Systemic Immune Parameters after Prior Radiation Therapy in Patients Receiving Immune Checkpoint Inhibitors

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Despite high-level interest, little is known about mechanistic links between ICI and RT in patients

Clinical observations and preclinical models have suggested a link between radiation therapy (RT) and anti-tumor immune responses.

- Focused RT appears to heighten immune function[1,2]
- RT depends on intact pre-existing immunity to exert cytotoxic effects[3]
- Abscopal Effect: in some cases, local RT results in tumor shrinkage at sites distant from the treatment field[3]

Links between immune checkpoint inhibitor (ICI) and RT are being studied.[4-6]

- Receipt of RT prior to initiation of anti-Programmed death 1 (PD-1) antibodies may enhance treatment efficacy[7]
- PD-L1 therapy after concurrent chemoradiation for locally advanced non-small cell lung cancer significantly improves both progression-free and overall survival[8-10]

However, numerous trials of combined ICI and RT have yielded discouraging results.[11-14]

This may be in part due to an inadequate mechanistic understanding of the combined therapy in the clinical setting.

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Overall objective

To characterize systemic immune parameters in patients according to receipt of RT prior to initiation of ICI therapy.

We collected clinical data and serial blood samples from ICI-treated patients

01
Blood samples were collected at pre-ICI baseline and approximately 6 weeks after ICI initiation.

02
Clinical data collected included age, sex, race, ethnicity, cancer type, ICI type, and date of ICI initiation

03
Retrospective review of medical records to identify RT exposure: organ site, number of fractions, dose per fraction, total dose, date of last RT administration

04
Demographic characteristics: Fisher's exact test for categorical variables, t-tests for continuous variables.
For cytokines and autoantibodies we generated heat maps for baseline and 6-week values.

We used broad eligibility criteria

- Planned for but not yet started immune checkpoint inhibitor therapy

- Any cancer type or stage

- Any checkpoint inhibitor (PD1/PDL1, CTLA4, LAG3) either as monotherapy, combination, or combined with other types of treatments such as chemotherapy, radiation therapy

25% of patients in our cohort received prior RT within 6 months

Characteristic	Median (range) or N (%)				P value
	Total	RT 0–3 months prior to ICI	RT 3–6 months prior to ICI	No RT 0–6 months prior to ICI	
Age	68 (27–92)	69 (38–90)	68 (27–78)	68 (29–92)	0.97
Sex					0.65
Female	111 (40)	19 (35)	7 (50)	86 (41)	
Male	166 (60)	36 (65)	7 (50)	122 (59)	
Race/ethnicity					0.81
NH White	211 (76)	40 (73)	11 (79)	160 (77)	
Other	66 (24)	15 (27)	3 (21)	48 (23)	
Cancer type					0.04
Lung	141 (51)	28 (51)	10 (71)	103 (50)	
Melanoma	61 (22)	16 (29)	1 (7)	44 (21)	
Other	75 (27)	11 (20)	3 (21)	61 (29)	

ICI, immune checkpoint inhibitor; NH, non-Hispanic; RT, radiation therapy.

