Incorporating biomarkers into cutaneous neurofibroma trials

REINS CUTANEOUS NEUROFIBROMA BIOMARKER WORKING GROUP

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Response Evaluation In Neurofibromatosis Schwannomatosis

INTERNATIONAL COLLABORATION

Disclosures

NFlection Therapeutics- advisory board member

Color genomics- consultant

Myotherix- consultant

Chemocentryx- consultant

Pellepharm- consultant

23andMe- research collaboration

Medivir- research collaboration

Objectives

- Review the existing data related to biomarkers for cutaneous neurofibromas
- Recommendations for incorporation of biomarkers into clinical trials for cutaneous neurofibromas
- Recommend methods for sample collection for incorporation into cutaneous neurofibroma trials

Definition of a biomarker

"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

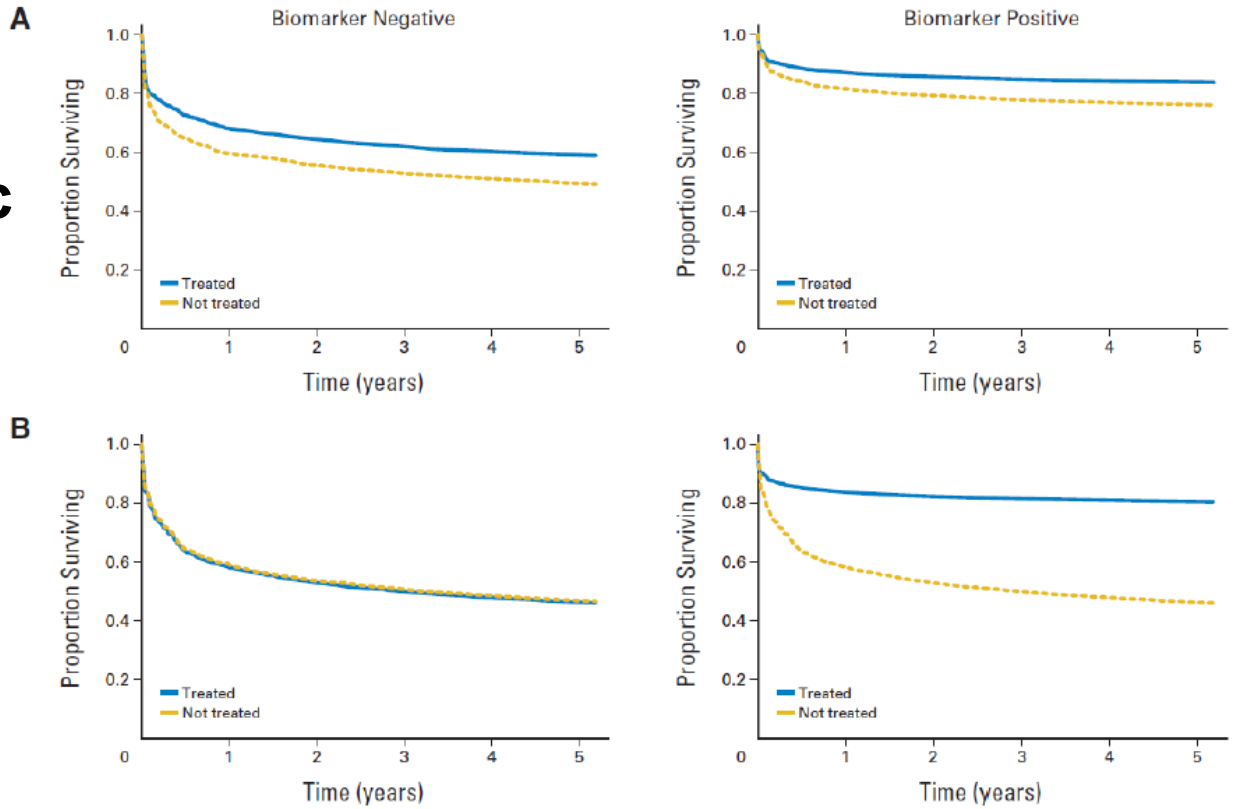
-National Institutes of Health
Biomarkers Definitions Working Group

Types of Biomarkers

Prognostic

Predictive

Pharmacodynamic



Ballman KV, J Clin Oncol, 2015

Prognostic biomarker

- Informs the likely outcome of a disease and whether additional therapy would be beneficial.

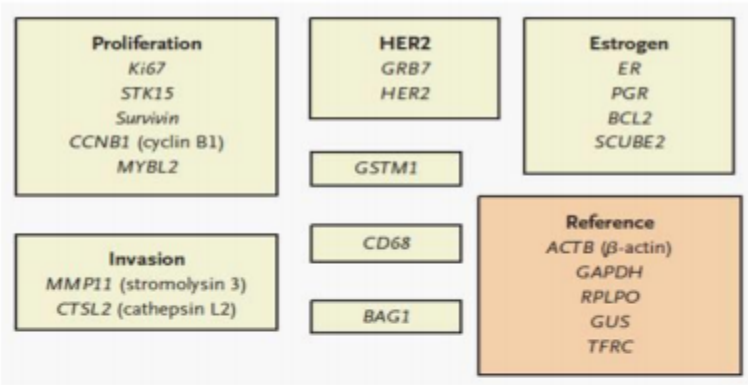
Prognostic Biomarker: Oncotype DX

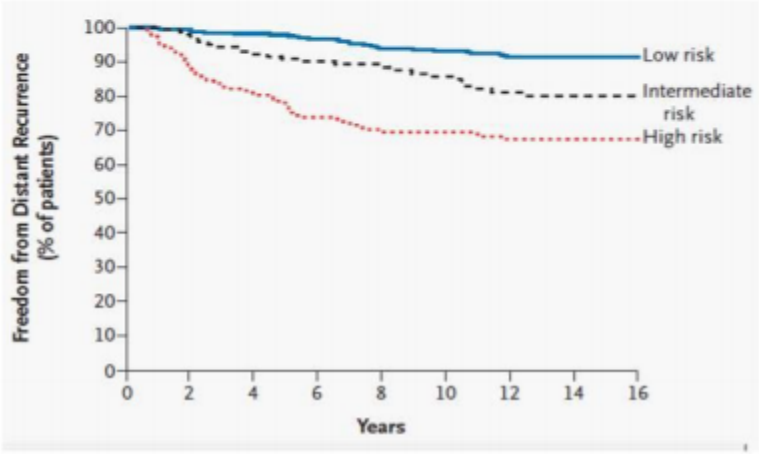
Hormone + node negative patients represent <u>half of breast cancer patients</u>.

