NCI Director's Consumer Liaison Group

The Challenge of Translating the Science of Oncology to Patient Care

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Framing the Question

- "The September meeting will explore how clinical trials need to change in order to take advantage of scientific advances"
- Hypothesis:
  - Current clinical trial designs are inadequate.

Outline

- Basic Clinical Trial Designs & Goals
- Advances in basic science
- Efforts to evolve oncology clinical trials
- Challenges for the future & concluding remarks.

Translating the Science of Oncology to Patient Care

Trial Design for Oncology Drug Approval

Clinical Trial Phases

- Preclinical
  - Target identification and validation
  - Medicinal chemistry and agent optimization
  - Pharmacokinetics/pharmacodynamics
  - Toxicology
- Phase I
  - Identify acute toxic effects
  - Determine dosing
  - Analyze drug metabolism and excretion (PK)
  - Interaction with drug target (PD)

Clinical Trial Phases

- Phase II
  - Assess for preliminary evidence of efficacy
  - Conducted in specific diseases/patient populations
  - Further safety data (acute and chronic)
- Phase III
  - Definitive assessment of efficacy
  - Usually compared to “standard treatment” i.e. randomized
  - Additional safety data and formulation of risk/benefit profile

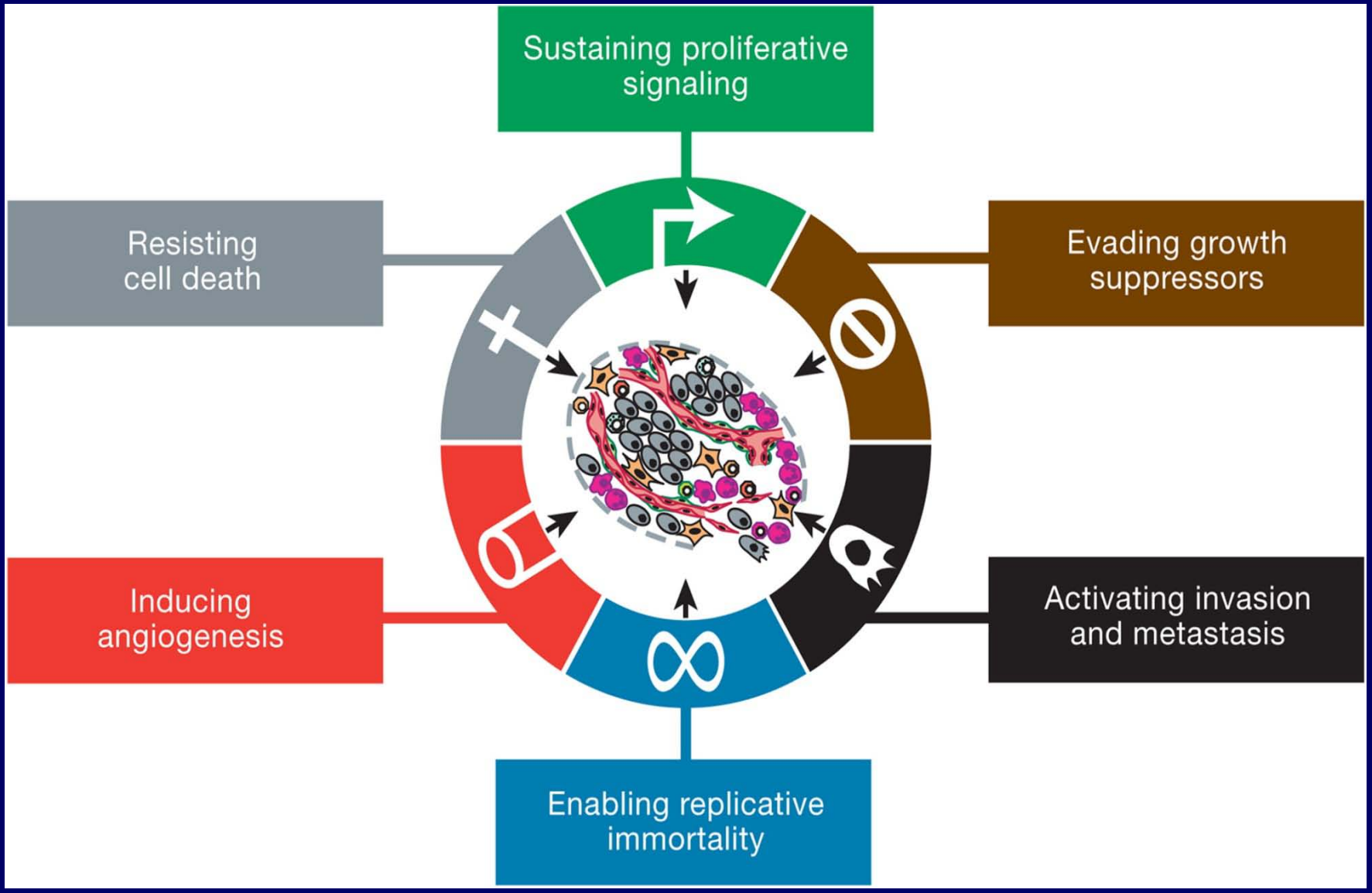
Clinical Trial Phases

- Phase IV
  - Product approved and marketed
  - Assess long term toxic effects, risks/benefits
  - Optimize use
  - Conduct studies in specific patient populations, e.g. children or patients with renal/hepatic dysfunction

Translating the Science of Oncology to Patient Care

Advances in Oncology Science

Hallmarks of Cancer



Hanahan and Weinberg. Cell 144:646-674, 2011

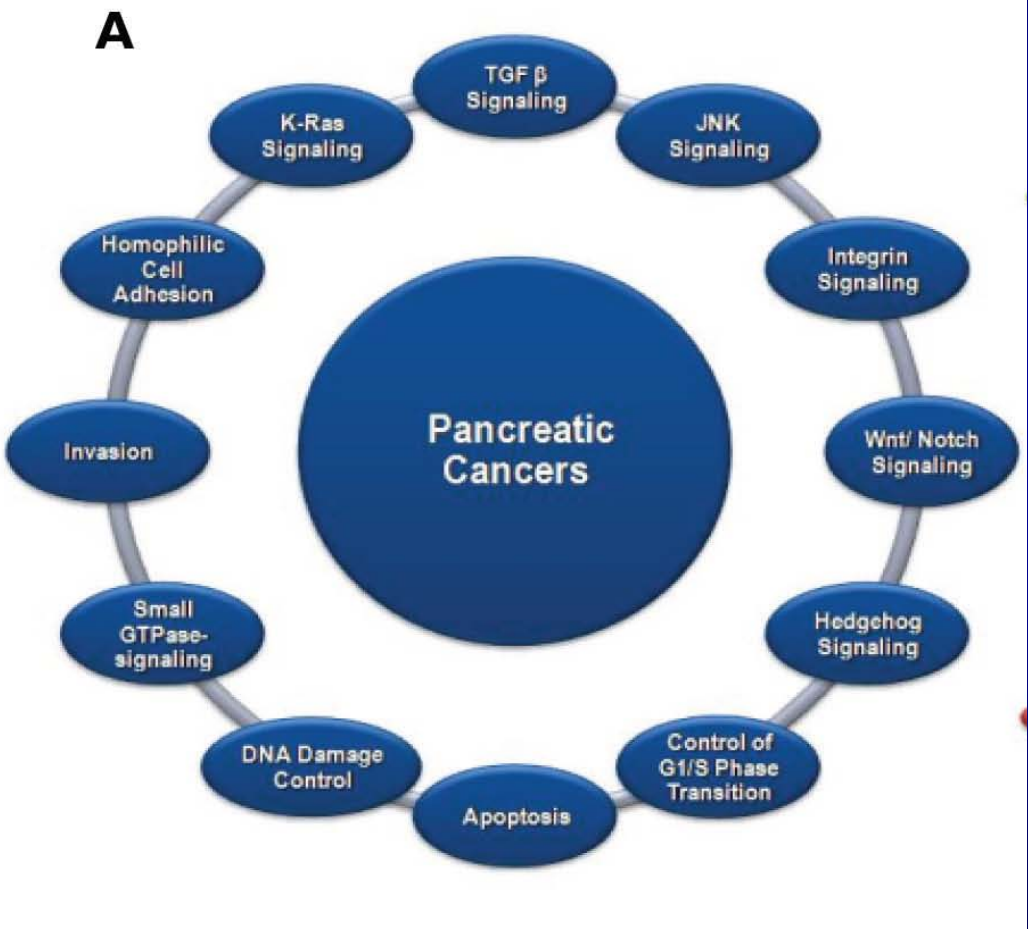
Advances in Basic Science

- Genomics
  - Dominant mutations & translocations
  - Regulatory RNA
- Signal Transduction
  - Cancer cell metabolomics
- Host/Tumor Interactions
  - Tumor stroma
  - Tumor immunology
- Animal models of human cancer

Molecular Events in Pancreatic Cancer

Exomic Sequencing/Mutational Analysis

- Average of 63 genetic alterations/cancer.
- Majority are point mutations.
- Core set of 12 cellular processes are altered.



