ATLAS OF MOLECULAR ONCOLOGY

EGFR Tumor Mutations and Markers of Acquired Resistance

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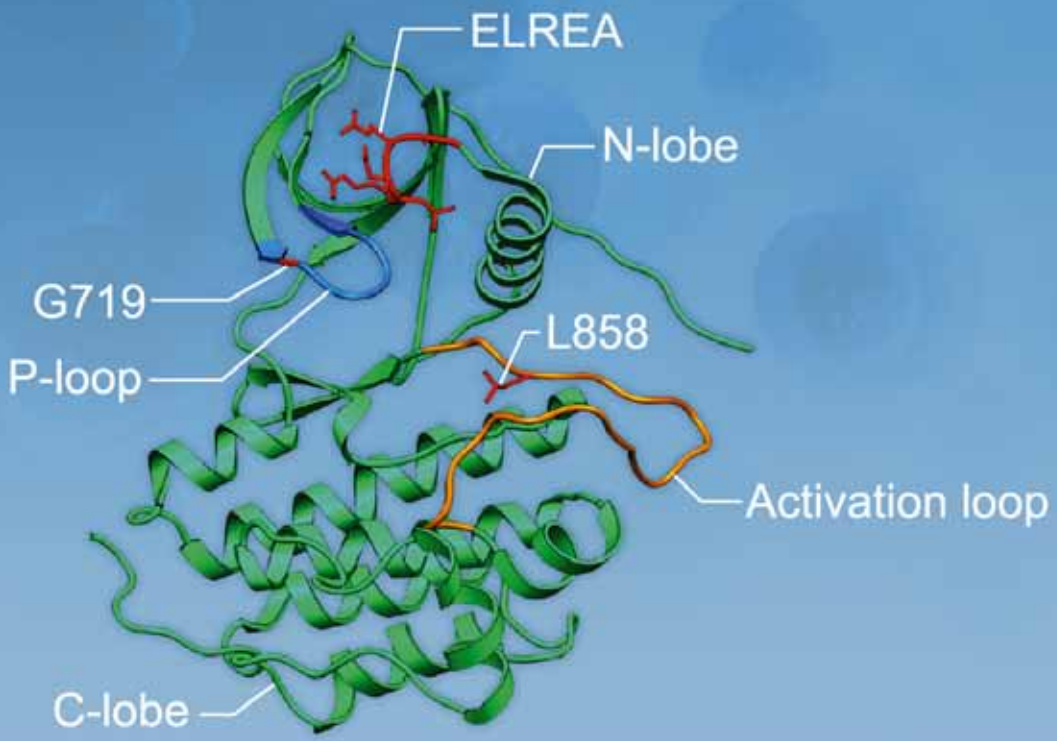
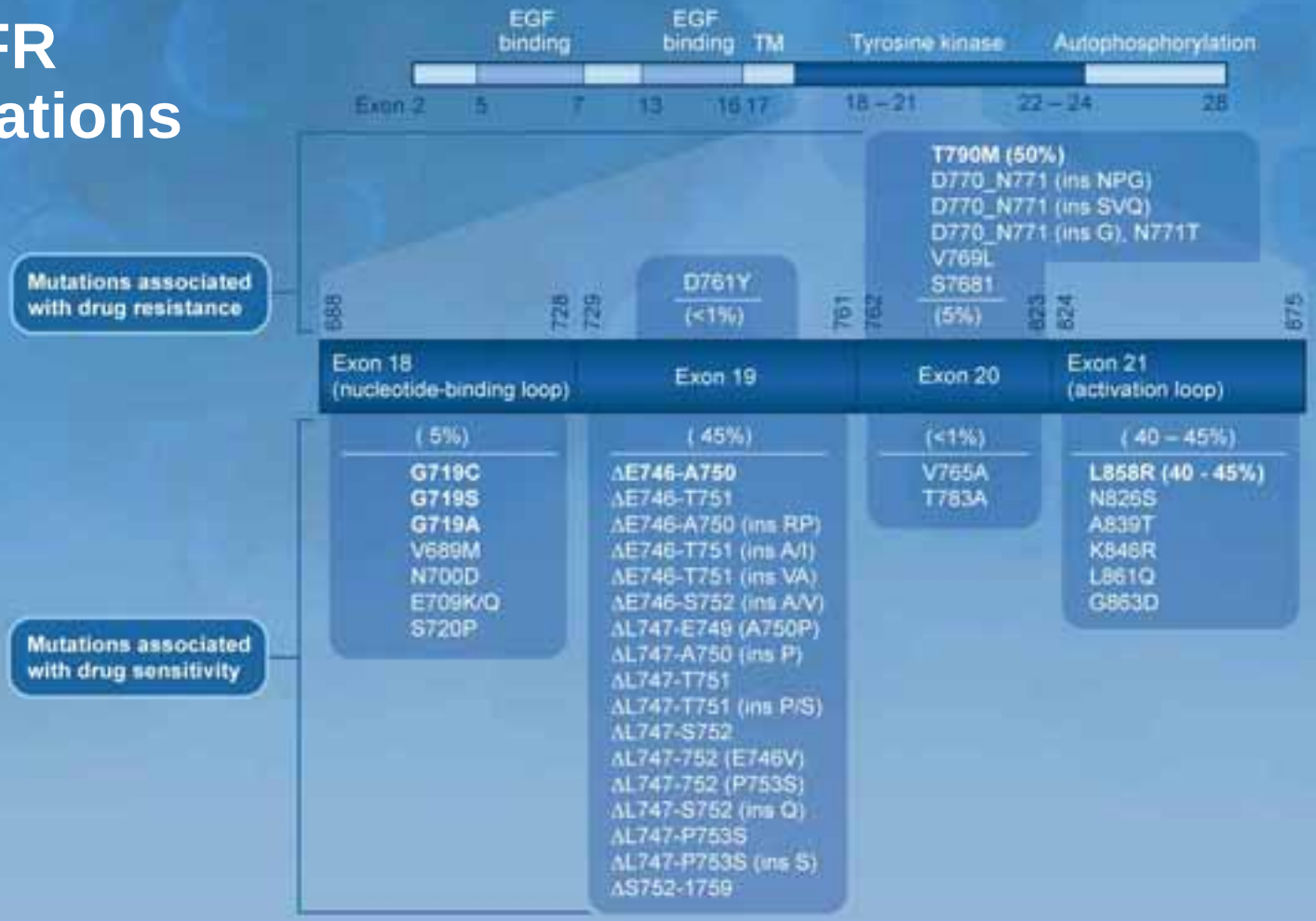
EGFR-TKI 2004-2006

- **Erlotinib prolongs survival as 2nd and 3rd line Rx compared to placebo**
  - **Benefit is best predicted by FISH +**
- **Erlotinib and gefitinib can cause dramatic responses and likely prolonged survival in a subset of patients (10%)**
  - **EGFR TK mutations best predict this group**
- **Combination with chemotherapy provides no benefit**