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Few cytokines and antibodies were associated with prior RT exposure
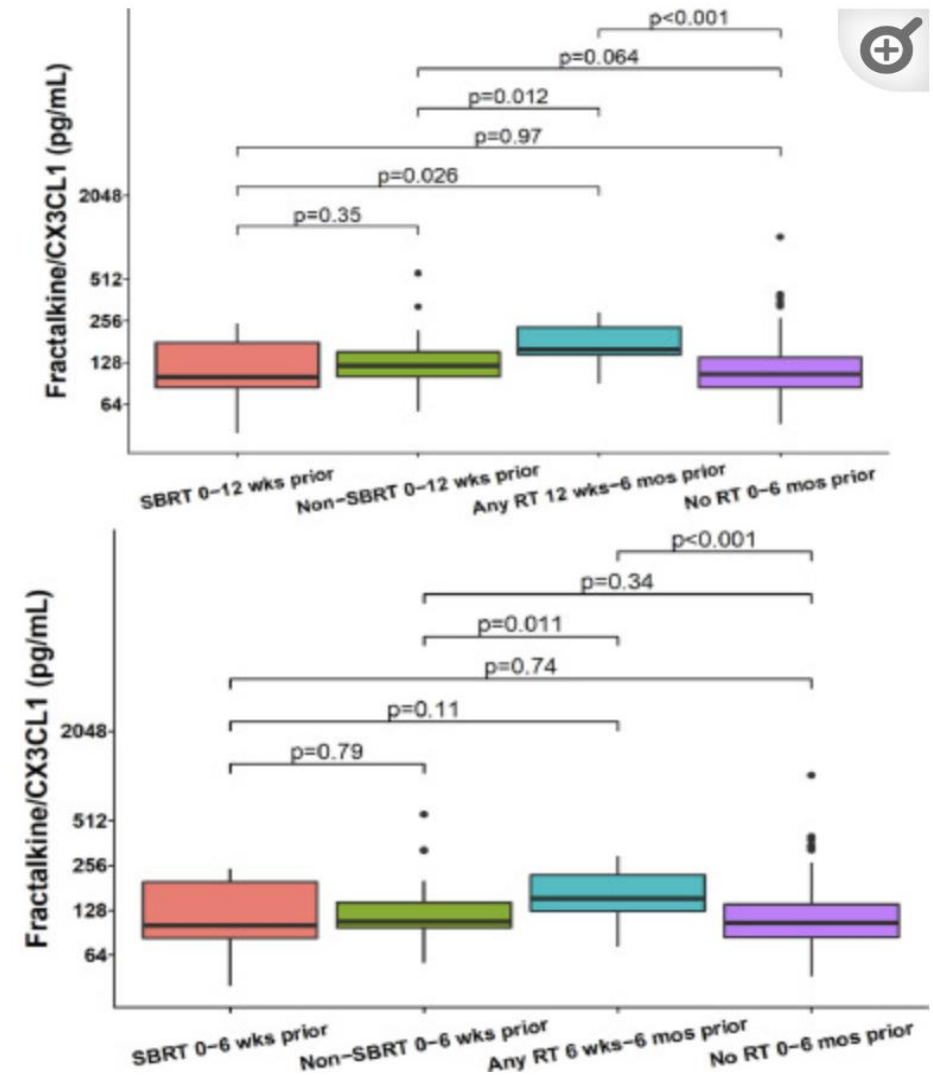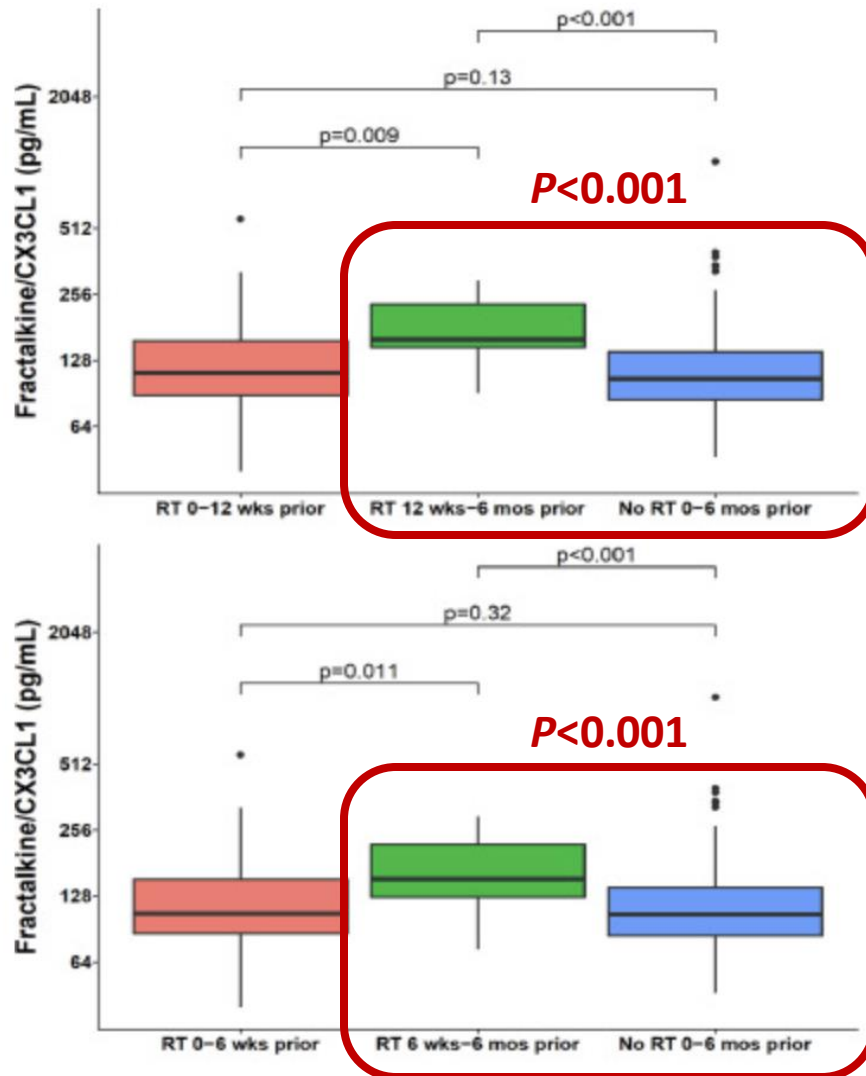
Cytokines (40 tested):

