GAPVAC

Glioma Actively Personalized Vaccine Consortium

-The GAPVAC for patients with newly diagnosed glioblastoma-

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Abstract Poster Number: O8

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Disclosure

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- I have no conflicts of interest to report in relation to this project.

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Thanks to

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- All patients and their families
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- EU FP7

SEVENTH FRAMEWORK PROGRAMME

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

REGION H

BCN PEPTIDES

immatics

BIONTECH

Heidelberg University Hospital

UNIVERSITÉ DE GENÈVE

FACULTÉ DE MÉDECINE

LUMC

LEIDS UNIVERSITAIR MEDISCH CENTRUM

Vall d'Hebron Hospital

CIMT Cancer Immunotherapy

TECHNION Israel Institute of Technology

UNIVERSITY OF Southampton

UCSF University of California San Francisco

Oncovir, Inc.

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Background

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- Gliomas have modest non-synonymous mutations (30-60/case)
- Checkpoint blockade therapies are not effective for gliomas with possible exception for hypermutated cases (e.g. mismatch repair deficiency)
- Nonetheless, encouraging T cell responses have been observed to **non-mutated glioma-associated antigens** in clinical trials (e.g. IMA-950)
- Personalized vaccines should exploit the **full repertoire** of antigens; both mutated (neo-epitopes) and non-mutated antigens which are overexpressed by glioma cells

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Objectives

- Primary endpoints were safety, tolerability, immunogenicity and the operational feasibility of the regimen in newly diagnosed glioblastoma (GB) patients.
- GAPVAC aims at integration with standard-of-care radiation therapy (RT) and temozolomide (TMZ)-based chemotherapy through an international study group.

Combining mutated and non-mutated peptides

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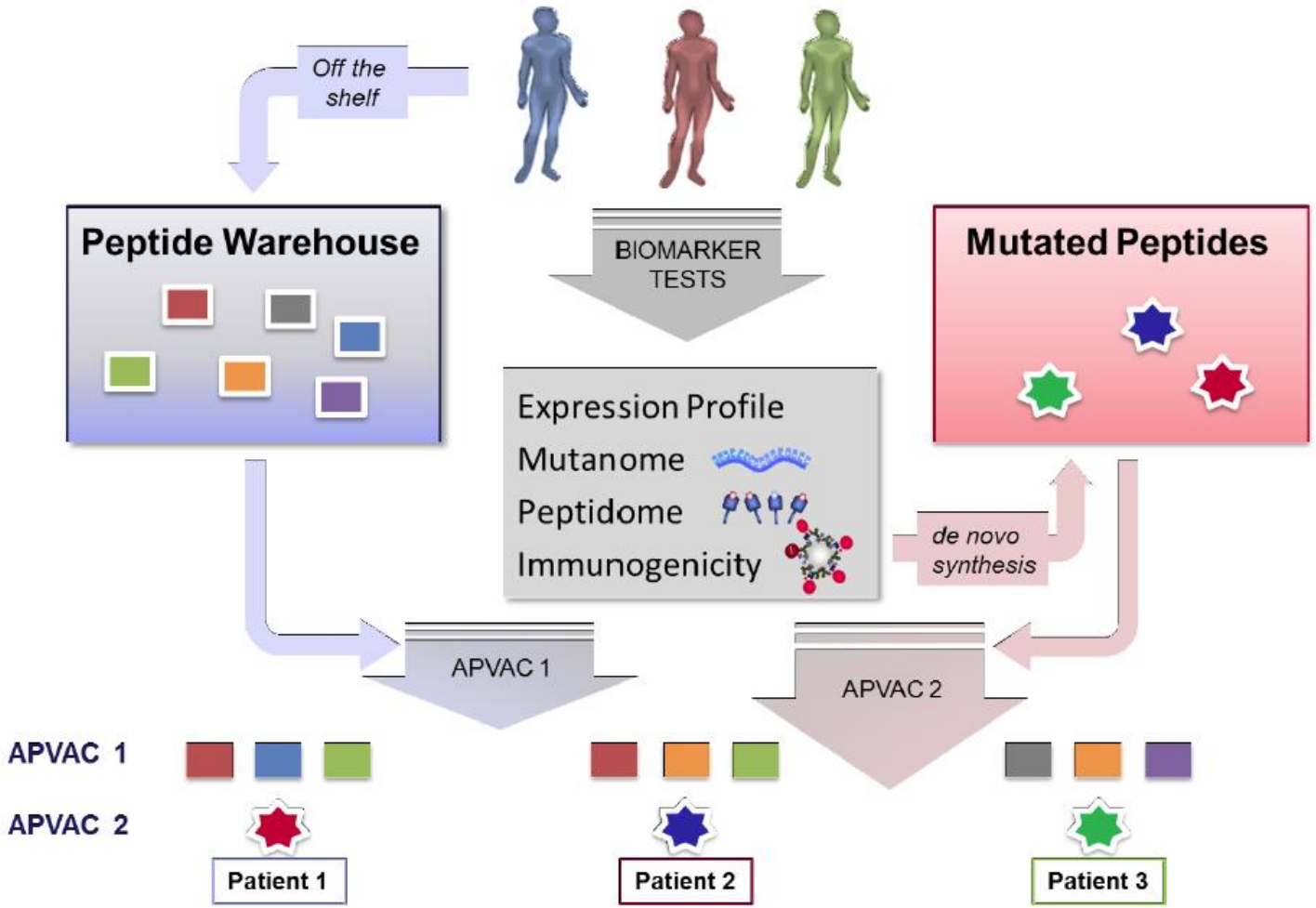
- APVAC1: Non-mutated, “off-the-shelf” peptides from the Peptide Warehouse (approx. 60 pep; Immatics)
- APVAC2: Patient-specific mutated peptides by “on-demand” synthesis



