

**Supplementary Table S1. PI3Ki + MEKi + PORCNI therapy results in tumor clearance in Pb-Cre;PTEN<sup>fl/fl</sup>Trp53<sup>fl/fl</sup> mice.** Pb-Cre;PTEN<sup>fl/fl</sup>Trp53<sup>fl/fl</sup> mice with established tumors were treated with copanlisib (C, 14 mg/kg, *iv*, every alternate day) + trametinib (T, 3 mg/kg, *po*, every day) + LGK`974 (L, 3 mg/kg, *po*, every day) for 28 days and approximately 7 months, as described in Methods section. At the end of treatment, harvested tumors were formalin fixed, paraffin embedded and individual slides were stained with H&E and scored in a blinded fashion by pathologist for histopathological response, as indicated in the table.

Pathological assessment of PTEN/p53-deficient murine prostate tumors <sup>#</sup>					
Treatments	Treatment response	Benign prostatic hyperplasia	High grade-prostatic intraepithelial neoplasia	Invasive adenocarcinoma	Sarcomatoid carcinoma
Untreated (28 days)	No	0/6	6/6	5/6	5/6
C+T+L (11 months)	Yes	3/3	0/3	0/3	0/3
C+T+L (28 days)	Yes	5/5**	0/5*	0/5*	0/5*
C+T (28 days)	Yes	4/4*	0/4*	0/4*	0/4*
	No	0/1	1/1	1/1	1/1
L (28 days)	No	1/3	2/3	2/3	2/3
T (28 days)	Yes	3/3*	0/3*	0/3*	0/3*
	No	2/3	1/3	1/3	3/3
C (28 days)	Yes	3/3*	0/3*	0/3*	0/3*
	No	1/4	2/4	1/4	2/4
<sup>#</sup> Number of tumors positive for given pathological characteristic/Total number of tumors evaluated					