Biomarkers – Lost in Translation: A Regulatory Perspective

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The views expressed are the personal views of the presenter and may not be understood or quoted as being made on behalf of or reflecting the position of EMA or its committees or working parties.
DISCLAIMERS and ACKNOWLEDGEMENTS

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EMA is not responsible for in vitro diagnostics (IVD) regulation/oversight in the EU, nor does it currently evaluate their clinical utility in guiding the use of drugs.

Jorge Martinalbo @EMA (till February 2017)
Scientific officer, Scientific Advice, R&D Support
Outline

- EMA biomarkers and companion diagnostics related activities and procedures

- EMA activities and experience IVD/BM+ cancer drugs 1995-2014

-(some) regulatory issues and emerging challenges

- Regulatory initiatives/WP:
  SA, Adaptive licensing
  EMA-HTA, SAG-O
  HPWP (collaboration with academia)
**EMA structure & functions**

**decentralised body EU**
- **headquarters** scientific secretariat, coordination (London > 1995)
- **network of national agencies** from 28 EU countries and > 5000 experts internal & external – scientific committees (multidisciplinary) & working parties

<table>
<thead>
<tr>
<th>centralised (EMA)</th>
<th>national</th>
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<tbody>
<tr>
<td>registration</td>
<td>price &amp; reimbursement</td>
</tr>
<tr>
<td></td>
<td>(access NHS, WTP)</td>
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<tr>
<td>guidelines</td>
<td>clinical trial approval</td>
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<td>scientific advice (opt)</td>
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<tr>
<td>orphan drug designation</td>
<td>devices incl. IVDs, coDx</td>
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<td>paediatric studies</td>
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<tr>
<td>EU pharmacovigilance</td>
<td>inspections</td>
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<td>coordination</td>
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BENEFIT-RISK ASSESSMENT


laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

THE B/R is key and it does not differ for drugs based on biomarkers

Robustness of the whole lot of data: biological plausibility, validity
Does a specific framework/regulatory pathway for the development of biomarker-driven drugs exist in EU?

NO

And yet....
Unselected/poorly selected population, huge numbers to detect marginal differences

**PARADIGM SHIFT**

**EMPIRICAL**

**STRATIFIED**

**INDIVIDUALISED**
EMA activities in the field of cancer BMs

*Drug approval* [IVDs, coDx: CE mark national]
- BM-restricted indications (also post-A), cut-off?

*R&D support*
- guidelines, scientific advice & qualification of novel methodologies (SAWP, PhGWP)
- orphan drug designation in BM+ subsets
- research consortia (Medicine Initiative_IMI OncoTrack, Cancer-ID)

*Workshops*
- 2016 CDDF immunotherapies; ESMO single-arm trials
Guideline on evaluation of anticancer medicinal products in man
Draft

Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man
Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials

Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man
Condition Specific Guidance

Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man
The use of patient-reported outcome (PRO) measures in oncology studies
Guideline on the evaluation of anticancer medicinal products in man

Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development

Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection

Guideline on good pharmacogenomic practice
Draft
EMA anticancer guideline

- Identify proper target population to optimize B/R

- Patient stratification, if convincing evidence of BM selectivity established early in non-clinical phases, confirmatory evidence in BM negative patients may not be required

- Tumor samples integral part; single biopsies may not be representative due to intra-tumor heterogeneity; multi-sampling, liquid biopsies?

- The development of biomarker diagnostic methods should be considered early in clinical development, maximising the clinical application of the technology. A diagnostic assay complying with the requirements laid down in IVD Directive (98/79/EC), as appropriate, should be available at time of licensure
For the use in confirmatory studies and e.g. as measures of efficacy, biomarkers must be *carefully and rigorously validated*, ideally following systematic evaluation in well designed *prospective clinical* trials (EMA/CHMP/446337/2011).

