

Type of EGFR Mutations and Treatment Responses to EGFR-TKI and Chemotherapy

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April 10, 2010

EGFR Sensitizing Mutations

- The discovery of mutations in the EGFR TK domain in 2004
- Mutations helped explain the clinical observations that
 - those with adenocarcinoma,
 - never smokers,
 - female, and
 - those of Asian descentappeared to benefit most from EGFR TK inhibitors.

Lynch T, et al. N Engl J Med 2004;350:2129-39

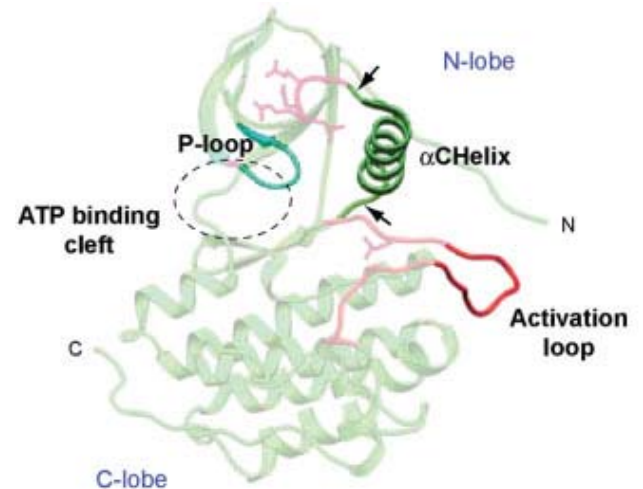
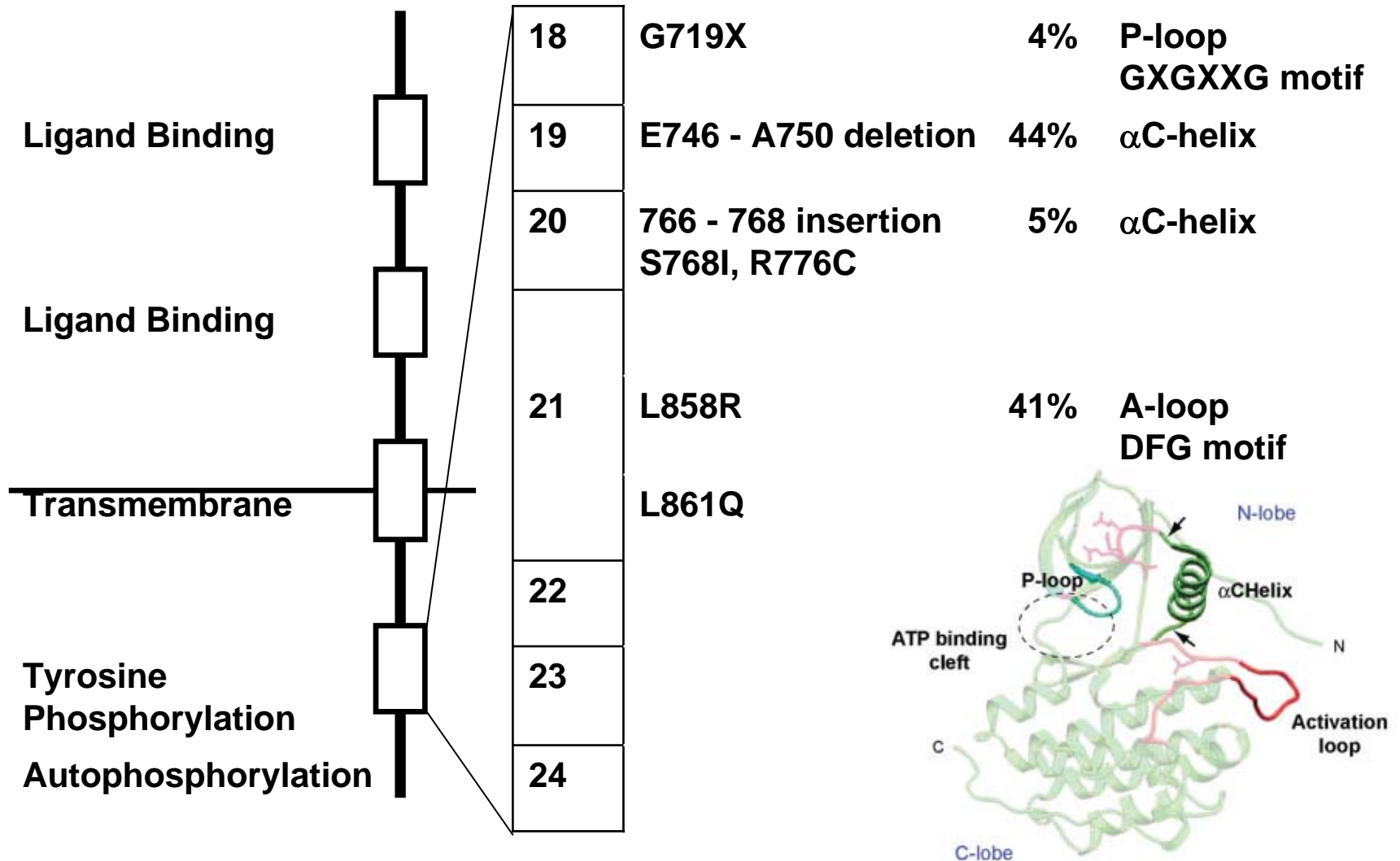
Paez J, et al. Science 2004;304:1497-50

