Dati generati da screening molecolari: piccoli trials e Big Data

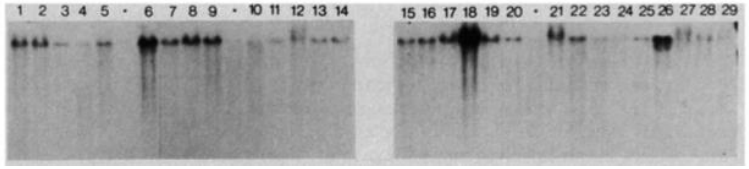
Luca Mazzarella, MD PhD
Istituto Europeo di Oncologia

An early example of targeted therapy developement

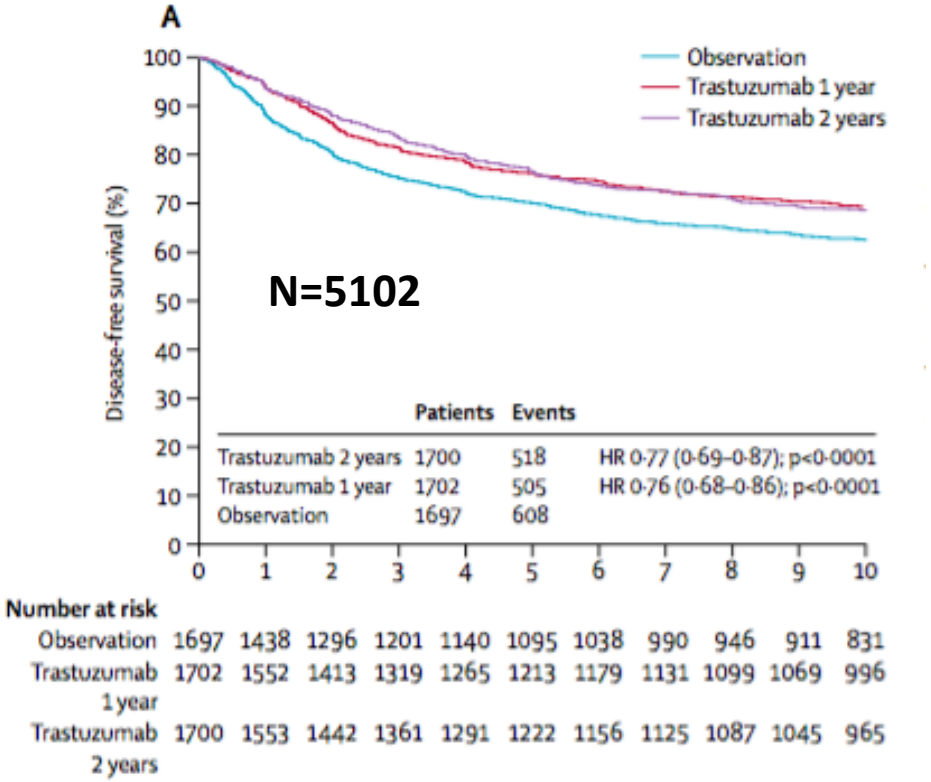
1987

Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, WILLIAM L. MCGUIRE

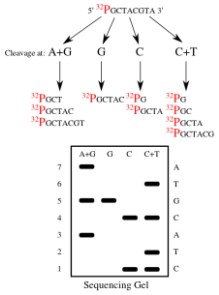


2005-2017

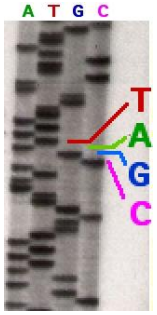


Evolution of genetic testing methods

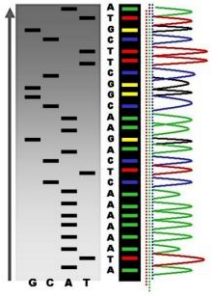
70's:
Maxam-Gilbert



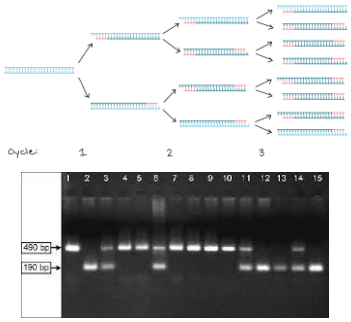
70's:
Sanger-radio



80's:
Sanger-fluorescent
(automated)

