Adaptive pathways: perspectives of patients and healthcare professionals on addressing patient needs

HCP representatives' views on the products selected for the adaptive pathways pilot

Adaptive pathways workshop
European Medicines Agency
London, 8 December 2016

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Adaptive Pathways

Prospectively planned adaptive approach to bring valuable drugs to pts in need

Authorised indication → iterative phases of evidence gathering→ progressive licensing adaptation

To maximize the positive impact of new drugs on public health by balancing

Timely access for patients

Need to provide adequate evolving information on benefits and harms

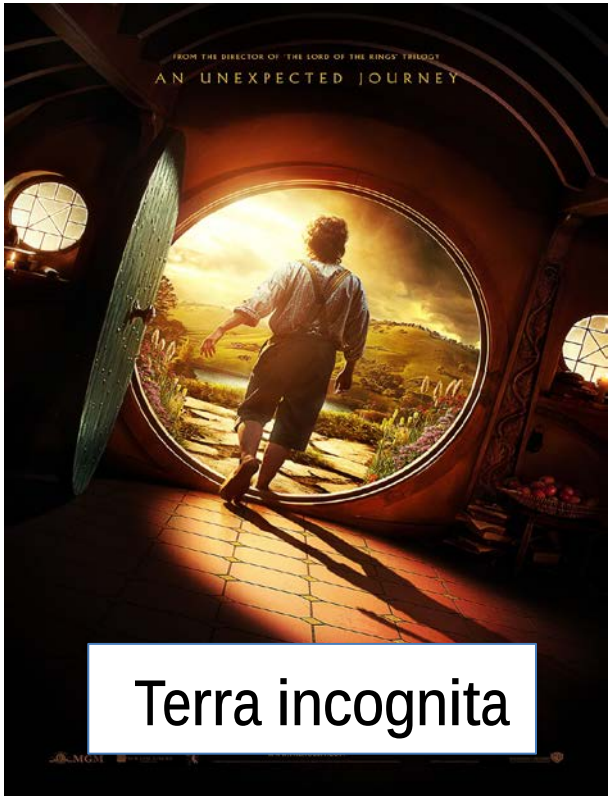
Adaptive pathways:

Pro

Biology

Engagement

Pragmatic approach (RWD)



