**Table S1. Clinicopathologic and molecular histories of patients with *NRG1*-rearranged lung cancers that did not respond to afatinib.** Note that these three additional cases are distinct from the patient detailed in Figure 1 who had a durable response to GSK2849330, and on progression of disease received afatinib without response.

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| Clinical History | Molecular Profiling |
| CASE 1. An 81 year-old man with a history of former cigar use (smoked for 1 year, no history of cigarette smoking) presented with a left lower lobe mass. He underwent a left lower lobectomy and mediastinal lymph node dissection, revealing a pT3N0M0 stage IIB invasive mucinous lung adenocarcinoma. The patient declined adjuvant chemotherapy and was managed with active surveillance. Repeat imaging 15 months after surgical resection revealed recurrent, advanced disease involving the contralateral lung (confirmed on biopsy of a right lung nodule). Afatinib administered at 40 mg daily after an *NRG1* fusion was identified. In contrast to the case above, anti-tumor response to therapy was not achieved. Stable disease (RECIST version 1.1, 7% disease shrinkage) was observed at 6 weeks. Repeat imaging at 13 weeks revealed disease progression with new and growing lung nodules. | Initial molecular profiling by next-generation sequencing (MSK-IMPACT) did not reveal actionable drivers (*FGFR1* amplification and *SMARCA4*, *NOTCH3*, and *STK11* rearrangements of uncertain significance were identified), and thus anchored multiplex polymerase chain reaction (MSK-Solid Fusion Assay, Archer FusionPlex) was performed. This revealed an in-frame *CD74-NRG1* fusion containing the EGF-like extracellular domain of NRG1. The rearrangement was an in-frame fusion between genes *CD74* exon8(NM\_001025159) and *NRG1* exon6 (NM\_013956).  |
| CASE 2. A 56 year-old woman with a 2 pack-year history of cigarette smoking was diagnosed with clinical stage IIIA invasive mucinous adenocarcinoma. She received neoadjuvant cisplatin and pemetrexed for four cycles followed by a left lower lobectomy revealing pT3N2M0 disease. Post-operative radiation therapy was thereafter administered. Give months later, she was found to have recurrent disease involving the bilateral lungs, lymph nodes, and pleura. Carboplatin, pemetrexed, and pembrolizumab were administered for 2 cycles with primary progressive disease. Thereafter, afatinib was initiated at 40 mg daily. Repeat imaging 5 weeks later revealed primary progressive disease with bilateral enlarging pulmonary metastases and a new adrenal mass. The patient passed away shortly thereafter from disease progression. | MSK-IMPACT did not initially reveal a targetable alteration. Only a *KMT2D* (MLL2) exon 39 mutation of unclear significance was identified (p.V3787\_L3802del; c.11355\_11402del). Subsequent targeted RNA sequencing (MSK-Solid Fusion Assay) identified an in-frame *SDC4-NRG1* fusion. The rearrangement was an in-frame fusion between genes *SDC4* exon2 (NM\_002999) and *NRG1* exon6 (NM\_004495). |
| CASE 3. A 51 year-old man with a <1 pack-year history of former smoking was diagnosed with clinical T4N2M0 stage IIIB invasive mucinous lung adenocarcinoma. He received neoadjuvant cisplatin and pemetrexed for four cycles followed by a left lower lobectomy and left upper wedge resection. Post-operative radiation therapy was thereafter administered. Three months later, he developed recurrent disease involving the lungs. Afatinib was initiated after an *NRG1* fusion was identified. Repeat imaging at 8 weeks showed primary disease progression with worsening disease in the chest and a new brain metastasis. | MSK-IMPACT identified an in-frame *CD74-NRG1* fusion (*CD74* exons 1-7 fused with*NRG1* exons 6-13): t(5;8)(q32;p12) (chr5:g.149782781::chr8:g.32584466). The only other genomic alteration identified was an *ARID1A* rearrangement: c.1138-11170\_c.4852del. This resulted in the deletions of exons 2-18, with a breakpoint within exon 18. The functional significance of this alteration is undetermined. |