

Molecular profiling of the PI3K δ inhibitor roginolisib in metastatic uveal melanoma and its correlation with clinical outcomes

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Abstract

Introduction : Uveal melanoma (UM) is a rare orphan disease with significant unmet clinical need. Unlike cutaneous melanoma, UM has a low tumor mutational burden and a highly immunosuppressive microenvironment, rendering it largely unresponsive to checkpoint inhibitor therapies. PI3K δ is involved in the pathophysiology of the disease, by enhancing regulatory T cell (Treg) activity and supporting tumor cell survival. Roginolisib, a PI3K δ inhibitor, was evaluated in 23 metastatic (m)UM patients at the 80 mg biological effective dose (BED). Here, we report the data from a comprehensive translational research program, including genomic, transcriptomic, proteomic and cellular data from these patients, supporting PI3K δ as a suitable therapeutic target for UM patients.

Methods: Study IOA-244-101 (NCT04328844) was conducted in patients with advanced cancer, which included mUM patients. Baseline and on-treatment blood and plasma samples were analyzed to evaluate circulating immune cells using mass cytometry, circulating tumor DNA (ctDNA) via whole exome sequencing, and circulating proteins through targeted proteomics. Additionally, biopsies at baseline and Day 28 of treatment were analyzed using whole transcriptome and whole exome sequencing.

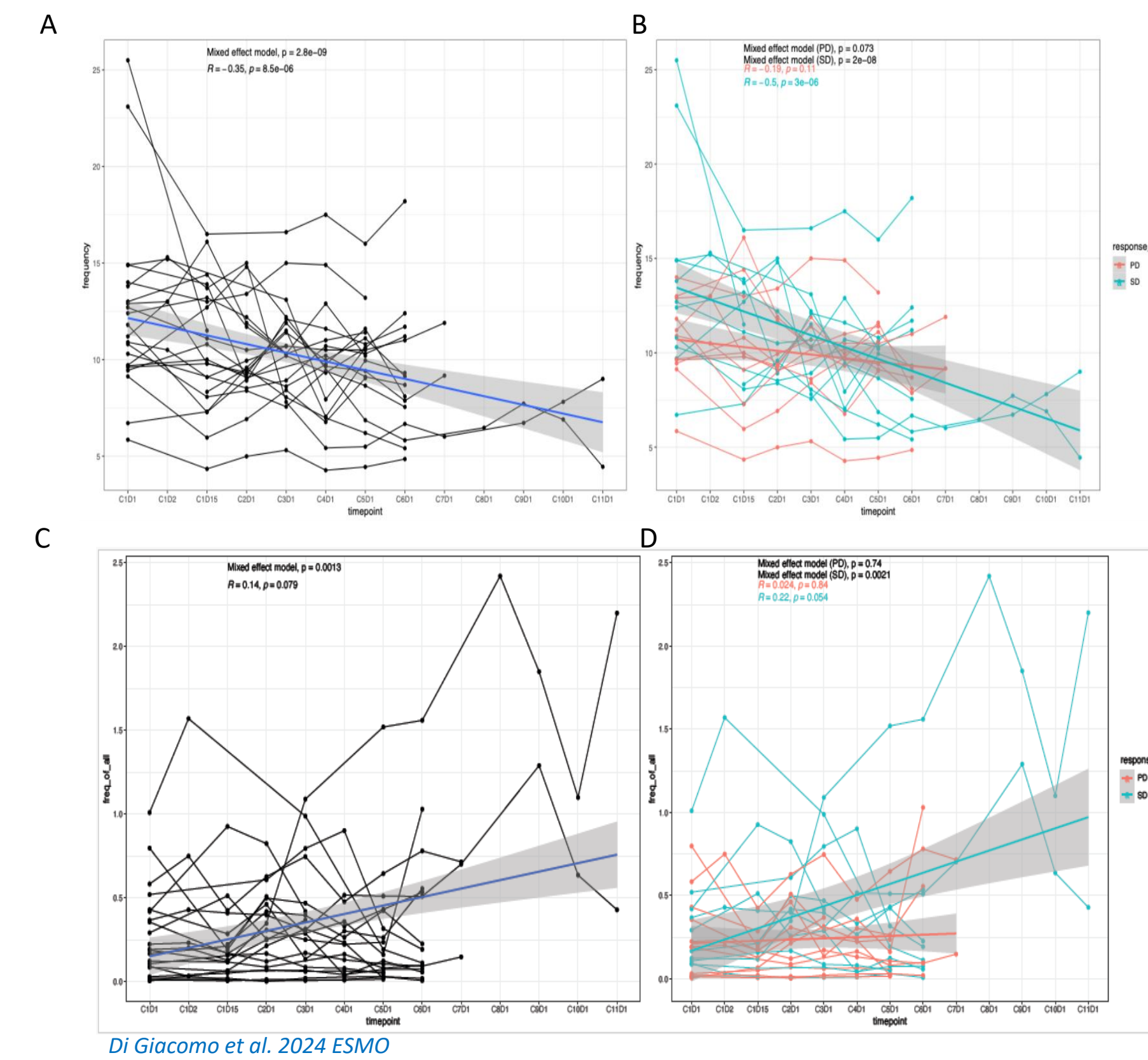
Results: Roginolisib treatment induced a progressive decrease of circulating Tregs and increased CD39⁺CD8⁺ T cells, accompanied by a reduction of soluble PD1, CCL22 and an increase of IL15 and IFNGR2. We identified a subpopulation of mUM patients that particularly benefited from roginolisib treatment. Patients with RECIST 1.1-defined stable disease (SD) at 16 weeks experienced significantly longer median overall survival (28.5 months) compared to those with progressive disease (PD) (10.9 months). SD patients had enhanced CD8⁺ T cell/Treg ratios and downregulation of PI3K/mTOR-associated proteins in plasma. Conversely, PD patients showed upregulation of these proteins after 8 weeks of treatment, suggesting a potential resistance mechanism.

