# Planning a Bayesian early-phase phase I/II study for human vaccines in HER2 carcinomas

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# Introduction (1)

- DNA vaccination can be envisaged as an efficient new way of preventing the slow progression of carcinogenesis in humans (Lollini et al. 2006)
- Cancer vaccines are much safer than cytotoxic agents (Hoos et al. 2007)

# Introduction (2)

Type of early phase drug development trial designs (Piantadosi 1997; Zohar et al. 2007)

- Phase I: trial design that has as a primary objective identifying the maximum tolerated dose (MTD) to administer
- Phase II: trial design with safety and efficacy estimation as a primary objective
- Phase I/II: aims to locate the most successful dose (MSD) i.e. the dose that maximizes the probability of observing a therapeutic response without toxicity

# Introduction (3)

- Commonly used phase I/II dose-finding designs use a Bayesian approach in order to determine the MSD. In this context, Bayesian inference requires incorporation of prior information on the dose-toxicity and dose-success relationships (Legezda 2001; Chaloner 2001).

# Introduction (4)

- Elicitation is the process of formulating a person's knowledge and beliefs about one or more unknown quantities of interest into a probability distribution for those quantities (Garthwaite et al. 2005).
- An elicitation is done well if the distribution that is derived accurately represents the experts' knowledge, regardless of how good this knowledge is.

# Introduction (5)

Motivation for eliciting prior beliefs in clinical trials: (Chaloner and Rhame 2001)

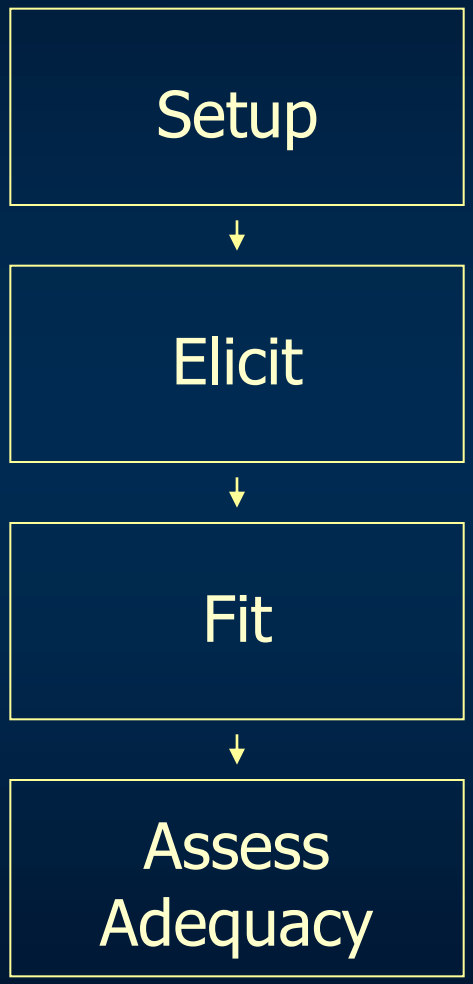
- Design and sample size
- Monitoring
- Bayesian methods
- Hindsight

# Objectives

The aims of this study were:

- to elicit prior probability distribution from physician's opinion about the available dose levels planned for phase I/II dose-finding clinical trials on human DNA vaccine in HER2 tumours
- to assess via simulations the impact of the choice of prior on the recommended dose level at the end of the trial

# Materials and Methods (1)




The elicitation process in four stages (O'Hagan 1998; Garthwaite et al 2005)

# Materials and Methods (2)

Prior elicitation process:

1. Expert's selection and identification of the aspects of the problem to elicit:

   13 researchers and physician selected

   initial guesses about toxicity and efficacy probability of the treatment per dose level (direct method)

2. Interaction with the experts:

   Questionnaire sent to the experts with a short cover letter

   They were asked not do discuss their answers with one another

# Materials and Methods (3)

3. Fit of probability distributions to the expert's summaries:

   Different priors for each dose level according to the choice of the percentile of the dose-toxicity distribution of the expert's opinion

   - enthusiastic prior 1 – the 10$^{th}$ p
   - enthusiastic prior 2 – the 25$^{th}$ p
   - informative prior – median p
   - skeptical prior 1 – the 75th p
   - skeptical prior 2 – the 90th p

# Materials and Methods (4)

4. Assessing the adequacy of the elicitation:

   Simulation study of 5000 independent dose-finding clinical trials. We investigated 100 different scenarios (each under the five different priors separately) in terms of dose-toxicity and dose-success relationship.