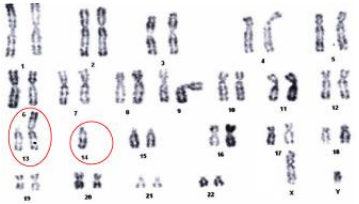


80's:
PCR

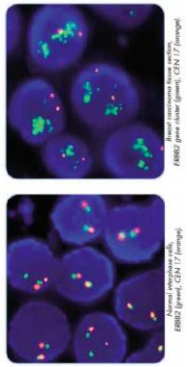


2000's:
Next-generation sequencing

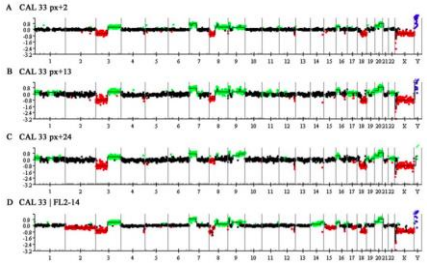
70's and before:
Kariotyping

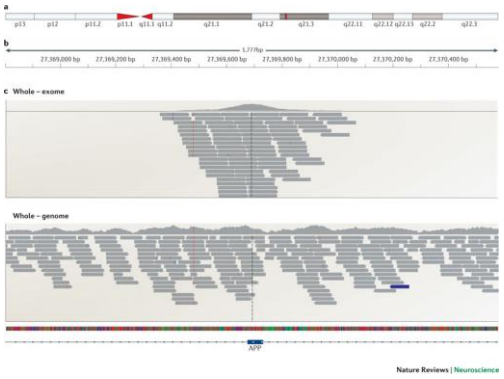


70's:
FISH

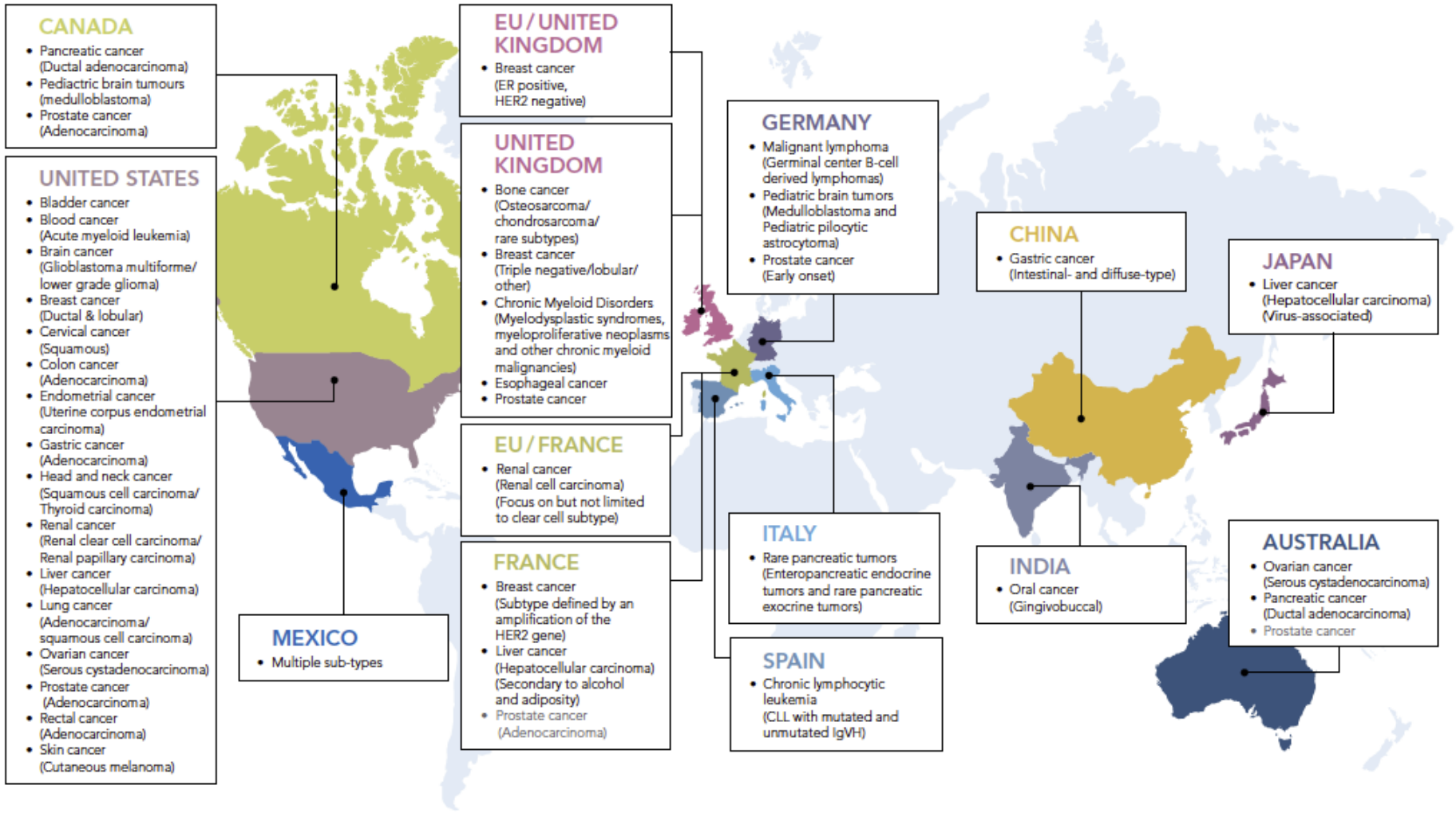


90's:
Comparative genome
hybridization



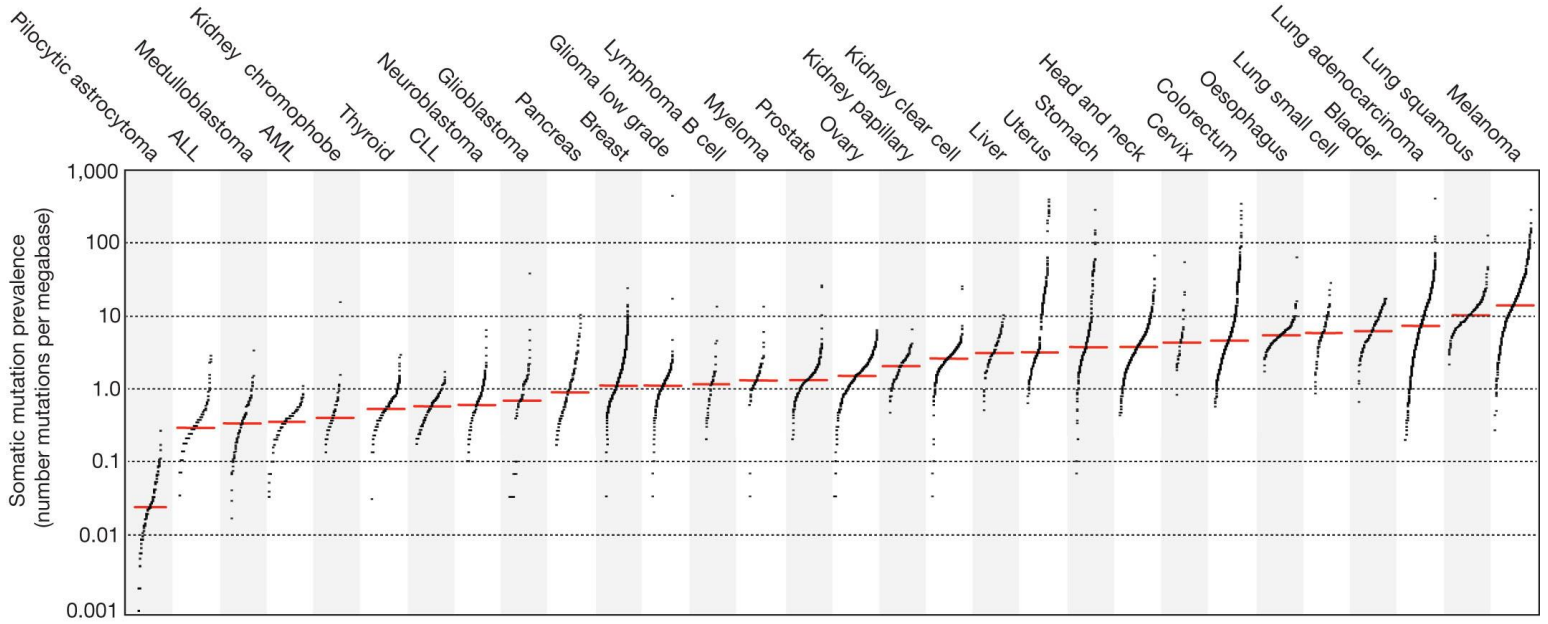


The International Cancer Genome Consortium



What we have learned so far

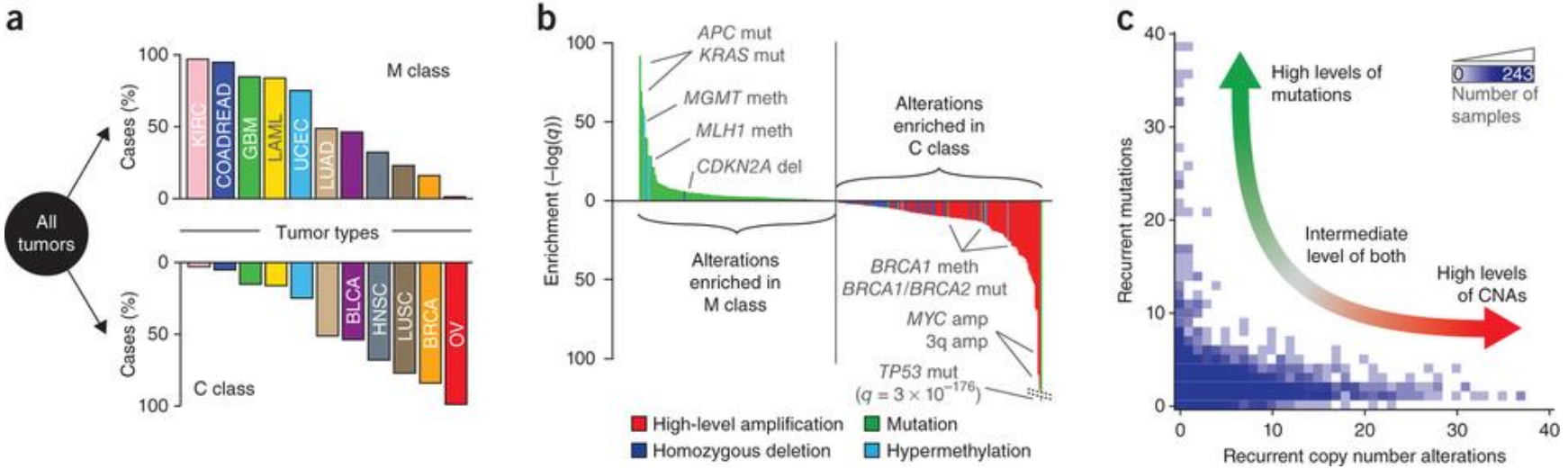
1. The prevalence of somatic mutations across human cancer types is extremely variable and influenced by the tissue of origin.



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

What we have learned so far

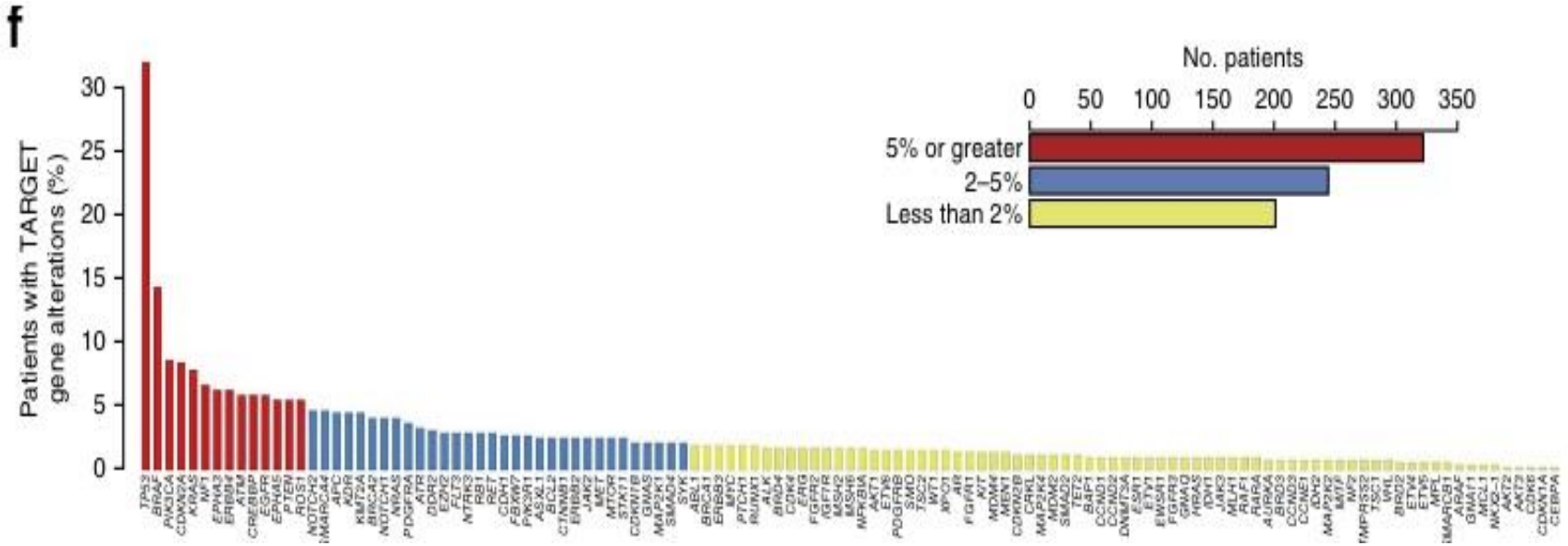
2. Some tumors are dominated by SNVs, others by structural variants



Ciriello et al, Nature Genetics 45, 1127–1133 (2013)

What we have learned so far

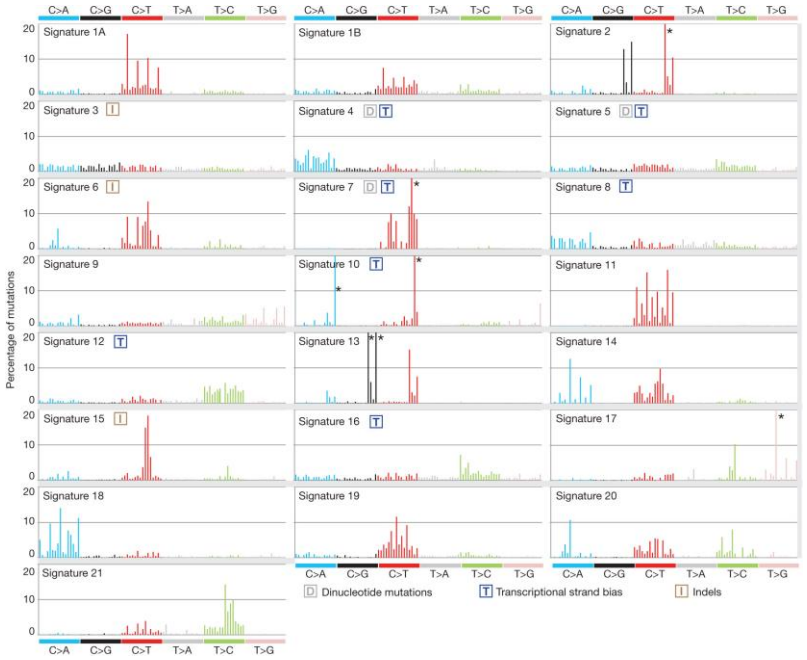
3. The tumor landscape is dominated by few frequent mutants (e.g. TP53, PIK3CA) and an ocean of rare mutants

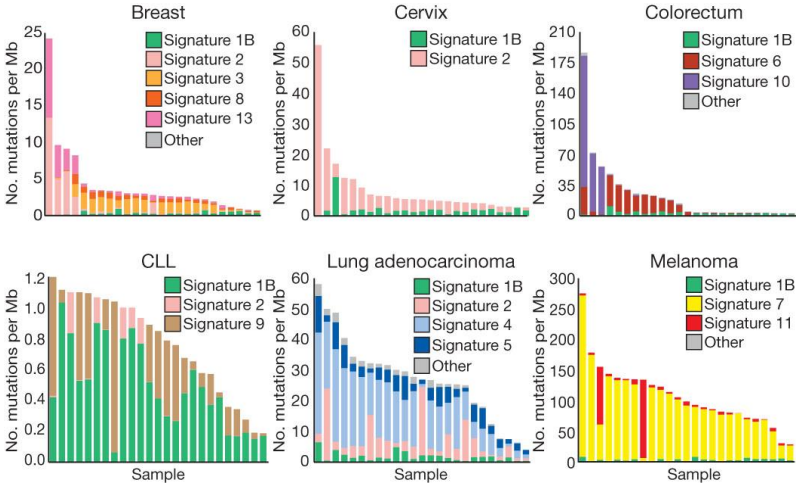


Van Allen et al, Nature Medicine 20, 682–688 (2014)

What we have learned so far

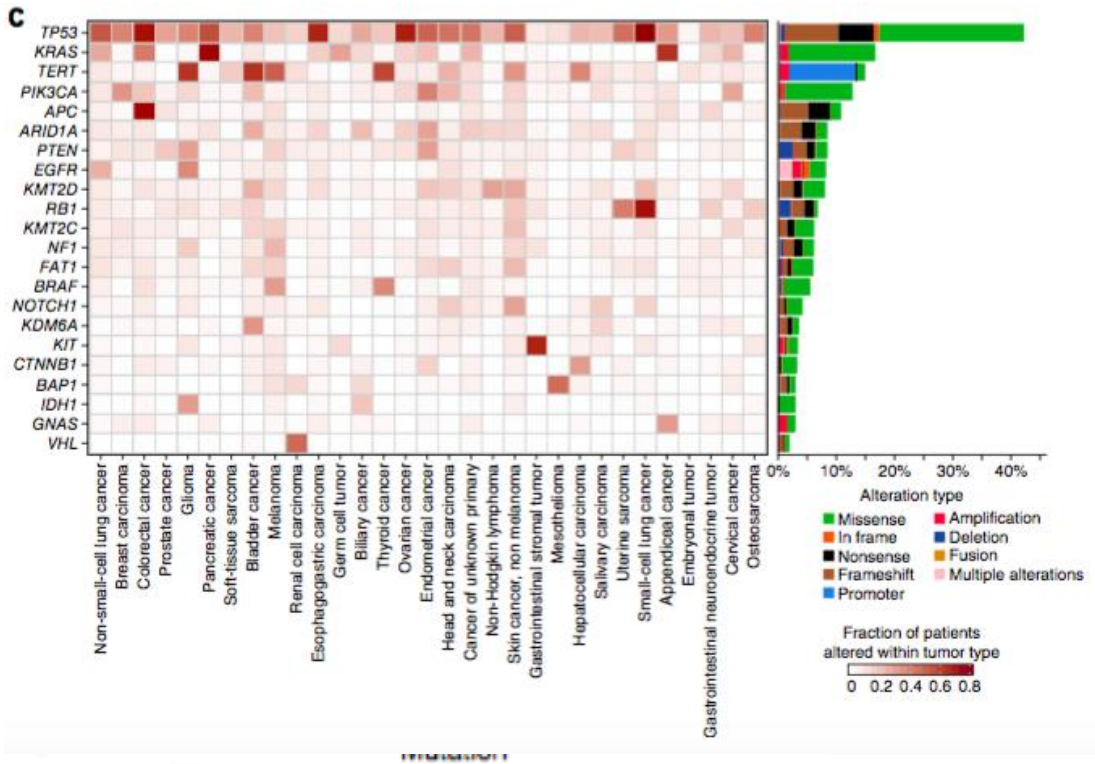
4a. Specific cancers are characterized by defining mutational signatures



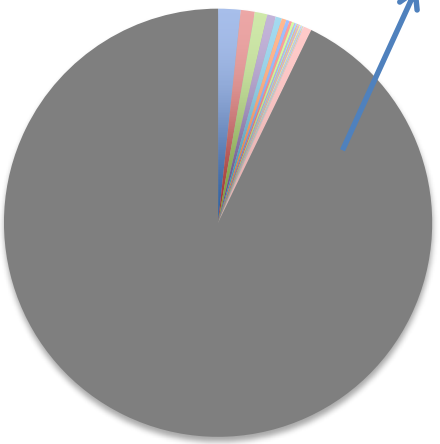


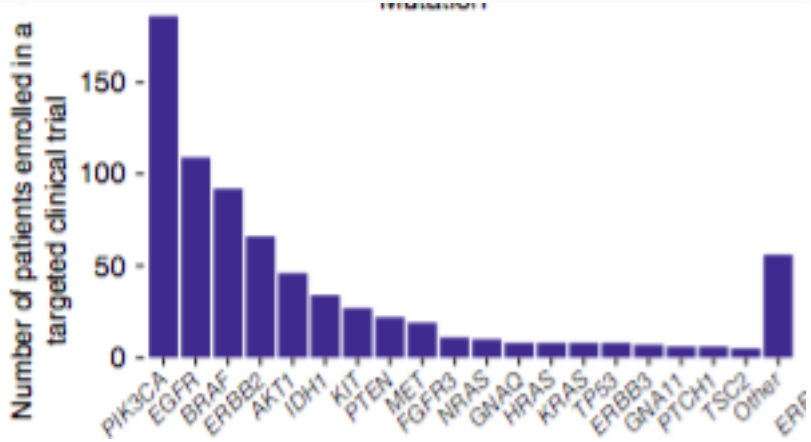
LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

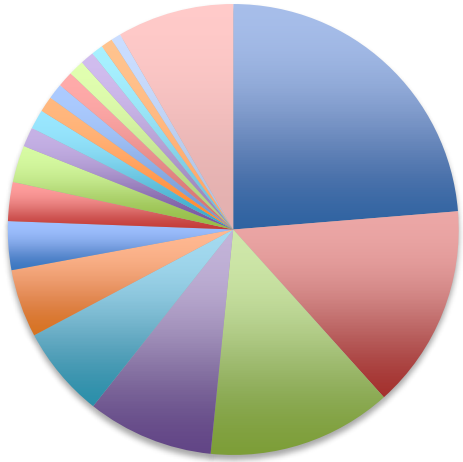
The issue: long tail of very rare biomarkers



Total screened







How to tackle the fragmentation of the biomarker-positive population?

