EMEA/EFPIA PGx in PK Workshop

Case 3: PGx Data Submission to Biomarker Scientific Advice

Task: What does the team do next?

Scenario 1

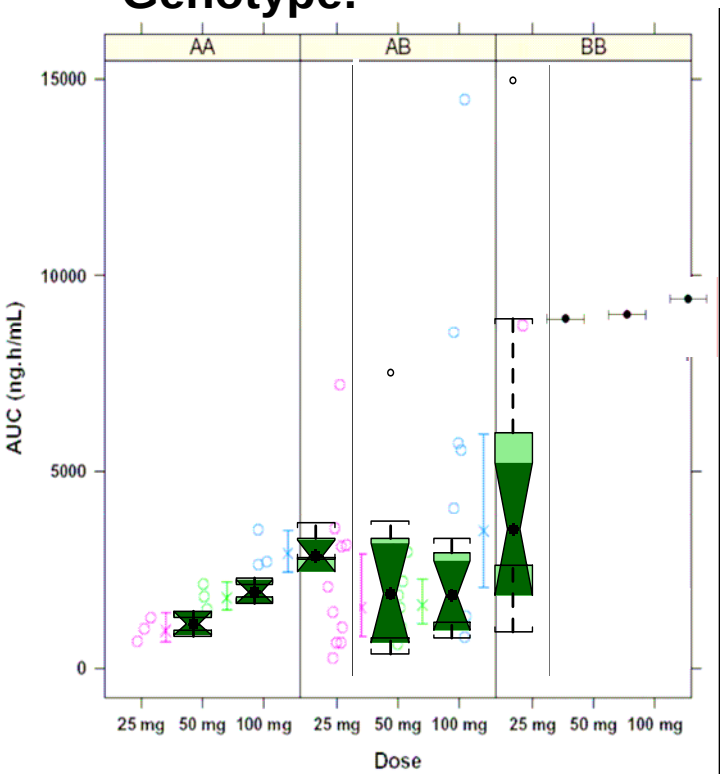
Hypothesis driven

Two Phase 1 studies available with PGx data

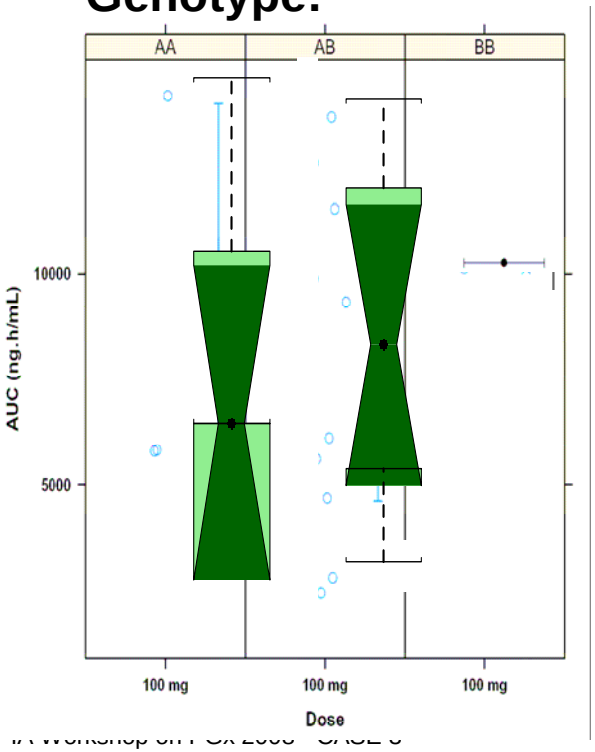
Genotyping:

- CYP2C8 pre-defined in the protocol, as there was preclinical evidence
- Gel-based assays for specific CYP2C8 alleles:
- All alleles (no selection for geographical selective alleles)
- Genotyping studies performed with Quality Management defined procedure

Genotype:



Genotype:



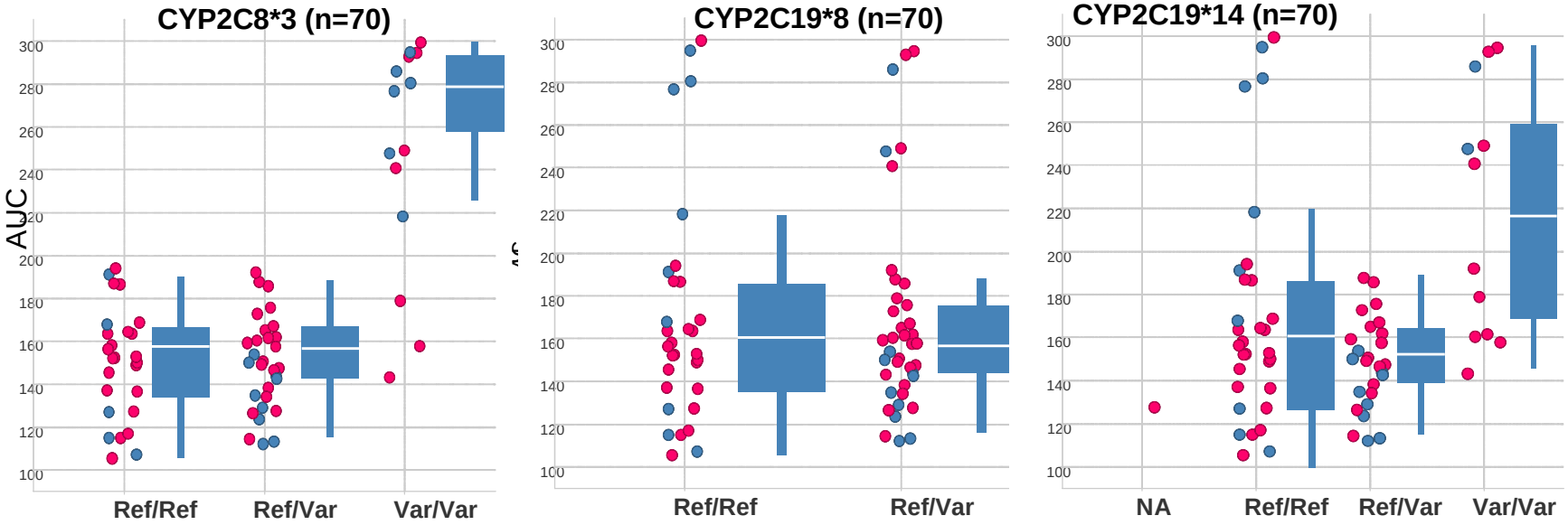
Scenario 2

Hypothesis driven / generation

Two Phase 1 studies available with PGx data

Genotyping:

- Several CYP450 genes genotyped, including CYP2C8 (as there was preclinical evidence)
- Commercially available assays used (internal research) – mixed platforms (TaqMan [red dots] and primer extension [blue dots] assays)
- All alleles (no selection for geographical selective alleles)
- Genotyping studies performed as exploratory research (without formal Quality Management defined procedure)



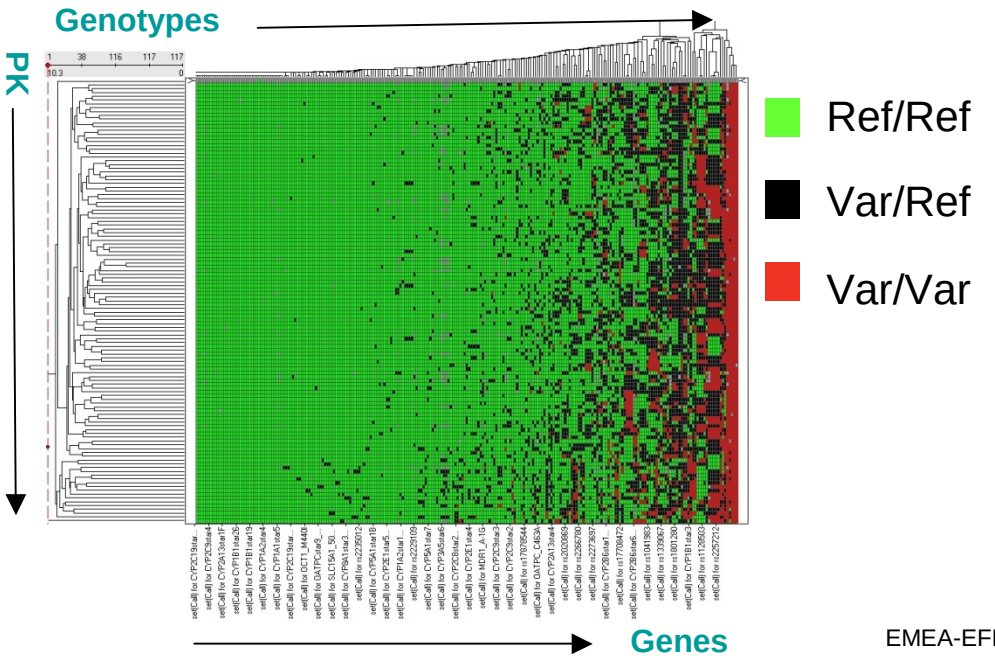
Scenario 3

Hypothesis generation

One Phase 2 study available with PGx data
(reason: explore PK and PD; test emerging technologies:DMET)

Genotyping:

- Affymetrix DMET chip
- Aim = Hypothesis generation
- Assays performed with Vendor
- Genotyping studies performed as exploratory research (without formal Quality Management defined procedure)
- Association with CYP2C8 and transporter gene



Chi-square test with Correction for multiple testing (Bonferroni)
Significance at P<=0.05