# Materials and Methods (5)

A phase I/II allocation scheme using an hybrid design (Ivanova 2003) was chosen:

- nonparametric response-adaptive design for the dose allocation scheme (up-and-down approach)

- estimation of the dose–toxicity relationship made using the Bayesian parametric modelling proposed for the continual reassessment method (O'Quigley et al 1990).

# Materials and Methods (6)

Dose space: $\Omega_d = \{d_1, ..., d_k\}$

$\Gamma$=maximal toxicity target

Binary indicators for toxicity (*Y=1 if toxicity, Y=0 otherwise*) and response (*V=1 if response, V=0 otherwise*)

$Q(d)$=probability of toxicity at dose $d$

$P(d)$=probability of response without toxicity at dose $d$

MSD: dose $d^*$ such that $P(d^*) = \max_{d \in \{d_1,...,d_k\} \& Q(d) \leq \Gamma} P(d)$

# Materials and Methods (7)

Allocation scheme:

Assuming that the most recent subject was treated with dose $d_j$ the dose level to be assigned to the next patient is:

- Dose $d_{j-1}$ if the most recent subject had toxicity
- Dose $d_j$ if the most recent subject had response with no toxicity
- Dose $d_{j+1}$ if the most recent subject had no response and no toxicity

# Materials and Methods (8)

The allocation scheme is adjusted by monitoring $Q(d)$.

Dose–toxicity relationship:

$$Q(d_j) = \alpha_j^a$$

$(\alpha_1, ..., \alpha_k)$: reflects elicited prior beliefs

$a$ : parameter with prior density taken to be $g(a) = e^{-a}$

# Materials and Methods (9)

After each patient's response, posterior toxicity probabilities at each dose are updated using Bayesian methods.

