EMA - roles in cancer drug development and approval

Jorge Martinalbo

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.
agenda

EMA structure & functions

approval

- evaluation procedure & criteria
- early access instruments, SATs

R&D support

- guidelines & scientific advice, qualification

EU market access

- multi-stakeholder dialogue, HTA
EU medicines regulatory network

EMA decentralised body EU

- headquarters scientific secretariat, coordination (London, 1995)
- network of national agencies from 28 EU countries and > 5000 experts internal & external – scientific committees & working parties - regular meetings, not permanently based at EMA
EMA human committees

- CHMP (medicinal products human use)
- PRAC (PhVig, risk assessment)
- COMP (orphans)
- PDCO (paediatrics)
- CAT (advanced therapies)

- HMPC (herbals)
- CVMP (veterinary)
<table>
<thead>
<tr>
<th>ACCESS</th>
<th>R&amp;D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>centralised</strong></td>
<td><strong>national</strong></td>
</tr>
<tr>
<td>registration (new cancer drugs)</td>
<td>price &amp; reimbursement (effective access NHS)</td>
</tr>
<tr>
<td>QSE guidelines</td>
<td>clinical trial approval VHP (opt)</td>
</tr>
<tr>
<td>scientific advice (opt)</td>
<td></td>
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<tr>
<td>orphan drug designation</td>
<td>devices, incl.</td>
</tr>
<tr>
<td>paediatric studies</td>
<td>in vitro diagnostics</td>
</tr>
<tr>
<td>ATMP classification</td>
<td></td>
</tr>
<tr>
<td>EU pharmacovigilance coordination</td>
<td>inspections (GXP)</td>
</tr>
</tbody>
</table>
**EMA drug approval**

Centralised procedure marketing authorisation application review: scientific opinion from a *single* multidisciplinary Committee for medicinal products for human use (CHMP), representatives each country (voting), all therapeutic areas

- 2 teams, active review time $\leq 210$ d (+ clock-stops)
- no evaluation of patient-level / raw data
assessment teams

assessors
- multidisciplinary
- chemistry/manufacturing/controls
- preclinical toxicology/pharmacology
- clinical pharmacology
- statistics
- medical reviewer
- safety, risk management

co/rapp (CHMP)

EMA product team
(regulatory, inspections, RMP, labelling, paediatrics...)

x2
benefit/risk paradigm

- ORR & DoR, PFS, OS
- improved symptoms & QoL
- beneficial effects

- type, frequency
- and severity of adverse effects

uncertainty
risk tolerance
objections **efficacy**

**effect magnitude (\& endpoint)**

- **negative trials:** claims on (exploratory) subgroup analysis
- **marginal/no clinically relevant efficacy** (“not just p-value”)
- **inconsistent data** on clinical efficacy (2EPs, subgroups)
- **(role in therapy/clinical usefulness – relative E? advances)**

**primary endpoint**
Pivotal CT EU approvals (ini+ext)
objections efficacy

methodological – trial design

- SATs - lack of randomised controlled data
- endpoint, validity of measurement; surrogacy?
- statistical analysis deficiencies – premature IAs
- comparator/backbone inadequate (evolution?) for population
- not isolating effect of individual drug
- population selected; enrichment (BM+?)
- dose/regimen justification; duration of treatment?
- long-term follow-up insufficient
- data validity (e.g. major protocol violations, GCP issues)
objections safety

in relation to severity of indication / unmet medical need / magnitude of clinical efficacy

- mortality, SAEs increased
- size safety DB limited
  - data quality, SATs non-comparative data
- long-term follow-up insuff.
- risk management plans

- DDI studies lacking
- special populations: renal and hepatic impairment (label)
cancer drugs EU approvals

>40% ‘targeted’ but no BM
EU assessment reports EPAR

European public assessment reports

This search allows you to find European public assessment reports (EPAR) for human medicines.

The European Medicines Agency publishes an EPAR for every medicine granted a central marketing authorisation by the European Commission. EPARs are full scientific assessment reports of medicines authorised at a European Union level.

Use this search to find information including a public-friendly summary in question-and-answer format and the package leaflet. You can also find information on medicines that have been refused a marketing authorisation or that have been suspended or withdrawn after being approved.

The Agency does not evaluate all medicines currently in use in Europe. If you cannot find the medicine you need through this search, please visit the website of your national health authority.

More information is available on the central authorisation procedure and on EPARs.

Browse A-Z

Browse by letter for medicines that have a European Public Assessment Report:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z View all

Or for other types of content pick from the navigation on the left.

Include:
- Authorised medicine
- Withdrawn post-approval
- Suspended
- Refused
EU CHMP assessment B/R

**Kadcyla**

*trastuzumab emtansine*

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### About

**Changes since initial authorisation of medicine**

<table>
<thead>
<tr>
<th>Name</th>
<th>Language</th>
<th>First published</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kadcyla : EPAR - Procedural steps taken and scientific information after authorisation</td>
<td>(English only) 03/12/2014</td>
<td>19/05/2016</td>
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</table>

### Authorisation details

#### Initial marketing-authorisation documents

<table>
<thead>
<tr>
<th>Name</th>
<th>Language</th>
<th>First published</th>
<th>Last updated</th>
</tr>
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<tbody>
<tr>
<td>Kadcyla : EPAR - Public assessment report</td>
<td>(English only) 19/12/2013</td>
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<tr>
<td>CHMP summary of positive opinion for Kadcyla</td>
<td>(English only) 20/09/2013</td>
<td></td>
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</tr>
</tbody>
</table>

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**SPC – product info**

**VARIATIONS**

**INDICATION EXTENSIONS**

**Q/S/E CHMP report initial approval**
early access instruments EU

**accelerated assessment** (~ US FDA priority review)
major public health interest, unmet need, innovative therapies
- 120/150 days *active CHMP review* (instead of 210 days)

**conditional approval** (~ US FDA accelerated approval)
unmet need: orphans, emergency threats, life-threatening
- B/R+ pending ongoing/new confirmatory studies
- valid for one year (*renewable*)
- conversion into normal: data package initial + obligations
- only initial approval (legal basis not + indications)

