Physiomics

Mathematical modelling in the age of Project Optimus

30 March 2023

FDA Project Optimus

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
Guidance for Industry
DRAFT GUIDANCE

Draft guidance structure:

A. Collection and Interpretation of Clinical Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Data
   - PKPD – modelling and simulation
   - Patient population is it relevant?
   - Analysis plan!

B. Trial Designs to Compare Multiple Dosages
   - Recommend a parallel dose-response trial
   - It does note need to be statistically powered to demonstrate superiority/non-inferiority

C. Safety and Tolerability
   - In addition to grading consider Patient Reported Outcomes

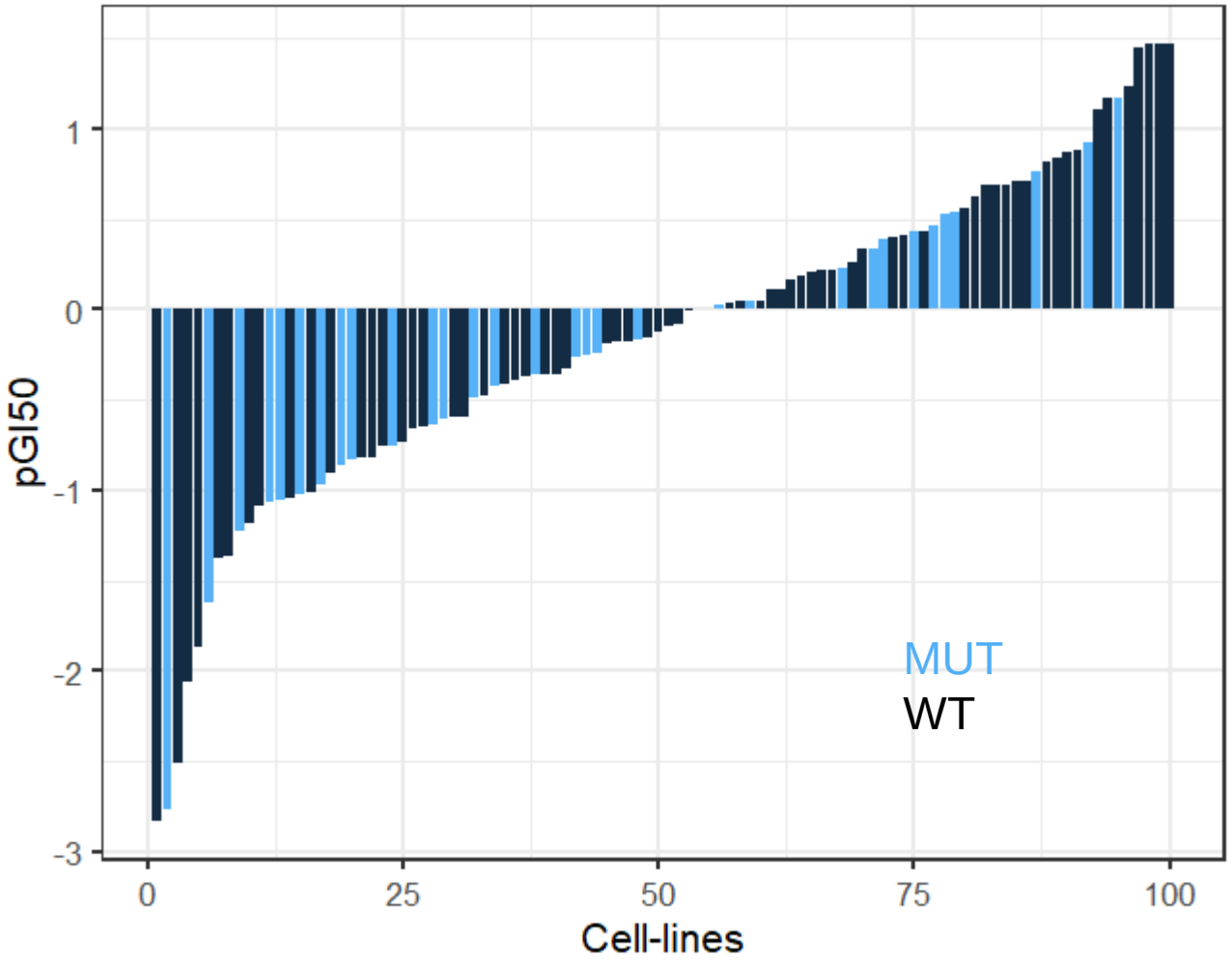
D. Drug Formulation
   - Ensure you have numerous dose strengths

E. Subsequent Indications and Usages
   - Be mindful that different doses may be needed for different indications

In this talk we'll take a closer look at some of this guidance starting with preclinical…