Transcriptomic analysis of tumor biopsies revealed that SD patients had higher baseline expression of 325 genes, including 61 G-protein coupled receptors (GPCRs), which were downregulated post-treatment. Longitudinal ctDNA profiling further demonstrated dynamic tumor evolution, with specific variants emerging or disappearing over time.

Conclusion: These findings highlight the importance of immune modulation, PI3K/mTOR signaling, and GPCR gene expression in potentially driving treatment outcomes, and encourage further evaluation of roginolisib in a randomized Phase 2 study.

Immunoregulatory activity of roginolisib in peripheral blood

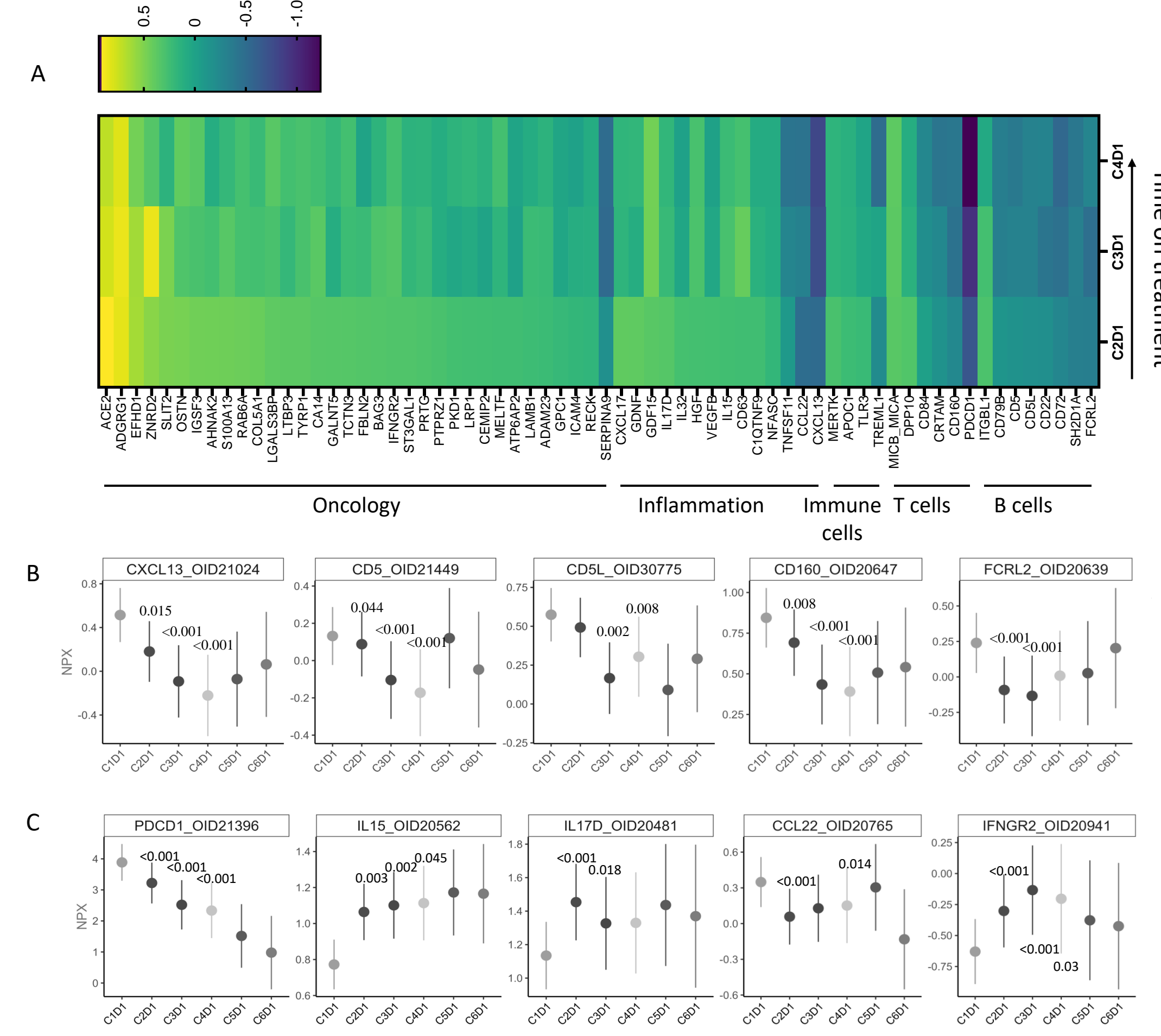
Figure 5: Longitudinal assessment of immune profiling via mass cytometry revealed reduction of Tregs and increase of CD39⁺ CD8⁺ T cells overtime



