Methodological issues (some) relating to patient selection-
CHMP Reflection paper

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Overview

- Background
- Personalised medicine and Regulation
- Why do we need a Guidance /RP?
- So what does the paper say?
- What next?

Biomarkers, patients and Regulation

BMs

- represent an additional test burden
- Need qualification and validation
- Need context of the BM.

(Why, When and How to replace 'old' with "new" ?

- Need 'reliability' and 'discriminatory ability'
- Need cut off points?!

Commonly asked Questions

- How do we qualify/ validate the marker
- Level of evidence required for a BM/PGBM in regulatory terms?
- Are RCT's mandatory for BM ??
- When will retrospective data be acceptable?
- BMs as Surrogate end points

Regulatory Objective!

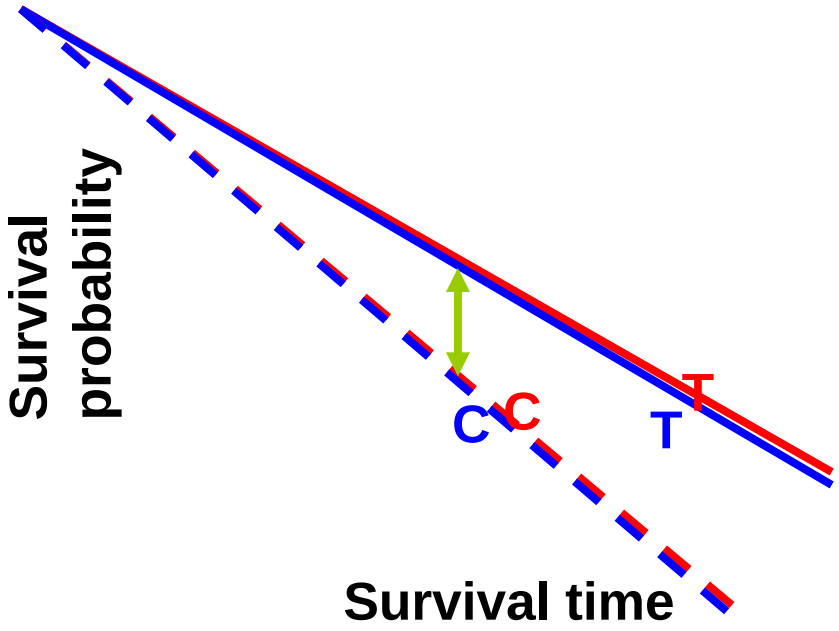
Evaluation & recommendations need to be

- Scientifically robust
- Clinically relevant
- Practical to implement

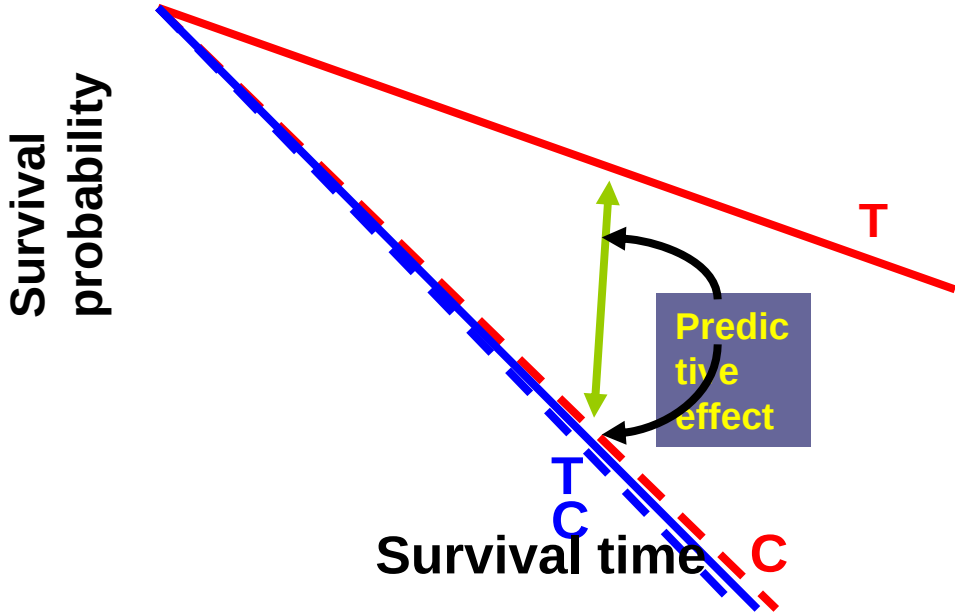
....to enable *Safe* and *Effective* use of the medicinal product **i.e., influence clinical practice**

