CLINICAL DEVELOPMENT OF A PROTOCOL

CLINICAL DEVELOPMENT OF A PROTOCOL

Where do we start?

- ***Pre NAC application***
  - Applicants supported by a pre-clinical project manager;
  - Review of an ‘office note’ by relevant teams.

- ***Post NAC application***
  - Wider CDD team convened;
  - Trial enters ‘Due Diligence’;
  - Key objectives set.

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What is Due Diligence?

- An opportunity to see how the application can be brought into the clinic.

What obstacles could there?:

- No toxicology, no formulated IMP; no clear PD markers.

So why are these things important?

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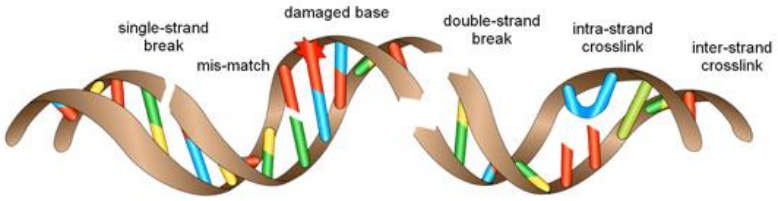
TOXICOLOGY STUDIES

Toxicology Studies



Does it damage DNA?

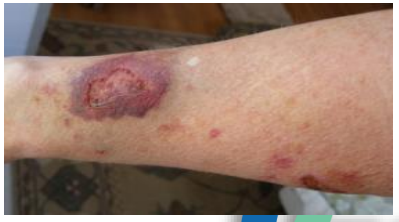
- Genotox & carcinogenicity

Does it damage animals?

- Single or Repeat Dose Toxicity

Does it damage reproduction?

- Repro and Development Toxicity



Does it damage where it is applied?

- Local Tolerance

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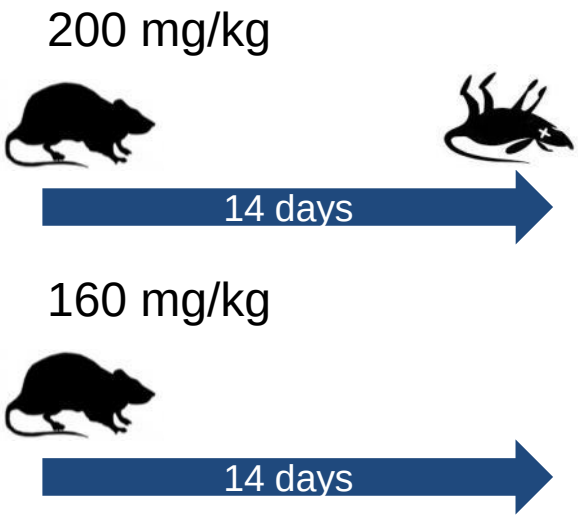
So what do we do?

Step 1:- Dose escalation to MTD

Step 2:- Escalation and increased duration



Take 160 mg/kg through to pivotal study

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Pivotal GLP study

Control

28 days dosing → 14 days off drug

40 mg/kg

28 days dosing

120 mg/kg

28 days dosing

160 mg/kg

28 days dosing → 14 days off drug

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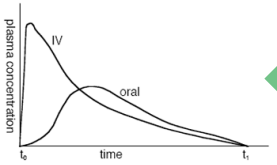
Endpoints

Ophthalmoscopy

Haematology

Urinalysis

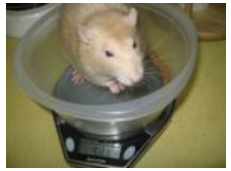
Toxicokinetics



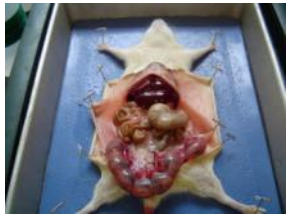
Food Consumption

Clinical chemistry

Body weight

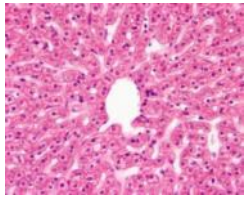


Necropsy



Behaviour

Histology



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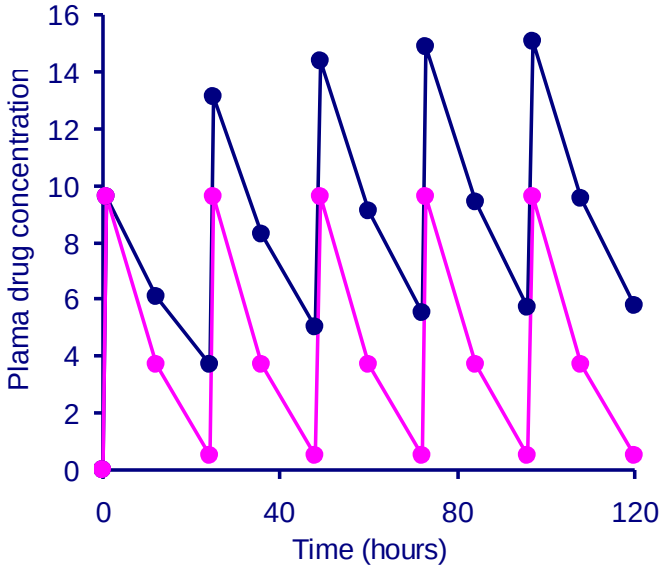
Toxicokinetics

- Toxicology based on exposure not dose or Cmax



Toxicity studies need TK:-

- To relate dose to toxicity
- To relate dose to exposure
- To understand dose proportionality
- To understand accumulation

What do we get from toxicology?

- What can we use to inform the clinical trial?
  - Estimate of therapeutic window;
  - Some basis for a starting dose;
  - An idea of the sensitive tissues and organs;
  - Know if the drug is likely to accumulate;
  - Whether dose is proportional to exposure.
- Much more safety data than a Phase 1 trial
- BUT how relevant is that information?

