

Figure S1

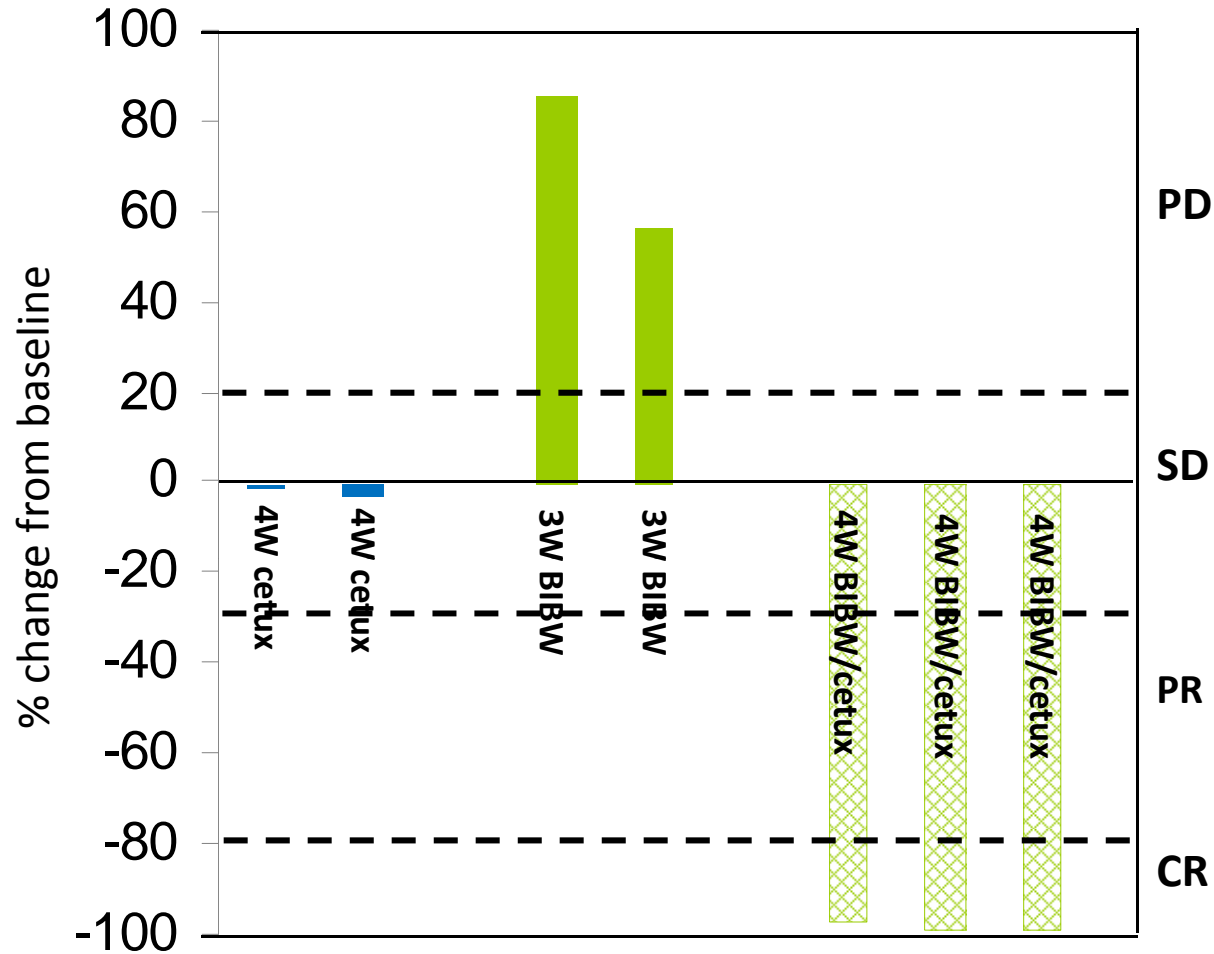


Figure S1. Change in radiographic tumor volume from baseline by treatment for individual lung tumor-bearing C/T790M animals. Graphed are the percent change in tumor volume calculated for individual animals pre- and post-treatment with cetuximab (cetux), BIBW-2992 (BIBW), or combinations of BIBW-2992 with cetuximab. Cutoffs of 20% growth, 30% shrinkage, and 80% shrinkage (dotted lines) are shown to delineate progressive disease (PD), partial response (PR), and complete response (CR), respectively. Mice that displayed less than 20% growth and less than 30% shrinkage in tumor volume were considered to have stable disease (SD). See methods for details.

