Precision Medicine and the Reclassification of Cancer
Divide and Conquer

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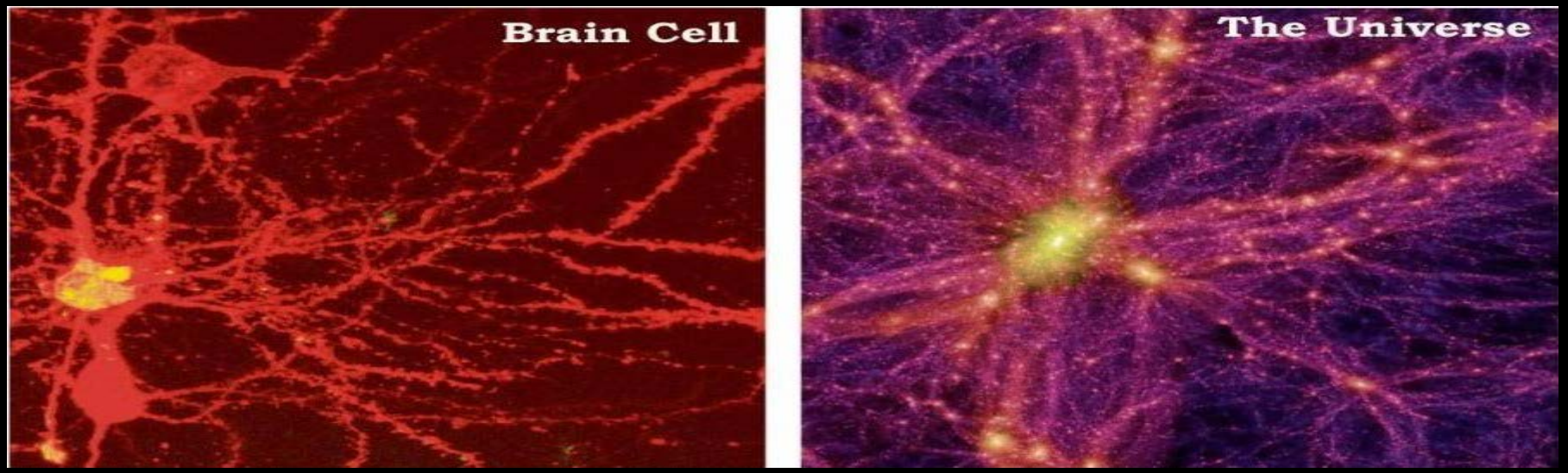
Director, Center for Personalized Cancer Therapy