What are we need with BMs

No biomarker effect



Predictive biomarker



Blue Line --Marker (–)

Red Line --Marker (+)

Genomic BMs, scope of inclusion in labelling.

Product	INN name	Biomarker	Scope
Ziagen	abacavir	HLA-B*5701	Safety
Herceptin	trastuzumab	HER2 receptor	Efficacy
Glivec	imatinib	c-kit	Efficacy
Trisenox	Arsenic trioxide	PML/RARa	Efficacy
Erbitux	cetuximab	EGFR/K-Ras	Efficacy
Tarceva	erlotinib	EGFR	Efficacy
Sprycel	dasatinib	PH+ Chromosome	Efficacy
Celsentri	maraviroc	CCR5 coreceptor	Efficacy
Tasigna	nilotinib	PH+ Chromosome	Efficacy
Vectibix	panitumumab	K-Ras	Efficacy
Tyverb	lapatinib	HER2	Efficacy
Iressa	gefitinib	EGFR	Efficacy
Multiple tradenames	carbamazepine	HLA-B*1502 HLA-A*3101	Safety
Multiple tradenames	Phenytoin	HLA-B*1502	Safety
Multiple tradenames	Tamoxifen	CYP2D6	Efficacy- Interactions
Multiple tradenames	Clopidogrel	CYP2C19	Efficacy
Abilify	aripiprazole	CYP2D6	Safety
Xeloda	capecitabine	DPD	Safety
Onsenal#	celecoxib#	CYP2C9	Safety
Faslodex	fulvestrant	Estrogen receptor	Efficacy
Viracept	nelfinavir	CYP2C19	Safety
Fasteurtec	rasburicase	G6PD	Safety

Reflection Paper

Aims;

- to identify products where genomic biomarkers influenced the development or raised questions
- to identify and streamline regulatory expectations
- to discuss the CHMP experience and concerns

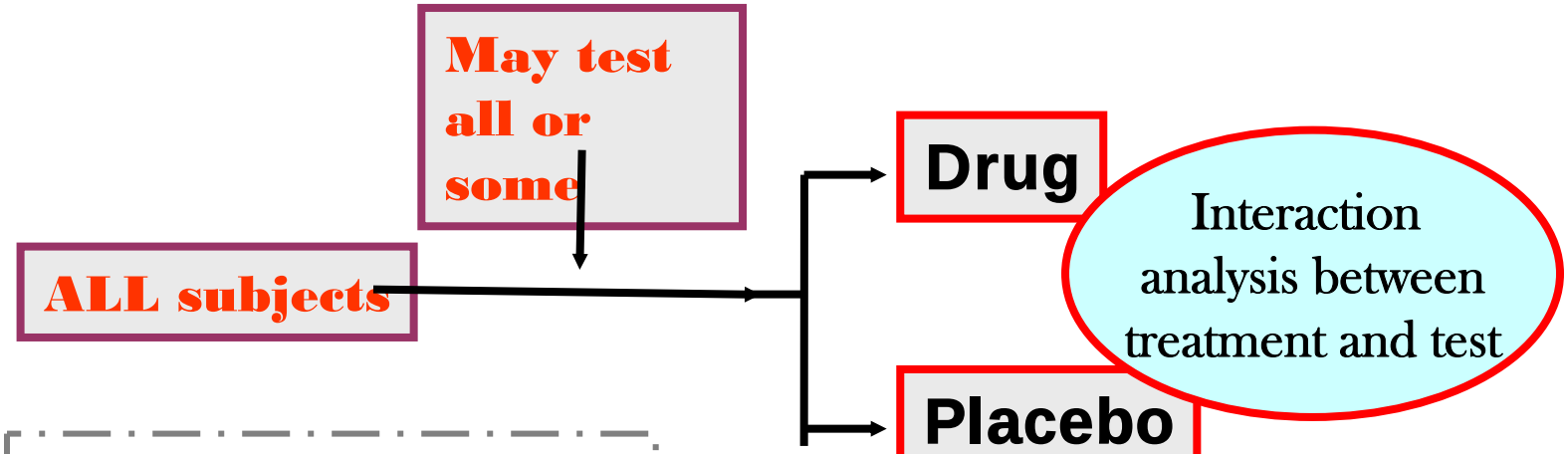
Scope;