Species choice








- For cytotoxics, species does not matter much - so choose well characterised species
- More targeted – more problematic

Species choice

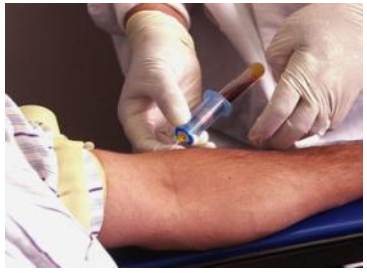
For a targeted small molecules:

- Presence or similarity of target
- Any difference in metabolism
- Well characterised species




For a biological – relevance, relevance, relevance





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PHARMACOLOGY
&
TOXICOLOGY

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Pharmacology vs Toxicology

Safety assessment involves both of the above

Primary/wanted Pharmacology

Secondary/unwanted Pharmacology

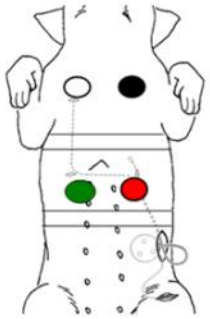
Toxicological effects

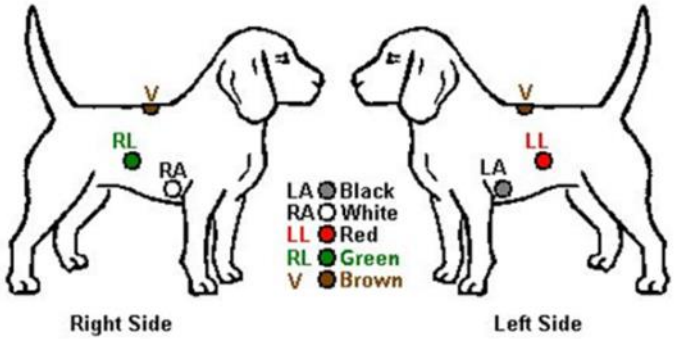
Safety Pharmacology

What target systems are evaluated ?

- **Cardiovascular**
- Respiratory
- CNS
- Renal
- GI system
- Immune system

Most drugs – Dog telemetered CV study





Cancer, stand-alone studies not required

But…?

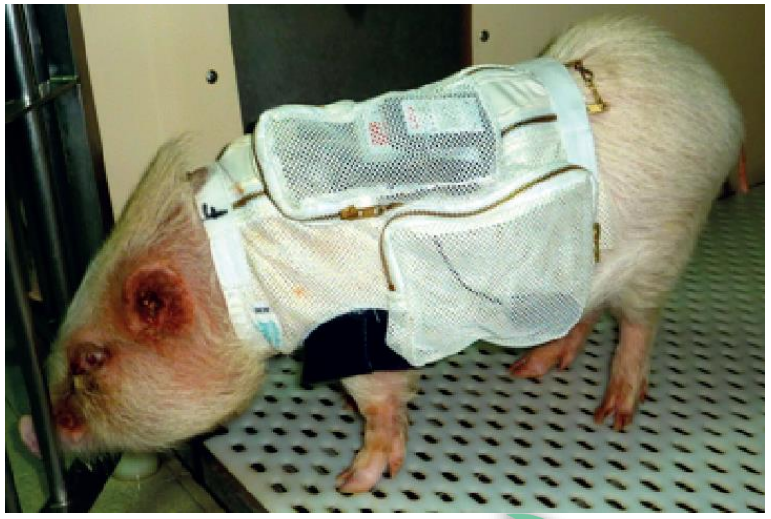
We might do…

Stand alone safety pharmacology

- Uses extra animals
- **Expensive**
- Generally only one dose

So bolt it onto a toxicity study

- Reduces animal use
- Fits in with Tox study
- Plus you get a pig in a waistcoat



Using the preclinical data clinically

Set starting dose based on:

- Doses where nothing bad happens (NOAEL)
- Maximum tolerated dose (MTD)
- Primary pharmacology (MABEL)
- Predicted PK modelling (doesn't work)

Inform dose escalation:

- How rapidly to dose escalate
- What doses (or plasma conc.) might efficacy and toxicity occur
- What might foreshadow toxicity

Inform risk mitigation:

- Extra safety endpoints (CV monitoring etc.)
- Risk mitigation plans (cytokine release etc.)

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Key points on preclinical safety

We perform safety studies to inform clinical trials

- Dose and schedule;
- **Endpoints;**
- Risk mitigations.

Species choice is key

- Does the drug behave as expected in human;
- Is the response to the drug relevant to human;
- More targeted the agent – bigger the headache.

Address both toxicology and pharmacology

- **Cardiovascular safety biggest concern;**
- **Do we need to address?**
- **Can we build into our tox studies?**

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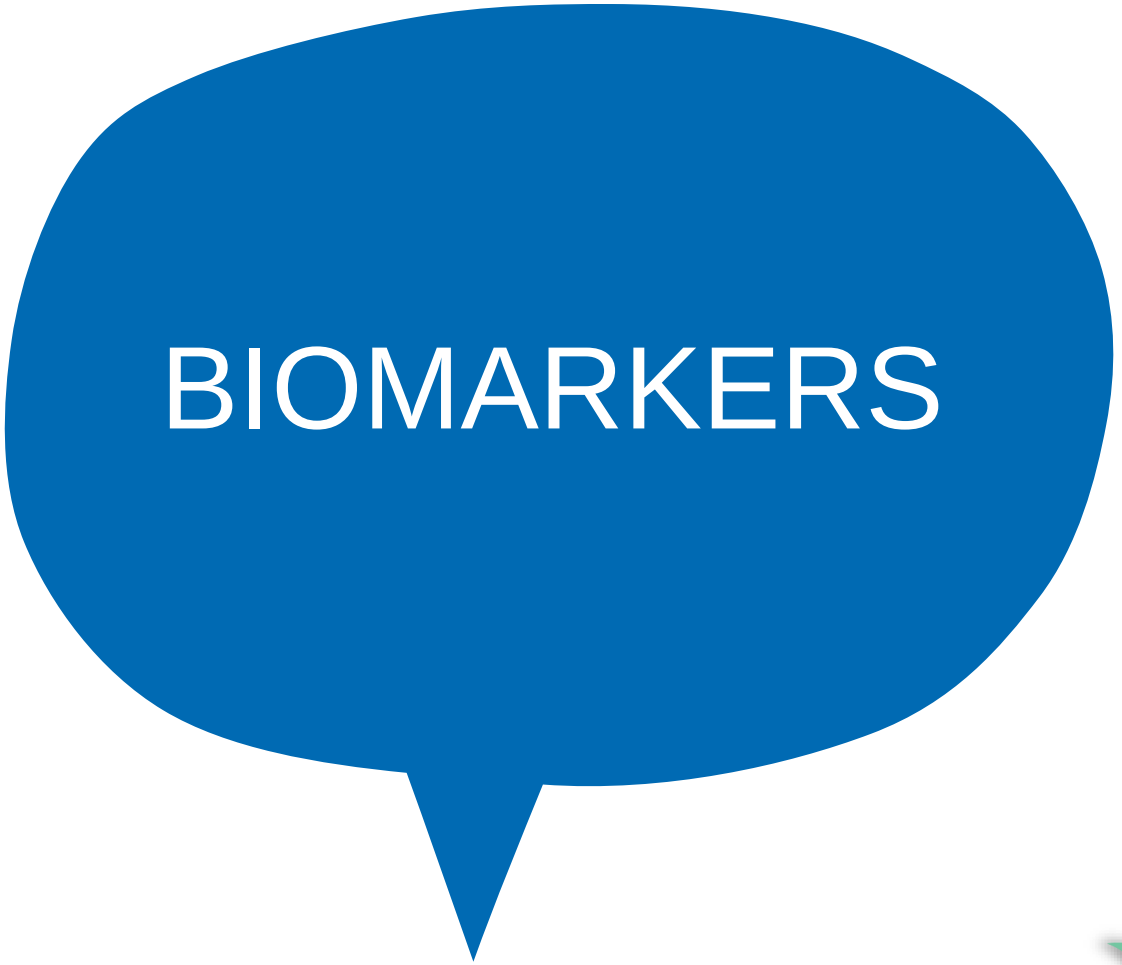


