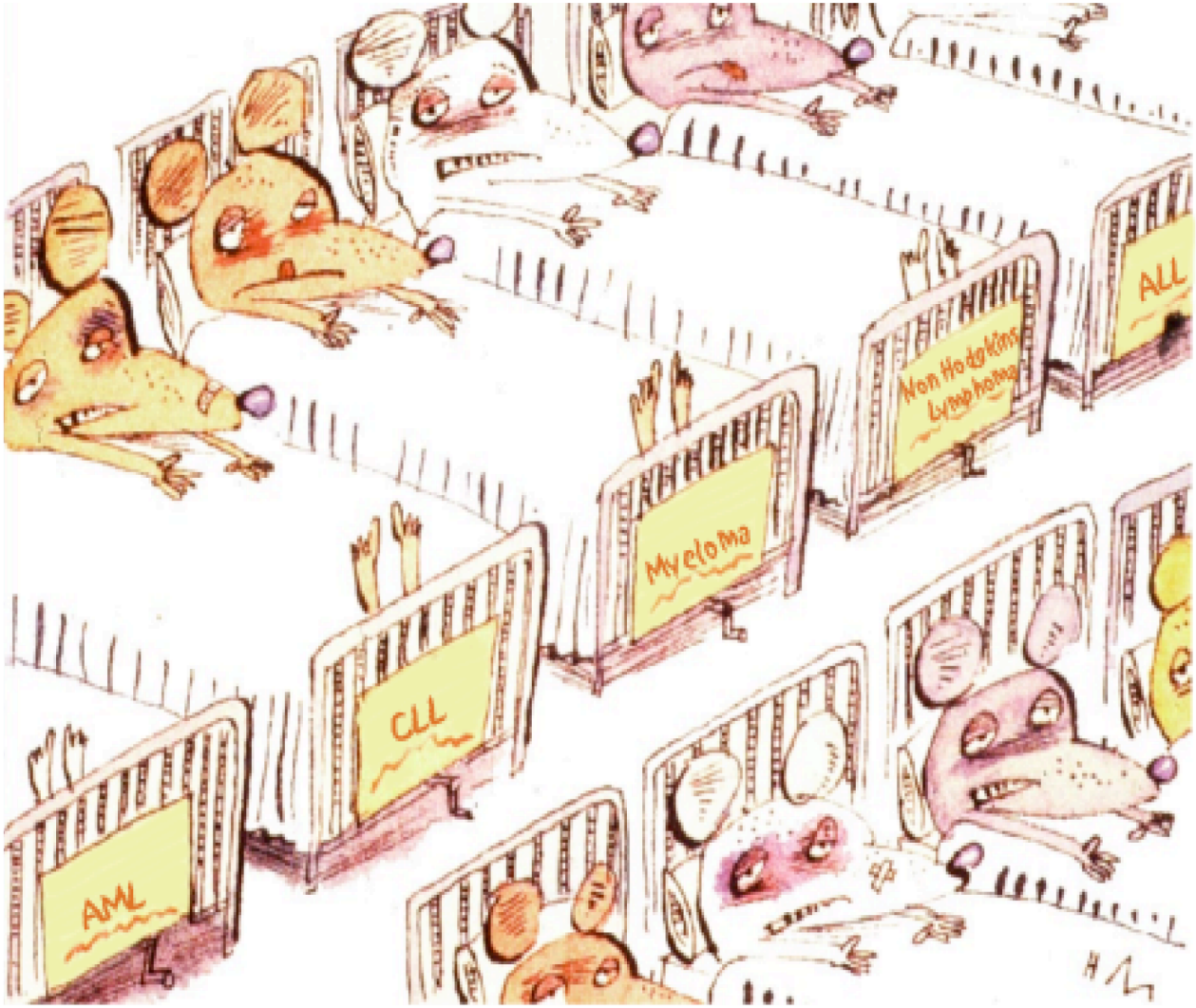
Advanced Tumor Biology Platforms for Drug Advancement

Drug Discovery & Designing -2015, Frankfurt, Germany

Neal Goodwin, PhD
Vice President, Corporate Research Development
Champions Oncology, Inc.
ngoodwin@championsoncology.com

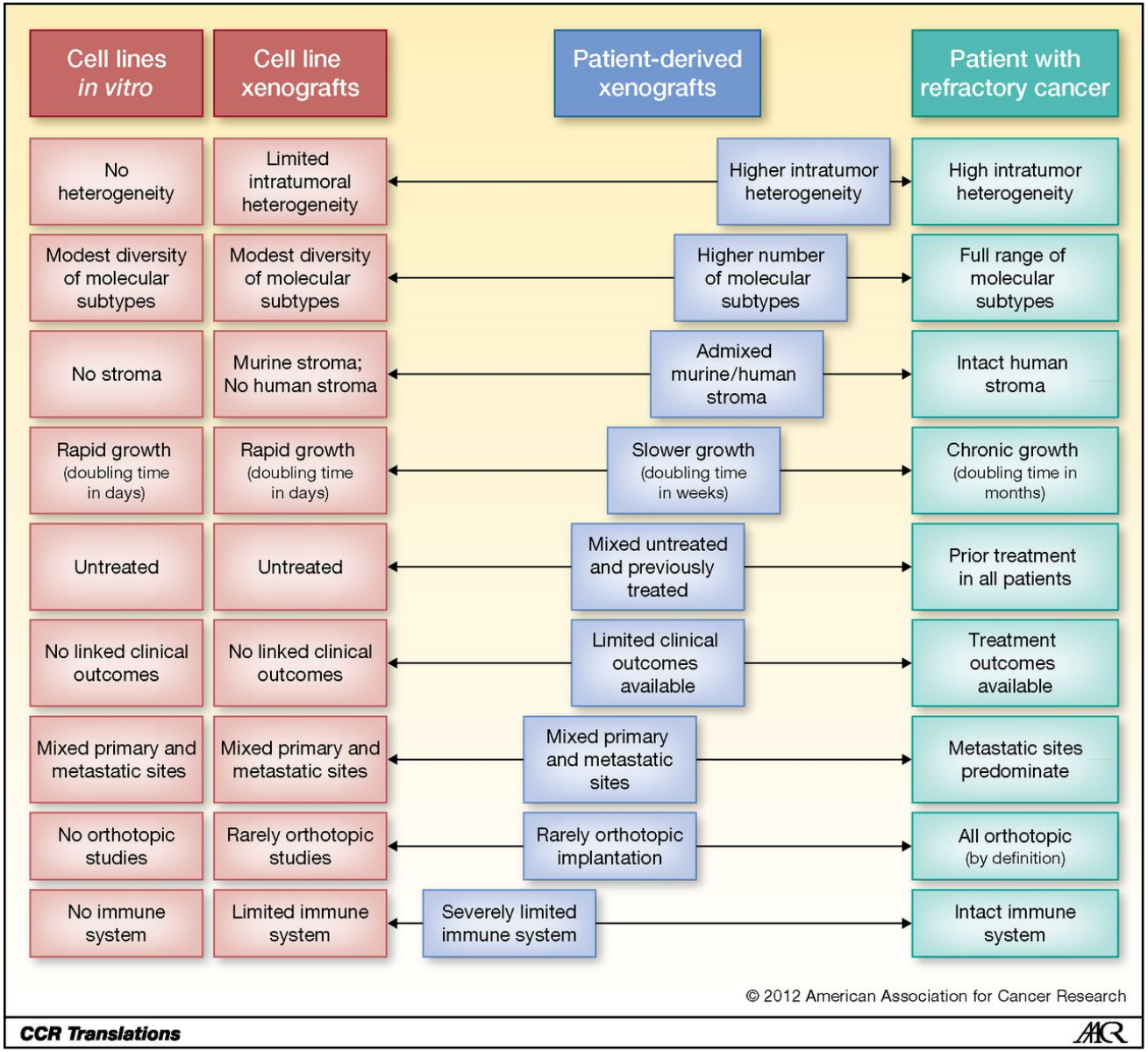
Humanized Mouse Avatars for Cancer Therapy



Mission & Opportunity

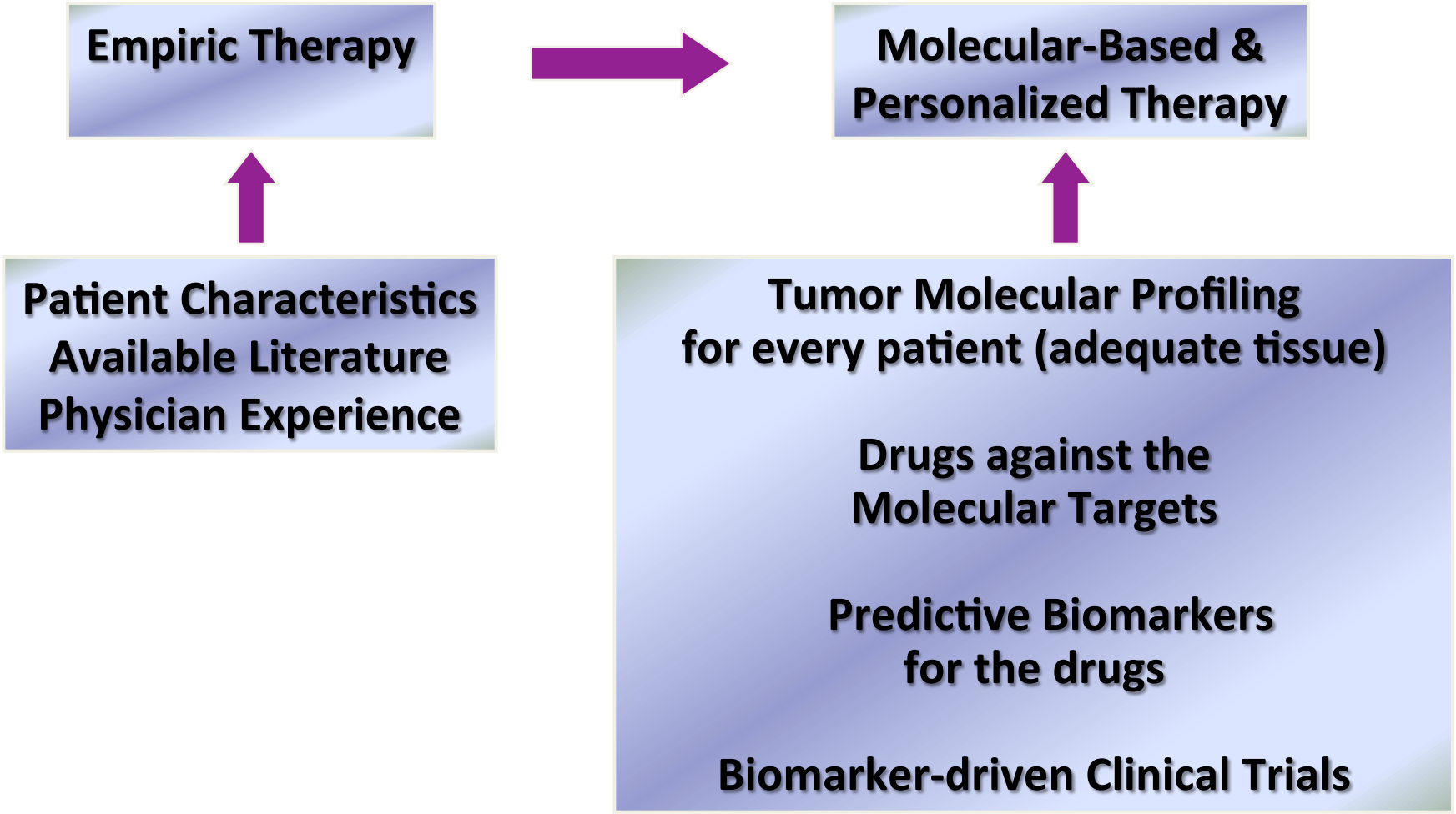
- ~95 percent of all investigations of new drugs for cancer fail
  - This contributes to the incredible expense of treating cancer and incredibly slow progress
- We need better tumor models & the biomedical research community needs a common, readily accessible tumor resource to support cancer drug development efforts
- Participate in something that may be a game-changer, improve cancer research and cancer care

Cell line–based models have been criticized for their poor ability to predict outcomes for advanced patients with cancer



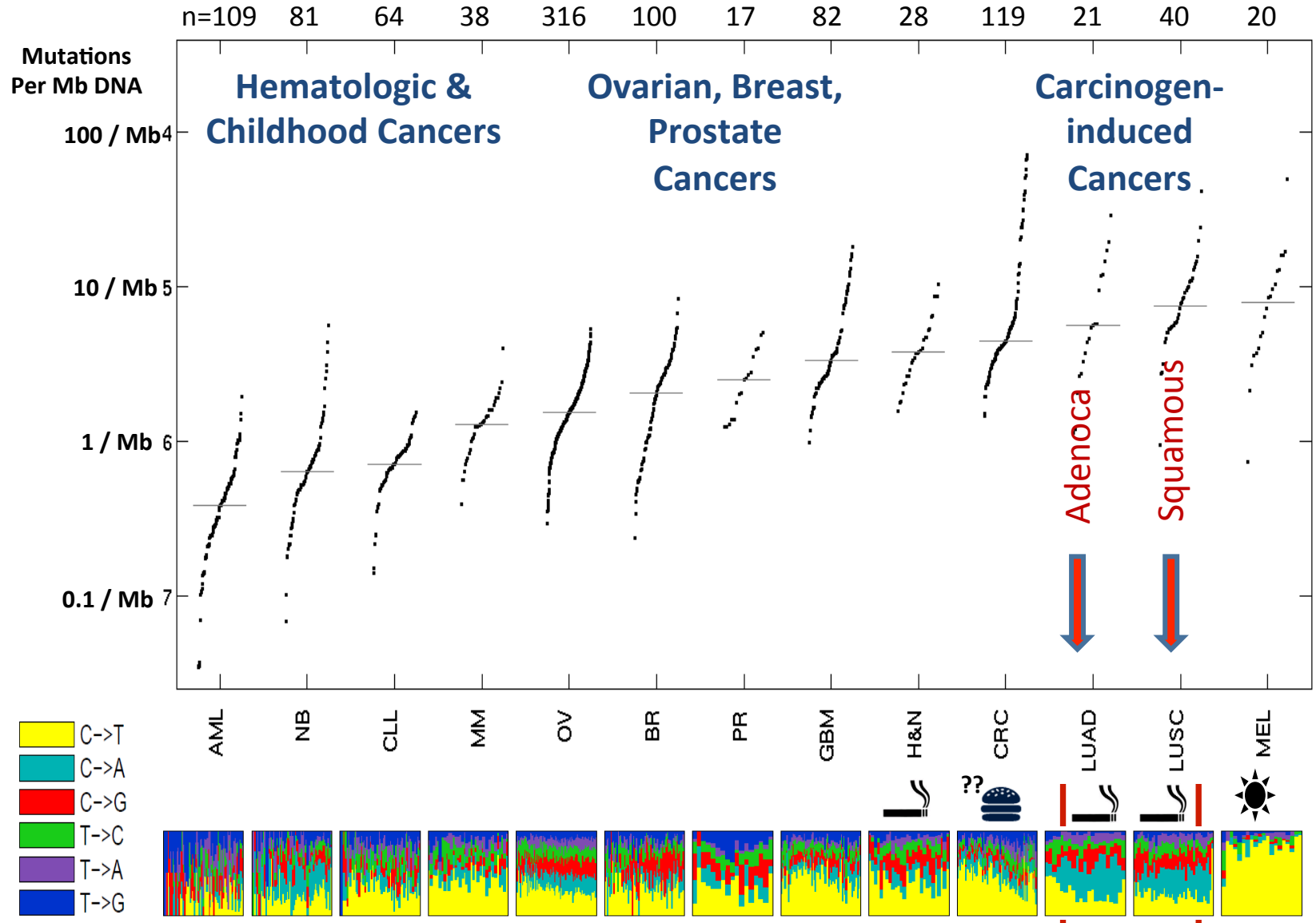
Kopetz S et al. Clin Cancer Res 2012;18:5160-5162