Terra incognita

Contra

Uncertainty

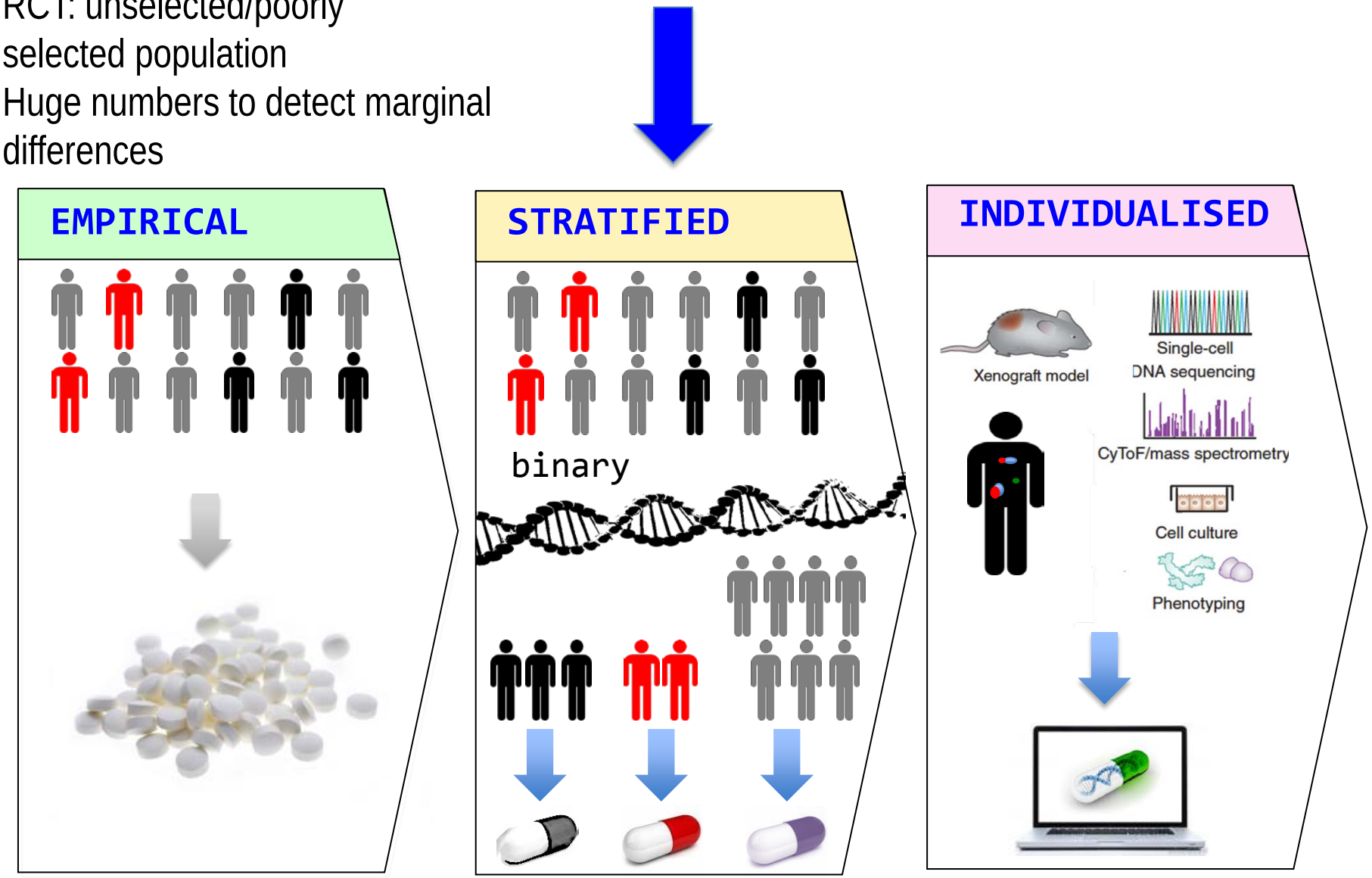
Safety

Real benefit
→B/R

Reliability of RWD

BIOLOGY:PARADIGM SHIFT

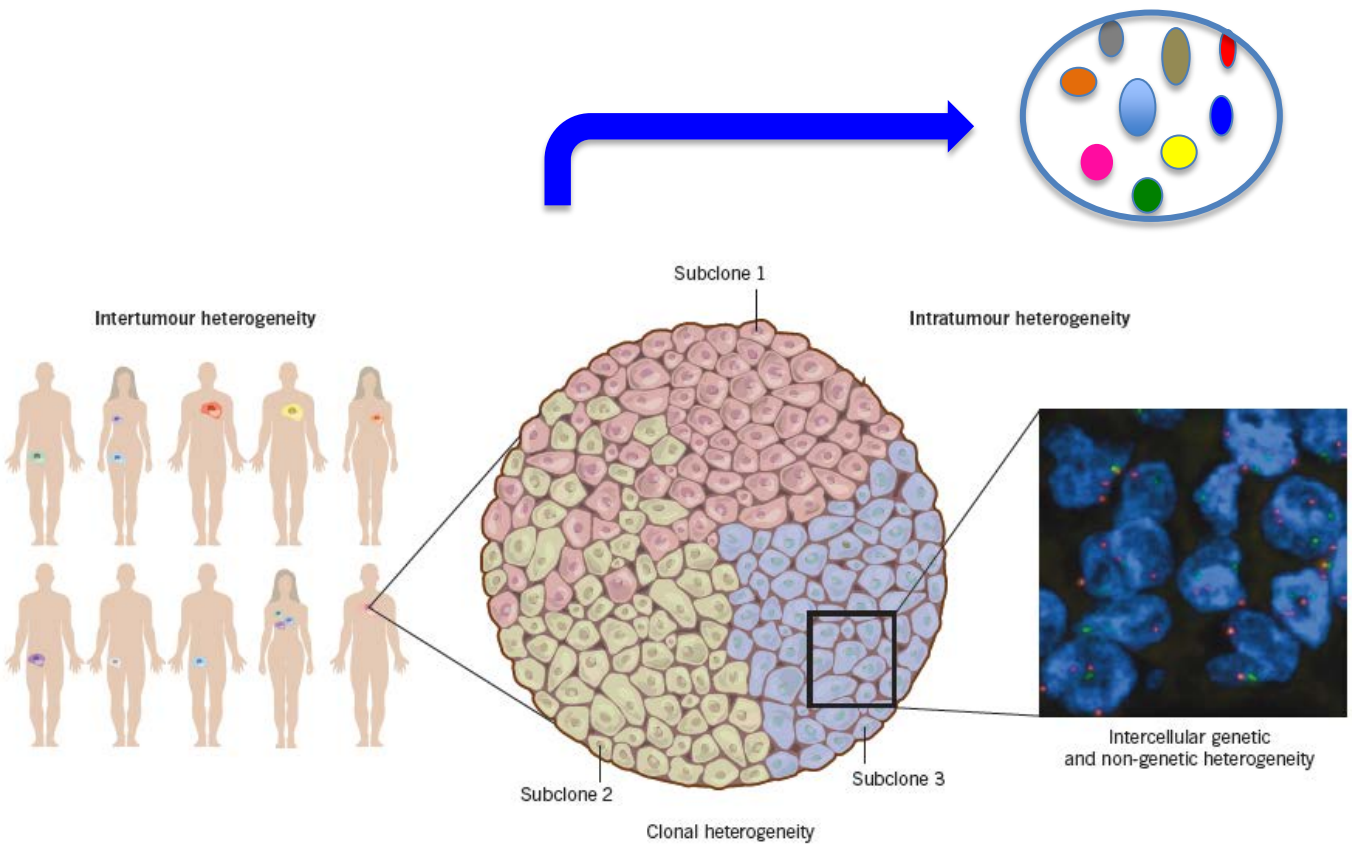
RCT: unselected/poorly selected population
Huge numbers to detect marginal differences



