Biomarkers of Brain Tumors to EGFR TKI

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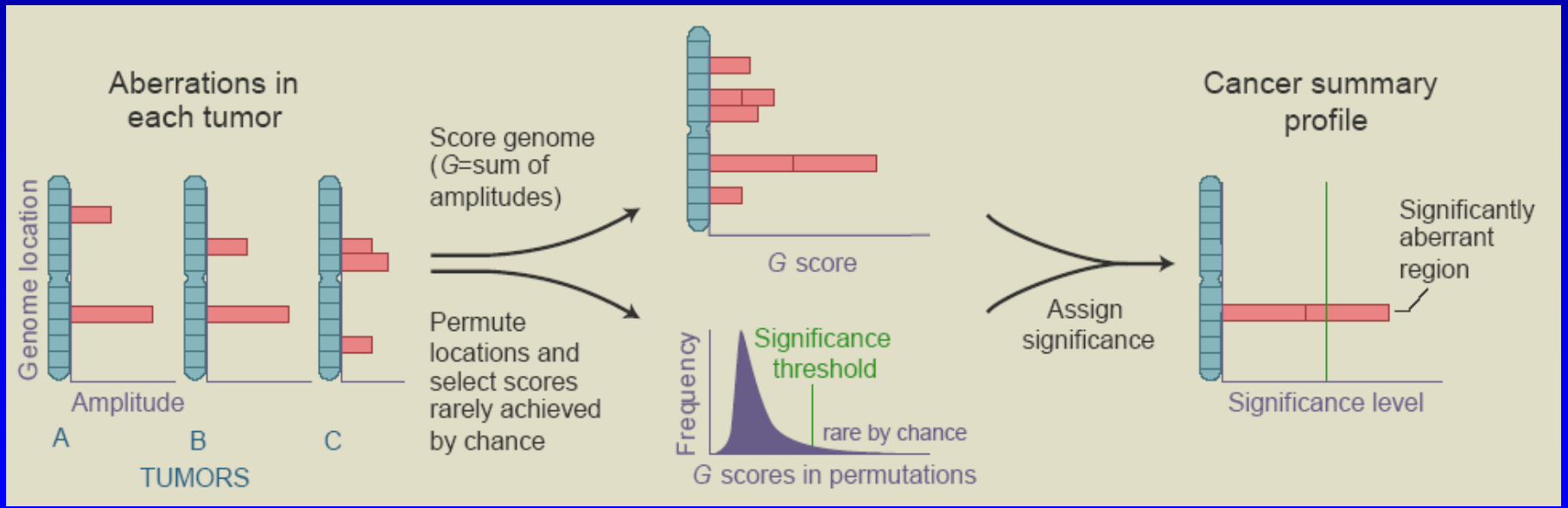
Signal transduction inhibitors for GBM
- Rationale -

- previous studies found mutations/gene copy number alterations in signal transduction pathways in a substantial fraction of clinical GBM samples
- genetically defined models have documented a role for (some of) these genetic aberrations in glioma formation
- clinical success of kinase inhibitors in other human cancers with mutational activation of a kinase/kinase pathway

