Becoming a multilingual statistician

Matt Whiley & Stuart Bailey

Bayes 2015 Basel

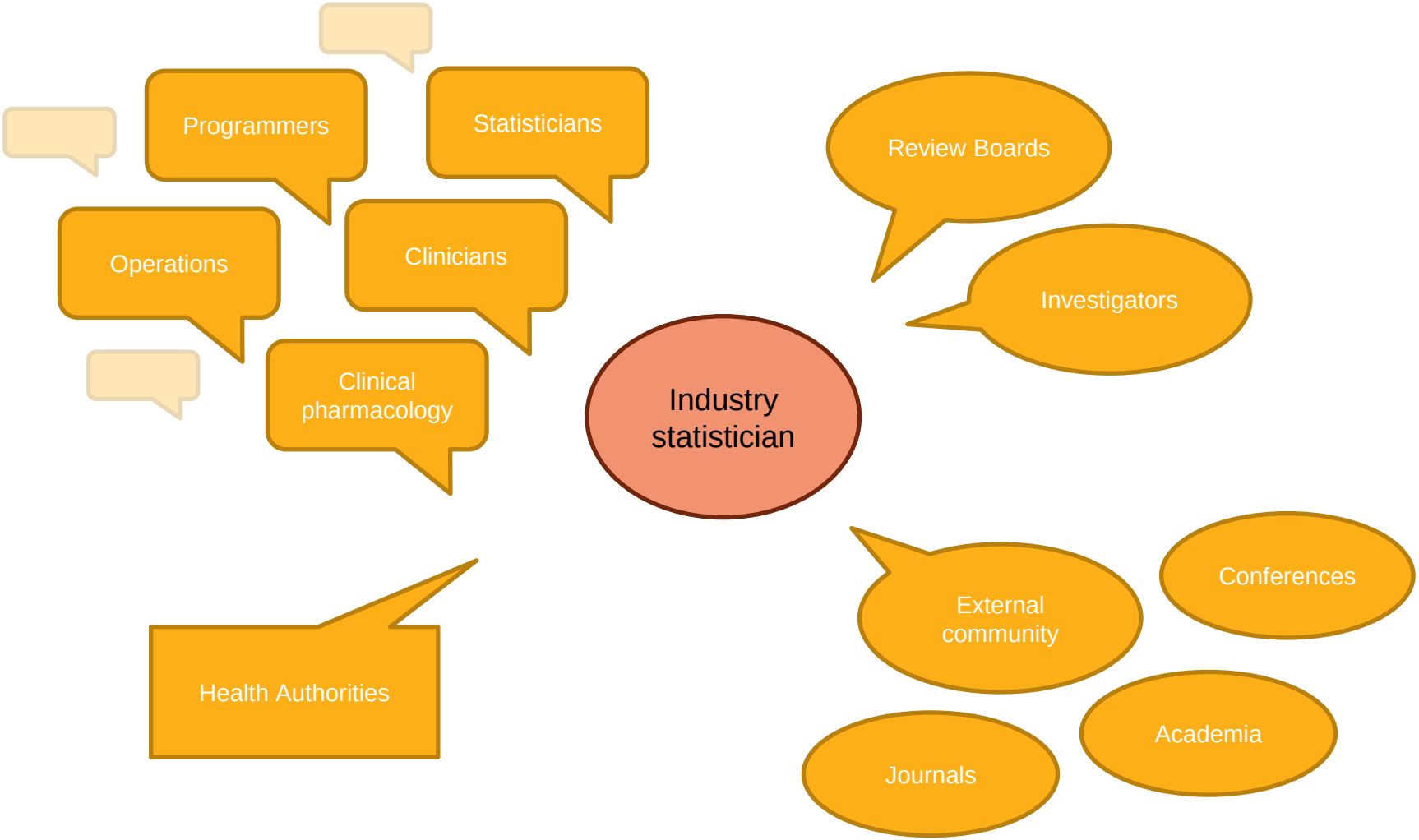
NOVARTIS

Novartis Oncology Early Clinical Biostatistics

Introduction

- Novartis Oncology Early Clinical Biostatistics
  - Oncology phase 1 (dose finding) and phase 2 (exploration of safety and efficacy)
- We work with (mostly) Bayesian solutions
- Phase I Bayesian model based designs are now our standard approach
- Our phase II designs are increasingly moving to a Bayesian estimation framework

Becoming a multilingual statistician



NOVARTIS

Presentation Structure

Introduction

- Statistical communication in Novartis Oncology
- In the context of Novartis Oncology's implementation of Bayesian model based dose escalation designs
  - Speaking up: The challenges of moving to a new paradigm
  - Translating ourselves
  - Lost in translation: Some unexpected miscommunications...
  - (Some future challenges)
  - Summary

Speaking up

- 3+3 designs seen as ‘gold standard’
  - Simple algorithmic approach
  - Easy to understand
  - Easy to implement
- Moving out of comfort zone
  - Costs for the team and the organization
    - More complex designs
    - More difficult to understand and communicate
    - More patients enrolled
    - More resources required

Creating internal engagement

Overcoming inertia

- Start with the problem, not the solution
  - Leave the stats to one side initially
- Dose escalation: Find the right dose
  - Accurately assess dose/toxicity relationship
  - Allow flexibility
    - Dose choice is not algorithmically driven
    - Adapt to new information (e.g., intermediate dose levels)
    - Can explore dose range, learn about PK, PD, etc.
    - Gather additional information where there is uncertainty
  - Use available information efficiently
  - Protect patient safety (high toxicity potential)

Creating internal engagement

Overcoming inertia

Design Requirements	3+3 Design	Bayesian Design
Escalating dose cohorts with **small numbers** of patients (e.g. 3-6 patients)	☺	☺
Accurately estimate MTD & select recommended dose for expansion (RDE)	☹	☺
Robustly avoid toxic doses ("**overdosing**")	☹	☺
Avoid sub-therapeutic doses while controlling overdosing	☹	☺
Enroll more patients at acceptable, active doses (**flexible cohort sizes**)	☹	☺
Use available **information efficiently**	☹	☺

Creating internal engagement

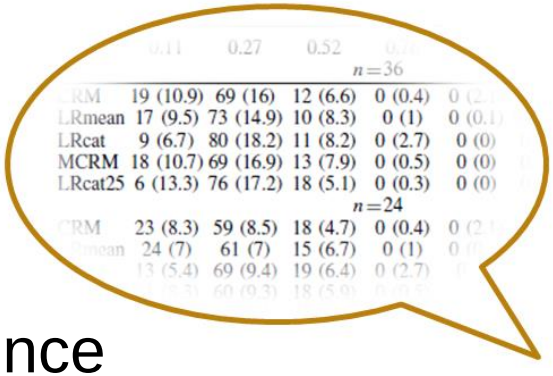
Gaining momentum

- Identifying the issues and knowing we have a statistical solution is only the beginning
- Have to bring the team on the journey
  - Avoid ‘black boxes’
- Together we have to:
  - Learn how to speak each others language
    - Helping clinicians understand our approach
    - Learning their language (for example, to help us set up priors)
    - Understand the practical and operational implications

Crossing the language barrier

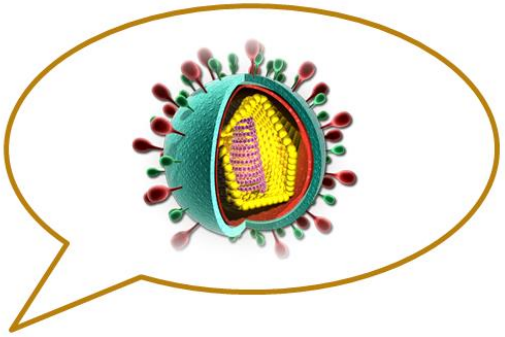
Translating our language

- Collaboration builds acceptance
  - Openness to questions and concerns
  - Consider and demonstrate benefits and risks



	0.11	0.27	0.52	
			$n=36$	
CRM	19 (10.9)	69 (16)	12 (6.6)	0 (0.4)
LRmean	17 (9.5)	73 (14.9)	10 (8.3)	0 (1)
LRcat	9 (6.7)	80 (18.2)	11 (8.2)	0 (2.7)
MCRM	18 (10.7)	69 (16.9)	13 (7.9)	0 (0.5)
LRcat25	6 (13.3)	76 (17.2)	18 (5.1)	0 (0.3)
			$n=24$	
CRM	23 (8.3)	59 (8.5)	18 (4.7)	0 (0.4)
Rmean	24 (7)	61 (7)	15 (6.7)	0 (1)
	13 (5.4)	69 (9.4)	19 (6.4)	0 (2.7)

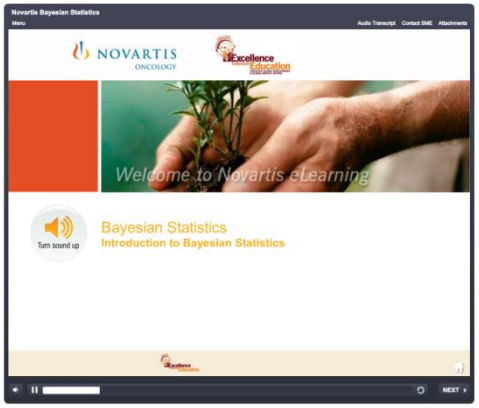
- The right communication for the right audience

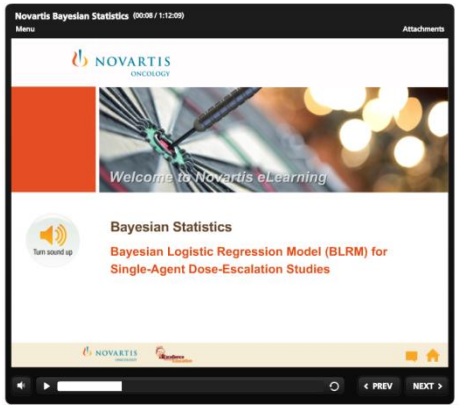


- Think conceptually
  - Simple, clear, non-technical, consistent
  - A picture is worth a thousand words
- Educate (and be educated)
  - Broad education in common concepts
  - Specific education in our commonly used designs