Jones S, et al. Science 321:1801-1806, 2008

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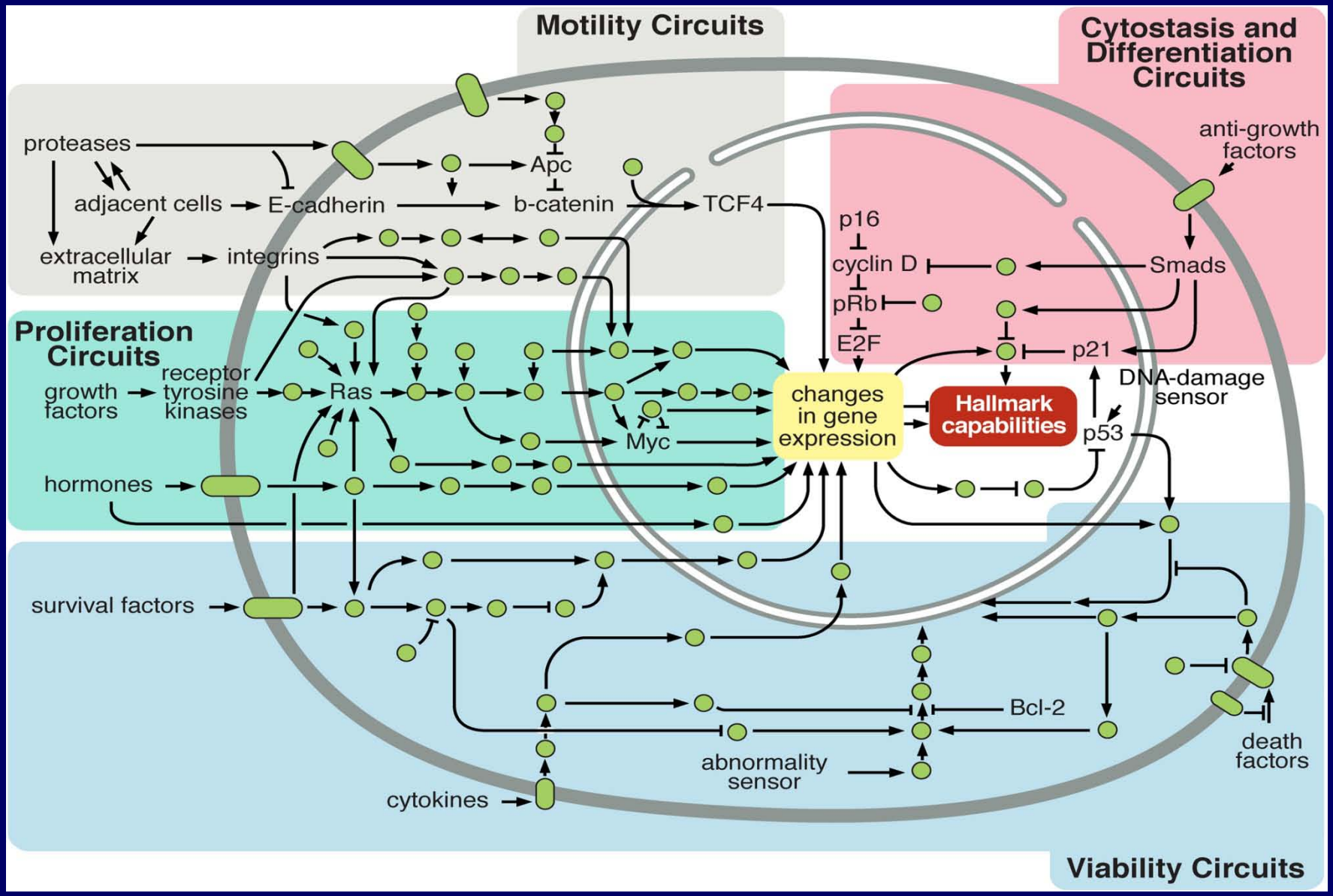
Signal Transduction



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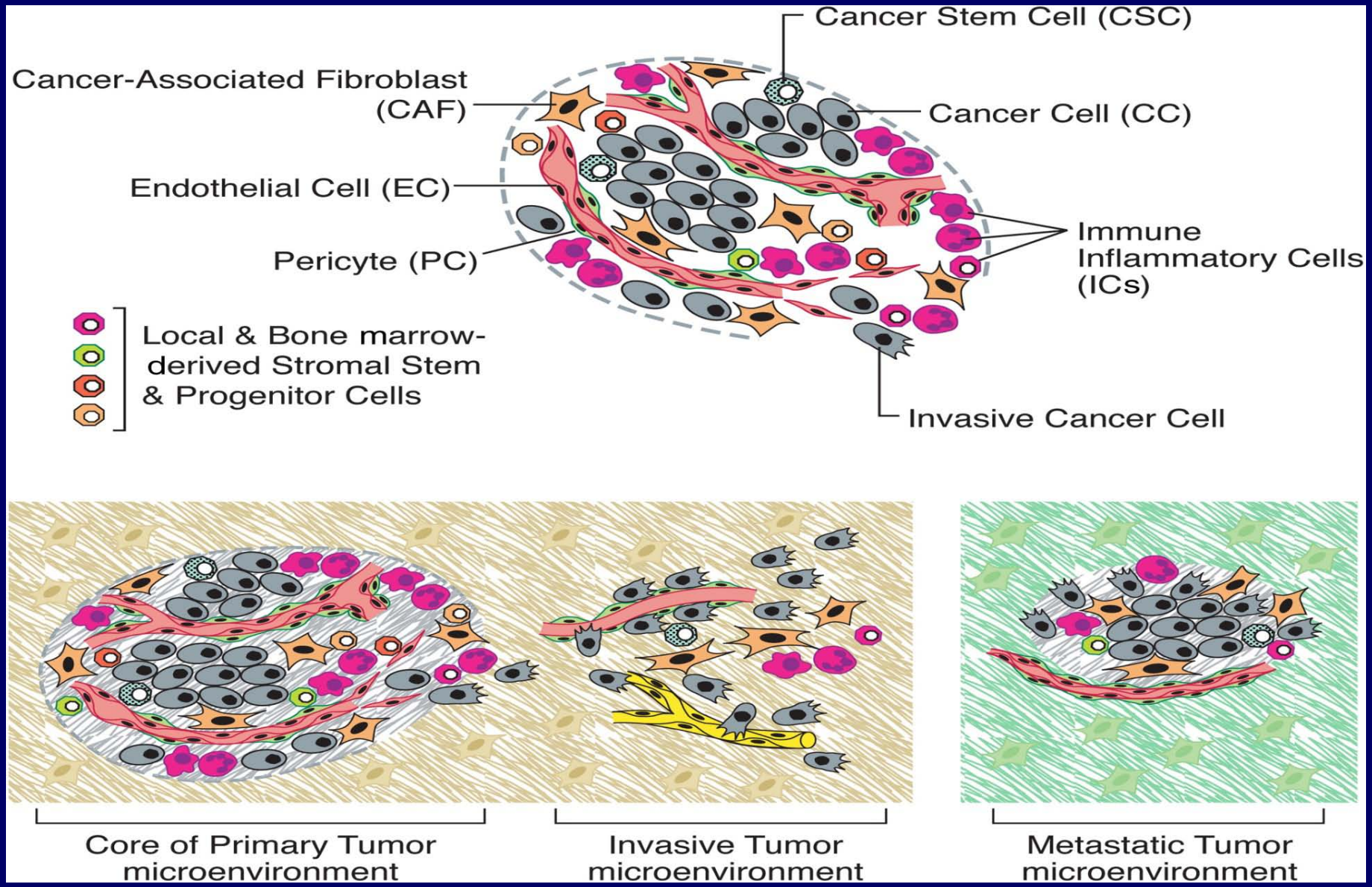
Host/Tumor Interactions



Hanahan and Weinberg. Cell 144:646-674, 2011

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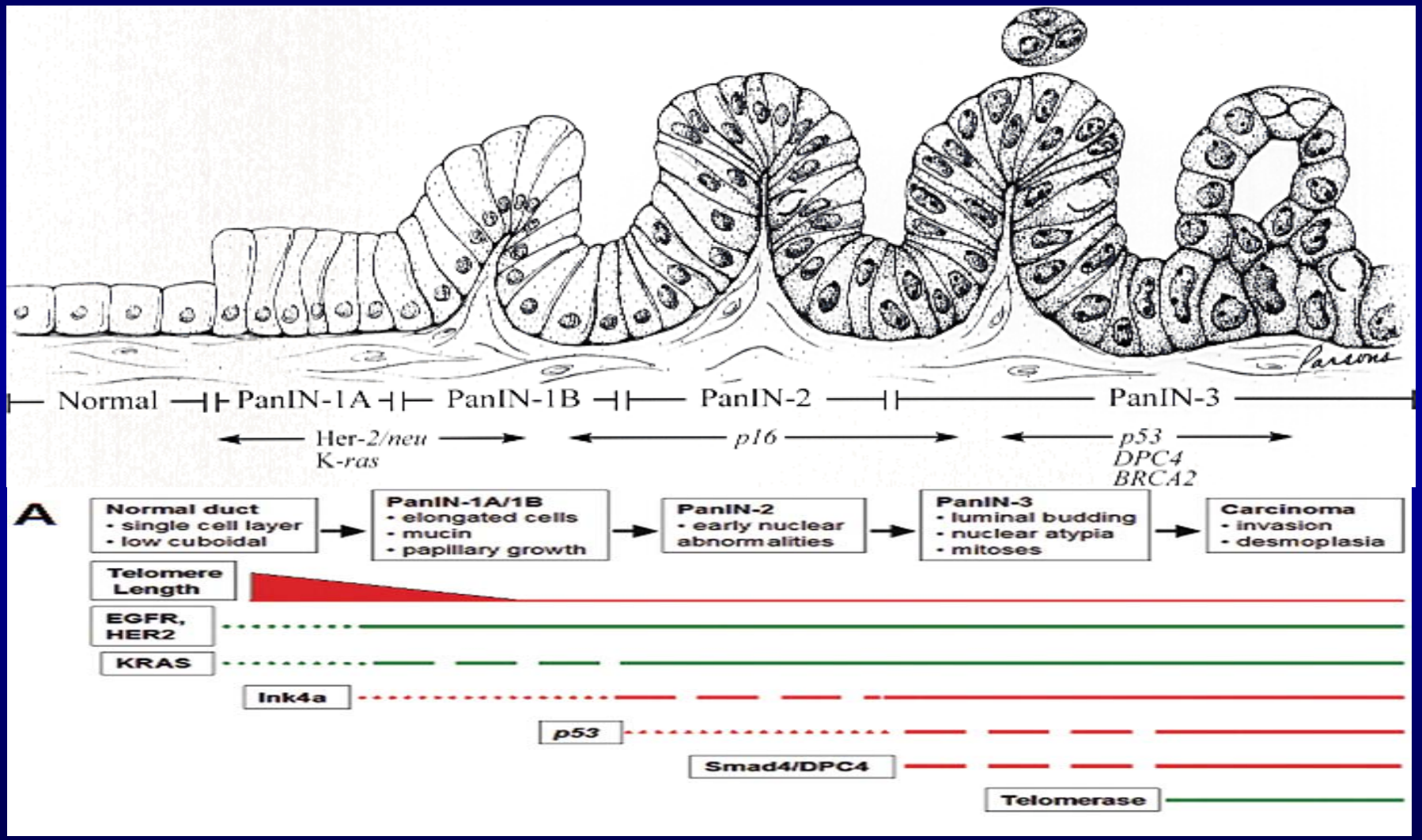
Molecular Progression Model