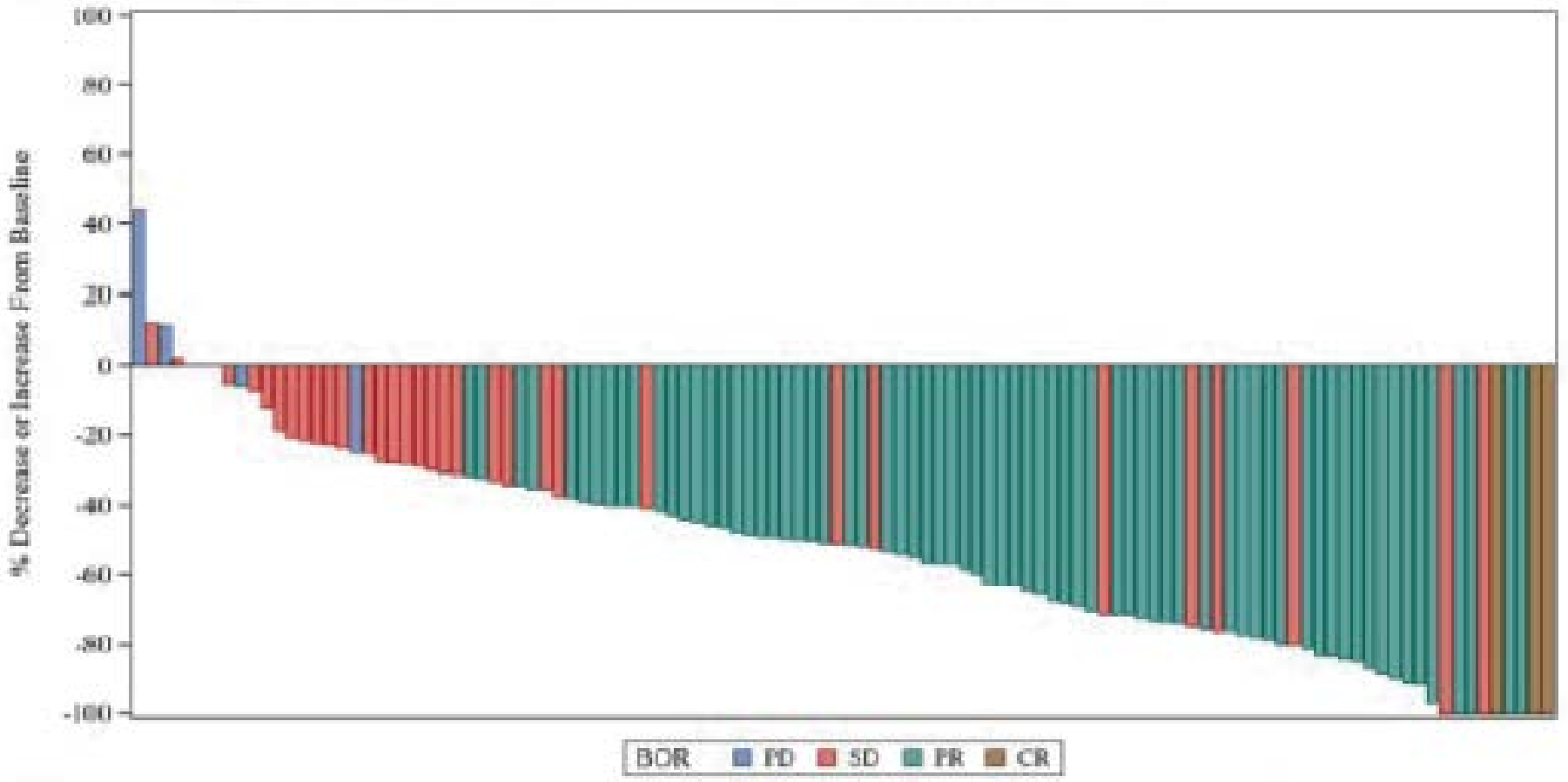
BIOLOGY MATTERS: CANCER HETEROGENEITY

FRAGMENTATION
(HETEROGENEITY)

CLUSTERING
(DIFFERENT
BENEFIT)

