SESSION 5: OPPORTUNITIES AND CHALLENGES WHEN IMPLEMENTING PHC CONCEPTS INTO CLINICAL TRIAL DESIGNS

A CLINICAL / REGULATORY PERSPECTIVE ON EXPERIENCE SO FAR WITH BIOMARKERS IN EU APPROVALS
OUTLOOK AND CHALLENGES

Rosa Giuliani, MD
Breast Unit, S. Camillo-Forlanini Hospital, Rome, IT
Scientific Advisory Group-Oncology_EMA

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.
Translating the Success of Imatinib to Other Malignancies

- Identify the appropriate therapeutic targets
- Match the right patient with the right drug
- Treat early in the course of the disease

At the right time (editor’s note ➔ me)
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>Registration</td>
<td>Price &amp; reimbursement</td>
</tr>
<tr>
<td></td>
<td>(access NHS, WTP)</td>
</tr>
<tr>
<td>Guidelines</td>
<td>Clinical trial approval</td>
</tr>
<tr>
<td><strong>Scientific Advice</strong> (opt)</td>
<td></td>
</tr>
<tr>
<td>Orphan drug designation</td>
<td>Devices incl. IVDs, coDx</td>
</tr>
<tr>
<td>Paediatric studies</td>
<td></td>
</tr>
<tr>
<td>EU pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td>Coordination</td>
<td>Inspections</td>
</tr>
</tbody>
</table>

**ACCESS**

**R&D**

**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>
</tr>
</thead>
<tbody>
<tr>
<td>Registration</td>
<td>Price &amp; reimbursement</td>
</tr>
<tr>
<td></td>
<td>(access NHS, WTP)</td>
</tr>
<tr>
<td>Guidelines</td>
<td>Clinical trial approval</td>
</tr>
<tr>
<td><strong>Scientific Advice</strong> (opt)</td>
<td></td>
</tr>
<tr>
<td>Orphan drug designation</td>
<td>Devices incl. IVDs, coDx</td>
</tr>
<tr>
<td>Paediatric studies</td>
<td></td>
</tr>
<tr>
<td>EU pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td>Coordination</td>
<td>Inspections</td>
</tr>
</tbody>
</table>

**ACCESS**

**R&D**
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 concept
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**

- Xenograft model
- DNA sequencing
- CyToF/mass spectrometry
- Cell culture
- Phenotyping
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

Under revision

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>
</tr>
</thead>
<tbody>
<tr>
<td>all-comers</td>
<td>sen, spe, PPV, NPV utility</td>
</tr>
<tr>
<td>▪ BM-stratified R</td>
<td></td>
</tr>
<tr>
<td>▪ pros-retrospective on archived specimens</td>
<td></td>
</tr>
<tr>
<td>adaptive</td>
<td></td>
</tr>
<tr>
<td>enrichment</td>
<td>PPV bio plausibility no data in BM-</td>
</tr>
<tr>
<td>vemurafenib/BRAF^{V600} MEL</td>
<td></td>
</tr>
<tr>
<td>crizotinib/ALK+ NSCLC</td>
<td></td>
</tr>
</tbody>
</table>
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.
Decision rules at interim analysis.

- **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)

Heterogeneity has an impact on biomarker validation

- 93% oncology drugs fail the transition from phase I to regulatory approval
- Success rate for drugs with and without biomarker: 85% vs 51%
A cruel truth of many solid tumors
From modest to extensive intratumoral heterogeneity, the rule rather than exception

Exogenous selective pressure

What do we expect from biopsies?
cfDNA

Data + biological noise

Biologically relevant?
Biologically neutral?

How do we integrate these two key points?

Presented By Barry Taylor at 2017 ASCO Annual Meeting
Molecular imaging to investigate heterogeneity

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’

tandem BM/target-histology
....till the new era of the tumor-agnostic drug development???
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 to 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.
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

Total number of procedures

Orphans
Therapeutic areas

Scientific-advice requests by therapeutic area - 2014

- Alimentary tract and metabolism: 48
- Anti-neoplastic and immunomodulating agents: 212
- Anti-parasitic products, insecticides, repellents: 2
- Blood and blood-forming organs: 26
- Cardiovascular system: 26
- Dermatomallosis: 8
- Diagnostic agents: 1
- General anti-infectives for systemic use: 59
- Genito-urinary system and sex hormones: 10
- Musculoskeletal system: 17
- Nervous system: 44
- Respiratory system: 25
- Sensory organs: 24
- Systemic hormonal preparations, ex. sex hormones: 14
- Various: 13
by clinical development phase:

- 2013
  - Phase I: 61%
  - Phase II: 25%
  - Phase III: 12%
  - Phase IV: 2%

EMA SA/PA requests by issues covered:

- 2013
  - Quality: 21%
  - Pre-clinical: 27%
  - Clinical: 52%
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
Relevance of advice

