Clinical Biomarkers and Diagnostics

October 12, 2023

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Outline

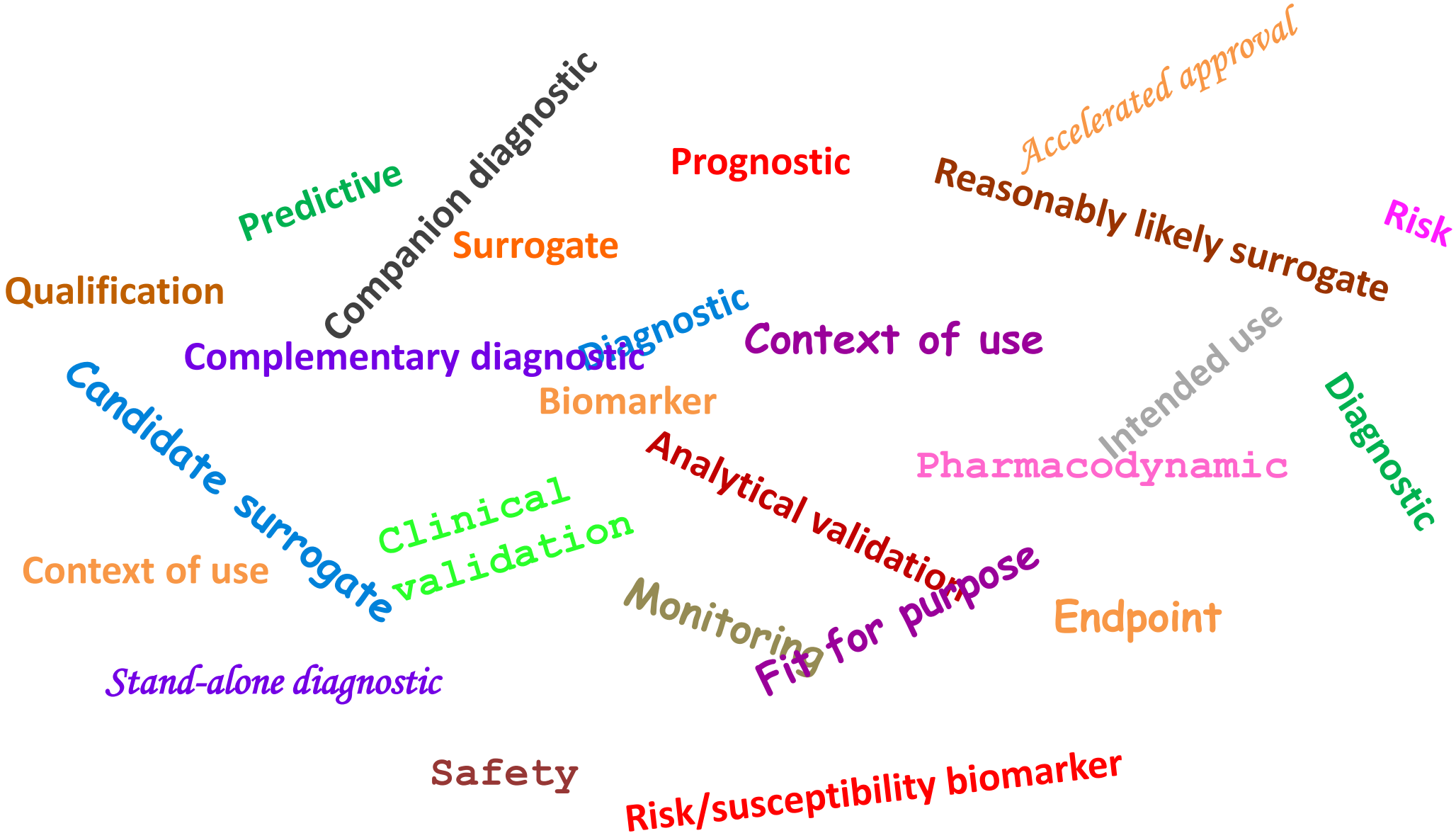
1. Introduction to Biomarkers
2. PD biomarkers

   BREAK
3. Predictive biomarkers
4. Companion and Complementary Diagnostics

   BREAK
6. Prognostic biomarkers
7. Safety biomarkers

   BREAK
6. BFAST Study
7. QUIZ

Understanding biomarker terminology



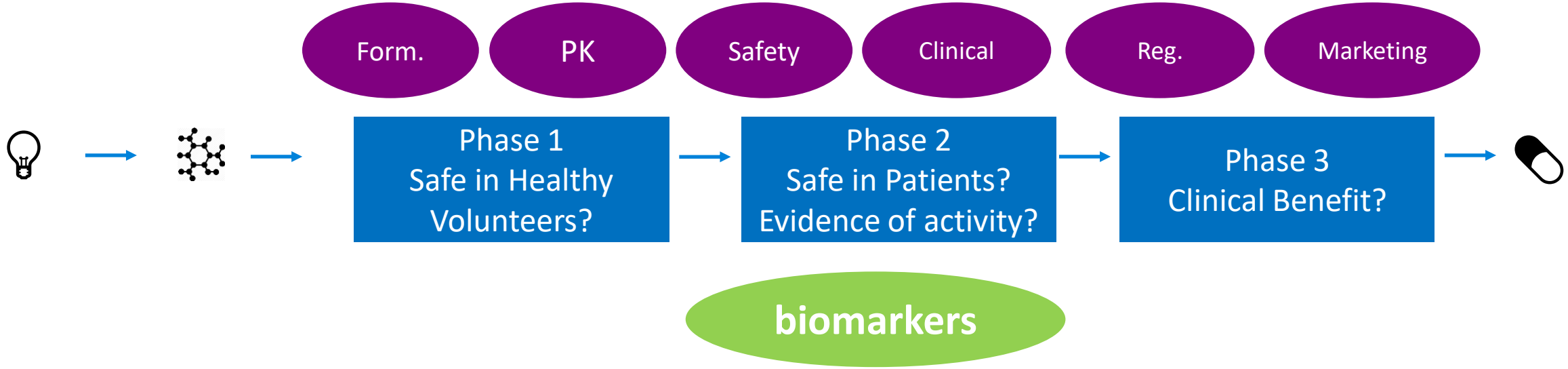
Definitions

Biomarker

A characteristic that is **objectively** measured and evaluated as an **indicator of normal biological or pathological processes, or pharmacologic responses** to a therapeutic intervention

FDA –NIH Biomarker Working Group BEST (Biomarkers, EndpointS and other Tools) resource

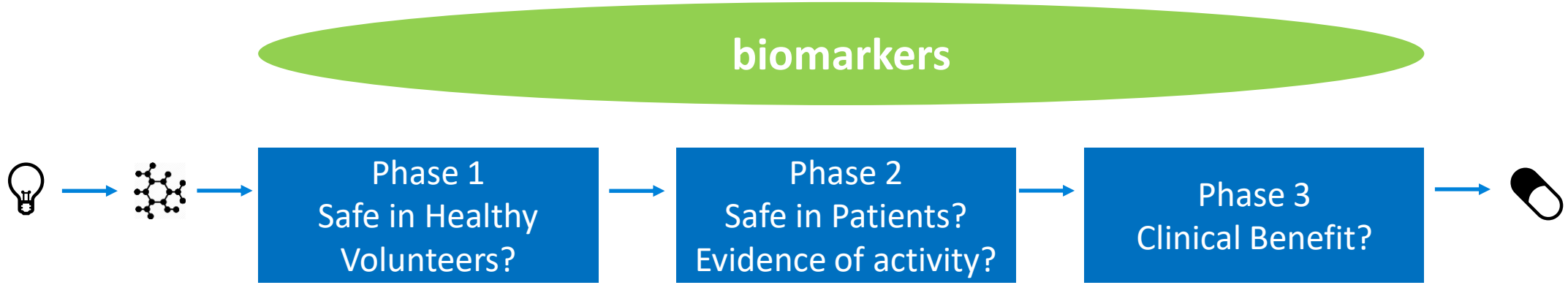
Why are biomarkers important?



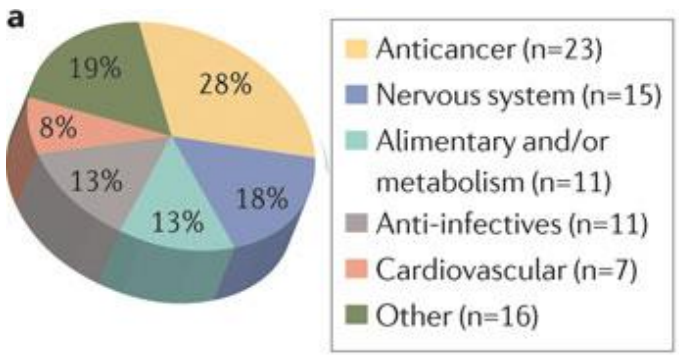
- Estimated cost per new approved drug - $2.5 Billion.[1]
- Overall success rate Ph 1 to launch - 10-14%.[2]
- Lack of efficacy is the major driver for attrition.[3]

1. DiMasi, J. A., Grabowski, H. G. & Hansen, R. W. Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics* **47,** 20–33 (2016).
2. Wong, C. H., Siah, K. W. & Lo, A. W. Estimation of clinical trial success rates and related parameters. *Biostatistics* **14,** 19–14 (2018).
3. Morgan, P. et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. Nature Publishing Group 17, 167–181 (2018).

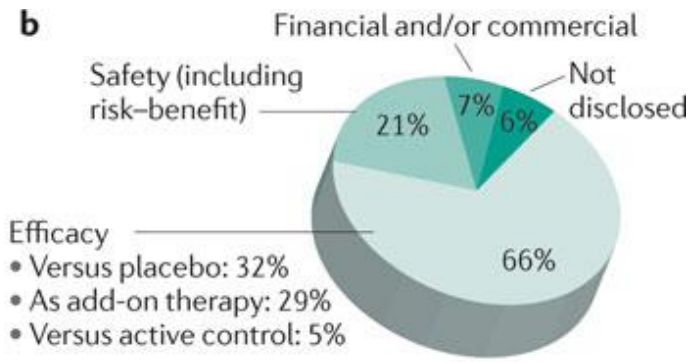
Biomarkers as Tools to Improve Clinical Development



Therapeutic Area



Reason for failure

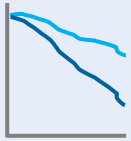


Industry wide Ph2 attrition 2007-2010

Nature Reviews | Drug Discovery

"The way to improve Phase III success rates is to avoid wishful **thinking** and to rely on high-quality scientific evidence by **fully testing mechanisms against each target indication, using well-defined end points in the right patient population in Phase II trials**." John Arrowsmith

Four Reasons Why Drug Candidates May Fail

	Wrong Target	• hypothesized target not a critical node in disease pathogenesis • safety issues associated with target
	Wrong Molecule	• insufficient affinity/avidity; off-target effects • poor PK/tissue penetration/inadequate dosing
	Wrong Outcomes	• clinical outcome measure not related to biology of target • clinical outcome measure not relevant in trial population
	Wrong Patients	• patients not properly stratified according to molecular, pathophysiological, or clinical heterogeneity • trials underpowered to detect an effect in the right subset

Biomarker Categories

1. Susceptibility/risk biomarker
2. Diagnostic biomarker
3. Monitoring biomarker
4. Prognostic biomarker
5. Predictive biomarker
6. Pharmacodynamic/response biomarker
7. Safety biomarker

FDA –NIH Biomarker Working Group BEST (Biomarkers, EndpointS and other Tools) resource

Biomarker Definitions

Susceptibility/risk Biomarker

A biomarker that **indicates the potential for developing a disease** or medical condition in an individual **who does not currently have clinically apparent disease** or the medical condition.

Monitoring Biomarker

A biomarker **measured serially for assessing status of a disease** or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

Safety Biomarker

A biomarker measured before or after an exposure to a medical product or an environmental agent **to indicate the likelihood, presence, or extent of toxicity** as an adverse effect.

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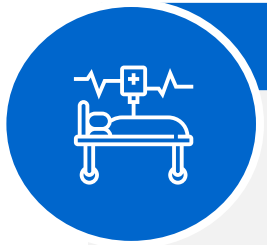
Biomarker Definitions

Pharmacodynamic Biomarker

A biomarker used to show that a **biological response has occurred** in an individual who has been exposed to a medical product or an environmental agent

Predictive Biomarker

A biomarker used to identify individuals who are **more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect** from exposure to a medical product or an environmental agent



Prognostic Biomarker

A biomarker used to identify **likelihood of a clinical event, disease recurrence or progression** in patients who have the disease or medical condition of interest

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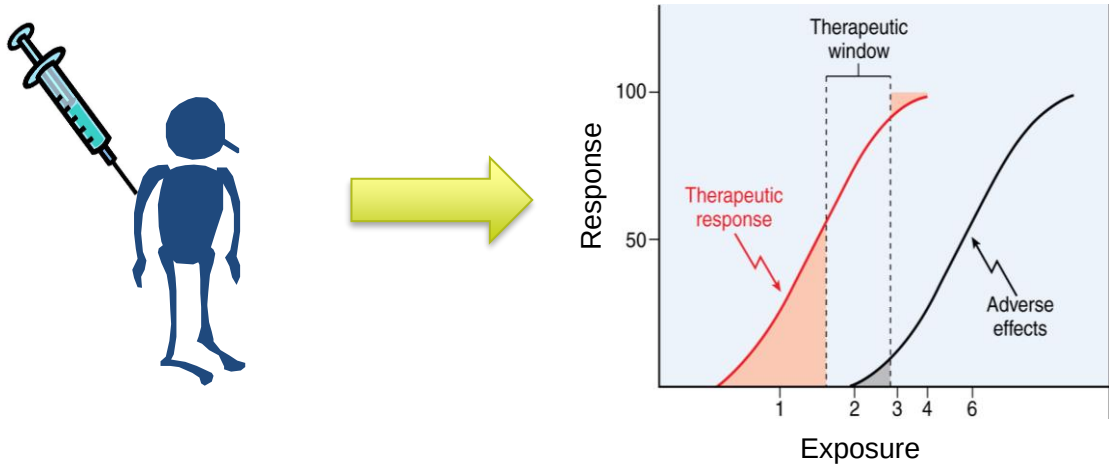
Pharmacodynamic (PD) Biomarker

PD biomarker

Pharmacodynamic Biomarker

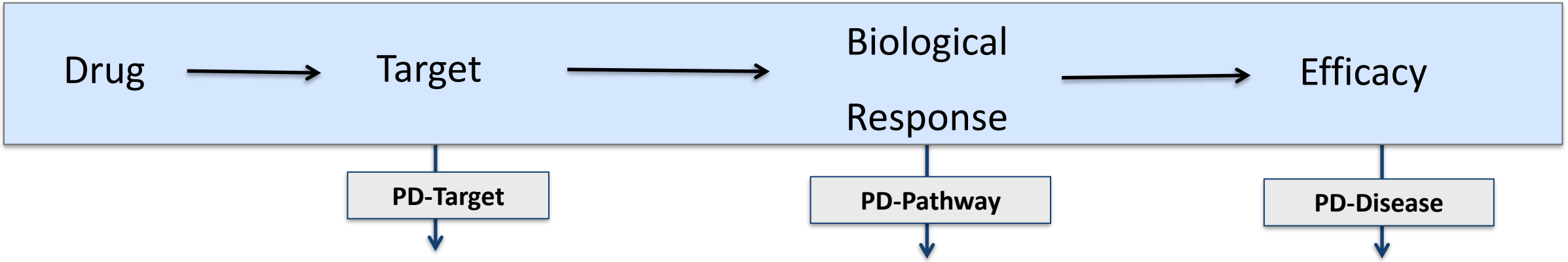
A biomarker used to show that a **biological response has occurred** in an individual who has been exposed to a medical product or an environmental agent



Intended uses of PD biomarkers

Roche

PD biomarker



Confirm target engagement	Demonstrate MOA	Confidence in efficacy
Biomarker capable of direct, quantitative measurement of target engagement at the site of action, suitable for PKPD and dose selection.	**Biomarker(s) that confirm (or not) the expected downstream pharmacology**	**Biomarker(s) that are linked to disease and increase (or decrease) our confidence that the drug will meet the Ph3 primary endpoint (efficacy)**

Key Questions PD biomarkers Aim to Answer

Roche

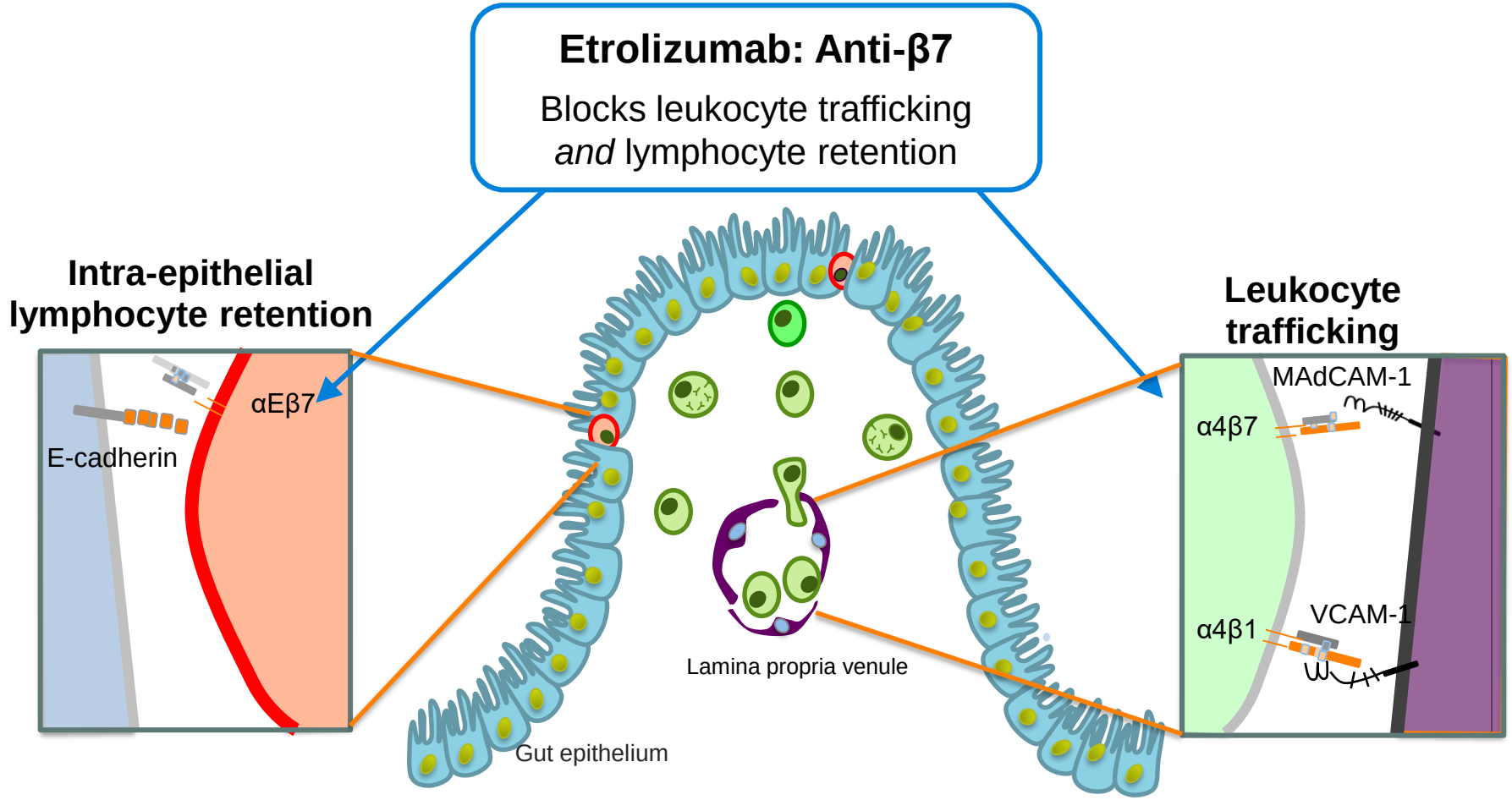
PD biomarker

1. Does dosing and subsequent exposure to therapeutic result in target engagement?
2. Does the target engagement result in expected downstream pharmacology and/or MOA?
   - Do we have mechanistic evidence of inhibition of biological pathway or process in patients? Confirmation of MOA
3. Does MOA predict or link to clinical outcome?
4. Do we understand the relationship between exposure, safety, efficacy?
   - Can we define the therapeutic window (safety/efficacy boundaries) and stay within it ?

