Engaging Patient Cohorts for Better Medicines, Faster

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Cancer Drug Development

- 833 industry sponsored Phase I trials ongoing 50% are targeted drugs (Cancer trials.gov)
- Cost is >1 billion per drug and 7 years for regulatory approval
- But only 5 % of drugs in phase I, will make it to market
- New drug approvals lowest in 20 years
- FDA Critical path Initiative (2004)
  - A paradigm change is required
  - Innovative trial designs
  - *Enrichment of patients*

We are using the evaluation tools and infrastructure of the last century to develop this century's advances

Robert Justice, MD, MS Division of Drug Oncology Products, FDA. 2006

Our Approach to Phase I Trials Emphasizes Patient Selection

- An unmet need, most patients with advanced cancer (>200,000 /year) will exhaust FDA approved treatments quickly
- “Rare Tumors” (new cases 40,000/year) no standard therapy in most cases
- Patients enroll to phase I trials in expectation of benefit
- Patients should be assigned to potential therapy of benefit if possible

Finding a Molecular Target

- Progress in cancer therapy impeded by inability to find a relevant target
- Most tumors are genetically heterogeneous
- Many over-expressed / mutated genes represent only a subset of the tumor cells
  - (i.e not an therapeutic target)
- Need to identify key oncogenic mutations that lead to the development of an invasive tumor

Simon R. Eur J Can. 4 4:2 7 0 7 –1 3: 2008

Contexts of Vulnerabilities "Oncogene Addiction"

Have been found for Rare Tumors

Tumor Type	Genomic Vulnerability	Go-to-Agent
CML	Bcr-abl fusion protein	imatinib (Gleevec)
GIST	c-kit mutations	Gleevec, sunitinib
Basal Cell	Patched mutation	GDC 0449
Adrenal Cancer Ewings sarcoma	IGFR	IGFR antibodies AMG 479; CP 751, 871
Castleman's Disease	Upregulated IL6	CNTO 328
Papillary renal cell	C-met amplification	XL888, MP470
Myxoid liposarcoma	12:16 translocation	ET743 (trabectadin)
Chondrosarcoma	TRAIL	TRAIL interactive
Synovial Cell Sarcoma	EGFR	erlotinib

Finding a Target-The 6th Vital Sign

- IHC assays + DNA microarray for up to 18 targets (e.g. Her2/neu, ER, c-kit, etc.)
- 91 patients with fresh frozen tumor
- IHC identified an average of 1.2 targets (for which a conventional therapeutic agent is available) per patient (range 0 - 4 targets).
- The DMA identified an average of 3.3 targets per patient (range 0 - 8 targets).
- Overall, a target was found for 89 (98%) of the patients.
- This data indicates that using IHC and DMA one can consistently find a potential target