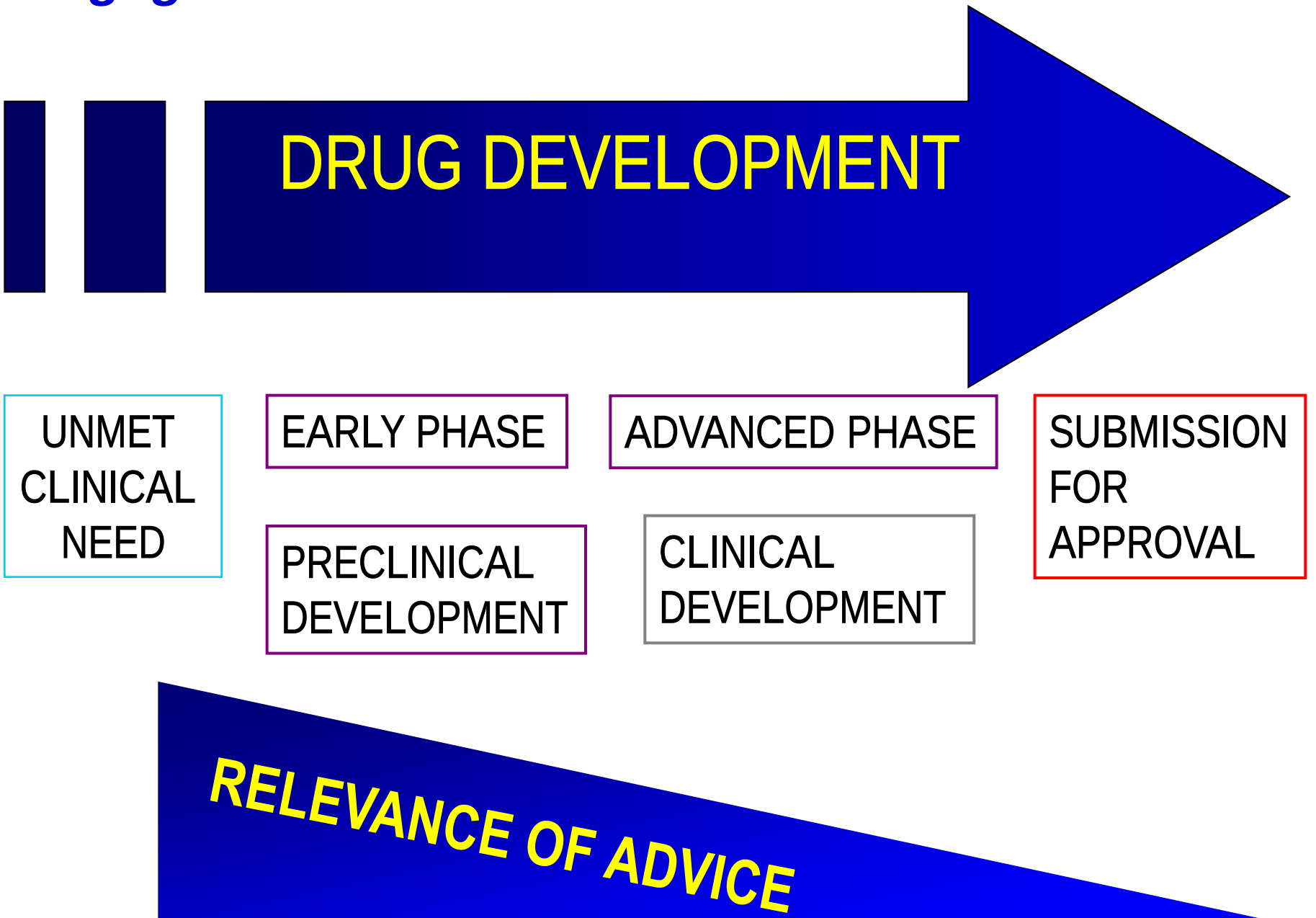


NOT ALL DRUGS ARE CREATED EQUAL



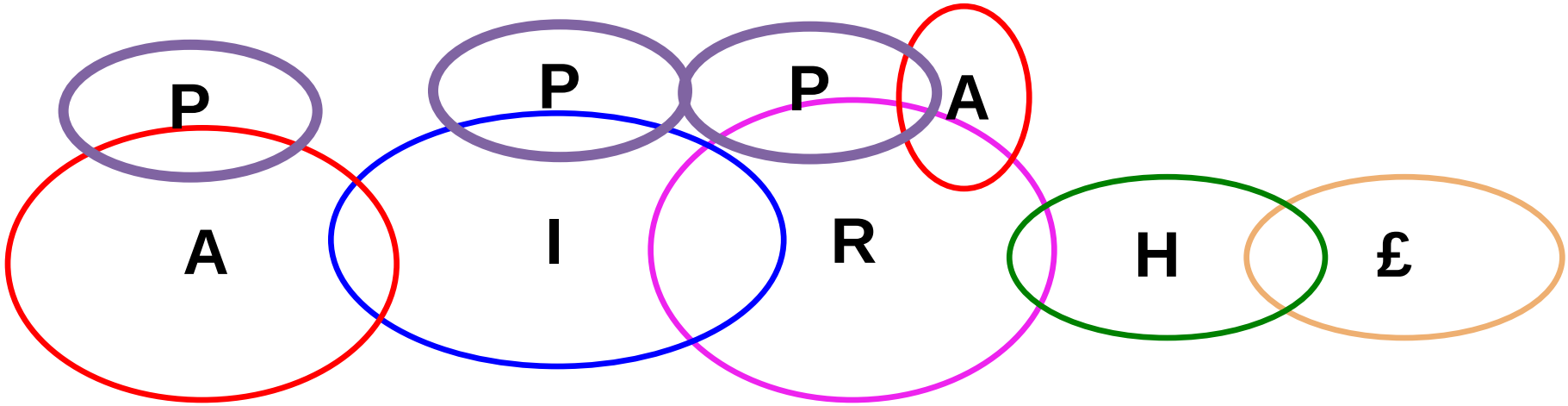
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002489/WC500134761.pdf

