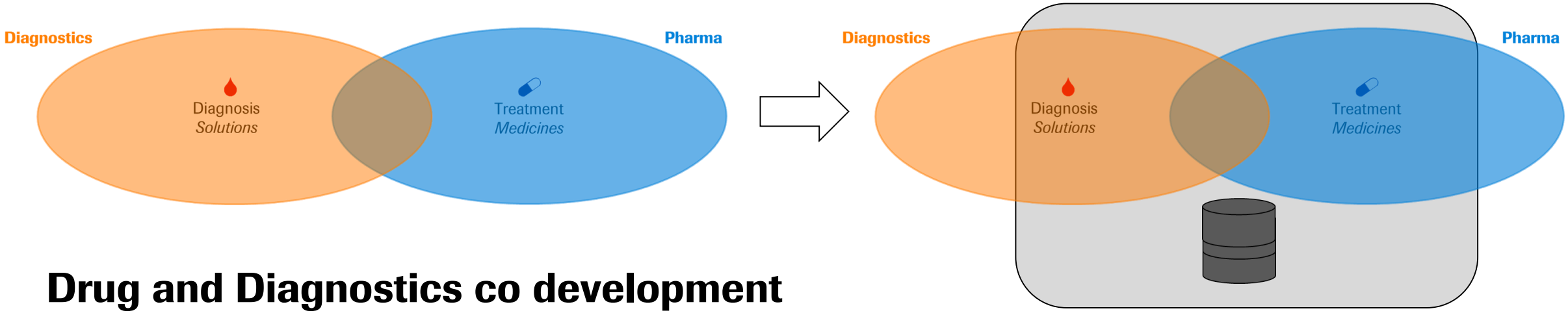
Examples of personalized Healthcare implementation At Roche: Statistical perspectives

