

ONE DRUG. ONE PATIENT.

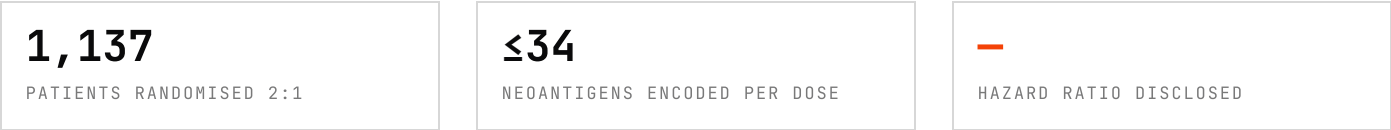
A therapy manufactured for a single person met its endpoints in a Phase 3 trial. This manual records what was disclosed, what was not, the pipeline that produces one dose, and a simulator built to make the underlying argument reproducible rather than asserted.

SUMMARY

On 19 August 2026 Merck and Moderna disclosed that intismeran autogene, an individualised neoantigen mRNA therapy, in combination with pembrolizumab, met its primary endpoint – recurrence-free survival (RFS) – and a key secondary endpoint – distant metastasis-free survival (DMFS) – in 1,137 patients with completely resected stage IIB-IV cutaneous melanoma, randomised 2:1.

Two claims of precedence are supportable from the disclosure: it is the first Phase 3 trial of an individualised neoantigen therapy to meet its primary endpoint, and the first to improve on pembrolizumab monotherapy in the adjuvant melanoma setting. The comparator was active, not placebo.

The disclosure contains no effect estimate. No hazard ratio, no confidence interval, no p-value; overall survival is described as not mature.



PROVENANCE RULE

Every figure in this manual is either (a) a published trial result with its citation, or (b) an output of the simulator described in section 05, in which case it is labelled **simulated** at the point of use. The two are never presented in the same register. Values are held in `research/FACTS.md`; a value not in that file does not appear here.

INDEPENDENCE

This document is independent work. It is not affiliated with, endorsed by, commissioned by or reviewed by Merck, Moderna, Washington University, the Icahn School of Medicine at Mount Sinai, OpenVax, or any other party named in it. All trial figures are taken from public disclosures and published literature.

WHAT WAS DISCLOSED, AND WHAT WAS NOT

INTERPATH-001 · PHASE 3	
Patients	1,137
Randomisation	2:1
Primary endpoint (RFS)	Met
Key secondary (DMFS)	Met
Hazard ratio	Not disclosed
Overall survival	Not mature
MERCK/MODERNA DISCLOSURE, 19 AUG 2026	

KEYNOTE-942 · PHASE 2B	
Patients	157
18-mo RFS, combination	79%
18-mo RFS, pembrolizumab	62%
Hazard ratio	0.561
95% CI	0.309-1.017
Grade ≥3 AEs	25% vs 18%
WEBER ET AL., LANCET 2024;403:632-644	

READING THE INTERVAL

The Phase 2b hazard ratio in general circulation derives from 157 patients, and its 95% confidence interval includes unity (two-sided $p=0.053$). At 18 months the result did not cross the conventional significance threshold. Five-year follow-up reports HR 0.51 (95% CI 0.294-0.887). The Phase 3 cohort is approximately sevenfold larger; effect estimates from small trials commonly attenuate on replication at scale. This is an expectation, not a prediction.

"Met endpoints" reports the crossing of a pre-specified threshold. It is uninformative as to magnitude. Any figure currently attached to the Phase 3 result is extrapolated from the Phase 2b, and should be described as such.

SIX STEPS TO ONE DOSE

Each dose is manufactured for a single patient from that patient's own tumour. Five of the six steps are established laboratory or manufacturing procedures. One is a prediction problem.