Identification of recurrent gene copy number alterations in glioblastoma



R. Beroukhim, G. Getz, E. Lander, W. Sellers

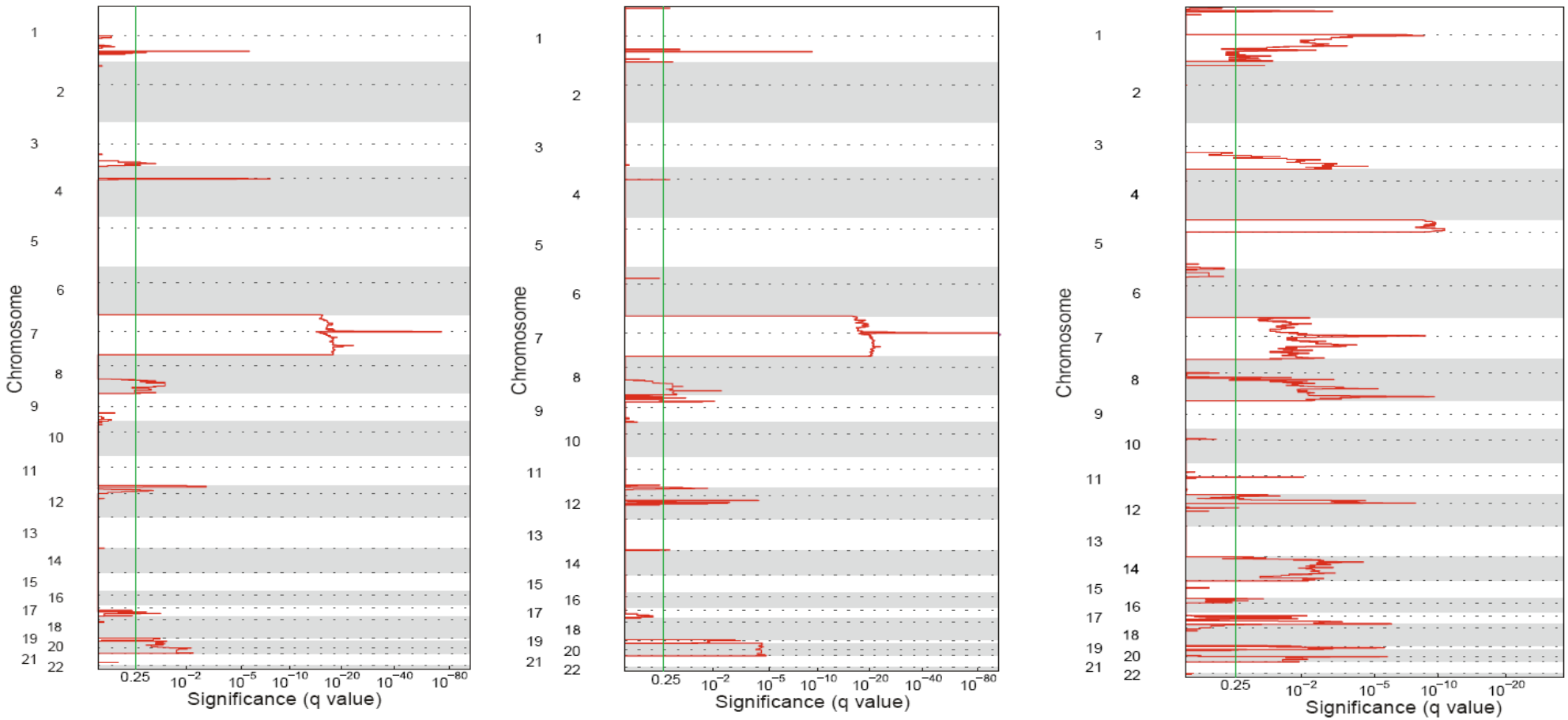
Example: Statistically significant recurrent amplifications

UCLA gliomas

other gliomas

Kotliarov et al. (100K SNP, n=178)

NSCLC (n=81)



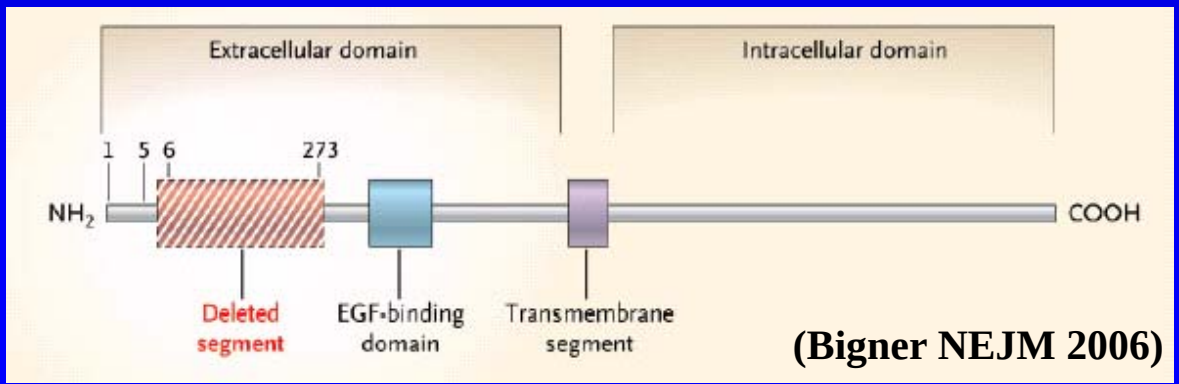
(Beroukhim et al., in press)

