



Henri Matisse, The Clown

Clinical Trial Design in the Era of Genomic Therapy

George W. Sledge MD
Stanford University

What We'll Discuss

- The era of targeted therapy in oncology
- Stupid and Smart cancers
- Genomic chaos and cancers as orphan diseases
- The Genomic era

The Targeted Therapy Era

- In contrast to a decade ago, almost all new cancer drugs are targeted agents
- These drugs are expensive and only briefly effective for most cancer patients

What is Targeted Therapy?



- Well-defined molecular target
- Target is correlated with biology
- Target measurable *in the clinic*, or so common it doesn't need to be
- Target correlated with therapeutic effect

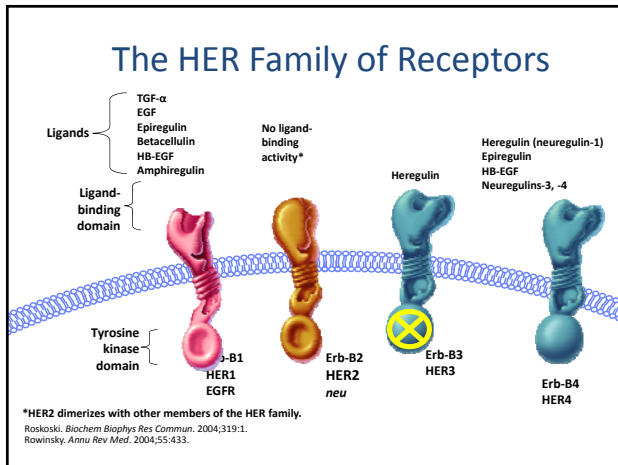
Why Targeted Therapy?

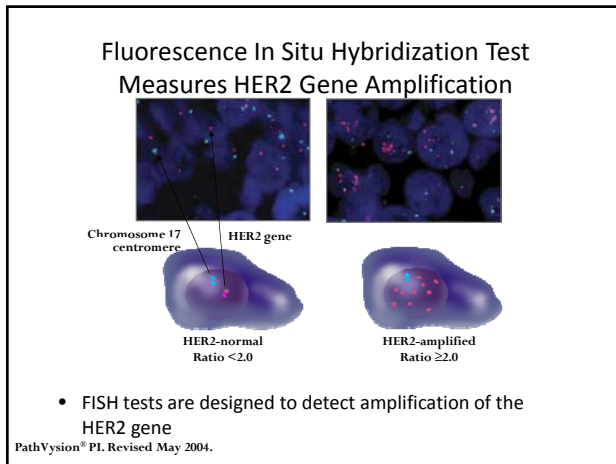
- More effective
- Avoid toxicity
- Clinical trials efficiencies

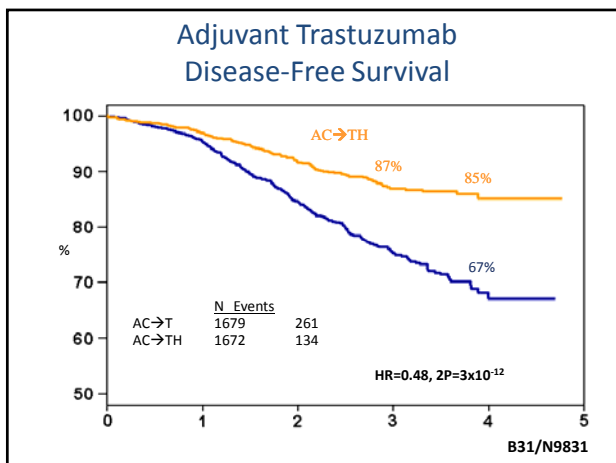


Current **Targets**/Cancers

- **Steroid receptors:** ER+ Breast Cancer, Prostate and B Cell hematologic cancers
- **HER2:** Breast and Gastric cancers
- **ALK:** NSCLC
- **BCR/ABL:** CML
- **c-Kit:** GIST
- **Hedgehog:** Basal Cell Ca and Medulloblastoma
- **RET:** Medullary Thyroid Cancer
- **B-RAF:** Melanoma
- **RAR:** Acute promyelocytic leukemia
- **CD20, CD30:** Lymphoma