Building engagement

Internal training



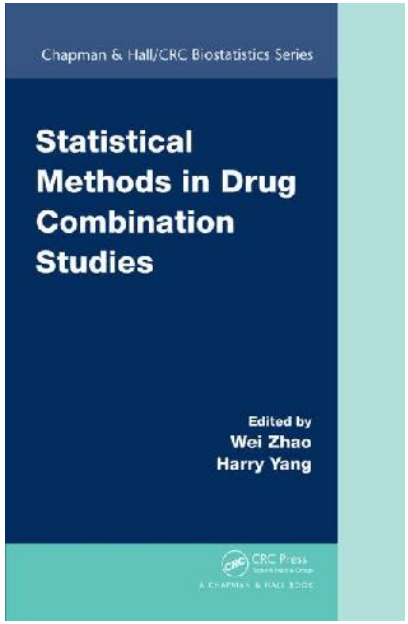


- Face to face, and online
- Statistical training
- Non-statistical training
  - Discuss design issues, and clinical questions
  - Implementation and operation
  - Offer statistical solutions
  - Case studies to provide context

NOVARTIS

Building engagement

External: Publications and presentations



Neuenschwander et al (2014)
Chapter: A Bayesian Industry Approach to Phase I Combination Trials


STATISTICS IN MEDICINE
Statist. Med. 2008; **27**:2420–2439
Published online 14 March 2008 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3230

Critical aspects of the Bayesian approach to phase I cancer trials

Beat Neuenschwander*,†, Michael Branson and Thomas Gsponer

Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland

SUMMARY

The Bayesian approach to finding the maximum-tolerated dose in phase I cancer trials is discussed. The suggested approach relies on a realistic dose–toxicity model, allows one to include prior information, and supports clinical decision making by presenting within-trial information in a transparent way. The modeling and decision-making components are flexible enough to be extendable to more complex settings. Critical aspects are emphasized and a comparison with the continual reassessment method (CRM) is performed with data from an actual trial and a simulation study. The comparison revealed similar operating characteristics while avoiding some of the difficulties encountered in the actual trial when applying the CRM. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: maximum-tolerated dose; continual reassessment method; logistic model

1. INTRODUCTION

Phase I cancer trials are aimed at finding the maximum-tolerated dose (MTD). This is traditionally achieved by exposing patients to dose levels that are adaptively selected based on cumulative toxicity data. The simplest and most widely used approach classifies safety events into two categories, dose-limiting toxicities (DLT) and non-DLTs, with the aim of finding the dose with probability of DLT closest to a targeted probability, usually 25 or 30 per cent.

Although there is agreement on the need for adaptive dose selection in phase I cancer trials, various designs have been discussed in the literature. They range from simple up-and-down schemes like the '3+3' design [1] to model-based approaches, the most prominent being the continual reassessment method (CRM) by O'Quigley *et al.* [2]. The impact of both designs on clinical practice has been considerable, and they have triggered new algorithmic and model-based designs.

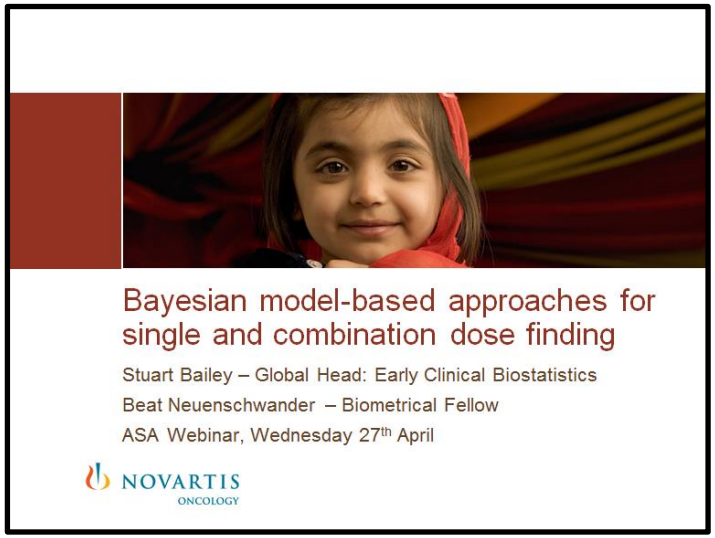
Up-and-down designs are algorithmic in that dose assignments follow from fixed rules that rely exclusively on observed toxicity data. The simplest up-and-down design—'go to next lower (higher) level if an (no) event has occurred'—targeting a probability of 50 per cent was introduced

*Correspondence to: Beat Neuenschwander, Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland.
†E-mail: beat.neuenschwander@novartis.com

Copyright © 2008 John Wiley & Sons, Ltd.

Received 19 November 2006
Accepted 27 December 2007

Neuenschwander et al (2008)
Critical aspects of the Bayesian approach to phase I cancer trials
Statistics in Medicine



Bailey & Neuenschwander (2011)
ASA Webinar

NOVARTIS

Building engagement

External: Publications and external presentations

Cancer Therapy: Clinical

Clinical Cancer Research

First-in-Human Phase I Dose-Escalation Study of the HSP90 Inhibitor AUY922 in Patients with Advanced Solid Tumors

Cristiana Sessa[1], Geoffrey I. Shapiro[2], Kapil N. Bhalla[3], Carolyn Britten[4], Karen S. Jacobs[4], Monica Mita[5], Vali Papadimitrakopoulou[6], Tim Pluard[7], Thomas A. Sarkar[8], Mikhail Akimov[9], Cornelia Quadt[9], Cristina Fernandez-Ibarra[9], Hong Lu[10], Stuart Bailey[9], Sandra Chica[10], and Udai Banerji[10]

Abstract

Purpose: A phase I study was conducted with the primary objective of determining the maximum tolerated dose (MTD) of AUY922 in patients with advanced solid tumors. Secondary objectives included characterization of the safety, pharmacokinetic, and pharmacodynamic profiles.

Patients and Methods: Patients with advanced solid tumors received 1-hour i.v. infusions of AUY922 once a week in a 28-day cycle. An adaptive Bayesian logistic regression model that employed observed dose-limiting toxicities (DLT) in the first treatment cycle was used to guide dose-escalation decisions, with the established MTD to be used in phase II studies.

Results: One hundred and one patients were enrolled and explored at doses in the range of 2 to 70 mg/m². DLTs occurred in 8 patients [22–70 mg/m²] and included diarrhea, asthenia/fatigue, anorexia, atrial flutter, and visual symptoms. At 70 mg/m², the AUY922 concentration achieved was consistent with active concentrations in a range of xenograft models. There was evidence of target inhibition in peripheral blood mononuclear cells (HSP70 induction) and tumor (client protein depletion and reduction of metabolic activity by ^{18}F-FDG-PET). The recommended phase II dose (RP2D) of 70 mg/m² was proposed on the basis of toxicity and pharmacokinetic and pharmacodynamic profiles.

Conclusions: At the RP2D of 70 mg/m², AUY922 exhibited acceptable tolerability, and phase II single agent and combination studies have been initiated in patients with HER2-positive breast, gastric, and non–small cell lung cancers. Clin Cancer Res; 19(13); 3671–80. ©2013 AACR.

Introduction

HSPs are a family of molecular chaperones that are ubiquitous in normal and cancer cells and are essential to the folding of a wide variety of oncogenic client proteins [1–4]. HSP90 client proteins influence the hallmark traits of cancer, including self-sufficiency in growth signals, evasion of apoptosis, tissue invasion, and angiogenesis [5]. The inhibition of HSP90 leads to misfolding of client proteins and degradation through the ubiquitin proteasome pathway [6]. HSP90 inhibitors target the postulated dependence of cancer cells on mutated or amplified oncoproteins, such as EGF receptor (EGFR) or human epidermal growth factor receptor 2 (HER2; refs. 7–10). In addition, the dependence of key signaling proteins such as RAF and AKT on the HSP90 chaperone complex can lead to a combinatorial blockade of signal transduction [1, 2, 6]. These properties suggest HSP90 inhibitors have potential as an anticancer treatment in a wide range of cancers, both as single agents and in combination with other anticancer agents [6]. Although increased expression of HSP90 is associated with poor prognosis in some tumors [11–13], predictive biomarkers of response to HSP90 inhibition are more likely to be linked to mutated or amplified oncogenic drivers [1, 2, 6].

The first generation of HSP90 inhibitors were geldanamycin derivatives, important in establishing a proof of concept that it was possible to achieve clinical responses related to HSP90 inhibition in a clinical setting. However, geldanamycin derivatives have disadvantages, including dependence on NAD(P)H:quinone oxidoreductase (DT-diaphorase) activity,

Authors' Affiliations: [1]Istituto Oncologico della Svizzera Italiana, Bellinzona, [2]Novartis Pharma AG, Basel, Switzerland, [3]Early Drug Development Unit, The Royal Marsden NHS Foundation Trust, Drug Development Unit, Sutton, [4]Novartis Pharmaceuticals, East Hanover, New Jersey, [5]University of Kansas Cancer Center, Kansas City, Kansas, [6]Jonsson Comprehensive Cancer Center and David Geffen School of Medicine, Los Angeles, California, [7]Nevada Cancer Institute, Las Vegas, Nevada, [8]Cancer Therapy and Research Center, San Antonio, [9]MD Anderson Cancer Center, Houston, Texas, [10]Washington University, St. Louis, Missouri, [11]Georgia Health Sciences University, Augusta, Georgia, [12]Novartis Pharmaceuticals, East Hanover, New Jersey, [13]Early Drug Development Unit, The Institute of Cancer Research and The Royal Marsden Hospital, Sutton, United Kingdom

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Prior presentation: Presented in part at the American Society of Clinical Oncology Annual Meeting 2010 (Abstract 3536, et al. abstract 3536).