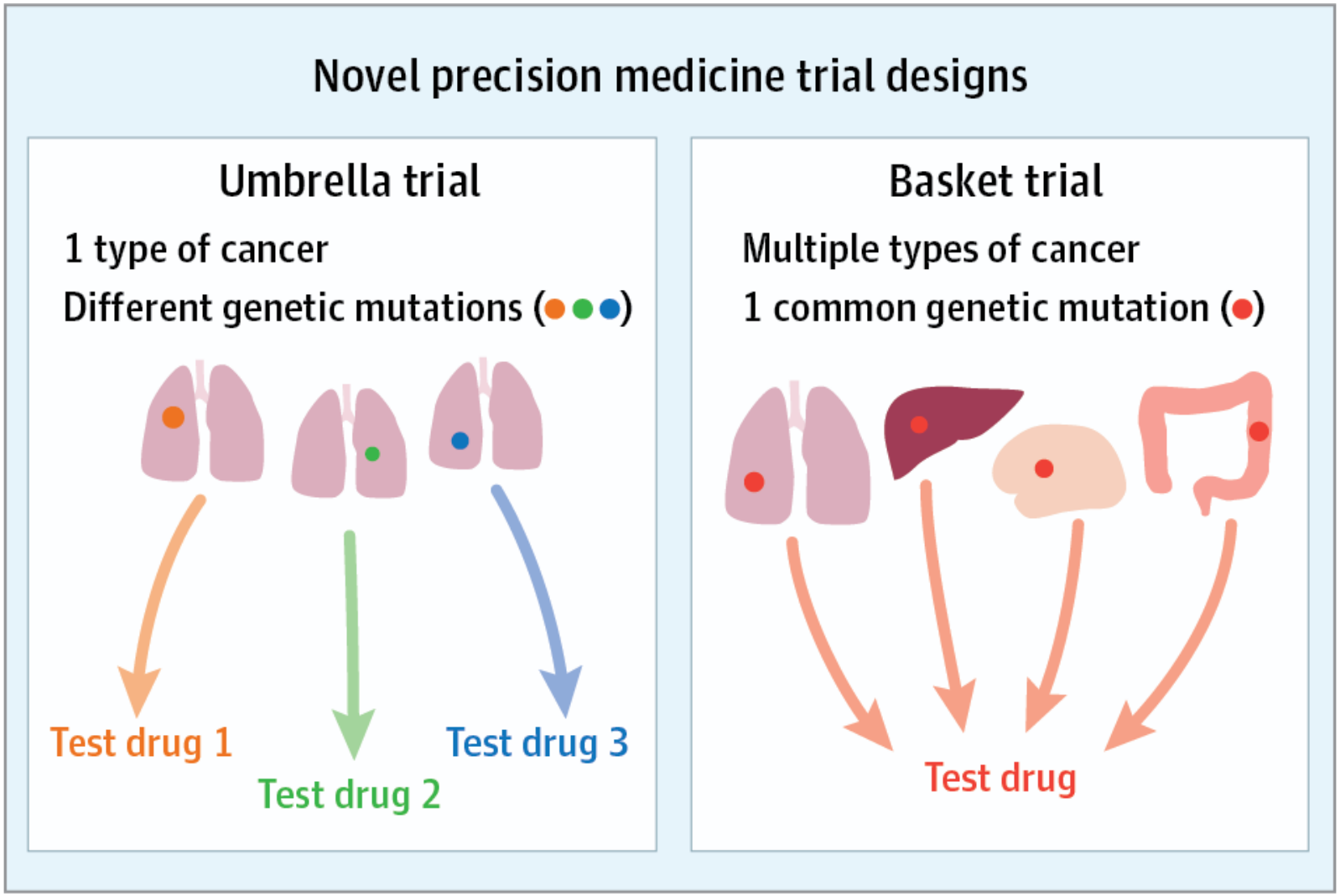


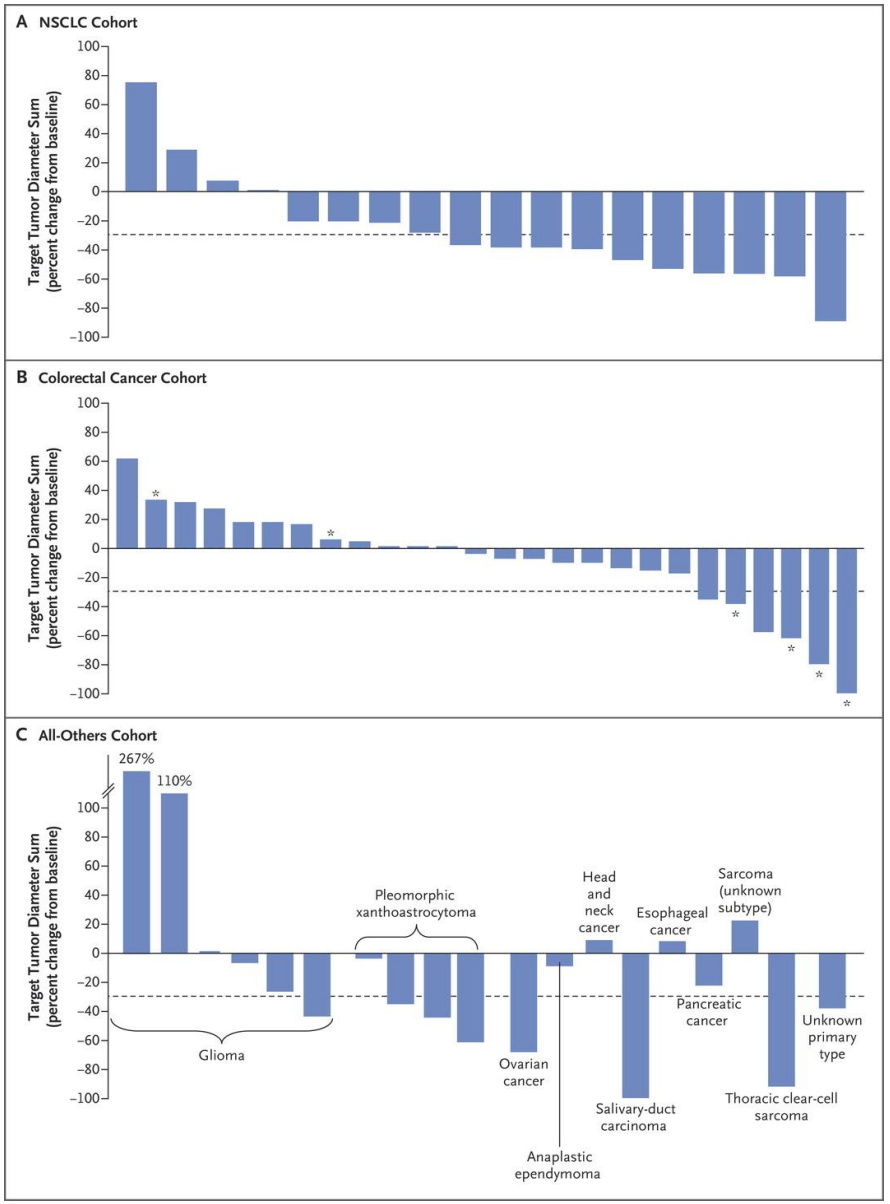
Table 2. Examples of Master Protocols in Cancer.*

Trial	Description	Design	Drug or Drugs	Disease and Target	Study Population	End Points
B2225[6]	Basket trial to determine cancers responsive to imatinib	Phase 2, multicenter, open-label, noncomparative trial	Single: imatinib (400 or 800 mg per day)	40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases	186 patients ≥15 yr of age	Tumor response (SWOG criteria and investigator's assessment)
BRAF V600[7]	Basket trial to evaluate the efficacy of vemurafenib in nonmelanoma cancers	Early phase 2, multicenter, open-label, noncomparative, adaptive trial using Simon's two-stage design	Vemurafenib monotherapy or (in some patients with colorectal cancer) vemurafenib plus cetuximab	Multiple nonmelanoma cancers with *BRAF* V600 mutations; eight tumor-specific cohorts plus an "all others" cohort	122 adults (≥18 yr of age)	Response rate (assessed by investigators according to RECIST or IMWG criteria) at wk 8
NCI-Match[8]	Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective	Exploratory, multicenter, noncomparative trial	Multiple: 30 treatments (as of May 2016), both FDA-approved and investigational, that target gene abnormalities	Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations	35 adults planned per substudy; pediatric study to begin in 2017	Tumor response (primary) and progression-free survival
BATTLE-1[9]	Umbrella trial to evaluate targeted therapies in chemotherapy-refractory NSCLC	Phase 2, single-center, comparative, adaptive randomization trial	Multiple: three monotherapies (erlotinib, vandetanib, and sorafenib) and one combination (erlotinib plus bexarotene)	Advanced NSCLC; targets included *EGFR* mutation, *KRAS/BRAF* mutation, VEGF expression, and RXRs/CyclinD1 expression	255 adults in whom ≥1 chemotherapy regimen had failed	Complete or partial response or stable disease according to RECIST criteria at wk 8 (primary), progression-free survival, overall survival, and toxicity
I-SPY 2[10-12]	Adaptive platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures	Phase 2, multicenter, comparative, adaptive randomization trial	Multiple: standard chemotherapy and five new drugs (initially) as add-on to chemotherapy; 12 treatments tested to date, with latest (patritumab) added October 2016	Early, high-risk breast cancer; three biomarkers (hormone-receptor status, HER2 status, and MammaPrint risk score) define eight genetic subgroups	1920 women (estimated) with invasive tumor ≥2.5 cm in diameter	Pathological complete response
Lung-MAP[13-15]	Master protocol to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC	Phase 2–3 comparative trial	Multiple: four investigational drugs plus one therapy for no-match control group (initially); three investigational drugs remain	Squamous-cell NSCLC; multiple targets (four molecular targets initially; three remain)	100–170 patients planned for phase 2 (40 are now enrolled); 300–400 planned for phase 3	Objective response rate, progression-free survival, and overall survival

Woodcock et al NEJM 2017

BASKET TRIALS: EXAMPLES

Vemurafenib in non-melanoma BRAF-mutated cancers



Hyman DM et al. N Engl J Med 2015;373:726-736.

Memorial Sloan Kettering Cancer Center

Oral CT001

Neratinib in *HER2*- or *HER3*-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study