Laurent Essioux, BBS 4th June 2019

Personalized Health Care evolution at Roche



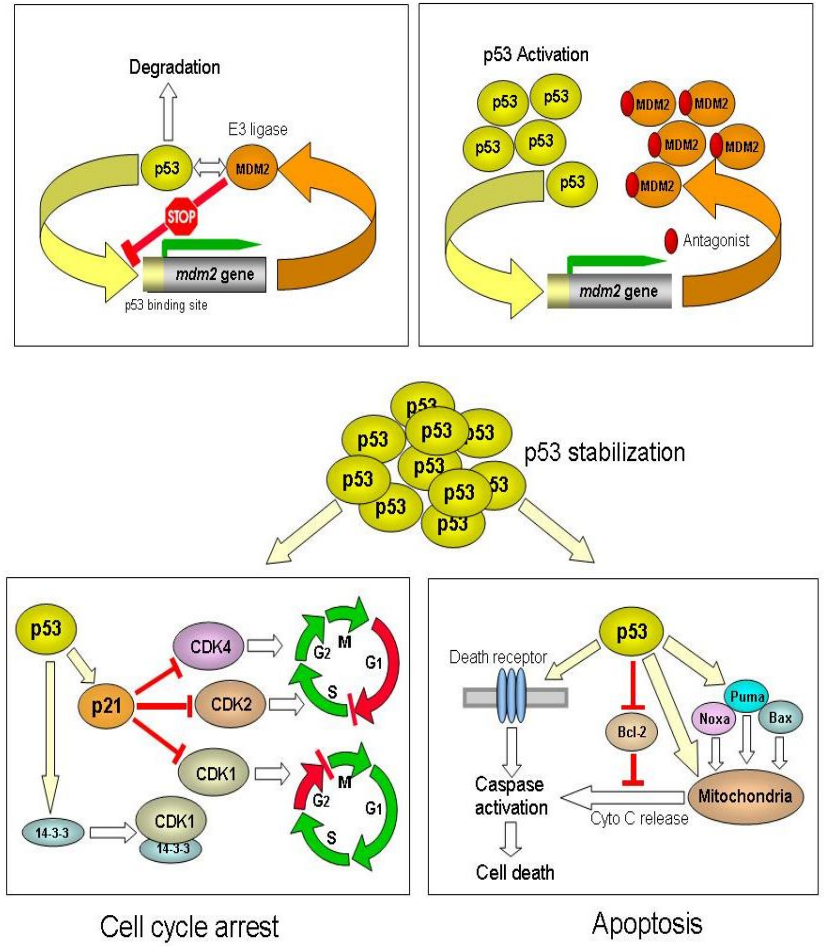
Drug and Diagnostics co development

Personalized Health Care

MDM2 inhibitor Gene signature response development

Identification of biomarkers associated with Immune related adverse effects

MDM2 Antagonist (idasanutlin) Program Background



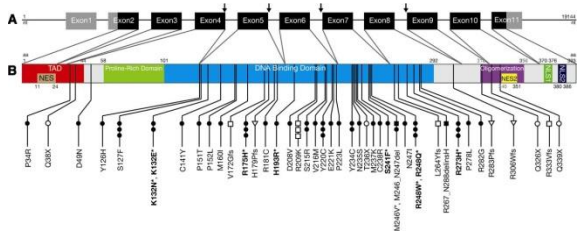
- MDM2 is a key negative regulator of the p53 tumor suppressor
- Idasanutlin blocks the MDM2-p53 interaction leading to stabilization and activation of p53 and tumor cell cycle arrest and apoptosis
- RO5045337 / MDM2(2) was the first MDM2 antagonist taken into the clinic
  - Showed exciting activity in AML Phase 1
  - Limited clinical development potential
- RO5503781 **/ Idasanutlin** is an optimized new generation MDM2 antagonist with same MOA
  - New chemical class, enhanced binding specificity and increased potency

Idasanutlin in Accelerated development in AML pivotal Phase 3 trial

Idasanutlin response biomarker strategy

Targeting patients with active p53 in Acute Myeloid Lymphoma (AML)

1 - Selection of p53 wild type patients using sequence-based test (83% of AML patients p53 wt)



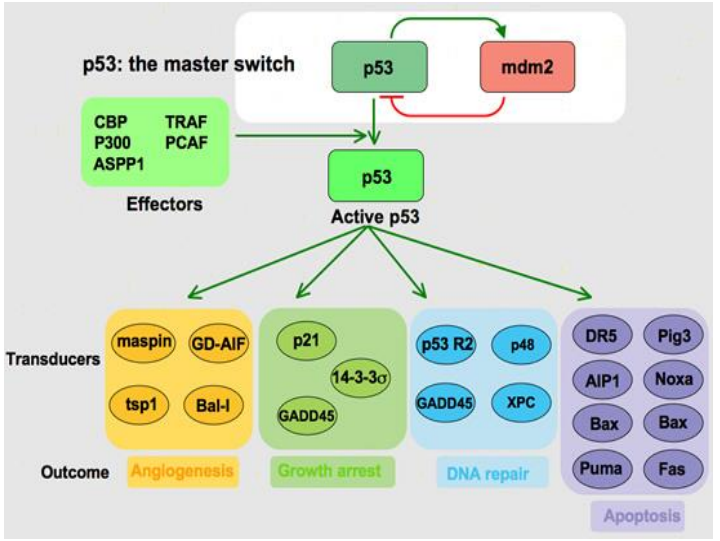
Dufour et al, blood 2013

2- Selection patients with activated p53 pathway

Can a gene expression-based signature informing p53 pathway activation status, prior to therapy, with clinical useful predictive value of response to MDM2 inhibitor be developed?

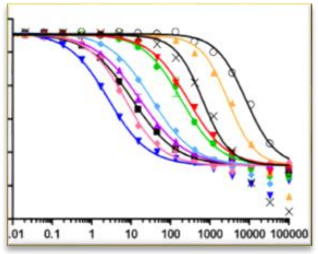
- **Can it outperform / complement p53 somatic mutation test?**
- **Does it outperform single gene assessment? (e.g MDM2 amplification assay)**

➔How to develop it using Phase I data to input Phase 3 assessment?