**exceptional circumstances**
comprehensive data *cannot be provided* (too *rare*, unethical...)
- data initial + obligations < normal
- annual reassessment B/R, focus safety, registries
conditional vs. exceptional

EU real?

ideal

'adequacy' of data

Normal

CMA

Exc Circ (too rare)

time to approval

### Early access tools FDA/EMA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>FDA</th>
<th>EMA</th>
<th>Review time (days)</th>
<th>Difference in dates FDA–EMA (days)</th>
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<tbody>
<tr>
<td>Pomalidomide (Imnovid)</td>
<td>Multiple myeloma</td>
<td>FT</td>
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<tr>
<td>T-DM1 (Kadcyla)</td>
<td>Breast HER2+</td>
<td></td>
<td></td>
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<tr>
<td>Radium 223 Cl₂ (Xofigo)</td>
<td>CRPC</td>
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<td>Dabrafenib (Tafinlar)</td>
<td>Melanoma BRAFm</td>
<td>FT</td>
<td>BTD</td>
<td>304</td>
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<tr>
<td>Trametinib (Mekinist)</td>
<td>Melanoma BRAFm</td>
<td>FT</td>
<td></td>
<td>299</td>
<td>17</td>
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<tr>
<td>Afatinib (Giotrif)</td>
<td>NSCLC EGFRm</td>
<td>FT</td>
<td></td>
<td>240</td>
<td>56</td>
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<tr>
<td>Obinutuzumab (Gazyvaro)</td>
<td>CLL CD20+</td>
<td></td>
<td></td>
<td>193</td>
<td>75</td>
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<tr>
<td>Ibrutinib (Imbruvica)</td>
<td>MCL, CLL</td>
<td>FT</td>
<td>FT</td>
<td>138</td>
<td>145</td>
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<tr>
<td>Ramucirumab (Cyramza)</td>
<td>Gastric</td>
<td>FT</td>
<td>FT</td>
<td>241</td>
<td>33</td>
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<tr>
<td>Ceritinib (Zykadia)</td>
<td>NSCLC ALK+</td>
<td>BTD</td>
<td>FT</td>
<td>126</td>
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<tr>
<td>Belinostat (Beleodaq)</td>
<td>PTCL</td>
<td>FT</td>
<td>FT</td>
<td>207</td>
<td>n/a</td>
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<tr>
<td>Idelalisib (Zydelig)</td>
<td>CLL, FL</td>
<td>FT</td>
<td>FT</td>
<td>229/315 FL</td>
<td>-16/70 FL</td>
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<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Melanoma</td>
<td></td>
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<tr>
<td>Blinatumomab (Blincyto)</td>
<td>ALL Ph-</td>
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<td>Olaparib (Lynparza)</td>
<td>Ovarian BRCA1/2m</td>
<td>FT</td>
<td>FT</td>
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<td>-131</td>
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<tr>
<td>Nivolumab (Opdivo)</td>
<td>Melanoma</td>
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<td>145</td>
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**EMA-ergering tools**

- **R&D:** PRIME (~breakthrough), early dialogue EMA-HTA joint advice
- **access:** adaptive pathways pilot (HTA), revisit AA/CMA
after conditional approval?

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**Early access of cancer drugs in the EU. Ann Oncol 27: 96–105, 2016**
SATs for approval?

RCTs remain gold standard for evaluating the B/R of cancer drugs, but single-arm trials (SATs) offer opportunities for early access, given RCT feasibility constraints in ‘precision medicine’

EU regulatory approval decisions case-by-case: limited guidance available about circumstances under which SATs are potentially acceptable for registration, e.g. ICH E10:

- **equipoise loss**: strong belief superiority exp. vs. alternatives
- **rarity** disease/subtype: randomisation impossible/unethical
- **disease course** predictable
- **treatment effect** dramatic
- **endpoint** objective

BMJ 2003
### EMA-ESMO SAT workshop 6/2016

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/05/event_detail_001285.jsp&mid=WC0b01ac058004d5c3

<table>
<thead>
<tr>
<th>Unmet Need</th>
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<tbody>
<tr>
<td>- <strong>prognosis</strong> (subset?)</td>
</tr>
<tr>
<td>- <strong>therapeutic alternatives</strong></td>
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<tr>
<td>- <strong>sparse evidence</strong></td>
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<table>
<thead>
<tr>
<th>Efficacy</th>
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</thead>
<tbody>
<tr>
<td>- <strong>endpoints</strong>: ORR &amp; DoR, novel clinically meaningful alternatives?</td>
</tr>
<tr>
<td>- <strong>threshold? context, risk</strong> false discovery - evidence: quality, design/conduct CT; other supportive, bio plausibility</td>
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<tr>
<th>Safety</th>
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<tr>
<td>- % &amp; grade AEs, DB, INI/EXT</td>
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<tr>
<th>Feasibility RCT</th>
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<tbody>
<tr>
<td>- <strong>actual prevalence</strong> (BM+)</td>
</tr>
<tr>
<td>- <strong>mol DG uptake screening</strong></td>
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<tr>
<td>- <strong>clinical equipoise</strong></td>
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<tr>
<td>- <strong>window of opportunity</strong></td>
</tr>
<tr>
<td>- <strong>timing</strong> - early results, approval - feasible RCT?</td>
</tr>
<tr>
<td>- alternatives confirmatory</td>
</tr>
<tr>
<td>- SATs, registries, RWD</td>
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<thead>
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<th>Controls</th>
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<tbody>
<tr>
<td>- data sharing</td>
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<td>- registries Dx+</td>
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<table>
<thead>
<tr>
<th>HTA, P&amp;R</th>
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<tbody>
<tr>
<td>- uncertainty - evidence family of data sources</td>
</tr>
<tr>
<td>- high price</td>
</tr>
<tr>
<td>- budget impact - off label use?</td>
</tr>
<tr>
<td>- patients’ pressure</td>
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</table>
RCT- & ‘SAT*-based approvals

<table>
<thead>
<tr>
<th></th>
<th>INI &amp; EXT</th>
<th>INITIAL</th>
<th>EXTENSIONS</th>
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<tr>
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<tr>
<td><strong>ALL</strong></td>
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<td></td>
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<tr>
<td>RCT</td>
<td>22%</td>
<td>33%</td>
<td>88%</td>
</tr>
<tr>
<td>SAT</td>
<td>78%</td>
<td>67%</td>
<td>90%</td>
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<tr>
<td><strong>SOLID</strong></td>
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<tr>
<td>RCT</td>
<td>13%</td>
<td>18%</td>
<td>9%</td>
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<tr>
<td>SAT</td>
<td>87%</td>
<td>82%</td>
<td>91%</td>
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<td><strong>HAEM</strong></td>
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<tr>
<td>RCT</td>
<td>59%</td>
<td>46%</td>
<td>22%</td>
</tr>
<tr>
<td>SAT</td>
<td>41%</td>
<td>54%</td>
<td>78%</td>
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</table>

*non-RCT - including also randomised uncontrolled (diff. dose/regimens), trials with external/historical controls, multi-cohort trials (e.g. 'basket') and observational*
framework - scenarios?