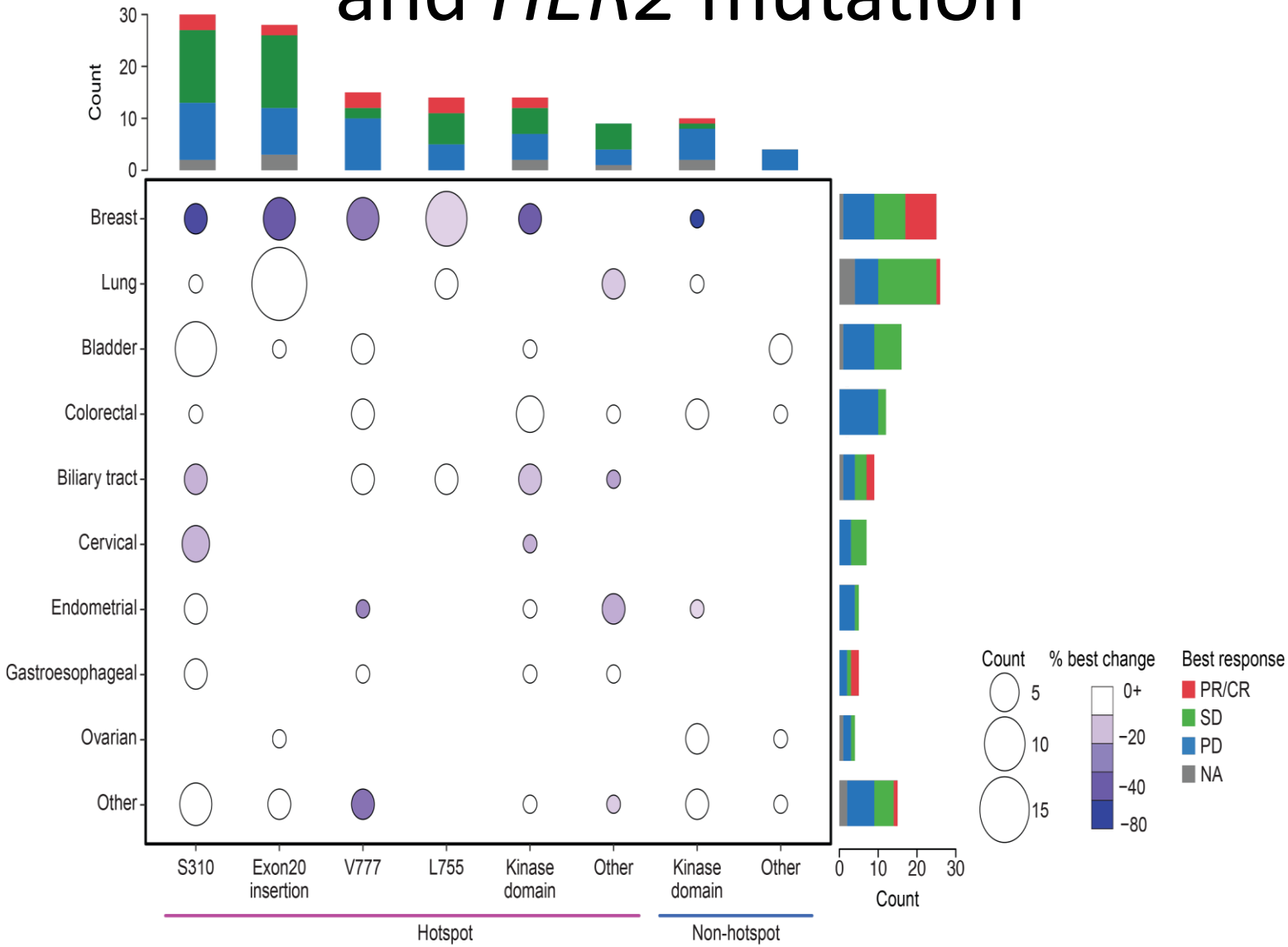
David M. Hyman,[1] Sarina Piha-Paul,[2] Jordi Rodon,[3] Cristina Saura,[3] Geoffrey I. Shapiro,[4] David I. Quinn,[5] Victor Moreno, [6] Ingrid Mayer,[7] Carlos Arteaga,[7] Valentina Boni,[8] Emiliano Calvo,[8] Sherene Loi,[9] A. Craig Lockhart,[10] Lillian M. Smyth,[1] Joseph Erinjeri,[1] Maurizio Scaltriti,[1] F Javier Carmona,[1] Gary Ulaner,[1] Jean Torrisi,[1] Juber Patel,[1] Jiabin Tang,[1] Fanli Meng,[1] Duygu Selcuklu,[1] Helen Won,[1] Nancy Bouvier,[1] Michael F. Berger,[1] Richard E. Cutler, Jr.,[11] Feng Xu,[11] Anna Butturini,[11] Lisa D. Eli,[11] Grace Mann,[11] Cynthia Farrell,[11] Alshad S. Lalani,[11] Richard Bryce,[11] Funda Meric Bernstam,[2] José Baselga,[1] David B. Solit[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Vall d'Hebron University Hospital, Barcelona, Spain; [4]Dana Farber Cancer Institute, Boston, MA, USA; [5] USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [6] START Madrid Fundación Jímenez Díaz, Madrid, Spain; [7]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [8]START Madrid Group, Madrid, Spain [9]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [10]Washington University in St. Louis School of Medicine, St. Louis, MO, USA; [11]Puma Biotechnology Inc, Los Angeles, CA, USA

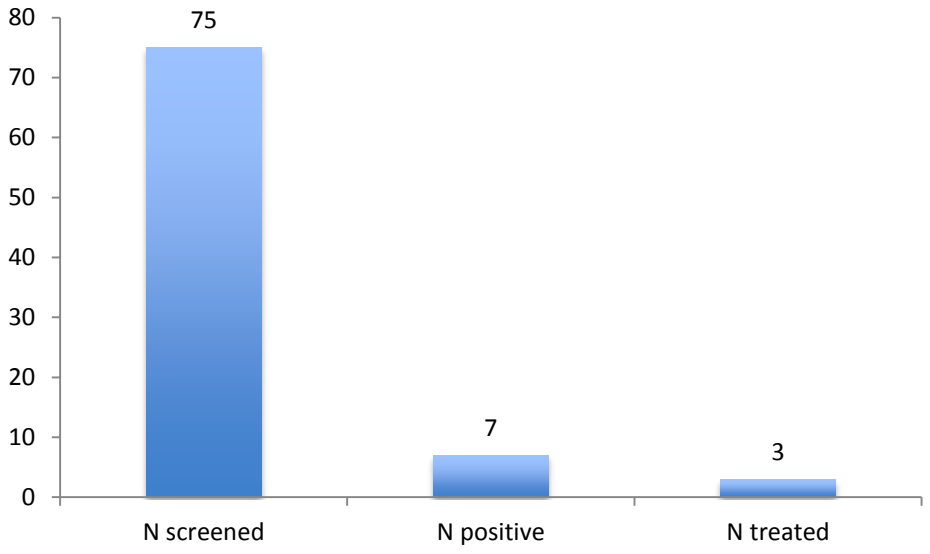
Enrollment by tumor type

	Neratinib monotherapy (n=141)
***HER2*-mutation positive**	
• Lung cancer	26 (18.4)
Breast cancer	25 (17.7)
• Bladder/urinary tract cancer	16 (11.3)
Solid tumors (NOS)	15 (10.6)
Colorectal cancer	12 (8.5)
• Biliary tract cancer	9 (6.4)
Endometrial cancer	7 (5.0)
Cervical cancer	5 (3.5)
Gastroesophageal cancer	5 (3.5)
Ovarian cancer	4 (2.8)
***HER3*-mutation positive**	
Solid tumors (NOS)	17 (12.1)

Integrated efficacy by tumor type and *HER2* mutation



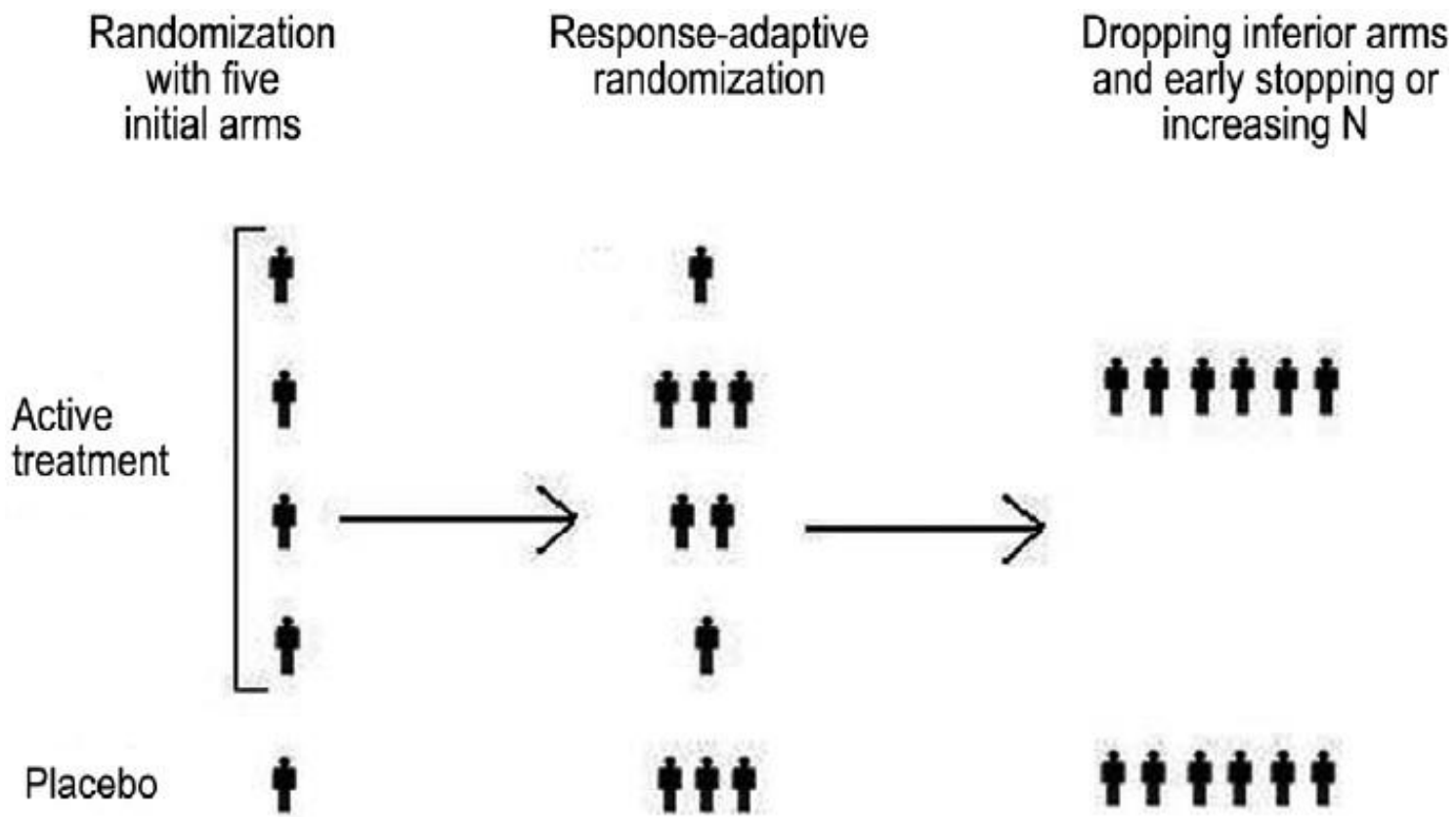
Some experience with a basket trial in IEO with FGFR inhibitors