Pao W, et al. Proc Natl Acad Sci 2004;101:13306-11

EGFR Sensitizing Mutations

- Shigematsu H, et al. Int J Cancer 2006;118:257-62
 - 9 studies, n = >2,000
 - Exon 19 del E746 - A750: 44%
 - Exon 21 L858R: 41%
 - Exon 20 ins: 5%
 - Exon 18 G719X: 4%
- Murray S, et al. J Thorac Oncol 2008;3:832-9
 - 202 studies, n = >12,244
 - Exon 19 del E746 - A750: 24%
 - Exon 21 L858R: 33%
 - Exon 20 ins: 5%
 - Exon 18 G719X: 3%

EGFR Sensitizing Mutations



EGFR Mutations As Predictors of TKI Response

- RR to TKI (retrospective)
 - Mutation-positive: 78%, (range, 30 - 100, with most series reporting >60)
 - Mutation-negative: 10% (range, 0 - 33)
- OS to TKI
 - Mutation-positive: improved (with an median OS up to 30 months)
 - Mutation-negative
- RR to TKI
 - Exon 19 deletions >
 - Exon 21 L858R
- OS to TKI
 - Exon 19 deletions >
 - Exon 21 L858R
- OS (untreated)
 - Exon 19 deletions < (?)
 - Exon 21 L858R

EGFR Mutations As Predictors of TKI Response

	Mutation positive		Mutation negative	
	No.	%	No.	%
Lynch	8 of 8	100%	1 of 8	13%
Paez	5 of 5	100%	0 of 4	0%
Pao	12 of 12	100%	5 of 23	22%
Kim	6 of 6	100%	2 of 21	10%
Mitsudomi	24 of 29	83%	2 of 21	10%
Han	11 of 17	65%	10 of 73	14%
Huang	7 of 8	87%	2 of 8	25%
Tokumo	8 of 9	89%	2 of 12	17%
Cappuzzo	8 of 15	53%	4 of 47	5%
Niho	4 of 4	100%	0 of 9	0%
Kimura	2 of 4	50%	0 of 9	0%
Yang	38 of 55	69%	7 of 35	20%

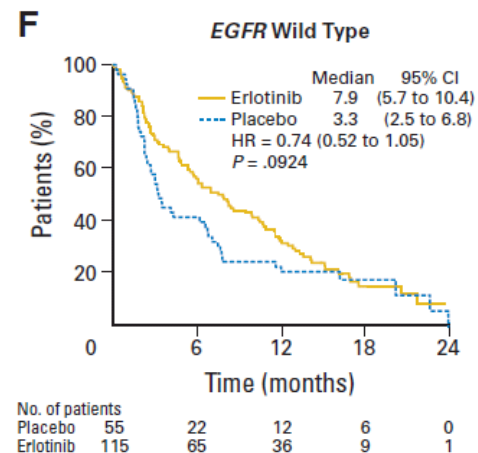
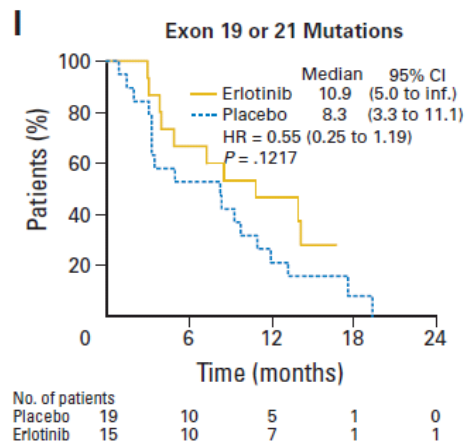
EGFR Mutations As Predictors of TKI Survival

