Translational analyses of the DeCidE[1] clinical study in advanced ovarian cancer patients reveal a substantial role for B cells in the clinical benefit derived from maveropepimut-S (MVP-S) treatment

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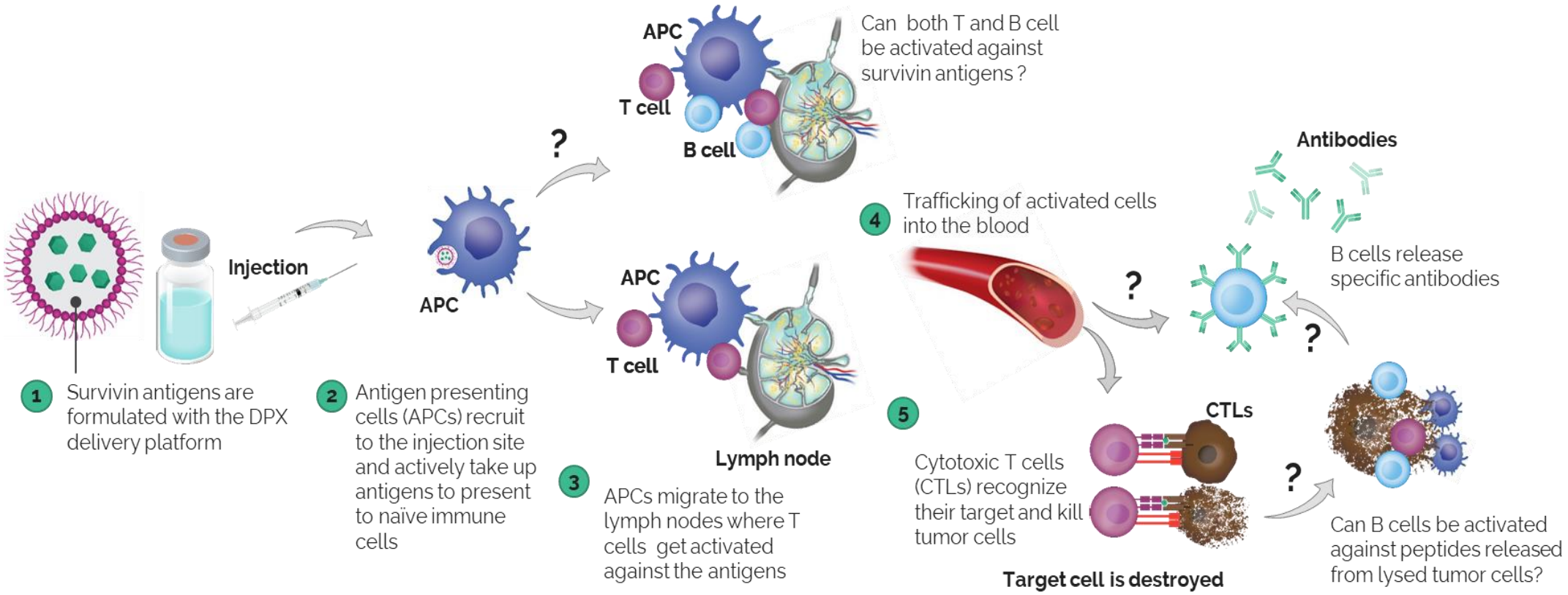
Maveropepimut-S (MVP-S) – a B Cell Activating Therapy?



- MVP-S, formerly DPX-Survivac, is an immune-educating therapy packaging 5 HLA class I peptides derived from the tumor antigen, survivin
- **Potential mechanism of action**: B cell activation driven by MVP-S is either directly by MVP-S or indirectly by antigens released from lysed tumor cells

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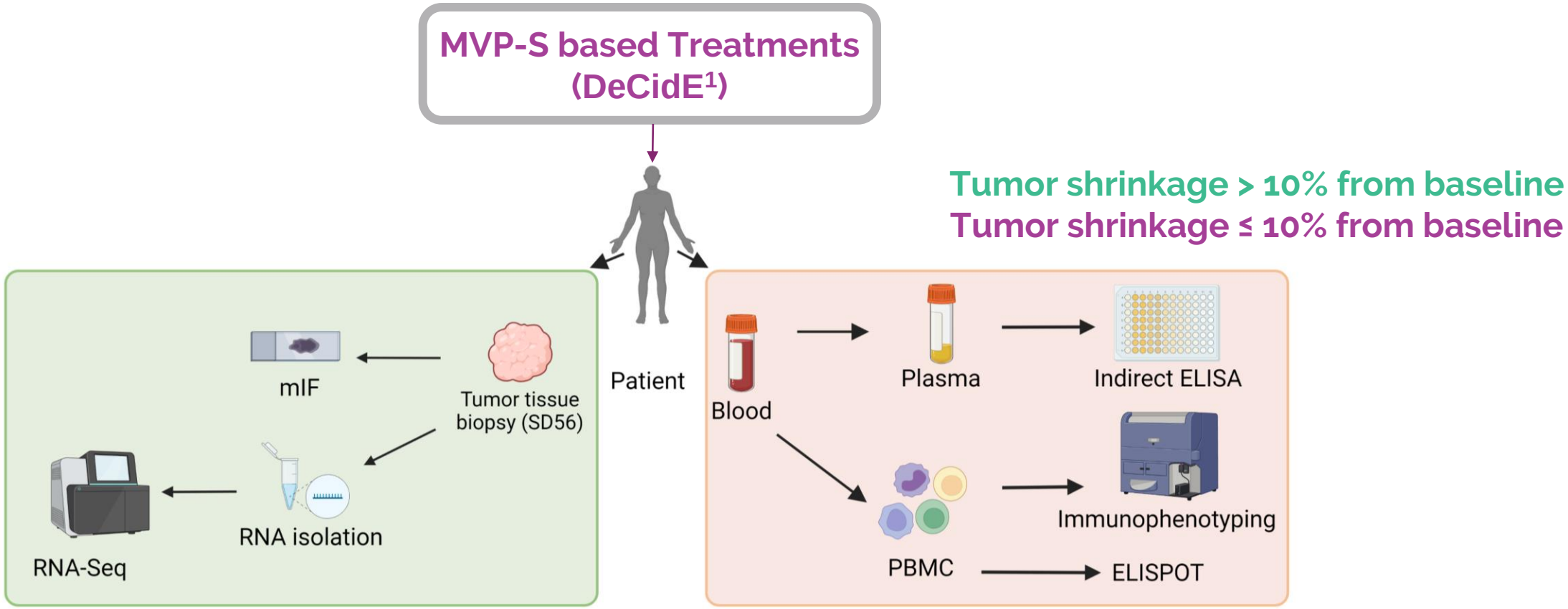
Materials & Methods