Oncotype Dx test:

-21 gene RT-PCR based assay

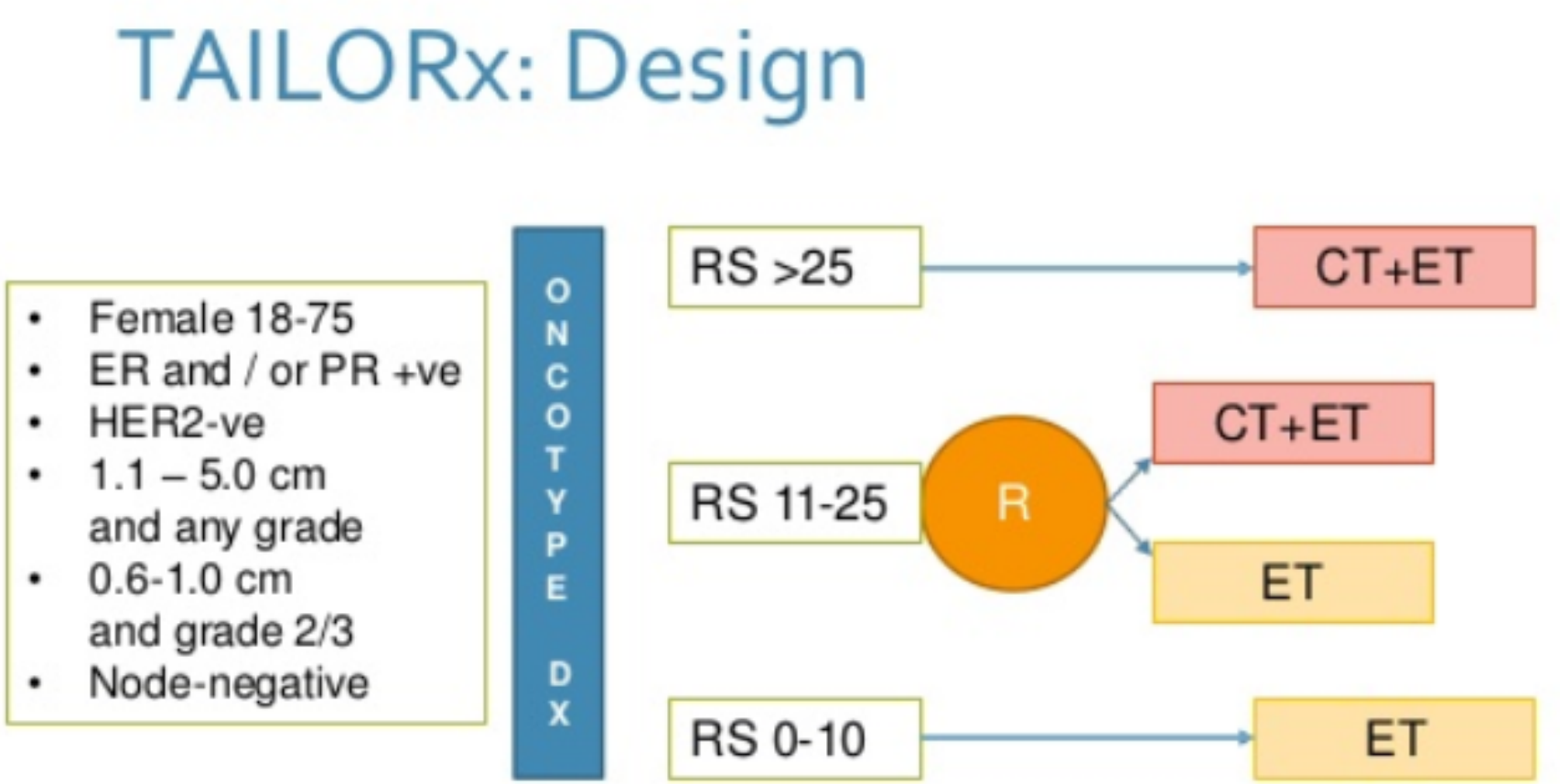
- Forecast probability of Breast cancer recurring after surgical intervention (called a 10-year recurrence score)