Transition from Empiric to Rationally Selected & Personalized Cancer Therapy

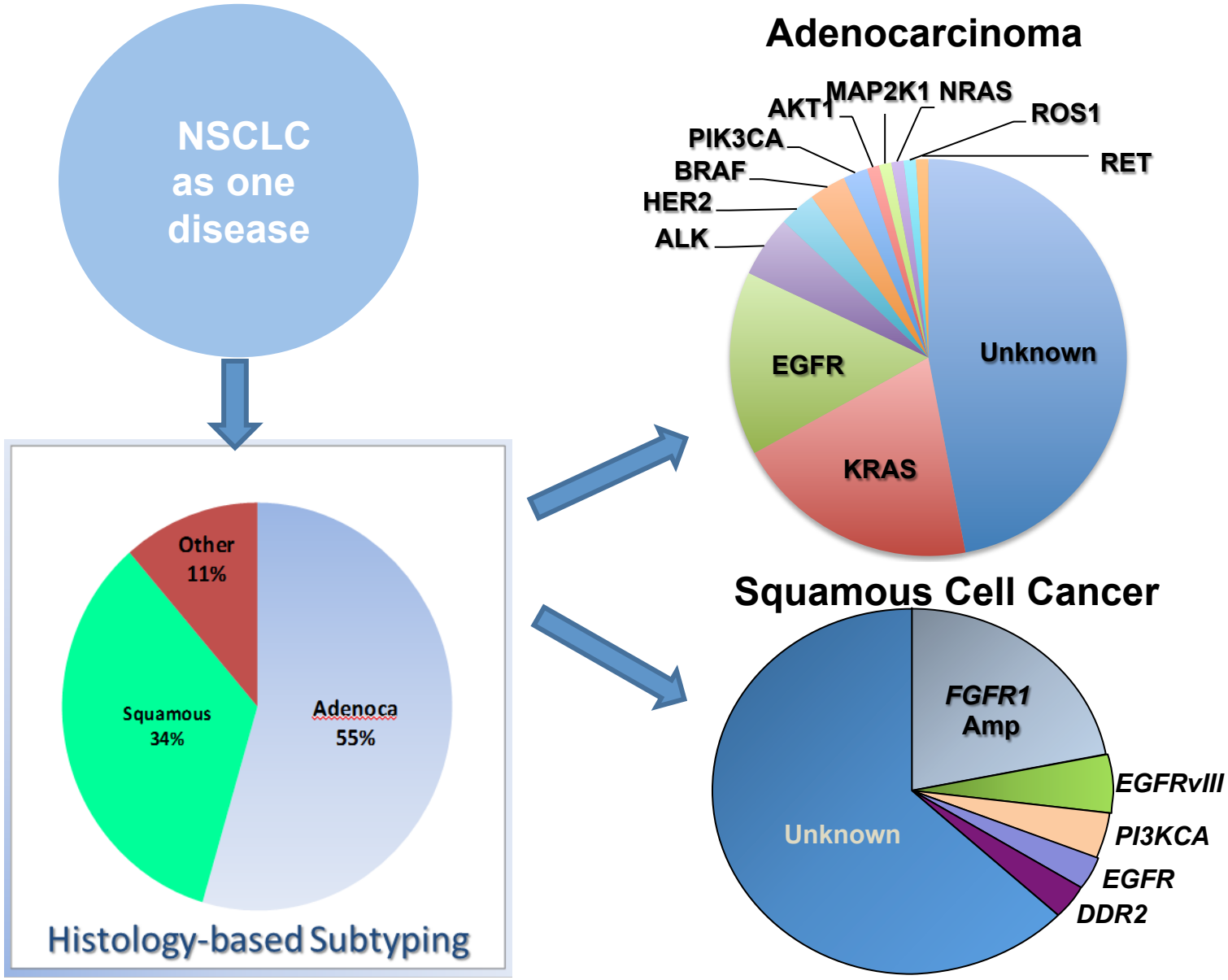


Gandara et al: Clin Lung Cancer, 2012

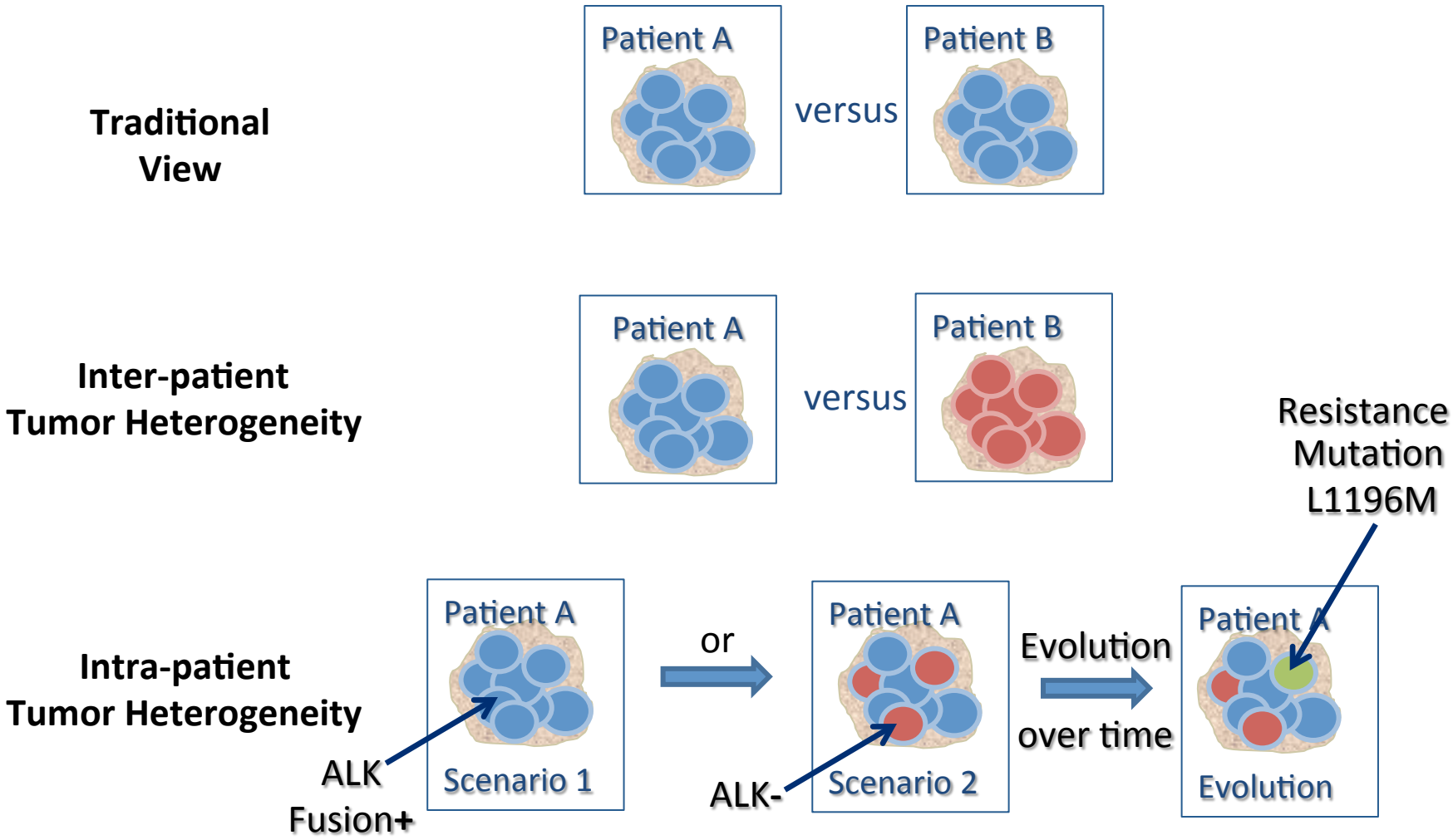
Magnitude of Genomic Derangement Cancer



The Cancer Genome Atlas Project: Govindan R. J Clin Oncol. 2012 (Proc ASCO Annual Meeting);30 (suppl): abstr 7006.


NSCLC as one disease
Other 11%
Squamous 34%
Adenoca 55%
Histology-based Subtyping
Adenocarcinoma
AKT1
MAP2K1
NRAS
ROS1
PIK3CA
RET
BRAF
HER2
ALK
EGFR
Unknown
KRAS
Squamous Cell Cancer
FGFR1 Amp
EGFRvIII
Unknown
PI3KCA
EGFR
DDR2

Models for Inter- and Intra-Patient Tumor Heterogeneity & Evolution Over Time



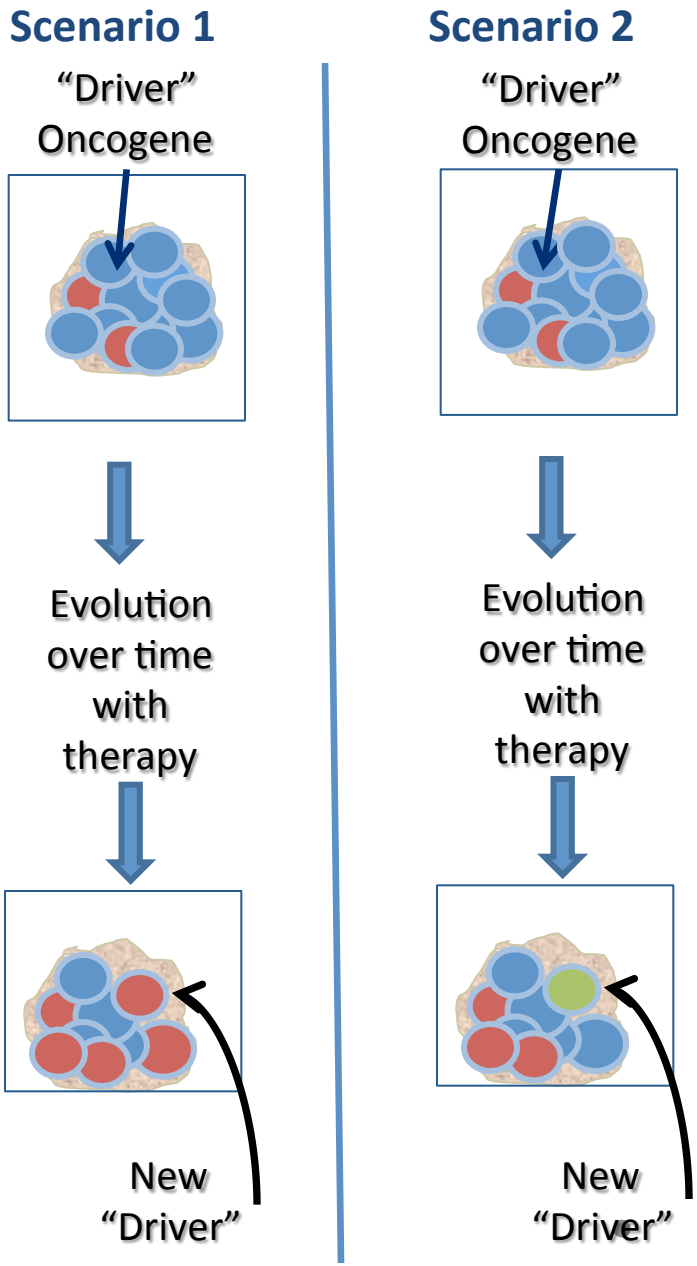
from Gandara et al: Clin Lung Cancer, 2012

Evolutionary Biology & Tumor Resistance

- **Intra-tumor heterogeneity** is present at baseline
- Reducing sensitive clones by therapy **permits unopposed growth of less fit resistant clones**

  or **emergence of a new clone ("Tumor Darwinism")**
- Separating **new "drivers"** from **emergent "passengers"** is becoming increasingly complex

from Gandara et al: Clin Lung Cancer, 2012



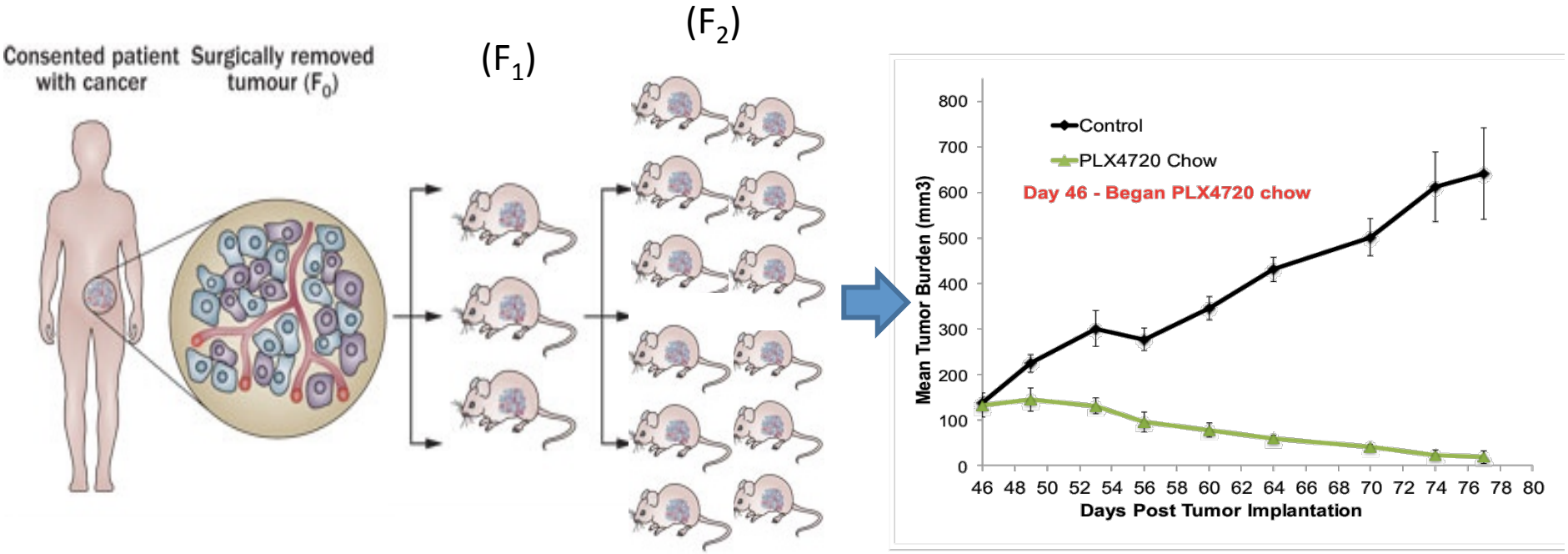
Cancer Treatment in 2020?