Epidermal Growth Factor Receptor (EGFR) Mutations



EGFR Mutations



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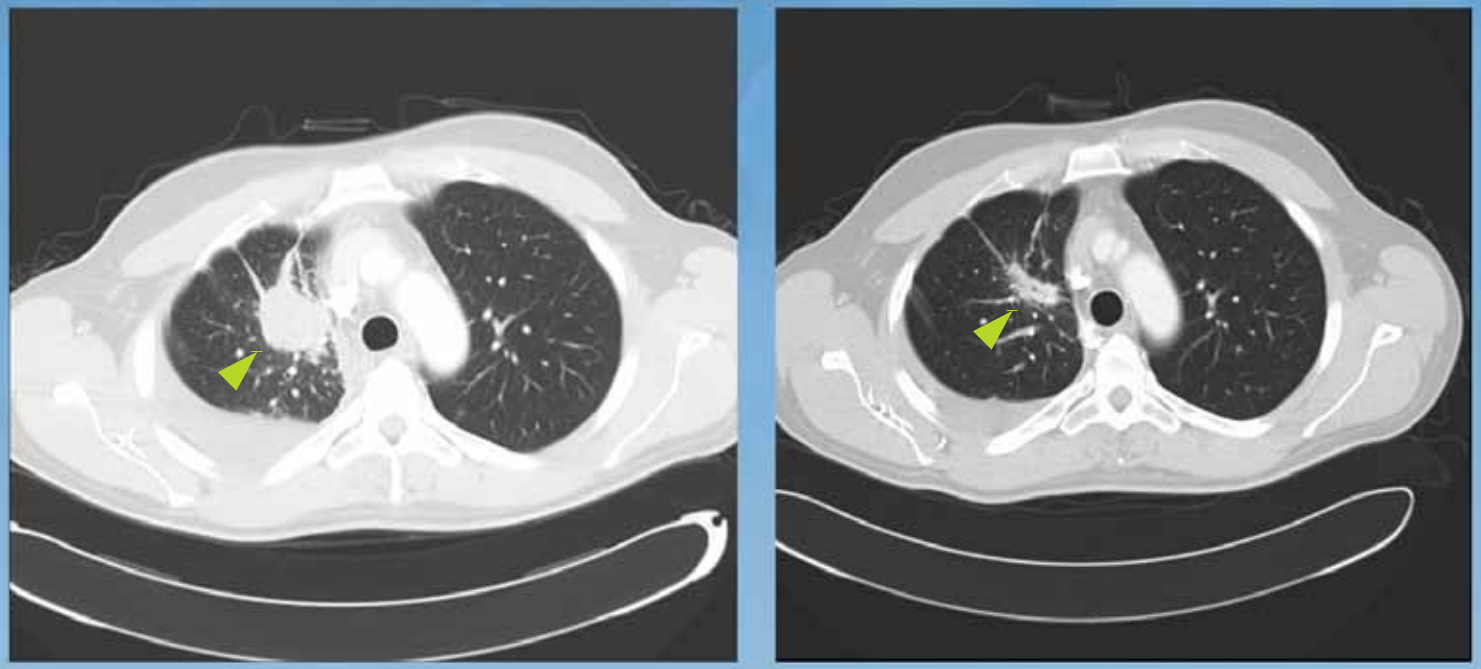
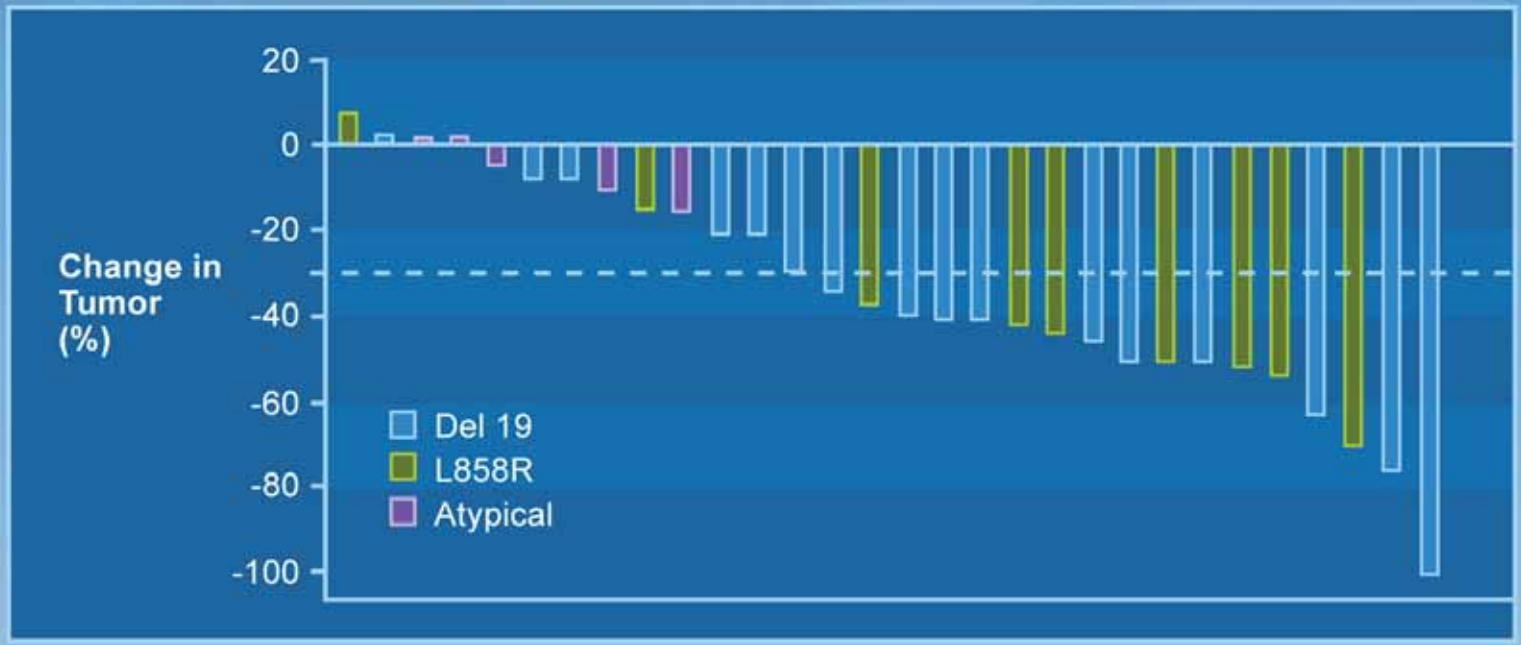
Patient with Prospectively Identified L858R Missense Mutation and Treated with Gefitinib



First Line Mutation Study with Gefitinib (Sequist et al. JCO 2008)

- 98 patients screened
- 34 EGFR mutations
- Results:
  - 55% response rate
  - 9.2 month median PFS
  - 17.5 month median OS

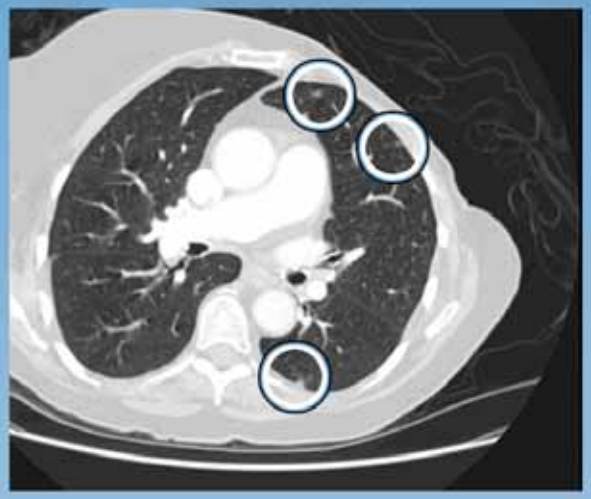
Percent Change in Measurable Tumor at Best Response by Individual Patient

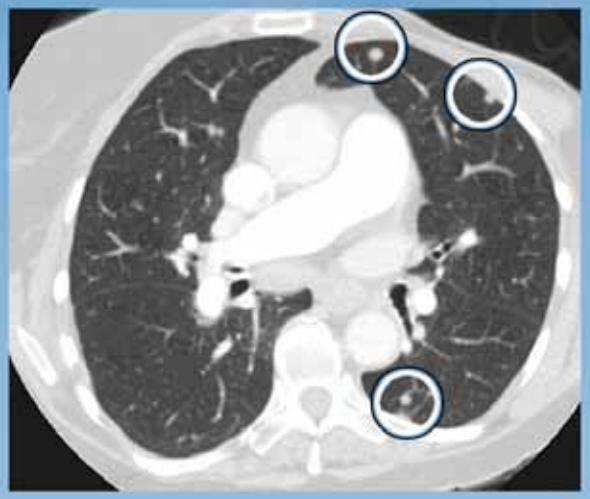


Source: With permission from Sequist, LV et al. *J Clin Oncol* 2008; 26:2442-2449, 2008