Example: etrolizumab, anti-B7 antibody, in development for IBD

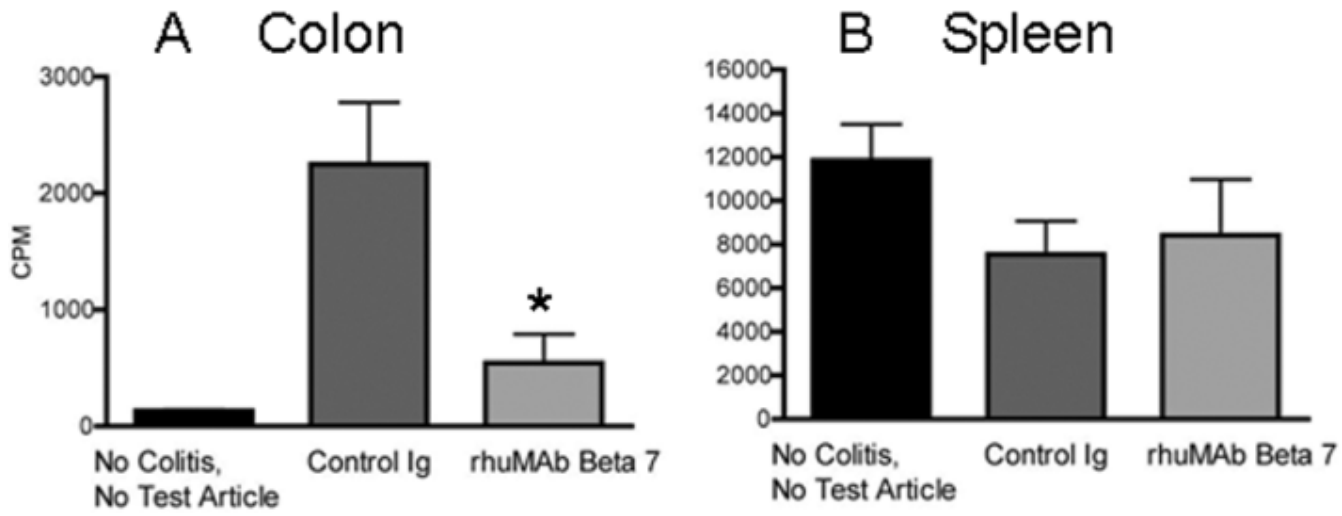
Roche

PD biomarker



Preclinical activity of anti-beta 7 antibodies

PD biomarker



Stefanich et.al, B.J.Pharm., 162, 2011.

- In a SCID mouse model of intestinal inflammation anti-beta 7 Ab treatment prevented homing of beta7+ CD4 T cells to the colon, but not to the spleen.

Receptor occupancy assay established preclinical PKPD relationship in cynomolgus monkeys

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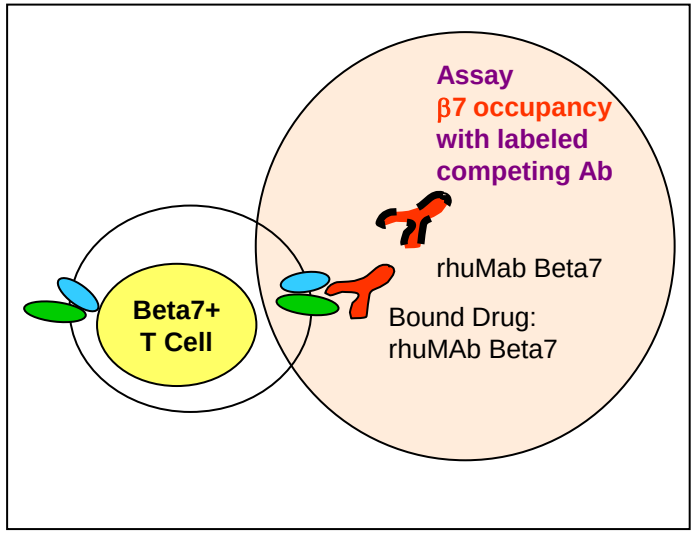
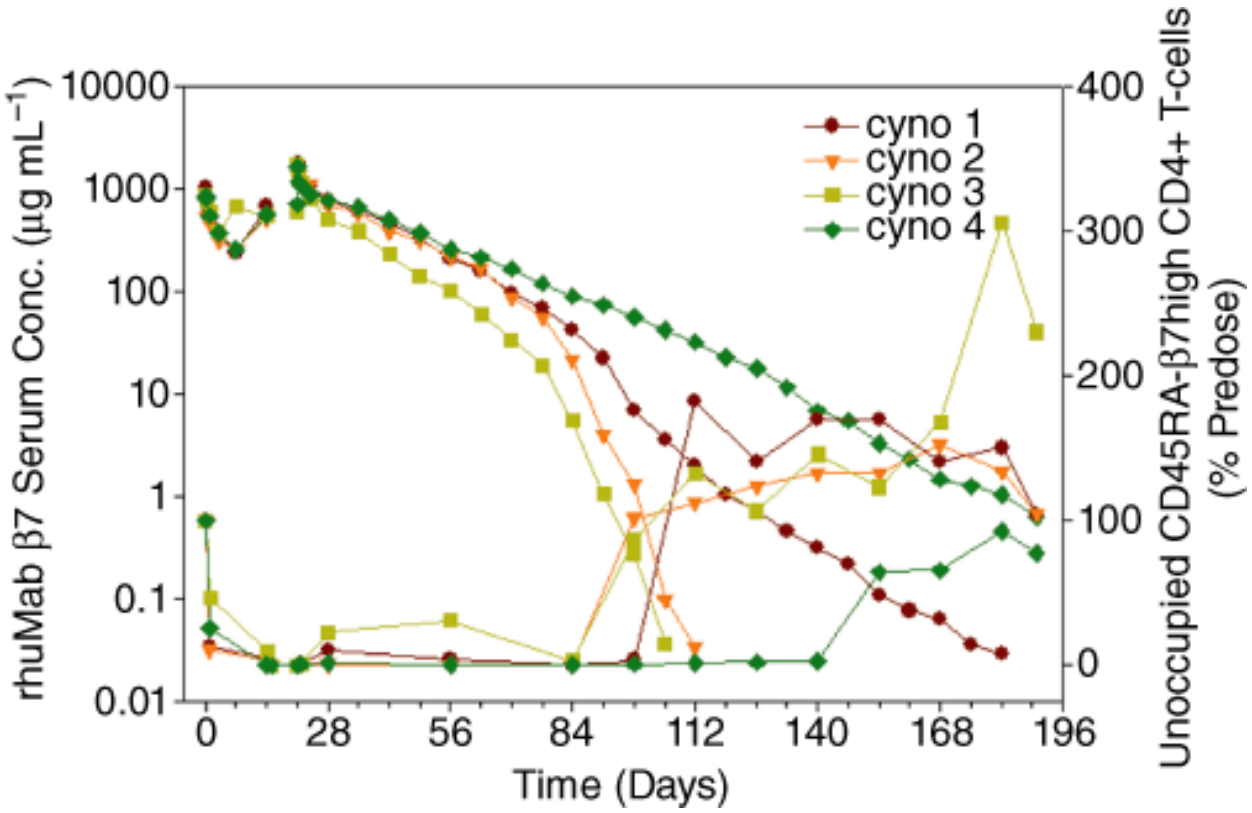
PD biomarker

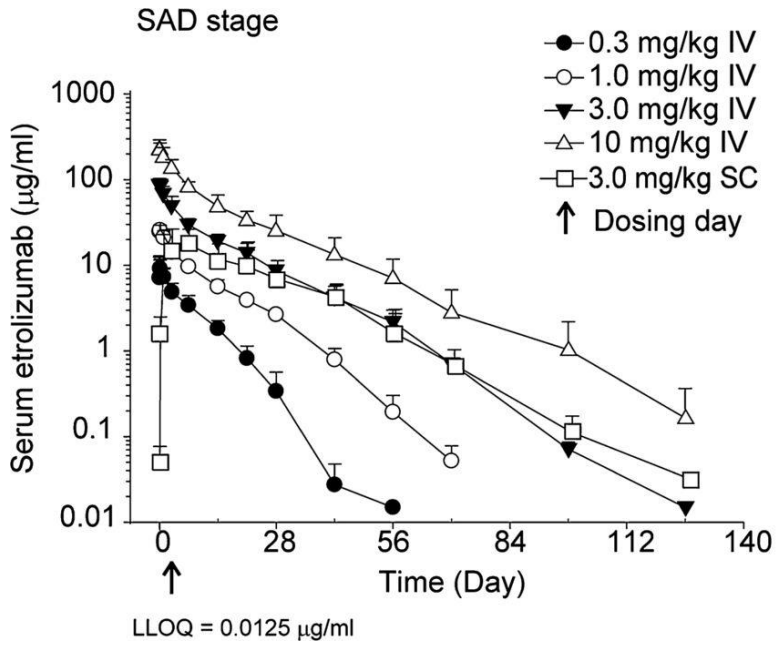


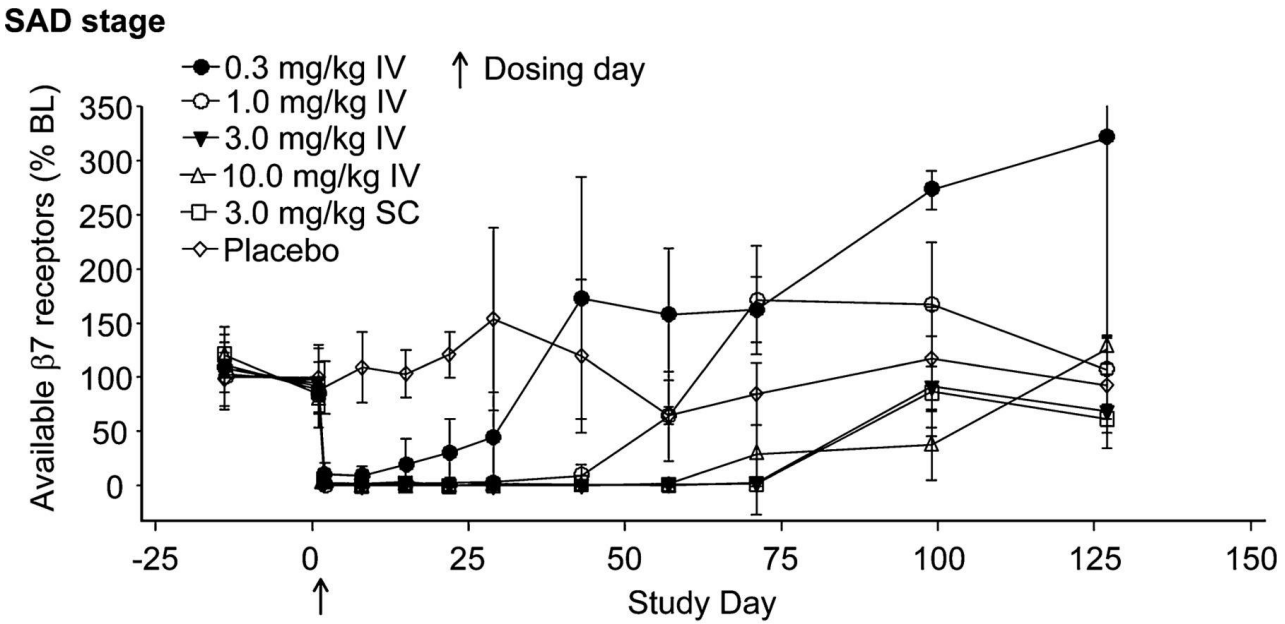


Stefanich et.al, B.J.Pharm., 162, 2011.

PKPD of etrolizumab in UC patients (phase 1)

PD biomarker





Paul J Rutgeerts et al. Gut 2013;62:1122-1130

Phase etrolizumab established PKPD in peripheral blood and gut (site of action)

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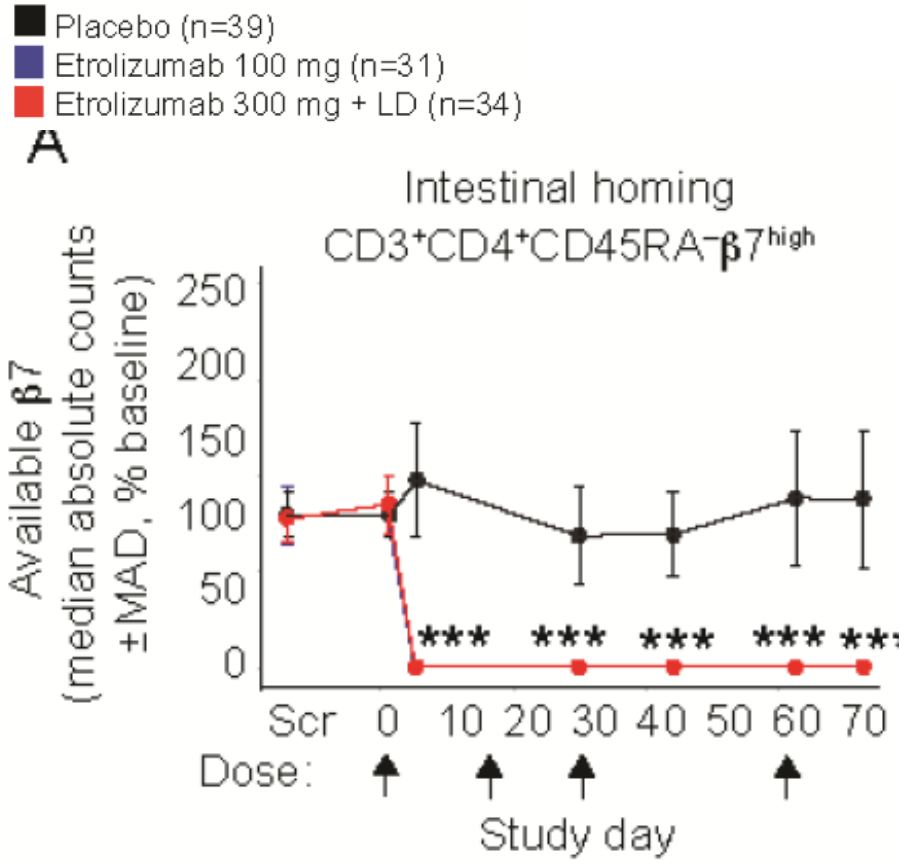
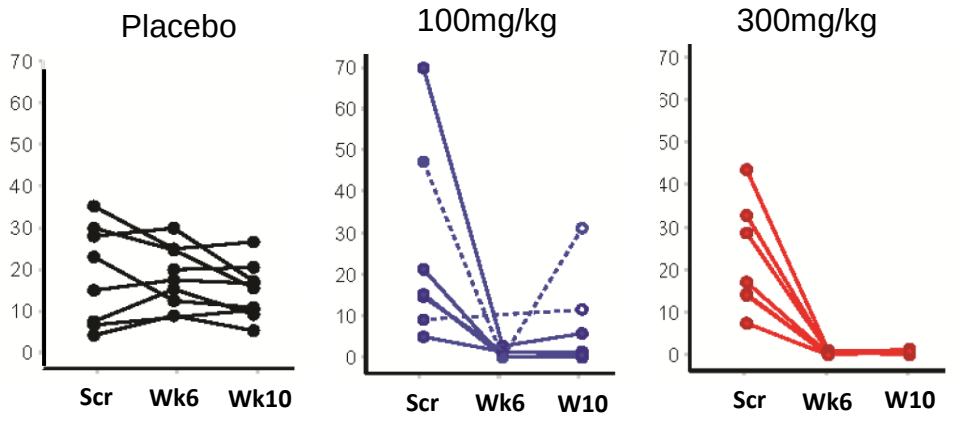
PD biomarker

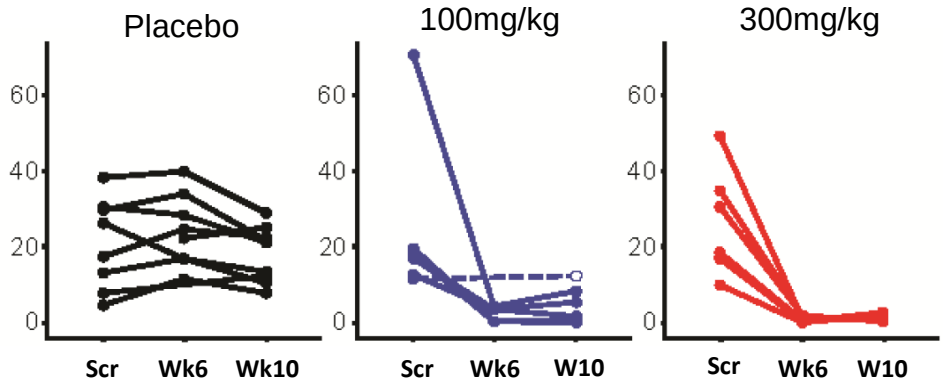
Blood



Available tissue αEβ7+ CD8+ T lymphocytes (%BL)



Available tissue α4β7+ CD8+ T lymphocytes (%BL)



Vermeire et al, *Lancet* **384**:309 (2014)

▪▪▪ *Patients received only one dose of Etrolizumab*

Etrolizumab reduces expression of inflammatory genes

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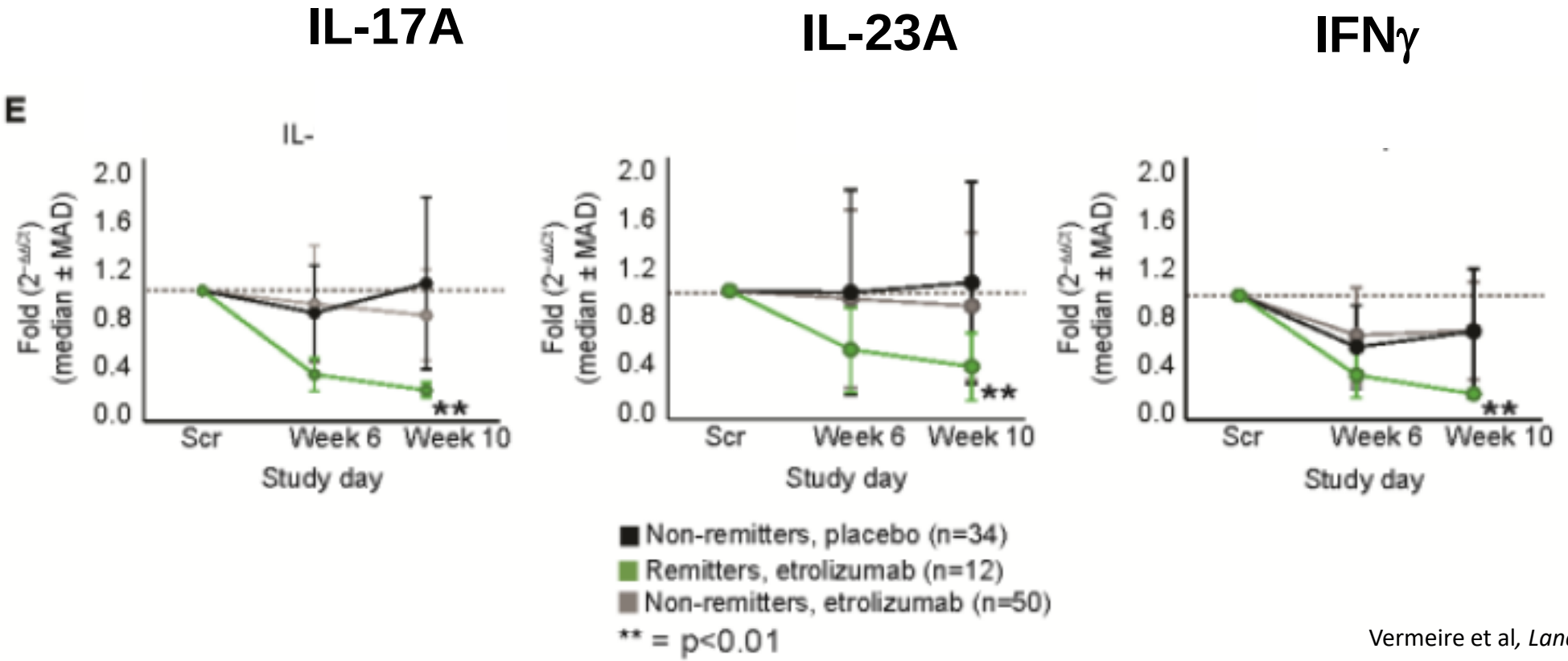
PD biomarker



Vermeire et al, *Lancet* **384**:309 (2014)

Impact of PD biomarkers on etrolizumab clinical development

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PD biomarker

Preclinical Animal studies

- Establish activity/efficacy
- Establish PK/PD relationship
- **Translatable** PD biomarker

Phase 1

- Establish PK/PD relationship

Phase 2

- Establish efficacy
- Establish PK/PD relationship
- Evaluate PK/PD/efficacy relationship