"Here's my sequence”

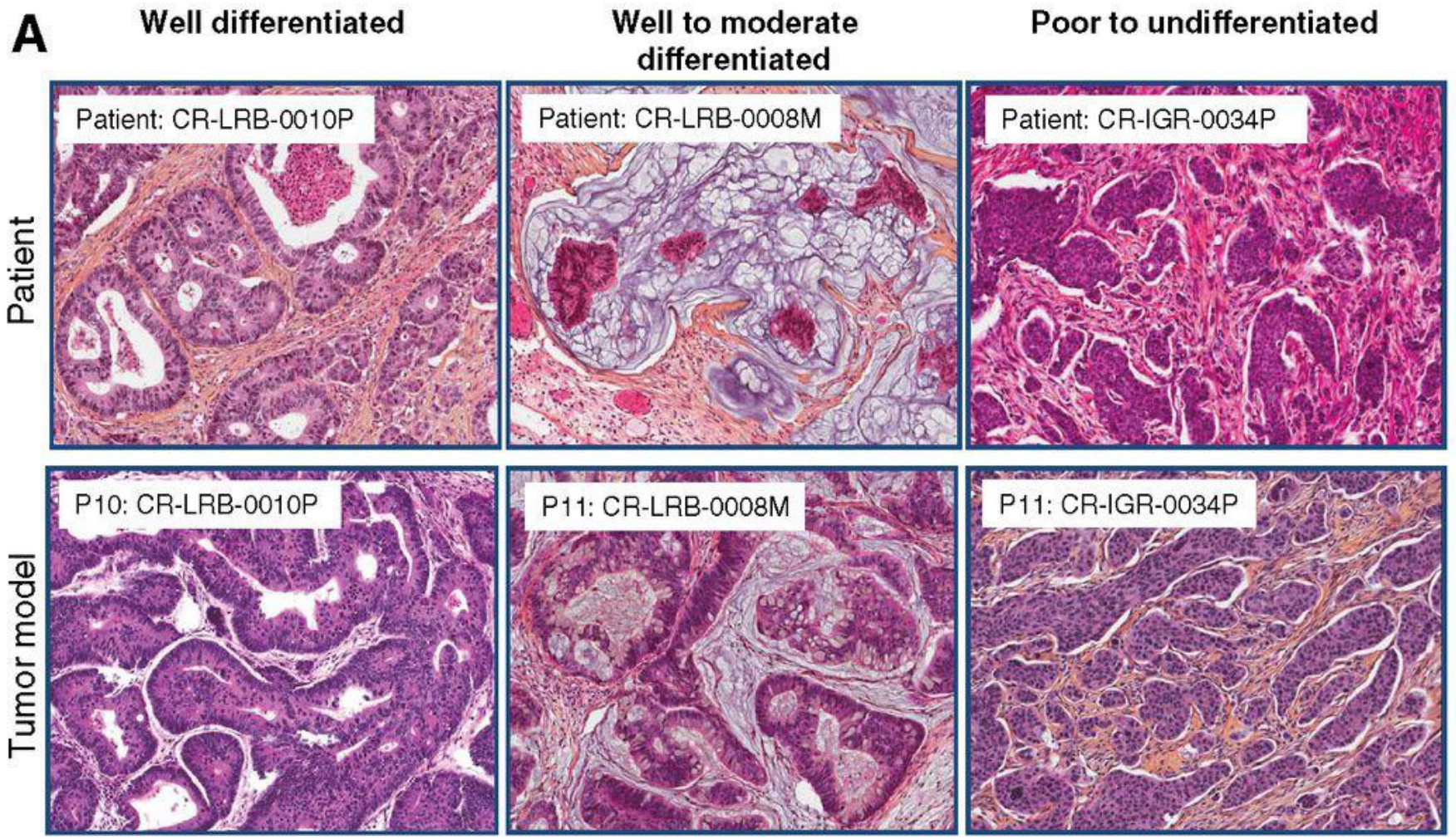
The New Yorker

PDX Platform Algorithm



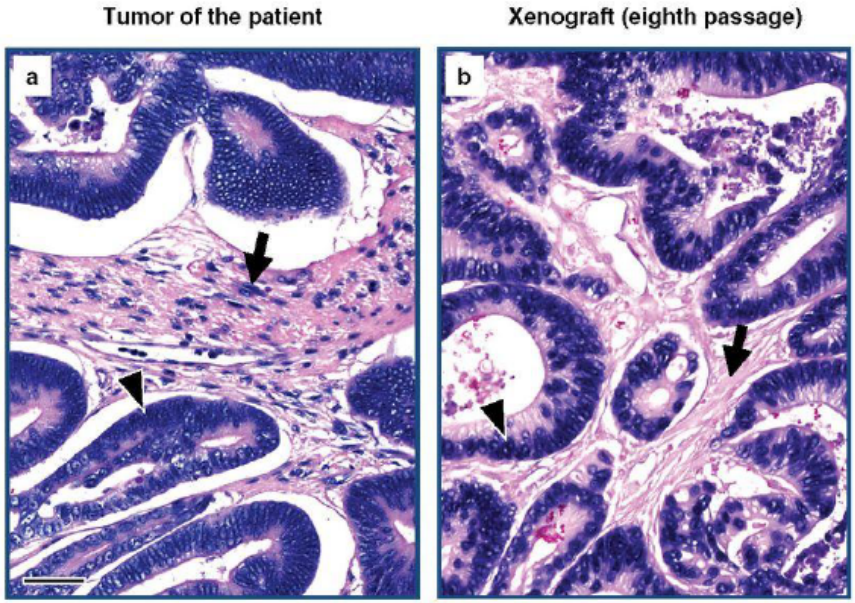
Adapted from: Tentler, *et al.* (2012) *Nat. Rev. Clin. Oncol*

Key PDX Features: Maintained Histology

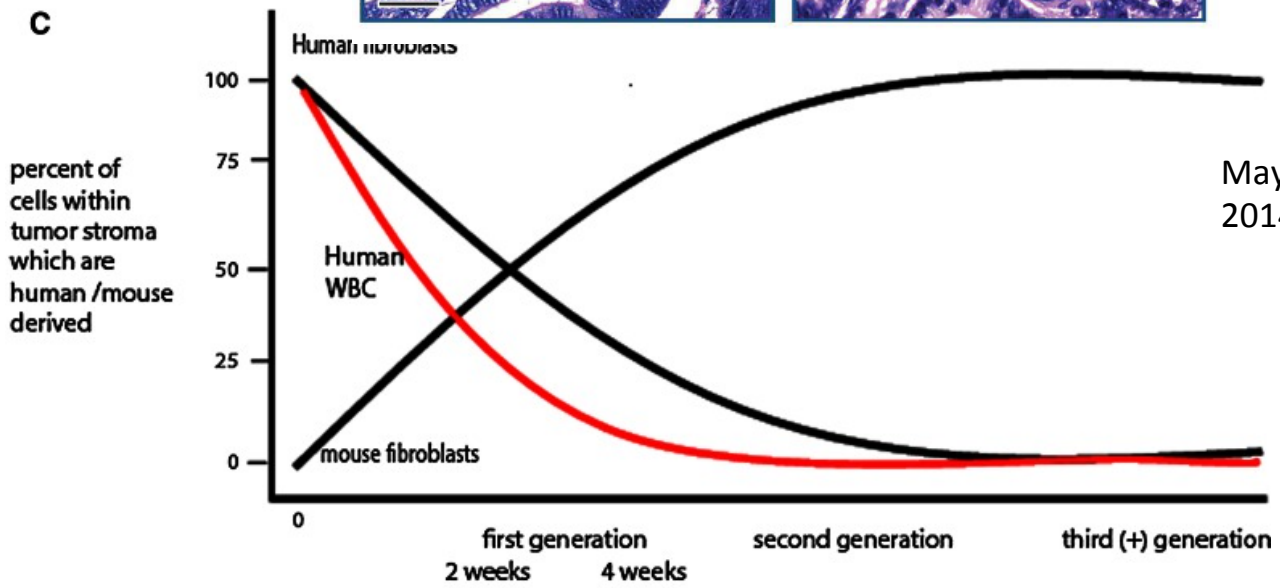


Julien S et al. Clin Cancer Res 2012;18:5314-5328

Key PDX Features: Preserved Stroma



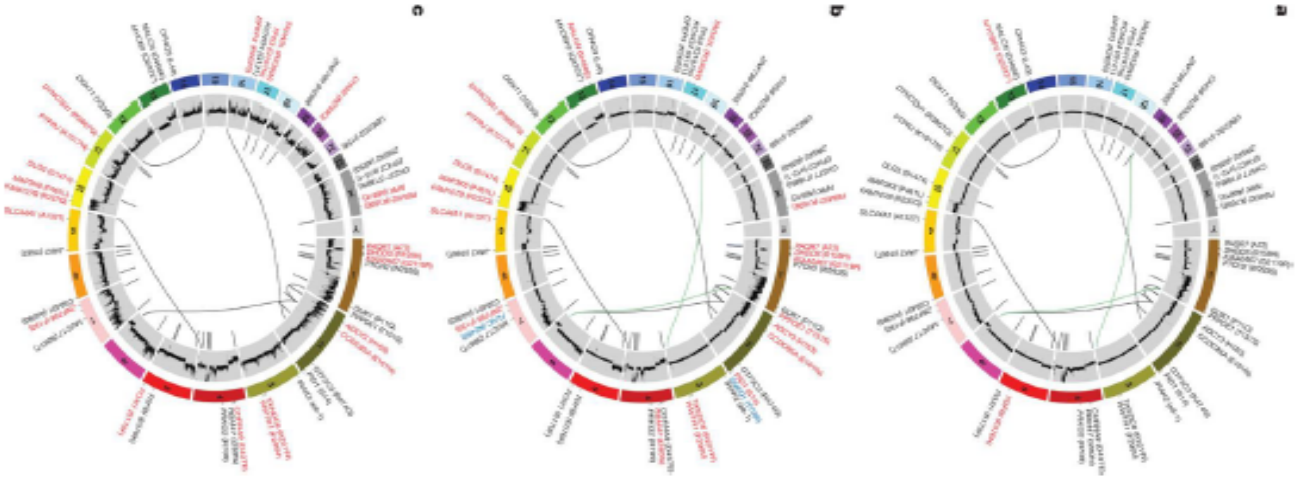
Julien S et al. Clin Cancer Res 2012;18:5314-5328



