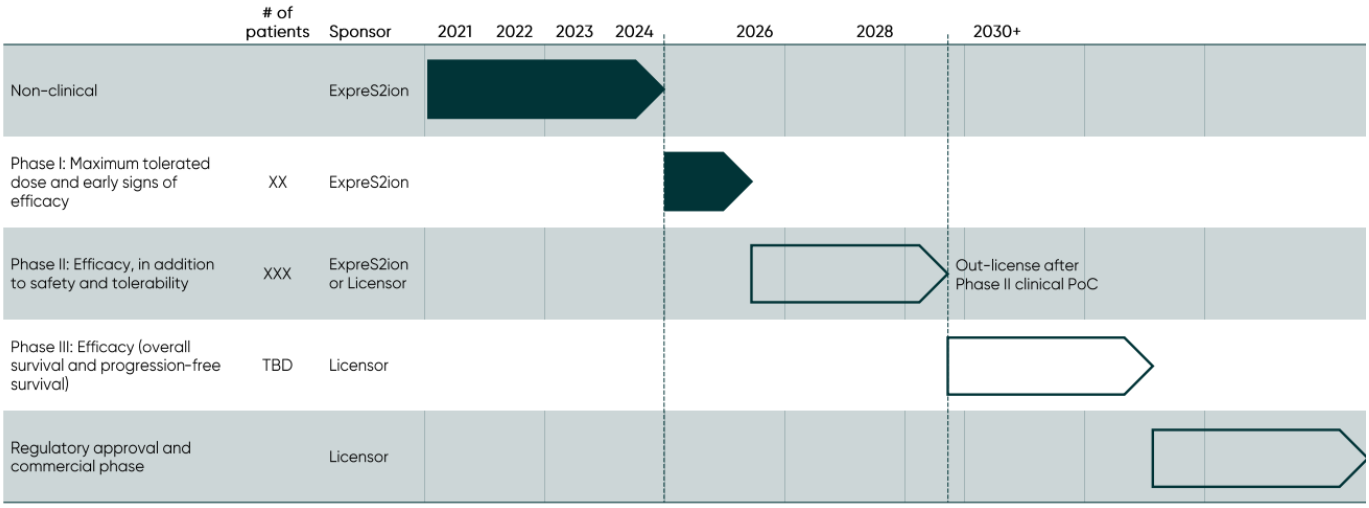
Flexible number of participants

Every dose level will include three patients, receiving five injections of ES2B-C001. In an optimal scheme, this would result in nine patients being tested in the first stage. It will be possible to expand the three-patient cohort as soon as signs of toxicity are registered and a final maximum tolerated dose (MTD) will be established.

The design allows for expanding the cohort at MTD with another 12 patients. However, there will also be inclusion of patients with unadjuvanted ES2B-C001 and an expected drop-out ratio, making the probable number of patients ending up around 27-30 subjects.

The study will be open-label and include no control from participants receiving placebo. As always in a first-in-human phase 1 study safety and tolerability will be the main focus. As soon as a maximum tolerated dose is established, the trial will be expanded to a cohort of 6-9 patients. We assume that this cohort will receive multiple doses.

Development schedule for ES2B-C001



Source: Company presentation, November 27

Topline results possible in 2026

As a secondary endpoint signs of clinical activity will be looked for. Immunogenicity elicited by the vaccine to the target protein HER2 is measured by the number of antibodies to HER2 proteins generated by the adaptive immune system in response to the antigen mounted on ES2B-C001.

Since the substance is polyclonal, binding to four different epitopes on the surface of the HER2 receptor, it is likely to give rise to four different clones of antibodies. Since patients may be under maintenance therapy it will also be of interest to see how the vaccine candidate interacts with the established treatments, such as Herceptin.

Based on a previous company presentation, we understand that patients will be followed up to five months after initiating vaccination. The original timeline included a recruitment period of 15 months, which then supposed a total of up to 36 patients. Since it is more likely that the study ends at 27-30 patients, some of which having low HER2 levels, we speculate that topline may be disclosed as early as in the first quarter of 2026.

Proof-of-concept trial may start in 2027

Assuming a safe profile of ES2B-C001 the company expects to launch a phase 2 proof-of-concept study involving +100 patients, either alone or in collaboration with a partner. We expect this study to be possible by 2027. A potential launch of the vaccine candidate would then be possible in 2032-33 after a major phase 3 studie and regulatory review.

In our base case scenario, we expect ExpreS2ion to reach a licensing deal in 2027 with an initial payment of EUR 25m.

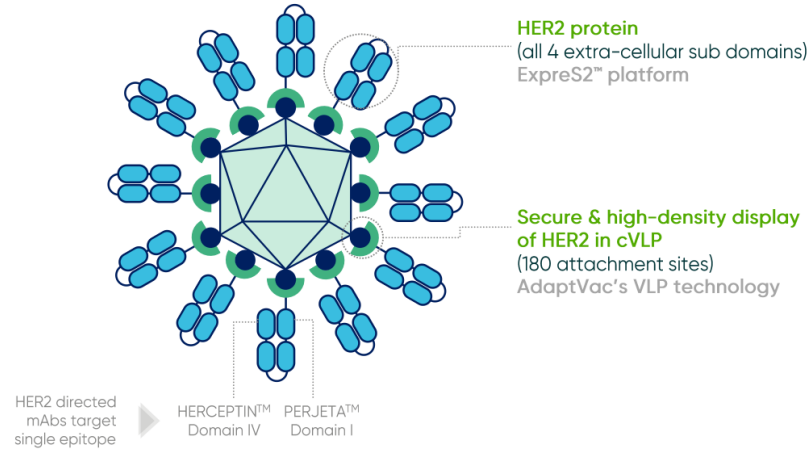
Polyclonal response distinguishes ES2B-C001

Current treatments of metastatic HER2-positive breast cancer are dominated by the monoclonal antibodies trastuzumab (Herceptin or generics) and pertuzumab (Perjeta). The monoclonal property means that the antibody has been expressed by a single B-cell clone, which is considered a safety measure but also narrows its action to one single epitope of the HER2 protein.