Resistance

- There are 2 robustly described TKI-resistance mechanisms: T790M in EGFR and MET amplification
- 1 patient with both T790M and L858R had a best response of SD and remained on treatment for 55 days

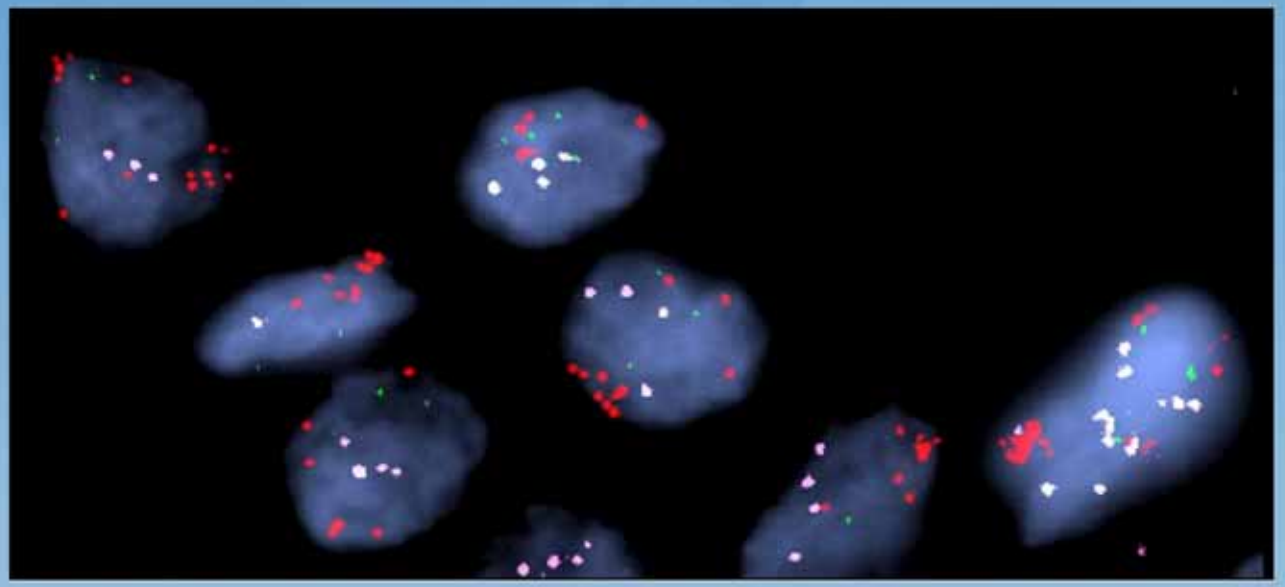




Source: With permission from Sequist LV et al. *Proc ASCO* 2007. Abstract 7504

Resistance

- 1 patient with both del 19 and MET amplification had rapid PD with new brain mets and malignant pleural and pericardial effusions and remained on treatment for 30 days



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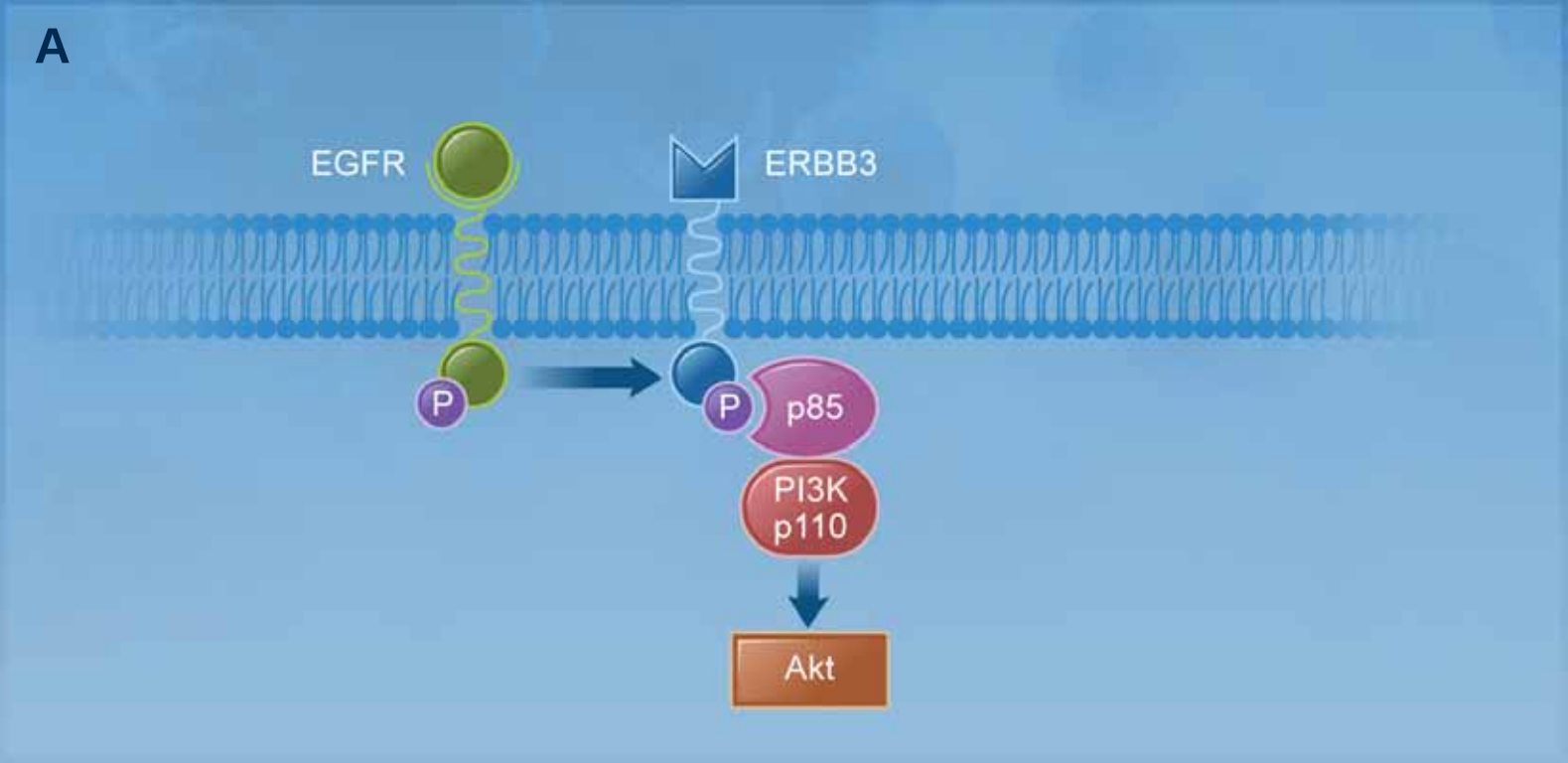
Resistance Mechanisms