Maykel J et al. Dig Dis Sci, 2014;59(6):1169-1179

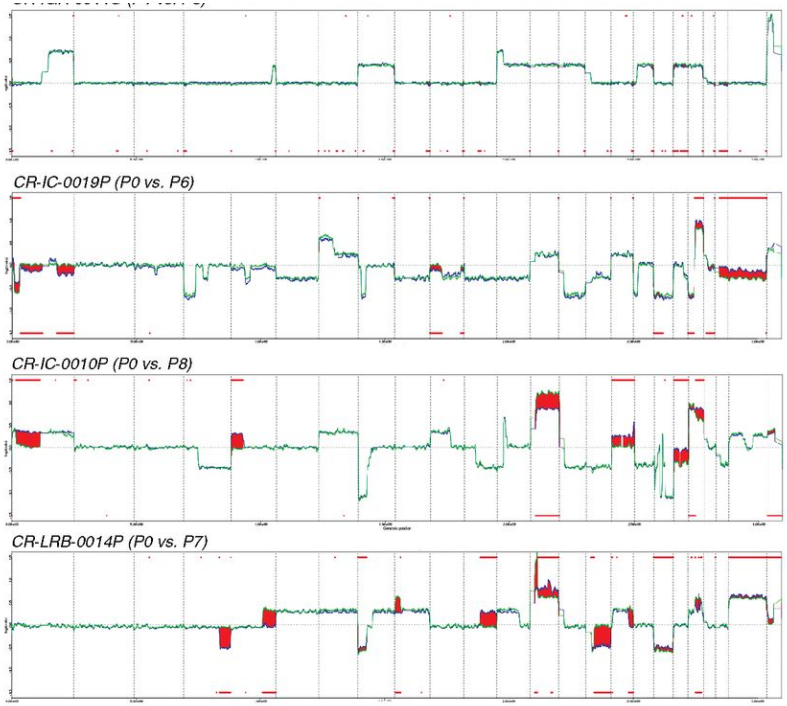
Key PDX Features: Genetic Fidelity

Translocations



Ding Nature '10

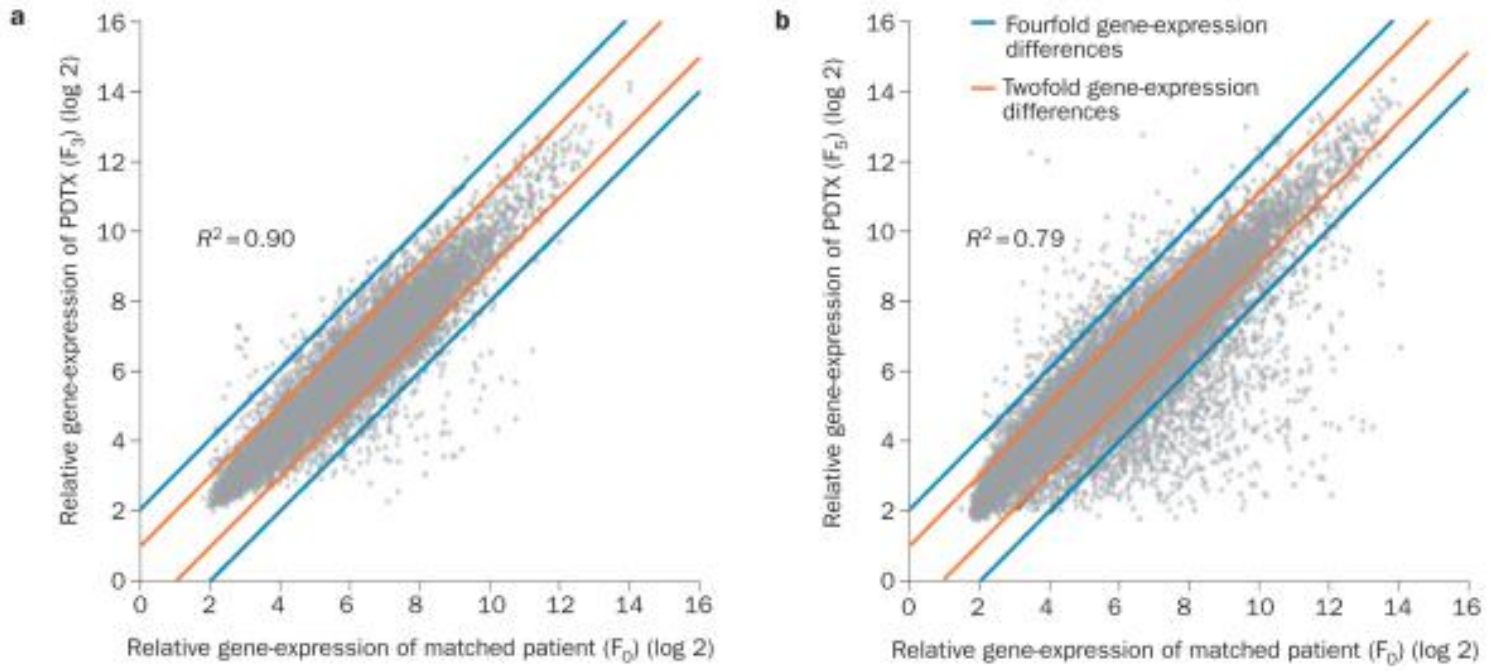
Copy number



Julien Clin Cancer Res 2012

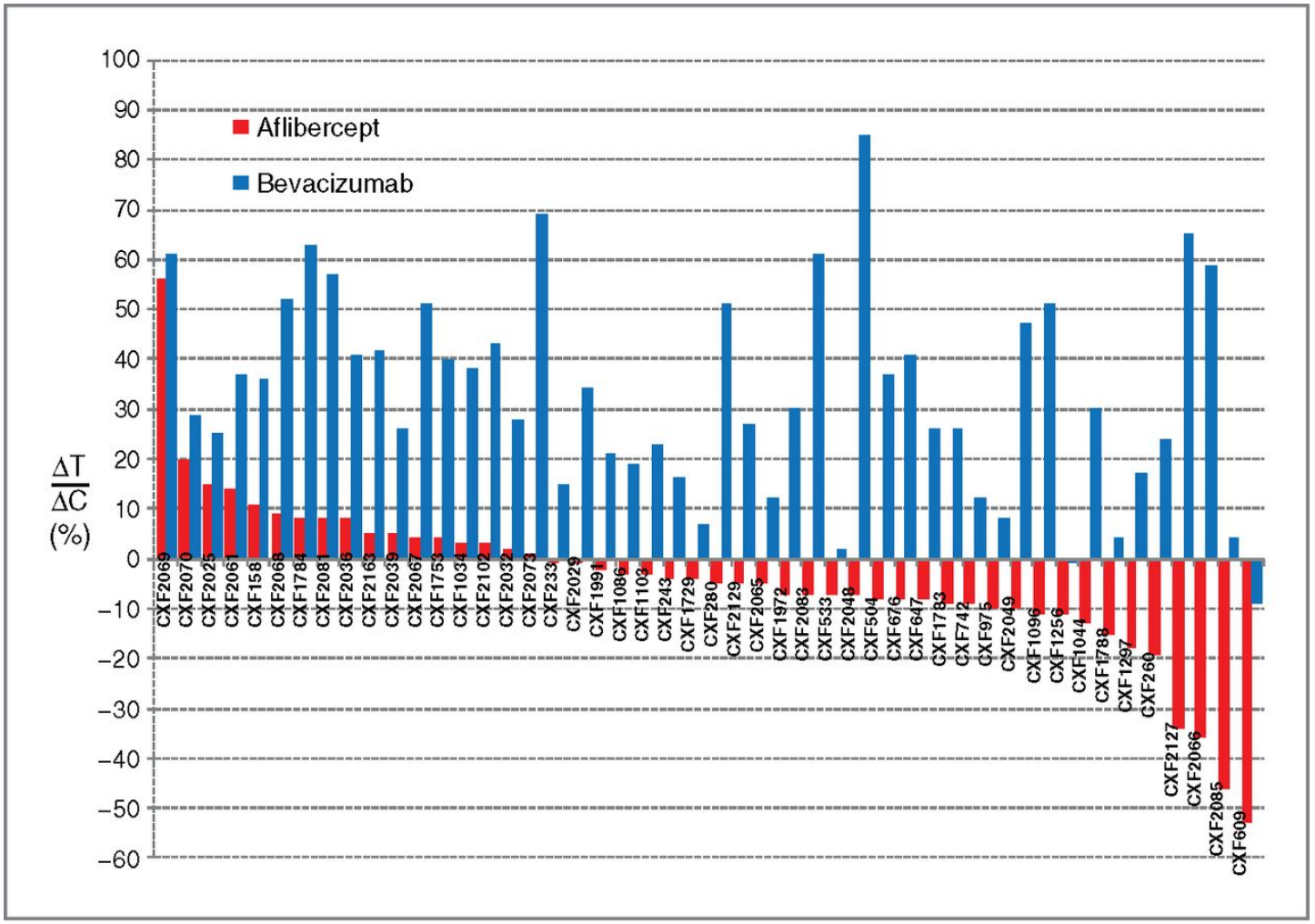
Key PDX Features: Genetic Fidelity

Gene Expression



Tentler J et al. Nat Rev Clin Oncol. 2012; 9(6):338-50

Key PDX Features: Tumor Diversity and Heterogeneity



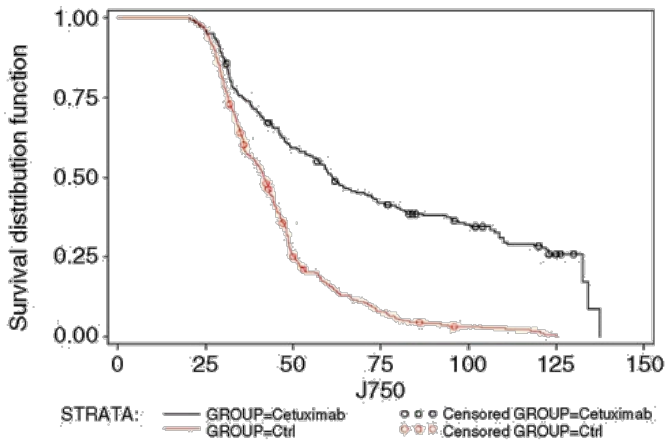
Chiron M et al. Mol Cancer Ther 2014;13:1636-1644

Key Features: Correlation with Patients Outcomes

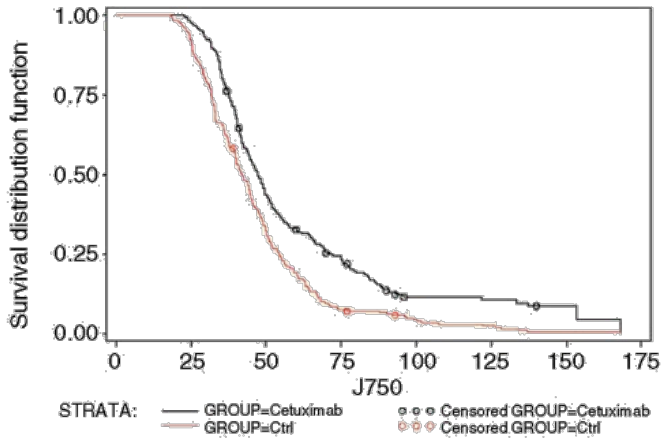
PDX Clinical Trial Simulation

PDX Trial

KRAS Wild Type



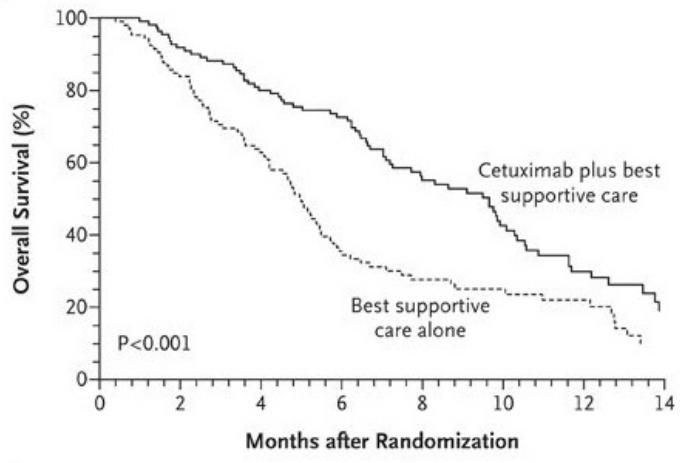
KRAS Mutant

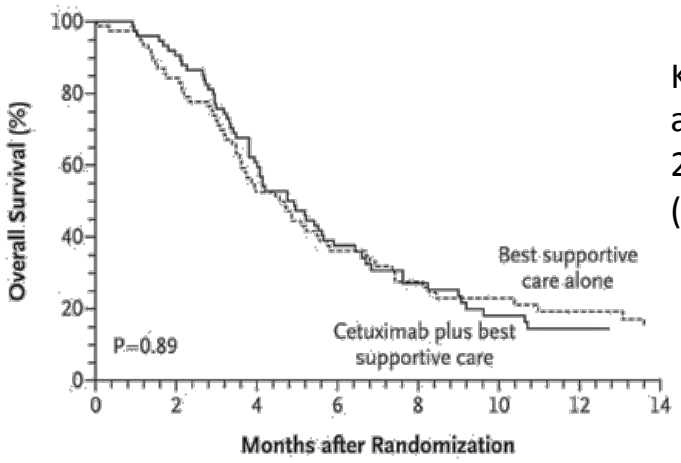


Julien S et al. Clin Cancer Res 2012;18:5314-5328

Julien S et al. Clin Cancer Res 2012;18:5314-53**28**

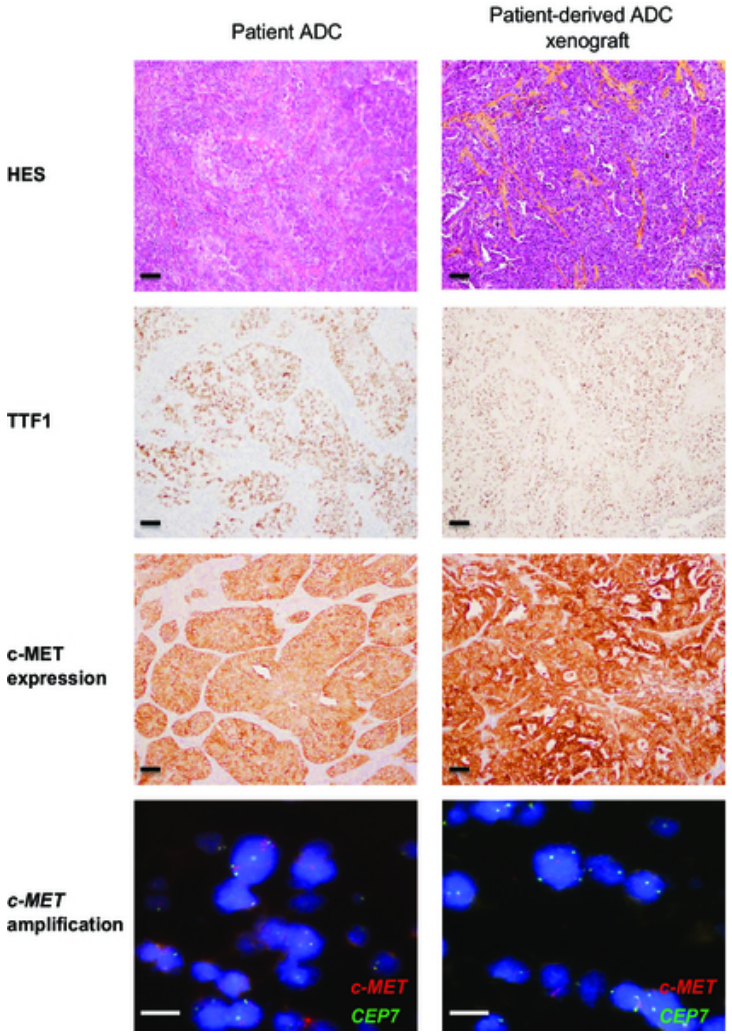
CO-17 Clinical Trial

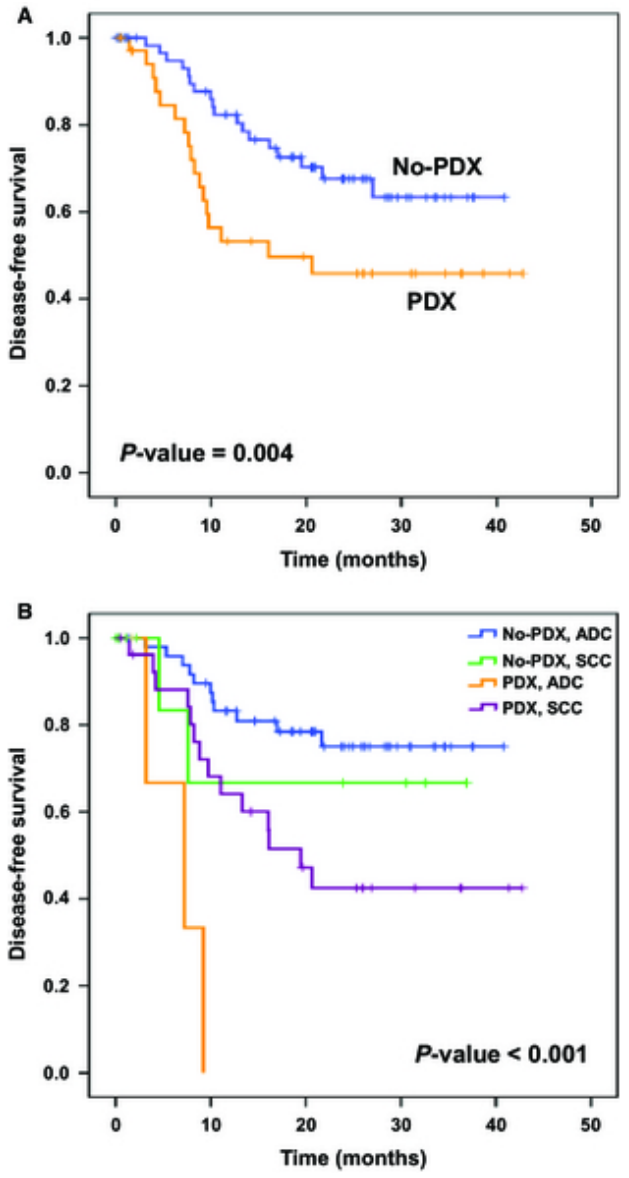




Karapetis et al. NEJM 2008, 359 (17): 1757

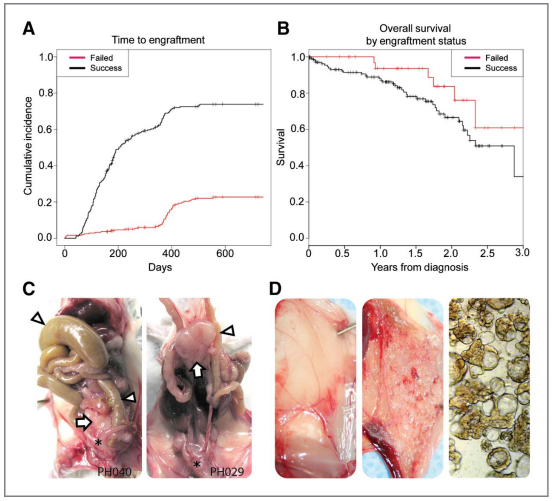
Correlation Between *Engraftability* and Patient Clinical Outcome Non-Small Cell Lung Cancer