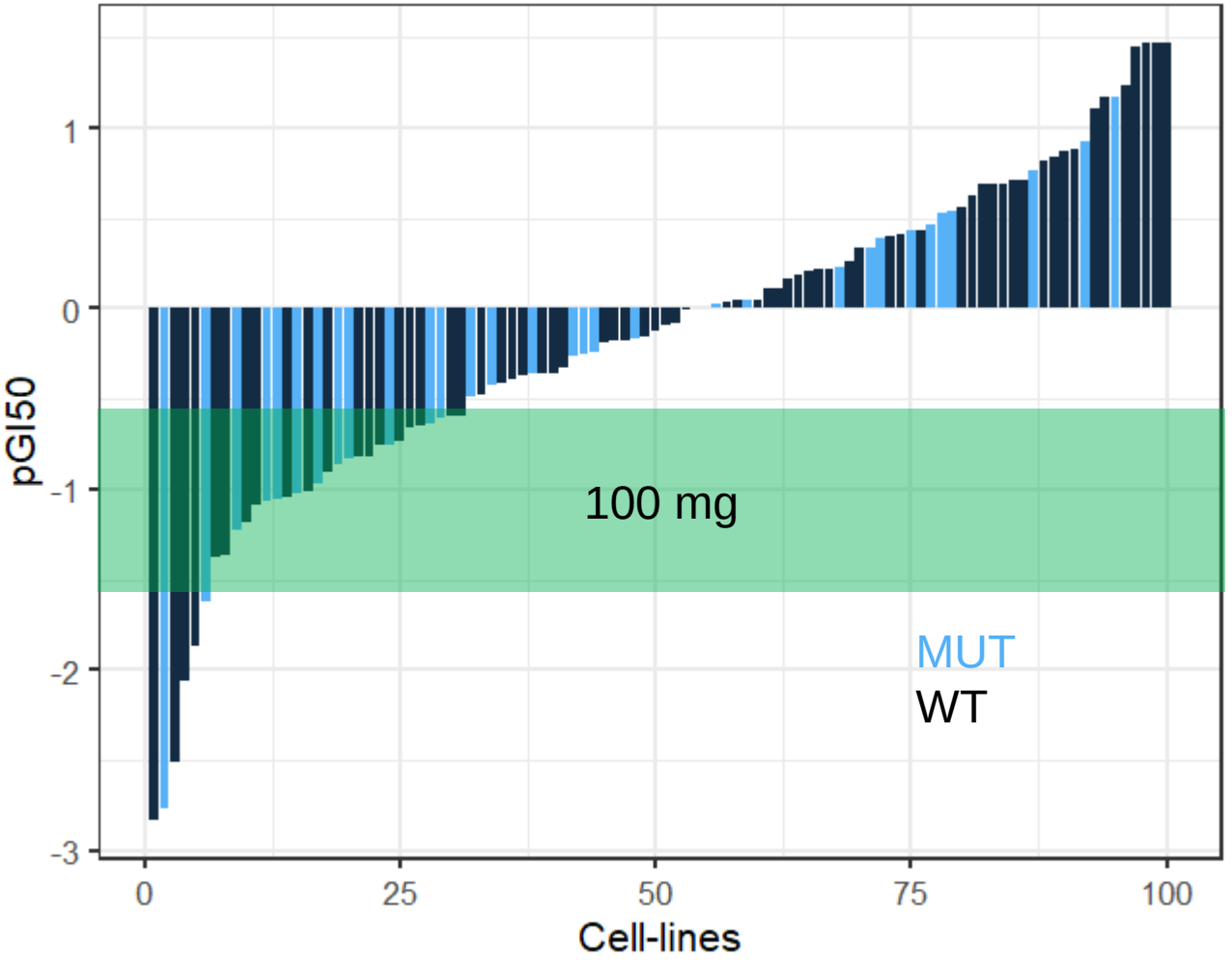
Efficacy: Response across panels of cell-lines

- Early in development we screen drugs across panels of cancer cell-lines for both small molecules and biologics (co-culture PBMCs and cancer cell-line)
- What we learn from these early studies is **inter-individual variability (IIV) clearly exists for efficacy**
- We know early on concentration matters!
- Every cell line has a unique concentration value that will inhibit their growth by 50% (GI50)
- pGI50 = log10(GI50 [uM])
- We'll put to one side the translational relevance of in-vitro assays…



Efficacy: Response across panels of cell-lines

- Inter-individual variability (IIV) clearly exists for efficacy
- We also know that there is IIV in concentration at a fixed dose
- Dose X mg gives a range of concentrations (green region)
- In all-comers we may not see a concentration-response – we hope that our patient selection strategy elucidates one!
- Now add in that we have IIV for toxicity too – picking a single “optimal” dose that works for everyone is impossible!



How do we handle IIV in PK, Efficacy and Safety/Tolerability?

- Dose Titration!
- Design Phase 1 studies to identify the best titration strategy
- Key advantage with regards Project Optimus – likely to negate the need for randomised parallel dose-response trial – very expensive!
- Two marketed small molecules with dose titration…

Venetoclax

- Target: BCL2 – apoptosis target
- Tumour Lysis Syndrome is a key issue
- Ramp-up is used for two different indications with different starting doses
- In the Phase 1 numerous ramp up regimens were tested
- Titration clearly helped in getting this drug approved

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Matthew S. Davids, Andrew W. Roberts, John F. Seymour, John M. Pagel, Brad S. Kahl, William G. Wierda, ...

