

## Phase IIa SAKK 11/16 Trial Evaluating Overall Survival With MVX-ONCO-1 Cell Encapsulation-Based Immunotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma After Progression on One or More Lines of Systemic Therapy

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### Abstract

Throughout the last two decades, the clinical advancement of most cancer vaccines has encountered significant setbacks. Insufficient activation of immune responses using tumor-specific antigens, along with suboptimal adjuvants, likely accounts for these disappointing outcomes. MVX-ONCO-1 represents an individualized cell therapy vaccine that merges inactivated patient-derived tumor cells with allogeneic human cells enclosed in capsules and modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). This design facilitates extended, localized release of a powerful adjuvant precisely at the site of administration. Combining these patient-specific tumor antigens with effective on-site adjuvant delivery targets two fundamental challenges and seeks to mirror the promising synergies documented in laboratory animal studies. SAKK 11/16 constituted a Phase IIa clinical study primarily assessing overall survival (OS). This marked the initial evaluation of MVX-ONCO-1's therapeutic potential. Eligible participants included individuals with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) whose disease had advanced following a minimum of one systemic treatment regimen—the trial aimed to demonstrate that 50% of patients would remain alive at 26 weeks. Within this difficult-to-treat cohort, the study achieved its main goal, with 68.8% of enrolled patients alive at six months. The median overall survival was 11.4 months, and 32% of participants survived beyond 18 months. Instances of complete and partial tumor regressions occurred during treatment with MVX-ONCO-1 as a single agent. Notably, all individuals who exhibited a positive delayed-type hypersensitivity (DTH) reaction to their autologous tumor cells following immunization survived for at least 12 months. Those who survived past the one-year mark also showed elevated antibody levels against tumor-associated antigens. An additional exploratory review revealed a median OS of 21.7 months calculated from the beginning of anti-PD-1 therapy. Safety assessments revealed no unanticipated risks, no systemic treatment-related adverse events (AEs), and smooth manufacturing processes throughout this multi-center investigation. The data support MVX-ONCO-1's ability to elicit an integrated immune response, translating into meaningful clinical improvements and extended patient survival when used independently. Prior treatment with immune checkpoint inhibitors may further augment these effects.

**Keywords:** Immunotherapy, Cell encapsulation device, Granulocyte-macrophage colony stimulating factor, Autologous irradiated tumor cells, Advanced solid tumors

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### Introduction

For nearly four decades, therapeutic cancer vaccines have largely been regarded as an elusive target, plagued by repeated disappointments despite major strides in cancer immunology research and technological innovations. Contributing factors to modest efficacy or barriers to late-

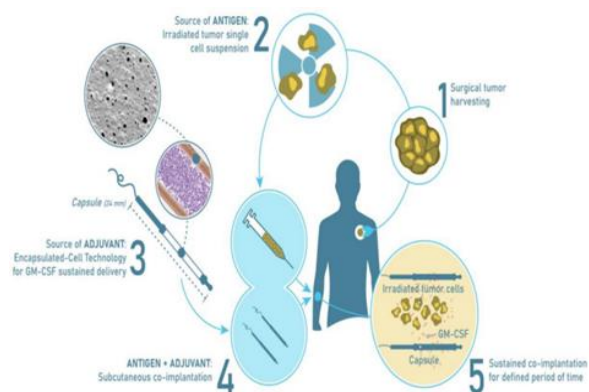
stage development include the scarcity of highly immunogenic tumor-specific targets, weak adjuvant systems, and the complexity of producing customized therapies for each patient [1-3]. Renewed optimism has emerged recently due to positive early data on personalized mRNA cancer vaccines administered in the post-surgical setting together with immune checkpoint blockade agents [4].

Presented here are the key outcomes from SAKK 11/16, the inaugural efficacy-focused trial of MVX-ONCO-1. This personalized cell-based vaccine leverages innovative cell-encapsulation methods and used OS at 26 weeks as its primary measure of success.

Over the past 20 years, robust anti-tumor vaccination effects have been reliably achieved in mouse models of diverse cancers by employing genetically altered tumor cells. Irradiated tumor cells modified to produce the cytokine GM-CSF [5, 6] have proven capable of establishing long-term protective immunity and improving survival across numerous cancer types, encompassing melanoma, sarcoma, leukemia, lymphoma, neuroblastoma, glioblastoma, and various carcinomas (e.g., lung, ovarian, gastric, hepatic, breast, colorectal, urothelial, and renal). Success in these models hinges on two pivotal components: the supply of relevant cancer antigens from the irradiated cells themselves, and the provision of controlled, localized GM-CSF secretion at the vaccination area lasting 5–7 days. Although the value of tumor antigens is widely acknowledged, the critical importance of adjuvant optimization is often minimized. GM-CSF's immunostimulatory potency is closely tied to its administration profile—modest, sustained local concentrations strongly promote both T-cell and antibody-mediated responses. In contrast, elevated local doses or widespread systemic exposure tend to induce immune tolerance [7, 8].

Many prior human trials involving advanced cancer patients have failed to replicate these essential conditions. Common shortcomings include reliance on high-dose injectable recombinant GM-CSF paired with peptide antigens, or on unmodified allogeneic tumor cells secreting GM-CSF (as in the GVAX approach [9, 10]). Neither strategy successfully delivered patient-matched tumor antigens nor achieved prolonged, tightly regulated local GM-CSF production, ultimately yielding limited immune activation and negative study results.

MVX-ONCO-1 introduces a distinctive vaccination platform that satisfies these requirements through the following features (**Figure 1**).



