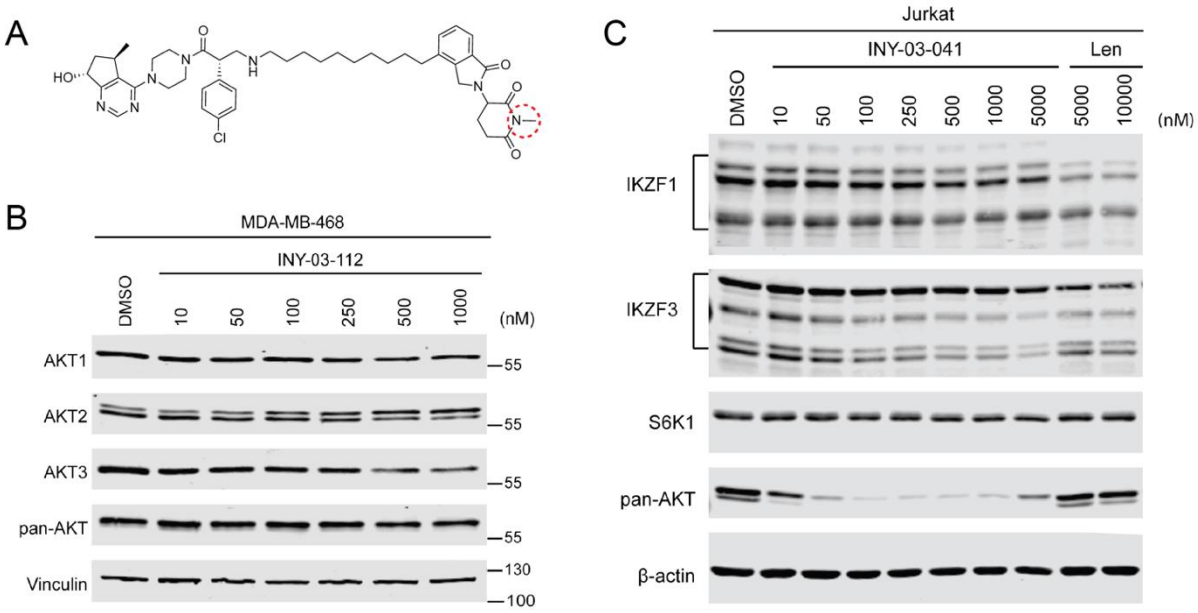

Figure S1. INY-03-041 requires CRBN binding to induce highly selective AKT degradation. *Related to Figure 1 and Figure 2*. (A) Chemical structure of negative control compound INY-03-112, with N-methylated glutarimide circled. (B) Immunoblots for AKT1, AKT2, AKT3, pan-AKT and Vinculin in MDA-MB-468 cells after 12-hour treatment with DMSO or INY-03-112 at the concentrations indicated (n=2). (C) Immunoblots for IKZF1, IKZF3, S6K1, pan-AKT and β-actin in Jurkat cells after 24-hour treatment with DMSO, INY-03-041, or lenalidomide (Len) at the concentrations indicated (n=3).

