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Challenges in developing Biomarker Assays for patient selection and Companion Diagnostic (CDx) Assays in early and late stage of drug development

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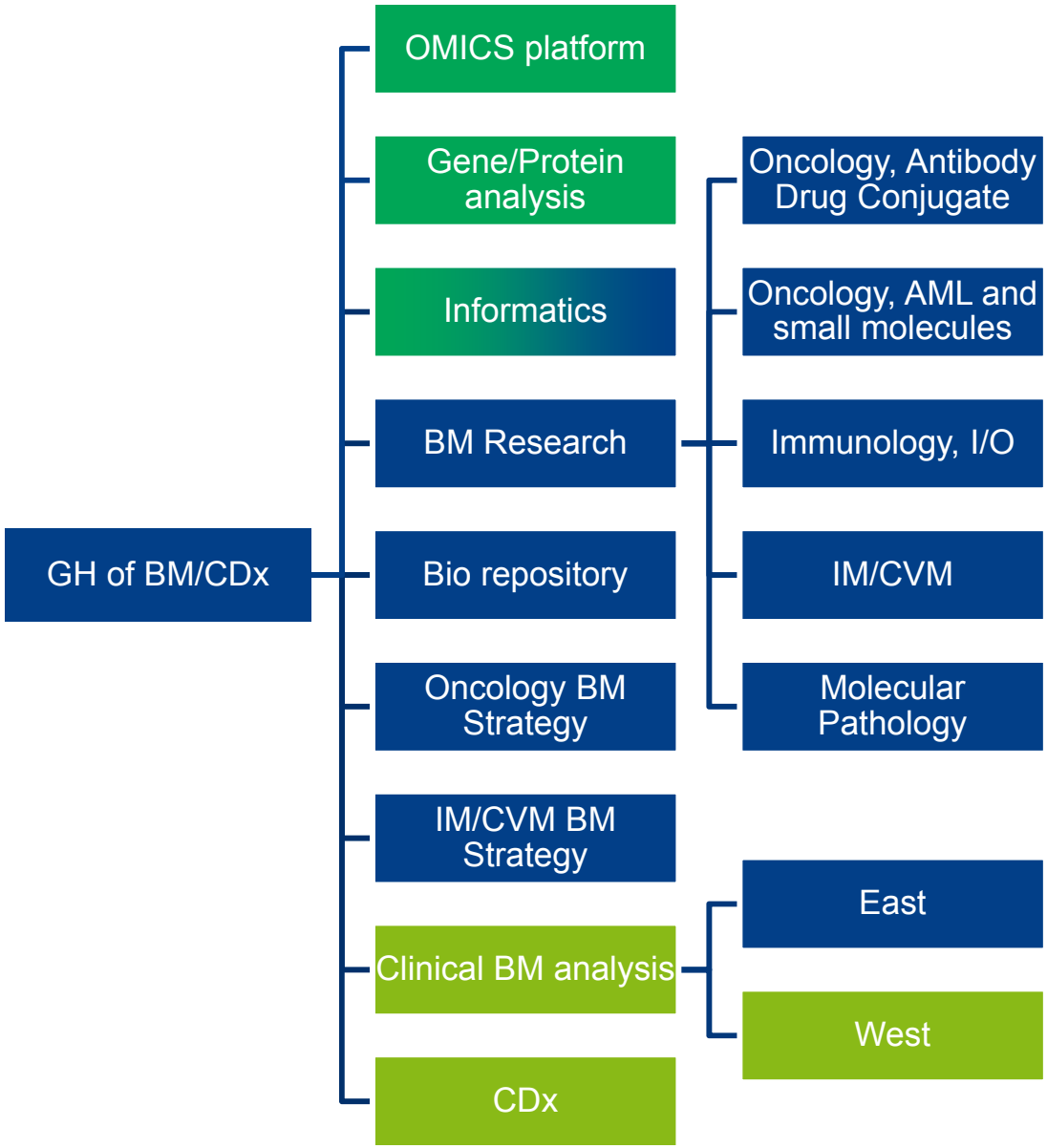
Global BM/CDx in Daiichi Sankyo



