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CDK4/6 blockade is as effective as immune-checkpoint inhibition in tumor growth control of Mlh1-/- and Msh2loxP/loxP villin-Cre mice

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Background

Mismatch-repair deficiency (dMMR) is a hallmark of Lynch syndrome-associated cancers, often resulting from inactivating mutations in *MLH1* or *MSH2*. These tumors have a high likelihood of responding to immune checkpoint inhibitors (ICI). Still, intrinsic or acquired resistance mechanisms impair patients' outcomes. Here, we compared the therapeutic potential of an anti-PD-L1 inhibitor with the CDK4/6 inhibitor abemaciclib in two preclinical mouse models of dMMR-driven carcinogenesis.

Methods

In this ongoing trial, $Mlh1^{-/-}$ or $Msh2^{loxP/loxP}$ Villin-Cre mice with gastrointestinal tumors were either treated with anti-PD-L1 monoclonal antibody (clone: 6E11, 2.5 mg/kg bw, i.p., q2wx3) or abemaciclib (75 mg/kg bw, p.o.,q1wx8). Control mice received the isotype (anti-IgG1 2.5 mg/kg bw, i.p., q2wx3) or were left untreated. Blood phenotyping was performed regularly. The tumor microenvironment was studied by immunofluorescence.

Results

Both therapies prolonged overall survival of mice significantly: $Mlh1^{-/-}$: 9.1 wks (6E11) vs. 11.1 wks (abemaciclib) vs. 3.5 wks (control); *$Msh2^{loxP/loxP}$Villin-Cre:* 6.0 wks (6E11, ongoing) and 8.2 wks (abemaciclib, ongoing) vs. 1.0 wk (control). One $Mlh1^{-/-}$ mouse received complete remission upon abemaciclib, while anti-PD-L1 therapy primarily induced stable disease at best (PET/CT). Therapeutic effects of abemaciclib were accompanied by increased numbers of tumor-infiltrating $CD4^+$/$CD8^+$ T-cells and lower numbers of M2-macrophages. Blood phenotyping revealed PD-L1 upregulation under abemaciclib therapy.

Conclusions

While ICI-based therapies are effective and FDA approved for dMMR cancer, abemaciclib constitutes a promising alternative therapy option. The strong immune stimulation upon abemaciclib treatment renders this compound ideal for ICI-refractory or intrinsically resistant tumors.

Legal entity responsible for the study

The authors.

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