Figure S2

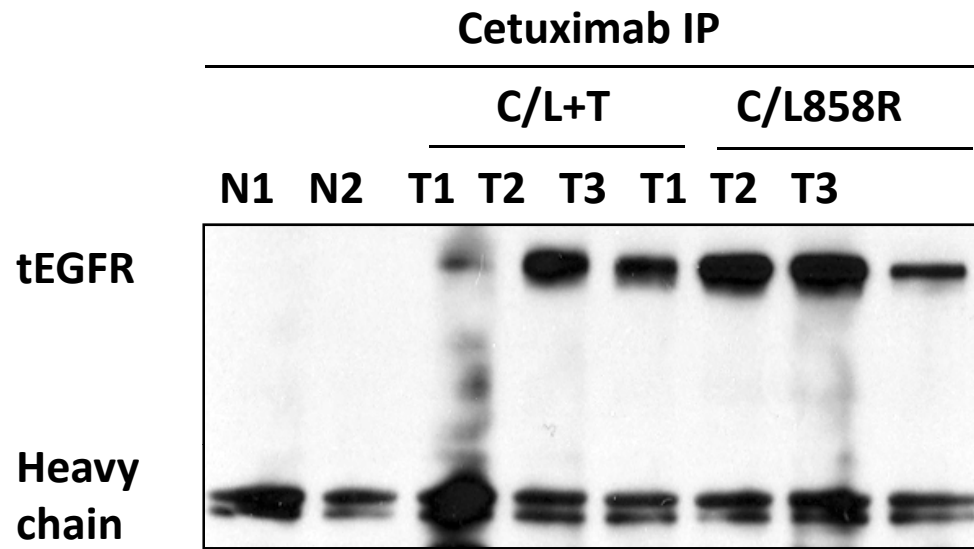


Figure S2. Cetuximab binds to EGFR^{L858R} and EGFR^{L858R+T790M}. Tumor cell lysates from C/L858R and C/L+T mice were immunoprecipitated with cetuximab and then subjected to immunoblotting with an antibody against total EGFR. N – normal lung; T – tumor.

Mouse	Genotype	Treatment	Response	Histology
1	C/L858R	BIBW-2992 (2W)	CR	No tumor
2	C/L858R	BIBW-2992 (2W)	CR	No tumor
3	C/L858R	BIBW-2992 (2W)	CR	No tumor
4	C/L858R	BIBW-2992 (2W)	CR	No tumor
1	C/L+T	BIBW-2992 (1W)	SD	Viable tumor
2	C/L+T	BIBW-2992 (2W)	SD	Viable tumor
3	C/L+T	BIBW-2992 (2W)	SD	Viable tumor
4	C/L+T	BIBW-2992 (3W)	SD	Viable tumor
5	C/L+T	BIBW-2992 (3W)	SD	Viable tumor
6	C/L+T	BIBW-2992 (4W)	PD	Viable tumor
1	C/L+T	Cetuximab (2W) + BIBW-2992	CR	No tumor
2	C/L+T	Cetuximab (4W) + BIBW-2992	PR	Necrotic tumor nodules
3	C/L+T	Cetuximab (4W) + BIBW-2992	CR	No tumor
4	C/L+T	Cetuximab (4W) + BIBW-2992	CR	No tumor
5	C/L+T	Cetuximab (4W) + BIBW-2992	CR	No tumor
6	C/L+T	Cetuximab (4W) + BIBW-2992	CR	No tumor
7	C/L+T	Cetuximab (4W) + BIBW-2992	CR	No tumor
8	C/L+T	Cetuximab (4W) + BIBW-2992	CR	Scant viable tumor nodules

Table S1. Summary of lung tumor-bearing C/L858R and C/L+T bitransgenic mice treated with BIBW-2992 alone or in combination with cetuximab.

Responses assessed by MRI; PD – progressive disease, SD – stable disease; PR – partial response; CR – complete response. See methods for details. nd – not determined. W – weeks.

Mouse	Genotype	Treatment	Response	Histology
1	C/T790M	BIBW-2992 (3W)	PD	Viable tumor
2	C/T790M	BIBW-2992 (3W)	PD	Viable tumor
1	C/T790M	Cetuximab (4W)	SD	Viable tumor
2	C/T790M	Cetuximab (4W)	SD	Viable tumor
1	C/T790M	Cetuximab (4W) + BIBW-2992	CR	No tumor
2	C/T790M	Cetuximab (4W) + BIBW-2992	CR	No tumor
3	C/T790M	Cetuximab (4W) + BIBW-2992	CR	No tumor

Table S2. Summary of lung tumor-bearing C/T790M bitransgenic mice treated with BIBW-2992 alone, cetuximab alone, or BIBW-2992 plus cetuximab.

