Glioblastoma, the disease

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Glioma: scope of the problem

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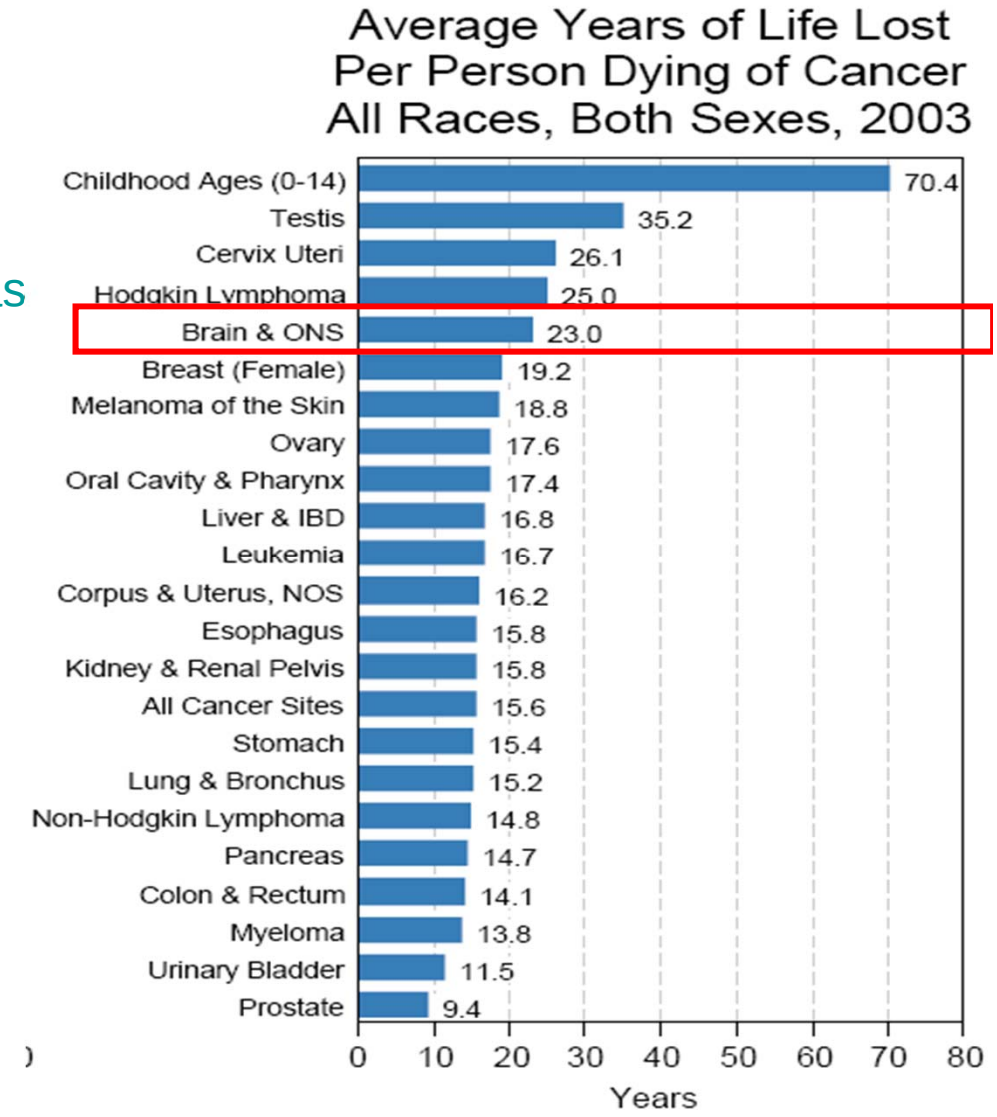
- Primary brain tumors
  - 7 per 100,000 worldwide
- Most common is gliomas:
  - astrocytoma, oligodendrogliomas or mixed
- WHO grade IV = glioblastoma
  - Median survival: 9 to 12 months
  - 2-years survival: 4-15%
- In US:
  - 17,000 new cases per year,
  - 12,000 deaths per year
- Disproportionate life years loss
  - ~2% of all primary tumors,
  - 7% of years of life lost from cancers before age 70



Statistics still hold, 15 years later….