MDM2 inhibitor sensitivity variable selection procedure

- Tumor growth inhibition assay – mdm2 (2) inhibitor



287 tumor cell lines

- RNA-sequencing -> building block of the expression-based signature
- Exome Sequencing -> p53 status

Univariate filtering step

- Spearman correlation (IC50, RNA-seq)
- Logisitic regression: Sensitivity~gene expression

Union the list with fdr<=0.05: **35 genes**

Functional annotation

p53-MDM2 pathway

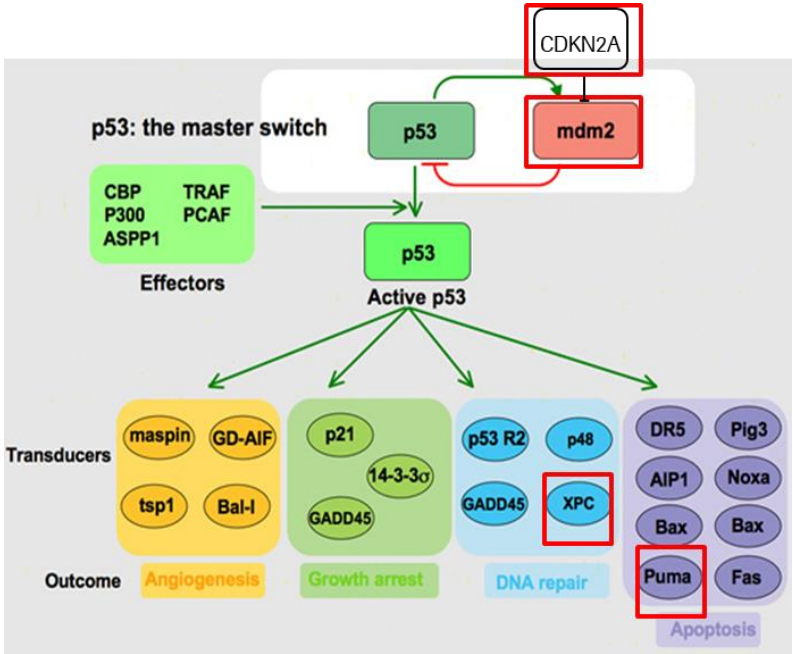
19 genes

Multivariate Variable selection

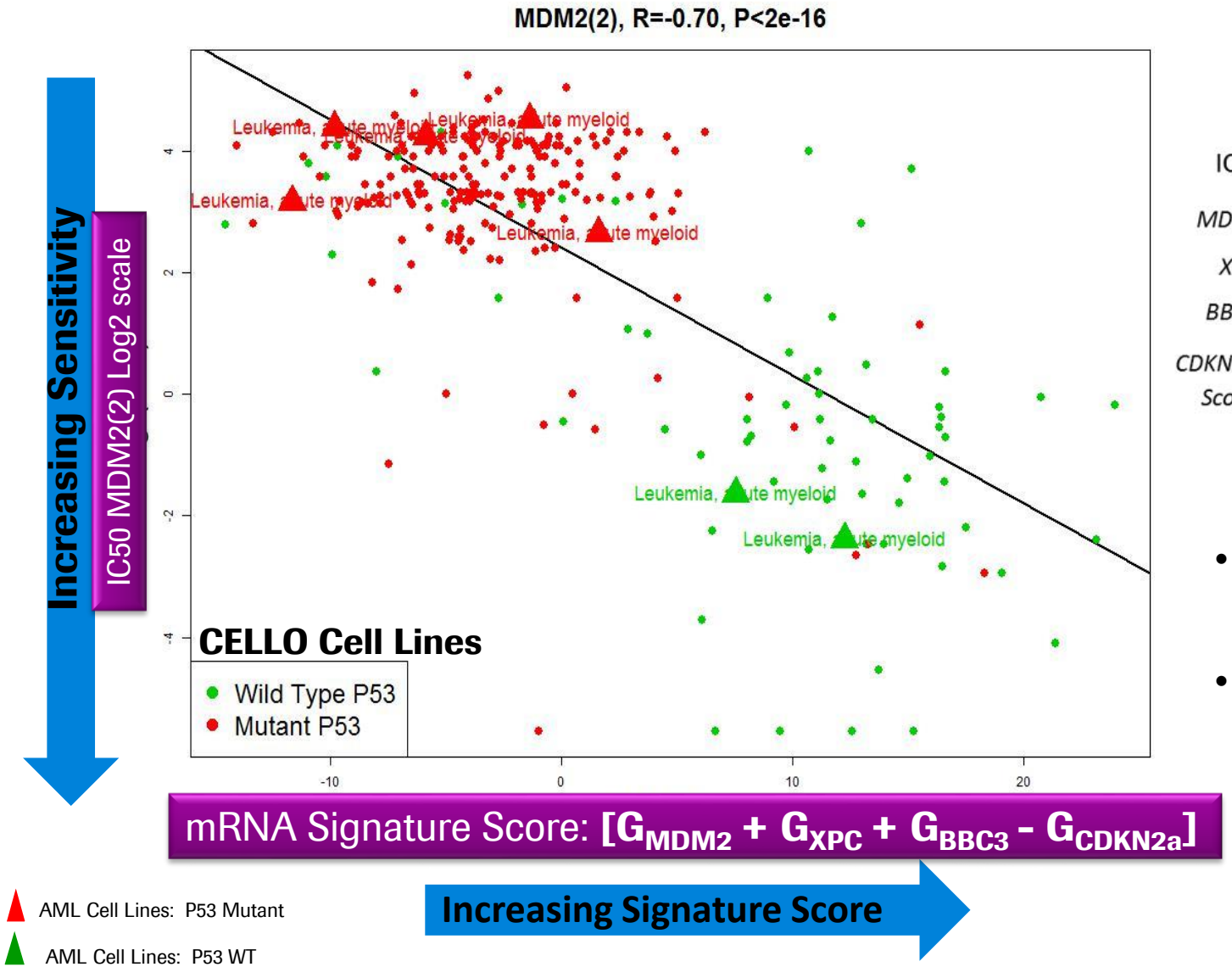
- Stepwise Multivariate regression selection (IC50)
- Stepwise Multivariate logistic regression selection (sens. vs res.)