Corresponding Author: Udai Banerji, The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust, Drug Development Unit, Sycamore House, Downs Road, Sutton, SM2 5PT, United Kingdom. Phone: 44-20-8661-3583; Fax: 44-20-8642-7976; E-mail: udai.banerji@icr.ac.uk

doi: 10.1158/1078-0432.CCR-13-0404

Sessa et al (2013)
First in human Phase I Dose-Escalation Study of the HSP90 Inhibitor AUY922 in Patients with Advanced Solid Tumors

Cancer Therapy: Clinical

A Phase I Study of Single-Agent Nilotinib or in Combination with Imatinib in Patients with Imatinib-Resistant Gastrointestinal Stromal Tumors

George D. Demetri,[1] Paolo G. Casali,[2] Jean-Yves Blay,[3] Margaret von Mehren,[4] Jeffrey A. Morgan,[1] Rossella Bertulli,[2] Isabelle Ray-Coquard,[3] Philippe Cassier,[3] Monica Davey,[4] Hossein Borghaei,[4] Daniel Pink,[4] Maria Debiec-Rychter,[5] Wing Cheung,[6] Stuart M. Bailey,[7] Maria Luisa Veronese,[7] Annette Reichardt,[8] Elena Fumagalli,[2] and Peter Reichardt[8]

Abstract **Purpose:** To study the safety, tolerability, and pharmacokinetics of the selective tyrosine kinase inhibitor nilotinib as a single agent or in combination with imatinib in patients with advanced imatinib-resistant gastrointestinal stromal tumors.

Experimental Design: A phase I interchoort dose-escalation trial was done in patients who received either (a) single agent nilotinib 400 mg twice daily or (b) escalating doses of nilotinib (200 mg once daily, 400 mg qd, or 400 mg bid) plus imatinib 400 mg bid (10- and 14-hour interval daily), or (c) nilotinib 400 mg bid plus imatinib 400 mg qd. Safety, pharmacokinetics, and tumor assessments were done.

Results: Oral clearance (CL/F) of nilotinib was similar across the combination groups (mean CL/F, 19.1-25.6 L/h), and lower than in the single-agent cohort (mean CL/F, 35.6 L/h). A linear relationship between nilotinib daily dose and peak concentration was observed in the combination cohorts. Observed adverse events (AE) were mostly nonhematologic. Frequently reported AEs were rash (40%), fatigue (38%), abdominal pain (36%), and nausea (36%). Severe AEs (grade 3 or 4) included abdominal pain (13%) and rash (9%), the latter mainly with the combination. Thirty-eight patients had stable disease and two patients achieved partial response with a median progression-free survival of 134 days for the entire group.

Conclusions: Nilotinib alone or in combination with imatinib was well tolerated overall and showed clinical activity in imatinib-resistant gastrointestinal stromal tumor patients. This phase I trial identified single-agent nilotinib 400 mg bid or combined with imatinib 400 mg qd as possible phase II doses for further evaluation. (Clin Cancer Res 2009;15(18):5910–8)

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract (1). The majority of GISTs (90%) harbor activating mutations in the *KIT* or platelet-derived growth factor receptor α (*PDGFRA*) receptor tyrosine kinases. The characteristic pathogenic feature of any GIST is the presence of aberrantly activated signaling through either KIT or PDGFRA receptor tyrosine kinases (2, 3).

Authors' Affiliations: [1]Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts; [2]Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico Istituto Nazionale del Tumori, Milan, Italy; [3]Centre Léon Bérard, Département de Medecine, Lyon, France; [4]Fox Chase Cancer Center, Philadelphia, Pennsylvania; [5]Helios Klinikum Bad Saarow, Department of Hematology, Oncology and Palliative Medicine, Bad Saarow, Germany; [6]Center for Human Genetics, Catholic University of Leuven, Leuven, Belgium; [7]Novartis Pharmaceuticals AG, Basel, Switzerland; and [8]Helios Klinikum Berlin-Buch, Sarcoma Center, Berlin, Germany

Received 3/16/09; revised 6/24/09; accepted 7/18/09; published OnlineFirst 9/1/09.

Grant support: Novartis Pharmaceuticals Corporation, Oncology Business Unit, Florham Park, NJ. G. Demetri received additional philanthropic support for this work from the following sources: The Virginia and Daniel K. Ludwig Trust for Cancer Research and the Stuttman GIST Cancer Research Fund. M. von Mehren was supported by grant number P30 CA006927 and CA106588 from the National Cancer Institute. The following authors received funding from Novartis Pharmaceuticals: G. Demetri, E. Fumagalli, P.G. Casali, P. Reichardt, M. von Mehren, and J.Y. Blay. The following authors received funding from Pfizer, Inc., for other projects: G. Demetri, E. Fumagalli, and P.G. Casali.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: This study has been presented in part at the annual meeting of American Society of Clinical Oncology, Atlanta, June 2006, at the European Society for Medical Oncology Congress, Istanbul, September 2006, and at the annual meeting of American Society of Clinical Oncology, Chicago, June 2007 and May 2008.

Requests for reprints: George D. Demetri, Ludwig Center, Dana-Farber Cancer Institute, Dana 1212, 44 Binney Street, Boston, MA 02115. Phone: 617-632-3960; Fax: 617-632-3408; E-mail: gdemetri@partners.org.

doi:10.1158/1078-0432.CCR-09-0542

Demetri et al (2009)
A phase I Study of Single-Agent Nilotinib or in Combination with Imatinib in Patients with Imatinib-Resistant Gastrointestinal Stromal Tumors

NOVARTIS

Building engagement

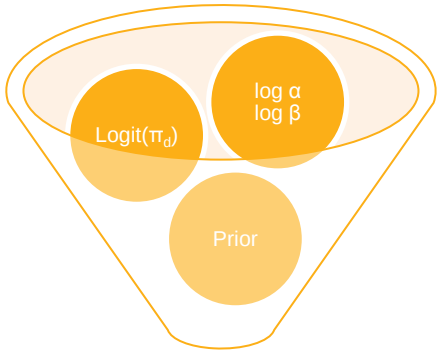
External: Health authority interactions

- **FDA**
  - Critical Path Initiative seeks to promote "new and innovative scientific approaches, such as the use of Bayesian Statistics"
- Committee for Medicinal Products for Human Use (**CHMP**) guideline for Clinical Trials in Small Populations
  - "Model-based approaches have been shown to provide better estimation of true MTDs compared to standard algorithmic approaches"

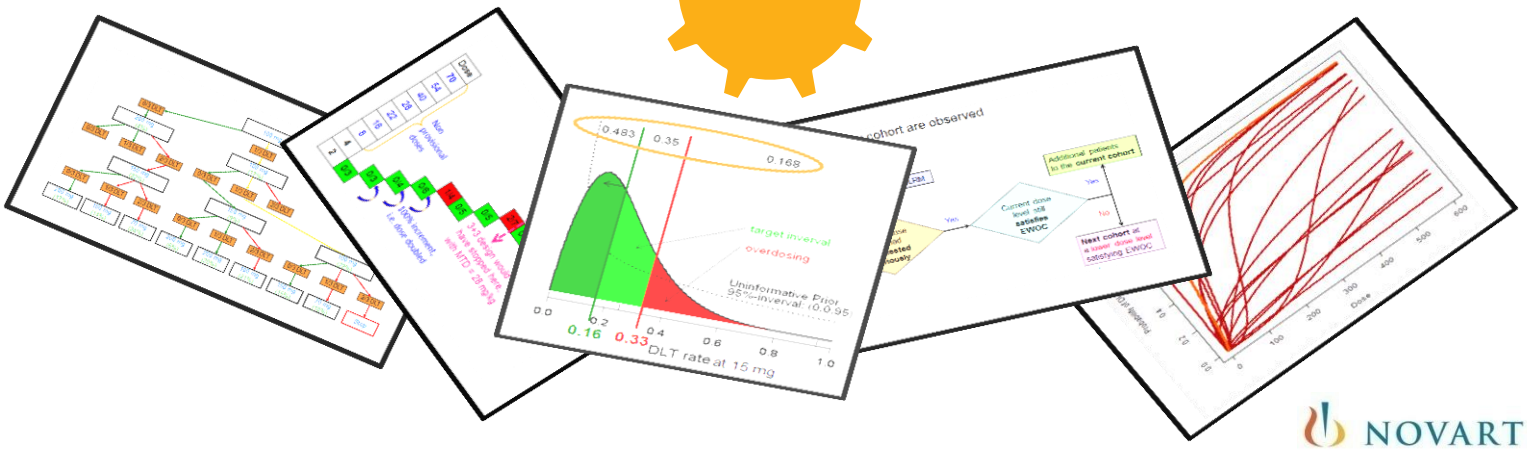
Building engagement

External: Health authority interactions

- **FDA**
  - Presentation to FDA Biostatisticians and Oncologists in Jun 2009
  - Novartis commented on Draft FDA Adaptive Design Guidance in May 2010
- **PMDA**
  - Presentation to PMDA in Nov 2010
- Novartis Bayesian Phase I designs are generally well accepted and challenges/questions from Health Authorities are more on the specifics of the application than on the general approach



Translating ourselves



NOVARTIS

Communication with Stats users

Difficult concepts and complex data

- Need to enable clinicians and others to understand
- Now a few examples taken from the model based approach we use for dose escalation studies in Novartis
  - Understanding priors
  - The EWOC (Escalation With Overdose Control) criterion
  - Dose escalation decision making

Phase I Dose escalations

Bayesian Logistic Regression

$$r_d \sim \text{Bin}(\pi_d, n_d)$$

$$\text{logit}(\pi_d) = \log(\alpha) + \beta \log(d/d^*)$$

- Model specifications
  - d is dose
  - r_d is the number of patients with DLT at dose d
  - π_d is P(DLT at dose d)
  - n_d is the total number of patients at dose d
  - Logistic regression
    - α and β are the logistic parameters
    - d* is a fixed reference dose