A challenge for monoclonal antibodies is the lack of durable therapeutic response and acquired resistance due to mutations in the HER2 receptors. Antibodies also tend to upregulate alternate pathways for tumor growth. In contrast, vaccines can induce polyclonal responses from several different antibodies which may induce a broader immunogenic effect at the target molecule.

The vaccine antigen included in ES2B-C001 thus has the potential to involve a broader B cell response by binding to numerous epitopes of all four domains of the HER2 protein, which is expressed on the surface of the tumor cell.

Illustration of ES2B-C001 interaction with HER2



Source: ExpreS2ion Biotech

Cancer vaccines are increasingly being studied as a possible strategy to both treat and prevent cancers in certain high-risk population. Several preventive vaccines for virus-caused cancers are already approved and used worldwide. However, the development of vaccines in breast cancer still has not yielded any approved products.

The human epidermal growth factor receptor-2 (HER-2) is a surface receptor-like tyrosine kinase which plays a role in many human breast carcinoma and in a few other tumor types, including bladder, colorectal, lung, stomach, and musculoskeletal cancers. In breast cancer, amplification of the HER2 gene and/or overexpression of its protein product occurs in 20–25% of all cases. This type is associated with a poor survival prognosis.

Base scenario involves licensing deal in 2027

Assuming a positive read-out late in 2026, we have an aggregated likelihood of 55 percent of a partnering deal in 2027. We have included an initial downpayment of EUR 25m in 2027, an optimistic assessment reflecting the innovativeness of the project.

We have assumed that ExpreS2ion will receive a 10 percent royalty on licensee sales and that AdaptVac will receive another 2 percent of sales. AdaptVac also has the right to receive a further SEK 3.5m upon initiation of the phase 1 study in 2025.

To arrive at a licensing deal in 2027, we have included full financing from TO 10 and 11, on top of the latest rights issue in June. An additional minor bridge financing in late 2026 or early 2027 may be necessary.

We have raised the likelihood of marketing approval (LOA) after partner-initiated phase 2b and 3 studies to 11 percent from 10 percent, based on the CTA and the establishment of manufacturing processes. Our base case is a marketing approval of ES2B-C001 by 2032.

Estimated sales potential of at least EUR 3.2bn

In a previous announcement, management defined the obtainable market opportunity for a HER2+ vaccine as more than EUR 2,8bn. A previous number in the annual report stated a total market

opportunity in breast cancer of more than EUR 10bn, which should be seen as broader definition of the market. Our NPV valuation is based on a peak sales estimate of EUR 3,2bn by 2037.

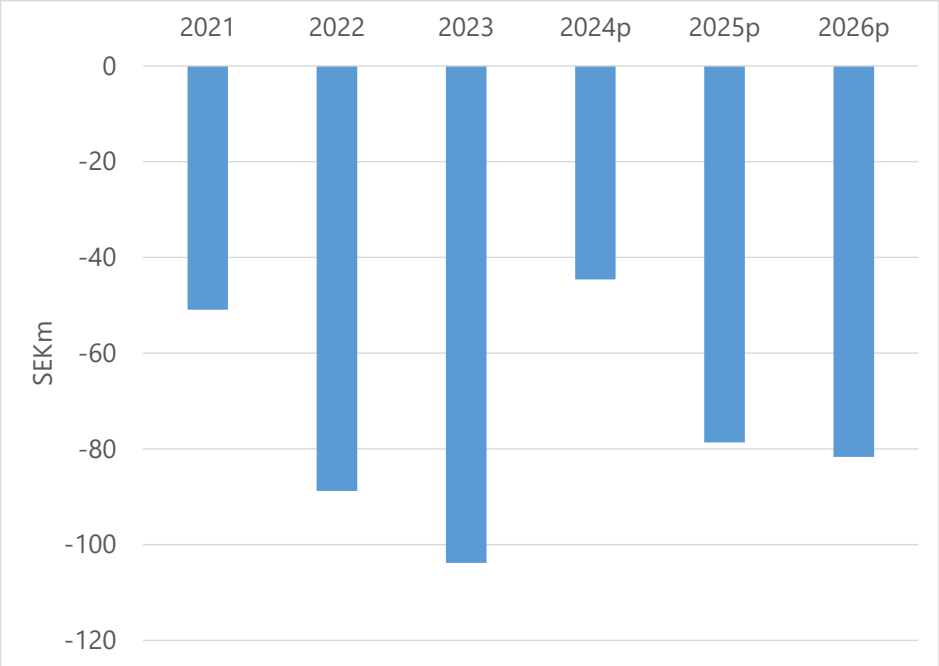
Financial discussion and valuation

We expect ExpreS2ion Biotech to enter 2025 with a cash position at SEK 70m, which would carry operations beyond the TO11 in September-October. This cash amount should be put in perspective of a market capitalization of SEK 57m, underscoring the negative outlook which is priced to the shares.

The subscription rate of TO10 at 69 percent adds gross proceeds of only SEK 10m. The negative share price development since the new share issues in July, with a subscription price at SEK 40 compared to SEK 17,9 in TO10, has put a dent in the financing capacity but we expect a positive news flow from the imminent phase 1 study to allow for a better start to 2025.

As for the TO11 warrant due in September-October 2025, we have assumed an VWAP of SEK 34, driven by the progression of patient recruitment in the phase 1 study, as well as preliminary safety conclusions in the lower doses. This scenario would grant the company another SEK 19m in October.