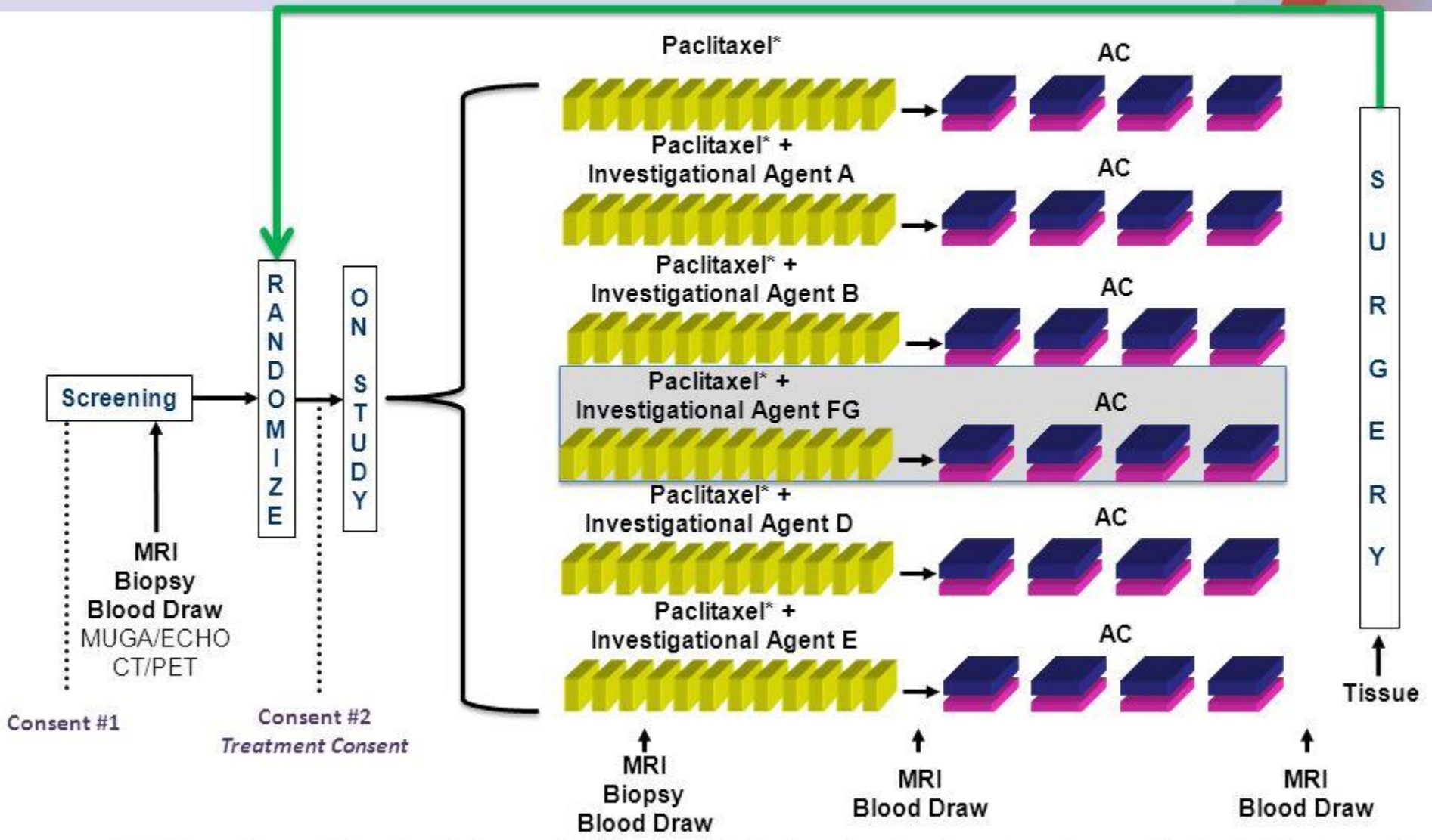
1 PD
1 SD
1 PR

UMBRELLA TRIALS: EXAMPLES

Adaptive randomization

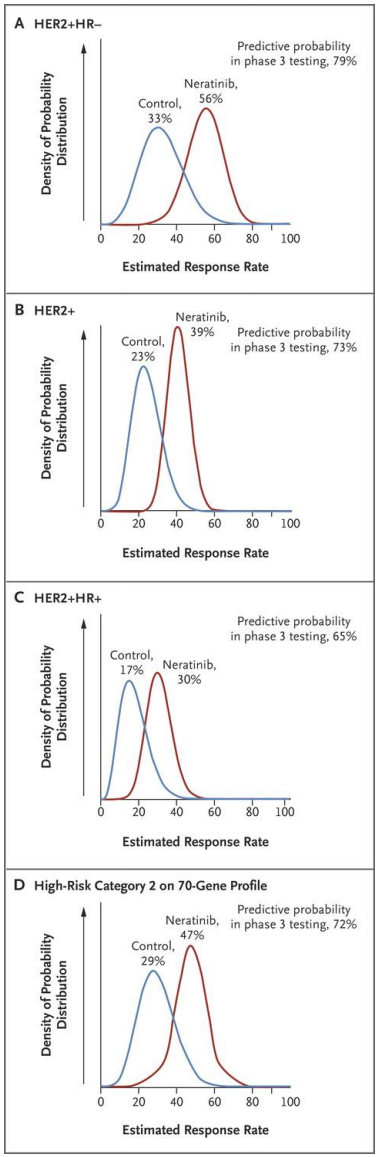


I-SPY 2 Adaptive Trial Design



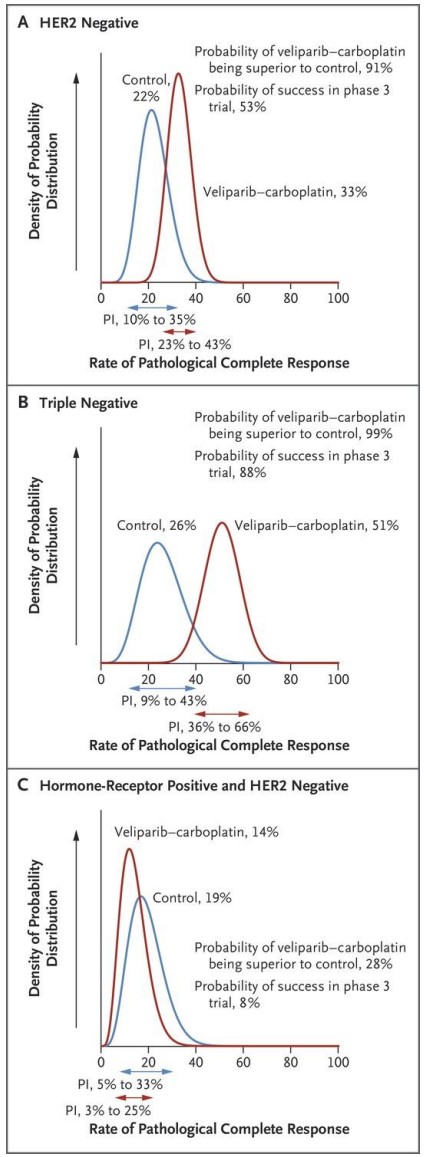
* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.

Neratinib



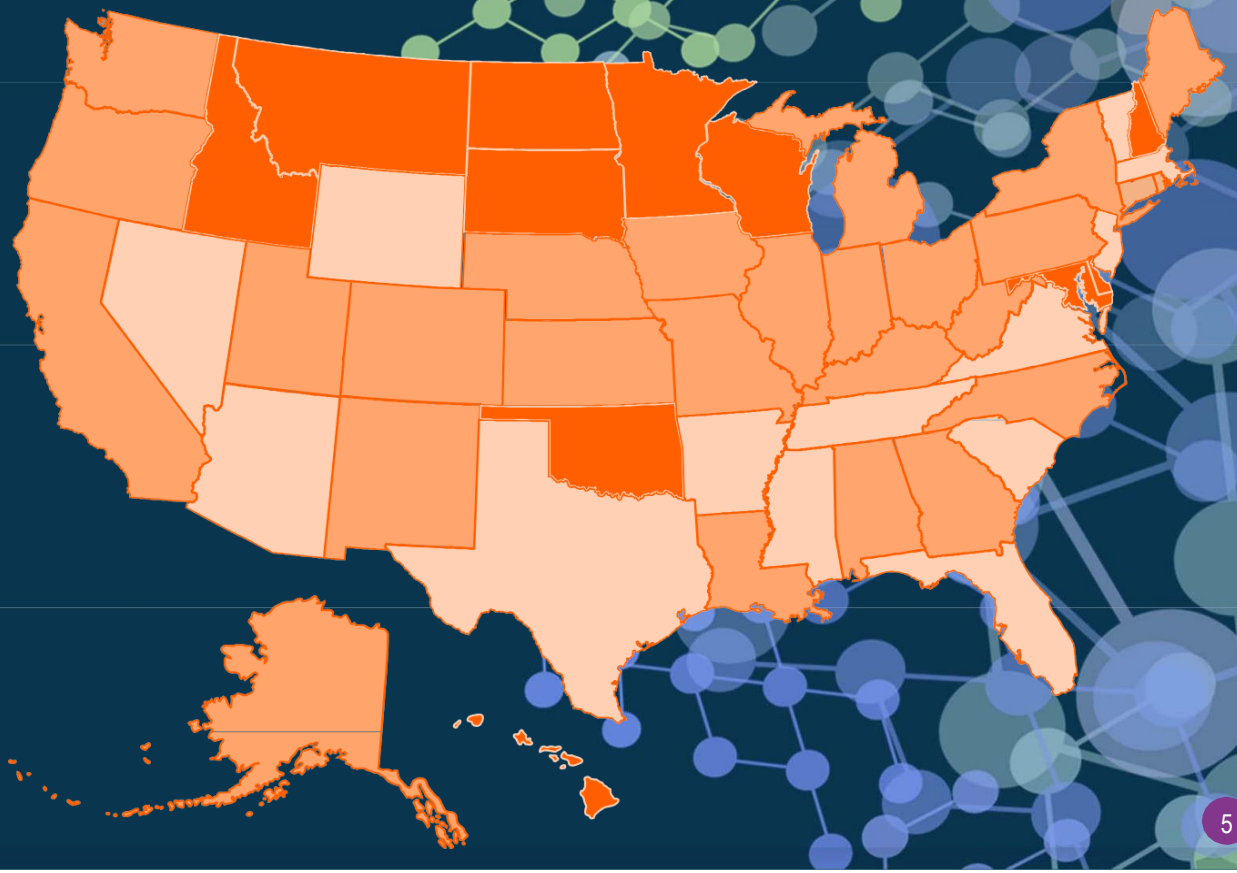
PARK ET AL NEJM 2016

Veliparib + CBDCA



RUGO ET AL NEJM 2016

NCI "MATCH" CANCER TREATMENT TRIAL: STATE BY STATE ENROLLMENT

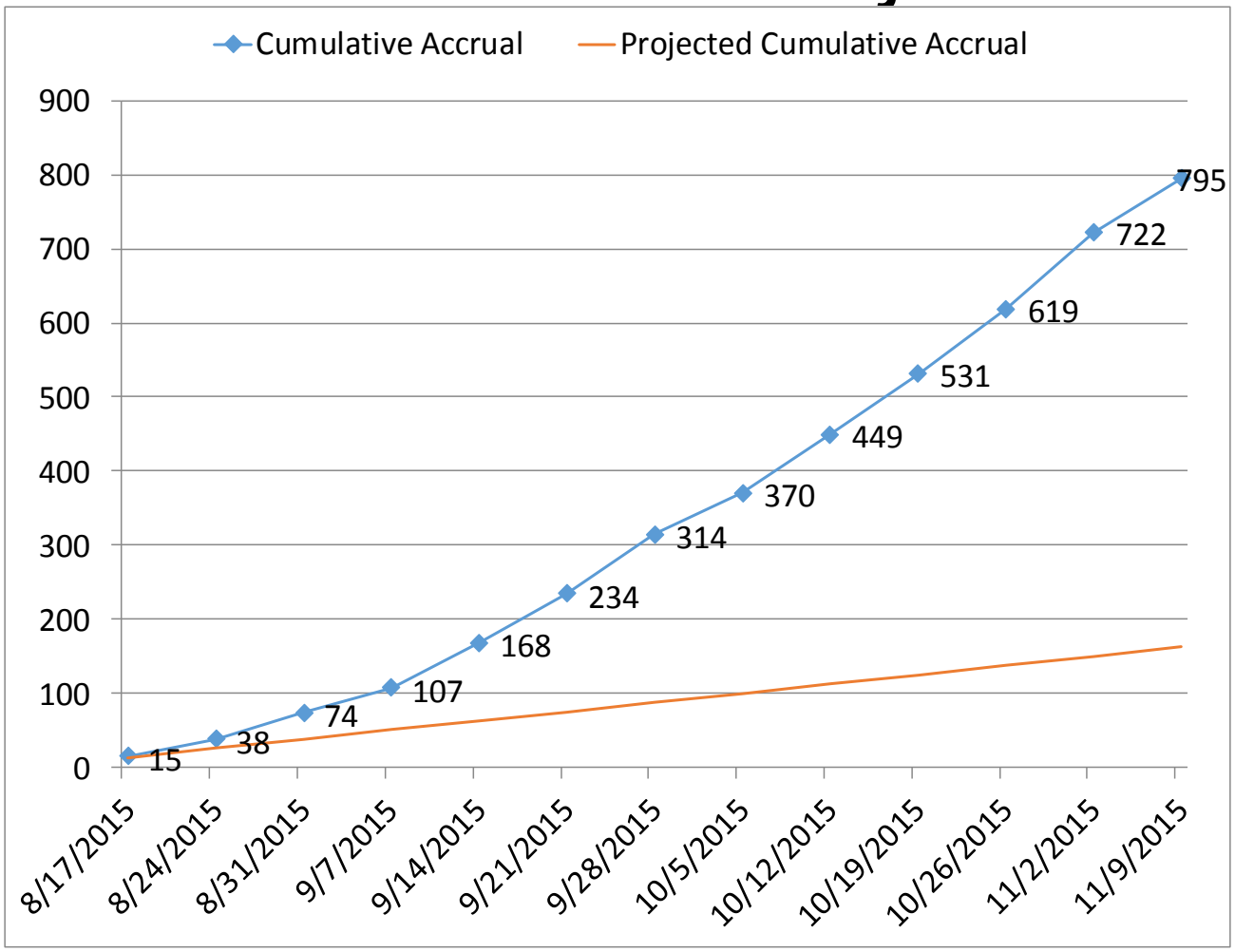


ENROLLMENT PER 1 MILLION POPULATION

- 30 – 65
- >8 – <30
- FEWER than 8

MATCH = Molecular Analysis for Therapy CHoice

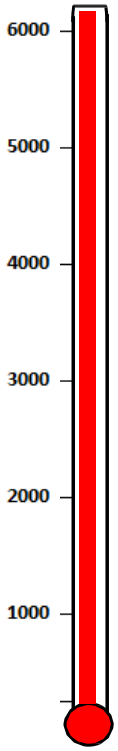
NCI-MATCH Weekly Accrual Far Exceeded Projections



Projected 50 Cases/Month at Start

Gradual Ramp-up in Year 1

NCI-MATCH Testing and Enrollment as of 6/18/17



6398 patients with tumor samples (N=6000)

5482 patients had received their test results

983 had a gene abnormality matching an available treatment

And proceeded to be further evaluated for the specific eligibility for the arm to which they matched

660 patients had enrolled for treatment

NOTE: These are strictly numbers reflecting a point in time and cannot be used to calculate overall rates; some are assigned and still in evaluation for eligibility for an arm; estimated 72% of those assigned will enroll

NCI MATCH INTERIM ANALYSIS

Activated 08/12/15; paused 11/11/15: 92 days		
Patient cases registered for screening	795	
Cases with samples submitted	739	
Cases where labs were able to complete tumor testing	645	87% (N=739)
Cases with mutation matching 1 of 10 available treatment arms	56	9% (N=645)
Patients matching specific eligibility criteria for, and assigned to, a treatment arm	33	5% (N=645)
Patients who entered 7 of 10 available treatment arms	16	2.5% (N=645)

NCI-MATCH Expanded to 25 Arms May 31, 2016

Arm / Target	Drugs(s)
A EGFR mut	Afatinib
B HER2 mut	Afatinib
C1 MET amp	Crizotinib
C2 MET ex 14 sk	Crizotinib
E EGFR T790M	AZD9291
F ALK transloc	Crizotinib
G ROS1 transloc	Crizotinib
H BRAF V600	Dabrafenib+trametinib
I PIK3CA mut	Taselisib
N PTEN mut	GSK2636771
P PTEN loss	GSK2636771
Q HER 2 amp	Ado-trastuzumab emtansine

Arm / Target	Drug(s)
R BRAF nonV600	Trametinib
S1 NF1 mut	Trametinib
S2 GNAQ/GNA11	Trametinib
T SMO/PTCH1	Vismodegib
U NF2 loss	Defactinib
V cKIT mut	Sunitinib
W FGFR1/2/3	AZD 4547
X DDR2 mut	Dasatinib
Y AKT1 mut	AZD 5363
Z1A NRAS mut	Binimetinib
Z1B CCND1,2,3 amp	Palbociclib
Z1D dMMR	Nivolumab
Z1I BRCA 1/2	AZD1775