Biomarkers in oncology drug development

"*A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*"

(FDA definition)

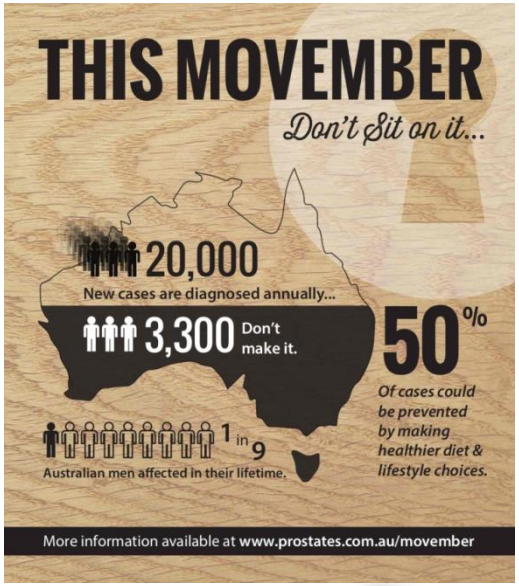
Examples of some well known biomarkers in current clinical practice

Body Temperature

Blood cholesterol

Blood pressure

beta sub unit of human chorionic gonadotropin (HCG) hormone



PSA

Biomarkers in oncology drug development

- Pharmacodynamic;
- Predictive – is this the optimal drug for the specific cancer?
- Prognostic – can we monitor a cancer's progression?
- Safety – does the drug cause any other adverse events to non-tumour targets?
- Early detection/screening biomarkers – how can we detect cancer early?

Right dose
Right schedule
Right patient

Terminology for PD biomarkers

1. Proof of mechanism (PoM): describes evidence of pharmacology.

Key questions to ask: does the compound bind to the target?

does the compound alter a signalling pathway ?

2. Proof of principle (PoP): describes a biological change associated with the disease and mechanism of action.

3. Proof of clinical concept: drug results in a clinical change on an accepted end point in patients with the disease. *e.g. Overall survival, PFS*

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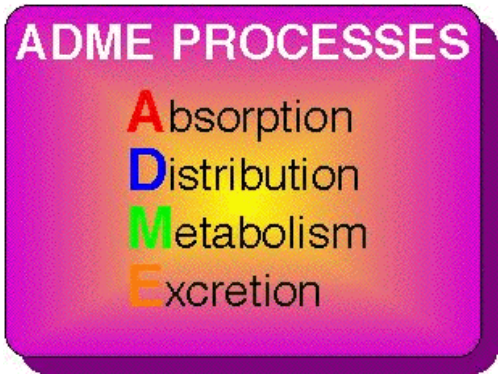
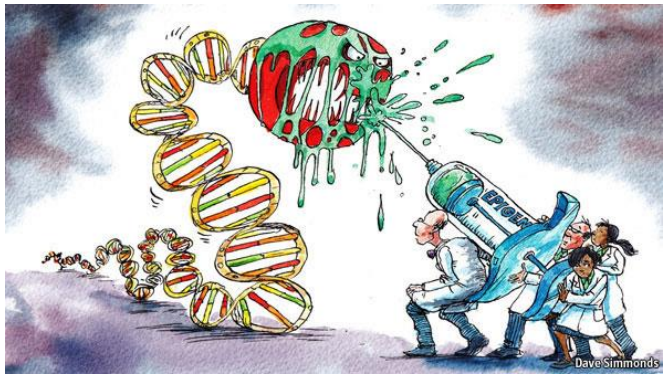
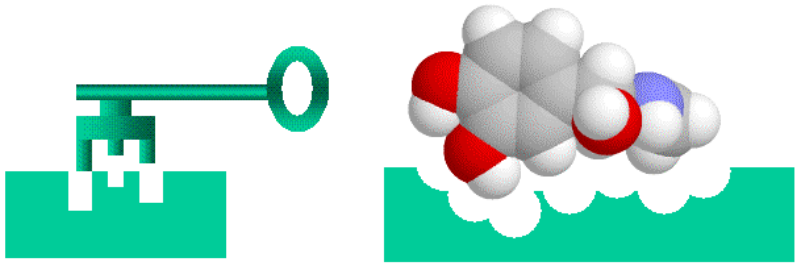
Ideal PD strategy



Plasma PK



Exposure in tumour



Proof of mechanism

Proof of principle – Inhibit proliferation ?

Proof of clinical Concept – increase In survival ?

Enrichment/ personalised

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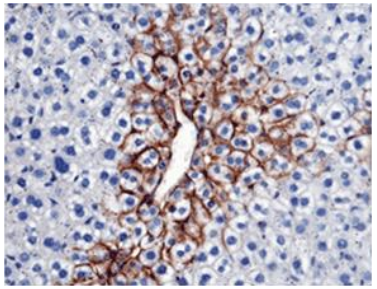
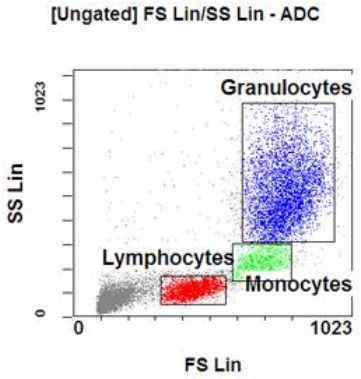
Biomarkers – why bother ?