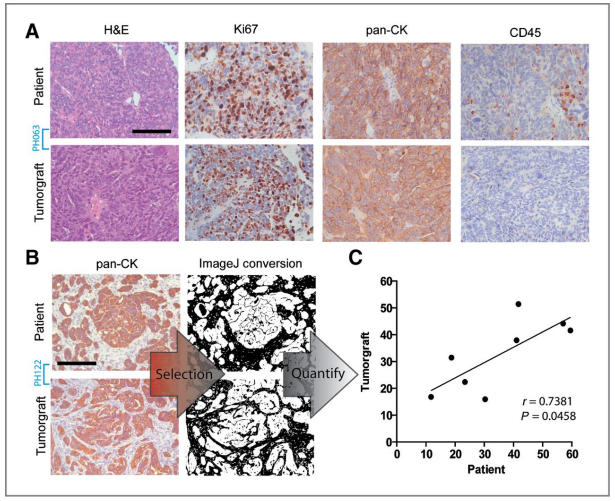


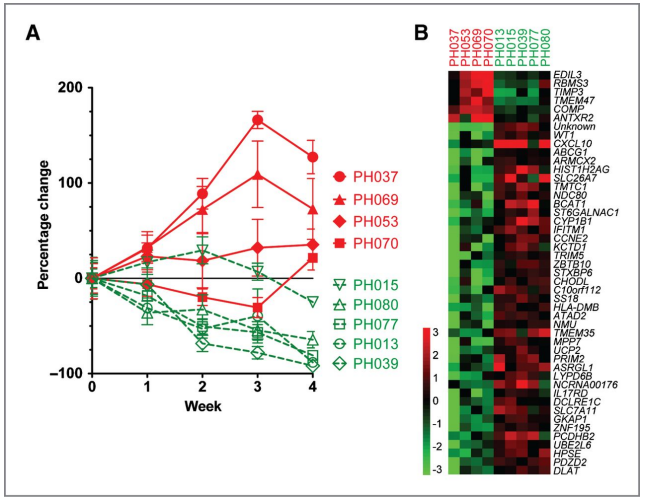


Ilie et al. Cancer Med. 2015 Feb;4(2):201-11

PDX Predict for Clinical Response in Ovarian Cancer







- PDX recapitulated molecular characteristics of tumor
- Accurately predicted platinum sensitivity (>90%)
- Exhibited gene signatures consistent with platinum resistance
- 328 models established across most subtypes
- 148 models BROC-HA sequenced
  - BRCA1 (8%), 6 BRCA2 (4%), and 4 PIK3CA (3%)
  - ATM, RAD51C, FANCM, FANCD2, FANCA, CHEK2, PALB2, MHS6, CDK12 and GEN1 loss of function mutations

Weroha et al. Clin Cancer Res 2014;20:1288-1297
Lodiha et al. Ann Oncol. 2015 Mar;26 Suppl 2:ii31

PDX Predict for Clinical Response in Sarcoma

Original Article

Patient-Derived Xenografts for Individualized Care in Advanced Sarcoma

Justin Stebbing, MA, FRCP, FRCPath, PhD[1]; Keren Paz, PhD[2]; Gary K. Schwartz, MD[3]; Leonard H. Wexler, MD[3]; Robert Maki, MD, PhD[4]; Raphael E. Pollock, MD, PhD[5]; Ronnie Morris, MD[2]; Richard Cohen, MD[6]; Arjun Shankar, MD[6]; Glen Blackman, MBBS[7]; Victoria Harding, MD[1]; David Vasquez, MD[2]; Jonathan Krell, MD, PhD[1]; Daniel Ciznadija, PhD[2]; Amanda Katz, MD[2]; and David Sidransky, MD[8]



Stebbing et al. Cancer. 2014 July 1; 120(13):2006-15.

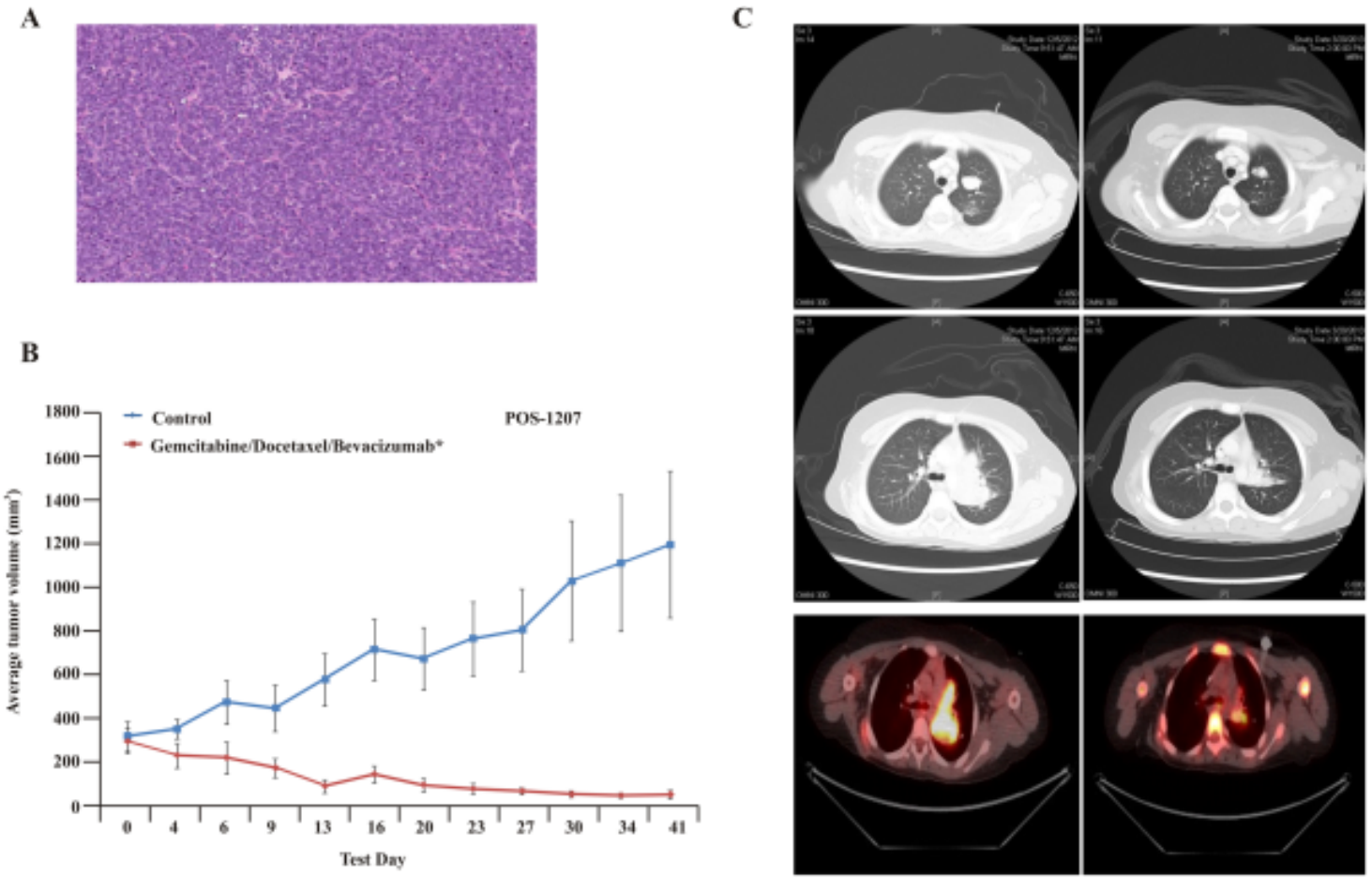
Results

- 22/29 (76%) tumors successfully engrafted
- PDX: Clinical response correlation accurate in 13/16 (81%)
- No patients progressed during the PDX-predicted therapy

Conclusion:

- PDX allowed for the testing of traditional and non-traditional therapies
- Accurately predicted for clinical benefit (81%)

Ewing Sarcoma with Pulmonary Metastases PDX-Directed Therapy Response

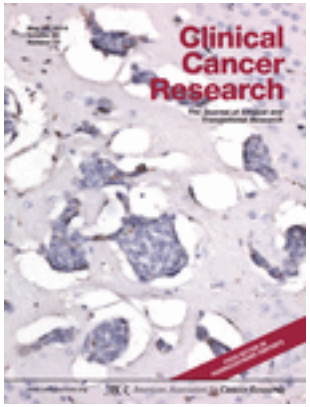


Stebbing et al. Cancer. 2014 Jul 1;120(13):2006-15

PDX Predict for Clinical Response in Sarcoma

Integrated Next Generation Sequencing and Avatar Mouse Models for Personalized Cancer Treatment

Elena Garralda[1], Keren Paz[2], Pedro P. López-Casas[1], Sian Jones[3], Amanda Katz[4], Lisa M. Kann[5], Fernando López-Ríos[6], Francesca Sarno[7], Fátima Al-Shahrour[1], David Vasquez[4], Elizabeth Bruckheimer[8], Samuel V. Angiuoli[5], Antonio Calles[9], Luis A. Diaz[10], Victor E Velculescu[11], Alfonso Valencia[12], David Sidransky[13], and Manuel Hidalgo[14,*]

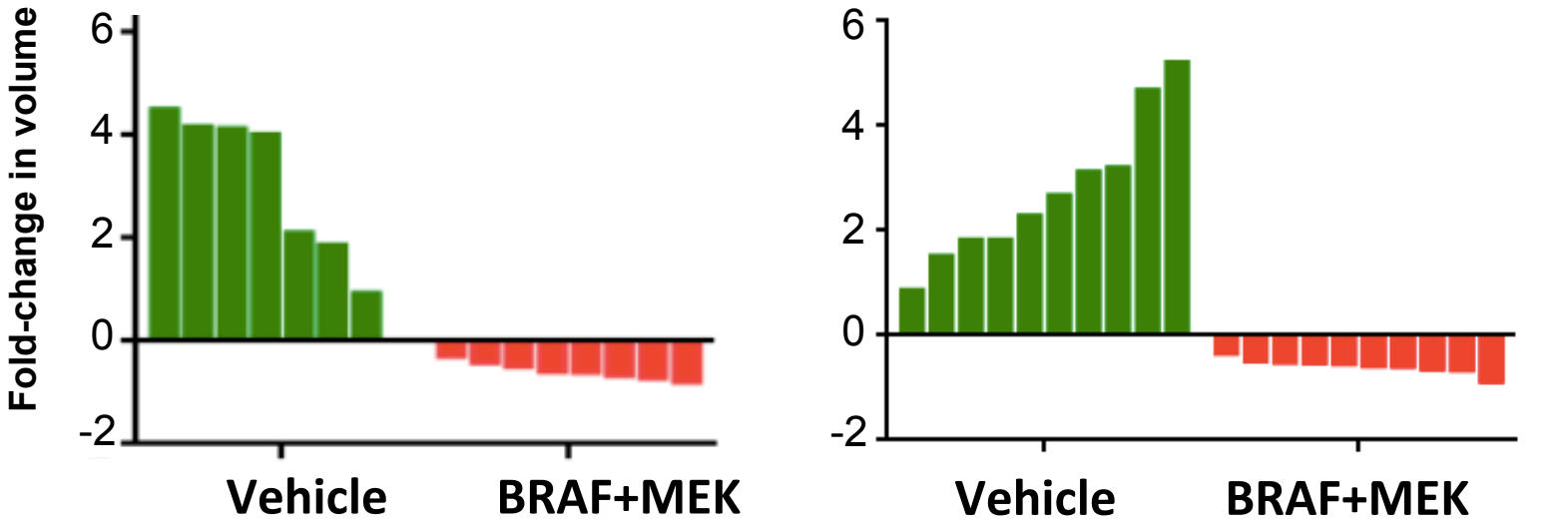


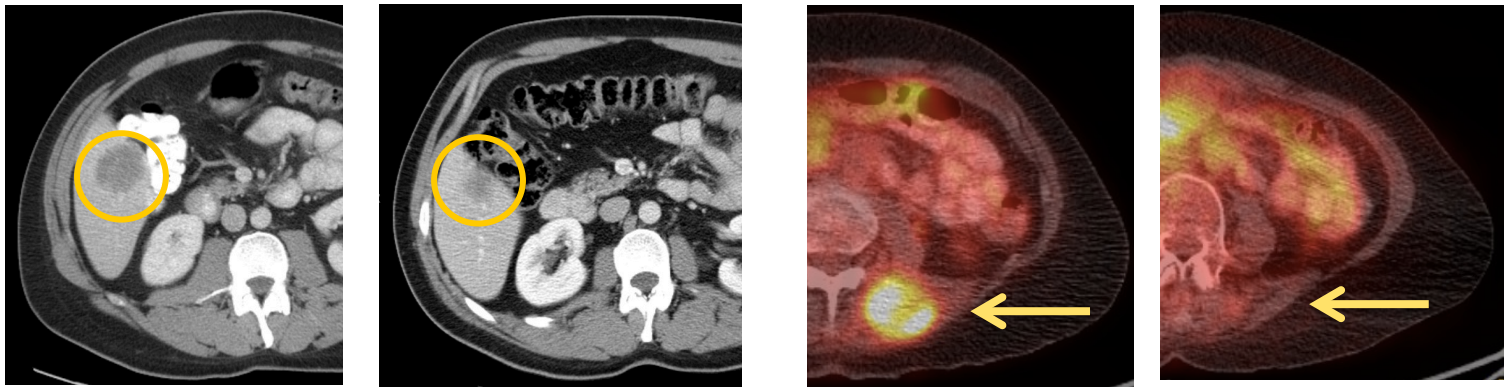
Garralda, et al. Clin Cancer Res May 1, 2014 20:2476-2484

RESULTS:

- Exome sequencing analyses obtained for 23 patients.
  - Tumor-specific mutations and copy-number variations were identified.
  - All samples profiled contained relevant genomic alterations.
- Tumor was implanted to create Avatar models
  - 13 patients have received a personalized treatment
  - 6 achieved durable partial remissions.
  - Drug candidate treatments in Avatar models correlated with clinical response and helped to select empirical treatments in some patients with no actionable mutations.