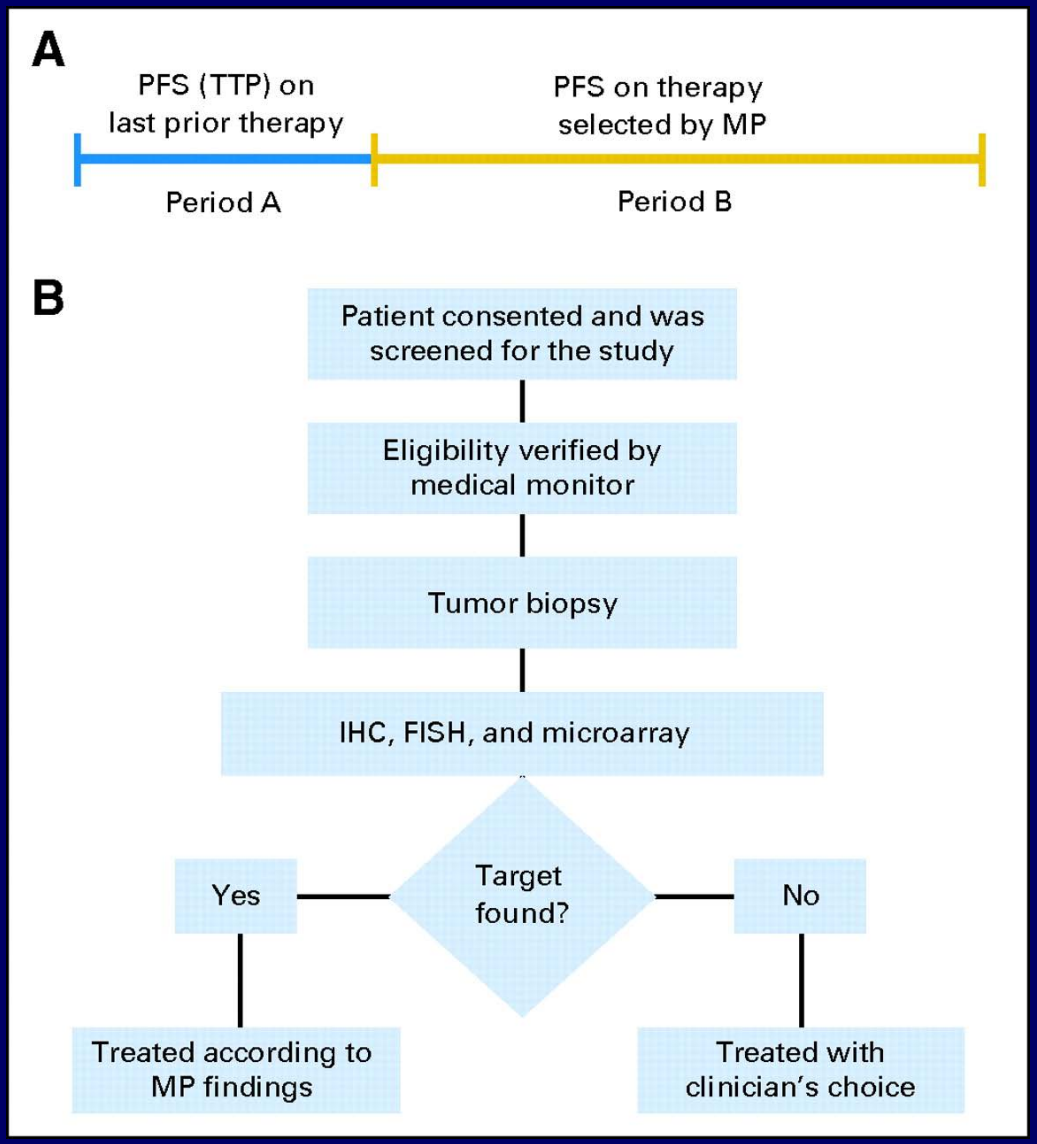
Von Hoff, Bittner, Penny et al. ASCO, A138s, 2006