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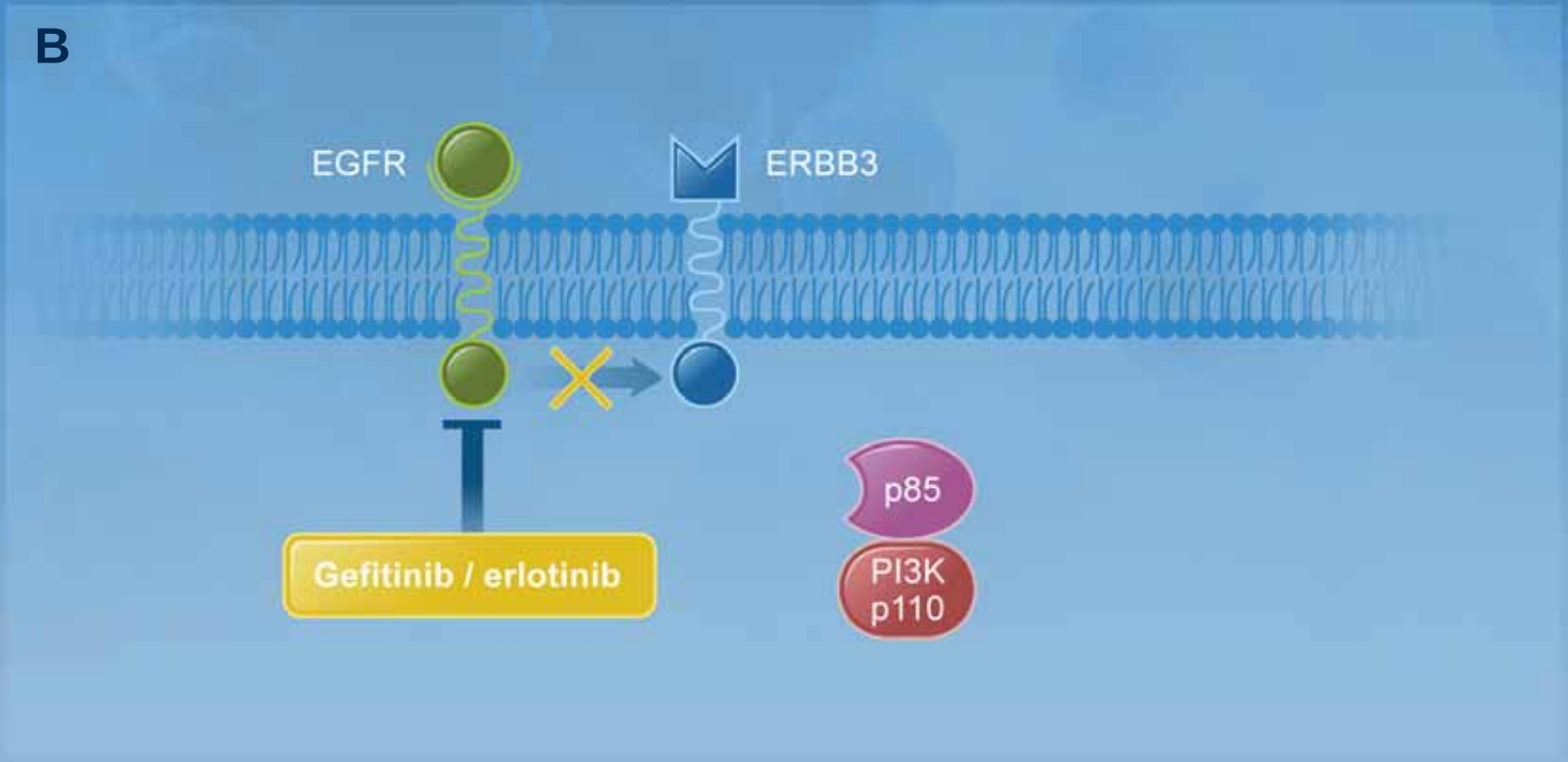
(Arteaga CL. HER3 and mutant EGFR meet MET. *Nat Med* 13:675-7), copyright 2007.

Resistance Mechanisms



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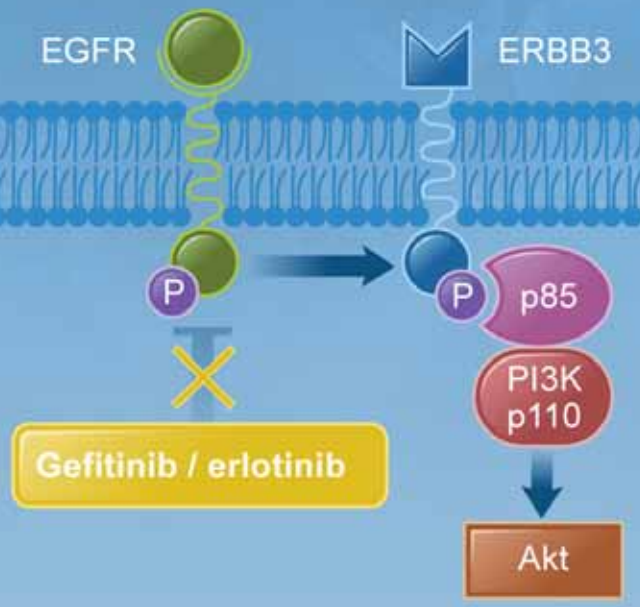
Resistance Mechanisms

C T790M



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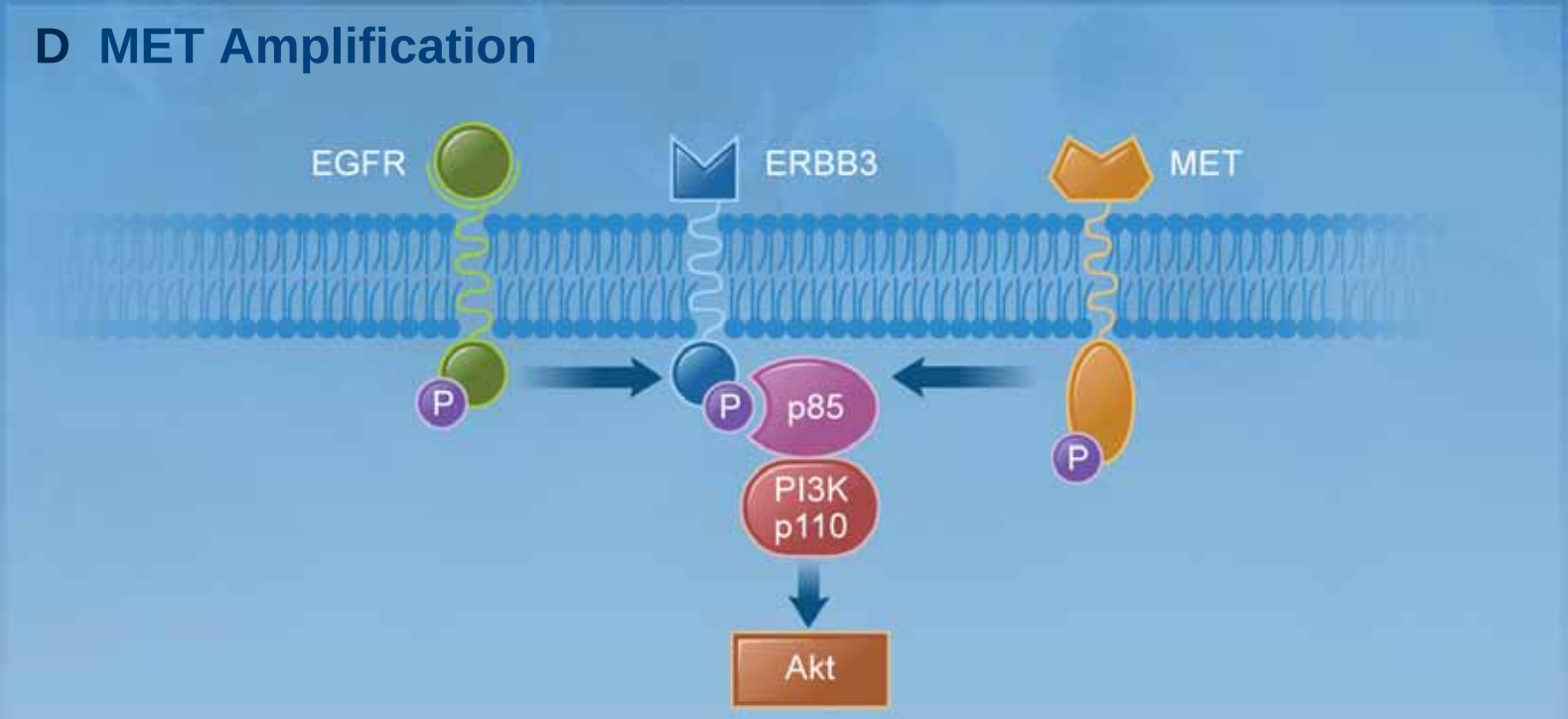
Resistance Mechanisms