Table A1. Intrapatient Ramp-Up Scheme in Arm B of the M12-175 Study

Study Cohort	No. of Patients	Dosing Regimen (mg)
Dose escalation		
B1	3	50-100-**200**
B2	3	100-200-**300**
B3	4	200-300-**400**
B4	8	200-400-**600**
B5	10	300-**600**
B6*	4	400-**900**
B7a MCL	7	20-50-100-200-**400**
B7b NHL	4	300-600-**900**
B8a MCL	7	20-50-100-200-400-**800**
B8b NHL	9	400-800-**1,200**
B8c DLBCL-RT	5	20-50-100-200-**400**
B9a MCL	6	100-200-400-800-**1,200**
Safety expansion		
FL and de novo DLBCL	36	400-800-**1,200**

Axitinib

- Target: VEGFR inhibitor – anti-angiogenic
- The label discusses both up and down dose modifications to essentially choose an MTDi (individualised MTD)

Dose increase or reduction is recommended based on individual safety and tolerability.

Over the course of treatment, patients who tolerate INLYTA for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the INLYTA dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy *[see Warnings and Precautions (5)]*. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

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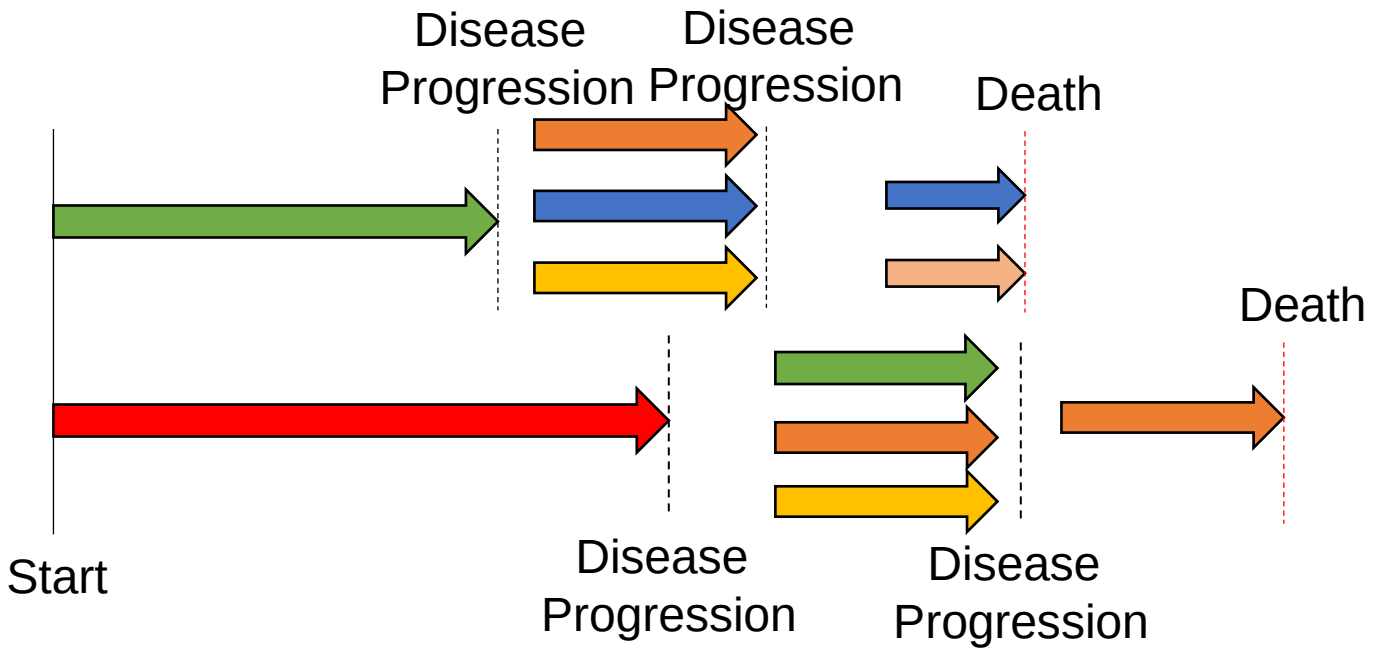
- Both Venetoclax and Axitinib are examples to a degree of individualised dosing and MTDi – note they don't continue increasing the dose beyond an upper limit
- The focus was on safety – when we think about the gold standard for efficacy Overall Survival we can see why….

Efficacy in Oncology – Overall Survival (OS)

The gold standard efficacy marker in oncology is overall survival

Below is a schematic of a Phase III trial exploring the efficacy of a new treatment A v Standard of Care (SoC)



Key Points

- OS is a measure of multiple lines of treatment
- Treatments post-progression are not always what you expect – an approved next line of treatment isn't always given
- Time between treatments is dependent on patient fitness and access to treatments
- The same treatment may be given more than once – sometimes right after each other
- **Key efficacy markers based on imaging, plasma/blood samples are only taken until 1st progression event to understand the difference between new treatment and SoC**