Baseline and on-treatment PBMCs, plasma, and tumor samples were collected from advanced ovarian cancer patients treated with MVP-S based therapy in the DeCidE[1] trial (NCT02785250). B cell populations were evaluated systemically using flow cytometry of PBMCs and by mIF and RNA sequencing of tumor tissue. Plasma IgG antibody responses against survivin peptides, recombinant survivin and TAAs were measured using indirect ELISA.

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Enriched B cell infiltration was detected in on-treatment tumor samples and was higher in patients with >10% tumor reduction

A

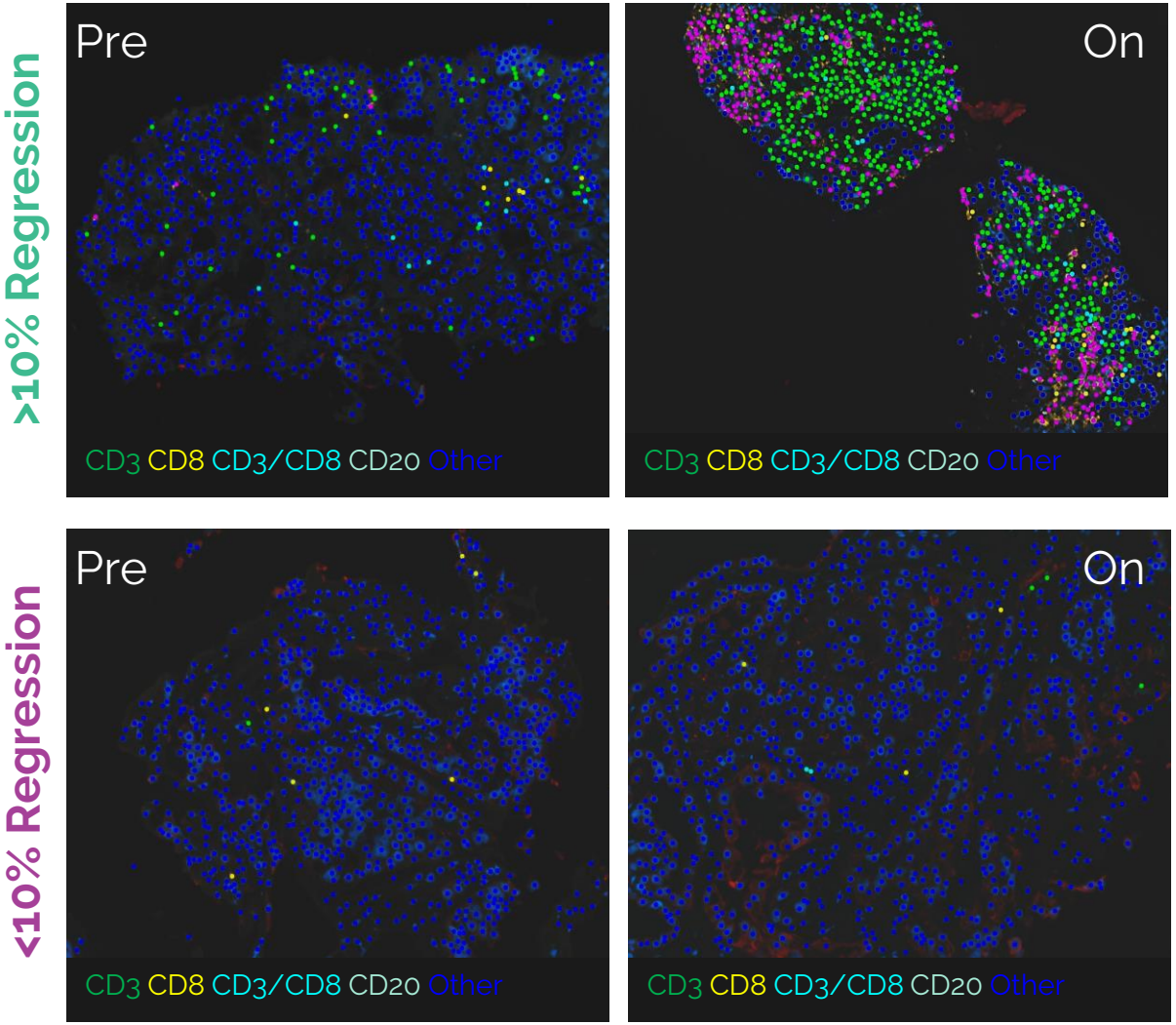

Figure 1A) Representative mIF images of pre- and on-treatment tumors from a patient with greater than **10% regression** of target lesion (top) and less than **10% regression** (bottom).