- For dose/exposure/duration/schedule selection
- Go/ No-go decisions on projects
- Portfolio prioritisation
- For the patient to get the best chance of response
- Scientifically based decisions
- Indicating or predicting toxicity

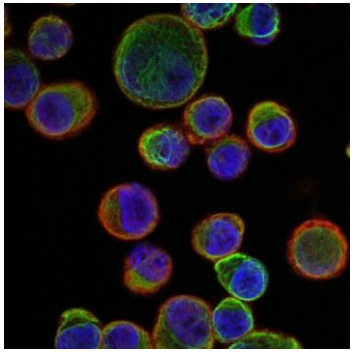
Assays and technologies to measure PD



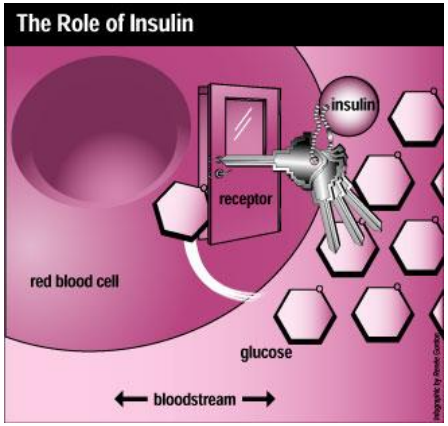
histology



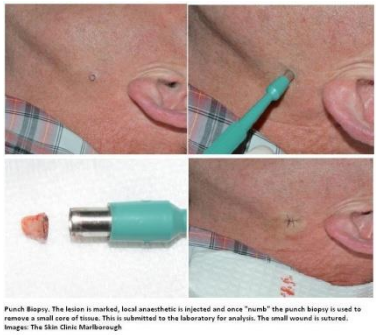
FACS/flow cytometry



Circulating cells - CTC

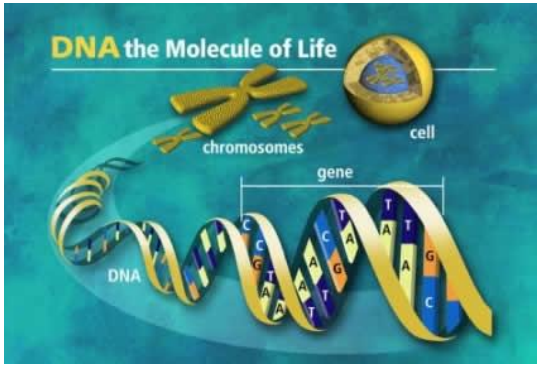


Circulating hormones/cytokines

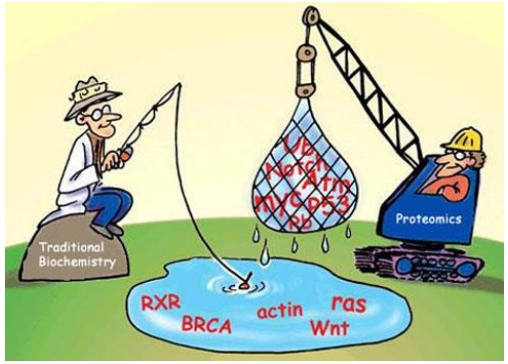


Skin punch biopsy

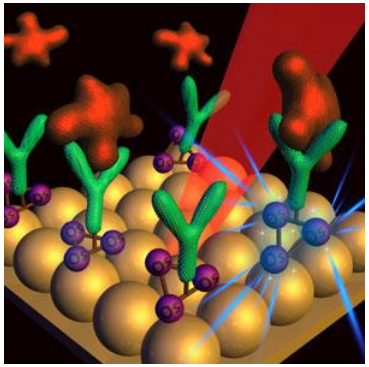
Hair follicle



Gene expression



Proteomic



Novel be-spoke assays/ others

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4S's - What makes a good biomarker

1. ***Science***

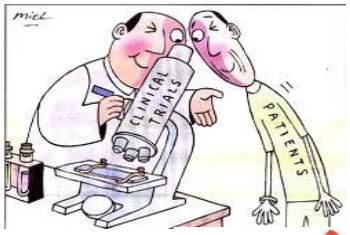
   Is there a "scientifically relevant" biomarker we can use. Need to understand deep biology

2. **Suitability**

   Pre-study assessment of sensitivity, specificity, magnitude of effect, reproducibility underlying "noise" of the assay

3. **Study design**

   When do we take samples ? How much ? Stats ?



4. **Sample**

   "What you get out of it, depend on how you collect the sample" *How much sample do you need ? Stability ? How quickly does it need analysing ? Freeze thaw? Shipping conditions etc.*

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Biomarker limitations

- **Currently:**
  - little evidence to correlate PD biomarker effect with clinical outcome;
  - Methodological limitations;
  - Often challenging to obtain repeat biopsies;
  - For FIC agents – your POM assay will be tested for the first time in the clinic;
  - Typically it will take more than 2 years to move a biomarker from hypothesis to fit-for-purpose validation prior to clinical use.

Tumour vs surrogate tissue

Tumour	Surrogate
Target site	Allows for rapid assessment of proof of mechanism for targeted therapies in dose escalation studies
Invasive	Amenable to repeated sampling, allows temporal dynamic monitoring of PD effect
Limited opportunity for repeat sampling – “one shot at goal”	Allows for PKPD and extrapolation from animal data
	Absence of associated molecular pathology
	Difference in drug concentrations between tumour and surrogate ?
	Emerging technology/assays that needs to be validated and tested appropriately
	Inability to always link changes in markers to clinical response

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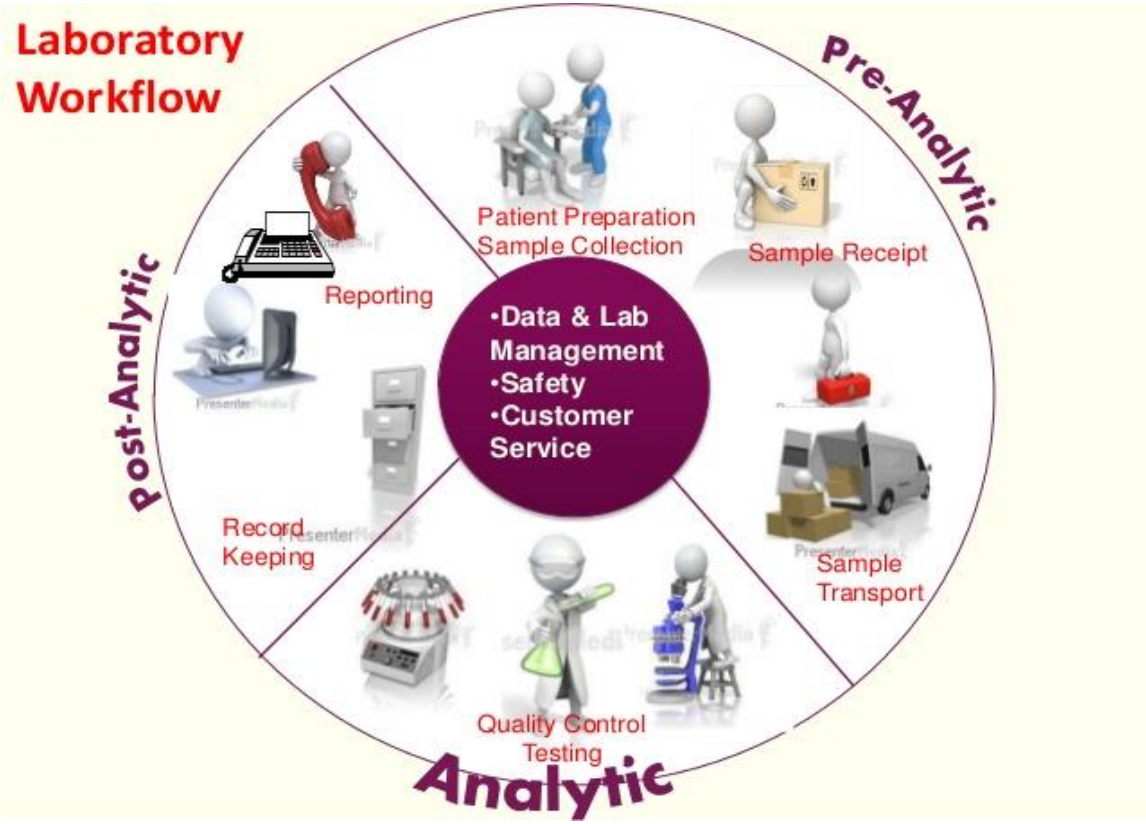
Quality is paramount

