

Moving from Full Development to Translational Medecine

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ABSTRACT

Programmers working for a big pharmaceutical company have the ability to internally change therapeutic area or development phase (either Translational Medicine (TM), Full Development (FD) or Global Medical Affairs (GMA)). One never knows before moving whether the grass is greener on the other side of the fence. I'd like to share my experience of moving from FD to TM and explain what is similar (same analyses, data management difficulties) and what is different (exploratory analyses for internal decision making on continuous data accrual, different processes, work according time and not month/years).

INTRODUCTION

One advantage of working for a big pharmaceutical company is the possibility to work across different therapeutic areas. Another one is the ability to follow a compound from early stage until marketing authorization and global medical affairs. As SAS ® programmer in clinical study reporting, you might want to know what to expect before changing project. In this paper, I'll explain what the similarities and differences are between early development (phase I-II) and full development (phase II-III) in the specific therapeutic area of oncology.

BACKGROUND ON STUDY DESIGNS

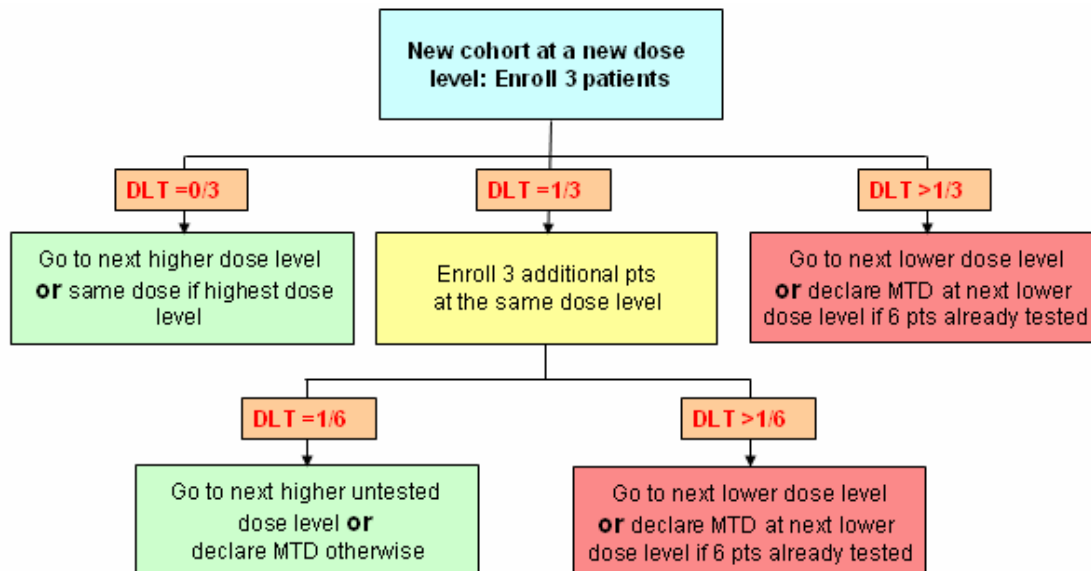
Novartis Oncology Biometric and Data Management has its own department of Translational Medicine split between exploratory development (ED) and clinical pharmacology (CP). I will focus on the particularities of Novartis Oncology phase I ED studies.

OBJECTIVES OF PHASE I ED STUDIES

The main objective of these studies is to identify the Maximum Tolerated Dose (MTD). These first-in-man studies focus on finding the highest dose with acceptable safety and pharmacokinetic profiles. The MTD will usually serve as the recommended dose for phase II studies. Patients are enrolled sequentially in small cohorts receiving increasing dose of the new compound. Toxicities and especially pre-defined Cycle 1 Drug Limiting Toxicities (DLT) are monitored. If no DLT is observed in the current cohort, then the dose is escalated to the next level.

TRADITIONAL STUDY DESIGN

The traditional design used to reach the MTD is the "3+3" rule.



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This has several disadvantages:

- does not use prior information
- ignores dosage history (0/3, 0/3, 0/3, 0/3, 0/3, 2/6 provides more information than 0/3, 2/6)
- same action under qualitatively different situations (0/3 and 1/6 lead to escalate to the next provisional dose, 2/6, 3/3, 2/6, 3/6 lead to de-escalate to the last provisional dose)
- inflexible cohort size (3 or 6)