PDX Predicts for Response in Metastatic CRC



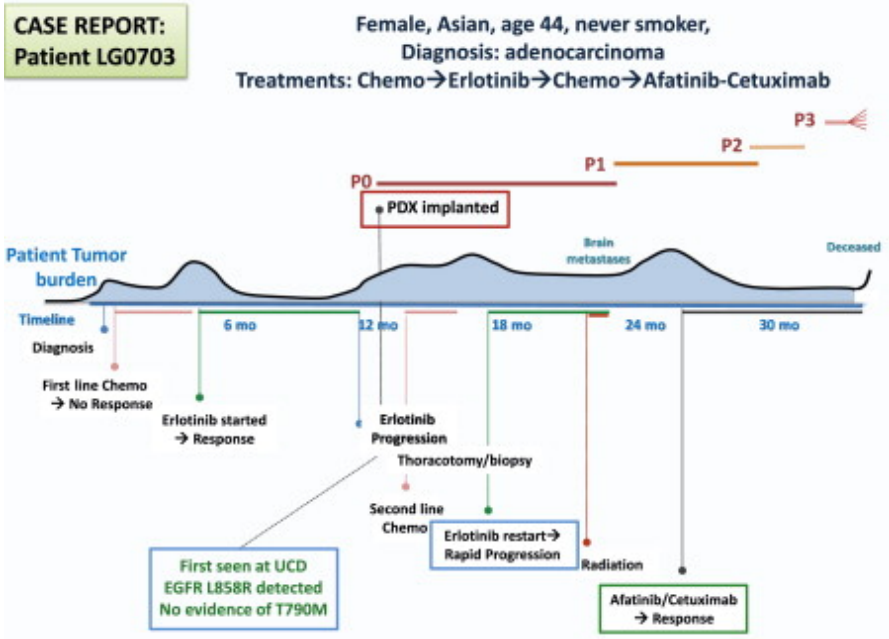


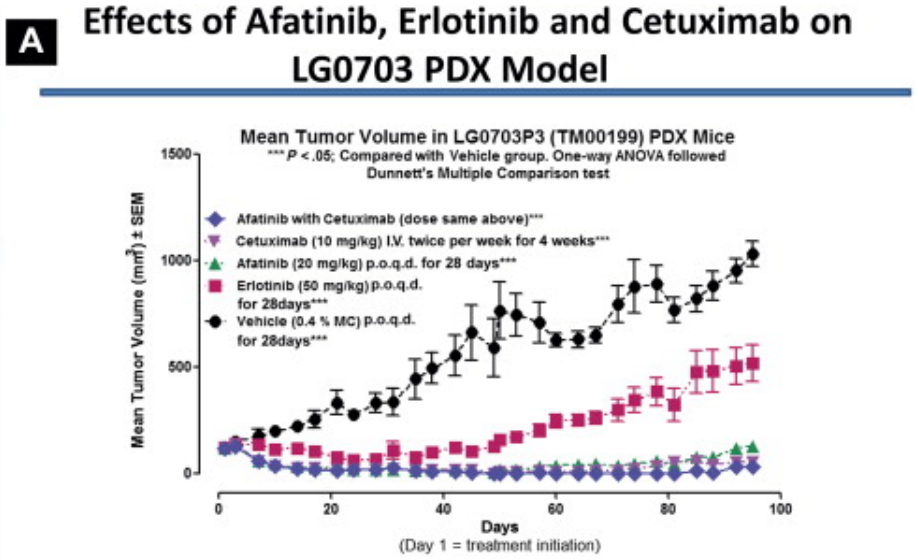
41% Regression

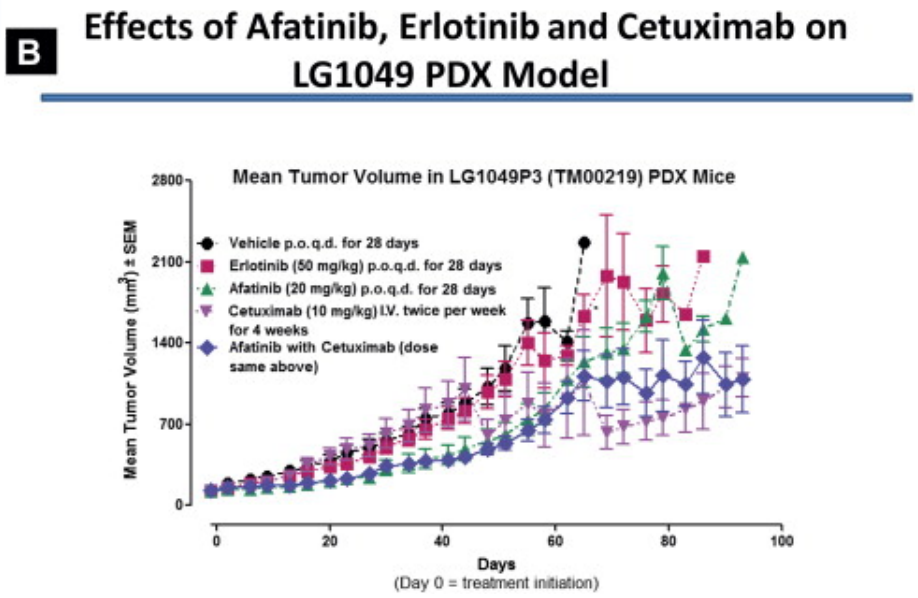
100% Regression

Corcoran et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 3517)

PDX Predict for Clinical Response in Non-Small Cell Lung Cancer



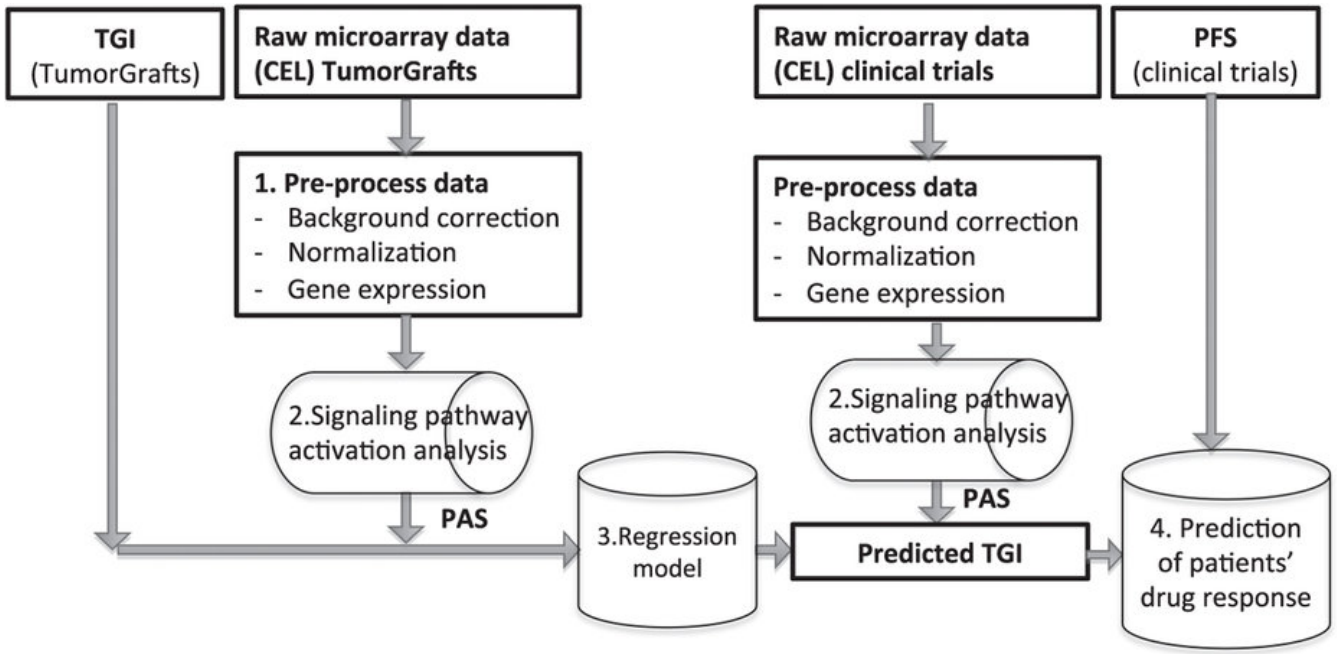




Preliminary data for SWOG Phase II/III S1403

Gandara et al. Clin Lung Cancer. 2015 Mar 18

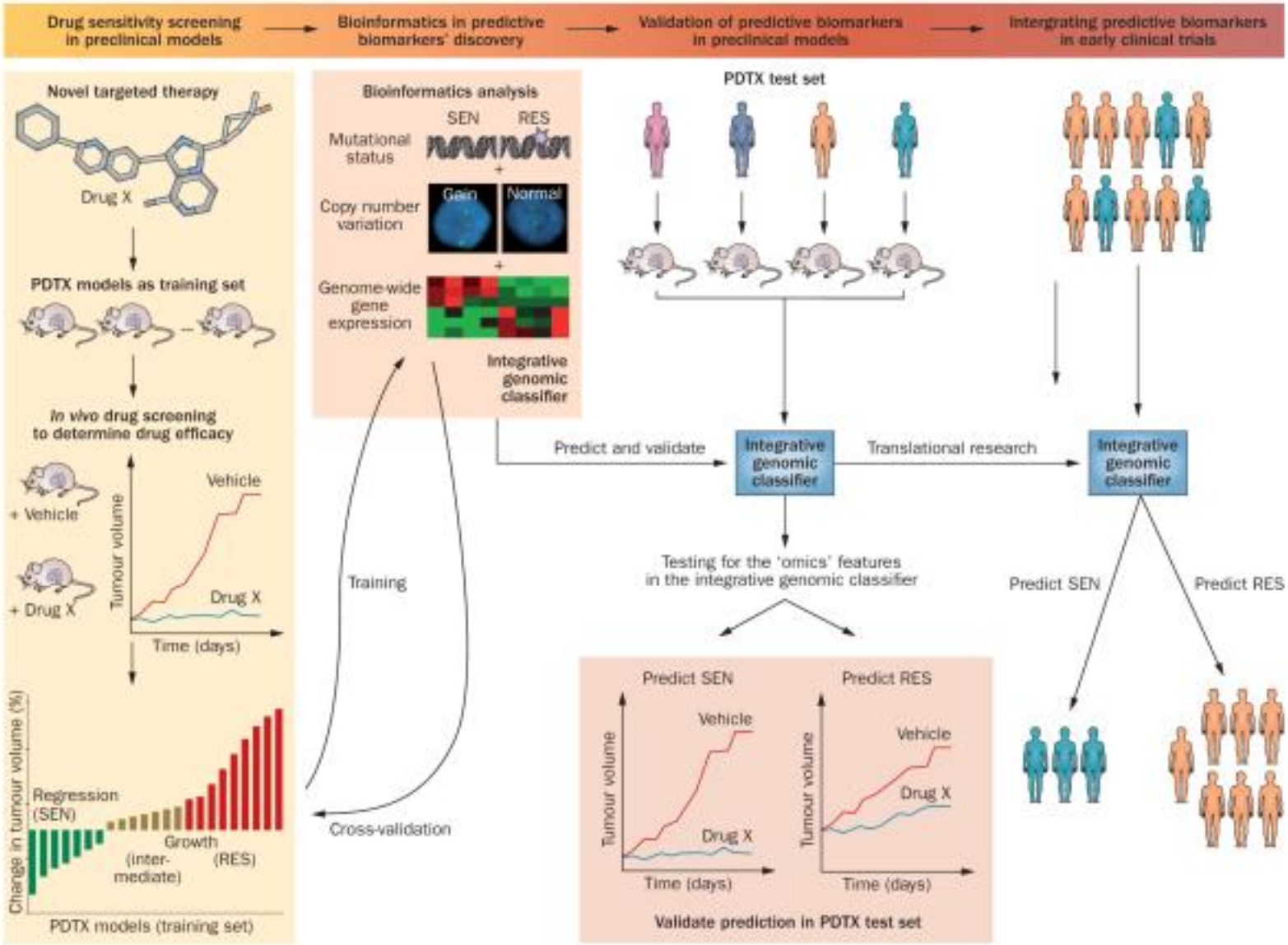
PDX Future: Analytical Approach for Predicting Patients' Drug Sensitivity



- Predicted cetuximab sensitivity in a set of transcriptomic data obtained from CRC PDX models.
- Forecasted the clinical outcome in patients with mCRC.
- Predicted clinical outcome for cetuximab in a cohort of mCRC patients using a pathway activation strength (PAS) profile derived from microarray gene expression data.
- Ability of PAS to predict cetuximab sensitivity in cancer patients as good as or even better than the predictive value of the K-*ras* mutation status.

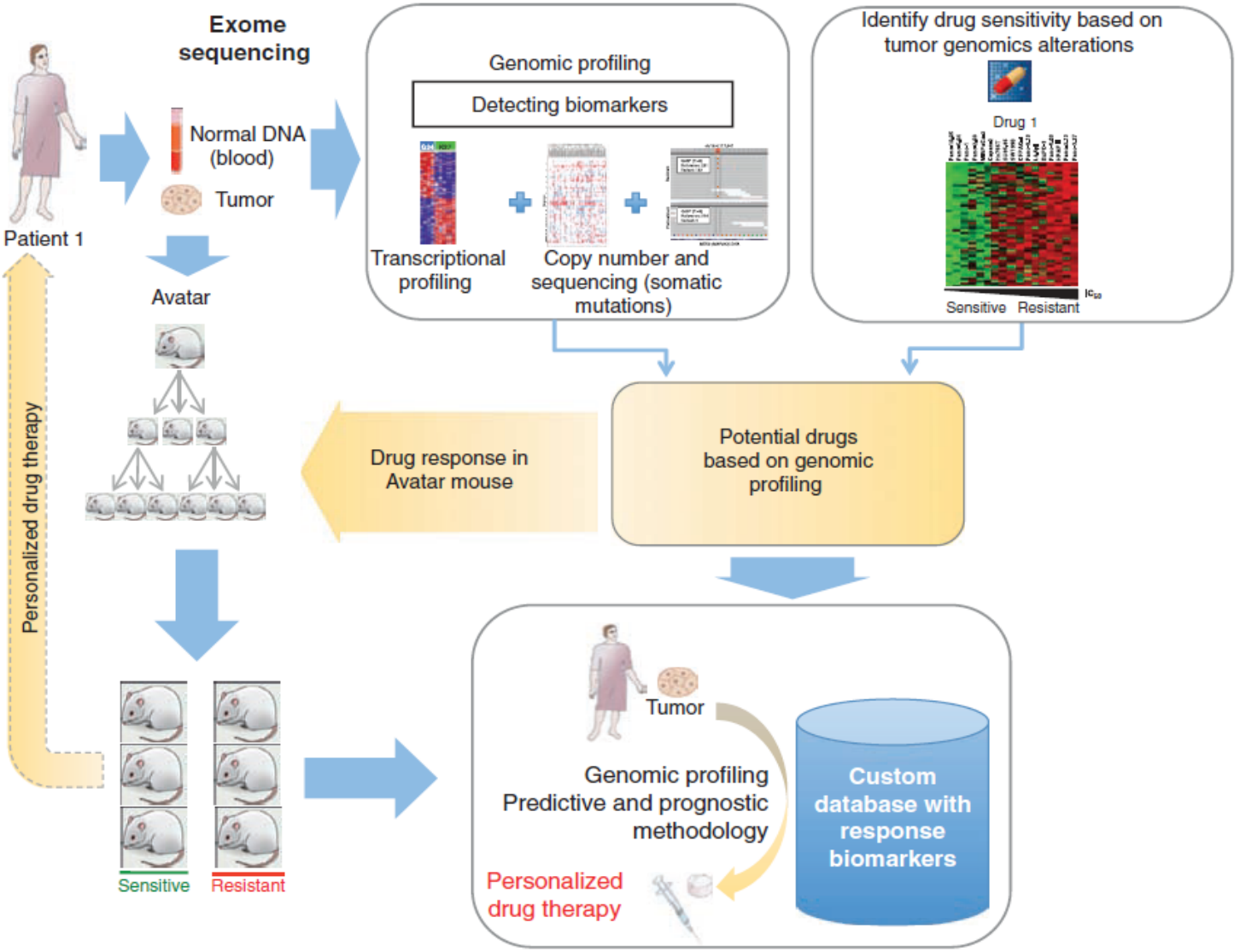
Zhu et al. 2015. Human Genome Variation **2**, Article number: 15009