Cash burn in SEKm, outcome and forecast



Source: ExpreS2ion Biotechnologies, Analysguiden forecasts

We expect an operative cash burn in 2025 of SEK 76m, up from this year's estimated SEK45m. Depending on the final number of patients in the phase 1 study, we expect this to cost SEK 30-40m, primarily during the course of 2025.

The next financing event is likely to occur in early 2026, possibly before the topline conclusions in the study. We estimate that ExpreS2ion will have to prepare for a gross SEK 110m capital raise, which would imply a 35 percent dilution at a subscription price of SEK 60.

This scenario would leave us with a fair value of SEK 91, down from SEK 96 in our latest report. In a more positive scenario, Expres2ion may be able to strike a licensing deal in late 2026 with a downpayment of SEK 100-200m, leaving a partner in charge of the phase 2 design.

Sum-of-The-Parts valuation of ExpreS2ion Biotech

	Project value (MSEK)	Value / share (SEK)	Peak sales (MEUR)	LOA*	WACC	Share of NPV	Comments
ES2B-C001	222	43,5	2 838	11%	15%	100%	Phase 1 started
Adaptvac holding	92	18,0		100%	12%	34%	Minority holder
Platform	42	8,2	0,6	100%	10%	100%	cash flow based
Malaria project	70	13,7	175	15%		6%	of consortium
Indigo (influenza)	17	3,3	952	3%		6%	of consortium
CMV program	18	3,6	900	3%	35%	100%	CD election 2025
Nipha program	25	4,9	100	3%		30%	of consortium
Administration	-20	-3,9					
Sum	465	91,3					

Projected no. of shares, end of 2026 (mln) 5,10

current number of shares (mln) 2,19

**) Likelihood of approval*

Forecasts by Analysguiden

Discussion of LOA at 11 percent

As a result of the BASG nod to the phase 1 study we raise our likelihood of approval (LOA) for ES2B-C001 to 11 percent from previously 10 percent. Our base scenario would be above the industry average in cancer drug development for a phase 1 project in its early stages. The industry average of an oncology product initiating a phase 1 is more in the region of 4-6 percent.

We justify this level by the vaccine approach of ES2B-C001, which may be associated with a lower development risk than a small molecule kinase inhibitor or a monoclonal antibody. Current preclinical data and a thorough manufacturing preparation adds to this optimism.

Assumptions of risk adjusted NPV calculation

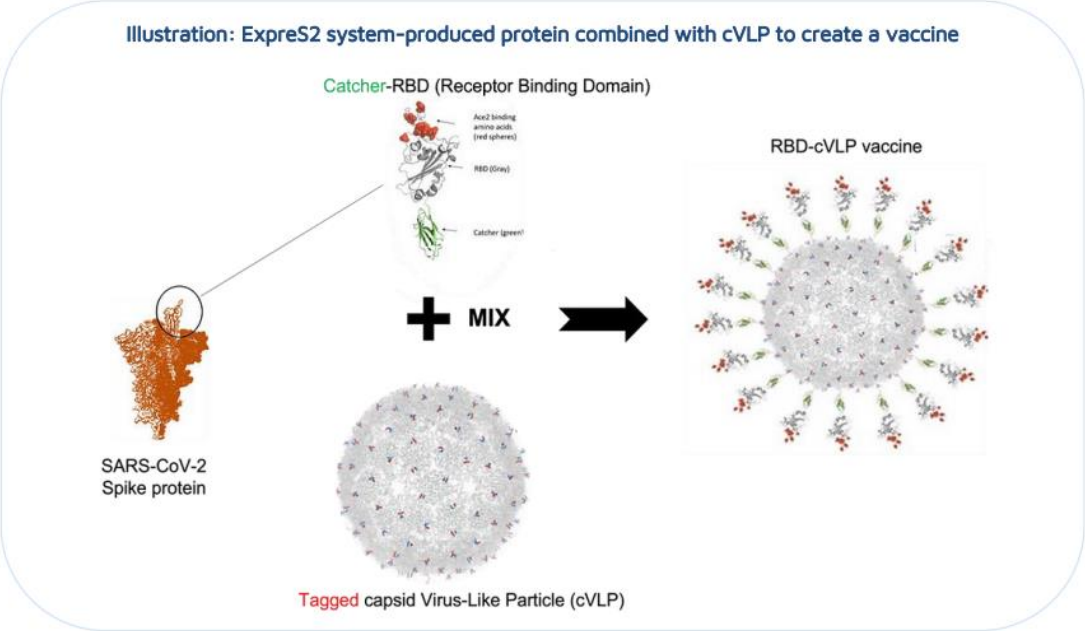
SEKm, ExpreS2ion Bio		2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Operating revenue		6	9	7	9	14	197	8	9	506
ES2B-C001				*0*	*0*	*0*	*189*	*0*	*0*	*497*
platform/services		*6*	*7*	*5*	*6*	*6*	*8*	*8*	*9*	*9*
EBIT		-127	-100	-43	-79	-81	139	5,7	6,0	
Cash		111	58	70	7	33				
AdaptVac		2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Net income				10	0	5	75	0	0	
Milestones, ERUm				*10*	*0*	*5*	*75*			
Risk adjustment				*1,0*	*1,0*	*1,0*	*1,0*	*1,0*	*1,0*	
Risk-adjusted NPV (SEKm)				64,3	-2,4	19,5	254,3	-1,2	5,0	
Risk-adjusted		*0,00*	*0,00*	*1,00*	*1,00*	*1,00*	*1,00*	0,00	0,00	
WACC	12%									
NPV, SEKm	29,1									
Likelihood of approval	100%									
ExpreS2ion share, SEK	18,0									
ES2B-C001 (SEKm)		2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Costs, preclinical / clinical		-70	-60	-24	-19	-16	0	0	0	0
milestones to Adaptvac				*-3,5*	*-3,5*	*0*	*0*	*0*	*0*	*0*
Sales, EURm									0	0
Total milestones, licensing	475					0	25	0	50	100
Royalty	*10%*									*0*
Expres2ion revenues, SEKm		-70	-60	-24	-19	0	189	0	575	1150
Risk-adjusted				*1,00*	*0,55*	*0,55*	*0,55*	*0,25*	*0,25*	*0,12*
Risk adjusted revenues, NPV (SEKm)				0	-10	-28	104	0	71	62
WACC	15%			Likelihhod of ph1 to ph2		55%				
NPV, SEKm	222			Likelihhod of ph2 to ph3		45%				
Likelihood of approval	11%			Likelihhod of succesful ph3		50%				
Diluted value/share, SEK	43,5			Likelihhod of regulatory approval		87%				