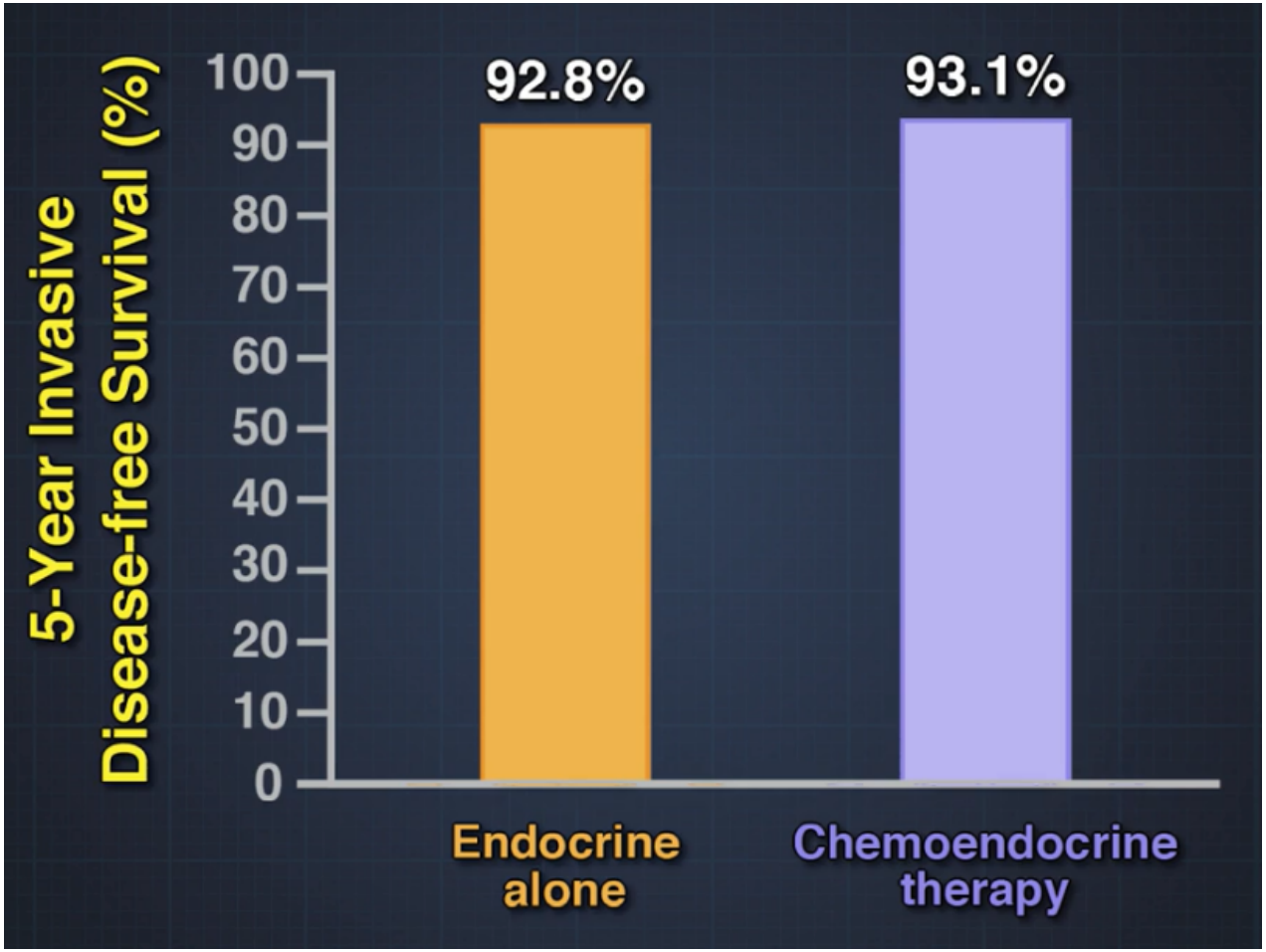
Paik NEJM 2004

Incorporating prognostic biomarkers into clinical trials



Sparano, N Engl J Med 2018; 379:111-121

Non-inferiority of ET therapy for patients with intermediate risk scores



Conclusions: Incorporation into clinical trials

- Prognostic biomarkers may be helpful in determining enrollment criteria into clinical trials

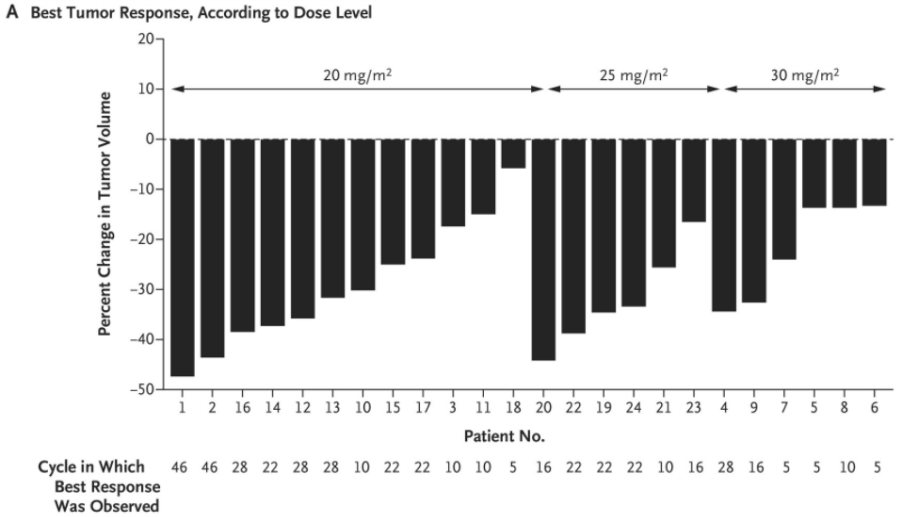
- They also may be used to substratify patients to determine which patients would benefit from the intervention.