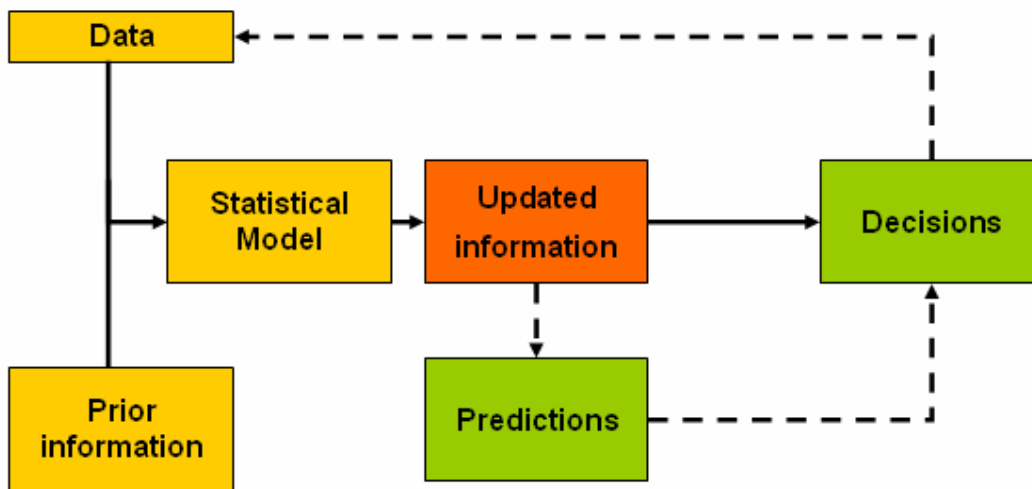
The known performances of this design are the following:

- Tends to underdose: targets 17-21% DLT rate rather than the expected 33% when up to 6 doses are investigated
- Anticonservative for toxic drugs: toxic doses assigned to relatively large number of patients
- Overly conservative for safe drugs: the MTD is consequently underestimated
- High variability in MTD estimates

To cope with this performance issues, a Bayesian model based can be applied.

BAYESIAN LOGISTIC REGRESSION MODEL – ESCALATION WITH OVERDOSE CONTROL (EWOC)

Bayesian methods formalize the learning process. Models begin with initial estimates of knowledge based on prior clinical data or pre-clinical data. Models are then updated with new information as it becomes available. Updated information forms the basis of dose escalation recommendations.



FORMALIZED LEARNING MECHANISM

The principles of Bayesian Logistic regression models are:

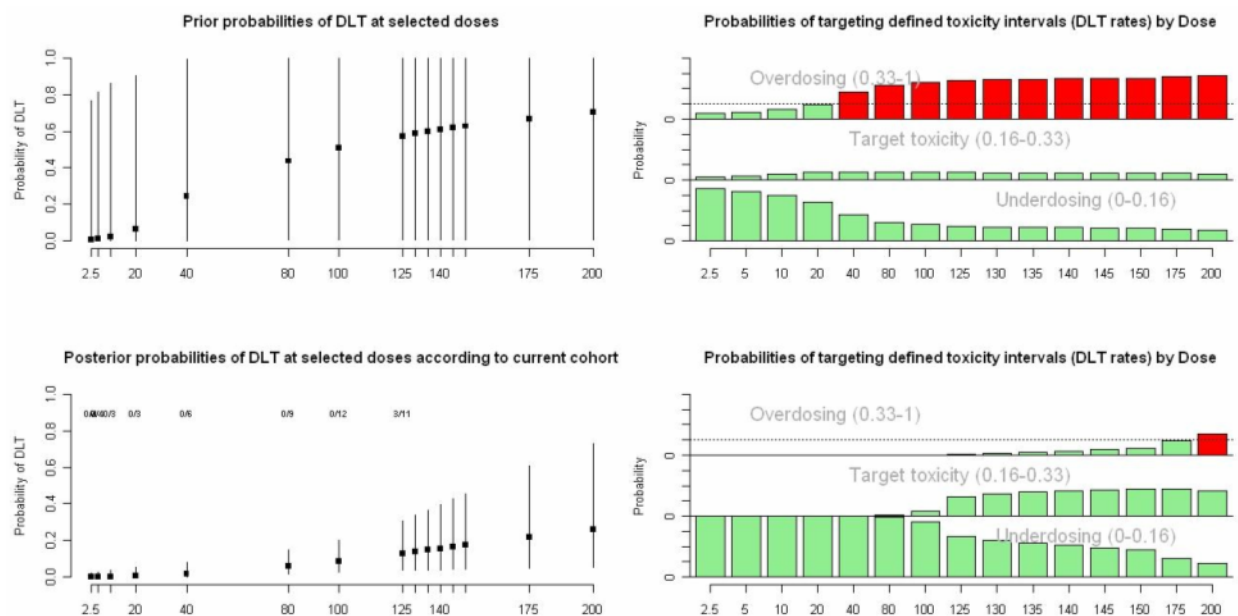
- precision of model estimates incorporated into dosing decisions
- restriction of the chance of exposing patients to excessive toxicity, whilst allowing clinicians to make informed dosing decisions based on estimated probabilities of under-dosing and targeted-dosing

When using the EWOC model, you usually need to specify intervals to summarize the probability of DLT. For example:

[0, 16.6)	Underdosing
[16.6, 33.3]	Targeted toxicity
(33.3, 100]	Excessive toxicity

You also need to specify EWOC criterion as the probability threshold for 'Excessive Toxicity' interval, for instance 0.25.

