B Cell Immunotherapy
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Development of the B Cell Cancer Vaccine HER-Vaxx for the Treatment of Her-2 Expressing Cancers

November 17 2022
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Imugene Ltd

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INTRODUCTION TO IMUGENE

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Imugene is a biotech company headquartered in Australia and publicly traded on the Australian Securities Exchange (ASX:IMU)

2013
Paul Hopper builds Imugene around technology originating from the Medical University of Vienna

2015
Leslie Chong from Genentech joins Imugene

2017
HER-Vaxx enters the clinic

2018
Licensed extensive B cell portfolio and platform from OSU & Mayo Clinic invented by Prof Pravin Kaumaya

2019
Completed the acquisition of a prolific oncolytic virus from City of Hope invented by Dr Yuman Fong

2021
Licensed onCARlytics from City of Hope invented by Dr Y Fong, Dr S Priceman & Dr A Park

2021
Strategic Partnership with **Celularity**

2021
CHECKvacc enters the clinic

2021
Strategic Partnership with **Eureka**

2021
HER-Vaxx Clinical Trial Supply Partnership with Merck KGaA & Pfizer

2021
PD1-Vaxx Clinical Trial Supply Partnership with Roche

2021
Entered the S&P/ASX 200 Index

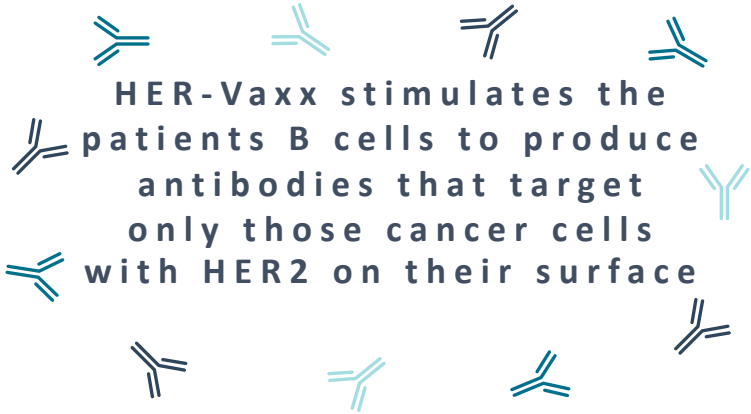
2022
VAXINIA enters the clinic

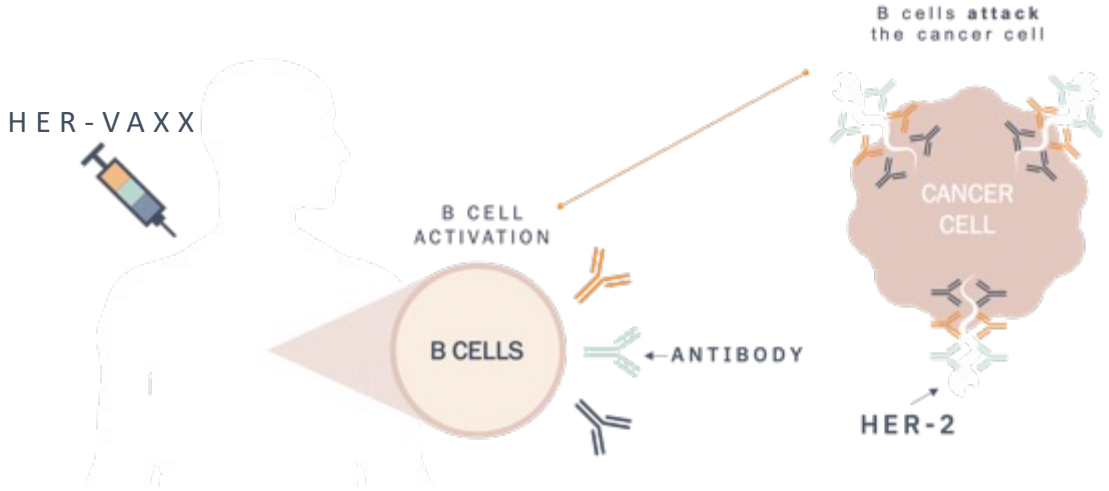
2022
HER-Vaxx Phase 2 Final OS

2022
Strategic Partnership with **Arovella**

HER-Vaxx B-CELL VACCINE SUMMARY

- HER-Vaxx is a B-cell immunotherapy designed to treat tumours that over-express the HER2/neu receptor, including gastric and breast cancer
- The immunotherapy is constructed from three B cell epitopes derived from the extracellular domain of HER2/neu (patent protected to 2036)
- HER-Vaxx is under development for the treatment of HER2-positive gastric cancer, and also has the potential to treat other HER2-overexpressing cancers (breast, CRC, lung)
- HER-Vaxx has been shown in pre-clinical studies and now in a Phase I and 2 studies to stimulate a potent polyclonal antibody response to HER2/neu, a well-validated cancer target





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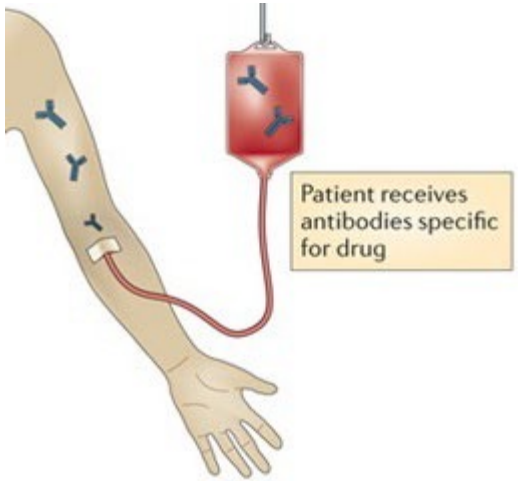
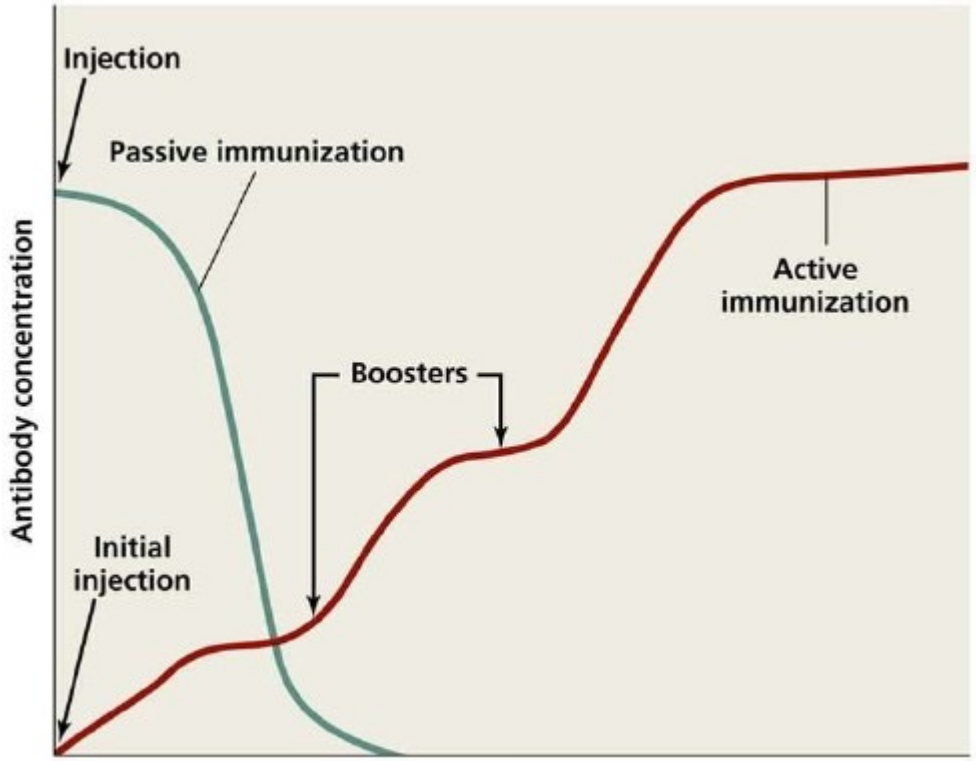
HER-Vaxx B Cell Vaccine

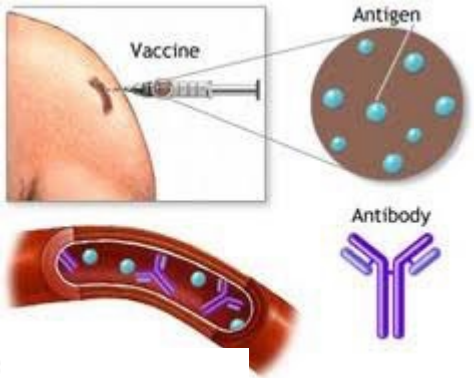
WHY ACTIVE IMMUNIZATION AGAINST CANCER?

Passive Immunotherapy Vs Active Immunization



Specificity	Memory
Yes	No





Specificity	Memory
Yes	Yes

B CELL BASED ANTIBODIES HAVE DISTINCT COMPETITIVE ADVANTAGES TO EXISTING TREATMENTS

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B cell vaccines offer a unique opportunity to intervene at multiple points in the immune system and create immune memory which enhances durability of response.