Analysguiden forecasts and assumptions

Appendices - Summary of the technology and programs

We classify the joint AdaptVac and ExpreS2ion platforms as a combined protein subunit antigen vaccine platform. Protein expression is provided by ExpreS2ion's EXPRES2 technology, coupled with a capsid Virus Like Particle (cVLP) of the AdaptVac platform. In the case of ABNCoV2, which has completed a phase 3 study, the capsid-like particle is coated with 60-80 particles of the recombinant RBD protein fragment. Researchers showed in a Nature article that RBD proteins glued to the CLP had a 3-4-fold higher immunogenicity compared to soluble RBD proteins injected without being mounted to the capsid-like particle, a strong rationale for the technology behind the ABNCoV2 cVLP vaccine.

Schematic figure of cVLP expression and construct



Source: Company presentation

Vaccine candidate in development

The breast cancer vaccine candidate ES2B-C001 is ExpreS2ion Biotechnologies in-house proprietary program which is progressing toward a clinical trial. It was licensed from AdaptVac based on an option agreement signed in 2020. In May 2022 ExpreS2ion Biotechnologies announced positive preclinical proof-of-concept results for this HER2-breast cancer vaccine candidate from a therapeutic study in HER2-transgenic mice. In the study, all transgenic mice vaccinated with ES2BC001 formulated in an adjuvant were metastasis-free, while all control mice had lung nodules. Furthermore, 73% of mice vaccinated with ES2B-C001 without adjuvant were metastasis-free.

Later ExpreS2ion initiated animal studies on non-human primates which now have been completed. In 2020 it was expected that the program would be ready for a CTA, Clinical Trial Application, by the

first half of 2022. This CTA has for several reasons been pushed into 2024.

In 2020 the program was developed by AdaptVac and called AV001. In the option deal which ExpreS2ion signed with AdaptVac in February 2020 described AV001, later to be ES2B-C001, as having shown proof-of-concept in animal testing on mice in an article published 2018 by researchers at the University of Bologna. However, this study was based on a non-proprietary tag catcher method and had to be redone with a proprietary tag catcher system developed by AdaptVac.

There are currently other vaccine candidates being developed for HER2 positive breast cancer in clinical trials. The list of preclinical programs is long and include candidates based on mRNA vaccine platforms. What may be the selling point of ES2B-C001 is the claim to both a preventive and therapeutic effect. ES2B-C001 is developed as a therapeutical vaccine for patients with HER2 positive breast cancer, having progressed after initial treatment with the standard anti-HER2 therapy Avastin (trastuzumab).

According to the 2023 prospect, two weeks after the inoculation of tumor cells, the first vaccine administrations were given. ES2B-C001 formulated in an adjuvant was found to totally block tumor development, whereas the control group progressively expanded with lung metastases and subcutaneously growing local tumors. Additionally, ES2B-C001 without adjuvant was found to inhibit, but not prevent, tumor development.

Vaccine candidates to HER2+ in clinical development

Study Title	Study Phase	Stage of Disease	Study Population	Tumor Type	Study Treatment	NCT Number
A Phase II Study of Concurrent WOKVAC Vaccination with Neoadjuvant Chemotherapy and HER2-Targeted Monoclonal Antibody Therapy	Phase II	I, II, III	Patients with HER2+ breast cancer, regardless of hormone receptor status, who are planning to receive neoadjuvant cytotoxic chemotherapy and HER2-targeted monoclonal antibody therapy prior to planned surgery.	Breast	Vaccine + chemo+HER2-targeted monoclonal antibody	NCT04329065
A Phase II Study to Evaluate the Efficacy and Safety of an Adjuvant Therapeutic Cancer Vaccine (AST-301, pNGVL3-hICD) in Patients with HER2 Low Breast Cancer (Cornerstone-001)	Phase II	I, II, III	Patients with histologically or cytologically confirmed HER2 low expression (1+ or 2+) and hormone receptor-negative (both ER- & PR-) breast cancer who have completed neoadjuvant systemic chemotherapy and have residual disease.	Breast	Vaccine	NCT05163223
A Phase I Dose Escalation Trial of Alpha-tocopheryloxyacetic Acid (α-TEA) in Patients with Treatment Refractory HER2+ Metastatic Breast Cancer	Phase I	IV	Stage IV HER2+ breast cancer who have been treated with definitive therapy and received maintenance HER2-targeted monoclonal antibody therapy; and currently have measurable disease not considered curable by conventional therapies.	Breast	Vitamin E derivative + HER2 targeted monoclonal antibody	NCT04120246
Phase I trial of intravenous administration of TAEK VAC-HerBy vaccine alone and in combination with HER2 antibodies in patients with advanced cancer (Stage 2 only)	Phase I	II, III, IV	Patients with HER2+ breast or gastric/gastroesophageal junction cancer who have locally advanced metastatic tumors	Breast and gastric/gastroesophageal junction	Vaccine + chemo+HER2-targeted monoclonal antibody	NCT04246671