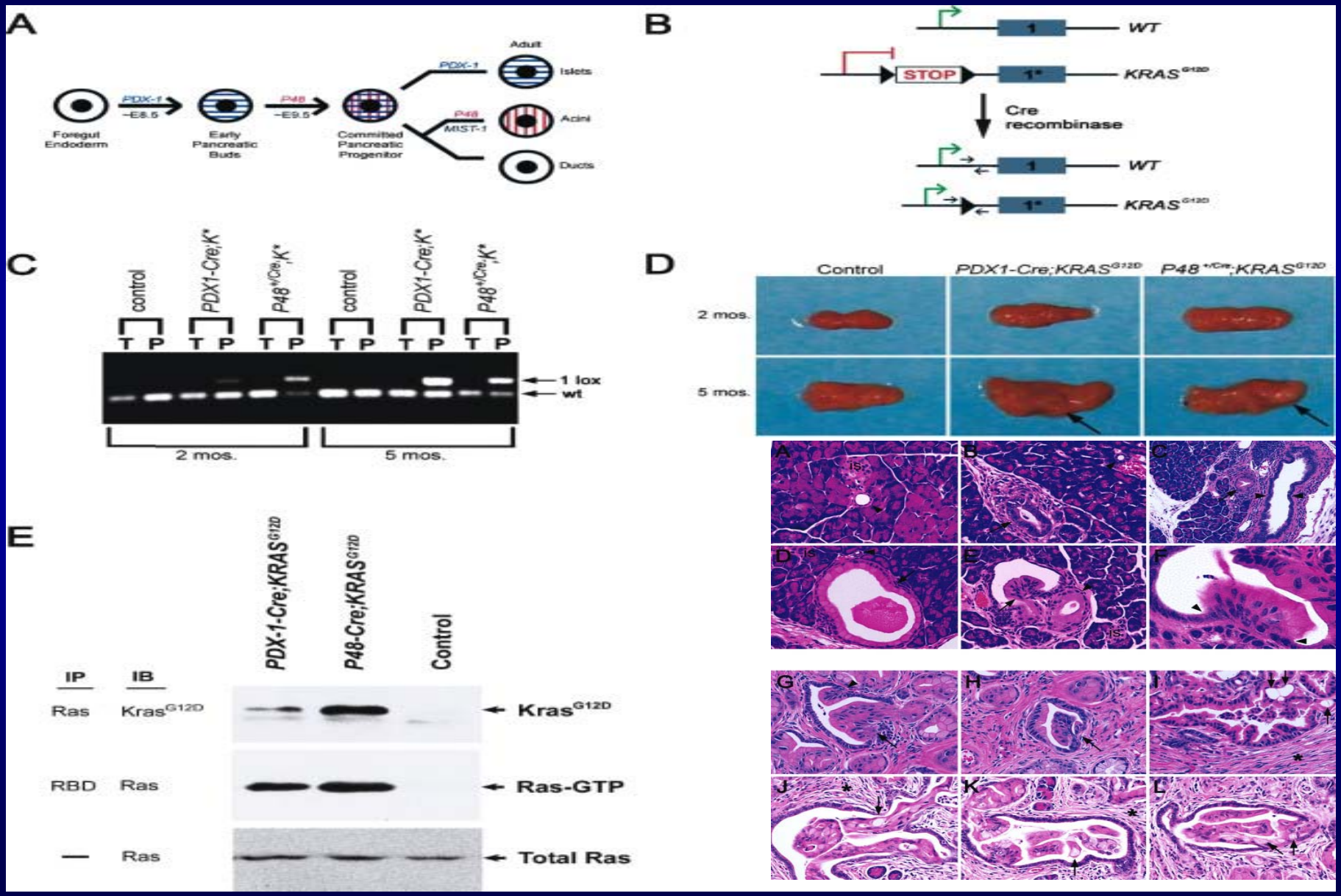
Pancreatic Intraepithelial Neoplasia (PanINs)



Hruban R, et al. Clinical Cancer Res, 2000

Aguirre A J et al. Genes Dev. 2003;17:3112-3126

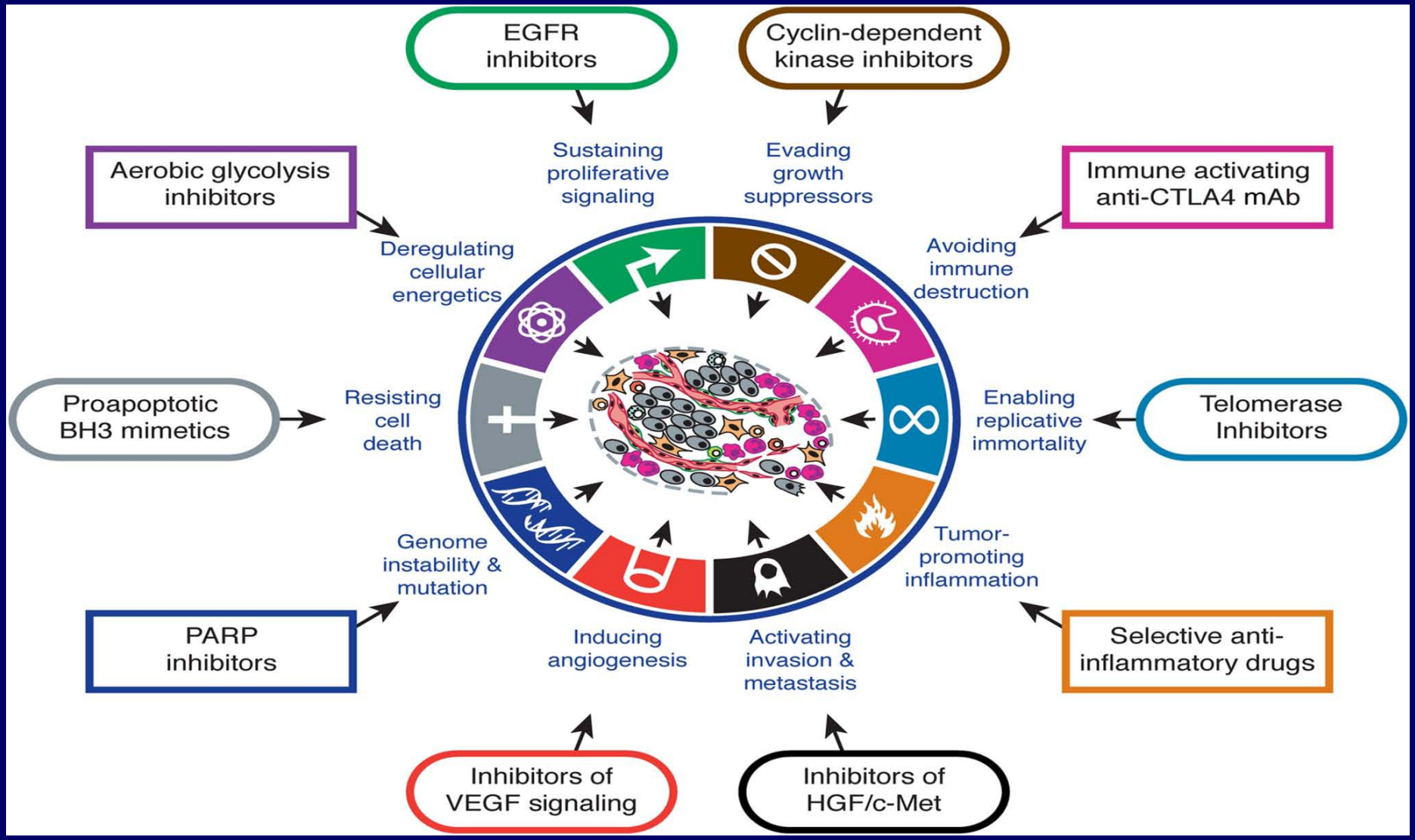
Animal model of human pancreatic cancer



Hingorani et al: Cancer Cell 4:437-450, 2003

Advances in Basic Science

Therapeutic Opportunities



Hanahan and Weinberg. Cell 144:646-674, 2011

Translating the Science of Oncology to Patient Care

Phase II Trials - A Critical Juncture in the Development of Successful Therapies

Phase II Trial Design

- Maximize the chances that you will draw an accurate conclusion about treatment effect
  - Choice of patient population
  - Treat a sufficient number of patients that you can be confident in the conclusion you draw…treatment is active or not.
  - Don’t treat too many participants with an inactive treatment (“early stopping rules”)
  - Optimal dose/schedule of treatment

Interpretation of a Phase II Trial
How will the results be used?

- Provide a “go/no go” decision regarding subsequent testing, usually in a phase III trial.
  - Negative predictive value high
  - Positive predictive value low
    - Ratain MJ, Clin Cancer Research 11:5661, 2005
- High degree of “activity” in an area of unmet medical need can result in accelerated approval

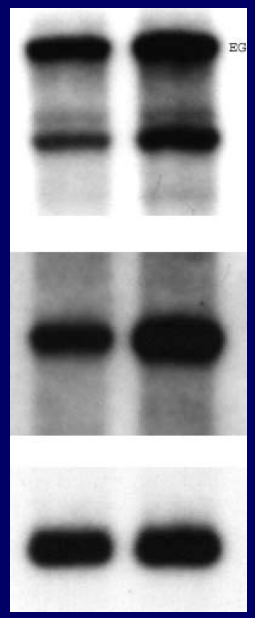
Phase II Trials
Conclusions

- Exploratory studies and rarely are definitive
  - Require confirmation
- Results must be interpreted cautiously
  - Especially in the absence of concurrent controls
- Critical assessment of efficacy and acceptable safety – important in the decision to move to phase III studies