- *baseline* **fractalkine/CX3CL1** and **MIP-1d/CCL15**

Autoantibodies (125 tested):

- *baseline* **anti-complement C8**

- *changes in* **anti-JO1, -nucleosome,** and **-GP2**
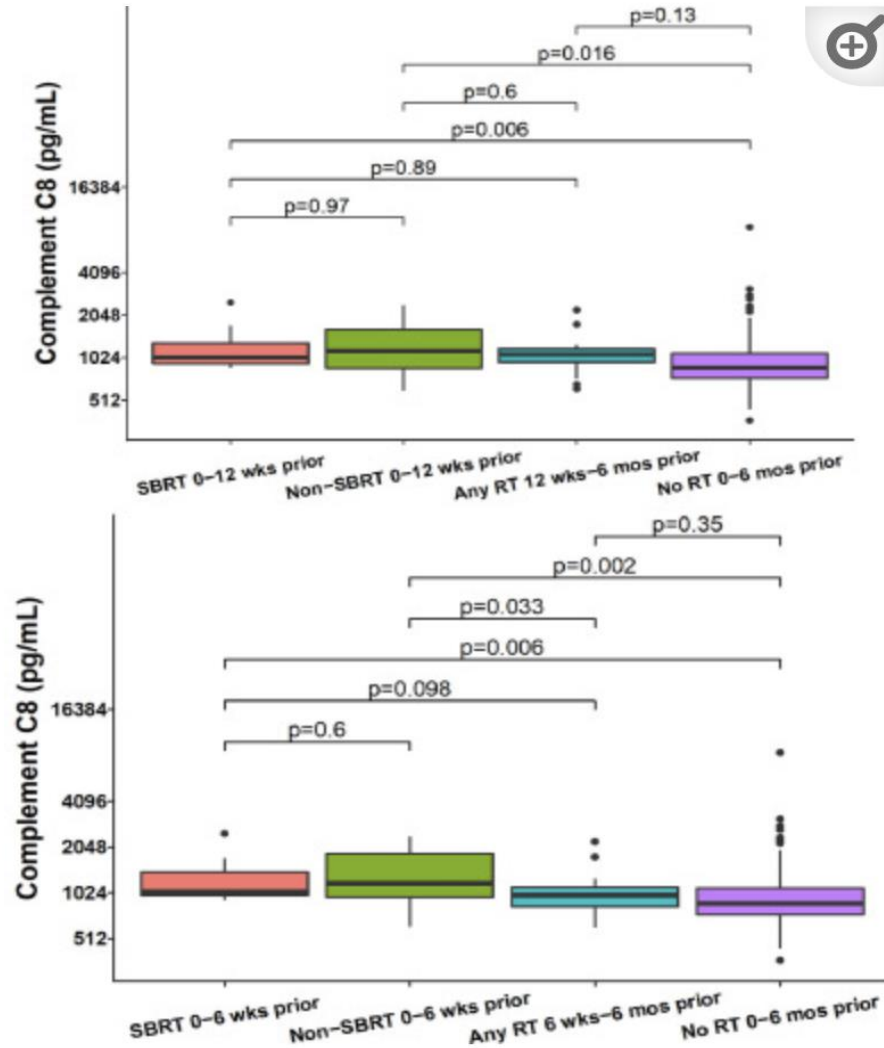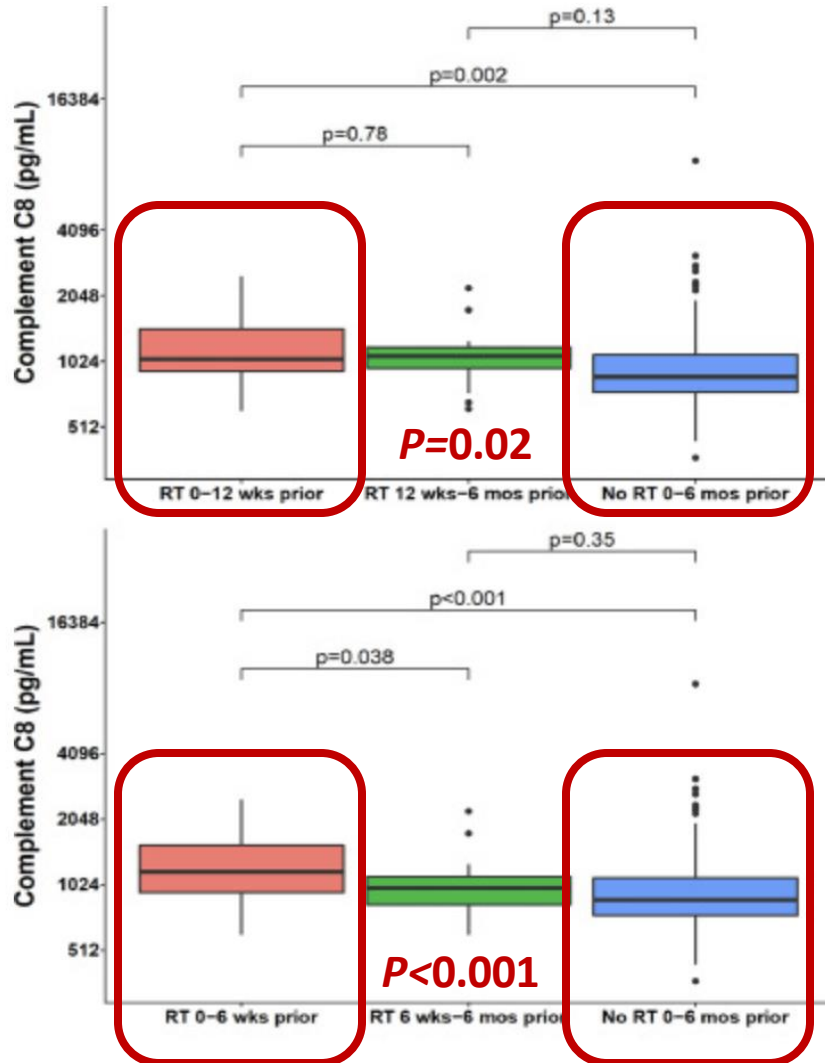