Source: Cancer Vaccine Institute, University of Washington

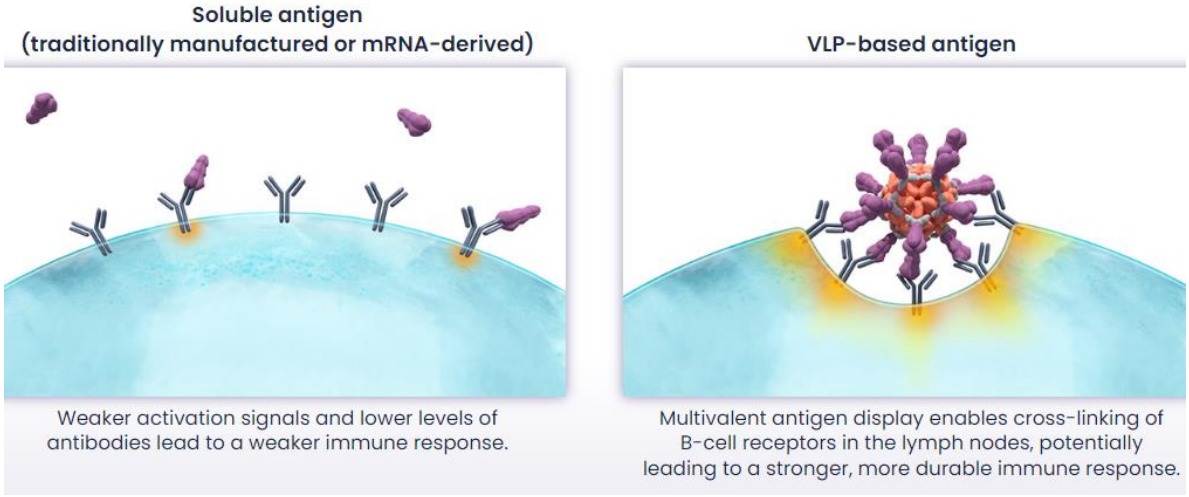
Competitive landscape in HER2+ breast cancer

Several earlier studies are also in different clinical phases with patients suffering from HER2 positive breast cancer. A sample is shown in the table above.

AstraZeneca acquisition of VLP vaccine

In 2023 AstraZeneca announced the acquisition of the US-based vaccine developer Icosavax, which is considered a market leader in the field of virus-like particle mounted vaccine development. Icosavax' most advanced project, IVX-A12, is ready to start phase 3 study in the prevention of infections of the respiratory syncytial virus (RSV) and human metapneumovirus (hMPV). The antigen protein of the vaccine is mounted on a virus-like particle (VLP) scaffold, much like the scaffold of AdaptVac.

Icosavax platform compared to traditional platform



Source: Icosavax home page

AstraZeneca pays upfront USD 838m for Icosavax, of which we estimate that the phase 3 program makes up at least 85 percent. Another approx. USD 300m are contingent on future milestones of the Icosavax pipeline.

We judge the AstraZeneca acquisition primarily as a way of boosting its position in the RSV market, where AstraZeneca has lost substantial market shares to newer products. But the acquisition clearly signals a belief in the VLP technology, which is an important vote of confidence in a vaccine industry otherwise focused on mRNA-based technology.

In a press statement AstraZeneca points out that the VLP technology is a proven technology with multiple products on the market, including vaccines for human papillomavirus and hepatitis B. So far, this technology has been limited to a smaller number of proteins which naturally fold into the VLPs, while the Icosavax protein VLP platform builds this success with the intention to create a more differentiated response.

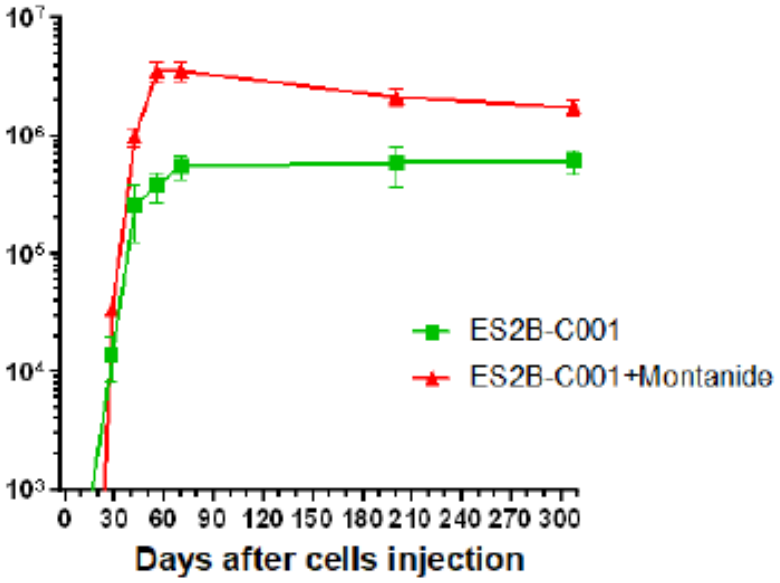
Icosavax's VLP platform technology is designed to enable multivalent, particle-based display of complex viral antigens, which it believes will induce durable virus protection. The AstraZeneca acquisition supports the notion that the VLP technology may induce a stronger

and more durable immune response versus traditional soluble antigens as well as mRNA-based approaches.

Proof-of-concept in mice model

The preclinical proof-of-concept of the breast-cancer program is based on an academic collaboration with researcher at the Universities of Bologna and Pavia in Italy[1]. ES2B-C001 was tested both prophylactically, in mice which later was injected with human carcinoma cells, and therapeutically in mice with tumor cells already present.

