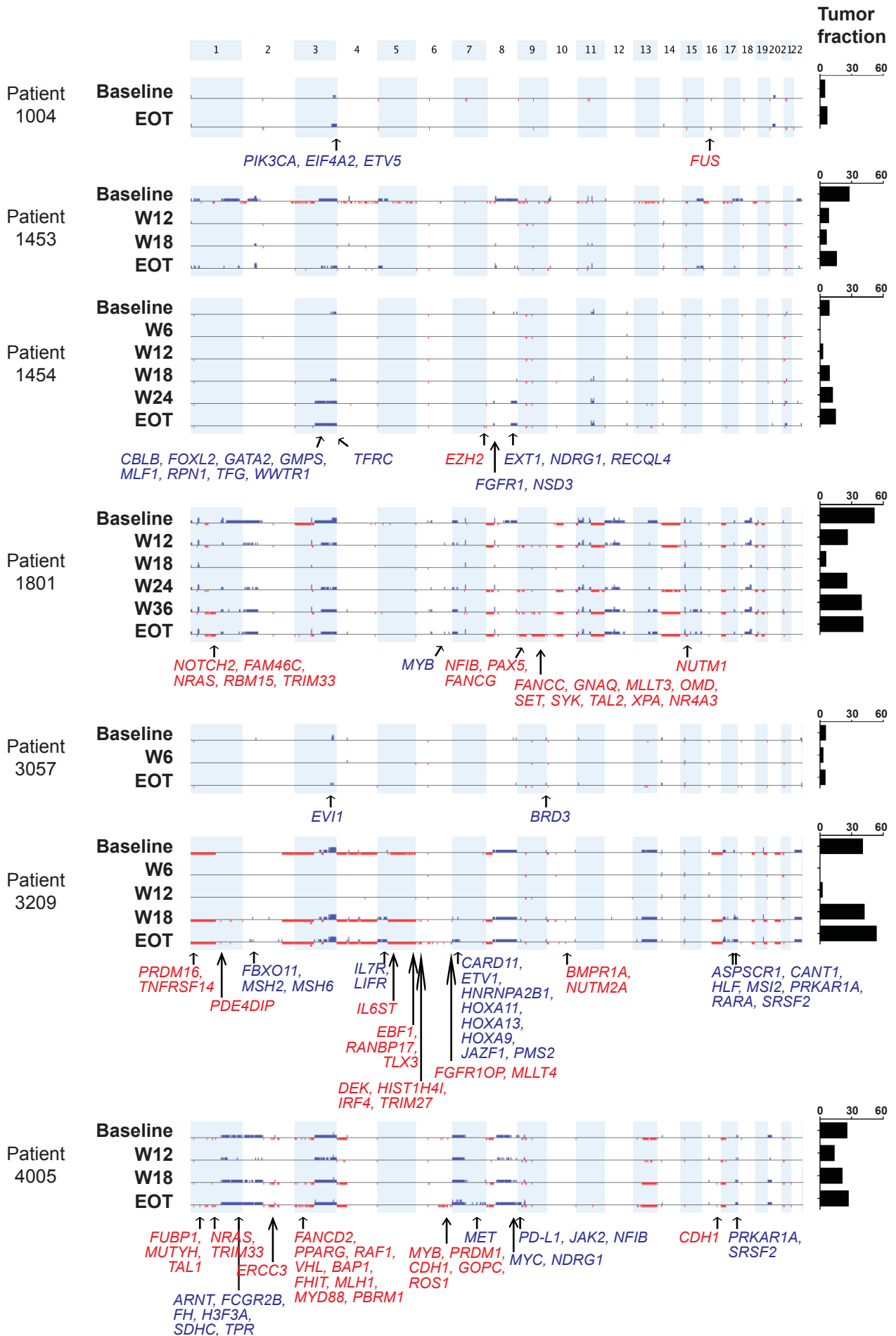


A



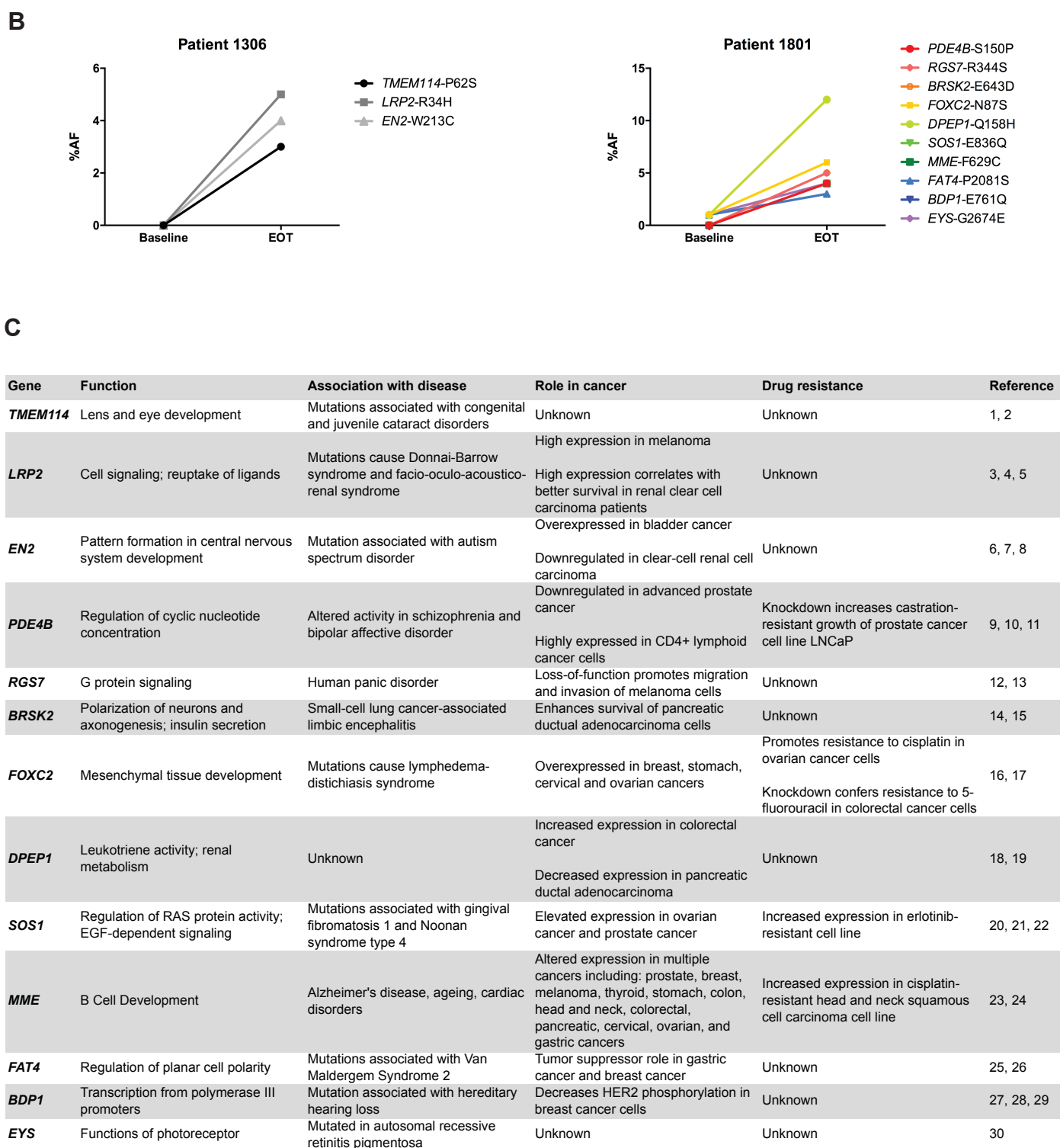


Figure S8.

A, CNV landscapes of 7 patients treated with pictilisib and had detectable CNVs at both baseline and EOT. COSMIC genes with CNVs not found at baseline but in EOT were annotated. Blue, copy number gain; red, copy number loss. **(B-C)** Somatic variants significantly increased in EOT compared to baseline cfDNA in two patients.

B, Gene mutation allele frequency at baseline and EOT. **C**, Known functions of all genes enriched in EOT and their roles in disease and drug resistance.