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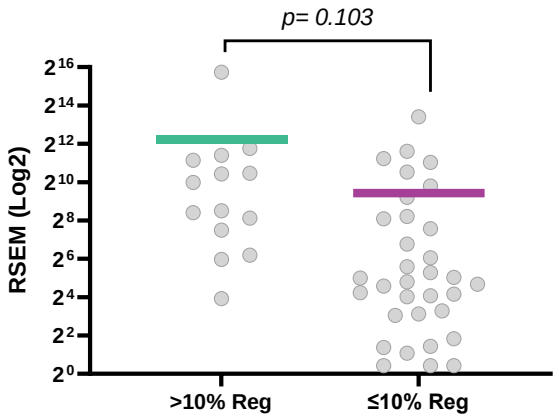
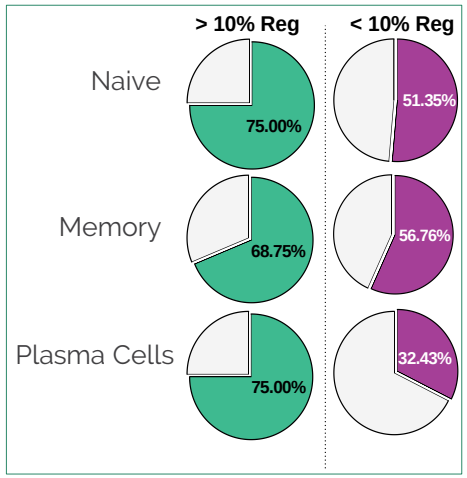
Enriched B cell infiltration was detected in on-treatment tumor samples and was higher in patients with >10% tumor reduction

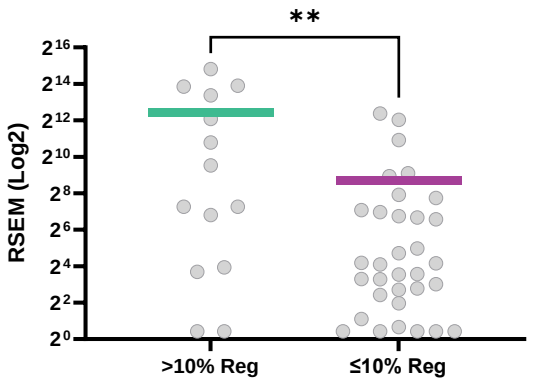
B Pre-treatment level of MS4A1 mRNA (CD20)



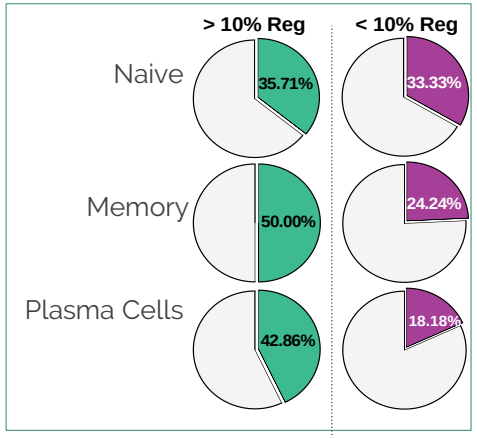
C % of subjects with infiltration pre-treatment



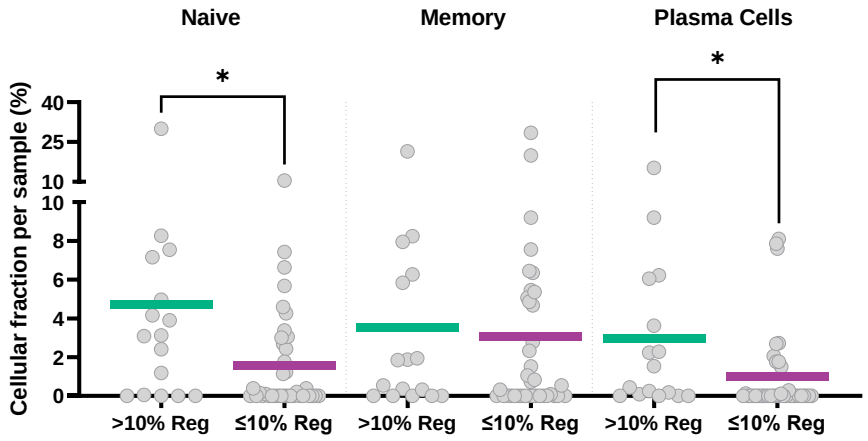
On-treatment level of MS4A1 mRNA (CD20)