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Class	Characteristics		Median Survival (Months)	2-Year Survival (%)
I	AA	<50 yr, normal mental status	58.6	76
II	AA	>50 yr, KPS 70-100, >3 mo time to first symptom	37.4	68
III	AA	<50 yr, abnormal mental status	17.9	35
	GBM	<50 yr, KPS 90-100		
IV	AA	≥50 yr, ≤3 mo time from first symptom	11.1	15
	GBM	<50 yr, KPS <90		
	GBM	KPS 70-100, >partial resection, "work" neurological functional status		
V	GBM	≥50 yr, KPS 70-100, ≥partial resection, "home" or "hospital" neurological function status	8.9	6
	GBM	>50 yr, KPS 70-100 biopsy only, received >54.4Gy; or ≥50 yr, KPS <70, normal mental status		
VI	GBM	≥50 yr, KPS 70-100 biopsy only, received ≤54.4Gy; or ≥50 yr, KPS <70, abnormal mental status	4.6	4

RTOG Recursive Partitioning Analysis of Prognostic Factor
by Curran WJ Jr. et al. *J Natl Cancer Inst*. 1993; 85:704-710.

GBM: two paths to a common endpoint

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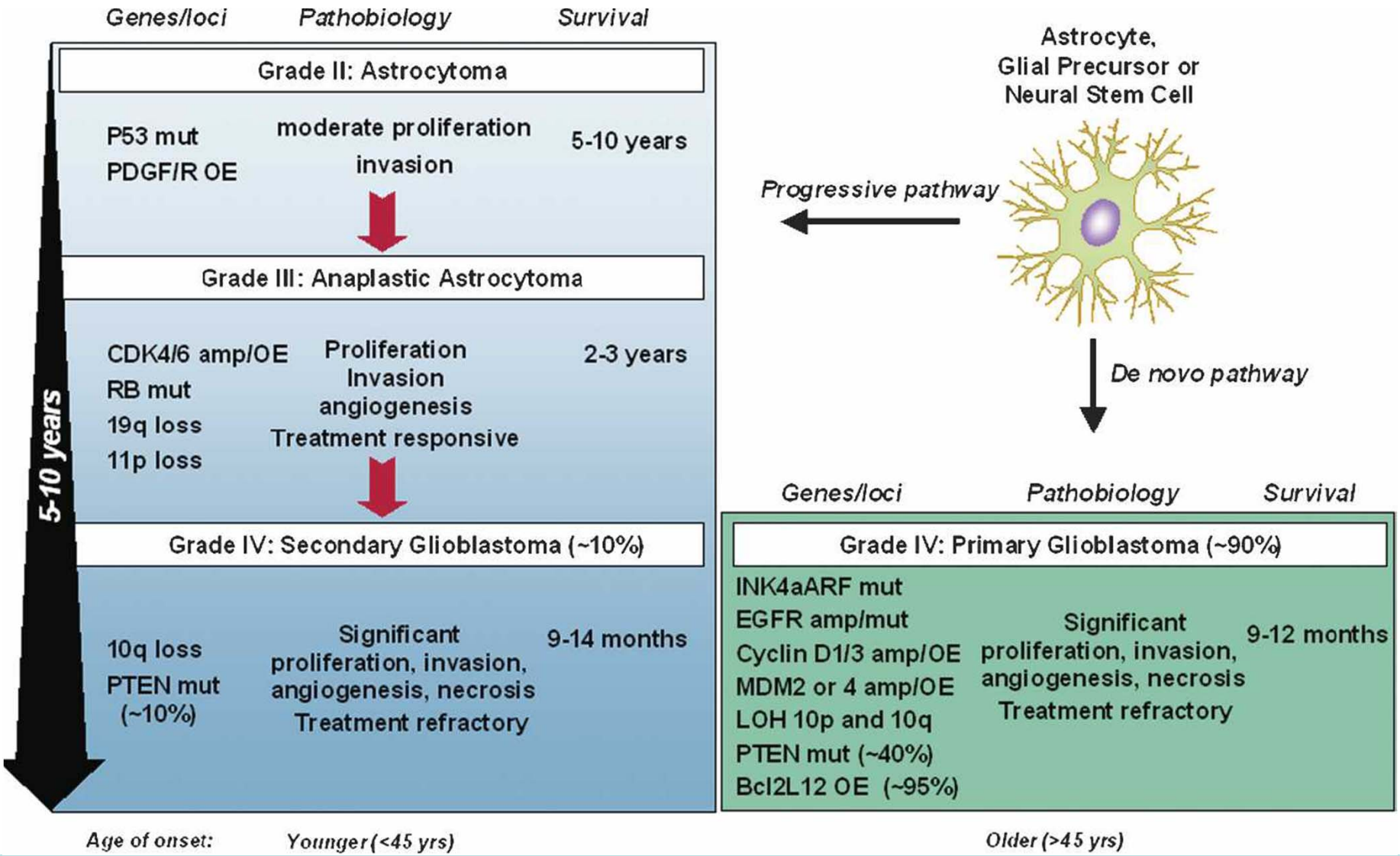
Furnari et al G&D 2007