	NATURAL B CELL DERIVED ANTIBODIES	MONOCLONAL ANTIBODIES
Safety	Stimulates the immune system to produce Abs, which may be potentially safer	Synthetic Ab, with side effects (including ventricular dysfunction, CHF, anaphylaxis, infusion reactions, immune mediation)
Efficacy	Polyclonal Ab response reduces risk of resistance and potentially increases efficacy	Monoclonal Ab – may develop anti-drug antibodies
Durability	Antibodies continuously produced with lasting immune response to potentially inhibit tumor recurrence	Half life necessitates recurrent dosing
Usability	After priming, low numbers of vaccinations required per year	Requires regular infusion
Cost	Low cost of production enables greater pricing flexibility facilitating combination	Expensive course of treatment >US$100K per year

HER-Vaxx: B-CELL IMMUNOTHERAPY VACCINE AGAINST HER-2

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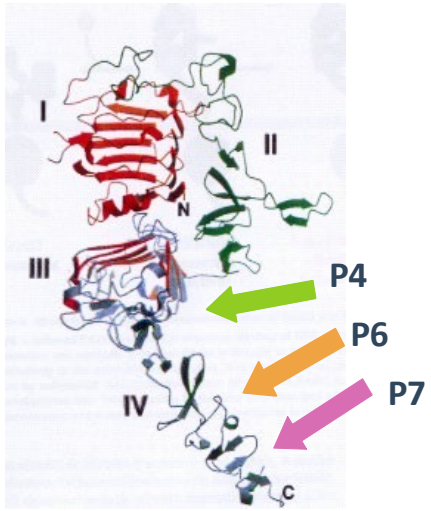
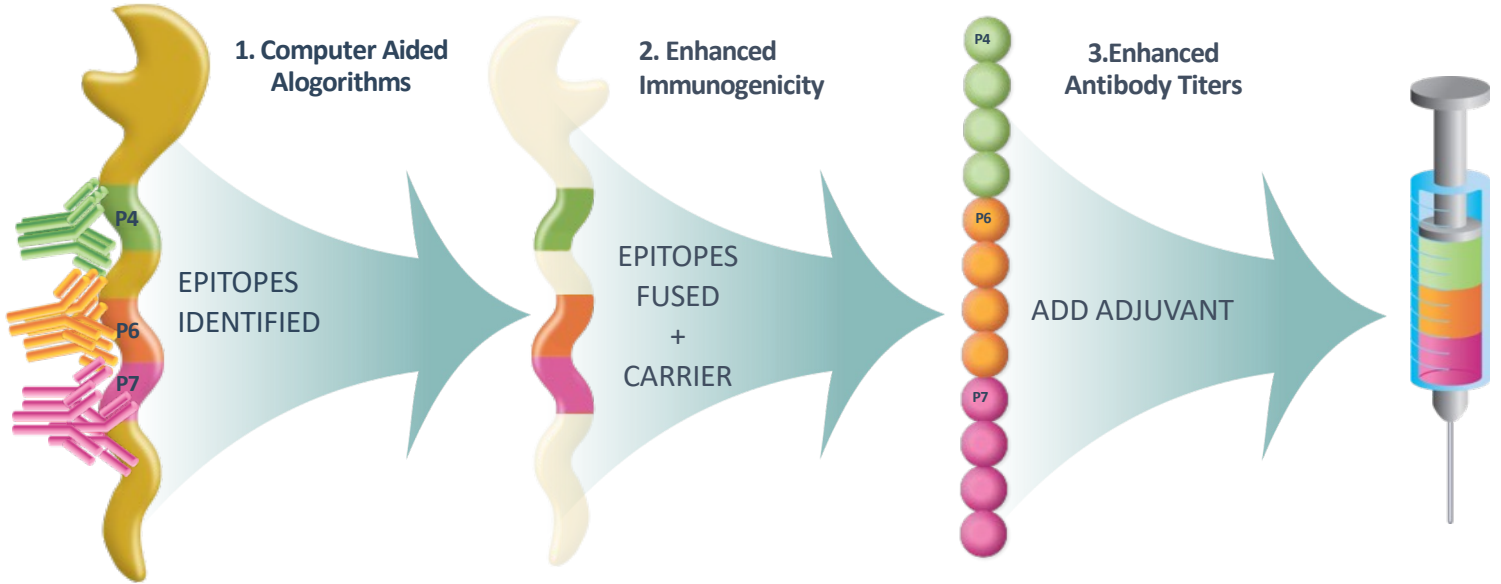
- B-cell cancer vaccine designed to stimulate a patient's own immune system to repeatedly target the HER-2+ cancer with HER-2 directed antibodies
- Stimulates a patient's B cells to produce polyclonal antibodies that target cells with overexpressing HER-2 receptors on their surface
- HER-Vaxx consists (1) of three fused B-cell epitope peptides (P4, P6, P7) from the HER-2 receptor conjugated to (2) a carrier protein CRM197 plus (3) an adjuvant Montanide ISA51. Injected as a water-in-oil emulsion.



HER-2 RECEPTOR



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HER-Vaxx Non Clinical Data

PUBLISHED HER-Vaxx B CELL VACCINE NON CLINICAL & PHASE 1b

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2017

Enhanced and long term immunogenicity of a Her-2/neu multi-epitope vaccine conjugated to the carrier CRM197 in conjunction with the adjuvant Montanide

BMC Cancer 2017, 17, 118 doi: 10.1186/s12885-017-3098-7

2021

Clinical and immunologic responses to a B-cell epitope vaccine in HER2/neu overexpressing advanced gastric cancer patients - results from Phase 1b trial IMU.ACS.001

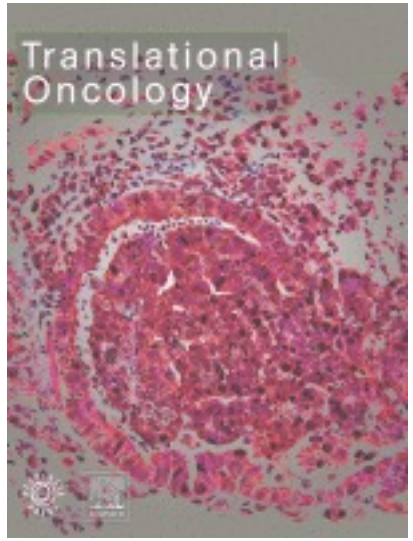
Clin. Can. Res. 2021, 27, 3649 doi: 10.1158/1078-0432.CCR-20-3742

2022

Vaccination against Her-2/neu, with focus on peptide-based vaccines

ESMO Open, 2022, 7, 100361 doi.org /10.1016/ j.esmoop.2021.100361

2022



Active immunization with a Her-2/neu-targeting Multi-peptide B cell vaccine prevents lung metastases formation from Her-2/neu breast cancer in a mouse model

Translational Oncology 2022, 19, 101378 doi: 10.1016/ j.tranon.2022.101378

PHASE 1 IN BREAST CANCER, COMPLETED AT MEDICAL UNIVERSITY OF VIENNA- SINGLE AGENT, NO CHEMO

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DESIGN

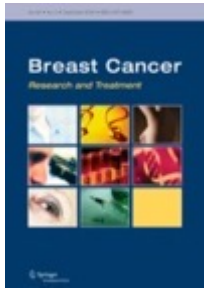
- 10 patients
- All late stage breast cancer patients
- HER-2 +/++
- Life expectancy > 4 months
- Conducted at Medical University of Vienna

RESULTS

- Patients developed anti-HER-2 antibodies
- Induction of cytokines (Th1 biased; IFNγ)
- Induction of memory T & B cells post vaccination
- Reduction in T reg cells post vaccination, indicating strong vaccine response
- Antibodies induced displayed potent anti-tumor activity
- Promising results - Patients were end stage and not primary target group

CLINICAL ENDPOINTS

1. Safety and Tolerability
2. Immunogenicity: antibodies and cellular responses



* Wiedermann et. al., Breast Cancer Res Treat. 2010 Feb;119(3):673-83.

Safety, Efficacy, Durability, Usability, Cost

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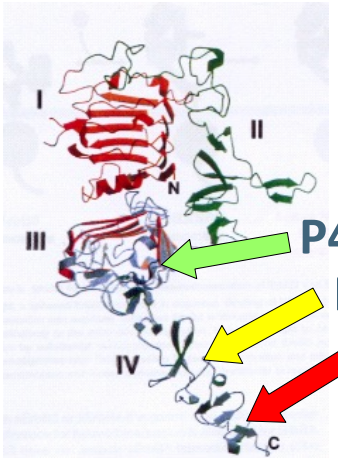
11

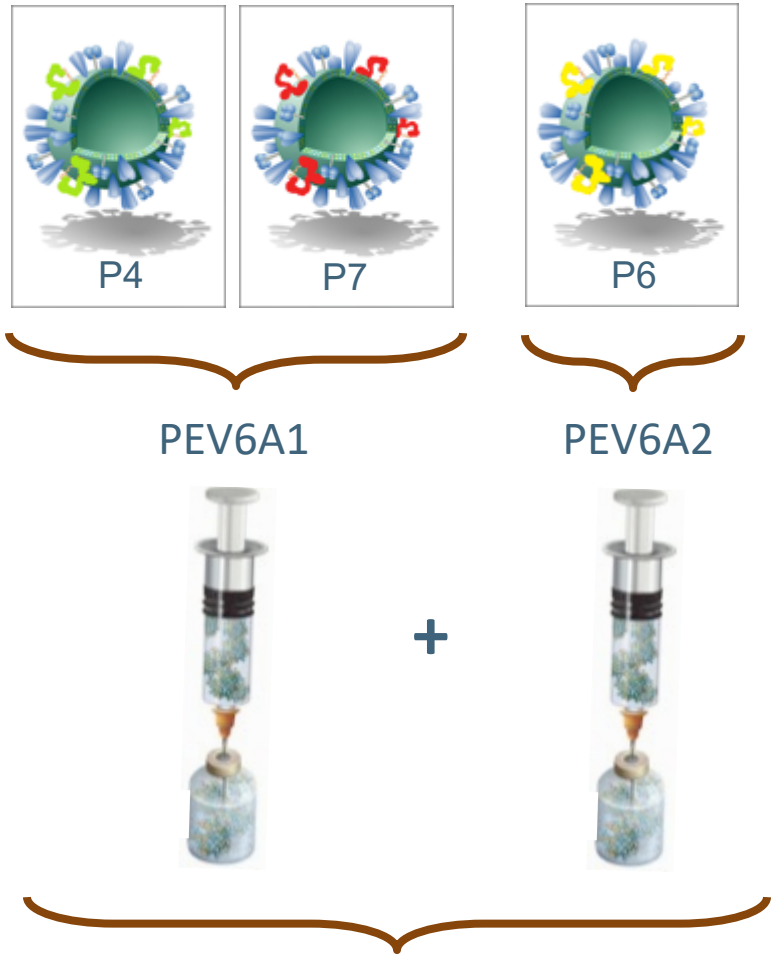
Phase I Vaccine Composition & Limitations