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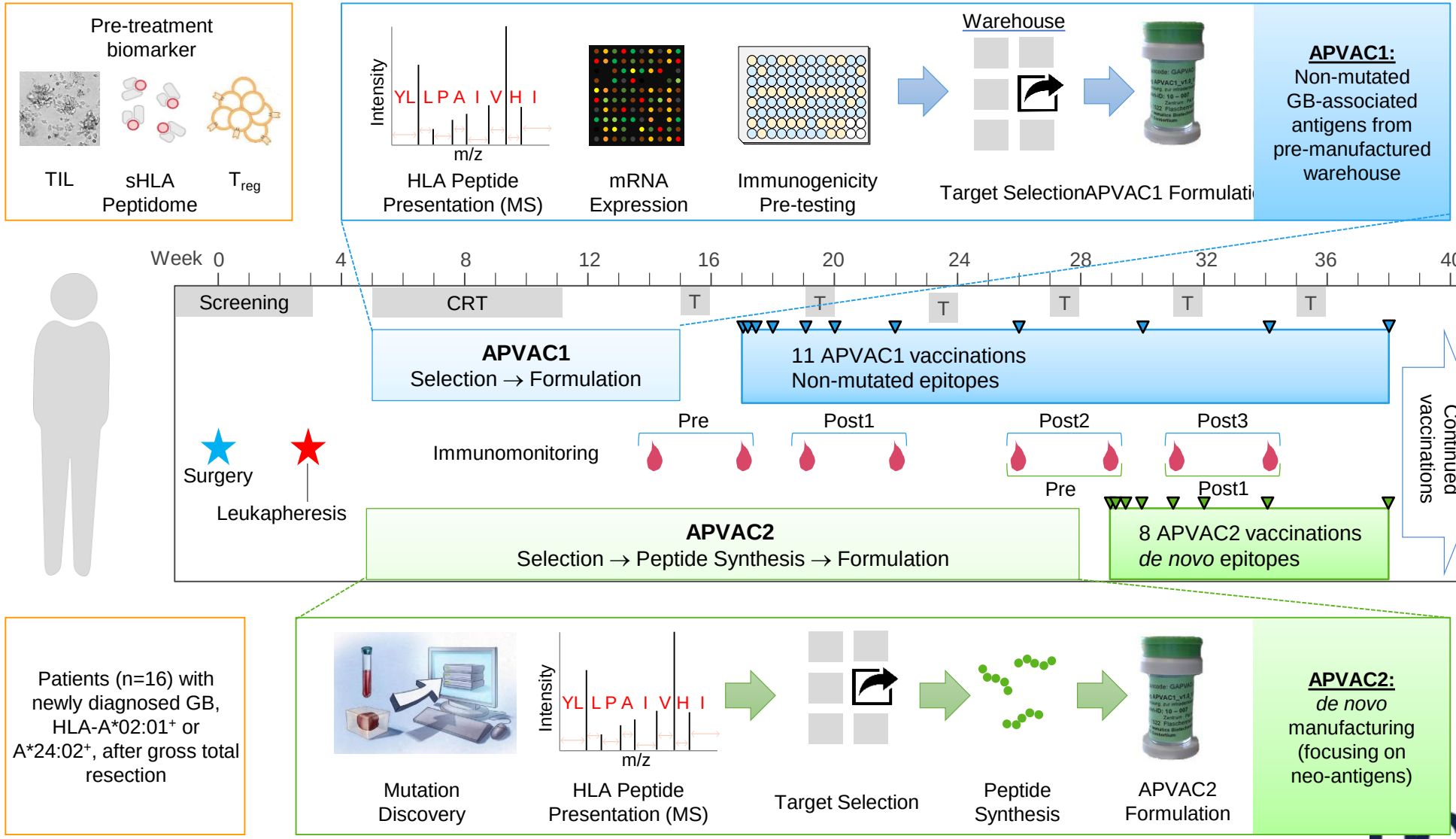
GAPVAC trial overview