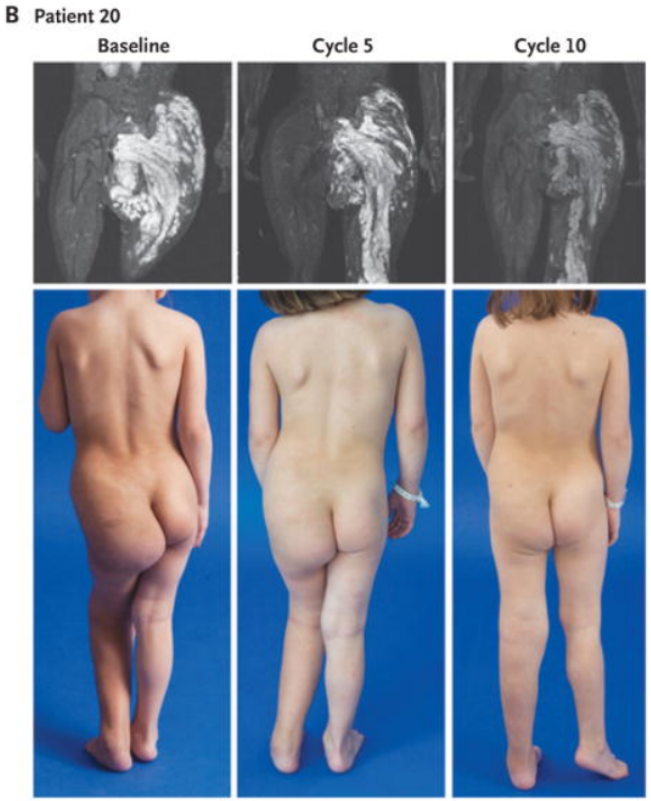
Pharmacodynamic Biomarker

Measures the effect of a drug on the disease process

Ex. Phosphorylation status of a substrate after inhibition of a protein kinase

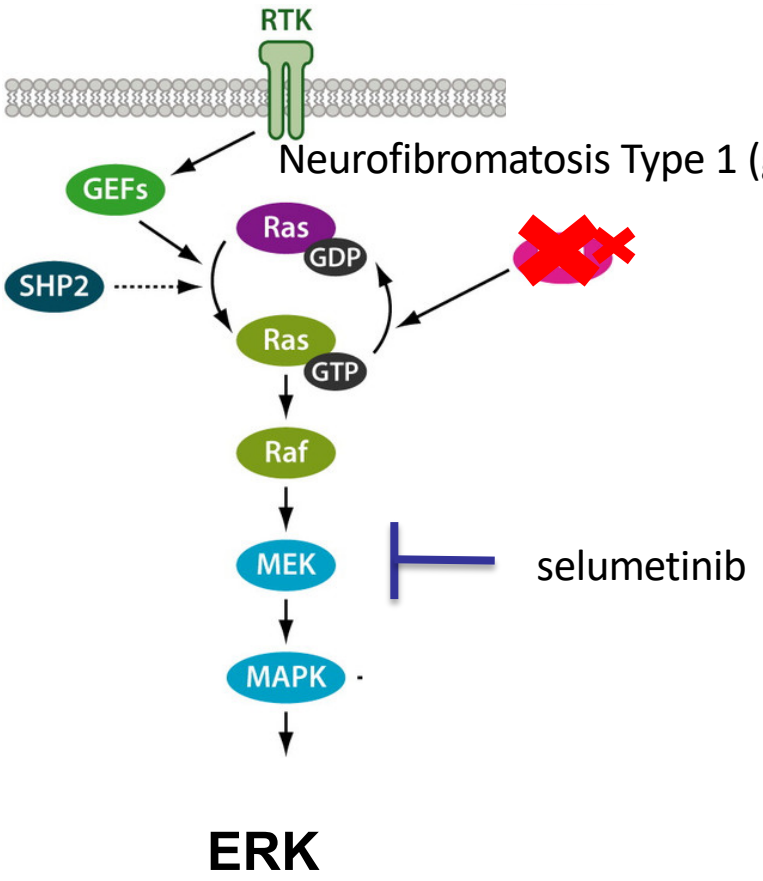
Phase 1 trial of selumetinib causes partial response in plexiform neurofibromas

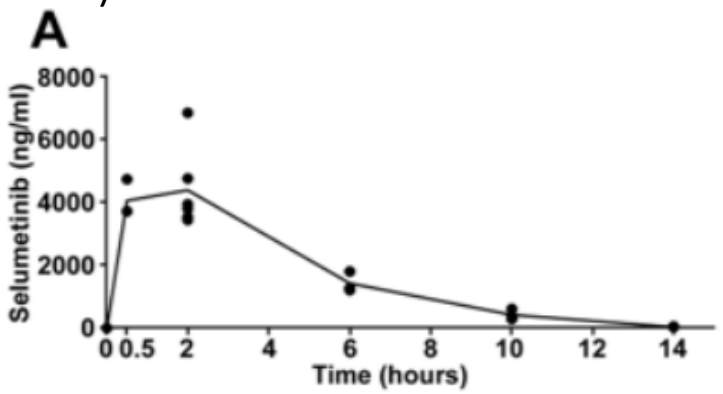


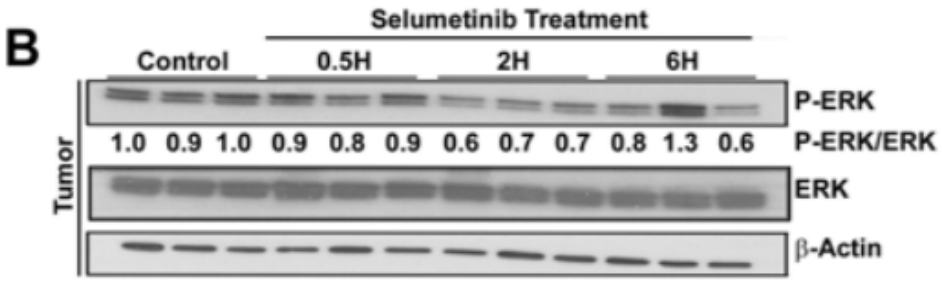


Dombi E, et al. Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas. *N Engl J Med*. 2016 Dec 29;375(26):2550-2560.

Pharmacodynamic analysis of selumetinib in murine neurofibromas







N Engl J Med 2016; 375:2550-2560

Conclusions: Incorporating pharmacodynamic biomarkers

- Pharmacodynamic markers can be used to assess target engagement of drug in preclinical and clinical trials