- **prospectively** identify when RCTs not strictly required for approval and HTA + P&R and/or feasible (ultra-rare entities or mol. subgroups in stratified medicine, equipoise loss) – ‘evidence pack’

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

EMA structure & functions

approval
- evaluation procedure & criteria
- early access instruments, SATs

R&D support
- guidelines & scientific advice, qualification

EU market access
- multi-stakeholder dialogue, HTA
dialogue with EU regulators

Pharm → Non-clinical → I → II → III → Post-mkt

Scientific Advice/Protocol Assistance (SAWP/CHMP/COMP-SB)
- Parallel SA (EMA - FDA)
- Qualification BMs (SAWP/CHMP)

ATMP Certification & Classification procedures (CAT)

Orphan Drug Designation (COMP)

Innovation Task Force (ITF), PhGWP

PhV, PSE (PRAC)

PIP (PDCO)

Qualification BMs (SAWP/CHMP)

Clinical development

ODD (COMP)
EU clinical trial approval

National Competent Authorities (NCA)
Ethics Committees

EU multi-national CTAs (current)  voluntary harmonisation procedure (VHP)

communication  time  outcome

sponsor  NCAs

communication  time  outcome

VHP-C  P-NCAs

+ (or -)
EMA guidelines

Clinical efficacy and safety guidelines

This section includes the European Medicines Agency's guidelines on the clinical efficacy and safety of medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing-authorisation applications for human medicines.

Guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy that are in the Community directives.

The Agency strongly encourages applicants and marketing-authorisation holders to follow these guidelines. Applicants need to justify deviations from guidelines fully in their applications at the time of submission. The Agency advises applicants to discuss any proposed deviations with EU regulators during medicine development through scientific advice.

Clinical efficacy and safety guidelines are provided for:

- Clinical pharmacology and pharmaco economics
- Nutritional scientific kaeterology
- Blood and blood forming organs
- Blood products (including biotechnological alternatives)
- Cardiovascular system

Guideline on the evaluation of anticancer medicinal products in man

<table>
<thead>
<tr>
<th>Draft Agreed by Oncology Working Party</th>
<th>September 2011</th>
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<tbody>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>15 December 2011</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 May 2012</td>
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<tr>
<td>Discussed at SAG-Oncology</td>
<td>05 November 2012</td>
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<td>Agreed by Oncology Working Party</td>
<td>28 November 2012</td>
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<td>Adopted by CHMP</td>
<td>13 December 2012</td>
</tr>
<tr>
<td>Date coming into effect</td>
<td>01 July 2013</td>
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</table>

This guideline replaces guideline / EMA reference.

Keywords: Cancer, malignancy, biomarker, targeted drugs, pharmacogenomics

Appendices

- PFS/DFS 1EP method.
- HRQoL/PROs
- condition-specific (CML, HSCT, MRD-CLL)
- paediatric addendum
R&D drug pipeline

Autoimmune/immunology
Cardiovascular
Endocrine
Hematology
Infectious disease
Metabolic
Neurology
Oncology
Psychiatry
Respiratory

Number of drugs
0  500  1,000  1,500  2,000  2,500
DeFrancesco Nat Biotech 2016

heterogeneity
EMA product R&D support

Scientific Advice (opt)

- Scientific Advice
  - Alimentary tract and metabolism: 39
  - Anti-neoplastic and immunomodulating agents: 1
  - Anti-parasitic products, insecticides, repellents: 25
  - Blood and blood-forming organs: 1
  - Cardiovascular system: 16
  - Dermatologicals: 14
  - Diagnostic agents: 2
  - General anti-infectives for systemic use: 52
  - Genito-urinary system and sex hormones: 12
  - Musculoskeletal system: 14
  - Nervous system: 59
  - Respiratory system: 20
  - Sensory organs: 14
  - Various: 29

Orphan Drug Designation (opt)

- Orphan Drug Designation
  - Cardiovascular diseases: 15
  - Endocrinology-gynaecology-fertility-metabolism: 7
  - Infectious diseases: 16
  - Oncology: 8
  - Immunology-rheumatology-transplantation: 7
  - Haematology-haemostaseology: 6
  - Neurology: 4
  - Gastroenterology-hepatology: 4
  - Pneumology-allergology: 4
  - Dermatology: 4
  - Pain: 3
  - Uro-nephrology: 2
  - Psychiatry: 2
  - Diagnostic: 2
  - Ophthalmology: 2
  - Vaccines: 2
  - Oto-rhino-laryngology: 1
  - Other: 4

Paediatric Inv. Plan

- Paediatric Inv. Plan
  - Cardiovascular diseases: 3
  - Endocrinology-gynaecology-fertility-metabolism: 7
  - Infectious diseases: 3
  - Oncology: 4
  - Immunology-rheumatology-transplantation: 4
  - Neurology: 4
  - Gastroenterology-hepatology: 2
  - Haematology-haemostaseology: 2
  - Pneumology-allergology: 1
  - Dermatology: 3
  - Pain: 6
  - Uro-nephrology: 2
  - Psychiatry: 2
  - Diagnostic: 1
  - Ophthalmology: 2
  - Vaccines: 2
  - Oto-rhino-laryngology: 1
  - Other: 4

by therapeutic area (2015)
**EM-MA scientific advice**

product-specific ‘case by case’

regulators
CTAs = national

- ph1
- phase 2
- phase 3

MAA

**EMA scientific advice & qualification**

**SAWP**: multidisciplinary expert group (n>50)
focus **phase 3 RCTs** - also exploratory, SATs
- **population** – all therapeutic areas
- **comparator**, blinding
- **endpoints**, SAP
- **safety**