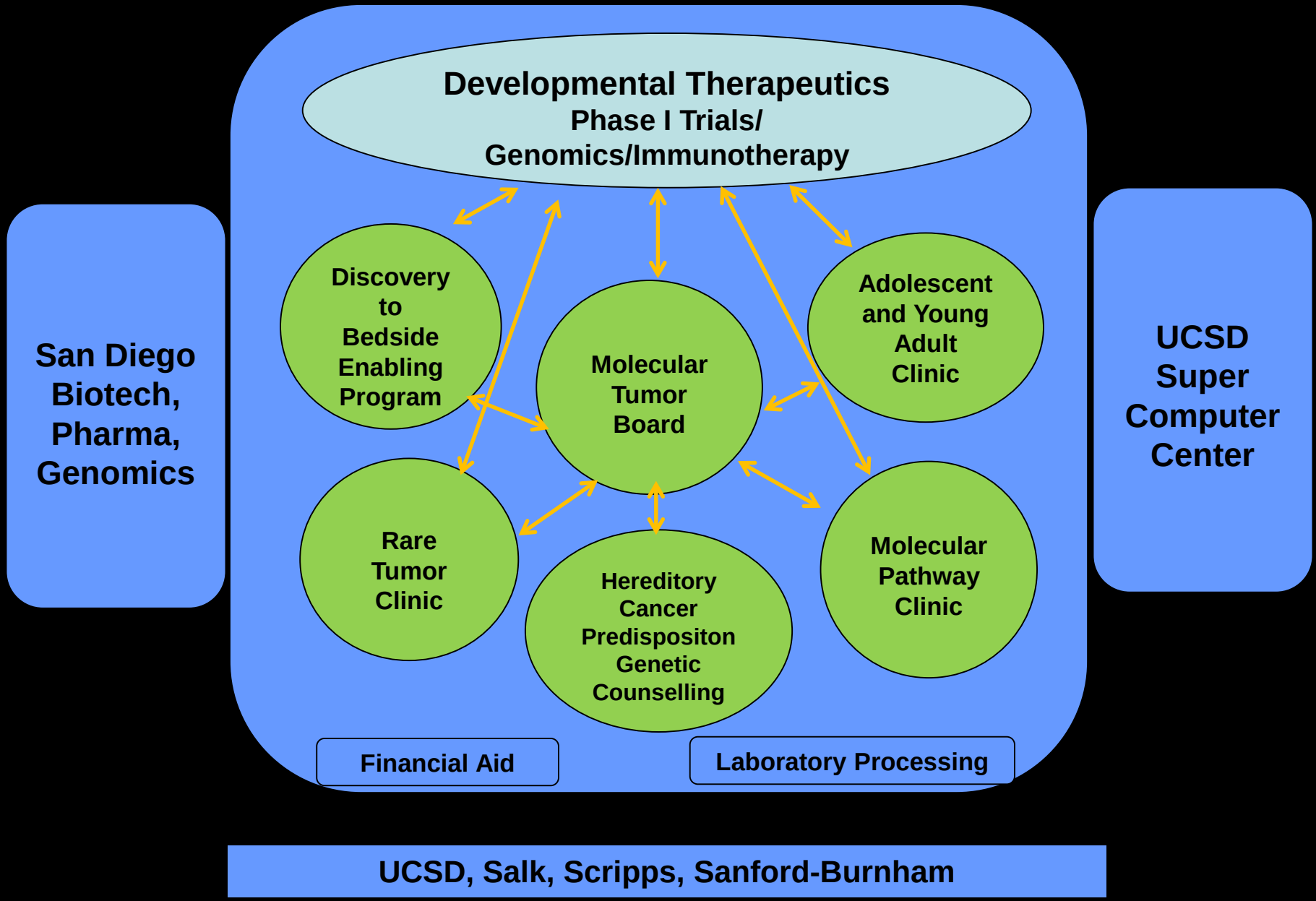
Director, Clinical Trials Office

Chief, Division of Hematology/Oncology

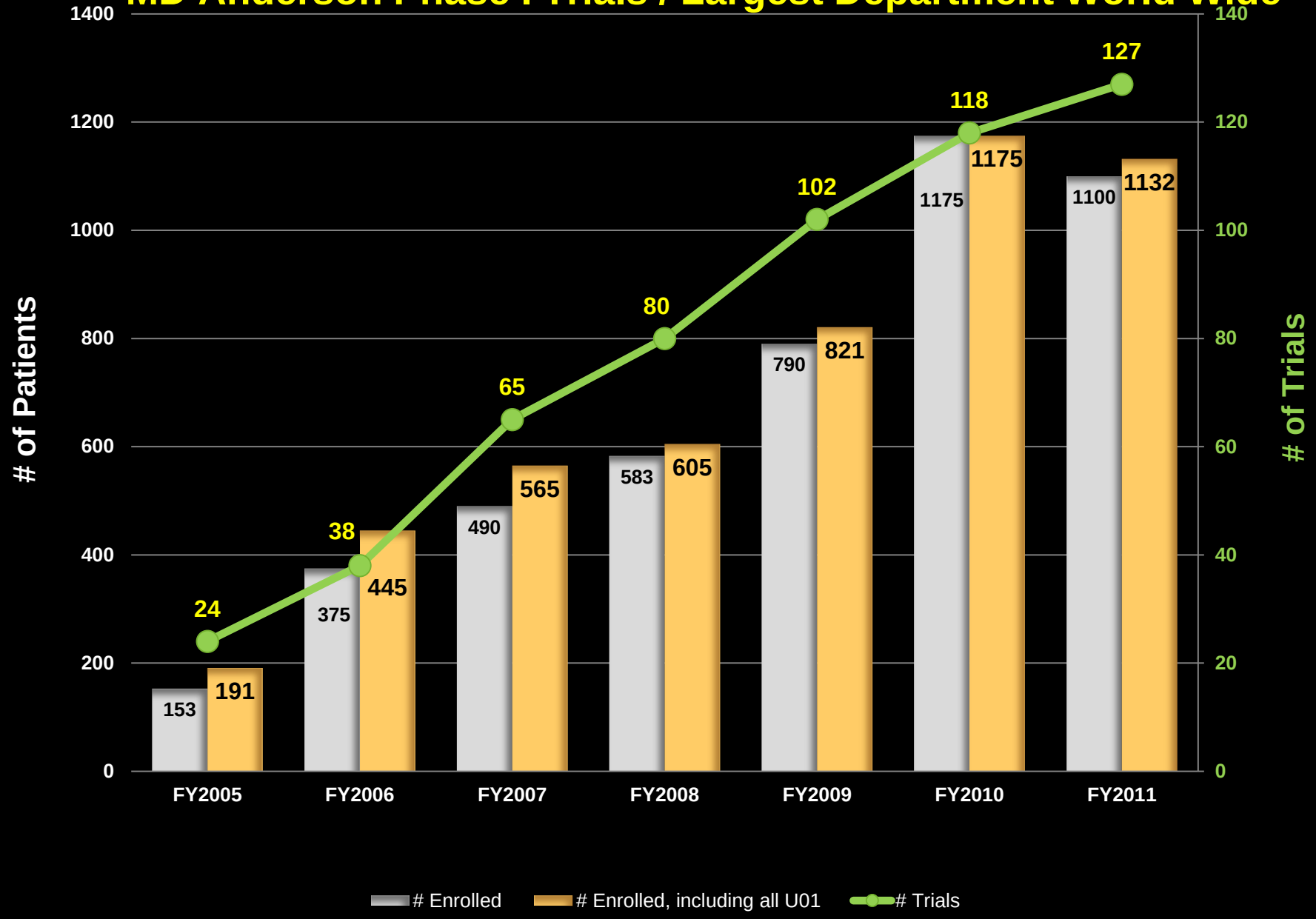
UCSD Moores Cancer Center



Center for Personalized Cancer Therapy at Moores Cancer Center



Kurzrock Experience
MD Anderson Phase I Trials / Largest Department World Wide



Question: Is it precision medicine or personalized medicine?

Answer: Both

“Precisionalized Medicine”

The Pillars of Precision Cancer Medicine

Genomics Immunotherapy

Precision Medicine
Lessons Learned

→ Use combinations of matched drugs for metastatic or complex tumors

→ Treat newly-diagnosed patients

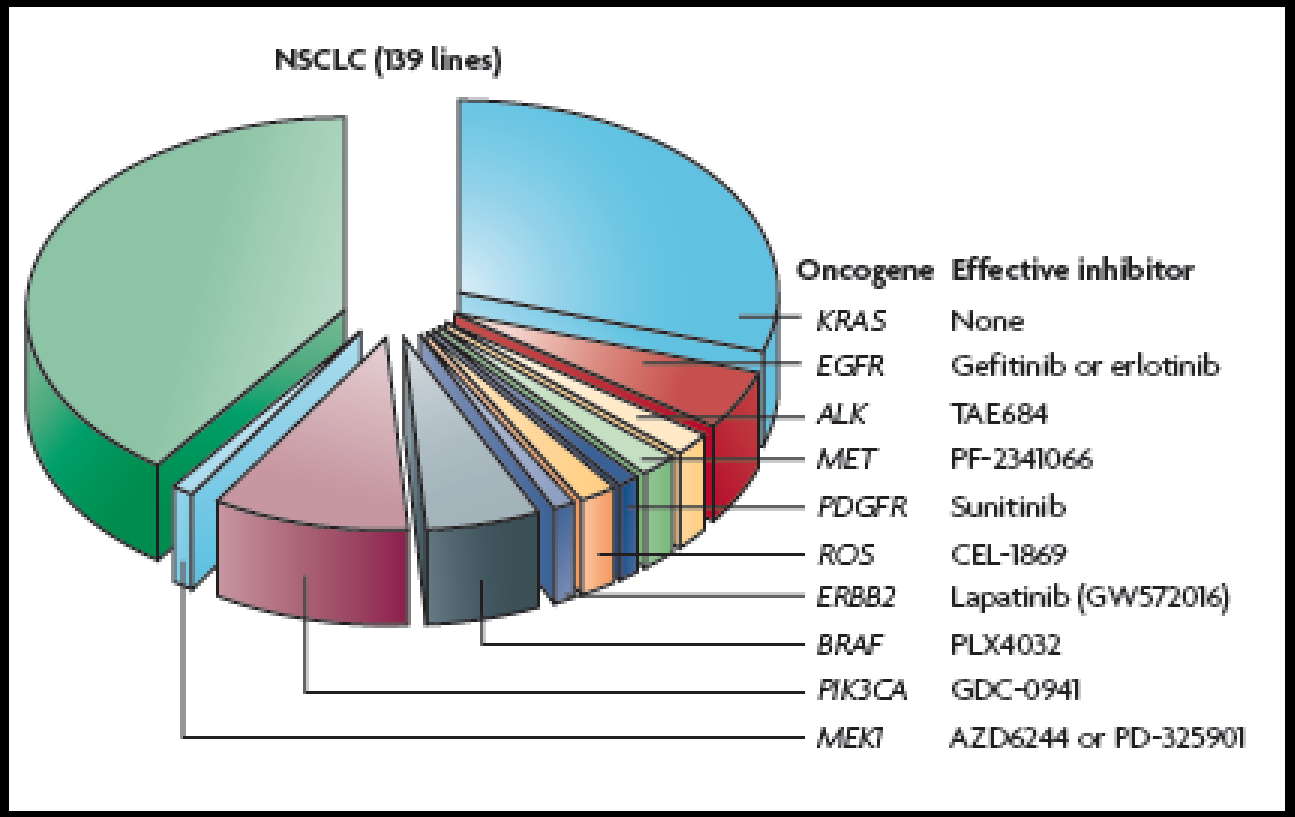
→ Omics is a disruptive technology; retrofitting the reality unveiled into traditional paradigms is suboptimal

→ Harness the immune system

→ Transformative changes will require new models for clinical research and practice

Why are cancers difficult to treat?

Divide and Conquer



Agents work only in those with a sensitizing aberration

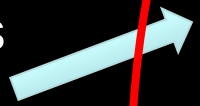
Braiteh….Kurzrock, MCT 2007

Munoz J, Swanton C, Kurzrock R, Molecular Profiling and the Reclassification of Cancer; Am Soc Clin Oncol Educ Book. 2013:

Sharma, Nat Rev Cancer 2010

What can patients expect from traditionally approved drugs ?

Drug	Tumor	Survival Gain	Complete remission
gemcitabine	pancreas	1.5 months	≈ 0%
bevacizumab	colon	2.2 months	≈ 0%
erlotinib	pancreas	11 days	≈ 0%
bevacizumab	NSCLC	2 months	≈ 0%
sorafenib	renal	2 months	≈ 0%
temozolamide	glioblastoma	2.5 months	≈ 0%
docetaxel	prostate	2.4 months	≈ 0%
cetuximab	colon	1.5 months	≈ 1-2 %



Master Protocol

Profile-Related Evidence Determining

Individualized Cancer Therapy

- **Histology-Independent targeted approach**
- **Multiple molecular aberrations assessed**
- **Patients matched with targeted agents**

The Reclassification of Cancer

PIK3CA mutations were found in 10% of 1,000 patients with advanced cancers

- Endometrial cancers (29%)
- Breast cancers (24%)
- Colon cancers (17%)
- Ovarian cancers (14%)
- Lung cancer (13%)
- Head and neck squamous cell cancers (13%)
- Pancreatic cancers (13%)

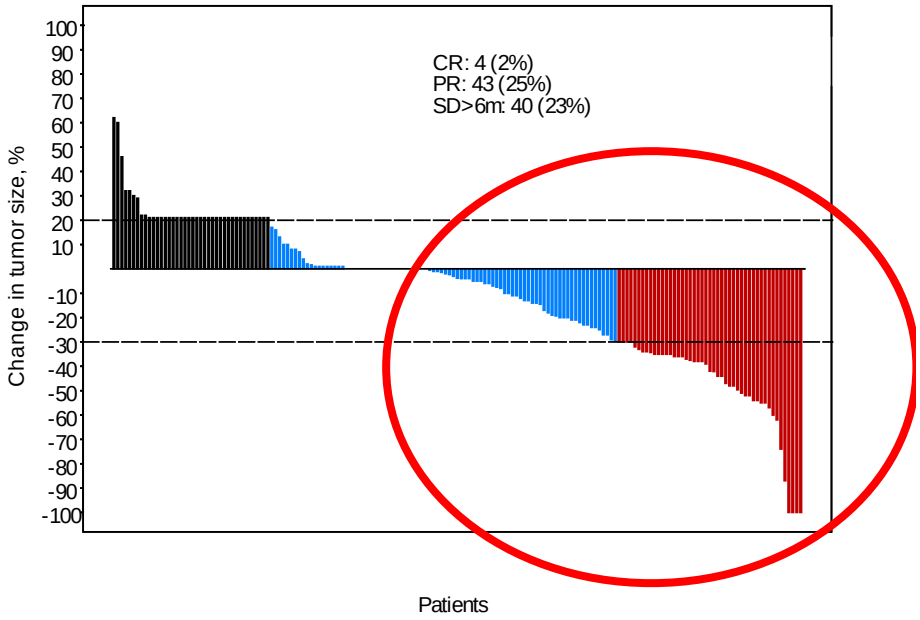
Molecular aberrations do not segregate well by organ of origin