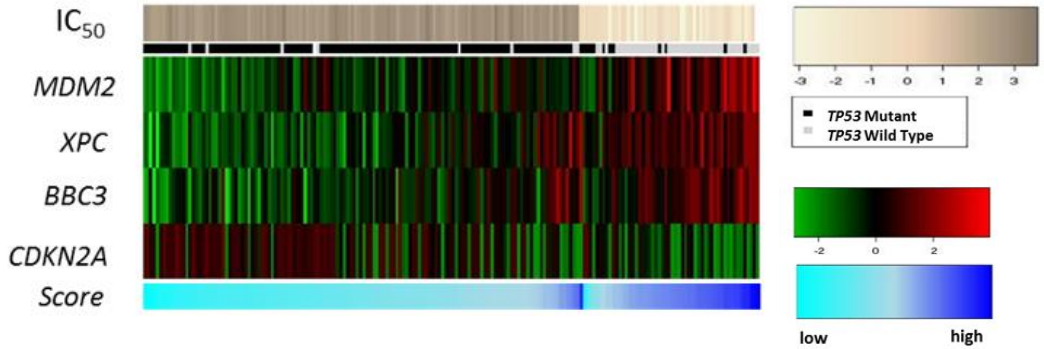
BIC criteria & biological interpretation

MDM2,CDKNa1, XPC,BBC3 (PUMA)



Multivariate Regression of molecular signature of MDM2 inh. Sensitivity: Score=$g_{MDM2}+g_{XPC}+g_{BBC3}-g_{CDKN2A}$



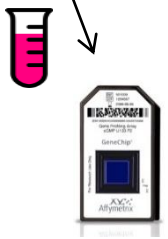


- p53 mutation status and RNA signature not completely redundant
- The signature was not associated with chemotherapy sensitivity (data not shown)

Translation to Phase I clinical trial

- NO212179 – mdm2 inh. (2)/ RO5045337

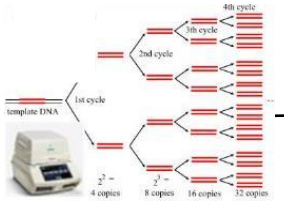
28 refractory/relapsed AML patients → QD Treatment at MTD x 10d + 18 d rest → Overall remission* at end of C1 (28 days)



4-gene Score computation

- NP28679 – Idasanutlin/ RO5503781

21 refractory/relapsed AML patients → QD X 5 days + 1g/m² cytarabine X 6 days → Overall remission* at end C1 (28-42 days)