Phase I Dose escalations

- Want to communicate to others
  - The principals underlying our model
  - Some key concepts that can help us to interpret the model
  - How we can use our model to guide dose escalation
- Need to think about key message
  - Might depend on circumstance
  - Will influence the way in which we share information

Phase I Dose escalations

- Perhaps we want to discuss with the team the set of curves the model is describing
  - This might be the case during study set up
    - Perhaps we want to demonstrate what our prior tells us about the dose/toxicity relationship
    - Or to help teams understand the flexibility of the model we are using
- Alternatively, we want to communicate with the team what the model is telling us about which doses are safe to use
  - This might be used to confirm the safety of the starting dose (prior)
  - Or to identify the maximum dose to which we can escalate for our next cohort (posterior)

Priors

- One of the first things we need to do it to build a prior for the logistic parameters
- If this is a first in human trial, we might want to use a non-informative prior
- If we have data from previous trials (perhaps in other indications) with the same drug then we may incorporate that data to produce a more informative prior

Non-informative prior

Informative prior

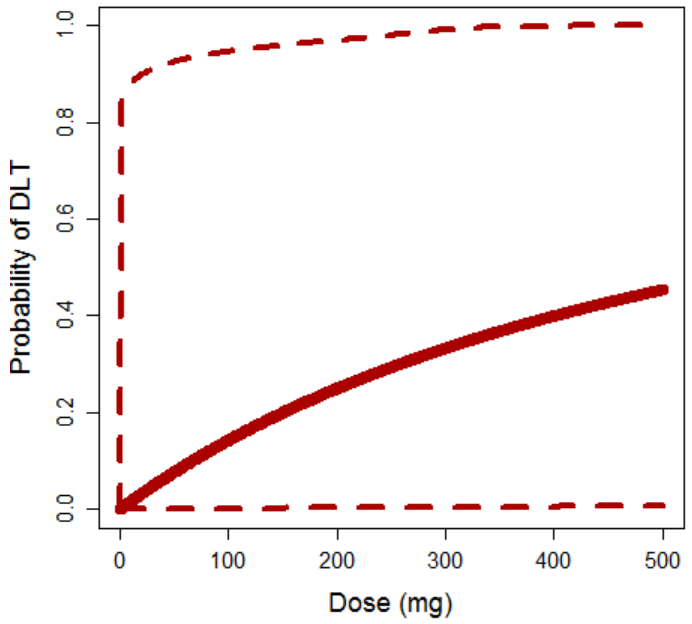
$$\begin{pmatrix}\log\alpha\\ \log\beta\end{pmatrix} \sim \text{BVN}\left(\begin{pmatrix}0.33\\ 0\end{pmatrix}, \begin{pmatrix}2, 0\\ 0, 1\end{pmatrix}\right) \quad \text{BVN}\left(\begin{pmatrix}-1.96\\ 0.479\end{pmatrix}, \begin{pmatrix}0.910, -0.235\\ -0.235, 0.634\end{pmatrix}\right)$$

- How can we help our colleagues understand what this means?
  - Does our prior match their prior beliefs about the dose/toxicity relationship

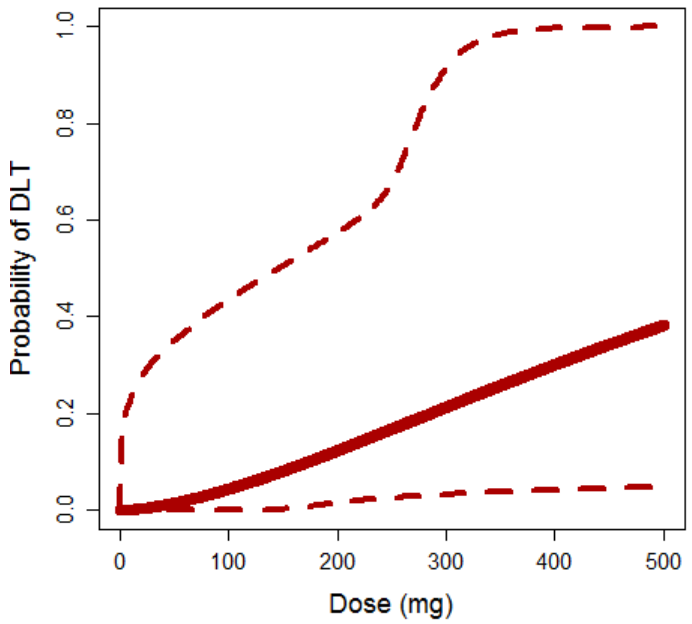
Priors

- Simple graphical summary to describe the ‘space’ of possible curves
- Simple explanation, clear and intuitive interpretation

Non-informative prior



Informative prior

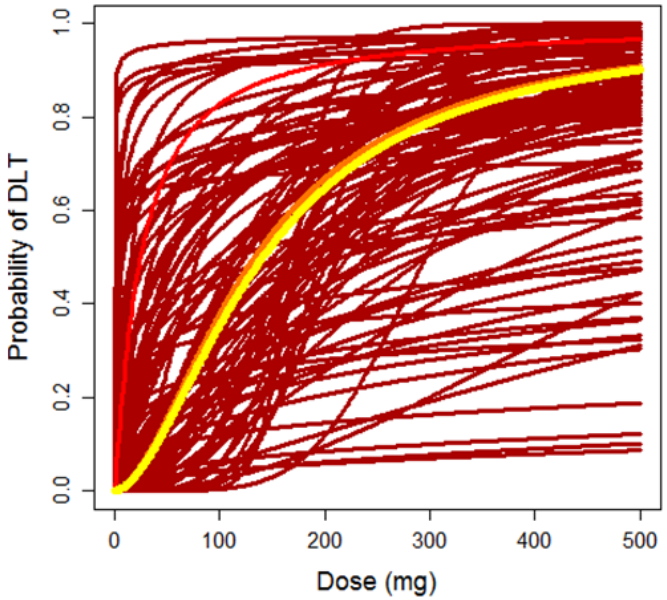


NOVARTIS

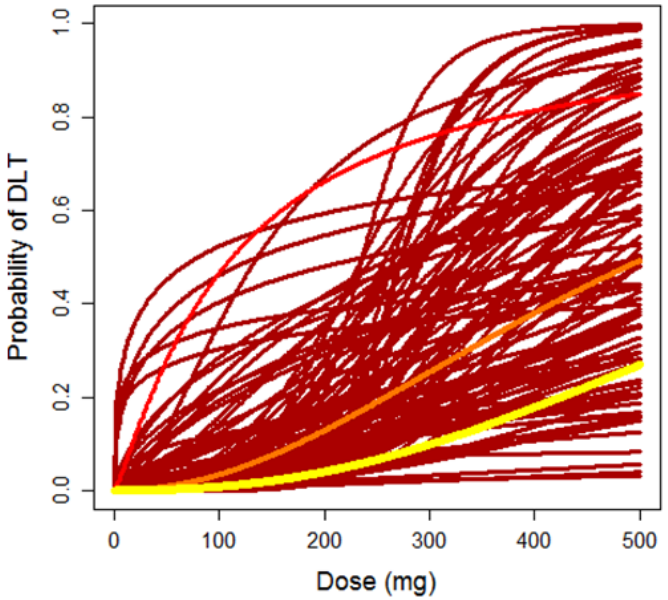
Priors

- We can illustrate further...
- What sort of curves are 'possible' based on our prior?

Non-informative prior



Informative prior

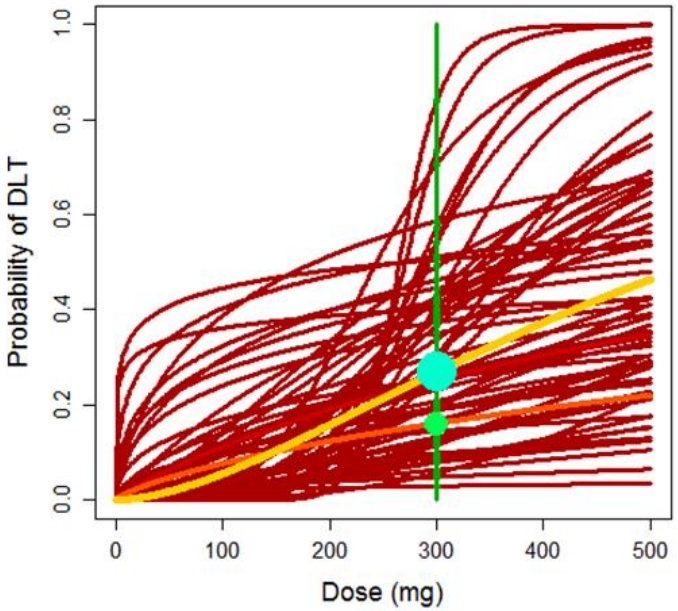


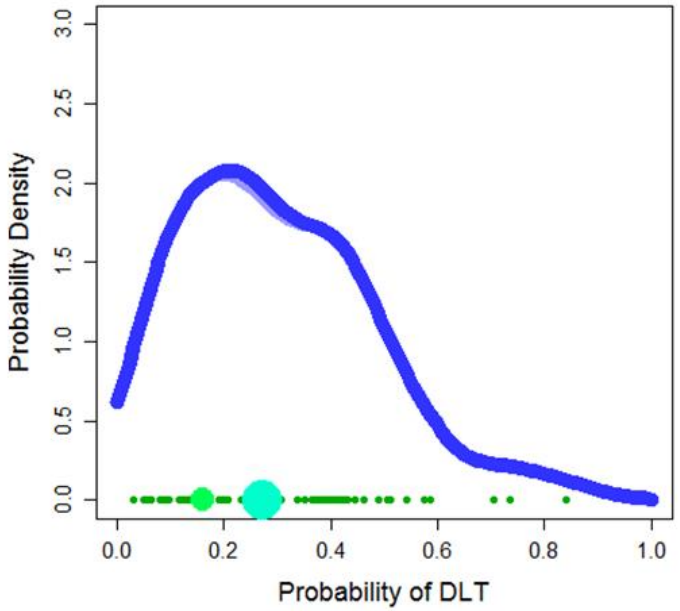
NOVARTIS

Learning about toxicity at a given dose

- And how do we turn these random curves into information about toxicity at a given dose?