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Fractalkine/CX3CL1 levels were significantly higher in patients who had received RT at least 6 or 12 weeks prior to ICI initiation
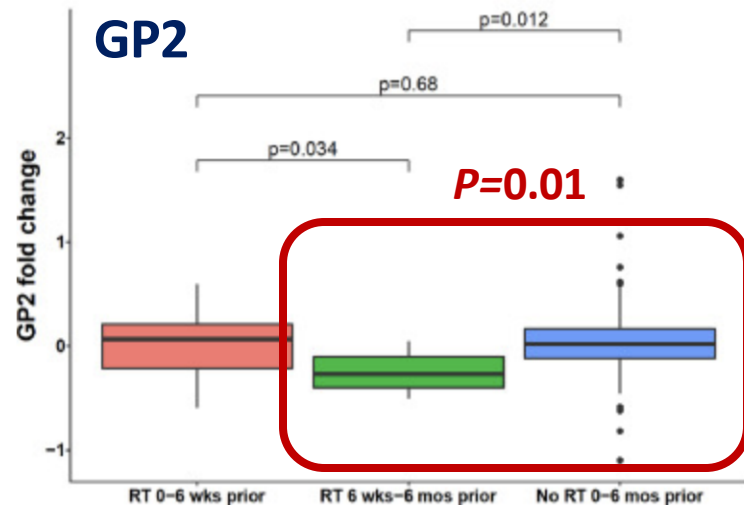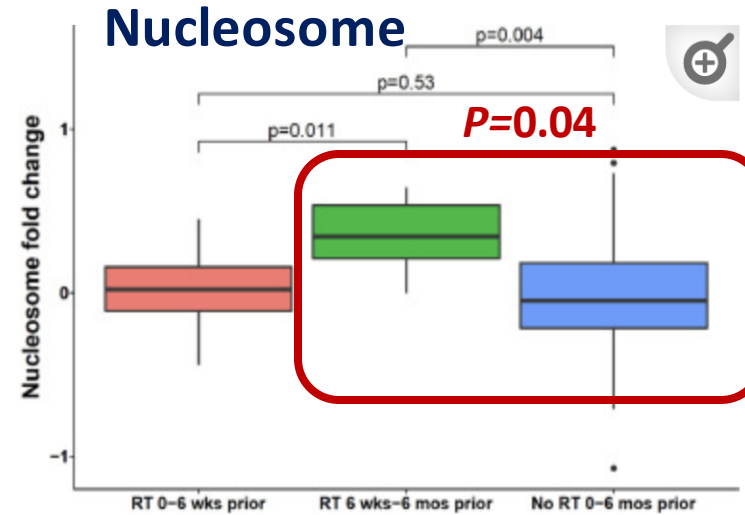