D MET Amplification



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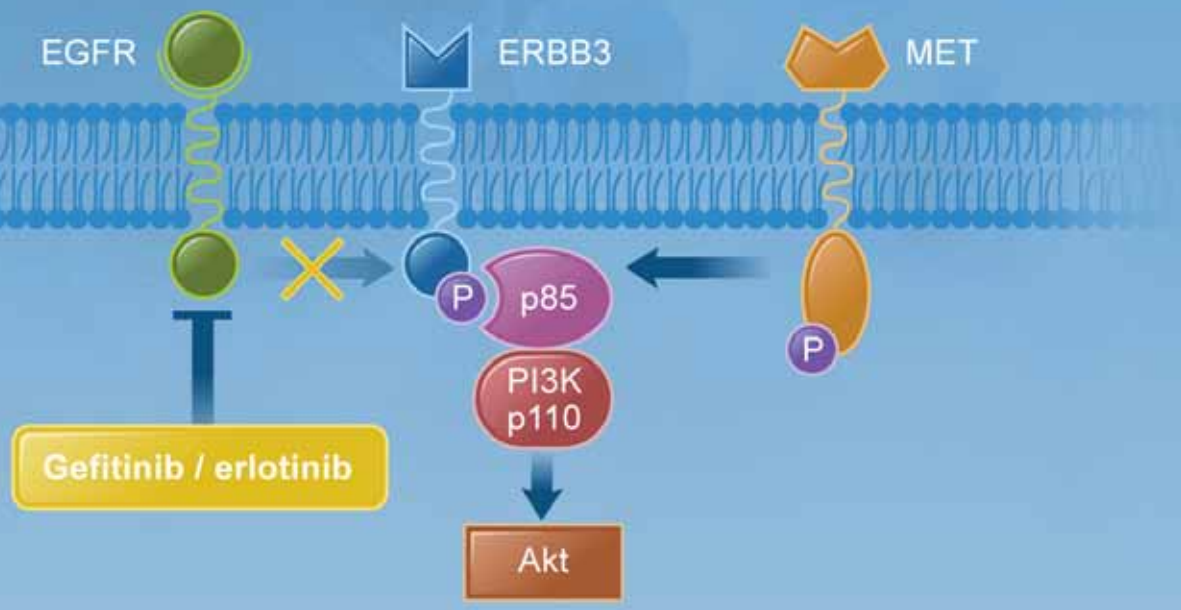
Resistance Mechanisms

E MET Amplification



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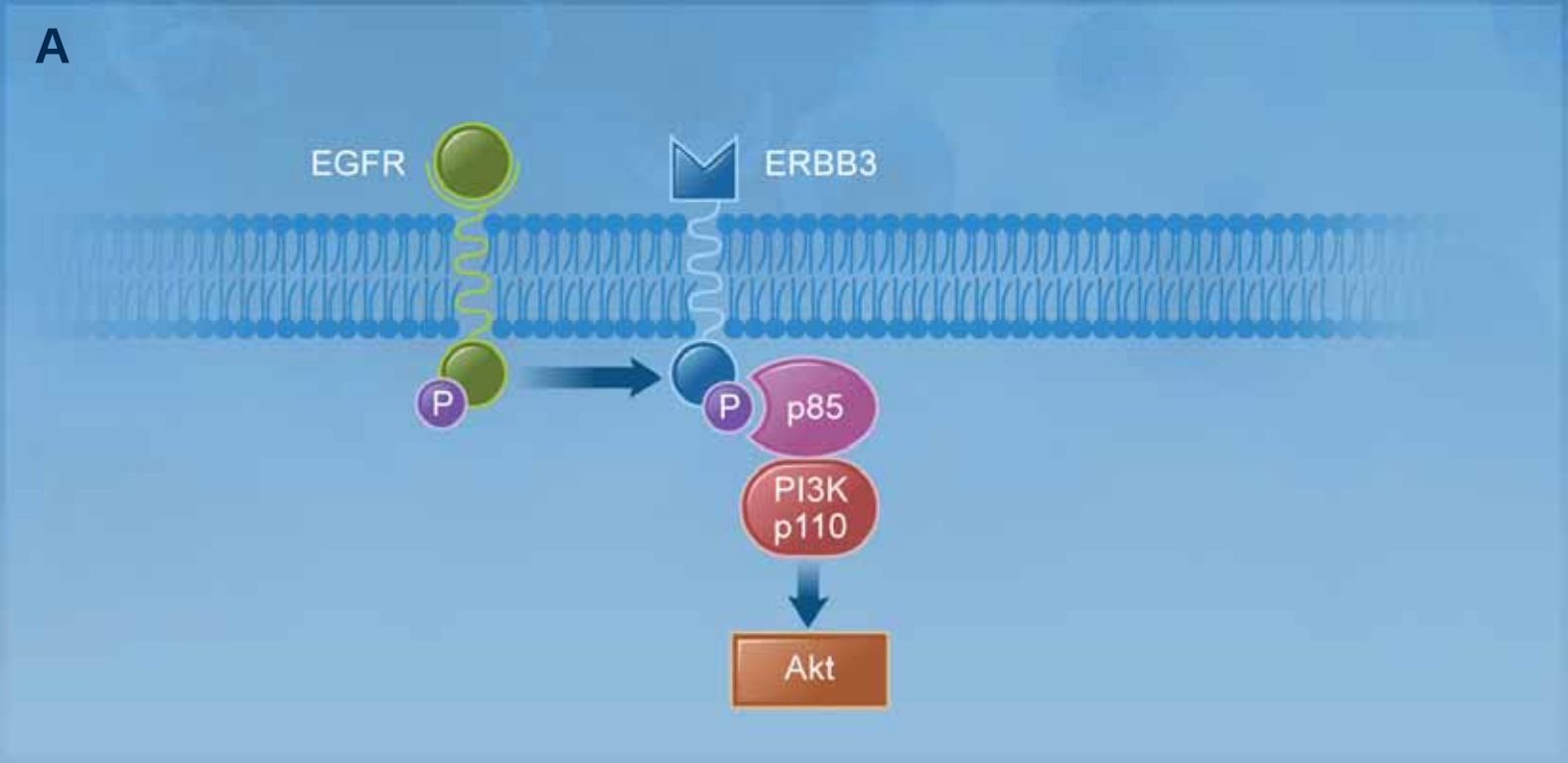
Is Activation of PI3K Sufficient to Induce Resistance?