Regulatory T cell percentages assessed longitudinally by mass cytometry (=CyToF) before and after treatment (C1D1 vs Cx1D1) in panels A (all UM patients) and B (SD at Week 16 patients in blue and PD at Week 16 patients in red). Activated CD39⁺CD8⁺ T cells assessed in panels C (all UM patients) and D (SD patients in blue and PD patients in red). Lines connect samples from individual patients

Roginolisib significantly modulates immuno-oncology associated proteins overtime

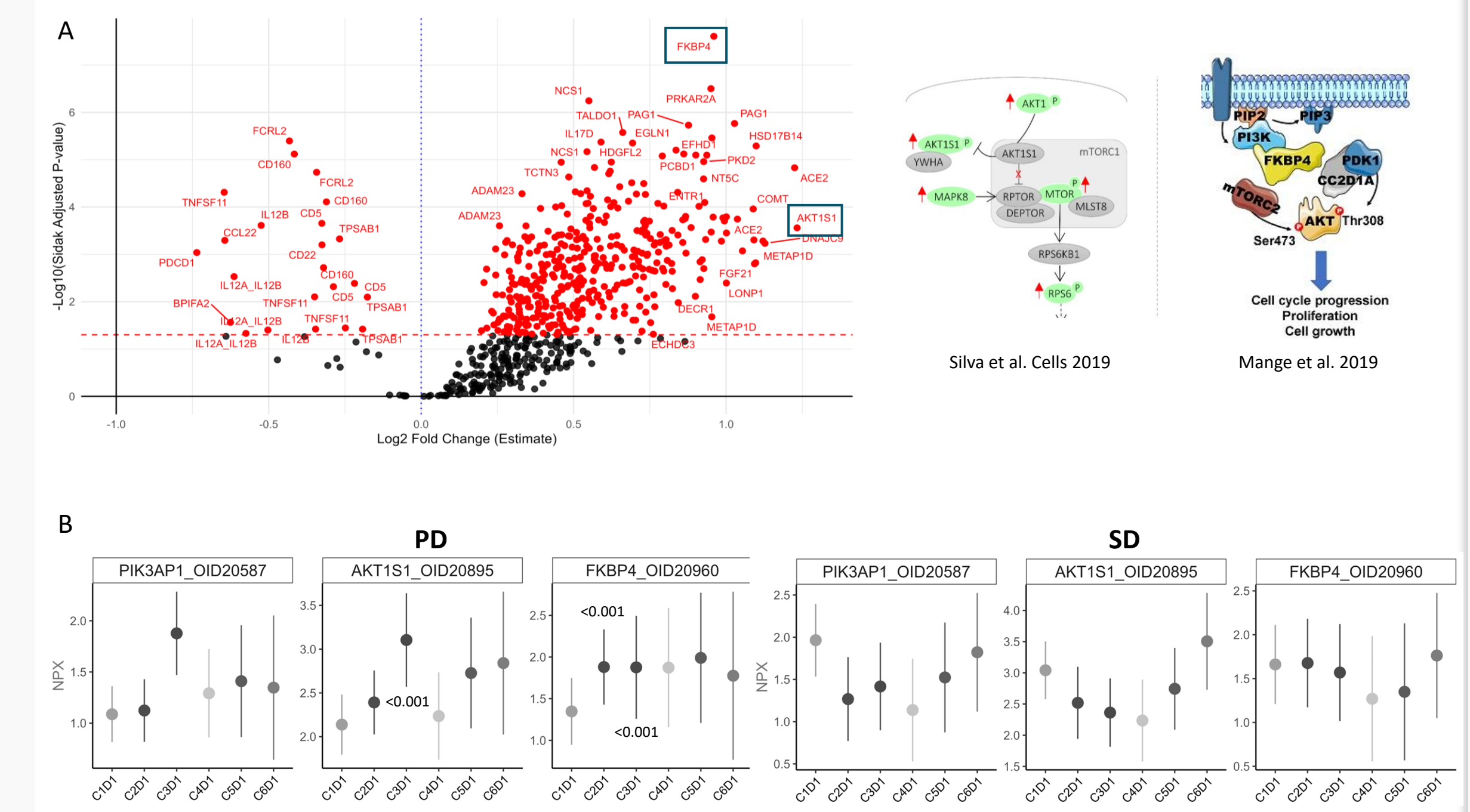
Figure 6. Longitudinal assessment of plasma proteins informed on pharmacodynamic and MoA activity of roginolisib