ECOG-ACRIN cancer research group | NIH NATIONAL CANCER INSTITUTE

Red = accrued 35 patients;
Green = nearing 35 patient

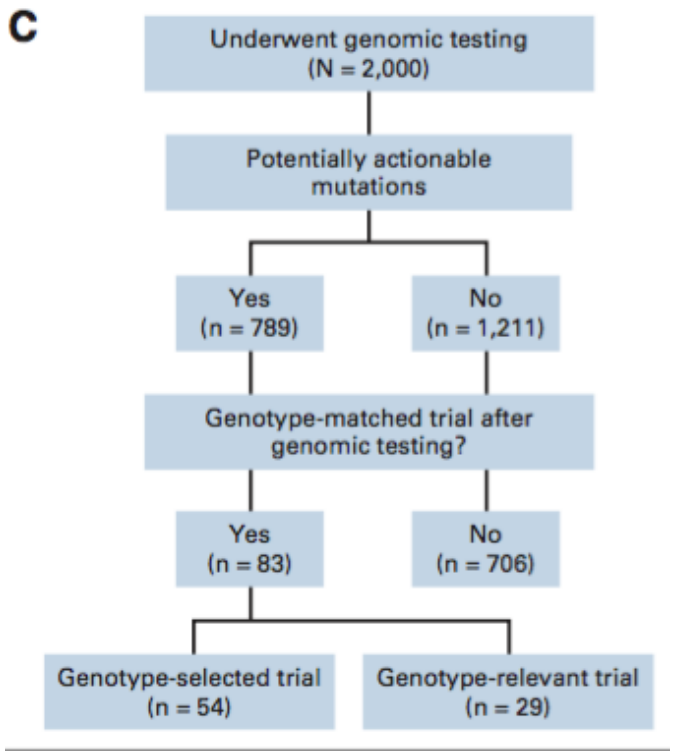
Arms added: March 13, 2017

- EAY131-J: Herceptin + Perjeta/HER2 Amp **(to follow Arm Q)**.
- EAY131-L: MLN0128/mTOR Mutations (**New target**)
- EAY131-M: MLN0128/TSC1/TSC2 Mutations (**New target**)
- EAY131-Z1C: Palbociclib/CDK4/CDK6 Amplification (**New target**)
- EAY131-Z1E: Loxo 101/NTRK Fusions (**New target**)
- EAY131-Z1I: AZD1775/BRCA1, BRCA2 mutations ***(New target)***

Current: as of June 18, 2017

- 25 treatment arms; ≈ 50% fully accrued; ≈ 25% well on the way; ≈ 25% will need additional accrual from **'rare variant study**'
- Assay success rate 94%
- Median assay turnaround time 16 days
- Toxicity acceptable
- Objective responses have been observed

High attrition rates for genome-driven targeted treatment



In a third of the patients, the genomic information from testing was not used for therapy planning (went elsewhere, progressed, died, or went on to a different therapy)

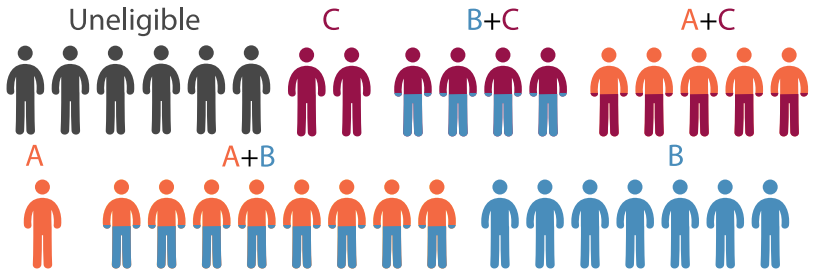
This may be due to the length in obtaining results (average 26 days)

Meric-Bernstam et al JCO 2015

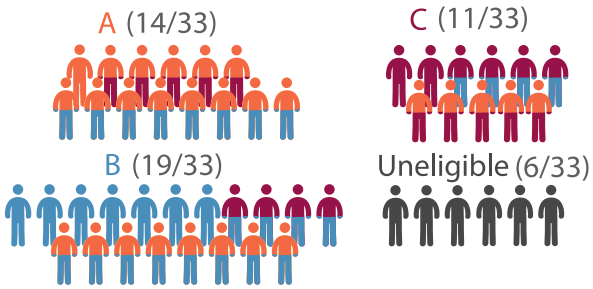
Issues with genetic biomarker-driven trials

- Actual drug allocation is still very low
- Require many drugs to become efficient
- Suffer from elevated attrition rates
  - Turnaround time is crucial and can be improved
- Are best performed as “platform” trials, where new drugs or biomarkers are continuously implemented
- Statistical design is very complex

Population

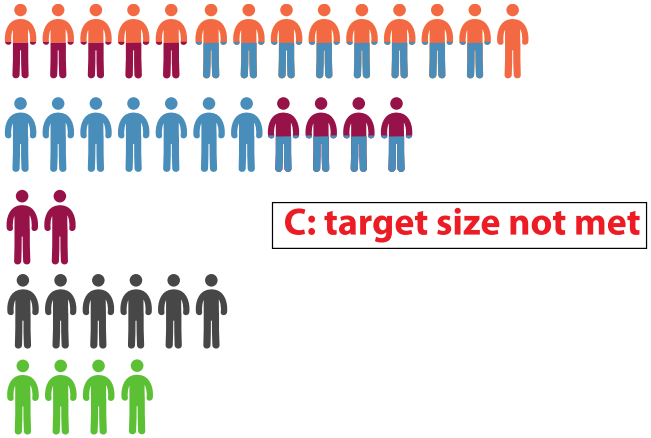


Drug eligibility



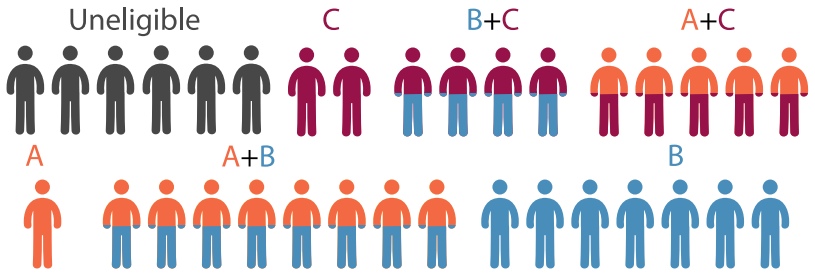
Target sample size

NON OPTIMAL DESIGN

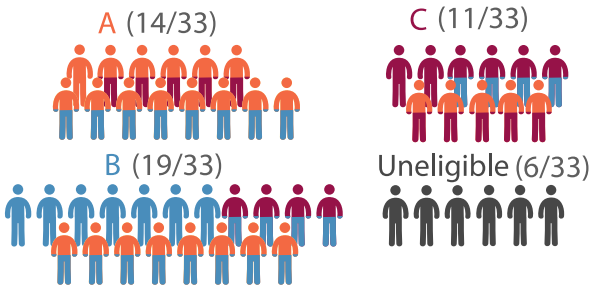


IF (A):
  THEN eligible for **drugA**
ELSE IF (B):
  THEN eligbile for **drubB**
ELSE IF (C):
  THEN eligibile for **drugC**
ELSE:
  Not allocated

Population

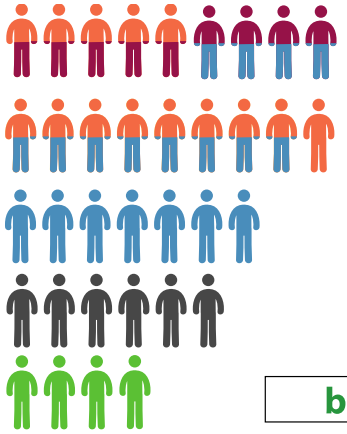


Drug eligibility



Target sample size

OPTIMAL DESIGN



balanced arms

IF (C):
  THEN eligible for **DrugC**
ELSE IF (A):
  THEN eligible for **Drug A**
ELSE if (B):
  THEN eligible for **DrugB**
ELSE:
  Not allocated

SHIVA: the biggest umbrella trial published to date

741 enrolled
496 with complete profile
293 with actionable alterations
195 randomized (98 lost at screening)

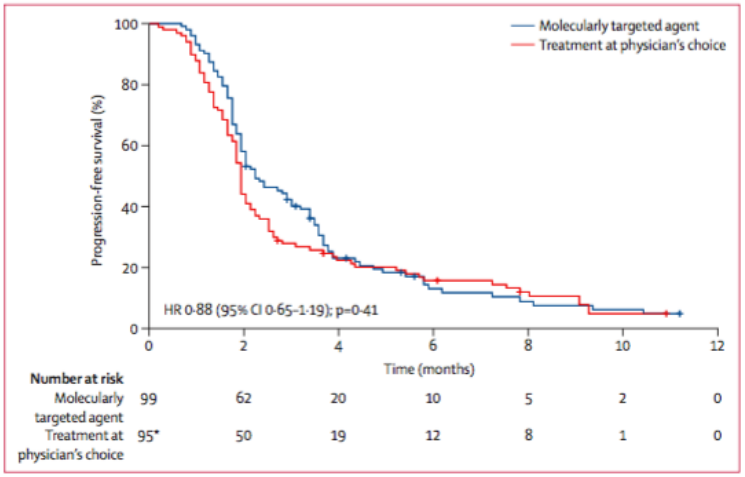


Figure 3: Progression-free survival
*One patient had a follow-up of zero days so is not shown here.

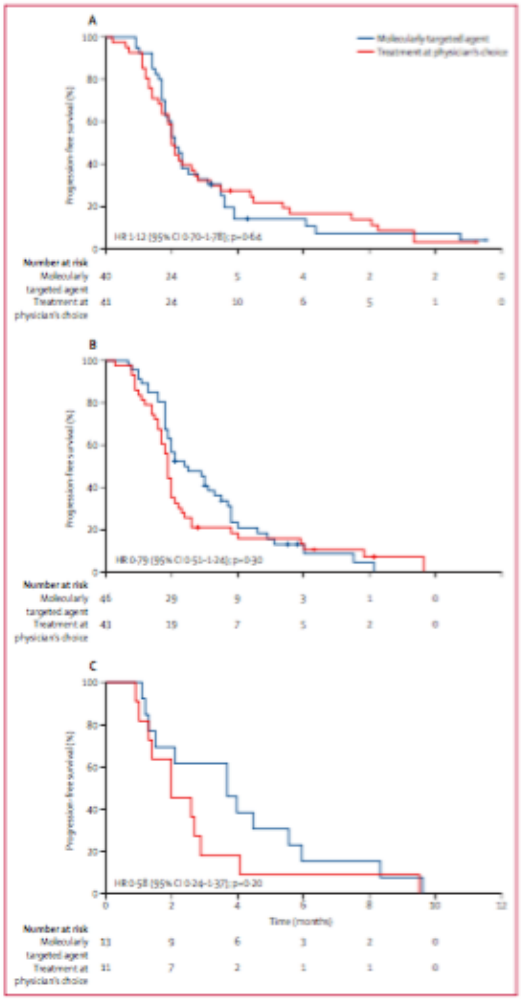


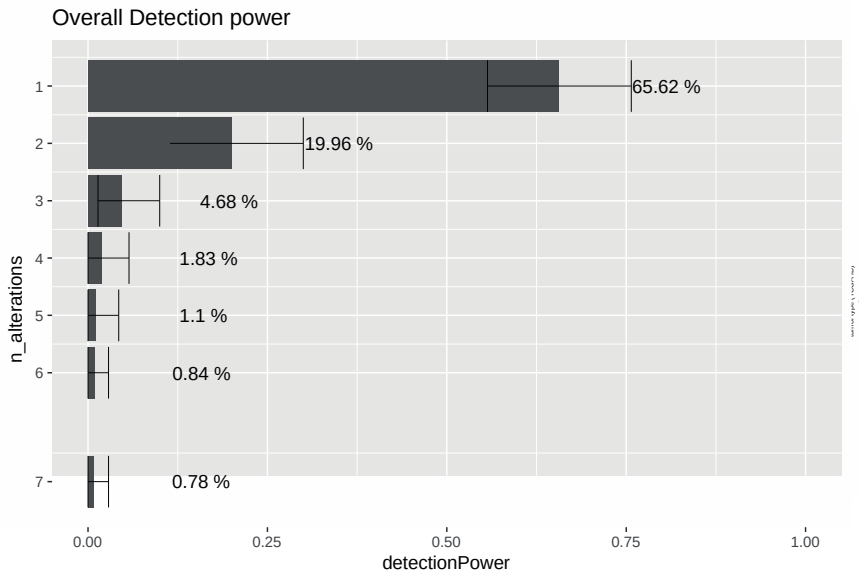
Figure 4: Progression-free survival by molecular pathway
Progression-free survival in patients with molecular alterations in the hormone receptor pathway (A), PI3K/AKT/mTOR pathway (B), and RAF/MEK pathway (C).