Gene name	haplotype	Ref/ Ref	Ref/Var	Var/ Var	G p-value*
CYP2C8	**CYP2C8star3**	**199**	**58**	**20**	**0.00004***
SLCO1B1	**OATPCstar10_A 1964G**	**187**	**63**	**25**	**0.0001***
CYP3A4	**CYP3A4star19_I VS10+12GA**	161	88	27	0.0007
CYP1A2	CYP1A2star1C	245	28	3	0.003
CYP2E1	rs2515641	179	76	22	0.003
FMO2	rs6671692	268	6	1	0.004
CYP3A43	rs800667	200	63	12	0.004
CYP2D6	CYP2D6star17_2 850CT	127	104	46	0.005
ABCB1	rs2032588	248	26	3	0.006
PTGIS	rs5626	271	5	0	0.007
CYP2D6	CYP2D6star17_1 023CT	254	14	8	0.007
CYP2A13	CYP2A13star1H_ 6432CT	224	46	7	0.007

Scenario 4 **Combined data from different studies**

Multiple clinical studies with PGx data available

Genotyping:

- CYP2C8 data available from **2 phase I** studies (QM-defined procedure) **(Scenario 1)**
- Data from **2 phase I** studies (exploratory research) **(Scenario 2)**
- Data from **1 phase II** study (ADME chip) **(Scenario 3)**
- Aim = Hypothesis driven (CYP2C8 + transporter) => Analysis / reporting with focus on CYP2C8 / transporter data only (pooling of PGx data in order to increase power)
- Assays performed on different platforms (See previous scenarios)

Scenario 1 : studies 1	(n=30) and 2 (n=38)	N=416
Scenario 2 : studies 3	(n=50) and 4 (n=20)	
Scenario 3 : study 5	(n=278)	

What were the issues for the Team?

Team Task:

1. What is reported for clinical analysis?
2. What is standard and format for team submission to EMEA Biomarker Scientific Advice?

- Expansion of haplotypes in different populations
- Predicted Phenotype (metaboliser genotype status)

- Scientist on team wanted Raw SNP data, allele, genotypes,
- Clinical pharmacologist only wanted predicted phenotype (no alleles)

Team Output on Data Submission to EMEA Scientific Advice

WHAT is reported ?

What is reported > **Dataset:**	Do not report	Report individual study results of QA-controlled studies only	Report only individual study results (of all studies)	Report meta-analysis results	Other (eg scientific publication)
Data from QA-controlled GT study (Scenario 1 hypothesis driven)	13				
Data from exploratory study (Scenario 2 hypothesis driven / generation)	13				
Data from exploratory studies (Scenario 3 Affy chip; hypothesis generation)					13 Go for briefing
Combined data from QA-controlled and exploratory studies (Scenario 4)			No meta-analysis (3 is sufficiently powered on ist own) Only scenarios 1 and 3 are reported		

Team Output on Data Submission to EMEA Scientific Advice

HOW are data reported ?

Meta analysis

How is reported> **Dataset:**	Do not report	Report as Genotyping Data	Report as predicted phenotype (EM, PM)	Weighted contribution of individual studies	Perform / include multiple testing correction
Data from QA-controlled GT study (Scenario 1 hypothesis driven)					
Data from exploratory study (Scenario 2 hypothesis driven / generation)					
Data from exploratory studies (Scenario 3 Affy chip; hypothesis generation)		Yes Individual SNP data and alleles in context of PK (All summary data)			
Combined data from QA-controlled and exploratory studies (Scenario 4)		Yes Individual SNP data and alleles in context of PK (All summary data) retorpective analysis for transporter in 1.			

conclusions

- Scenario 1: trend towards association, not signifcant, too premature to make a decision, but assays performed under QA procedure
- Scenario 2: QA issue with assays, no conficence in data
- Scenario 3: Well powered study which needs replication (can be done retrospectively) No Metanalysis required, no QA, still confident?
- Standards may be needed with regard to quality of technical platforms and performance
- Scenario 4: No meta-analysis required but report data from 1 and 3, because 3 was an independent replication of scenario 1.

- Overall conclusion : pre-clinical data is insuffiecient to define a complete hypothesis (multiple pathways with escape routes).
- As the story emerges from the different types of studies, confidence on assays became key, also with regard to share data with EMEA
- Scenario's nevertheless gave a tendency towards CYP2C8 which was consistent despite quality issues.

Items that are under GCP

As per other established clinical lab practices, no need to describe:

- Blood Collection
- Blood Storage pending DNA use
- Shipping
- DNA Extraction
- DNA storage
- DNA qualification as indicated

Not part of submission

- Specimen collection most likely blood but sometimes other specimens (buccal swab, sputum, etc…) are collected
- Specimen storage
- Specimen shipment
- DNA extraction from specimen
- DNA dilution
- DNA storage
- Genotyping using a specific method / assay
- Genotype calling
- Reporting of genotypes

Team consults….

- Is there a Standard rating procedure to increase confidence towards confirming genomic biomarker?
- SNP nomenclature, NCBI (or not)
- (We'll need to invite SDO expert on this case to share their learnings… eg Standards Development Organizations (SDOs) such as ISO, CEN, HL7, and CDISC)