Anti-HER2 antibodies (ng/ml) in active cohorts



All untreated transgenic mice exposed to HER2+ mammary carcinoma cells developed progressive tumors, whereas mice vaccinated with ES2B-C001 plus an additional adjuvant (Montanite ISA 51) remained tumor-free. Seventy percent of mice vaccinated with ES2B-C001 monotherapy without additional adjuvant remained tumor-free. Treated mice remained tumor-free for more than one year after cell injection, whereas all control mice developed progressive tumor within 1–2 months. Interestingly, ES2B-C001 inhibited lung metastases in mice exposed to the cancer cells. As for the elicitation of anti-HER-2 antibody responses there was a marked improvement in the cohort receiving Montanide adjuvanted ES2B-C001 compared to ES2B-C001 monotherapy (see table above).

In mice already infected with cancer cells ES2B-C001 and the antibody trastuzumab were effective in trastuzumab-responsive tumor cells, while as expected ES2B-C001 alone did show a potent effect in trastuzumab-resistant cells. The article also pointed out the potential of a longer duration of the elicited antibody response compared to the therapeutic antibody trastuzumab. In immunotherapeutic terminology, monoclonal antibodies are

[1] Ruzzi et al; Biomedicines 2022, vol 10, 2654

classified as passive immunotherapy, whereas vaccines are called active immunotherapy.

Potential mechanistical advantage

A potential advantage of the ES2B-C0001 vaccine candidate is the mechanistic fact that it binds to all four extracellular domains of the HER2 protein, while trastuzumab only binds to one of all four domains. On the other hand, virus-like particles might theoretically interfere negatively with anti-tumor immunity through the induction of anti-VLP antibodies, an effect termed carrier-induced epitopic suppression (CIES)[2]. We note that no such adverse events were reported in the phase 3 program with ABN-CoV2

The ES2B-C001 vaccine candidate administered in the Ruzzi study published in Biomedicines in 2022 was a re-engineered version for human administration with 50 antigens per particle, the maximum number of HER2 antigens which can be mounted on a VLP scaffold. In the first published research on ES2B-C001 in 2018, the scaffold was presented as a carrying 360 HER2 peptides[3]. By that time, no additional adjuvant was added to the mice model. Somewhat contradictory, in the latest poster presented by Ruzzi at last year's AACR meeting, it is referred to a version based on 180 antigens per particle. This may point to the evolving status in the program by that time and we expect the maximum number attached to the scaffold to be limited to 50.

Academic research in VLP based HER2 vaccines

Cell Line	Mouse Model	Tumor Antigen	VLP Platform	Adjuvant or Combination Therapy
MamBo89 (HER2-positive cell line derived from a hHER2 transgenic mouse model)	FVB (FVB/NCrl) F1 HER2/Delta16 (FVB background)	HER2	AP205 phage	None
D16-BO-QD (HER2-positive cell line derived from a hHER2 transgenic mouse model)	FVB Delta16 (FVB background)	HER2	AP205 phage	Montanide ISA 51
DDHER2 (mouse cell line expressing rat HER2)	BALB/c	CH401 (rat HER2-derived epitope)	Physalis mottle virus (PhMV)	CpG (TLR-9 agonist loaded on VLPs)
TuBo (HER2-positive cell line derived from a NeuT transgenic mouse model)	BALB/c	HER2	Recombinant baculovirus (rBV)	Glycosylation patterns AddaVax Poly (I:C)
TuBo	BALB/c	GP2 (HER2/neu derived peptide)	Bacteriophage lambda (λF7)	None
TuBo	BALB/c	E75 (HER2-derived peptide)	λF7	None
D2F2/E2 (mouse cell line transfected with hHER2)	BALB/c	GPI-HER2	rBV	None
TuBo 4T1	BALB/c	xCT	MS2	None
4T1	BALB/c	IL-33	HBcAg	None
4T1	BALB/c	P53 and MUC1	VP2 B19	None
4T1	BALB/c	NeoAG	Qβ	G10 (TLR-9 agonist loaded on VLPs)

Source: Ruzzi et al; Int. J. Mol. Sci. 2023, 24

Competing academic research

Due to its proven effectiveness in the metastatic setting, HER2 is becoming a popular target for BC immunotherapy. However, due to the loss of HER2- specific immunity, its modest adaptive immune

[2] Vaccine, 2010 Jul 26;28(33):5503-1

[3] Palladini et al; ONCOIMMUNOLOGY 2018, VOL. 7, NO. 3,

response leads to reduced drug efficacy following disease progression, despite HER2 still being overexpressed (Ritter et al. 2007).[4]

Different vaccine approaches, based on both mRNA and VLP technologies, are currently being pursued in many oncology areas. The most advanced mRNA programs are in late clinical testing. Several anti-HER-2 cancer vaccines based on VLP platforms have shown to be effective in inducing specific antibody responses and having anticancer activity in preclinical trials. Below is a table reprint from a scientific article published last year by the same research group which has been involved in the ES2B-C001 program.

As far as we can judge, ExpreS2ion has taken the lead in the field of developing a VLP-mounted HER2 vaccine to treat and prevent breast cancer. All the projects listed in the table above are examples of published animal research with breast cancer vaccine candidates based on a VLP platform. The ES2B-C001 program is represented in the two upper quotations, both making use of AP205 phage display.

Like in all cancer research and development, which is funded by both public and industrial means, there is a lot of competition. However, it is our impression that none of the other academic groups have progressed to a clinical stage with an VLP-based candidate in HER2+ breast cancer.