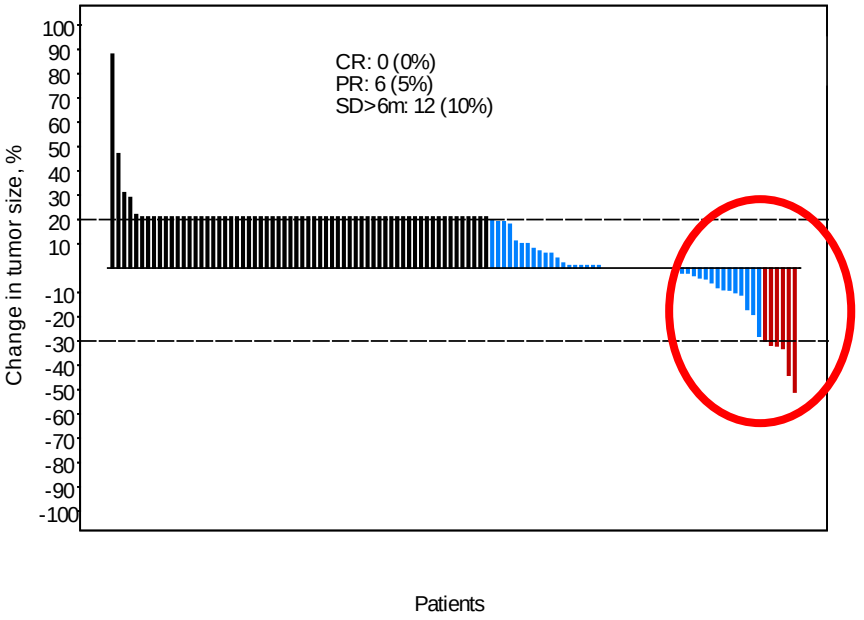
Matching patients with targeted drugs increases response rates

Matched therapy
N=175
Complete/Partial Response = 27%

Therapy without matching
N=116
Complete/Partial Response = 5%

p<.0001

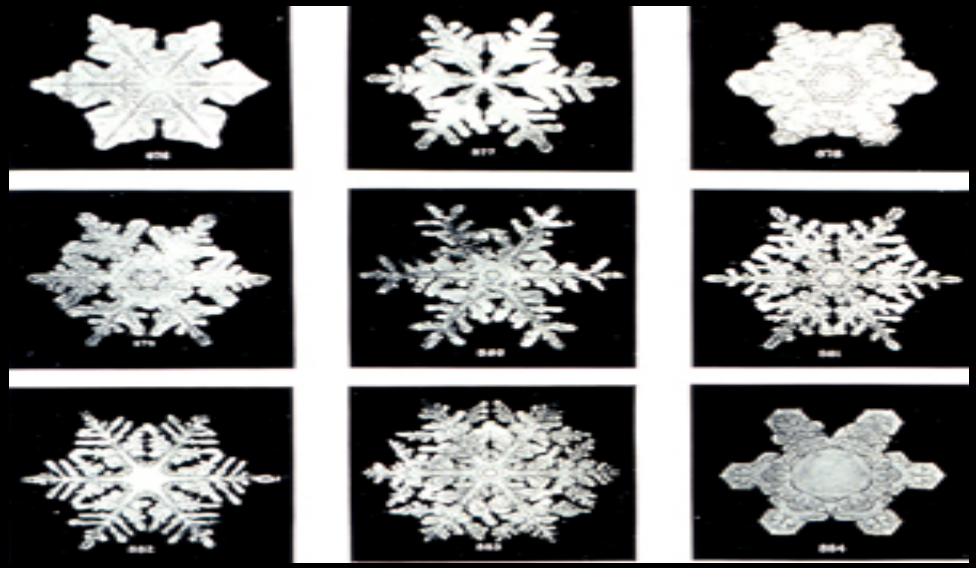




Janku….Kurzrock, MCT, 2011; Tsimberidou….. Kurzrock, CCR, 2012;
Janku…..Kurzrock, JCO, 2012; Janku…..Kurzrock, Cell Reports, 2014

Partnering with the UCSD SuperComputer Center

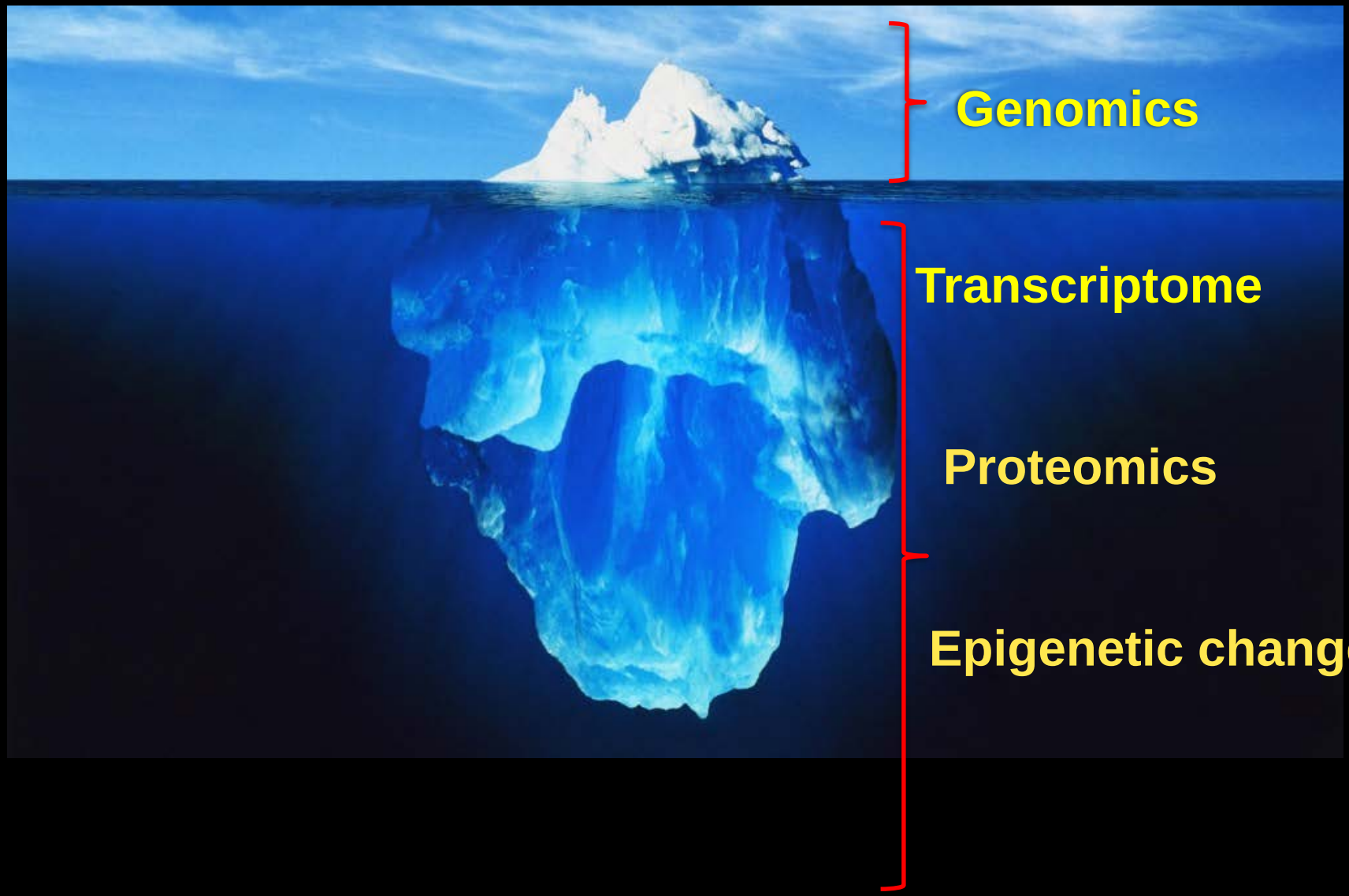
What if every patient with metastatic disease is different?