Challenges in the clinical development of signal transduction inhibitors for glioma

- uncertain drug delivery (blood-brain barrier)
- limited access to tumor tissue
- heterogeneity

EGFR TKI therapy for glioblastoma
- Rationale -

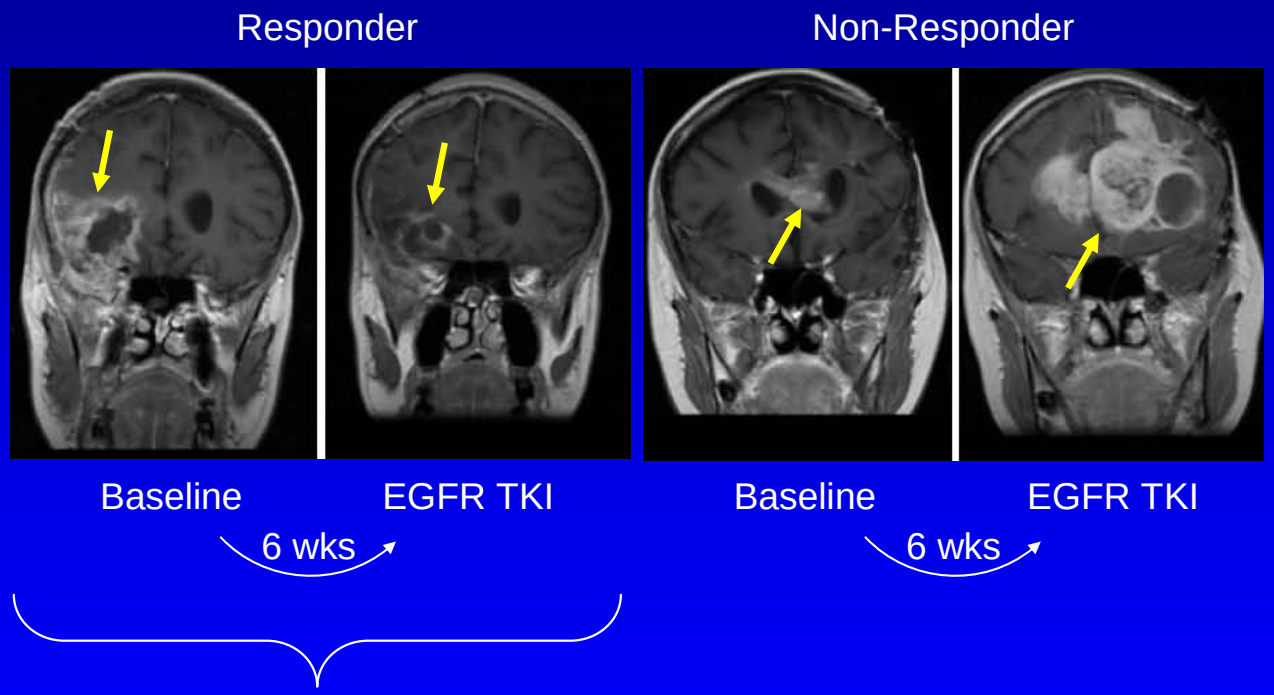
- Amplification of EGFR gene locus in 40 % of glioblastomas
- EGFRvIII-mutant in ~ 20 % of glioblastomas:
  - lacks AA 6-273 of extracellular EGFR domain
  - constitutively activated
  - Oncogenic in cell transformation assays



(Bigner NEJM 2006)

EGFR TKI therapy for GBM
- Clinical Activity -

- 49 patient with recurrent glioblastoma
- radiographically “measurable” disease
- single-agent EGFR kinase inhibitor (erlotinib or gefitinib)



9/49 patients (18 %)

