Dose-escalation designs for combination & dose-schedule studies

Lecture 6: Intro to combination/schedule problem

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Motivation

There is growing clinical interest in

- **Combining** several agents;
  - To achieve a better efficacy (synergistic/additive effect on efficacy);
  - To achieve better tolerability (antagonistic effect on toxicity)
- Studying various administration **schedules**:
  - Less intensive schedules (but with a higher dose) can result in similar efficacy but could be better tolerated by patients
- A shift to **integrate both** Phase I and Phase II clinical trials for Molecularly Target Agents (MTA)
  - efficacy reaches a plateau after a particular level
  - efficacy has an inverted-U shape

Single agent dose-escalation designs

Model-based methods

- CRM
- EWOC

Model-Assisted methods

- mTPI
- BOIN

Fundamental assumption - a **monotonic** dose-response relation.

Cannot be applied to:

- Combination trials with many treatments.
- Scheduling of drugs
- Non-monotonic relationships;

Overreaching theme: **unknown ordering** of combination/schedules/doses

Unknown ordering problem: Illustration

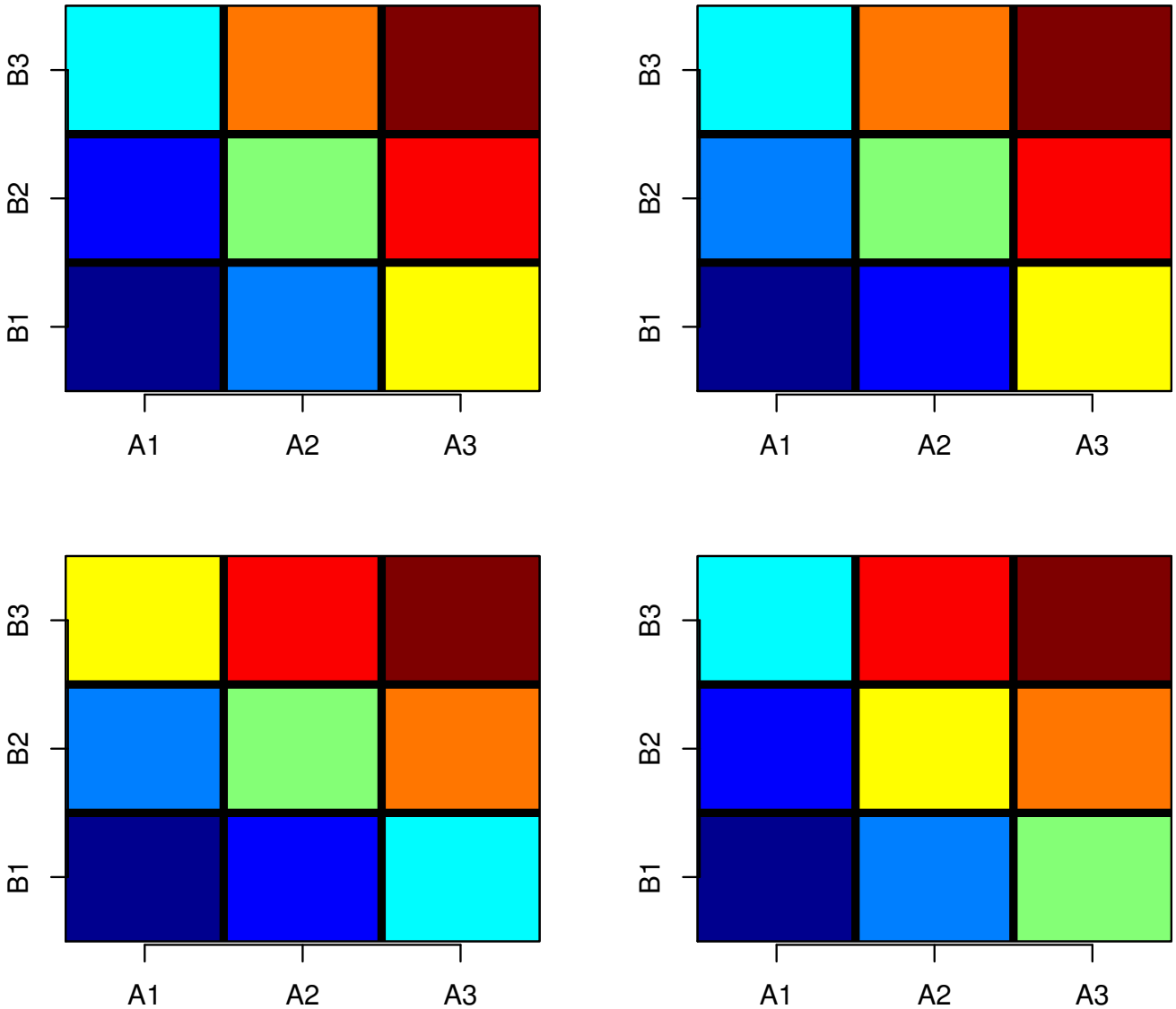
Let us consider drugs combination dose-escalation trial with

