**Supplementary Figure 1:** Representative example of tissue microarray (TMA) punched out from a combined large-cell neuroendocrine carcinoma (LCNEC) with adenocarcinoma. This is the same case illustrated in Figure 1. (A) (B) (C) Sample obtained from the LCNEC component. (A) Low-power field image (H.E). (B) High-power field image of the part surrounded by a square mark. (C) IHC staining of CD56. Cancer cells showed positive reaction. (D) (E) (F) Sample obtained from adenocarcinoma component. (D) Low-power field image on H&E. (E) High-power field image of the part surrounded by a square mark. (F) IHC staining of CD56. No positive cells were observed.

**Supplementary Figure 2:** Validation of five mutations on the PI3K/AKT/mTOR pathway by Sanger sequencing (LCNEC 68c: *PIK3CA* E545K, LCNEC 9c: *PTEN* K342\*, LCNEC 13c: *PTEN* S59\*, LCNEC 4c: *RICTOR* R910H, LCNEC 11p: *MTOR* E2419K).

**Supplementary Figure 3:** Correlation of gene copy number, calculated using the total depth on the covered region of each of 244 targeted genes and those obtained from the Oncomine® Cancer Research Panel (OCP).

**Supplementary Figure 4:** Validation of the copy number gains or amplifications of 13 samples (8 LCNEC samples, 1 SCLC biopsy samples and 4 SCLC surgically resected cases) for *MYCL1*, *MYC* and *FGFR1* by a quantitative real-time polymerase chain reaction (qPCR).

**Supplementary Figure 5**: Overview of the key driver alterations and other activating alterations in small cell lung cancer (SCLC). Genetic alterations in the PI3K/AKT/mTOR pathway were detected in 24 (17%) of the tumors: *PIK3CA* (4%), *PTEN* (6%), *AKT2* (2%) and *RICTOR* (6%). Copy number gains of each *MYC* family member were mutually exclusive.

**Supplementary Figure 6:** Relationship between *RB1* mutation and IHC staining of RB and p16. The mutual exclusivity of the protein expression between RB and p16 was distinct.

**Supplementary Figure 7:** Relationship between genetic alteration and protein expression in large-cell neuroendocrine carcinoma (LCNEC) of the lung. Comparison of the over expression of receptor tyrosine kinases (RTKs) with the genetic alterations in resected LCNEC specimens (51 of 65 resected cases) revealed no significant relationship between strongly positive RTKs (*KIT*, *EGFR*, *IGF1R*, *KDR*, *ERBB2*) expression and genetic alterations.