Engagement: relevance of interaction

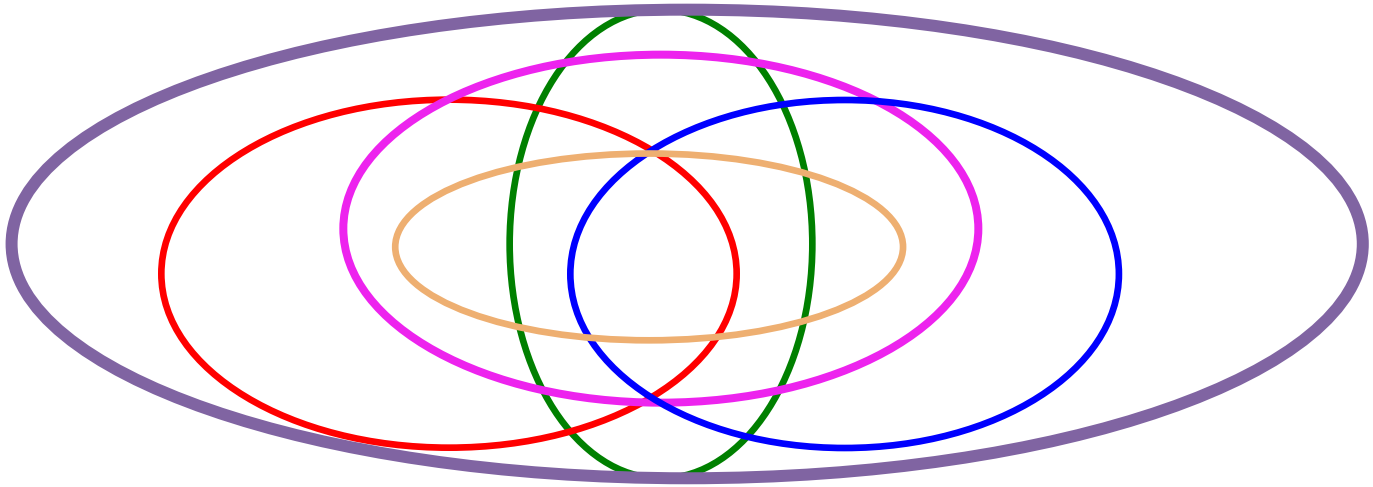


Shift in the model of interaction between stakeholders

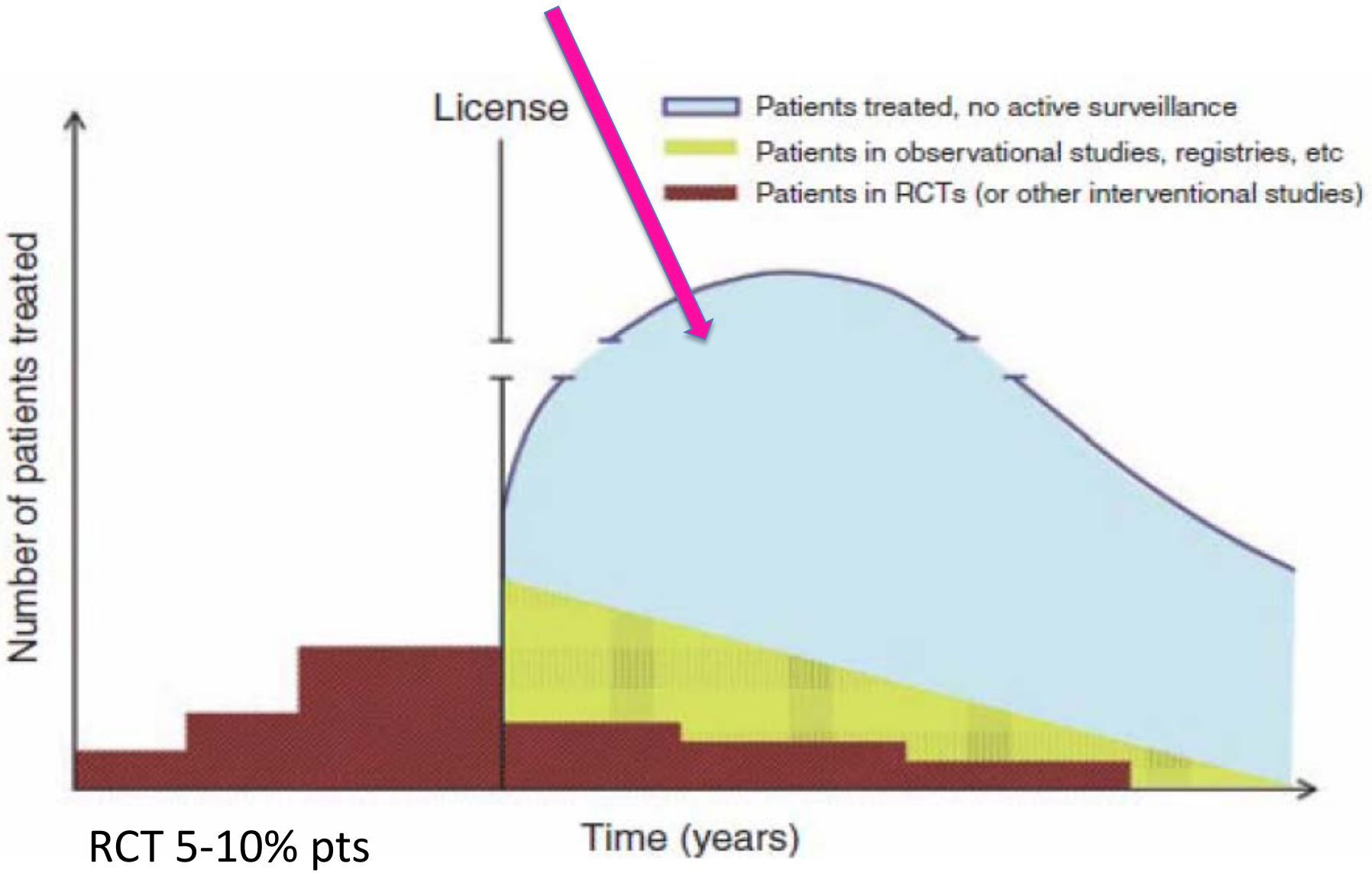
CURRENT



IDEAL



My “real” patients are here



RCT 5-10% pts

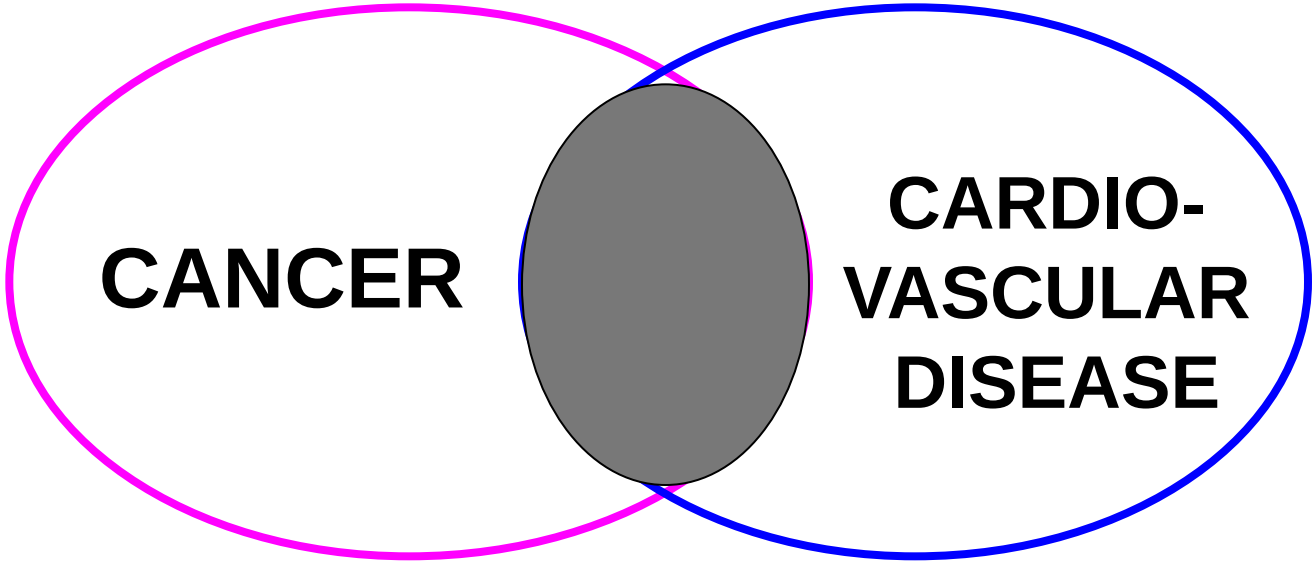
“Athletes with cancers”

Clin. Pharm. Ther. Vol 91, March, 2012

Will it be this the first time that we deal with uncertainty?