HER-2



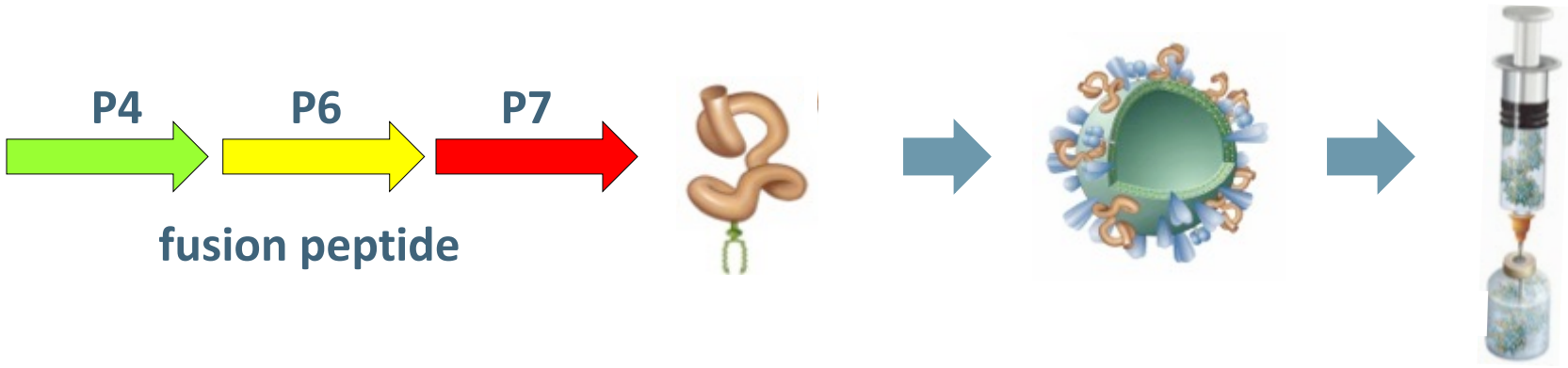
3 peptide antigens

- Limited / insufficient stability of P6 and P7 (short shelf life) – oxidation of Met in P7
- P4, P6, P7 not compatible in one formulation
- Separate formulation steps necessary
- Application in 2 injections necessary



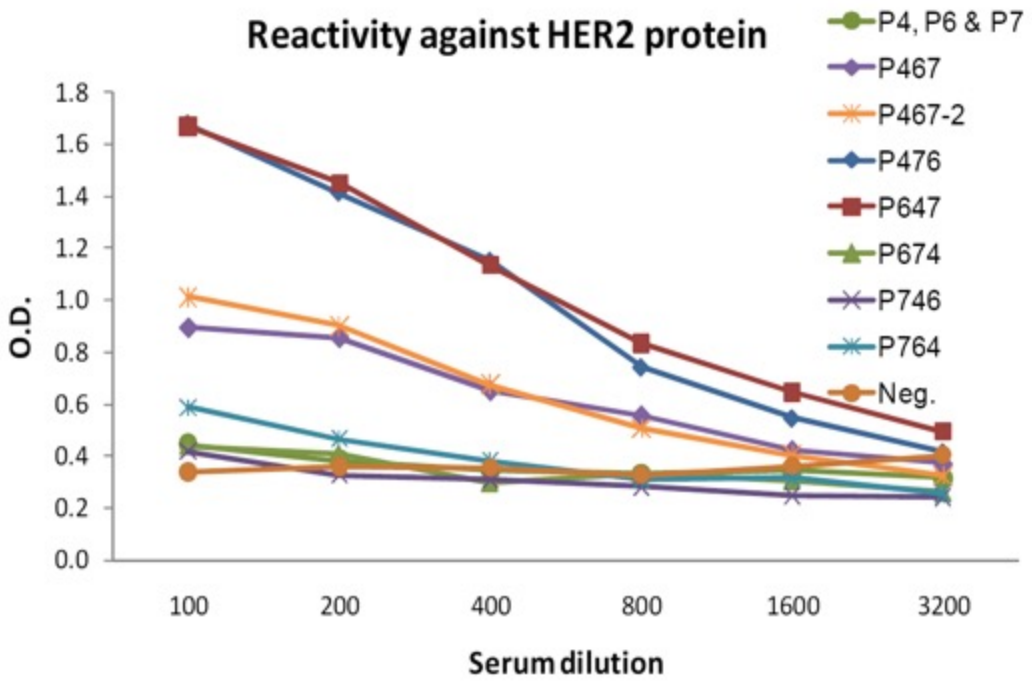
Product Optimization - Multi-Epitope Fusion Peptide

- Single formulation process
- Equal dosing of the three antigens guaranteed
- Quantification simplified (QA)
- One injection per dose
- New IP generated – IP protection until 2030



Fusion Peptide Shows Even Better Immunogenicity / Target Reactivity

- Combinatorial variants tested in mice
- Induction of antibodies with even higher reactivity against HER-2 protein as compared to single peptide immunization
- P467 selected for development – P647 had issues
- New patent filed and granted in US and EU



Name	Combinatorial variants of fusion peptide sequence
P467	PESFDGDPASNTAPLQPRVLQGLPREYVNARH**S**YMPIWKFPDEEGAC
P476	PESFDGDPASNTAPLQPYMPIWKFPDEEGA**S**RVLQGLPREYVNARHC
P647	RVLQGLPREYVNARH**S**PESFDGDPASNTAPLQPYMPIWKFPDEEGAC
P674	RVLQGLPREYVNARH**S**YMPIWKFPDEEGA**S**PESFDGDPASNTAPLQPC
P746	YMPIWKFPDEEGA**S**PESFDGDPASNTAPLQPRVLQGLPREYVNARHC
P764	YMPIWKFPDEEGA**S**RVLQGLPREYVNARH**S**PESFDGDPASNTAPLQPC

Acknowledgement: Kammer, Amacker, Zurbriggen (Pevion Biotech)

Structure and Sequence P467

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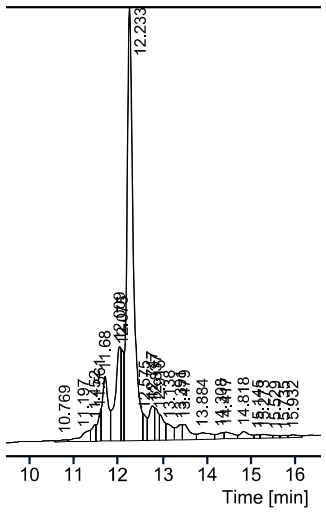
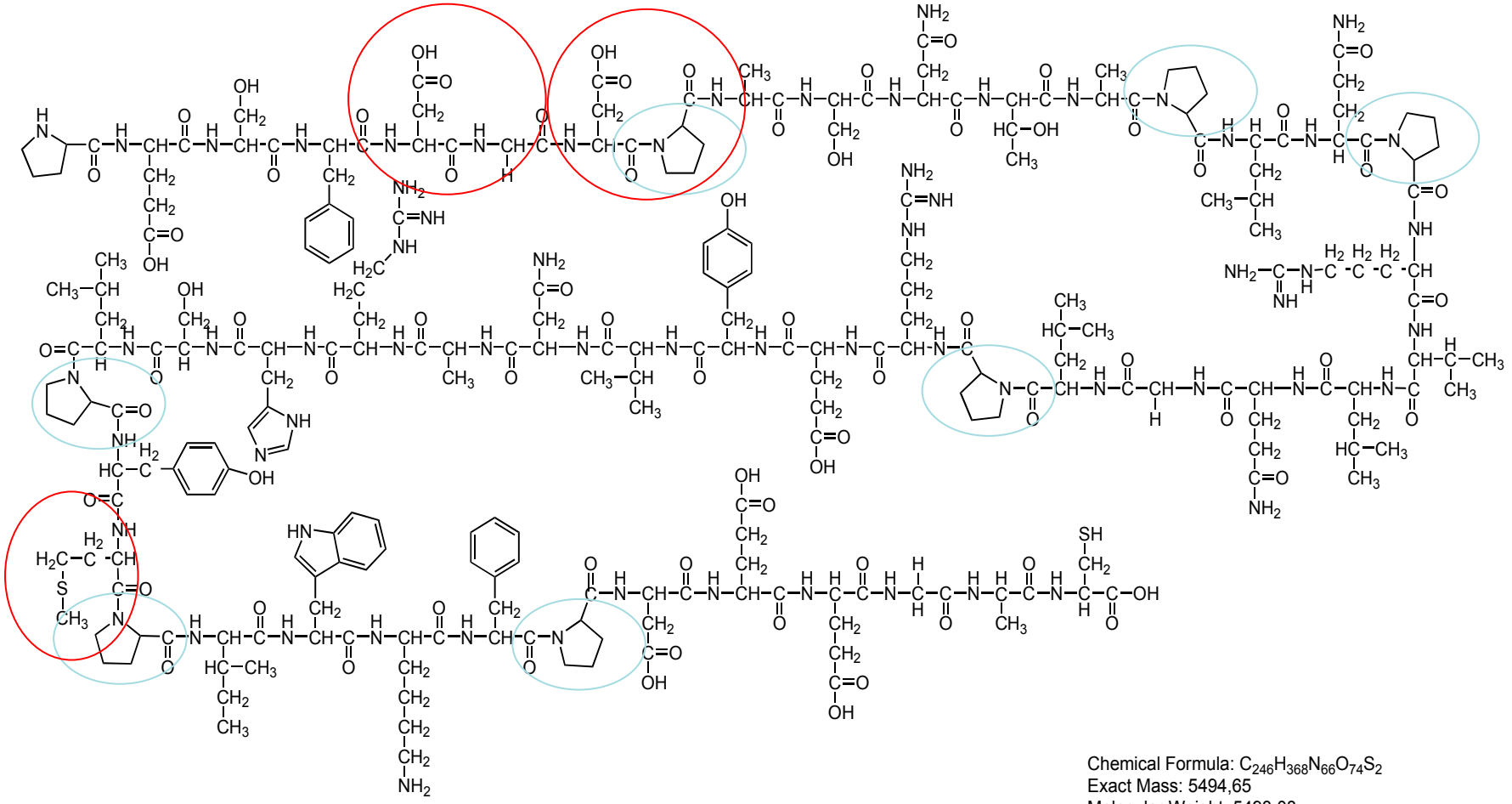
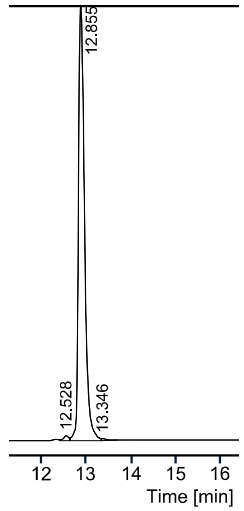
P467 Batch-ID: AP6
PESFDGDPAS NTAPLQPRVL QGLPREYVNA RHSLPYMPIW KFPDEEGAC