% of subjects with increase in infiltration on-treatment



D B cell infiltration pre-treatment



Changes in B cell subsets in response to treatment

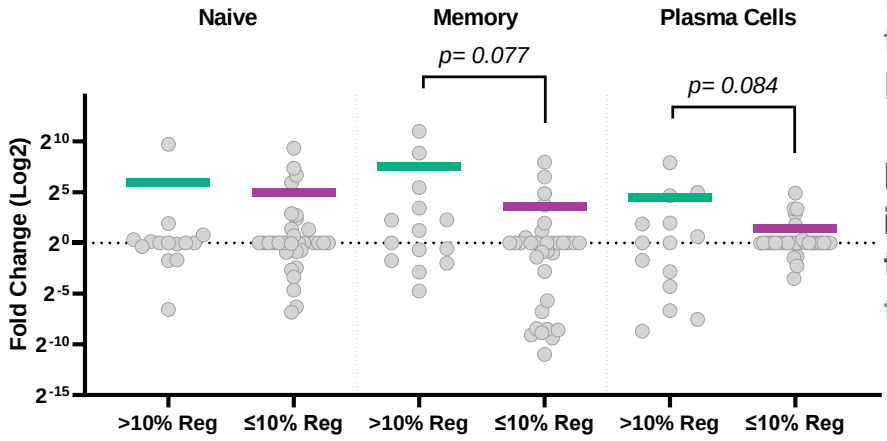


Figure 1 (B) Levels of total B cells represented by the levels of MS4A1 mRNA (CD20) in pre-treatment tumors (top) and in paired on-treatment tumors (bottom). **(C)** Percent of subjects in each response group with detectable infiltration of B cell subsets pre-treatment (top) and percent of subjects with increase in B cell infiltration on-treatment (bottom). **(D)** Relative frequencies of different B cell subsets in pre-treatment samples (top); and changes in B cell subset frequencies induced by treatment (bottom) presented as Log2 fold-change.

MVP-S treatment promotes infiltration of T and B cells into the tumors in subjects with >10% tumor reduction

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The frequency of systemic plasmablasts increased on-treatment

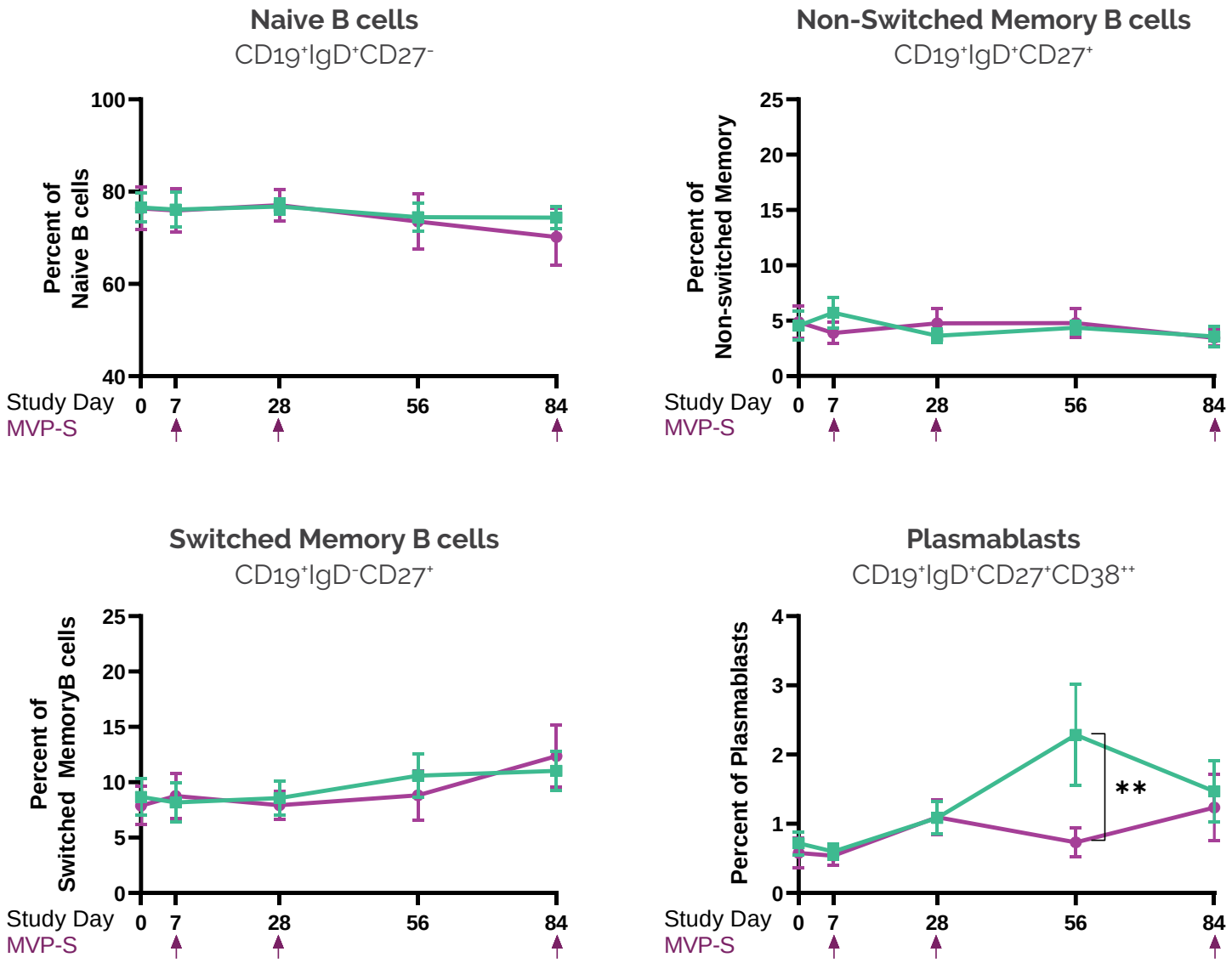

Figure 2. Frequency of naive, non-switched and switched memory B cell subsets sustain through the treatment. Consistent with detection of antibodies specific to MVP-S antigens in plasma samples frequency of plasmablasts increase after two MVP-S treatments in subjects with **>10% tumor reduction**.