Support dose selection
Increase PTS

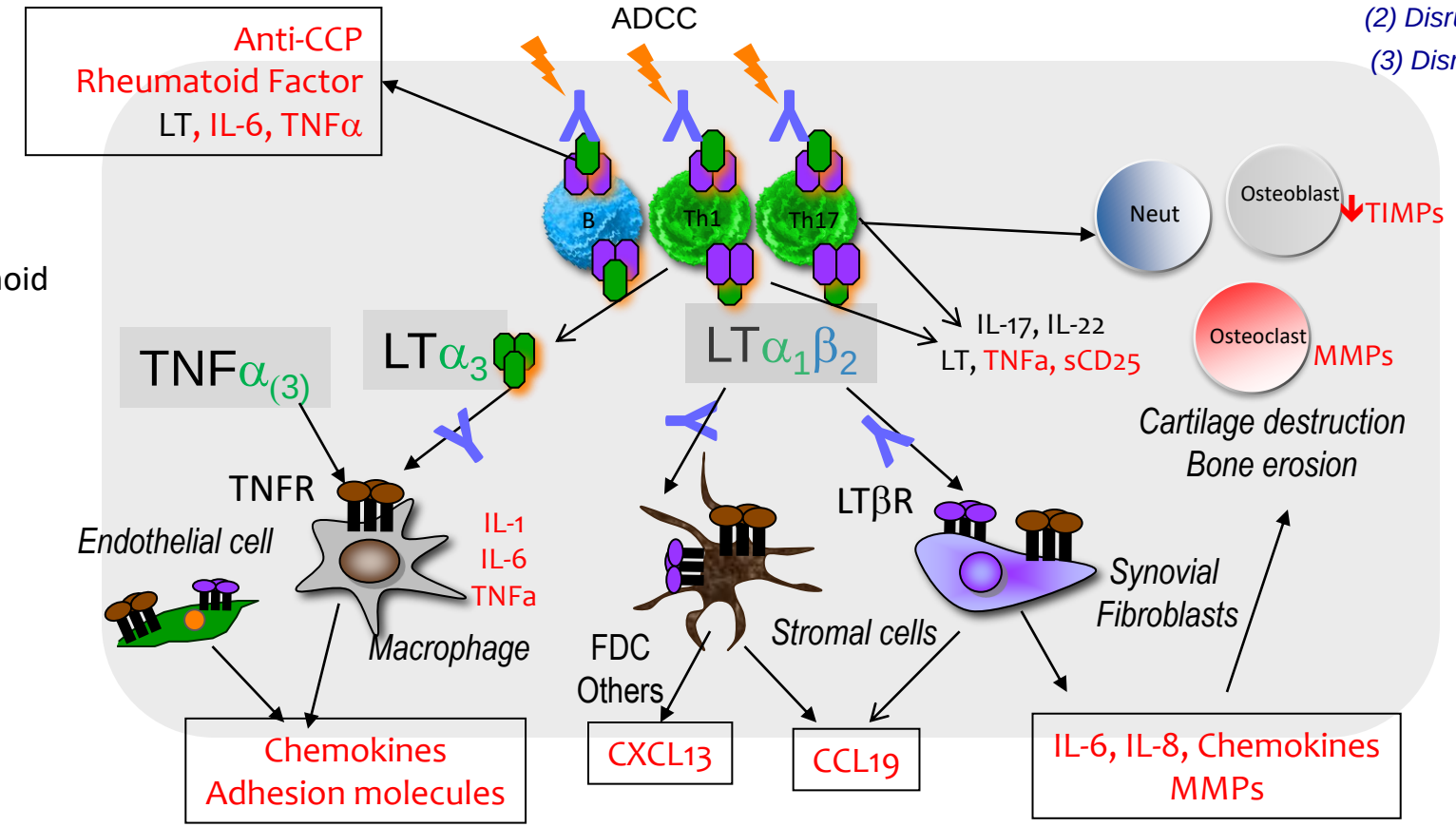
Example: pateclizumab, anti-Lta, for RA

Roche

PD biomarker

(1) Depletion of Lt$\alpha\beta$-bearing lymphocytes (ADCC)
(2) Disruption of LTα3 signaling (TNF-R pathway)
(3) Disruption of Lt$\alpha\beta$ signaling (FDC networks)

RA synovium
&
ectopic lymphoid
structures



PD biomarkers
highlighted in red

Pateclizumab Phase 2 PD Biomarkers established proof of activity and supported NO GO decision

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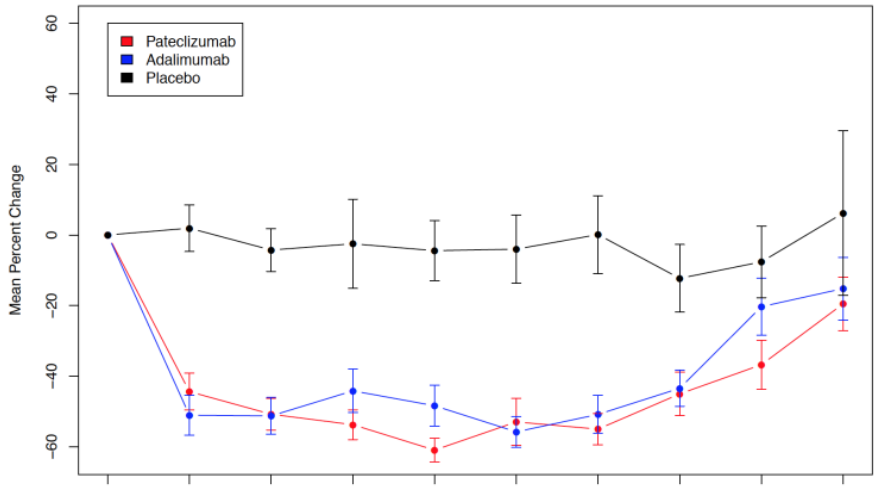
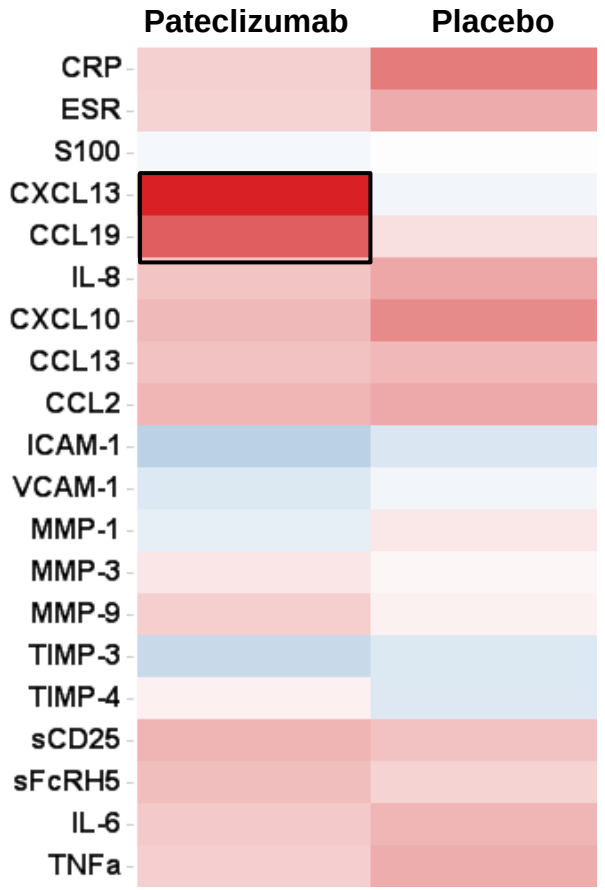
PD biomarker

Serum CXCL13



Inhibition of pathway biomarker CXCL13 confirms target engagement



Median % Change from Baseline:

Exploratory analysis of raw data,
no subjects were excluded
Non QC'd, Non-validated

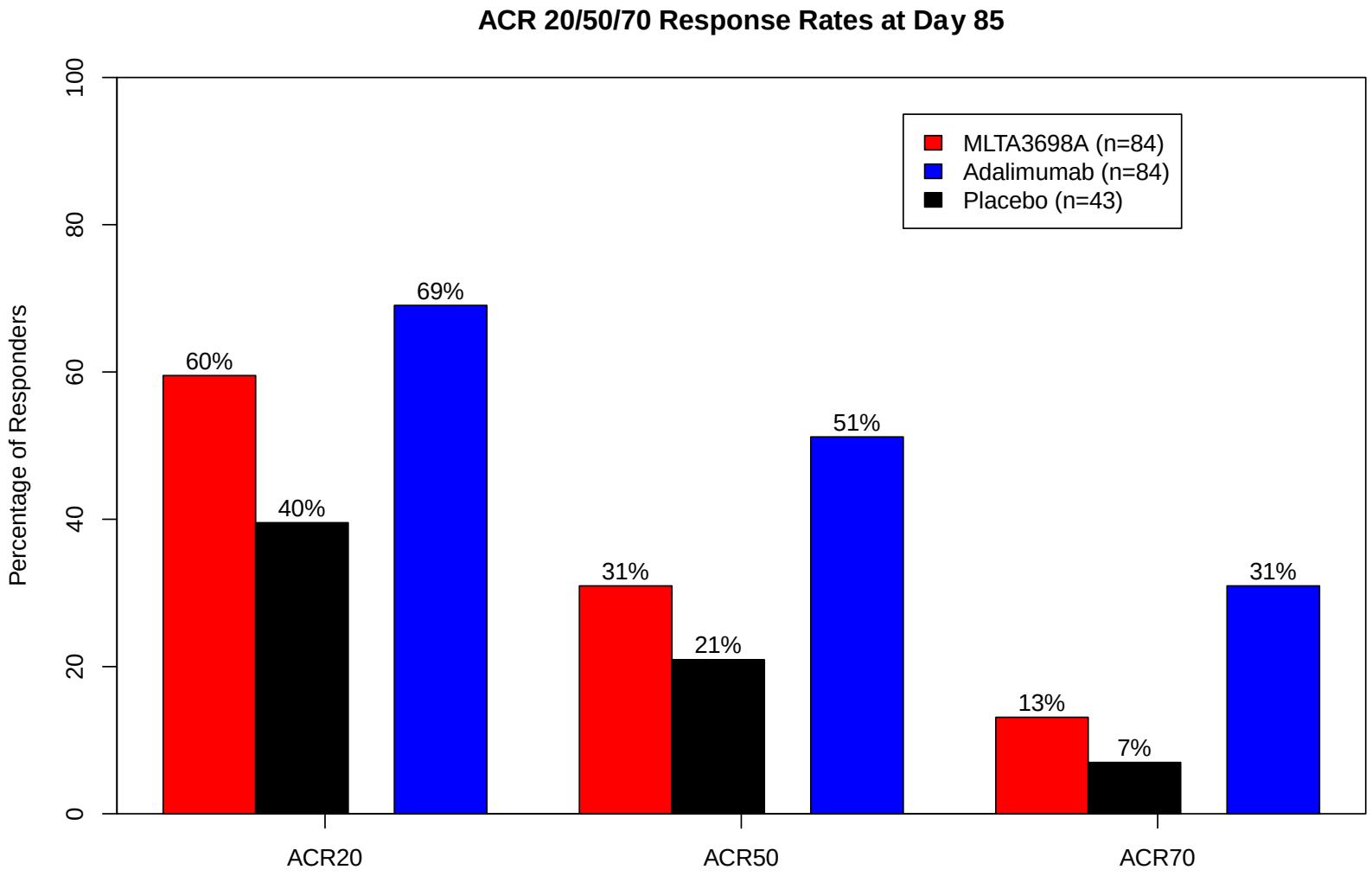
Kennedy et.al, Arthritis Res Ther, 2014.

Lack of robust effect on disease pathway biomarkers supports NO GO decision and conclusion that pateclizumab is not a suitable drug for RA.

Pateclizumab demonstrated efficacy in ACR20 response…. but was not superior to anti-TNFa (SOC)

Roche

PD biomarker

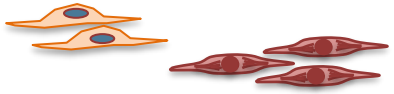


Example: Small molecule inhibitor of TRPA1 for asthma

Roche

PD biomarker

Non-neuronal TRPA1 MoA:



ASM, fibroblasts:
IL-8 release, ASM contraction

Direct activation:
AITC, Cinnamaldehyde, d15PGF2

Indirect activation & potentiation
bradykinin, tryptase, eiocosanoids, neurotrophins

Immune cell activation

Edema & granulocyte influx

Mucus

Substance P
Neurokinin A
CGRP

ASM contraction

Ca^{2+}

Ca^{2+} channels

TRPA1

PLC/IP3

GPCRs

Ca^{2+}

NaV mediated action potential to CNS (cough)

Sensory neuron

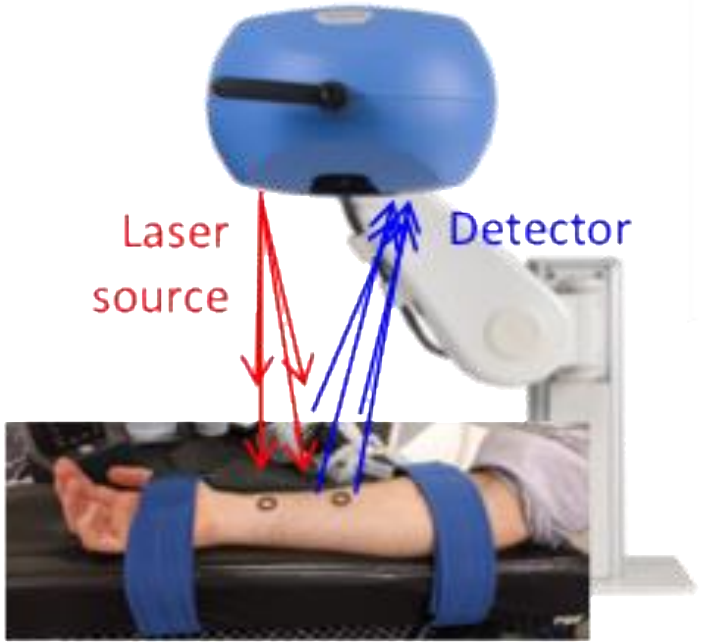
Demonstrating PD activity in Phase 1: TRPA1 agonist skin challenge

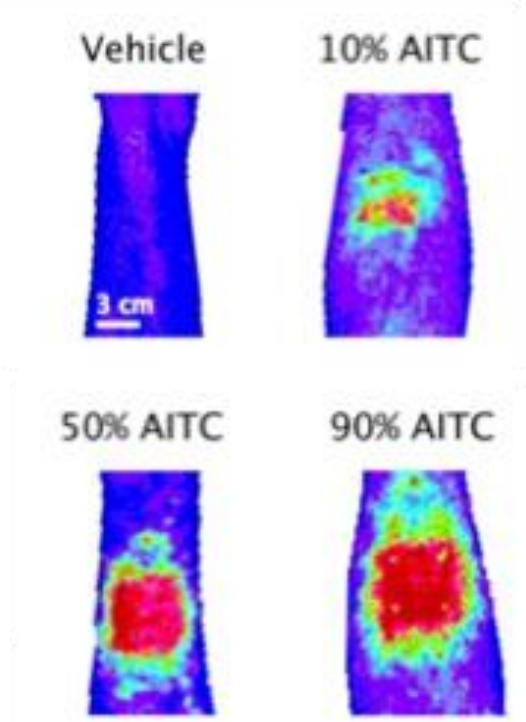
Roche

PD biomarker

- TRPA1 is a ligand gated calcium channel expressed on sensory neurons in the **lung**, GI, and **skin**
  - AITC application to the skin activates TRPA1 and induces dermal blood flow
  - Dermal blood flow can be imaged by Laser Speckle Contrast Imaging
  - Non-invasive, rapid, technically simple method to monitor PD activity in Ph1

Laser Speckle Contrast Imaging (LSCI) of dermal blood flow[1,4]

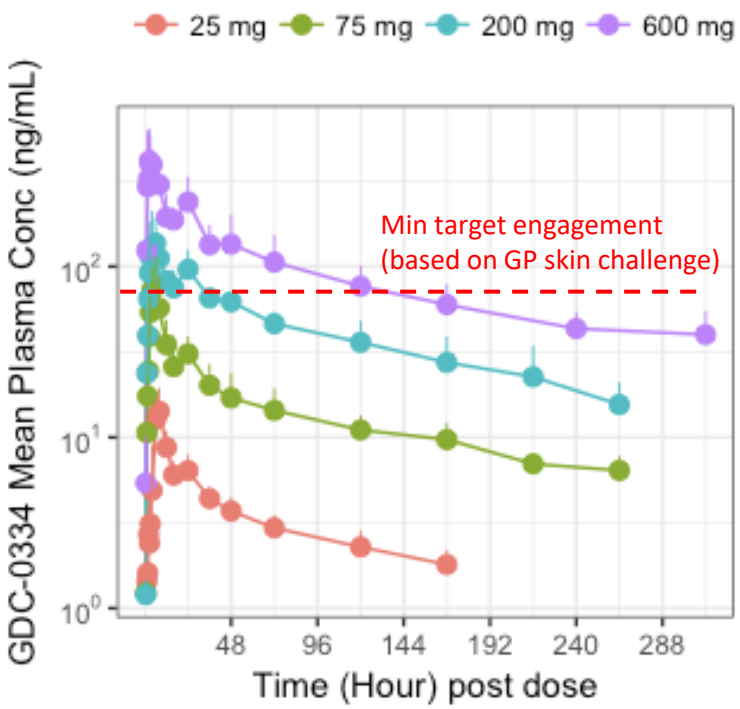




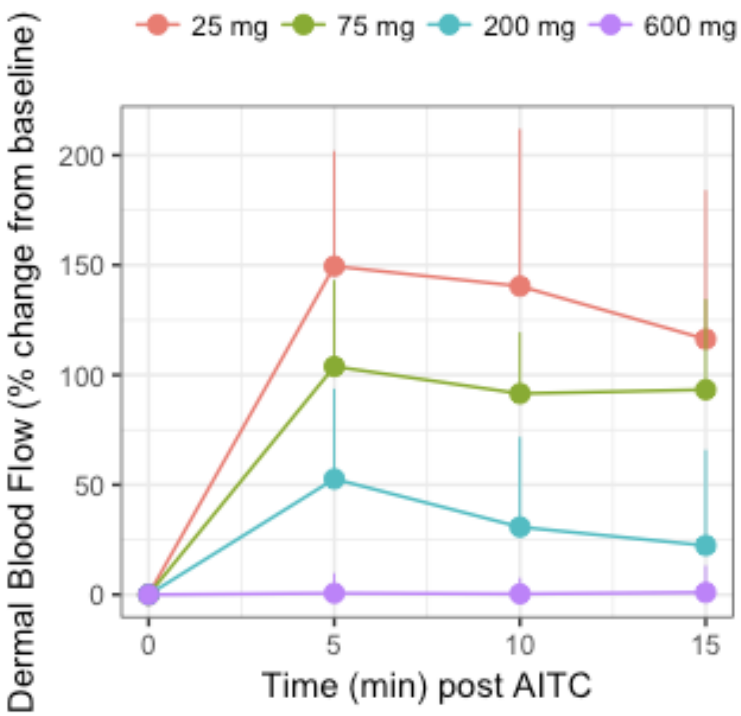
Dose proportional increases in exposure and PD modulation

PD biomarker

Phase 1 SAD Plasma PK



Phase 1 SAD Skin Dermal Blood Flow



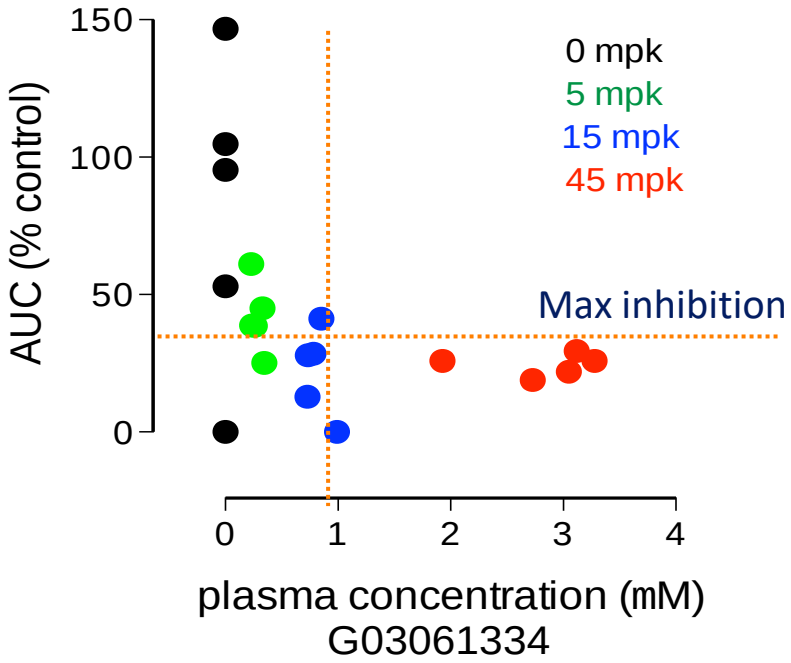
AITC application on the skin activates TRPA1 causing an increase in dermal blood flow that is inhibited by increasing exposure of TRPA1i