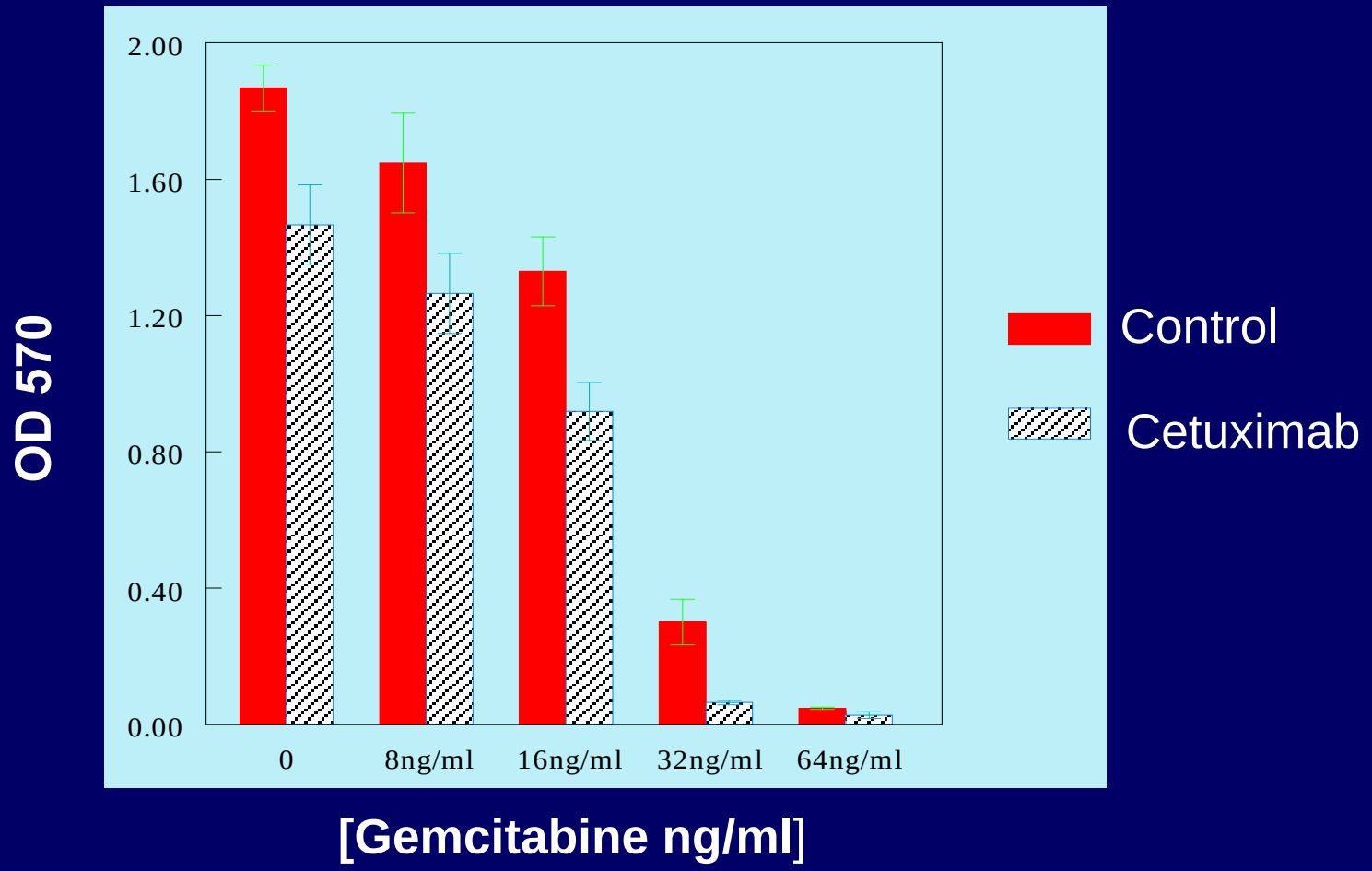
Challenges Inherent in Translating Cancer Science to the Clinic

- **Targeting EGFR in pancreatic cancer**
  - **In vitro effects on pancreatic carcinoma cell lines**
  - **Growth and metastasis of orthotopic pancreatic tumors**
  - **Animal studies combining gemcitabine and Cetuximab**
  - **Human studies combining gemcitabine and Cetuximab**

Expression of EGF-R and TGF-a in FG and L3.6pl Human Pancreatic Carcinoma cells



In vitro growth Inhibition of L3.6pl Pancreatic Carcinoma Cells with Cetuximab + Gemcitabine



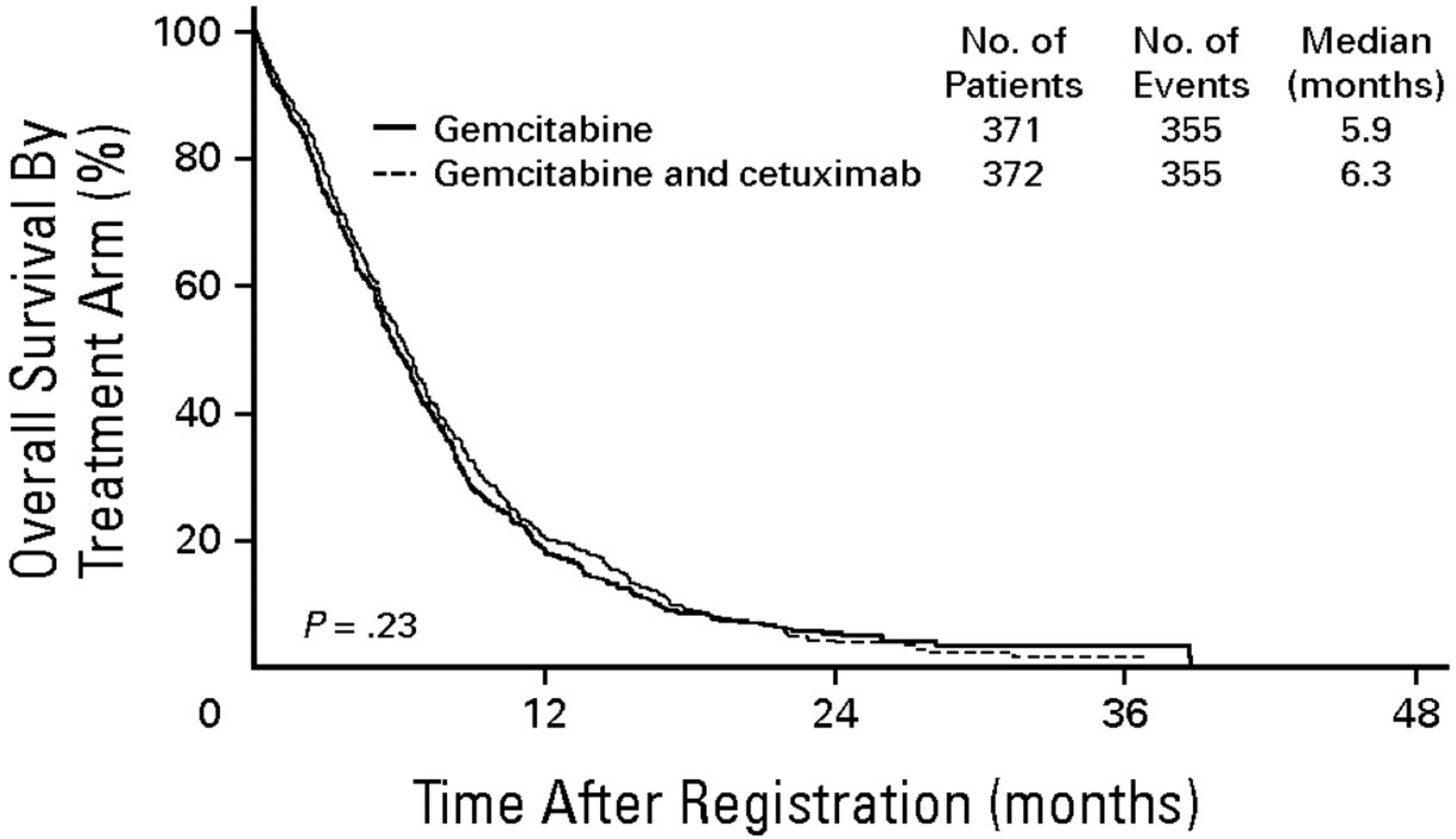
Phase II Trial of Cetuximab in Advanced Pancreatic Cancer

Disease Control Following Cetuximab and Gemcitabine

- The median time to progression: 105 days
  - 63 days for gemcitabine*
- Progression free survival at 1-year: 17.5%
  - 9% for gemcitabine
- Median survival: 202.5 days
  - 169.5 days for gemcitabine
- Survival at 1 year: 32.5%
  - 18% for gemcitabine

*Burris, et al. J Clin Onc 15:2403-2413, 1997.

Overall Survival – Advanced Pancreas Cancer Gemcitabine alone or Gemcitabine plus Cetuximab.



Philip P A et al. JCO 2010;28:3605-3610

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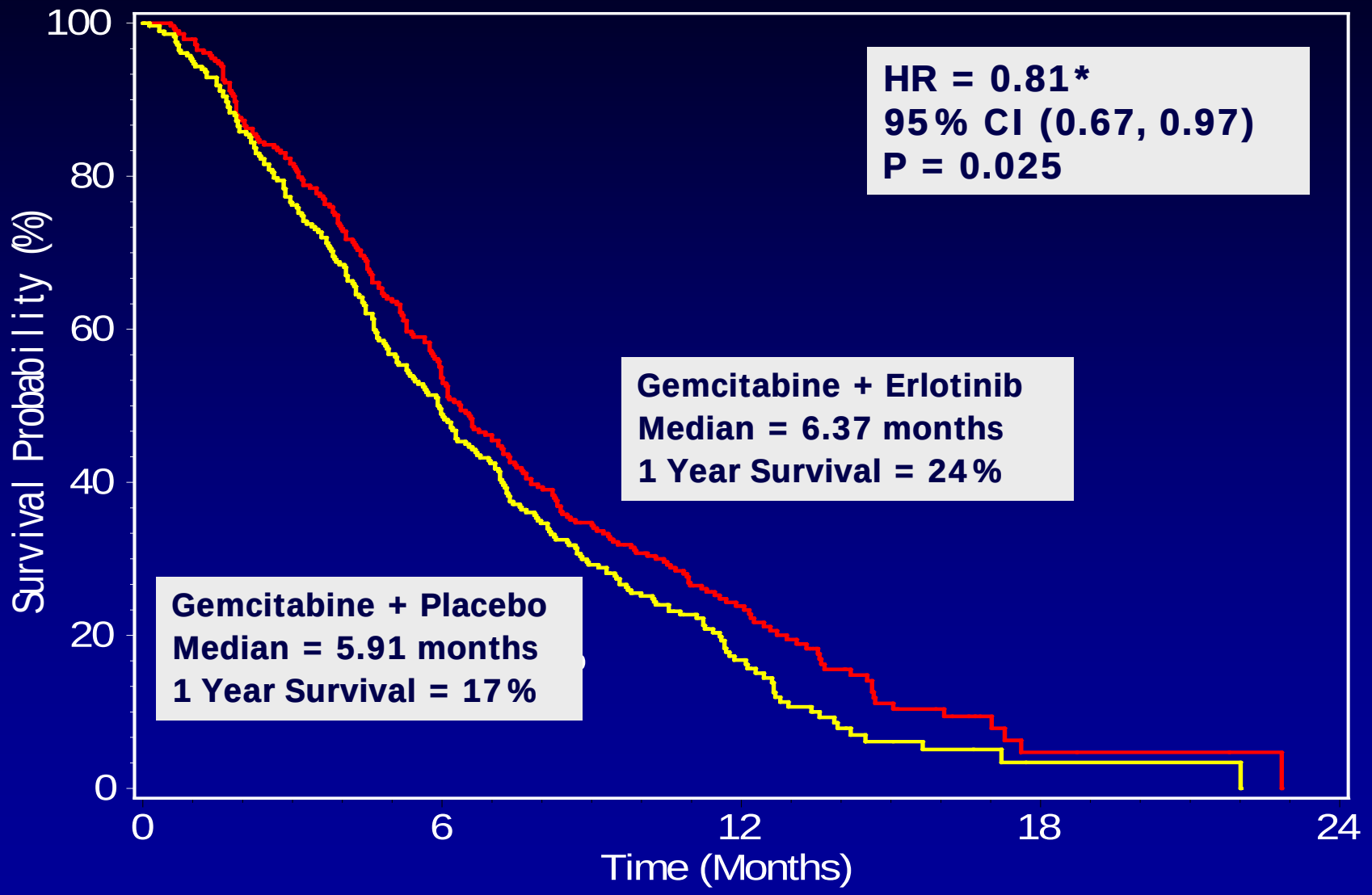
Erlotinib - Overall Survival for All Patients



* Adjusted for PS, pain and disease extent at randomization

Take Home Messages

- Unselected phase II designs may not be adequate for development of many targeted agents
- Target validation is complex
- Identification of predictive biomarkers – even more difficult
- Future requirements
  - Improved preclinical models
  - Predictive biomarkers

Can Novel Clinical Trial Designs Increase Success Rates?