GAPVAC



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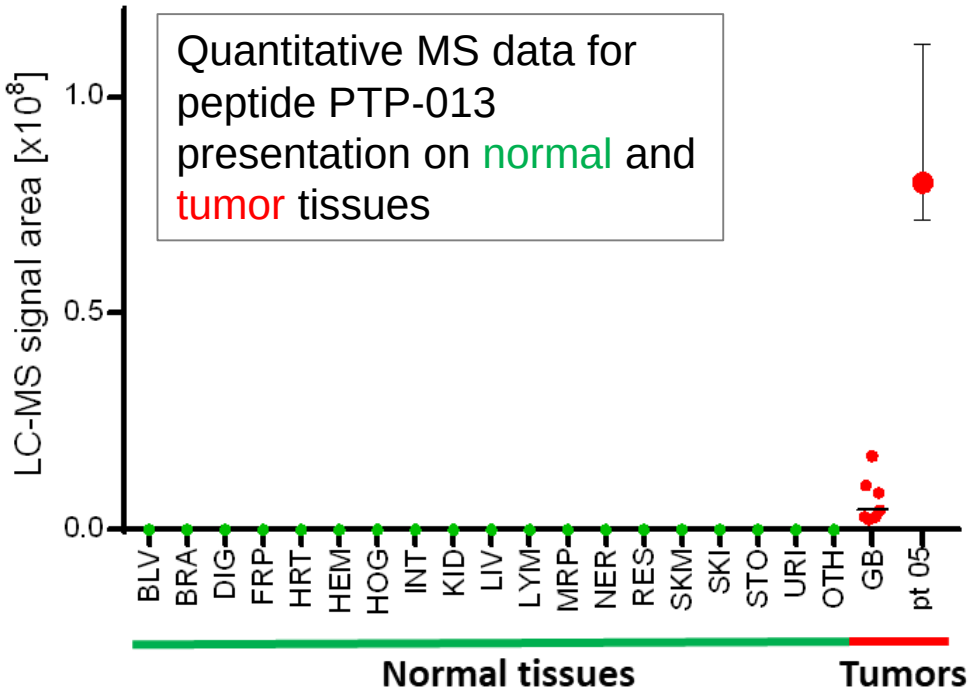
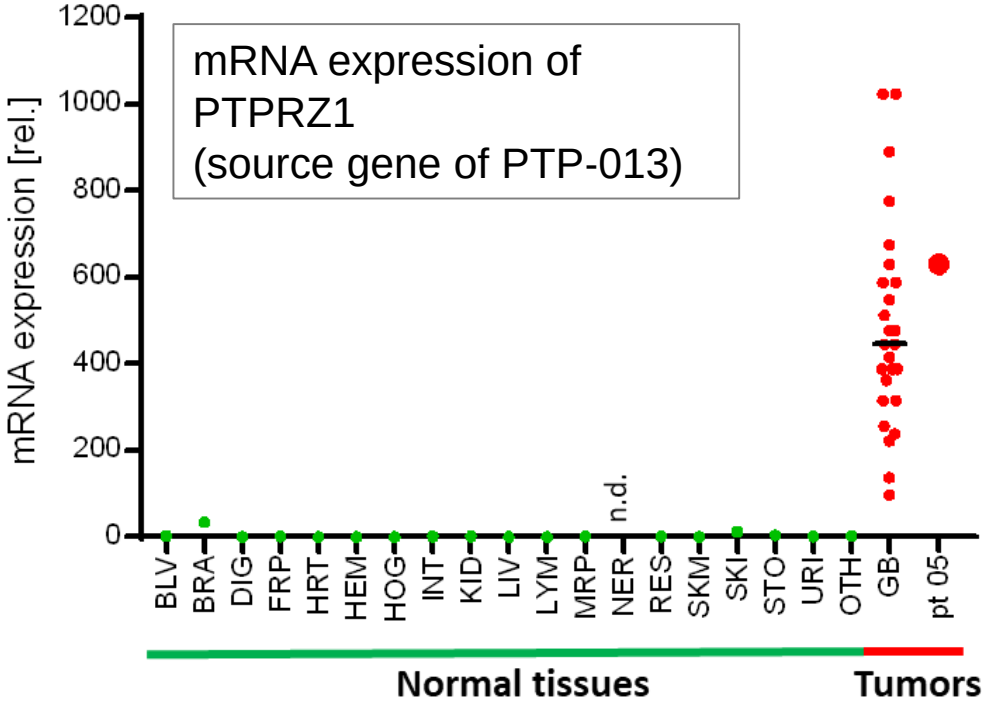
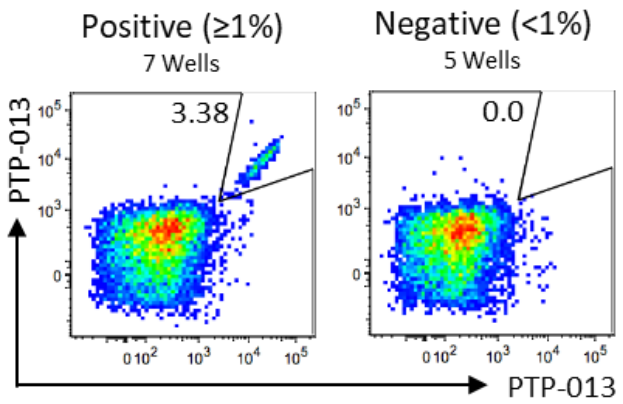
APVAC1: From a warehouse of non-mutated antigens to truly personalized vaccine formulations

GAPVAC







Immunogenicity testing data for PTP-013 in pre-treatment leukapharesis-derived PBMC of patient 05