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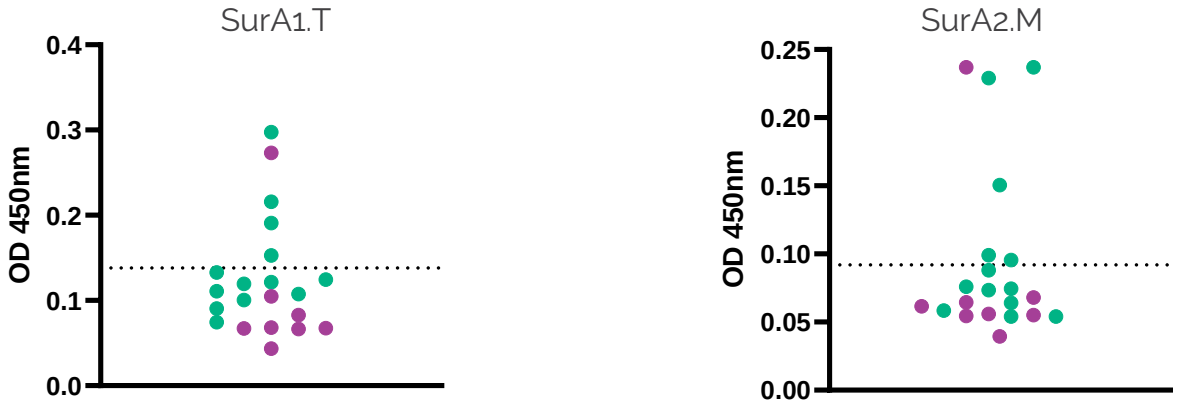
Antigen-specific antibodies are increased on-treatment and elevated in plasma of patients who achieved >10% tumor reduction (2 of 5 survivin peptides)

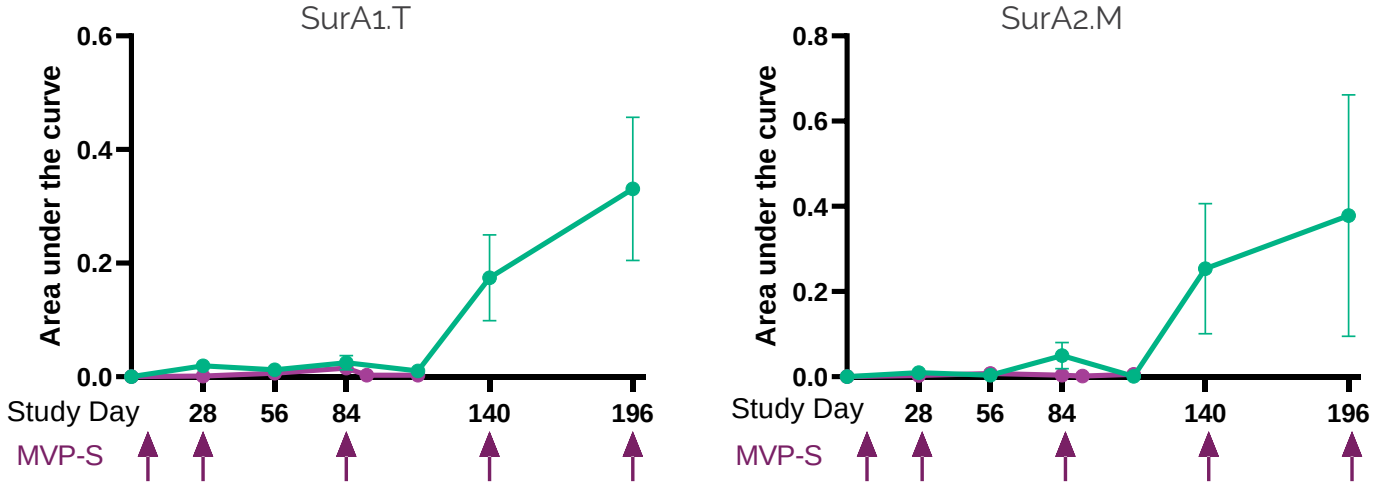
A

Pre-treatment levels



B

Increases on-treatment



N of samples

Study Day	0	28	56	84	92	112	140	196
>10% Regression (N)	13	5	13	10	--	1	8	6

N of samples

Study Day	0	28	56	84	92	112	140	196
≤10% Regression (N)	8	6	8	3	1	2	--	--

Figure 3 (A) Immunoreactivity against all five MVP-S peptides was detected in subset of samples collected prior to the first MVP-S treatment, demonstrating existence of natural survivin antibodies in a subset of cancer patients. Figure presents OD values obtained at the lowest sera dilution in indirect ELISA, healthy control samples were analyzed in parallel. **(B)** Strong peptide-specific IgG antibody responses to all five MVP-S peptides were elicited in patients that achieved **>10% tumor reduction** on MVP-S based treatment. Antibody levels (mean±SEM) presented as area under the curve, calculated relative to Day 0.