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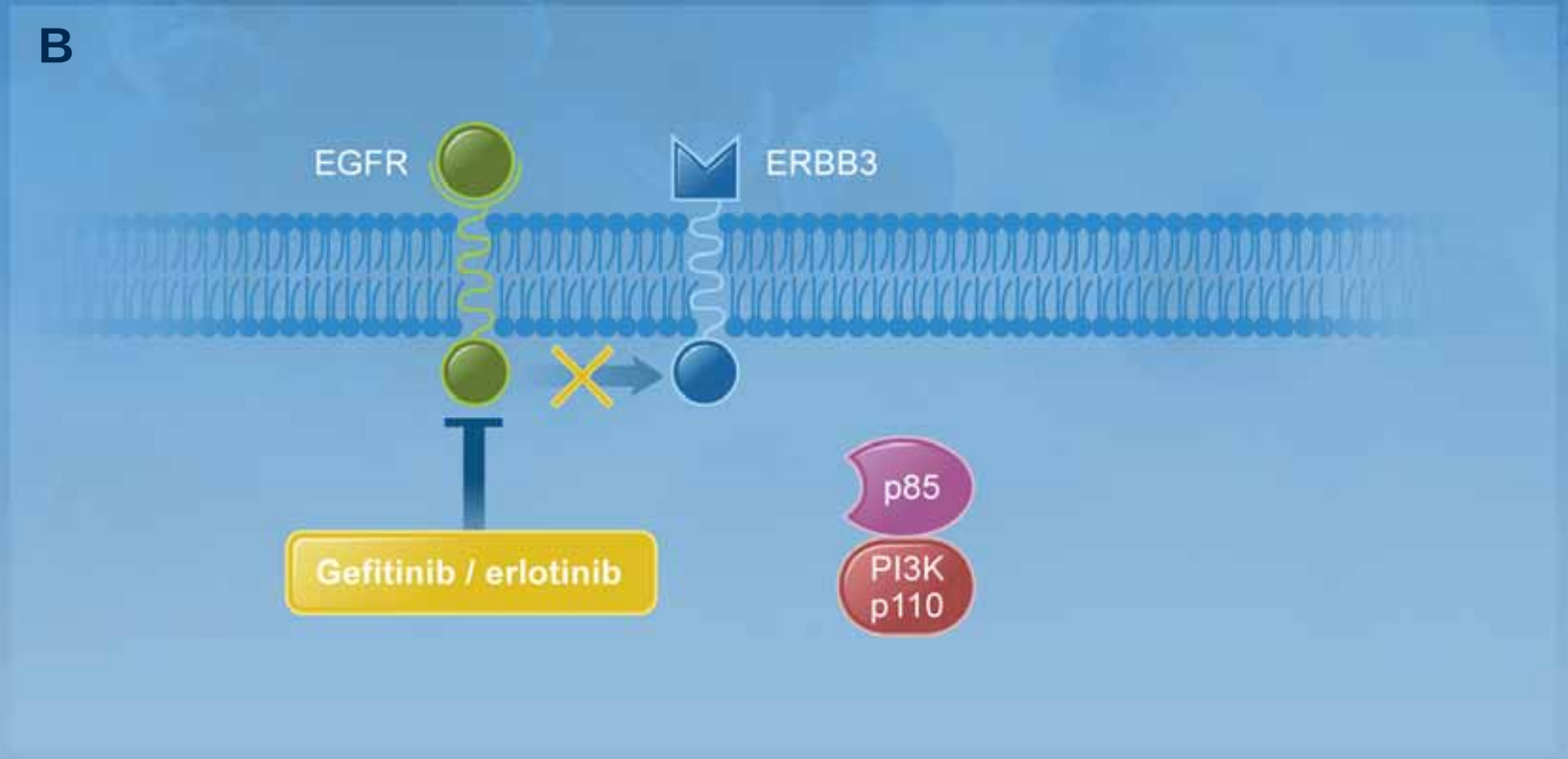

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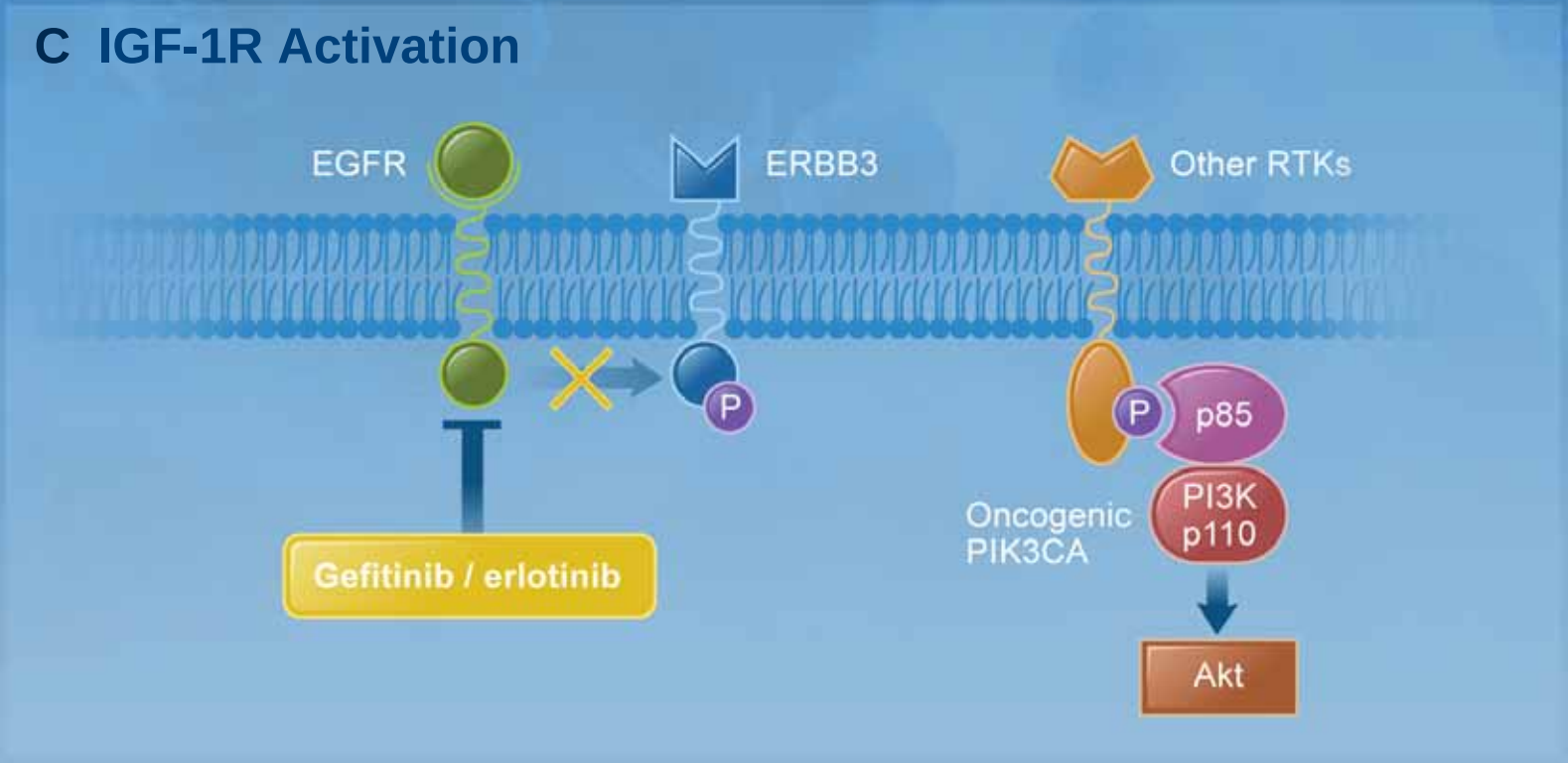

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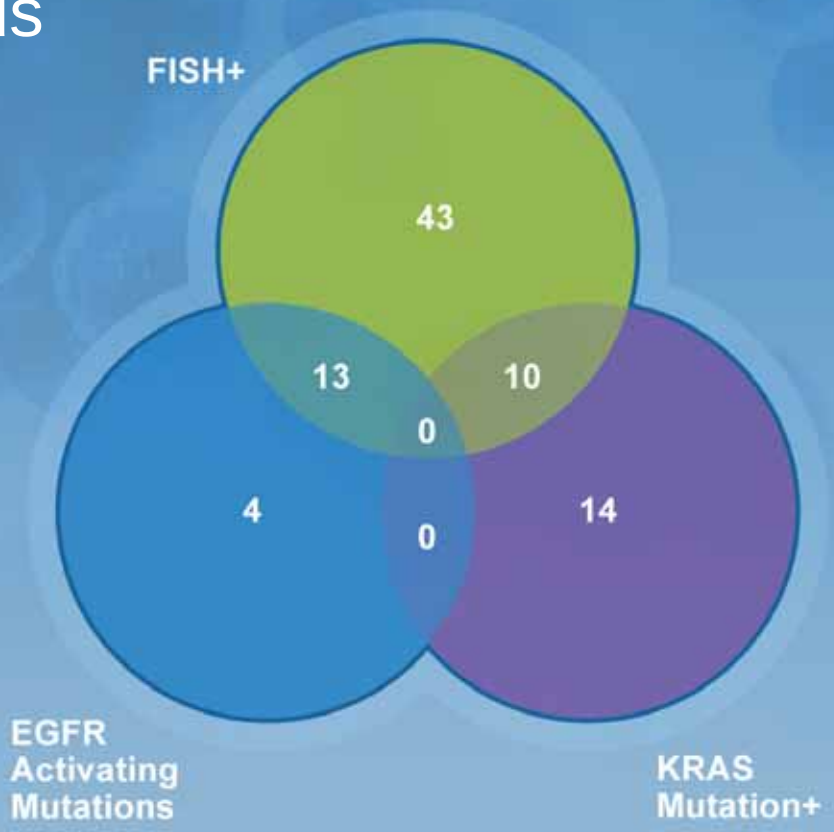
OSI-774-203 ("BUNN" Study)
Patient Biomarker Status