GAPVAC Warehouse

33 A*02-restricited peptides

NLGN4X-001	NLDTLMTYV
NRCAM-001	GLWHHQTEV
PTP-005	KVFAGIPTV
PTP-013	MIWEHNVEV

26 A*24-restricited peptides

GMP drug substance pre-manufactured

APVAC1 for patient 05

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Main eligibility criteria

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- Histologically confirmed, newly diagnosed GB
- HLA-A*02:01 or HLA-A*24:02 positivity
- Gross total resection (< 1 cm^2 residual tumor on < 48 h MRI T1Gd+)
- At least 0.5 g tumor tissue freshly cryopreserved during surgery
- Age ≥ 18 years, KPS ≥ 70%
- Candidate for and willing to receive standard RT+TMZ
- Steroids ≤ 2 mg/day dexamethasone
- Availability of an APVAC manufacturing slot confirmed by the sponsor

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APVAC compositions

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Day	1	2	4	8	15	22	36	every 4 wks.
APVAC (400 µg i.d.)	●	●	●	●	●	●	●	●
GM-CSF (75 µg i.d.)	●	●	●	●	●	●	-	-
poly-ICLC (1.5 mg s.c.)	●	-	●	●	●	●	●	●

	APVAC1 (warehouse selected)	**APVAC2 (*de novo* manufact-ed)**
Composition	I. Up to **7 non-mutated HLA class I** peptides; individually selected and formulated from a pre-manufactured warehouse of GB-associated peptides **II. 2 pan-DR binding HLA class II**-restricted tumor-associated peptides III. 1 HLA class I viral marker peptide	**2 peptides** via one of the following tracks: I. mutation-containing, **MHC-presentation confirmed by MS** (HLA class I or class II) II. mutation-containing, predicted HLA presentation **and immunogenicity** (19mers) **III. non**-mutated HLA class I peptides (**presentation confirmed by MS**, not part of warehouse)
Vaccination	**11 x within 21 wks. starting day 15 of 1st TMZ cycle**	**8 x within 9 wks. starting day 15 of 4th TMZ cylce**

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Safety profile was as expected from the underlying disease and the vaccine's mechanism of action

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- All 15 patients presented Grade 1 or 2 adverse events (AE) that were related to the study drug.
- Injection site reactions, mainly of grade 1 or 2, were the most frequent study drug-related events.
- 2 patients experienced an anaphylactic reaction after receiving APVAC vaccines, poly-ICLC and GM-CSF.
- One patient experienced a potentially regimen-related Grade 3 brain edema.

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Summary of immune responses to APVAC1 (N=13)

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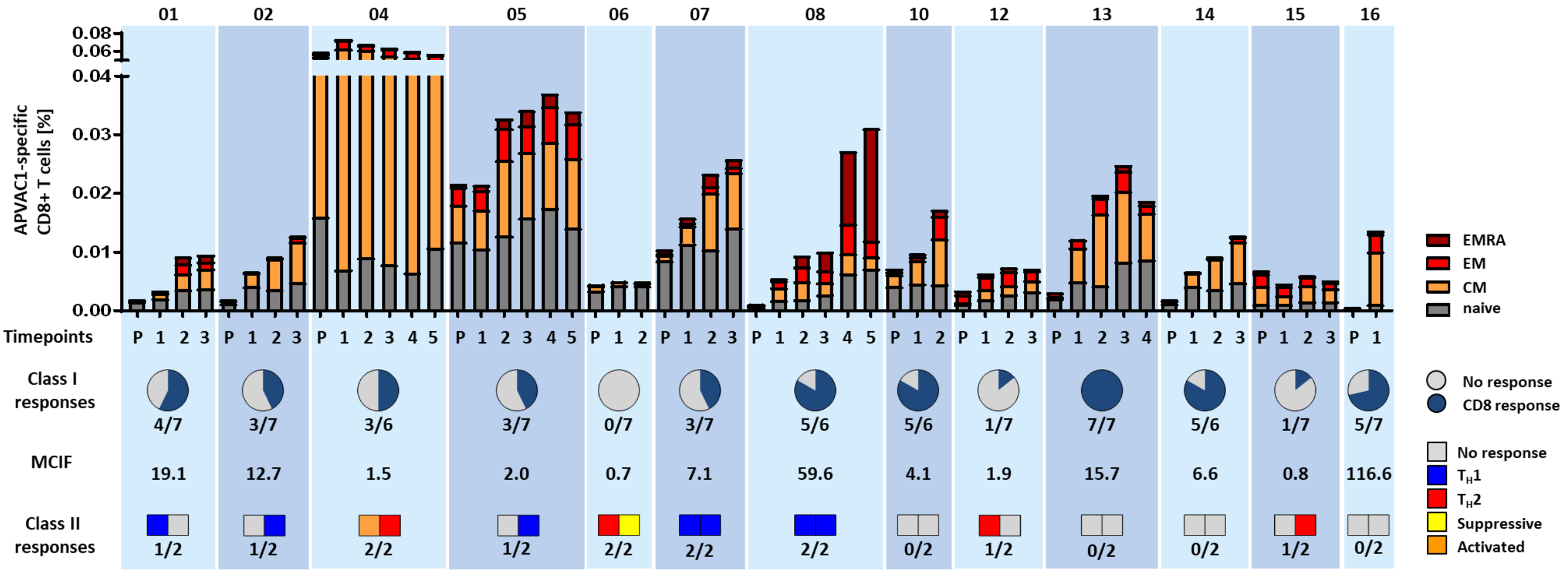

