

Table S1. Estimated free energy differences and their components based on the Generalized Born (GB) or Poisson Boltzmann (PB) model, for different EGFR mutant-afatinib covalent systems. This table lists the free energy difference and its components (ΔE and $\Delta\Delta G_{solv}$), between each EGFR mutant-afatinib covalent complex and the corresponding two isolated molecules, for the NSCLC patients involved in this study. Based on these patient data, the afatinib-related response level and PFS were recorded for each EGFR mutation, and these values are now presented below.

GB model											
Mutation	E				ΔG				$\Delta E + \Delta\Delta G$	Response Level	PFS (month)
	Complex	Mutant	Afatinib	ΔE	Complex	Mutant	Afatinib	$\Delta\Delta G$			
L858R	-25217.358	-25279.281	6.451	55.472	-4782.848	-4646.473	-20.892	-115.483	-60.011	2	15.87
L858R_T790M	-25301.406	-25427.035	7.780	117.849	-4771.399	-4612.634	-19.919	-138.845	-20.997	3	9.59
delE746_A750	-24977.633	-25076.333	8.100	90.600	-4702.502	-4471.861	-20.484	-210.157	-119.557	2	16.85
delL747_P753insS	-25330.408	-25003.324	8.576	-335.660	-4380.815	-4604.566	-19.912	243.663	-91.997	2	6.57
delL747_T751	-25008.885	-25178.346	8.893	160.568	-4665.909	-4572.609	-21.044	-72.256	88.312	2	13.9
L861Q	-25529.024	-25425.139	8.599	-112.484	-4594.504	-4660.102	-21.040	86.638	-25.846	3	10.94
S768I	-25431.583	-25529.753	6.332	91.838	-4687.421	-4500.002	-21.457	-165.962	-74.124	3	6.64
P772S_dulS768_D770	-25700.492	-25614.781	8.904	-94.615	-4684.279	-4714.262	-21.585	51.568	-43.047	4	3.25
T790M_delE746_A750	-25212.140	-25094.471	5.023	-122.692	-4474.421	-4566.332	-21.085	112.996	-9.696	3	1.94
T790M_L833V_delE746_A750	-25246.210	-25290.698	8.383	36.105	-4431.836	-4341.390	-20.561	-69.885	-33.780	3	5.89
WT	-25385.914	-25438.477	9.104	43.459	-4747.221	-4657.497	-20.047	-69.677	-26.218	NIL	NIL
T790M	-25085.107	-25084.231	12.447	-13.324	-4951.380	-4932.630	-24.102	5.351	-7.973	NIL	NIL
PB model											
Mutation	E				ΔG				$\Delta E + \Delta\Delta G$	Response Level	PFS (month)
	Complex	Mutant	Afatinib	ΔE	Complex	Mutant	Afatinib	$\Delta\Delta G$			
L858R	-25217.358	-25279.281	6.451	55.472	-4500.369	-4354.595	-20.265	-125.509	-70.037	2	15.87
L858R_T790M	-25301.406	-25427.035	7.780	117.849	-4471.990	-4338.635	-19.357	-113.999	3.850	3	9.59
delE746_A750	-24977.633	-25076.333	8.100	90.600	-4419.099	-4205.851	-19.981	-193.267	-102.667	2	16.85
delL747_P753insS	-25330.408	-25003.324	8.576	-335.660	-4078.354	-4303.582	-19.485	244.713	-90.947	2	6.57
delL747_T751	-25008.885	-25178.346	8.893	160.568	-4371.630	-4277.846	-20.501	-73.283	87.285	2	13.9
L861Q	-25529.024	-25425.139	8.599	-112.484	-4291.379	-4359.465	-20.369	88.455	-24.029	3	10.94
S768I	-25431.583	-25529.753	6.332	91.838	-4379.188	-4201.936	-20.971	-156.281	-64.443	3	6.64
P772S_dulS768_D770	-25700.492	-25614.781	8.904	-94.615	-4370.848	-4423.675	-20.828	73.655	-20.960	4	3.25
T790M_delE746_A750	-25212.140	-25094.471	5.023	-122.692	-4171.335	-4283.592	-20.500	132.757	10.065	3	1.94
T790M_L833V_delE746_A750	-25246.210	-25290.698	8.383	36.105	-4157.110	-4044.473	-20.113	-92.524	-56.419	3	5.89
WT	-25385.914	-25438.477	9.104	43.459	-4428.539	-4386.151	-19.472	-22.916	20.543	NIL	NIL
T790M	-25085.107	-25084.231	12.447	-13.324	-4653.393	-4621.047	-23.445	-8.900	-22.224	NIL	NIL

Table S2. Inhibitory constants (nM) of afatinib to representative EGFR-family receptors, determined in molecular and cellular assays. Inhibitory constant can be an important indicator for inhibitor potency in cancer treatment. All presented values, confirmed in multiple (*n*) biological experiments, were collected from a number of literatures.

Receptor Index	ErbB-4 Kinase	EGFR (<i>WT</i>) Kinase	EGFR (<i>L858R</i>) Kinase	EGFR (<i>L858R_T790M</i>) Kinase	ErbB-2 Kinase
Value	1	0.5	0.2	9	14
Range	0.7~1.7	0.2~0.7	0.2~0.4	9~10	7~25
<i>n</i>	4	5	2	2	5