Restricted mainly to centralised MAAs and other major safety issues discussed at CHMP relating to genomic biomarkers

So;

It is not a detailed review of literature on methodologies of genomic marker application

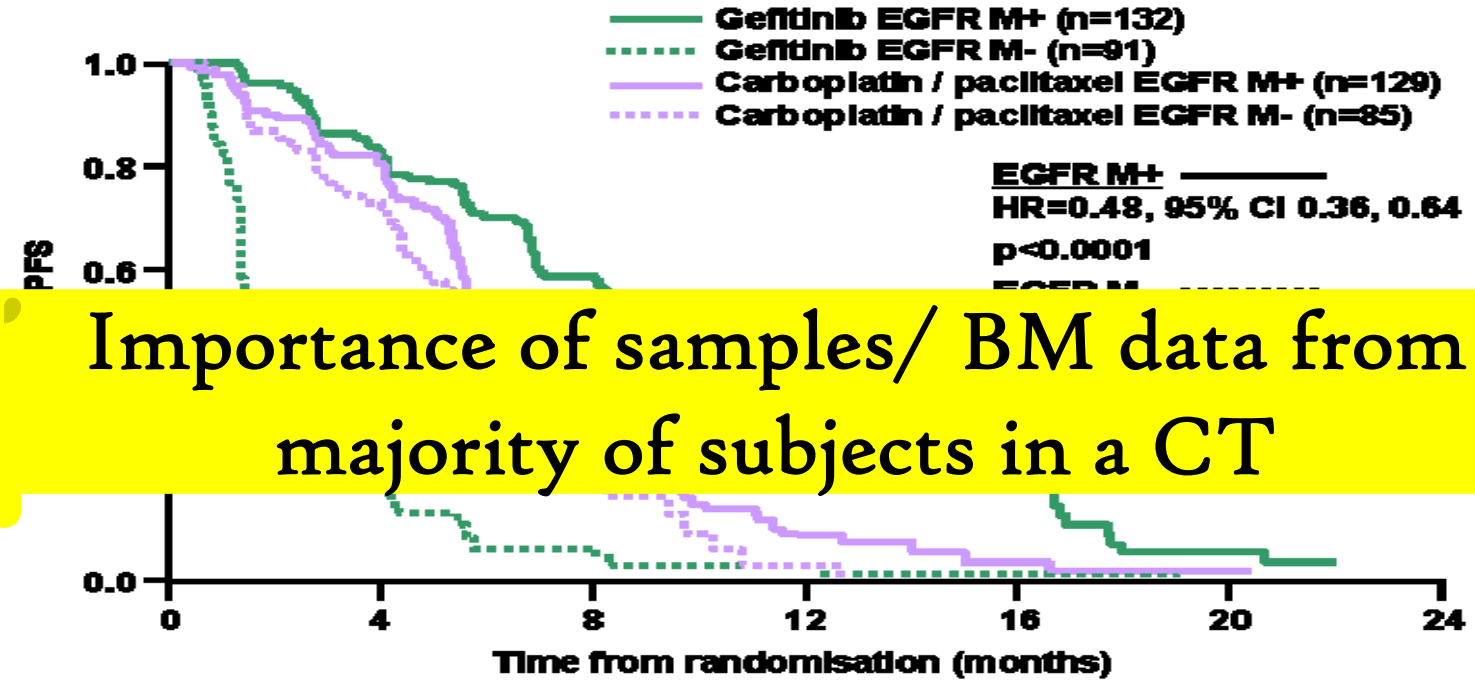
Clinical Trial Designs (1)