Genomes of Primary and Secondary GBM

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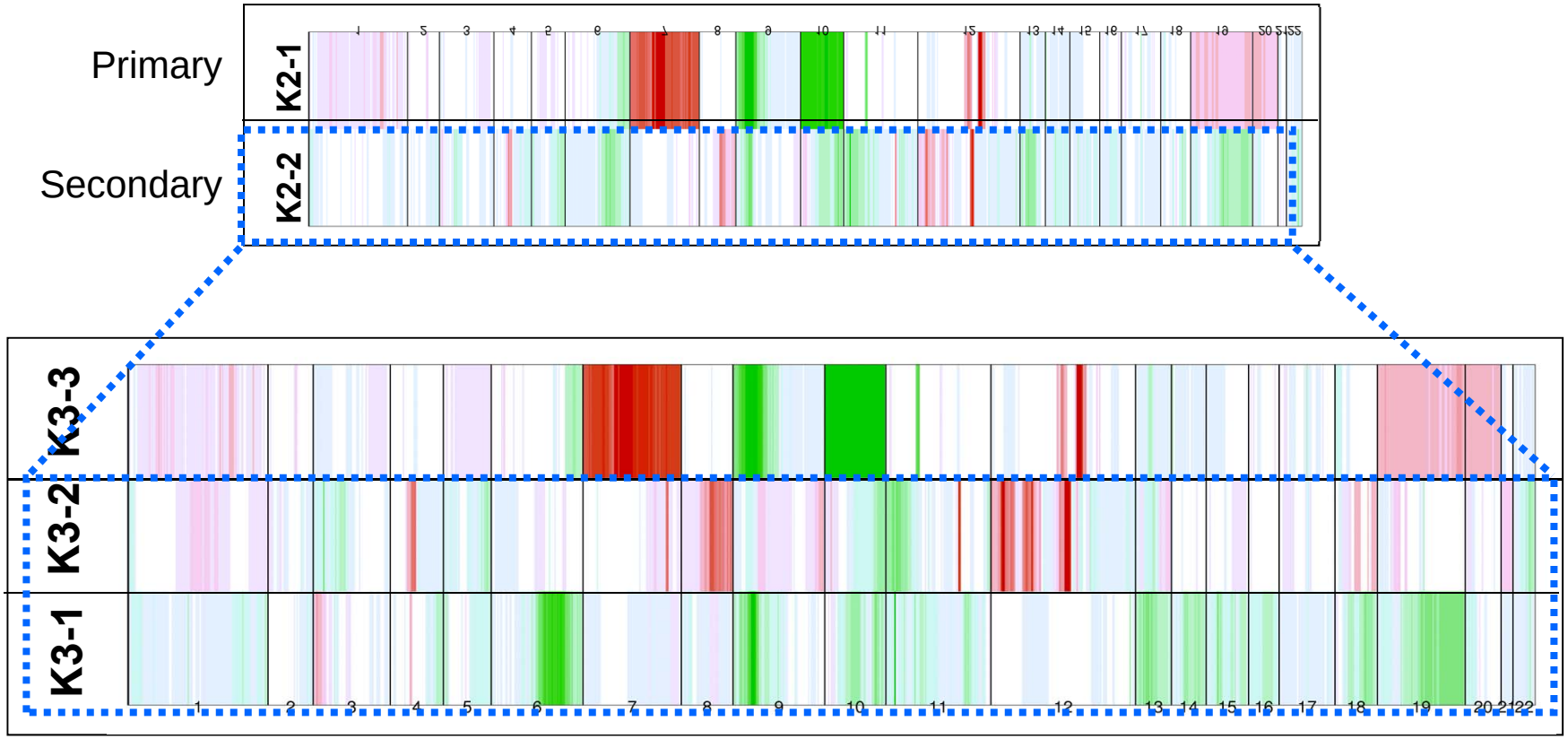

- Subclass of primary GBM has not been defined on the genomic level
- Secondary GBM can be stratified into two distinct subclasses, with different Time-To-Progression