	Progression-free (months)		Overall (months)	
	Mutant	Wild-type	Mutant	Wild-type
Han	21.7	1.8	30.5	6.6
Cappuzzo	9.9	2.6	20.8	8.4
Chou	7.6	1.7	14.7	4.7
Cortes-Funes	12.3	3.6	13.0	4.9
Zang	10.0	3.0	—	7.0
Takano	12.6	1.7	20.4	6.9
Yang	8.0	3.4	24.0	12.9

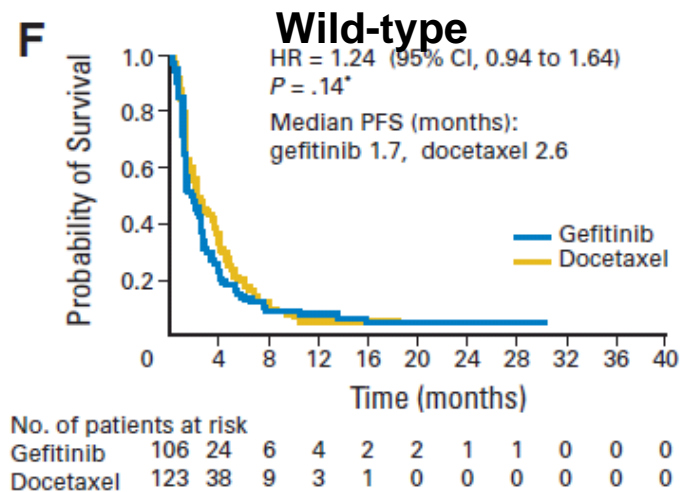
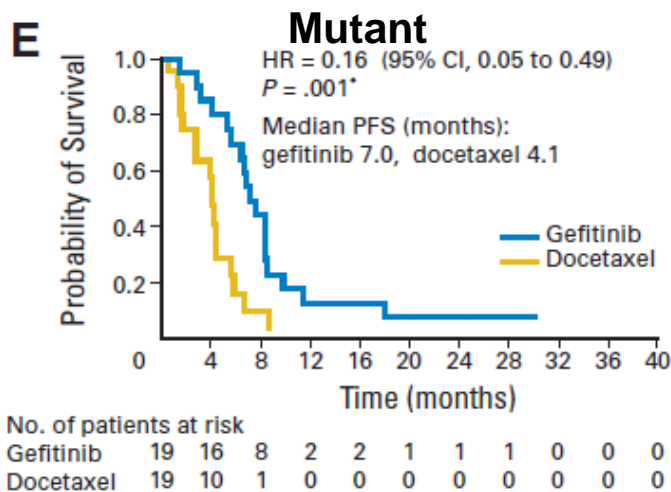
EGFR Mutations As Predictors of TKI Response

	Mutation positive		Mutation negative	
	No.	%	No.	%
BR.21 E vs. P 3 rd	10 of 37	27%	12 of 171	7%
Zhu C-Q, et al. J Clin Oncol 2008;26:4268-75				
ISEL G vs. P 3 rd	6 of 16	37.5%	3 of 115	2.6%
Hirsch FR, et al. J Clin Oncol 2006;24:5034-42				
V-15-72 G vs. D 2 nd	6 of 9	67%	0 of 22	0%
Maruyama R, et al. J Clin Oncol 2008;26:4244-52				
INTEREST G vs. D 2 nd	8 of 19	42.1%	7 of 106	6.6%
Douillard JY, et al. J Clin Oncol 2010;28:744-52				

EGFR Mutations As Predictors of TKI Survival: BR.21 & INTEREST



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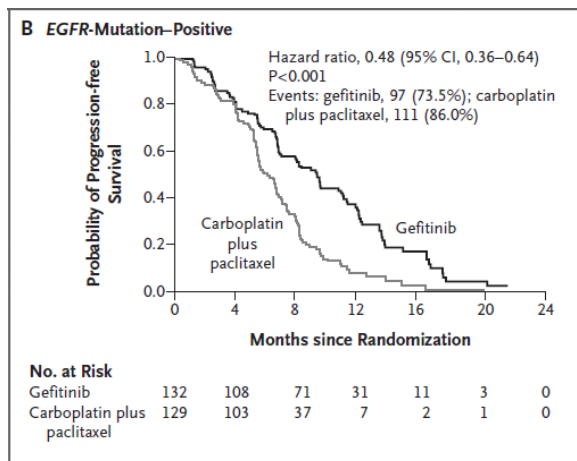