- **N=119, 24 patients not included due to missing/unknown**
- **14% EGFR mut; 20% KRAS mut; 47% FISH+**
- **35 patients (29%) *KRAS* WT, FISH-, and EGFR WT**



Source: Hirsch FR et al. *IASLC.* 2008 (abst. #11)

BR.21: Role of KRAS Biomarker in Response and Survival

- 206 tumors from BR.21 study analyzed for KRAS mutational status
- 30 (15%) of patients had KRAS mutations
- Small numbers preclude a robust analysis, but high HR favors placebo in patients with KRAS mutation

	Response			Survival Benefit				
	# Pts Assessed for ORR	ORR	P-value	# Pts	MS: Erl vs Plac (mon)	HR	95% CI	P-value
Total	427	8.9%	NA	731	6.7 vs 4.7*	0.70	0.58 – 0.85	<0.001
KRAS Mutation	20	5.0%	0.69	30	3.7 vs 7.0	1.67	0.62 – 4.50	0.31
KRAS WT	98	10.2%		176	7.5 vs 3.4	0.69	0.49 – 0.97	0.03

* Shepherd FA et al. *J Thor Oncol*. 2007; 2(6): S68-S76

Source: Zhu et al. *J Clin Oncol*. 2008; 26:4268-75.

KRAS and EGFR Mutation Data

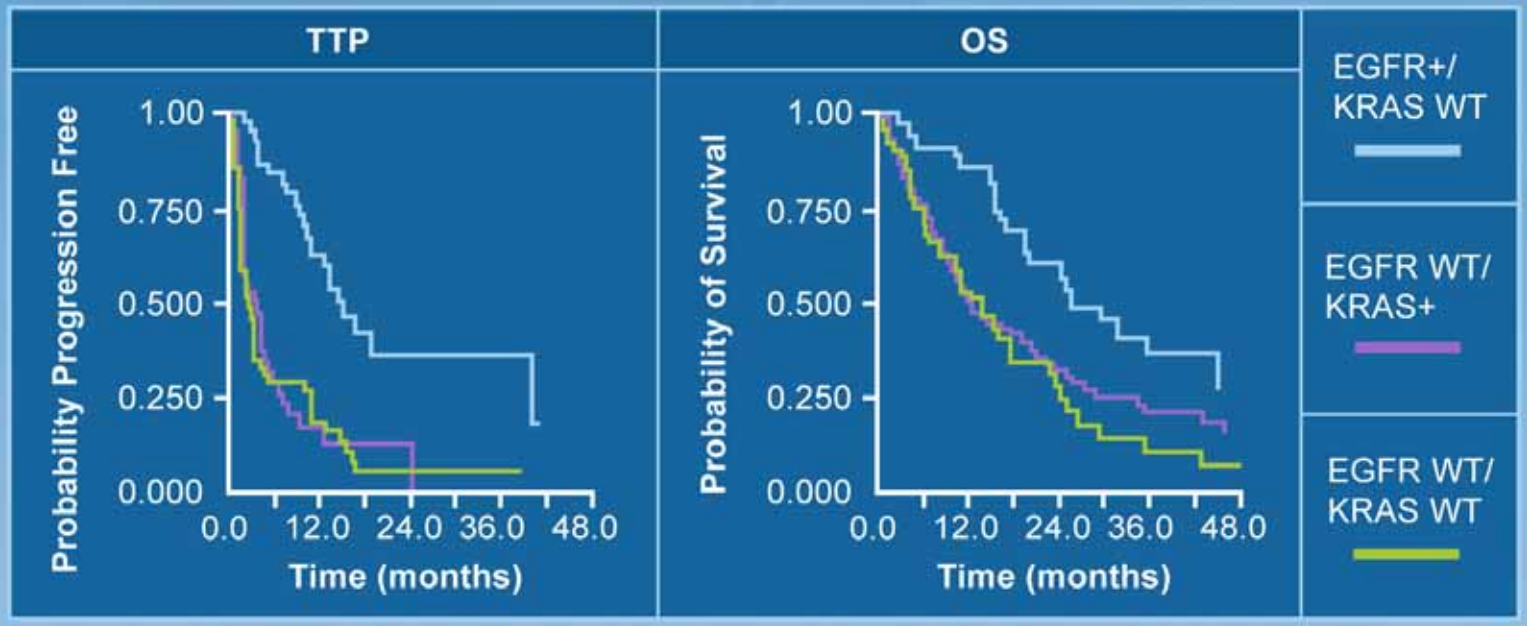
- Patients with *EGFR* mutations did significantly better than the 2 other groups. There was no significant difference between patients with KRAS mutations and patients who were EGFR WT/KRAS WT.

Clinical Outcomes by EGFR and KRAS Status				
	EGFR+/KRAS WT	EGFR WT/KRAS+	EGFR WT/KRAS WT	P
N	46	41	83	
Best Response				
CR	0	0	0	
PR	31 (67%)	0	4 (5%)	
SD	14 (30%)	19 (46%)	35 (42%)	
PD	0	18 (44%)	35 (42%)	
NE	1 (2%)	4 (10%)	9 (11%)	
Response Rate	31 (67%)	0	4 (5%)	<0.001
Median TTP (Months)	15.1	3.3	3.1	<0.0001
Median OS	24.5	13.0	11.8	0.002

Source: With permission from Jackman et al. Molecular Markers Meeting, Oct. 2008

KRAS and EGFR Mutation Data

- **When EGFR mutants are pulled out, there is no difference in TTP or OS between KRAS mutants and KRAS WT**



Source: With permission from Jackman et al. Reprinted with permission from *Clin Cancer Res* 2009;15(16):5267-73, fig 1. Molecular Markers Meeting, Oct. 2008