Maher et al Can Res 2006

EGFR, a signature oncogene

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- Amplified in ~43% of GBM
- 20-30% with EGFRvIII (exon 2-7 deletion):
  - constitutively active receptor
  - *Sugawa et al PNAS 1990*
- 14% oncogenic missense mutations in the extracellular domain of EGFR in glioblastoma
  - *Mellinghoff et al., PLoS Med., 2006*

- *Rational target of TKI against EGFR?*

Lack of EGFR TKI efficacy

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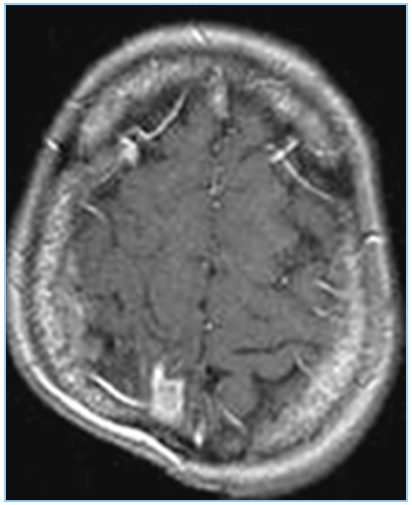
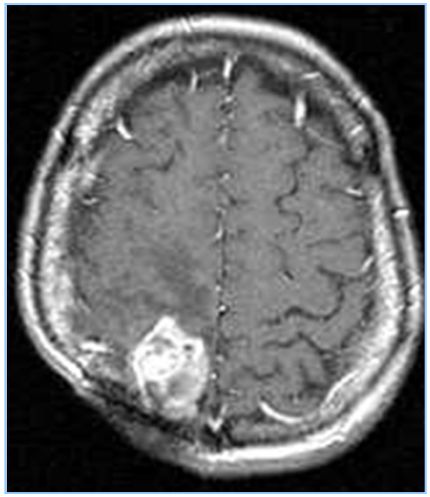
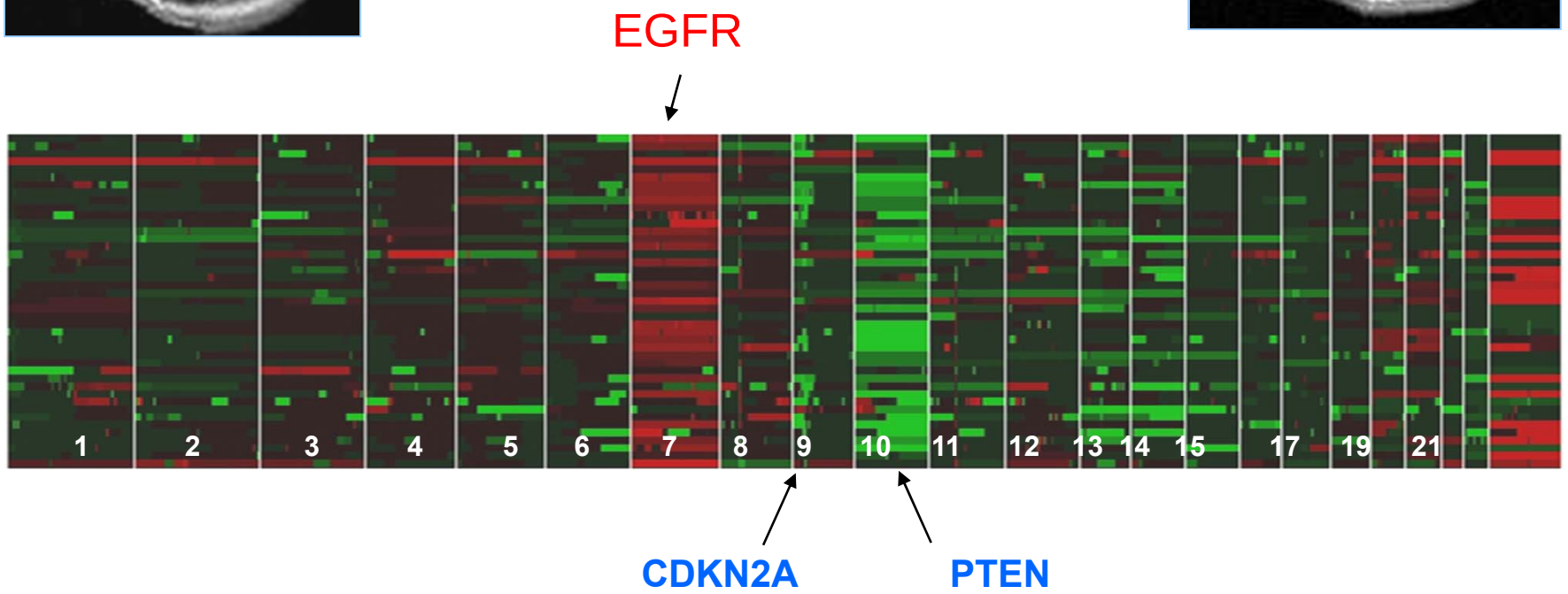