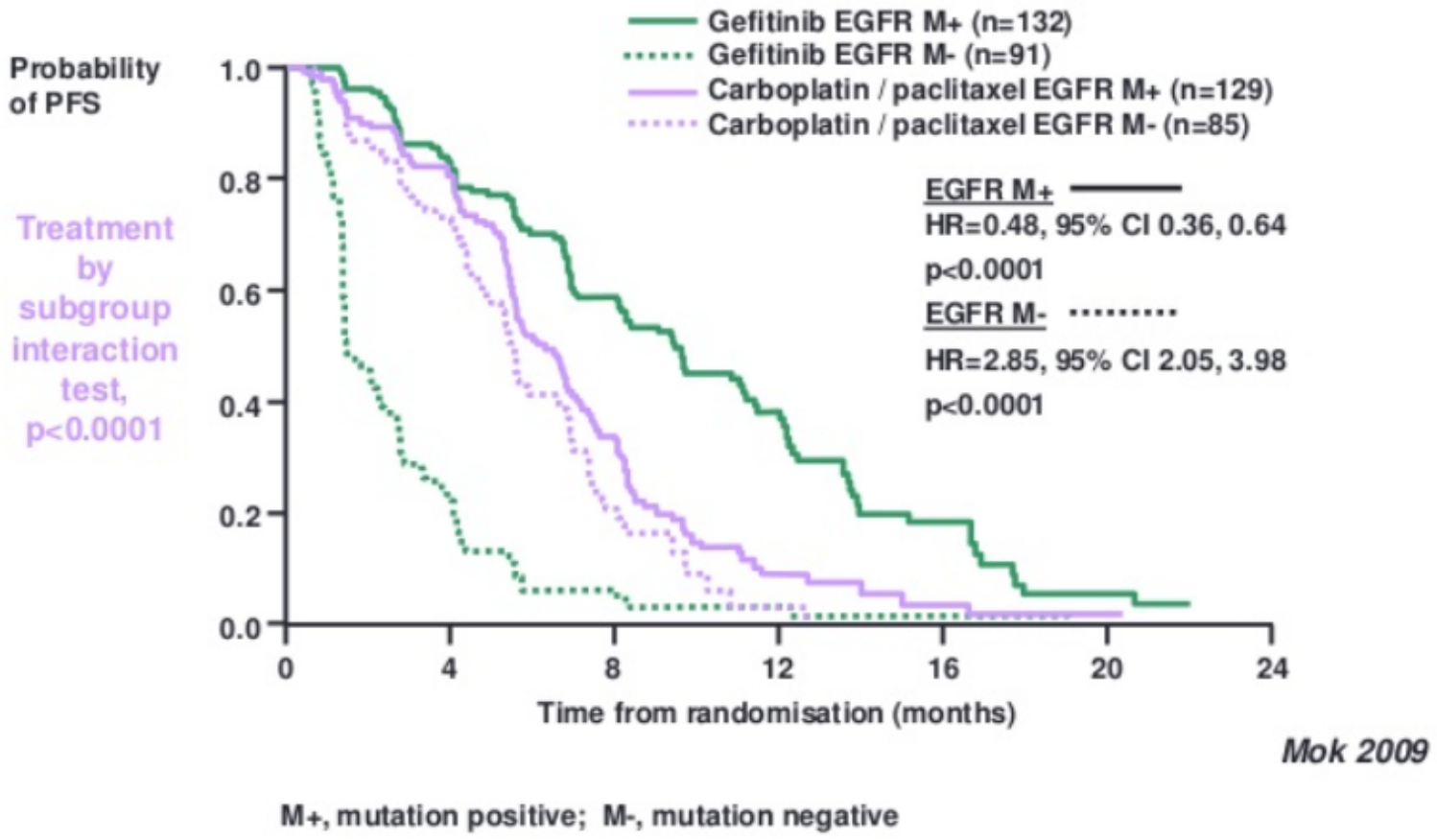
- Pharmacodynamic markers can be analyzed in clinical trials to determine level of target engagement required for therapeutic effect/ on-target side effects.

Predictive biomarkers

Assess the likelihood the tumor will respond to the drug.

- CML and BCR-ABL
  - Philadelphia chromosome (t 9:22)
  - Fusion protein has high tyrosine kinase activity
  - Imatinib: Tyrosine kinase inhibitor

