Epithelial-mesenchymal transition (EMT) progression and AKT activation were observed in both BR cell lines. Knockdown of CNTN1 re-sensitized BR cells to BCT-100 treatment and reversed the EMT progression via inhibiting AKT pathway. **Conclusion:** Contactin 1 modulates BCT-100 resistance through induction of EMT by activating AKT pathway in SCLC. **Keywords:** Contactin 1, small cell lung cancer, pegylated arginase (BCT-100)

P3.12-09
Smad4 Mutation Confers Acquired Neuroendocrine Phenotype in Transformation of Lung Adenocarcinoma to Small Cell Lung Cancer

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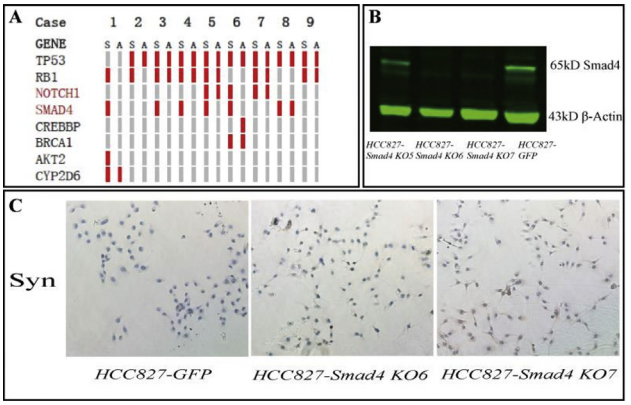
Background: Along with the widely use of EGFR-TKI therapy, transformation from lung adenocarcinoma (LAC) to small cell lung cancer (SCLC) has been recognized and accepted as a reason of drug resistance , but the mechanism remains unclear . **Method:** At first, we detected mutated genes in LAC and SCLC component from 9 combined SCLC cases independently by NGS, and analyzed the gene expression in pairs to find the targeted genes. And then, we knocked out the putative gene in HCC827 cell line by CRISPR/Cas9 to detect the changes of classic neuroendocrine markers (CgA, Syn, CD56). **Result:** A high mutation rate of Smad4 gene is observed in SCLC component from 9 combined SCLC cases (66.7%, 6/9, Figure 1A), which is much higher than that in pure SCLC (1.8%, available on http://www.cbioportal.org) samples. HCC827-Smad4$^{-/-}$ cell line is successfully established (Figure 1B), and by IHC assay, the expression of Syn is obviously enhanced in HCC827-Smad4$^{-/-}$ cells when compared with HCC827-GFP cells (Figure 1C). **Conclusion:** The dysfunction of Smad4 protein confers the neuroendocrine phenotype of LAC, which plays a potential role in transformation to SCLC. **Keywords:** small cell lung cancer, SMAD4 mutation, transformation



P3.12-10
Immunogenomic Characteristics of SCLC and LCNEC Redefined Molecular Subgroups

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Background: While small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) are distinct classes of high-grade neuroendocrine carcinomas, the differential diagnosis between SCLC and LCNEC remains challenging. In fact SCLC and LCNEC overlap in clinical, histopathologic, cytologic, morphologic and genetic characteristics. Molecular profiling with microarray or next-generation sequencing has provided growing evidence suggesting that both SCLC and LCNEC are biologically heterogeneous and a great part of them are borderline neuroendocrine carcinomas falling between typical SCLC and LCNEC. On account of accumulated knowledge, we speculated that immunogenomically characterizing SCLC and LCNEC collectively as one group, or rather morphologically or cytologically separating SCLC from LCNEC has superior clinical value. **Method:** We analyzed gene expression profiles of 44 SCLCs, 56 LCNECs and 25 normal lung samples obtained from Gene Expression Omnibus. Unsupervised and supervised analyses were performed to understand molecular characteristics of samples. Pathway and CIBERSORT analyses were employed to obtain immune landscape of SCLC and LCNEC. **Result:** Unsupervised clustering with 1189 differentially expressed genes revealed 2 distinct molecular subgroups (G1 and G2) of SCLC and LCNEC, which is not associated with histopathology. Targeted pathway analysis found that G1 was marked by activated IL-17, MAPK and Hippo signaling pathways. In contrast, transcriptional factors, such as ASCL1, INSM1, SOX2, and NKX2-1 were significantly up-regulated in G2, but not in G1. Moreover, in silico analysis of cellular composition and expression of immune genes disclosed unique immunoprofiles for G1 and G2. G1 was characterized by enriched CD4 memory cells, M1 macrophages and activated dendritic cells. While G2 was composed of high fractions of memory B cells and naïve CD4 cells. Strikingly, expression of both immunoinhibitors (IL10, PDL1, IDO1) and immunomodulators (OX40L, BAFF, GITR, IL6), as well as MHC class I and II molecules was higher in G1 compared to that in G2. **Conclusion:** We identified the common intrinsic features and molecular subgroups of SCLC and LCNEC, which are beyond conventional histopathology and better associated with immunogenomics of tumors. Further research is warranted to identify potential clinical implication of SCLC and LCNEC molecular subgroups. **Keywords:** immunogenomic, molecular subgroup