PK/PD relationship in skin translates across species

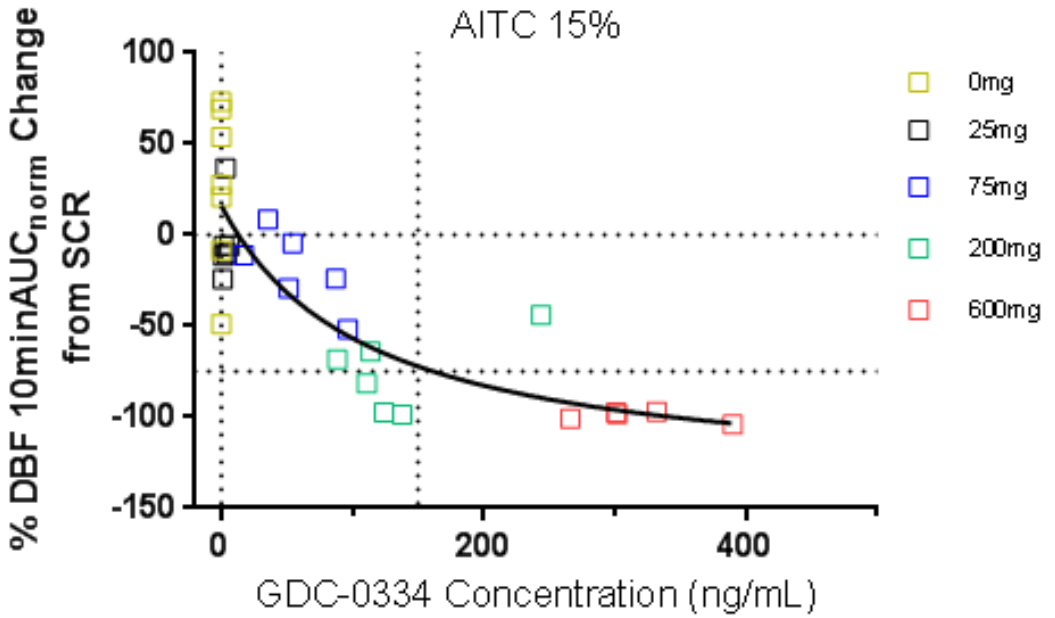
Roche

PD biomarker

Guinea Pig



Human Phase 1



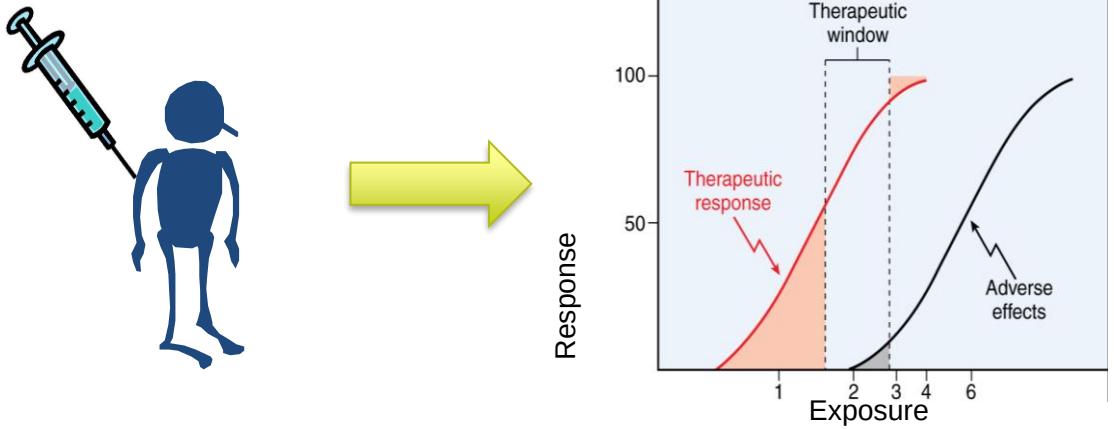
In humans, complete inhibition of dermal blood flow observed at drug concentrations ≥ 300 ng/mL

PD Biomarkers

PD biomarker

Pharmacodynamic Biomarker

A biomarker used to show that a **biological response has occurred** in an individual who has been exposed to a medical product or an environmental agent



- PD biomarkers improve clinical development
  - Inform early go/no-go decisions
  - Inform dosing
  - Increase the probability of success

Categorization of Pharmacodynamic Biomarkers

Biological: Dynamic change may not be associated with clinical efficacy

a) Drug hits target (eg. Receptor occupancy, copies of infused product per ug of PBMC DNA for cell therapies)

- Can be assessed systemically for PK/PD modeling
- Observed in all patients

b) MOA related (eg. Tumor infiltration of CD8+ T-cells, change in pathway signaling)

- requires site of action context eg tumor or disease state
- may not be dose related
- may not be observed in all patients
- may not be associated with efficacy

Categorization of Pharmacodynamic Biomarkers

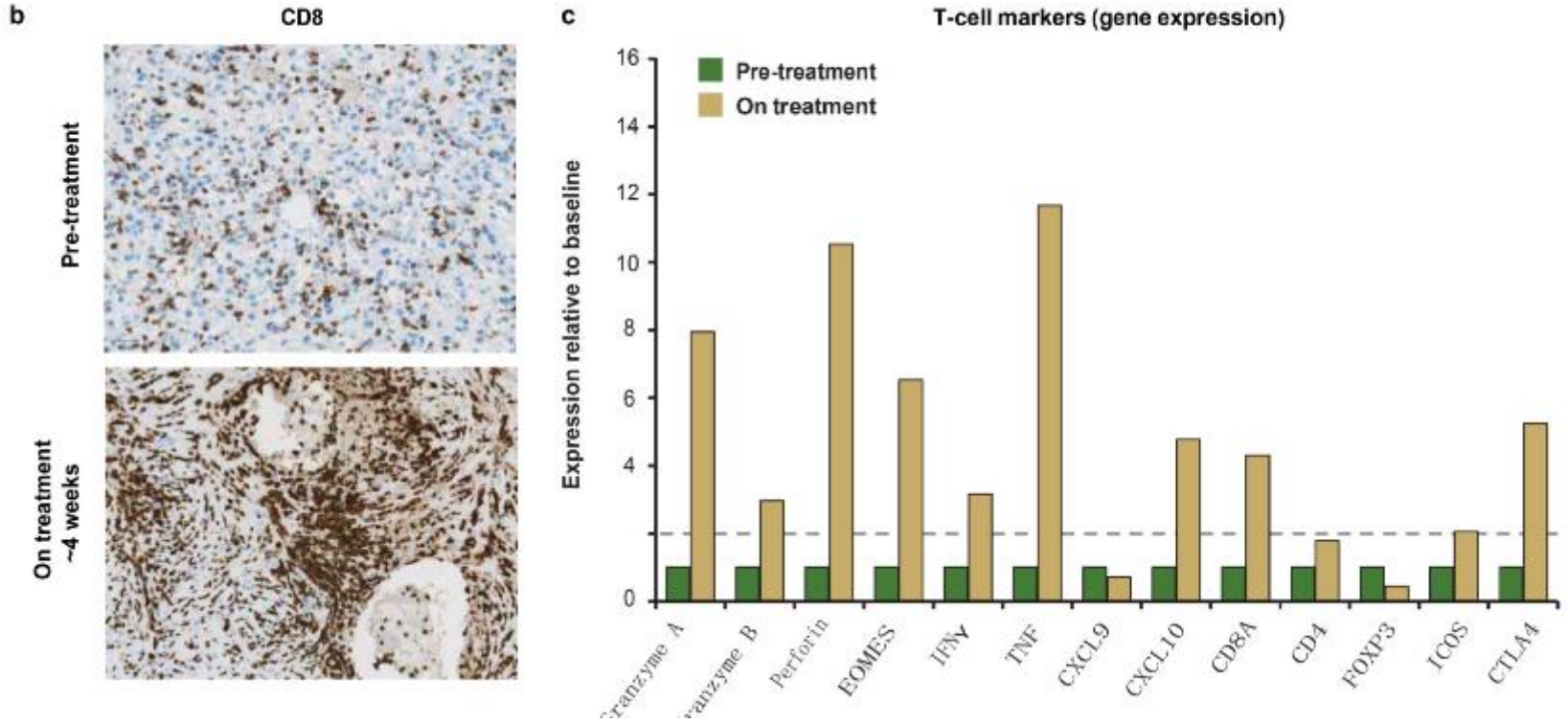
Clinical: Dynamic change is associated with clinical efficacy

Examples include change in tumor markers CA-125, PSA, change in circulating tumor DNA, radiologic imaging

- Markers can be evaluated systemically
- confirms clinical translation of biological pharmacodynamics
- Unequivocally related to outcomes
- requires a high quality, regulatory grade tool to inform clinical decisions
- may be employed as an endpoint in clinical trials

MOA related biomarkers

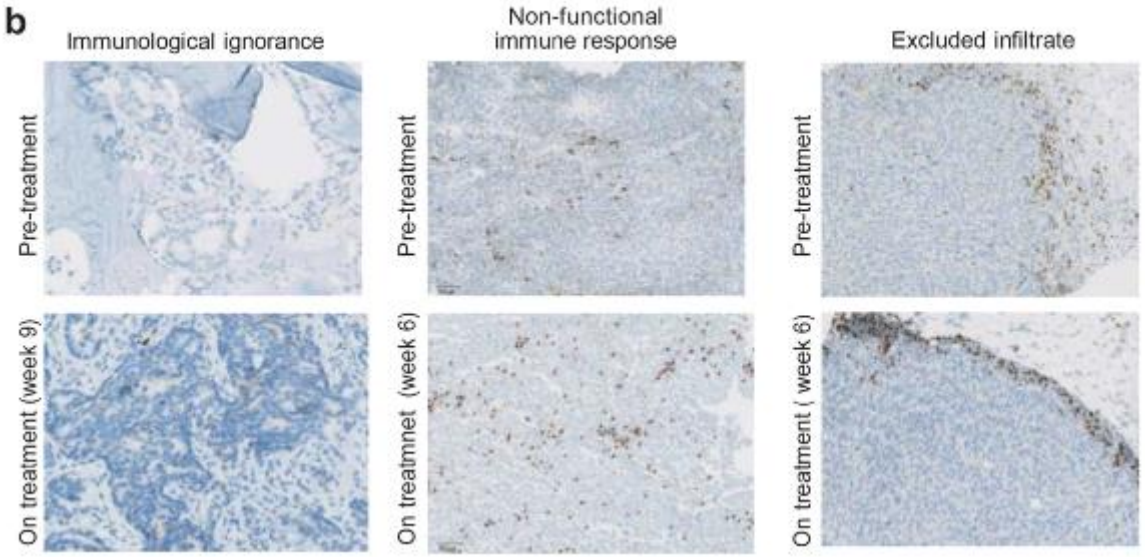
Example in Cancer Immunotherapy



Herbst et al., Nature 2014

Infiltration of activated CD8+ T-cells in the tumor microenvironment upon treatment with atezolizumab (anti-PDL1)

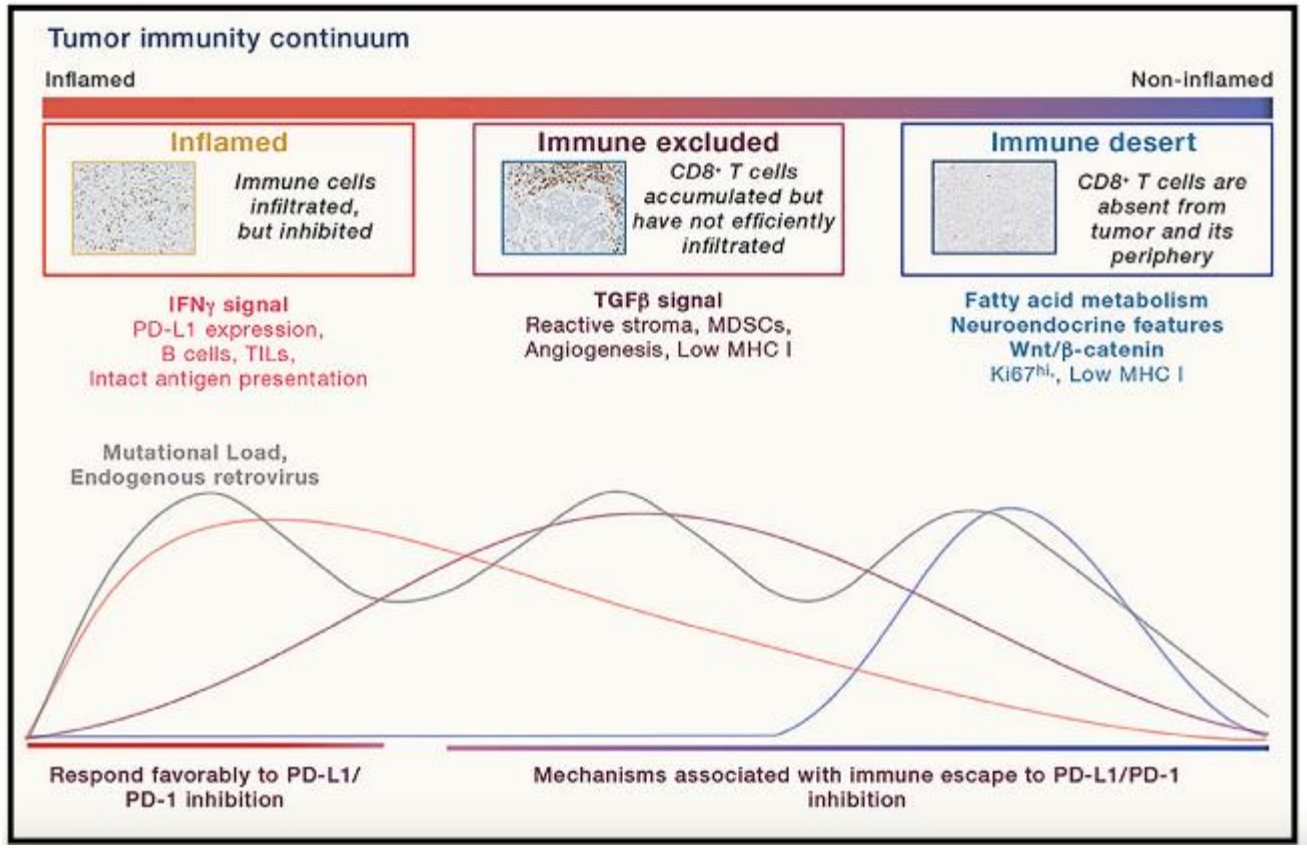
MOA related biomarkers may help understand response/innate resistance patterns



Herbst et al., Nature 2014

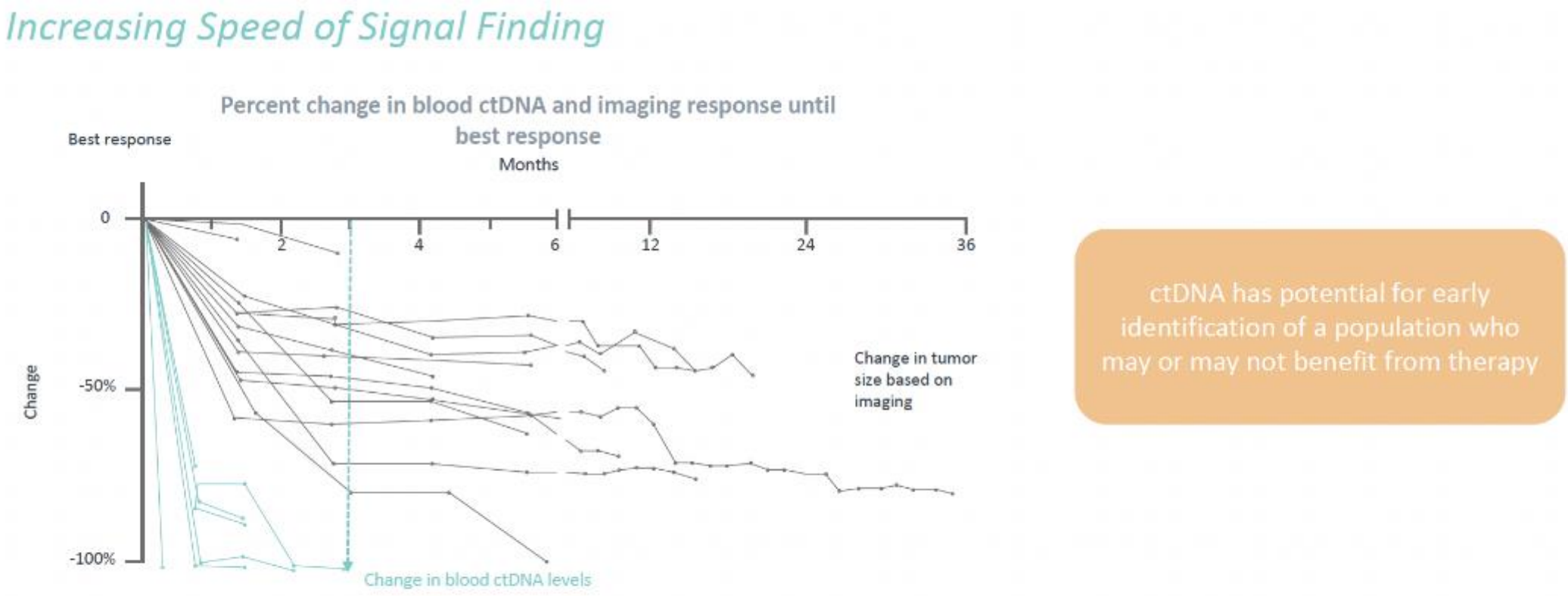
Pattern of tumor infiltration of T-cells associated with T-cell contexture in baseline biopsies

Tumor Immunity Continuum across 8 distinct cancer types



PD marker correlations to clinical outcomes

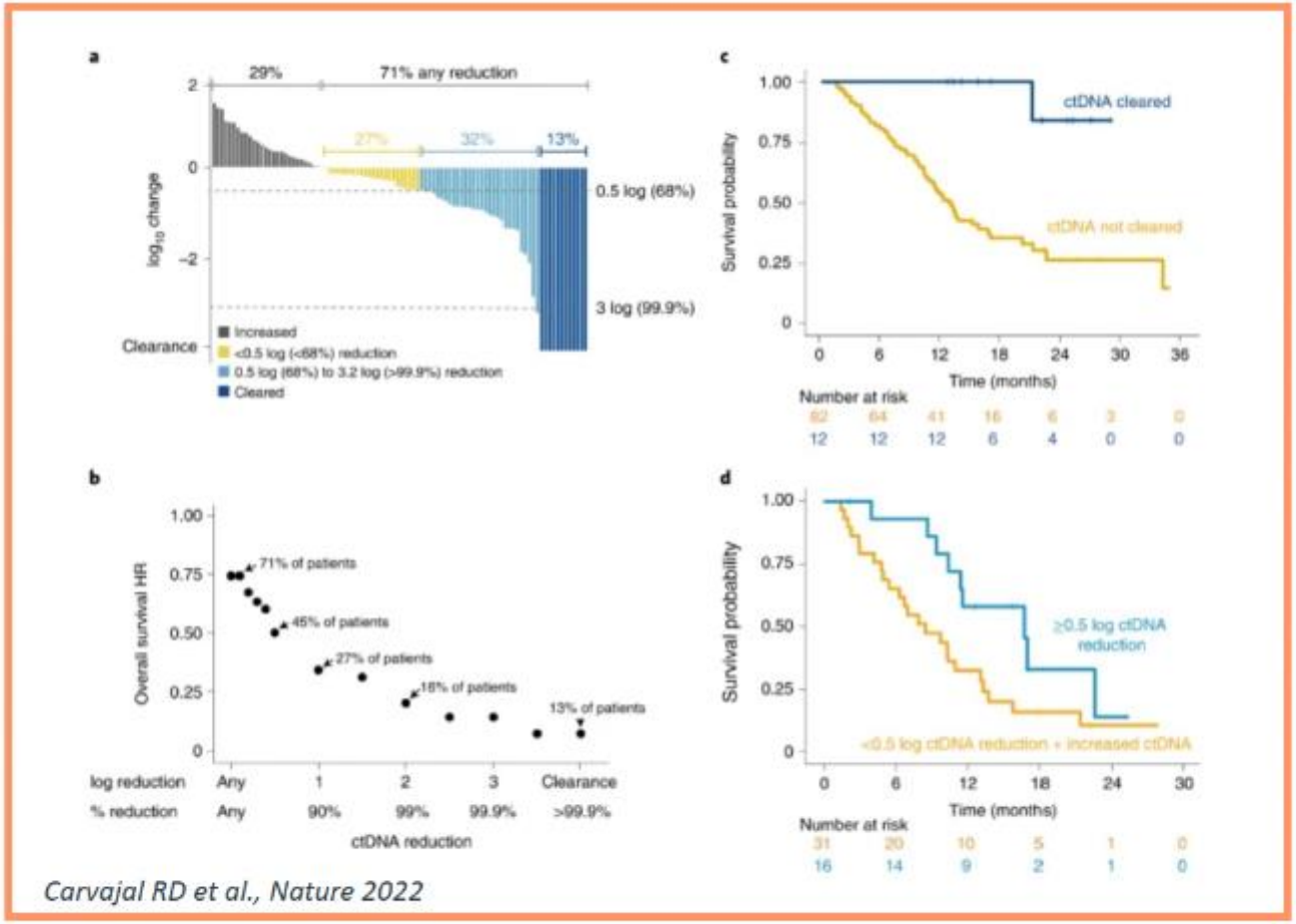
Dynamic changes in circulating tumor DNA delivers quantitative response data earlier than imaging



ctDNA = circulating tumor DNA.
Cheng ML et al. JCO Precis Oncol 2021;5:393–402.