EGFR TKI therapy for glioblastoma
- Molecular Determinants of Drug Response -

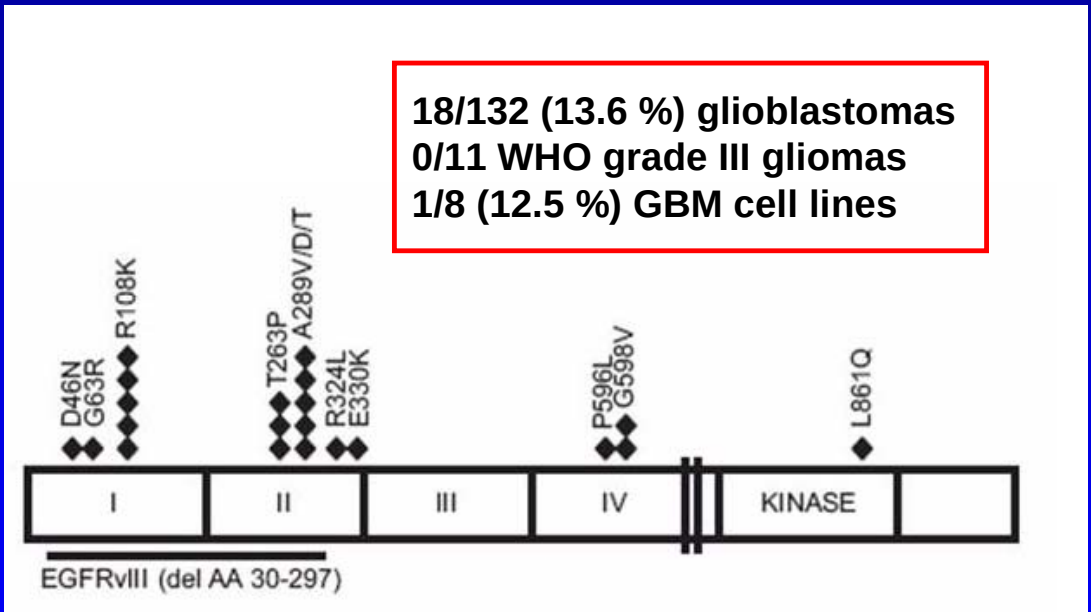
Table 3. Biomarkers of a Response to EGFR Kinase Inhibitors.*

Group	Response	No Response	P Value	Odds Ratio (95% CI)
	no. (%)			
UCLA patients				
Molecular biomarkers — no./total no. (%)				
EGFR amplification or polysomy	6/7 (86)	13/18 (72)	0.66	NC
EGFRvIII expression	6/7 (86)	6/19 (32)	0.03	13 (1–130)
PTEN expression	7/7 (100)	6/19 (32)	0.005	NC†
Coexpression of EGFRvIII and PTEN‡	6/7 (86)	2/19 (11)	<0.001	51 (4–669)
UCSF patients				
Molecular biomarkers — no./total no. (%)				
EGFRvIII expression	7/8 (88)	11/25 (44)	0.05	9 (1–84)
PTEN expression	5/8 (62)	4/25 (16)	0.02	9 (1.5–52)
Coexpression of EGFRvIII and PTEN¶	5/8 (62)	1/25 (4)	0.001	40 (3–468)

* CI denotes confidence interval, and NC not calculated.
† An odds ratio could not be calculated because none of the UCLA patients with PTEN-deficient tumors had a response, but if 0.5 is added to each cell count, the odds ratio is 31 (95 percent confidence interval, 1.5 to 633.0).
‡ The test had a sensitivity of 86 percent and a specificity of 89 percent in the UCLA group and a positive predictive value of 75 percent.
§ A subgroup of patients in the UCSF study received concurrent temozolomide. All UCLA patients received monotherapy with an EGFR kinase inhibitor.
¶ The test had a sensitivity of 63 percent, a specificity of 96 percent, and a positive predictive value of 89 percent.