$d^{**}$ : maximum dose-level such that $P(d^{**}) \leq \Gamma$

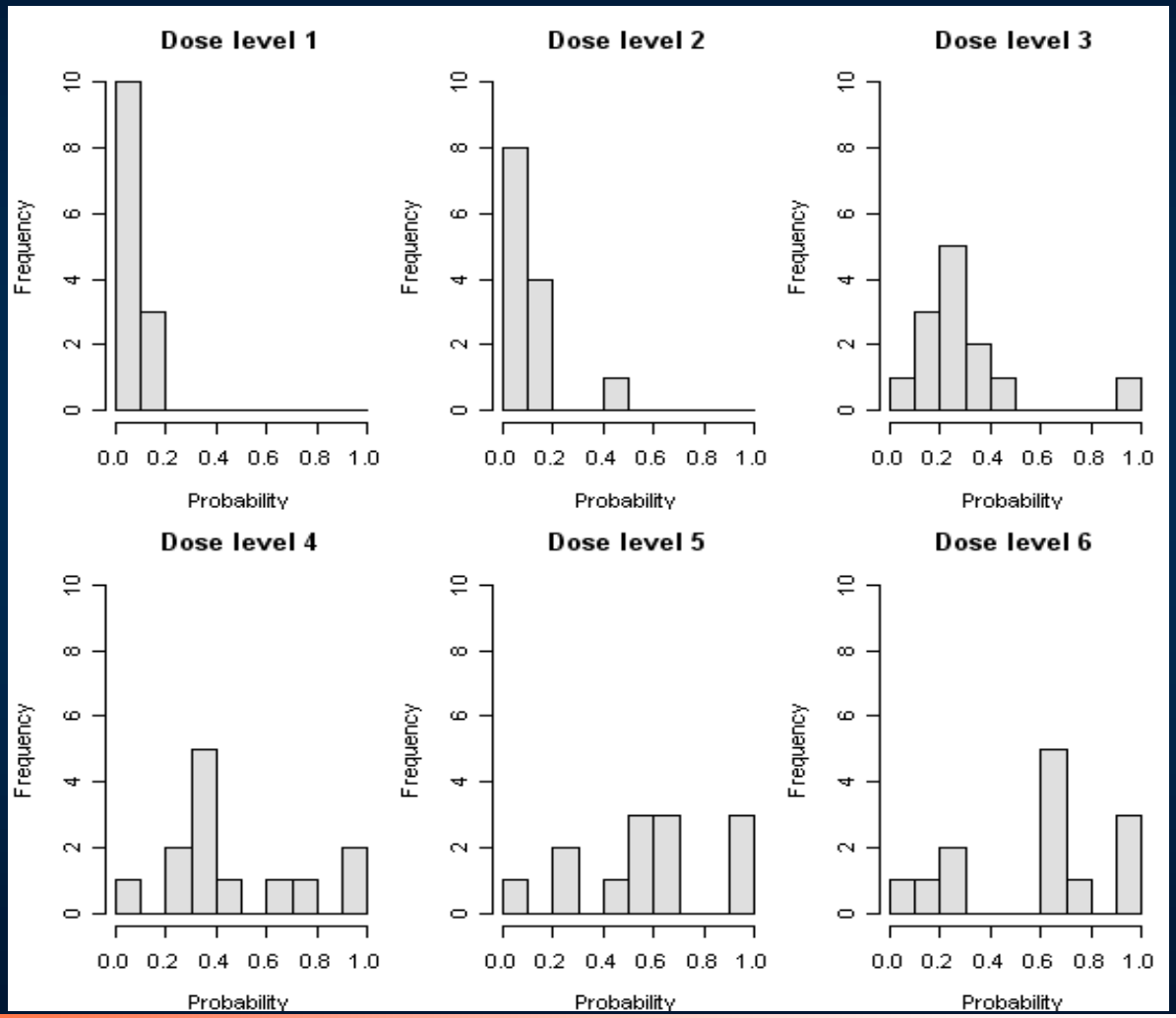
Next patient assigned to the dose $min(d^{**}, d_{allocation\ scheme})$

# Materials and Methods (10)

Stopping: decision taken based on the Sequential Probability Ratio Test (Wald 1947; O'Quigley 2001) to stop the trial for efficacy or futility