The Ideal Target

- A driving mutation in a
- “Stupid cancer” that is
- Easily druggable
- And the mutation is really common

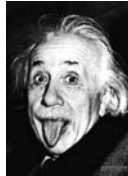
Stupid Cancers

- Single dominant mutation
- Small mutational load
- Monotherapy is effective
- Resistance rare, late, same pathway



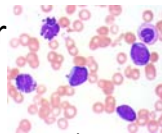
Smart Cancers

- Multiple mutational drivers
- Large mutational load
- Multi-targeted therapy required
- Resistance common, early

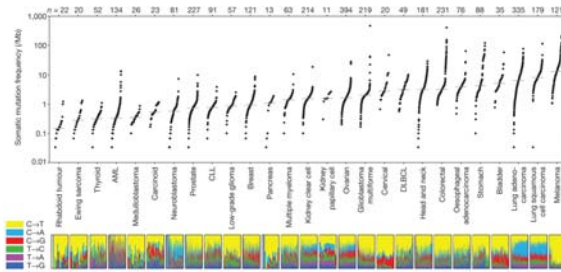


CML: A Stupid Cancer

- Driven by a single chromosomal translocation (BCR-ABL)
- High response rate, long OS for the *first* drug that came along (imatinib—89% @5y!)
- Imatinib doesn't work?
 - Use an “ib” targeting the *same* kinase domain
- A Stupid Cancer

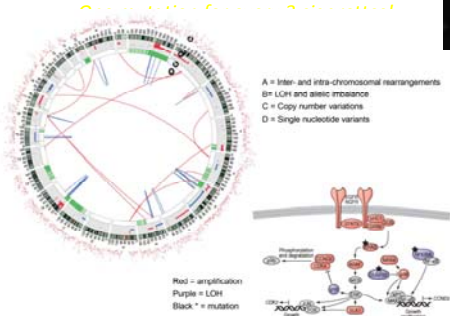


Cancers Vary in Genomic Complexity: Somatic mutation frequencies observed in exomes from 3,083 tumour-normal pairs.



MS Lawrence *et al. Nature* **000**, 1-5 (2013) doi:10.1038/nature12213

NSCLC: Smart Cancers are Genomically Complex



Lee *et al. Nature* **465**: 473-7, 2010

Melanoma: Complexity Affects Drug Sensitivity



Baseline

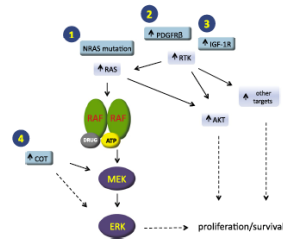
15 weeks

22 weeks

Wagle, N *et al. JCO* 2011 epub ahead of print

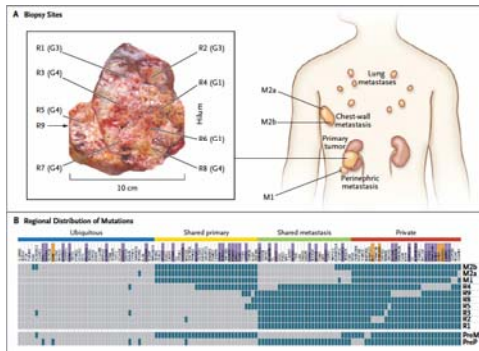
Mechanisms of Resistance to BRAF Inhibition

- MAP3K8 (COT) overexpression
- PDGFR β upregulation
- N-RAS mutation
- PTEN loss
- MEK1 mutation
- IGF1R activation



Poulikakos and Rosen, Cancer Cell 19: 11-15, 2011

Genomic Complexity → Heterogeneity



Gerlinger, M et al. NEJM 366: 883-92, 2012

Oncology as Whack-a-Mole



Rapid emergence of compensatory mechanisms of resistance

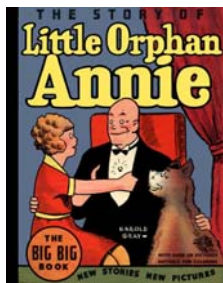
Genomic Chaos

- “Smart tumors” = genomic chaos
- This is a *quantitative*, not just a *qualitative*, problem
- They are not hard targets just because we haven’t found a single “magic bullet”
- We don’t need a magic bullet, we need a magic shotgun