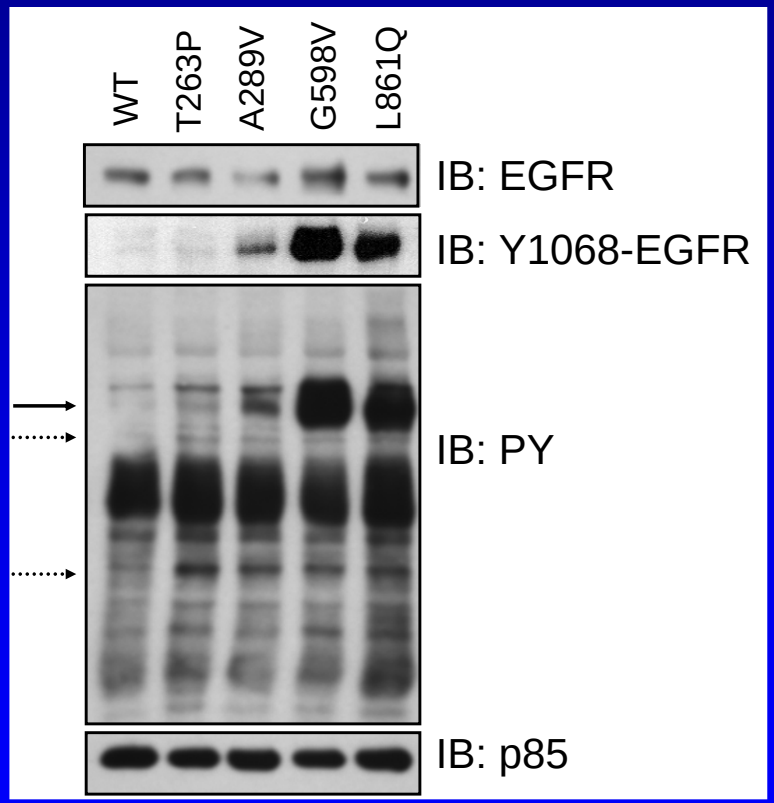
(T. Cloughesy, C. Sawyers, P. Mischel)

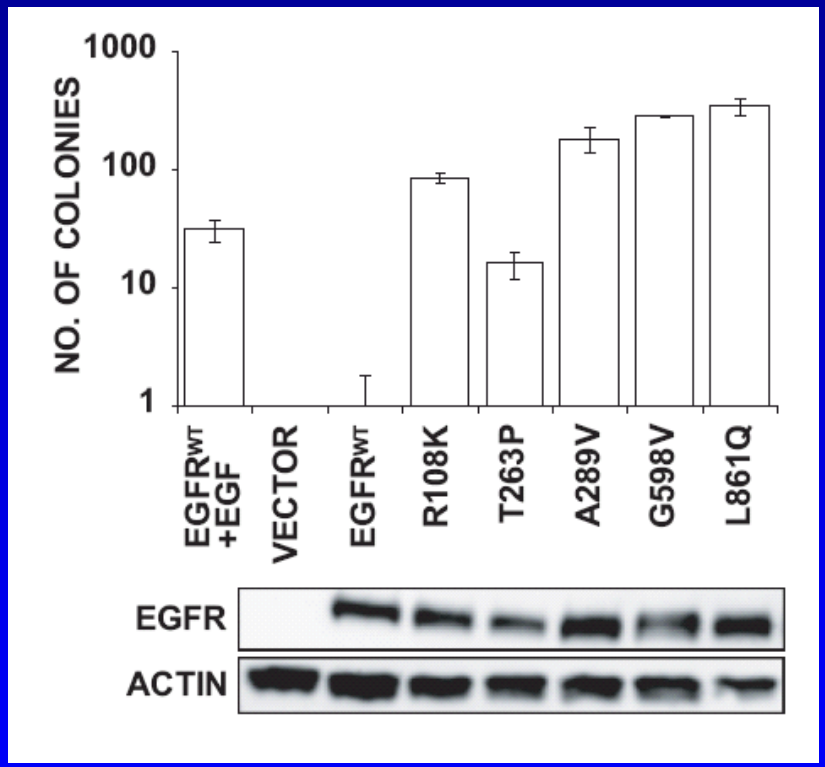
Discovery of missense mutations in EGFR extracellular domain



