curves and corresponding Gehan-Breslow-Wilcoxo tests were used to evaluate the statistical differences between groups in survival studies. $P < 0.05$ was considered to be significant.

T cell analysis for MC38 implanted tumors. MC38 implanted tumors were established by subcutaneously injecting 1×10^5 of MC38 cells were injected into the right flank of 6 week old C57BL/6 female mice (Jackson Lab). On the day of the tumor cells injected, mice were randomly divided into four groups: control antibody treatment, PD-1 mAb treatment, CDK4/6 inhibitor treatment, and PD-1 mAb plus CDK4/6 inhibitor treatment. Control and PD-1 mAb treatments were conducted by intraperitoneal injection (200 μg/mouse in 200 μl HBSS saline buffer) every three days for a total of 4 injections. The treatment of palbociclib was given by oral gavage with the dosage of 200 mg/kg for 9 days, with a break after 7 days. Tumors were then collected and single cell was generated from tumor tissues as described in section "Single Cell Generation from Tumor Tissue and Flow Cytometry analysis". After cells were filtered through 40 μm strainer, cells were fixed in 0.5 ml/tube Fixation buffer (420801, Biolegend) in the dark for 20 minutes at room temperature. Cells were then washed with 1 × PBS with 2% BSA. The fixed cells were suspended in Intracellular Staining Perm Wash Buffer (421002, Biolegend) after centrifuge for two times to permeabilize the cells. Cells were then co-stained with antibodies against CD3 (100236, APC conjugated, Biolegend), Granzyme B (515403, FITC conjugated, Biolegend), IFN-γ (505808, PE conjugated, Biolegend) to check the activities of T cells. Or cells were co-stained with antibodies against CD3 (100236, APC conjugated, Biolegend), CD4 (100510, FITC conjugated, Biolegend), CD8 (100708, PE conjugated, Biolegend). The corresponding isotype IgG1 controls were used for controls. The cells were incubated with corresponding antibodies for 30 minutes at room temperature. Cells were washed by 1 × PBS with 2% BSA and analyzed by flow cytometry.

Data Availability. Source data for gels in Figs 1–4 and Extended Data Figs 1–9 are available in Supplementary Fig. 1. Source data for Figs 2j and 2k are available in Table 1. Source data for Figs 3j-n, 3o are available in Table 2. Source data for Fig. 4k, l are available in Table 3. Source data for Extended Data Figs 3c, d are available in Table 4. Source data for Extended Data Figs 6j, l, o, p, r, s are available in Table 5. Source data for Extended Data Figs 10b-j are available in Table 6. All other data supporting the findings of this study are available from the corresponding author upon a reasonable request.

31. Gan, W. *et al.* SPOP Promotes Ubiquitination and Degradation of the ERG Oncoprotein to Suppress Prostate Cancer Progression. *Molecular cell* **59**, 917–930 (2015).
32. Dai, X. *et al.* Prostate cancer-associated SPOP mutations confer resistance to BET inhibitors through stabilization of BRD4. *Nat Med* **23**, 1063–1071 (2017).
33. Wan, L. *et al.* The APC/C E3 Ligase Complex Activator FZR1 Restricts BRAF Oncogenic Function. *Cancer Discovery* **7**, 424–441(2017).
34. Gao, D. *et al.* Phosphorylation by Akt1 promotes cytoplasmic localization of Skp2 and impairs APC^{Cdh1}-mediated Skp2 destruction. *Nat Cell Biol* **11**, 397–408 (2009).
35. Yu, Q. *et al.* Requirement for CDK4 kinase function in breast cancer. *Cancer Cell* **9**, 23–32 (2006).
36. Sicinska E. *et al.* Requirement for cyclin D3 in lymphocyte development and T cell leukemias. *Cancer Cell* **4**, 451–61 (2003).
37. Hamanishi, J. *et al.* Programmed cell death 1 ligand 1 and tumor-infiltrating $CD8^+$ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A* **104**, 3360–3365 (2007).
38. Wang, H. *et al.* The metabolic function of cyclin D3-CDK6 kinase in cancer cell survival. *Nature* **546**, 426–430 (2017).
39. Wan, L. *et al.* APC(Cdc20) suppresses apoptosis through targeting Bim for ubiquitination and destruction. *Developmental cell* **29**, 377–391 (2014).
40. Kozar, K. *et al.* Mouse development and cell proliferation in the absence of D-cyclins. *Cell* **118**, 477–491 (2004).
41. Choi, YJ. *et al.* The requirement for cyclin D function in tumor maintenance. *Cancer cell* **22**, 438–451 (2012).
42. Sicinski, P. *et al.* Cyclin D1 provides a link between development and oncogenesis in the retina and breast. *Cell* **82**, 621–630 (1995).