- **DS BM/CDx function is one global accountability includes BM researches, clinical BM, CDx and informatics**
- **Cross-organization structure to accumulate required expertize and capability into one accountability**
  - **DS Tokyo**
  - **DS RD Novare**
  - **DSI US**
- **Members from function teams work together and provide a seamless collaboration with drug project teams in DS**

Topics

- Hypothesis creation
  - How to identify biomarkers to aid drug discovery and development?
  - How evaluate the biomarkers in non-clinical researches?
- Clinical assay development
  - What need to be done for successful BM assay transition from non-clinical to clinical?
  - Need to understand the reality in clinical study, sample collection, quality, handling and operation
- Companion diagnostics (CDx) development
  - CDx is not just a BM assay
  - Understanding of regulatory and business requirements for CDx development

Definition of Biomarker Types

- **Predictive biomarker- predict efficacy before treatment, select responder, stratify population**
  e.g. Her2 IHC/FISH, ALK fusion
- Target engagement biomarker - was the molecular target engaged?
  e.g. phosphorylation of target molecule of TKIs
- PD biomarker - measures drug's effect on organism target and organism's effect on drug
  e.g. apoptosis in tumors after anti cancer drug treatment
- Surrogate biomarker – predict efficacy at early time point and accelerates clinical decisions
  e.g. tumor shrinkage for anti cancer drugs, decrease of blood glucose for DM drugs
- Progression biomarker (surrogate endpoint) –Disease biomarkers – measures pathogenic phenotype (responder/non-responder).
  e.g. PFS and ORR for anti cancer drugs
- Safety biomarker - Early indicators of Toxicity/Adverse Events.
  e.g. troponin for cardiac safety issue

Hypothesis creation

Hypothesis creation (BM discovery)

Possible approaches of biomarker research

1. Driven by known mechanism of drug and disease
   - Expression of target molecule, e.g. cell surface Her2 expression for anti Her2 antibodies

2. Hypothesis free discovery
   - Identification of new biomarker using “omics” technologies
   - Use number of models, like cell line panel e.g. CCLE

3. “Forward” and “reverse” translational research
   - Forward: Create hypothesis in established non-clinical models, and translate it into clinical / patient by using biomarkers
   - Reverse: Create hypothesis by utilizing clinical samples / data from trials, hospitals, consortium, etc. and bring it to “controllable” non-clinical researches for confirmation

BM discovery and evaluation before going to clinical stage

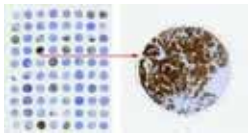
Select BM

From known biology

Hypothesis free discovery

Drug effect in BM positive model vs. BM negative model

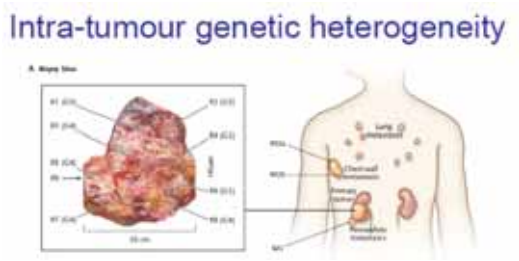
Confirm in human samples
- Frequency
- Disease
- Population



Appropriate model of target disease?

How to find / establish appropriate model?

Samples of target disease?



Gerlinger et al. NEJM 2012

How to obtain right samples?
- Hospitals? Consortium?
- Biobank?
- Own trials?

Good quality?

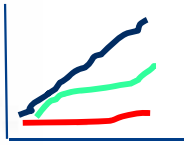
Right assay for human samples?

How to develop reliable assay?