New program adds value to portfolio

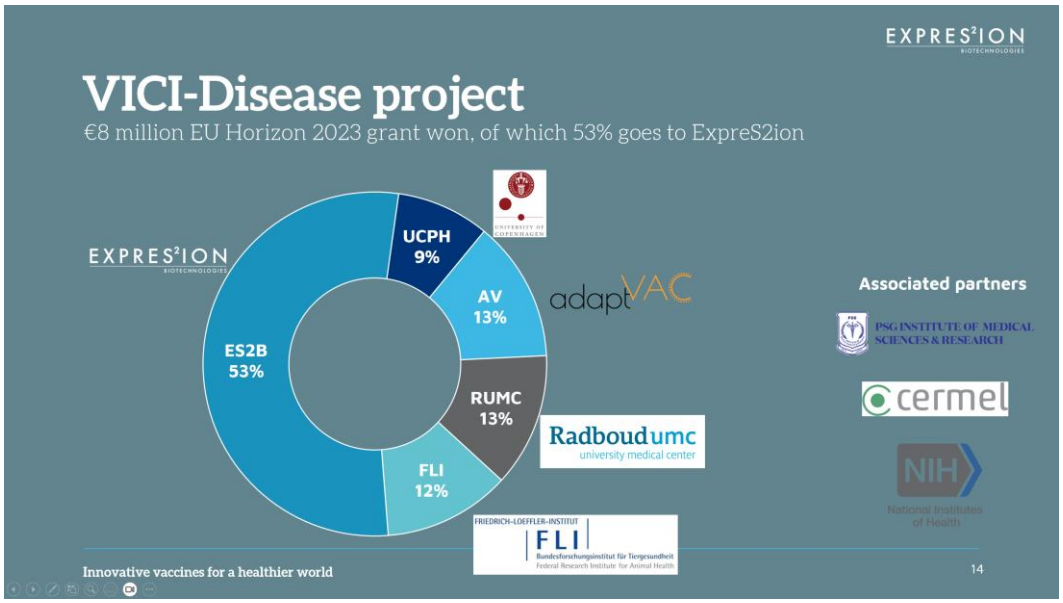
In December ExpreS2ion announced that it will be part of a new consortium, the VICI-Disease consortium, with the aim to develop a vaccine against viruses with pandemic or endemic potential, starting with the Nipah virus. This virus causes severe infections such as acute respiratory infection and fatal encephalitis in humans primarily in tropical regions. Mortality rate is estimated at 40% to 75%.

The virus is transmitted to humans from animals (such as bats or pigs), or contaminated foods and can also be transmitted directly from human to human. Fruit bats of the *Pteropodidae* family are the natural host of Nipah virus. There is no treatment or vaccine available for either people or animals.

Horizon Europe is granting 8 million EUR, approximately 90 million SEK, to the consortium, of which 53% is direct contribution for ExpreS2ion’s part of the project costs. The aim is to obtain clinical proof-of-concept of a Nipah virus (NiV) vaccine candidate within four years.

[4] mRNA vaccination in breast cancer; Journal of Cancer Research and Clinical Oncology, Jiang et al; 2023.

Several vaccine institutions in VICI collaboration



Source: ExpreS2ion Biotechnologies

Cooperation with Oxford University

Malaria is a major public health problem in developing countries. It is a mosquito-borne disease and places a particularly high burden on children in the African Region. There were around 240 million cases of malaria and 627,000 deaths worldwide in 2020, mostly children.

For 20 years the University of Oxford has been carrying out extensive research in this field and has several programs ongoing. In October, this year the WHO recommended the R21/Matrix-M vaccine, which has been sponsored by University of Oxford in collaboration with the Serum Institute of India and Novavax. Novavax is the proprietary owner of the Matrix-M adjuvant and will market the vaccine in non-endemic countries. The vaccine is expected to be launched by the Serum Institute and Novavax next year.

This is the second malaria vaccine to be approved and recommended by WHO after RTS,S/AS01 (Mosquirix, GlaxoSmithKline), which was developed in the late 80's and received a WHO recommendation only in 2021. Both vaccines have shown to be safe and effective in preventing malaria in children and, when implemented broadly, are expected to have a high public health impact.

The R21/M vaccine shows a reduction of symptomatic cases of malaria by 75% during the 12 months following a 3-dose series. Mosquirix is believed to be less efficient in the region of 50 percent. In a phase 3 trial, Mosquirix efficacy was 56% in children aged 5–17 months.

Last year UNICEF paid up to USD 170 million to access eighteen million doses of Mosquirix over a three-year period, corresponding to a price per dose of 9,4 USD. We estimate that Mosquirix is selling at around EUR 75m annually. Low unit prices are likely to remain but the launch of the second more efficient vaccine should expand the market. ExpreS2ion refers to a Data Bridge study projecting an EUR

1,8 bn malaria market by 2029, which should assume the entry of more efficient vaccines.

ExpreS2ion vaccine will have to prove higher efficacy

ExpreS2ion is currently involved in four different projects undergoing in total six clinical studies, all sponsored by University of Oxford. All these studies have progressed to a clinical phase or are currently preparing to recruit. A cooperation with the world leader in malaria research and development is an asset for ExpreS2ion. However, to enter this vaccine market, a new vaccine will have to prove higher immunogenicity than the two marketed products.

Oxford publishes malaria study

ExpreS2ion Biotech is a prominent supplier of antigens to the clinical efforts by Oxford University in the research after a more potent and convenient malaria vaccine. In June researchers linked to the university published results in the medical review Lancet Infectious Diseases.

The authors conclude that the RH5.1/Matrix-M vaccine candidate shows an acceptable safety and reactogenicity profile in both groups. The vaccine candidate is meant to be a second line of defense in blood-stage malaria infection after vaccination with the current type of products. The antigen which targets the RH5.1 protein is produced by ExpreS2, ExpreS2ion Biotech's proprietary protein expression platform.

