Supplementary Figure Legends

Mechanism of drug efficacy within the epidermal growth factor receptor revealed by microsecond molecular dynamics simulation

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Figure S1. Time evolution of the first two principal components (PCs) and the relative non-overlapped volumes for gefitinib. The PCs show that it takes about 3μs for wild-type EGFR to equilibrate, and about 5μs for the L858R mutation. The relative volumes are correlated with the two principal components, which all reflect the inter-lobe movement of EGFR and the capacity of the binding site.

Figure S2. The binding positions of gefitinib ((a) and (b)) and ATP ((c) and (d)) in the binding site of EGFR, from x-ray crystallography ((a) and (c)) and docking calculations ((b) and (d)). The x-ray structures 2GS6 and 2ITY are displayed in the figures. The labelled nitrogen atoms of gefitinib and ATP were used to calculate the distances of gefitinib and ATP to the hinge residue Met793. The "correct" docking modes are shown for the anchor fragments ((b) and (d)). The tails of gefitinib and ATP have large deviations in their docking positions, and are not shown for clarity. The x-ray structures of EGFR in (b) and (d) are used for reference only; the conformations for each docked ligand are taken from MD simulations and have large fluctuations (see "Extensive conformations are sampled from microsecond simulations" in Results section of main text).

Figure S3. Backbone root-mean-square fluctuations (RMSF) from the average structures of wild-type (black line) and L858R mutant (red line) EGFRs. The α-helices and β-sheets remain well defined throughout the simulations, except for the N-terminal end of the αC-helix and the αG-helix which is located on the periphery of the C-lobe helical core. The αG-helix usually shows large fluctuations, or is deformed in many x-ray structures of EGFR and other protein kinases. The results show that for mutant EGFR the overall mobility of residues is larger than that for the wild-type, although similar patterns are displayed in most regions for the two molecular systems. Obvious differences are evident at the αC-helix and the A-loop, where the formation of hydrogen bonds between residues (cyan dots, see also Figure 4 in main text) in two regions stabilizes the wild-type conformation.