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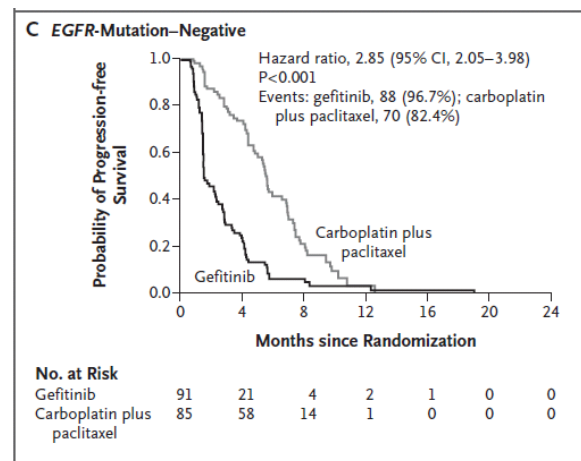
EGFR Mutations As Predictors of TKI Response

	Mutation positive		Mutation negative	
	No.	%	No.	%
IPASS G vs. C 1 st	94 of 132	71.2%	1 of 91	1.1%
Mok TS, et al. N Engl J Med 2009;361:947-57				
WJTOG G vs. C 1 st	36 of 58	62.1%	—	—
Mitsudomi T, et al. Lancet Oncol 2010;11:121-8				
TRIBUTE C+E vs. C	8 of 15	53%	18 of 99	18%
Eberhard DA, et al. J Clin Oncol 2005;23:5900-9				
INTACT C+G vs. C	13 of 18	72%	84 of 152	55%
Bell DW, et al. J Clin Oncol 2005;23:8081-92				

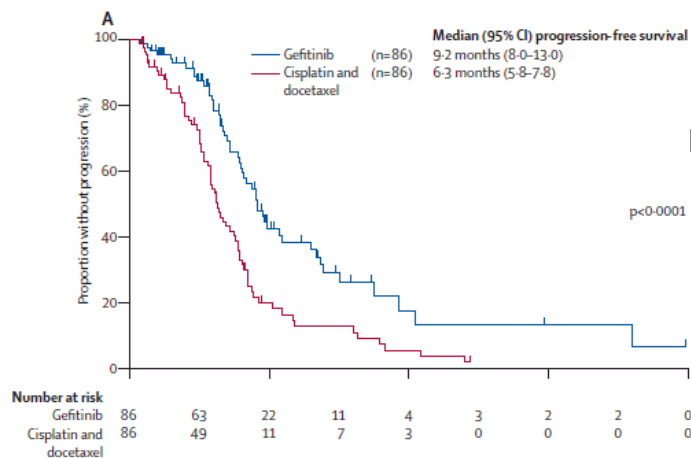
EGFR Mutations As Predictors of TKI Survival: IPASS & WJTOG



HR = 0.48



Mok TS, et al. N Engl J Med 2009;361:947-57



HR = 0.49

Mitsudomi T, et al. Lancet Oncol 2010;11:121-8

Exon 19 Del vs. Exon 21 L858R

- RR to TKI (retrospective)
 - Mutation-positive: 78%, (range, 30 - 100, with most series reporting >60)
 - Mutation-negative: 10% (range, 0 - 33)
- OS to TKI
 - Mutation-positive: improved (with an median OS up to 30 months)
 - Mutation-negative
- RR to TKI (N America)
 - Exon 19 deletions >
 - Exon 21 L858R
- OS to TKI (N America, not E Asia)
 - Exon 19 deletions >
 - Exon 21 L858R
- OS (untreated)
 - Exon 19 deletions < (?)
 - Exon 21 L858R

Exon 19 Del vs. Exon 21 L858R

	RR (%)		PFS* or OS (months)	
	Exon 19 Deletions	Exon 21 L858R	Exon 19 Deletions	Exon 21 L858R
Inoue (25 / 75)	67%	86%	—	—
Sequist (34 / 98)	59%	78%	—	—
Asahina (20 / 82)	83%	67%	—	—
Sutani (38 / 100)	75%	86%	—	—
Riely CCR '06 (retrospective)	—	—	12* or 34	5* or 8
Jackman CCR '06 (retrospective)	73%	50%	24* or 38	10* or 17
Rosell NEJM '09	OD = 3.08		HR = 1.92* or 2.98	
Takano JCO '08	—	—	29.2	27.2
Yang JCO '08	95%	74%	8.9*	9.1*
Wu AJRCCM '08	69%	65%	—	—