Oxford programs involving S2-expressed antigens

Trial abbreviation	Phase	Sites	Vaccines in trial	Trial status	Year started
VAC-085	I	Oxford, UK	Pfs48/45	Vaccinations on-going	2023
VAC-086	Ib	MRC Unit, The Gambia	RH5.2-VLP in Matrix-M R21 in Matrix-M	Vaccinations on-going	2023
VAC-089	Ia	Oxford, UK	RH5.1 in Matrix-M R78C in Matrix-M	Vaccinations on-going	2023
VAC-091	IIb	IRSS CRUN, Burkina Faso	RH5.1 in Matrix-M RH5.2-VLP in Matrix-M	Vaccinations on-going	2023
BIO-001	I/IIa	Oxford, UK	RH5.2-VLP in Matrix-M RH5.1 in Matrix-M	Screening & vaccinations on-going	2023
BIO-002	I	Sheffield, UK	RH5.1 in Matrix-M	Vaccinations on-going	2023
BIO-003	I	IHI Bagamoyo, Tanzania	RH5.1 and R78C in Matrix-M	In set-up	N/A

Source: ExpreS2ion Biotech

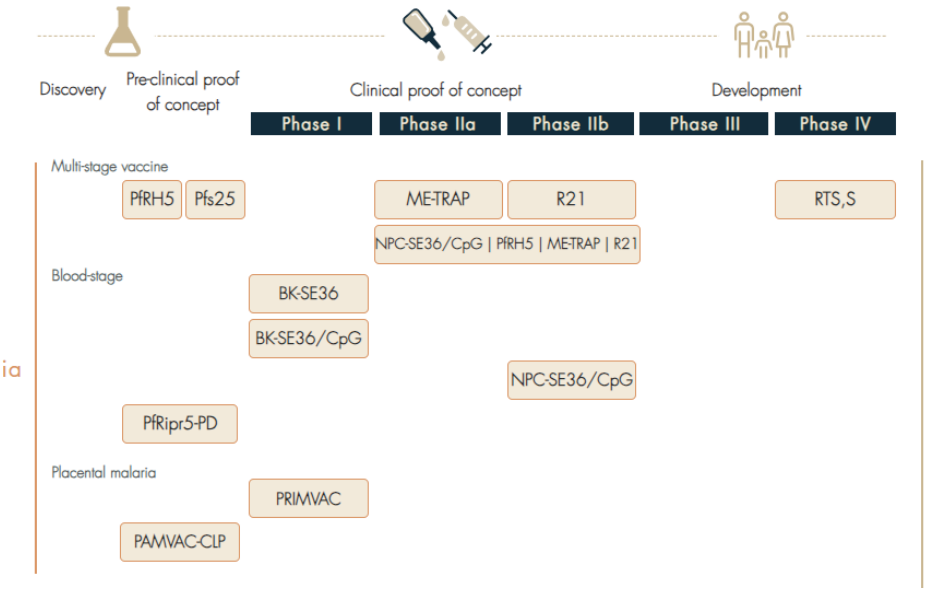
The article makes no mentioning of the antigen producer and at the moment there is no commercial agreement entered between ExpreS2ion Biotech and Oxford University. If the product advances to a phase 3 set-up, ExpreS2ion has the right to negotiate a license agreement. We have so far not made any assumption of the possibility of a commercial scenario materializing in the Oxford collaboration before 2027. ExpreS2ion Biotech is involved as

antigen supplier to Oxford University in seven different clinical studies on four different vaccine candidates.

According to clinicaltrials.gov University of Oxford is currently sponsoring thirty-five ongoing trials in malaria vaccination. Four of these trials involve ExpreS2ion as a subcontractor of the RH5 expression protein. The most advanced is VAC091 (NCT05790889) which will involve 360-460 participants in Burkina Faso and report results late in next year. At this point in time, we find it difficult to assess the possibility for this row of programs to reach success, but serving as a subcontractor to University of Oxford is a meriting feature. We view the continuous efforts of University of Oxford in this field as a second or third wave of new Oxford malaria cures.

However, in absence of a commercial agreement between University of Oxford and the involved parties, such as ExpreS2ion Biotech, we remain cautious on the value of these programs.

Malaria portfolio of the European Vaccine Initiative



Source: European Vaccine Initiative

A second factor behind a cautious approach to the value of AdaptVac is the lack of external validations other than from Bavarian Nordic. There are several different virus-like particle (VLP) vaccine platforms, both involving capsids or other scaffolds. The VLP technology was first described in animal models in 2007. Since then, VLPs are considered as promising nanotools for the development of subunit vaccines due to high immunogenicity and safety. The proprietary knowledge of AdaptVac is based on a method of displaying the isopeptide (spike protein) on the surface of the VLP, a method which we believe has distinctive features over similar generic techniques, such as the SpyTag/Catcher system.

The most advanced program in AdaptVac after ABNCoV2 is PAMVAC-VLP (also PAMVAC-CLP). This program is a malaria vaccine candidate sponsored and coordinated by the European Vaccine Initiative (EVI) in collaboration with the Oxford University.

The PAMVAC program is still in a phase of preclinical proof-of-concept. The basis of the project was invented by University of

Copenhagen and later transferred to AdaptVac. A randomized phase 1 clinical trial was conducted in Germany and Benin in 2015-17. It was published in 2019[5] and the authors concluded that a follow-up trial in in women before first pregnancies in an endemic area was to come next. Since then, the program has not advanced to a new clinical trial.

The parties received financing of EUR 10m by the European Union in 2022 which is expected to last until 2027. The PAMVAC-VLP program is a placenta-borne concept as opposed to the RH.5 blood stage programs of ExpreS2ion. In the ExpreS2ion Q3 report it was announced that the company is discontinuing collaboration in the placenta-borne malaria program after the decision of University of Copenhagen to contract a different manufacturer of the expressed protein.

[5] *Clinical Infectious Diseases*, Volume 69, Issue 9, 1 November 2019, Pages 1509–151

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