Marker stratified (posthoc): EGFR and gefitinib in NSCLC

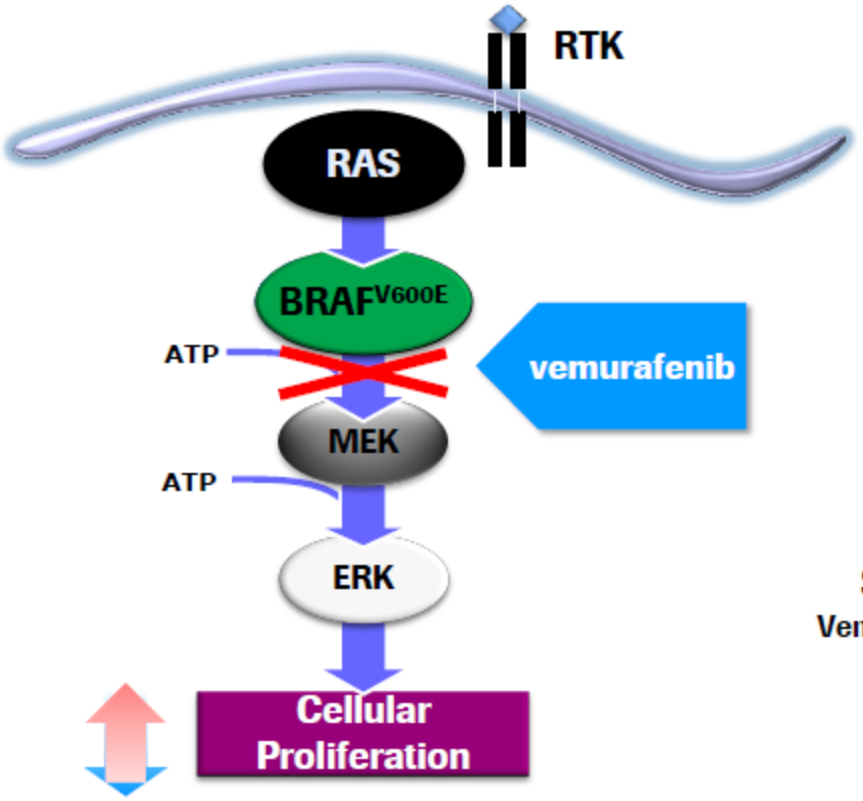


M+, mutation positive; M-, mutation negative

N Engl J Med 2004; 350:2129-2139

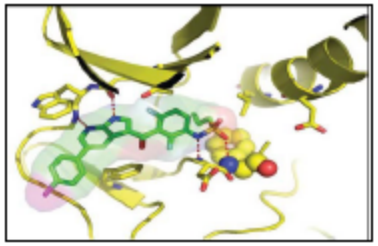
Science 2004;304:1497-1500

Marker-enriched design: vemurafenib for melanoma



BRAF oncogenic mutations

– ~50% melanoma



Structure-Guided Discovery

Vemurafenib (RG7204, PLX4032) co-structure with kinase domain of BRAF^{V600E}

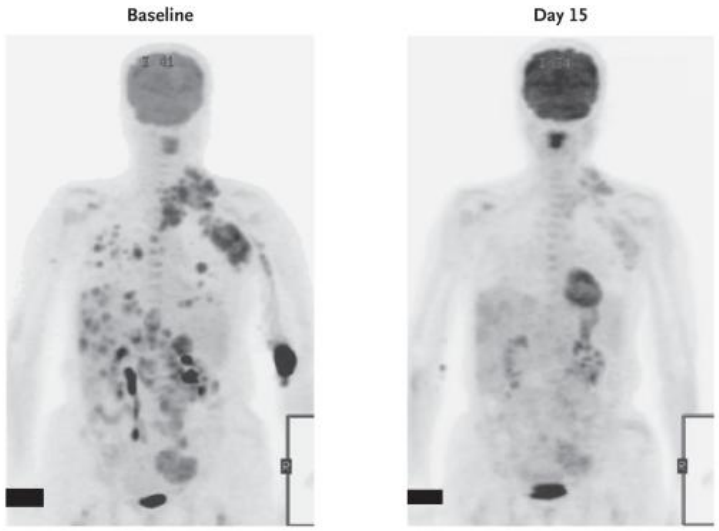
(Bollag et al. Nature 2010)

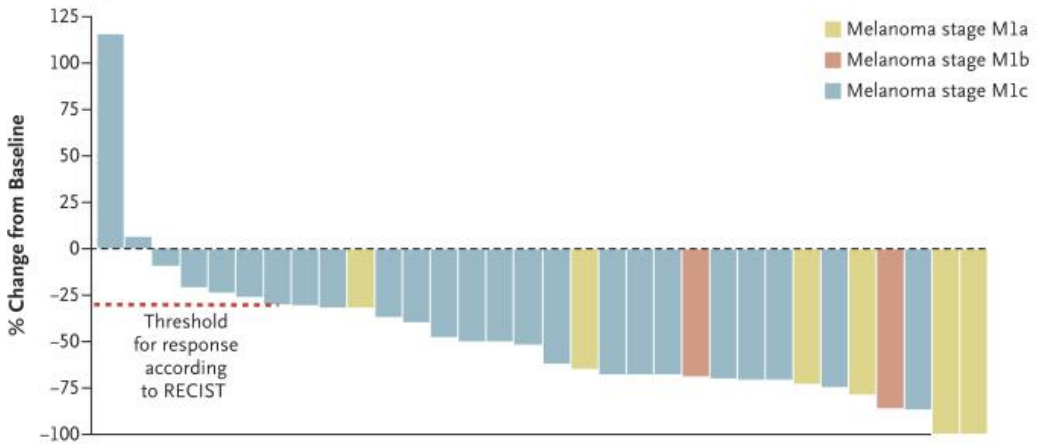
Vemurafenib: 6 years from IND to FDA-approval

2006 2007 2008 2009 2010 2011 2012

IND

FDA Approval





Flaherty et al. N Engl J Med. 2010 Aug 26; 363(9): 809–819.

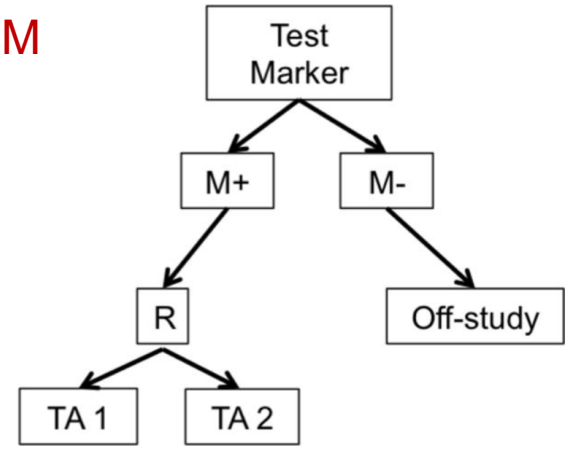
Predictive biomarkers used in oncology treatment

Biomarker	Cancer type	Drug therapy	Drug target
HER2 (gene amplification)	Breast	Trastuzumab	HER2
Estrogen receptor (protein expression)	Breast	Tamoxifen	Estrogen receptor
BCR–ABL (gene translocation)	CML	Imatinib, dasatinib, nilotinib	BCR–ABL
EGFR ± KRAS (KRAS mutation)	CRC	Cetuximab, panitumumab	EGFR
EGFR (kinase domain mutation)	NSCLC	Erlotinib, gefitinib	EGFR
PML–RAR (gene translocation)	APL	All trans retinoic acid	PML–RAR
BRCA1/2 (mutation)	Breast	Olaparib, veliparib	PARP
BRAF V600E (mutation)	Melanoma	Vemurafenib	BRAF
ALK (rearrangements)	NSCLC	Crizotinib	ALK