piCHEM







Chemical Formula: $C_{246}H_{368}N_{66}O_{74}S_2$
Exact Mass: 5494,65
Molecular Weight: 5498,08

Decision made in Feb 2015 to change virosome delivery to CRM197 carrier protein

P467-CRM197

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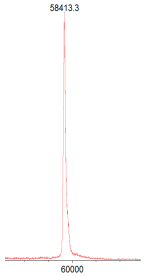
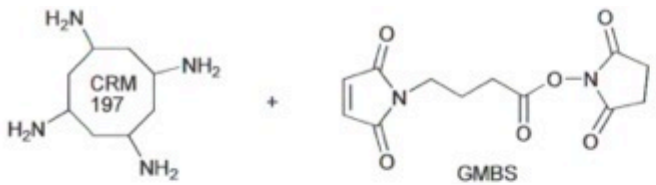
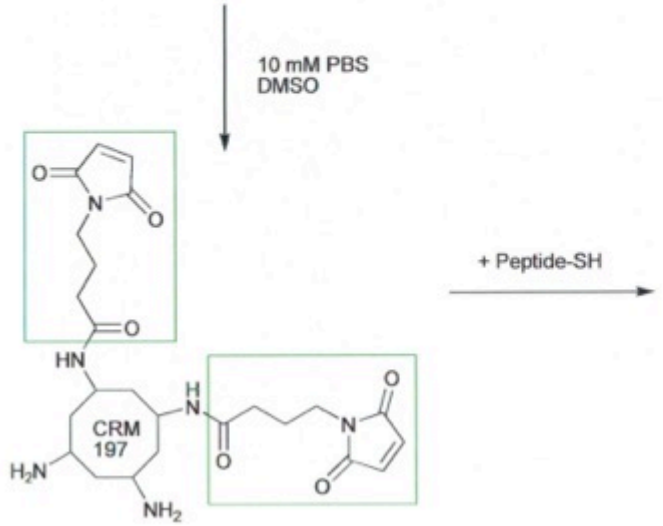
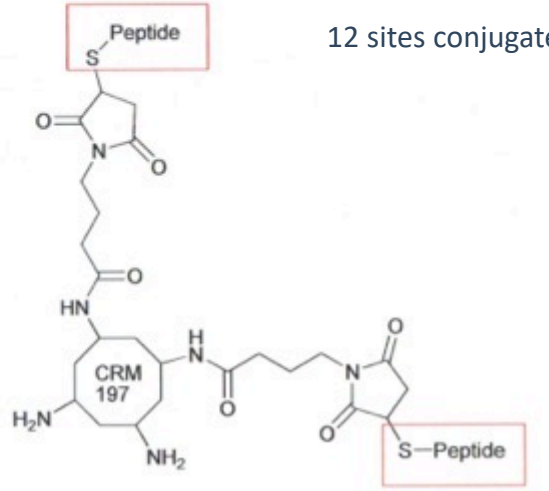
41 possible sites



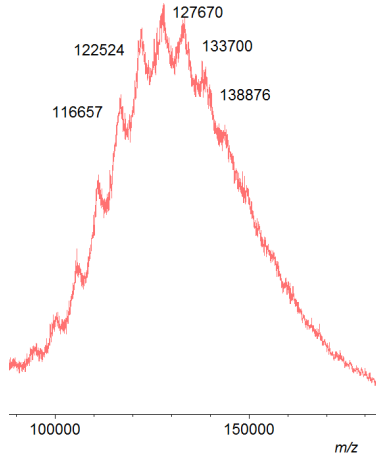


piCHEM

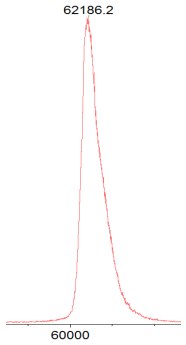




12 sites conjugated



23 sites activated



- cGMP batch completed (piCHEM) and aseptically filled (Baccinex)
- Mean MW MALDI-TOF MS – 127,494 g/mol
- Mean peptide / P467-CRM197 – 12mol/mol
- **Three R&D batches and three cGMP batch completed**
- 48-month stability established

BACCINEX SA

HER-Vaxx: SELECTION OF CRM197 CARRIER PROTEIN

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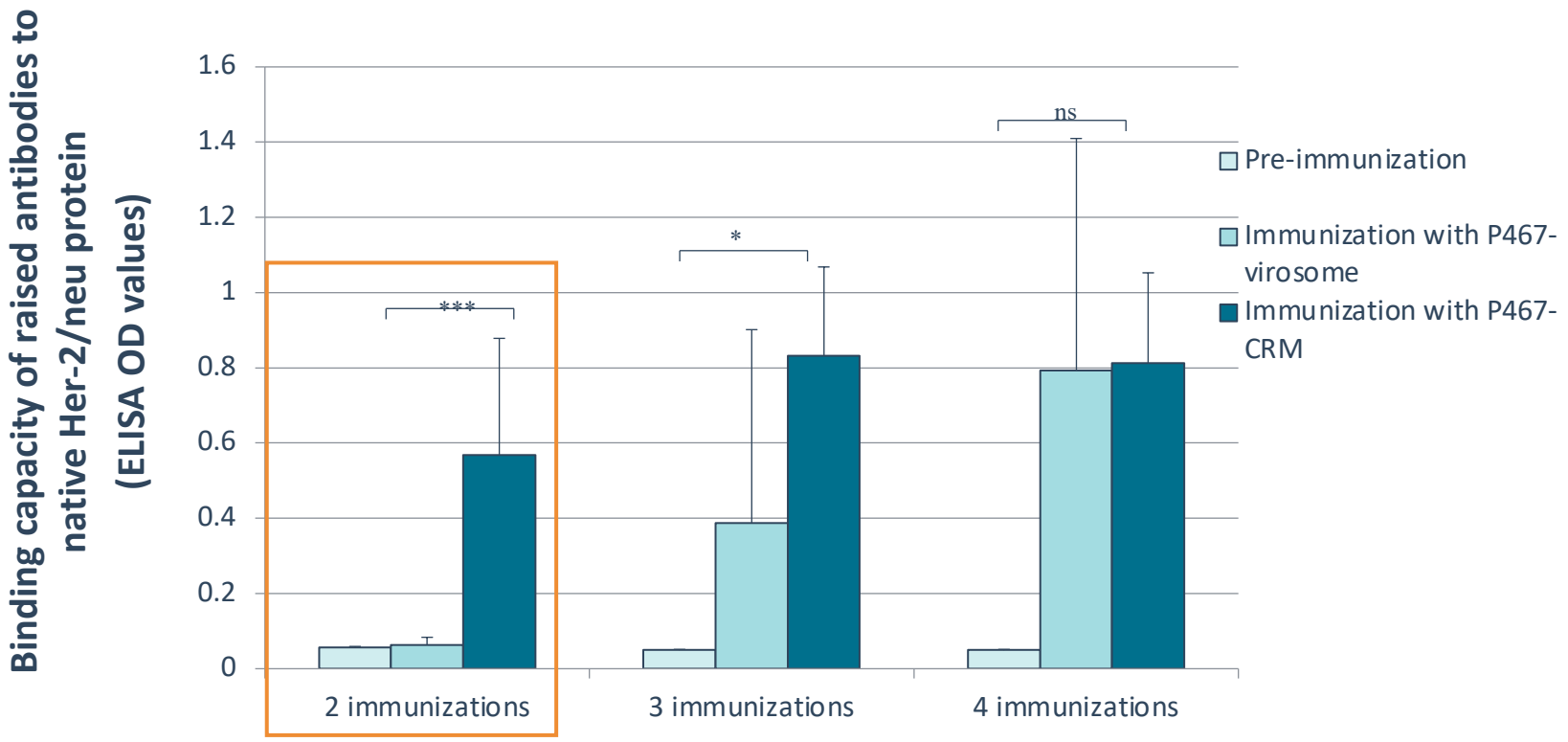
P467-CRM induces faster and higher antibody responses, compared with P467-virosomes*



