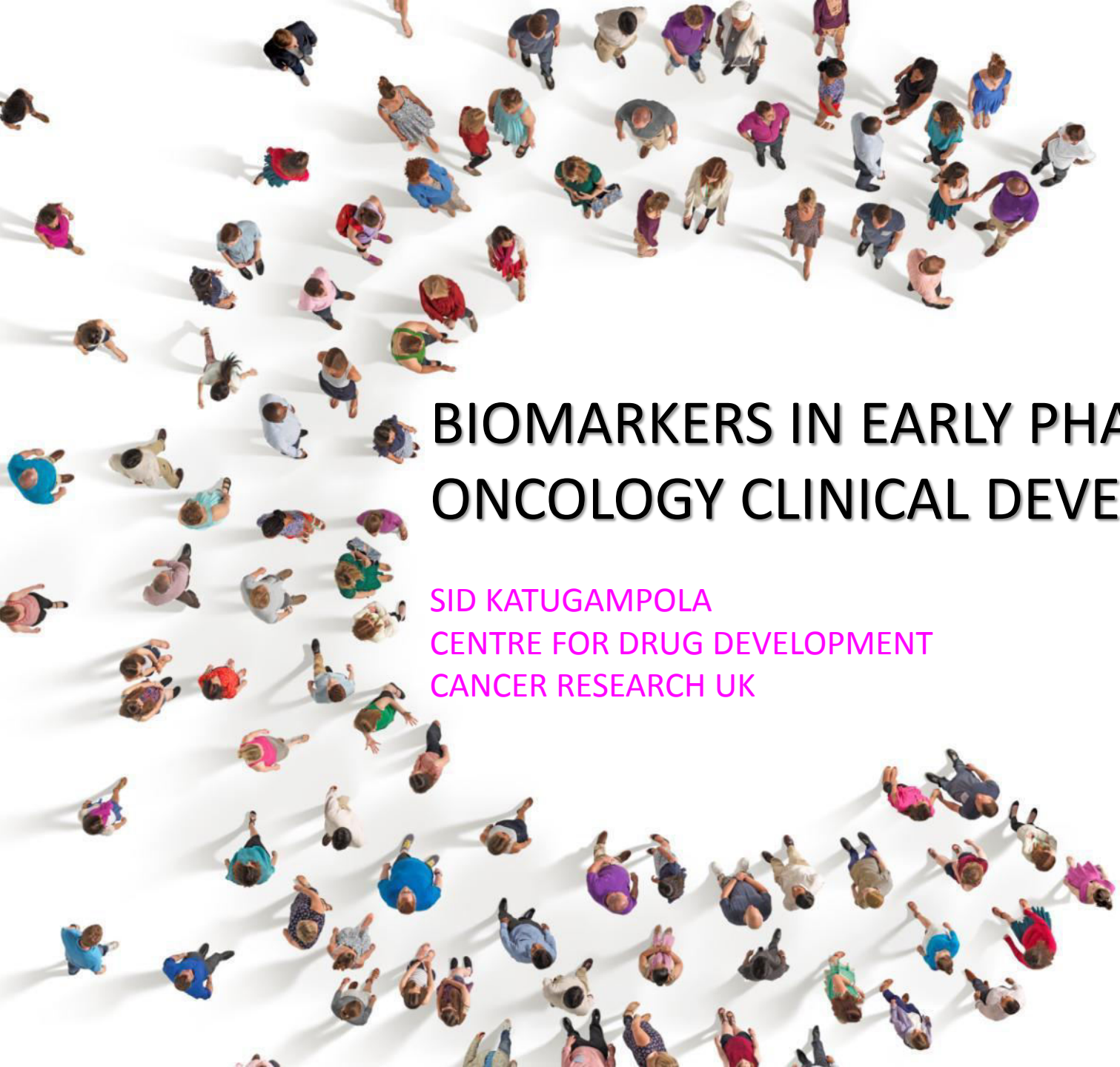
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BIOMARKERS IN EARLY PHASE ONCOLOGY CLINICAL DEVELOPMENT

SID KATUGAMPOLA
CENTRE FOR DRUG DEVELOPMENT
CANCER RESEARCH UK

Cancer; Some Sobering Thoughts

- Getting cancer is one of our greatest fears.
- Over 300,000 new cases of cancer are diagnosed every year in the UK.
- Someone in the UK is diagnosed with cancer every 2 minutes.
- 1 in 2 of people in the UK will develop cancer.
- It is predicted that the global incidence of cancer will double over the next 20 years.
- A disease that kills when metastasised and where **new treatments are desperately needed**

So what is Cancer Research UK doing to provide new treatments ?