Bioinformatic estimate of biomarker-positive populations in Genomics-driven trials using Precision Trial Designer (PTD)

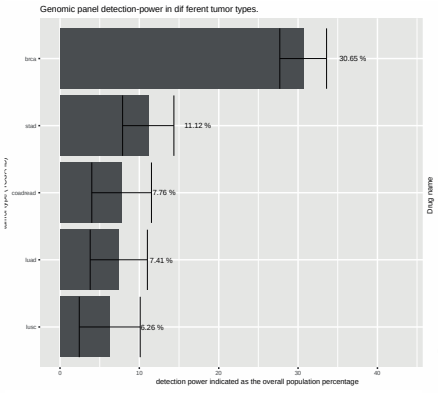
L.Mazzarella1, G.Melloni2, A.Guida 1, G.Curigliano1, E.Botteri3, A.Esposito1, M.Kamal4, C. Le Tourneau4, L. Riva5, P. Pelicci6

1New Drug Development, Istituto Europeo di Oncologia, Milan, IT, 2Biomedical Informatics, Harvard Medical School, Boston, MA, US, 3Norwegian National Advisory Unit on Women's Health, Oslo University Hosp., Oslo, NO, 4Dept of Medical Oncology, Institut Curie, Paris, FR, 5Center for Genomic Science, Italian Institute of Technology, Milan, IT, 6Department of Experimental Oncology, European Institute of Oncology, Milan, IT

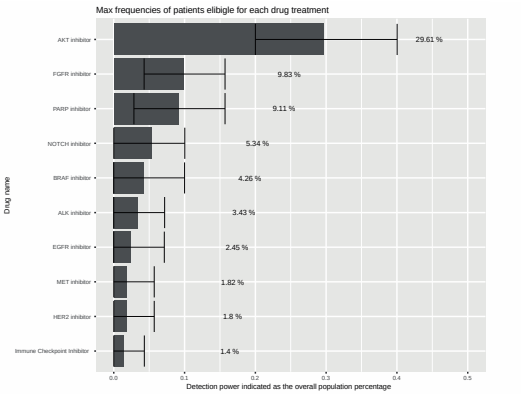
Fondazione IEO Istituto Europeo di Oncologia

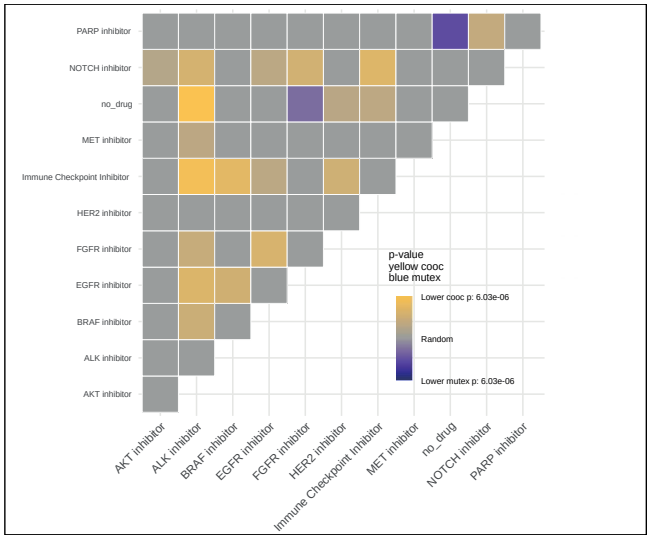


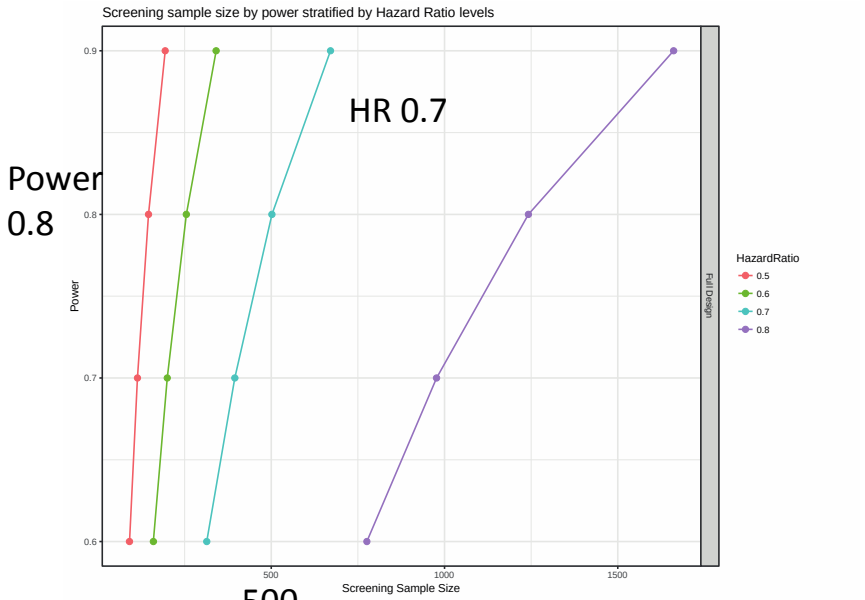
By histology



By drug

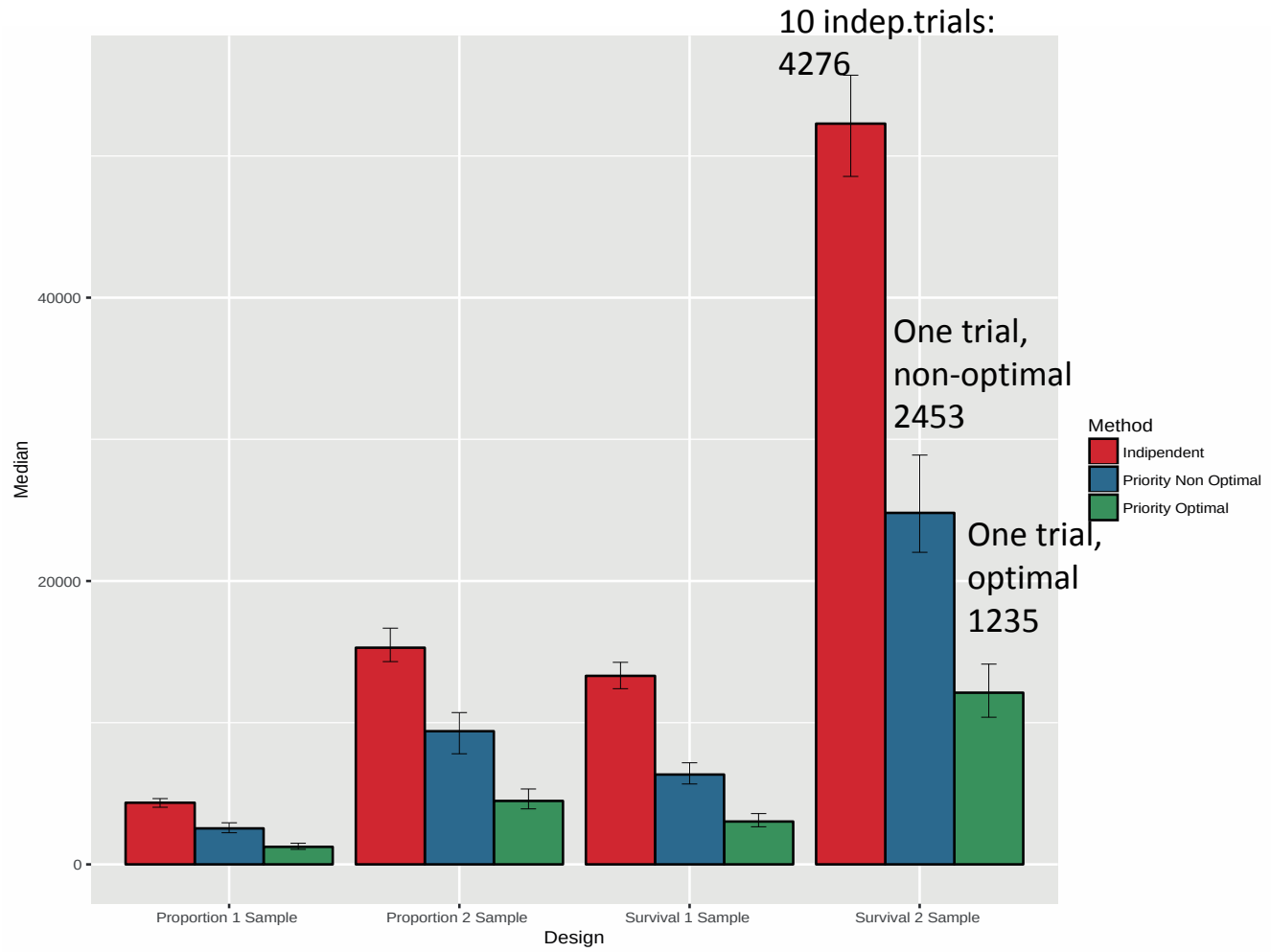






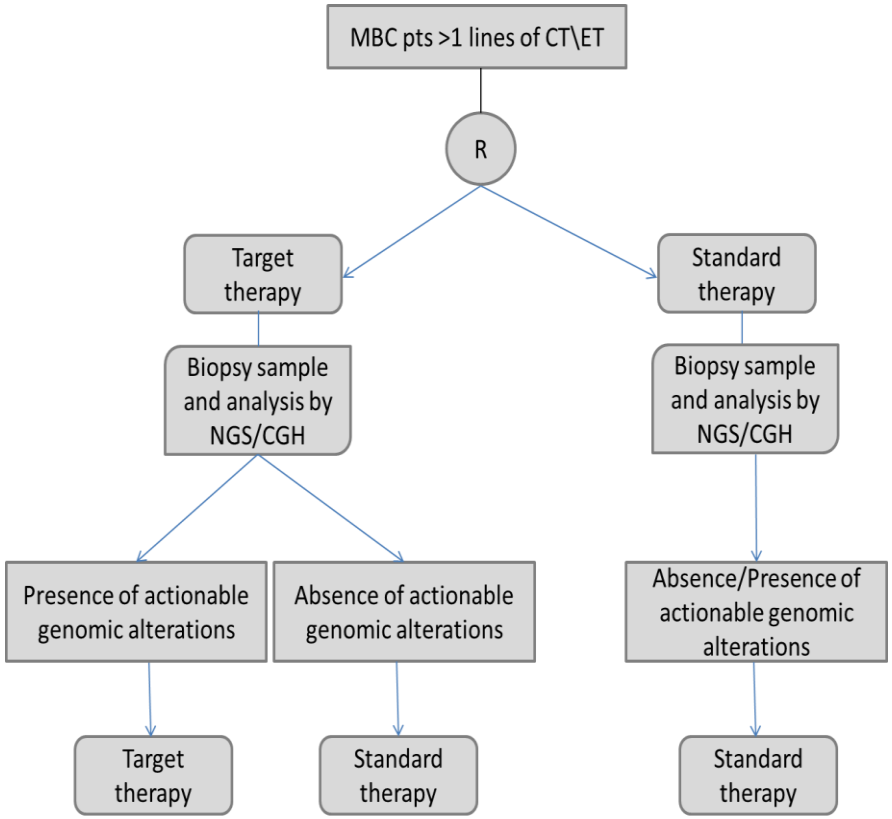
500

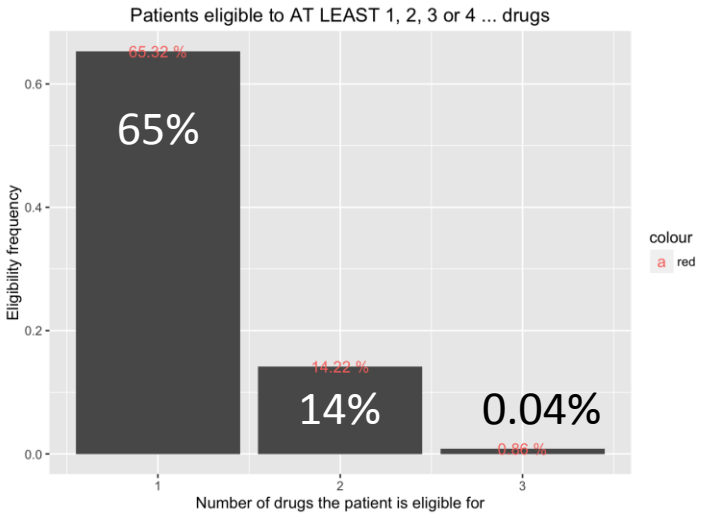
Quantifying the advantage of an umbrella trial

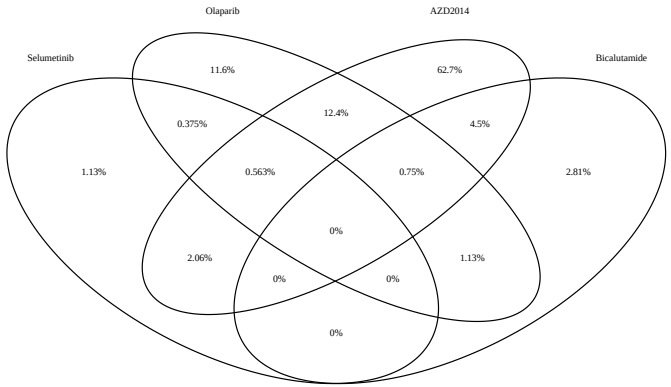


we simulated a 10-arm (inhibitors of PARP, NOTCH, MET, HER2, FGFR, EGFR, BRAF, ALK, AKT and immune checkpoints) imaginary trial on multiple cancers, based on genetic alterations suggested by the past Molecular Analyses for Personalized medicine (MAP) conference.