**Figure 1.** Graphic Illustration of the Investigational Medicinal Product (IMP)

MVX-ONCO-1 uses the individual patient's unique tumor antigens to create a fully customized therapy matched to each person's cancer's specific molecular profile, bypassing the need to pinpoint, extract, or produce specific antigen targets. The platform is suitable for all cancer types, operates independently of Human Leukocyte Antigen (HLA) matching, and is appropriate for both adjuvant and advanced metastatic disease settings. This individualized antigen approach is paired with precise, prolonged release of GM-CSF confined to the vaccination site for approximately 7 days, avoiding unwanted systemic exposure to the adjuvant.

This controlled, extended delivery is achieved through biocompatible macrocapsules containing MVX-1 cells, an engineered human cell line that continuously secretes GM-CSF. Although the tumor cell component is patient-specific, the GM-CSF-secreting capsules are consistent across individuals and can be manufactured in bulk. Both elements are cryopreserved for storage. Administration consists of a short 30-minute outpatient procedure in which the irradiated tumor cells and loaded capsules are placed subcutaneously in proximity to the normal skin, away from any tumor masses.

In addition, the production of MVX-ONCO-1 follows a relatively simple workflow that avoids intricate genetic manipulation of the patient's tumor cells or extended laboratory culturing. This efficient process supports reliable and consistent manufacturing. The entire preparation timeline for MVX-ONCO-1 spans seven days, determined through biosafety evaluations, enabling rapid progression from tumor tissue collection to treatment initiation and thereby reducing delays in patient management.

Results from the initial first-in-human Phase I trial, involving 34 participants with different advanced treatment-resistant solid tumors, have been published recently [11, 12]. That study successfully achieved its main goals of demonstrating safety and practicality. Beyond these, encouraging clinical signals were observed, including partial responses (PRs), clear evidence of immune priming, and extended survival. Particularly noteworthy were the outcomes in two patients with R/M HNSCC who had progressed after chemotherapy and/or anti-PD-1 treatment: one experienced a partial response, and the other remained alive for more than seven years, including over five years without any further anticancer therapy.

These promising early clinical observations, combined with a very low toxicity profile and evidence of immune activation, led to the development and execution of SAKK 11/16—a multi-center Phase IIa study focused on efficacy, using overall survival as the primary endpoint in patients with R/M HNSCC progressing after at least one line of systemic therapy [13].

## Materials and Methods

### *Study design and participants*

SAKK 11/16 was designed as a multi-center, prospective, single-arm, open-label Phase II clinical trial. It targeted patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) whose disease had progressed following first-line treatment for metastatic disease (either chemotherapy or immunotherapy). This population typically faces a grim outlook, lacks a clear standard of care, and has median survival times of roughly 6 to 9 months.

### *Sample size calculation*

The trial initially employed a single-arm, single-stage Phase II design based on A'Hern [14] to evaluate the following one-sided hypotheses:

- H0: OS rate at 26 weeks  $\leq 30\%$ .
- H1: OS rate at 26 weeks  $\geq 50\%$ .

Under the assumption of a 50% OS rate at 26 weeks with MVX-ONCO-1 treatment, 39 patients were planned to achieve a one-sided type-I error ( $\alpha$ ) of 0.05 and 80% statistical power.

During an unplanned interim assessment, data from 10 patients showed that 7 had survived beyond 26 weeks. Using this information, the sample size was recalculated via the conditional power approach outlined by Kieser *et*

*al.* [15]. The revised total enrollment target, maintaining the original power and error rates, was set at 20 patients. An exact binomial test served as the basis for the final analysis. In this adaptive framework, the null hypothesis would be rejected if at least 11 of the 20 patients survived to 26 weeks or longer. With 7 survivors already observed in the interim group, a minimum of 4 additional survivors were needed from the remaining 10 patients.

### *Statistical methods*

The primary endpoint was analyzed using a one-sided exact binomial test to assess whether the 26-week OS rate exceeded 30%. The observed proportion of patients alive at 26 weeks after enrollment was reported along with the exact 95% lower confidence limit.

For secondary time-to-event outcomes, median values were estimated using the Kaplan–Meier (KM) method, with 95% confidence intervals (CI). Event counts for each endpoint were summarized descriptively using frequencies and percentages.

The original sample size determination was performed with R version 3.1.0 using the *clinfun* package version 1.0.6. The interim-based re-estimation utilized R version 4.1.2. All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.3.3 (The R Foundation; [www.r-project.org](http://www.r-project.org)).

### *Study population*

**Safety Population:** Included all patients who received at least one administration of study treatment.

**Full Analysis Set (FAS):** Comprised all enrolled patients who received at least one dose of study treatment (modified intention-to-treat principle, mITT), excluding those with major eligibility deviations. Receipt of at least one dose was defined as implantation lasting at least one day without premature capsule removal.

**Per Protocol Set (PPS):** Derived from the FAS but excluded patients with significant protocol deviations, those who did not complete the planned treatment (fewer than 6 implantations of 2 capsules each, or any vaccination site explantation occurring less than 6 days after placement).

### *Procedure*

As outlined previously [12] (**Figure 1**), MVX-ONCO-1 consists of two main constituents. Tumor tissue was collected from an accessible lesion and dissociated into a single-cell suspension. These cells were subjected to lethal irradiation (100 Gy), divided into portions, and

cryopreserved in liquid nitrogen until use. Separately, a genetically engineered human K562 cell line secreting GM-CSF was loaded into biocompatible macrocapsules. The treatment schedule involved subcutaneous implantation of two macrocapsules, spaced about 1 cm apart, with irradiated autologous tumor cells injected between them. This was repeated weekly for the first four weeks, followed by additional doses at weeks 6 and 8. Capsules were explanted one week after each implantation. Delayed-type hypersensitivity (DTH) testing using irradiated autologous tumor cells was conducted on three occasions: before treatment initiation and again at weeks 6 and 12.