A) Heatmap of significantly up or downregulated proteins in the blood of UM patients at Day 1 of Cycle 2, 3 and 4 compared to baseline (Cycle 1 Day 1), measured by linear mixed effects model. B-C) Proteins significantly up or downregulated over time in the blood of patients after treatment with roginolisib for up to 5 cycles. B) Panel of proteins confirming the on-target activity of roginolisib. C) Panel of proteins involved in the mechanism of action of roginolisib. Timepoints with Sidak adjusted p-values are significant timepoints compared to C1D1 and calculated by Analysis of Variance (ANOVA) and linear mixed effects (lmer) model.

Protumoral proteins released from PD patients, including PI3K/mTOR pathway components, may indicate therapy resistance

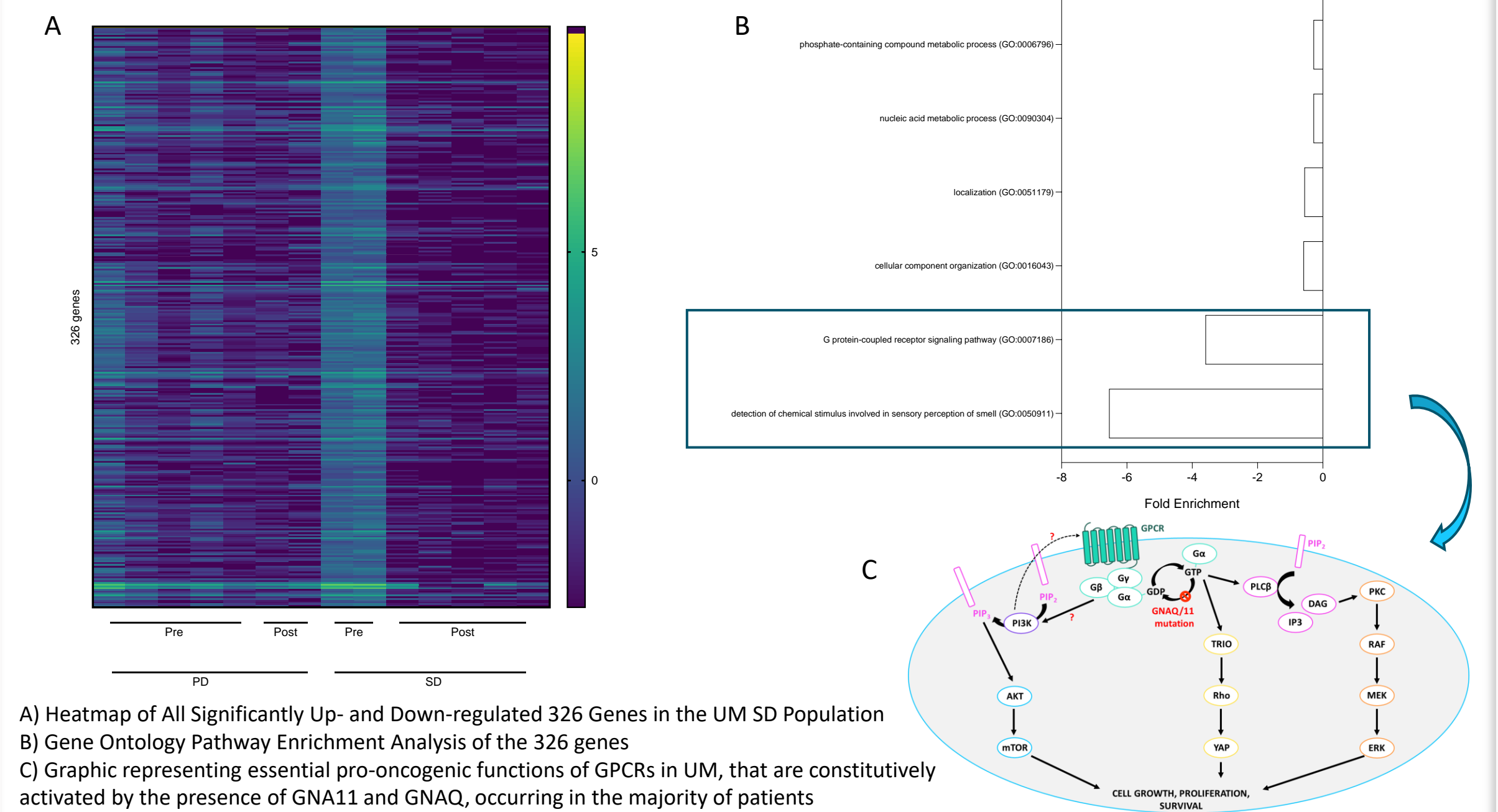
Figure 7: Proteomic analysis of PD patients unraveled potential signs of emerging resistance to roginolisib