Iressa x 2 months





Molecular determinants of therapeutic responses

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Table 3. **Biomarkers of response to EGFR kinase inhibitors**

UCLA dataset	Responders (n=7)	Non-Responders (n=19)	P Value	Odds Ratio	95% C.I.
EGFRvIII expression	83% (6/7)	32% (6/19)	0.03	13	1.3-133
PTEN expression	100% (7/7)	32% (6/19)	0.005	NC*	NC*
EGFRvIII/PTEN coexpression***	83% (6/7)	11% (2/19)	<0.001	51	3.9-669
UCSF dataset *	Responders (n=8)	Non-Responders (n=25)	P Value	Odds Ratio	95% C.I.
EGFRvIII expression	87.5% (7/8)	44% (11/25)	0.05	8.9	0.95-84
PTEN expression	62.5% (5/8)	16% (4/25)	0.02	8.8	1.5-52
EGFRvIII/PTEN coexpression****	62.5% (5/8)	4% (1/25)	0.001	40	3.4-468

- PTEN status dictates response to EGFR tyrosinse kinase inhibitor in GBM with EGFRvIII mutation
- However, responses are not durable…

Mellinghoff….Mischel, *NEJM* 2005

Co-activated RTKs in GBM

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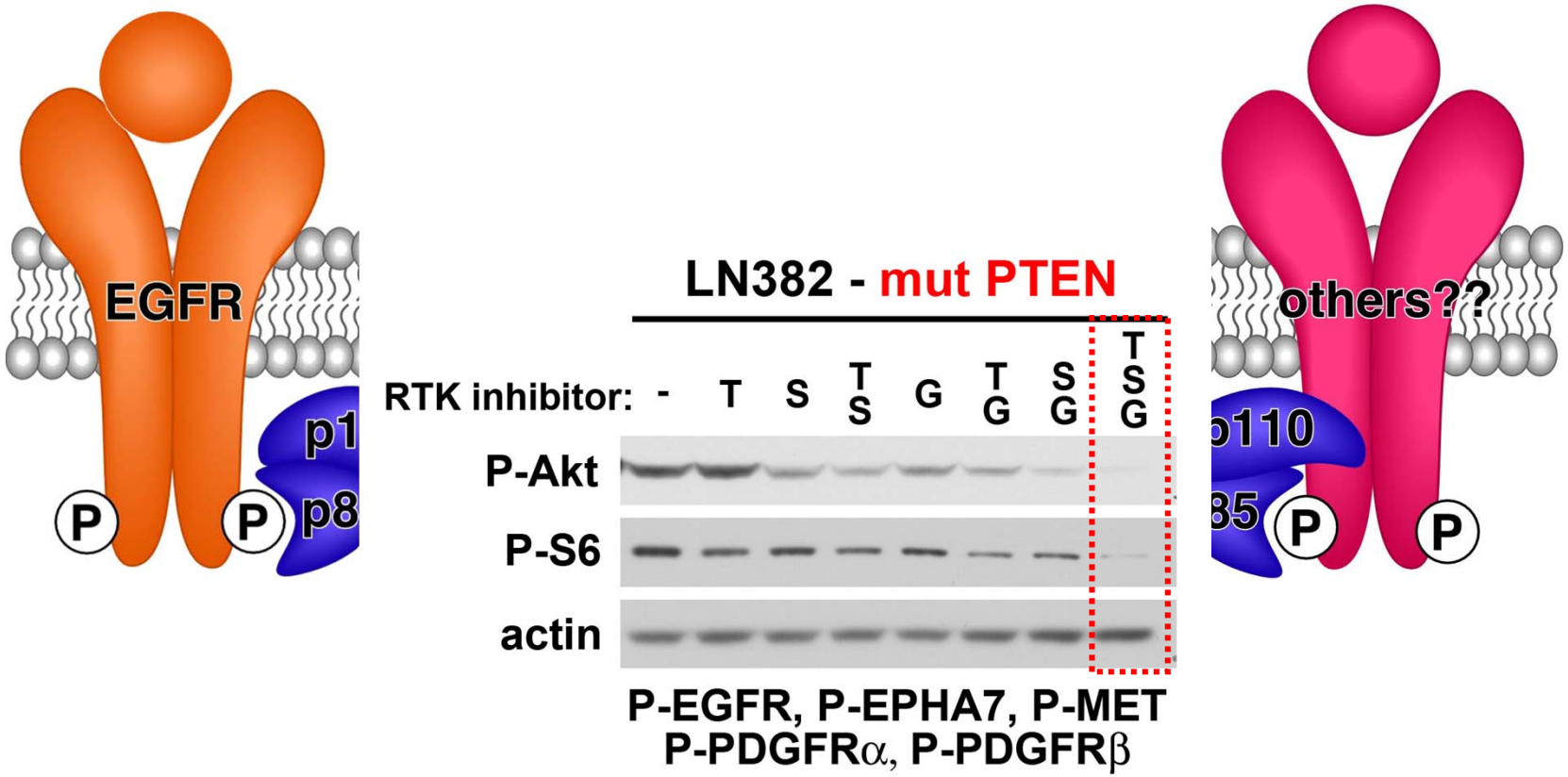