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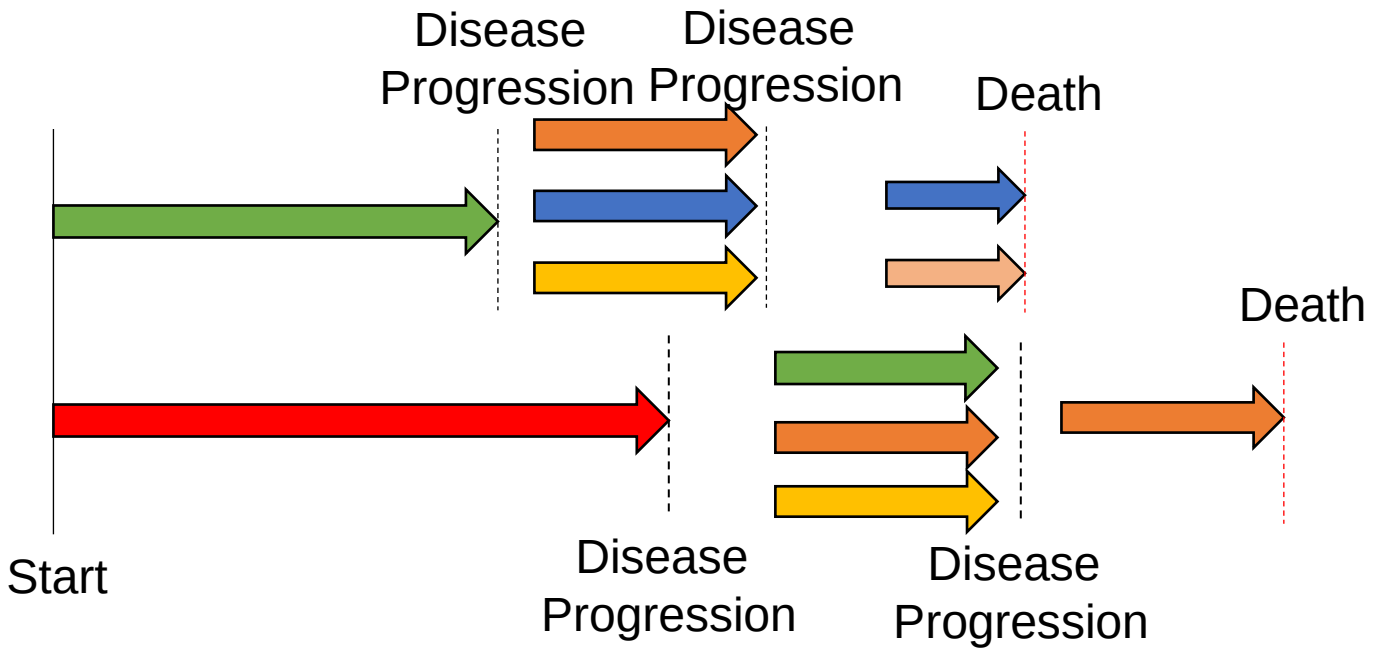

We don't know…

- How the resistance that emerges under treatment A will respond to subsequent lines of treatment
- How long a patient will need to recover from toxicities related to treatment A to start next line of treatment

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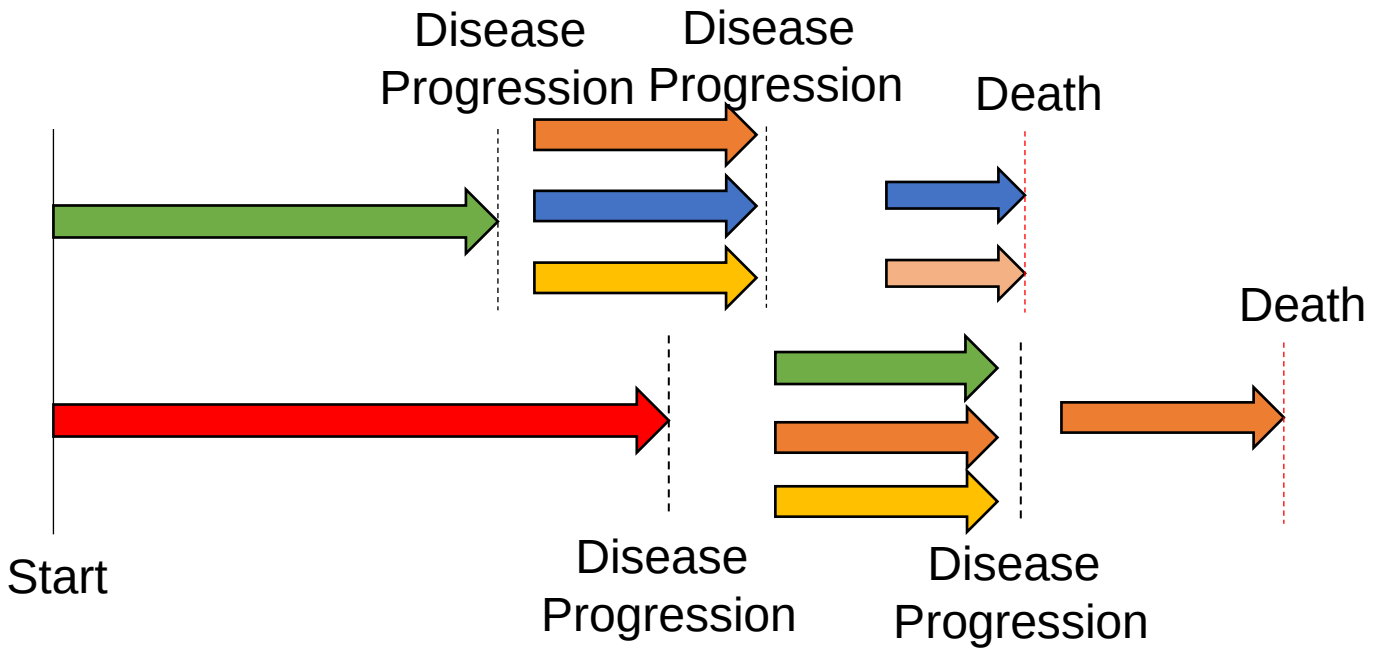
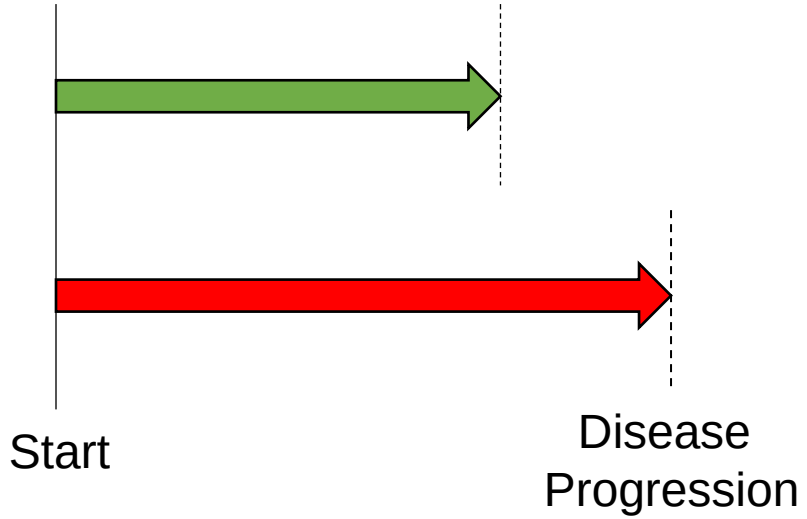