Centre for Drug Development (CDD)

- Based in London.
- Manages preclinical development and sponsors phase I and II trials of new anticancer agents (currently~ 30 active projects) .
    - agents in multiple tumor types, including on CRUK priority areas (Pancreatic, Lung, Brain, Oesophageal)
    - Small molecule therapeutics, antibodies, cell therapies, gene therapies, imaging agents.
    - Global partnerships with academia and industry
- Development function established in 1982.

Over 100 compounds taken into early phase trials and 6 agents have reached the market – eg. Temodar (Temozolomide) & Zytiga (Abiraterone)

So what is the focus of CDD ?

- Develop novel agents where expertise and /or resources to support further development are lacking.

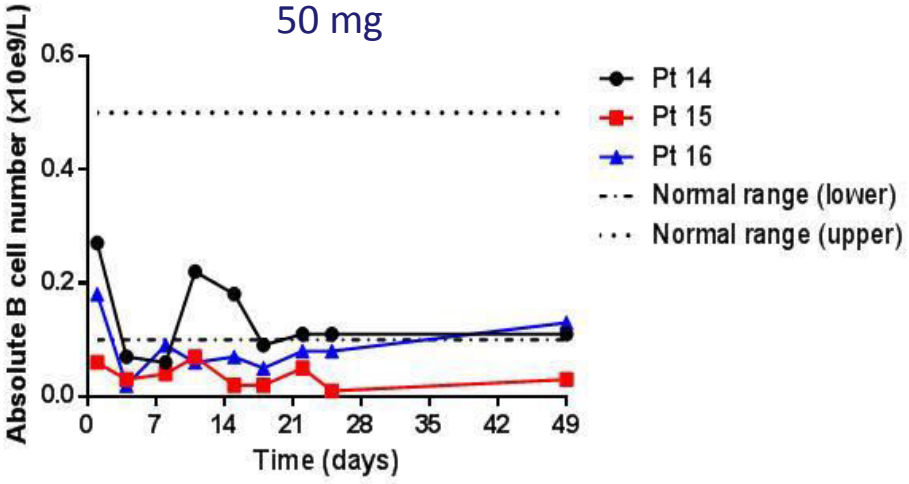
COMPANY	DRUG	KEY CRUK ACTIVITIES
Immatics Biotechnologies	IMA950 Multipeptide vaccine	FIH clinical trial
GSK	GSK1070916A Small molecule Aurora Kinase B/C inhibitor	FIH clinical trial
AstraZeneca	AZD3965 Small molecule MCT-1 inhibitor	FIH clinical trial

- 'Sweet-spot' around translation from preclinical to FIH
- First in class agents – highly desirable
- Focus on **biomarkers**

