anti-PD-1 antibody to palbociclib treatment restored essentially normal numbers of TILs (Extended Data Fig. 10d-j).

A recent study revealed that another inhibitor of CDK4/6, abemaciclib, increased immunogenicity of cancer cells via an *Rb*-dependent mechanism, which activates tumor cell expression of endogenous retroviral elements, thereby stimulating production of type III interferons and antigen presentation by tumor cells[30]. Together with our demonstration that cyclin D-CDK4 regulates PD-L1 stability through Cullin 3^{SPOP} (Extended Data Fig. 10k), these studies provide complementary molecular rationale for combining CDK4/6 inhibitor treatment with anti-PD-1/PD-L1 immunotherapy to enhance tumor regression.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

Received 12 July; accepted 8 November 2017.
Published online 16 November 2017.

1. Zou, W., Wolchok, J. D. & Chen, L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. *Sci Transl Med* **8**, 328rv324 (2016).
2. Boussiotis, V. A. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. *N Engl J Med* **375**, 1767–1778 (2016).
3. Gotwals, P. *et al.* Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer* **17**, 286–301 (2017).
4. Sharma, P. & Allison, J. P. The future of immune checkpoint therapy. *Science* **348**, 56–61 (2015).
5. Mahoney, K. M., Rennert, P. D. & Freeman, G. J. Combination cancer immunotherapy and new immunomodulatory targets. *Nat Rev Drug Discov* **14**, 561–584 (2015).
6. Herbst, R. S. *et al.* Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* **515**, 563–567 (2014).
7. Iwai, Y. *et al.* Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A* **99**, 12293–12297 (2002).
8. Otto, T. & Sicinski, P. Cell cycle proteins as promising targets in cancer therapy. *Nat Rev Cancer* **17**, 93–115 (2017).
9. Casey, S. C. *et al.* MYC regulates the antitumor immune response through CD47 and PD-L1. *Science* **352**, 227–231 (2016).
10. Dorand, R. D. *et al.* Cdk5 disruption attenuates tumor PD-L1 expression and promotes antitumor immunity. *Science* **353**, 399–403 (2016).
11. Li, C. W. *et al.* Glycosylation and stabilization of programmed death ligand-1 suppresses T-cell activity. *Nat Commun* **7**, 12632 (2016).
12. Lim, S. O. *et al.* Deubiquitination and Stabilization of PD-L1 by CSN5. *Cancer Cell* **30**, 925–939 (2016).
13. Schiff, P. B. & Horwitz, S. B. Taxol stabilizes microtubules in mouse fibroblast cells. *Proc Natl Acad Sci U S A* **77**, 1561–1565 (1980).
14. Malumbres, M. & Barbacid, M. Mammalian cyclin-dependent kinases. *Trends Biochem Sci* **30**, 630–641 (2005).
15. Hydbring, P., Malumbres, M. & Sicinski, P. Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases. *Nat Rev Mol Cell Biol* **17**, 280–292 (2016).
16. Bates, S. *et al.* CDK6 (PLSTIRE) and CDK4 (PSK-J3) are a distinct subset of the cyclin-dependent kinases that associate with cyclin D1. *Oncogene* **9**, 71–79 (1994).
17. Lees, E., Faha, B., Dulic, V., Reed, S. I. & Harlow, E. Cyclin E/cdk2 and cyclin A/cdk2 kinases associate with p107 and E2F in a temporally distinct manner. *Genes Dev* **6**, 1874–1885 (1992).
18. Takaki, T. *et al.* Preferences for phosphorylation sites in the retinoblastoma protein of D-type cyclin-dependent kinases, Cdk4 and Cdk6, in vitro. *J Biochem* **137**, 381–386 (2005).
19. Fry, D. W. *et al.* Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther* **3**, 1427–1438 (2004).
20. Parry, D., Bates, S., Mann, D. J. & Peters, G. Lack of cyclin D-Cdk complexes in Rb-negative cells correlates with high levels of p16INK4/MTS1 tumour suppressor gene product. *EMBO J* **14**, 503–511 (1995).
21. Lukas, J. *et al.* Retinoblastoma-protein-dependent cell-cycle inhibition by the tumour suppressor p16. *Nature* **375**, 503–506 (1995).
22. Soucy, T. A. *et al.* An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. *Nature* **458**, 732–736 (2009).
23. Genschik, P., Sumara, I. & Lechner, E. The emerging family of CULLIN3-RING ubiquitin ligases (CRL3s): cellular functions and disease implications. *EMBO J* **32**, 2307–2320 (2013).
24. Barbieri, C. E. *et al.* Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. *Nat Genet* **44**, 685–689 (2012).
25. Cancer Genome Atlas Research, N. The Molecular Taxonomy of Primary Prostate Cancer. *Cell* **163** (2015).
26. Sato, Y. *et al.* Integrated molecular analysis of clear-cell renal cell carcinoma. *Nat Genet* **45**, 860–867 (2013).
27. Xu, J. *et al.* Genome-wide association study in Chinese men identifies two new prostate cancer risk loci at 9q31.2 and 19q13.4. *Nat Genet* **44**, 1231–1235 (2012).
28. Gan, W. *et al.* SPOP Promotes Ubiquitination and Degradation of the ERG Oncoprotein to Suppress Prostate Cancer Progression. *Mol Cell* **59**, 917–930 (2015).
29. da Fonseca, P. C. *et al.* Structures of APC/C(Cdh1) with substrates identify Cdh1 and Apc10 as the D-box co-receptor. *Nature* **470**, 274–278 (2011).
30. Goel, S. *et al.* CDK4/6 inhibition triggers anti-tumour immunity. *Nature* **548**, 471–475 (2017).

Supplementary Information is available in the online version of the paper.

Acknowledgements We thank members of the Wei, Freeman, Sicinski, and Pandolfi laboratories for discussions. J.Z. is supported by the career transition award (1K99CA212292-01). W.W. is a Leukemia & Lymphoma Society (LLS) research scholar. This work was supported in part by the NIH grants GM094777 and CA177910 (W.W.), R01 CA083688, P01 CA080111 and R01 CA202634 (to P.S.), and P50CA101942 (G.J.F).

Author Contributions J.Z., X.B. and H.W. performed most of the experiments with assistance from Y.Z. Y.G., N.T.N, Y.T., Y.C., F.W., X.D., J.G., Y.H., C.F., S.R., and Y.S. Y.Z, S.R., and Y.S performed IHC staining for human prostate cancer samples. Y.G., Y.T., and Y.C. helped mice work. J.Z., X.B., H.W. P.S. and W.W. designed the experiments. G.F., P.S., and W.W. supervised the study. J.Z. and W.W. wrote the manuscript with help from X.B, H.W., P.S. and G.F. All authors commented on the manuscript.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details are available in the online version of the paper. Readers are welcome to comment on the online version of the paper. Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. Correspondence and requests for materials should be addressed to G.F. (gordon_freeman@dfci.harvard.edu), P.S. (peter_Sicinski@dfci.harvard.edu) or W.W. (wwei2@bidmc.harvard.edu).

Reviewer Information *Nature* thanks J. Bartek, C. Klebanoff and S. Ogawa for their contribution to the peer review of this work.