(post-authorisation safety & efficacy studies, pragmatic trials, registries, meta-analyses)
FAQs SA clinical
dev. strategy, (pivotal) study design

- single-arm – conditional?

population

- definition entry criteria, stratification
- feasibility: orphan, mol. stratified

dose/regimen

- pre/clinical S&E, PK/PD, model & simulation, duration

comparator

- vs. active control(s)? equipoise?
- ‘basket’ investigator’s choice? global dev
- effective use – medical diversity, ESMO/NCCN
FAQs SA clinical endpoints

- OS vs. PFS, surrogates; 2EPs
- effect size - clinical relevance
- PROs / HRQoL - choice instruments, collection, analysis

statistical methodology

- SAP, interim analyses, adaptive designs, TIE control
- adjustment OS confounding next-line /cross-over

safety

- size DB registration, AEs monitoring
SA procedure

SAWP1

Coords 2 FRs

40-day

SAWP2

70-day

SAWP3

CHMP

LoI

Discussion meeting (SAWP)
EMA-FDA parallel SA

- **voluntary:** formal *eligibility request* to EMA-FDA
- briefing doc & questions identical to FDA and EMA
- **logistics:** steps / discussions scheduled per SAWP dates
  - fits 60-day Type B meetings and 70-day SA procedure
  - joint discussion meeting (F2F/TC) with Sponsor (day 60)

- exchange reports/responses (TC, LoQ common), but separate responses from each agency - aligned or increased requirements?

- <50 parallel EMA-FDA SA applications since 2006
- importance of *ad-hoc* and ‘cluster’ EMA-FDA SA interactions e.g. trilateral HC-EMA-FDA oncology TC
qualification novel methodologies

- pharmacological screening
  - mechanism of action
  - predict activity/safety
    - PK/PD modelling
    - toxicogenomics
  - verify mechanism
    - dose-response
    - proof of concept
    - input CT design
      - population
      - surrogate endpoint
- optimise population
  - guide treatment regimen

- PhGen predictive/prognostic BMs to enrich/select population
- surrogate E endpoints (e.g. MRD CLL)
- patient reported outcomes (PRO) questionnaires
market access

quality, safety, efficacy

clinical evidence E&S
assoc. uncertainty
single EU framework

budget impact, C/E, REA
national frameworks

B/R

P&R
<table>
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<tr>
<th></th>
<th>regulators</th>
<th>HTAs &amp; payers</th>
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<tr>
<td><strong>evaluation, decision</strong></td>
<td><strong>single</strong> EU + EFTA</td>
<td><strong>28+ frameworks</strong> normative &amp; methodological</td>
</tr>
<tr>
<td><strong>criteria, questions</strong></td>
<td><strong>benefit / risk QSE E vs. CT comparator not economic</strong></td>
<td><strong>costs / effectiveness relative to relevant comp. affordability, resources</strong></td>
</tr>
<tr>
<td><strong>population &amp; SoC endpoints</strong></td>
<td><strong>&quot;compromise&quot; global developments</strong></td>
<td><strong>representative individual healthcare system</strong></td>
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<tr>
<td><strong>uncertainty</strong></td>
<td><strong>early access (CMA)</strong></td>
<td><strong>patient benefit, HRQoL; clinical relevance threshold; modelling</strong></td>
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<tr>
<td><strong>global developments</strong></td>
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<td><strong>managed entry schemes</strong></td>
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</table>
NHS access - P&R, HTA

C/E → R?

REA → P

? → P&R

+1 y
EMA-HTAs multi-stakeholder SA

EMA-HTA to discuss/align evidence requirements **early** in development so drug developers can address information needs of both regulators and payers/HTAs

- **population & comparator**: relevance NHS, indirect comparisons / REA?
- **endpoints, SAP**: PFS vs. OS – patient relevant? HRQoL instruments? FU?
- **other evidence**: real-world data, economic - resource utilisation
glossary

- AR: Assessment Report
- ATMP: Advanced Therapy Medicinal Product
- B/R: benefit-risk
- BM: Biomarker
- CAT: Committee for Advanced Therapies
- CHMP: Committee for Medicinal Products for Human Use
- CMA: Conditional Marketing Authorisation
- COMP: Committee for Orphan Medicinal Products
- CP: Centralised Procedure
- CTA: Clinical Trial Application
- EPAR: European Public Assessment Report
- FUM: follow-up measure
- HTA: Health Technology Assessment
- ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- IMP: Investigational Medicinal Product
- MAA: Marketing Authorisation Application
- NCA: National Competent Authority
- PASS/PAES: Post-authorisation Safety/Efficacy study
- PDCO: Paediatric Committee
- PRAC: Pharmacovigilance Risk Assessment Committee
- Rapp: Rapporteur
- SAG: Scientific Advisory Group
- SB: Significant benefit (orphan)
- SAWP: Scientific Advice Working Party
EMA - roles in cancer drug development and approval

Jorge Martinalbo

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.
agenda

EMA structure & functions

approval

- evaluation procedure & criteria
  - early access instruments, single-arm trials

R&D support

- guidelines & scientific advice, qualification

EU market access

- multi-stakeholder dialogue, HTA
EU medicines regulatory network

- EMA decentralised body EU
  - headquarters scientific secretariat, coordination (London, 1995)
  - network of national agencies from 28 EU countries and > 5000 experts internal & external - scientific committees & working parties - regular meetings, not

~ 50 national regulatory authorities  European Commission  European Medicines Agency

global
EMA human committees

- CHMP (medicinal products human use)
- PRAC (PhVig, risk assessment)
- COMP (orphans)
- PDCO (paediatrics)
- CAT (advanced therapies)

- HMPC (herbals)
- CVMP (veterinary)
interactions + WP/WG

PKWP  BMWP (biosim)  BSWP (stats)  M&S WG

PRAC

CAT

OWP (onco)

IDWP (infect)