Such a design may be adopted if the results of the testing will not be readily available at the clinical sites for informing randomisation

[redacted]

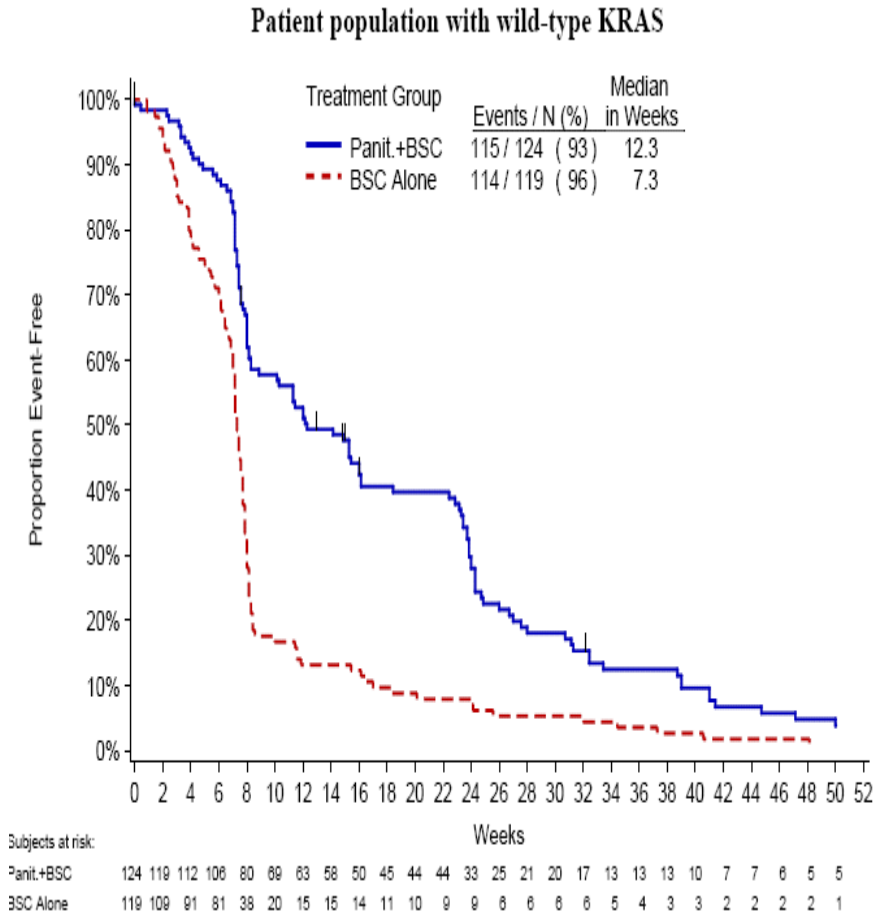
Comparison of gefitinib and carboplatin/paclitaxel treatment arms for PFS based on their EGFR mutations status – IPASS study



Important of samples/ BM data from majority of subjects in a CT

Gefitinib (N=609)	Carboplatin / Paclitaxel (N=608)