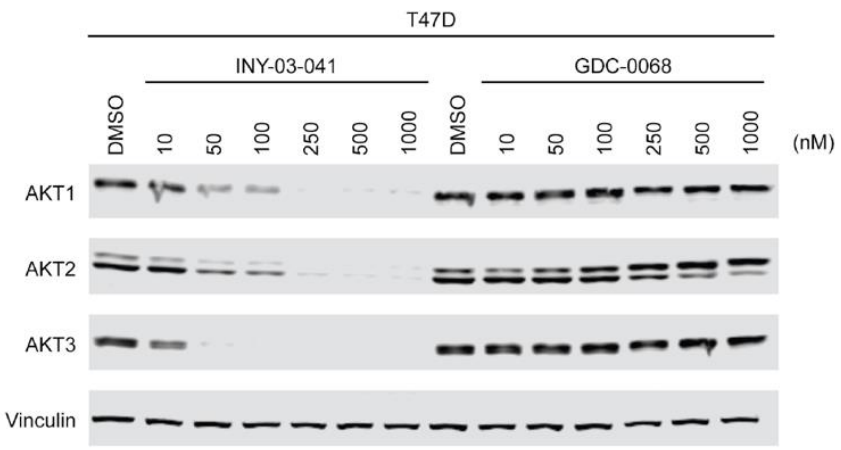

Figure S2. INY-03-041 induces degradation of AKT isoforms in T47D cells. *Related to Figure 4.* Immunoblots of AKT1, AKT2, AKT3 and Vinculin after treating T47D cells for 24 hours with DMSO, INY-03-041, or GDC-0068 at the concentrations indicated (n=3).