- Evidence of documentation, quality manual, validation reports, training records, equipment logs, SOPs, computer software, CVs, JD, staff GCP training



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Challenges

- Does the original application provide supporting data for PoM, PoP and PoC data and how robust & reproducible is the data?
- Seek earliest opportunity to embark on a selected hypothesis driven approach to biomarker ID – this will take time and may never get there!
- Prioritise list of biomarkers;
- Cost of assays? Value for money vs working collaboratively vs investigators favourite technology of the month!
- Agreements/SUAs.

CLINICAL DEVELOPMENT OF A PROTOCOL

Take home messages

- For novel targets, cast your net wide then triage to the most “robust” marker;
- Conduct detailed and critical evaluation of all data available immediately post NAC to identify gaps, concerns and challenges.
- For targeted therapies proof of mechanism/principle/concept markers are key
- As a minimum, for all studies, need to show PoM;
- Consider how stratification/selection markers can be included;
- Consider how surrogate end point assays can complement biopsy read outs;
- Be clear on the expectations of the assay and its purpose - Remember “fit for purpose” validation;
- Don’t forget sample collection, processing, storage, logistics and GCLP.

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CLINICAL DEVELOPMENT OF A PROTOCOL

Drug Supply & Formulation

- Active Pharmaceutical Ingredient (API)
  - The active molecule in the drug
- Investigational Medicinal Product (IMP)
  - The material given to patients
- Small Molecules
  - Something less than 10000 g in molecular weight
- Biologicals
  - Generally administered by injection, usually IV

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Drug Supply & Formulation (2)

- Antibodies
  - Made from a mammalian cell line by fermentation in a similar way to beer;
  - The protein needs to be isolated from the cellular matter and fed material, purified, concentrated and formulated into a stable medium to allow aseptic filtration into product vials;
  - This is almost a continuous process from the fermentation of the cells through to the bulk drug substance and then filling into vials;
  - Biggest challenges are keeping a larger process sterile and free from contamination by virus, mycoplasma etc. and not really know what is in your product in addition to the protein.

All work has to be in compliance with EU GMP (Dir 2003/94/EC) and the final product to be administered to the patient has to be certified and released for use by a Qualified Person.

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API

- To start with usually only a few grams at most available
- Scaling up
  - assessment based on experience
  - Oral: for small molecules to support a clinical trial you would need about 2.4kg (@1000 x starting amount)
  - Intravenous: usually made on a much small scale i.e. <500 g and the formulation needs to have sufficient aqueous solubility and be sufficiently stable to undergo sterilisation via filtration (0.2 micron filter) or by autoclave and then stored as liquid or lyophilised products.
- Work with a CRO for chemical development work
  - make the chemistry safe;
  - larger up scales;
  - reproducibility;
  - purity;
  - analytical methods to monitor the API and IMP.

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IMP

- **Bioavailability**
  - test the solubility of the drug to determine if it is likely to be 'bioavailable' (the degree to which a drug or other substance becomes available to the target tissue after administration);
  - if we need to add materials (called excipients) to the active molecule to aid it's dissolution in the body, without which it will not have any biological effect.

- **Manufacture**
  - perform a test run to check reproducibility;
  - manufacture final IMP (capsules; powder/vials; vaccines) to ensure reproducibility, and suitable purity to give to patients.

- **Storage and stability**
  - develop analytical methods to monitor the purity and stability of the formulated drug;
  - carry out stability studies to determine the storage conditions under which the drug is stable;
  - determine the shelf life so it does not degrade and produce any potentially harmful by-products;
  - package and label in accordance with the regulations (Eudralex Volume 4: Annexe 13 'Investigational Medicinal Products' of the EU Guide to Good Manufacturing Practice) and distribute to clinical sites where the pharmacy then dispenses to patients in line with the clinical trial protocol.

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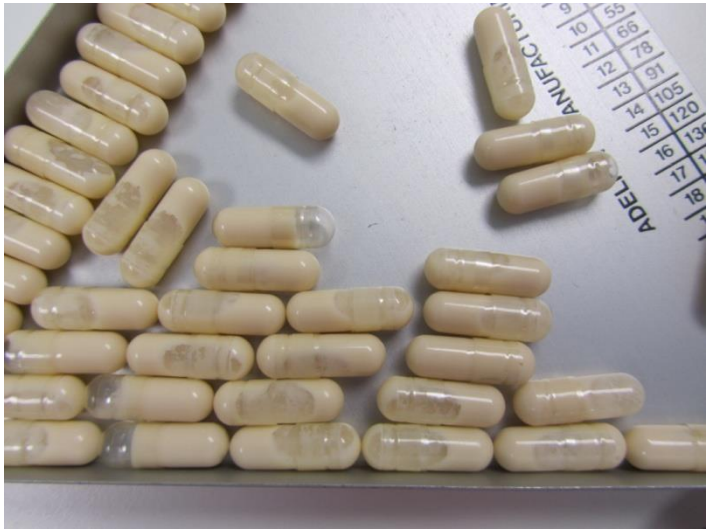
IMP – Final Product

20mg capsules AZD0424 in 70:30 PEG300:PEG1500



XXX capsules 20mg of AZD0424 in 70:30 PEG 300:1500
Protocol Number CRUKD/07/061
For oral administration according to protocol
Store between 2°C to 8°C
FOR CLINICAL TRIAL USE ONLY
KEEP OUT OF REACH OF CHILDREN
Sponsor: Cancer Research UK, London, EC1V 4AD
Tel. 0207 242 0200

Batch No.: XX-XX Expiry Date: DDMMMYYYY

BDU

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Designing the trial

What, When, Where and How?