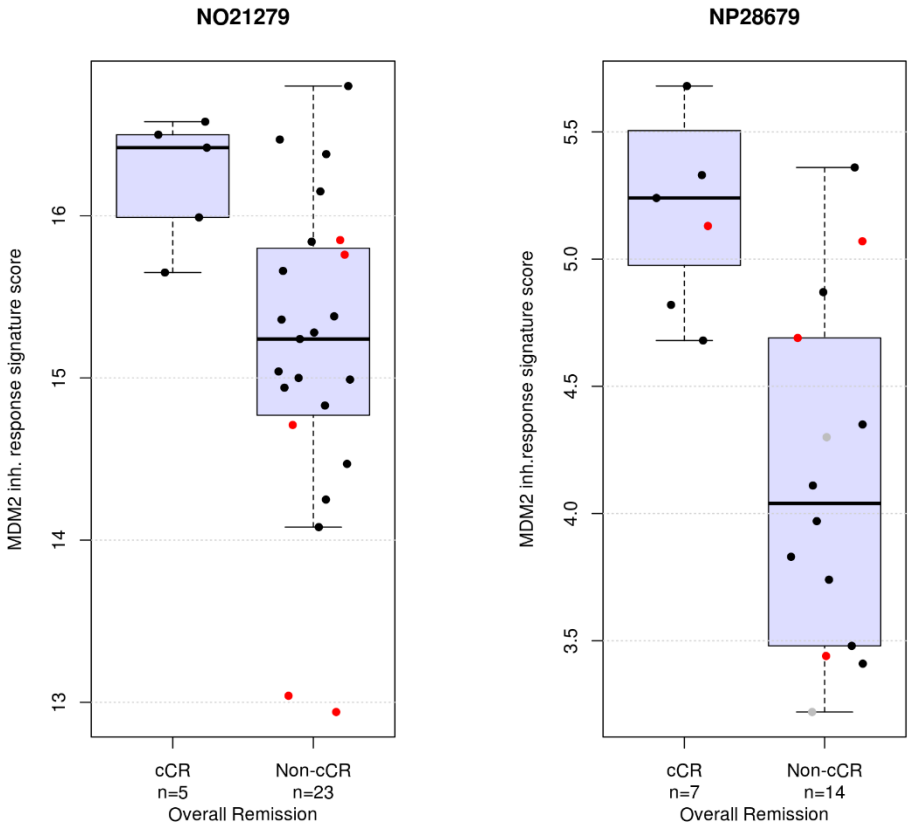


4-gene Score computation

* Overall remission: Bone marrow blast <=5%, with or without complete blood count recovery and with/without platelet count recovery

Level of Evidence for MDM2 Signature

Reproducible signature in the two MDM2 antagonists



		Non Overall Remission	Overall Remission	p-value	AUCROC [95% CI]
NO21279					
	Sample size	23	5		
	TP53 mutations	5	0	ns	-
	RNA expression score median (IQR)	15.2 (14.8, 15.8)	16.4 (16.0, 16.5)	0.005	0.86 [0.71;1]
NP28679					
	Sample size	14	7		
	TP53 mutations	3	1	ns	-
	RNA expression score median (IQR)	4.0 (3.5, 4.6)	5.2 (5.0, 5.54)	0.001	0.90 [0.76;1]

bjh correspondence

MDM2 antagonist clinical response association with a gene expression signature in acute myeloid leukaemia