- Converge to sustain the activation of PI3K pathway
- A new therapeutic strategy
  - ➔ simultaneous inhibition of co-activated RTKs

Stommel….DePinho, *Science* 2007

Co-amplification of RTK in GBM

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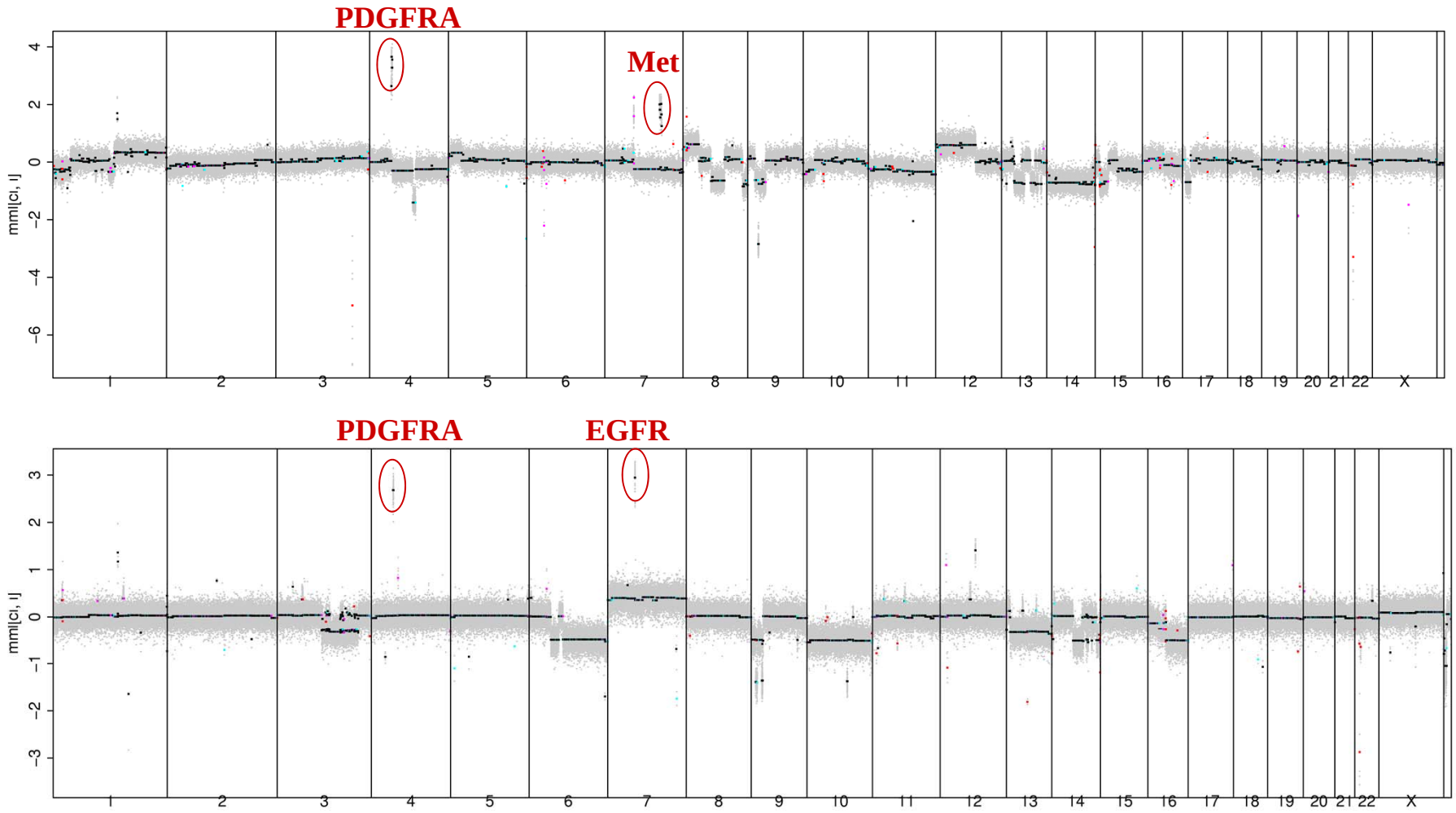
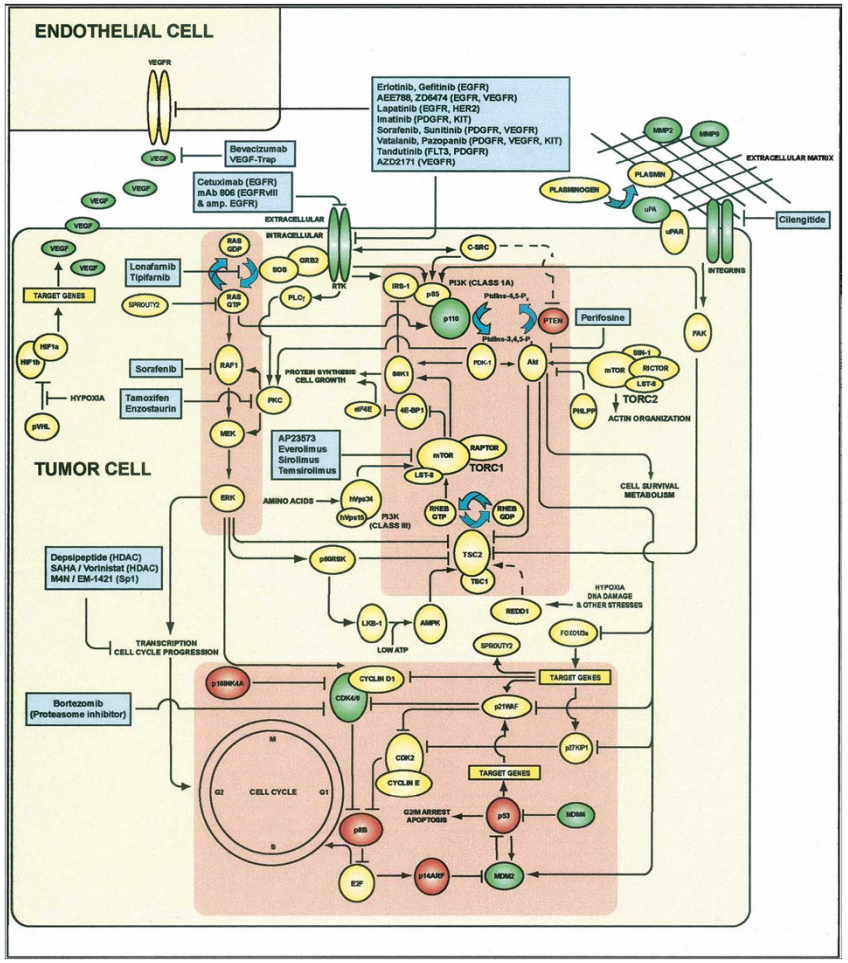


Cameron Brennan; TCGA

Furnari et al G&D 2007



Deregulation of complex signaling network, not linear pathway, driven by underlying genetic and epigenetic alterations