#### *Endpoints and assessments*

The trial's primary outcome measure focused on overall survival (OS) at 26 weeks, specifically the percentage of participants alive 26 weeks after study entry. Success was predefined as more than 50% of patients surviving to this point. The final analysis was completed after all enrolled individuals had their tumor status evaluated at 52 weeks from the start of therapy.

Among the secondary endpoints were the interval until the start of next-line treatment, the length of response as measured by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, objective response rates (ORR) determined by RECIST 1.1 at weeks 6, 13, 26, 39, and 52 following registration, disease control rates (DCR) via RECIST 1.1 at those same intervals, the best overall response according to RECIST 1.1 criteria, objective responses evaluated with iRECIST (iOR), progression-free survival (PFS) based on RECIST 1.1, iRECIST-based PFS (iPFS), PFS rates at the specified time points using RECIST 1.1, overall survival, PFS during the initial subsequent therapy per RECIST 1.1, and the best response achieved under that subsequent therapy per RECIST 1.1, in addition to the frequency of adverse events and serious adverse events (SAEs).

Exploratory goals involved detailed immune system assessments and delayed-type hypersensitivity (DTH) evaluations performed before treatment (baseline), at week 6, and once treatment had concluded. Other planned investigations included biomarker studies on biopsies from the tumor site at baseline and four weeks after the final capsule removal, optional histological examination of tumors at baseline and at weeks 13, 26, and 52 post-registration (only when clinically safe), quality-of-life evaluations, pain assessments, and any available tumor response data according to RECIST 1.1

during extended follow-up, interpreted in relation to subsequent therapies where relevant.

Safety monitoring included routine clinical examinations, tracking of vital signs, evaluation of local reactions and systemic tolerability, standard laboratory testing, and electrocardiogram recordings conducted from study start through week 18. Discontinuation of study treatment was permitted in cases of severe toxicity, confirmed pregnancy, or upon patient request. All adverse events were categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. General AE reporting extended until 30 days after the last capsule explantation, whereas treatment-related AEs and SAEs continued to be documented until study participation ended. Long-term surveillance for survival and serious adverse events proceeded until the patient's death or the five-year mark, whichever came sooner.

Efficacy monitoring tracked survival status at 6, 12, and 18 months and used RECIST 1.1 for disease assessments at baseline and at weeks 6, 12, and 18, with all data locked as of June 29, 2023. For selected participants, supplementary tumor information was collected after week 18 following a protocol amendment.

#### *Delayed type hypersensitivity*

DTH reactions were tested by injecting  $1 \times 10^6$  irradiated patient-derived tumor cells intradermally into normal skin at three time points: before treatment began, at week 6, and after therapy completion. A response was classified as positive if the induration reached or exceeded 5 mm. Assessments of erythema, induration, and ulceration occurred 48–72 hours post-injection in accordance with recognized international protocols. When positive, punch biopsies were collected to study the influx of immune cells at the site.

#### *Multiplex immunofluorescence staining and acquisition*

Automated multiplex immunofluorescence (Multi-IF) staining was executed on the BOND RX instrument (Leica Biosystems) through successive rounds of primary antibody application, each linked to TSA-OPAL fluorophores from Akoya Biosciences. Four-micrometer FFPE tumor sections were first deparaffinized and rehydrated, followed by antigen retrieval in ER1/ER2 buffers. After blocking, primary antibodies were added, then a horseradish peroxidase-conjugated secondary antibody, tyramide-based signal amplification, and

OPAL dye deposition. This process cycled through all six antibodies. Each batch included a tonsil section as a positive control. Sections were finally counterstained with spectral DAPI (Akoya Biosciences) and scanned in their entirety at 20× resolution on a Vectra Polaris multispectral system (Akoya Biosciences).

#### *Ex-vivo modified IFN- $\gamma$ enzyme-linked immuno spot (ELISpot)*

PBMCs were isolated, cryopreserved, thawed into X-Vivo 15 medium (Lonza, BE02-060F), and rested overnight at 37°C with 5% CO<sub>2</sub>. They were subsequently co-cultured for 24 hours with freshly thawed irradiated autologous tumor cells (1:2 ratio) in Mabtech pre-coated 96-well plates. Plates were washed according to the manufacturer's guidelines and read on a Mabtech IRIS 2 device. Spot-forming units (SFU) were quantified after correcting for background activity from control wells containing only PBMCs or tumor cells.

#### *Auto-antibody analysis — seromic profiling*

Autoantibody profiling was performed externally by Cambridge Protein Arrays utilizing HuProt™ v4.0 Human Proteome Microarrays.

## Results and Discussion

### *Feasibility*

**Figure 1** provides an overview of the personalized cancer vaccine studied in this trial. Each prepared dose contained  $4 \times 10^6$  irradiated autologous tumor cells sourced from either metastatic lymph nodes or distant metastatic lesions, along with two macrocapsules holding  $0.8 \times 10^6$  cells each. These engineered cells were designed to secrete at least 20 ng of GM-CSF per day. The two components were placed subcutaneously in proximity to one another, at locations removed from any tumor sites. Capsules were retrieved after 7 days using an attached retrieval filament, based on prior pharmacokinetic studies in animal models. A total of 6 vaccinations were administered over 8 weeks (at weeks 1, 2, 3, 4, 6, and 8). All implantation sites used healthy skin distant from tumors. To target different immune regions, doses were administered in rotation across limbs: first on the left arm, then on the left thigh, then on the right thigh, then on the right arm, and so on. No maintenance doses were given afterward.