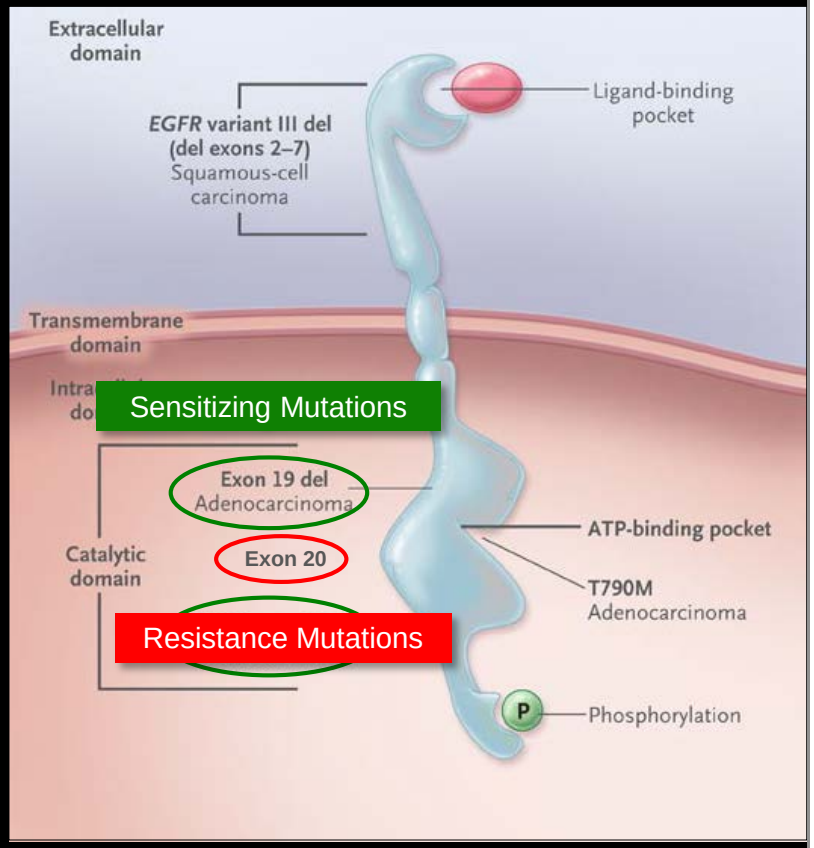
Malignant Snowflakes

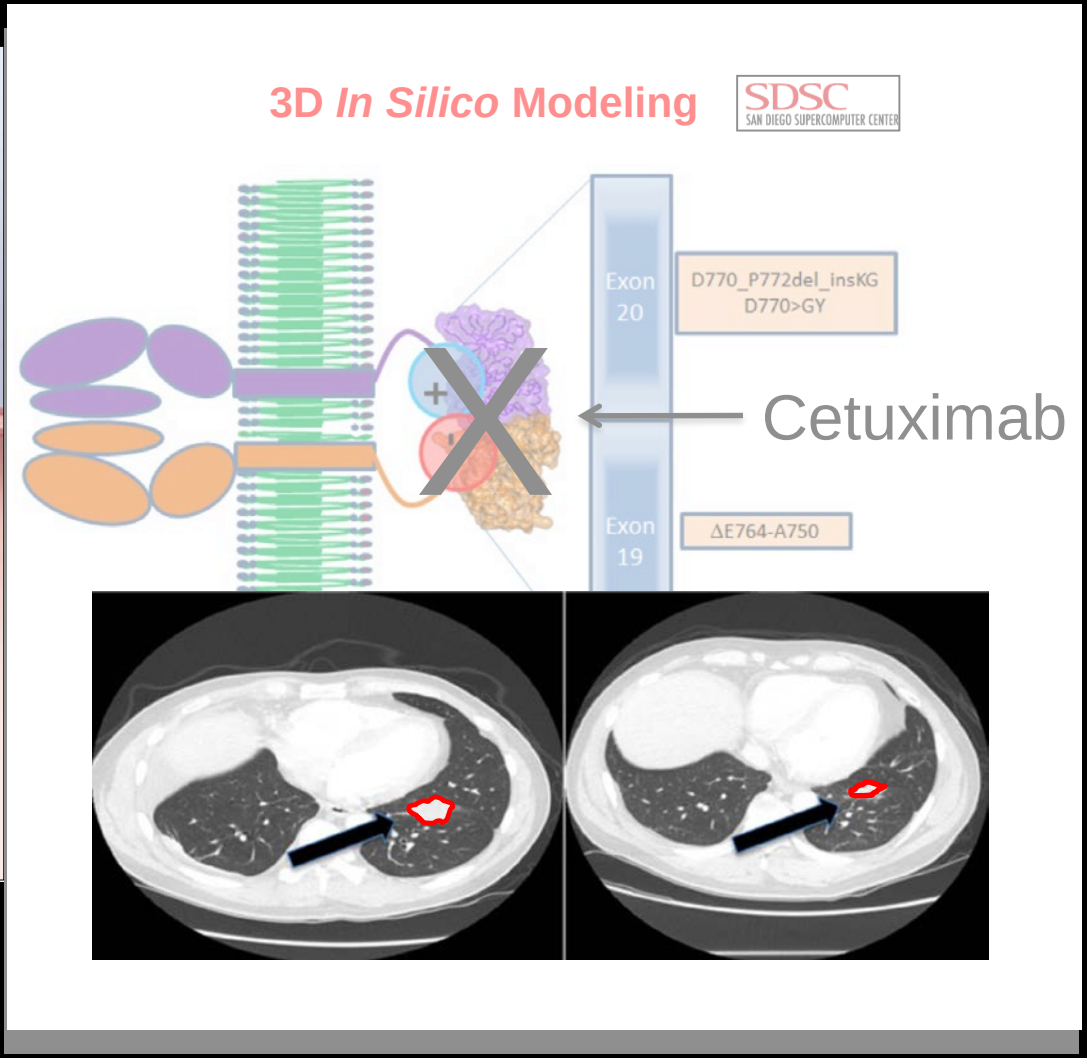
Pt number	Molecular Results (Foundation Medicine)
1	PIK3CA amplification, SOX2 amplification, TP53 G302fs*42, FLT3 L260*
2	AKT1 (E17K)
4	EGFR amplification, CCND1 amplification, CDKN2A/B loss, FGFR1 amplification, MYC amplification, TP53 P151A
42	ERBB2 amplification, PIK3CA H1047L, AURKA amplification, TP53 R342P, CREBBP P858S, ZNF217 amplification
25	ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*
7	ESR1 Y537S
13	GATA3 *445fs*2+
16	RET C634R, GATA3 P436fs*11+
18	AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q
54	NF1 R1276Q

Tip of the Iceberg



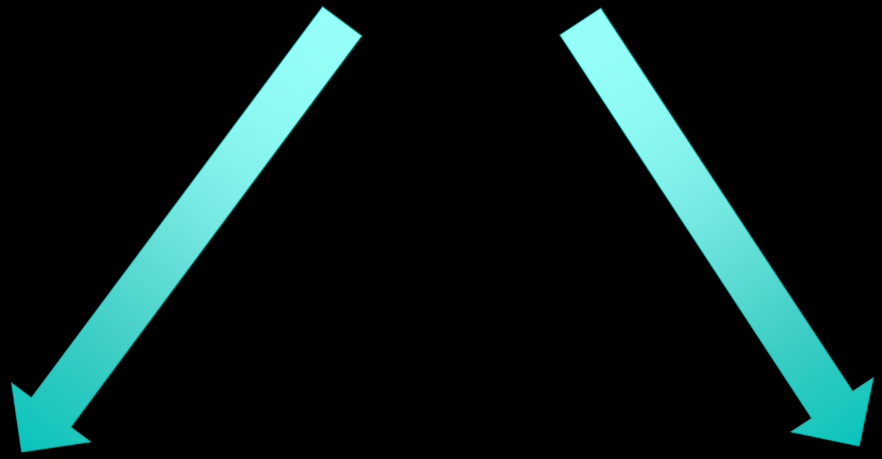
Epidermal Growth Factor Receptor (EGFR) *In Silico* Modelling in Lung Cancer