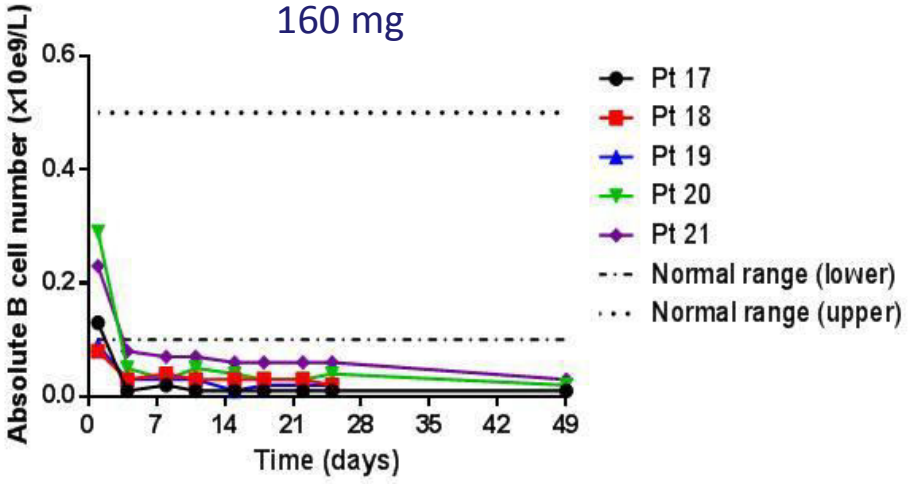
CASE STUDY 1: Chi Lob 7/4

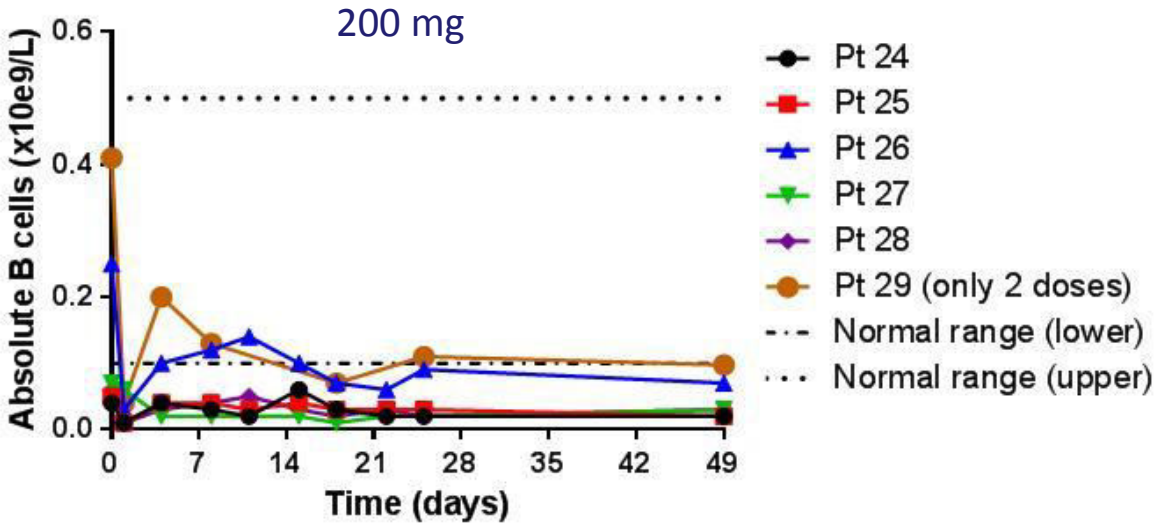
- CD40 is expressed on B cells, monocytes and tumours
- Anti-CD40 agonist antibodies – stimulate the immune system to induce anti-tumour T cell responses in patients
- Dose escalation in 28 patients dose levels of 0.5, 1.6, 5, 16, 50, 160, 240 mg
- Aim – to establish safety, tolerability, PK, HACA, PD, RP2D