Of note, this guideline also opens for the *possibility retrospective validation* through replication of findings.
**TAILORED TRIAL DESIGNS**

- **Enrichment designs**: only BM+ are included  
  Cons: no info on BM-ve pts

- **Stratified designs**: stratification by BM status

- **Adaptive enrichment**: BM+ and BM- pts are included → option to restrict randomisation  
  To BM+ only, after interim analysis

Stratified and adaptive designs support the value of BM at predicting outcome (response), but require large sample size

In cases when info on BM-ve pts is insufficient, such studies may be requested after approval
CT designs co-dev ‘simple’ coDx + BM-stratified drugs

<table>
<thead>
<tr>
<th>Design</th>
<th>Dx parameters</th>
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<tbody>
<tr>
<td>all-comers</td>
<td>sen, spe, PPV, NPV</td>
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<tr>
<td></td>
<td>utility</td>
</tr>
<tr>
<td>adaptive</td>
<td></td>
</tr>
<tr>
<td>enrichment</td>
<td></td>
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</tbody>
</table>

- BM-stratified R
- pros-retrospective on archived specimens

vemurafenib/BRAF<sup>V600</sup> MEL
crizotinib/ALK+ NSCLC

bio plausibility
no data in BM-
Adapted phase II-III BELLE 4 study
1° line MBC
R 1:1, placebo controlled
Stratification: PI3K activation and HR status

Interim analysis: no improvement of PFS in the full and in the PI3K pathway activated population. Trial stopped for futility at the end of phase II
PI3K activated tumors in 35.3% pts, Determined mainly in archival tissues

PIK3CA 72.8%
PTEN gene mut 18.4%
Loss pf PTEN expression 19%
Cancer heterogeneity (population → single-cell level)

-93% oncology drugs fail the transition from phase I to regulatory approval
-Success rate for drugs with and without biomarker: 85% vs 51%

Heterogeneity has an impact on biomarker validation
EU approvals 1995-2014: BM+ve vs not

High rate (>40%) ‘targeted’ but no BM
Drugs with BM+ indication EU

different meaning e.g. Ph+ CML hallmark defines entity vs. ALKm NSCLC rare molecular subgroup with distinct natural history
‘CLUSTERS’

- **CML & ALL Ph+**
  - imatinib
  - dasatinib, nilotinib, ponatinib, bosutinib

- **LUNG**
  - EGFRm erlotinib, gefitinib, afatinib, osimertinib
  - ALK+ crizotinib, ceritinib

- **CRC**
  - KRASwt (EGFR+)
  - cetuximab, panitumumab

- **BREAST**
  - HER2+ trastuzumab, pertuzumab, lapatinib, trastuzumab, emtansine
  - HR+ toremifene, fulvestrant

- **MELENOAMA**
  - BRAFm vemurafenib, dabrafenib, trametinib

- **<EXT>**
  - imatinib: GIST KITm & HES/CEL PDGFR-t & MDS&MPD PDGFR-t
  - trastuzumab: gastric HER2+
Solid tumors

BM+

Cytotoxic

Targeted
Biomarkers

The European Medicines Agency pays close attention to research into the use of biomarkers in the development of medicines.

Biomarkers are tests that can be used to follow body processes and diseases in humans and animals. They can be used to predict how a patient will respond to a medicine or whether they have, or are likely to develop, a certain disease. For example, the levels of chemicals in the fluid surrounding the brain may be able to predict the likelihood that a patient with mild memory problems will go on to develop dementia due to Alzheimer’s disease.

Biomarkers are playing an increasingly important role in the development of new medicines. The Agency expects that their use in research will contribute to faster public access to new medicines.

Activities at the Agency

On request, the Agency can give an opinion on the qualification of the use of a biomarker, to indicate its acceptability for a specific use in pharmaceutical research and development.