Tobias et al, BMC Cancer 2017, 17, 118

HER-Vaxx: SELECTION OF OPTIMAL ADJUVANT

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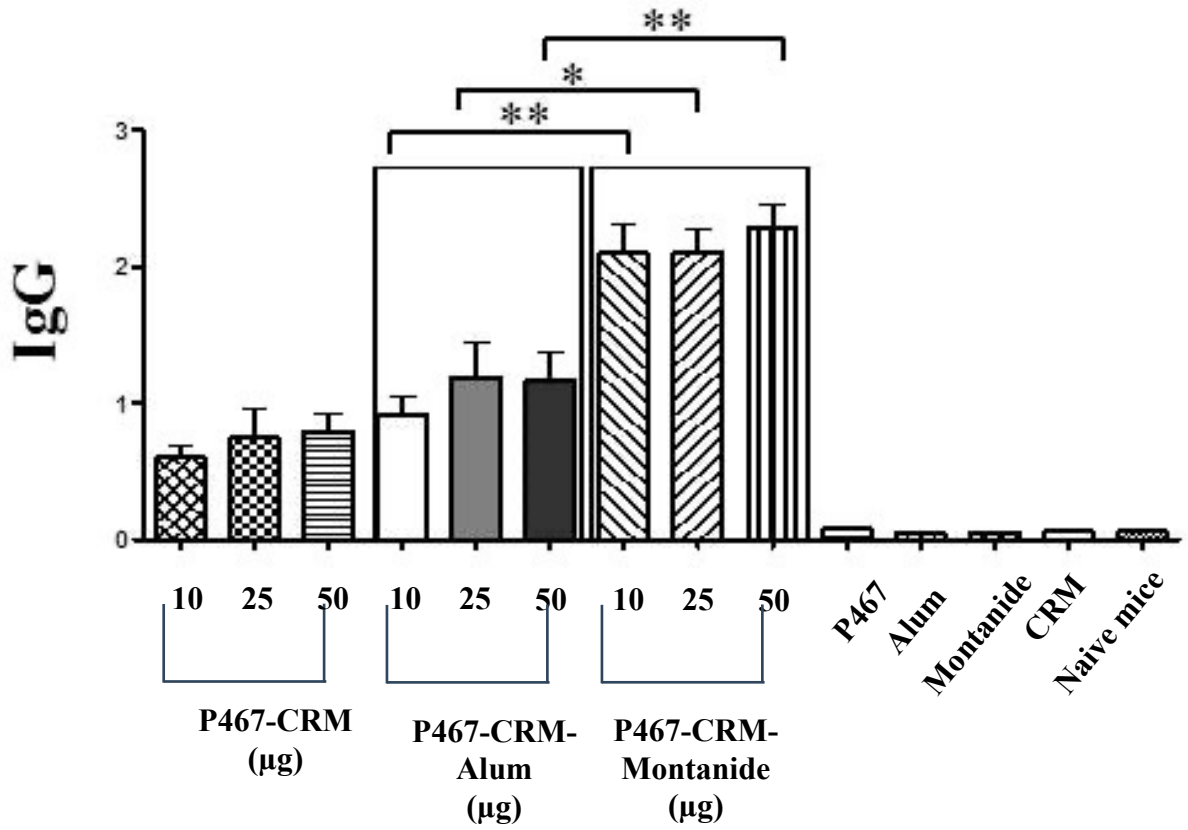
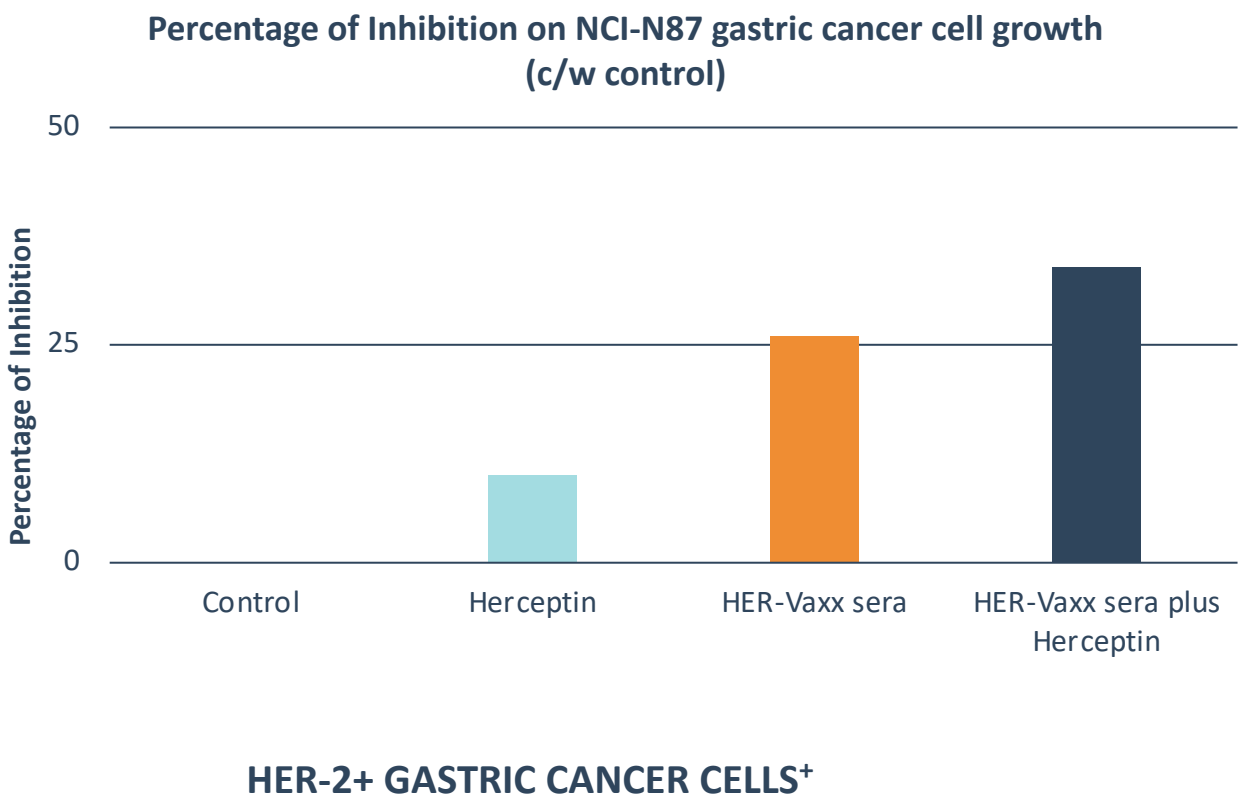
P467-CRM-Montanide induces higher titers of IgG, as well as IgG1 and IgG2a, compared with P467-CRM-Alum



Tobias et al, BMC Cancer 2017, 17, 118

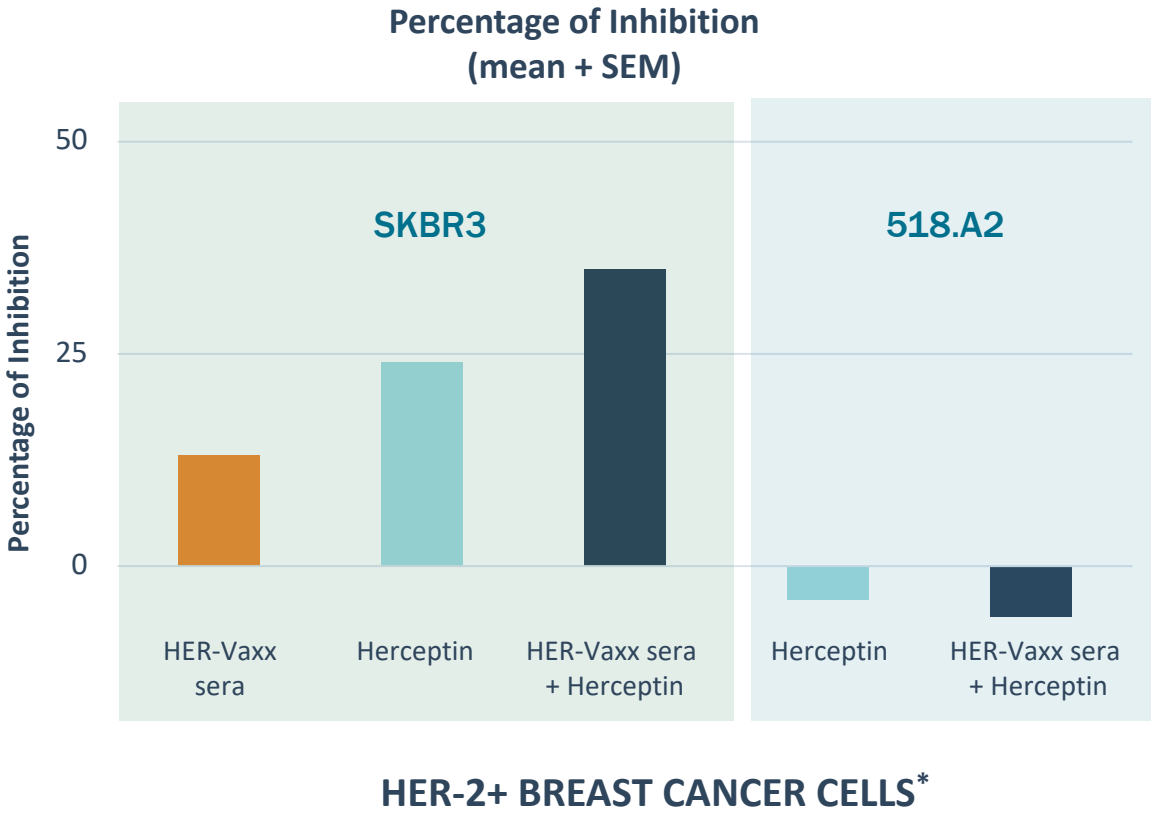
HER-Vaxx INHIBITS HER-2 EXPRESSING CELL GROWTH