- Phase 0 Trials
- Randomized discontinuation designs
  - Sorafenib
- Adaptive designs
  - BATTLE NSCLC trial

Translating the Science of Oncology to Patient Care

Phase 0 Trials

Exploratory IND studies

<u>OVERALL GOAL:</u> Provide initial rationale and guiding principles for further agent development based on studies in humans.

Characteristics of a Phase 0 trial

- First-in-human, single agent or combination:
  - Limited number of subjects (≈10-12)
  - Very limited drug exposure
    - Low, theoretically non-toxic doses
    - Limited duration of dosing (≈ ≤7 days)
    - One course
  - No therapeutic (or diagnostic) intent
    - Ethical issues
- Conducted prior to traditional Phase 1 trial
- Can be initiated with a less extensive pre-clinical data package than traditional Phase 1 trials

Phase 0 Trials may Improve the Efficiency of Subsequent Trials

- Determine whether a pre-specified mechanism of action can be observed in humans
- Provide PK/PD data for an agent prior to definitive Phase 1-2 testing
  - Eliminating an agent early in clinical development because of poor PD or PK properties
- Refine biomarker assay using human tumor tissue and/or surrogate tissue
- Evaluate PD and/or PK of two or more analogs directed at the same target and select the most promising candidate for further development
- Evaluate biodistribution and target effects with imaging

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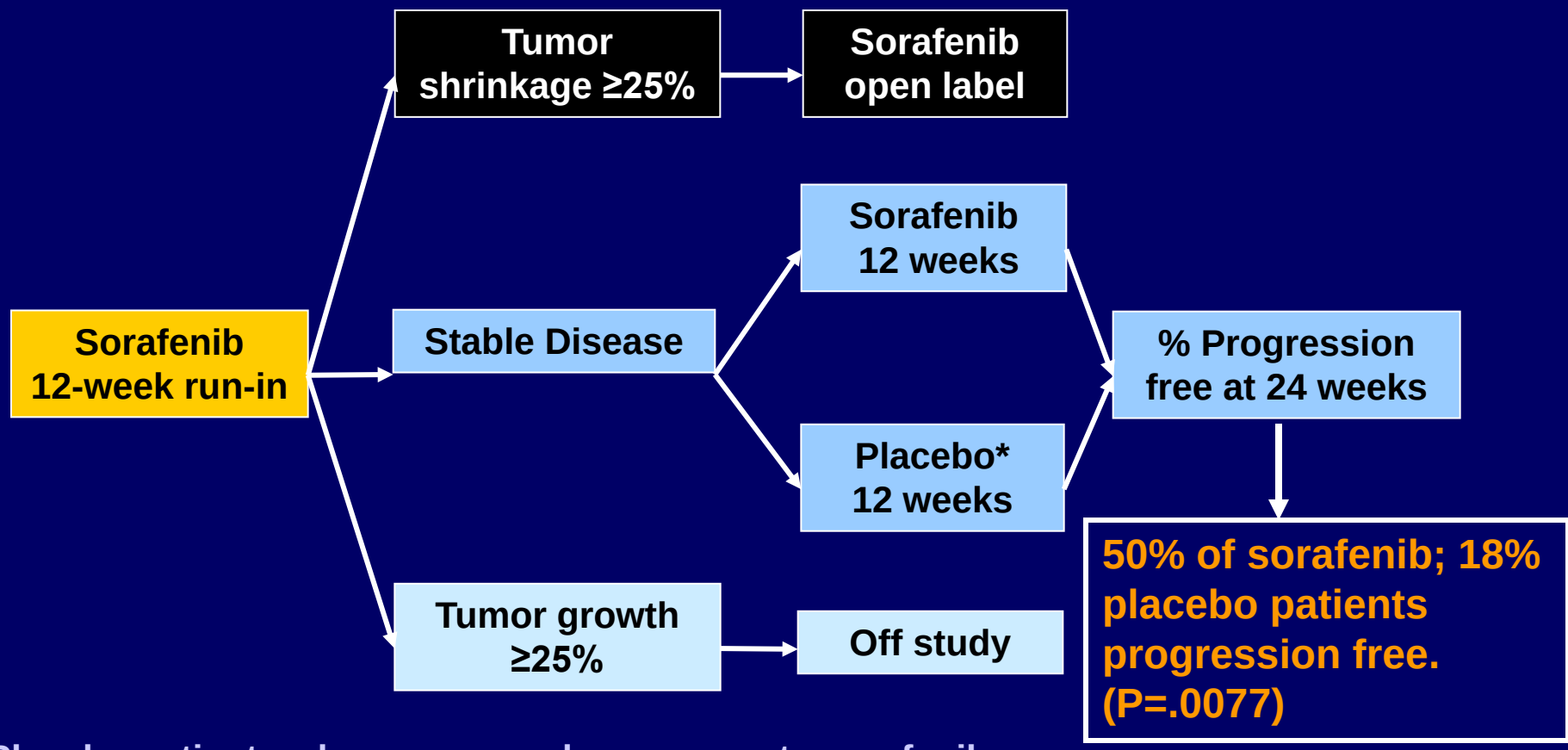
Randomized Discontinuation Trials

- Randomized discontinuation trials enable assessment of disease stabilization effects through an enrichment design comprising a run-in period, followed by randomization of potential ‘responders’ to study drug or placebo.
- Particularly useful for diseases where “response” has been a poor surrogate for clinical effectiveness.
  - Melanoma
  - Renal Cancer

Randomized Discontinuation Design

Sorafenib



*Placebo patients who progressed cross over to sorafenib

Ratain et al. JCO 24:2505-2512, 2006

Can Novel Clinical Trial Designs Increase Success Rates?

- Phase 0 Trials
- Randomized discontinuation designs
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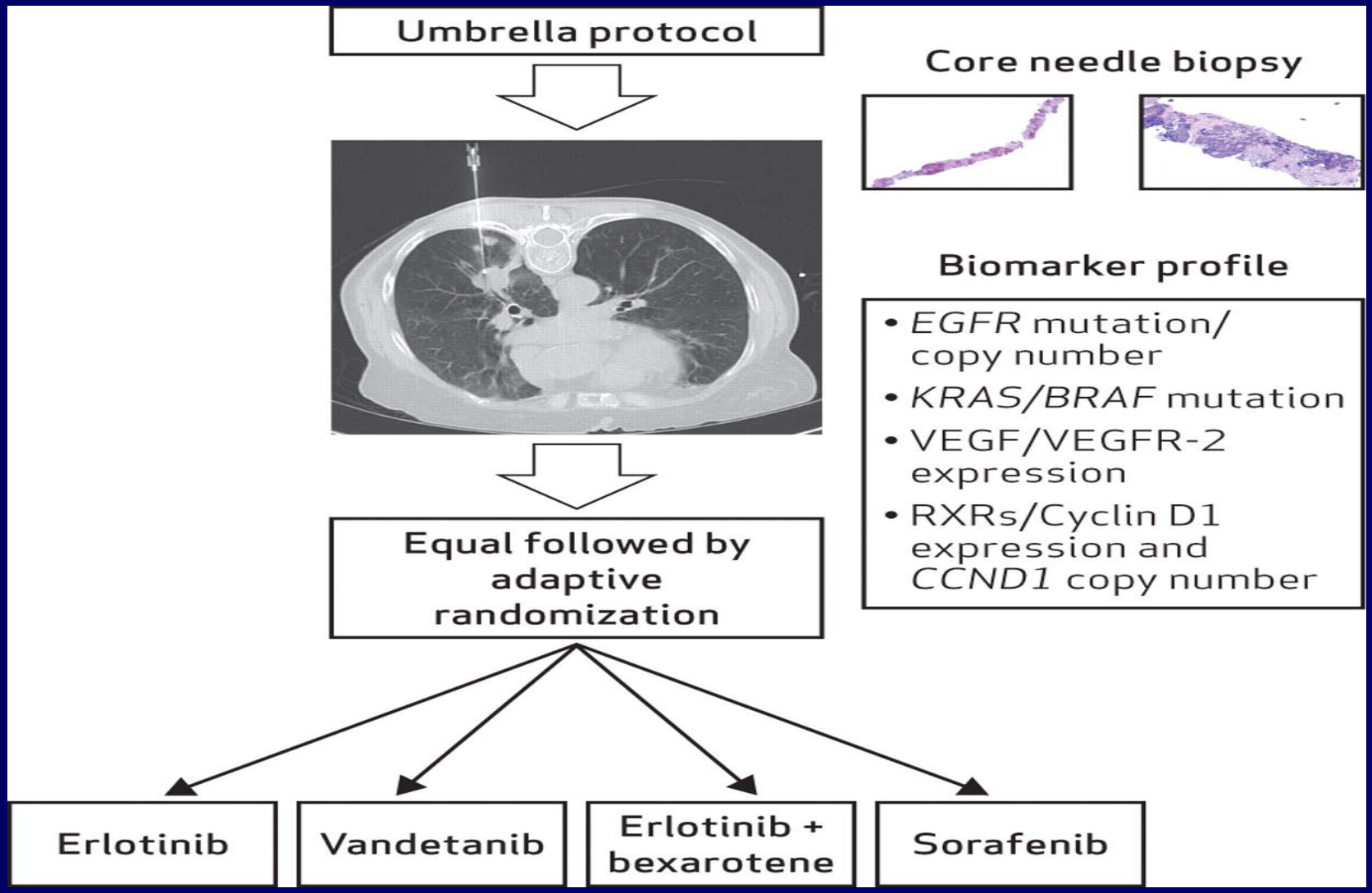
  - BATTLE NSCLC trial