Dynamic changes in ctDNA correlate with survival

Molecular response to tabentafusp in previously treated advanced uveal melanoma

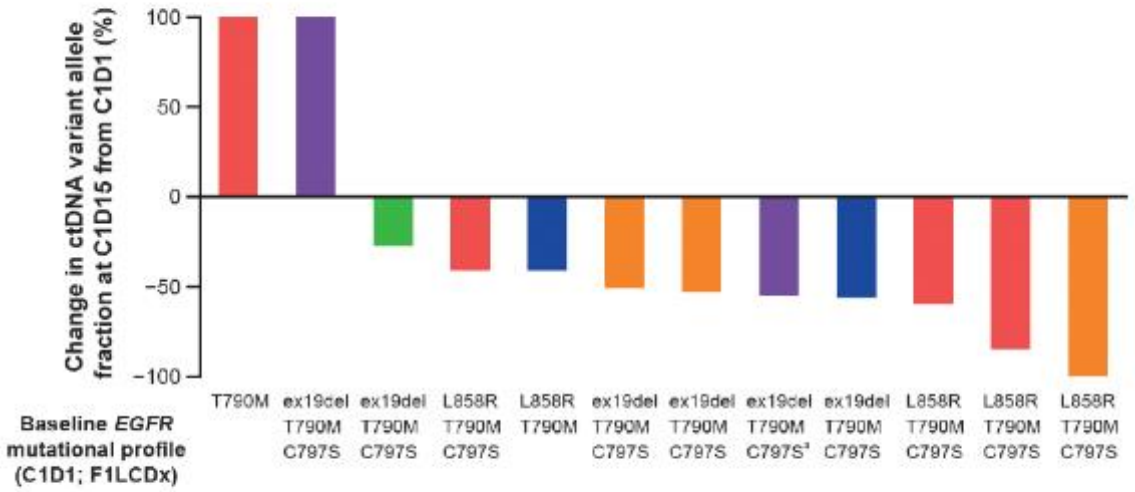


Carvajal RD et al., Nature 2022

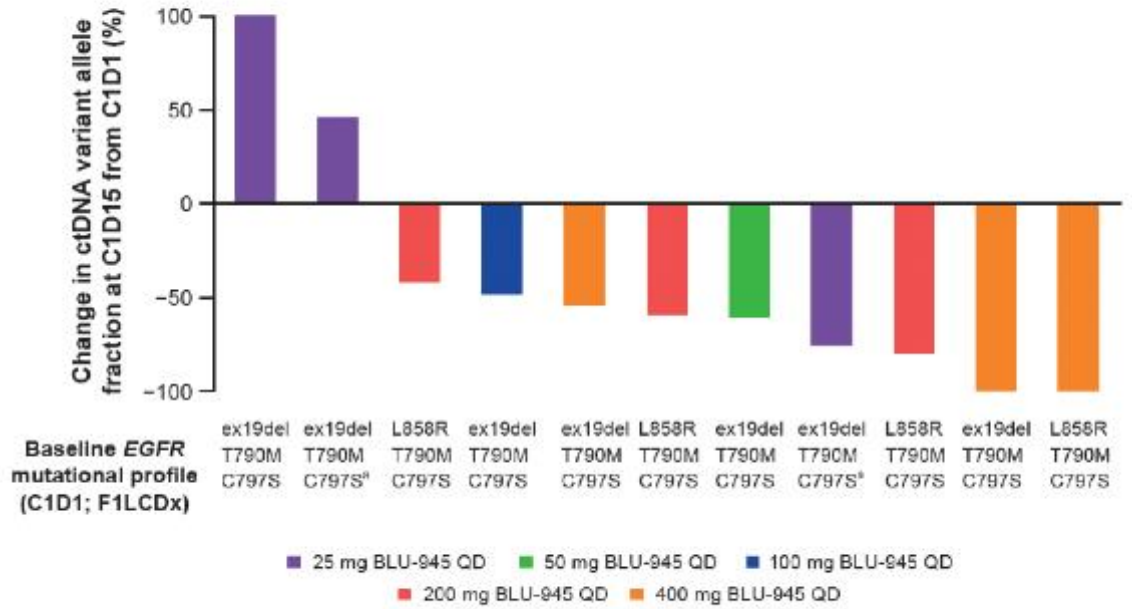
Monitoring of drug target ctDNA

Activity on EGFR T790M & C797S VAF after 14 days of therapy

A. Modulation of *EGFR*-T790M ctDNA levels



B. Modulation of *EGFR*-C797S ctDNA levels



Assessing VAF% change on treatment provides insight into response when tissue is not available

*CTA – clinical trial assay
VAF: Variant allele frequency

1. Shum E, Elamin Y, Reckamp KL, Piotrowska Z, et al. Emerging evidence of activity of BLU-945 in patients with advanced EGFR-mutant NSCLC utilizing circulating tumor DNA in the phase ½ SYMPHONY study. AACR 2022. New Orleans, LA.

FOUNDATION MEDICINE

Q&A

BREAK

Outline

1. Introduction to Biomarkers
2. PD biomarkers

   BREAK
3. Predictive biomarkers
4. Companion and Complementary Diagnostics

   BREAK
6. Prognostic biomarkers
7. Safety biomarkers

   BREAK
6. BFAST Study
7. QUIZ

Predictive Biomarkers

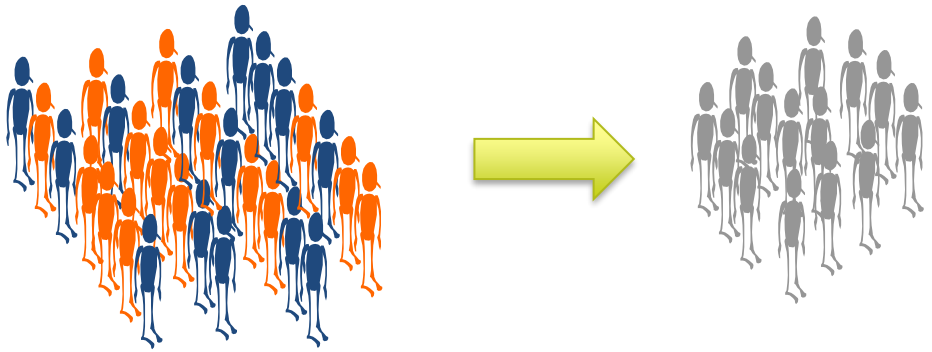
Roche

Predictive biomarker

Predictive Biomarker

A biomarker used to identify individuals who are **more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect** from exposure to a medical product or an environmental agent

→ **Predict patients who might respond better to a drug**
→ **Predict drug safety and efficacy**



= Patient Selection

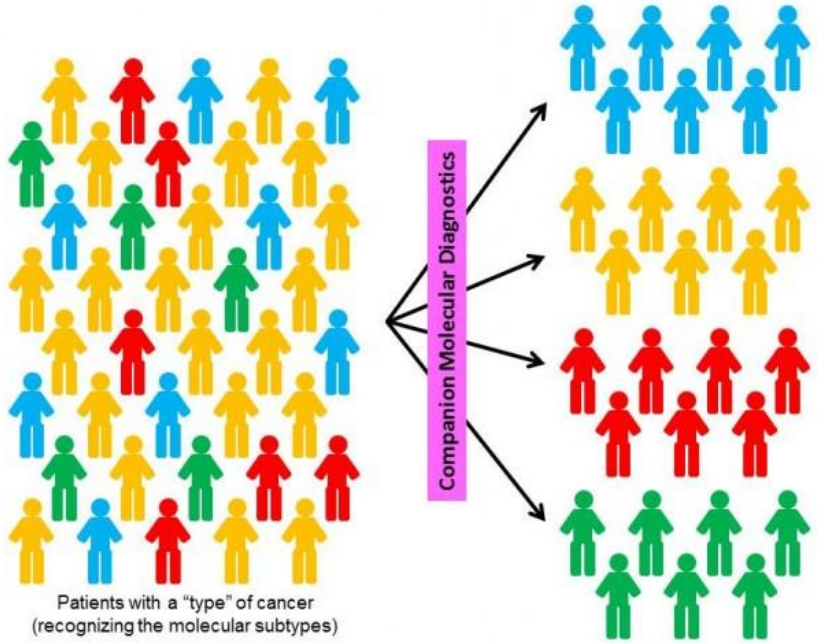
Intended use of predictive biomarkers?

Roche

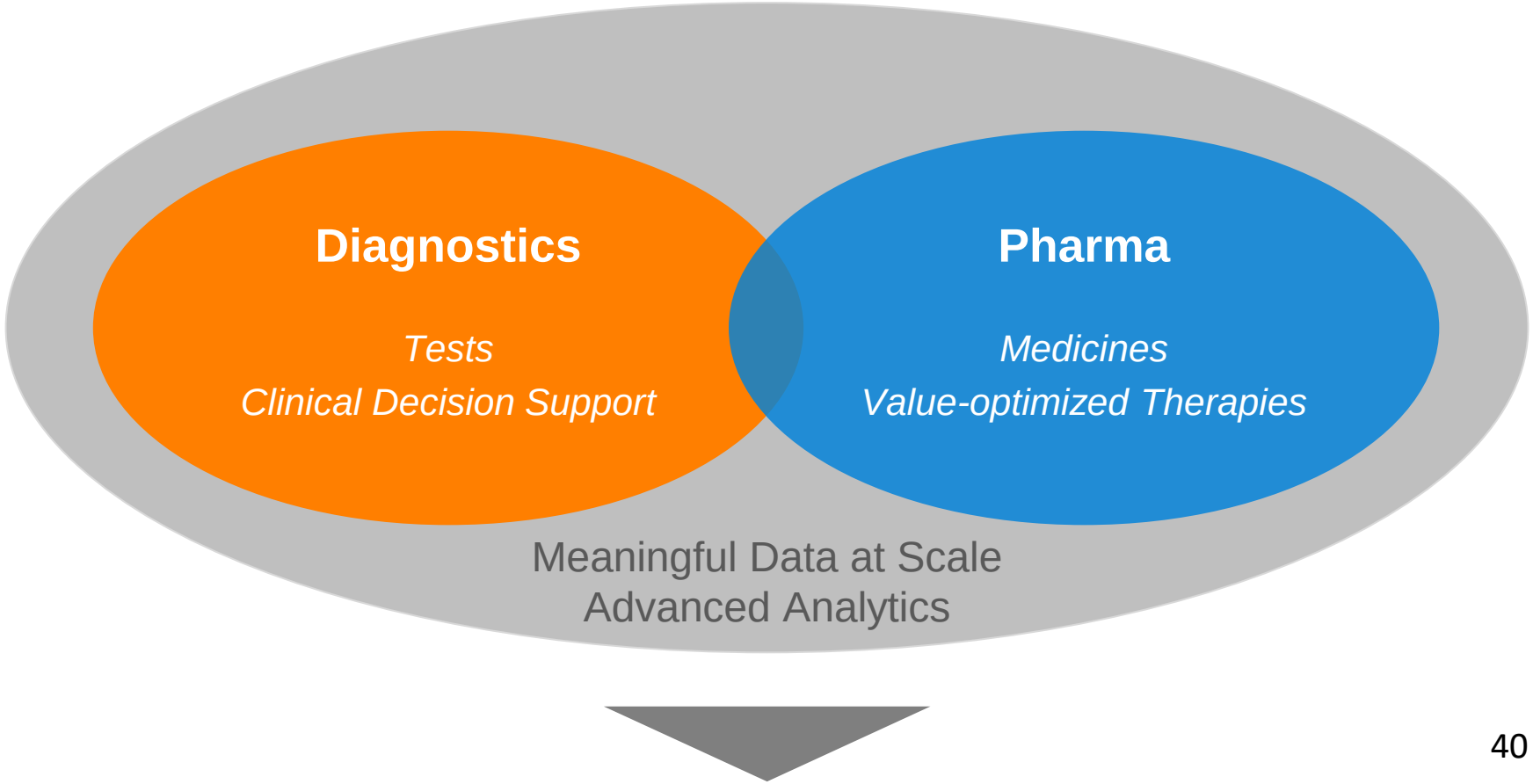
Predictive biomarker

- Many diseases are heterogenous, of unknown etiology, and often a compilation of syndromes/symptoms
- Often only a subgroup of patients derives great benefit from a therapeutic
- Predictive biomarker aim to identify that subgroup of patients, resulting in enhanced benefit/risk ratio
  - Also reduces number of patients treated that do not derive great benefit

Personalized Healthcare



Driving the vision of Personalized Healthcare PHC

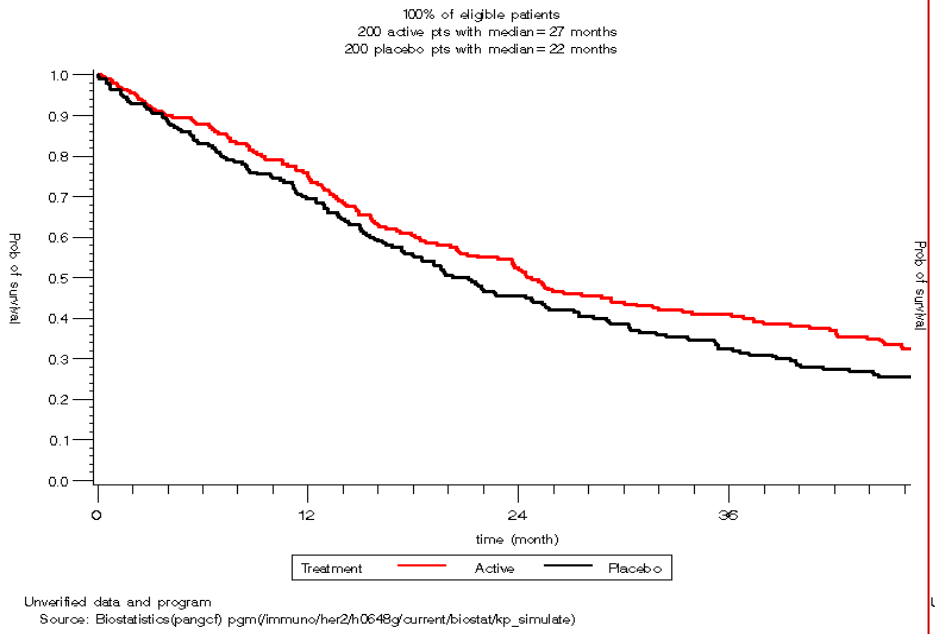


The right treatment for the right patient at the right time

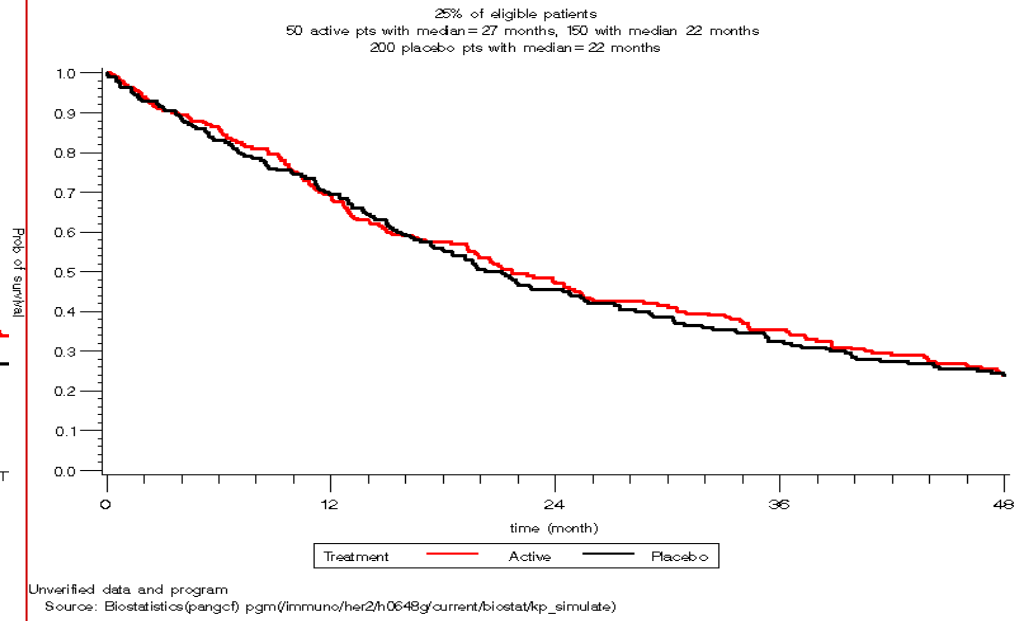
Herceptin example: The Power of Patient Selection

Predictive biomarker

A Phase III in which *only* patients capable of showing a treatment effect are included



Phase III in which only 25% of patients are capable of showing a treatment effect, but *all* are included

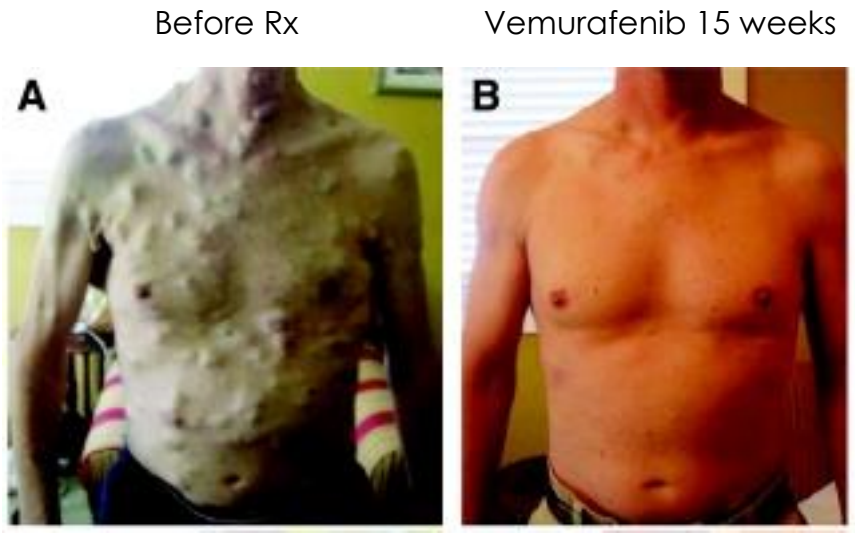


Zelboraf example: targeted therapies

Roche

Predictive biomarker

- About half of all melanomas carry a mutant BRAF gene that drives tumor initiation/growth
- Vemurafenib is a BRAF inhibitor that inhibits the altered BRAF protein and was approved for the treatment of patients with BRAF-mutant metastatic melanoma
- Most patients have an impressive initial response to treatment, but, unfortunately, resistance to the drug may develop quickly



Wagle et al., Journal of Clinical Oncology, 2011

Example Indication Statement:

Zelboraf® vemurafenib

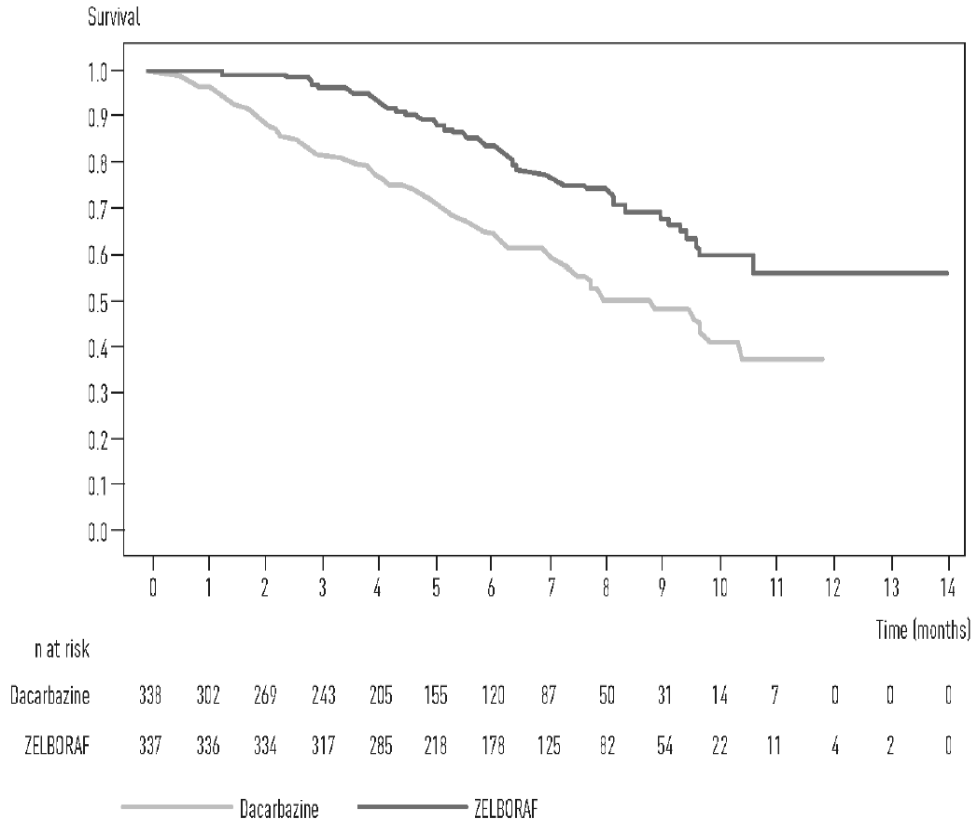
Roche

- ZELBORAF is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma **with BRAF V600E mutation as detected by an FDA-approved test**
- ZELBORAF is not indicated for use in patients with wild-type BRAF melanoma.

BRAF V600E status is essential for the safe and effective use

Companion Diagnostic (CDx)

Figure 1 Kaplan-Meier Curves of Overall Survival – Treatment-Naïve Patients



Companion Diagnostics Example: ZELBORAF

Roche Diagnostics

ZELBORAF™ (vemurafenib) tablets

Co-approval in 2011

Intended Use:
The cobas® 4800 BRAF V600 Mutation Test is a real-time PCR test on the cobas 4800 system,
and is intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib.