Zhong at al, Br. J. Haematol, 2015

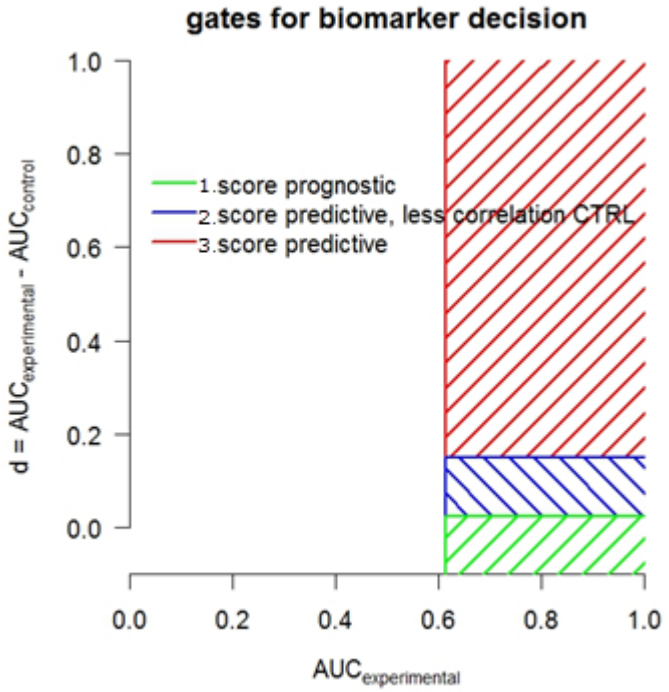
Gene Signature included as an exploratory endpoint in the Phase III trial

➔ To be developed as a *complementary* diagnostic

Guidance to iDMC to assess biomarker utility at IA

For AML Phase III Pivotal Study

2:1 randomization idasanutlin + Cytarabine vs Cytarabine



Probability for each recommendation (**bold** = correct decision):
Interim Analysis after 120 patients, response after two cycles (d56)

Truth	P(declare useless)	P(declare Case 1)	P(declare Case 2)	P(declare Case 3)
score useless	**0.95**	0.01	0.02	0.02
score prognostic	0	**0.62**	0.31	0.07
score predictive, less correlation in controls	0	0.21	**0.39**	0.39
score predictive	0.01	0.04	0.16	**0.79**

Conclusions – Part I

- Development of response/predictive biomarkers requires a tight collaboration between biological research, clinical research, and statistical analysis rigor
  - Importance of analysis transparency
  - Pre-specification in hypothesis testing
  - Data exploration needs to be contained, especially with Sparse data
- The development of predictive markers is contingent on the development plan and available data, which can be limiting
  - In vitro data suggested that the mdm2 inhibitor response signature was not associated with chemotherapy, its prognosis value could not be tested before the phase III design
  - Limited information of the association with p53 mutations in AML

Moving into the ‘data’ era – The hidden cost of clinical trial data

Planned

- CRF Data: curation, mapping transformation of data from CRF to SDTM to ADAM dataset, and documentation
- Exploratory biomarkers: Procuring and managing patient samples, Running the assay (e.g., WGS, RNA)