Immunogenicity summary for non-mutated warehouse antigens and neoantigens

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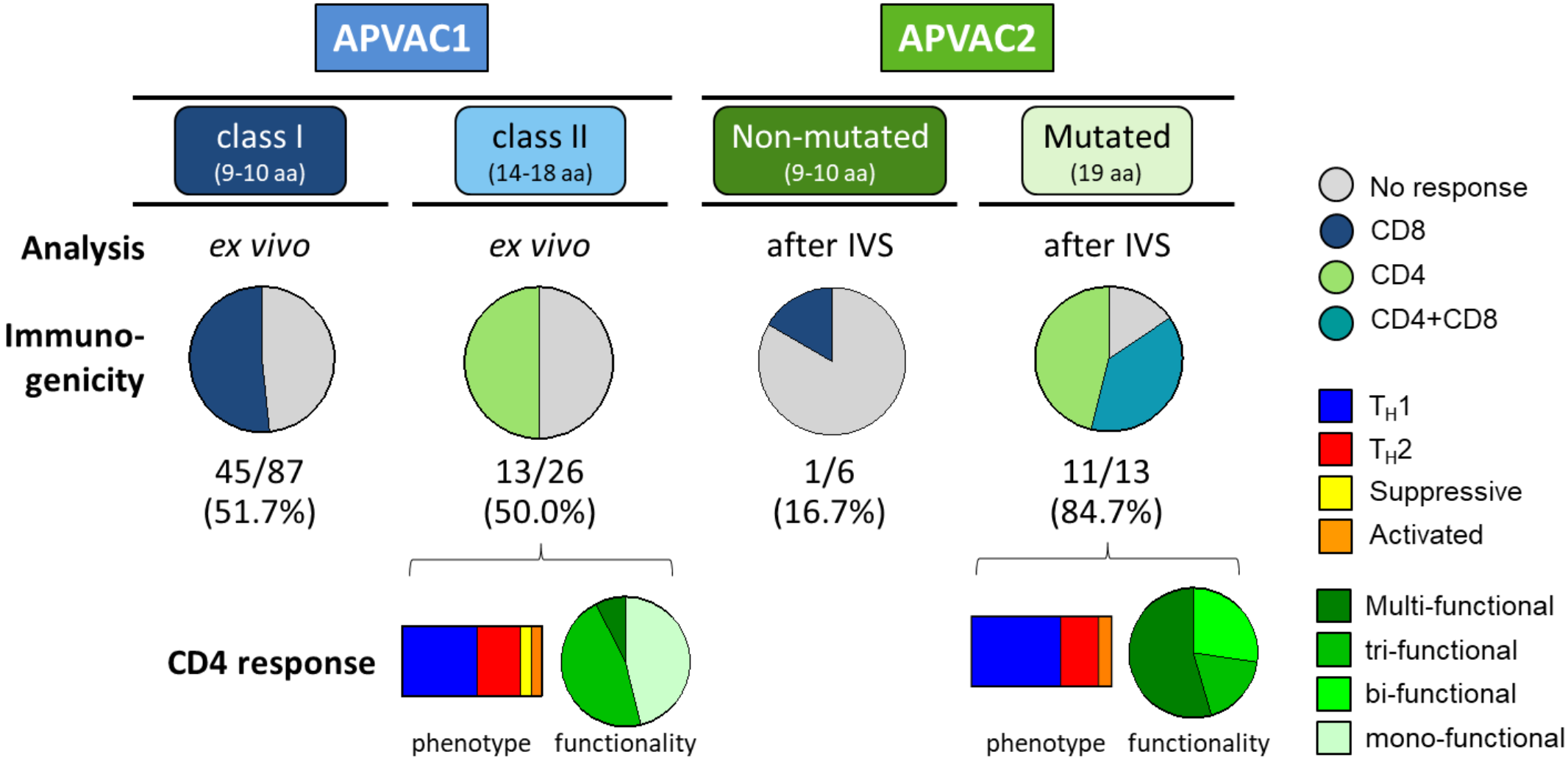