Informative prior





NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

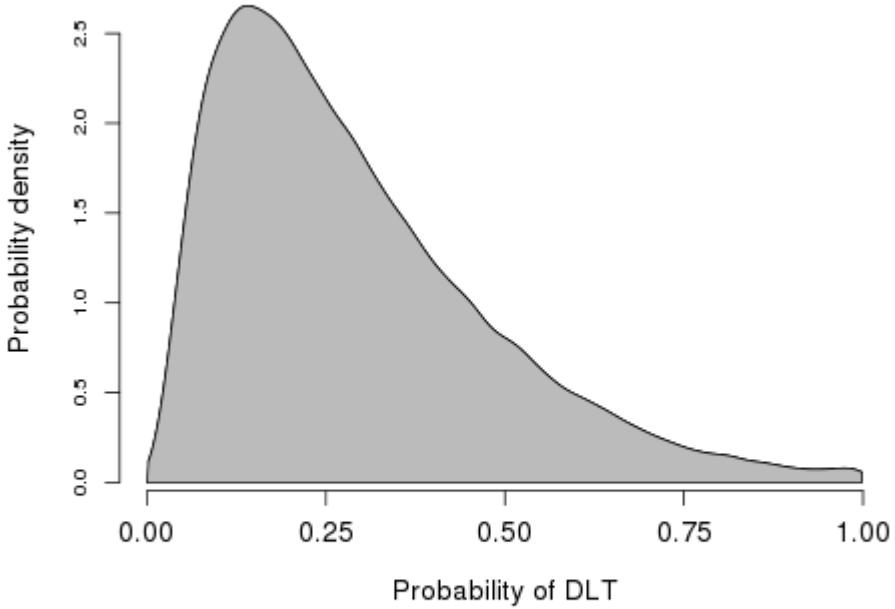
- Patients will not receive a dose for which there is a posterior probability greater than 25% that the probability of DLT will exceed 33%
- Tricky concept: ‘Probability of a probability’, ‘25%’, ‘33%’?
- Break into manageable chunks
  - Define ‘excessive toxicity’
    - If risk of DLT exceeds 33%, dose is excessively toxic
  - But we’re never sure of the true risk, we only have an estimate with error

Reference: Babb et al.