EXTRAPOLATION

Kimmick, ASCO 2012



ELDERLY PTS: By 2030 70% all cancer diagnosis

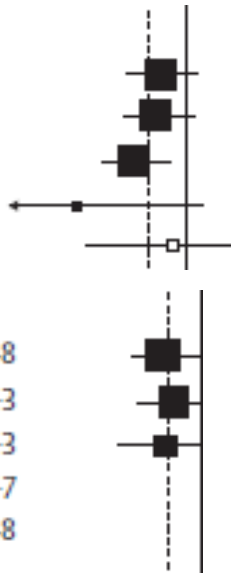
(*Smith JCO 2009, Gravanis ASCO 2012*)

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Lancet 2011

	Deaths/women		Taxane deaths		Ratio of annual death rates
	Allocated taxane	Allocated non-taxane	Log-rank O–E	Variance of O–E	Taxane:Non-taxane
(D) Entry age (trend χ^2_1=3·5; 2p=0·06)					
<45 years	871/5930 (14·7%)	928/5927 (15·7%)	−36·7	384·6	
45–54 years	835/7747 (10·8%)	932/7720 (12·1%)	−41·4	372·3	
55–69 years	735/6572 (11·2%)	877/6570 (13·3%)	−69·0	346·5	
>70 years	51/314 (16·2%)	81/343 (23·6%)	−11·4	24·4	
Unknown	149/1565 (9·5%)	150/1563 (9·6%)	−2·5	48·6	
(D) Entry age (trend χ^2_1=0·0; 2p=0·9; NS)					
<45 years	871/3398 (25·6%)	991/3454 (28·7%)	−54·8	422·8	
45–54 years	738/3399 (21·7%)	773/3356 (23·0%)	−30·6	344·3	
55–69 years	375/1961 (19·1%)	396/1920 (20·6%)	−20·2	169·3	
>70 years	18/106 (17·0%)	25/112 (22·3%)	−2·2	8·7	
Unknown	7/79 (8·9%)	5/84 (6·0%)	2·4	1·8	



For 70 years-old denominators are in the range of hundreds, wheresas for younger pts are of thousands

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 12, 2012 VOL. 366 NO. 2

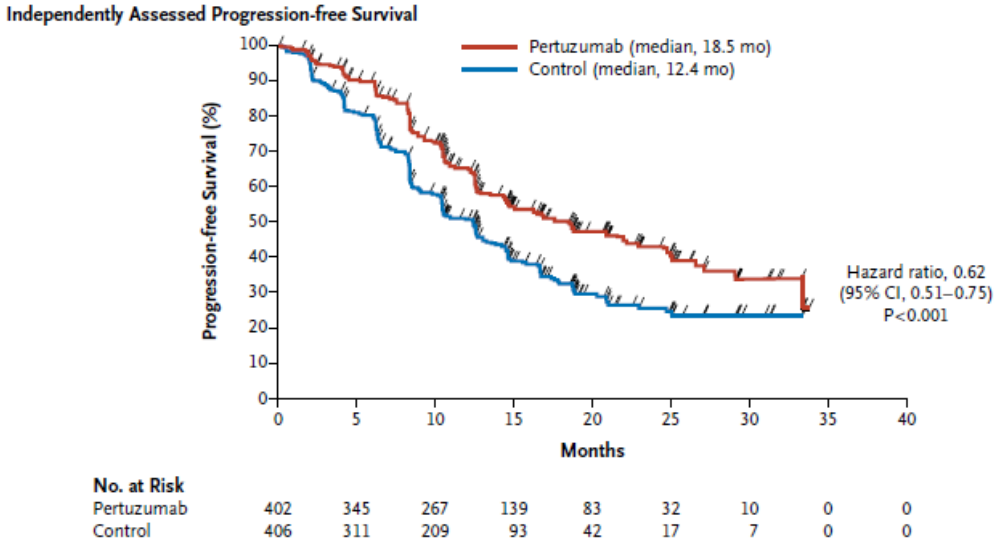
Baselga, NEJM, 2012

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

806 pts

CT H Placebo

CT H Pertuzumab



11 pts (2.8%)

5 pts (1.2%)

LEFT VENTRICULAR DYSF.

Prior neo/adjuvant chemo	CT H Placebo	CT H Pertuzumab
No	214 (52.7%)	218 (54.2%)
Yes	192 (47.3%)	184 (45.8%)
Anthracycline	164 (40.4%)	150 (37.3%)
Taxane	94 (23.2%)	91 (22.6%)
Trastuzumab	41 (10.1%)	47 (11.7%)

TRICKY POINT: RDW

Are RWD as good as data from RCT?

Depends on data

WHAT IS RWD and how will it be captured?

E-HR
Phase IV trials
Pragmatic trials
Registries
Post-authorization safety/efficacy studies
Observational studies (prospective and retrospective)
Pharmacoeconomics studies
Expanded access/ compassionate use program
Data collected by NCA (e.g. MEA)

-Agreement on scope of collection
-Clear plan: avoid duplication (my data, your data…)

Nearly half of all investigational drugs that successfully complete phase II studies fail in phase III, mostly because of lack of safety or efficacy. If new drugs are approved on the basis of phase II trials there is a 50:50 chance that they are unsafe,ineffective, or both.

Article type: Original Article

Title: A randomized adaptive phase II/III study of buparlisib, a pan-Class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2– advanced breast cancer (BELLE-4)