A) Volcano plot representing all proteins significantly down and upregulated at any cycle in PD patients. B) Expression levels of proteins before (pre-dose C1D1) and after treatment (C2D1, C3D1, C4D1, C5D1, C6D1) in PD population and SD population. Timepoints with Sidak adjusted p-values are significant timepoints compared to C1D1 and calculated by ANOVA and lmer model.

Pre- and post-treatment tumor biopsy transcriptomics reveals downregulation of GPCR signaling in SD patients

Figure 8: 326 genes are significantly affected by roginolisib treatment in SD patients only



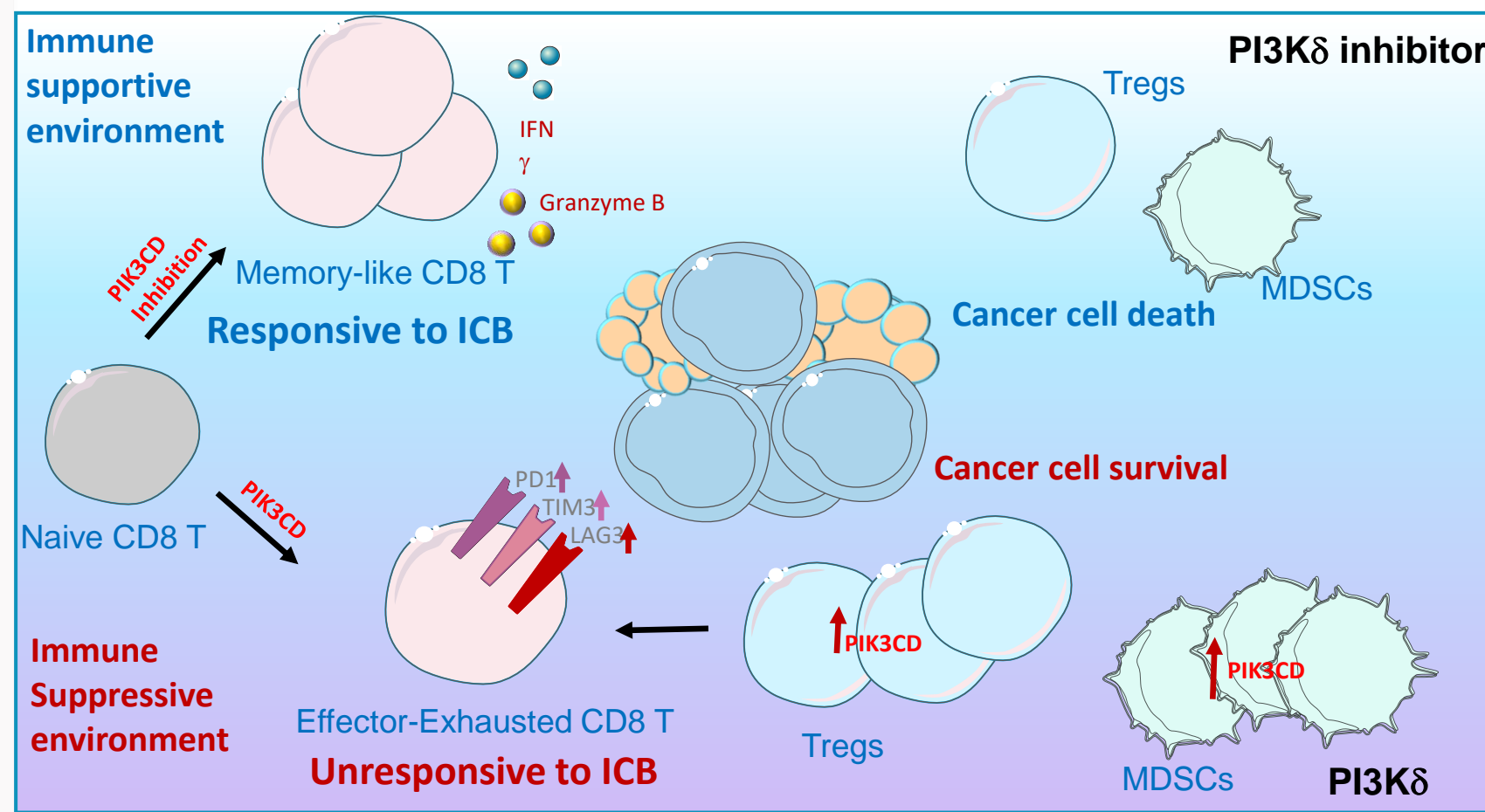
A) Heatmap of All Significantly Up- and Down-regulated 326 Genes in the UM SD Population. B) Gene Ontology Pathway Enrichment Analysis of the 326 genes. C) Graphic representing essential pro-oncogenic functions of GPCRs in UM, that are constitutively activated by the presence of GNA11 and GNAQ, occurring in the majority of patients