Concept of translational eco-system

MoA analysis
Model creation





Preclinical Data generation

Research Data
Analysis
Hypothesis
creation

verification

hypothesis

Adjustment
New strategy

Clinical strategy

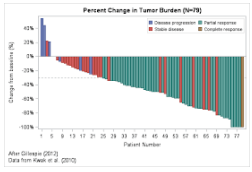
hypothesis

verification

TR Data Analysis
Hypothesis
modification

Sample
acquisition

Clinical Data generation


Clinical Study

BM analysis
Discovery

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Clinical assay development

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What is “analyzing biomarkers” in clinical space?

- A lot of uncertainty compare to non-clinical space
  - Population, quality, handling, processing, skill, logistics, human error, etc.

- Higher level of requirement
  - Regulatory requirement
    - Analytical validity, GLP, CAP/ CLIA certification
  - Clinical requirement
    - Clinical validity, study design
  - Operational feasibility
    - not always handled by a skilled technician

Analytic Validity of a Biomarker Assay

Analytical validity is the ability to accurately and reliably measure the molecule of interest

- Analytic sensitivity (analytic detection rate)
  - Correctly identifying presence of biomarker
- Analytic specificity
  - Correctly identifying absence of biomarker
- Quality controls
  - Ensure results fall within specified limits. Ensure assay performance is maintained throughout the entire duration of the clinical trial.
- Assay robustness
  - Resistance of assay to change in pre-analytical and analytical variables. For example: Different labs, instruments, technicians, temp, time, lot of reagents, shipping conditions, sample processing.

Clinical Biomarker Assay Development

Make every attempt to

- Develop the assay on platforms commonly found at global CROs
- Use assay reagents and analytical protocols that are commonly used in global CROs.
- Even better, use the exact same assay protocol and reagents that are used in the CRO assay (if available). This eliminates the need to tech transfer the assay. Saves time and money.
- The goal is to develop an assay that can be easily tech transferred and run in a CRO. The goal is NOT to develop the absolute best assay (e.g. most sensitive, too technically challenging, too many steps) that doesn't fit into a CROs workflow.

K. Nakamaru, F. Berisha, K. Ito, S. Iwai, R. Weiner, M. Murakami, BM/CDx, Daiichi Sankyo

Challenges in Evaluating Clinical Samples

Many types of different tissues are the targets of BM assay

As part of method validation one should evaluate disease state clinical samples that are as representative as possible to the expected patient samples that will be collected on study. A word of caution:

- Patient samples purchased from a single vendor

  may not be the same as

- Patient samples purchased from multiple vendors (recommended path)

  may not be the same as

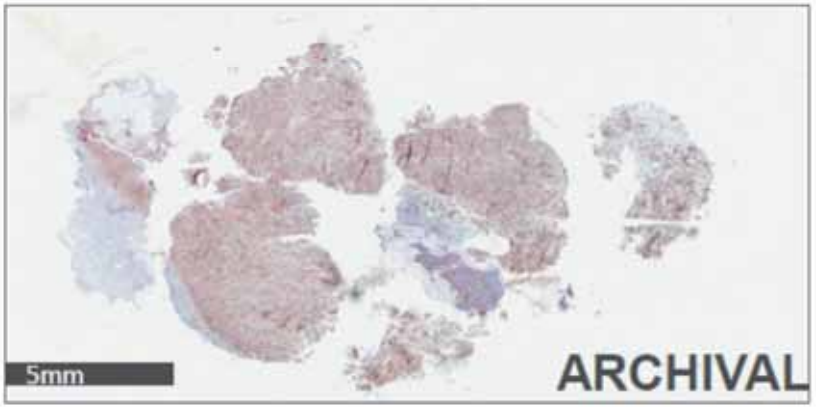
- Patient samples obtained during a well controlled clinical study with specific inclusion/exclusion criteria

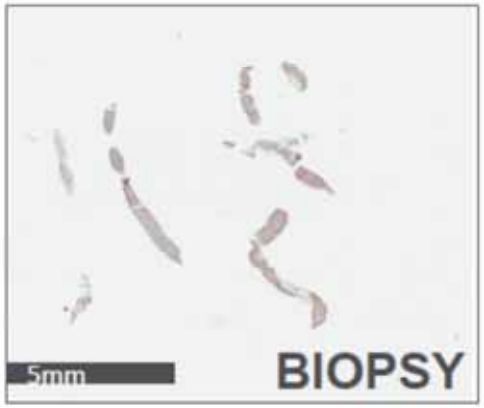
Sample collection error

You must make sure the lab accepting the sample knows what to expect.