Responses assessed by MRI; PD – progressive disease, SD – stable disease; PR – partial response; CR – complete response. See methods for details.

	C/L+T vs NORMAL	
Gene	FC	FDR
<i>Prm1</i>	287.08	2.75E-09
<i>Prm1</i>	260.91	3.36E-09
<i>Kng1</i>	128.20	1.24E-07
<i>Dlk1</i>	100.50	4.78E-05
Ereg	90.88	5.61E-09
<i>Gtl2</i>	58.60	4.10E-06
Areg	29.28	1.33E-07
<i>Gtl2</i>	27.70	2.56E-06
<i>Gtl2</i>	24.26	6.68E-06
<i>Gtl2</i>	23.94	7.06E-06

	C/T790M vs NORMAL	
Gene	FC	FDR
<i>Prm1</i>	348.81	1.35E-13
<i>Prm1</i>	327.21	2.87E-13
<i>Kng1</i>	187.55	1.28E-11
<i>Dlk1</i>	133.84	2.24E-09
Ereg	73.06	3.20E-14
<i>Gtl2</i>	46.31	2.14E-09
<i>Slc26a4</i>	33.98	1.41E-08
<i>Gtl2</i>	32.88	2.84E-11
<i>Gtl2</i>	28.52	4.12E-10
<i>Gtl2</i>	28.43	4.62E-10
Areg	28.11	1.00E-11

	C/L858R vs NORMAL	
Gene	FC	FDR
<i>Prm1</i>	689.29	6.82E-10
<i>Prm1</i>	625.20	6.82E-10
<i>Kng1</i>	65.39	4.02E-07
<i>Dlk1</i>	56.32	0.000165
<i>Ear1</i>	51.82	1.07E-08
Ereg	45.38	4.52E-08
<i>Gtl2</i>	43.97	8.65E-06
<i>Arg2</i>	26.07	2.29E-06
<i>Cd200r4</i>	25.92	2.34E-09
Areg	24.15	2.39E-07

Table S3. Genes Most Highly Overexpressed in Tumors From Various EGFR Mutant Mice vs. Normal Lung. FC – fold change; FDR – false discovery rate.

Mouse	Genotype	Treatment	Response	Histology
1	C/L858R	Cetuximab (2W)	CR	No tumor
2	C/L858R	Cetuximab (2W)	CR	No tumor
3	C/L858R	Cetuximab (2W)	CR	No tumor
4	C/L858R	Cetuximab (2W)	CR	No tumor
5	C/L858R	Cetuximab (2W)	CR	No tumor
1	C/L+T	Cetuximab (2W)	SD	nd
2	C/L+T	Cetuximab (2W)	PR	nd
3	C/L+T	Cetuximab (4W)	SD	Viable tumor
4	C/L+T	Cetuximab (4W)	SD	Viable tumor
5	C/L+T	Cetuximab (4W)	SD	Viable tumor
6	C/L+T	Cetuximab (4W)	SD	Viable tumor
7	C/L+T	Cetuximab (4W)	PR	nd
1	C/L+T	Cetuximab (4W) + erlotinib	PD	Viable tumor
2	C/L+T	Cetuximab (4W) + erlotinib	SD	Viable tumor
3	C/L+T	Cetuximab (4W) + erlotinib	SD	Viable tumor
4	C/L+T	Cetuximab (4W) + erlotinib	PR	Viable tumor

Table S4. Summary of lung tumor-bearing C/L858R and C/L+T bitransgenic mice treated with cetuximab alone or in combination with erlotinib. Responses assessed by MRI; PD – progressive disease, SD – stable disease; PR – partial response; CR – complete response. See methods for details. nd – not determined. W – weeks.

Mouse	Genotype	Treatment	Response	Histology
1	C/L+T	Paclitaxel (4W)	PD	Viable Tumor
2	C/L+T	Paclitaxel (4W)	PD	Viable Tumor
3	C/L+T	Paclitaxel (4W)	PD	Viable Tumor
4	C/L+T	Paclitaxel (4W)	SD	Viable Tumor
5	C/L+T	Paclitaxel (4W)	SD	Viable Tumor
1	C/L+T	Pemetrexed (2W)	PD	Viable Tumor
2	C/L+T	Pemetrexed (2W)	PD	Viable Tumor
3	C/L+T	Pemetrexed (2W)	PD	Viable Tumor
4	C/L+T	Pemetrexed (2W)	SD	Viable Tumor

Table S5. Summary of lung tumor-bearing C/L+T bitransgenic mice treated with pemetrexed or paclitaxel. Responses assessed by MRI; PD – progressive disease, SD – stable disease. See methods for details. W – weeks.