Supplementary Figure 1: Box plot of lesion numbers in the wildtype, *UroIICRE*$^{+}$ *β-catenin*$^{exon3/+}$ and *UroIICRE*$^{+}$ *β-catenin*$^{exon3/exon3}$

Box plot of lesion numbers in the wildtype, *UroIICRE*$^{+}$ *β-catenin*$^{exon3/+}$ and *UroIICRE*$^{+}$ *β-catenin*$^{exon3/exon3}$ cohorts at 3, 12 and 18 months of age (n=3). We show that at 3, 12 and 18 months the number of lesions in the *UroIICRE*$^{+}$ *β-catenin*$^{exon3/+}$ (e3/+) and *UroIICRE*$^{+}$ *β-catenin*$^{exon3/exon3}$ (e3/e3) are significantly higher than the corresponding wildtype (WT) time point (*, $p<0.001$, Mann Whitney Test). Similarly lesions at both 12 and 18 months in the *UroIICRE*$^{+}$ *β-catenin*$^{exon3/+}$ and *UroIICRE*$^{+}$ *β-catenin*$^{exon3/exon3}$ cohorts are significantly higher than the corresponding cohort at 3 months ($^{\#}$, $p<0.001$, Mann Whitney Test).

Supplementary Figure 2: **Proliferation of lesions in Rapamycin treated mice versus vehicle control**

Boxplot indicating reduction in percentage of BrdU positive cells in bladder tumours treated with Rapamycin versus those treated with vehicle control ($p<0.01$, Mann Whitney Test).

Supplementary Figure 3: Histology of *AhCreER*^{T} *GSK3αβ* $^{fl/fl}$ mice

AhCreER^{T} *GSK3αβ* $^{fl/fl}$ mice reveal bladder lesions (A), which demonstrate proliferation as well as accumulation of nuclear β-catenin and PTEN (B-D).

Box plot of average number of BrdU positive cells per lesion in both *AhCreER^{T} APC$^{fl/fl}$* and *AhCreER^{T} APC$^{fl/fl}$ PTEN$^{fl/fl}$* mice of each cohort at 7 days after first induction (n=3) (E).

Black bar measures 200µm (20x magnification).

Supplementary Figure 4: **Histology of *UroIICRE^{+}PTEN$^{fl/fl}$* mice**

Comparison of 12 month old wildtype and *UroIICRE^{+}PTEN$^{fl/fl}$* urothelium. The H&E demonstrates that the urothelium of *UroIICRE^{+}PTEN$^{fl/fl}$* (B) is comparable to wildtype (A) with no hyperplasia, dysplasia or tumour formation. We notice lower levels of PTEN in the *UroIICRE^{+}PTEN$^{fl/fl}$* urothelium *(*D) in comparison to wildtype (C) with similar levels of pAkt(Ser473) (E,F) .

Black bar measures 200µm (20x magnification).

Supplementary Figure 5: Boxplot of Histoscore of total Akt and total mTOR in *UroIICRE^{+} β-catenin$^{exon3/exon3}$* and *UroIICRE^{+} β-catenin$^{exon3/exon3}$ PTEN$^{fl/fl}$* mice

Histoscore of age matched lesions in *UroIICRE^{+} β-catenin$^{exon3/exon3}$* (e3/e3) and *UroIICRE^{+} β-catenin$^{exon3/exon3}$ PTEN$^{fl/fl}$*(fl/fl) demonstrates no stastically significant increase in total Akt (p=0.19) (A) and total mTOR (p=0.07) (B) using the Mann Whitney Test.

Supplementary Figure 6: *UroIICRE^{+} β-catenin$^{exon3/exon3}$ PTEN$^{fl/fl}$* mice treated with Rapamycin

Addition IHC for pmTOR reveals significant downregulation of this pathway in *UroIICRE^{+} β-catenin$^{exon3/exon3}$ PTEN$^{fl/fl}$* mice after treatment with Rapamycin (A,B). Similarly we also demonstrate that p-4EBP1 and p-S6 Kinase, a know target of the mTOR pathway, is downregulated after treatment (C-F).

Black bar represents 100µm (all magnifications at 40x).

Supplementary Figure 7: **Proliferation of tumours in Rapamycin treated mice versus vehicle control**

Boxplot indicating reduction of BrdU positive cells per 20x field view of bladder tumours treated with Rapamycin versus those treated with vehicle control ($p<0.05$, Mann Whitney Test) (A). Boxplot demonstrating reduction in percentage of BrdU positive cells in tumours and (*UroIICRE+ β-catenin$^{exon3/exon3}$ PTEN$^{fl/f)}$*) and lesions (*UroIICRE+ β-catenin$^{exon3/exon3}$*) after treatment with Rapamycin (B).