DRUG DEVELOPMENT

UNMET NEED

EARLY PHASE

PRECLINICAL DEVELOPMENT

ADVANCED PHASE

CLINICAL DEVELOPMENT

SUBMISSION for APPROVAL

HTA/Price & reimbursement

Early dialogue is needed

RELEVANCE OF INTERACTION
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 eg 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
• 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 to 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.
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>
<td></td>
</tr>
<tr>
<td></td>
<td>- endpoints (MRD)</td>
<td></td>
</tr>
</tbody>
</table>

- 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
Challenges

- Rare mol. subsets, SATs, ‘novel’ designs (basket)
- Move from coDx to multiplex panels, WES/WGS
- Combining?
- 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?
assay divergences

→ BluePrint PD-L1 IHC

<table>
<thead>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>target</td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td>sample</td>
<td>archival</td>
<td>recent</td>
<td>archival/recent</td>
<td>archival/recent</td>
<td>fresh cut slides</td>
</tr>
<tr>
<td>IHC assay</td>
<td>Dako 28-8* COMPLEM</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
SAT framework – scenarios

- 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…

ULTRA-RARE

RARE MOL

BREAKTHROUGH

screening IVD BM+
NOT ALL DRUGS ARE CREATED EQUAL
EARLY ACCESS vs COMPLETE INFORMATION

Timely (early) access to innovative agents
Flexibility
Foster progress & health

MAJOR CHALLENGE

EARLY REGULATORY APPROVAL

EARLY ACCESS for PATIENTS

BENEFIT
RISK

Robust evidence
Quality of data
Miss the “magic moment” for OS

MIND THE GAP
Market access EU

- quality, safety, efficacy
- clinical evidence E&S assoc. uncertainty
- single EU framework
- budget impact, C/E, REA
- national frameworks

Courtesy of J. Martinalbo
The “FUNNEL effect”

(Too) Many variables at each stage
Some more transparent, other less

I am (stuck) here
Collaboration with academia to be reinforced

03/04/2017

Collaboration with academia to be reinforced

EMA publishes framework and action plan for closer interaction

As a science-driven organisation, the European Medicines Agency (EMA) has developed a framework to formalise, structure and further develop interactions with the academic community in the context of the European medicines regulatory network.

The framework and an action plan for the next three years were adopted by EMA’s Management Board at its March 2017 meeting.

"Academia play an important role in helping the EU medicines regulatory network keep abreast of the opportunities and challenges brought by science, be it in the context of the development, assessment or safety monitoring of medicines," says EMA’s Executive Director Guido Rasi. "The framework will allow us to integrate cutting-edge scientific knowledge more tightly into our activities. It will also help academic start-ups benefit from advice from the EU regulatory network to translate their discoveries into patient-focused medicines."

Related content
- Academia: Information for you
- Partners & networks: Academia
- European medicines regulatory network

Related documents
- Framework of collaboration between the European Medicines Agency and academia (03/04/2017)
- Framework of collaboration between the European Medicines Agency and academia - Annex I - Action plan (03/04/2017)

Contact point:
EMA press office
First ever trial of penicillin at the Radcliffe Infirmary in Oxford

RANDOMIZED TRIAL \(\rightarrow\) 12 PTS…Penicillin enough for 6!

BIOLOGIC EXPLOSION IN THE MIDST OF ECONOMIC CRISIS

PHASE TWO TRIAL CAN BE MISLEADING, PHASE III ARE ENOURMOUSLY EXPENSIVE FOR VIRTUALLY EVERYONE

COOPERATION IS NOT AN OPTION ANYMORE, IT’S a NEED

RATIONAL DESIGN IMPLEMENTED WITH BIOMARKERS
In the bookshop ironically on the same shelf
A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

The European Society for Medical Oncology (ESMO) has developed a validated and reproducible scale, the ESMO-MCBS to assess the magnitude of clinical benefit for cancer medicines.

This scale uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment.
• When a new anticancer drug is EMA approved, its benefit will be «scaled» by a dedicated ESMO committee

• Drugs which obtain the highest scores (A&B or 5&4):

1. will be highlighted in the ESMO guidelines
2. represent the highest priority for rapid endorsement by national bodies across Europe

[Diagram showing curative and non-curative categories with scores A, B, C, 5, 4, 3, 2, 1]
### Challenges in Drug Development

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Patients Selection</th>
<th>Study Design</th>
</tr>
</thead>
</table>
| Tumor heterogeneity:  
how precise can we be?  
Single dominant clone vs multiple co-existing subclones,  
Intratumoral heterogeneity:  
reliability and precision of the biopsy/sampling  
-Heterogeneity over life-time of cancer | Technical feasibility and validity of biomarkers (including genome sequencing) | Interpretation of ever-increasing volume data  
-Extrapolation of indication  
-Endpoint  
-Integration of new techniques  
-new designs |

**Value and cost-effectiveness in personalised medicine**
Factors taken into account for ESMO-MCBS

- HR, Long term survival, RR
- Overall survival, Progression free survival
- Quality of Life
- Prognosis of the condition
- Toxicity
- Costs

Magnitude of Clinically Benefit

Not analyzed in view of significant “Heterogeneity” across Europe

V 1.1 exp Sept 2017
SAT
The concept of personalized medicine is so appealing that seemingly only curmudgeons could criticize it.