Phase II Study of Molecular Profiling for Refractory Solid Tumors

The Bisgrove Study Group

The Stardust and Scottsdale Healthcare Foundations

Von Hoff D D et al.
JCO 2010;28:4877-4883



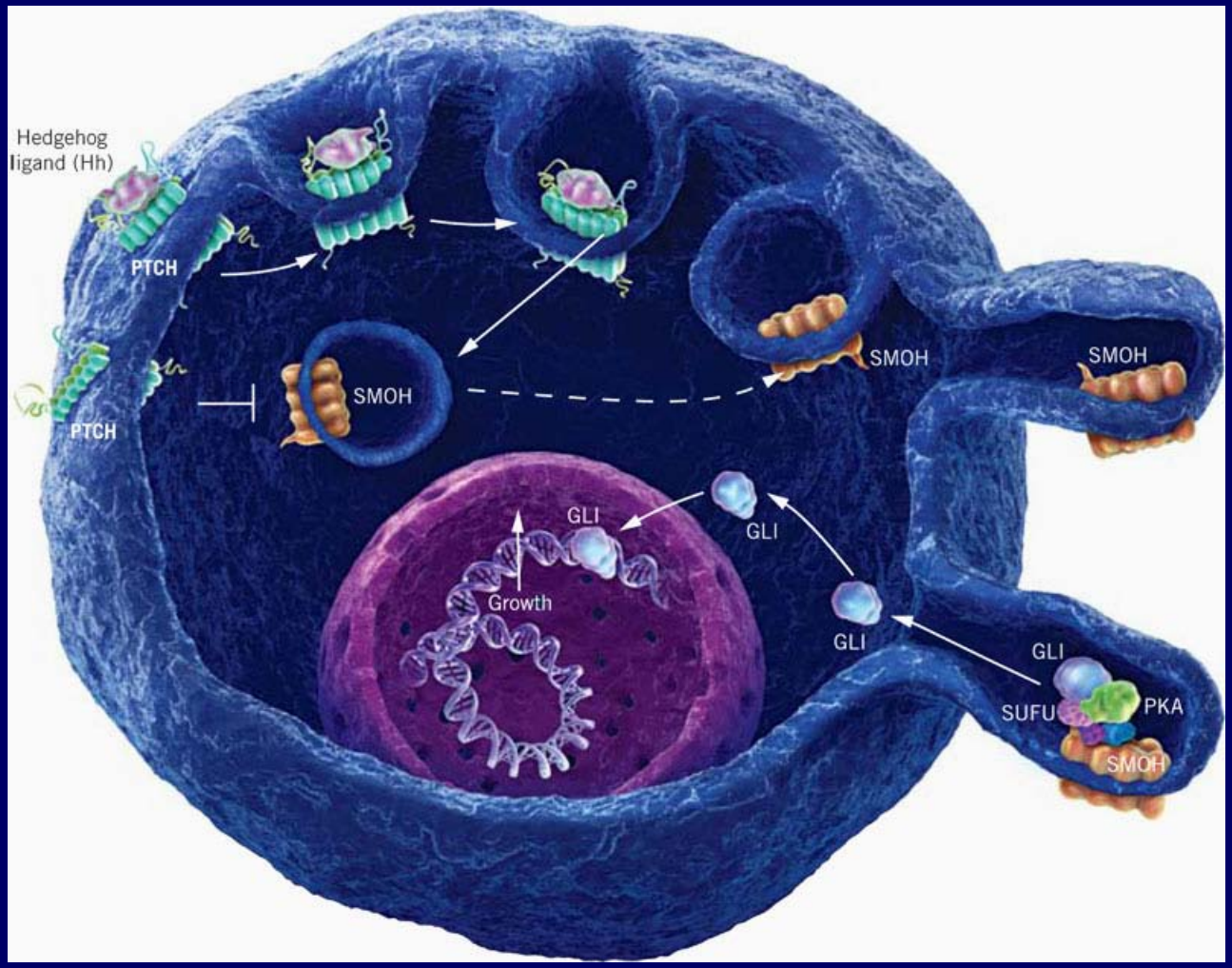
Results: Primary Endpoint – PFS Ratio ≥ 1.3

1. In 66 patients treated according to MP results
    - Number of patients with PFS ratio ≥ 1.3 = 18/66 (27%)
    - 95%CI 17-38%,
    - One-sided one-sample; p=0.007
2. The null hypothesis was that ≤ 15% of this patient population would have a PFS ratio of ≥ 1.3.
3. Therefore the null hypothesis is rejected and our conclusion is that this molecular profiling approach is promising

Conclusions for this Prospective Study

1. It is possible to measure molecular targets in patient's tumors from 9 different centers across the U.S.
2. This Molecular Profiling approach and treatment selection showed benefit in some cases
3. We consider this a promising result worth pursuing
4. Newer technologies such as whole genome sequencing may refine patient selection

Treatment Based on Inhibiting the Hedgehog Pathway:



2 Key Receptors

-Smoothened

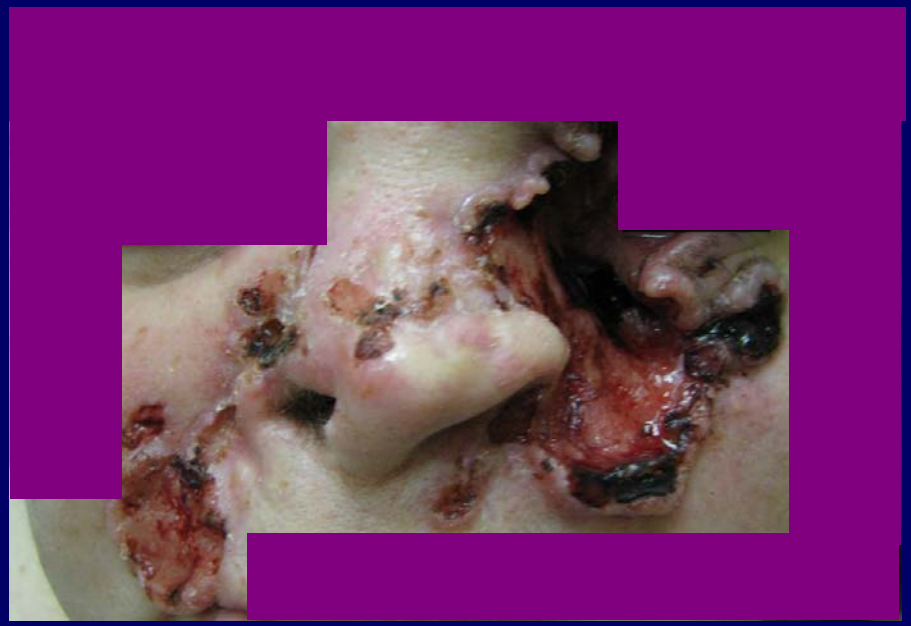
-Patched (Tumor suppressor)

