**Supplementary Materials and Methods.**

***Apoptosis assays***

Induction of apoptosis in Aldefluor+ and Aldefluor- cells was measured by Annexin V binding and Caspase 3/7 assays. Briefly, SUM159 cells were treated with VS-5584 or DMSO control for 24h. Cells were first stained with Aldefluor reagents for 30 min followed by Annexin V-FITC (EBioscience, San Diego, CA) and PI staining for 10 min. Alternatively, SUM159 cells were first stained with Aldefluor reagent. FACS-sortedAldefluor+ and Aldefluor- cells were then cultured overnight before compound incubation for 24h. Caspase3/7 Glo assay (Promega, Madison, WI) was carried out.

***siRNA Transfection:***

Two different siRNA sequences purchased from Qiagen (Velencia, CA) were used for each of PI3K (SI02622207, SI02665369), PI3K (SI02622214, SI02622221) and mTOR (SI00300244, SI02662009) along with scrambled negative control AllStar siRNA (Qiagen).

***in vivo tumor xenograft stidies and cell dissociation***

*MDA-MB-231 xenograft study*: 4x106 MDA-MB-231 cells admixed with matrigel (BD Biosciences) were injected orthotopically in the mammary fat pad of six to eight weeks old female Nu/Nu mice. After tumors reached average size of 100-150 mm3 (approximately 3-4 weeks), mice were randomized into 2 groups (n=7) and treated with either vehicle alone or 25 mg/kg VS-5584 QD on day 1-5 and 8-9 by oral administration.

*MCF7 xenograft study*: 107 MCF7 cells were admixed with matrigel and injected orthotopically in the mammary fat pad of six to eight weeks old female Nu/Nu mice in which estrogen pellet was inserted 1 day prior to cell injection. After tumors reached an average size of 100-150 mm3 (approximately 3-4 weeks), mice were randomized into 3 groups of 10 animals per group and were administered with vehicle, 20 mg/kg VS-5584 or 5 mg/kg everolimus orally on a QDx10 dosing schedule.

*NCI-H841 xenograft study:* 5x106 NCI-H69 SCLC cells admixed with matrigel were injected subcutaneously in the right flank of female athymic nude mice. When tumors reached an average size of 400 mm3, mice were randomized into 2 groups (n=8) and treated with vehicle control, or 20 mg/kg VS-5584 administered orally on Monday, Wednesday and Friday for 3 weeks.

*NCI-H69 xenograft study:* 4x106 NCI-H69 SCLC cells admixed with matrigel were injected subcutaneously in the right flank of female athymic nude mice. When tumors reached average size of 150 mm3, mice were randomized into 5 groups (n=10) and treated with vehicle control, cisplatin (i.p. once a week for 2 weeks), 15 mg/kg VS-5584 (PO, QDx5 weekly for 8 weeks), and combination of cisplatin and VS-5584 with the same dosing schedules. Tumor measurements and body weights were taken twice weekly.

*Cell dissociation:*To dissociate single cells, xenograft tumors or human tissue fragments were minced into smaller pieces and incubated in HEPES-Eagle's medium containing 50 μg/ml Liberase (Roche Applied Science, Indianapolis, IN) in case ofxenograft models or a mixture of 50 μg/ml collagenase and 50 μg/ml dispase in case of human tumors for 1h at 37°C under agitation. Tissue fragments were triturated by pipetting through pipettes with progressively smaller orifices (25, 10 and 5 ml) every 15 minutes. Dissociated cells were filtered through a 100 µm nylon mesh, centrifuged at 800 x g for 5 min and washed 3 times in RPMI medium supplemented with 20% FBS, 100 U/ml penicillin, and 100 g/ml streptomycin. To remove mouse cells from xenografted human tumors, 2x106 live cells were suspended in 1 ml RPMI supplemented with10% FBS. Ten µl of biotin anti-mouse CD45 (BioLegend) and 10 µl biotin anti-mouse H-2Kd (BioLegend) were added and incubated for 15 min on ice with occasional rocking. Fifty l washed Dynabeads Biotin Binder (Invitrogen) were added and incubated for 20 min on ice with occasional rocking. Beads were separated with magnet and free cell suspension transferred into new tubes.