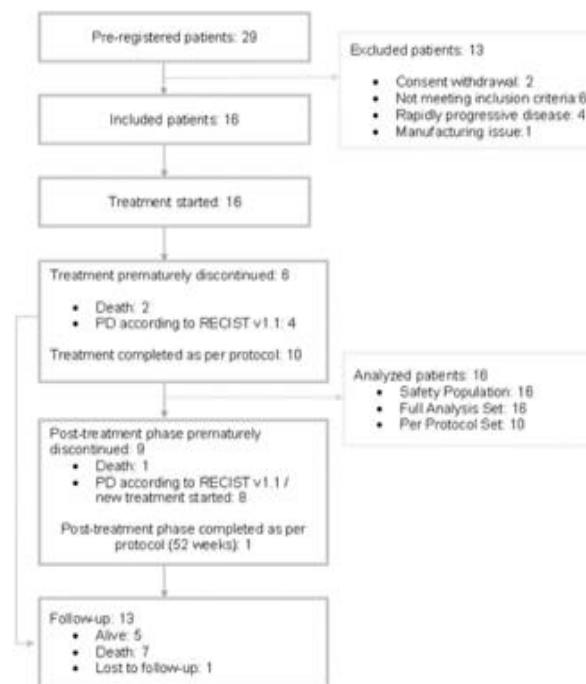
Sixteen patients were recruited from four Swiss centers between August 13, 2018, and July 25, 2022. Using the

reverse Kaplan–Meier technique, the median follow-up duration for the full analysis set (FAS) reached 23.8 months (95% CI 11.1–not reached). The median observation period for censored cases in the FAS was 19.2 months, ranging from 11.1 to 55.5 months. Baseline patient characteristics and medical histories are detailed in **Table 1**, with the CONSORT flowchart presented in **Figure 2a**.

**Table 1.** Patients' medical history and baseline characteristics

| Characteristic                                       | Category           | % or range | n    |
|------------------------------------------------------|--------------------|------------|------|
| Sex                                                  | Female             | 6.3        | 1    |
|                                                      | Male               | 93.8       | 15   |
| Age                                                  | Median             | 42.0–76.0  | 59.5 |
| WHO performance status                               | 0                  | 50.0       | 8    |
|                                                      | 1                  | 37.5       | 6    |
|                                                      | 2                  | 12.5       | 2    |
| CPS score                                            | < 1                | 18.8       | 3    |
|                                                      | 1–19               | 62.5       | 10   |
|                                                      | ≥ 20               | 12.5       | 2    |
|                                                      | Missing            | 6.3        | 1    |
|                                                      | Hypopharynx        | 12.5       | 2    |
| Location of primary tumor                            | Oral cavity        | 43.8       | 7    |
|                                                      | Oropharynx         | 43.8       | 7    |
| HPV result for Oropharynx Location                   | Negative           | 28.6       | 2    |
|                                                      | Positive           | 42.8       | 3    |
|                                                      | Unknown            | 28.6       | 2    |
| Did a relapse occur?                                 | No                 | 62.5       | 10   |
|                                                      | Yes                | 37.5       | 6    |
| Metastatic disease?                                  | No                 | 12.5       | 2    |
|                                                      | Yes                | 87.5       | 14   |
| Location(s) of metastasis (more than one applicable) | Bone               | 18.8       | 3    |
|                                                      | Distant lymph node | 43.8       | 7    |
|                                                      | Kidney             | 6.3        | 1    |
|                                                      | Liver              | 12.5       | 2    |
|                                                      | Lung               | 68.8       | 11   |
|                                                      | Pleura             | 0.0        | 0    |
|                                                      | Soft tissue        | 6.3        | 1    |
|                                                      | Negative           | 50.0       | 8    |
| P16 result                                           | Positive           | 31.3       | 5    |
|                                                      | Unknown            | 18.8       | 3    |

|                                             |        |         |     |
|---------------------------------------------|--------|---------|-----|
| Time from diagnosis to registration (years) | Median | 0.8–9.0 | 2.1 |
| Previous systemic therapy                   | Yes    | 100.0   | 16  |
| Pre-treatment with checkpoint inhibitor     | No     | 12.5    | 2   |
|                                             | Yes    | 87.5    | 14  |
| Previous radiotherapy                       | No     | 12.5    | 2   |
|                                             | Yes    | 87.5    | 14  |
| Previous tumor surgery                      | No     | 50.0    | 8   |
|                                             | Yes    | 50.0    | 8   |
| Relevant concomitant diseases               | No     | 25.0    | 4   |
|                                             | Yes    | 75.0    | 12  |



a)

| Highest grade | Baseline symptoms | All AEs   | AEs related to any treatment | AEs related to MVX-ONCO-1 | AEs related to implantation/explantation |
|---------------|-------------------|-----------|------------------------------|---------------------------|------------------------------------------|
| 0             | 4 (25.0%)         | 0 (0.0%)  | 7 (43.8%)                    | 12 (75.0%)                | 9 (56.3%)                                |
| 1             | 5 (31.3%)         | 3 (18.8%) | 4 (25.0%)                    | 3 (18.8%)                 | 3 (18.8%)                                |
| 2             | 4 (25.0%)         | 5 (31.3%) | 5 (31.3%)                    | 1 (6.3%)                  | 4 (25.0%)                                |
| 3             | 3 (18.8%)         | 3 (18.8%) | 0 (0.0%)                     | 0 (0.0%)                  | 0 (0.0%)                                 |
| 4             | 0 (0.0%)          | 0 (0.0%)  | 0 (0.0%)                     | 0 (0.0%)                  | 0 (0.0%)                                 |
| 5             | 0 (0.0%)          | 5 (31.3%) | 0 (0.0%)                     | 0 (0.0%)                  | 0 (0.0%)                                 |

b)

**Figure 2.** Study Patients: (a) CONSORT Diagram; (b) Baseline symptoms and AEs highest grade per patient—Safety population.