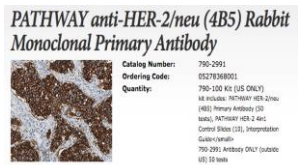
Dx CO-APPROVALS SUPPORTING ROCHE DRUG PRODUCTS

Roche Diagnostics

Herceptin® trastuzumab — SEPT 1998

VENTANA

PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody



HER2 ISH assay

Tarceva® erlotinib — NOV 2004

EGFR Cobas assay

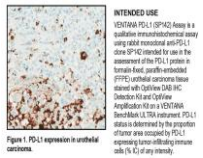
Zelboraf® vemurafenib — AUG 2011

BRAF mutation assay

TECENTRIQ™ atezolizumab — OCT 2016

VENTANA

VENTANA PD-L1 (SP142) Assay



PD-L1 IHC assay

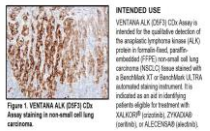
VENCLEXTA® venetoclax tablets — APR 2016

17p deletion FISH assay

ALECENSA® — NOV 2017

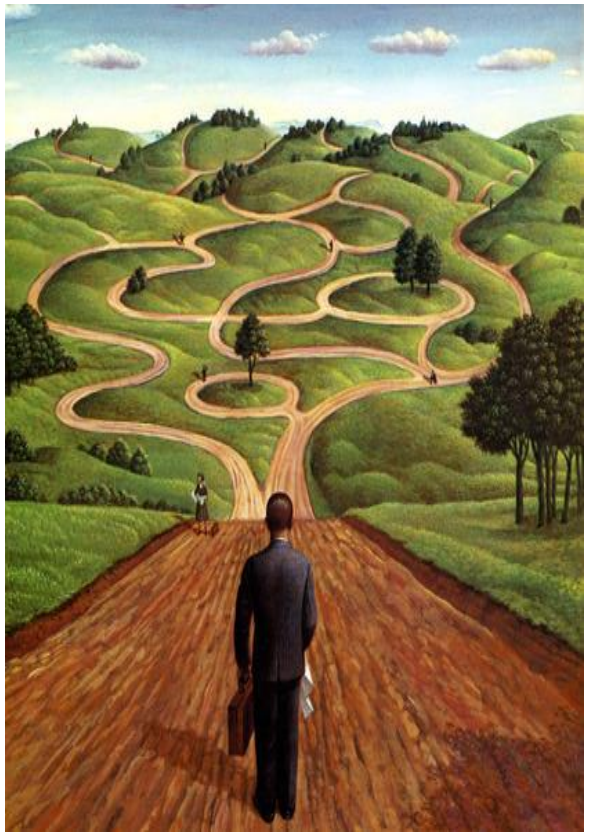
VENTANA

VENTANA ALK (D5F3) CDx Assay



ALK positive

Evolution of CDx Develoment



Addressing the complexity of biomarker development and the rapidly evolving technology landscape will require **flexible and efficient** CDx development strategies.

Companion and Complementary Diagnostics

Predictive Biomarkers

Roche Diagnostics

- **Companion Diagnostic Test (CDx)**
  - A companion diagnostic is a medical device, often an *in vitro* device, which provides information that is **essential for the safe and effective use** of a corresponding drug or biological product.
  - Restricted labeling: therapeutic is only approved for the biomarker subgroup of patients

- **Complementary Diagnostic Test**
  - Test that aids in the benefit-risk decision making about use of the therapeutic.
  - **Difference in benefit-risk is clinically meaningful.**
  - Complementary IVD information is included in the therapeutic product labeling.
  - “All-Comers” labeling with a predictive claim

Complementary Diagnostics Example: TECENTRIQ and PD-L1

Roche Diagnostics

- Indication: Tecentriq is a PD-L1 blocking antibody indicate for the treatment of patients with locally advances or metastatic urothelial carcinoma
- Clinical efficacy described for all patients, as well as based on PD-L1 IHC assay (SP142)

No patients excluded from receiving Tecentriq therapy based on SP142 status

Complementary Diagnostic

	All Patients	PD-L1 Expression Subgroups	
TECENTRIQ™ atezolizumab	N=310	PD-L1 Expression of < 5% in ICs[1] (N=210)	PD-L1 Expression of ≥ 5% in ICs[1] (N=100)
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	**14.8% (11.1, 19.3)**	**9.5% (5.9, 14.3)**	**26.0% (17.7, 35.7)**
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
Median DoR, months (range)	NR (2.1+, 13.8+)	12.7 (2.1+, 12.7)	NR (4.2, 13.8+)

NR = Not reached

+ Denotes a censored value

[1] PD-L1 expression in tumor-infiltrating immune cells (ICs)

What about Predictive Biomarkers outside of oncology?

Roche
Diagnostics

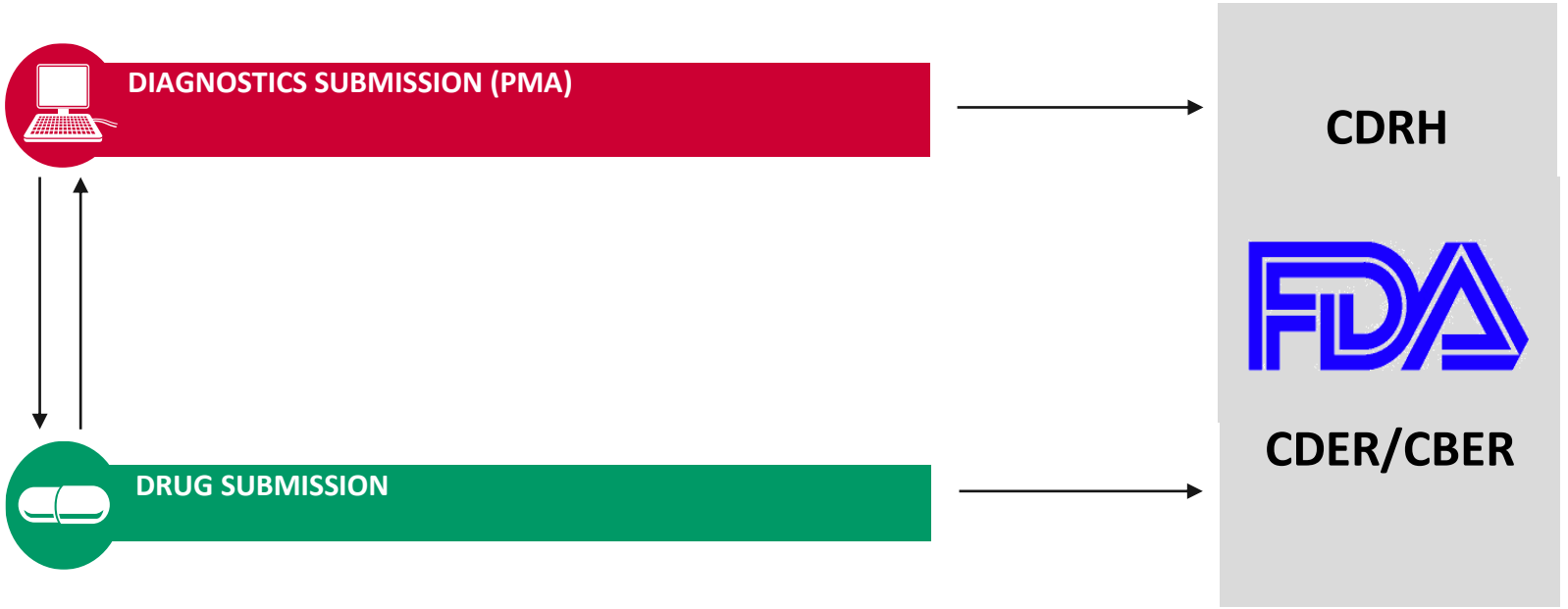
Examples of predictive biomarkers in asthma

Xolair® Omalizumab FOR SUBCUTANEOUS USE	**positive skin test or in vitro reactivity to a perennial aeroallergen (allergic)**
Nucala® (mepolizumab) for Subcutaneous Injection 100 mg/vial	**Eosinophilic phenotype**

- These predictive biomarkers were already **existing diagnostic clinical tests** so no new companion/complementary diagnostic assay development was required

Companion/Complementary Diagnostics Regulatory Pathway

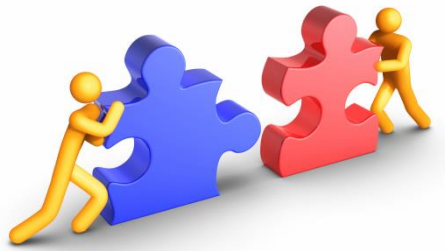
US Registration



Companion/Complementary Diagnostics

Considerations

- Determination of **Companion** vs **Complementary** will be made by FDA only after the clinical data is submitted.
  - *Pre-sub meetings beneficial but not binding*
- Reimbursement:
  - If drug label does not state that an FDA approved test is required, how does this impact assay use and reimbursement?
- Challenges around when and why to order the Complementary Dx test



CDx Layers of Complexity

- One Indication, One Drug, One Test, One Allele
- One Indication, More Than One Drug, One Test, Same Alleles
- One Indication, More Than One Drug, Two Tests, Multiple Alleles
- Multiple disease indications, IHC tests (2 discrete antibodies), molecular targets, mRNA expression (PD-L1)
- One Test, Multiple Indications, Multiple Drugs, Different Genes, Multiple Variants/Allele Representation (NGS)

Future needs for a consolidation of diagnostic testing to enable a single test or a few tests to garner all the necessary information for therapeutic decision making.

Stand-Alone Dx

- Relates to a **disease or condition**, not a therapy
- Can be for screening, diagnosis, prognosis, monitoring
- Can be referenced in Rx labeling (e.g. “Warnings & Precautions)
- Part of the existing lab infrastucture in most cases
- Often high-volume

Complementary Dx

- Is **NOT** required for the sale and effective use of a therapy
- Dx is in Rx label in “Clinical Studies” section
- Rx is in Dx label in the “intended use”
- Identifies patients “most likely to benefit” based on either safety or efficacy

Companion Dx

- Is **REQUIRED** for the safe and effective use of a therapy
- Dx is in Rx label in “Indications and Usage” section
- Rx is in Dx label in the “intended use”
- Dx identifies patients not likely to benefit from Rx
- Requires resources from Rx to support Dx

Q&A

BREAK

Outline

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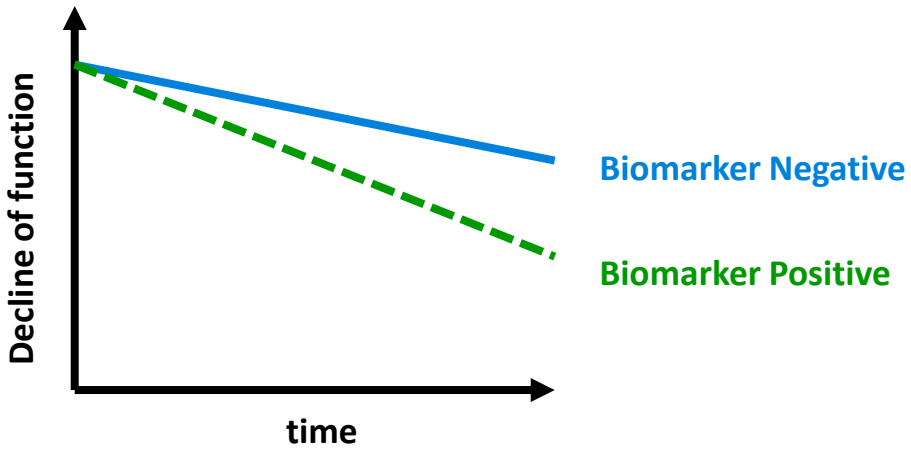
   BREAK
6. BFAST Study
7. QUIZ

Prognostic Biomarker

Prognostic Biomarker

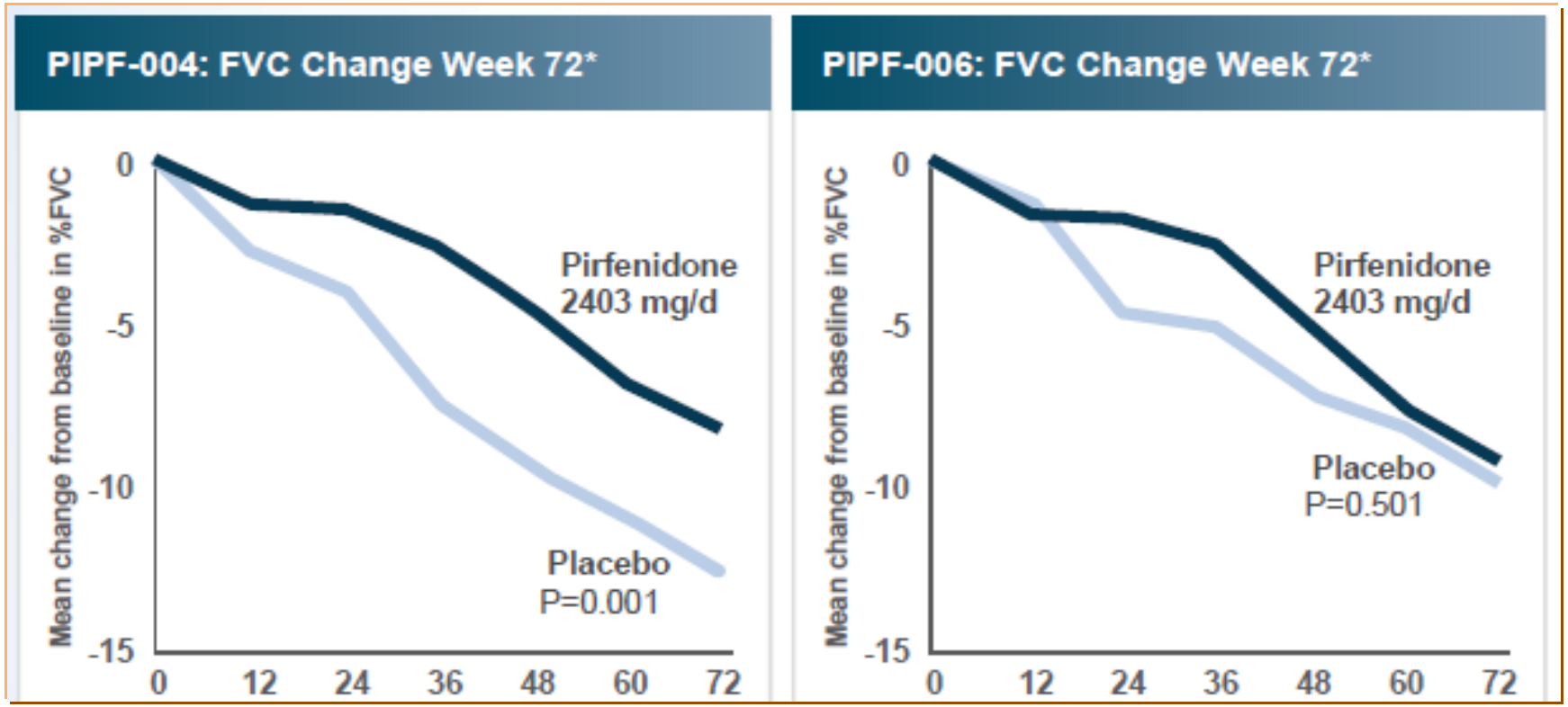
A biomarker used to identify **likelihood of a clinical event, disease recurrence or progression** in patients who have the disease or medical condition of interest



Prognostic Biomarkers can help support trial design

Roche

Prognostic biomarker



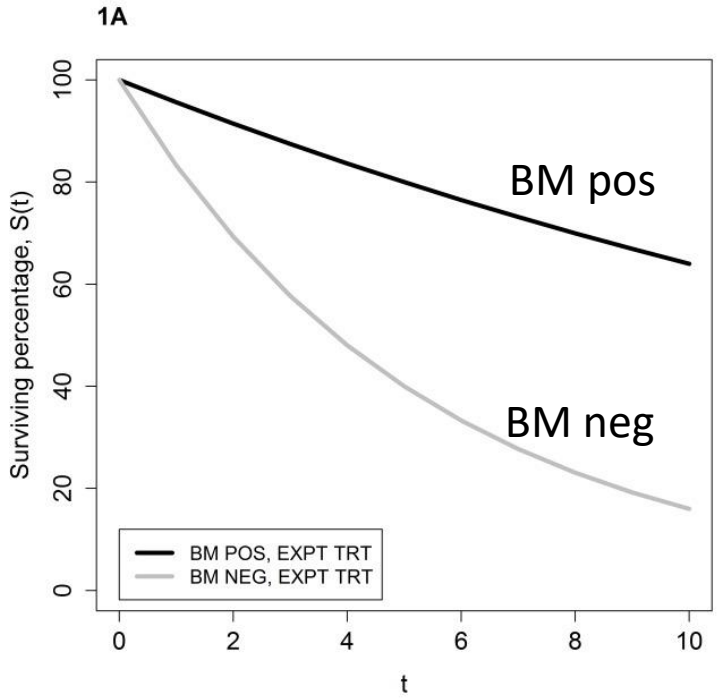
- Primary endpoint met in only one trial (004)
  - No clear reason for failure in 006 – different rate of progression in placebo arm?

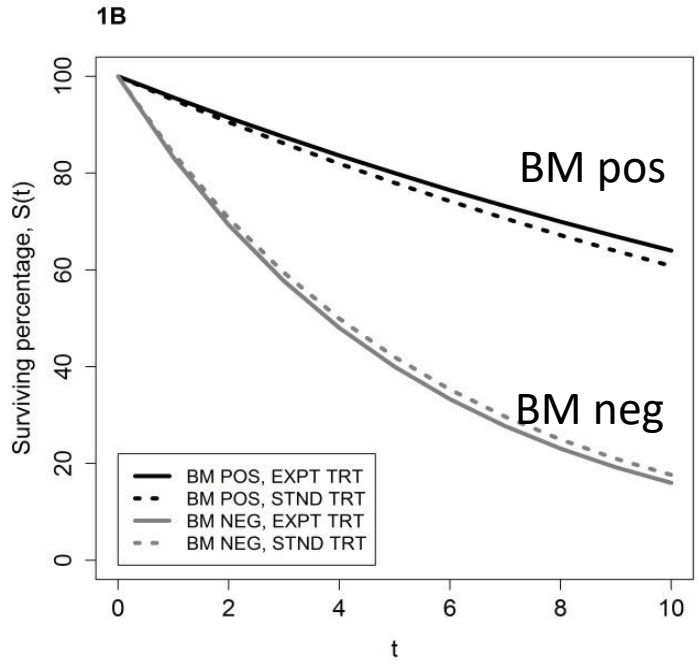
Prognostic biomarker does not have to be predictive of treatment effect

Roche

Prognostic biomarker

Assume that patients have been randomized to the experimental and standard therapies





- For patients receiving the **experimental therapy**, those who are positive for the biomarker (black curve) survive longer than those who are negative for the biomarker (gray curve).
- The biomarker is associated with the same difference in survival for those patients receiving the **standard therapy** (black dashed curve versus gray dashed curve)

Prognostic biomarkers can be predictive biomarkers as well - example in IPF

Roche

Prognostic biomarker

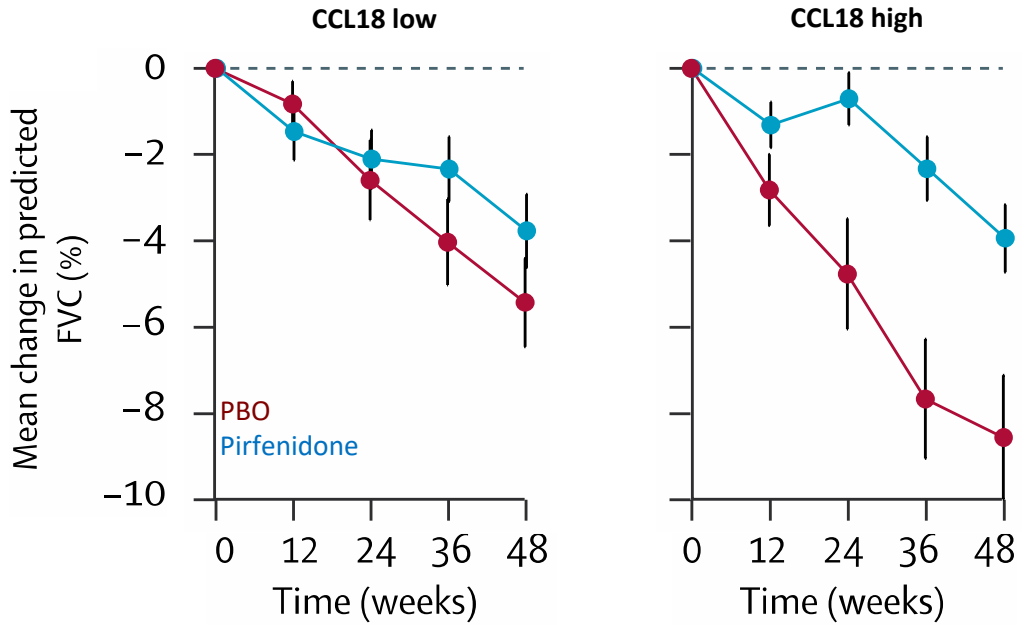
Serum CCL18 is

prognostic for disease progression

and

predictive for pirfenidone treatment

Serum CCL18 is prognostic for disease progression (FVC%pred)