Tsigelny….Kurzrock, Oncotarget

Strategies



Customized Combinations and Immunotherapy for Advanced Disease

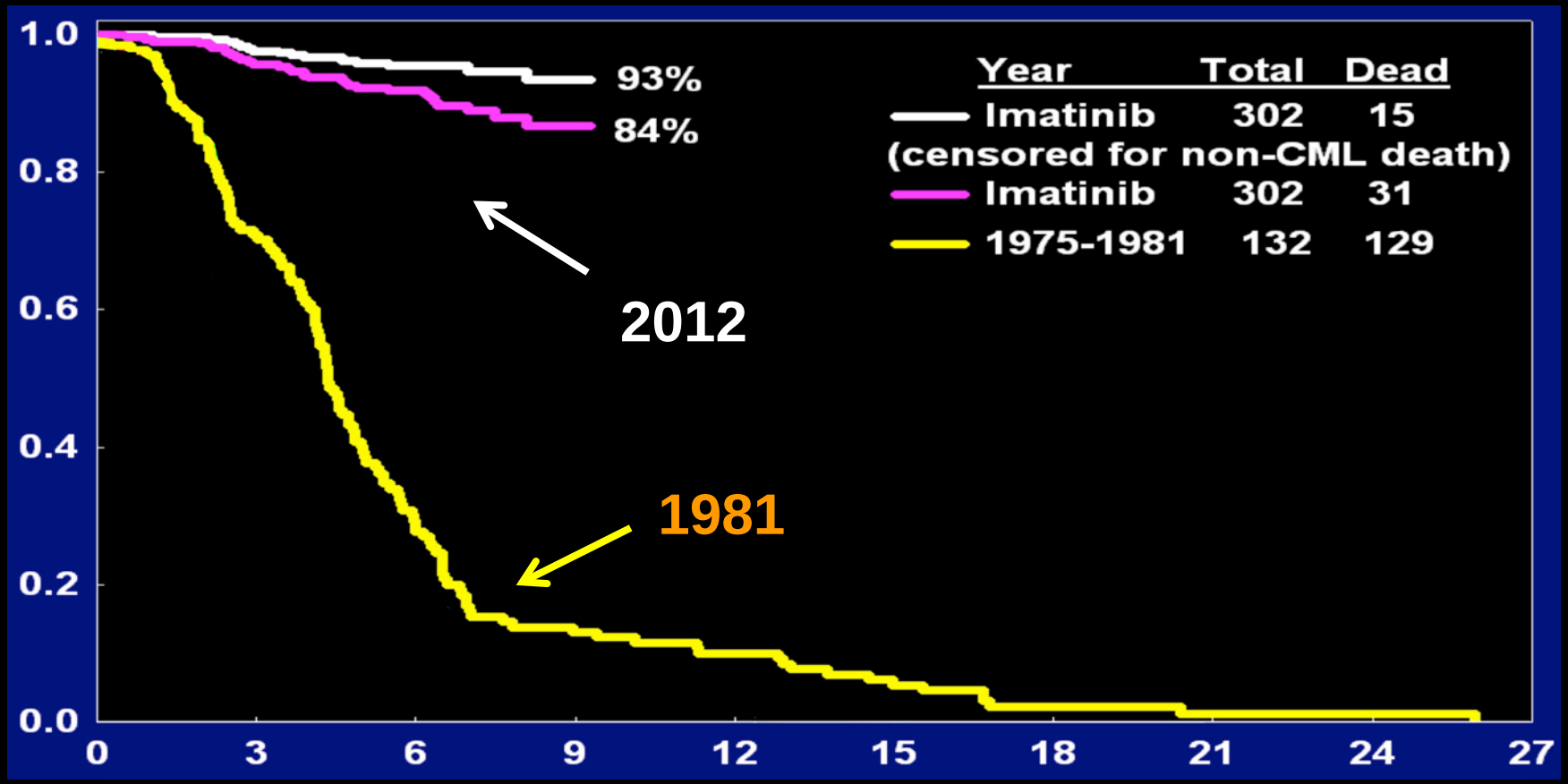
Treat Newly-Diagnosed Disease

Transforming Outcomes in Solid Tumors?

Is It About Time?

Lessons from the Chronic Myelogenous Leukemia (CML) Story
A Fatal Disease Transformed

- Median survival in 1980s was about 4 years
- Median survival in 2012 is 20+ years



Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

N ENGL J MED 361;12 NEJM.ORG SEPTEMBER 17, 2009

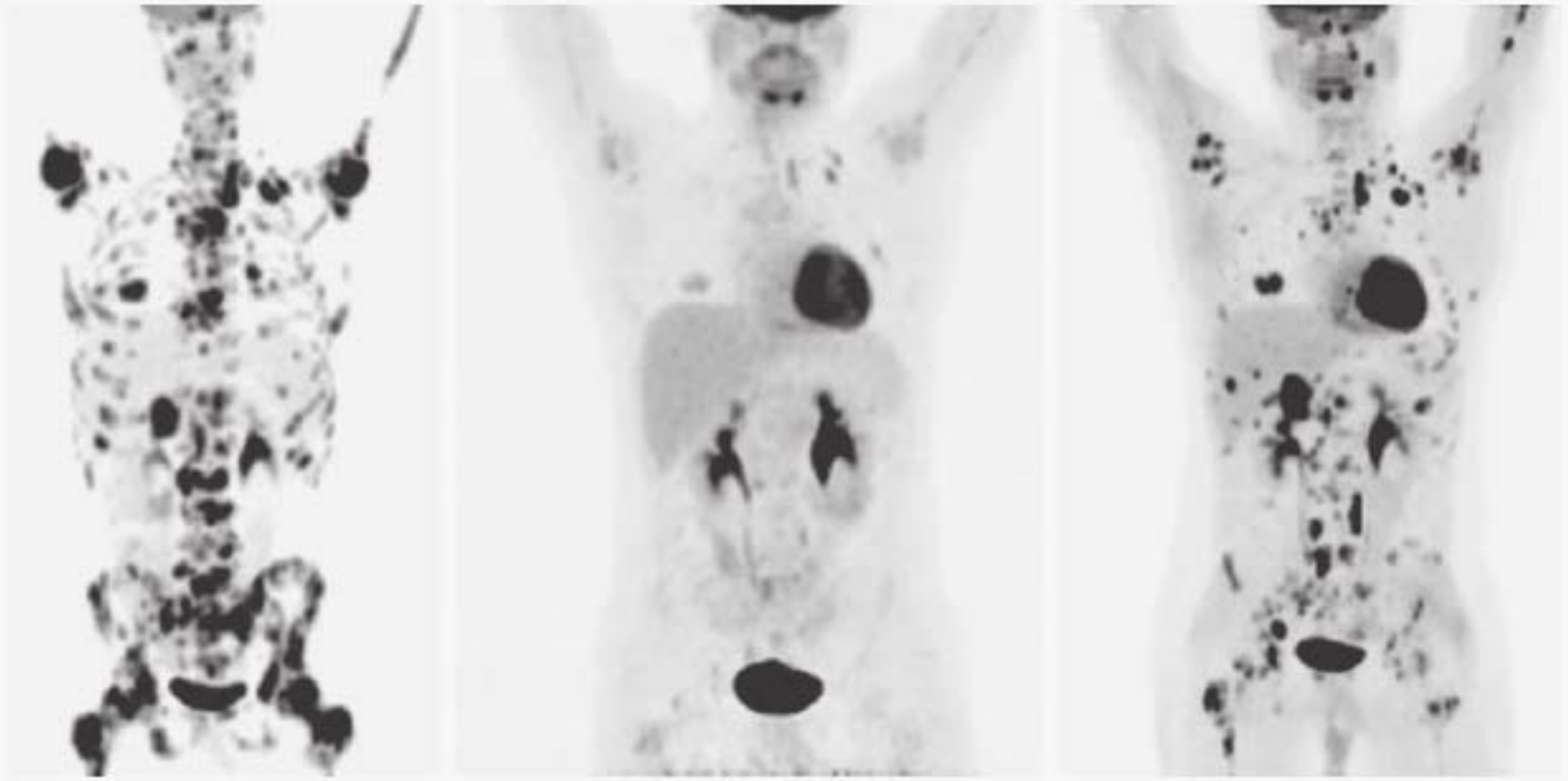
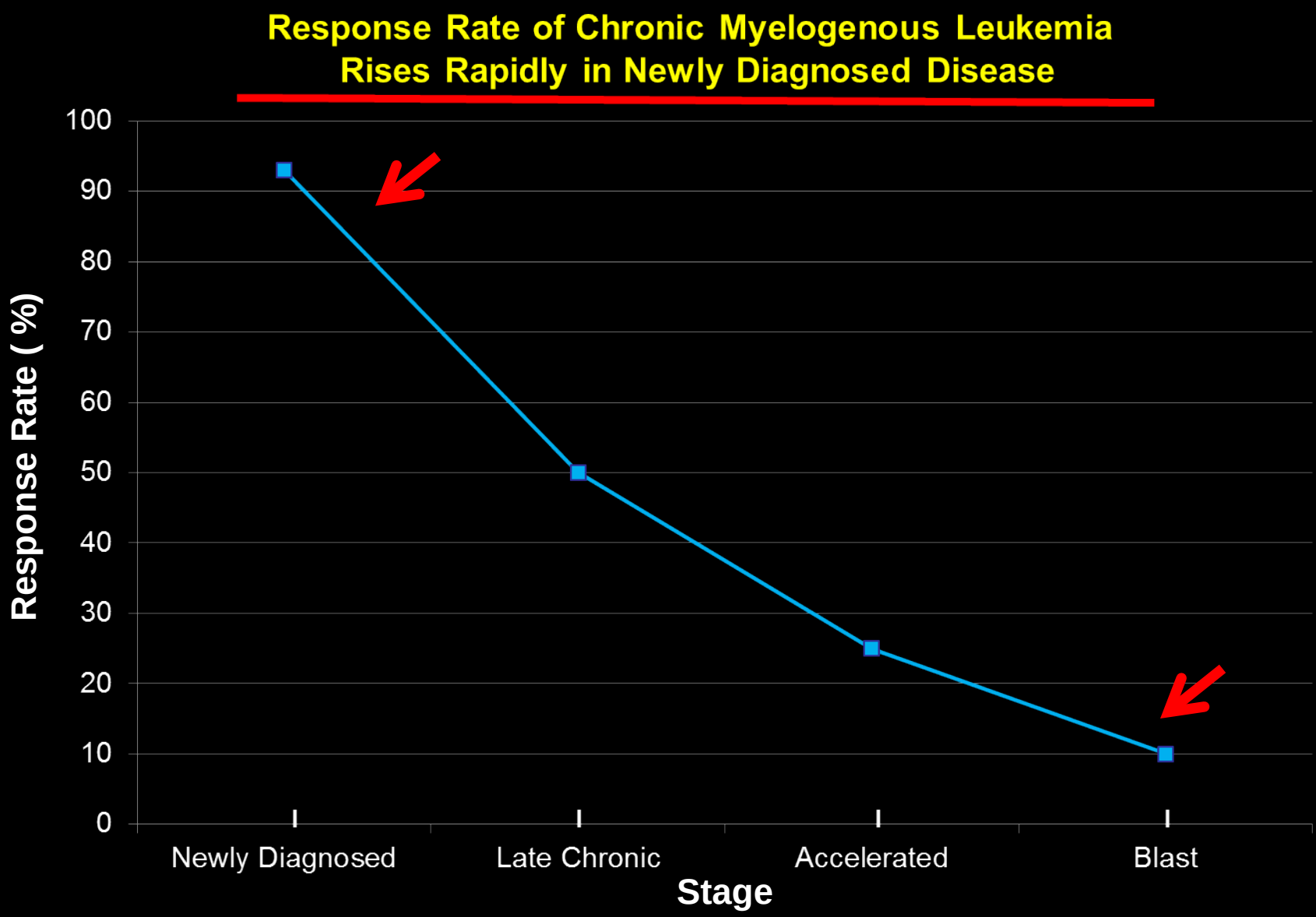