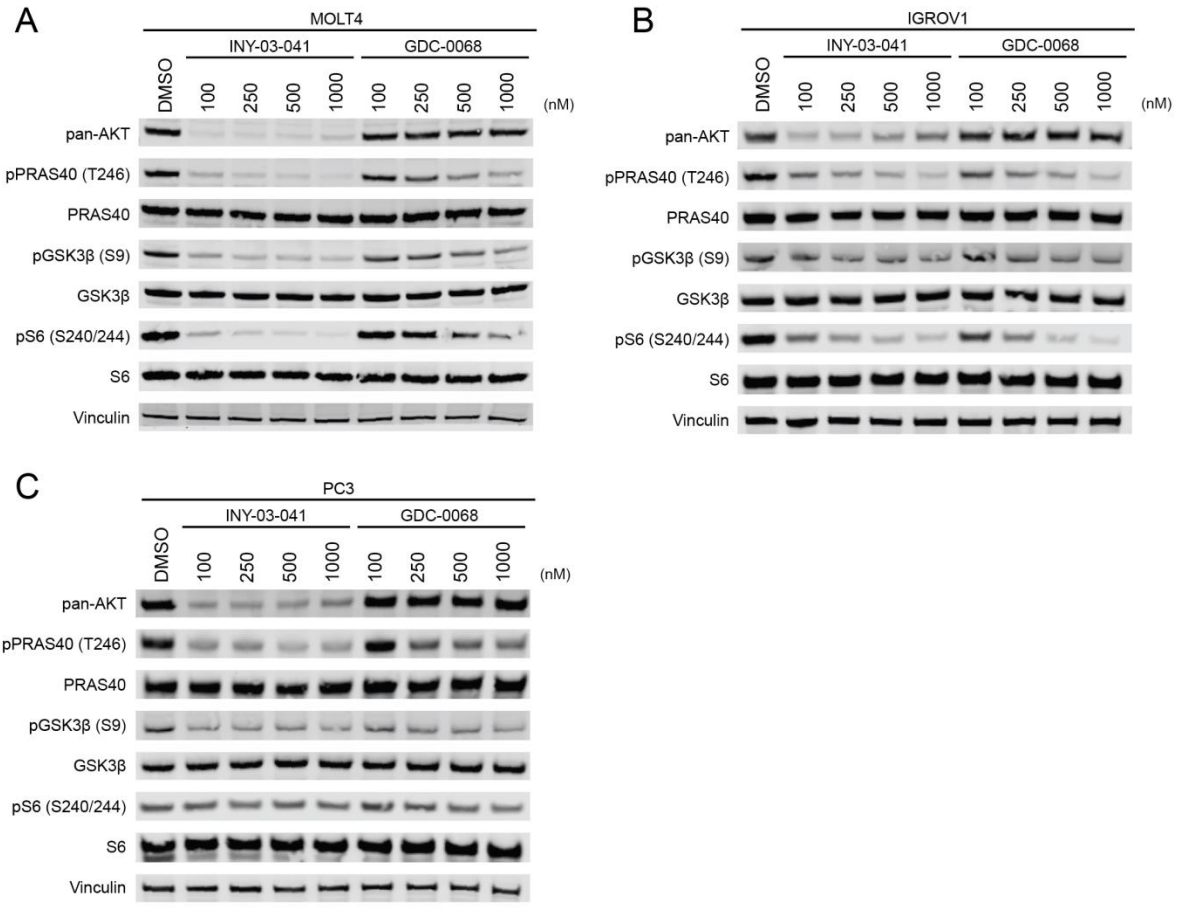

Figure S3. INY-03-041 induces potent downregulation of AKT signaling in MOLT4, IGROV1 and PC3 cells. *Related to Figure 4.* Immunoblots of pan-AKT, phospho-PRAS40 (T246), total PRAS40, phospho-GSK3β (S9), total GSK3β, phospho-S6 (S240/244), total S6 and Vinculin in (A) MOLT4, (B) IGROV1 and (C) PC3 cells after treatment with DMSO, INY-03-041, or GDC-0068 for 24 hours at concentrations indicated (n=2).