MIP-1d/CCL15 levels were higher in patients who had received relatively recent stereotactic RT
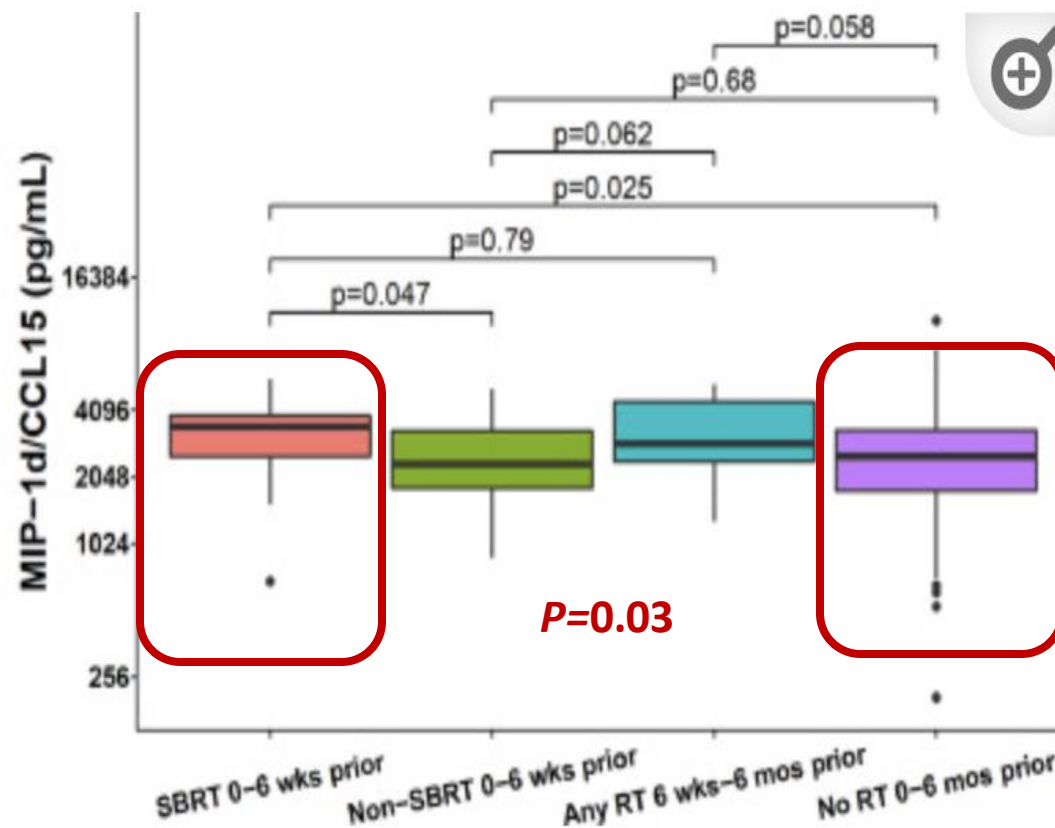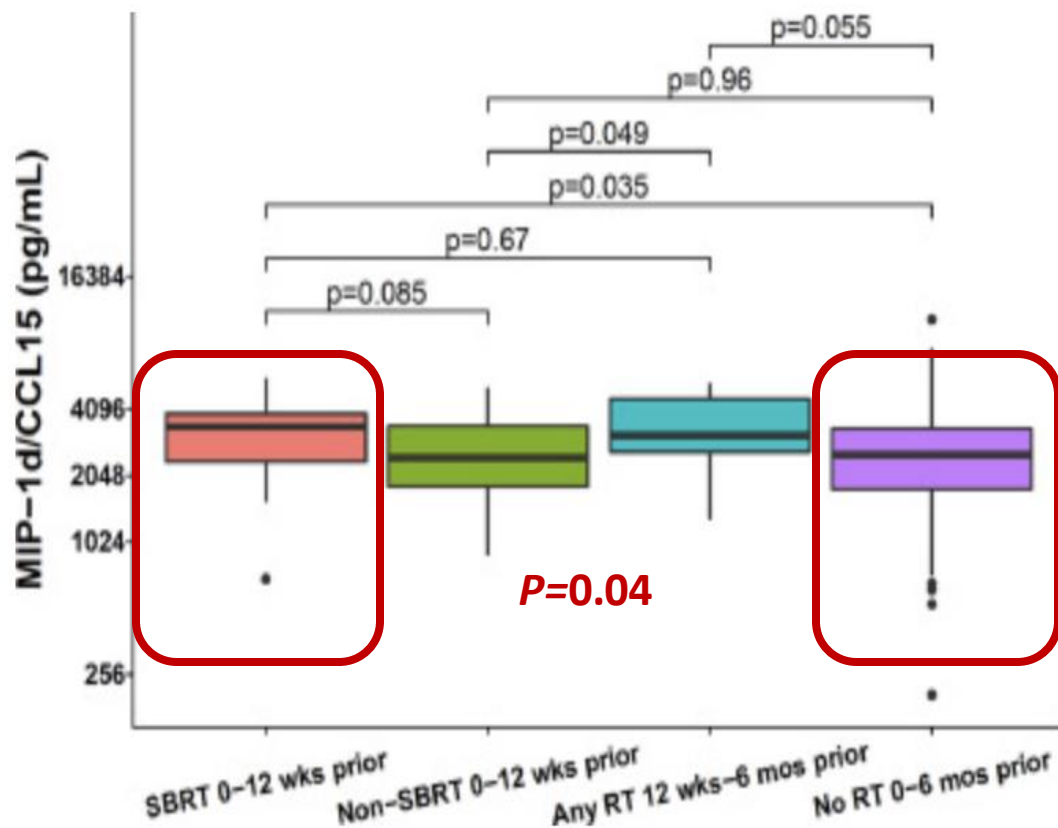
Anti-complement C8 antibody levels higher with near-term prior RT