For more information, see qualification of novel methodologies and biomarkers.
EMA activities in the field of cancer BMs

- **Biomarker qualification**
  The EMA qualification process is a new, voluntary, scientific pathway leading to either a scientific opinion or scientific advice on innovative methods or drug development tools. The EMA can issue an opinion on the acceptability of a specific use of a method, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to nonclinical or clinical studies, such as the use of a novel biomarker.

- **Innovation Task Force (ITF)**
  The ITF is a multidisciplinary group that includes scientific, regulatory, and legal competences. It was set up to ensure coordination across the EMA and to provide a forum for early dialogue with applicants. The scope of the ITF activities encompasses emerging therapies and technologies and borderline therapeutics for which there is no established EMA scientific, legal, and regulatory experience. Recent areas of ITF engagement have included nanomedicines, pharmacogenomics, synthetic biology, biomaterials, modeling and simulation, and mobile health.

- **Scientific advice**
  The EMA offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals. The advice is designed to facilitate the development and availability of high-quality, effective, and acceptably safe medicines, for the benefit of patients. Companies can request scientific advice from the EMA at any stage of development of a medicine.

- **Combined advanced therapy medicinal products (ATMP) and medical devices**
  ATMPs are medicinal products including gene therapy, somatic cell therapy, and tissue-engineered products. ATMPs may incorporate, as an integral part of the product, one or more medical devices, in which case they are referred to as "combined" ATMPs. Those devices must meet the essential requirements laid down in the relevant directive and notified body for medical devices may be involved in the assessment of quality and safety of the device.

- **EMA consultation on ancillary substances in medical devices**
  If medical devices contain as an integral part "ancillary substances" that, used separately, may be considered to be a medicinal product, notified bodies must verify the quality, safety, and usefulness of such ancillary substances. To do this, the Notified Body must seek a scientific opinion from one of the competent authorities designated by the Member States or the EMA.

Pignatti, CCR 2014
Relevance of advice

Early dialogue is needed
**Scientific Advice Working Party**

**Multidisciplinary expert group of the CHMP**
- 30 members (+ alternates) selected by expertise, not by EU MS, with complementary scientific competence
  - NCAs, academia, some co-members of COMP, CAT, PDCO, CHMP

- monthly face-to-face (F2F) 4-day meetings, 11/year
  - approx. 30-40 new products/each, 20 discussion meetings sponsors

- interaction with other EMA WPs, WGs, committees
- letter peer-reviewed/adopted by CHMP, *ad hoc* discussions

**Network external experts**
- NCA, academia; CoI check

**Patient involvement**
SA/PROTOCOL ASSISTANCE PROCEDURES 2001-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Number of Procedures</th>
<th>Orphans</th>
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<tbody>
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<td>2003</td>
<td>86</td>
<td>23</td>
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<td>2002</td>
<td>71</td>
<td>14</td>
</tr>
<tr>
<td>2001</td>
<td>67</td>
<td>7</td>
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</table>
EMA SA/PA

- by clinical development phase:

  - Phase I: 61%
  - Phase II: 12%
  - Phase III: 25%
  - Phase IV: 2%

  2013

EMA SA/PA requests by issues covered

- Quality: 21%
- Pre-clinical: 27%
- Clinical: 52%

2013

EMA annual report 2013
BM issues scientific advice

No access to raw data; ‘strategy’

Biomarker
- scientific plausibility (target/related?)
- non/clinical evidence for qualification
- context of use: MoA, anatomical-histo tumour type…

Assay/test
- establish analytical & clinical validity, cut-off
- pre- (biospecimens) and post-analytical
- platform, development and bridging
EXPERTS selected according to their specific expertise

CORE GROUP (3-yrs)
- CONTINUITY
- CONSISTENCY

ADDITIONAL EXPERTS
On a case by case basis
- RELEVANT PROFESSIONAL EDUCATION
- TRAINING & EXPERIENCE
e.g. patients & pts advocates

SAGs are convened by CHMP to deliver answers, on a consultative basis, to specific questions, abt drugs at advanced stage of development
Biomarkers often used to “garnish”

Biomarkers as rescuers of drugs on the verge of failure
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Pignatti, CCR 2014
BM Qualification Procedure in EU

Qualification of novel methodologies for drug development: guidance to applicants

- Agreement by SAWP: 27 February 2008
- Adoption by CHMP for release for consultation: 24 April 2008
- Final Agreement by CHMP: 22 January 2009

A qualified BM can be used in drug development without the confirmation of acceptance.