IVS = *in vitro* sensitized

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Patients' clinical course

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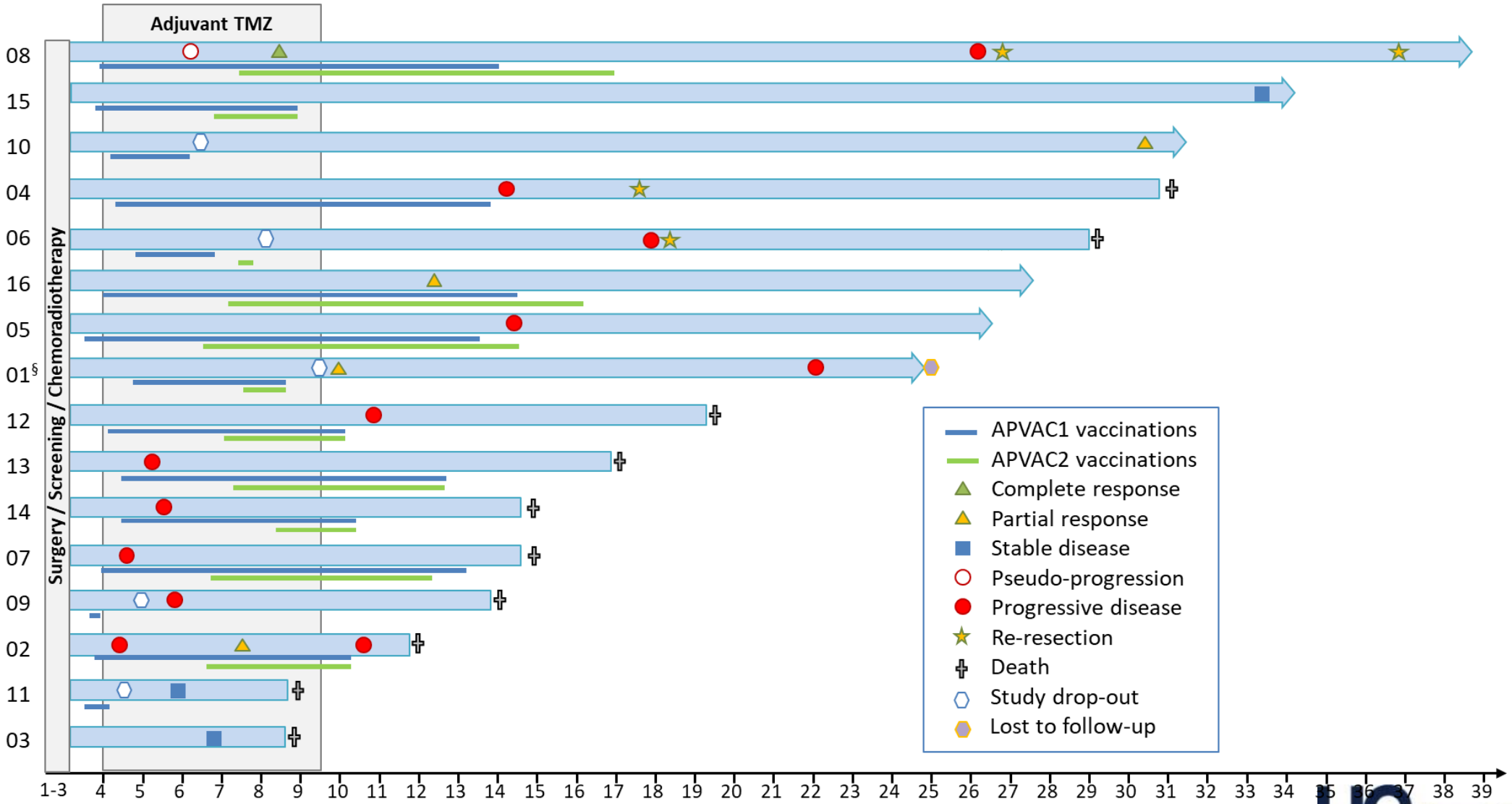

§ after V7* patient started a different experimental therapy

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Intratumoral T cells in patient 08 and response to the APVAC1 class II peptide PTP-010

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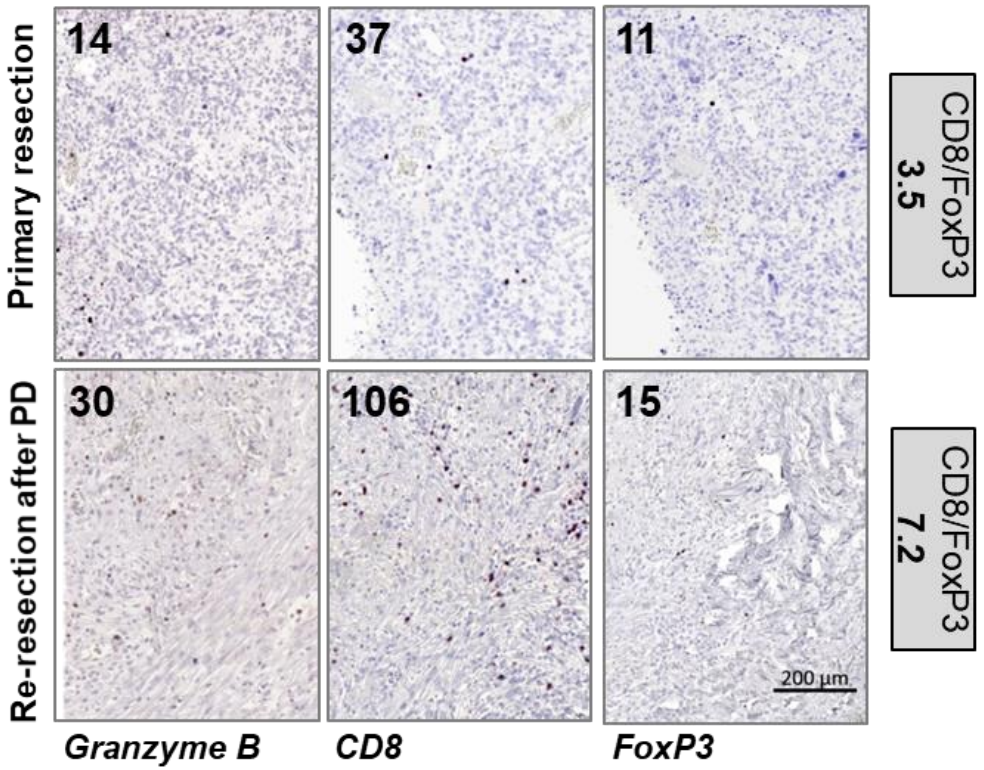
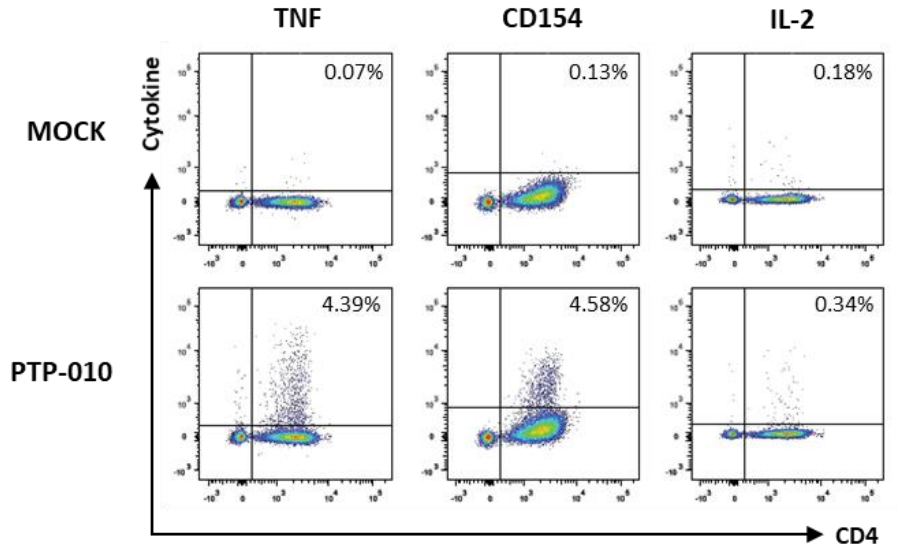
Immunohistochemistry on tumor sections