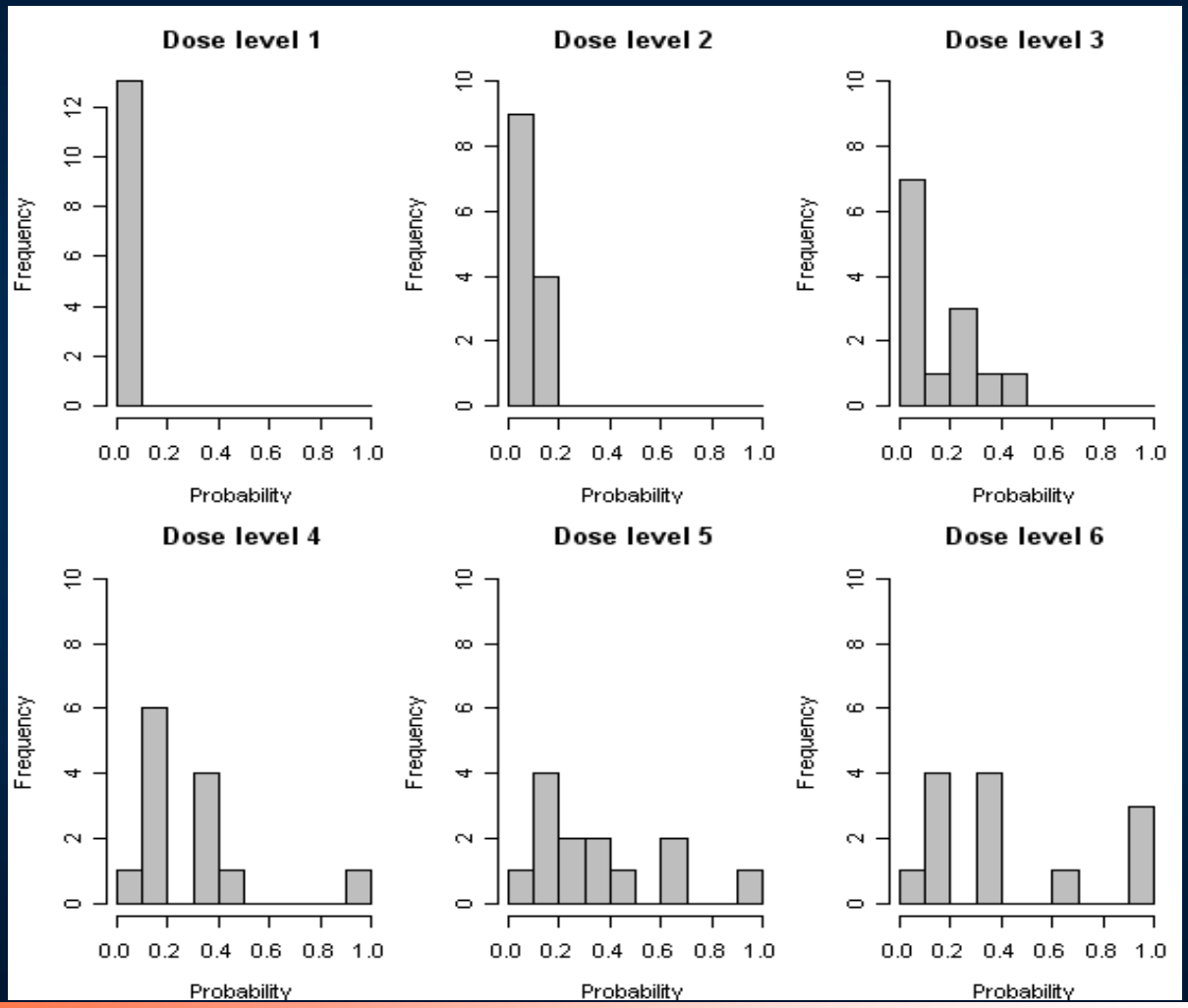
# Results (1)

Response distribution according to the expert's opinion by dose level.