The Genomic Landscape of Cancer

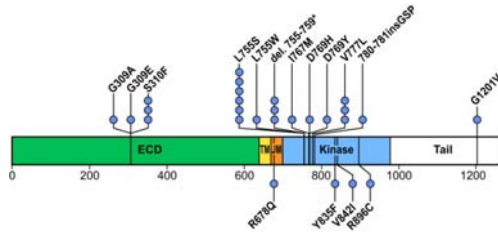
- Most common cancers lack a single driver mutation
- HER2 and bcr/abl (“low-hanging fruit”)-driven cancers are uncommon
- Common mutations (Ras, p53) are undruggable
- Rare driver mutations are frequent
- Tumors with multiple driver mutations are common
- **Result: Cancer is becoming a collection of orphan diseases**

The Orphan Disease Era



- A myriad of rare diseases
- Many genomic drivers
- IT-driven
- Complex biology
- Uncertain therapeutics
- Phase III trials difficult

25 Patients with HER2 Somatic Mutations



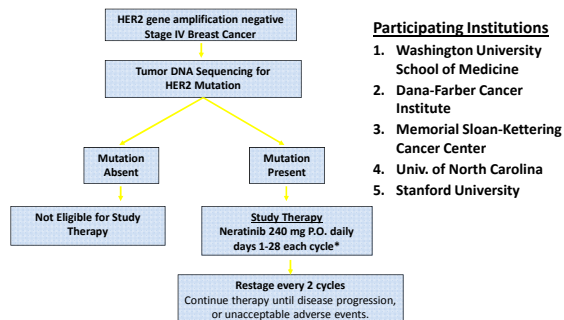
- Each blue circle represents a patient.
- From 8 publications with a total of 1,499 patients.
- 20% of patients have mutations at amino acids 309 or 310.
- 68% of patients have mutations at amino acids 755-781.

San Antonio Breast Cancer Symposium – December 4–8, 2012

HER2 Somatic mutations

- Occur in $\leq 2\%$ of breast cancers
- Activating
- IHC and FISH negative
- Sensitive to small molecules but not trastuzumab in preclinical models

Phase II Clinical Trial of Neratinib for HER2 Mutation Positive Breast Cancer



San Antonio Breast Cancer Symposium – December 4–8, 2012

Studying HER2 Mutations

- Patient requirements
 - 29 patients studied = minimum of 1450 metastatic patients screened
- Logistic requirements
 - Clinical trials consortium
 - CLIA-certified lab(s)

Studying one driver in one disease is an inefficient use of patient/trial resources