VWP (vaccines)

RIWG (immuno)

CHMP

SAWP

PhGWP

SAG-O
dangerous liaisons
## functions: EU / national

<table>
<thead>
<tr>
<th>ACCESS</th>
<th>R&amp;D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>centralised</strong></td>
<td><strong>national</strong></td>
</tr>
<tr>
<td>registration (new cancer drugs)</td>
<td>price &amp; reimbursement (effective access NHS)</td>
</tr>
<tr>
<td>QSE guidelines scientific advice (opt)</td>
<td>clinical trial approval VHP (opt)</td>
</tr>
<tr>
<td>orphan drug designation paediatric studies ATMP classification</td>
<td>devices, incl. <em>in vitro</em> diagnostics</td>
</tr>
<tr>
<td>EU pharmacovigilance coordination</td>
<td>inspections (GXP)</td>
</tr>
</tbody>
</table>
EMA drug approval

centralised procedure marketing authorisation application
review: scientific opinion from a single multidisciplinary Committee for medicinal products for human use (CHMP), representatives each country (voting), all therapeutic areas

- 2 teams, active review time ≤ 210 d (+ clock-stops)
- no evaluation of patient-level / raw data
benefit/risk paradigm

ORR & DoR, PFS, OS
improved symptoms & QoL
beneficial effects

uncertainty
risk tolerance

type, frequency
and severity of
adverse effects
objections efficacy

effect magnitude (& endpoint)

- negative trials: claims on (exploratory) subgroup analysis

- marginal/no clinically relevant efficacy (“not just p-value”)

- inconsistent data on clinical efficacy (2EPs, subgroups)

methodological – trial design

- SATs - lack of randomised controlled data

- (role in therapy/clinical usefulness – relative endpoint, validity of measurement; surrogacy? E? advances)

- statistical analysis deficiencies – premature IAs

- comparator/backbone inadequate (evolution?) for population, not isolating effect of individual drug

- dose/regimen justification; duration of treatment?
primary endpoints

INI+EXT

- OS
- PFSp
- RRP
- other
objections safety

- in relation to severity of indication / unmet medical need / magnitude of clinical efficacy

- mortality, SAEs increased
- size safety DB limited
  - data quality, SATs non-comparative data
- long-term follow-up insuff.
- risk management plans

- DDI studies lacking
- special populations: renal and hepatic impairment (label)
cancer drugs EU approvals

>40% 'targeted' but no BM
drugs with BM+ indication EU 25%

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

toremifene (Fareston)
breast HR+

imatinib (Glivec)
CML Ph+

arsenic trioxide (Trisenox)
APL PML-RARα

ibritumomab tiuxetan (Zevalin)
iNHL-FL CD20+

cetuximab (Erbilux)
CRC EGFR+ -> KRASwt 2008

panitumumab (Vectibix)
CRC EGFR+ KRASwt

lapatinib (Tyverb)
breast HER2+

vemurafenib (Zelboraf)
melanoma BRAFV600

fulvestrant (Faslodex)
breast HR+

rituximab (Mabthera)
DLBCL CD20+ var/ext

trastuzumab (Herceptin)
breast HER2+

dasatinib (Sprycel)
CML & ALL Ph+

nilotinib (Tasigna)
CML Ph+

gefitinib (Iressa)
NSCLC EGFR

erlotinib (Tarceva)
NSCLC EGFRm var/ext

crizotinib (Xalkori)
NSCLC ALK+

pertuzumab (Perjeta)
breast HER2+

trastuzumab emtansine (Kadcyla)
breast HER2+

olaparib (Lynparza)
ovarian BRCAm

trametinib (Mekinist)
melanoma BRAFV600

dabrafenib (Tafinlar)
melanoma BRAFV600

afatinib (Giotrif)
NSCLC EGFRm

tronetinib (Iclusig)
CML & ALL Ph+

brentuximab vedotin (Adcetris)
sALCL, Hodgkin CD30+

bosutinib (Bosulif)
CML Ph+

toxotuzumab (Fulvestrant)
breast HER2+

toxotuzumab (Bosutinib)
CML Ph+
## 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><strong>Target</strong></td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>archival</td>
<td>recent</td>
<td>archival/recent</td>
<td>archival/recent</td>
<td>?</td>
</tr>
<tr>
<td><strong>IHC assay</strong></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><strong>Cell types</strong></td>
<td>TC</td>
<td>TC</td>
<td>TC</td>
<td>IC &amp;/or TC</td>
<td>TC</td>
</tr>
<tr>
<td><strong>Cut-offs NSCLC</strong></td>
<td>TC≥5%</td>
<td>TC≥1% TC≥50%</td>
<td>TC≥25%</td>
<td>TC or IC≥1% TC or IC≥5% TC≥50% or IC≥10%</td>
<td>TC≥1%</td>
</tr>
</tbody>
</table>

No harmonised meaning of PD-L1+, clinical implications in decision making, ordering tests and comparing agents.
EU assessment reports EPAR
EU CHMP assessment B/R

SPC – product info

VARIATIONS
INDICATION EXTENSIONS

Q/S/E CHMP report initial approval
early access instruments EU

accelerated assessment (~ US FDA priority review)

- major public health interest, unmet need, innovative therapies
- 120/150 days active CHMP review (instead of 210 days)

conditional approval (~ US FDA accelerated approval)

- unmet need: orphans, emergency threats, life-threatening
- B/R+ pending ongoing/new confirmatory studies
- valid for one year (renewable)
- conversion into normal: data package initial + obligations
- only initial approval (legal basis not + indications)

exceptional circumstances

- comprehensive data cannot be provided (too rare, unethical…)
- data initial + obligations < normal
- annual reassessment B/R, focus safety, registries
conditional vs. exceptional

EU real?