Per protocol requirements, every participant presented with metastatic disease featuring at least one tumor site suitable for minimally invasive, sterile surgical removal,

plus at least one additional measurable lesion evaluable under Response Evaluation Criteria in Solid Tumors (RECIST), RECIST 1.1, and iRECIST standards.

The investigation demonstrated that deploying a personalized cell-based cancer immunotherapy platform relying on encapsulated cell technology can be successfully implemented across multiple centers. The SAKK 11/16 research group effectively managed the production, coordination, and distribution of the biological therapeutic materials between the manufacturing facility and participating clinical sites.

### Safety

This study did not identify any novel safety concerns beyond those previously documented in the Phase I trial population [12]. No treatment-related systemic adverse events (AEs) associated with the investigational medicinal product (IMP) occurred (**Figure 2b**). All observed systemic AEs were attributed to the underlying malignancy or pre-existing comorbidities. A few individuals reported mild local skin reactions at the implantation sites. In two cases, capsule retrieval on day 8 proved difficult and necessitated ultrasound assistance. Overall, the results confirm that this innovative immunization approach is well tolerated among patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). With 50 individuals now having received MVX-ONCO-1 (34 from the Phase I study and 16 from this Phase IIa trial), a comprehensive safety profile has emerged, showing no significant acute or delayed systemic side effects.

Quality of life was evaluated using validated questionnaires, and pain levels associated with both implantation and explantation procedures were recorded (data not presented here).

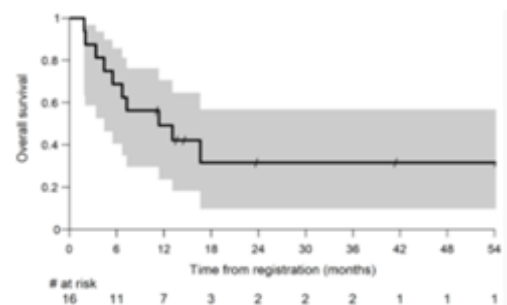
### Efficacy

The primary analysis was conducted on the full analysis set (FAS) population. All participants were monitored for a minimum of 11 months, with only one patient lost to follow-up after 413 days.

The majority of enrolled patients had already undergone more than two lines of treatment for metastatic disease, and 87.5% had progressed following anti-PD-1 therapy before joining the study.

In this challenging patient group with limited therapeutic options, the trial met its primary objective of OS at 26 weeks. This key target was achieved earlier than anticipated, with just 16 patients recruited. Eleven of the

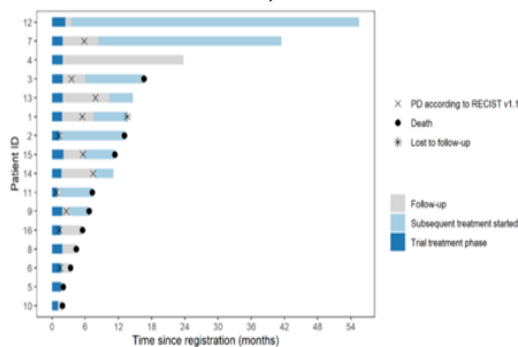
16 participants survived to the 26-week time point, resulting in an OS rate of 68.8% and prompting the decision to halt further enrollment (**Figure 3a**). Because the lower limit of the two-sided 90% confidence interval exceeded 30%, the null hypothesis of an OS rate at 26 weeks of 30% or lower could be statistically rejected. Additionally, the two-sided 95% confidence interval also remained entirely above 30% (**Figure 3b**).



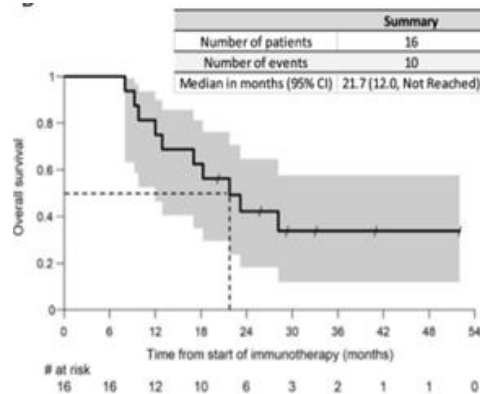
a)

| Characteristic               | Category | n  | %     | 90% CI         | 95% CI       |
|------------------------------|----------|----|-------|----------------|--------------|
| Survival status at 26 weeks  | Alive    | 11 | 68.8% |                |              |
|                              | Death    | 5  | 31.2% |                |              |
| Overall Survival at 26 weeks |          | 11 | 68.8% | [45.2%, 86.8%] | [41.3%, 89%] |

b)



c)



d)

| Total (N=16)    |           |                  |
|-----------------|-----------|------------------|
| Variable        | Estimator | 95% CI           |
| OS at 26 weeks  | 100.0%    | [100.0%, 100.0%] |
| OS at 12 months | 75.0%     | [46.3%, 89.8%]   |
| OS at 18 months | 62.5%     | [34.9%, 81.1%]   |
| OS at 24 months | 42.2%     | [18.1%, 64.6%]   |

e)

**Figure 3.** Efficacy results—Primary endpoints

(a) Kaplan–Meier Plot for Overall Survival; (b) Descriptive Summary of Overall Survival at 26 Weeks; (c) Swimmer Plot; Exploratory Analysis (d) Median Overall Survival and Kaplan–Meier Plot for Overall Survival from Start of Immunotherapy; (e) Overall Survival from Start of Immunotherapy at Fixed Time Points