Adaptive Trial Designs

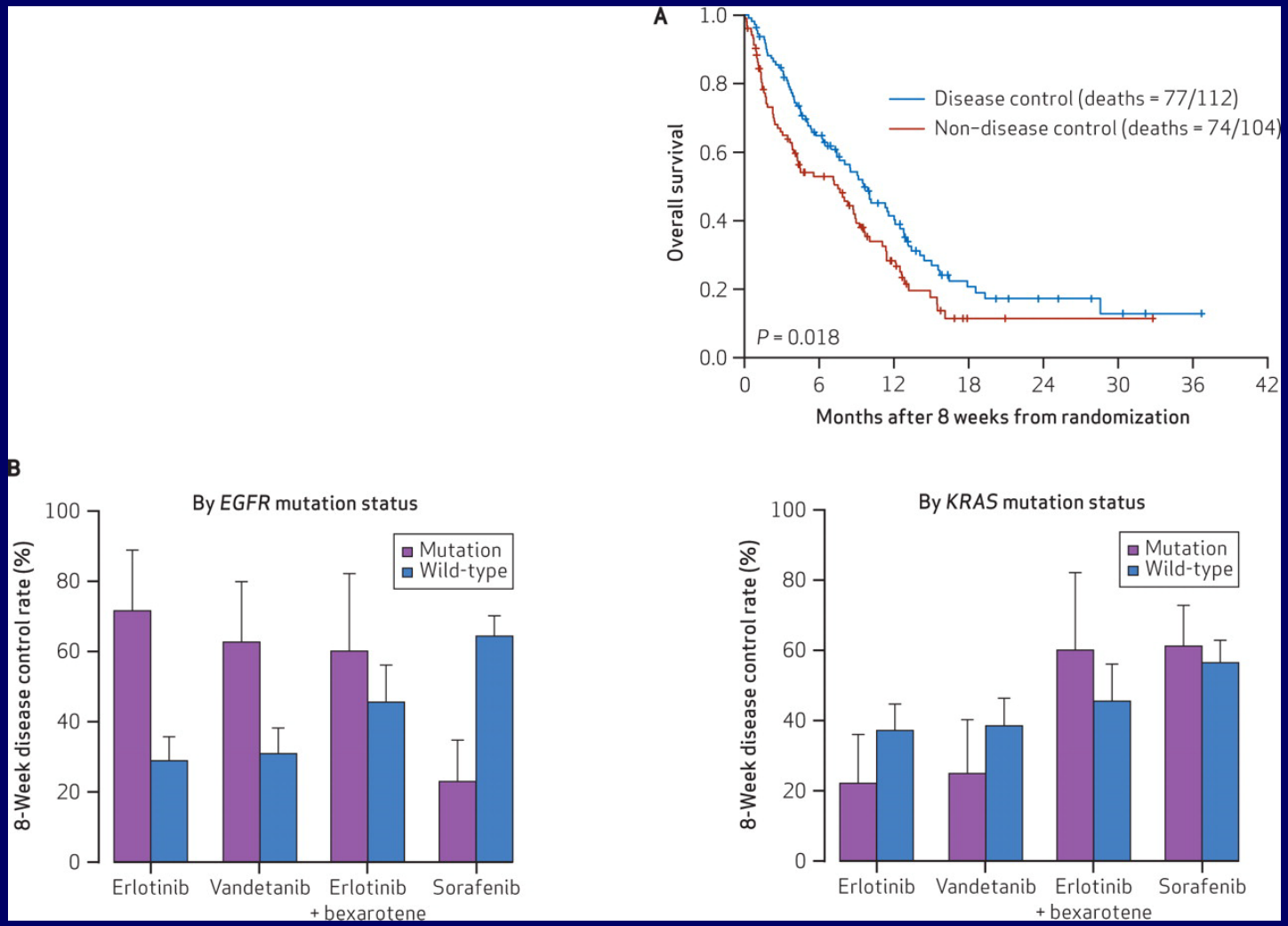
- **Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination - BATTLE**

Schema for BATTLE study.



Kim E S et al. Cancer Discovery 2011;1:44-53

Major efficacy results of BATTLE study.



Kim ES, et al. Cancer Discovery 2011;1:44-53

BATTLE Trial for NSCLC

Accomplishments

- Biopsy and assignment to treatments feasible
- Some results confirm current understanding of predictive biomarkers

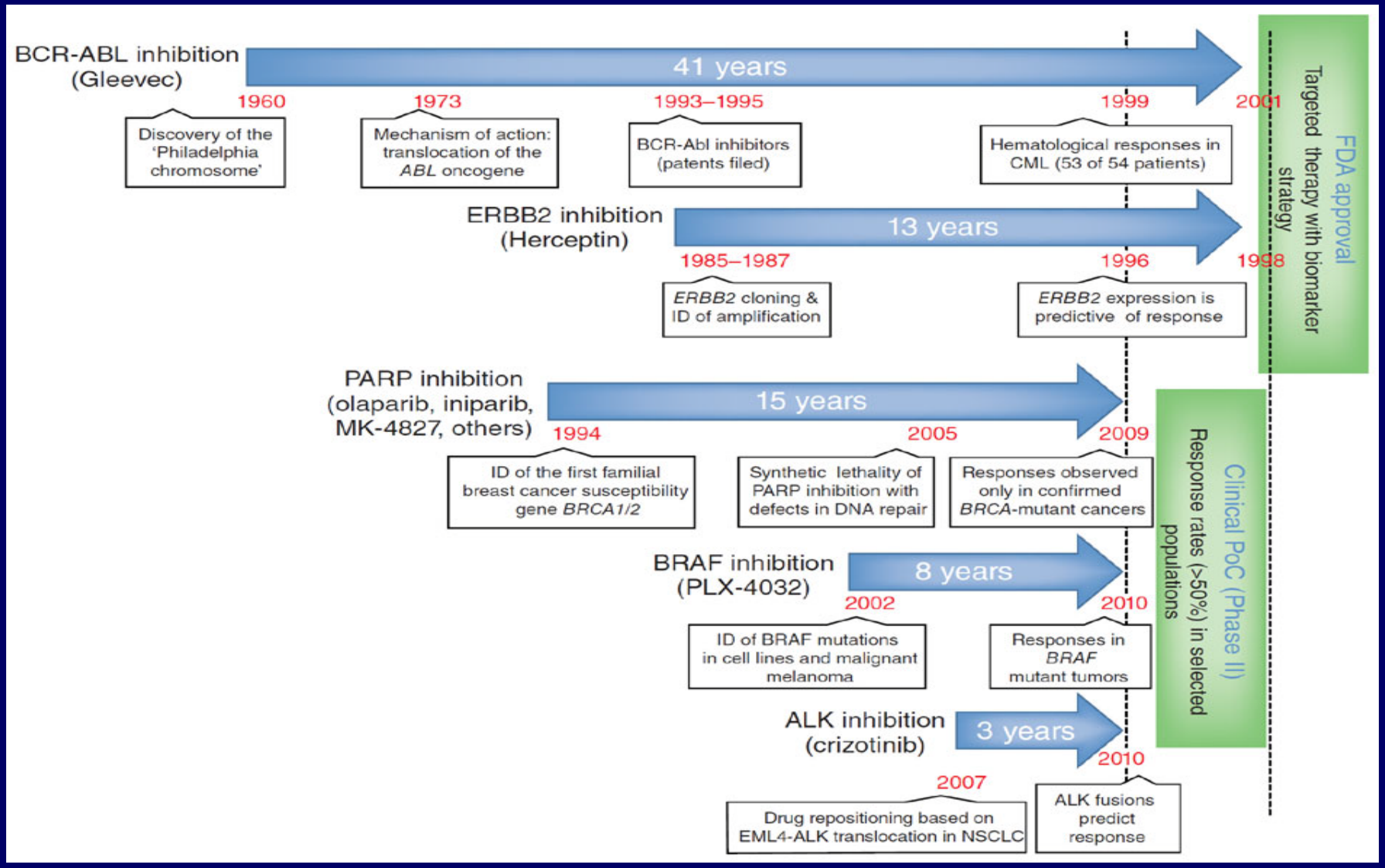
Questions

- Results are hypothesis generating rather than validating
- Assay cutoffs unclear and biomarkers do not remain state-of-the-art
- Large patient numbers
- Expense

Can Genomic Medicine Lead the Way?

- Identification of targetable dominant oncogenes and translocations leads to rapid alterations in the standard of oncologic care
  - Examples
    - Bcr/Abl – imatinib
    - EGFR* - erlotinib
    - Alk/EML4 translocation – crizotinib
    - BRAF* - vemurafenib

Can Genomic Medicine Lead the Way?