ideal

'adequacy' of data

Normal

CMA

Exc Circ (too rare)

time to approval
### Early Access Tools: FDA/EMA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>FDA Review Time (days)</th>
<th>EMA Review Time (days)</th>
<th>Difference in Dates (days)</th>
<th>bCMA</th>
<th>bAccAs</th>
<th>Rev. start</th>
<th>dApproval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomalidomide (Imnovid)</td>
<td>Multiple myeloma</td>
<td>FT</td>
<td>304</td>
<td>71</td>
<td>NO</td>
<td></td>
<td></td>
<td>178</td>
</tr>
<tr>
<td>T-DM1 (Kadcyla)</td>
<td>Breast HER2+</td>
<td>FT</td>
<td>182</td>
<td>26</td>
<td>266</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radium 223 Cl₂ (Xofigo)</td>
<td>CRPC</td>
<td>FT</td>
<td>154</td>
<td>49</td>
<td>172</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar)</td>
<td>Melanoma BRAFm</td>
<td>FT</td>
<td>304</td>
<td>17</td>
<td>89</td>
<td></td>
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<tr>
<td>Trametinib (Mekinist)</td>
<td>Melanoma BRAFm</td>
<td>FT</td>
<td>299</td>
<td>208</td>
<td>397</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Afatinib (Giotrif)</td>
<td>NSCLC EGFRm</td>
<td>FT</td>
<td>240</td>
<td>-56</td>
<td>75</td>
<td></td>
<td></td>
<td>264</td>
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<tr>
<td>Obinutuzumab (Gazyvaro)</td>
<td>CLL CD20+</td>
<td>FT</td>
<td>193</td>
<td>30</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ibrutinib (Imbruvica)</td>
<td>MCL, CLL</td>
<td>FT</td>
<td>138</td>
<td>145</td>
<td>342</td>
<td></td>
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<tr>
<td>Ramucirumab (Cyramza)</td>
<td>Gastric</td>
<td>FT</td>
<td>241</td>
<td>33</td>
<td>242</td>
<td></td>
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<td></td>
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<tr>
<td>Ceritinib (Zykadia)</td>
<td>NSCLC ALK+</td>
<td>FT</td>
<td>126</td>
<td>92</td>
<td>372</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belinostat (Beleodaq)</td>
<td>PTCL</td>
<td>FT</td>
<td>207</td>
<td>92</td>
<td>372</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idelalisib (Zydelig)</td>
<td>CLL, FL</td>
<td>FT</td>
<td>229/315 FL</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Melanoma</td>
<td>FT</td>
<td>189</td>
<td>118</td>
<td>321</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinatumomab (Blincyto)</td>
<td>ALL Ph-</td>
<td>FT</td>
<td>75</td>
<td>n/a</td>
<td>321</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Olaparib (Lynparza)</td>
<td>Ovarian BRCA1/2m</td>
<td>FT</td>
<td>319</td>
<td>-131</td>
<td>-3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nivolumab (Opdivo)</td>
<td>Melanoma</td>
<td>FT</td>
<td>145</td>
<td>56</td>
<td>182</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n/total (%)</td>
<td></td>
<td>FT</td>
<td>200</td>
<td>49</td>
<td>210</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### EMA-ergering tools

- **R&D**: PRIME (~breakthrough), early dialogue EMA-HTA joint advice
- **access**: adaptive pathways pilot (HTA), revisit AA/CMA

after conditional approval?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Pivotal clinical trial design (N)</th>
<th>Primary efficacy results (95% CI)</th>
<th>EU CMA</th>
<th>Outcome HTA/P&amp;R</th>
<th>Time from authorisation (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (Sutent)</td>
<td>GIST 2L mono</td>
<td>Phase 3 RCT versus BSC (312)</td>
<td>PFS 6.5 versus 1.46 months—HR 0.33 (0.23–0.47)</td>
<td>July 06</td>
<td>R</td>
<td>32 n/a 2 4</td>
</tr>
<tr>
<td>RCC 2L. mono</td>
<td>2 x phase 2 single-arm (106, 63)</td>
<td>ORR 25.5% (17.5%–34.9%)</td>
<td></td>
<td></td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Panitumumab (Vectibix)</td>
<td>CRC KRASwt 2L+ mono</td>
<td>Phase 3 RCT versus BSC (463)</td>
<td>PFS 8 versus 7.3 months—HR 0.54 (0.44–0.663)</td>
<td>December</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Lapatinib (Tyverb)</td>
<td>Breast HER2+ 2L comb. chemo</td>
<td>Phase 3 RCT add on to capecitabine (399)</td>
<td>PFS 6.23 versus 4.26 months—HR 0.57 (0.43–0.77)</td>
<td>June 08</td>
<td>R</td>
<td>66 n/a 7 4</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra)</td>
<td>CLL 3L mono</td>
<td>Phase 2 single-arm (154)</td>
<td>ORR 58% (40%–74%)</td>
<td>April 10</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>RCC 1L mono</td>
<td>Phase 3 RCT versus BSC (435)</td>
<td>PFS 9.2 versus 4.2 months—HR 0.46 (0.34–0.62)</td>
<td>June 10</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Everolimus (Votubia)</td>
<td>SEGA paediatric 1L mono</td>
<td>Phase 2 single-arm (28)</td>
<td>Volume 0.93 versus 1.74 cm³ (0.4–1.2)</td>
<td>September</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Vandetanib (Caprelsa)</td>
<td>Thyroid, MTC 1L mono</td>
<td>Phase 3 RCT versus BSC (331)</td>
<td>PFS 30.5 versus 19.3 months—HR 0.46 (0.31–0.69)</td>
<td>February</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Pixantrone (Pixuvri)</td>
<td>DLBCL 2L mono</td>
<td>Phase 3 RCT versus BSC (140)</td>
<td>CR 20 versus 5.7% (3.5–25.1); P = 0.021</td>
<td>May 12</td>
<td>5 n/a NO</td>
<td>22 12 n/a 14</td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>NSCLC ALK+ 2L mono</td>
<td>Phase 1 single-arm + phase 3 RCT versus chemo (125, 318)</td>
<td>phase 1 ORR 60%, phase 3 PFS 7.7 versus 3 months—HR 0.49 (0.37–0.64)</td>
<td>October</td>
<td>NO</td>
<td>17 29/5</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>sALCL CD30+ 2L mono</td>
<td>Phase 2 single-arm (58)</td>
<td>ORR 75%, CR 33%, DoR 6.7 months</td>
<td>October</td>
<td>4 III R</td>
<td></td>
</tr>
<tr>
<td>Hodgkin CD30+ 3L mono</td>
<td>Phase 2 single-arm (102)</td>
<td></td>
<td></td>
<td>October</td>
<td>4 III R</td>
<td></td>
</tr>
<tr>
<td>Bosutinib (Bosulif)</td>
<td>CML Ph+ 2L+ mono</td>
<td>Phase 2 single-arm (four cohorts: 502)</td>
<td>MCR 2L 53.4% (47.2–59.5), 3L 27% (19–36)</td>
<td>March 13</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Vismodegib (Erivedge)</td>
<td>Basal cell, met. 1L mono</td>
<td>Phase 2 single-arm (two cohorts: 104)</td>
<td>ORR 30.3% (15.6–48.2), 42.9% (30.5–56.0)</td>
<td>July 13</td>
<td>3/5 IV R</td>
<td></td>
</tr>
<tr>
<td>Cabozantinib (Cometriq)</td>
<td>Thyroid, MTC 1L mono</td>
<td>Phase 3 RCT versus BSC 2: 1 (330)</td>
<td>PFS 11.2 versus 4 months—HR 0.28 (0.19–0.4)</td>
<td>March 14</td>
<td>3 IV n/a</td>
<td></td>
</tr>
</tbody>
</table>