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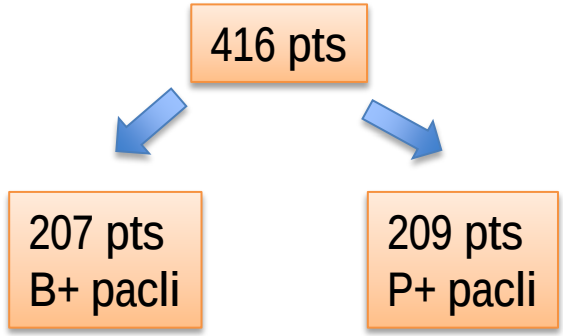
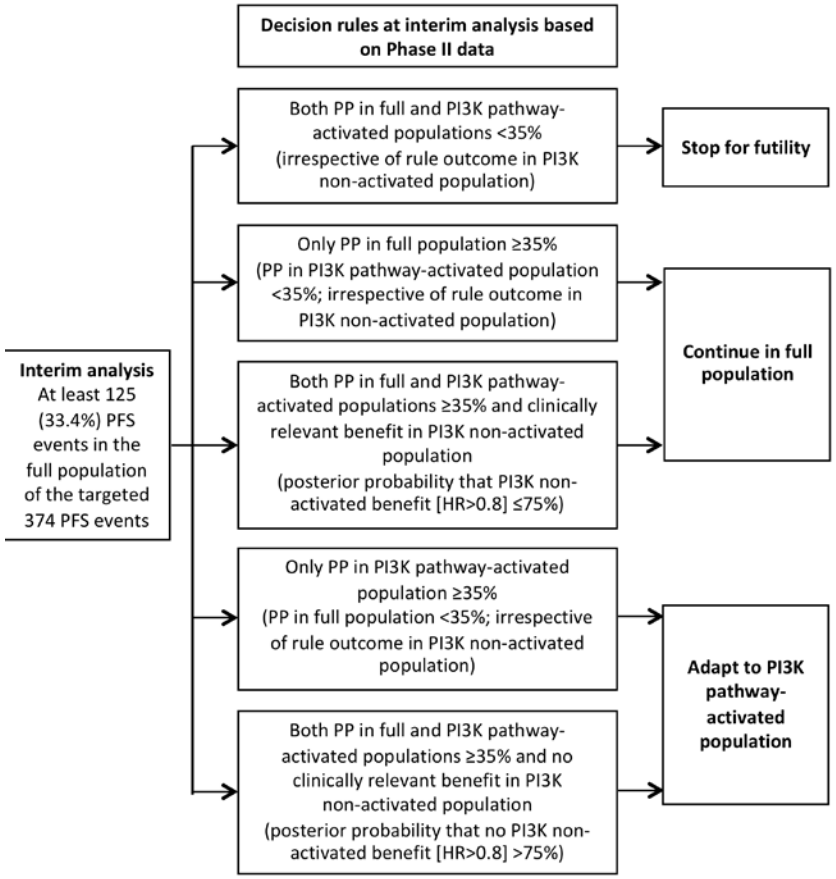
Ann Oncol,Nov 2016
accepted manuscript

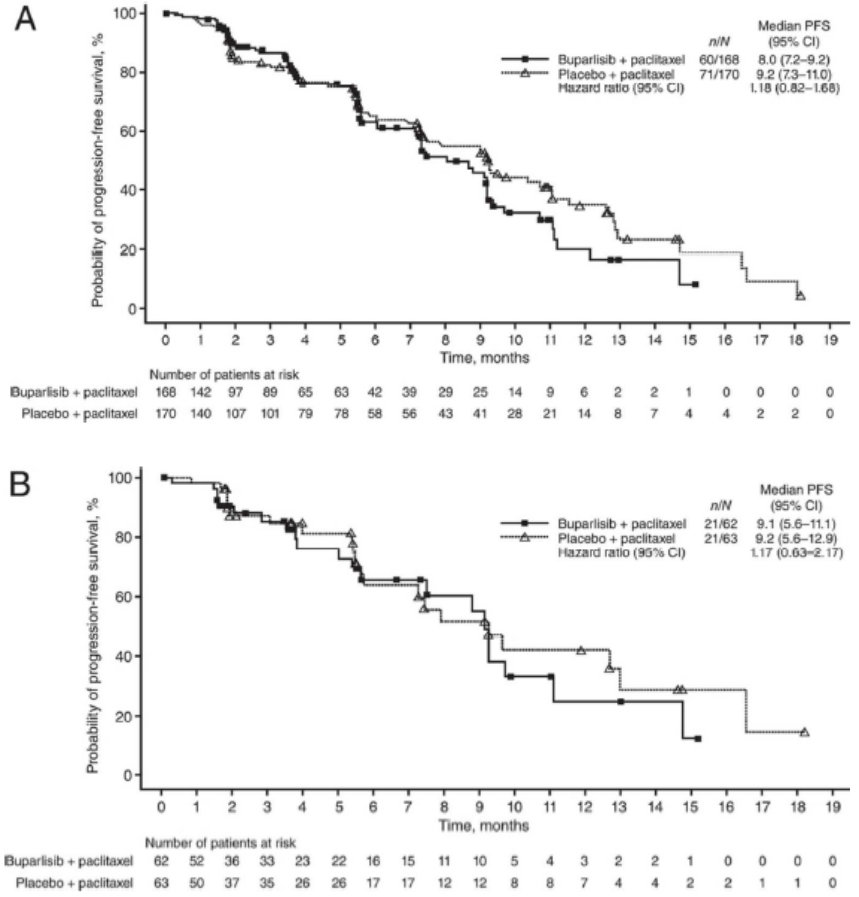
Adaptive phase II-III BELLE 4 study
1° line MBC
R 1:1, placebo controlled
Stratification: PI3Kactivation and HR status



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.