Encouraged parallel EMA & FDA application (confidentiality agreement), communication during assessment, joint meetings.
**EMA qualification novel methodologies**

<table>
<thead>
<tr>
<th>preclinical</th>
<th>clinical</th>
<th>drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ pharmacological screening</td>
<td>▪ dose-response</td>
<td>▪ optimise population</td>
</tr>
<tr>
<td>▪ PK/PD modelling</td>
<td>▪ proof of concept</td>
<td>▪ guide treatment regimen</td>
</tr>
<tr>
<td>▪ toxicogenomics</td>
<td>▪ population selection</td>
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<tr>
<td></td>
<td>▪ endpoints (MRD)</td>
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In-depth assessment (raw data, protocols...), **possible FDA parallel** VXDS, platform for multi-sponsor pre-competitive collaboration – outcomes:

*Underused in oncology, missed opportunities (PD-L1?)*

0 requests for EMA qualification procedures BMs for cancer patient selection since 2008, all SA on ‘approach’
Qualification outcomes

CHMP Qualification Opinion (public document)
- on the acceptability of a **specific use** of the proposed **method** (e.g. use of a biomarker in R&D non-/clinical studies), based on the assessment of submitted data, not product-specific

CHMP Qualification Advice (confidential document)
- on **future protocols** and methods for further method development towards qualification, based on evaluation of **scientific rationale** and on **preliminary data**

Letter of support (public, subject to sponsor’s agreement)
- when novel methodology under evaluation cannot yet be qualified but is shown to be **promising** based on preliminary data – to **encourage data-sharing** and facilitate eventual studies towards qualification
Current framework: IVD definition

Co-Dx are regulated within the medical devices legal framework (IVD Directive 98/79/EC)

Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system

- used alone or in combination
- intended by the manufacturer to be used *in vitro* for the examination of *specimens*, including blood and tissue donations, derived *from the human body*, solely or principally for the purpose of *providing information*:
  - concerning a *physiological or pathological state*
  - concerning a congenital abnormality
  - to determine the safety and compatibility with potential recipients
  - to *monitor therapeutic measures*
List categories according the Directive

NB: 3\textsuperscript{rd} party independent certification organisation, on which regulatory national competent authorities ‘delegate’ tasks of conformity assessment.
In EU the licenced indication of a Pharmaceutical may require the use of a Co-Dx, but the specific test is not normally stipulated.

Range of proprietary and “in-house” tests
All consistent with the MA

-Vary levels of diagnostic accuracy:
Different subpopulations?
Proposed revision vs current status

Co-Dx will be required to demonstrate analytic performance and clinical performance (Dx sensitivity, specificity, PPV, NPV). Expected value in normal or affected populations.

Competent authority consulted → opinion in 60 days.

Life-cycle of Co-DX: post-market surveillance plan.
New IVD regulation

- **Timelines**: final legal-linguistic review, planned formal adoption early 2017, 5-y transition period, apply 2021/22
- All IVDs subject to demonstration of compliance with general safety and performance evaluations
- Majority of IVD manufacturers engaging NBs as part of conformity assessment procedures; responsible person for regulatory compliance appointed

- **CoDx definition**: “essential to define patients’ eligibility to specific treatment” and classified as 2\(^{nd}\) highest risk category (class C) NB + EMA consultation (?)
  - details on 60-day procedure and criteria to be outlined in a dedicated guideline
# Drug/IVD evolution