EWOC: Understanding a concept

Escalation with overdose control

300mg

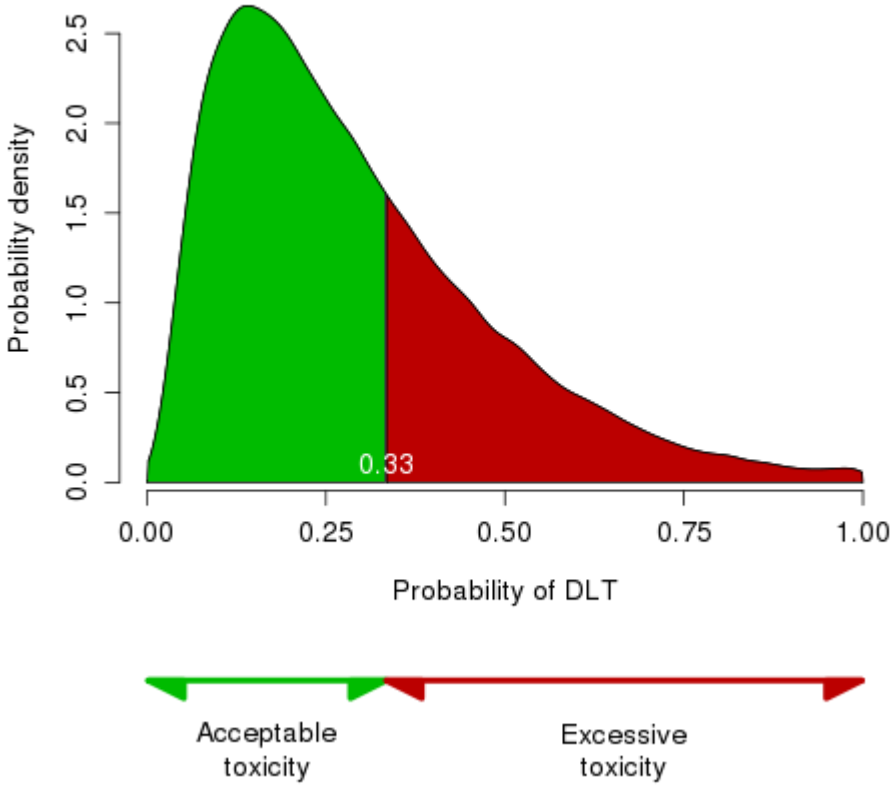


NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

300mg

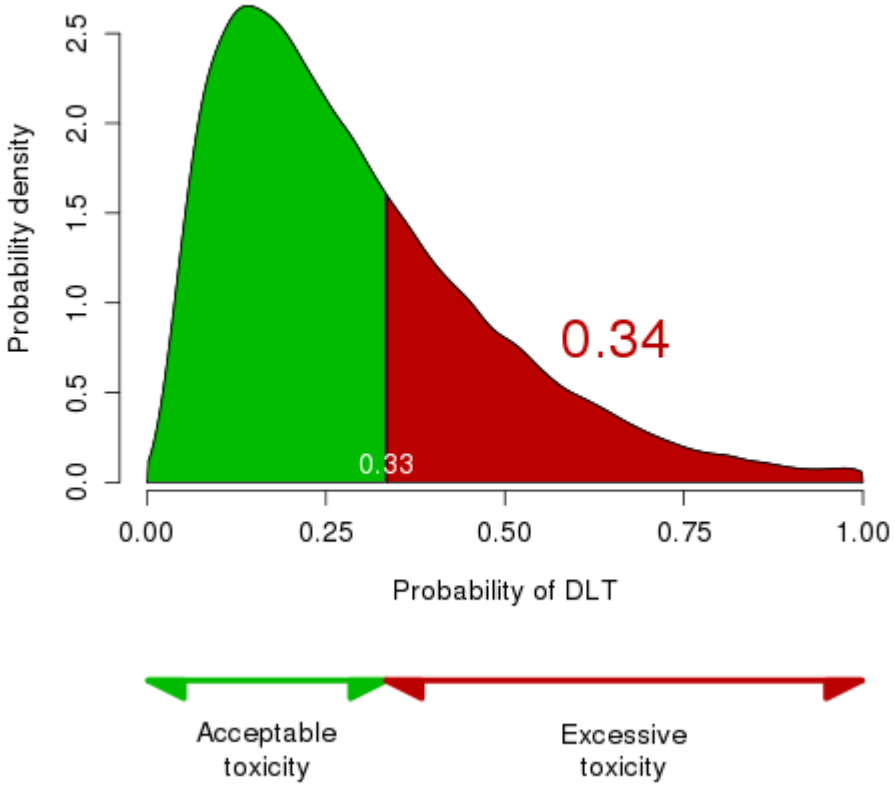


NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

300mg

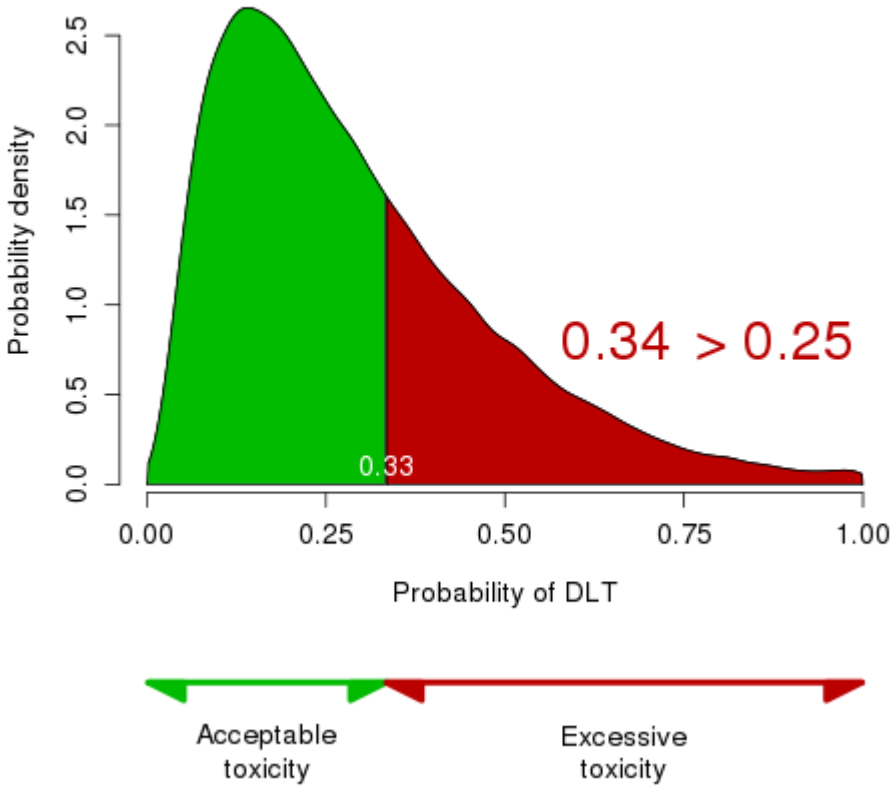


NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

300mg

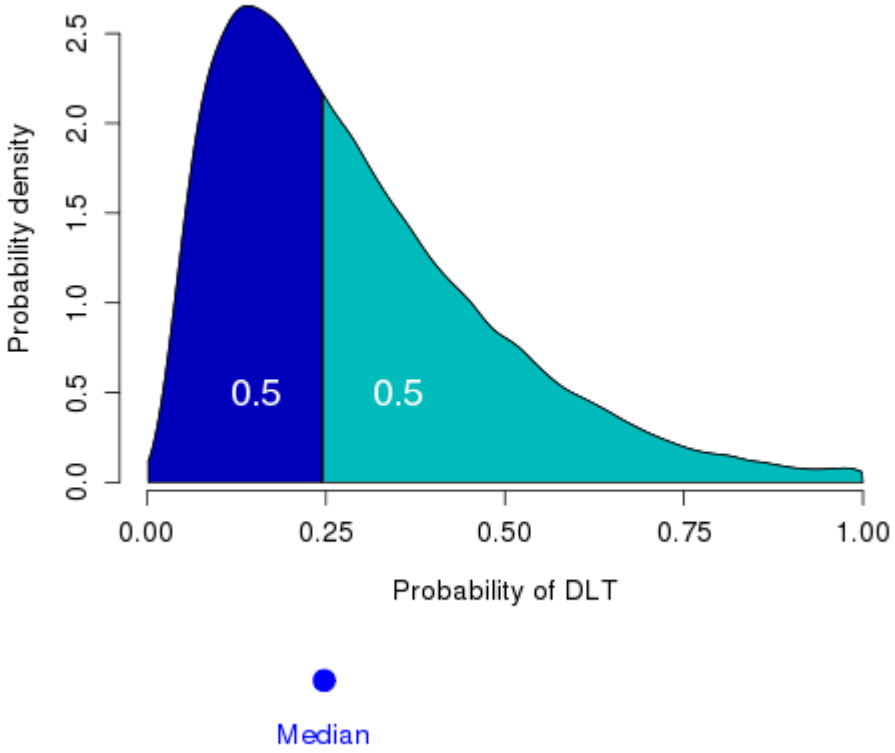


NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

300mg

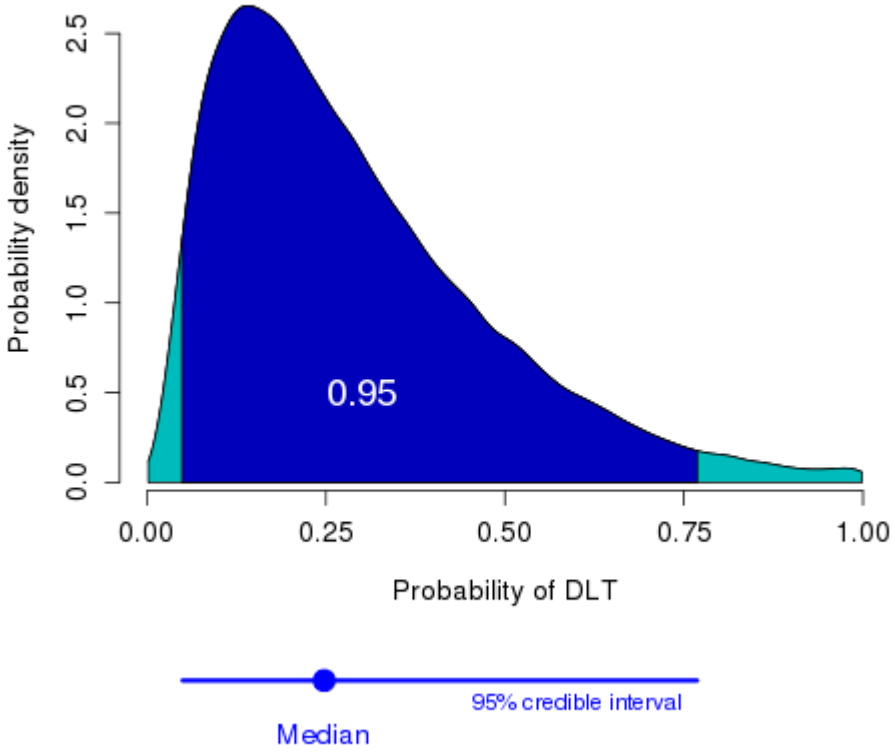


NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

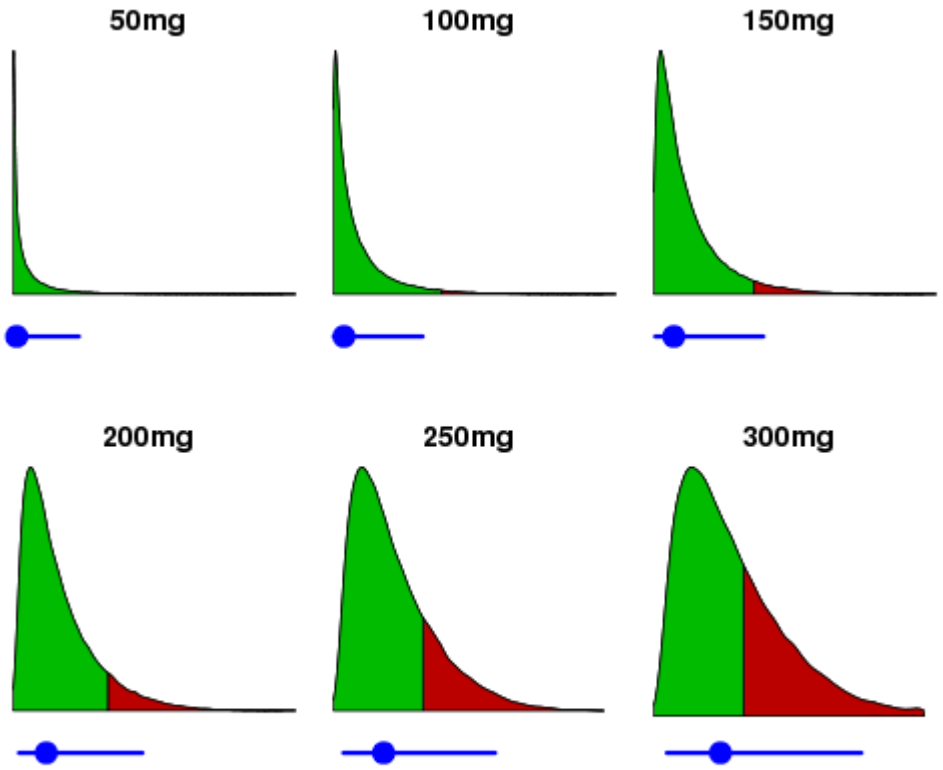
300mg



NOVARTIS

EWOC: Understanding a concept

Escalation with overdose control

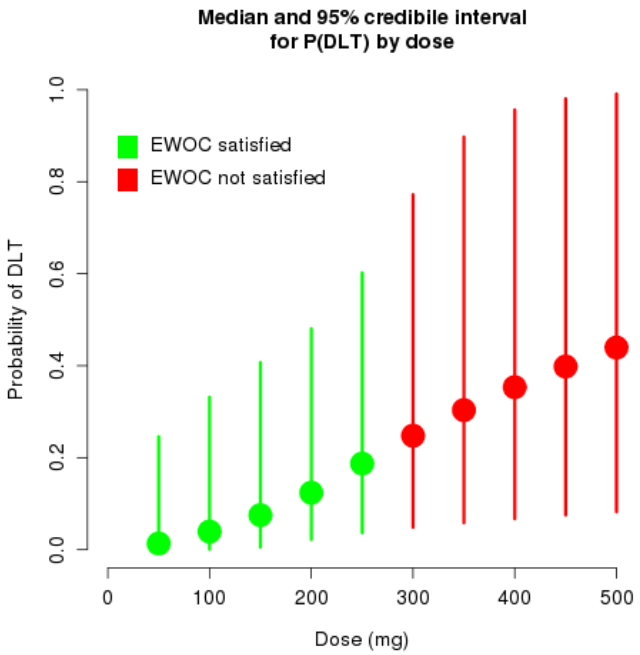


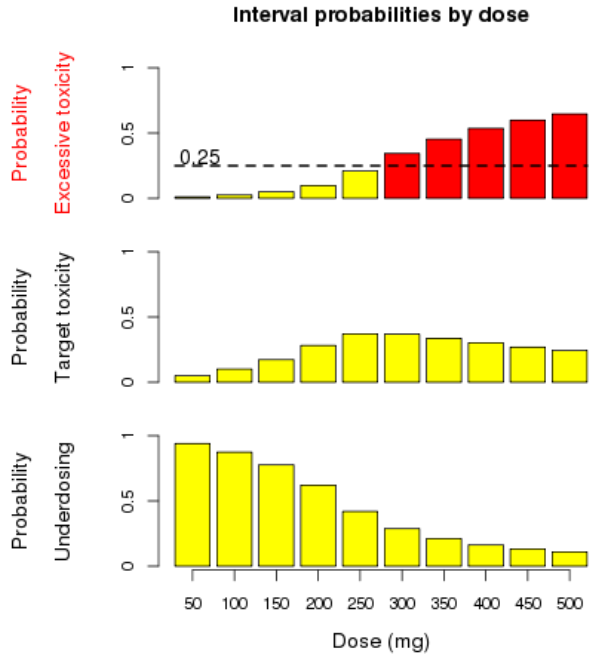
NOVARTIS

Dose decisions

Supporting a dose recommendation

- Graphical summaries used to support dose escalation decisions
  - To the point – what doses may be safely used?