- 3 dose levels of drug A: A_1, A_2, A_3
- 3 dose levels of drug B: B_1, B_2, B_3

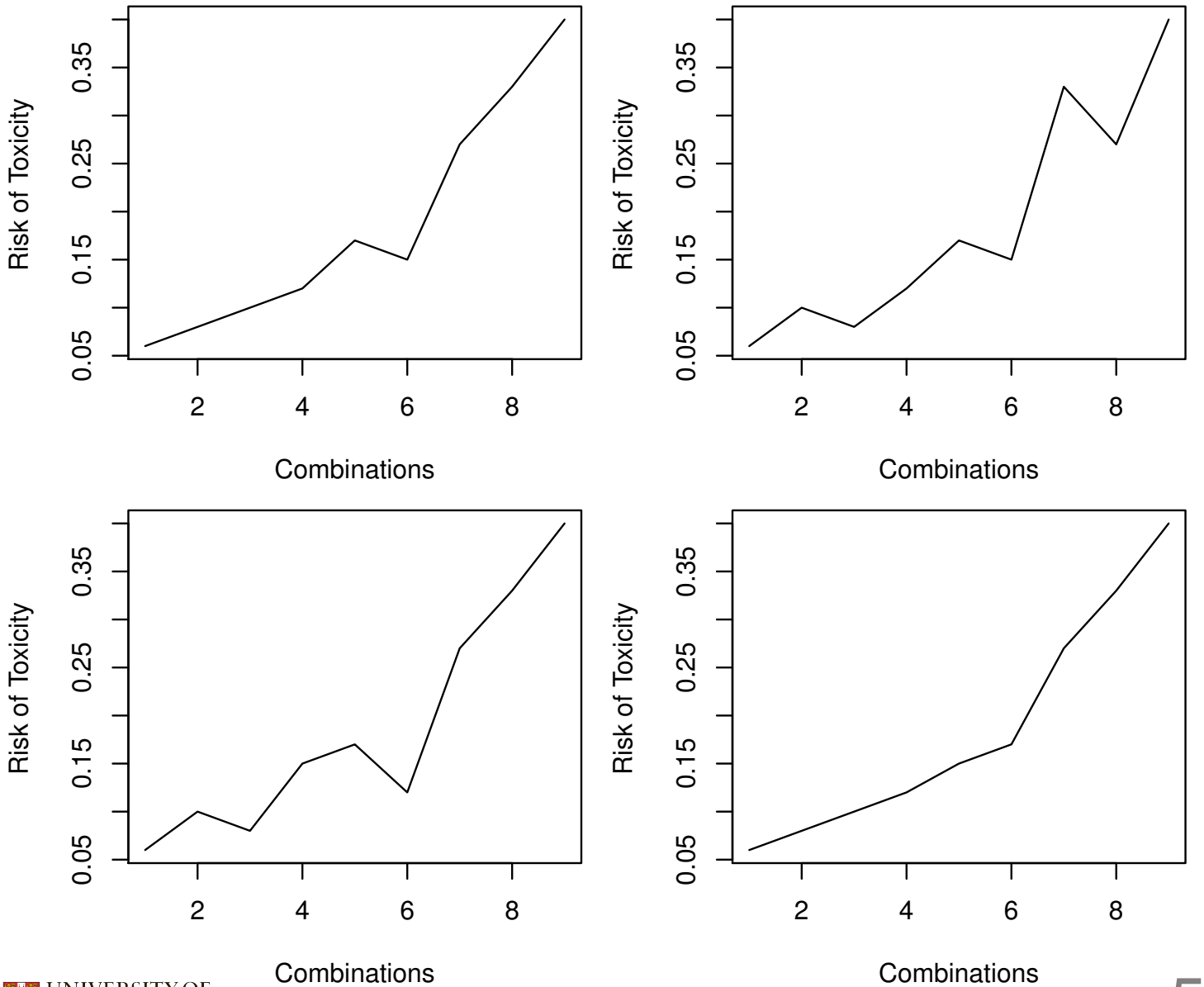
$(A_1; B_3)$	$(A_2; B_3)$	$(A_3; B_3)$
$(A_1; B_2)$	$(A_2; B_2)$	$(A_3; B_2)$
$(A_1; B_1)$	$(A_2; B_1)$	$(A_3; B_1)$