Supplementary References

1. Jamieson RV, Farrar N, Stewart K, Perveen R, Mihelec M, Carette M, *et al.* Characterization of a familial t(16;22) balanced translocation associated with congenital cataract leads to identification of a novel gene, TMEM114, expressed in the lens and disrupted by the translocation. *Hum Mutat* **2007**;28(10):968-77 doi 10.1002/humu.20545.
2. Mihelec M, St Heaps L, Flaherty M, Billson F, Rudduck C, Tam PP, *et al.* Chromosomal rearrangements and novel genes in disorders of eye development, cataract and glaucoma. *Twin Res Hum Genet* **2008**;11(4):412-21 doi 10.1375/twin.11.4.412.
3. Christ A, Herzog K, Willnow TE. LRP2, an auxiliary receptor that controls sonic hedgehog signaling in development and disease. *Dev Dyn* **2016**;245(5):569-79 doi 10.1002/dvdy.24394.
4. Gonias SL, Karimi-Mostowfi N, Murray SS, Mantuano E, Gilder AS. Expression of LDL receptor-related proteins (LRPs) in common solid malignancies correlates with patient survival. *PLoS One* **2017**;12(10):e0186649 doi 10.1371/journal.pone.0186649.
5. Andersen RK, Hammer K, Hager H, Christensen JN, Ludvigsen M, Honore B, *et al.* Melanoma tumors frequently acquire LRP2/megalin expression, which modulates melanoma cell proliferation and survival rates. *Pigment Cell Melanoma Res* **2015**;28(3):267-80 doi 10.1111/pcmr.12352.
6. Hnoonual A, Sripo T, Limprasert P. Whole-exome sequencing identifies a novel heterozygous missense variant of the EN2 gene in two unrelated patients with autism spectrum disorder. *Psychiatr Genet* **2016**;26(6):297-301 doi 10.1097/YPG.0000000000000153.
7. Li Y, Liu H, Lai C, Su Z, Heng B, Gao S. Repression of engrailed 2 inhibits the proliferation and invasion of human bladder cancer in vitro and in vivo. *Oncol Rep* **2015**;33(5):2319-30 doi 10.3892/or.2015.3858.
8. Lai CY, Xu Y, Yu GS, Wu X, Li YF, Pan B, *et al.* Engrailed-2 might play an anti-oncogenic role in clear-cell renal cell carcinoma. *J Mol Histol* **2016**;47(3):229-37 doi 10.1007/s10735-016-9665-4.
9. Feng Y, Cheng D, Zhang C, Li Y, Zhang Z, Wang J, *et al.* Association of PDE4B Polymorphisms with Susceptibility to Schizophrenia: A Meta-Analysis of Case-Control Studies. *PLoS One* **2016**;11(1):e0147092 doi 10.1371/journal.pone.0147092.
10. Kashiwagi E, Shiota M, Yokomizo A, Itsumi M, Inokuchi J, Uchiumi T, *et al.* Downregulation of phosphodiesterase 4B (PDE4B) activates protein kinase A and contributes to the progression of prostate cancer. *Prostate* **2012**;72(7):741-51 doi 10.1002/pros.21478.
11. Nagy ZS, Ross JA, Rodriguez G, Balint BL, Szeles L, Nagy L, *et al.* Genome wide mapping reveals PDE4B as an IL-2 induced STAT5 target gene in activated human PBMCs and lymphoid cancer cells. *PLoS One* **2013**;8(2):e57326 doi 10.1371/journal.pone.0057326.