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EGFR TKIs 2006-2008

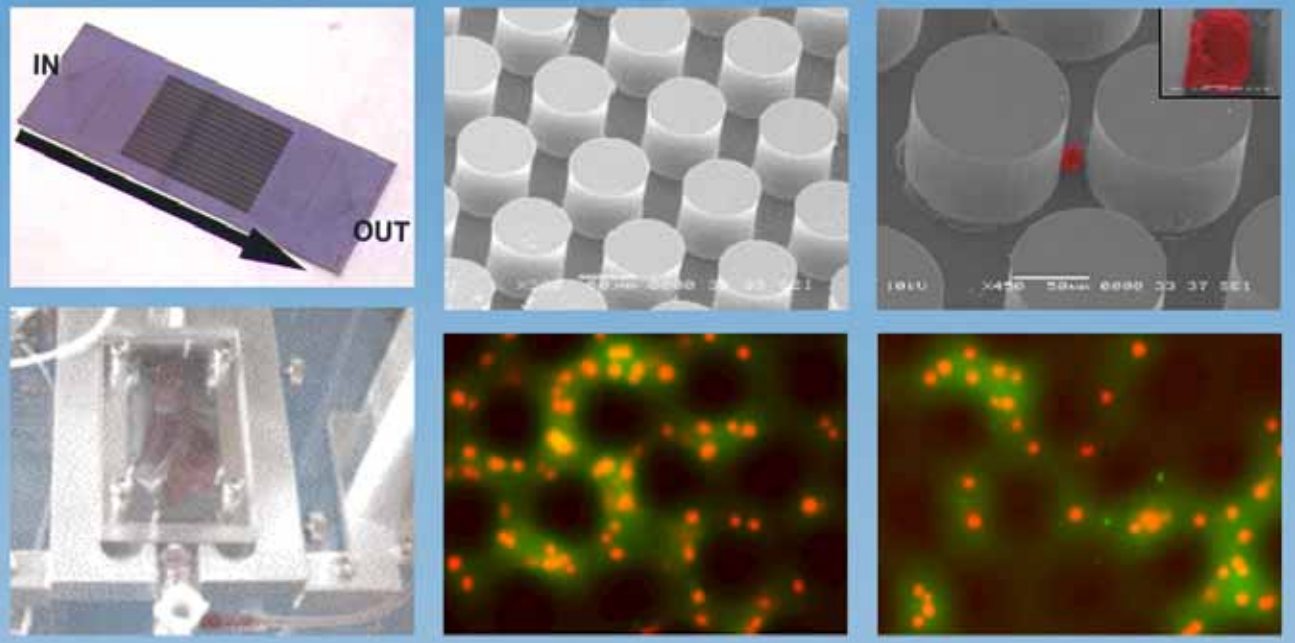
- **Resistance Mechanisms**
  - **T790M 50%**
  - **c-MET amplification and IGF-1 signaling 25%**
  - **Non-Kinase role of EGFR**
  - **Unknown (40%)**
- **Overcoming Resistance**
  - **Role of dual kinase inhibitors for T790M**
  - **Benefit to irreversible inhibitors?**
  - **c-MET inhibitors**
  - **IGF-1 based Rx**

EGFR Mutation Testing: Ready for Prime Time

- Test can be done reliably on 10 unstained slides from a core biopsy.
  - Almost always from a larger resection specimen
  - Occasionally from a fine needle aspiration
- Two to three week testing interval remains a challenge
- Re-biopsy of patients who initially respond can often reveal mechanisms of resistance
  - MSK data from ASCO 2009
- Analysis of circulating tumor cells and circulating tumor DNA may offer simpler, less invasive option

CTC-Chip

- **Array of microposts that separates cells by size and captures epithelial cells against the walls of anti-Ep-CAM coated posts**



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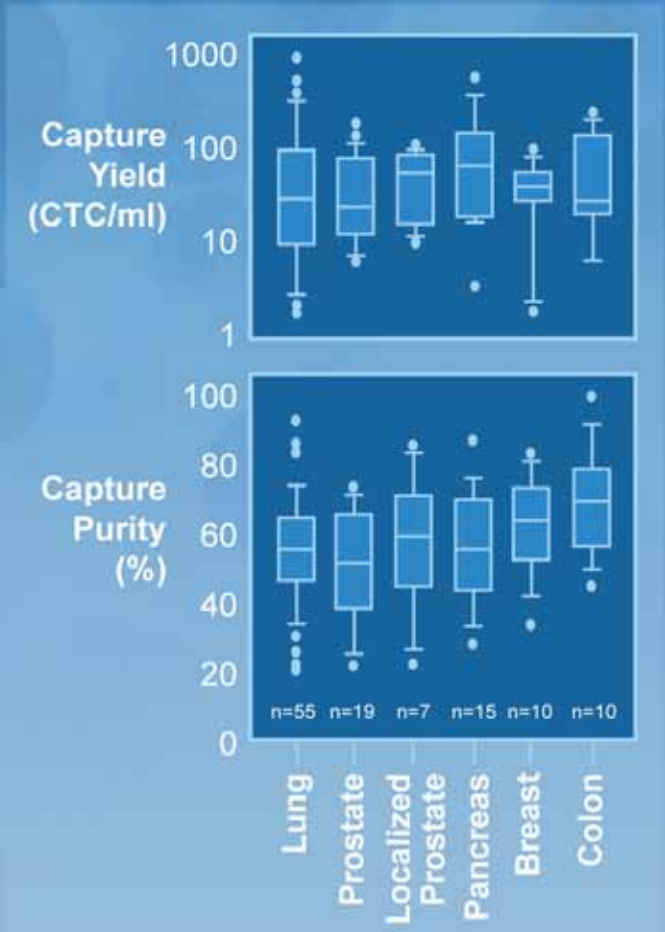
CTC-Chip

Cohort	Total Number of Samples	Samples with >5 CTC/ml (%)
Healthy Subjects	20	0
Lung Cancer	55	100
Prostate Cancer	19	100
Localized Prostate Cancer	7	100
Pancreatic Cancer	15	100
Breast Cancer	10	100
Colon Cancer	10	90



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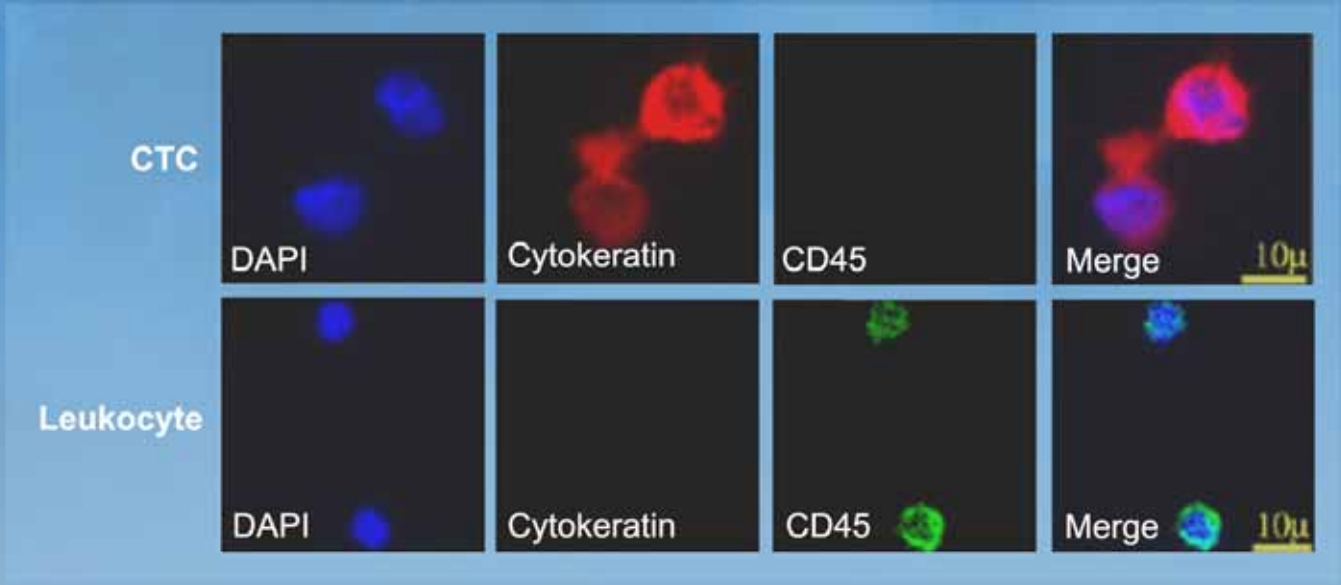

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EGFR Mutations 2009

- Mutated EGFR provides a model for the paradigm of oncogene addiction
- TKI shrinks tumor in 70% of patients with EGFR mutations and should be considered as a care standard for patients harboring these activating mutations
- Never and light smokers with adenocarcinoma should be tested as early in the course of therapy as possible
- Re-biopsy of responders at the time of progression can be helpful clinically