Types of predictive biomarker trials

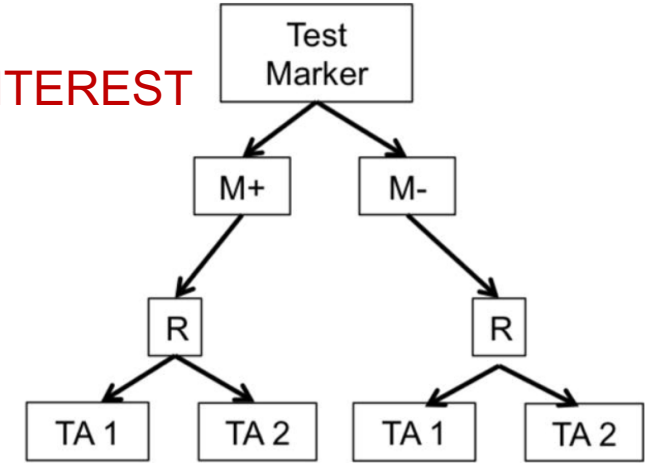
Marker enriched

BRIM



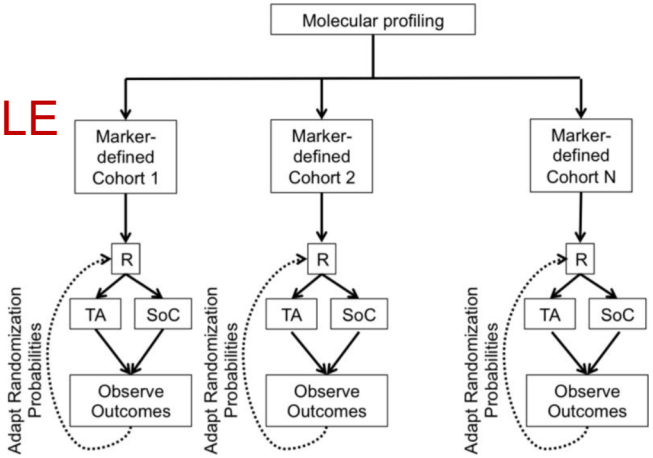
Marker stratified

INTEREST



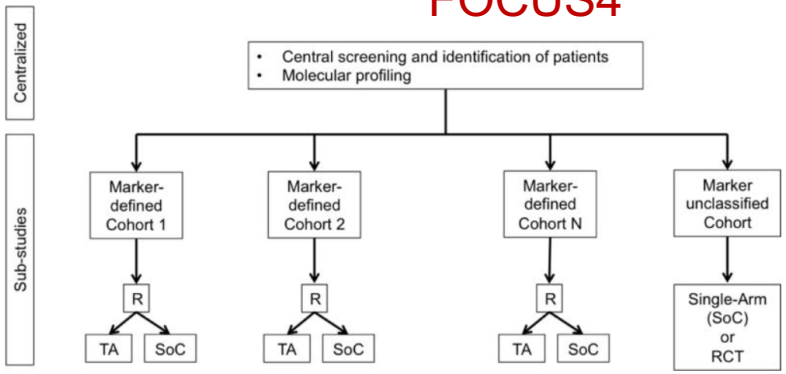
Adaptive marker

BATTLE



Umbrella: trial

FOCUS4



L.A. Renfro et al. Cancer Letters 387 (2017)

Incorporating biomarkers into clinical trials

Advantages:

- May enable earlier go/no go decisions for therapeutic trials
- Biomarkers associated with drug mechanism of action can provide reassurance that compounds are having intended effect
- Can be helpful in dose selection (bioavailability, target tissue exposure, safety)
- May inform inclusion/exclusion criteria of trial enrollment for Phase II studies

Disadvantages:

- Increase complexity of study (patient enrollment, specimen handling)
- Danger of over interpreting results
- Quality and reliability of assays
- Use of multiple biomarkers can increase complexity

Stages of incorporation of predictive biomarkers during clinical trial development

- Preclinical: clear relationship between exposure of the target to the drug, desired biomarker effect and model efficacy

- Early clinical trials for proof of mechanism: show that the candidate drug engages at a reliable and quantifiable level at humans, indicating a functional effect

- Early clinical: show that the candidate drug results in a biologic and/or clinical change associated with the disease and mechanism of action

- Proof of concept: show that the candidate drug results in a clinical change on an accepted endpoint in patients with disease

Considerations in evaluating a candidate predictive biomarkers

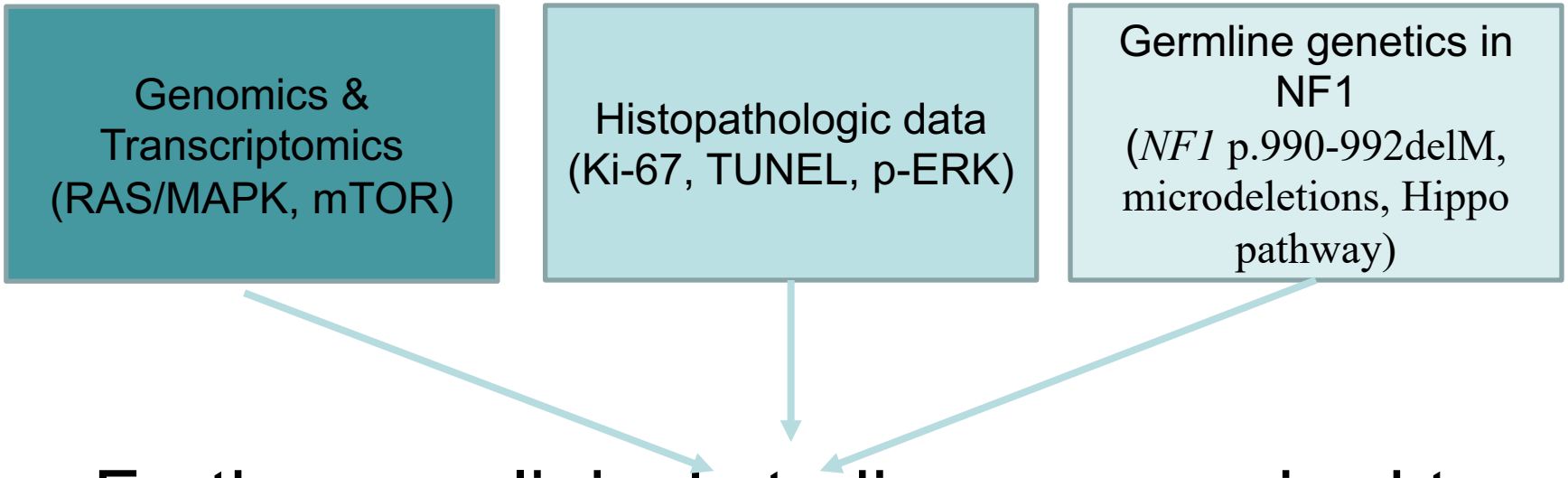
- Clinical relevance/scientific rationale— The biomarker should ideally be related to the mechanism of action of the drug and/or the clinical endpoint
- Sensitivity and specificity to treatment effects — Ability to detect the biomarker or change in biomarker in the target population
- Reliability — Ability to measure the biomarker analytically with accuracy, precision, robustness and reproducibility
- Practicality — Non-invasive or minimally invasive biomarkers are preferable — The biomarker should be suitable to implement in multi-site trials
- Simplicity — Simpler is better for translating a biomarker from lab bench to bedside