12. Sabater L, Gomez-Choco M, Saiz A, Graus F. BR serine/threonine kinase 2: a new autoantigen in paraneoplastic limbic encephalitis. *J Neuroimmunol* **2005**;170(1-2):186-90 doi 10.1016/j.jneuroim.2005.08.011.
13. Saiyin H, Na N, Han X, Fang Y, Wu Y, Lou W, *et al.* BRSK2 induced by nutrient deprivation promotes Akt activity in pancreatic cancer via downregulation of mTOR activity. *Oncotarget* **2017**;8(27):44669-81 doi 10.18632/oncotarget.17965.
14. Hohoff C, Neumann A, Domschke K, Jacob C, Maier W, Fritze J, *et al.* Association analysis of Rgs7 variants with panic disorder. *J Neural Transm (Vienna)* **2009**;116(11):1523-8 doi 10.1007/s00702-008-0097-5.
15. Qutob N, Masuho I, Alon M, Emmanuel R, Cohen I, Di Pizio A, *et al.* RGS7 is recurrently mutated in melanoma and promotes migration and invasion of human cancer cells. *Sci Rep* **2018**;8(1):653 doi 10.1038/s41598-017-18851-4.
16. Wang T, Zheng L, Wang Q, Hu YW. Emerging roles and mechanisms of FOXC2 in cancer. *Clin Chim Acta* **2018**;479:84-93 doi 10.1016/j.cca.2018.01.019.
17. Tavian D, Missaglia S, Maltese PE, Michelini S, Fiorentino A, Ricci M, *et al.* FOXC2 disease-mutations identified in lymphedema-distichiasis patients cause both loss and gain of protein function. *Oncotarget* **2016**;7(34):54228-39 doi 10.18632/oncotarget.9797.
18. Eisenach PA, Soeth E, Roder C, Kloppel G, Tepel J, Kalthoff H, *et al.* Dipeptidase 1 (DPEP1) is a marker for the transition from low-grade to high-grade intraepithelial neoplasia and an adverse prognostic factor in colorectal cancer. *Br J Cancer* **2013**;109(3):694-703 doi 10.1038/bjc.2013.363.
19. Zhang G, Schetter A, He P, Funamizu N, Gaedcke J, Ghadimi BM, *et al.* DPEP1 inhibits tumor cell invasiveness, enhances chemosensitivity and predicts clinical outcome in pancreatic ductal adenocarcinoma. *PLoS One* **2012**;7(2):e31507 doi 10.1371/journal.pone.0031507.
20. Xiao ZH, Linghu H, Liu QF. [Expressions of Ras and Sos1 in epithelial ovarian cancer tissues and their clinical significance]. *Nan Fang Yi Ke Da Xue Xue Bao* **2016**;36(11):1502-7.
21. De S, Dermawan JK, Stark GR. EGF receptor uses SOS1 to drive constitutive activation of NFkappaB in cancer cells. *Proc Natl Acad Sci U S A* **2014**;111(32):11721-6 doi 10.1073/pnas.1412390111.
22. Timofeeva OA, Zhang X, Ransom HW, Varghese RS, Kallakury BV, Wang K, *et al.* Enhanced expression of SOS1 is detected in prostate cancer epithelial cells from African-American men. *Int J Oncol* **2009**;35(4):751-60.
23. Mishra D, Singh S, Narayan G. Role of B Cell Development Marker CD10 in Cancer Progression and Prognosis. *Mol Biol Int* **2016**;2016:4328697 doi 10.1155/2016/4328697.
24. Fukusumi T, Ishii H, Konno M, Yasui T, Nakahara S, Takenaka Y, *et al.* CD10 as a novel marker of therapeutic resistance and cancer stem cells in head and neck squamous cell carcinoma. *Br J Cancer* **2014**;111(3):506-14 doi 10.1038/bjc.2014.289.

25. Cai J, Feng D, Hu L, Chen H, Yang G, Cai Q, *et al.* FAT4 functions as a tumour suppressor in gastric cancer by modulating Wnt/beta-catenin signalling. *Br J Cancer* **2015**;113(12):1720-9 doi 10.1038/bjc.2015.367.
26. Hou L, Chen M, Zhao X, Li J, Deng S, Hu J, *et al.* FAT4 functions as a tumor suppressor in triple-negative breast cancer. *Tumour Biol* **2016** doi 10.1007/s13277-016-5421-3.
27. Girotto G, Abdulhadi K, Buniello A, Vozzi D, Licastro D, d'Eustacchio A, *et al.* Linkage study and exome sequencing identify a BDP1 mutation associated with hereditary hearing loss. *PLoS One* **2013**;8(12):e80323 doi 10.1371/journal.pone.0080323.
28. Gouge J, Guthertz N, Kramm K, Dergai O, Abascal-Palacios G, Satia K, *et al.* Molecular mechanisms of Bdp1 in TFIIIB assembly and RNA polymerase III transcription initiation. *Nat Commun* **2017**;8(1):130 doi 10.1038/s41467-017-00126-1.
29. Thaler S, Schmidt M, Robetawag S, Thiede G, Schad A, Sleeman JP. Proteasome inhibitors prevent bi-directional HER2/estrogen-receptor cross-talk leading to cell death in endocrine and lapatinib-resistant HER2+/ER+ breast cancer cells. *Oncotarget* **2017**;8(42):72281-301 doi 10.18632/oncotarget.20261.
30. Gu S, Tian Y, Chen X, Zhao C. Targeted next-generation sequencing extends the phenotypic and mutational spectrums for EYS mutations. *Mol Vis* **2016**;22:646-57.