Exon 20

Retrospective Studies

- 515 patients for EGFR TK mutation from Jan 2000 to Jun 2007
- 23 patients (22 adeno, 20 never smokers) with EGFR exon 20 mutations, 9 with co-existing EGFR mutations (7 with co-existing EGFR exon 21 L858R / L861Q).
- 16 patients (16 adeno, 15 never smokers) with EGFR exon 20 mutations received gefitinib.
- 4 patients (25%) with EGFR exon 20 mutations received gefitinib and had a partial response.

Exon 18 G719X

- G719X comprises <5% of EGFR mutations and had been associated with sensitivity to gefitinib / erlotinib.
- Preclinical models showed that
 - erlotinib (reversible EGFR inhibitor) may be more selective for exon 19 deletion mutations;
 - neratinib (HKI272) (irreversible EGFR, HER2 inhibitor) may be more selective for point mutations, including exon 18 G719X.

Exons 18 and 20 Prospective Studies

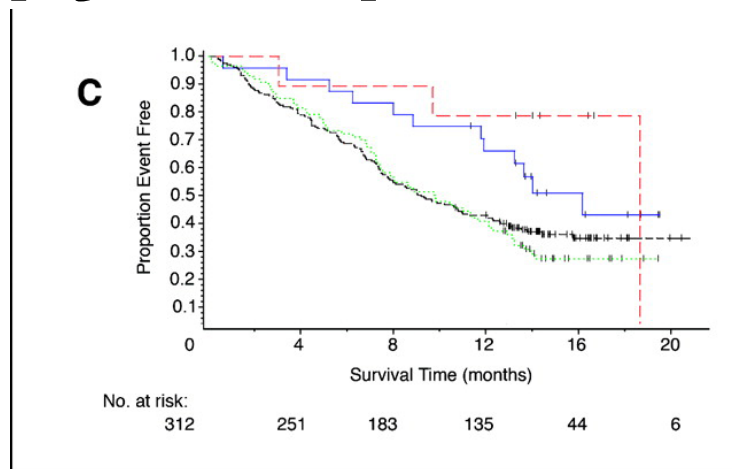
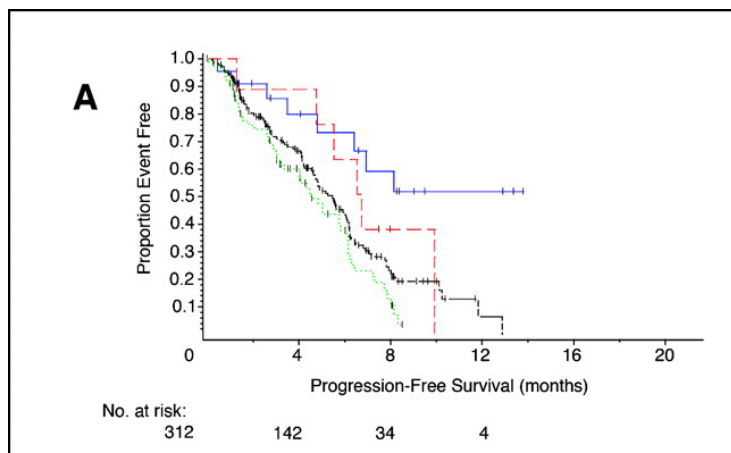
	Exon 18 mutations		Exon 20 mutations	
	G719X	Responses		Responses
Yang Phase II 55 / 90 Gefitinib	(n = 0)	—	SVD768- 770ins (n = 3)	1 PR, 2 PD
Douillard Phase III 44 / 297 Gefitinib	(n = 2)	Not reported	(n = 0)	—
Sequist Phase II 102 / 167 Neratinib	(n = 4)	3 PR, 1 SD	Ins (n = 3) V774M (n = 1)	0 PR

EGFR Mutations As Predictors of Chemotherapy Response

- TALENT and INTACT
 - Phase III chemotherapy + erlotinib or gefitinib vs. chemotherapy
 - OS of EGFR mutation (+) patients was significantly longer than OS of EGFR mutation (-) patients who received chemotherapy alone without gefitinib or erlotinib.
- IPASS
 - Phase III gefitinib vs. chemotherapy
 - RR (47.3%) of EGFR mutation (+) patients was significantly higher than RR (23.5%) of EGFR mutation (-) patients who received chemotherapy.
 - PFS was not different between patients with and patients without EGFR mutation in the chemotherapy arm.

