*Supporting Information for*

# Effect of Double Mutations T790M/L858R on Conformation and Drug-Resistant Mechanism of Epidermal Growth Factor Receptor Explored by Molecular Dynamics Simulations

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**Table S1** Energy contributions of individual residues to binging free energy of inhibitors to the WT and T790M/L858R EGFRs[a]

| | | TAK-285 | | | W2P | | | HKI-272 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $\Delta E_{vdw}$ | $\Delta E_{ele}$ | $\Delta G_{ele + pol}$ | $\Delta E_{vdw}$ | $\Delta E_{ele}$ | $\Delta G_{ele + pol}$ | $\Delta E_{vdw}$ | $\Delta E_{ele}$ | $\Delta G_{ele + pol}$ |
| L718 | WT | -1.31 | -0.45 | 1.00 | -2.61 | -0.46 | 0.80 | -1.88 | -0.43 | 0.20 |
| | T790M/L858R | -1.72 | -0.26 | 0.83 | -1.55 | -0.40 | 0.98 | -1.84 | -0.32 | 0.18 |
| V726 | WT | -2.15 | -0.33 | 0.29 | -1.79 | -0.47 | 0.21 | -1.03 | -0.37 | 0.16 |
| | T790M/L858R | -1.56 | -0.17 | 0.37 | -1.67 | -0.13 | 0.17 | -1.49 | -0.57 | 0.34 |
| M766 | WT | -1.03 | -0.37 | 0.07 | --- | --- | --- | -1.19 | -0.63 | -0.18 |
| | T790M/L858R | -0.65 | -0.08 | 0.19 | --- | --- | --- | -0.68 | -0.05 | 0.16 |
| L777 | WT | -1.22 | -0.26 | 0.09 | --- | --- | --- | --- | --- | --- |
| | T790M/L858R | -0.30 | 0.01 | 0.10 | --- | --- | --- | --- | --- | --- |
| L788 | WT | -1.89 | -0.06 | 0.42 | -1.41 | -0.31 | 0.32 | -1.75 | -0.10 | 0.19 |
| | T790M/L858R | -1.82 | 0.32 | 0.41 | -1.73 | -0.00 | 0.59 | -1.12 | -0.21 | 0.08 |
| M790 | WT | -1.79 | 0.08 | 0.43 | -1.50 | 0.01 | 0.54 | -1.39 | -0.36 | 0.34 |
| | T790M/L858R | -2.12 | 0.04 | 0.50 | -2.24 | 0.21 | 0.72 | -1.96 | -0.25 | 0.36 |
| M793 | WT | -1.25 | -2.12 | -0.10 | -1.24 | -2.03 | 0.19 | -1.47 | -3.00 | 0.06 |
| | T790M/L858R | -0.94 | -2.08 | -0.03 | -0.92 | -1.87 | 0.21 | -1.75 | -2.05 | 0.43 |
| G796 | WT | --- | --- | --- | --- | --- | --- | -1.43 | 0.24 | 0.30 |
| | T790M/L858R | --- | --- | --- | --- | --- | --- | -1.26 | 0.19 | 0.33 |
| C797 | WT | --- | --- | --- | -1.29 | -2.06 | -0.34 | -0.92 | -1.08 | 0 |
| | T790M/L858R | --- | --- | --- | -0.92 | -0.62 | 1.13 | -1.06 | -0.77 | 0.16 |
| L844 | WT | -2.51 | -0.19 | 0.22 | -2.15 | 0.44 | 0.19 | -2.07 | 0.47 | 0.19 |
| | T790M/L858R | -1.75 | -0.08 | 0.14 | -1.06 | 0.48 | 0.12 | -1.56 | 0.62 | 0.28 |

[a] All values are given in kcal/mol.

$\Delta^{E_{vdw}}$: van der Waals interaction energy.

$\Delta^{E_{ele}}$: electrostatic interaction energy.

$\Delta G_{ele + pol} = \Delta E_{ele} + \Delta G_{pol}$.