CAPACITY multivariate analysis p = 0.032

Prognostic effect size = -3.1

Prognostic biomarkers can be predictive biomarkers as well - example in asthma

Roche

Prognostic biomarker

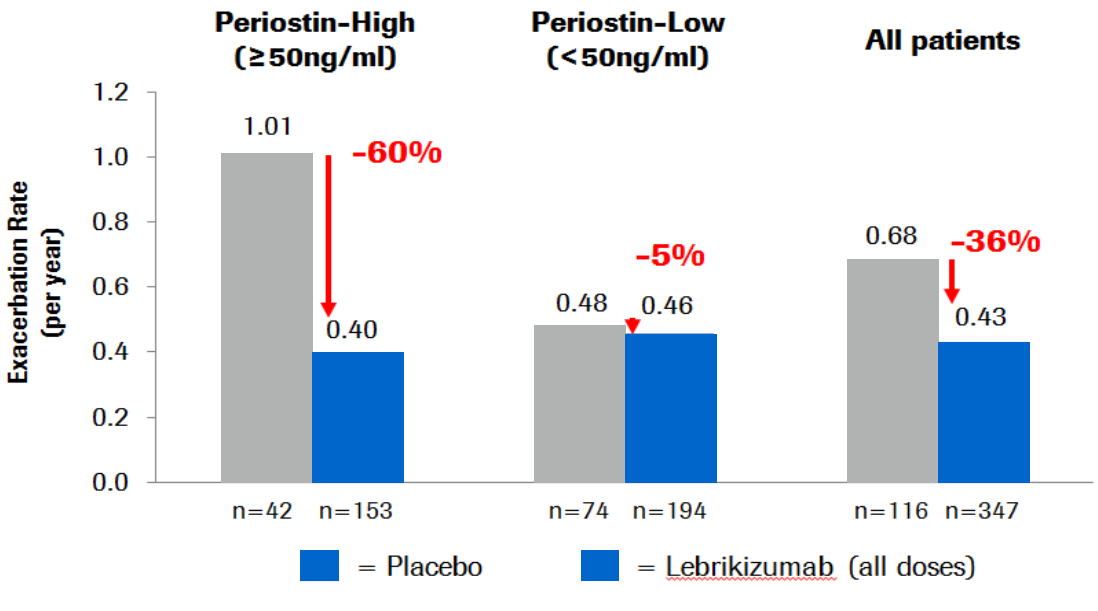
Serum periostin was both

prognostic for exacerbations

and

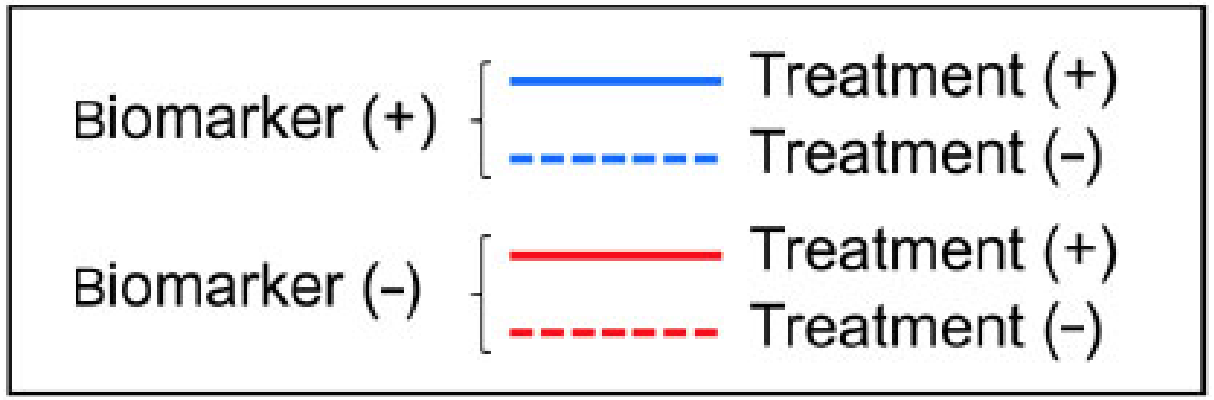
predictive of lebrikizumab response

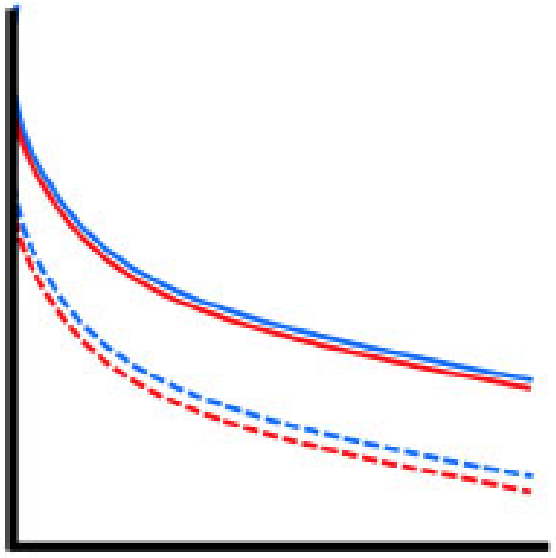
Efficacy of lebrikizumab in T2-high as defined by serum periostin



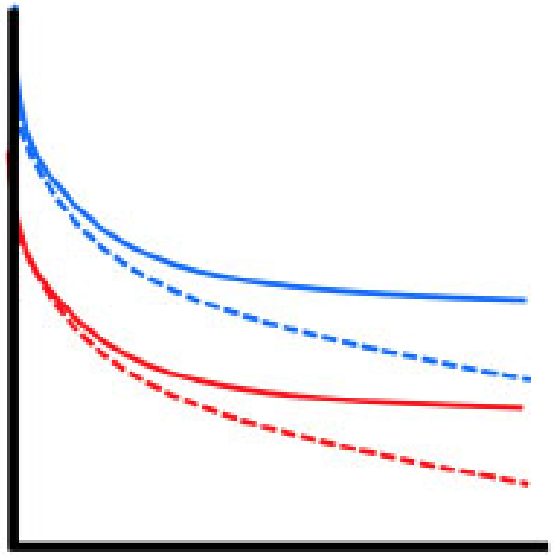
Source: LUTE & VERSE Phase 2 Trials

Recap: Prognostic vs Predictive biomarkers

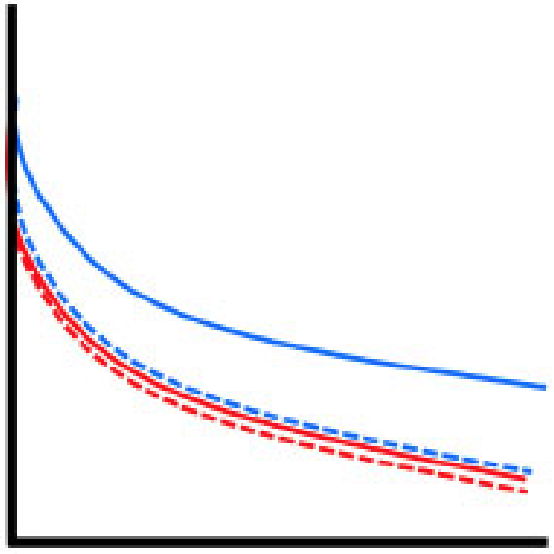




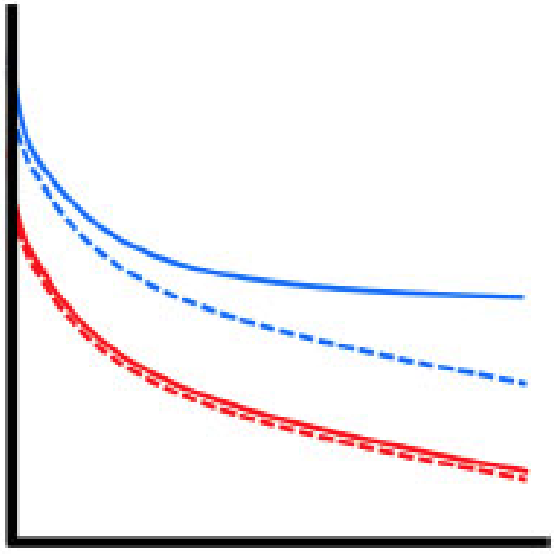
Neither prognostic nor predictive



Prognostic but not predictive



Not prognostic but predictive



Prognostic and predictive

Summary Prognostic Biomarkers

Prognostic biomarker

- A biomarker used to identify the **likelihood of a clinical event, disease recurrence or progression** in patients

- Important for clinical trial design
  - More homogeneous patient subgroup
  - Fewer patients
  - Shorter duration

- Prognostic biomarkers can be both predictive and pharmacodynamic biomarkers at the same time

Safety Biomarker

Roche

Safety biomarker

Safety Biomarker

A biomarker measured before or after an exposure to a medical product or an environmental agent **to indicate the likelihood, presence, or extent of toxicity** as an adverse effect.

- Common to all safety biomarkers is the ability to detect or predict these adverse drug or exposure effects.

Intended use of Safety Biomarkers

Roche

Safety biomarker

Safety biomarkers can be sub-defined according to other biomarker types by its intended use for safety

Monitoring Safety Biomarker	Predictive Safety Biomarker	Susceptibility/Risk Safety Biomarker
Signal toxicity by the detection of or change in a biomarker, allowing dose modification or treatment interruption before toxicity becomes severe and or can indicate the type of needed treatment.	Identify individuals with increased or decreased likelihood of experiencing a particular toxicity when an individual is subjected to drug exposure	Identify individuals without clinically apparent disease for whom particular therapies should not be initiated (or should be monitored more closely) because of significant potential to develop toxicity when subjected to drug exposure.

The Intended Use of a Biomarker drives the discovery, validation process

Enrollment

Stratification

Prognostic

Target Engagement

PK/PD – dose selection

Proof of Activity

Safety Monitoring

Pharmacodynamic

Surrogate Endpoint

Companion Dx

MOA, Differentiation

Complementary Dx

Predictive

Darker color reflects greater impact, requirement for validation (assay & clinical), regulatory, etc.

Q&A

BREAK

Roche

BFAST

BLOOD FIRST ASSAY SCREENING TRIAL

BFAST: BLOOD FIRST ASSAY SCREENING TRIAL

BFAST

A PHASE II/III MULTICENTER STUDY

EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TARGETED THERAPIES

AS TREATMENTS FOR PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

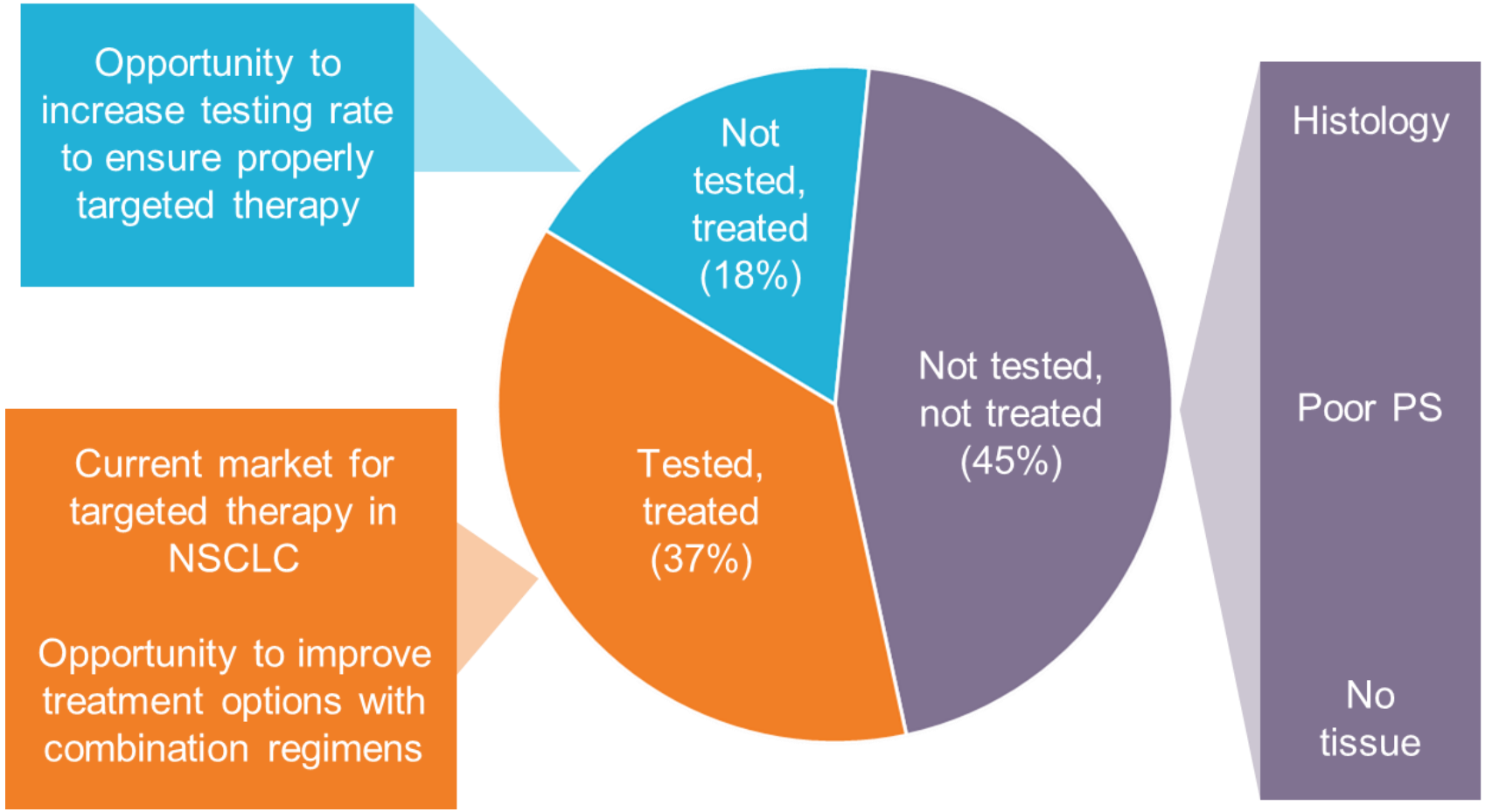
HARBORING ACTIONABLE SOMATIC MUTATIONS DETECTED IN BLOOD

The first prospective study to use only blood-based next generation sequencing (NGS) to detect specific fusions with the aim of selecting treatment for people with advanced non-small cell lung cancer (NSCLC), without the need for tissue biopsy.

First line therapy: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead.

BFAST

Many Patients are Never Molecularly Diagnosed in NSCLC



NSCLC = non-small cell lung carcinoma; PS = performance status

Source: US Commercial, testing and treatment rates for chemo doublets

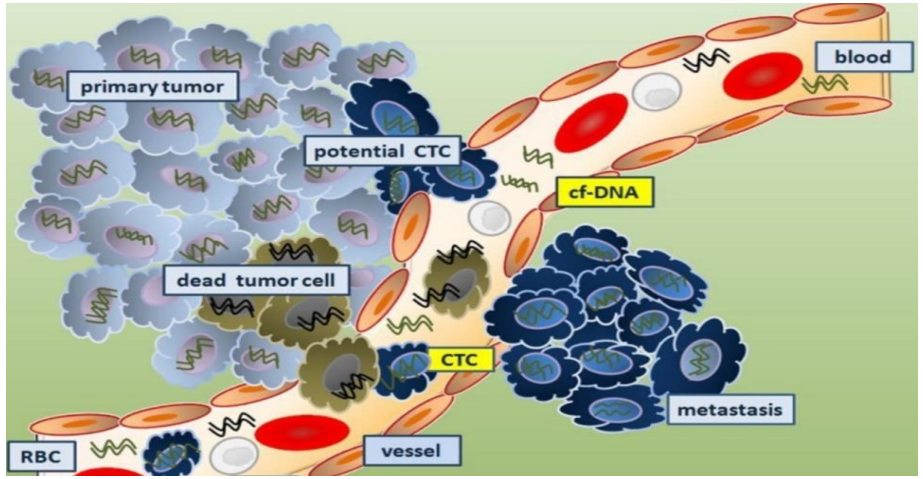
Identifying actionable biomarkers in NSCLC samples : biopsy vs blood

Standard-of-Care (Conventional) Biopsies in Lung Cancer

- Surgical resections, core needle biopsies, FNAs
- Derived directly from 1º or metastatic tumor
- Typically FFPE
- FNAs and CNBs used to diagnose and stage cancer
- Surgical specimens required for molecular diagnosis *but up to 30% NSCLC patients do not have these tissue samples available*
- Single lesion and time point
- Limited quantity and quality

DNA from Blood samples

- DNA derived from normal cells and tumor cells
- Tumor DNA is tested (circulating tumor DNA, ctDNA)
- Tumor DNA derived from all lesions.
- Samples taken over time
- Next generation sequencing is the basis for the ctDNA tests used in BFAST
- Identify individual mutations (ie, ALK rearrangements)
- Identify tumor mutational burden (TMB)



http://cdn.intechopen.com/pdfs-wm/38575.pdf

The BFAST trial will address central challenges:

Lung cancer challenges	BFAST solution
• Some patients do not have sufficient tissue for one biomarker • As number of biomarkers increases, fewer single-plex tests can be completed with limited amount of tissue	• Expands testing by introducing multiplex blood-based testing (eliminating tissue limitations and barriers for rare mutation testing) • Multiplex testing platform can increase testing rates for all relevant alterations in NSCLC
• Individual trials for rare mutations require screening and reject many biomarker-negative patients • The trials can be prohibitively expensive and slow	• Trial enrols patients with or without mutational testing by tissue • Umbrella design reduces time and costs • Trial provides data for new indications in rare tumour types • Can test for both common and rare mutations in one procedure

BFAST

Foundation Medicine, Inc. (FMI)

Founded in 2010
in Cambridge, MA

>1200 employees and growing

The leading platform for **comprehensive genomic profiling** of cancer

Launched the first **FDA approved universal companion diagnostic** in 2017

Connects physicians and their patients to the latest cancer treatment approaches

Molecular insights **accelerate oncology R&D** through biopharma partnerships

Acquired by Roche in 2018

FMI remains operationally independent

www.foundationmedicine.com

FoundationOne Liquid CDx (F1L CDx)

324 genes

Detects all 4 classes of genomic alterations:
- Base substitutions, insertions/deletions, rearrangements and copy number alterations

bTMB and MSI included in assay

Analytically validated and implemented in a CAP-CLIA lab

FDA IVD approved, CE-IVD marked, Japan MHLW-approved
- intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms

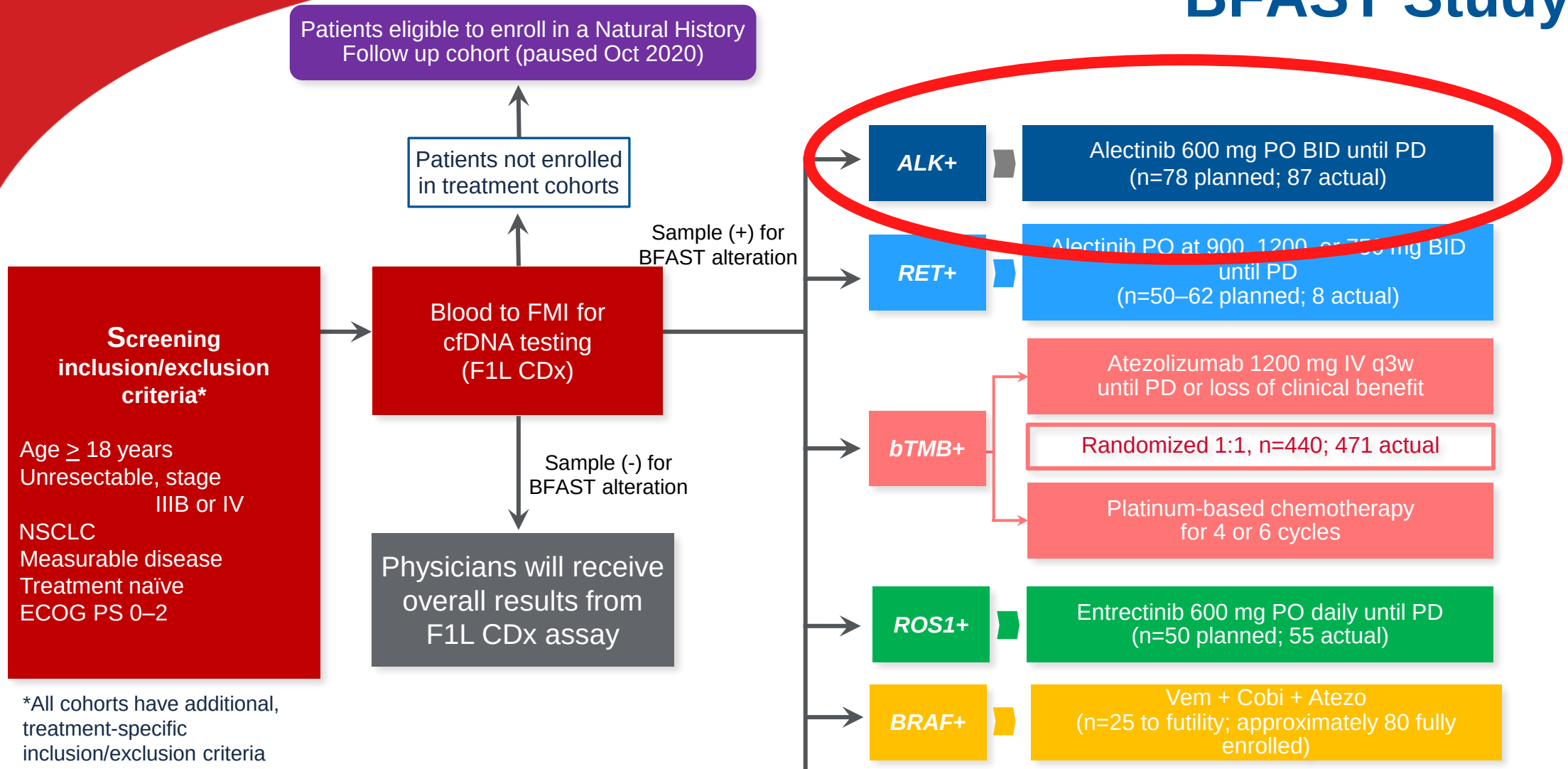
F1L CDx Technical Specifications:
https://www.foundationmedicine.com/test/foundationone-liquid-cdx

