**Supplemental Figure 1. Compound *EGFR* S768I+V769L (*EGFR*-SV768IL) mutations confer resistance to osimertinib.** **A**, The *EFGR*-SV768ILmutation was introduced by site-directed mutagenesis and confirmed by Sanger sequencing. **B**, Plasmids containing *EGFR* or *EFGR*-SV768IL were stably introduced into PC9 and HCC827 cells via lentiviral transduction and then expression of EGFR confirmed by Western blotting. **C**,Isogenic PC9 (left panel) and HCC827 (right panel) cells were treated with osimertinib for 96 h and then growth determined using alamarBlue viability dye (top panel). IC50 values were determined by non-linear regression analysis using GraphPad Primsm (bottom panel). Isogenic PC9 cellswere treated with osimertinib for 48 h and then caspase 3/7 activity determined. Results represent the fold change in caspase 3/7 enzymatic activity above the corresponding untreated cell line. All experiments were repeated 3 times and included triplicate determinations of each condition. Results represent the mean ± SD. EV: empty vector. \*\*p<0.01, \*\*\*p<0.001.

**Supplemental Figure 2. Contextual landscape of resistance to osimertinib by line of therapy and type of alteration.** Summary of mechanisms of resistance reported in recent prospective studies and the largest retrospective series of acquired resistance mechanisms to osimertinib in the first-line and later-line.(5,6,15,34-36)