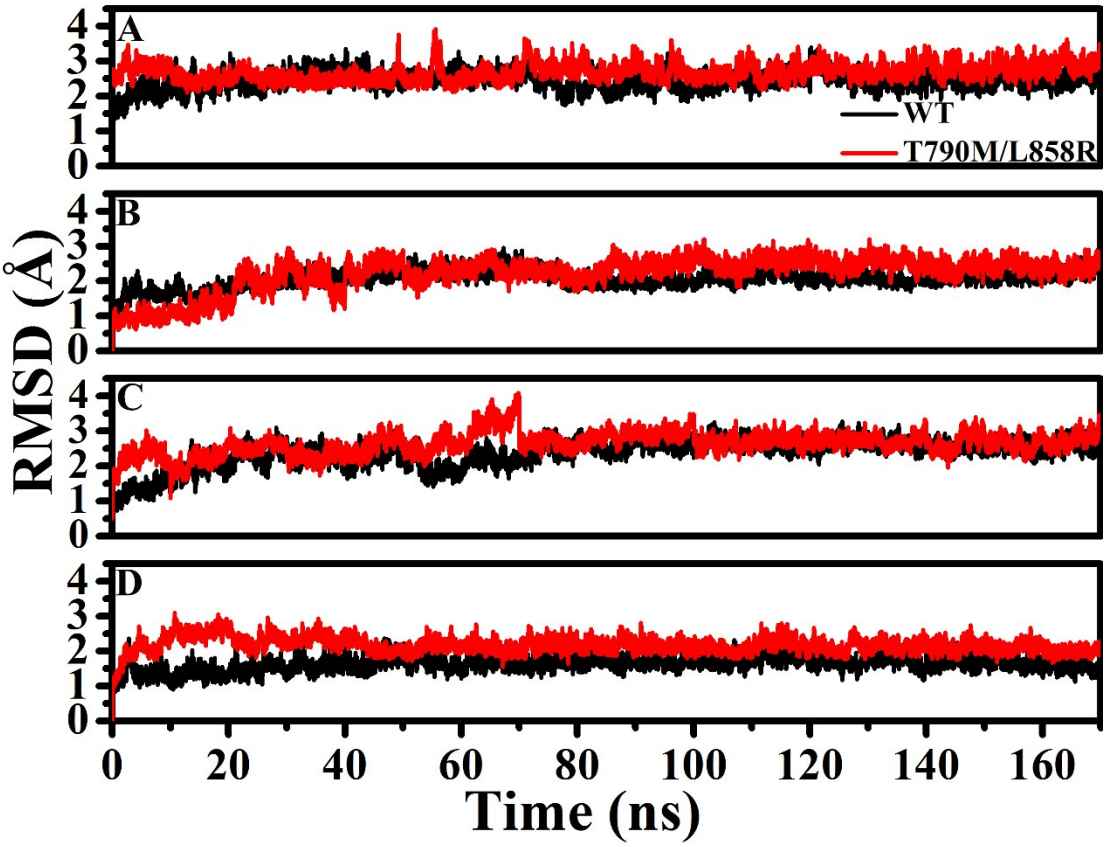


**Fig. S1** Root-mean square displacements (RMSDs) of backbone atoms relative to their initial structures as function of simulated time. The WT and T790M/L858R apo state of EGFR (A) and EGFRs associated with TAK-285 (B), W2P (C) and HKI-272 (D).

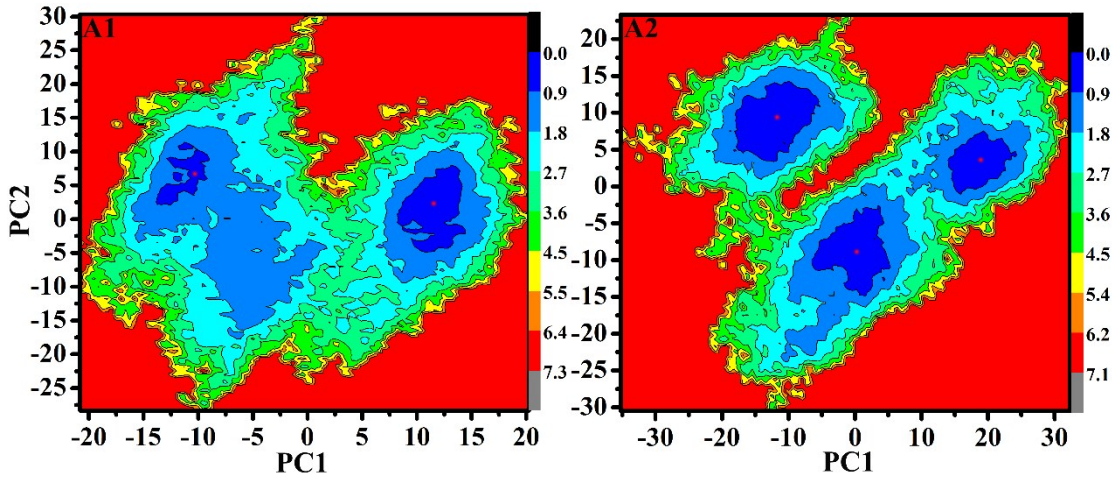


**Fig. S2** A1 and A2 respectively represent the free energy landscapes of the WT/mutated apo EGFRs constructed by projecting MD trajectories on the first two principal components PC1 and PC2.