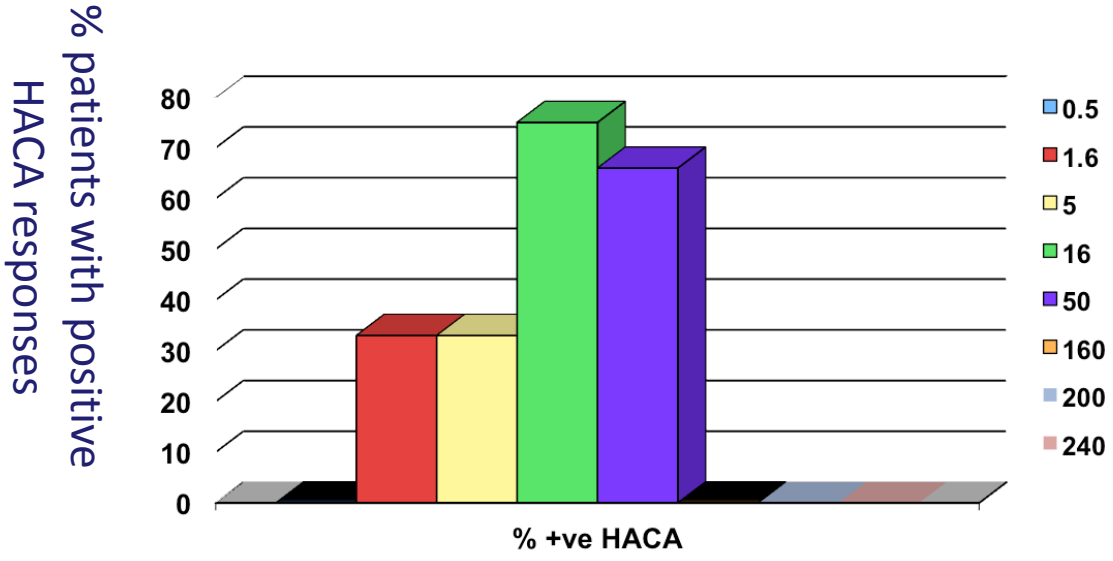
50 mg



160 mg





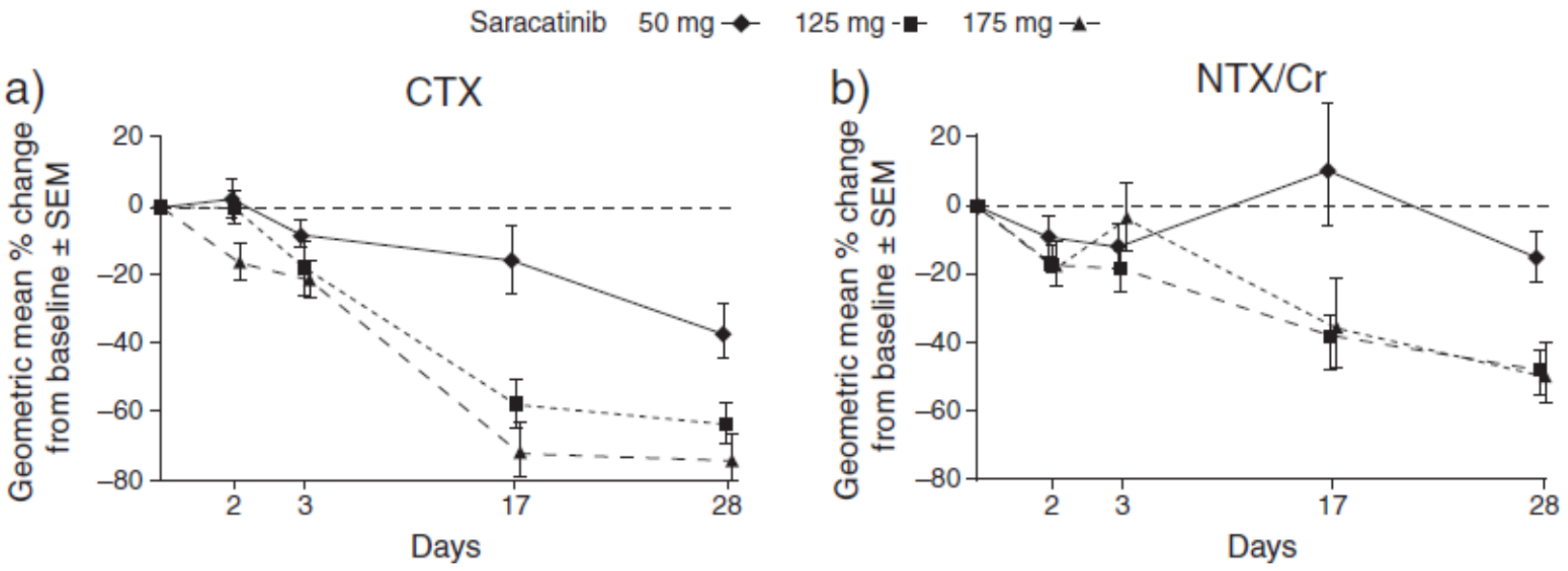


- Well tolerated
- Significant decrease in B cell (particularly at doses > 160 mg) with increase in doses
- NK, monocyte activation and IL-12 production occur above 160 mg
- HACA response lost at higher doses due to B cell depletion

Presented at flow cytometry UK 2013

CASE STUDY 2: Saracatanib (AZD0530)

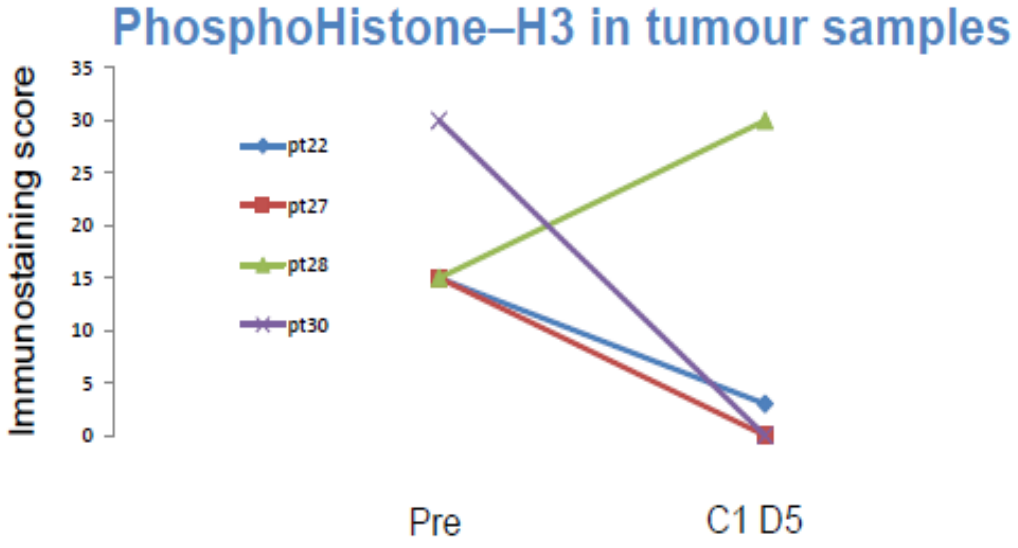
- Saracatanib is a Src kinase inhibitor
- In a phase 1 study of solid tumours 50, 125 or 175 mg doses
- Serum CTX and urinary NTX/creatinine ratio measured
- Inhibition of osteoclast activity used to define dose and time point to progress