What we do know…

- Eradicating as much of the disease for as long as we can is what the patient would clearly want and gives us our best chance of increasing OS but does not guarantee it i.e. **a necessary but not sufficient condition**
- Drugs that don't shrink tumours/reduce tumour burden are not being used clinically!

Efficacy in Oncology – Biomarkers

If we now focus on the 1st treatment period…

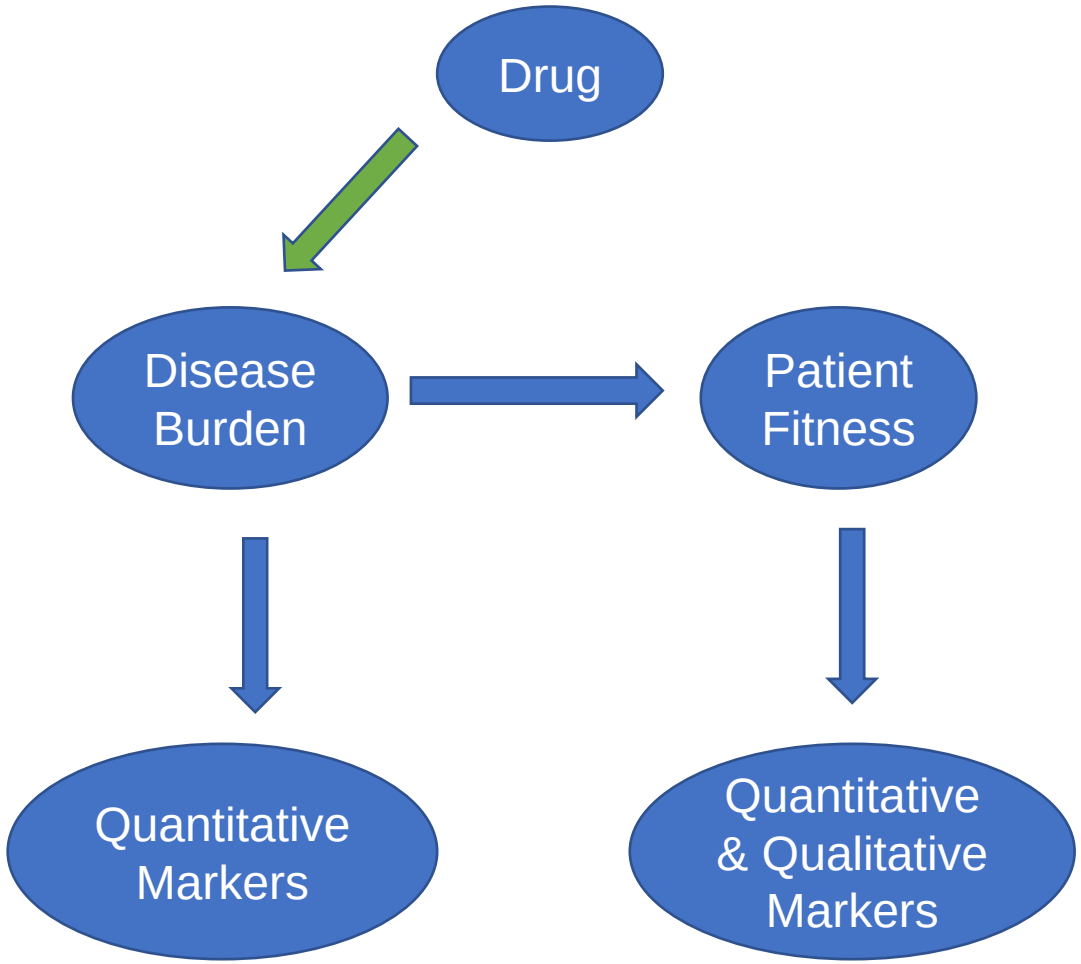


There are numerous measures of efficacy via biomarkers

1. Imaging:
   - Tumour Size both continuous and categorical
   - Time to new lesions
   - Location of lesions
2. Blood borne:
   - Circulating Tumour Cells
   - Circulating tumour DNA
   - Circulating cytokines, growth factors, epithelial cell death markers etc.
   - Organ function e.g. liver enzymes
   - Many more!
3. Qualitative measures of patient well being via questionnaires

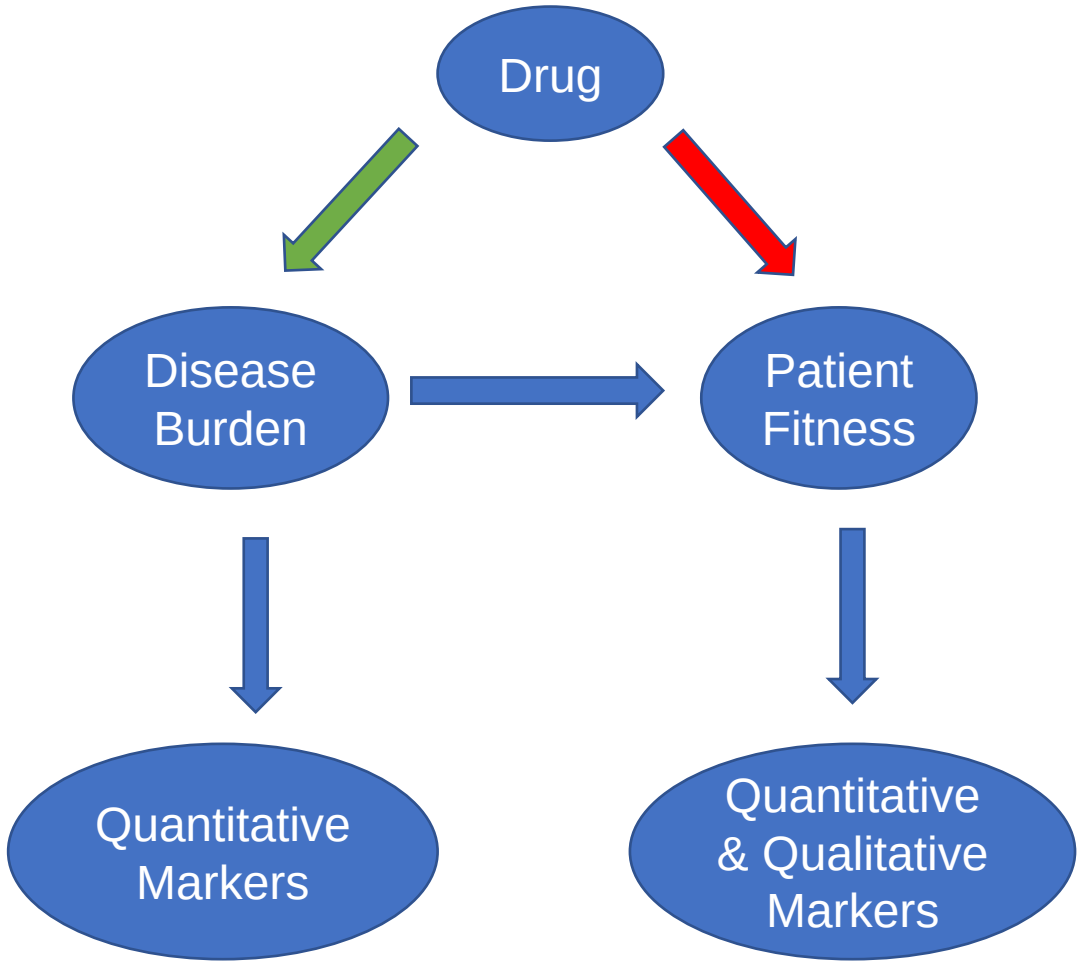
- All of the above should play a role when making choices about dose/dose-titration
- There is no single measure that fully captures disease burden and its effect on a patient
- **In order to integrate all of them we need mathematical/statistical models that link dose/exposure to changes in the above**

Efficacy in Oncology – Biomarkers



- Dose/exposure of drug designed to affect disease burden, which we can't measure precisely, we have numerous measurements via biomarkers
- What happens to these markers dictates decisions we make:
  - Should we progress the drug to next stage of development
  - What dose/schedule should we use
- In early stages of development where the efficacy signal can be very heterogenous due to the drug possibly being given to all-comers – it may be pertinent to combine preclinical and clinical data on efficacy to make decisions
- Mathematical/statistical modelling techniques can be used to combine both preclinical and emerging clinical data, with clinical data eventually outweighing preclinical evidence

