Radiotherapy (RT) is used in the treatment of >50% of cancer patients, but RT-resistance is common. We have recently identified RT-associated genomic small deletion signatures (RTscars), marking tumors that have developed resistance (Kocakavuk et al. 2021, Nature Genetics). Here, we used longitudinal molecular profiles to explore non-genetic mechanisms of RT-resistance.

**RESULTS (Figures)**

- **Treatment scars associated with longitudinal increase in proliferating stem-like cell state**
  - Kaplan-Meier overall survival plot for IDHmut glioma samples, log-rank test.
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- **Increase in proliferating stem-like cell state associated with worse overall survival**
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- **RT-associated small deletion**
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- **Boxplots depicting T-cell fraction in bulk tumor at recurrence**
  - Mann-Whitney-U test.

- **Longitudinal change in the number of frameshift-induced neoantigens**

**CONCLUSION**

Our analyses revealed a longitudinal increase in the proliferating stem-like cell state associated with RT-resistance and unmans the cell cycle pathway as an actionable target. The RT-associated deletion signature (RTscars) correlated with increased frameshift-neoantigens and T-cell fractions at recurrence, suggesting a potential benefit of a combinational immune-targeted therapy in this specific patient population.

No conflicts of interest.