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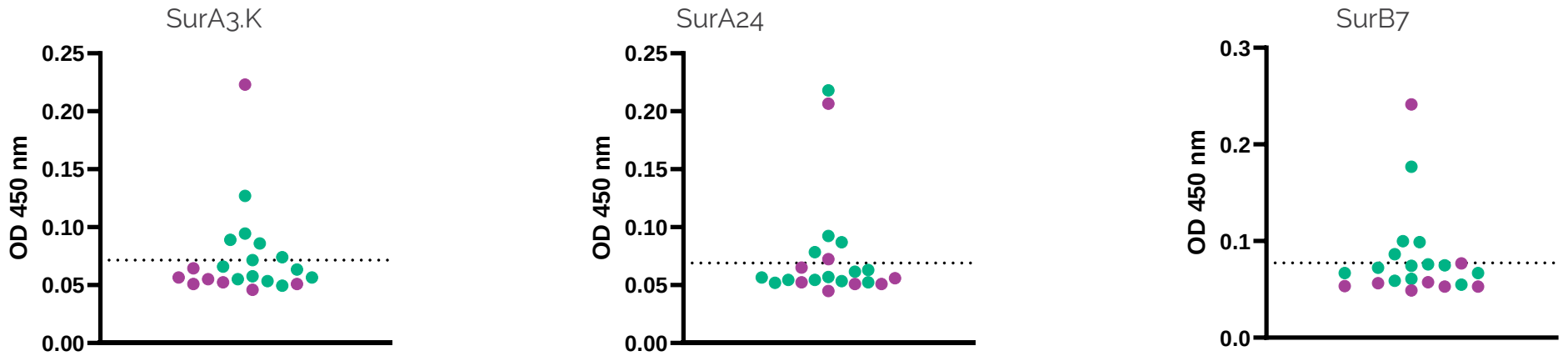
Antigen-specific antibodies are increased on-treatment and elevated in plasma of patients who achieved >10% tumor reduction (3 of 5 survivin peptides)

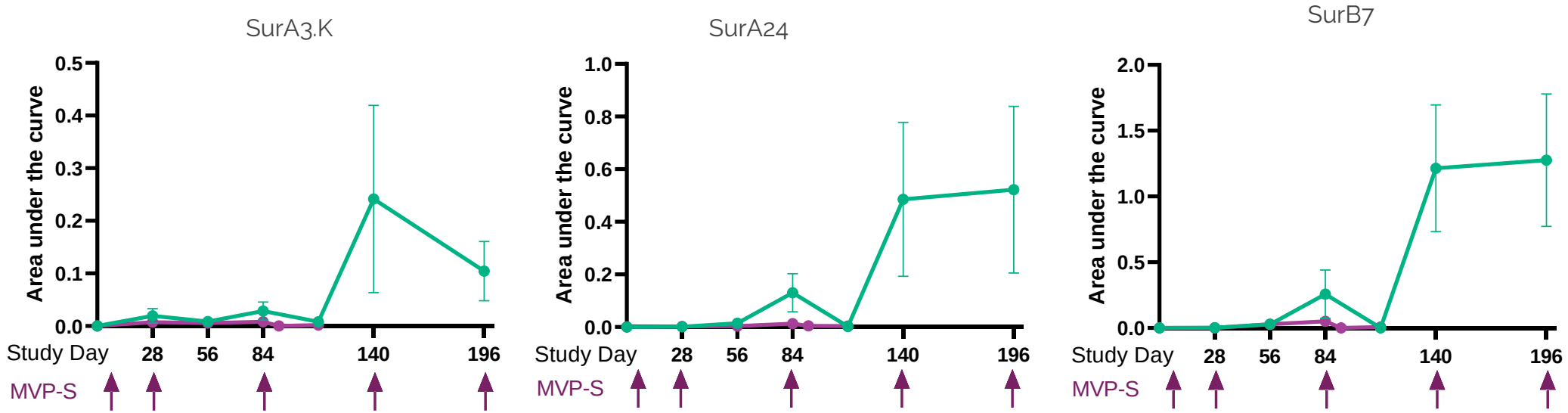
A

Pre-treatment levels



B

Increases on-treatment



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Antigen-specific antibodies are increased on-treatment and elevated in plasma of patients who achieved >10% tumor reduction