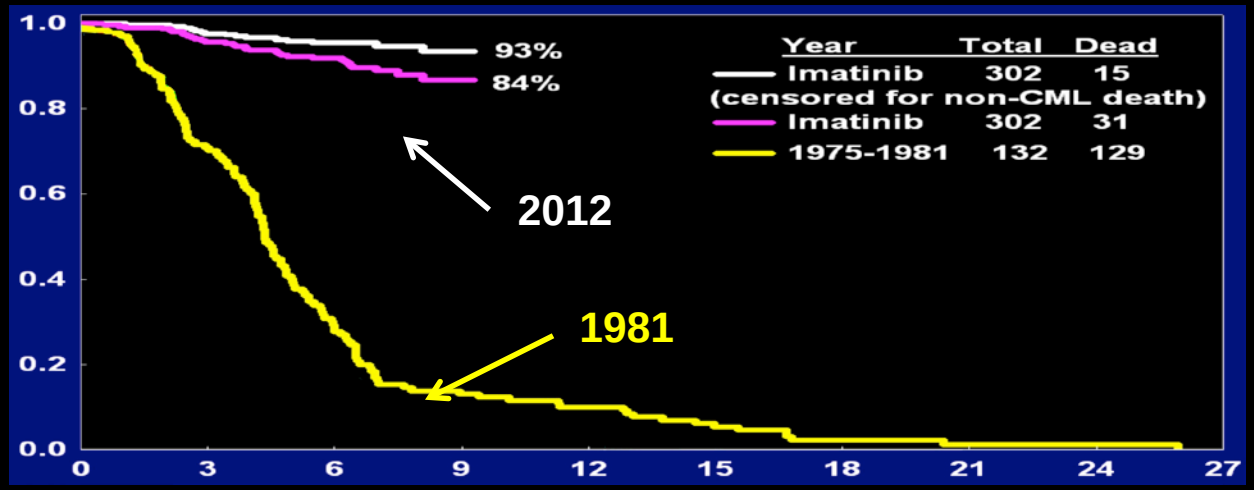
Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.

Whole-body projections from ^{18}F-fluorodeoxyglucose (FDG)–PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.


Response Rate of Chronic Myelogenous Leukemia
Rises Rapidly in Newly Diagnosed Disease
Response Rate (%)
100
90
80
70
60
50
40
30
20
10
0
Newly Diagnosed
Late Chronic
Accelerated
Blast
Stage

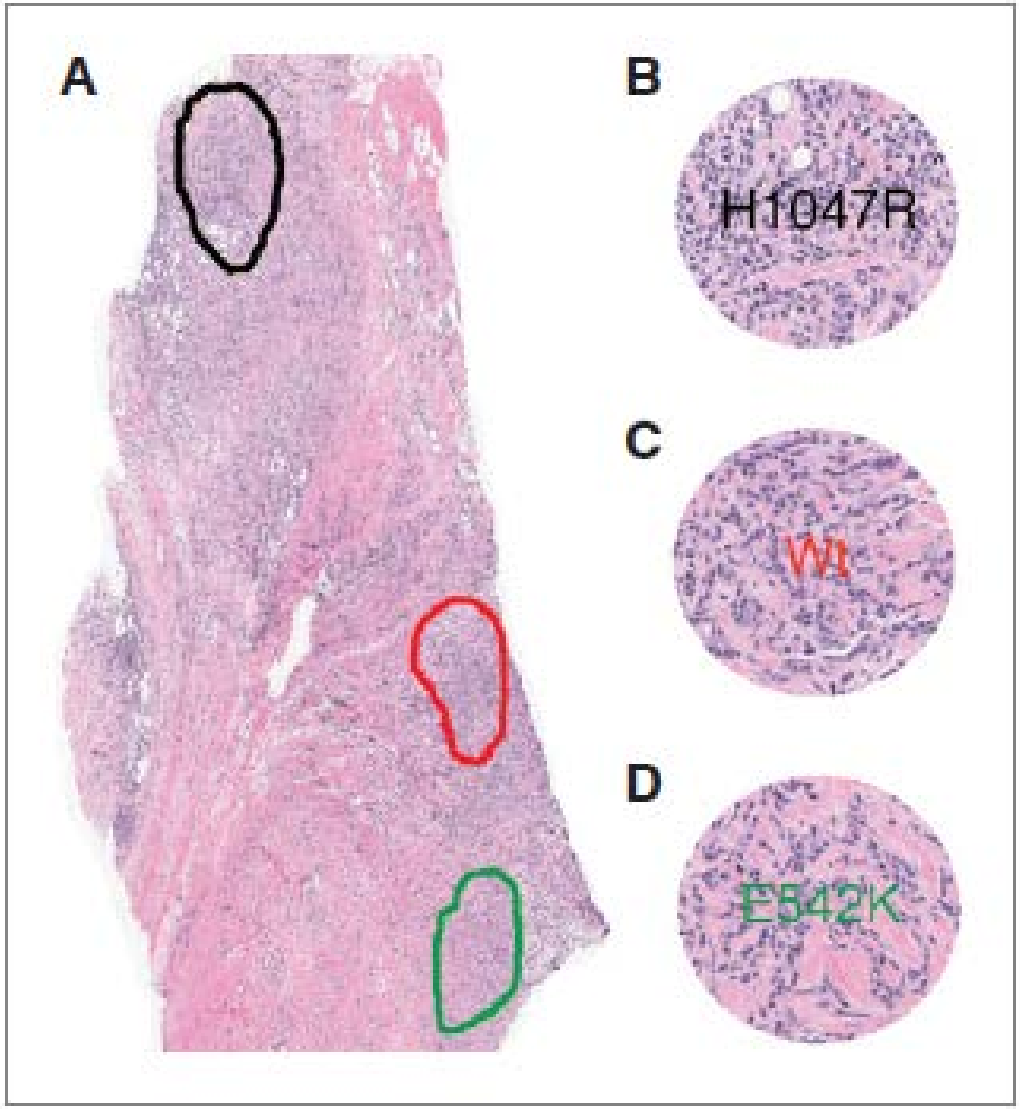
Key factors leading to the revolution in outcome of chronic myelogenous disease