KRAS story



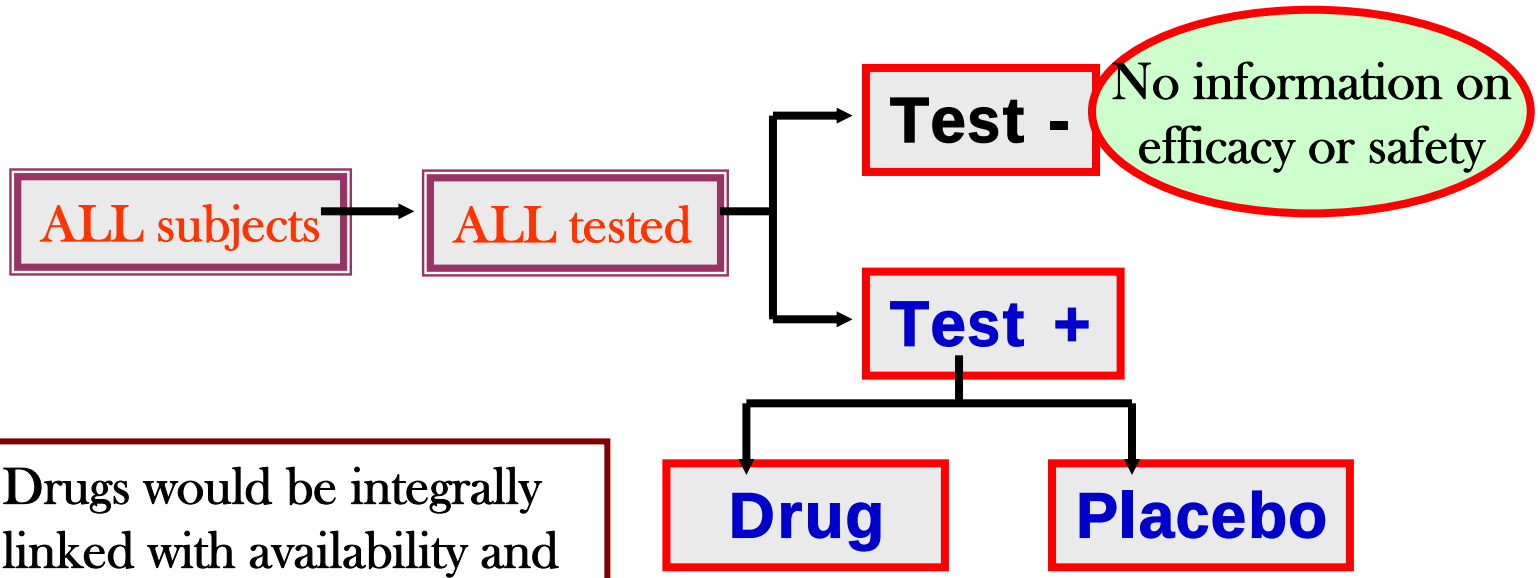
- Wild type vs mutant KRAS, Impact on PFS;
- Retrospective analysis; (prosp defined)

Several Interesting issues;

- Prognostic or Predictive
- 2nd Renewal- suggested that *use of Vectibix in mutated KRAS may be detrimental* –a marker of safety.
- Relationship with B RAF, NRAS, Not defined *De Rook W et al; Lancet oncol, 11:753-62, 2010*

Clinical Trial Designs (2)

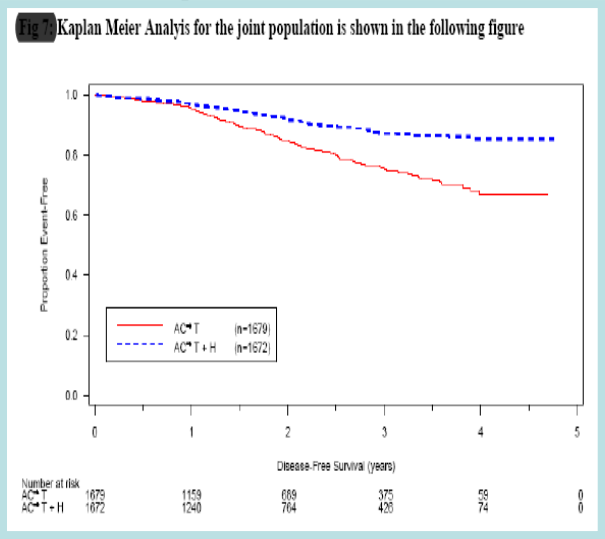
Enriched or targeted design



Drugs would be integrally linked with availability and use of the biomarker test at the time of approval.