The effect of this new individualized anticancer vaccine on reducing tumor size remains unclear. It is widely recognized that in the current immunotherapy landscape, objective response rates or progression-free survival (PFS) often fail to serve as dependable predictors of overall survival [16]. In the present trial, objective responses were infrequent: one patient (6.3%) achieved a complete response (CR) and another (6.3%) had a partial response. Ten patients (62.5%) achieved stable disease (SD) as their best response, while four patients (25%) experienced disease progression. Disease control rate (DCR) was calculated as the percentage of patients attaining CR, PR, or SD at specified assessment times after enrollment and before initiating any new anticancer regimen. At 26 weeks, the DCR stood at 18.8% (3 patients), with a 95% confidence interval of 4–45.6%. Median overall survival in the study reached 11.4 months as of the data cutoff date, at which point five patients were still alive. One had been lost to follow-up (**Figure 3c**). Patient 4, who presented with multiple lung and mediastinal lymph node metastases and had progressed on prior nivolumab treatment, attained a complete remission that lasted 16.5 months and remained ongoing at the time of data cutoff.

Several participants displayed atypical clinical trajectories, including periods of tumor stabilization or responses that emerged only after starting subsequent palliative immunotherapy or chemotherapy. In this heavily pre-treated group, later-line palliative therapies produced tumor control or partial responses in multiple cases. For instance, patient 12 achieved stable disease as the best response to MVX-ONCO-1. This individual then received nivolumab despite undetectable PD-L1

expression on both tumor cells and the surrounding microenvironment (CPS = 0). Remarkably, the patient went on to experience a durable complete response characterized by the complete disappearance of large bilateral pulmonary metastases. This remission has persisted for more than three years and was still ongoing at data cutoff (**Figure 3c**).

Given that 14 of the 16 patients had entered the trial with progressive disease following anti-PD-1 treatment as their most recent line of therapy for metastatic cancer, an exploratory survival analysis was conducted starting from the initiation of immune checkpoint inhibitor therapy. This evaluation showed a median OS of 21.7 months from the start of anti-PD-1 treatment — substantially longer than durations typically reported in published literature (**Figures 3d and 3e**).

Further analysis examined the interval until subsequent palliative therapies (such as chemotherapy, cetuximab, nivolumab, or participation in other clinical trials). From the time of study registration to the documented start of the next treatment, the median duration was 7.5 months (95% CI 3.5–8.3 months).

#### Exploratory endpoints

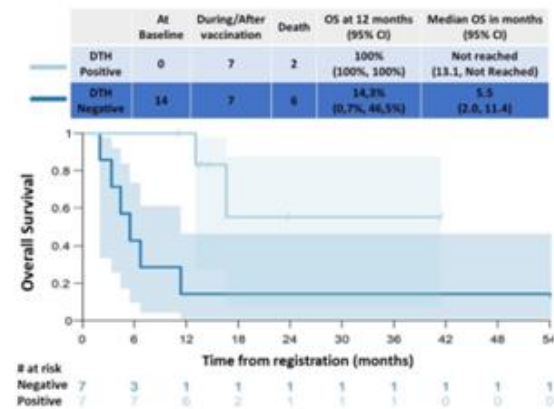
##### Immunomonitoring

All secondary endpoints were evaluated in the full analysis set (FAS) unless otherwise specified.

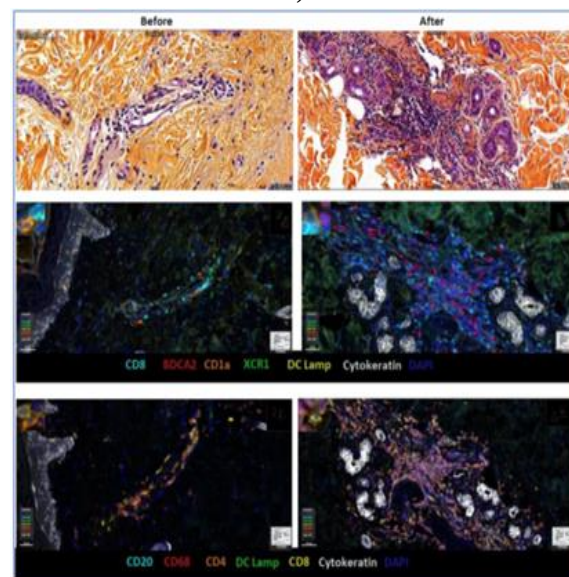
To better understand the differences between long-term survivors (patients alive beyond 12 months) and short-term survivors (those alive for less than 12 months), a comprehensive translational research program was undertaken. This included assessment of several immune-related markers, notably the delayed-type hypersensitivity (DTH) response, ex-vivo lymphocyte activation via ELISpot, and humoral immunity indicators.

The capacity to mount an immune response against the patient's own tumor cells, as indicated by the DTH test, was associated with prolonged survival. Before vaccination, all 16 patients (100%) tested negative on the DTH assay. Among the 14 evaluable participants for post-treatment DTH testing, 7 out of 8 patients (87.5%) who survived to 12 months converted to a positive DTH reaction. In contrast, among those who remained DTH-negative, 6 out of 7 (85.7%) succumbed at earlier time points. No notable differences in baseline clinical or biological characteristics were observed between the DTH-positive and DTH-negative groups. Three DTH-negative patients had only a single post-baseline