**move from coDx to multiplex?**

= NGS-based multiplex panels, WES/WGS

<table>
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<tr>
<th>tumor/BM</th>
<th>drug</th>
<th>IVD/coDx initial</th>
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<tbody>
<tr>
<td>NSCLC</td>
<td>erlotinib</td>
<td>Roche Cobas EGFR Mut</td>
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<tr>
<td>EGFRm</td>
<td>gefitinib</td>
<td>Qiagen thesascreen EGFR RGQ (RT-PCR)</td>
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<tr>
<td></td>
<td>afatinib</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>crizotinib</td>
<td>Abbott VYSIS ALK Break Apart (FISH)</td>
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<tr>
<td>ALK+</td>
<td></td>
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<tr>
<td>GIST</td>
<td>imatinib</td>
<td>Dako c-Kit pharmDx (IHC)</td>
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<tr>
<td>KIT+</td>
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<td>CRC</td>
<td>cetuximab</td>
<td>[EGFR+ IHC Dako PharmDx- obsolete]</td>
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<td>panitumab</td>
<td>Qiagen thesascreen KRAS RGQ PCR Kit</td>
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<tr>
<td>breast</td>
<td>trastuzumab*</td>
<td>HercepTest Dako (IHC, semiquant.)</td>
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<tr>
<td>HER2+</td>
<td>pertuzumab</td>
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<td>vemurafenib</td>
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<td>dabrafenib</td>
<td>BioMérieux THXID BRAF</td>
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<tr>
<th>IVDs alternatives + LDTs</th>
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<tr>
<td>Qiagen thesascreen EGFR RGQ Plasma</td>
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<tr>
<td>IHC screening -&gt; confirm</td>
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<tr>
<td>LDTs</td>
</tr>
<tr>
<td>Dako, Zymed, Invitrogen, DxS, Qiagen, Transgenomic</td>
</tr>
<tr>
<td>IHC: Leica Bond Oracle, Ventana PATHWAY, BioGenex…</td>
</tr>
<tr>
<td>FISH: Abbott PathVysion, Ventana INFORM</td>
</tr>
<tr>
<td>ISH: Dako HER2 CISH PharmDx, Ventana INFORM Dual ISH, etc.</td>
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<td>LDTs?</td>
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</table>
# assay divergences

→ **BluePrint PD-L1 IHC**

<table>
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<tr>
<th>drug</th>
<th>nivolumab BMS</th>
<th>pembrolizumab MSD</th>
<th>durvalumab AstraZeneca</th>
<th>atezolizumab Roche</th>
<th>avelumab Merck/Pfizer</th>
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<tr>
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<td>recent</td>
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<td>fresh cut slides</td>
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<td>IHC assay</td>
<td>Dako 28-8* COMPLEX</td>
<td>Dako 22C3* coDX</td>
<td>Ventana SP263</td>
<td>Ventana SP142</td>
<td>Dako</td>
</tr>
<tr>
<td>cell types</td>
<td>TC</td>
<td>TC</td>
<td>TC</td>
<td>IC &amp;/or TC</td>
<td>TC</td>
</tr>
<tr>
<td>cut-offs NSCLC</td>
<td>TC≥5%</td>
<td>TC≥1% TC≥50%</td>
<td>TC≥25%</td>
<td>TC or IC≥1%</td>
<td>TC≥1%</td>
</tr>
</tbody>
</table>

no harmonised meaning of PD-L1+, clinical implications in decision making, ordering tests and comparing agents
CRITERIA FOR ADAPTIVE PATHWAYS CANDIDATE SELECTION

✓ An iterative development plan: start in a well defined subpopulation and expand, or have a Conditional Marketing Authorisation, maybe surrogate endpoints and confirm

✓ Real World Data (safety and efficacy) can be acquired to supplement Clinical Trials