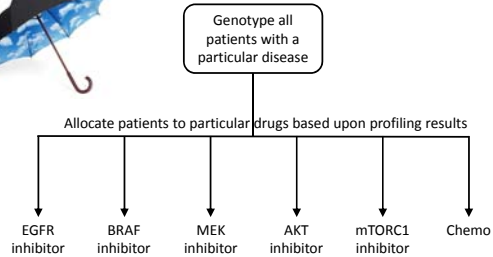
- Two alternatives:
 - Umbrella trials



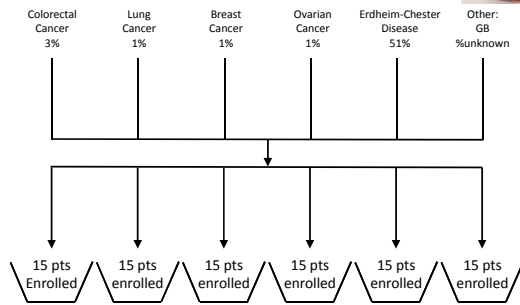
- Basket trials



Genotyping study: Umbrella Trials



An alternative approach – The “Basket” study

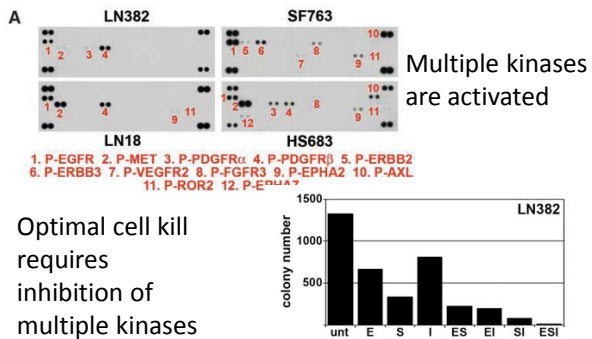


The Mutational Landscape of Breast Cancer

- 100 breast cancers genomes analyzed
- Driver mutations found in at least 40 different cancer genes
- 73 different combinations of driver mutated cancer genes
- 28 cancers had a single driver mutation, but some had as many as 6 driver mutations
- **WE HAVE NEVER TARGETED 6 DRIVERS!**

Stephens, PJ et al. Nature 486: 400, 2012

Multi-Kinase Activation Requires Multi-Kinase Inhibition



Stommel et al. SCIENCE VOL 318: 287,2007

- Toxicity increases significantly with each added drug
- New toxicities occur
- Cost of regimen increases dramatically
--\$8-10K/drug/month
- At the same time, potential study population decreases

Combination Kinase Inhibition is
Difficult

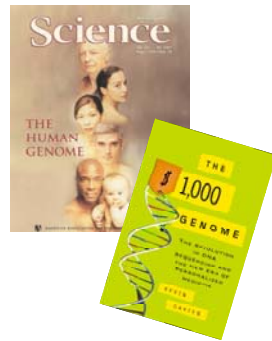
The Genome Era

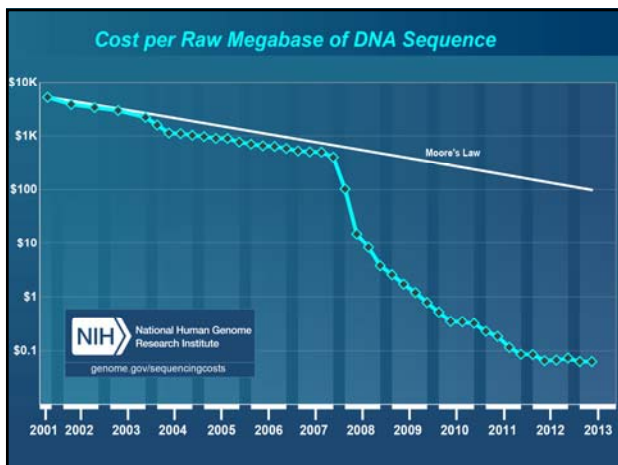
First human genome:
2001

First cancer genomes:
2009

Large-scale sequencing:
NOW

Population-based
sequencing: **SOON**





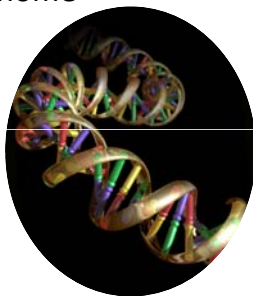


**"Here's my
sequence..."**

The New Yorker

Implications of the \$1000 Genome

- Every cancer informs our understanding of tumor biology
- Things become very complicated
- "In Your Face" genomic chaos



Today's Clinical Trials System is Not Designed for Chaos

- Emphasizes single agents
- Combination trials never biomarker-based
- Biomarker development is secondary
- Regulatory apparatus ill-suited to modern biology



A“Next-Gen” Clinical Trials System

- Therapeutic individualization based on personal genomics
- Real-time bioinformatics
- HIT network supporting clinical trials and cancer care
- Increased collaboration
- Trial designs focused around multi-targeting
- Redesigned informed consent process
- Fundamentally different regulatory apparatus





“The future is already here — it's just not evenly distributed.”

William Gibson

THANK YOU