SATs for approval?

RCTs remain gold standard for evaluating the B/R of cancer drugs, but single-arm trials (SATs) offer opportunities for early access, given RCT feasibility constraints in ‘precision medicine’

EU regulatory approval decisions case-by-case: limited guidance available about circumstances under which SATs are potentially acceptable for registration, e.g. ICH E10:

- equipoise loss: strong belief superiority exp. vs. alternatives
- rarity disease/subtype: randomisation impossible/unethical
- disease course predictable
- treatment effect dramatic
- endpoint objective

BMJ 2003
unmet need
- prognosis (subset?)
- therapeutic alternatives
- sparse evidence

efficacy
- endpoints: ORR & DoR, novel clinically meaningful alternatives?
- threshold? context, risk false discovery - evidence: quality, design/conduct CT; other supportive, bio plausibility

controls
- data sharing
- registries Dx+

feasibility RCT
- actual prevalence (BM+)
- mol DG uptake screening
- clinical equipoise
- window of opportunity
- timing - early results, approval - feasible RCT? alternatives confirmatory - SATs, registries, RWD

HTA, P&R
- uncertainty - evidence family of data sources
- high price
- budget impact - off label use?
- patients’ pressure

safety
% & grade AEs, DB, INI/EXT
framework – scenarios?

- prospectively identify situations when RCTs may not be strictly required for approval (e.g. unequivocal loss of equipoise) and/or feasible (ultra-rare clinical entities or molecular 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 Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Cossi1*, P. Bruzzi2, J. Bogaerts3 & J.-Y. Blay4 on behalf of the Rare Cancers Europe (RCE) Consensus Panel

**RARE MOL**

**BREAKTHROUGH**

screening IVD BM+
RCT- & SAT-based approvals

initial

RCT
SAT

extensions
## RCT- & ‘SAT’-based approvals (1995-2014)

<table>
<thead>
<tr>
<th></th>
<th>INI &amp; EXT</th>
<th>INITIAL</th>
<th>EXTENSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>78%</td>
<td>67%</td>
<td>88%</td>
</tr>
<tr>
<td>SAT</td>
<td>22%</td>
<td>33%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>SOLID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>87%</td>
<td>82%</td>
<td>91%</td>
</tr>
<tr>
<td>SAT</td>
<td>13%</td>
<td>18%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>HAEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>59%</td>
<td>46%</td>
<td>22%</td>
</tr>
<tr>
<td>SAT</td>
<td>41%</td>
<td>54%</td>
<td>78%</td>
</tr>
</tbody>
</table>
EMA review success & time

**INITIAL MAA**

- **N total (N SAT)**: 141 (46)
- **40 (13)**
- **101 (33)**

**success rate 72% (72%)**

**EXTENSION**

- **122 (18)**
- **19 (5)**
- **103 (13)**

**success rate 84%**

**2006-2014**

<table>
<thead>
<tr>
<th>Authorisations (n)</th>
<th>SAT</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>initial (18/50)</strong></td>
<td>334 (183 - 556)</td>
<td>343 (176 - 757)</td>
</tr>
<tr>
<td><strong>regular (10/39)</strong></td>
<td>294 (183 - 512)</td>
<td>328 (176 - 757)</td>
</tr>
<tr>
<td><strong>conditional (5/8)</strong></td>
<td>363 (211 - 491)</td>
<td>410 (211 - 547)</td>
</tr>
<tr>
<td><strong>exc circ (3/3)</strong></td>
<td>419 (337 - 556)</td>
<td>357 (216 - 638)</td>
</tr>
</tbody>
</table>

**success rate 72%**

**SAT 72%**

**RCT 87%**
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 initial approval on RR

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

- regulatory success rate
- INI: 72% SAT vs. 72% RCT; EXT: 72% SAT vs. 87% RCT
EU clinical trial approval

- National Competent Authorities (NCA)
- Ethics Committees

EU multi-national CTAs (current) and voluntary harmonisation procedure (VHP)
EMA guidelines

Guideline on the evaluation of anticancer medicinal products in man

<table>
<thead>
<tr>
<th>Draft Agreed by Oncology Working Party</th>
<th>September 2011</th>
</tr>
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<tbody>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>15 December 2011</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 May 2012</td>
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<tr>
<td>Discussed at SAG-Oncology</td>
<td>05 November 2012</td>
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<td>Agreed by Oncology Working Party</td>
<td>28 November 2012</td>
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<td>Adopted by CHMP</td>
<td>13 December 2012</td>
</tr>
<tr>
<td>Date coming into effect</td>
<td>01 July 2013</td>
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</tbody>
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This guideline replaces guideline / MRG Reference.