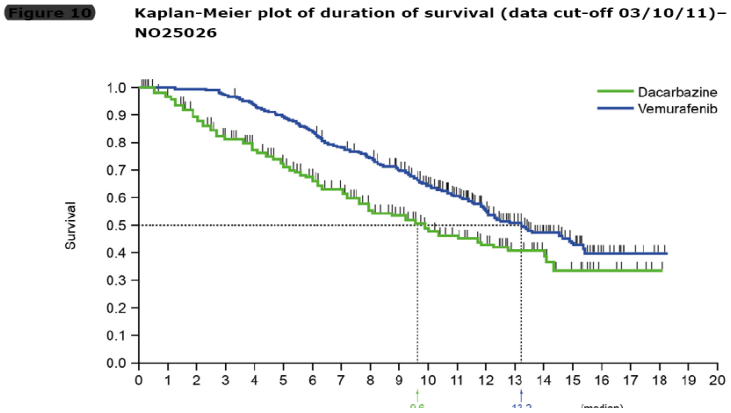
Do we need marker –ve subjects??

Breast cancer and Herceptin



- ~ 30% of all Br Ca are Her-2 (+)
- IHC staining 1+ to 3 + is not infallible
- *(~20% discordance between CTA & test)*
- Reports of response in Her (-) ve subjects?