Hannon et al., 2012

CASE STUDY 3: GSK1070916A

- GSK1070916A is a potent selective inhibitor of Aurora kinase B and C
- Phase I (37 patients in total, 24 at MTD) study in collaboration with GSK as part of the CDP programme
- Patients with advanced/metastatic solid cancers
- GSK1070916A (1 hour IV infusion for 5 days every 21 days).
- The primary objectives were to determine the safety profile, DLT and MTD.
- Cycle 1 blood and healthy skin biopsies were obtained for PK and PD assays (M30 and M65)
- The expanded cohort included 6 pts having paired tumour biopsies for PD studies using immunohistochemistry.



- Limited evidence of clinical activity
- No effect on circulating M30 or M65
- No PD modulation in skin
- No correlation between PD modulation and clinical outcome
  - is it the right patient group ?
  - was the right dose/scheduling selected ?
  - more objective/quantitative end points ?

Presented at ASCO 2013

Tool box for measuring PD in early phase oncology

- Tumour markers
  - Histology based – Immunohistochemistry
  - Genetic – miRNA, NGS, nanostring
  - Proteomic – LCMS, NMR
  - Metabolomic – LCMS, NMR
  - Imaging – CT, MRI, PET
- Surrogate markers
  - Flow cytometry – cell surface markers, target occupancy
  - Circulating tumour associated – CTC, ctDNA, CEC, CEPC
  - Circulating markers – cytokines, growth factors, hormones
  - Immune cell phenotype and functionality
  - Skin biopsies/ hair follicles

Limitations and challenges in the real world

- Currently, little evidence to correlate PD biomarker effect with clinical outcome.
- How long, to what degree, in what tissue do you need to see PD
- Often challenging to obtain repeat biopsies. Therefore tumour PD markers not dynamic. Correlation between tumour and blood borne markers – not there yet.
- For first in class agents – likely that your POM assay will be tested for the first time in the clinic. High risk of failure
- It will take time to have a good biomarker ready to be used in the clinic. Often this needs to start in parallel to identifying a new drug. Need investment in time, cost and resource
- Resistance and tumour heterogeneity associated with targeted therapies

Take home messages

- Biomarkers are key to the success of early phase oncology trials and help minimise phase II attrition
- Be clear on what markers you want to use for a particular trial design, during which part of your trial and the expectation of the assay
- It is challenging to discover, develop and have a robust clinical assay, particularly for FIC agents. However, without such a pharmacodynamic assay, minimising phase 2 attrition remains a significantly bigger hurdle to overcome

Thank You & Questions?