- What is the IMP, is there an indication in mind, what information do we already have?
  - Is it a small molecule; a vaccine; an antibody etc?
  - Is it targeting anything specific such as CHK1, HER2?
  - Will it be for all comers with cancer or a specific tumour type?
  - Is there any information that is outstanding?
  - Does this need to go to the MHRA Scientific Advice Committee?
- When are you going to open the trial?
  - Is it going to be open in 1, 2, 3 years or more?
  - What needs to be in place for opening the trial?
  - Will the landscape be the same or will this trial/IMP have passed its sell by date?
- Where will it be run?
  - Who will be the Chief Investigator?
  - How many sites do you need?
  - Are there any key requirements e.g. PET scans?
- How will you deliver it, how much will it cost?
  - With aplomb!
  - Work out what is needed and make it happen.

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Clinical Concept through to final protocol

Where do we start?

Clinical Concept

- Overview of what we want to achieve
- Includes:
  - success criteria;
  - Objectives;
  - Proposed biomarkers;
  - Patient population;
  - Eligibility criteria etc.
- This is a working document and forerunner of a protocol outline and then the full clinical protocol.
- When it is ‘baselined’ depends on when the study exits ‘due diligence’

<IMP name> Clinical trial concept

<Author is CDD Medical Advisor>

Title:

Indication: *<description of patient population>*

Success criteria: *<particularly relevant for CDP studies; may inform proposed endpoints>*

Proposed primary objective(s)	**Proposed primary endpoint(s)**
1.	
2.	
Proposed secondary objective(s)	**Proposed secondary endpoint(s)**
1.	
2.	

Existing data on IMPs:

- Intended schedule(s) (and route) -
- Estimated starting dose -
- Estimated efficacious dose -
- Estimated Maximum Tolerated Dose (MTD) -

Study design:

- Dose escalation scheme -
- Dose escalation stopping criteria -
- Expansion cohort –
- Combination or comparator agent (if applicable) –
- Estimate of number of patients (per cohort and total) –
- Any special design features - <e.g. adaptive design, randomised discontinuation design>

Safety considerations: *<clinical mitigation planning, anticipated toxicity in man>*

Selection and purpose of biomarkers:

- PD biomarkers -
- Stratification -
- Other biomarkers - *<e.g. imaging or proposed tertiary assays>*

Key patient eligibility criteria:

Inclusion

Exclusion

This is our starting point: Information taken from NAC application and other supporting documents

Objectives and Endpoints

Common Objectives for a Phase I/II trial:

Primary Objective	Endpoint
Propose a recommended Phase II dose by: Assessing the toxicity and safety profile of the IMP	 Document and determine causality of AEs, SAEs, abnormal laboratory parameters etc
Establishing the maximum tolerated dose of IMP (at planned route/schedule)	a) Determining a dose at which no more than one patient out of up to six patients at the same dose level experience a highly probable or probable <IMP> related dose limiting toxicity, (defined in protocol).
Or: Establishing the biologically active dose (BAD)	Decrease of <x> % of <x marker> in <x> % of patients. Decrease of <x> % of <x marker> in <x> % of patients and there is a plateau in activity between two dose levels (i.e. <x>% absolute difference).

Objectives and Endpoints

Common Objectives for a Phase I/II trial:

Secondary Objective	Endpoint
To investigate the pharmacokinetic behaviour of <IMP> in man.	Determining the correlation between pharmacokinetic studies and toxicity and/or efficacy. *Include measures wherever possible*
To investigate the pharmacodynamic behaviour of <IMP> in man.	Determining magnitude and duration of effect of biomarkers following < IMP> administration. *Include measures wherever possible.*
To document possible anti-tumour activity in patients.	Any/percentage/numbers response (stable disease, partial response or complete response) in any of the patients as determined by the Response Evaluation Criteria in Solid Tumours (RECIST). *<TTP and PFS may also be used as endpoints for examining possible anti-tumour activity, calculate baseline date according to disease response criteria e.g. RECIST or indication specific criteria.* *<Overall survival should be calculated from the date of first study-related treatment which should be defined for each study in discussion with the CI and MA. Usually this is first dose of IMP but this may be first intervention or first dose of non-IMP if this will precede first dose of IMP. You could refer to disease assessment section for details of calculation of endpoint.>*

Objectives and Endpoints

Common Objectives for a Phase I/II trial:

Tertiary Objective	Endpoint
To explore the use of <imaging modality or laboratory assay> as biomarkers for detection of early tumour response.	Determining the magnitude of change in <imaging parameter or laboratory parameter> calculated from <imaging modality or laboratory assay> data and the uptake of <tracer or compound> by tumour tissue quantified by <imaging modality or laboratory assay> during the first cycle of <IMP> treatment and their relation with response.
To characterise mutation expression to identify predictive biomarkers of disease response to <IMP>.	Correlation of anti-tumour activity with the expression of clinically relevant mutations including <XXXX>.

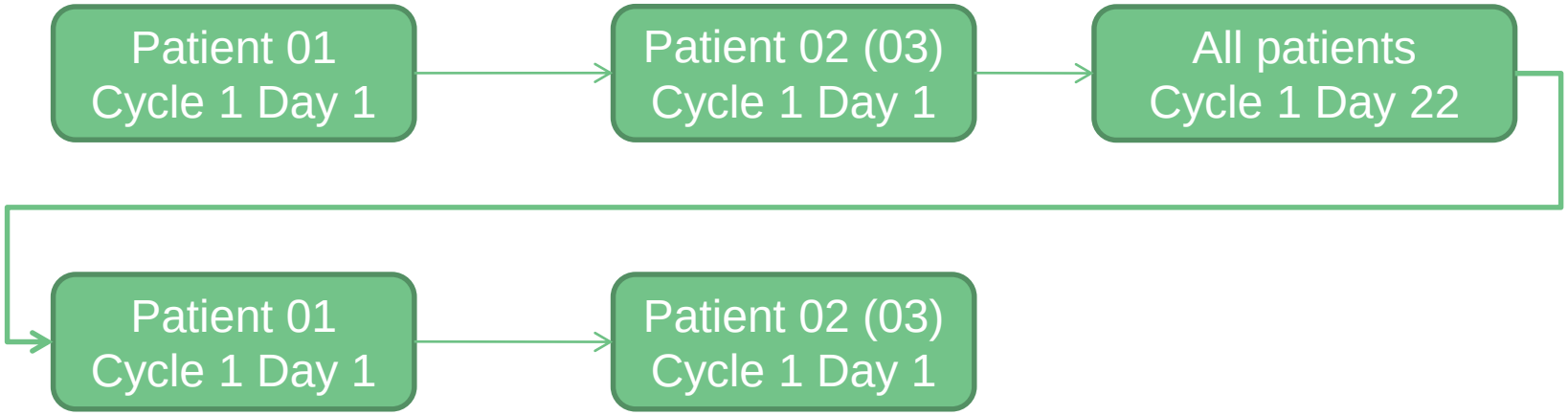
Study Design and Escalation Schedule

Schedule is dependent on toxicology studies etc.