Conclusions

- There are currently no validated predictive biomarkers for cutaneous neurofibromas that meet the criteria listed

- **We have a unique opportunity. Biomarker development should be incorporated into cNF clinical trials.**
  - **Ease of access to tissue samples**
  - **High number of samples for analysis**

Potential biomarkers from literature

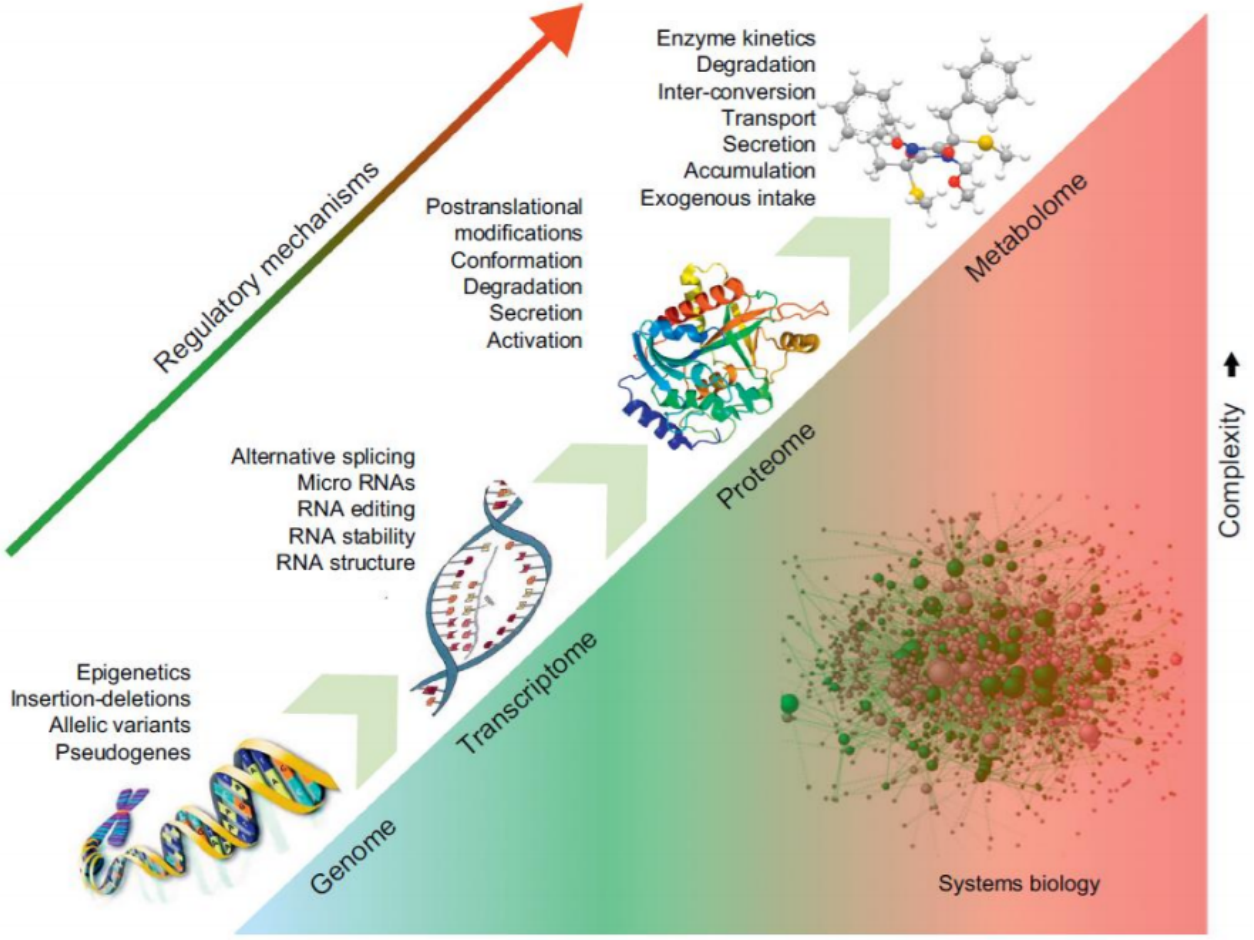


- Further preclinical studies are required to define biomarkers, drug targets, and the molecular pathways important for NF1.

Exploratory analysis

- We recommend incorporating a standard set of tissue collection protocols into cutaneous neurofibroma trials:

Emerging biomarkers



Barallobre-Barreiro J et al. Rev Esp Cardiol, 2013

Recommended Tissue collection for all clinical trials

- Normal skin
  - pre and post-treatment [Optional]
- Cutaneous neurofibroma pre and post-treatment
- Plasma pre and post-treatment

Methods for collection

- Serum collection
  - PAX tubes
  - Snap-Freeze serum
- Tissue collection
  - RNA Later
  - Formalin
  - Snap-Freeze

Goal: to preserve protein, RNA, DNA for future analyses.

Dataset Annotation

Host

1. germline NF1 mutation
2. tumor burden
3. current age/gender/ethnicity
4. comorbidities
5. age of cNF onset

Tumor

1. somatic NF1 mutation
2. tumor size
3. tumor consistency
4. tumor growth rate
5. tumor location

We need a concerted effort to create standardized phenotypic databases with biobanking capabilities to aid in biomarker discovery

Potential pitfalls of including biomarkers in clinical trials

- Infrastructure issues among sites which can impede adequate and timely sample collection
- Non-compliance among investigators
- Study subjects may not want biopsy or may have wound healing, toxicities or other skin issues that preclude biopsy

- **Compliance: pre-planned and real-time infrastructure to confirm samples are collected in a timely and adequate manner.**


"Planning is bringing the future into the present so that you can do something about it now."
- Alan Lakein

Biomarker working group

- Anat Stemmer-Rachamimov
- Deeann Wallis
- Sarah Adsit
- Bruce Korf
- Dominique Pichard
- Jaishri Blakely
- Dawn Siegel
- Kavita Sarin

- REiNS cutaneous neurofibroma group