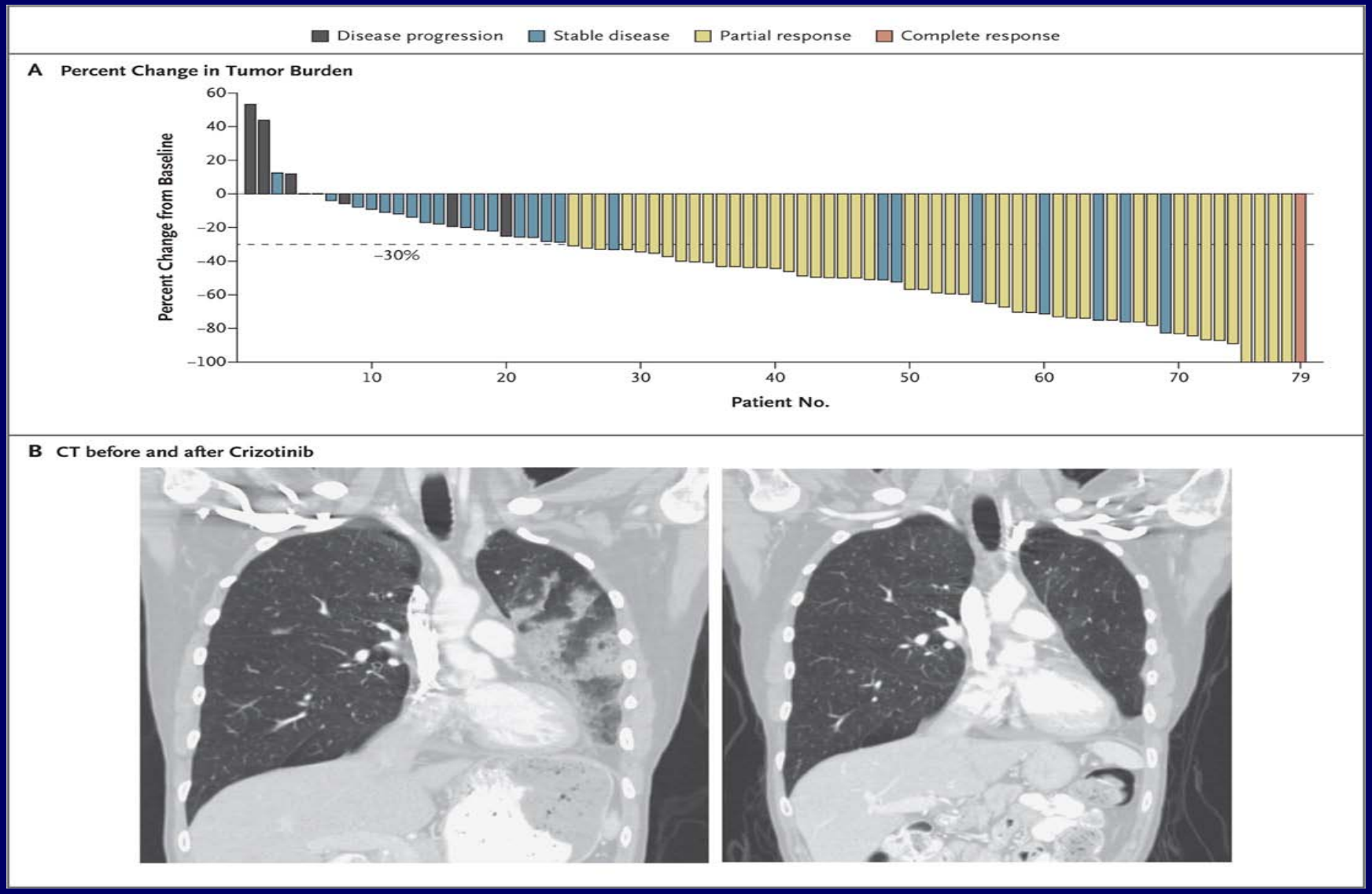


Chin L, et al. Nature Medicine 17:297-303, 2011

Crizotinib in Alk+ NSCLC

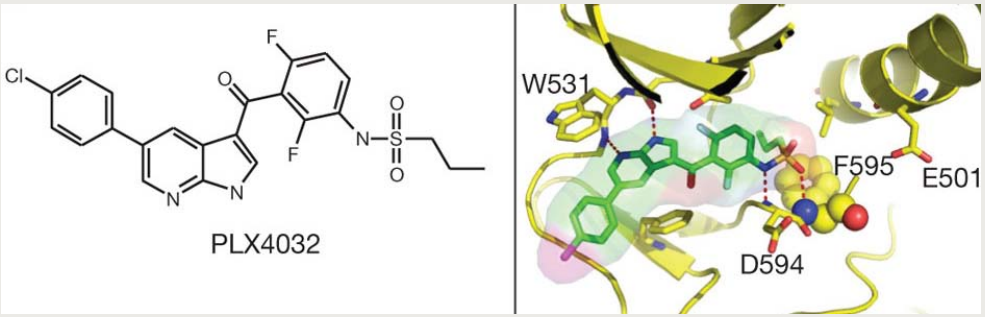
- Two Phase II trials
  - Study A ORR 50%; duration of response 42 weeks
  - Study B ORR 61%; duration of response 48 weeks
- FDA accelerated approval 8/26/11.

Crizotinib in Alk+ NSCLC



Kwak EL, et al. NEJM 363:1693-1703, 2010

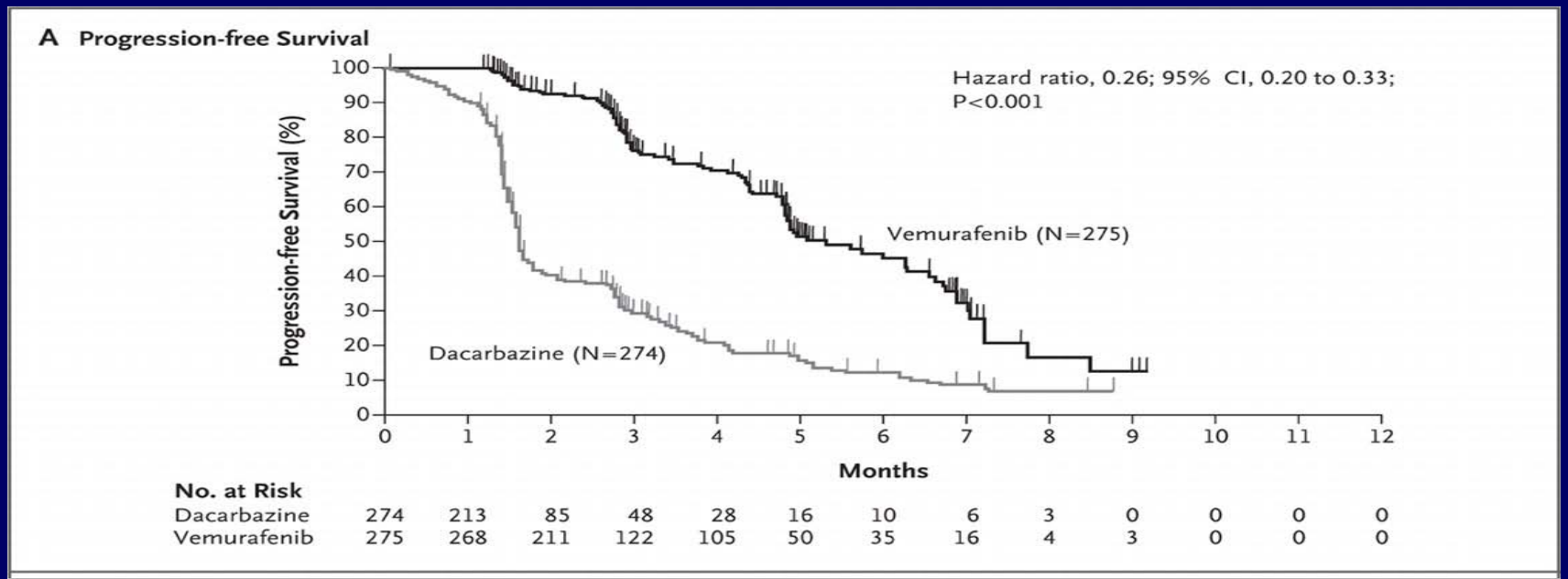
Mutant V600E BRAF Inhibitor: Vemurafinib

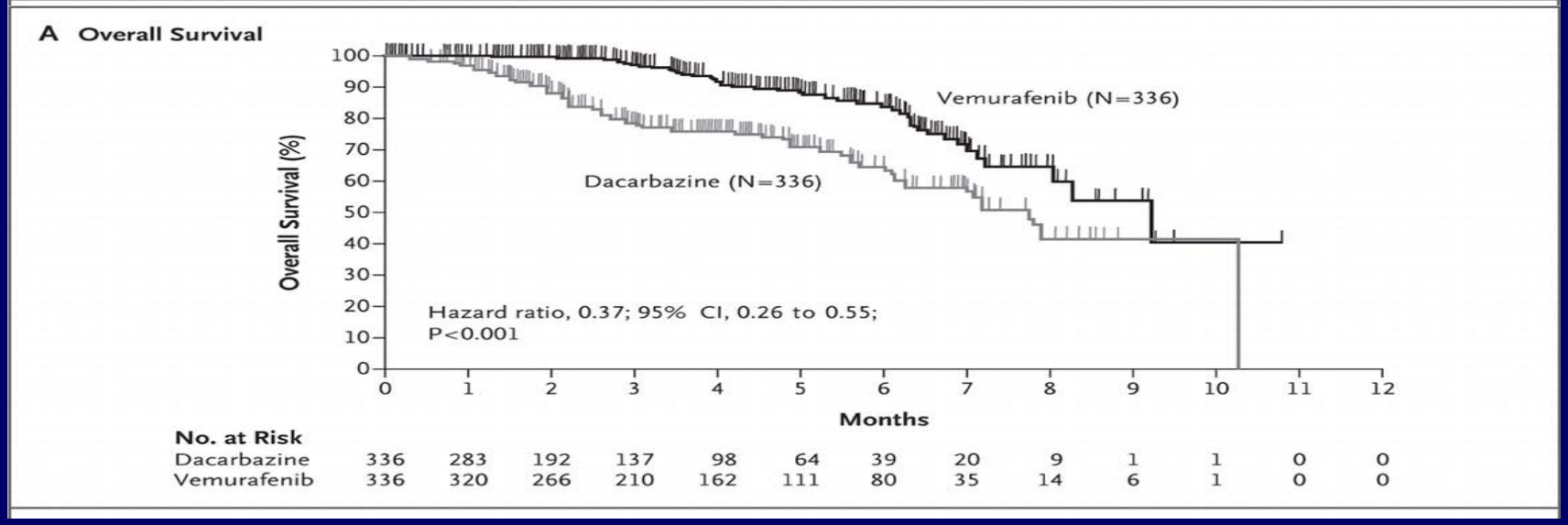


Phase I escalation (n=55) → Phase IB: Patients with V600E mutations → Melanoma (n=32); Colorectal (n=21)