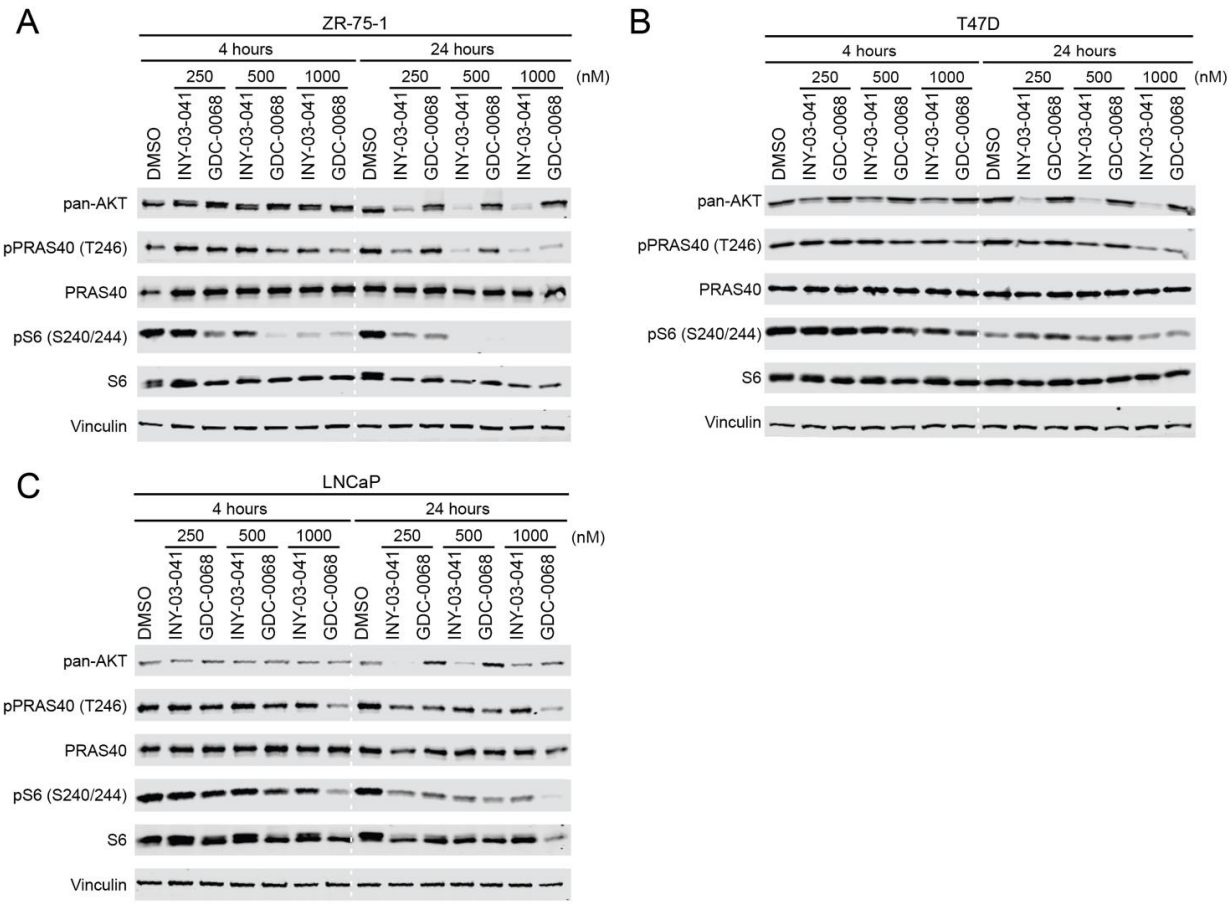

Figure S4. **INY-03-041 requires longer time points than GDC-0068 to display inhibition of downstream AKT signaling.** *Related to Figure 4*. Immunoblots of pan-AKT, phospho-PRAS40 (T246), total PRAS40, phospho-S6 (S240/244), total S6 and Vinculin in (A) ZR-75-1, (B) T47D and (C) LNCaP cells after treatment with DMSO, INY-03-041, and GDC-0068 for 4 or 24 hours at indicated concentrations (n=2).

Table S3. **Hormone receptor and mutational status of PIK3CA and PTEN in cancer cell line panel.** *Related to Figure 3.* The tissue, cancer subtype and status of each gene (Meric-Bernstam et al., 2012; Vlietstra et al., 1998) as wild-type (wt), mutated (mut) or deleted (del) is indicated. Triple negative breast cancer (TNBC).

Cell Line	Tissue	Cancer Subtype	PIK3CA	PTEN
ZR-75-1	Breast	Luminal A	wt	mut (L108R)
T47D	Breast	Luminal A	mut (H1047R)	wt
LNCaP	Prostate	Androgen-dependent	wt	del/mut
MCF-7	Breast	Luminal A	mut (E545K)	wt
MDA-MB-468	Breast	TNBC – Basal A	wt	del
HCC1937	Breast	TNBC – Basal A	wt	del

Table S4. **GR values indicate anti-proliferative advantage of INY-03-041.** *Related to Figure 3.* (A) GR values were calculated after 72-hour treatment with the compounds indicated over a range of concentrations. GR_{50} values represent compound potency, GR_{max} values measure the efficacy of the drug at high concentrations. GR_{AOC} captures changes in potency and efficacy and is calculated by integrating GR curve over a range of concentrations.

GR_{50} (μM)

Cell Line	INY-03-041	INY-03-112	GDC-0068	Lenalidomide
ZR-75-1	0.016	0.413	0.229	inf
T47D	0.178	1.34	1.53	inf
LNCaP	0.130	1.38	1.32	inf
MCF-7	0.148	1.49	1.72	inf
MDA-MB-468	1.69	2.70	12.9	inf
HCC1937	1.65	2.42	inf	inf

GR_{max}

Cell Line	INY-03-041	INY-03-112	GDC-0068	Lenalidomide
ZR-75-1	-0.688	-0.517	-0.384	0.744
T47D	-0.321	-0.163	0.054	0.999
LNCaP	0.011	0.212	0.017	0.829
MCF-7	-0.305	-0.332	0.218	0.910
MDA-MB-468	-0.819	-0.832	0.518	0.940
HCC1937	-0.813	-0.726	0.538	0.905

GR_{AOC}

Cell Line	INY-03-041	INY-03-112	GDC-0068	Lenalidomide
ZR-75-1	1.17	0.329	0.705	0.085
T47D	0.630	0.198	0.285	-0.010
LNCaP	0.549	0.186	0.330	0.042
MCF-7	0.627	0.320	0.243	0.021
MDA-MB-468	0.430	0.319	0.140	0.033
HCC1937	0.415	0.313	0.156	-0.008