STEP	PROCEDURE	CLASS
01	Resection of the primary tumour	Surgical
02	Whole-exome and RNA sequencing, tumour and matched normal	Laboratory
03	Somatic variant calling against the normal	Established computation
04	Prediction of HLA presentation; ranking; selection of ≤ 34 epitopes	Prediction problem
05	Synthesis of one encoding mRNA strand, LNP-formulated	Manufacturing
06	Administration with pembrolizumab, 1 mg q3w $\times 9$ / 400 mg q6w	Clinical

WHY STEP 04 IS THE CONSTRAINT

Of the several thousand somatic variants typical of a cutaneous melanoma, only peptides presented at the cell surface by the patient's own HLA alleles are available to T-cell recognition. Binding affinity is necessary but not sufficient. Four further constraints act independently:

- **Expression** – a transcript that is not made cannot be presented.
- **Clonality** – a subclonal epitope leaves the remaining subclones untouched, and selects for them.
- **Self-similarity** – a peptide too close to the self-proteome has no untolerised repertoire to recruit.
- **Demonstrated reactivity** – prior evidence of T-cell response against the epitope or a close analogue.

Assembling that evidence stack, per candidate and per patient, is a retrieval and inference problem over genomes, expression atlases, immunopeptidomics data, assay results and the literature. It is the component that scales with compute.

THE STEP IS ALREADY OPEN SOURCE

Open implementations of epitope prediction and vaccine composition exist, are maintained, and are in clinical use. Any serious effort begins by integrating them.

pVACtools

GRIFFITH LAB, WASHU.
SUBSTITUTIONS, INDELS, FUSIONS,
SPLICE VARIANTS, VECTOR DESIGN,
REVIEW UI. >164,000 PYPI
DOWNLOADS REPORTED.

MHCflurry

ALLELE-SPECIFIC CLASS I BINDING
PREDICTION USING NEURAL
NETWORKS. OPEN SOURCE.

OpenVax

MOUNT SINAI. TUMOUR/NORMAL READS
TO VACCINE COMPOSITION. IN USE
IN THREE REGISTERED TRIALS.

REGISTERED TRIAL	PIPELINE
NCT02721043	OpenVax
NCT03223103	OpenVax
NCT03359239	OpenVax

WHERE THE OPEN PROBLEM ACTUALLY SITS

Not in binding affinity, which is well served. In the evidence stack beneath an affinity score, and in doing that assembly reliably enough, per patient, to justify occupying one of thirty-four slots.

THE SIMULATOR

A three-compartment model of a treated tumour, published on the study site and running in the browser. It exists so that the argument in section 06 can be reproduced rather than asserted.

```
dS/dt = rs·S·(1 - T/K) - (targeted + chemo + immune)·S
dR/dt = rr·R·(1 - T/K) - (chemo·0.60 + immune)·R
dE/dt = re·E·(1 - T/K) - (chemo·0.90 + immune·0.35)·E
T = S + R + E
```

S DRUG-SENSITIVE · R DRUG-RESISTANT · E IMMUNE-ESCAPED (ANTIGEN OR HLA LOSS)

LOAD-BEARING ASSUMPTION

Immune clearance is implemented as **saturating in tumour burden**: per-cell killing declines as total population rises, on the reasoning that a large tumour outruns a finite effector pool. That single assumption reproduces efficacy in minimal residual disease and failure in bulky disease – which is the rationale for an adjuvant trial design. It is order-of-magnitude reasoning, not a fitted parameter.

CALIBRATION

Parameters were chosen so that two independently published medians fall where they do. No parameter was fitted to the Phase 3 result, which has published no effect estimate to fit to.

CONDITION	SIMULATED	PUBLISHED MEDIAN
Continuous maximum dosing, targeted agent	15.8 mo	14.3 mo
Adaptive schedule	33.8 mo	33.5 mo

PUBLISHED MEDIANS: ZHANG ET AL., ELIFE 2022;11:E76284 (N=17 VS 16)

WHAT THE MODEL REPRODUCES

ALL FIGURES ON THIS PAGE ARE SIMULATED OUTPUT.

OBSERVATION	PROTOCOL	RESULT
Vaccine contribution is burden-dependent	Resected melanoma, CPI ± vaccine	Progression 14.7 mo → cleared
Cold tumour gains almost nothing	Resected PDAC, CPI ± vaccine	+0.3 mo
Burden separates strata within one tissue	Colorectal MSI-high vs MSS	Cleared vs progression
Monotherapy selects its own escape route	Targeted agent alone, continuous	96% resistant at progression
Immune pressure selects the other route	CPI + vaccine + targeted	Escaped compartment dominant
Scheduling changes outcome and toxicity	Adaptive vs continuous, mCRPC	23.6 vs 20.2 mo
Concurrent maximal therapy self-limits	All seven modalities	Toxicity hold

MUTATIONAL BURDEN BY TUMOUR TYPE

Approximate median mutations per megabase. Four entries in the full catalogue are flagged extrapolated rather than anchored.