Eberhard DA, et al. JCO 2005;23:5900-9
Bell DW, et al. JCO 2005;23:8081-92
Mok TS, et al. NEJM 2009;361:947-57

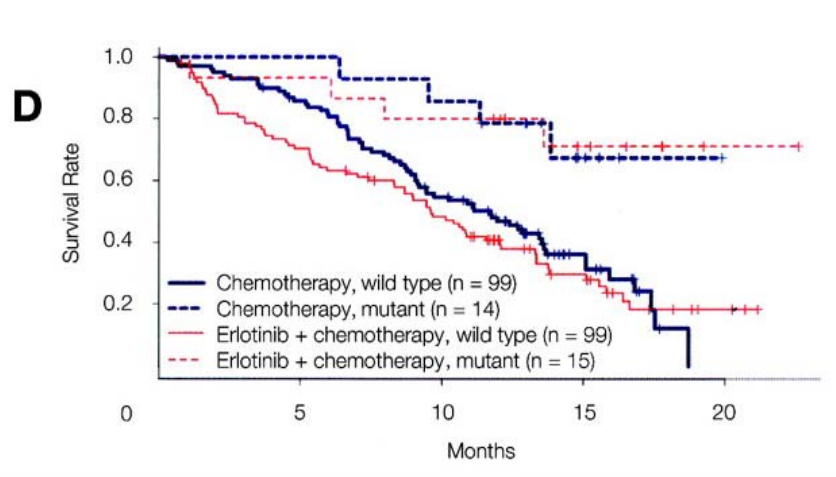
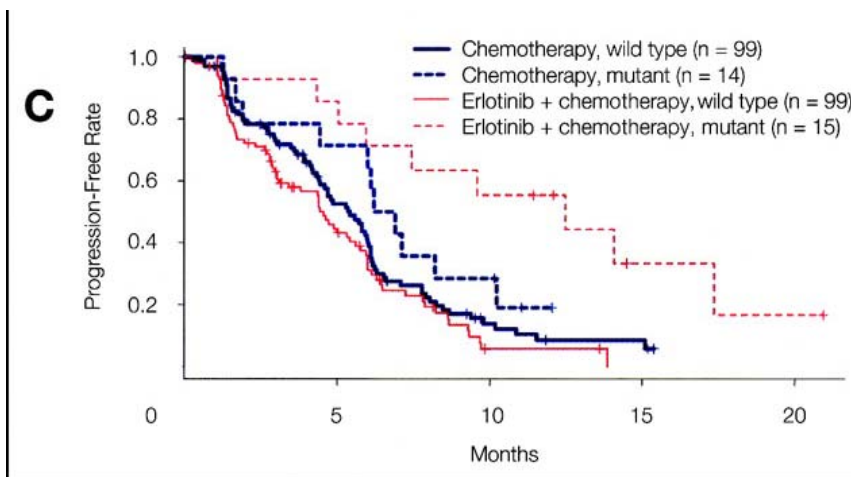
EGFR Mutations As Predictors of Chemotherapy Response



TRIBUTE: Chemo + E vs. Chemo
INTACT: Chemo + G vs. Chemo

— EGFR mutation-positive (chemotherapy & gefitinib)
— EGFR mutation-negative (chemotherapy & gefitinib)
- - - EGFR mutation-positive (chemotherapy & placebo)
- - - EGFR mutation-negative (chemotherapy & placebo)

Eberhard DA, et al. JCO 2005;23:5900-9
Bell DW, et al. JCO 2005;23:8081-92



Summary

- Tyrosine kinase inhibitor
 - Response rate
 - TK mutation: 78%, (range, 30 - 100, with most series reporting >60)
 - Wild type: 10% (range, 0 - 33)
 - Exon 19 deletions > exon 21 L858R >> Exon 20 mutations (esp. insertion / duplication / deletion)
 - Overall Survival
 - TK mutation: improved (with an median OS up to 30 months)
 - Wild type
 - Exon 19 deletions > exon 21 L858R (in N America, but not in E Asia)
- Chemotherapy
 - Response rate
 - TK mutation > wild type
 - Progression-free or overall survival
 - TK mutation = wild type