✓ Input of all stakeholders, particularly HTAs, is fundamental

UNMET MEDICAL NEED and INNOVATION are prerequisites
ADAPTIVE PATHWAYS/MAPPs
prospectively identify when RCTs not strictly required for approval (e.g. unequivocal equipoise loss) and/or feasible (ultra-rare entities or mol. subgroups in the context of stratified medicine)

- key elements: RCT feasibility, compelling efficacy thresholds on valid endpoints (ORR, DoR, others?), adequate external controls, indirect comparisons, supportive & confirmatory evidence…

**SAT framework – scenarios**

**ULTRA-RARE**

- Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

**RARE MOL**

- screening IVD BM+

**BREAKTHROUGH**

- Courtesy of J. Martinalbo
EMA experience summary

- ~22% cancer drug approvals (33% INI, 11% EXT) in EU based on non-RCT evidence
  - haematological (54% INI, 22% EXT)
  - solid (18% INI, 9% EXT)
  - >30% targeted drugs in BM+ tumors INI approval on RR

- regulatory review initial approval
  - 1995-2004: SAT 385d vs. RCT 315d, but last 10y both ~ 335d
  - SAT: conditional (28%), exceptional circumstances (17%)

- regulatory success rate
  - INI: 72% SAT vs. 72% RCT; EXT: 72% SAT vs. 87% RCT
BM-stratified trials

Basket

Umbrella
Challenges

- Rare mol. subsets, SATs, ‘novel’ designs (basket)
- Move from coDx to multiplex panels, WES/WGS
- Combinations?
- Divergences in IVDs for same BM in a drug class, data-sharing & cross-validation
- Intra-tumor heterogeneity implications for registrational CTs, multiregion/mets sampling, subclonal %, ‘liquid biopsies’…
- Drug label: BM+, uncertainty cut-offs – evolution during lifecycle
- P&R national – IVD ‘gatekeeper’ - informational needs patients, clinicians, HTAs/payers - differential C/E by BM thresholds?
<table>
<thead>
<tr>
<th>CANCER TYPE</th>
<th>PATIENTS SELECTION</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Tumor heterogeneity: how precise can we be?</td>
<td>-Technical feasibility and validity of biomarkers (including genome sequencing)</td>
<td>Interpretation of ever-increasing volume Data</td>
</tr>
<tr>
<td>Single dominant clone vs multiple co-existing subclones, Intratumoral heterogeneity: reliability and precision of the biopsy/sampling</td>
<td></td>
<td>-Extrapolation of indication -Endpoint -Integration of new techniques -new designs</td>
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<td>-Heterogeneity over life-time of cancer</td>
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Value and cost-effectiveness in personalised medicine
Market access EU

quality, safety, efficacy

clinical evidence E&S assoc. uncertainty
single EU framework

budget impact, C/E, REA
national frameworks

B/R

P&R
RATIONAL DRUG DEVELOPMENT

PATIENTS SELECTION

STUDY DESIGN

CANCER TYPE

1) DISEASE
2) MECHANISMS
3) TIME

TARGETS

DRIVERS vs PASSENGERS

BIOMARKERS

INNOVATIVE TRIALS

CLINICAL VS STATISTICAL RELEVANCE

PATHWAYS
Clear and in depth knowledge of the *druggable* disease

- **Selection** of population
- **Mechanisms** of action/resistance
- The *variable time* taken on board (evolution of the disease under treatment)
- **Innovative studies**

- Approval granted first for patients who could benefit more ("superlative" B/R)
- Extended observation (RDW)
GLOBAL collaboration

Acadia/Regulators: generation & validation of data

HTA/payers ‘clinical utility’

Pharma & Dx – pre-competitive, data sharing?

NCI, ASCO, EORTC/
Academic networks ‘broker’ biobanks?

Rational allocation of resources

Patients selection

......

Anticipation of resistance

Avoid unnecessary toxicity

The biomarkers novel