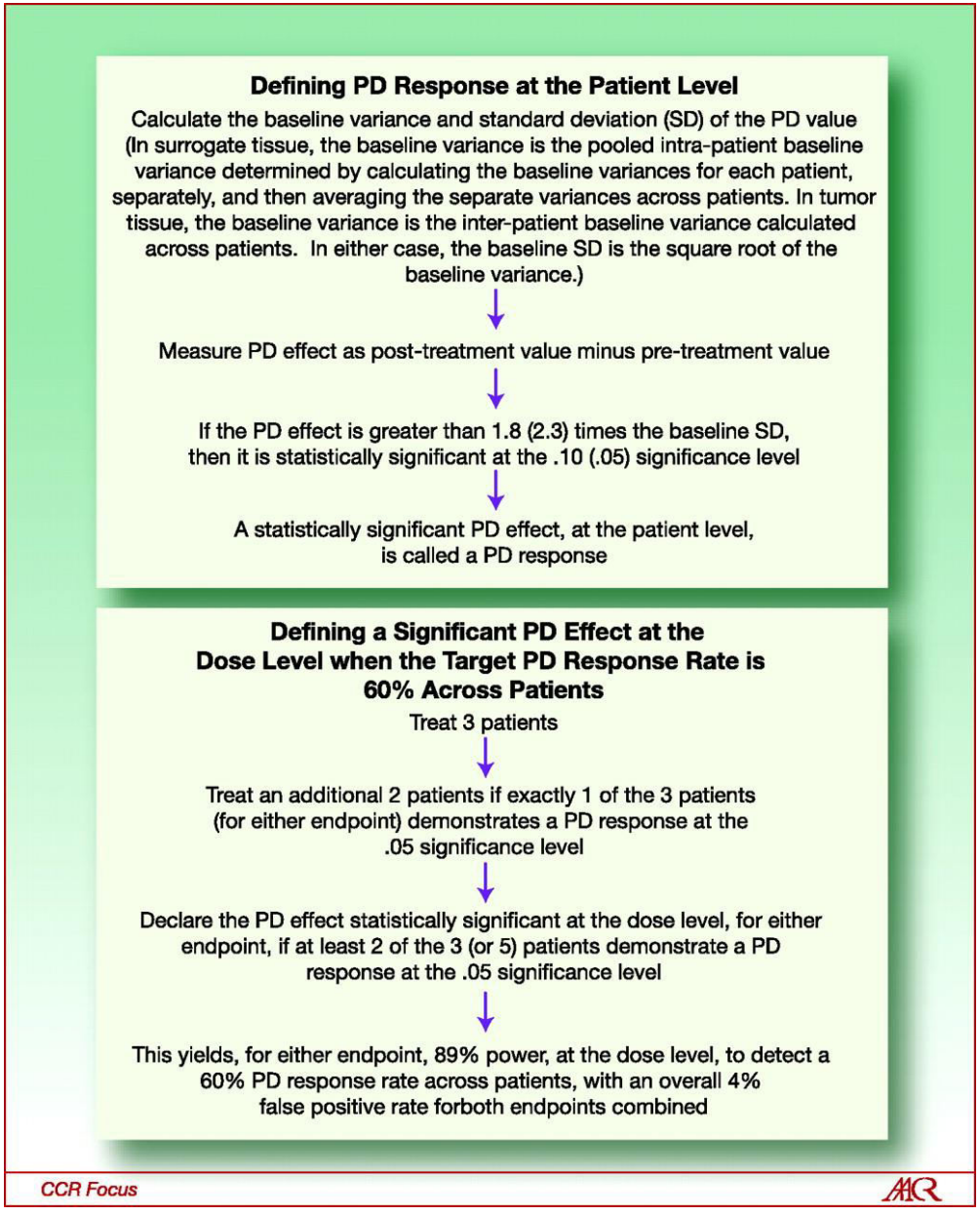
Sidath Katugampola
Centre for Drug Development
Cancer Research UK
0203 469 6876

Sidath.Katugampola@cancer.org.uk

BACK-UP

From hypothesis to validated clinical assay

Description	Aim	What will it measure	End result
Hypothesis testing and discovering assay	Optimisation and characterisation of assay	Have we got an assay that can measure a response	Assay to take forward to next stage
Further optimisation of assay	To get best signal:noise	Is there a workable assay with a good window	Assay to take forward for validation
Pre-study validation	Determine assay performance characteristics	Is the assay fit-for-purpose to be used in a clinical trial	Validated assay with an SOP ready to be used in a clinical trial
Use assay in clinical trial	To deliver trial end points	Confidence in robustness of assay	Data to support trial and knowledge on future direction of assay



S. Percy Ivy et al. Clin Cancer Res 2010;16:1726-1736

What makes a good biomarker – (4S's)

1. **Science**

   - is there a "scientifically relevant" biomarker we can use. For FIC agents, translation of the biomarker to the clinic will be risky. Need to understand deep biology

2. **Suitability**

   - Pre-study assessment of sensitivity, specificity, magnitude of effect and reproducibility are essential to understand the underlying "noise" of the assay. Include patient material where relevant

3. **Study design**

   - statistics ? when do we take samples ? Escalation or expansion or both, Use preclinical PKPD as a guide.

4. **Sample**

   - how much sample do you need ? Stability ? How quickly does it need analysing ? Freeze thaw? Shipping conditions etc

Team Biomarkers welcomes you all to the next chapter – 7th International Conference on Biomarkers & Clinical Research scheduled for Nov 28-30, 2016 in Baltimore, USA

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