Biopsy sample collection concern

- Will there be tumor in the core biopsy?
- Should multiple passes be taken to obtain multiple cores?
- Will there be an impact from intra- and inter-tumor heterogeneity?
- Will the same biomarker result come from:
    - Archival versus newly obtained biopsies?
    - Primary versus metastatic site samples?





Clinical Validity of Biomarker Assay

- Clinical sensitivity (or the clinical detection rate)
  - Measures the proportion of individuals who have or will get the clinical disorder and whose test values are positive
- Clinical specificity
  - Measures the proportion of individuals who do not have the clinical disorder and whose test results are negative
- Positive and negative predictive values (PPV and NPV)
- Prevalence
  - Measures the proportion of individuals in the selected setting who have, or who will develop, the disorder
- Notes on prevalence:
  - Prevalence results determined during the discovery stage or at a single academic site, which generally use a non-validated assay and a more homogeneous patient population, are often not reproduced when using the highly optimized validated assay.
  - Prevalence ALWAYS seems to decrease from discovery through clinical development.

CDx development

Business Case for Clinical Biomarkers

Quote from US FDA:
"Biomarkers represent opportunities to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into therapies."

FDA U.S. Food and Drug Administration U.S. Department of Health and Human Services

Biomarker Analysis = Value proposition for R&D

What creates the need for a CDx product?

Other considerations

- ✓Development program need
  - Patient stratification is a means of controlling cost and duration of studies
- ✓Commercial Need
  - Differentiate product from competitors
  - Earlier launch
- ✓Health economics
  - Payers are becoming more sensitized to drugs providing value in outcomes for the patients

It's going to be slower and/or more expensive than we thought - probably both

Timelines

- Typical diagnostic development programs take 6-18 months from proof of concept to a test ready for use in clinical studies
- An additional 6-9 months is required to progress to a submission-ready product

Cost

- Can be substantial, depending on the model

Impact on Rx development plans

- The diagnostic test has separate verification and validation requirements, but they likely must be integrated with the drug clinical studies and may impact on schedule and design

Regulatory

- Separate submissions are required; review schedules differ and must be coordinated

The Diagnostic Product is not Just the Assay


Sample Collection

Shipment


Accessioning


Sample Processing


Analyte Extraction


Assay Preparation


Marker Detection


Data Analysis


Data Archive


Physician Interpretation

A diagnostic product is a complex system of reagents, instruments, software, algorithms and procedures, all of which comprise the final regulated product

Possible scenarios of drug and CDx development

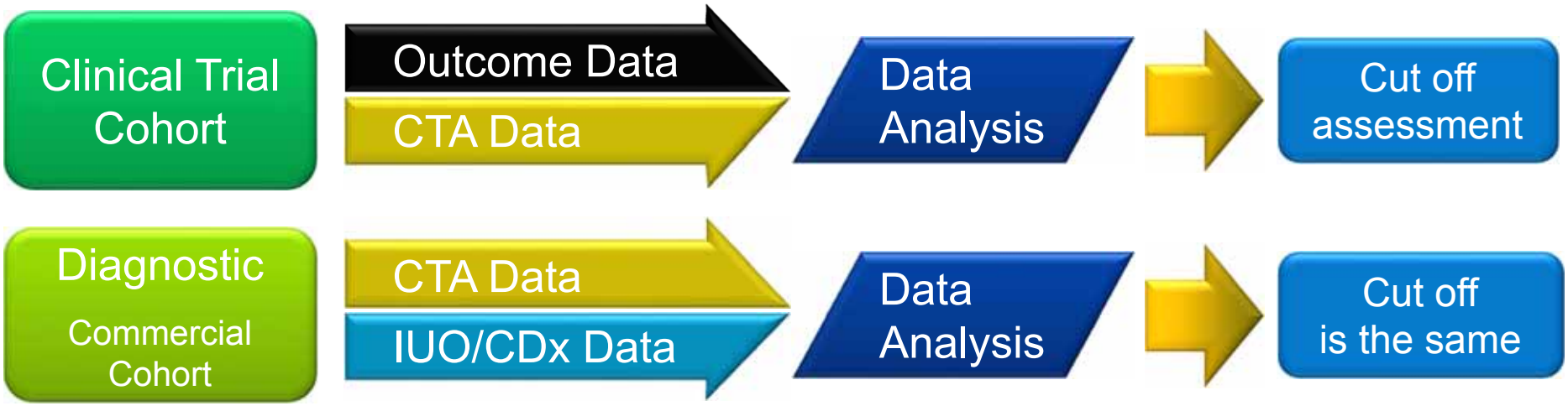
Model 1: Best Scenario of CDx Development processes Minimum risk