PDX Clinical Trial Schema: Biomarker Directed Patient Selection



Tentler J et al. Nat Rev Clin Oncol. 2012; 9(6):338-50

Integrating PDX Models Into Clinical Drug Development



Hidalgo, M. et al. Canc. Disc. 2014. 4(9): p.998

The Breast Cancer Genome Guided Therapy Study (BEAUTY)
PDX Program

- PDX in the neoadjuvant setting before and after chemotherapy
  - Peripheral node biopsies from 83 patients implanted in mice
  - 31.3% PDX take rate (26/83)
    - 51.9% TN
    - 41.7% ER+/Her2+ 41.7%
    - 27.3% ER-/Her2+
    - 17.4% Luminal B; ER expression was lost in PDXs from Luminal B tumors (2/2)
    - 0% Luminal A
  - Residual tumor at surgery from 17 pts was injected into mice
    - 17% take rate (all TN grade III tumor)

Boughey et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 11130)

PDX Future: Humanized Mice Predicting Immunotherapy Sensitivity

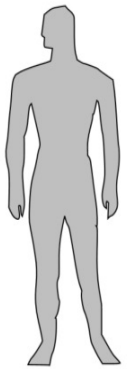
CD34+ HSC NOG Mice



- NOG mice (truncated IL-2Rγ)
- Impaired B,T, and NK cells

Myeloablation to further immune suppress

Tumors from patients or banked tumor fragments





Commercial CD34+ HSCs

Autologous CD34+ HSCs

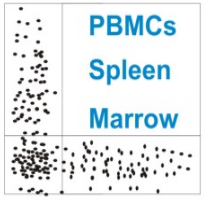
Reconstitute with CD34+ hematopoietic stem cells (HSCs)

10-12 weeks

huCD45+ leukocytes

huCD3+ T cells

huCD19+ B cells



Flow cytometry on reconstituted animals

Removal of tumor

Implant tumor fragments

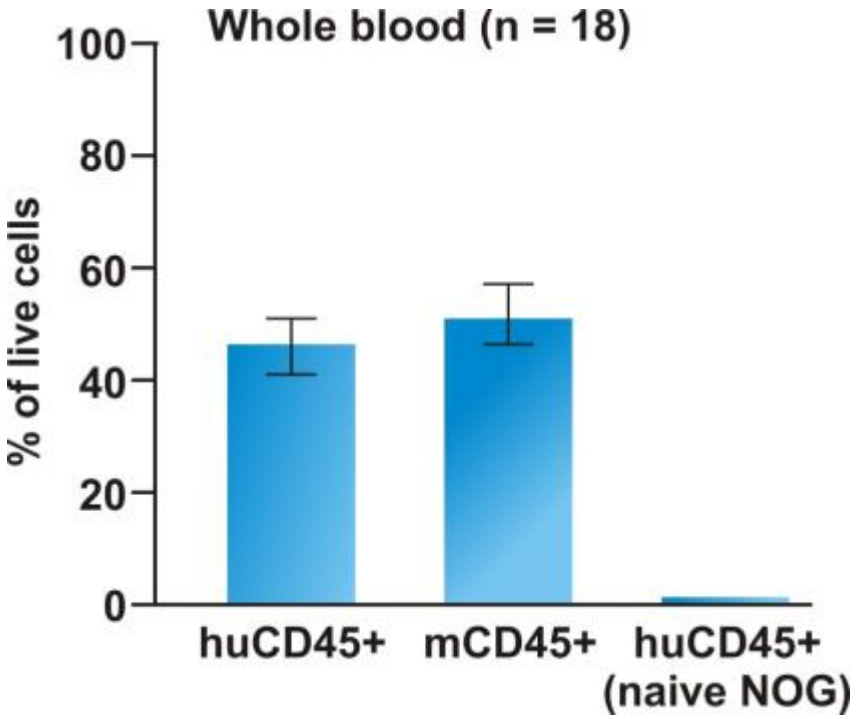
IMMUNOGRAFT

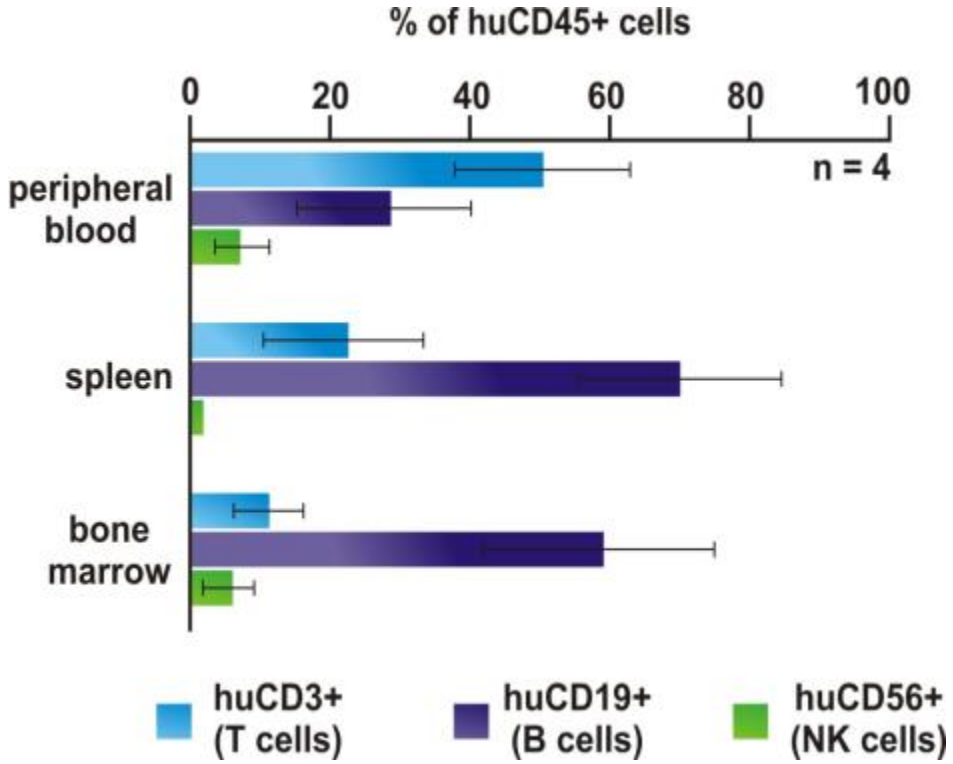
Screen against immunotherapy

* Tumor growth inhibition
* Activation of huCD8+ T cells
* Level of huCD4+/CD25+ regulatory T cells
* Level of huCD4+/CD69+ helper T cells
* Tumor-infiltrating huCD8+ lymphocytes

Key Leukocyte Surface Markers

in huNOG mice

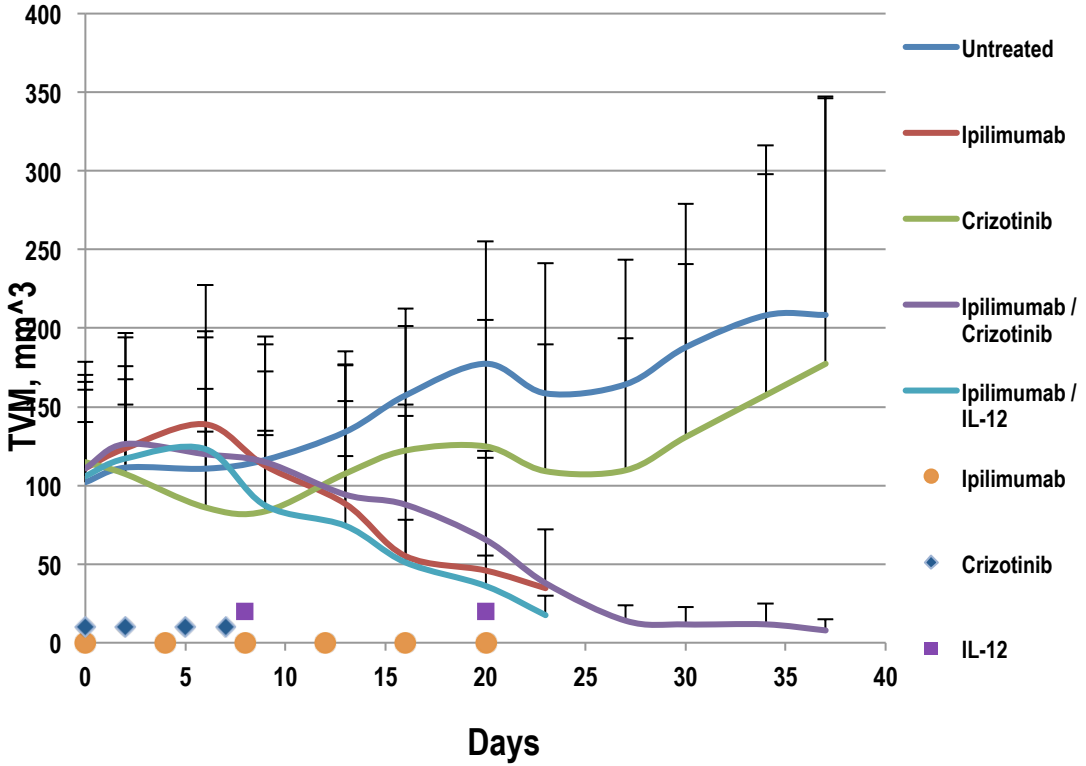




Baia et al. AACR 2015

NSLC Growth in huNOG Mice

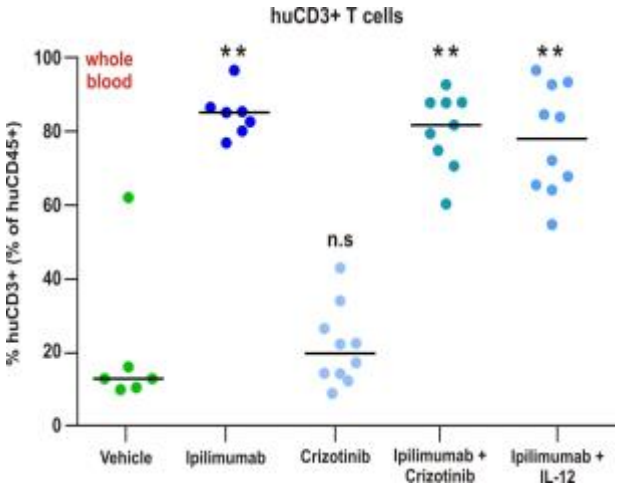
CTG – 0852; HLA-A2 matched

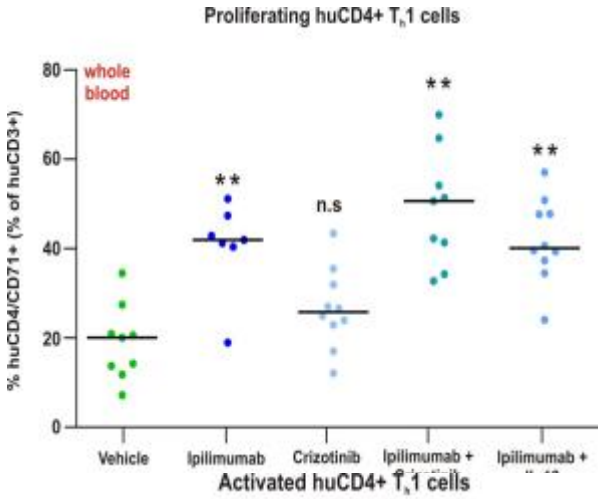


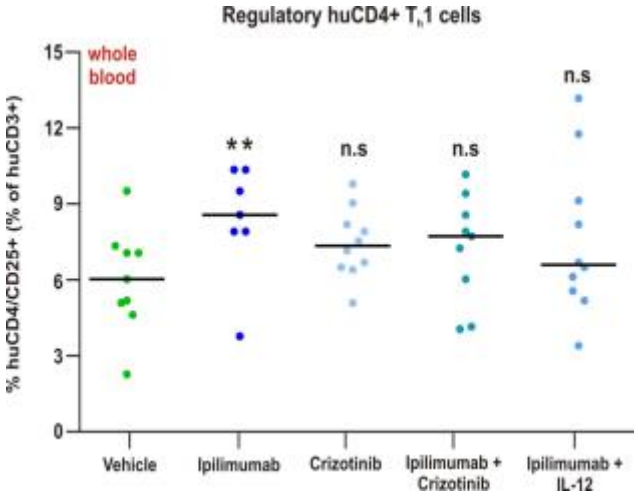
- Tumor regression in Ipilimumab treated mice Induction of T-Cell proliferation and expansion overall observed in peripheral blood
  - ↑CD8+ cytotoxic T-Cells
- An allogeneic response?