C

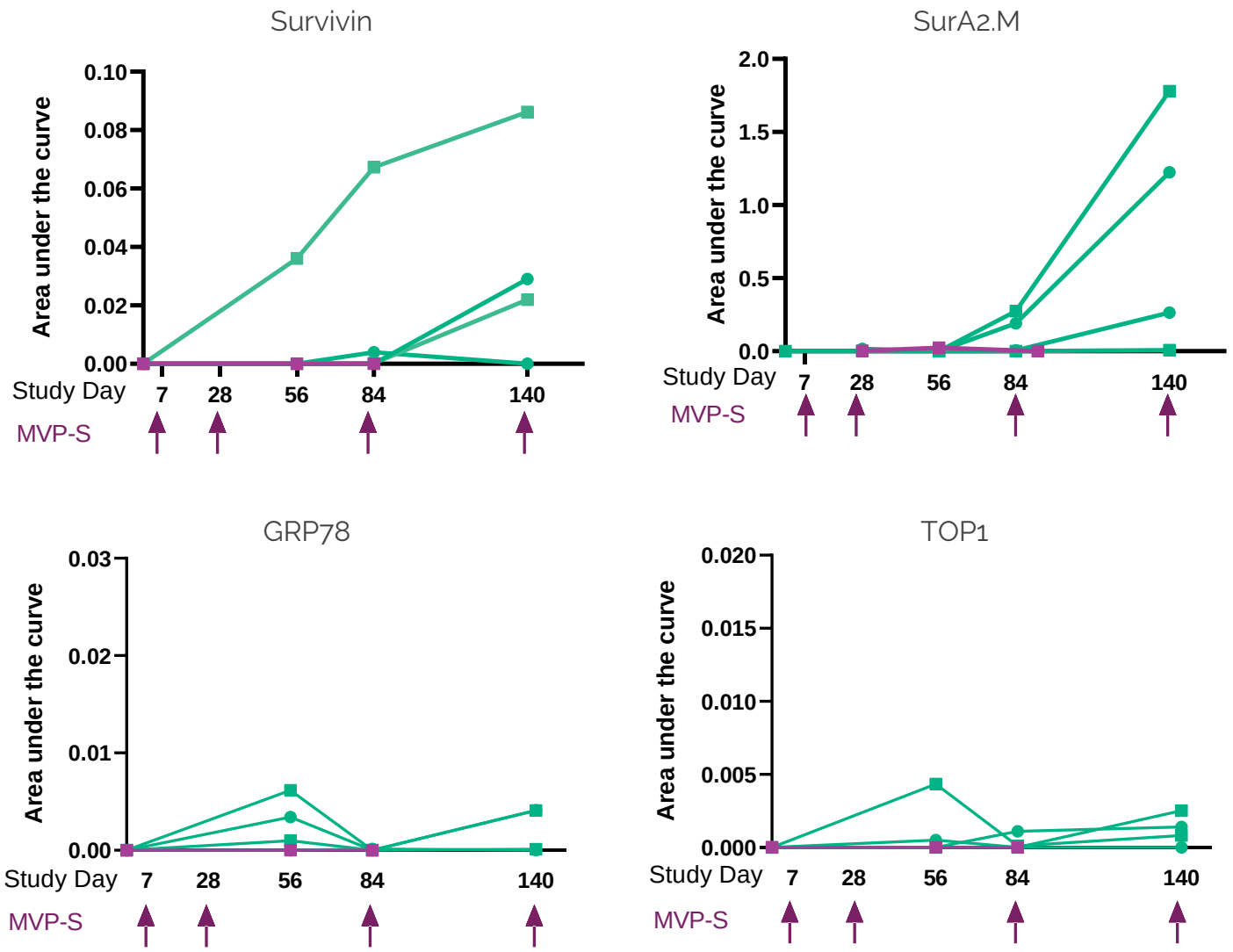

Figure 3 (C) Antibodies against survivin, but not against other tumor-associated proteins such as DNA topoisomerase I (TOP1) and glucose-regulated protein 78 (GRP78), were detected in plasma samples of MVP-S treated patients.

Antigenic peptides delivered by MVP-S induce survivin-specific antibody responses. These findings suggest that tumor lysis and antigenic spread may not play a significant role in the generation of anti-tumor antibodies with MVP-S based treatment.

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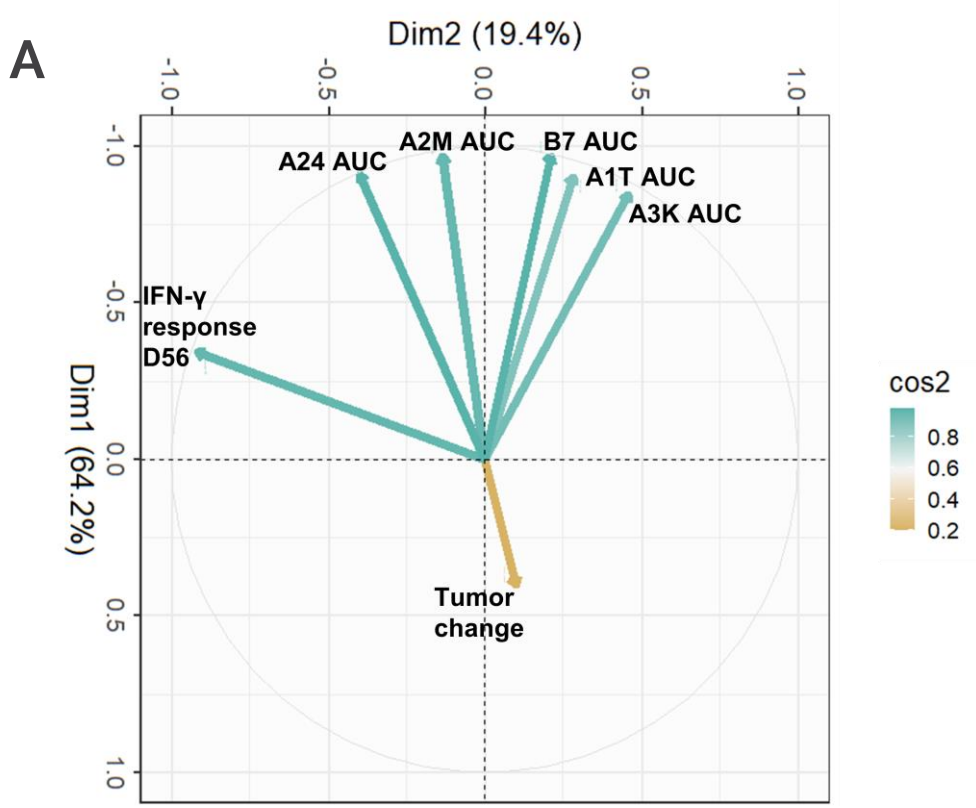
Levels of antibody responses against MVP-S peptides positively correlate with each other and with T cell responses, and tend to inversely correlate with tumor growth