Phase I Study of GDC-0449

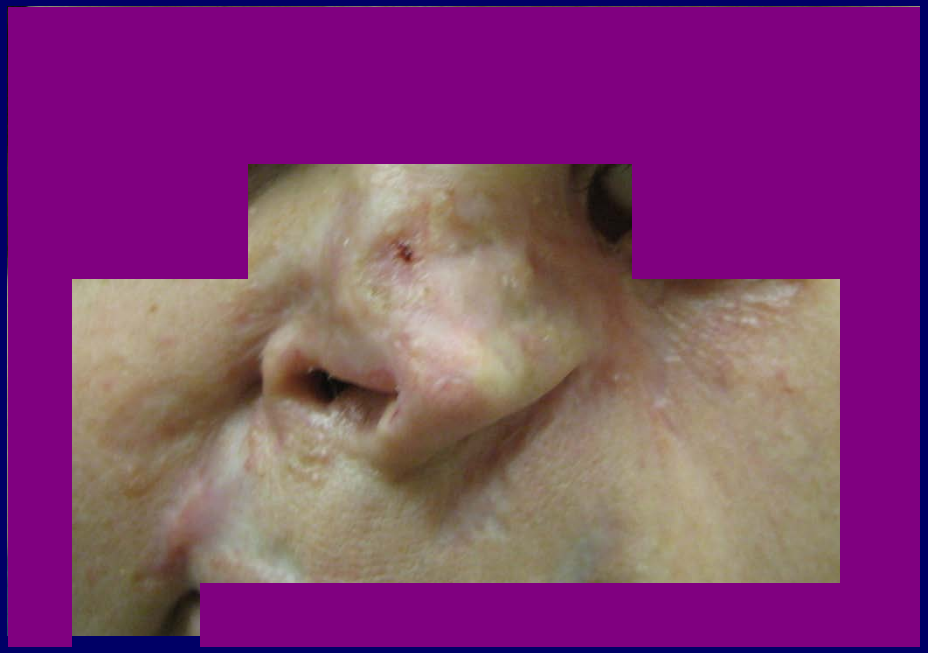
- Metastatic/ locally advanced basal-cell carcinoma
- Only 800-1000 cases/year
- 3 dose levels (n=33) treated with GDC-0449
  - 150 mg/d (n=17)
  - 270 mg/d (n=15)
  - 540 mg/d (n=1)
- Minimal side effects, Grade 3/4 AEs in only 6 patients
  - Fatigue (n=4), hyponatremia (n=2),
  - muscle spasm/ atrial fibrillation (n=1 each).

41yo With Multiple Advanced Facial BCCs

Baseline



After 5 months



Clinical Activity Summary of GDC0449 in Basal cell cancer

Best Response	Patients, N=33
Duration of Treatment	9.8 months
Response (2CR)	18
RECIST	7
Physical exam	10
Both	1
Stable Disease	11
Disease Progression	4
Patched mutations	9/10 specimens

Von Hoff ,D., LoRusso, P., Rudin, C. et al ., NEJM 361:1164-1172, 2009

Whole Genome Sequencing for Treatment is now a Reality

Scientists Crack Cancer Codes

Nature; December 16, 2009

- Scientists are hailing the unlocking of the complete genetic code of two of the most common cancers as "a fundamental moment in cancer research".
- The scientists have discovered 30,000-odd errors in the DNA code of melanoma and about 23,000 errors in the DNA of lung cancer.