- Key factors:
  - Known driver target (Bcr-Abl)
  - Targeted agent (imatinib)
  - Treat newly-diagnosed patients



Metastases = Blast Crisis in Leukemia

Tumor Microhetergoeneity

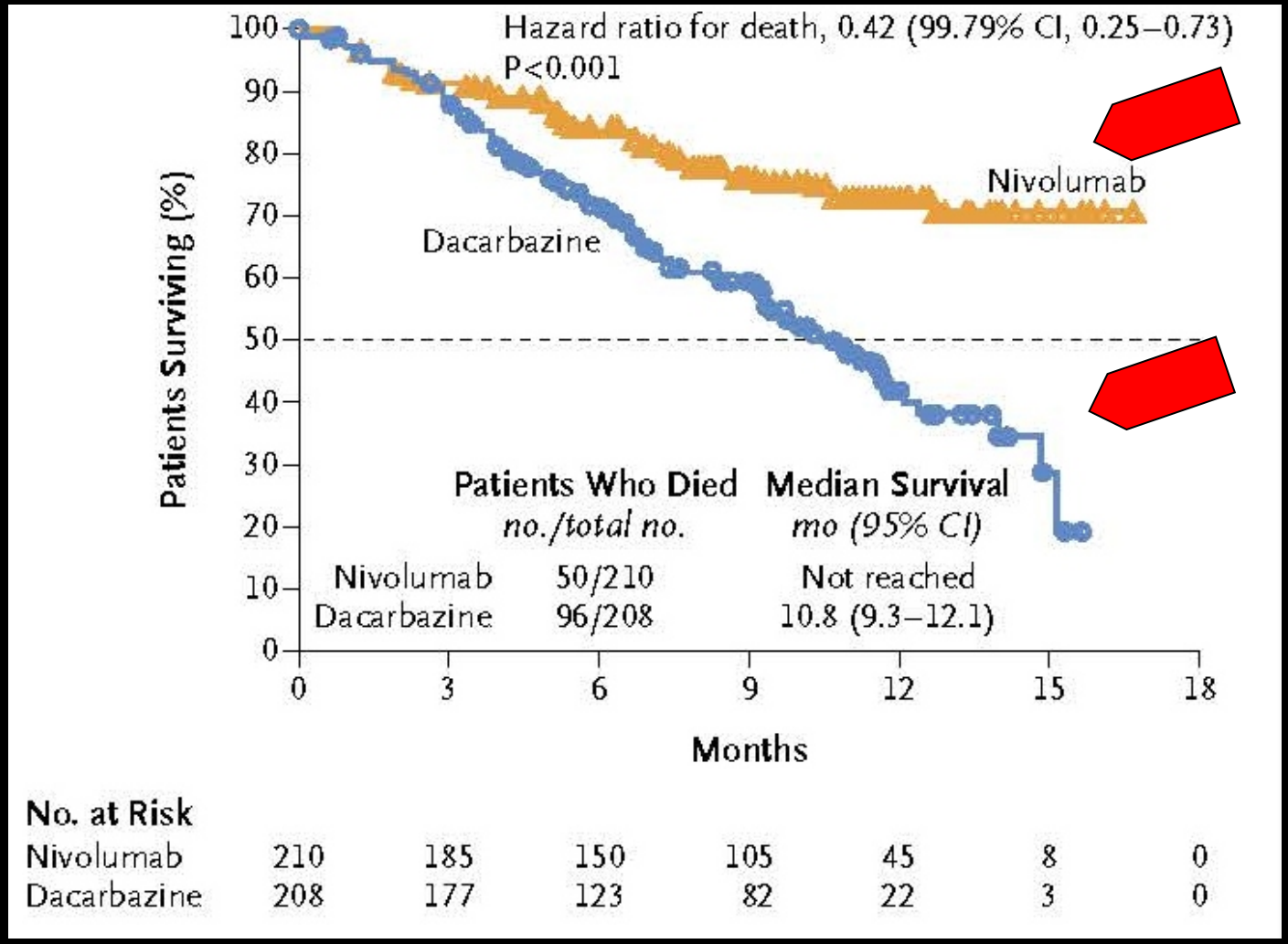


- Molecular profile can differ even within the single lesion
- Discrepancy between molecular profile of primary and metastic lesion (~20%).

Harnessing the immune system

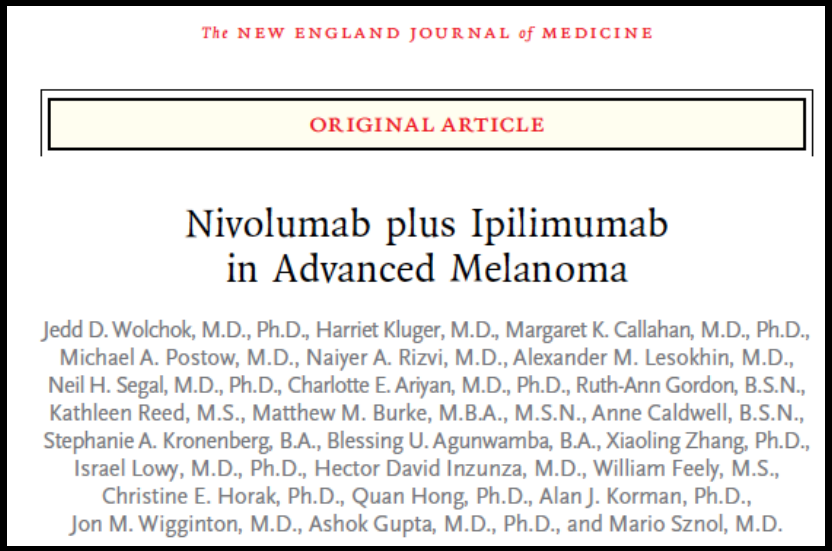
Immunotherapy is revolutionizing cancer care

Metastatic Melanoma: Long-term remissions



Robert et al. ….. Melanoma…..N Engl J Med 2015; 372:320-330

Combinatorial immune blockade is likely the rule, not the exception



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

- ASCO 2014 update
  - 2 year survival rate- 79%
    - Comparison: dacarbazine monotherapy 2 year survival rate- 18%
    - Prior therapies (1-3+) in 38%

Wolchok JD et al. N Engl J Med 2013;369:122-133

Predicting super-responders to immunotherapy

Biomarker

- PDL-1 negative: 0-17%
- PDL-1 positive: 36-100%

Patel and Kurzrock, MCT 2015

Unique characteristics

- Delayed responses with initial progression
- Subset of patients with advanced disease that have long-term complete remission (?cure)