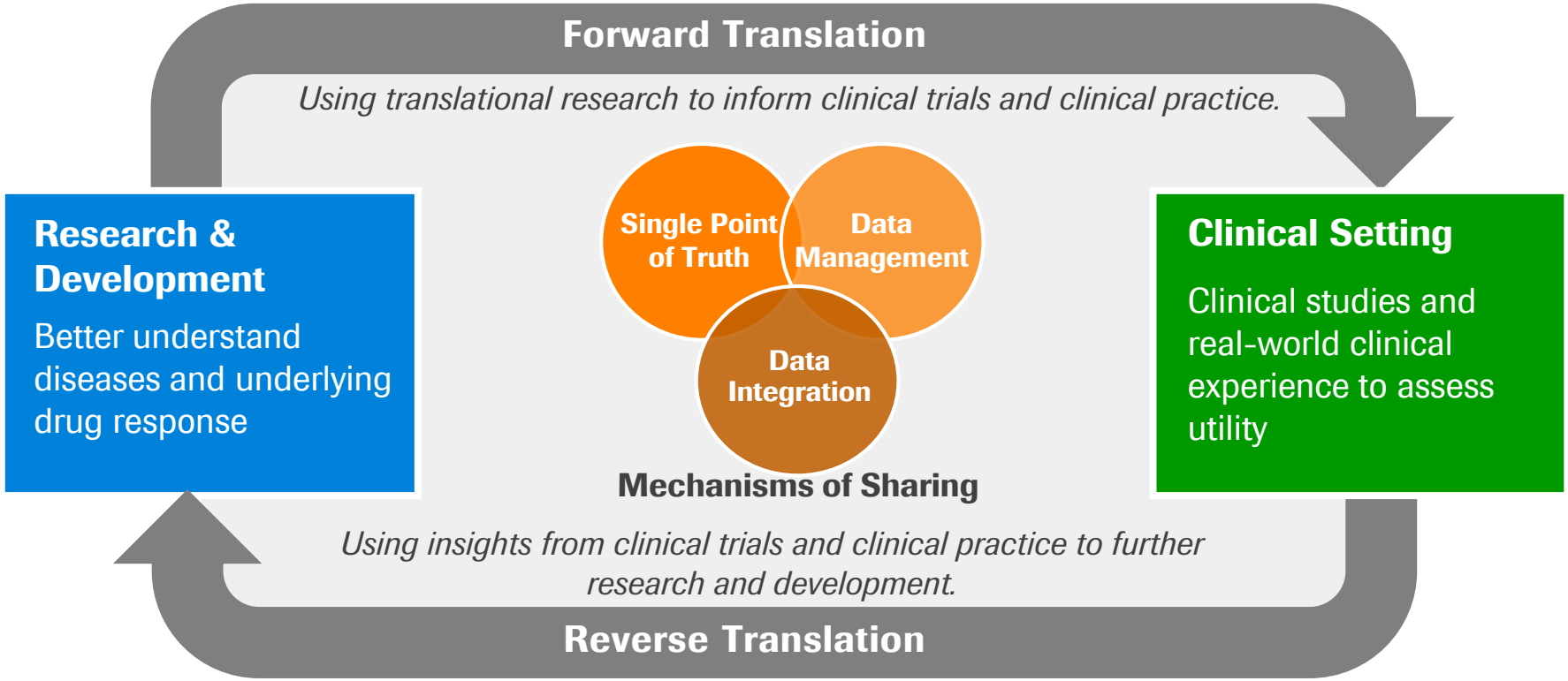
Unplanned

- Variation on adherence to standards
- Secondary use of data (e.g data harmonization)
- Data cataloging and curation of exploratory biomarkers
- Integration
- Enabling infrastructure (e.g. network, storage, compute)

Enhanced Data and Insights Sharing (EDIS)

Accelerate reliable insights generation from data

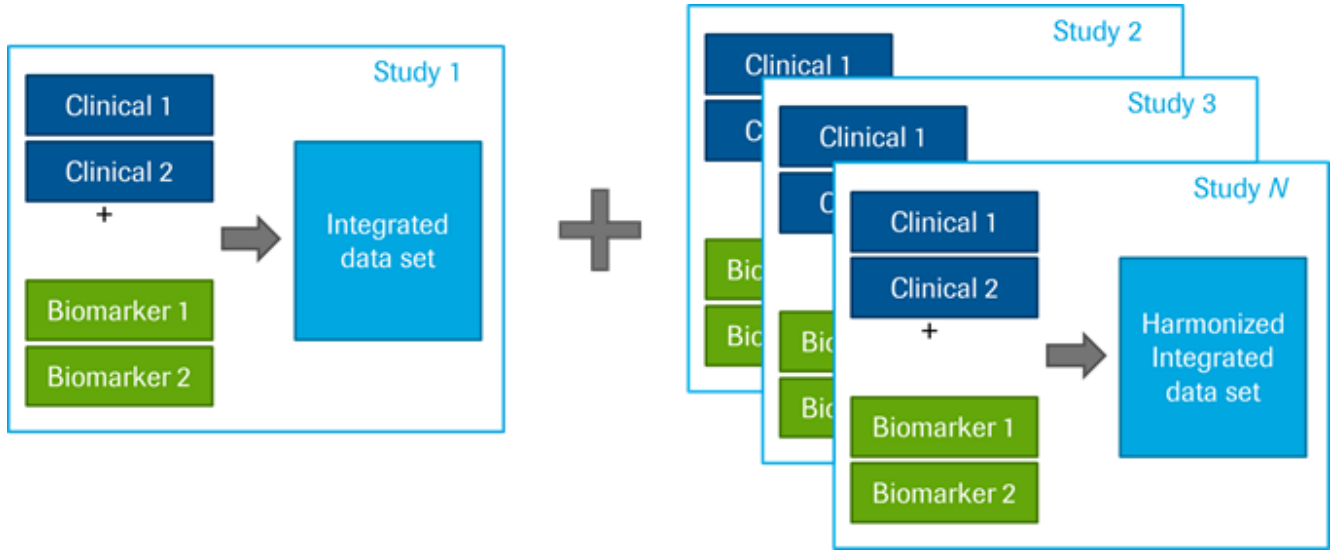
EDIS intends to make our internal data **F.A.I.R.*** and **SHARED** to accelerate generating meaningful insights from the data we have access to for R&D.