Typical IV trial:

- IMP given on Day 1 of a 3 week/22 day cycle (q3/52) in cohorts of 3 patients

Cohort 1 to 2 etc:

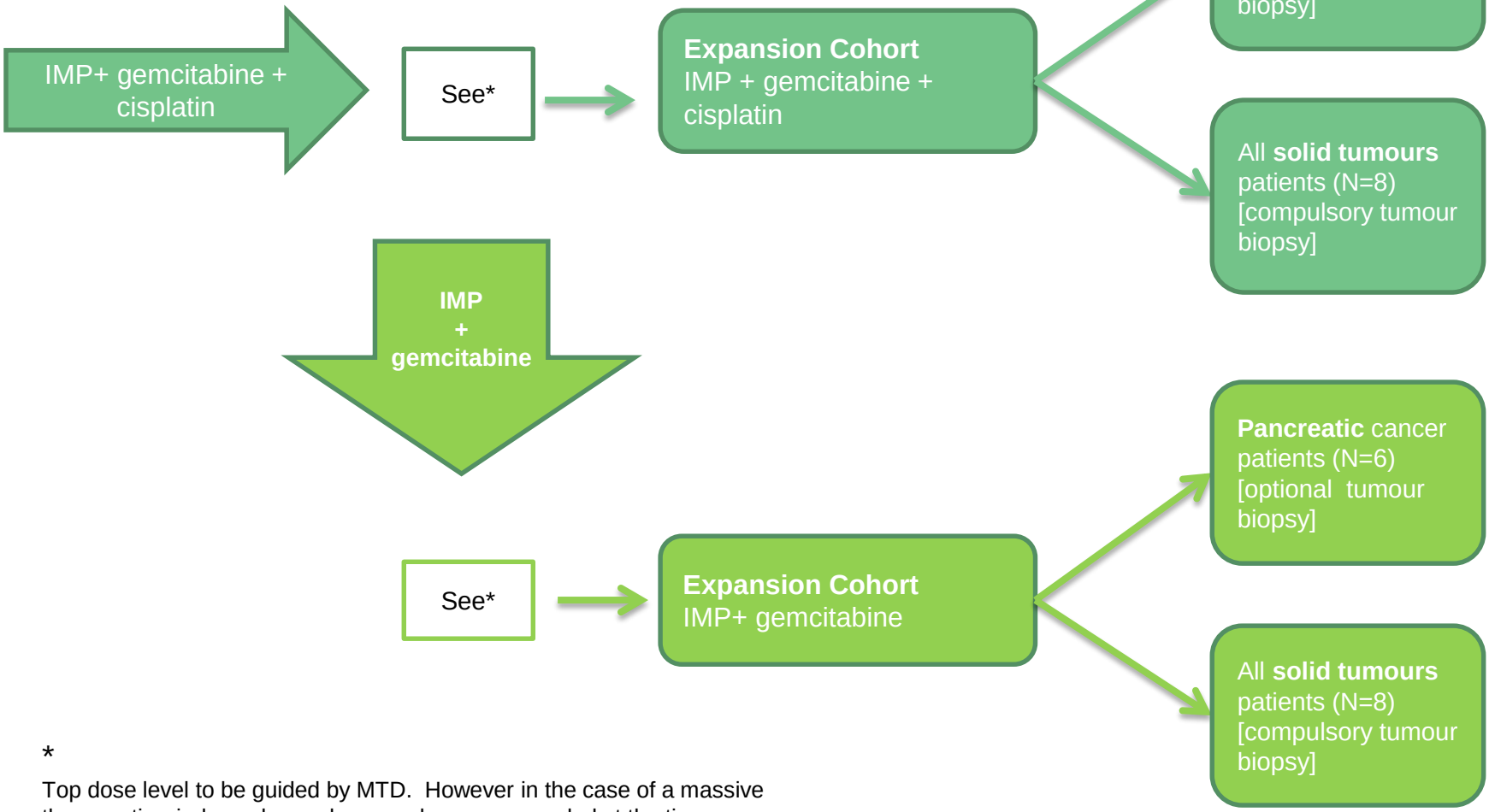


Dose doubled in consecutive cohorts until the emergence of Grade 2 IMP-related toxicity. Doses then escalated by up to 50%

Oral trials follow a similar pattern but IMP likely to be taken daily or twice daily.