P3.12-11
Association of the Lung Immune Prognostic Index (LIPI) with Outcomes for Immune Checkpoint Inhibitors in Diffuse SCLC Patients

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Background: Pretreatment LIPI (Lung Immune Prognostic Index), based on derived NLR (neutrophils/[leucocytes-neutrophils] ratio) and lactate dehydrogenase (LDH) has been associated with outcomes for immune checkpoint inhibitors (ICI) in advanced NSCLC patients. We tested whether LIPI has the same role in diffuse small cell lung cancer (SCLC) patients. **Method:** Baseline dNLR and LDH and clinical data were retrospectively collected in SCLC patients, treated with ICI (PD1 inhibitor, PDL1 inhibitors +/- CTLA4 inhibitor) from April 2014 to Jan. 2018 (N=66) from 6 European centers. LIPI was calculated combining

dNLR and LDH, stratifying 3 risk groups: good (dNLR<3+LDH<upper limit of normal (ULN), intermediate (dNLR>3 or LDH>ULN), poor (dNLR>3+LDH>ULN). The primary endpoint was overall survival (OS), and secondary endpoint was progression-free survival (PFS). **Result:** Fifty-three patients (80%) were males, 58 (88%) smokers and all patients had PS ≤1, with median age 63 years (41-82). PDL1 was ≥ 1% by immunohistochemistry in 6 patients, and unknown in 60 patients. The median of prior lines was 1 (0-6). Platinum-based therapy was the prior line in 63 (95%) patients, with ORR of 88%. The median PFS and OS with ICI were 2.7 months (m) [95% CI 1.87-4.43] and 10.3 m [95% CI 5.8-12.6]. dNLR was greater than 3 in 16 (25%) and LDH> Upper Limit of Normal (ULN) in 33 (50%) patients. Based on both, LIPI stratified the population in 3 groups: 26 patients as good (40%), 29 (45%) as intermediate and 10 (15%) as poor LIPI risk groups. LIPI was an independent factor for OS (HR 2.77, 95% CI 1.07-7.14, *P*=0.03) and PFS (HR 3.13, 1.37-7.16, *P*=0.01). Median OS for good, intermediate, and poor risk groups were 11.4 m [95% CI 5.5-27.3], 11 m [95% CI 6.8-not-reached (NR)] and 2.3 m [95% CI 0.7-NR], respectively (*P*=0.004). Median PFS for good, intermediate, and poor risk groups were 3 m [95% CI 1.9-12.6], 2.8 m [95% CI 1.6-6.0 and 1.2 m [95% CI 0.47-NR], respectively (*P*=0.004). **Conclusion:** Baseline LIPI poor risk group is associated with poor outcomes for ICI in diffuse SCLC patients. LIPI effect in a validation cohort is currently evaluated.

P3.12-12
Genomic Profiling of Pulmonary Large-Cell Neuroendocrine Carcinoma (LCNEC) Reveals Distinct Mutational Landscape