Efficacy/Toxicity in Oncology – Biomarkers



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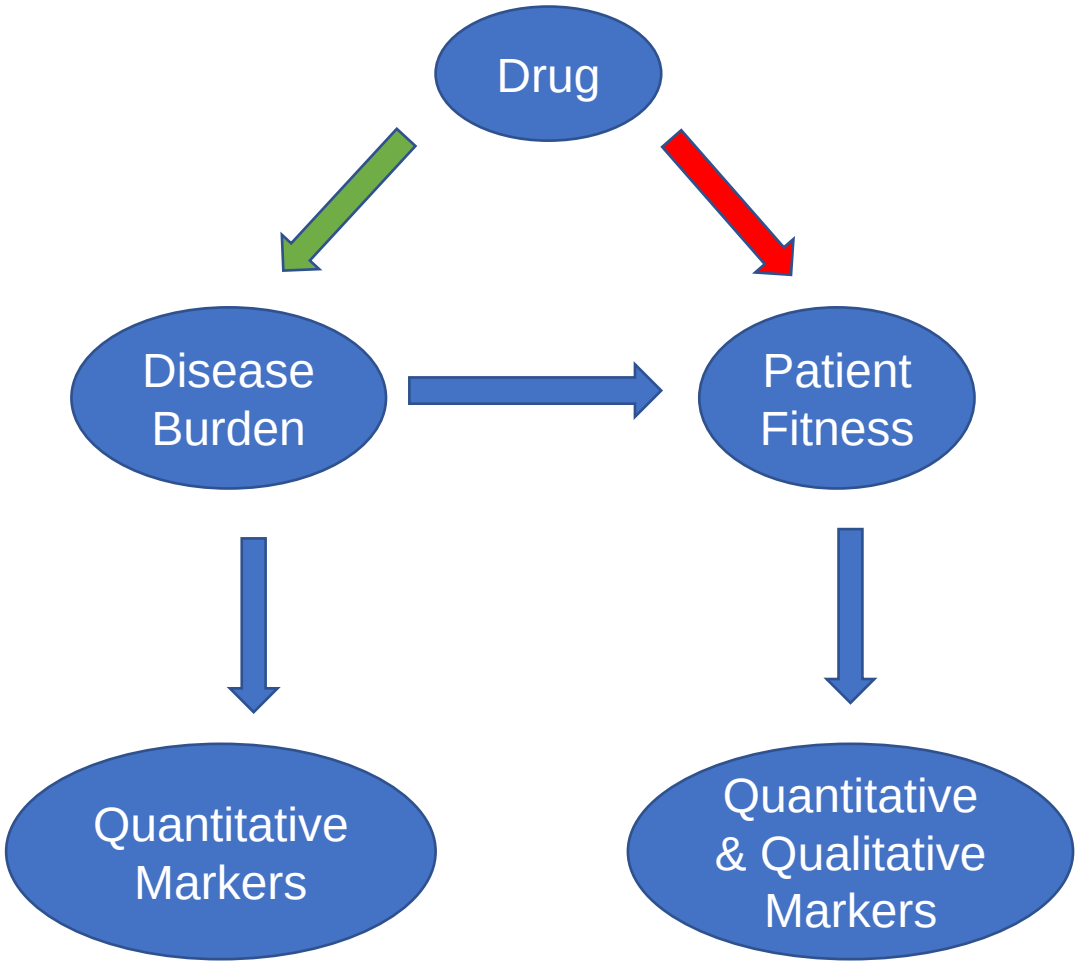
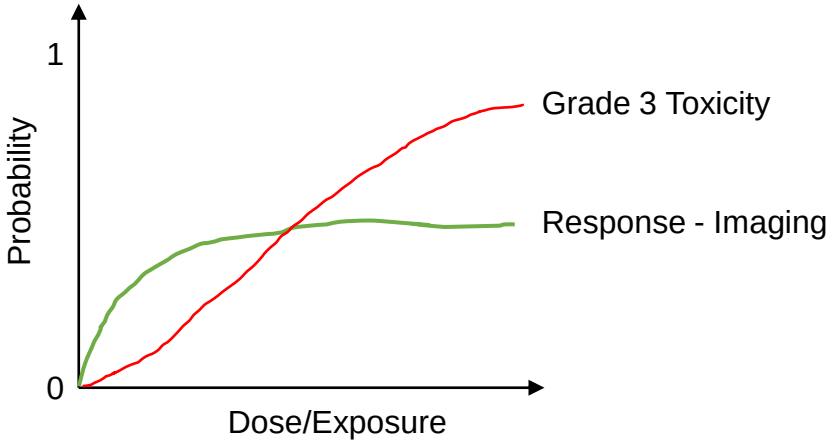
- In early stages of development where the efficacy signal can be very heterogenous due to the drug possibly being given to all-comers – it may be pertinent to combine preclinical and clinical data on efficacy to make decisions
- Mathematical/statistical modelling techniques can be used to combine both preclinical and emerging clinical data, with clinical data eventually outweighing preclinical evidence
- We also know the drug can effect patient fitness in an undesirable way…toxicity…which can be measured both quantitatively and qualitatively!