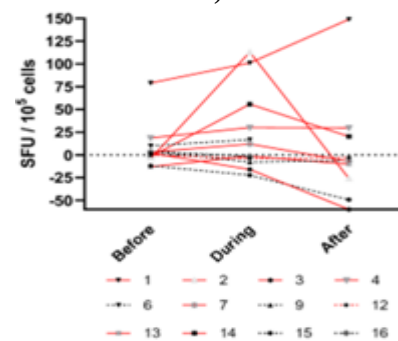
measurement due to rapid disease progression or early death. Median OS for DTH-negative patients was 5.5 months (95% CI 2.0–11.4 months), whereas median OS was not reached for DTH-positive patients (95% CI 13.1–not reached) (**Figure 4a**).



a)



b)



c)

**Figure 4.** In vivo and In vitro Stimulation of Patient Immune Cells.

a) Kaplan–Meier Plot of Overall Survival According to DTH Status (Negative vs Positive after Vaccination). Overall Survival Rate at 12 Months and Median Overall Survival by DTH Group.

b) Example Multiplex Immunofluorescence Images Showing Immune Cell Infiltration in Punch Skin Biopsies from the DTH Site Before and After Vaccination. The upper panels display hematoxylin phloxine saffron staining; the middle and lower panels show multiplex immunofluorescence staining.

c) Measurement of IFN- $\gamma$  Release from PBMCs via Modified Ex-vivo ELISpot Following Exposure to Irradiated Autologous Tumor Cells. Red lines mark patients who survive for more than 12 months; black lines mark those who survive for less than 12 months. Solid lines correspond to individuals with positive delayed-type hypersensitivity (DTH) reactions, while dotted lines indicate negative DTH responses.

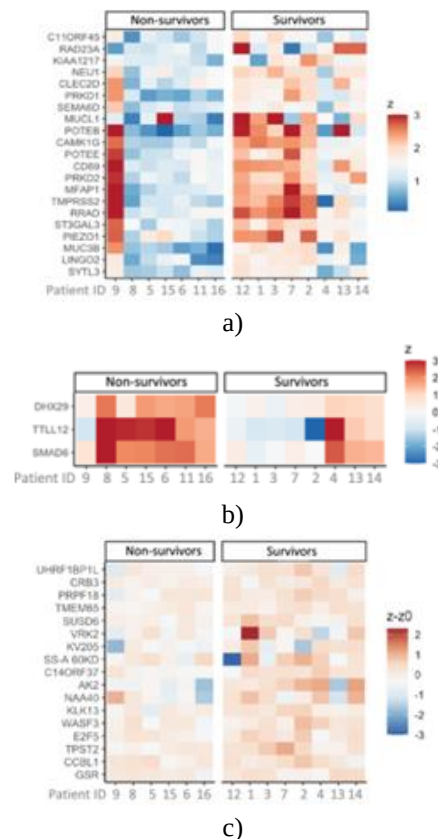
Skin punch biopsies were taken from the DTH test site in certain participants and analyzed histologically. Typical examples are shown in **Figure 4b**. While the assessment was qualitative rather than strictly quantitative, the images clearly depict substantial infiltration by multiple immune cell populations — notably CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes, B cells, and antigen-presenting cells — specifically when the DTH test turned positive. These results reinforce that a positive DTH reaction is accompanied by effective immune cell recruitment at the site, which plays a central role in generating anti-tumor immunity.

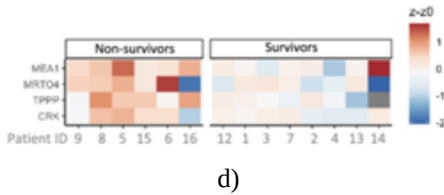
Results from the ex vivo ELISpot assay further confirmed that the vaccination protocol successfully activated immune cells. As depicted in **Figure 4c**, an increase in T-cell reactivity relative to pre-treatment baseline levels was observed in 67% of the patients who lived beyond 12 months. In contrast, no meaningful change occurred in those with shorter survival.

Of particular interest, among patients who survived more than 12 months and developed a positive DTH response, 5 of 7 (71.4%) also showed ELISpot positivity. On the other hand, in the group surviving less than 12 months, none of the 6 patients (0%) became DTH-positive, and only 1 of 6 (16.7%) became ELISpot-positive. Moreover, all 5 patients (100%) who tested positive on both DTH and ELISpot assays survived for more than 12 months. Conversely, 3 out of 4 patients (75%) who stayed negative on both tests did not reach the 12-month survival mark. Taken together, these data indicate a

strong association between the emergence of coordinated immune reactivity and improved long-term survival.

Furthermore, prior research has established that GM-CSF-secreting cell-based immunotherapies can elicit humoral (antibody) responses [17-20]. In light of this, an exploratory seromic analysis was performed to evaluate the antibody repertoire. This profiling showed that the majority of patients surviving for more than 12 months exhibited substantially higher baseline antibody titers (**Figure 5a**) directed against multiple tumor-associated antigens, such as the mucin family members MUCL-1 [21] and MUC3B [22], and the cancer-testis antigen POTEE [23], compared with short-term survivors. Long-term survivors additionally displayed antibodies against various proteins implicated in tumor progression (e.g., PIEZO1 [24]), increased malignancy (TMPRSS2 [25]), and epithelial-mesenchymal transition processes (KIAA1217 [26], C11orf45 [27]), some of which relate to immune checkpoint pathways. By comparison, individuals surviving less than 1 year had elevated antibody levels against SMAD6 [28] (**Figure 5b**). This suggests heightened immune targeting of SMAD6 in patients with poorer prognosis, a protein previously linked to unfavorable clinical outcomes.





**Figure 5.** Antibody Profile Level at Baseline.

(a) Higher levels in long-term survivors (survival exceeding 12 months) versus short-term survivors (survival under 12 months). (b) Higher levels in short-term survivors compared to long-term survivors. Antibody Profile: Top shifts observed during treatment. Comparison between baseline and on-treatment samples (Patient 11 contributed only a baseline seromic sample, so no longitudinal comparison was performed). (c) Rise in antibody levels in long-term survivors relative to short-term survivors. (d) Rise in antibody levels in short-term survivors relative to long-term survivors.