HER-Vaxx antibodies demonstrate anti-tumour effect by inhibiting validated HER-2+ gastric cell line



HER-2+ GASTRIC CANCER CELLS+

Combination with Herceptin shows significantly higher inhibition than Herceptin alone



HER-2+ BREAST CANCER CELLS*

+ Charles River Laboratories, Morrisville NC

* Tobias et al, BMC Cancer 2017, 17, 118

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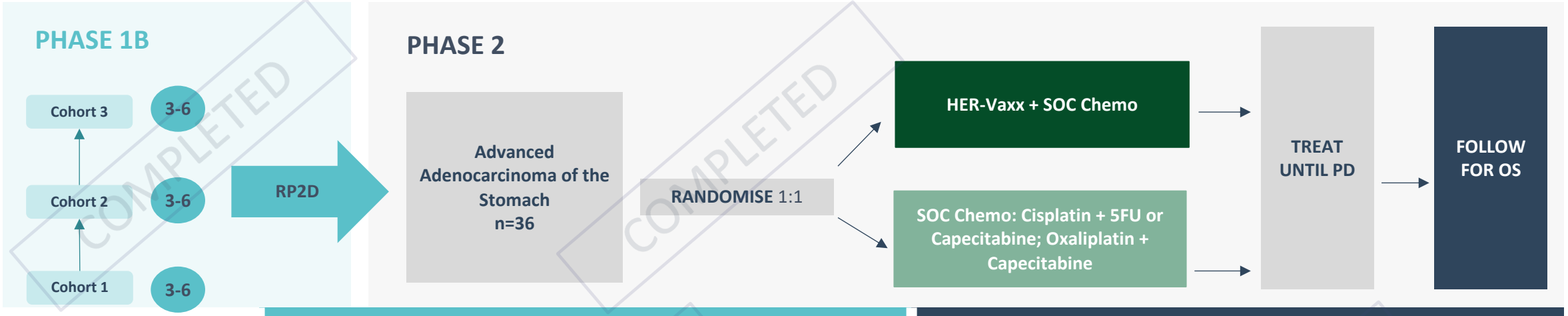
HER-Vaxx Clinical Data

HERIZON:

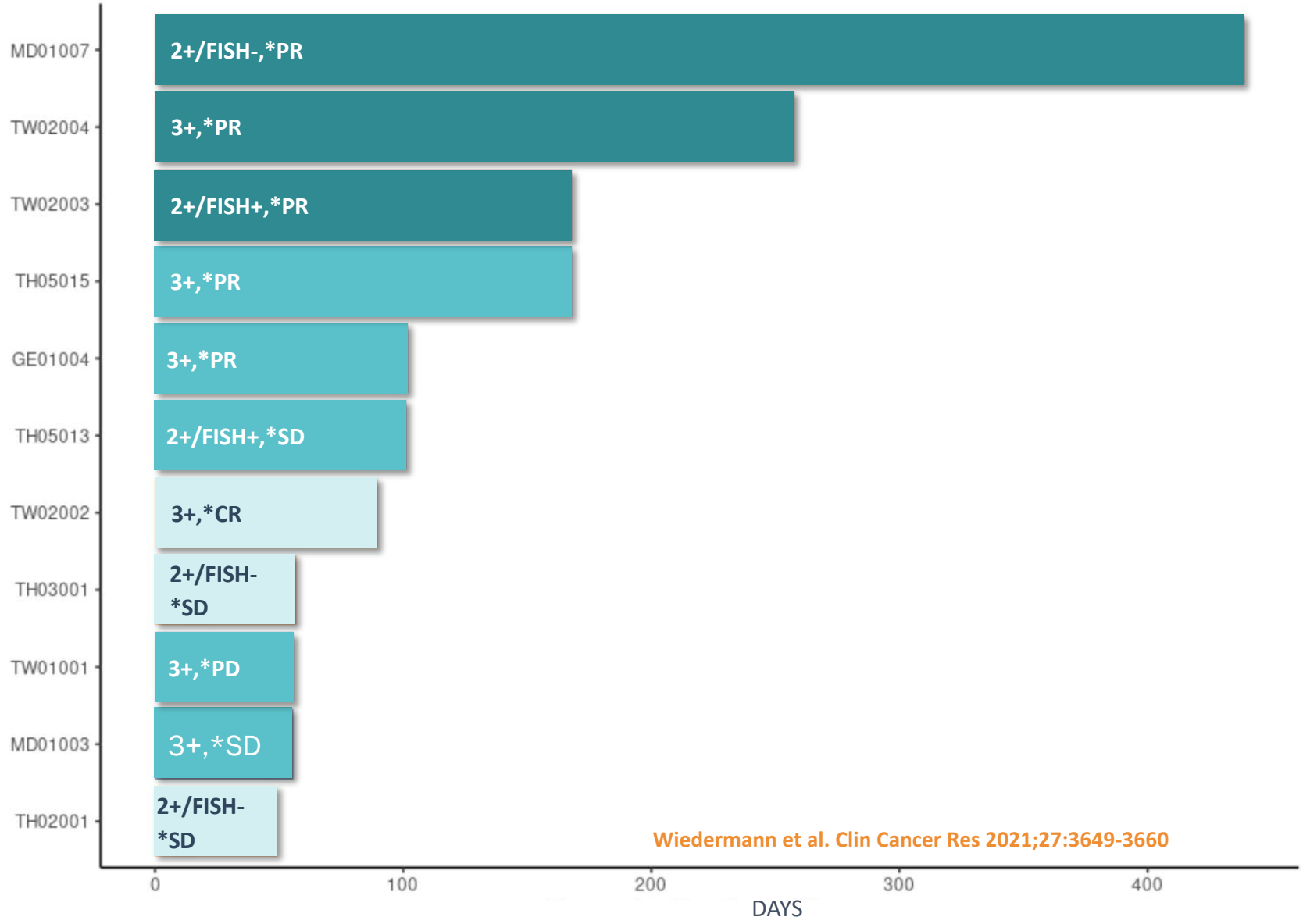
HER-Vaxx PHASE 1b/2 IN METASTATIC GASTRIC CANCER (GC)



PHASE	PHASE 1B	PHASE 2
INDICATION	Newly diagnosed HER2+ gastric cancer	Newly diagnosed HER2+ gastric cancer
OBJECTIVES	Safety & Tolerability, Immunogenicity, RP2D	Primary: OS Secondary: PFS, Safety & Tolerability, Immune Response
NO. OF PATIENTS	14	36
SITE LOCATION	Asia, Eastern Europe	Eastern Europe, India

HERIZON HER-Vaxx PHASE 1B:

EFFICACY



Wiedermann et al. Clin Cancer Res 2021;27:3649-3660

HER-Vaxx Phase 1b: Biomarker analysis of native HER2 receptor binding assay (by FACS) on N87 gastric cancer cells with patient sera

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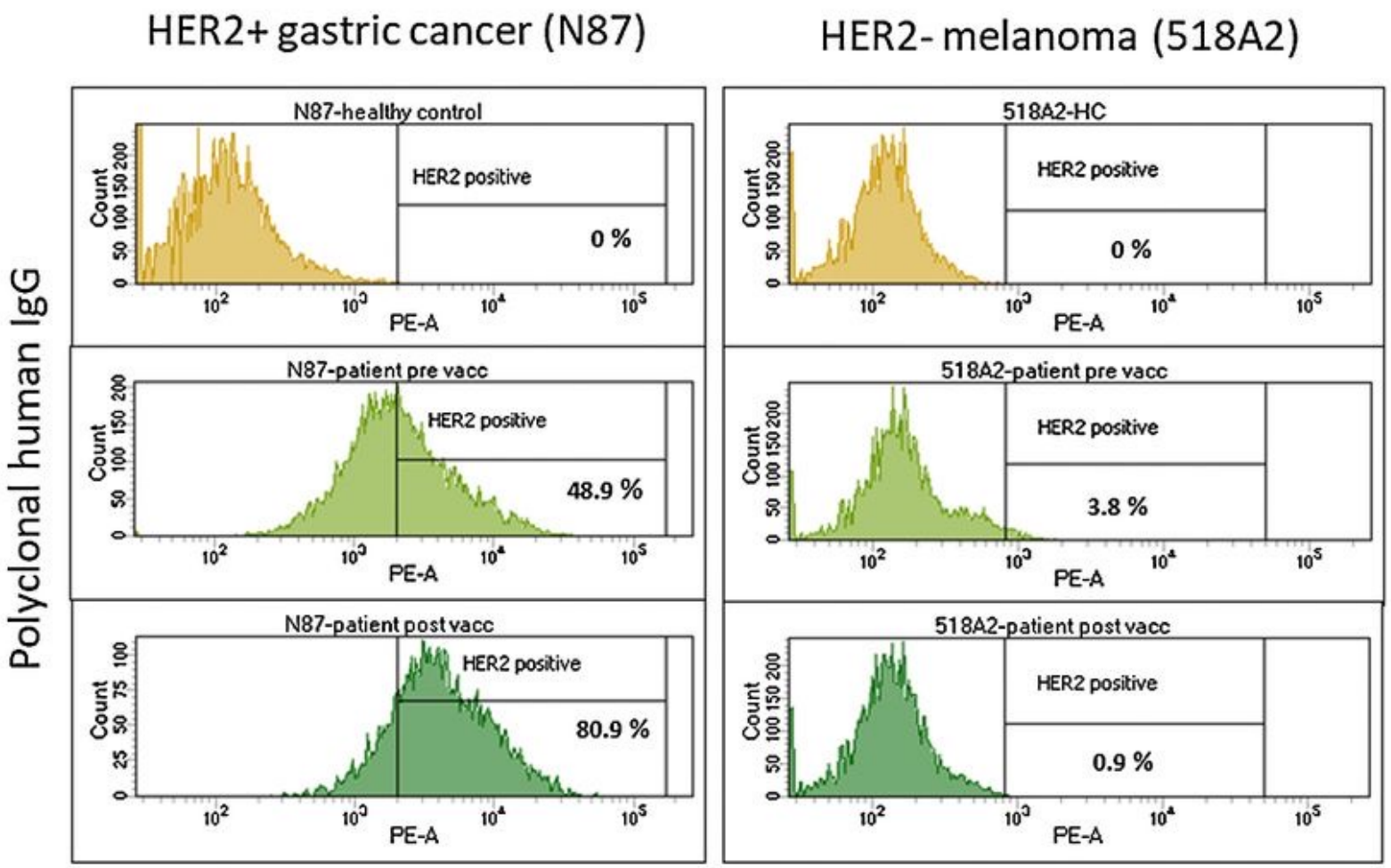