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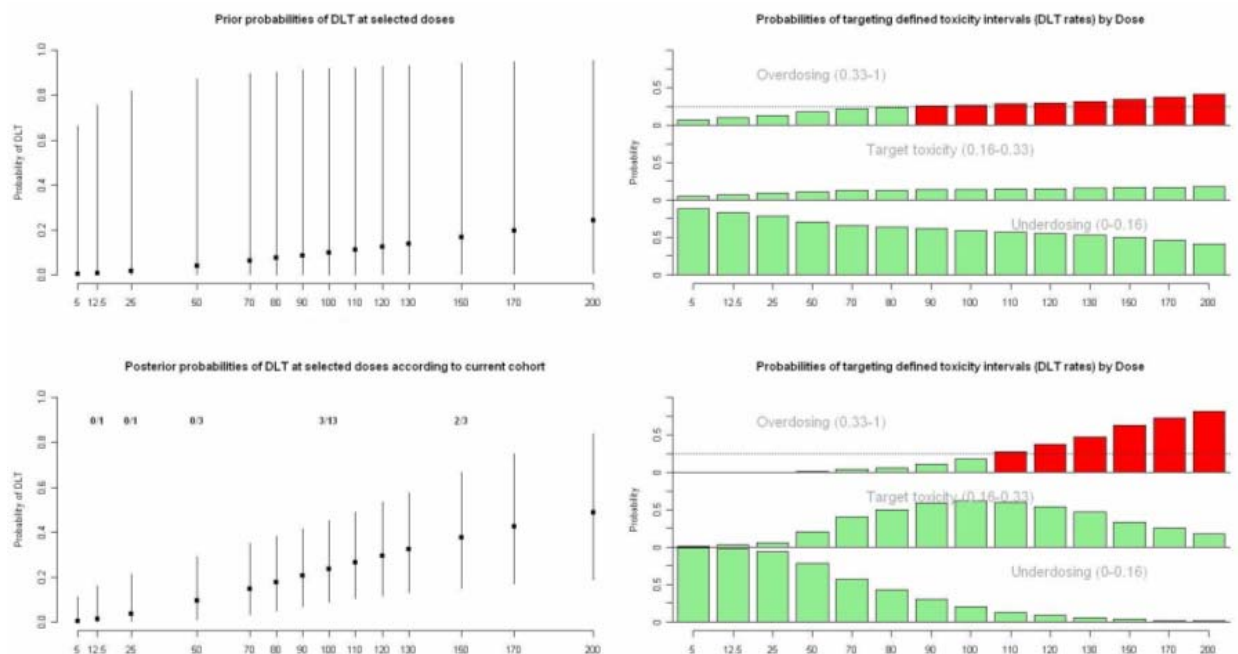


In this example, on the plots at the top display the probabilities before starting the study. These are prior probabilities of DTLs. Uncertainty (i.e., 95% probability interval for dose) is obviously huge since no information on patients is available.

The plots at the bottom display posterior probabilities once 60 patients have been enrolled at doses of up to 125mg and 3 DTLs have been observed overall. The plot on the left quantifies how much has been learned about the dose-DLT relationship. (updated point estimates and narrower probabilities intervals at each dose), while the plot on the right indicates that the maximum dose that can be investigated by the next cohort is 175mg (risk of overdosing less than 25%).

RULES TO DECLARE MTD

Before a drug dosage can be declared to be the MTD, at least 21 evaluable patients must have been treated, with at least six evaluable patients treated at the MTD.



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In this example, we can't escalate. Posterior probabilities of DLT at selected doses of up to 150mg show that maximized probability in the target toxicity is at a dose of 100 mg. The risk of overdose is less than 25% and in addition, sufficient patients are under the MTD dose cohort (13). Based on this data, the MTD could be declared at 100 mg.

DOSE EXPANSION PART

Once MTD is declared, the MTD cohort is usually expanded to further characterize the safety and tolerability of the investigated drug. Secondary objectives are efficacy endpoints and/or characterization of pharmacokinetic and pharmacodynamic profiles.

WHAT DOES THIS MEAN IN TERMS OF REPORTING

RESOURCE PLANNING

Since the timing of the MTD cannot be planned exactly, programmers have to be ready and well prepared so that as soon as the MTD is declared, programmers are able to produce and deliver the required analyses.

Organize yourself so that your programs are ready any time during the dose escalation part.