Liquid Biopsy Program

Doing genomics on DNA from a small tube of blood sample

No tissue biopsy

~700 patients

Liquid Biopsy Program

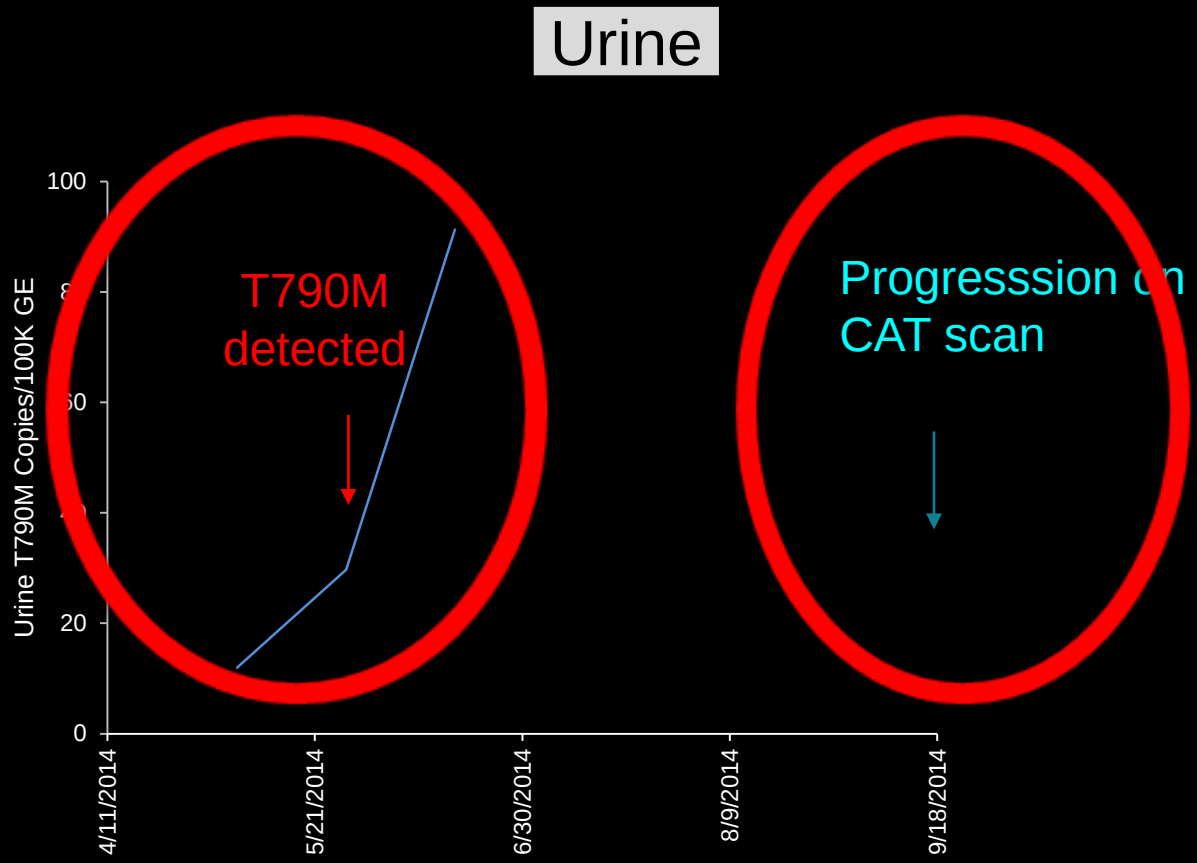
→ Blood

→ Urine

→ Ascites

Theoretically samples shed
DNA from multiple metastatic sites.

Lung Cancer
Early Detection of Progression



Liquid Biopsy (N = 171 Patients)

Circulatory Tumor DNA

N = 54 genes

	No. of Patients/Total (%)
All	99/171 (58%)
Glioblastoma	9/33 (37%)
Actionable	67/171 (39%)
Healthy Volunteer	1/222 (0.45%) [p53]

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Detecting EGFR Amplifications in Ascites in Lung Cancer

Case No.	Age/Sex	Diagnosis	Tissue NGS[a]	Ascites ctDNA[b]
1	64/man	Adenocarcinoma of the lung, metastasis to pleura and peritoneum	*CDK4* amplification[c] *MDM2* amplification [Also, PCR-based assay (Response Genetics) of primary lung tumor in December 2010 was negative for EGFR, ROS1 and ALK aberrations] (March 2013, Pleural mass)	**Somatic Mutations:** ***EGFR*** amplification **Total CNVs detected:** 23 (May 2014)

Liquid biopsy applications

Customized combinations for advanced disease.

Need to know all genomic aberrations from multiple metastases

Follow newly-diagnosed disease

Monitor resistance

Precision Medicine

Lessons from meta-analyses of 70,253 patients

Meta-Analyses Conducted

1) Trials leading to FDA approval from trastuzumab (1998) until June 2013
   → 38,104 patients; 112 trials

2) Phase II studies published between
   → 32,149 patients; 570 trials

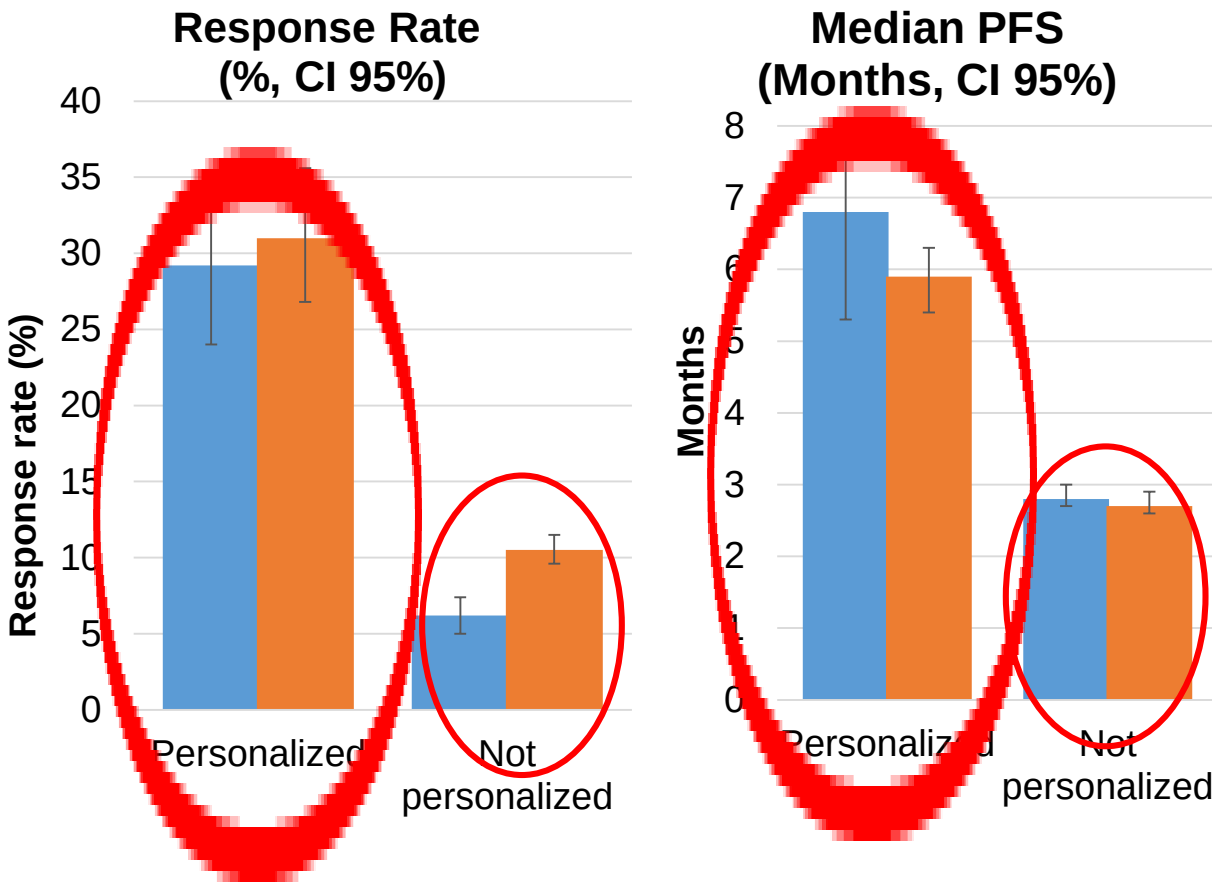
Summary of results
Multivariable analysis: N = 38,104

Randomized trials meta regression

Characteristic	P-value
RRR meta-regression	
Personalized therapy strategy	0.03
Progression Free Survival	
Personalized therapy strategy	<0.001
Ctrl arm placebo vs. active drug	<0.001
Hematologic tumor vs solid	0.004
Cross-over allowed	<0.001
Overall Survival	
Personalized therapy strategy	0.07
Hematologic tumor vs solid	0.006

All trials meta-regression (RR) and weighted pooled multilinear regression (PFS/OS)

Characteristic	P-value
Response rate	
Personalized therapy strategy	<0.001
Hematologic tumor vs solid	<0.001
Progression Free Survival	
Personalized therapy strategy	0.002
Overall Survival	
Personalized therapy strategy	0.041



Pooled analysis

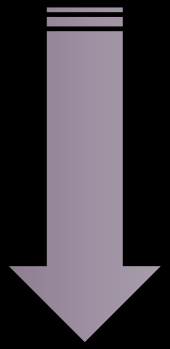
Meta-analysis

CONCLUSIONS

- **Non-personalized targeted arms led to poorer outcomes than cytotoxics arms**

  (All P<0.0001, except P=0.048 for OS meta-analysis).

Worst outcome



Best outcome

	POOLED Analysis			Meta-analysis		
ARMS type	RR (%)	PFS (Mos)	OS (Mos)	RR (%)	PFS (Mos)	OS (Mos)
Non-personalized targeted	4	2.6	8.7	7.5	2.5	8.3
Cytotoxic	12	3.3	9.4	16.1	3.3	9.3
Personalized targeted	30	6.9	15.9	31.3	6.1	13.7

THANK YOU
for your time and interest

Questions??

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teoam2011@gmail.com