Changes in Jo-1, GP2, and Nucleosome antibody levels differed in cases with earlier prior RT (>6 weeks before ICI initiation)
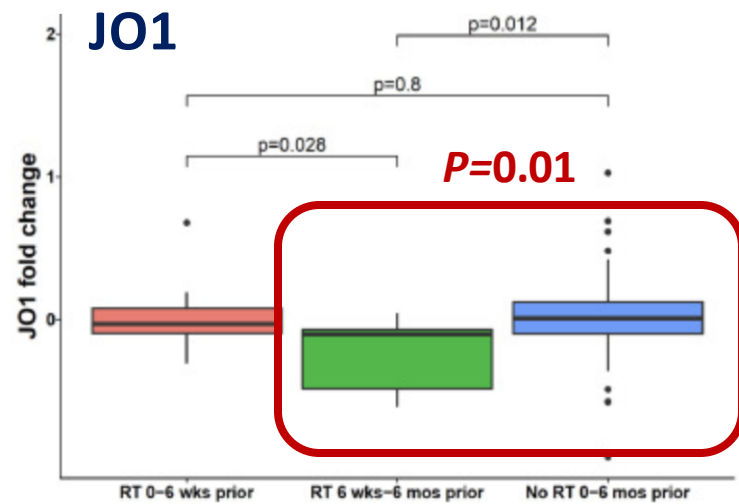
What do we know about these immune parameters?

- ## CX3CL1

  - Member of the CX3C chemokine subclass

  - Chemoattractivity for monocytes, neutrophils, natural killer cells, and T cells

- ## Complement C8

  - Plays key role in the formation of the membrane attack complex

  - Membrane attack complex may target and lyse pathogens and contribute to tissue damage when directed against host cells

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Limitations of the analysis

- Role of RT on immune function

  - RT may affect cell populations and functions (which we did not analyze)

  - RT may affect immune parameters not included in our panels

  - RT biologic effects may occur in tumor microenvironment (which we did not capture in peripheral blood draws)

- Heterogeneity of study cohort (especially RT indications and regimens)

Conclusions

- In a cohort of patients treated with ICI, the administration of pre-ICI RT with varying timing, schedules, and indications was associated with few differences in cytokines and autoantibodies

- Further research needed to elucidate the biologic effects of this strategy are critical to optimizing the rationale and outcomes of combination ICI + RT regimens

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