FAIR*: Findable, Accessible, Interoperable and Reproducible

The integrated Data Mart Portfolio

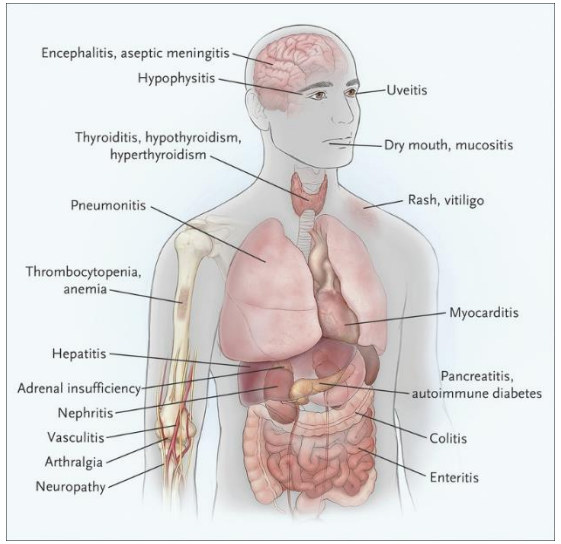
Data mart Portfolio
Cancer immunotherapy
Cancer Immunotherapy Safety
Heme (NHL/FL)
Breast Cancer (TNBC)
Autism
Ophthalmology
Asthma/COPD
Inflammatory Bowel Disease
MIND4AD (AD)



Cancer immunotherapy and immune related adverse effect

Background

- Immune Check point inhibitor (PD-1 /PD-L1 inhibitor , CTLA4-inhibitor) increases anti-tumor immunity
- The activation of the immune system can lead to inflammatory side effects called immune related adverse effects



Postow et al. (2018), NEJM

Most frequent IrAE (PD-L1 inh.)
- Skin (Rash),
- Liver (Hepatitis)
- Endrocrinal (hypo/hyperthyroidism)

Objectives:

Identification of factors associated with occurrence of IrAEs upon PD-L1 inhibitor treatment

Identification of high-risk patients

➔ Improve patient monitoring and selection, and differentiation of risk/benefit ratio

➔ Based on patient's baseline and on-treatment characteristics

9 RCTs with PD-L1 inhibitor (>6000 patients, lung and bladder)

Multi-dimensional Data
Treatment regimens
Presence/Absence of AEs and/or ADA
Demographics and clinical information
Medicinal chemistry , blood flow cytometry
Germline DNA sequencing (HLA, WGS)
(Microbiome)
tumor genomic • RNA seq, • Somatic mutation panel

Statistical approach

Time to first Immune related Adverse effect

- Exploratory Data Analysis
  - Define the right follow-up time window
  - Incidence between indications, treatment arms
  - Descriptive analysis of covariates….
- For selected sets of covariates
  - Use an Individual Participant Data (IPD) meta-analysis framework

$$\ln(\lambda_{ij}) = \ln\left(\lambda_{0j}(t)\right) + \widetilde{\theta}_j x_{ij} + \gamma_{ij}^T X_{ij} + \varepsilon_{ij}$$

  - Flexible modeling to account for the adjustment covariates (γ_{ij}) and estimation of the parameter of interest (θ_{ij})
  - One-step IPD meta-analysis favored: some organ-specific IrAEs have small # of events

Conclusions

- Use of existing clinical data is a key component of the PHC strategy evolution at Roche
  - Legacy RCT is a key data source
- Allows to enrich the development of the co-development of compounds and diagnostics
- Allows to extend the scope of clinical research questions
  - Assess benefit/risk ratio depending on patient's characteristics
  - Identify prognostic / predictive biomarkers
- Brings new statistical challenges…

Doing now what patients need next