Flaherty et al, NEJM 2010, Kopetz et al ASCO 2010

Vemurafenib in Melanoma

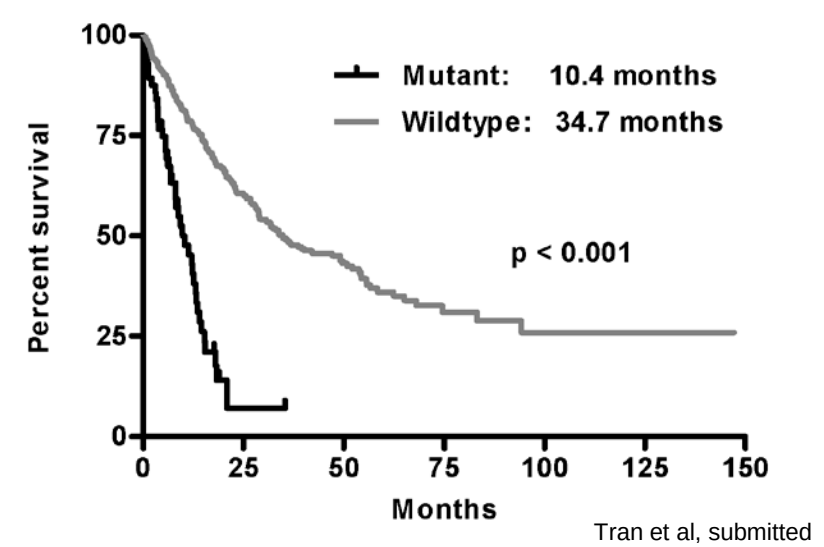




Chapman PB, et al. NEJM 364:2507=2516, 2011

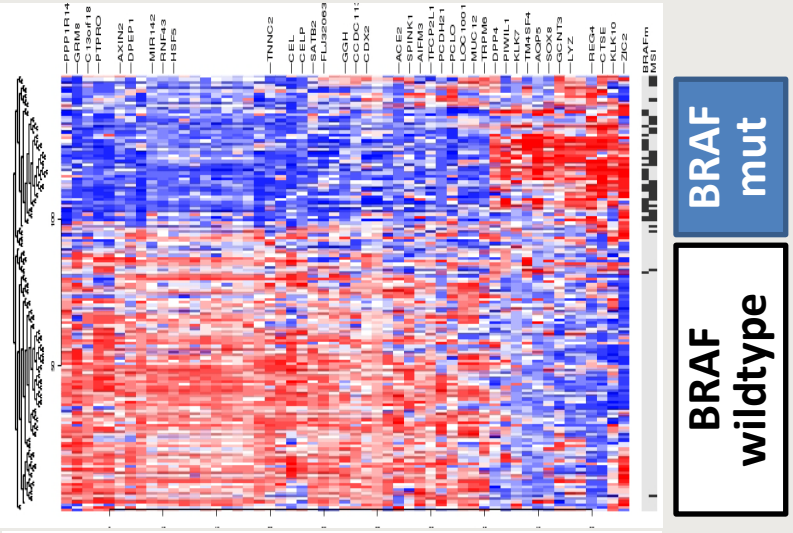
BRAF mutations in Colon Cancer

BRAF mutation appears to define a clinically **distinct** subset of mCRC tumors



Tran et al, submitted

…that is biologically distinct from other CRC



Tejpar et al, ASCO '10

Can we use BRAF inhibitors in this subset of patients?

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

BRAF Inhibitor Vemurafinib in CRC

Small 21 patient study, Phase IB Expansion Cohort

Only predicted to work in BRAF^{mut} tumors (6-8%)

Would have required a 300 patient study without enrichment to acquire the same information in patients with BRAF^{mut} tumors

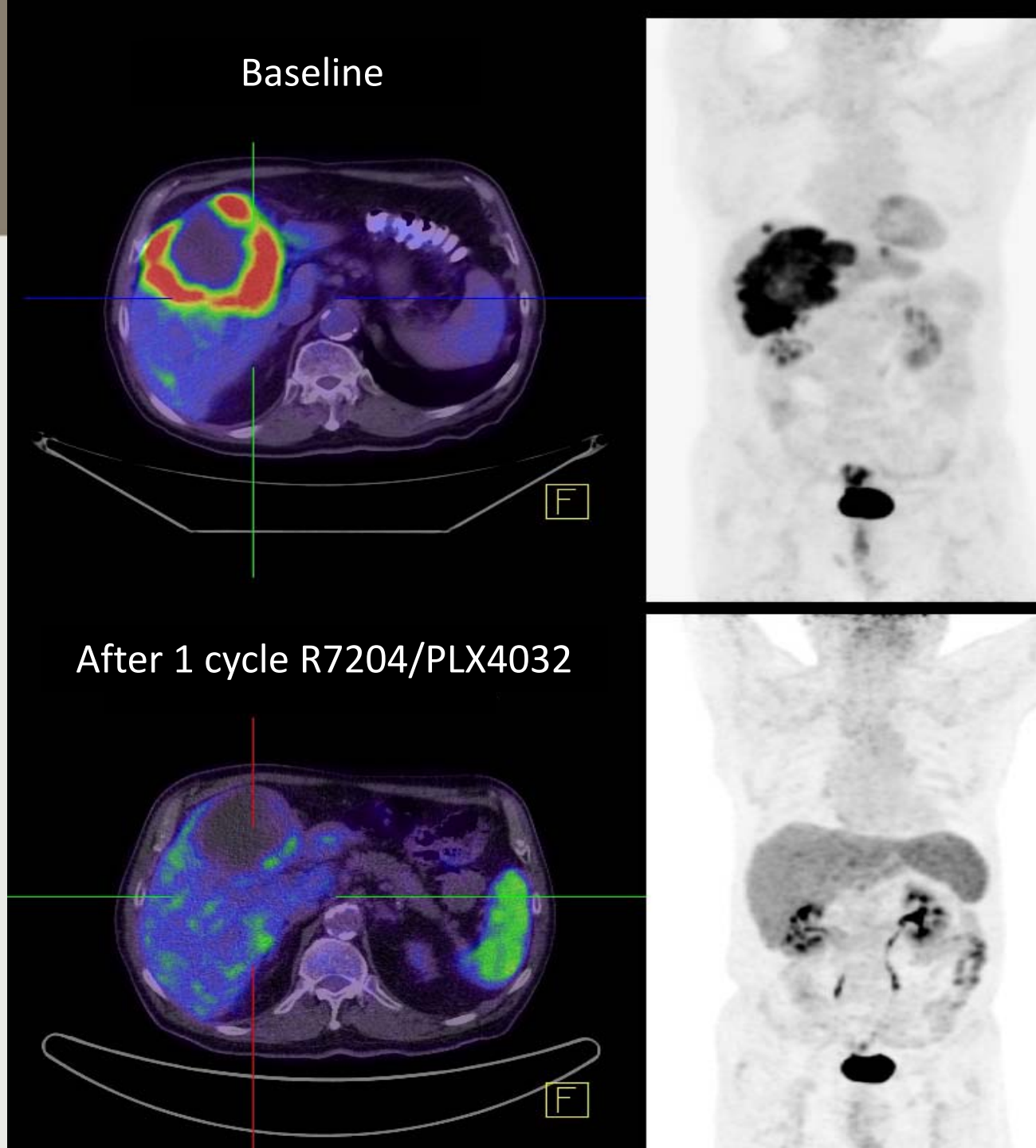
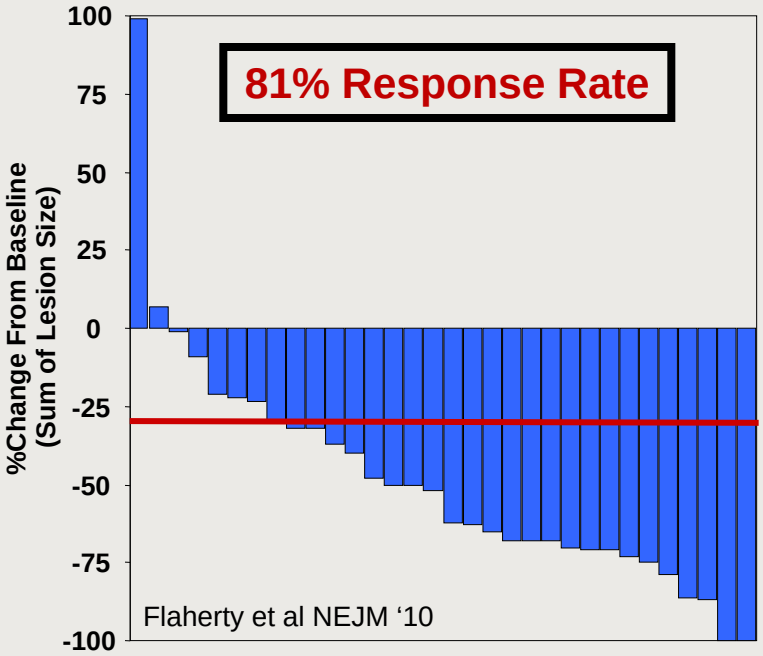


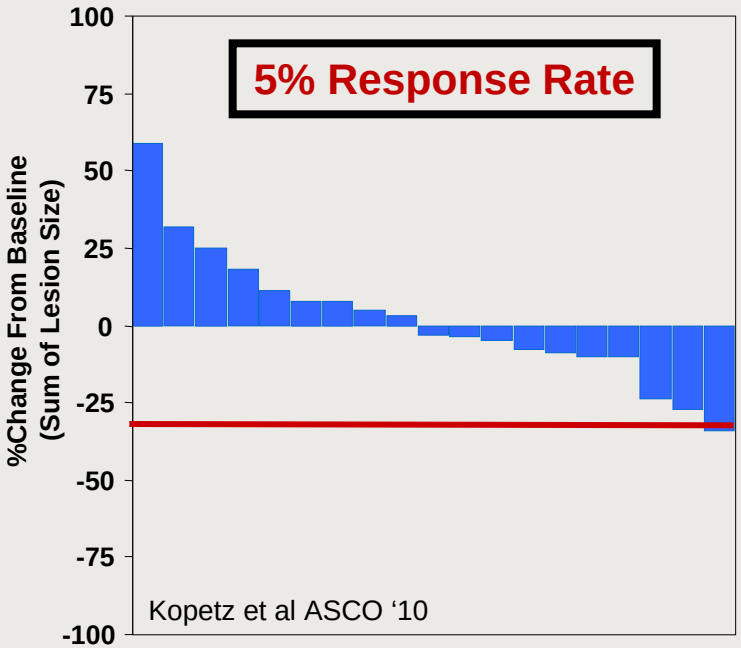
Figure compliments of Jayesh Desai
Kopetz, et al. ASCO '10

Vemurafenib in Colon Cancer

Refractory Melanoma



Refractory Colorectal



Hurdle : Oncogene mutation does not imply oncogene dependence

Understand the biological context in which particular mutations occur.

Challenges for the Future

- Cancer Genomics to define dominant mutations/translocations
  - Therapeutic target and predictive biomarker are the same!
  - Overall molecular context matters
- Increase sophistication of preclinical models with greater emphasis on identification of predictive biomarkers.

Concluding Thoughts

- When the science dictates, current clinical trial designs are fully capable of identifying highly active agents.
- It remains uncertain whether novel clinical trial designs can substitute for lack of basic scientific understanding of cancer.
- Generation of basic science data <u>with potential for high clinical impact</u> should remain the highest priority.

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