NOVARTIS

Communication with Statisticians

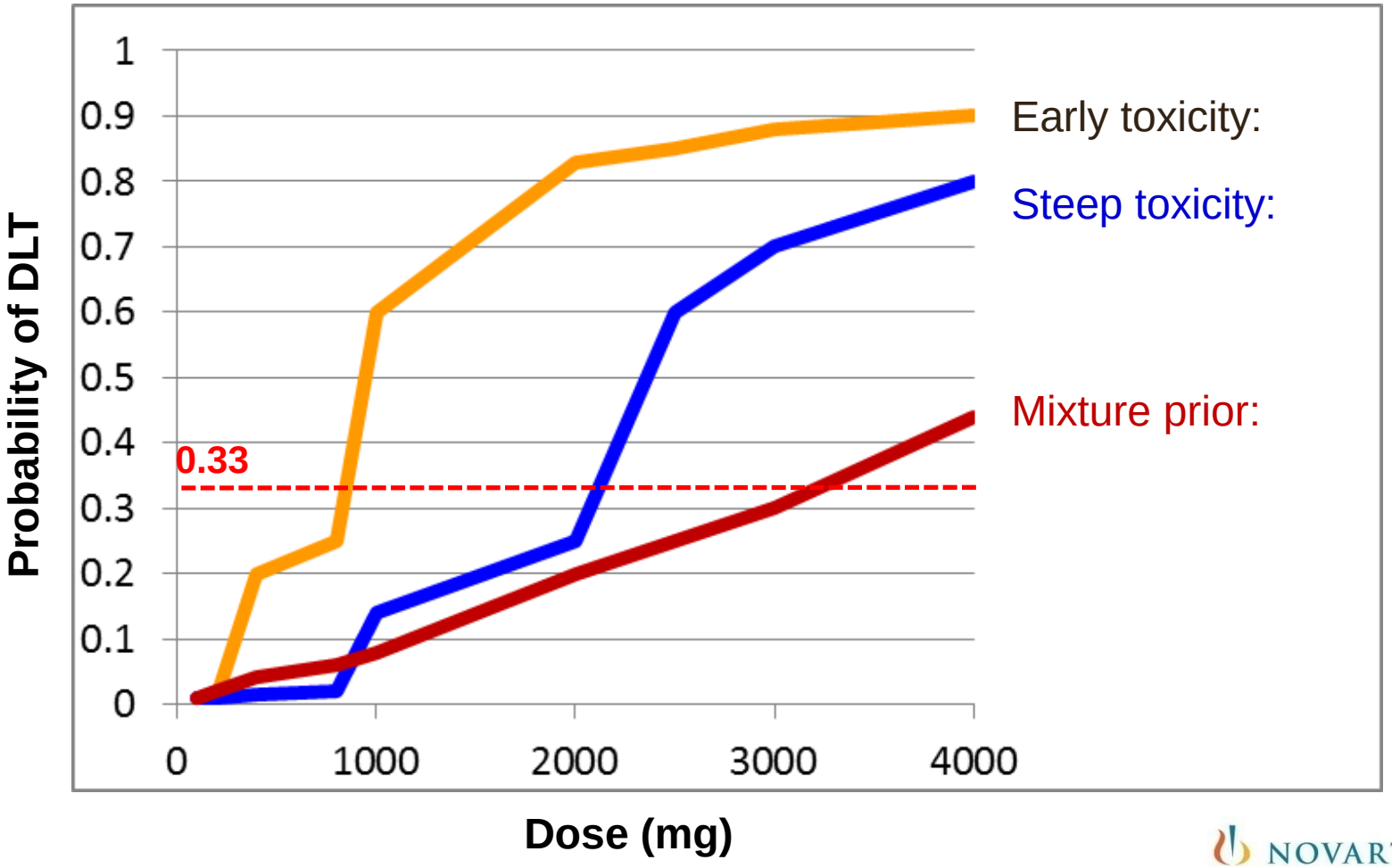
Statistically bilingual

- We need to be statistically bilingual
- Enable a frequentist to understand the properties of our Bayesian design
  - For our model based Phase I approach this typically includes an investigation of operating characteristics

Communication with Statisticians

Statistically bilingual

- How does our model operate under a number of 'true' scenarios

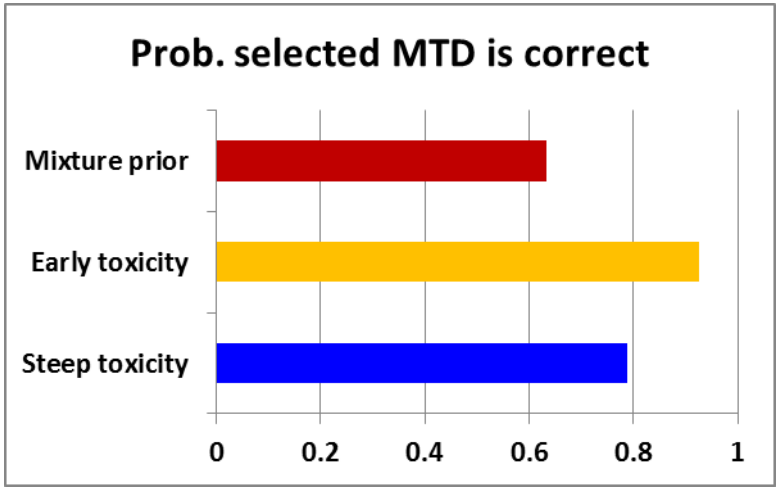


NOVARTIS

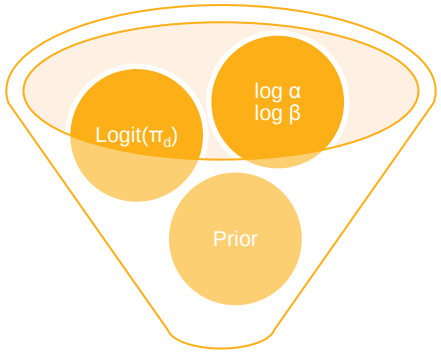
Communication with Statisticians

Statistically bilingual

- Summary metrics:
  - Do we have a high (long run) probability of correctly identifying the MTD?
  - Is our approach successful at minimizing the risk of a patient being exposed to an excessively toxic dose?



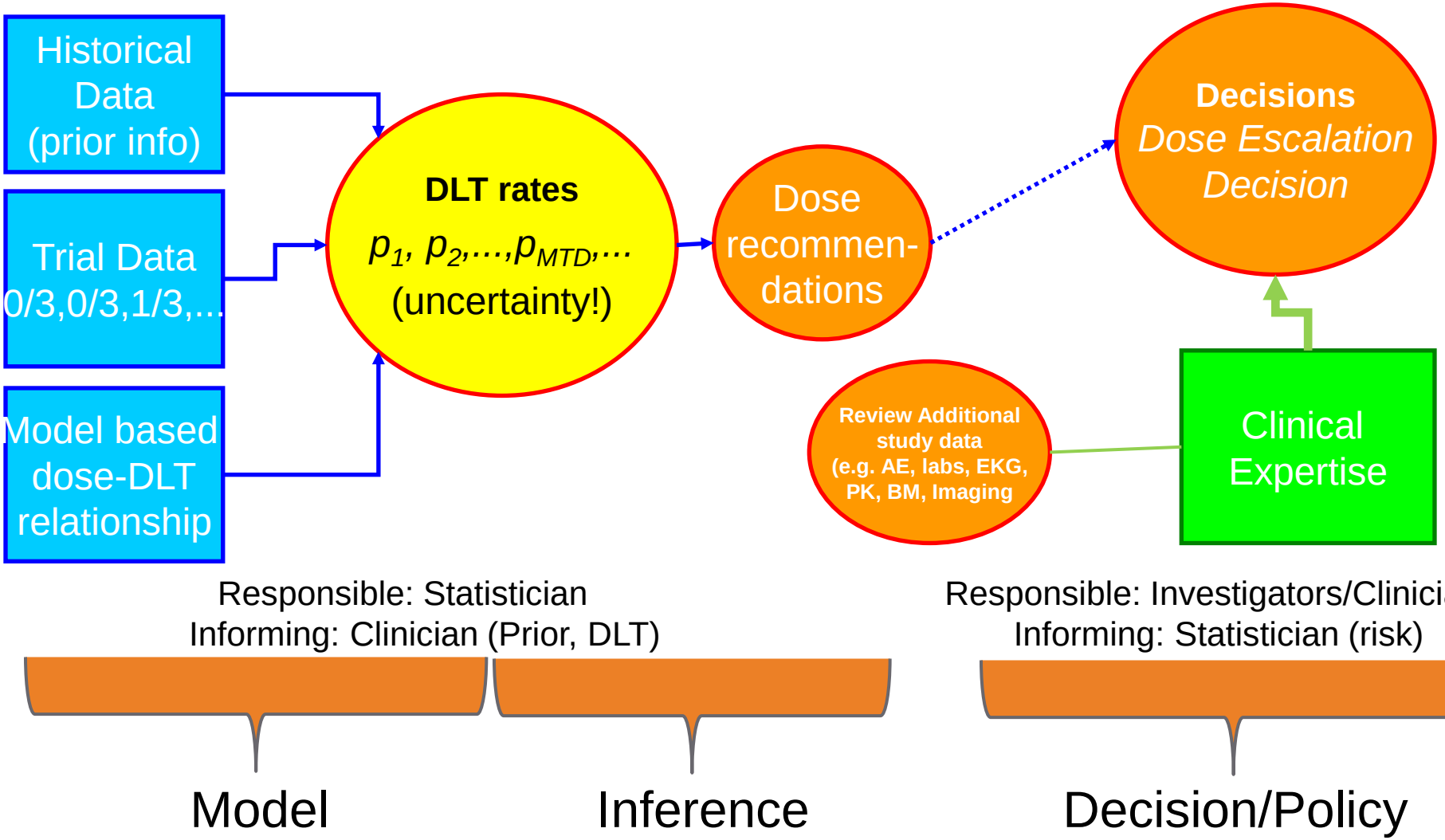
True Scenario	I	II	III	IV	V	VI	VII
Mixture prior	**63.3**	8.1	28.6	28.0	5.1	25.2	3.5
Early toxicity	**92.5**	4.3	3.2	58.4	13.5	24.7	5.2
Steep toxicity	**78.8**	0.6	20.6	36.8	9.9	25.7	3.8