Whole Genome Sequence Analysis of a Pancreatic Ampullary Adenocarcinoma-TGEN

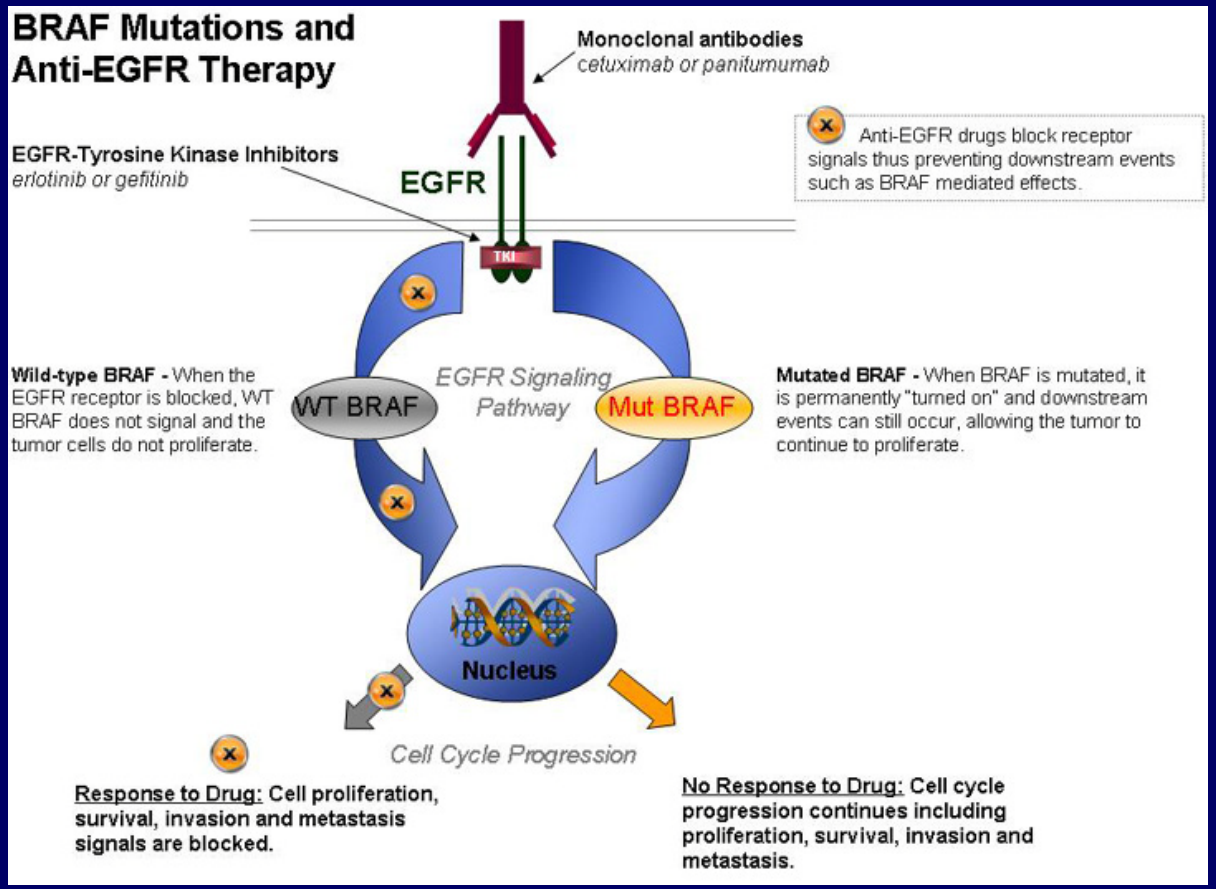
63 y.o. man with Pancreatic Ampullary Adenocarcinoma

- 5 year survival rate is ~ 40%
- Used frozen tumor specimen 300mg total tissue (≈ 70% tumor)
- Peripheral blood cells for normal DNA
- Timeline: 3-4 weeks data generation; 3 weeks analysis

SNP/Mutation statistics

- 30X coverage of tumor and 25X for normal
- number of total germline SNPs = 2,641,540
- 2284316 in dbSNP (86.5%)
- number of de novo mutations = 9,017
- number of non-synonymous coding mutations = 81
- Druggable genes: Kras and PTEN found