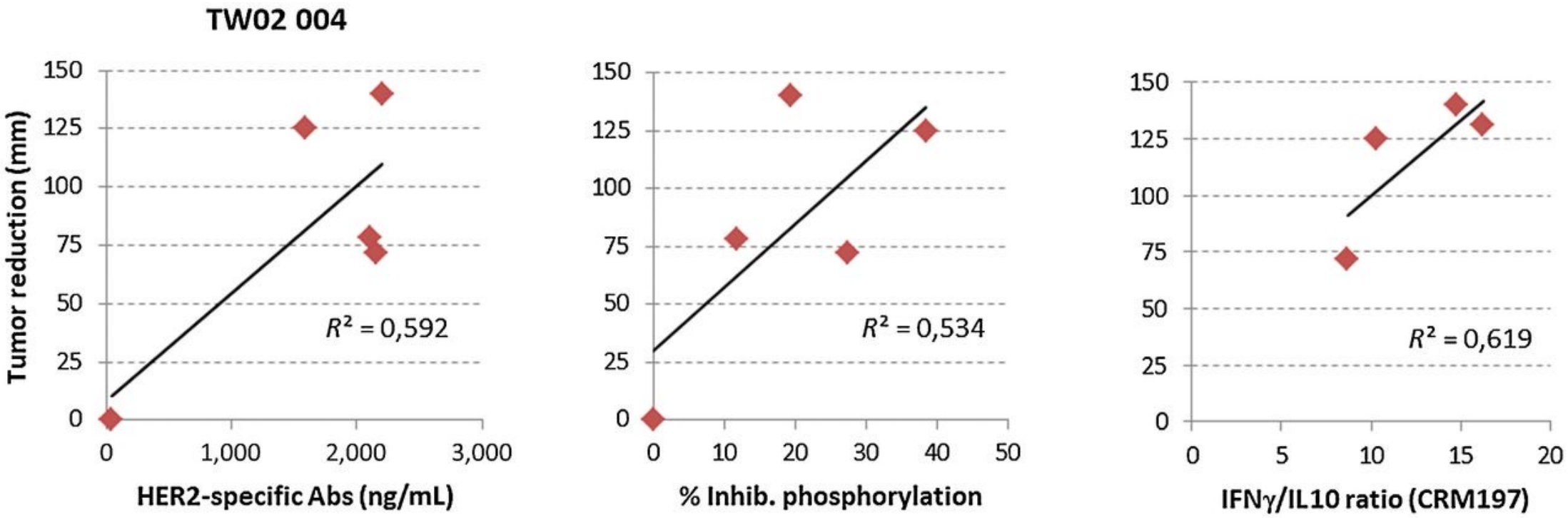
Flow cytometric binding analysis of patient Abs to N87 gastric cancer cells (15 µg of polyclonal patient IgG from d0 and after third vaccination).

Pre-vaccination patient IgG shows background binding on 48.9% of N87 cells, while post-vaccination IgG binds on 80.9% of cells.

No difference in IgG binding was observed on human HER2-negative 518A2 melanoma cells.

Wiedermann et al. Clin Cancer Res 2021;27:3649-3660

HER-Vaxx Phase 1b: Correlation of tumor reduction and (1) HER2-specific IgG, (2) inhibition of HER2 phosphorylation, and (3) CRM197-specific cytokine ratios



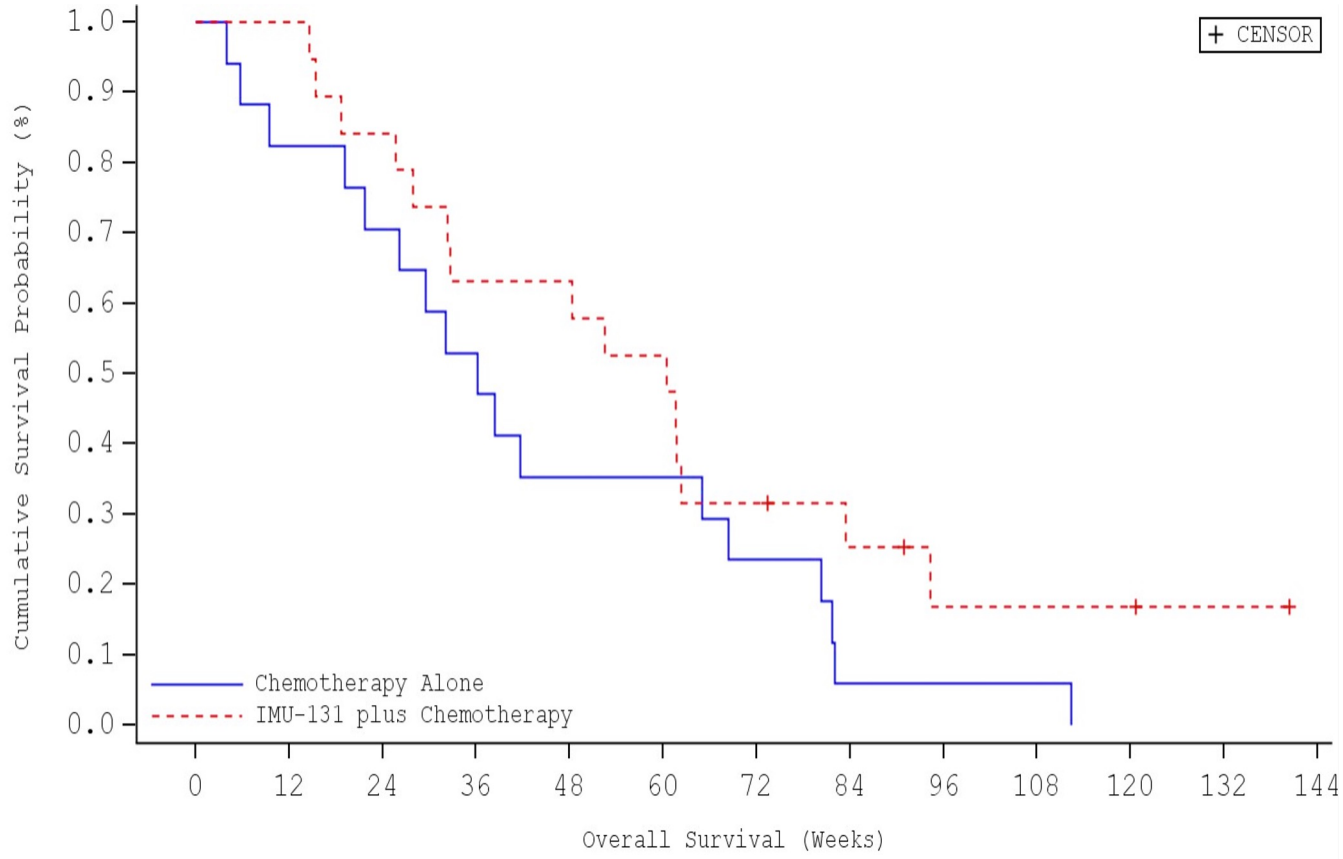
Changes in tumor size (SODs in mm vs. d0) correlated with HER2-specific IgG Abs levels, with percent inhibition of HER2 phosphorylation and with CRM197-specific IFNγ/IL10 ratios for patient TW02004 (Cohort 3): coefficient of determination r^2 (+ or −) shown in graph.