The FoundationOne Liquid CDx assay interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 [Exons 4-9]	CASP8	**DDR2 [Exons 5,17,18]**	FGFR4	KDR	**MYD88 [Exon 4]**	PPP2R2A	**SMO**
ACVR1B	CBFB	DIS3	FH	KEAP1	NBN	PRDM1	SNCAIP
AKT1 [Exon 3]	CBL	DNMT3A	FLCN	KEL	**NF1**	PRKAR1A	SOCS1
AKT2	**CCND1**	DOT1L	FLT1	**KIT [Exons 8,9,11,12,13,17]**	NF2	PRKCI	SOX2
AKT3	CCND2	EED	**FLT3 [Exons 14,15,20]**	KLHL6	NFE2L2	PTCH1	SOX9
ALK [Exons 20-29, Introns 18,19]	CCND3	**EGFR [Intron 7]**	**FOXL2**	KMT2A (MLL)	NFKBIA	**PTEN**	SPEN
ALOX12B	CCNE1	EP300	FUBP1	KMT2D (MLL2)	NKX2-1	**PTPN11**	SPOP
AMER1	CD22	EPHA3	GABRA6	**KRAS**	NOTCH1	PTPRO	SRC
APC	CD70	EPHB1	GATA3	LTK	NOTCH2	QKI	STAG2
AR	CD74* {Introns 8-6}	EPHB4	GATA4	LYN	NOTCH3	RAC1	STAT3
ARAF [Exons 4,5,7,11,13,15, 16]	CD79A	**ERBB2**	GATA6	MAF	**NPM1 [Exons 4-6,8,10]**	RAD21	**STK11**
ARFRP1	CD79B	**ERBB3 [Exons 3,6,7,8,10,12,20,21,23,24,25]**	GID4 (C17orf39)	**MAP2K1 [Exons 2,3]**	**NRAS [Exons 2,3]**	RAD51	SUFU
ARID1A	**CD274**	ERBB4	**GNA11 [Exons 4,5]**	**MAP2K2 [Exons 2-4,6,7]**	NT5C2	RAD51B	SYK
ASXL1	CDC73	ERCC4	GNA13	MAP2K4	**NTRK1 [Exons 14,15, Introns 8-11]**	RAD51C	TBX3
ATM	**CDH1**	ERG	**GNAQ [Exons 4,5]**	MAP3K1	NTRK2	RAD51D	TEK
ATR	**CDK12**	**ERRFI1**	**GNAS [Exons 1,8]**	MAP3K13	**NTRK3 [Exons 16,17]**	RAD52	TET2
ATRX	**CDK4**	**ESR1 [Exons 4-8]**	GRM3	MAPK1	NUTM1* {Intron 1}	RAD54L	TERC* {ncRNA}
AURKA	**CDK6**	ETV4* {Introns 5, 6}	GSK3B	MCL1	P2RY8	**RAF1 [Exons 3,4,6,7,10,14,15,17]**	**TERT* {Promoter}**
AURKB	CDK8	ETV5* {Introns 6, 7}	H3F3A	**MDM2**	**PALB2**	RARA	TGFBR2
AXIN1	CDKN1A	**ETV6* {Introns 5,6}**	HDAC1	MDM4	PARK2	**RB1**	TIPARP
AXL	CDKN1B	EWSR1* {Introns 7, 13}	HGF	MED12	PARP1	RBM10	TMPRSS2* {Introns 1-3}
AP1	**CDKN2A**	**EZH2 [Exons 4,16,17,18]**	HNF1A	MEF2B	PARP2	REL	TNFAIP3

BARD1	CDKN2B	EZR* {Introns 9-11}	**HRAS [Exons 2,3]**	MEN1	PARP3	**RET [Exons 11,13-16, Introns 9,10,11]**	TNFRSF14
BCL2	CDKN2C	FAM46C	HSD3B1	MERTK	PAX5	RICTOR	**TP53**
BCL2L1	CEBPA	FANCA	ID3	**MET**	PBRM1	RNF43	TSC1
BCL2L2	CHEK1	FANCC	**IDH1 [Exon 4]**	MITF	PDCD1	**ROS1 [Exons 31,36-38,40, Introns 31-35]**	TSC2
BCL6	**CHEK2**	FANCG	**IDH2 [Exon 4]**	MKNK1	**PDCD1LG2**	RPTOR	TYRO3
BCOR	CIC	FANCL	IGF1R	MLH1	**PDGFRA [Exons 12,18]**	RSPO2* {Intron 1}	U2AF1
BCORL1	CREBBP	FAS	IKBKE	**MPL [Exon 10]**	**PDGFRB [Exons 12-21,23]**	SDC4* {Intron 2}	**VEGFA**
BCR* {Introns 8, 13, 14}	**CRKL**	FBXW7	IKZF1	MRE11A	PDK1	SDHA	VHL
BRAF [Exons 11-18]	CSF1R	FGF10	INPP4B	MSH2	PIK3C2B	SDHB	WHSC1
BRCA1	CSF3R	FGF12	IRF2	MSH3	PIK3C2G	SDHC	WHSC1L1
BRCA2	CTCF	FGF14	IRF4	MSH6	**PIK3CA [Exons 2,3,5-8,10,14,19,21]**	SDHD	WT1
BRD4	CTNNA1	FGF19	IRS2	MST1R	PIK3CB	SETD2	XPO1
BRIP1	**CTNNB1 [Exon 3]**	FGF23	JAK1	MTAP	PIK3R1	SF3B1	XRCC2
BTG1	CUL3	FGF3	**JAK2 [Exons 14]**	**MTOR [Exons 19,30,39,40,43-45,47,48,53,56]**	PIM1	SGK1	ZNF217
BTG2	CUL4A	FGF4	**JAK3 [Exons 5,11,12,13,15, 16]**	MUTYH	PMS2	SLC34A2* {Intron 4}	ZNF703
BTK [Exons 2,15]	CXCR4	FGF6	JUN	MYB* {Intron 14}	POLD1	SMAD2	
C11orf30	CYP17A1	**FGFR1**	KDM5A	**MYC**	POLE	SMAD4	
CALR	DAXX	**FGFR2 [Intron 17]**	KDM5C	MYCL	PPARG	SMARCA4	
CARD11	DDR1	**FGFR3 [Exons 7, 9,14, 18, Intron 17]**	KDM6A	**MYCN**	PPP2R1A	SMARCB1	

BFAST Study Design



*All cohorts have additional, treatment-specific inclusion/exclusion criteria

BFAST NCT03178552

ALK+ / Alecensa Results

- BFAST is the first trial to show that by using a blood-based next-generation diagnostic, it is possible to identify the ALK mutation in people with NSCLC using a blood draw alone
- In the study, 87.4% (95% CI: 78.5-93.5) of people with advanced NSCLC who were identified by the FoundationOne Liquid biopsy assay to have ALK fusions had a confirmed response to treatment with Alecensa (overall response rate; ORR) as measured by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
- This is consistent with the ORR for Alecensa observed in the pivotal Phase III ALEX trial, which identified people using tissue-based testing.
- These data demonstrate that the FoundationOne Liquid assay can help to test and identify a broader population of people with advanced NSCLC who may benefit from Alecensa, for whom current diagnostic tests are not suitable, such as for those who cannot provide tissue samples due to insufficient or absent tumor tissue, or where tissue diagnostics are not available

https://www.gene.com/media/press-releases/14814/2019-09-29/genentech-to-present-results-of-first-pr

ALK+ CDx approval
&
ALECENSA® (alectinib)
label update to include plasma

FDA Approves FoundationOne Liquid CDx for 3 New Companion Diagnostic Indications

October 27, 2020
Hannah Slater

The FDA approved the FoundationOne Liquid CDx for 3 new companion diagnostic indications to help match patients who could benefit from treatment with specific FDA-approved targeted therapies.

The FDA has approved the FoundationOne Liquid CDx for 3 new companion diagnostic indications to help match patients who could benefit from treatment with specific FDA-approved targeted therapies, according to Foundation Medicine, the developer of the test.

The new indications are for alpelisib (Piqray) in advanced or metastatic breast cancer, rucaparib (Rubraca) in advanced ovarian cancer, and alectinib (Alecensa) in a certain type of metastatic non-small cell lung cancer (NSCLC). In addition, the agency also approved a label expansion which now allows the FoundationOne Liquid CDx to report additional select copy number alterations and genomic rearrangements.

BFAST Summary

- The collaboration with Foundation Medicine is a key component to the development of multiplex, next generation diagnostics
- Blood-based diagnostic testing (liquid biopsies) will enable more patients access to personalize cancer therapy
- The BFAST study is an innovative trial utilizing blood based testing to screen patients for targeted therapy in **1L NSCLC** to expand testing and treatment options for patients
  - Additional trial arms are being added

https://clinicaltrials.gov/ct2/show/NCT03178552

Liquid biopsy in COVID times –
Drive-up window
for blood draws!

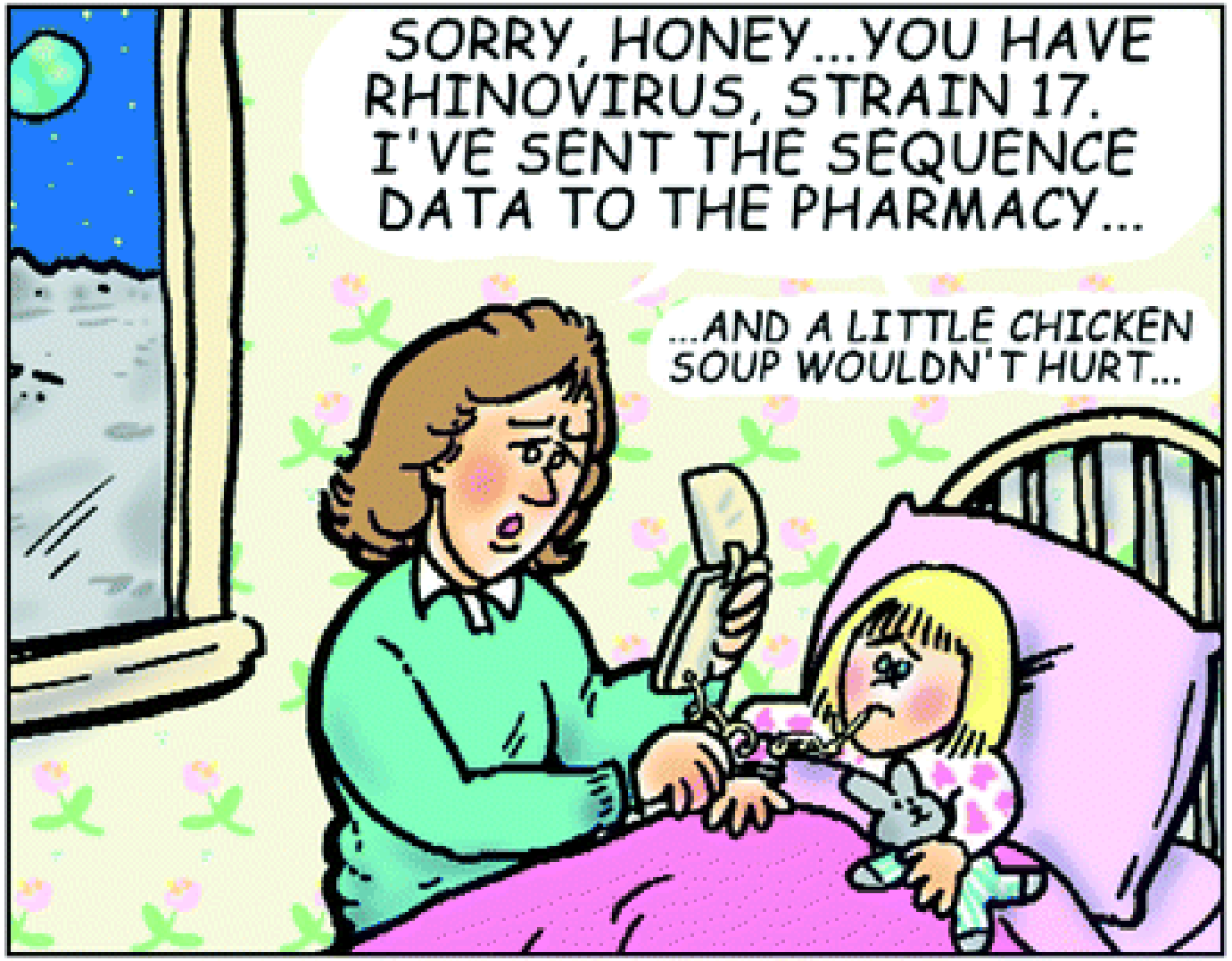
CLOSING & QUIZ

Combining Good Drugs with Good Biomarkers = PHC
---- Good for all Parties

Patient and Physician	- More effective therapies and ability to monitor - Better ability to tailor therapy to patient - Less trial and error
Drug Companies	- Helps focus efforts on high value/ high PTS projects - Enable more informed development - Better R&D productivity - Better uptake and reimbursement
Regulatory Authorities	- Strengthens therapeutic rationale - More targeted labeling - Helps ensure better risk:benefit
Payers	- Less expenditure on ineffective therapies - Easier reimbursement decisions - Better justification for high cost drugs

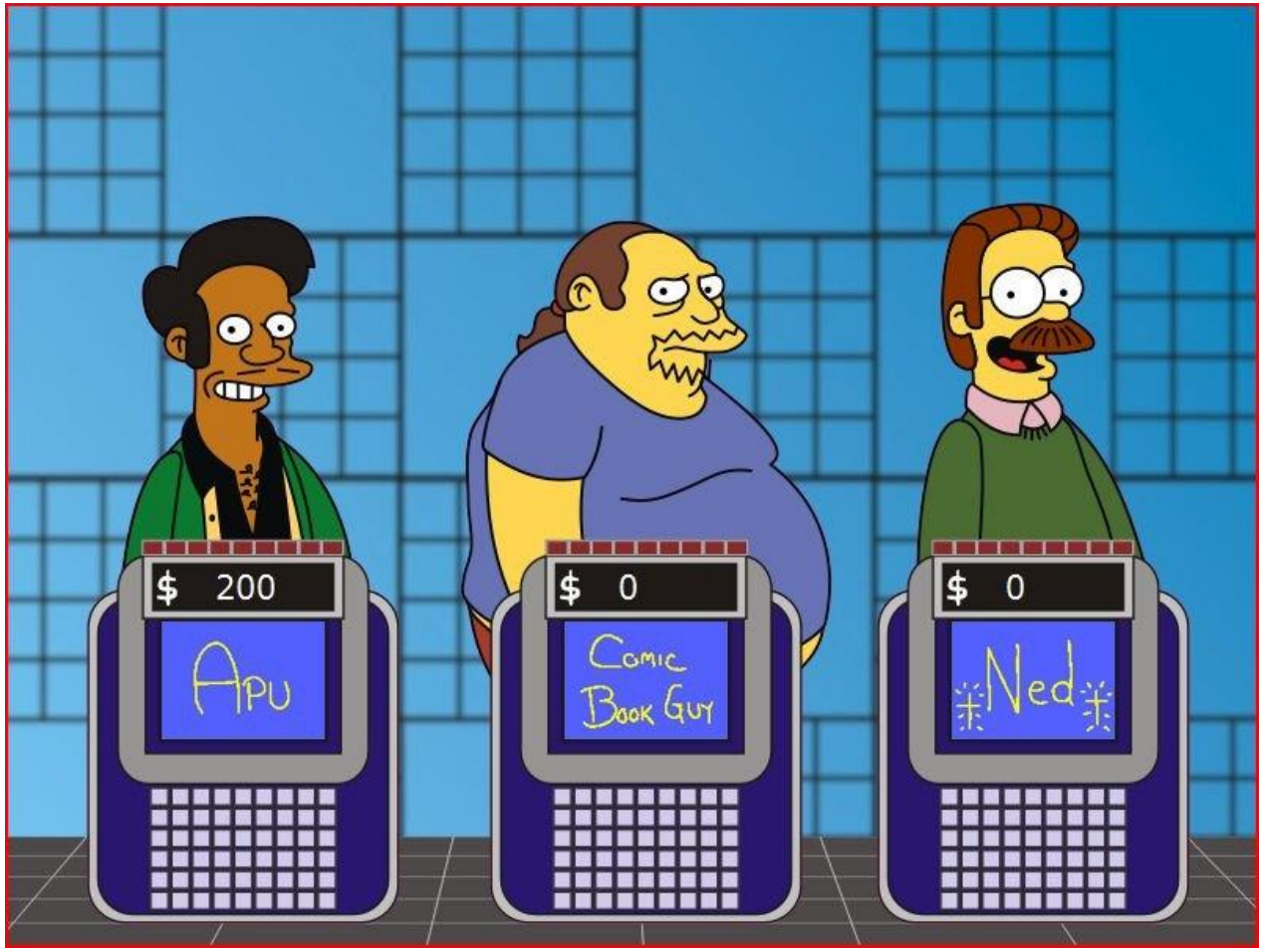
A good biomarker can make a good drug better,
but it can not make a bad drug good

Personalized Healthcare….



What biomarker and diagnostic is it??

Based on the
Intended Use



Question 1

- The subgroup of women with breast cancer who overexpress the human epidermal growth factor receptor 2 (HER2) protein derive clinically meaningful responses to trastuzumab (HERCEPTIN), an anti-HER2 monoclonal antibody. **A positive result confirming overexpression is required for patients to receive trastuzumab** (HERCEPTIN), and other HER2-directed therapies such as pertuzumab (PERJETA) and ado-trastuzumab emtansine (KADCYLA)

- **What type of biomarker is HER2?**
- **What type of assay is the diagnostic?**

Question 2

- PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is **associated with increased objective response rate** (ORR) in a nonrandomized study of TECENTRIQ™ (atezolizumab).

- **What type of biomarker is PD-L1 expression?**
- **What type of assay is the diagnostic SP142?**

Question 3

- The xTAG® Cystic Fibrosis 60 Kit v2 is a qualitative genotyping test which provides information intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and in **confirmatory diagnostic testing** in newborns and children.

- **What type of biomarker is xTAG?**
- **What type of assay is the diagnostic?**

Question 4

- BRACAnalysis ® is a genetic test that **detects the presence of a BRCA1 or BRCA2 gene mutation**. BRCA mutations are responsible for the majority of hereditary breast and ovarian cancers. People with a mutation in either the BRCA1 or BRCA2 gene have risks of up to 87 percent for developing breast cancer and 39-63 percent for developing ovarian cancer by age 70. Mutation carriers previously diagnosed with cancer also have a **significantly increased risk** of developing a second primary cancer. In fact, patients with these types of mutations have an up to 64 percent chance of developing a second breast cancer by age 70.

- **What type of biomarker is BRCA1 or BRCA2 gene mutation?**
- **What type of assay is the diagnostic?**

Question 5

- The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 (v2.0) is an in vitro nucleic acid amplification test for the **quantitation of** human immunodeficiency virus type 1 **(HIV-1) RNA** in human plasma…. This test is intended for use in **conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients.**

- **What type of biomarker is HER2?**
- **What type of assay is the diagnostic?**

Question 6

- HemosIL Fibrinogen-C is intended for the **quantitative determination of fibrinogen**, based on the Clauss method, in human citrated plasma on IL Coagulation Systems.
- Plasma fibrinogen may be used as a biomarker to select patients with chronic obstructive pulmonary disease at high risk for exacerbation and/or all-cause mortality for inclusion in interventional clinical trials.

- **What type of biomarker is fibrinogen?**

Question 7

- A creatinine test system is a device intended to **measure creatinine quantitatively in plasma and urine**. Creatinine measurements are used in the **diagnosis and treatment of certain renal disease**, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

(Serum creatinine may be used to evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity.)

- **What type of biomarker is creatinine?**

THANK YOU!

QUESTIONS