Selection of Patients Can Result in Efficacy: The Braf Story



- Seen in 60% of melanomas
- 10% of solid tumors

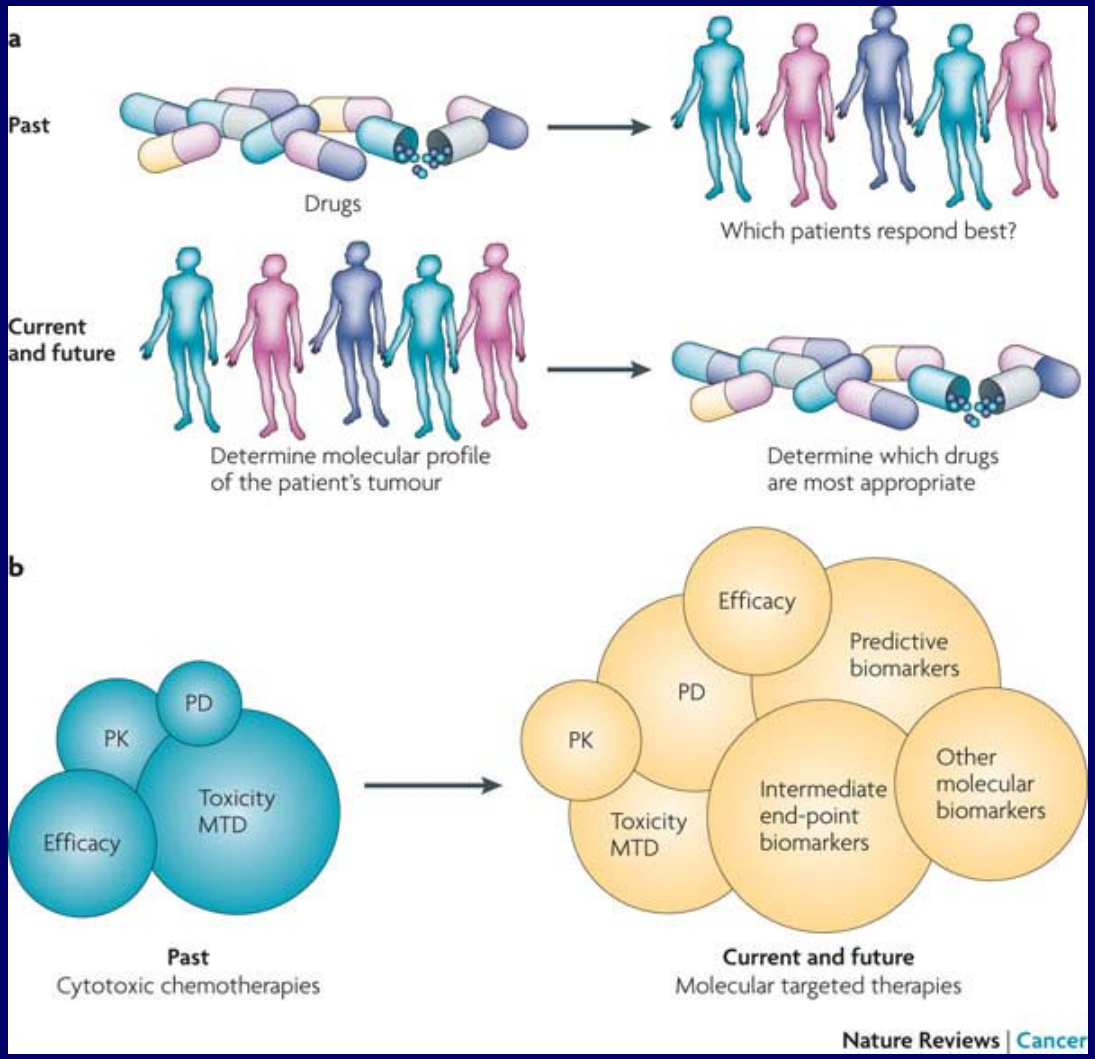
PLX4032

- oral inhibitor of Braf
- Phase I study
- N=27
- Dose 960 mg bid
- 70% response in Braf mutated melanoma!!

Other Examples

- ALK fusion Gene Inhibition.
  - Crizotinib in NSCLC. (A3, ASCO 2010).
- BRACA1/2-PARP Inhibition.
  - Olafarib (Fong PC et al, NEJM 2009)
- HDAC Inhibition.
  - HBI-8000 in Adenoid Cystic carcinoma (A 3529. ASCO 2009)
- CDK/TRKA Inhibition.
  - PHA-848125 Thymic cancer (A3531, ASCO 2008). Now a phase II study

Drug Development-The New Paradigm To Accelerate Discoveries into the clinic



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