NOVARTIS

Dose decisions

Clinically driven, statistically supported decisions



NOVARTIS

Dose decisions

Clinically driven, statistically supported decisions

- Maximum dose recommended by the Bayesian logistic regression model
- Statistician thinks:
  - I've run the model using the latest data. I've applied the EWOC criterion, and considered the protocol specified rules for dose escalation. Taking all of this into account tells us that this is the maximum dose that can safely be given to future patients. Now it's up to the team to make an informed choice about which dose to investigate next...
- Clinician thinks:
  - This is the dose

Efficiency

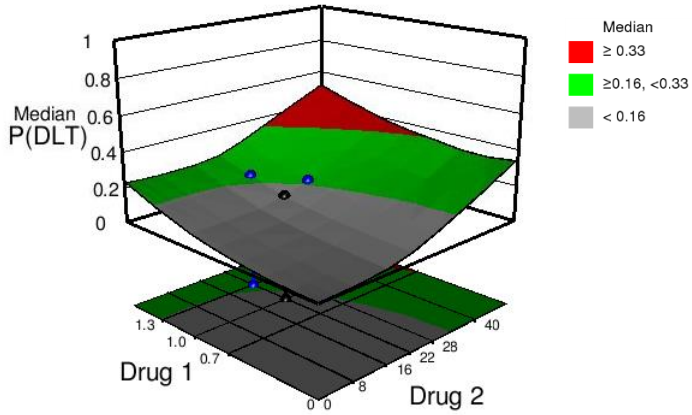
- We aim to use the available information efficiently
- To a statistician this is shorthand for many things:
  - We won't make decisions based purely on the current cohort
  - We will formally incorporate prior information into the analysis
  - The team will have flexibility to consider other data to make an informed decision
  - We can recruit additional patients if we need to explore further
- The clinicians response:
  - But my dose escalation has enrolled more than 50 patients
  - If I used 3+3 I could do this with just 12 patients!
  - This approach is not efficient!

Lost in translation

- Don’t assume we have a common understanding
- Need to develop a shared vocabulary
- These aren’t necessarily statistical concepts
- But clear communication is important

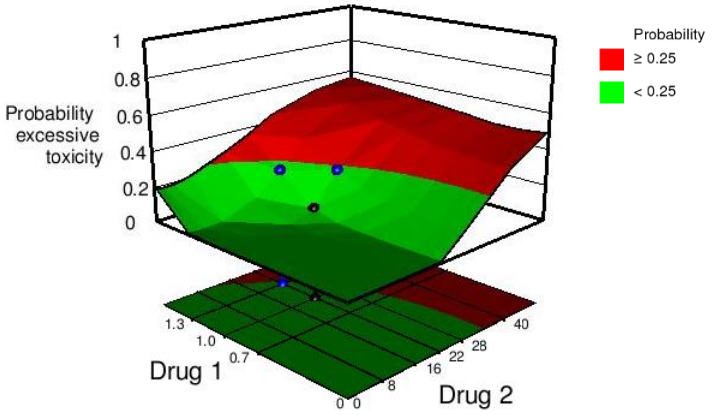
Beyond single agent

- Dual combination
  - More complex visualizations
- Triple (or more!) combinations
  - How to maintain simplicity and clarity of communication?



P(Excessive toxicity)

Drug 1 (mg) \ Drug 2 (mg)	8	16	22	28	40
0.7	0.00	0.00	0.01	0.15	0.40
1.0	0.00	0.00	0.05	0.23	0.45
1.3	0.01	0.09	0.21	0.35	0.50



NOVARTIS

Combination dose escalation

Drug-drug interaction

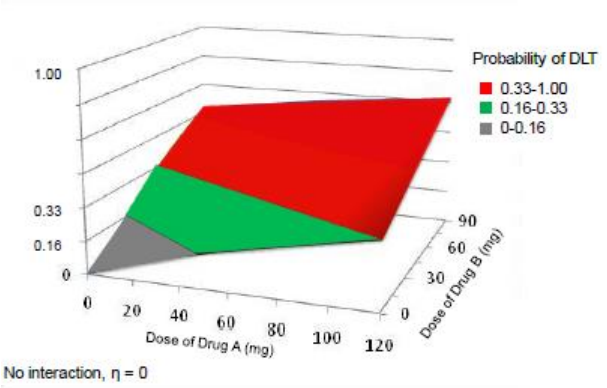
$$odds(\pi_{A(dA)B(dB)}) = odds(\pi^{0}{}_{A(dA)B(dB)})\exp(\eta)$$

- Flexible model, allowing for DDI
- DDI is modeled as an odds multiplier
  - How to translate this concept for a non-statistical audience?

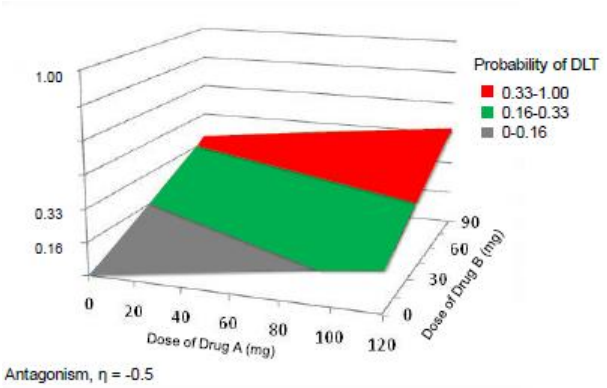
Combination dose escalation

Drug-drug interaction

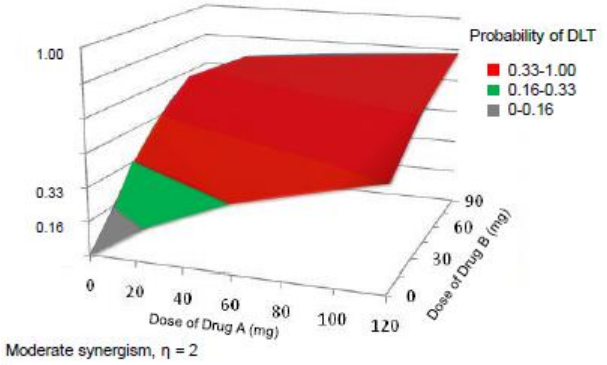
$$odds(\pi_{A(dA)B(dB)}) = odds(\pi^{0}{}_{A(dA)B(dB)})\exp(\eta)$$



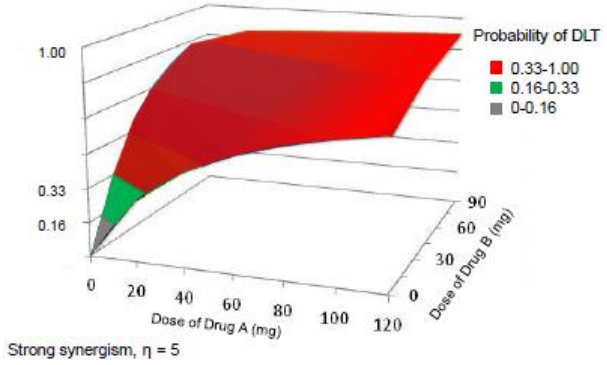
No interaction, η = 0



Antagonism, η = -0.5



Moderate synergism, η = 2



Strong synergism, η = 5

NOVARTIS

Combination dose escalation

Drug-drug interaction

$$odds(\pi_{A(dA)B(dB)}) = odds(\pi^{0}{}_{A(dA)B(dB)})\exp(\eta)$$

- Here DDI is introduced on a safety scale
  - Perhaps our colleagues are more accustomed to thinking of DDI in terms of PK rather than safety
  - Not the same, but not unrelated - PK interaction may inform safety interaction

Combination dose escalation

Drug-drug interaction

$$odds(\pi_{A(dA)B(dB)}) = odds(\pi^{0}{}_{A(dA)B(dB)})\exp(\eta)$$

- New challenge:
  - How to we help teams better understand and interpret our interaction parameter?
  - How do we elicit prior distributions
  - Do we look for more complex statistical solutions?
    - Do we even need to ‘tease apart’ PK and safety interaction? Or is it enough that we have a flexible model to guide escalation?

Summary

- The move to Bayesian model based dose escalations shows how we can motivate change by:
  - Engaging colleagues
  - Demonstrating tangible advantages for the team, and for patients
  - Use conceptual thinking to help the team understand a more challenging design
- Good communication requires:
  - Engagement
  - Ingenuity
  - Constant refinement
  - Hard work!

References

- Babb, Rogatko, Zacks. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Statistics in Medicine*1998
- Bailey, Neuenschwander, Laird, Branson. A Bayesian case study in oncology phase I combination dose-finding using logistic regression with covariates. *JBS* 2009
- Demetri GD, Casali PG, Blay JY, von Mehren M, Morgan JA, Bertulli R, Ray-Coquard I, Cassier P, Davey M, Borghaei H, Pink D, Debiec-Rychter M, Cheung W, Bailey SM, Veronese ML, Reichardt A, Fumagalli E, Reichardt P. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2009 Sep 15;15(18):5910-6
- Neuenschwander, Branson, Gsponer. Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in Medicine*2008
- Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S: A Bayesian Industry Approach to Phase I Combination Trials in Oncology in Zhao W and Yang H. Statistical Methods in Drug Combination Studies. Chapman & Hall/CRC, 2014.
- Sessa C, Shapiro GI, Bhalla KN, Britten C, Jacks KS, Mita M, Papadimitrakopoulou V, Pluard T, Samuel TA, Akimov M, Quadt C, Fernandez-Ibarra C, Lu H, Bailey S, Chica S, Banerji U. First-in-human phase I dose-escalation study of the HSP90 inhibitor AUY922 in patients with advanced solid tumors. Clin Cancer Res. 2013 Jul 1;19(13):3671-80.

NOVARTIS