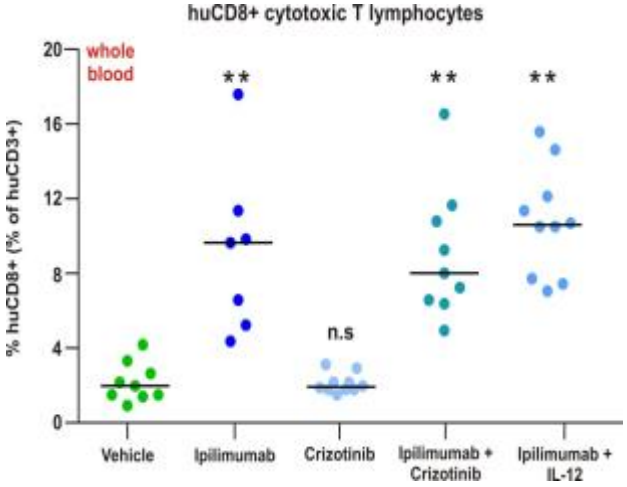
Baia et al. AACR 2015

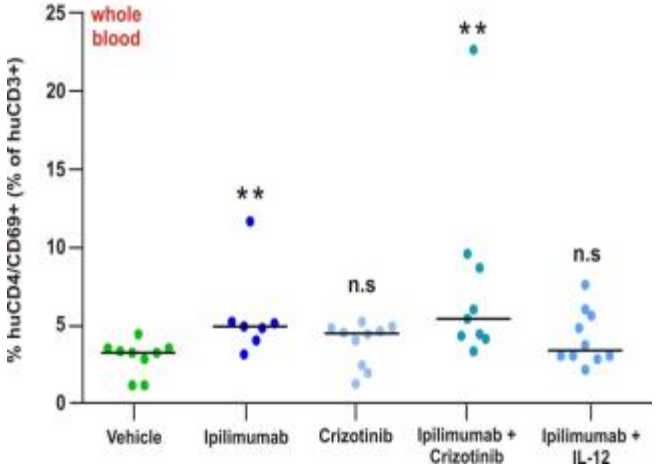
T-Cell Proliferation









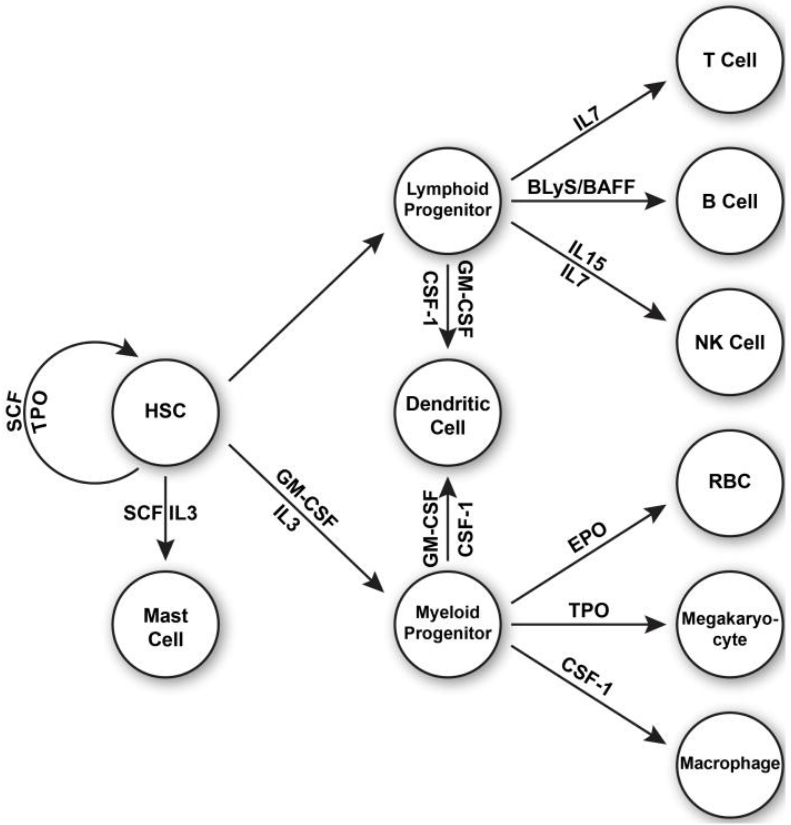


Non-parametric Mann-Whitney:
** p <0.05, n.s non-significant

Baia et al. AACR 2015

PDX Future: Humanized Mice Predicting Immunotherapy Sensitivity

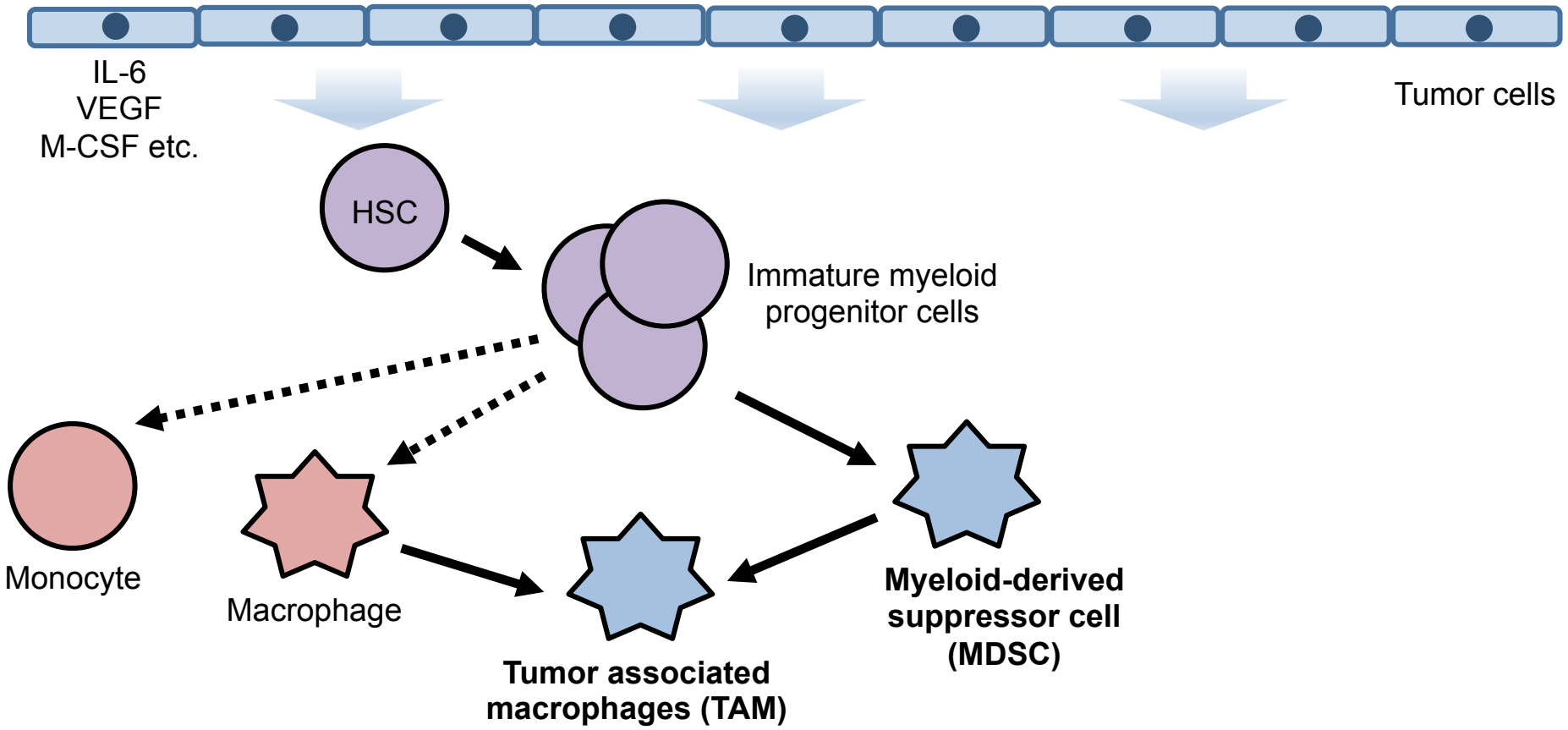
Transgenically Expressed Cytokines and HLA to enhance HSC Engraftment



- NOG/HLA-DR4/I-Aβ$^{-/-}$ mice
  - T-cell homeostasis differentially regulated
  - Antigen inducible antibody class switching
- NOG/HLA-A2
- NOG/HLA-A2/DR4/GM-IL-3 Tg
  - T-cell homeostasis differentially regulated
  - Antigen inducible antibody class switching
  - Myeloid tumor suppressive cells

Shultz et al. Nat Rev Immunol. 2012 Nov; 12(11): 786–798
M. Ito manuscript in preparation 2015
Suzuki et al. Int Immunol. 2012 Apr;24(4):243-52

PDX Future: Enhanced Humanized Mice for Tumor Microenvironment Effector Studies

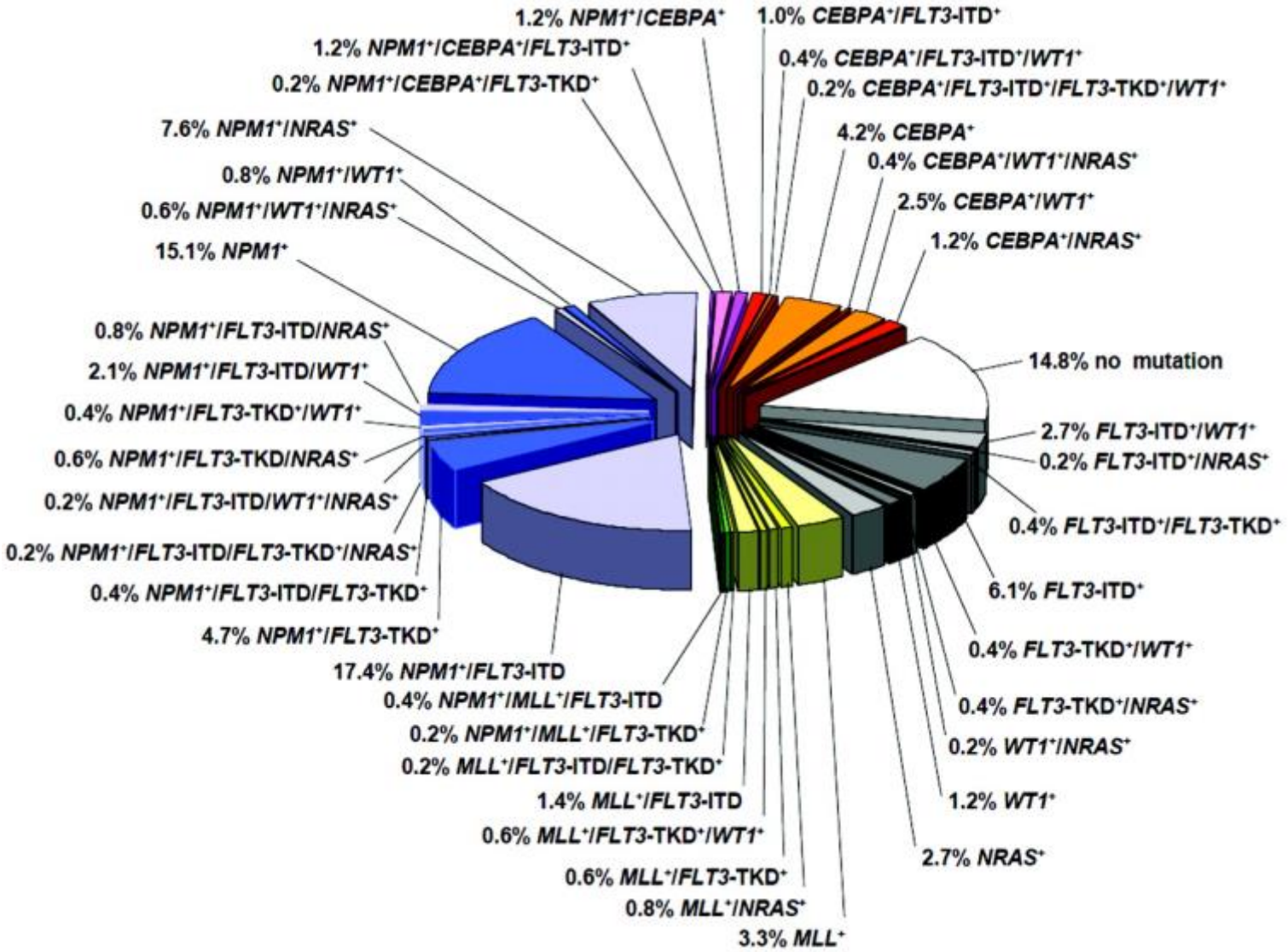


Immflamatory myeloides ⟺ **Immune suppressive myeloides**

- Non-specific suppression of immune system
- Produce cytokines and soluble factors that support tumor angiogenesis

M. Ito et al CIEA, 2015, manuscript in preparation

AML is a genetically heterogeneous disease



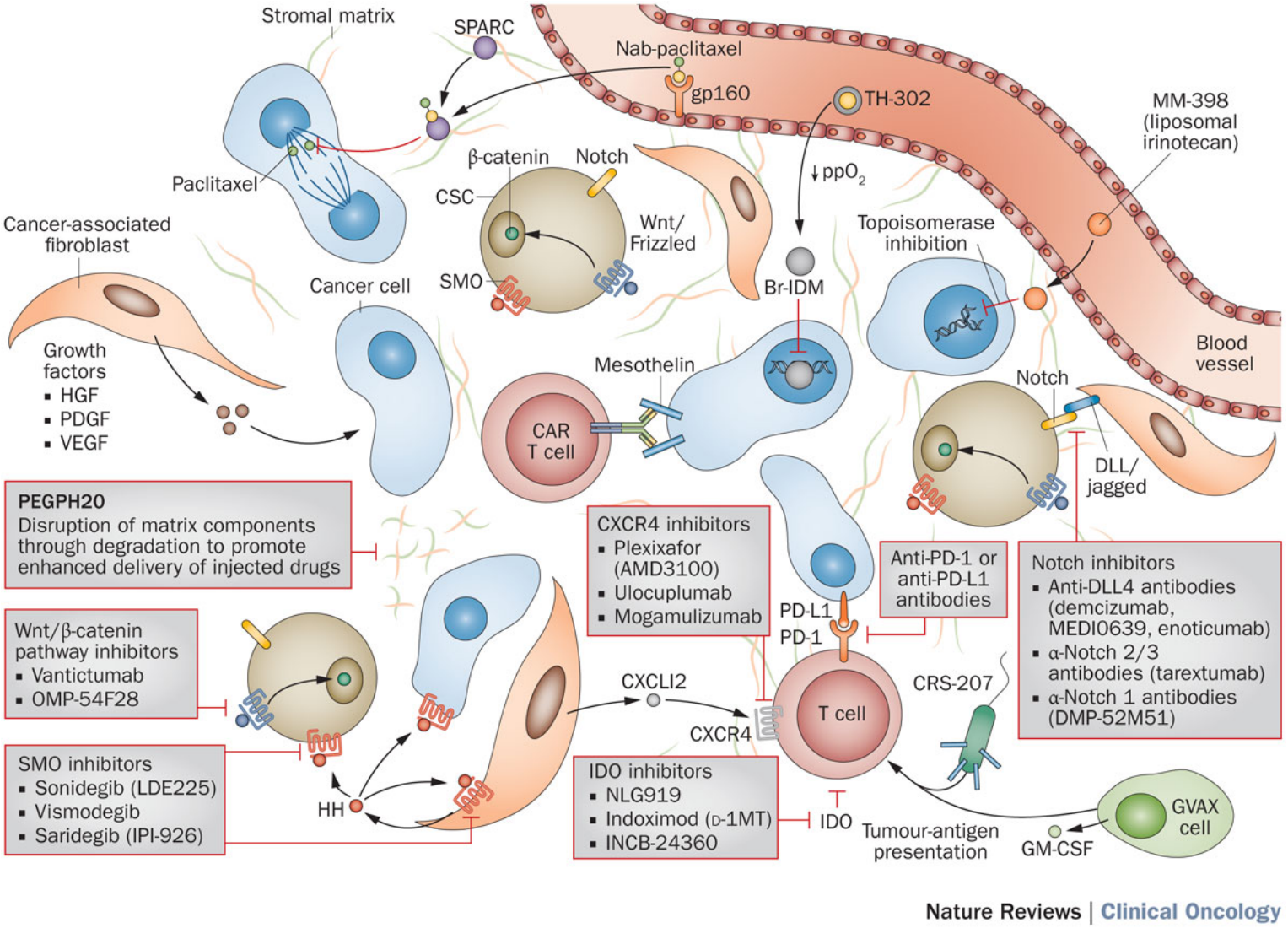
Roboz G (2011) Hematology

Methods

1) Source material: Apheresis from consented patient
   a) Apheresis typically yields 10^{19} cells
   b) Bank for ~10K P1 mice
2) Implantation into myeloablated NOG mice
3) Time coursed-flow cytometry phenotyping of huCD45+/ huCD33+/huCD3+ cells at 12 & 16 weeks post injection
4) Efficacy studies



Complexity of Drug Development: Novel Therapies and Targets in Pancreatic Cancer



Garrido-Laguna, I. & Hidalgo, M Nat Rev Clin Oncol. 2015 Mar 31

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