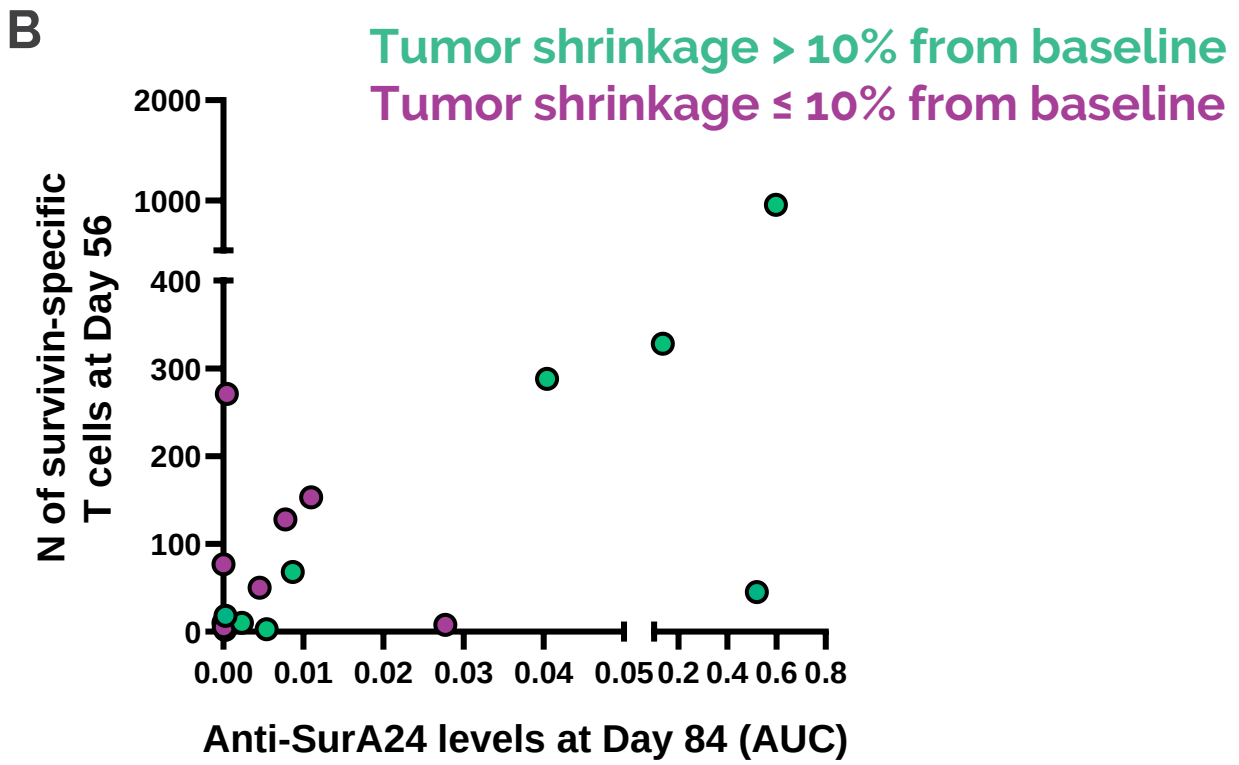


Figure 4 (A) Principal Component Analysis (PCA) of peptide-specific-antibody levels, T cell responses determined by IFN-γ ELISPOT and change in tumor volume. Arrows pointing in a similar direction correlate positively, color of the arrows dictate the strength of correlation **(B)** Example; correlations between anti-SurA24 levels at Day 84 in plasma and number of survivin-specific T cells per 10^6 PBMCs determined by IFN-γ ELISPOT at Day 56.

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Conclusion

- Increases in both T and B cell immune infiltration in tumors are associated with >10% tumor reduction in patients treated with MVP-S based therapy,
- Natural antibodies against survivin peptides can be detected in some cancer patients prior to MVP-S treatment and can be further increased by MVP-S treatment,
- MVP-S-based treatment can elicit *de novo* antibody responses against all 5 survivin antigens. Immune responses were maintained for at least 6 months after treatment initiation,
- Antigen-specific humoral responses to MVP-S antigens are more prominent in patients with **>10% tumor reduction**,

Results of this study provide new insight into the mechanism of action of MVP-S and suggest that **both cellular and humoral survivin-specific immune responses are important for the anti-cancer efficacy driven by MVP-S based immunotherapy.**

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Contact Information

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