Notably, long-term survivors (beyond 12 months) also displayed elevated baseline antibody titers against immune-regulatory genes such as SEMA6D [22], along with treatment-associated increases in antibodies targeting the transmembrane protein SUSD6 (**Figures 5c and 5d**) compared to short-term survivors. According to published studies [29, 30], SUSD6 suppresses MHC-I expression on tumor cells. Inhibiting SUSD6 has been shown to enhance T-cell responses and produce synergistic effects when combined with anti-PD-1 agents.

Patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) who no longer respond to initial chemo- or immunotherapy generally face a grim prognosis [31]. Results from various Phase III trials in the second-line setting consistently show limited survival: median OS of 7.6 months with durvalumab [32] (Eagle study), 7.7 months with nivolumab [33, 34] (CheckMate 141), 8.0 months with avelumab [35, 36] (JAVELIN), and 8.4 months with pembrolizumab [37, 38] (KEYNOTE-040). Two-year survival rates in these trials ranged from 16.9% to 18.4%. Cetuximab as a single agent has received approval in the United States after platinum-based therapy failure, based on single-arm studies reporting median OS of 5.2-6.1 months [39]. Palliative regimens using methotrexate or taxanes are frequently used despite lacking clear evidence of benefit from randomized trials (per European Society for Medical Oncology (ESMO) recommendations [40]). A randomized Phase 3 study of

docetaxel with or without gefitinib also failed to show a benefit, with a median OS of approximately 6 months [41]. Consequently, effective new options are urgently needed for patients progressing after chemotherapy and/or immunotherapy [42, 43].

Encouraged by promising signals seen in heavily pre-treated HNSCC patients receiving MVX-ONCO-1 during the Phase I trial [11, 12], the multi-center Phase IIa SAKK 11/16 study was initiated.

SAKK 11/16 successfully met its primary OS endpoint earlier than planned. In this difficult-to-treat group — patients with R/M HNSCC progressing after at least one systemic therapy line, with 85% having failed prior anti-PD-1 treatment — 68.8% (well above the 50% target) were alive at 6 months. Since the primary goal was reached with only 16 participants, enrollment was closed, and all treated patients continued protocol-specified follow-up. Median OS reached 11.4 months (95% CI 4.4–not reached), with 31.6% of patients alive at 18 months, including several exceptionally long survivors. Complete and partial tumor responses were documented with MVX-ONCO-1 used alone in this refractory setting.

Because nearly all patients (14/16) had previously received anti-PD-1 therapy and two more received it later, an exploratory analysis examined survival from the first dose of anti-PD-1 treatment. This yielded a median OS of 21.7 months from the start of checkpoint inhibition — markedly longer than the 7–8 months typically reported in pivotal second-line Phase III trials of pembrolizumab (KEYNOTE-040 [38]) and nivolumab (CheckMate 141 [34]).

Importantly, the treatment showed no new safety concerns and did not cause any systemic adverse events linked to the investigational product. Manufacturing and logistical processes proceeded smoothly across centers, with all vaccine doses prepared and available within 10 days of tumor cell collection.

Understanding the immunological mechanisms behind MVX-ONCO-1 is essential to interpret the observed clinical benefits and extended survival. To date, reliable prognostic or predictive markers remain elusive for HNSCC patients who progress after standard chemotherapy and immunotherapy.

A striking finding was that every patient who developed a cancer-specific immune response to their own irradiated tumor cells — as evidenced by a positive DTH test after vaccination — survived for at least 12 months. In sharp contrast, only one patient with survival of less

than 12 months showed DTH positivity. This resulted in a substantial gap in median OS: 6 months for DTH-negative patients versus not reached (95% CI 11.1–not reached) for DTH-positive patients. Thus, post-treatment DTH positivity emerges as a potential strong predictor of durable survival. This association held regardless of Human Papillomavirus (HPV) status.

Furthermore, tumor responses (partial and complete) were seen with vaccine monotherapy, and enhanced responses to later anti-PD-1 therapy occurred even in PD-L1-negative tumors. These observations support the idea that MVX-ONCO-1 can generate meaningful anti-tumor immunity on its own and may synergize with checkpoint inhibitors. Exploratory immune monitoring, including detailed seromic profiling, offers insights into the underlying processes. Such data are hypothesis-generating and help clarify how the vaccine stimulates immunity in patients with advanced disease. The cell-encapsulation approach for local GM-CSF delivery likely enhances the recruitment and activation of antigen-presenting cells [44] while preserving MHC-I expression by modulating SUSD6.

SAKK 11/16 represents the first personalized cell-based cancer vaccine trial to demonstrate positive overall survival results in relapsed/refractory metastatic head and neck squamous cell carcinoma, alongside an excellent safety profile and clear evidence of immune activation.

Further clinical investigations are warranted, both in R/M HNSCC and other malignancies, including combination strategies with immune checkpoint inhibitors, to fully assess the promise of this distinctive vaccination platform.

## Conclusion

This work highlights the potential of MVX-ONCO-1 as an innovative immunization platform. By employing encapsulated, genetically engineered allogeneic cells to deliver sustained adjuvant activity together with inactivated autologous tumor cells, it overcomes key limitations of earlier cancer vaccines. The approach induces targeted, clinically relevant immune responses. These findings could open the door to a broadly applicable new form of cancer immunotherapy.

In summary, MVX-ONCO-1 exhibited strong safety, practical feasibility, and meaningful clinical activity in patients with recurrent or metastatic cancer who had exhausted standard treatment options.

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