Conclusion

- Roginolisib is a differentiated PI3K δ inhibitor that has shown safety and efficacy in a FIH study (NCT04328844)
- At the biologically effective dose (BED) of 80 mg, roginolisib reduced peripheral regulatory T cells and increased activated CD39⁺CD8⁺ T cells in patients with metastatic uveal melanoma (mUM), particularly in those with confirmed stable disease (SD) at Cycle 5 (C5, Week 16)
- Proteomic analysis of longitudinal plasma samples identified treatment-driven modulation of 83 proteins across all patients, including soluble PD-1 and IL-15. Notably, increased levels of PI3K-associated proteins may indicate the emergence of resistance mechanisms in patients who progressed at C5 (=Week 16).
- Patients with stable disease at C5, who exhibited an impressive 28 months mOS, had a baseline GPCR gene signature that is significantly downregulated by roginolisib.

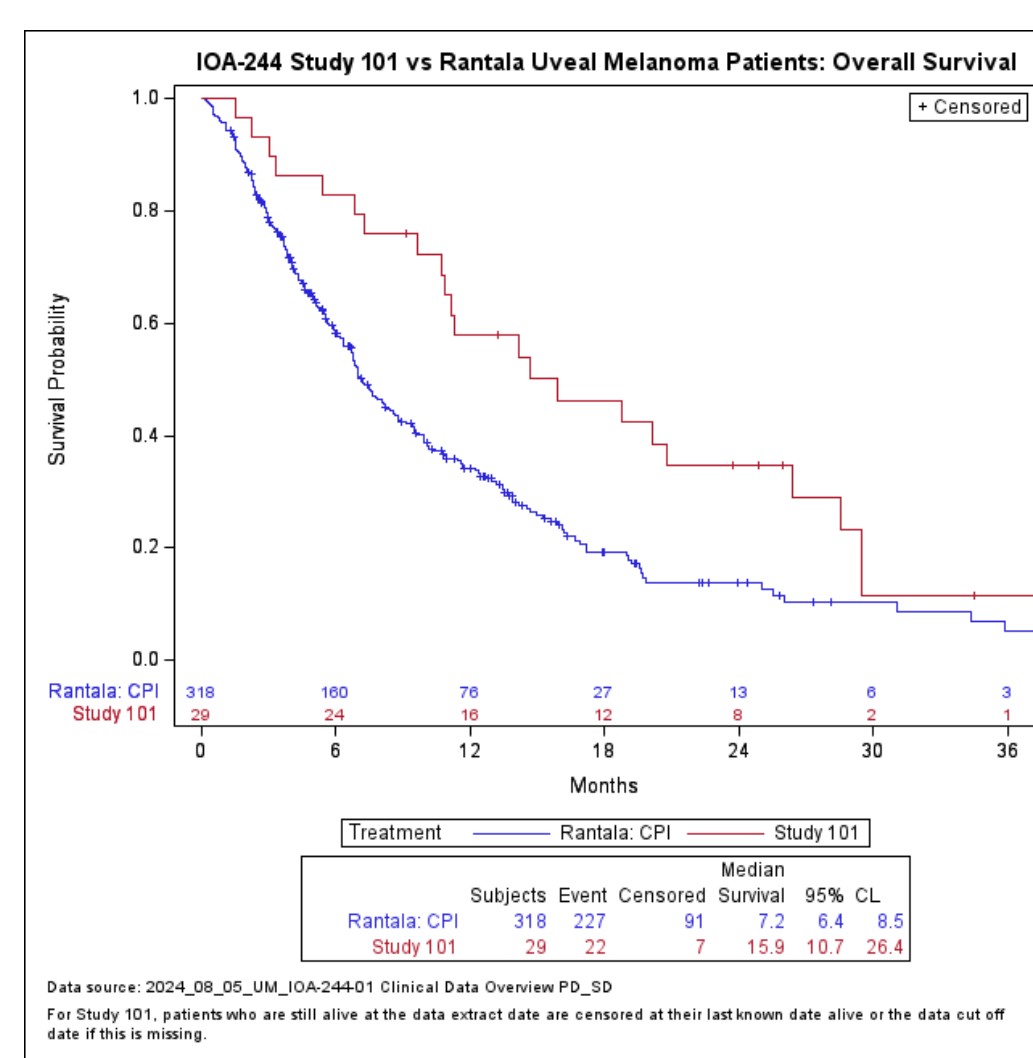
Introduction and preliminary data

Figure 1: Cartoon depicting MoA of a PI3K δ inhibitor in solid tumors



Ali et al., Nature 2014
Abu Di et al., Cancer research, 2017
Yoon et al., JTC 2021
Johnson et al., Cancer research Comm, 2023