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Background: The controversial classification of lung neuroendocrine tumor has been amended a few times since recognised as a separate entity. LCNEC shares clinical features with small cell lung carcinoma (SCLC) and they were both classified as lung neuroendocrine carcinoma according to the 2015 WHO lung primary pathology classification, numerous studies have revealed barely satisfactory outcomes when it was treated as SCLC. However the underlying molecular basis for such commonalities and discrepancies are poorly understood. In this study, we interrogated the genomic landscape of LCNEC and SCLC along with their histologically related subtypes: carcinoids and atypical carcinoids to define the molecular pattern of LCNEC. **Method:** We performed targeted sequencing in 35 tissue samples using a panel covering 520 cancer related genes, spanning 1.6MB of human genome, with an average sequencing depth of 1,418x. Among them, 15 were diagnosed with SCLC, 9 with LCNEC, 6 with carcinoid and 5 with atypical carcinoid. **Result:** On average, LCNEC exhibited 13.5 mutations per million base pairs (Mb) and a C:G>A:T transversion rate of 34%, which is indicative of tobacco exposure. LCNEC had SCLC (16.7 Mb) had comparable TMB (p=0.18), which is significantly higher than carcinoids (1.2/Mb, p<0.001) and atypical carcinoids (2.4/Mb, p<0.001). The most frequently mutated gene in LCNEC is *TP53* (89%, 8/9), followed by *NOTCH1* (33%), *KEAP1* (22%), *RB1* (22%) and a few chromatin modifiers, including *KMT2D* (33%), *KMT2C* (33%). Co-mutation in *TP53* and *RB1*, a hallmark of SCLC, was found in 22% (2/9) of LCNEC patients; in contrast, 80% of SCLC patients harbored concurrent mutation. 67% carcinoid (4/6) and 20% (1/5) atypical carcinoid patients had no mutation identified from this panel. No classic lung adenocarcinoma driver mutations were found in any subtype. Copy number analyses revealed significantly higher copy number variation (CNV) in SCLC and LCNEC comparing with carcinoids and atypical carcinoids, which yield virtually no CNV. Our analysis revealed a comparable CNV status of SCLC and LCNEC (p=0.158), with an enrichment in amplification of chromatin modifiers. **Conclusion:** Our study, comprehensively characterized 4 subtypes of neuroendocrine tumors, revealed a high TMB and CG:AT transversion rate in LCNEC patients as well as a distinctive mutation landscape, with an enrichment of mutations occurring at chromatin remodelers. Furthermore, LCNEC has comparable TMB and CNV status as SCLC, which are significantly higher than carcinoid and atypical carcinoids. **Keywords:** lung neuroendocrine carcinoma, large-cell neuroendocrine carcinoma, targeted sequencing

P3.12-13
Expression of the Immune Checkpoint Axis-PVR/TIGIT in Small Cell Lung Cancer

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Background: The poliovirus receptor (PVR) is an immune checkpoint protein expressed on tumor cells. It has been reported to mediate activation of T cells via CD226 or inhibition through binding to T-cell Ig and ITIM domain (TIGIT). TIGIT competes with CD226 for binding to PVR, and exhibits stronger affinity for PVR. Recently we have found that PVR is highly expressed in SCLC cell lines. Characterizing the expression and significance of the PVR-TIGIT axis in SCLC will help us to better understand the immunology of SCLC and may lead to novel therapeutic strategies to combine checkpoint blocking agents for improved SCLC immunotherapy. **Method:** Immunohistochemistry (IHC) was performed to evaluate PVR protein expression in a TMA of 39 SCLC cell lines and a cohort TMA of 77 limited stage SCLC patients with clinical data. We analyzed both PVR and TIGIT in an independent cohort of 27 resected, limited-stage SCLC tumors. **Result:** Thirty-seven cell lines (95%, 37/39) demonstrated staining for PVR and of those, 4 cell lines (10.3%, 4/39) showed strong staining (H-score ≥ 270). In the 77 SCLC patients cohort, PVR expressed predominantly in the membrane of tumor cells, with minimal expression observed on immune cells. PVR expression in the SCLC patient cohort was 82% with an arbitrary H-score cut-off of ≥ 50. Higher PVR expression was found for male patients (P=0.040). The expression of PVR increased with the tumor progressing from stage I to stage III (p =0.007). SCLC patients who had higher PVR expression demonstrated poorer prognosis and the difference was near statistically significant (p=0.050). Using the same cut-off (H-score ≥ 50) in the independent SCLC cohort, the prevalence of high PVR expression was 89% (24/27). In the independent SCLC cohort, TIGIT was found to be expressed membranous or cytoplasm on the immune cells with weak to moderate staining. Immune cells with TIGIT staining were typically seen as variable size and aggregated toward the periphery of the tumor nest. TIGIT protein staining was demonstrated in 20 cases (74%). No association was