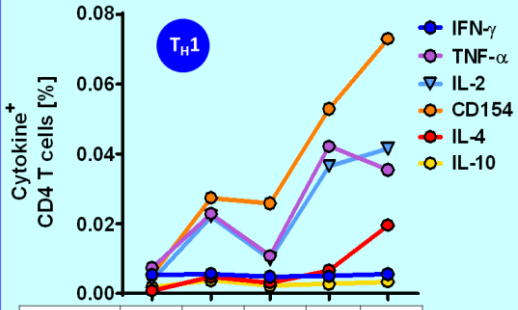
ICS from TIL at re-resection – PTP-010



Intratumoral

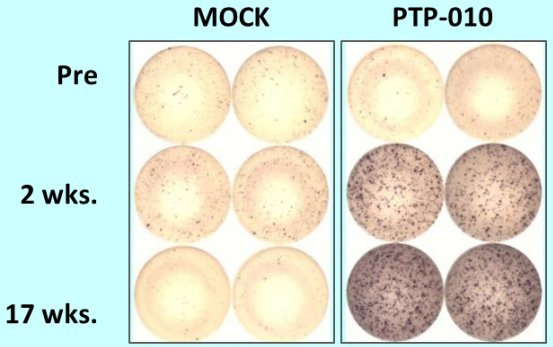
PBMC

Ex vivo ICS – PTP-010



	Pre	Post1	Post2	Post3	Post4
APVAC1 vaccinations	-	4/6	7/8	9	11
Weeks post 1st APVAC1	-	2/5	11/15	21	29

IFN-γ ELISpot – PTP-010



GAPVAC-101 – Trial conclusions

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- Safety: expected safety profile, well tolerated
- Feasibility:
  - Selection and manufacturing was successful
  - However, MS-peptidome analysis did not detect any of the predicted mutated epitope for APVAC2 from > 600 mutations.
- Immunogenicity:
  - Short, non-mutated APVAC1 antigens induced sustained central memory $CD8^+$ T-cell responses
  - Predicted neo-epitopes in APVAC2 demonstrated high immunogenicity predominantly as $CD4^+$ T_H1 T-cell responses
- Clinical effects: encouraging signals, but small sample size

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GAPVAC-101 – Implications

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- APVAC1: In tumors with low mutation load, inclusion of carefully selected, off-the-shelf (i.e. warehouse) non-mutated antigens is reasonable.

- APVAC2: Inclusion of *on demand*-manufactured neo-antigen peptides is possible, but still challenging.
  - Need to improve mass-spect/peptidome-based identification of HLA-presented mutated peptides.
  - Chemical properties of peptides- Other modalities may also be considered (e.g. RNA with other drawbacks)
  - Regulatory guidelines for individualized peptide drugs may be refined.

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I am stopping my talk

But our work will never stop at any time!

THANK YOU!