Figure 2: Roginolisib-treated uveal melanoma patients showed extended mOS compared to historical control



Based on extract from 05 Aug 2024 - Di Giacomo et al. ASCO 2024

Kaplan Mayer curve representing mOS of metastatic uveal melanoma patients treated with roginolisib in FIH study (red line) and comparison with historical control in the same patient population (blue line).

mOS historical control: 7.2 months
mOS roginolisib trial: 15.9 months

Biomarker of FIH study: Layout and correlation with clinical outcome

Figure 3: Cartoon depicting biomarker experimental layout in the FIH study

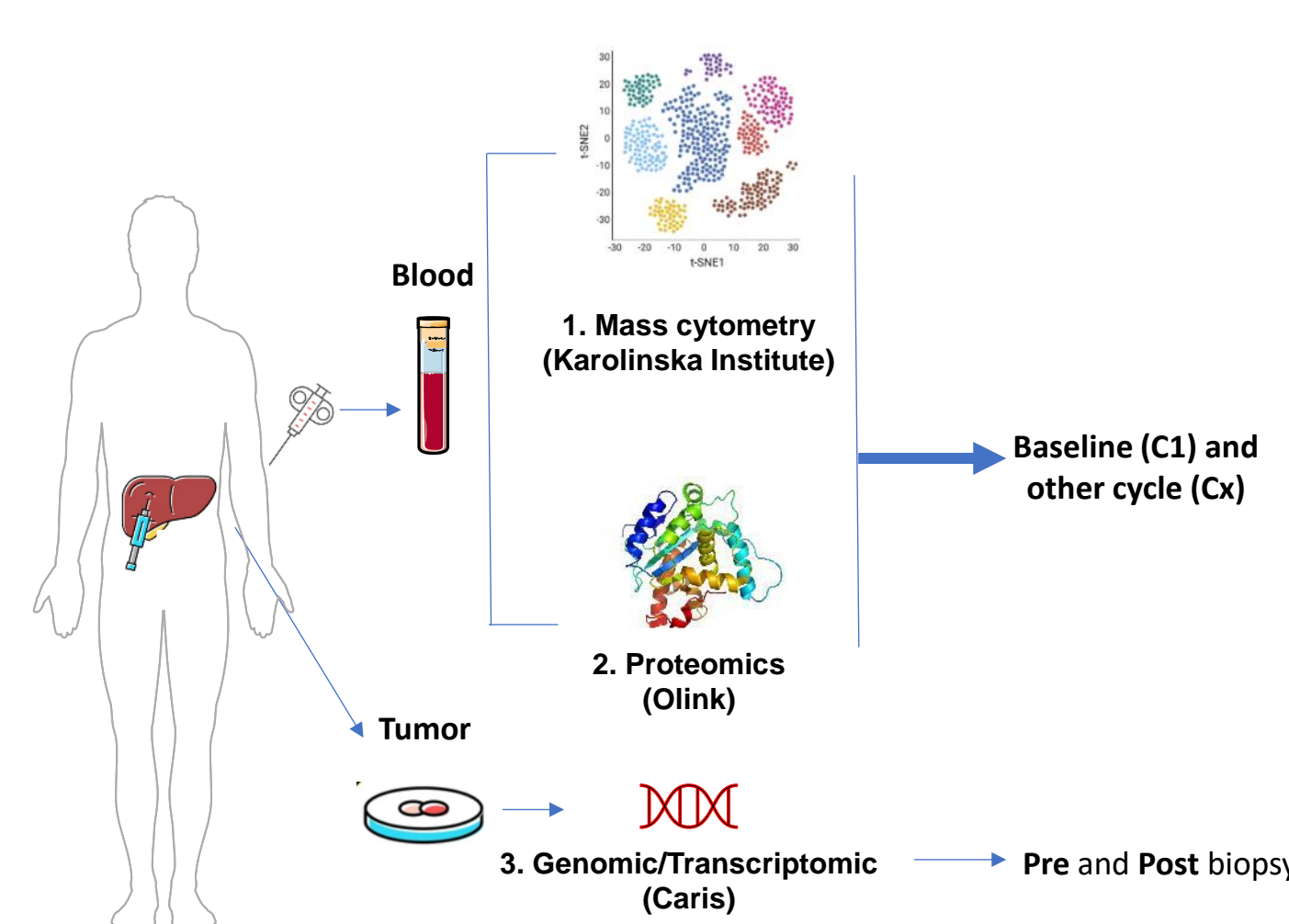
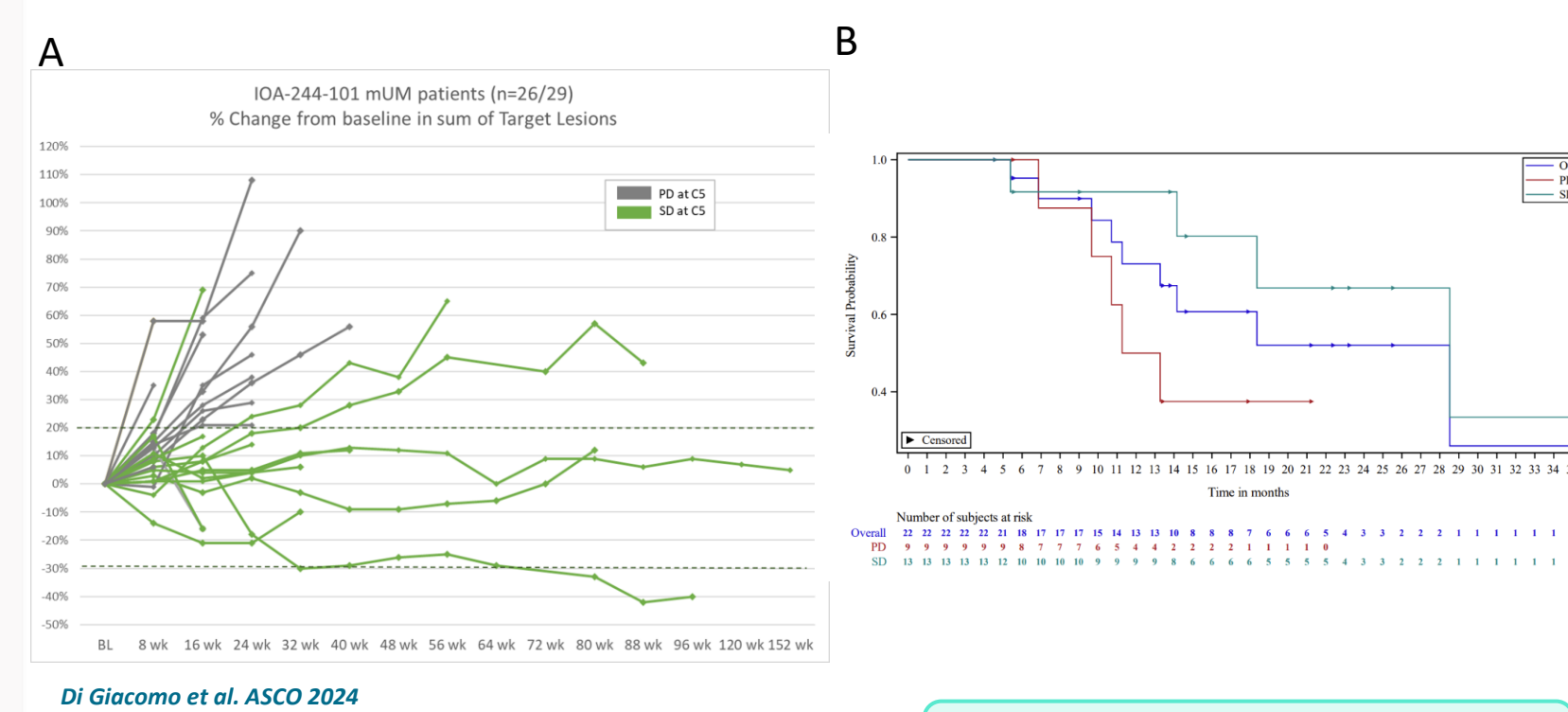


Figure 4: A spider plot of mUM patients (n=26/29) treated with roginolisib shows distinct tumor growth patterns at Cycle 5 (3.8 months): SD and PD at Week 16



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mOS of PD at Week 16: 11.1 months
mOS of SD at Week 16: 28.5 months

A) Spider Plot of Percent Change in Target Lesions for All Uveal Melanoma Patients with Measurable Disease as per RECIST 1.1. PD (grey) indicate patients with progressive disease at C5 (week 16). SD (green) indicate patients with stable disease at C5 (week 16) B) Kaplan Mayer curve representing mOS of metastatic uveal melanoma patients treated with roginolisib overall (Blue line), SD patients (green line) and PD patients (red line).