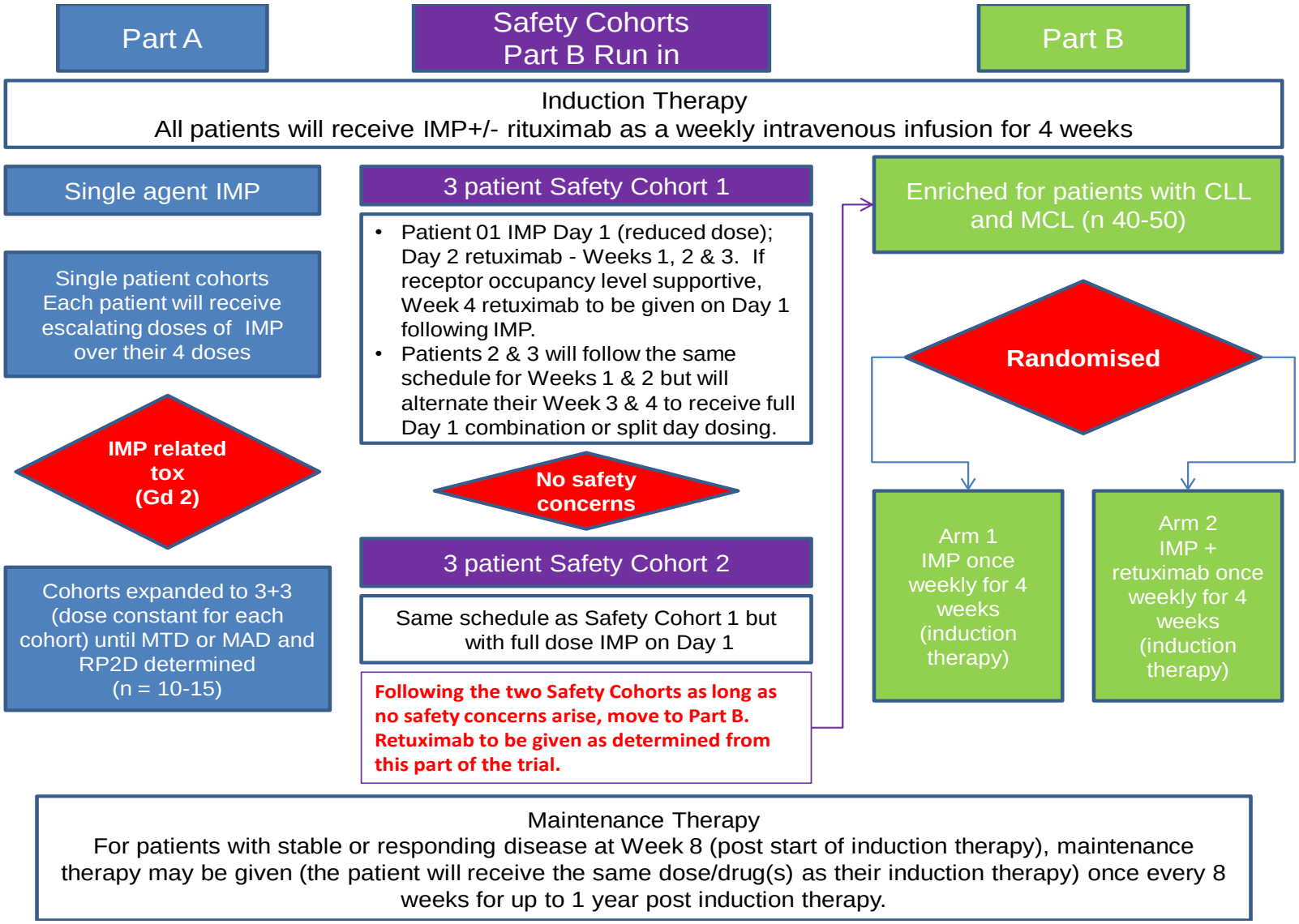
Study Design: Combination Trial

Dose escalation in solid tumour patients n=3-6 per cohort



*

Top dose level to be guided by MTD. However in the case of a massive therapeutic window a lower dose can be recommended at the time.


Part A
Safety Cohorts
Part B Run in
Part B
Induction Therapy
All patients will receive IMP+/- rituximab as a weekly intravenous infusion for 4 weeks
Single agent IMP
Single patient cohorts
Each patient will receive escalating doses of IMP over their 4 doses
IMP related tox (Gd 2)
Cohorts expanded to 3+3 (dose constant for each cohort) until MTD or MAD and RP2D determined (n = 10-15)
3 patient Safety Cohort 1
Patient 01 IMP Day 1 (reduced dose); Day 2 retuximab - Weeks 1, 2 & 3. If receptor occupancy level supportive, Week 4 retuximab to be given on Day 1 following IMP.
Patients 2 & 3 will follow the same schedule for Weeks 1 & 2 but will alternate their Week 3 & 4 to receive full Day 1 combination or split day dosing.
No safety concerns
3 patient Safety Cohort 2
Same schedule as Safety Cohort 1 but with full dose IMP on Day 1
Following the two Safety Cohorts as long as no safety concerns arise, move to Part B. Retuximab to be given as determined from this part of the trial.
Enriched for patients with CLL and MCL (n 40-50)
Randomised
Arm 1
IMP once weekly for 4 weeks (induction therapy)
Arm 2
IMP + retuximab once weekly for 4 weeks (induction therapy)
Maintenance Therapy
For patients with stable or responding disease at Week 8 (post start of induction therapy), maintenance therapy may be given (the patient will receive the same dose/drug(s) as their induction therapy) once every 8 weeks for up to 1 year post induction therapy.

CLINICAL DEVELOPMENT OF A PROTOCOL

CLINICAL DEVELOPMENT OF A PROTOCOL

Can we do it?

Points to consider

- **Is it attractive to patients or is it patient centric?**
  - How much time will the patient have to spend in hospital?
  - What investigations will they undergo?
  - Will they need to have a biopsy or more than one biopsy?
  - How much blood will they need to give?
  - Do they need to stay in overnight or attend at weekends?
  - Is this a rare tumour type?
  - How well will they feel?
  - Is there a particular age group?
  - Will they have to take multiple capsules/tablets a day and do they have to fast before and after?
  - Are there better alternatives out there?

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CLINICAL DEVELOPMENT OF A PROTOCOL

Can we do it?

Points to consider

- **What facilities/equipment/resource is needed at site?**
  - What is their experience and have we worked with them before?
  - Does the protocol call for special investigations? e.g. PET scans or ophthalmology on a regular basis?
  - Would the patient have to travel to another hospital for tests?
  - Does the site have accredited Haematology and Biochemistry laboratories?
  - Does the site have enough staff?
  - Including: doctors, research nurses, data managers etc.
  - Does the site have competing trials?
  - Does the site have sample processing and storage facilities?
  - Can samples be taken outside of normal working hours/weekends?
  - Is there a dedicated Clinical Trials Pharmacist?
  - Is there monitoring space and availability?

ECMC

So how can we make it easier?

Making it easier on patients

- **Do you need biopsies from every patient?**
  - If no, define the ideal number but then have a ‘settle for’ number in mind (and a time limit).
- **During Cycle 1, does the patient need to stay in hospital for PK/PD samples?**
  - Are all the timepoints practical or necessary?
  - Is there a window around timepoints that would allow the patient to go home?
  - Would it be easier on the patient to let them stay in hospital?
  - Do they need to fast? If so how long and can they drink?
- **After Cycle 1, does the patient need to attend hospital on every visit?**
  - If there is no specific need, consider a telephone call to the patient rather than a visit?
  - If the patient has had all PK/PD tests done, consider reducing the number of visits required and whether routine bloods could be done locally or at GP/District Nurse?

ECMC

CLINICAL DEVELOPMENT OF A PROTOCOL

Cost?

How much does a clinical trial cost?

- How long is a piece of string?
- Costs are dependent on type of trial, type of IMP, manufacture, toxicology, number of amendments, number of patients etc.
- Clinical costs minimal (AcoRD* and ECMCs) in most cases

"Health & social care research is a core NHS activity and as such, the NHS is committed to supporting a portfolio of commercially and non-commercially funded research. This guidance note provides a transparent and consistent basis for attributing the costs of health & social care research studies."

*Attributing the costs of health and social care Research & Development

CLINICAL DEVELOPMENT OF A PROTOCOL

Summary

- By the time you see a protocol, the trial could be 5 years old or more;
- The average Phase I trial from start (NAC) to finish (Archive) can take 6 years or more;
- Reluctance to change after so much work, so need to include the right people earlier;
- Scientists and medics can get carried away with the science;
- Need to have clear objectives and go-no-go rules;
- Need to keep the patient as the focus, without them, we don't have a trial;
- Biomarkers should enhance a trial not make it harder;
- We can't run trials without data and support;
- We won't have the perfect trial or protocol at the start, it will need to be amended from time to time.

ECMC

Thank you and Questions

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