This means that you should :

- 1 Have a proper analysis plan in place; Make sure imputation rules make sense; Censoring of time to event variables are well defined; Treatment assignment is understood by your team (a new formulation/regimen of the compound could be introduced in the middle of the study, how would you identify these patients?). You do not want to discover unclear definitions at the MTD declaration...
- 2 Make sure all collected data is available sufficiently in advance so that you know what to expect.
- 3 Expect the unexpected, the MTD can happen anytime but you might need to help for a very important exploratory analysis which will lead to modifying your planned analysis.

PROGRAMMING DONE ON CONTINUOUS ACCRUAL OF DATA

As you have to be ready anytime during the dose escalation part, you have to work and develop your code on data that is constantly changing since it is collected while you are programming. Changes in term of data structure and/or changes because of the ongoing data cleaning can be expected.

This means that you should:

- 1 Be proactive and anticipate any potential issues (whether issue is coming from data and/or a trend in data collection).
- 2 Develop as much as possible the use of defensive coding in order to avoid your program crashing simply because of a data issue (incorrect character date of 31JUN for example). Flag these data issues and send them to data management so that data cleaning activities are eased.
- 3 Avoid as much as possible data driven programming: data might be collected in a certain way when the study starts but suddenly, the team realizes that the data was not properly entered (this can happen when unusual data is collected such as a study specific biomarker (parameters with incorrect unit recorded for a particular center)).
- 4 Follow protocol amendments and understand implications on data collected. As the study move forward, more and more data is collected. Sometime, it is found that a collected parameter is not of interest anymore but another one may become relevant to assess the activity of the compound. As a result, database could be updated to allow collection of this new parameter. Make sure to identify and minimize the impact of these kind of changes,
- 5 Expect the unexpected: Data will be analyzed by dose level but you do not know in advance how many levels will be displayed. Take this into account when developing your reporting programs.

ANALYSES

In addition to the planned analyses, exploratory analyses are often requested by the clinical team. By its nature of dose finding, a lot of possible exploratory analyses arise in the dose escalation part. If your clinical team is really imaginative, you might be faced with priority setting problems.

1. Planned analyses

- MTD – Dose expansion

Requested analyses are usually the same as those needed in Full development studies. Although the DLT rate is the primary end point, secondary endpoints are often safety and tolerability as well as efficacy. Similar analyses as those done in Full development are made:

- o Safety and tolerability: adverse event rates, summary of laboratory values, CTC grading, change from baseline in ECG, laboratory values, vital signs, drug exposure, concomitant medications, patient disposition
- o Efficacy: evaluation of responses according different criteria: RECIST, metabolic, biomarkers

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- o Pharmacokinetic: full profiles, PKPD

Differences with full development are the following:

- o For these studies, you carefully look at the exact time the dose was taken to identify pre-dose data and post dose data. This is a main difference with FD as in FD time is not systematically collected. You need to know exactly when the patient took study drug in order to assess drug activity,
 - o Time on study is not as long as in full development. When in full development, patients are followed up for years, in ED, patients follow up is usually in months. This is due to the fact that these patients are refractory to standard therapies,
 - o In ED studies, less patients take part in the study compared to FD studies
- Anniversary report

There are limited regulatory activities when working in ED such as Investigator Brochure (IB) and Investigational New Drug (IND). Safety analysis has to be performed (usually laboratory data, adverse events, drug exposure, PK).

2. Unplanned analyses

Depending on the company pipeline, you might have several compounds within the same class. Companies usually choose the best compound to put in development. So an internal analysis may be decided to compare compounds and take decisions on which compound to select.

Exploratory Development studies, as stated in the name, collect a large panel of data. This opens the door to a nearly unlimited cross analysis between study endpoints. For example, if lesions are measured by CT scans but also PET scans, you might want to check correlations in responses between scans (RECIST vs metabolic). Or even follow a particular lesion as measured by CT and PET. Exploratory biomarkers are often used to gain a preliminary understanding of the tumor activity of the drug.

Most of the time, these analyses are planned in the statistical analysis plan. Nevertheless, you can be asked to provide this analysis anytime during study, for decision making. Although it will be known that data might not be 100% clean and complete, your programs will have to be ready.

CONCLUSION

The use of Bayesian models for ED studies allows for the incorporation of prior as well as newly available study information. In addition, it minimizes risk of overdosing and eases decision making.

Due to the nature of these studies, programmers should try to use company standards as much as possible (standard tools for reporting, company/project standard derivation rules). When no such standards are available, programmers should strive to develop flexible and robust code.

Similar to Bayesian models, programmers learn about particularities of ED studies with passing time. Programmers can consequently put in practice this knowledge in their daily work, and errors that may have made before will just be bad memories.

REFERENCES

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