Vemurafenib in melanoma

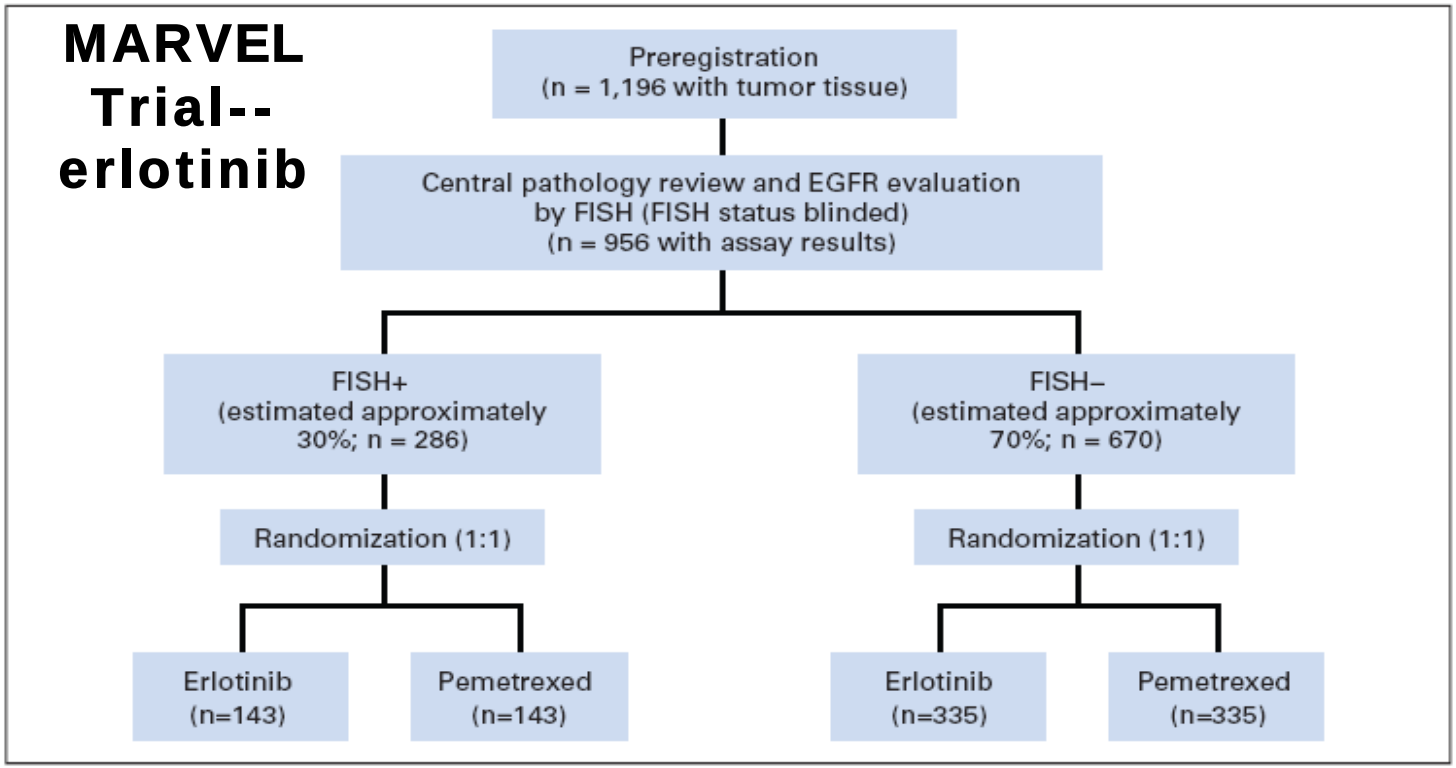


Number
Dacarba
Vemuraf

Kinase	Anticipated frequency in V600 mutation-positive melanoma [f]	Inhibitory Concentration 50 (nM)
$BRAF^{V600E}$	93.2%	10
$BRAF^{V600K}$	5.6%	7
$BRAF^{V600R}$	1%	9
$BRAF^{V600D}$	<0.1%	7
$BRAF^{V600G}$	<0.1%	8
$BRAF^{V600M}$	<0.1%	7
$BRAF^{V600A}$	0	14

BM+ or negative frequency is not such an issue

Marker by RX- Interaction Design



Answers limitations of unselected or enriched designs;
but impacts sample size and expense..

Science to Clinic workshop; London Oct 2012

Observations on Trial designs

- Predictive values need to be generated in populations that reflect anticipated clinical use.
- Enriched design often does not validate the marker (!) or define its utility in the broad population.

Safety markers and clinical trials

	Abacavir	*Carbemazepine*	*Warfarin*
Marker	HLA-B*5701	HLA B* 1502	CYP 450 SNPs+ VKORC1
Discovery	Retrospective	Retrospective	Retrospective
Confirmatory evidence	Prospective study	Retrospective Prospective study not feasible	Variable
Replication	Yes	Yes	ongoing
Validity	Clear evidence	Clear evidence of harm	Evidence of association Dosing alteration??
Utility	Clear	Clear	Contradictory

Population and predictive ability;
recent example

Gene/allele	p-value
DRB1*1501	6.8×10^{-25}
DQB1*0602	1.1×10^{-22}
DRB5*0101	1.6×10^{-20}
DQA1*0102	1.2×10^{-18}

- DRB1*1501-DQA1*0102-DQB1*0602-DRB5*0101 are part of a very well-characterized haplotype

its risks, particularly its risk of liver toxicity. The Committee was not convinced that screening patients for the DQA1*0102 gene variant sufficiently reduced this risk.

Population and predictive ability;
'Old' example

Populations	Genetic markers	Comments
Han Chinese and Thai	HLA-B*1502	If you carry this genetic marker, the risk for carbamazepine induced rare serious skin reaction known as Steven Johnson Syndrome, is increased.
European Caucasians and Japanese	HLA-A*3101	If you carry this genetic marker, the risk for carbamazepine induced delayed skin hypersensitivity reactions (mild or severe) may be increased.

Predictive ability in a particular population will be event/incidence dependent. Rarer the event, more difficult to establish evidence.

Retrospective data/analyses

- Often based on associations..
- Inability to replicate the results
  - Winner's Curse (first result is usually best)
  - often -overestimation of Effect size
  - underpowered FU studies (sample sizes)
  - Phenotype heterogeneity..
- Bias (various)

Caveats for Retrospective data analysis

- Ideally, data from well conducted RCT
- Biological sample or BM status availability from all or majority of the subjects (from RCT)
- Prospectively stated hypothesis & appropriate analysis plan
- Replication
- Biological plausibility &
- difference between BM+ vs BM- is clear

Experience at CHMP:

'A lot of post-hoc analyses' and
"Pharmacoepi-PGx" experience is limited

A Number of open questions

- When is a RCT mandatory?
- Is retrospective identification and validation BM acceptable?
- Are BM (-) patients be required in trials ?
- **Can we use Adaptive designs??**

Answers (May be !?)

- **Most of the time (almost everytime)**
- **Yes –depends on the circumstances.**
- **Clearly situation dependent**

Adaptive designs

On second thoughts.....

Ask Martin Posch !!

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Thank you