SHARP: precision medicine trial on metastatic breast cancer



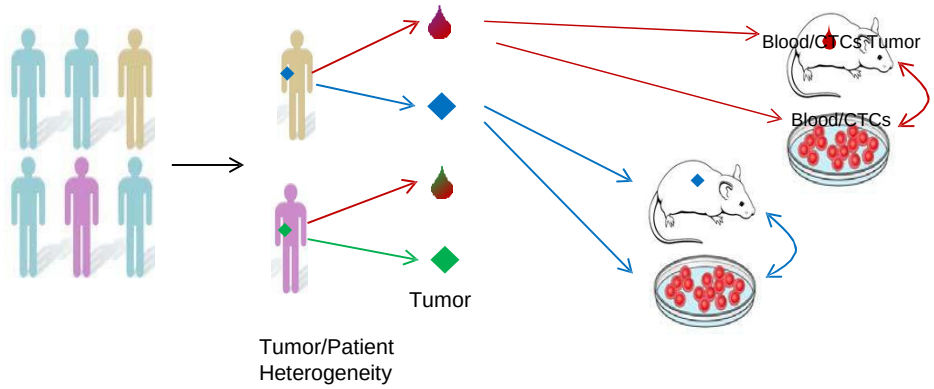


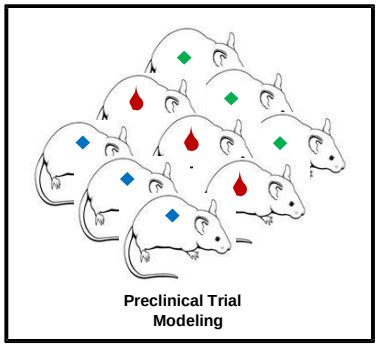


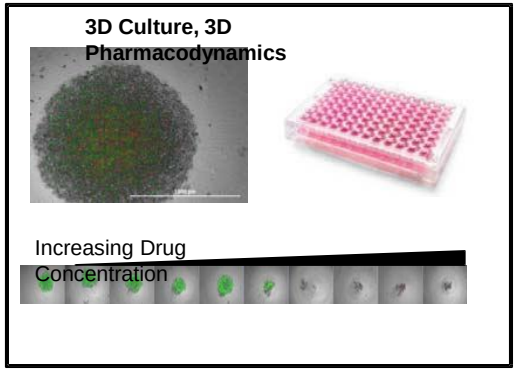
AZD2014: 54.2%
Olaparib: 17.5%
Selumetinib: 2.7%
Bicalutamide: 6%

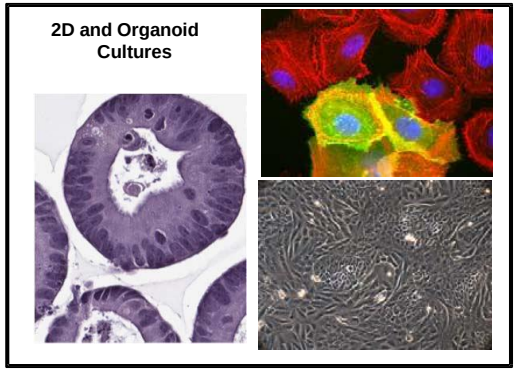
NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

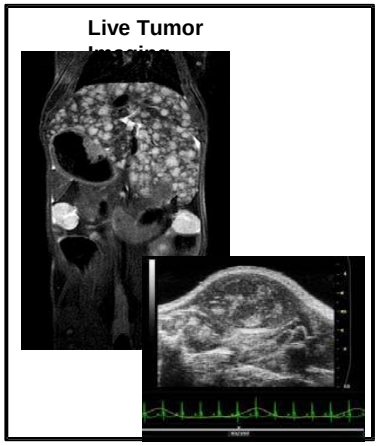
Develop PDX Models and PDC (Tumor & Fibroblast) Lines DNA, RNA, Protein, WES, RNASeq, Targeted Sequencing





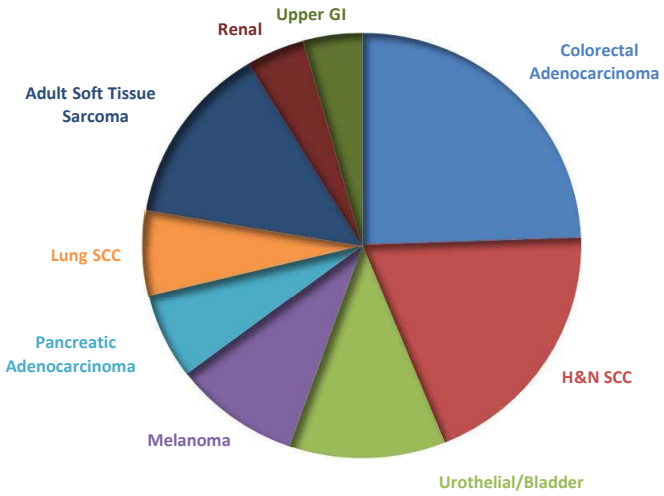






National Cancer Institute Patient-Derived Models Repository

NCI Patient-Derived Models Repository (PDMR)
Initial Distribution Types



- PDX Pathology Confirmed
- Whole Exome Sequence, NCI Cancer Gene Panel, and RNASeq Available
- Human Pathogen Screening and STR Profile Available
- Confirmed Re-growth from Cryopreserved Fragments

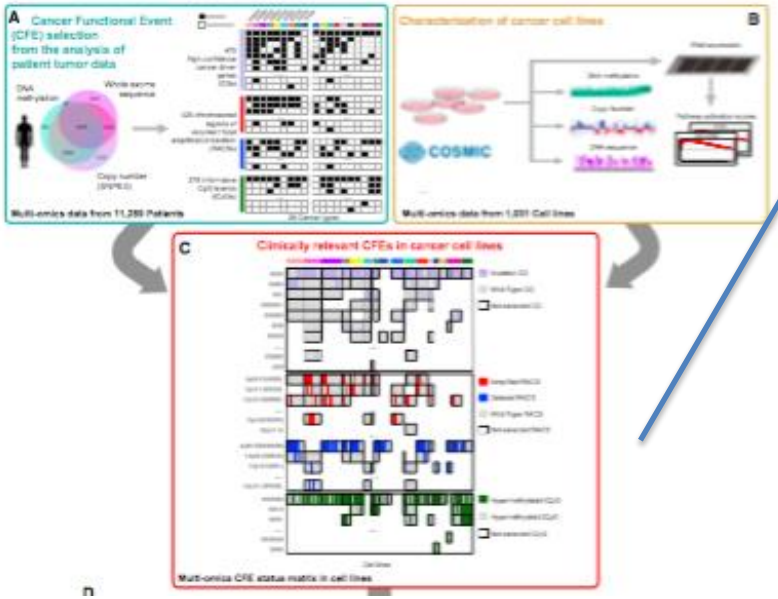
Distribution Groups (N=100 Models)
Colorectal Adenocarcinoma
Head & Neck Squamous Cell Carcinoma •Pharyngeal, Laryngeal, Lip/oral cavity, NOS
Urothelial/Bladder
Melanoma
Pancreatic Adenocarcinoma
Lung Squamous Cell Carcinoma
Adult Soft Tissue Sarcoma •Ewings, Leiomyosarcoma, Malignant fibro. histiocytoma, Fibrosarcoma, Non- Rhabdosarcoma NOS, Rhabdosarcoma NOS
Renal
Upper GI •Stomach, Sm. Intest, GIST, Appendiceal

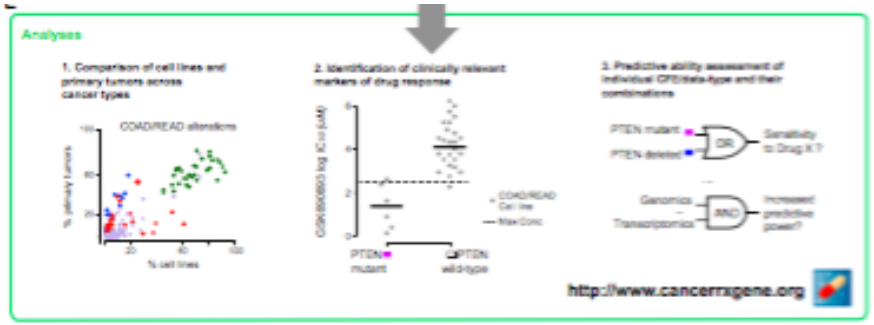
National Cancer Institute Patient-Derived Models Repository

Personalizing treatment using integrated in vivo-in silico approaches: cell lines

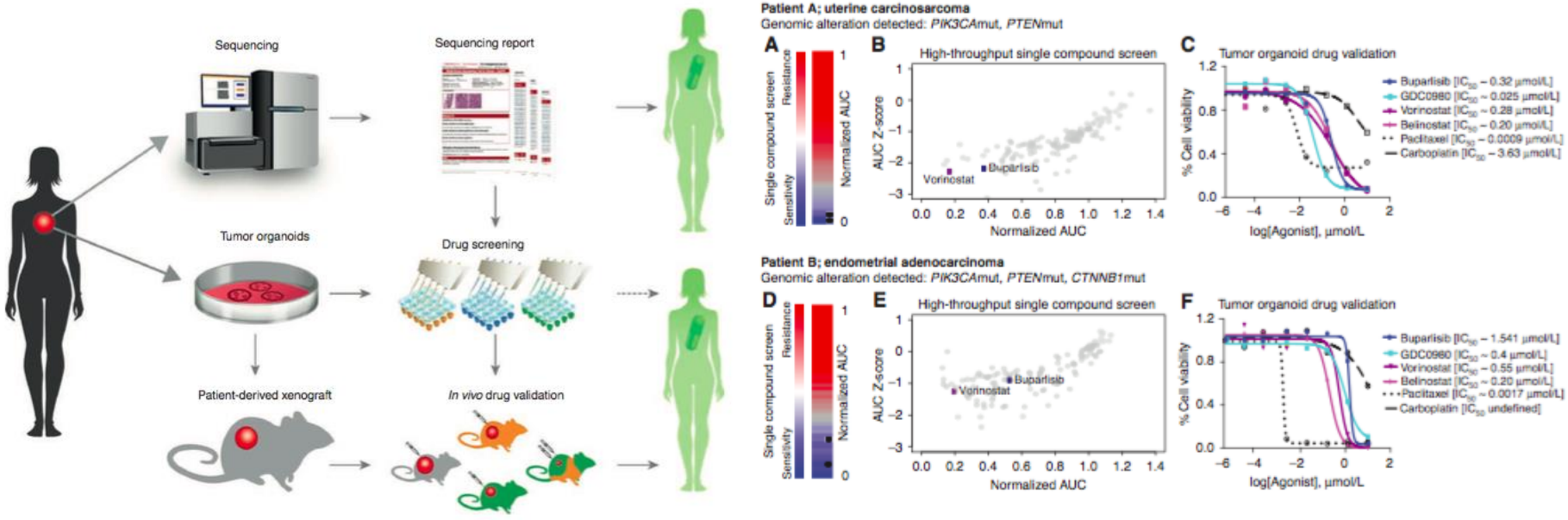
A Landscape of Pharmacogenomic Interactions in Cancer

Francesco Iorio,[1,2,20] Theo A. Knijnenburg,[3,4,20] Daniel J. Vis,[4,20] Graham R. Bignell,[2,20] Michael P. Menden,[1,5,20] Michael Schubert,[1] Nanne Aben,[4,6] Emanuel Gonçalves,[1] Syd Barthorpe,[2] Howard Lightfoot,[2] Thomas Cokelaer,[1,2,17] Patricia Greninger,[7] Ewald van Dyk,[4] Han Chang,[8] Heshani de Silva,[8] Holger Heyn,[9] Xianming Deng,[10,11,18] Regina K. Egan,[7] Qingsong Liu,[10,11] Tatiana Mironenko,[2] Xeni Mitropoulos,[7] Laura Richardson,[2] Jinhua Wang,[10,11] Tinghu Zhang,[10,11] Sebastian Moran,[9] Sergi Sayols,[9,19] Maryam Soleimani,[2] David Tamborero,[12] Nuria Lopez-Bigas,[12,13] Petra Ross-Macdonald,[8] Manel Esteller,[9,13,14] Nathanael S. Gray,[10,11] Daniel A. Haber,[7,15] Michael R. Stratton,[2] Cyril H. Benes,[7] Lodewyk F.A. Wessels,[4,6,16,21] Julio Saez-Rodriguez,[1,5,21] Ultan McDermott,[2,21,*] and Mathew J. Garnett[2,21,*]





Personalizing treatment using integrated in vivo-in silico approaches: organoids



Pauli et al Cancer Disc 2017

Take home messages

- Old school large randomized phase trials are no more feasible due to fragmentation of the target population
- Efficacy demonstration for new drugs is based on sophisticated trial designs
  - Basket and umbrella trials still have big attrition rate issues
- Genetic biomarkers are increasingly accessible due to declining costs
- Non-genetic, functional biomarkers are increasingly accessible and will allow to even further personalize treatment

Luca.mazzarella@ieo.it

GRAZIE DELL'ATTENZIONE