Even assuming monotonicity with each drug, we cannot order
$(A_1; B_2)$ and $(A_2; B_1)$;
$(A_1; B_3)$ and $(A_2; B_1)$;
$(A_1; B_3)$ and $(A_3; B_1)$ and so on...

Unknown ordering problem: Illustration



Unknown ordering problem: Illustration



Dose-schedule problem

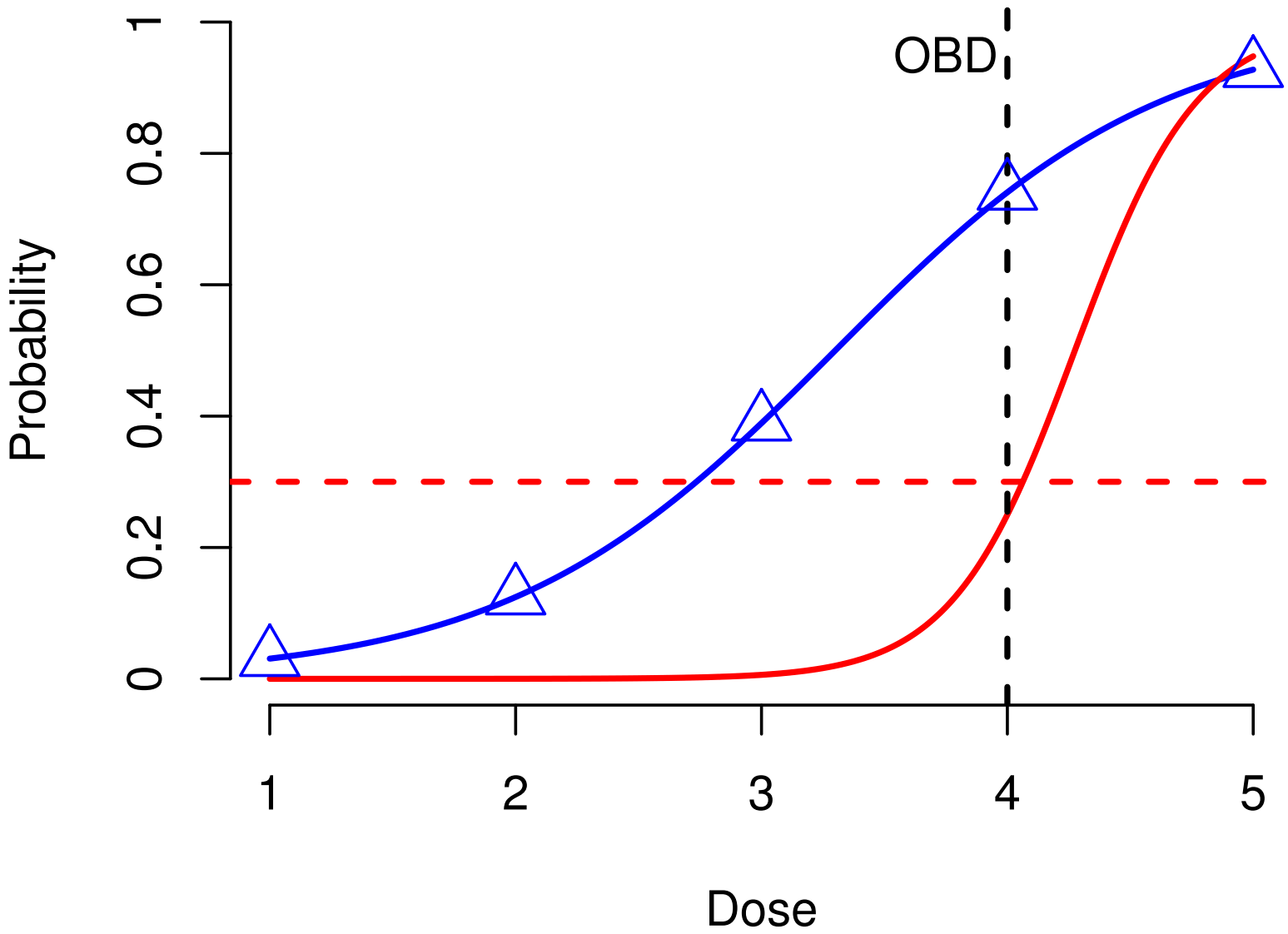
Consider a 6 days treatment of an experimental treatment:

- 10 mg, every day
- 15 mg, 2d on / 2d off
- 20 mg, 3d on / 3d off
- 5 mg, 3 times per day every day.

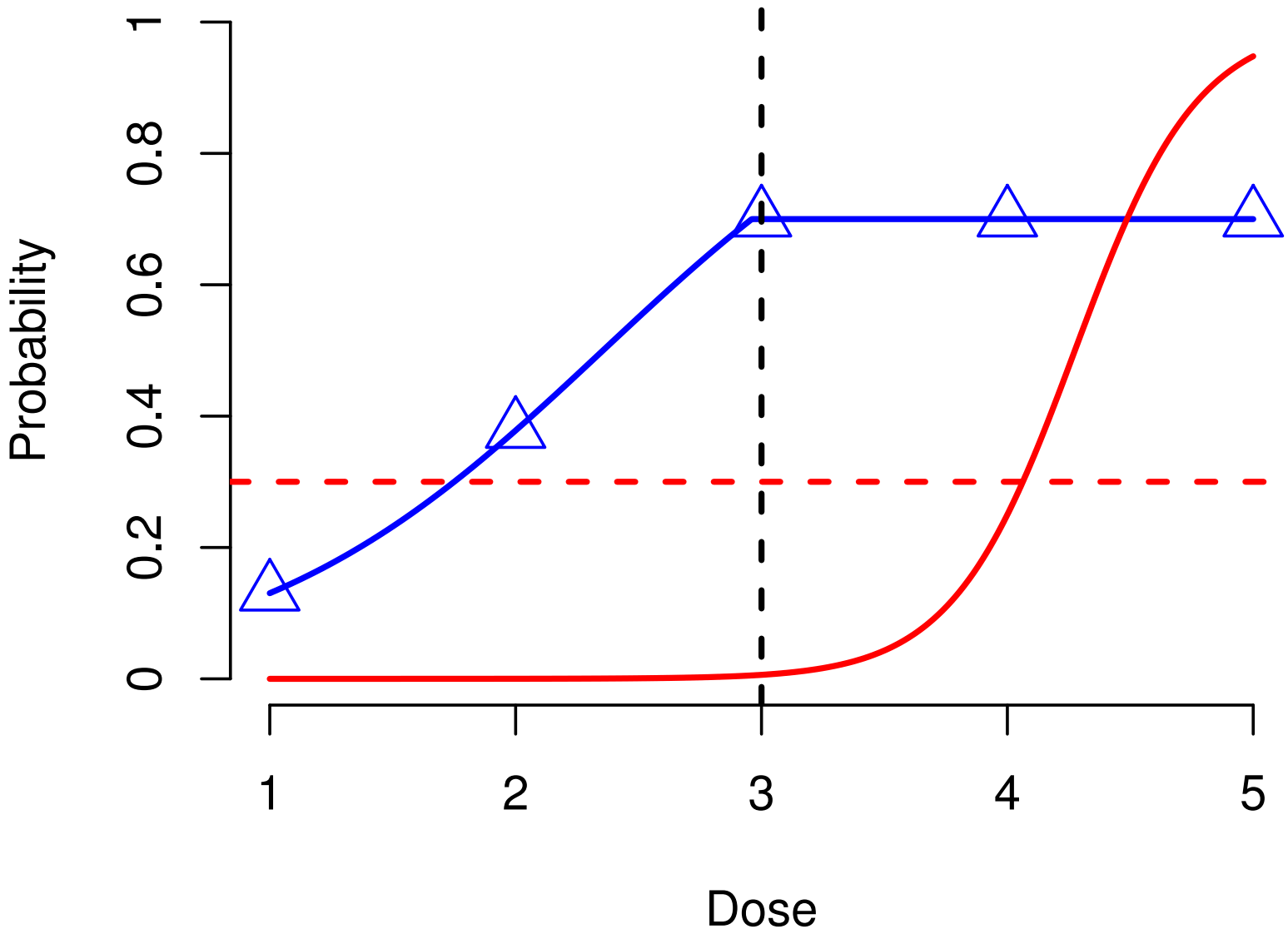
Possible **drivers of toxicity**:

- Single dose;
- Total dose;
- Schedule;
- Combination of the above?

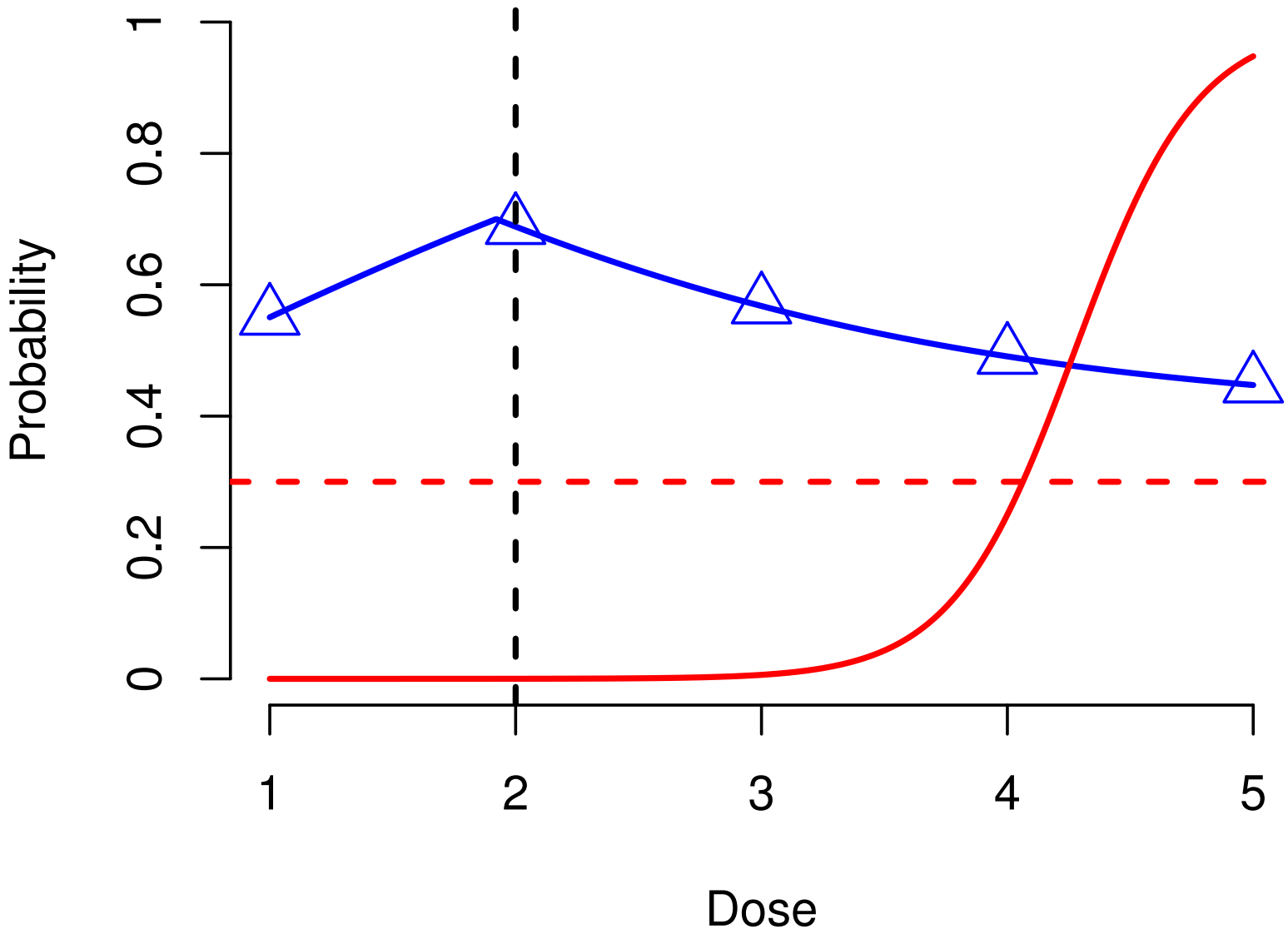
Dose-escalation for MTAs



Dose-escalation for MTAs



Dose-escalation for MTAs



Combination-schedule for MTAs

Combinations (immunotherapy + chemo) under different schedules:

- 2 days immunotherapy AFTER chemotherapy (S_1)
- 3 days immunotherapy AFTER chemotherapy (S_2)
- 4 days immunotherapy OVERLAP with chemotherapy for 1 days (S_3)
- 4 days immunotherapy OVERLAP with chemotherapy for 2 days (S_4)

Six regimens are considered in the trial:

Regimen	R_1	R_2	**R_3**	**R_4**	**R_5**	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

Single-agent design in combination-schedule problem

	R_1	R_2	R_3	R_4	R_5	R_6	Stop	Mean	DLTs
				Scenario 1.1					
True	0.05	0.10	0.20	**0.30**	0.45	0.70			
CRM	0.00	5.54	23.21	**47.60**	21.71	2.07	0.01	29.99	8.85
mTPI	2.68	12.32	32.20	**38.65**	13.71	0.41	0.03	29.99	7.08
				Scenario 1.2					
True	0.05	0.10	**0.30**	0.20	0.45	0.70			
CRM	0.06	8.50	18.65	**40.14**	29.55	3.10	0.00	30.00	8.59
mTPI	2.77	28.75	22.71	**31.68**	13.66	0.40	0.03	29.99	6.84
				Scenario 1.3					
True	0.05	0.10	0.20	0.45	**0.30**	0.70			
CRM	0.00	9.03	34.87	**35.80**	16.36	3.94	0.01	30.00	8.89
mTPI	2.68	12.42	**58.45**	14.28	11.73	0.41	0.03	29.99	7.07

Content of this course

- While these problems look different, the associated statistical challenges are similar (if not the same);
- In this part of the course, we will introduce the methods allowing to relax monotonicity assumption in;
  - combination trials with one agent being fixed;
  - combination trials with both agents being escalated;
  - dose-schedule trials;
  - Phase I/II trials;
- And learn how to implement them in `R`.