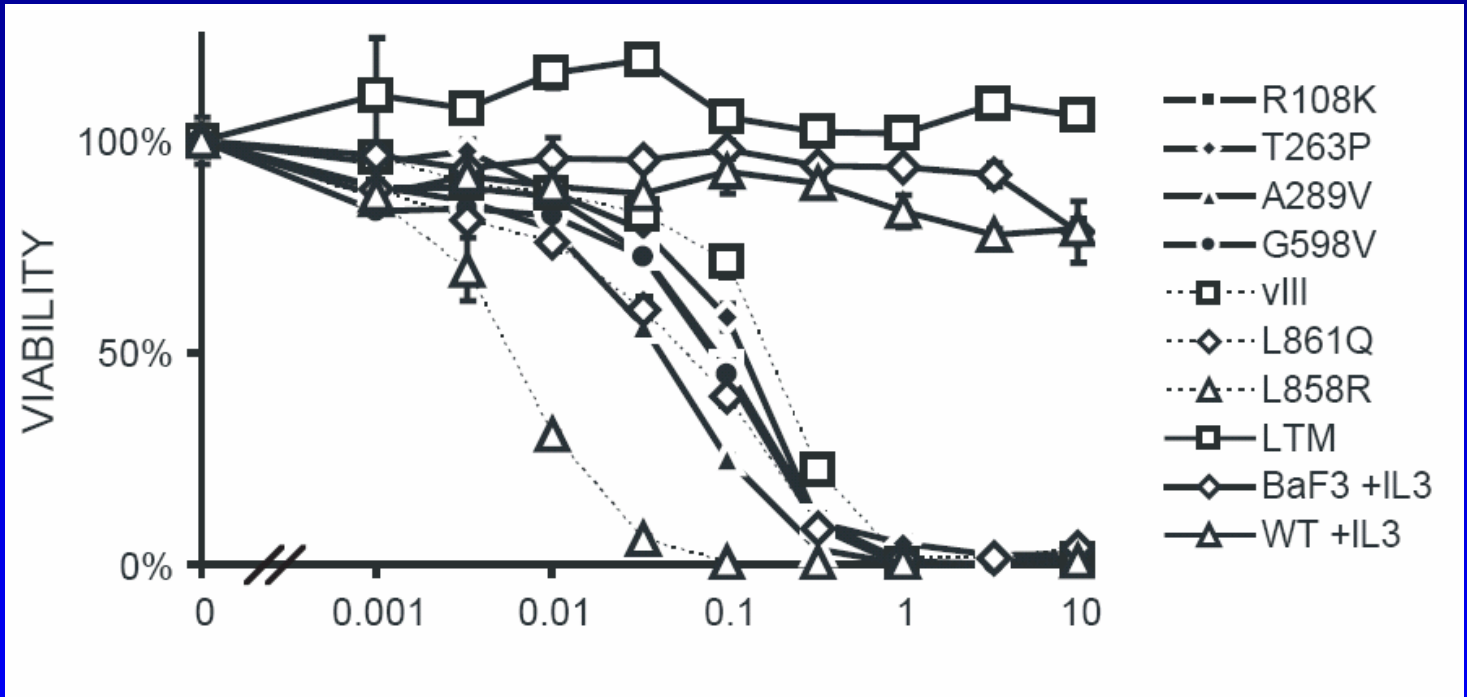
(in collaboration with M. Meyerson)

EGFR EC mutants are constitutively active and transforming





EGFR EC mutants are responsive to EGFR TKIs



(Lee et al., PLoS Med 2006)

Compressing drug development timelines

Table 1 | **Role of phase 0 clinical trials in cancer-drug development**

Current challenges in cancer-drug development	Phase 0 trials
Suboptimal use of target assessment and imaging techniques in early-phase clinical trials	Biomarker development and assay qualification in human tissues before the initiation of the trial
	The evaluation of imaging studies that provide functional and metabolic information about the effects of a drug on its target(s)
	The integration of such assays and/or imaging studies in phase 0 trials to establish the mechanism of action *in vivo* in actual patient samples
Establishment of the maximum tolerated dose as a primary endpoint in trials with molecularly targeted agents	Evaluation of target modulation is a primary endpoint
Late-stage failures with low rates of anticancer drug approvals	Allow for the systematic de-prioritization of investigational agents that do not show expected biological effects
Long timelines for the development of promising agents	The early initiation of first-in-human, proof-of-concept trials that provide data to better inform and expedite subsequent clinical development should shorten drug-development timelines
Increasing number of complex trials that require substantial resources	Investing resources in early-phase trials that involve a small number of patients should help prioritize resource allocation for subsequent larger trials

James Doroshow, Nat Rev Cancer Feb 2007)

Approach to clinical development of signal transduction inhibitors for GBM

- Characterize molecular determinants of response in tumors from patients on clinical trials with signal transduction inhibitors (retrospective) – e.g., EGFR TKI
- Clinical trials for molecularly defined patient populations – e.g., rapamycin for PTEN deficient GBM