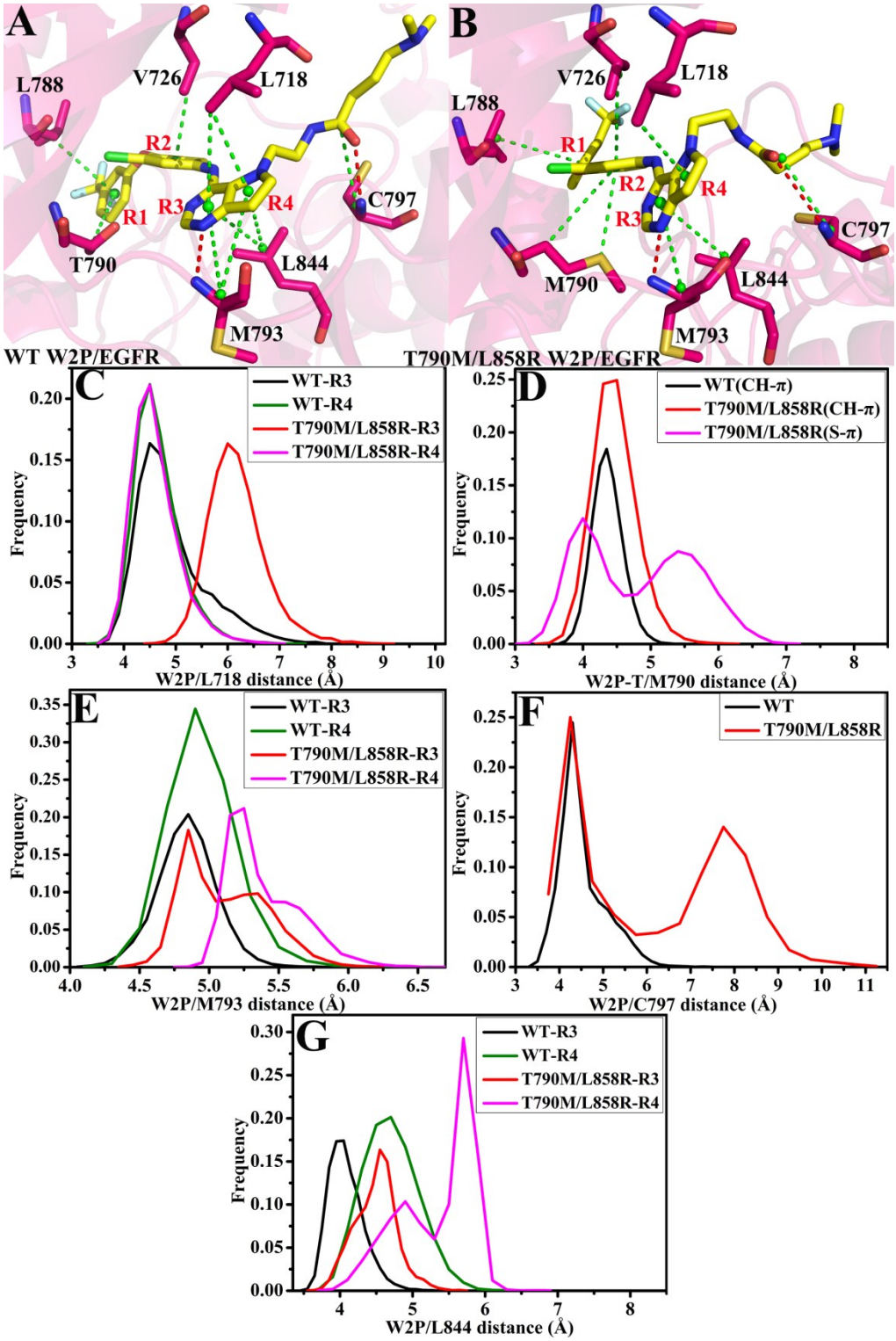


**Fig. S3** Geometric positions of inhibitor W2P relative to the key residues in the WT and mutated EGFRs and the hydrogen bonds are shown in the red line: (A/B) the WT/double mutant EGFRs associated with W2P. (C)-(G) depict the frequency distribution of distances between W2P and the key residues.

