INTERMITTENT DOSING OF THE ATAXIA TELANGIECTASIA AND RAD3-RELATED (ATR) INHIBITOR CERALASERTIB PROMOTES ANTITUMOR IMMUNITY BY REMODELLING THE TUMOR IMMUNE MICROENVIRONMENT IN PRE-CLINICAL MODELS

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Background The combination of an ATR inhibitor ceralasertib and anti-PD-L1 antibody durvalumab is being tested in Phase III clinical trials in patients who have progressed on prior immunotherapy. Preclinical experiments were performed to build a greater understanding of the potential immune driven mechanisms-of-action by which ceralasertib enhances antitumor efficacy in combination with anti-PD-L1 in the context of the clinical dose and schedule.

Methods To assess the antitumor efficacy and associated pharmacodynamic effects ceralasertib was administered to CT26 tumor-bearing BALB/c immunocompetent mice twice daily with continuously and intermittently 7 day-on/7 day-off schedules alone or in combination with PD-L1 blockade. Flow cytometry and immunohistochemistry was used to quantify CD8+ T-cells when on and off ceralasertib treatment. Immunophenotyping was performed using single-cell CyTOF protein expression mass cytometry and bulk tumor or single-cell RNA sequencing (scRNA-seq) transcriptomics analysis to evaluate intratumoral T-cell populations.

Results Modelling of intermittent ceralasertib dosing regimen in mouse tumor models revealed CD8+ T-cell and type I interferon (IFNI) dependent antitumor activity, which was enhanced in combination with anti-PD-L1 immune checkpoint blockade. Ceralasertib suppressed highly proliferating CD8+ T-cells when on-treatment which was rapidly reversed when off-treatment. This was linked to significant relative reductions in T-cells which displayed markers commonly associated with an exhausted phenotype and a concomitant increase in cells with naïve non-activated phenotypes with improved T-cell function in the tumor microenvironment. Continuous daily administration of ceralasertib led to the sustained suppression of CD8+ T-cells and impaired antitumor activity compared to intermittent dosing. In addition, ceralasertib caused up-regulation of type I interferon (IFNI) which may promote an inflammatory environment and drive direct anti-proliferative effects on tumor cells.

Conclusions Broad immunostimulatory and immunomodulatory changes following intermittent ATR treatment in combination with immune checkpoint blockade may underpin the durable clinical therapeutic benefit observed in patients and indicates its potential wider impact on antitumor immunity.

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