Cancer is a disease of the genes

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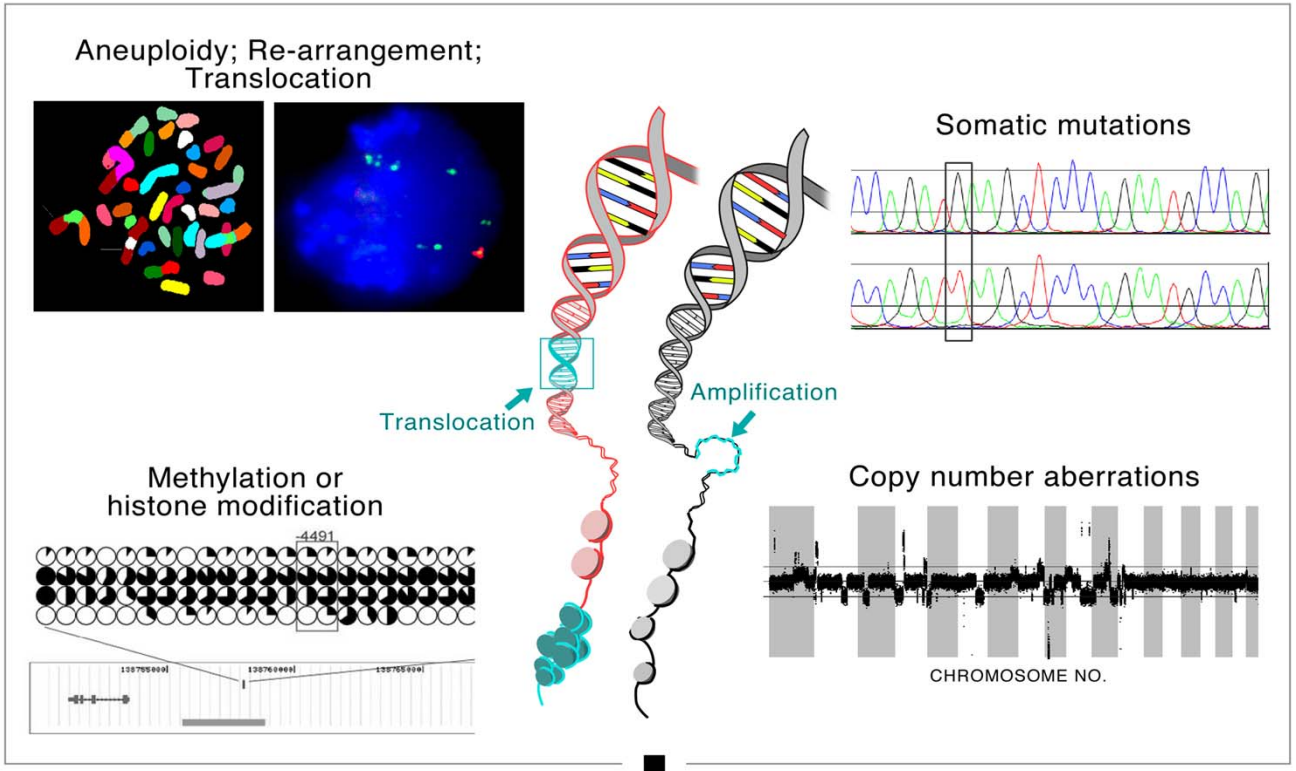
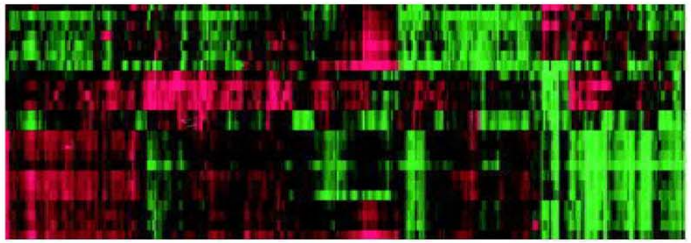
Genomic and Epigenomic Alterations

Chin and Gray, *Nature*, in press



Altered expression

- Coding messenger RNA
- Non-coding micro RNA



- Level of expression
- Shift in patterns of splicing variants
- Aberrant transcripts e.g. fusiion transcripts

The Cancer Genes Atlas (TCGA)

THE CANCER GENOME ATLAS

- To define the atlas of genomic and epigenomic alterations in GBM, lung and ovarian cancers
- To identify genomic subtypes that can stratify patients for therapies
- To discover predictive or prognostic biomarkers
- To identify rational targets (and combination thereof) for therapeutic intervention
- To improve survival of patients

Update from TCGA

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- Generation of multi-dimensional genomic data on clinically annotated GBM and matched normals
- Preliminary integrative analyses of 165 samples
- Disease Working Group to interface with biology and clinical experts
- Reports:
  - Cameron Brennan (MSKCC): Copy number and translocation
  - Joe Gray (LBNL): RNA expression and methylation profiles
  - Rick Wilson (Wash U): Targeted re-sequencing of Phase I genes