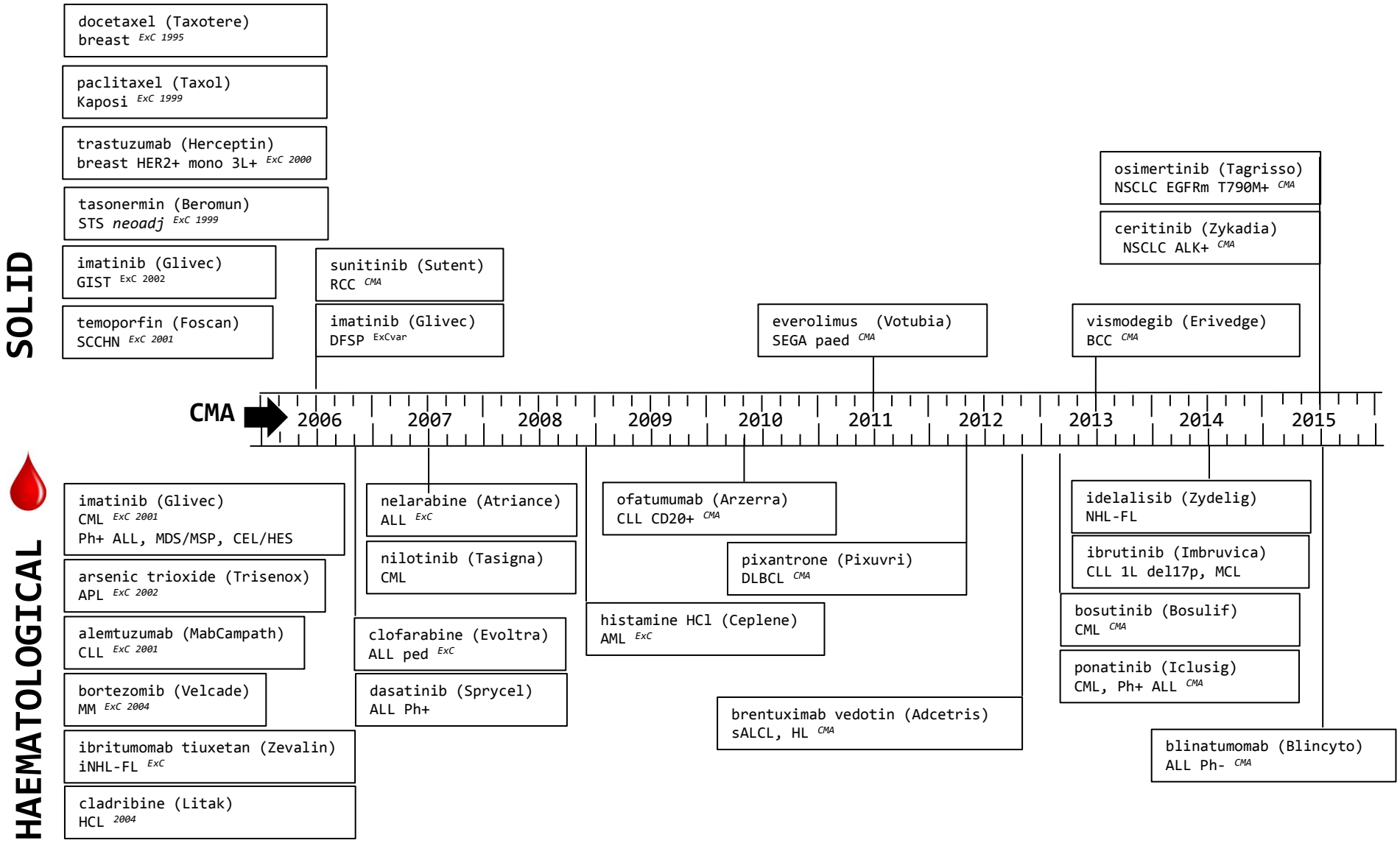




PI3K activated tumors
in 35.3% pts,
Determined mainly
in archival tissues

PIK3CA 72.8%
PTEN gene mut 18.4%
Loss pf PTEN
expression 19%

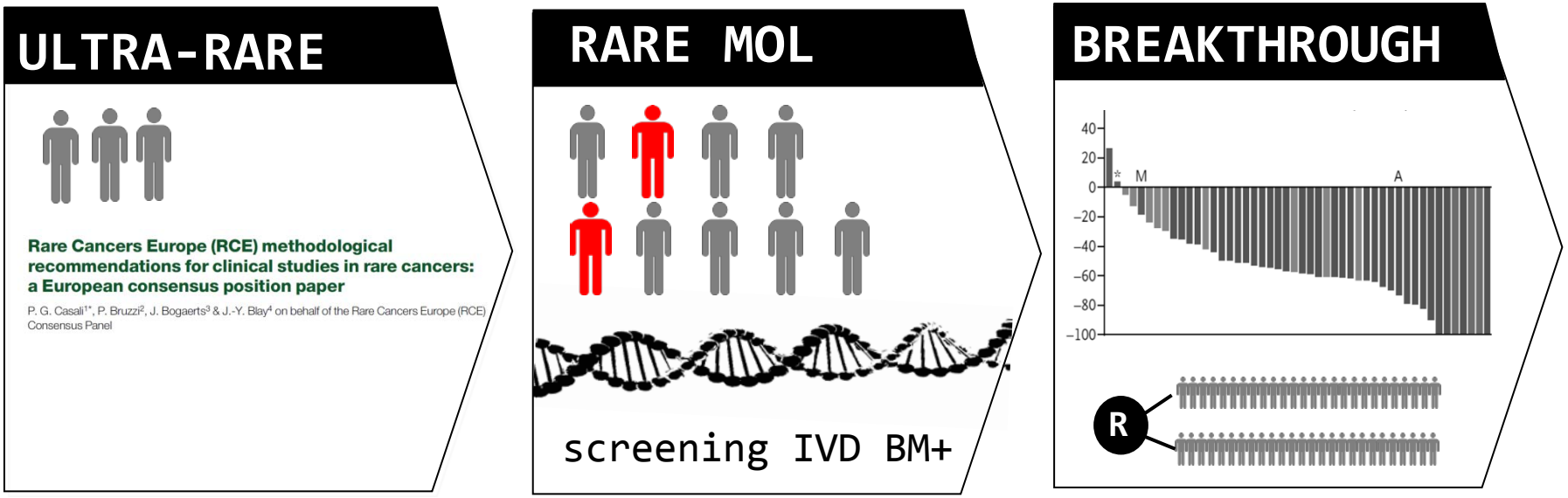
EU approvals on SATs



Courtesy of J. Martinalbo

SAT: 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**…



Courtesy of J. Martinalbo

RISK MITIGATION

RATIONALE DRUG DEVELOPMENT

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 (molecularly driven)

-RWD lacking reliability both in terms of quality

-Study required post-peri approval difficult to complete (once the drug is avaialble)

PATIENTS SAFETY