Colorectal, MSI-high	42
Melanoma, cutaneous	13.5
NSCLC, adenocarcinoma	8.5
Urothelial, bladder	7.5
Colorectal, MSS	3.5
Renal cell carcinoma	2.5
Pancreatic ductal adenocarcinoma	1.5

LIMITATIONS

Stated here rather than in an appendix, because the limitations constrain every figure in section 06.

1. **The model is not calibrated for prediction.** It is parameterised to reproduce two published medians. It has no validation cohort and produces no confidence intervals.
2. **Three compartments is a simplification.** Real tumours carry many subclones, spatial structure, stromal interaction and an immune system with memory. None of that is represented.
3. **Per-cancer parameters are order-of-magnitude.** Mutational burden and checkpoint response rates are approximate medians; four of thirteen entries are extrapolated rather than anchored to a published source, and are flagged as such in the interface.
4. **Anatomical barriers are not modelled.** The glioblastoma entry ignores the blood-brain barrier, which flatters every result produced for it.
5. **The saturating-immunity assumption is reasoning, not measurement.** It is load-bearing. If it is wrong, section 06 is wrong.
6. **"Cleared" is a model state, not a clinical outcome.** It denotes burden below a detection threshold sustained for six simulated months. In a clinic that is a follow-up appointment.
7. **The adaptive-therapy comparison rests on a small trial.** Its initial report described eleven patients and was challenged in print for incomplete reporting of patient characteristics and comparison against historical controls (Mistry, Nat Commun 2020).

WHAT THIS DOCUMENT DOES NOT CLAIM

That the Phase 3 effect size is known. That the simulator predicts patient outcomes.
That any protocol expressible in it should be administered. That any organisation named in it has reviewed, endorsed or participated in it.

SOURCES

FIGURE USED	SOURCE
n=1,137; endpoints met; no HR; OS not mature; dosing schedule	Merck / Moderna joint disclosure, 19 August 2026
n=157; 79% vs 62%; HR 0.561 (0.309–1.017); p=0.053; grade ≥3 AEs 25% vs 18%	Weber JS et al., Lancet 2024;403:632–644
Five-year RFS HR 0.51 (0.294–0.887)	Merck / Moderna five-year update, 2026
TTP 33.5 vs 14.3 mo; OS 58.5 vs 31.3 mo; HR 0.41 (0.20–0.83); n=17 vs 16; 54% time on drug	Zhang J et al., eLife 2022;11:e76284
Adaptive-therapy protocol and first cohort	Zhang J et al., Nat Commun 2017;8:1816
Reporting critique of the adaptive trial	Mistry HB, Nat Commun 2020
≤34 neoantigens; WES + RNA-seq; HLA typing	Moderna technical disclosures; AACR abstract 6539
pVACtools scope and adoption	pVACtools v6, arXiv:2606.26659
OpenVax trial usage	openvax.org; NCT02721043, NCT03223103, NCT03359239
Mutational burden and ORR by tumour type	Approximate medians; see research/FACTS.md §I for per-entry anchoring
All timings, fractions and outcomes in section 06	Simulation output – this document's own model

VOLUNTEER COMPUTATION, IF THAT IS THE INTEREST

DreamLab (Imperial College London with the Vodafone Foundation) and World Community Grid's Mapping Cancer Markers have run genuine biomedical workloads on donated cycles for years. This project runs none. Anyone wishing to contribute compute to cancer research should contribute it there.

NOT A TREATMENT. JUST A MODEL.

Metastasis is a study and a simulator. The model is a teaching instrument parameterised to reproduce published medians; it is not calibrated for prediction. Nothing in it diagnoses, treats or funds anything. No sequencing runs on any reader's device and no data leaves the browser.

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