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Survival data

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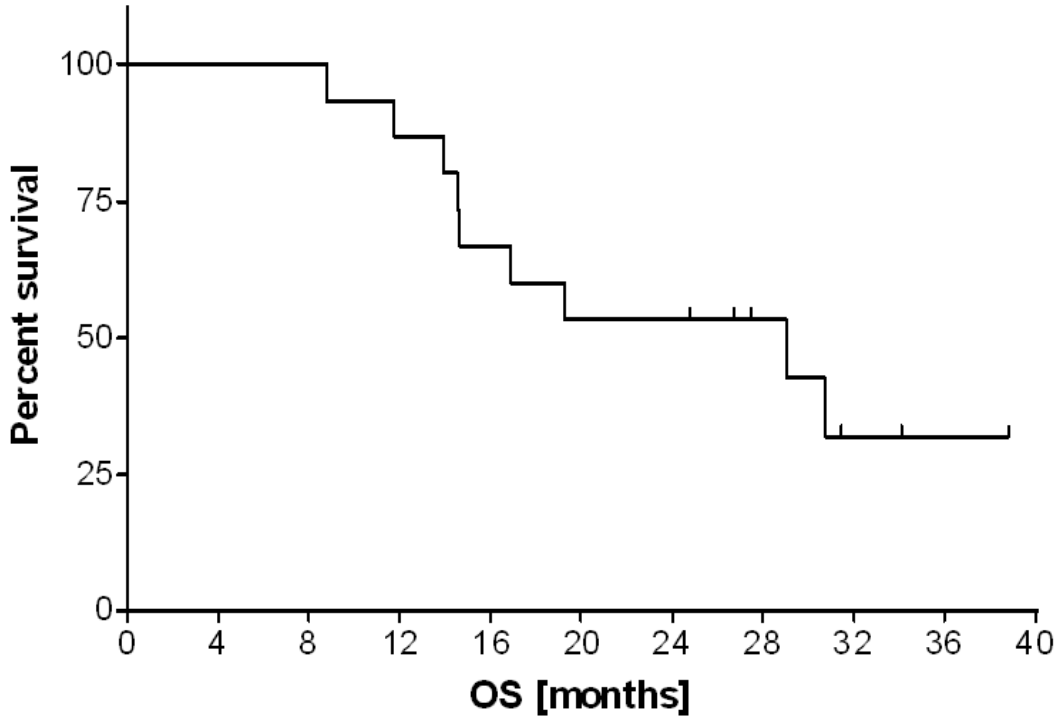

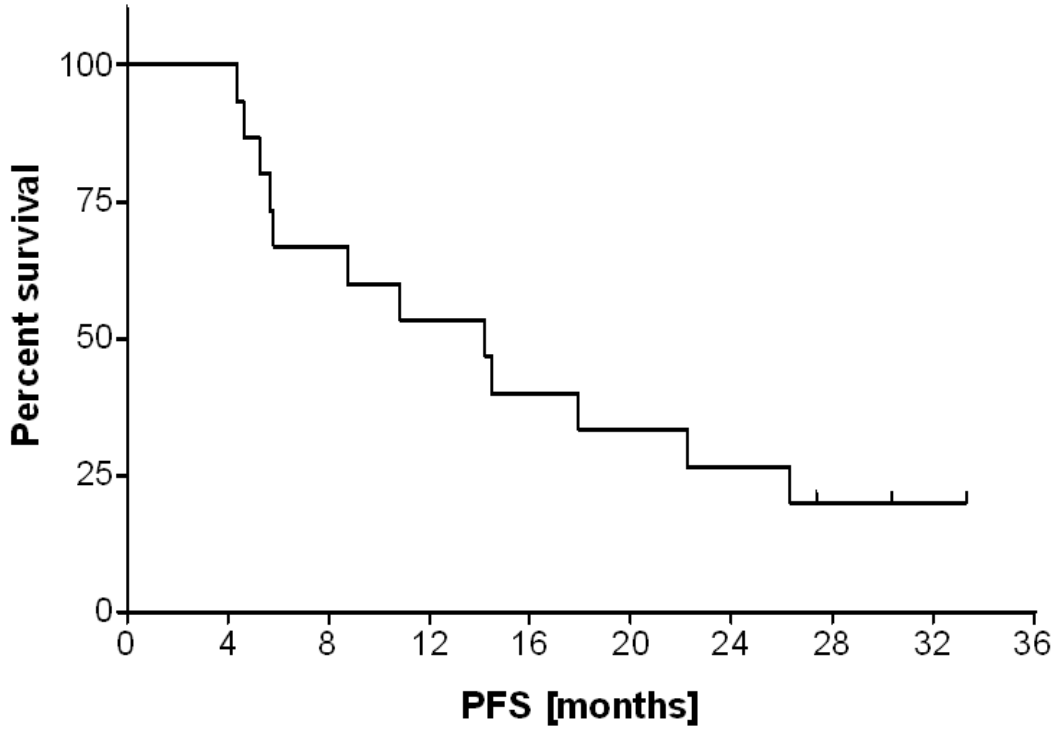

Censored subjects	6 (40%)
Deaths	9 (60%)
Median OS [months]	**29.0**
Median follow-up [months]	31.5

Censored subjects	3 (20%)
Events	12 (80%)
Median PFS [months]	**14.2**

Median OS in historical control for newly diagnosed GBM with GTR =18.9 months

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APVAC composition

GAPVAC

	APVAC1
Composition	**I. Up to 7 non-mutated HLA class I peptides**; individually selected and formulated from a pre-manufactured warehouse of GB-associated peptides **II. 2 pan-DR binding HLA class II-restricted tumor-associated peptides** (not personalized) **I. 1 HLA class I viral marker peptide** (not personalized)
Formulation	**578 µg peptide per vial in 700 µL 33% DMSO** **(500 µL ≈ 400 µg per peptide per vaccination**
Vaccinations	**11 x within 21 wks. starting day 15 of 1st TMZ cycle**

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