Keywords: Cancer, malignancy, biomarker, targeted drugs, pharmacogenomics

Appendices
- PFS/DFS 1EP method.
- HRQoL/PROs
- condition-specific (CML, HSCT, MRD-CLL)
- paediatric addendum
EMA product R&D support

Scientific Advice (opt)

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Plans agreed</th>
<th>Waivers</th>
</tr>
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<tbody>
<tr>
<td>Alimentary tract and metabolism</td>
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<tr>
<td>Anti-neoplastic and immunomodulating agents</td>
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<tr>
<td>Anti-parasitic products, insecticides, repellents</td>
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<tr>
<td>Blood and blood-forming organs</td>
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<tr>
<td>Cardiovascular system</td>
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<td>Dermatologicals</td>
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<tr>
<td>Diagnostic agents</td>
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<td>General anti-infectives for systemic use</td>
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<tr>
<td>Genito-urinary system and sex hormones</td>
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<td>Nervous system</td>
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<td>Respiratory system</td>
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<td>Sensory organs</td>
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Orphan Drug Designation (opt)

<table>
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<th>Therapeutic Area</th>
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<tbody>
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<tr>
<td>Endocrinology-gynaeology-fertility-metabolism</td>
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<tr>
<td>Infectious diseases</td>
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<tr>
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<tr>
<td>Immunology-rheumatology-transplantation</td>
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<tr>
<td>Neurology</td>
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<td>Gastroenterology-hepatology</td>
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<td>Haematology-haemostaseology</td>
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<td>Pneumology-allergology</td>
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<tr>
<td>Dermatology</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Uro-nephrology</td>
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<td>Psychiatry</td>
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<tr>
<td>Diagnostic</td>
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<tr>
<td>Ophthalmology</td>
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<td>Vaccines</td>
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<tr>
<td>Oto-rhino-laryngology</td>
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<tr>
<td>Other</td>
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</table>

Paediatric Inv. Plan

<table>
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<th>Therapeutic Area</th>
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<th>Waivers</th>
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<td>Cardiovascular diseases</td>
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<tr>
<td>Endocrinology-gynaeology-fertility-metabolism</td>
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<tr>
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<tr>
<td>Immunology-rheumatology-transplantation</td>
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<tr>
<td>Neurology</td>
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<tr>
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<tr>
<td>Haematology-haemostaseology</td>
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<td>Oto-rhino-laryngology</td>
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</tr>
<tr>
<td>Other</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

by therapeutic area (2015)
EMA scientific advice

product-specific ‘case by case’

regulators
CTAs = national

ph1 phase 2 phase 3 MAA

SAWP: multidisciplinary expert group (n>50)
focus phase 3 RCTs - also exploratory, SATs
- population – all therapeutic areas
- comparator, blinding
- endpoints, SAP
- safety

(post-authorisation safety & efficacy studies, pragmatic trials, registries, meta-analyses)
qualification novel methodologies

- pharmacological screening
  - mechanism of action
  - predict activity/safety
    - PK/PD modelling
    - toxicogenomics
- verify mechanism
  - dose-response
  - proof of concept
  - input CT design
    - population
    - surrogate endpoint
- optimise population
  - guide treatment regimen

- PhGen predictive/prognostic BMs to enrich/select pop (PD-L1?)
- surrogate E endpoints (e.g. MRD CLL, pCR neoadjuvant BC)
- patient reported outcomes (PRO) questionnaires
market access

quality, safety, efficacy

clinical evidence E&S
assoc. uncertainty
single EU framework

budget impact, C/E, REA
national frameworks
differences?

<table>
<thead>
<tr>
<th>regulators</th>
<th>HTAs &amp; payers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>evaluation, decision</strong></td>
<td><strong>single EU + EFTA</strong></td>
</tr>
<tr>
<td><strong>criteria, questions</strong></td>
<td><strong>benefit / risk QSE</strong></td>
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<tr>
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<td><strong>E vs. CT comparator</strong></td>
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<td><strong>population &amp; SoC endpoints</strong></td>
<td><strong>“compromise”</strong></td>
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<tr>
<td></td>
<td><strong>global developments</strong></td>
</tr>
<tr>
<td></td>
<td><strong>“hard” or established surrogates (&lt;HRQoL)</strong></td>
</tr>
<tr>
<td><strong>uncertainty</strong></td>
<td><strong>early access (CMA)</strong></td>
</tr>
</tbody>
</table>
NHS access - P&R, HTA

C/E → R?

REA → P

¿ → P&R

CDF

NICE

(5-30m)

ΔP

(1-10m)

HAS

(4-19m)

AIFA

(5-19m)

(?m)
EMA(-HTAs) scientific advice

evidence / criteria among market access decision-makers?

Regulators
CTAs = national

ph1 > phase 2 > phase 3 > MAA

SAWP: multidisciplinary expert group (n>50)

SATs prospective discussion
- unmet need and clinical relevance of effect vs alternatives
- ORR, durability – novel endpoints?
- vs. benchmark? mol. subgroups?
- post-authorisation studies, registries registration pathway – R, CMA, ExcCir? AP?

EMA-HTA-multi-stakeholder discussions

PRIME – PRIority MEdicines breakthroughs, enhanced interaction with EMA
questions?

“Everything you always wanted to know about regulators

*But were afraid to ask”
adaptive pathways pilot

start 3/2014 as non-binding, safe-harbor pilot, prospectively planned systems approach to lifecycle incl. P&R and utilisation existing regulatory framework process/tools

Criteria for candidate selection

- preliminary evidence PoC, unmet need, but not necessarily a breakthrough
- adaptation: early stage of development, plan includes iterative phases of evidence collection – evaluation – adapt license
- RWD real-world data (registries, post-A S&E studies, observational trials…), also ‘unconventional’ designs e.g. basket
- stakeholders’ input (+HTAs/payers)
Number of Patients Treated vs. Time (years)

- **Initial License**
  - Natural history of disease,
  - Patient population,
  - Resource utilisation,
  - Safety and Efficacy

- **“Full” License**
  - Safety,
  - Efficacy,
  - Open label studies

- **Phase IV Trials**
  - Patients treated,
  - no active surveillance

- **Registries**
  - Patients in RCTs
  - (or other interventional studies)

- **Hospital data**

- **Surveys**

- **Health Insurance Data**

- **Biobanks**

- **EHR**
  - Patients treated,
  - no active surveillance

- **RWE through the lifecycle**
  - Registries
  - Hospital data
  - EHR
  - Surveys
  - Biobanks

- **Patients in observational studies, registries, etc**