Wiedermann et al. Clin Cancer Res 2021;27:3649-3660

HERIZON HER-Vaxx PHASE 2:

OVERALL SURVIVAL

END POINT	OVERALL SURVIVAL Final OS Readout	
Treatment	HER-Vaxx + Chemotherapy	Chemotherapy Only
Sample Size	19	17
Events	15	17
Median OS (2-sided 80% CI)	13.9 months (7.5, 14.3)	8.3 months (6.0, 9.6)
Median Duration of Response	30 weeks	19 weeks
HR	0.585	
2-sided 80%CI	(0.368, 0.930)	
Log-rank Test (1-sided p-value)*	0.066 +	



* Pre-specified alpha at 0.10
\+ Statistically Significant

HERIZON HER-Vaxx PHASE 2:

SAFETY

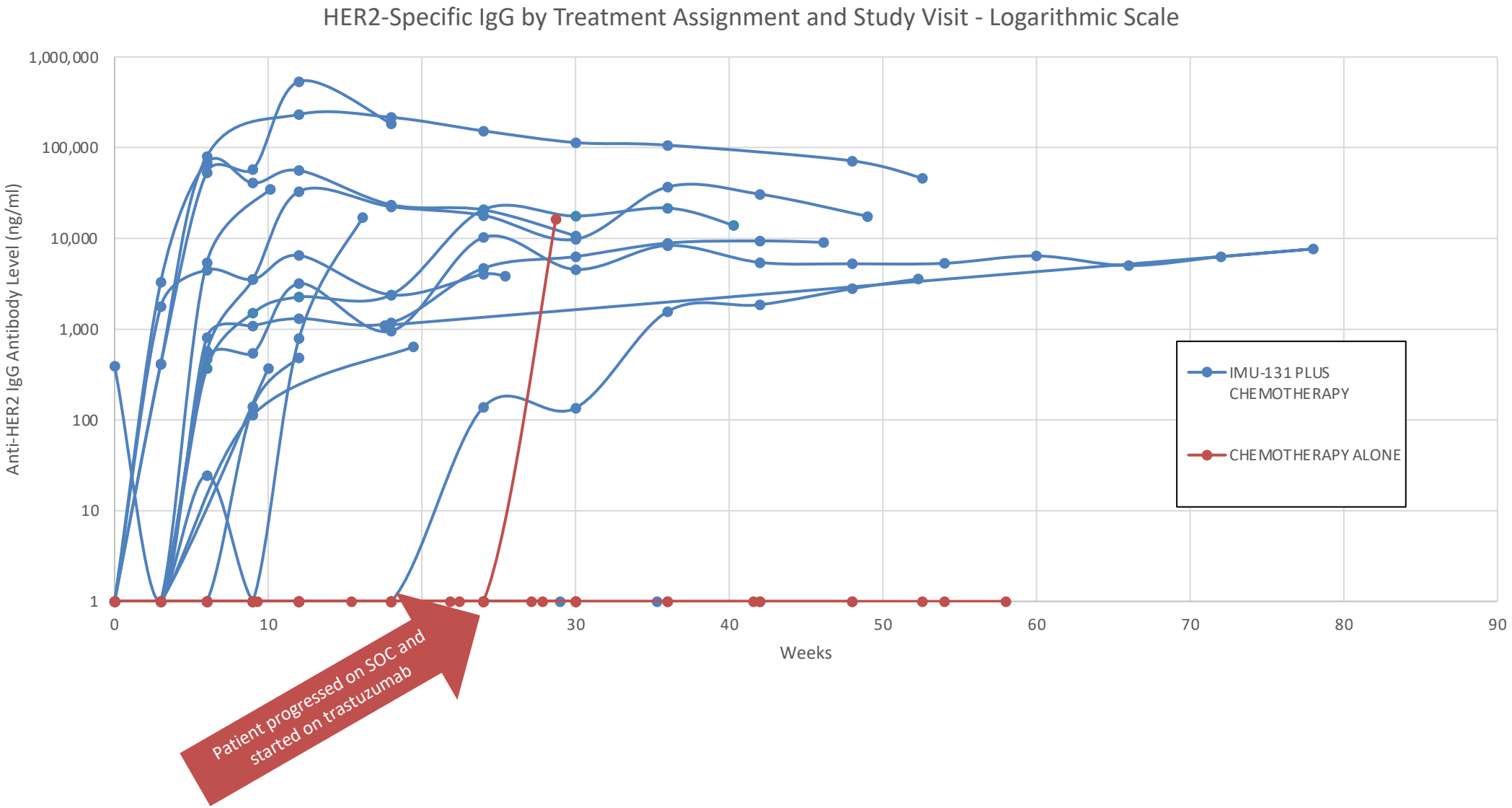
TREATMENT EMERGENT ADVERSE EVENTS

	HER-VAXX + CHEMOTHERAPY (N =1 9) n (%)	CHEMOTHERAPY ONLY (N =1 7) n (%)
Patients with at least one TEAE	18 (94.7%)	16 (94.1%)
Grade 1 / 2	10 (52.6%)	9 (52.9%)
Grade ≥ 3	8 (42.1%)	7 (41.2%)
Serious AE*	2 (10.5%)	5 (29.4%)
Fatal AE	1 (5.3%)	1 (5.9%)

*SAEs are also included in the ≥3 AE. N = number of patients in the treatment arm at final analysis. n = number of patients who experienced the event.

HERIZON HER-Vaxx PHASE 2:

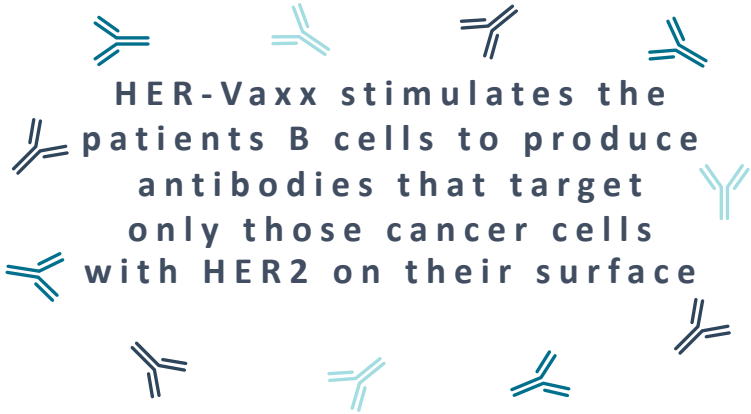
HER-2 ANTIBODY DEVELOPMENT PER PARTICIPANT

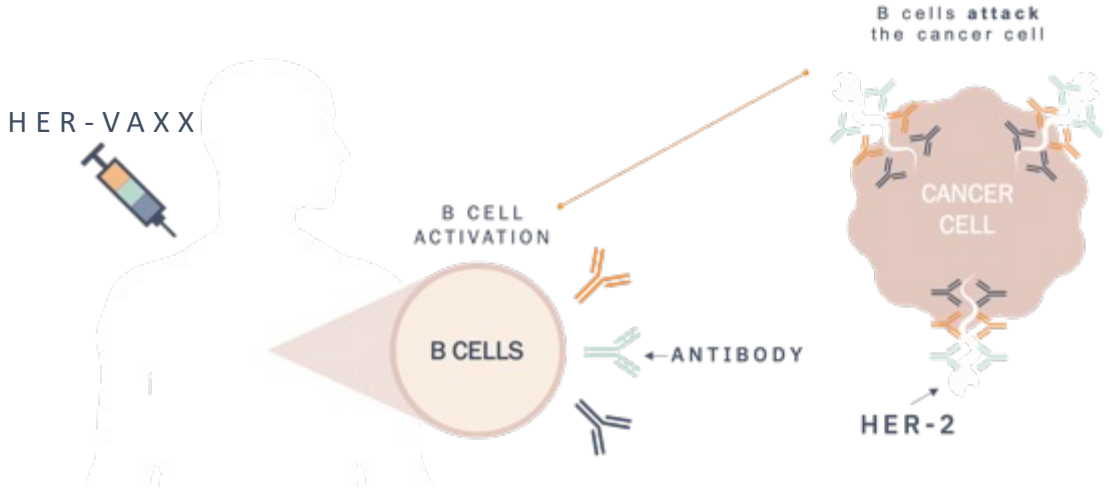


Note: Antibodies were analysed from all enrolled patients. Values below LLOQ are represented as “1”.

HER-Vaxx B-CELL VACCINE SUMMARY

- HER-Vaxx is a B-cell immunotherapy designed to treat tumours that over-express the HER2/neu receptor, including gastric and breast cancer
- The immunotherapy is constructed from three B cell epitopes derived from the extracellular domain of HER2/neu (patent protected to 2036)
- HER-Vaxx is under development for the treatment of HER2-positive gastric cancer, and also has the potential to treat other HER2-overexpressing cancers (breast, CRC, lung)
- HER-Vaxx has been shown in pre-clinical studies and now in a Phase I and 2 studies to stimulate a potent polyclonal antibody response to HER2/neu, a well-validated cancer target
- HER-Vaxx available for territorial partnering and/or licensing



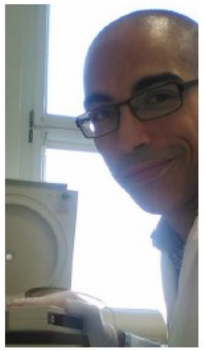


Special Acknowledgements – R&D team in Vienna

B Cell Immunotherapy
IMUGENE

MEDICAL UNIVERSITY OF VIENNA

Prof. Dr. Ursula Wiedermann



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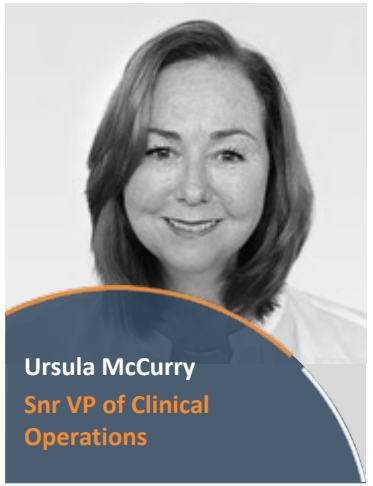
piCHEM

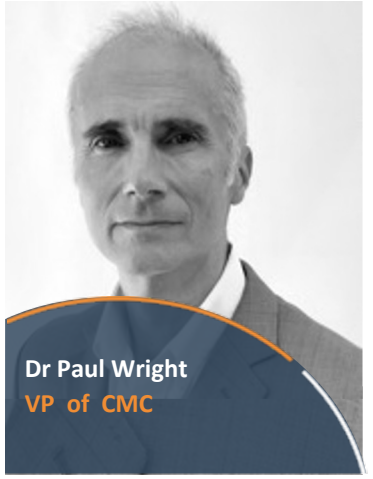
BACCINEX SA

IMUGENE'S MANAGEMENT TEAM

IMUGENE
Developing Cancer Immunotherapies

Experienced management team with significant clinical development expertise





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