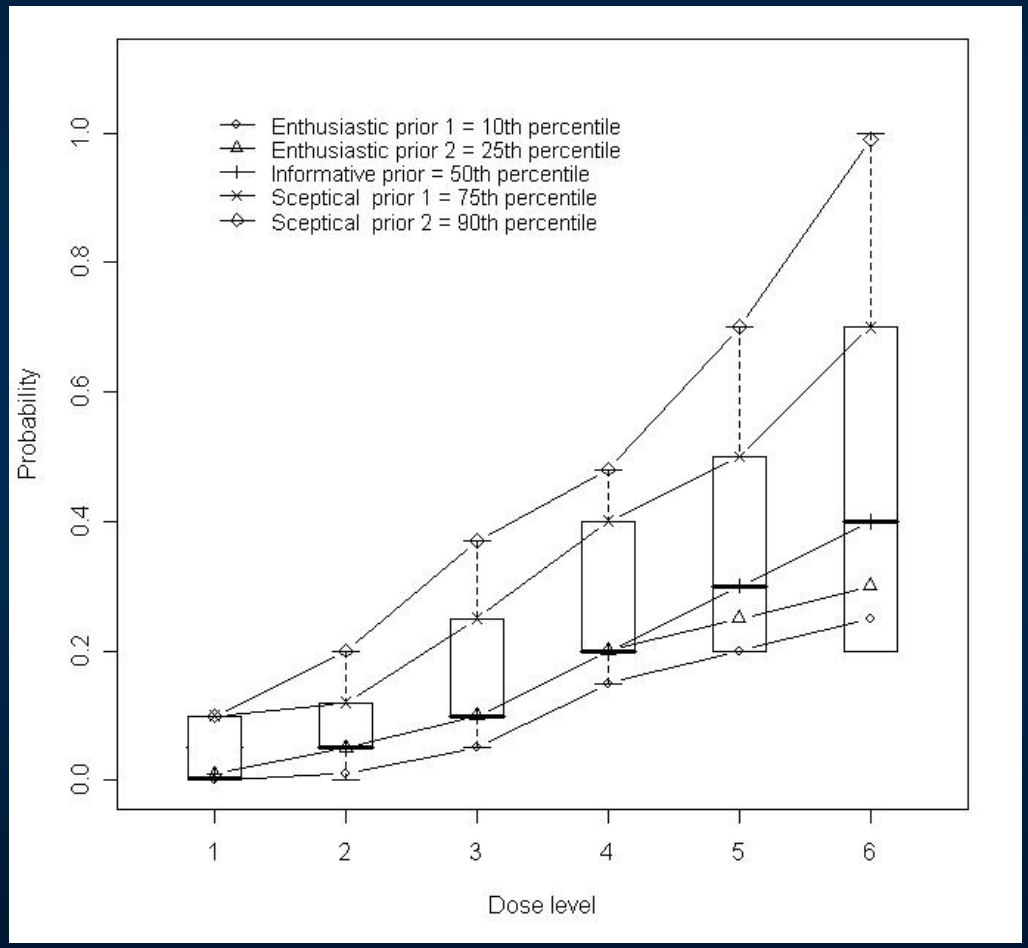
# Results (2)

Toxicity distribution according to the expert's opinion by dose level.



# Results (3)

Prior dose-toxicity relationships defined according to the expert's dose-toxicity distribution.



# Results (4)

| PRIOR (DOSE-TOXICITY) | MSD-1 | MSD | MSD+1 | Median sample size at stopping (Q1-Q3) | Mean % observed toxicities |
|---|---|---|---|---|---|
| **Enthusiastic prior 1:** 0.001 , 0.01 , 0.05 , 0.15 , 0.2 , 0.25 | 0.19 | 0.69 | 0.06 | 42 (36-54) | 10.8 |
| **Enthusiastic prior 2:** 0.01 , 0.05 , 0.1 , 0.2 , 0.25 , 0.3 | 0.21 | 0.65 | 0.09 | 44 (37-54) | 11.6 |
| **Informative prior:** 0.01 , 0.05 , 0.1 , 0.2 , 0.3 , 0.4 | 0.24 | 0.59 | 0.12 | 30 (28-34) | 8.1 |
| **Skeptical prior 1:** 0.1 , 0.12 , 0.25 , 0.4 , 0.5 , 0.7 | 0.21 | 0.63 | 0.07 | 38 (33-50) | 9.3 |
| **Skeptical prior 2:** 0.1 , 0.2 , 0.37 , 0.48 , 0.7 , 0.99 | 0.26 | 0.58 | 0.07 | 40 (33-49) | 8.4 |

# Results (5)

- The rate of finding the true MSD is not higher than 70%.
- Enthusiastic prior 1 always gave the higher percentage of correct selection (mean MSQ=0.006)
- Enthusiastic prior 2 always gave the higher median sample size at stopping.
- The informative prior gave the lower percentage of correct selection with the lower median sample size.

# Conclusion

- Introducing subjectivity into a scientific process by using expert opinion is a controversial issue.
- Caution must be taken when using predefined questionnaires since appropriate training for the clinicians to properly understand what exactly is expected from them is required.
- Including in a trial protocol a detailed section on the conduct of the elicitation process and the resulting assessments could be a first step to make the use of assessed distributions acceptable.