- Identify target BM in early researches, validate the CTA in phase I, develop a cut off the commercial assay in parallel in phase II, and use commercial assay and validate the cut off in phase III
- **No bridging is Required!!**
- BUT, higher cost and longer time

Model 2: Tailored for rapid CDx development process, in parallel with early filing trials. Reality… Moderate risk

- Develop Formulation Lock assay (FLA*) at diagnostic company, and analyze clinical trial cohort using FLA.
  *FLA is the final design (analytically) of commercial assay as a result
- **Bridging will not be required.**
- Higher price than CTA!!! A lot less than final commercial assay.

Model 3: Early filing, no CDx Development
Higher risk of bridging of CTA and CDx



- Develop clinical trial assay (CTA) at CRO, and analyze clinical trial cohort using data generated by CTA.
- CTA may or may not identify correct Intend To Treat (ITT) Population
- If CDx assay is required by Regulatory Authorities, bridging is required
  - CTA is linked to clinical outcome, CDx is linked to CTA cut off to identify correct treatment population, i.e. no direct link of CDx to outcome

Bridging of CTA and CDx assay is necessary! But bridging study may fail!!

If the bridge fails, the FDA/PMDA may request extension of the trial to validate the utility of the test which ultimately will delay the drug approval unless we qualify for a breakthrough approval (True only for FDA)

Risks associated with Bridging

Heath Authorities require minimum of 90% concordance of the CTA and CDx commercial assay.

- ✓ **Do we have the freedom to use the archived samples?**
  - Include in the Informed consent that the samples will be used for CDx development
  - Ethical issues among regions, should be taken in consideration
- ✓ **Do we know sample stability?**
  - Trials vary in length from 3-5 years, sample stability a major concern.
  - Preferable blocks instead of slides (IHC case)
- ✓ **Have the clinical team standardized the protocol for samples/tissue collection?**
  - Early plan for sample collection and stability studies is key
- ✓ **How do we mitigate the risk for not having samples for all patients?**
  - Prepare a detailed statistical analysis plan and discuss as early as possible with HA.

Drug and CDx launch planning needs to be accounted for:

- Product distribution – ensuring supply chain at launch
- Instrument base and providing access to testing
  - Worldwide considerations
  - Turn-around time
- Training programs for sales, physicians, support staff, etc.
- Customer support , including reporting between companies of product issues
- Technical support in the field

Diagnostic test adoption
- it can't be an afterthought

- Post-marketing commitments

  Commonly required, minimally to monitor performance but frequently to answer questions not addressed by initial clinical studies

- Supporting clinical evaluations beyond validation

  Adoption is best supported by a body of evidence, not just a study done for regulatory approval

- Incorporation into treatment/diagnosis recommendations

  Supports routine use and reimbursement

- Demonstration of health economic value

  Critical to payers and reimbursement

- Coding and payment considerations

  Must be addressed to get physicians to use the test

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