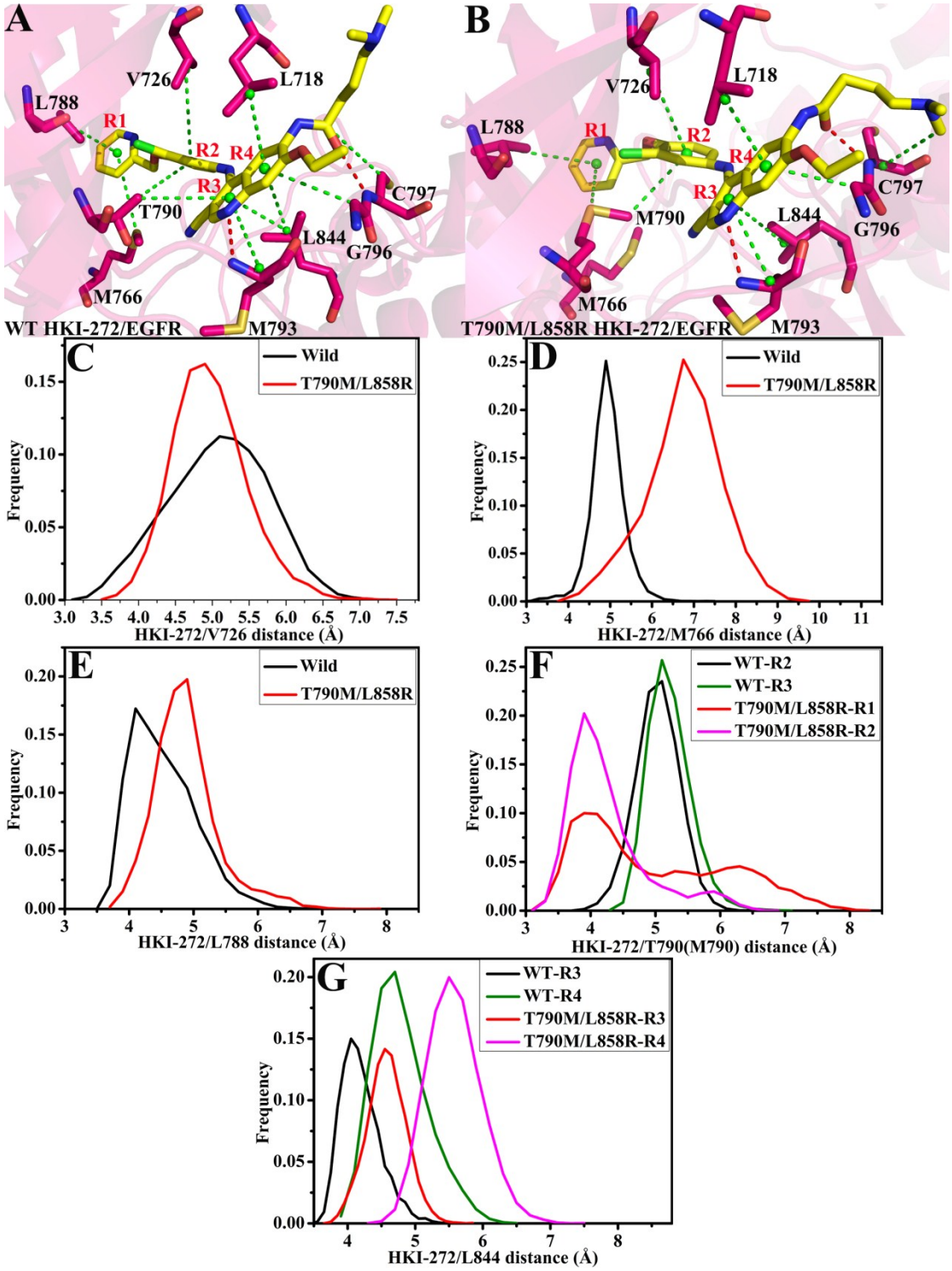


**Fig. S4** Geometric positions of inhibitor HKI-272 relative to the key residues in the WT and T790M/L858R EGFRs and the hydrogen bonds are shown in the red line: (A/B) the WT/double mutant EGFRs associated with HKI-272. (C)-(G) display the frequency distribution of distances between HKI-272 and the key residues.