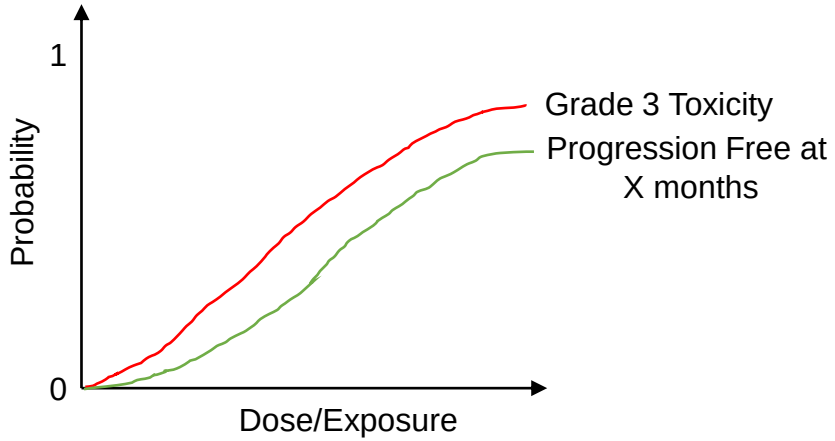
Toxicity in Oncology – Biomarkers

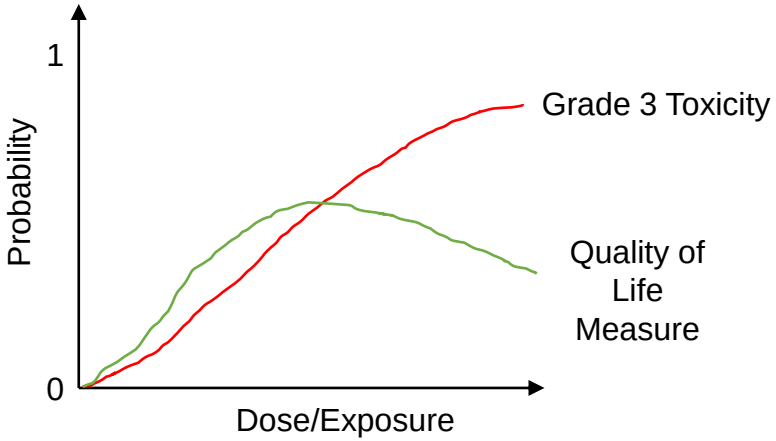


- Again toxicity can be measured using both quantitative and qualitative markers
- Effects on blood borne markers: liver enzymes, immune system (cytokines and cell types) etc.
- Nausea and vomiting - a less dynamical marker
  - Grading systems
- Certain markers could relate to both efficacy and safety…markers of epithelial cell-death
- In order to understand the complexity between all these markers, mathematical/statistical modelling techniques are crucial to help make the right choice about dose/dose titration algorithms

Relationships between efficacy & safety







- It may be that the different efficacy measures do not all agree exactly when compared to toxicity when we look at population level of seeing certain events
- Next add to this that each patient has their own tolerability and cancer sensitivity profile i.e. we know there is inter-individual variability in both efficacy and safety.
- For efficacy think back to early discovery/development & the panel of cell-lines – they all had different GI50 values when drug was administered

FDA Project Optimus – Modelling & Simulation

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Draft guidance structure:

A. Collection and Interpretation of Clinical PK, PD, & Pharmacogenomic Data
   - ❖ *Engage early and use all available data to help with designing Phase 1 dose-escalation and expansion studies*

B. Trial Designs to Compare Multiple Dosages
   - Recommend a parallel dose-response trial
   - ❖ *An alternative to this could be to simply consider a dose-titration algorithm developed using modelling & simulation techniques – this would account for all the IIV discussed*

C. Safety and Tolerability
   - In addition to grading consider Patient Reported Outcomes
   - ❖ *Using techniques such as ordinal logistic regression and item response theory could be useful*

D. Drug Formulation
   - Ensure you have numerous dose strengths
   - ❖ *Preclinical PK-PD-TGI modelling may assist with this together with knowledge of the starting dose based on tox or MABEL etc.*

E. Subsequent Indications and Usages
   - Be mindful that different doses may be needed for different indications

Summary

- We know there is inter-individual variability in the IC50 for efficacy and safety – then in addition we have inter-individual variability in exposure – **IIV is everywhere!**
  - Dose titration is the only solution if you want to account for IIV
- There is no single efficacy marker that is a true surrogate for OS – think about post-progression treatments
- We do know that shrinking tumours is good!
- There are a plethora of efficacy and safety markers collected in early development

❖ Modelling and simulation can clearly help with integrating all the markers and help in ranking the different sources of variation to assist in one of two dosing options:

- Develop the best titration algorithm
- If a single dose is required – choose the best option that gives as many patients as possible the chance to benefit
- Titration though is likely to lead to the best chance of success for a drug program

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Thank you

Time for Questions…

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