Phase I clinical trials in oncology

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Phase I oncology trials vs other diseases: how are they different?

	Oncology	Most other diseases
Overriding concern	Avoid or delay a fatal outcome	First do no harm
Subjects	With advanced, refractory disease	Healthy volunteers
Preferable dose	Maximum tolerated	Minimum effective
Direct subject benefit	At therapeutic doses	None expected

Phase I oncology trials vs other diseases: how are they similar?

	Oncology	Most other diseases
Number of subjects	As limited as possible (ethics and cost)	As limited as possible (ethics and cost)
Surrogates desirable	For activity / efficacy	For safety
Information obtained for later trials	Toxicity, early signs of activity	PK/PD
Move quickly to trials in	Patients with target tumor	Patients with target disease

Objectives of phase I trials in oncology

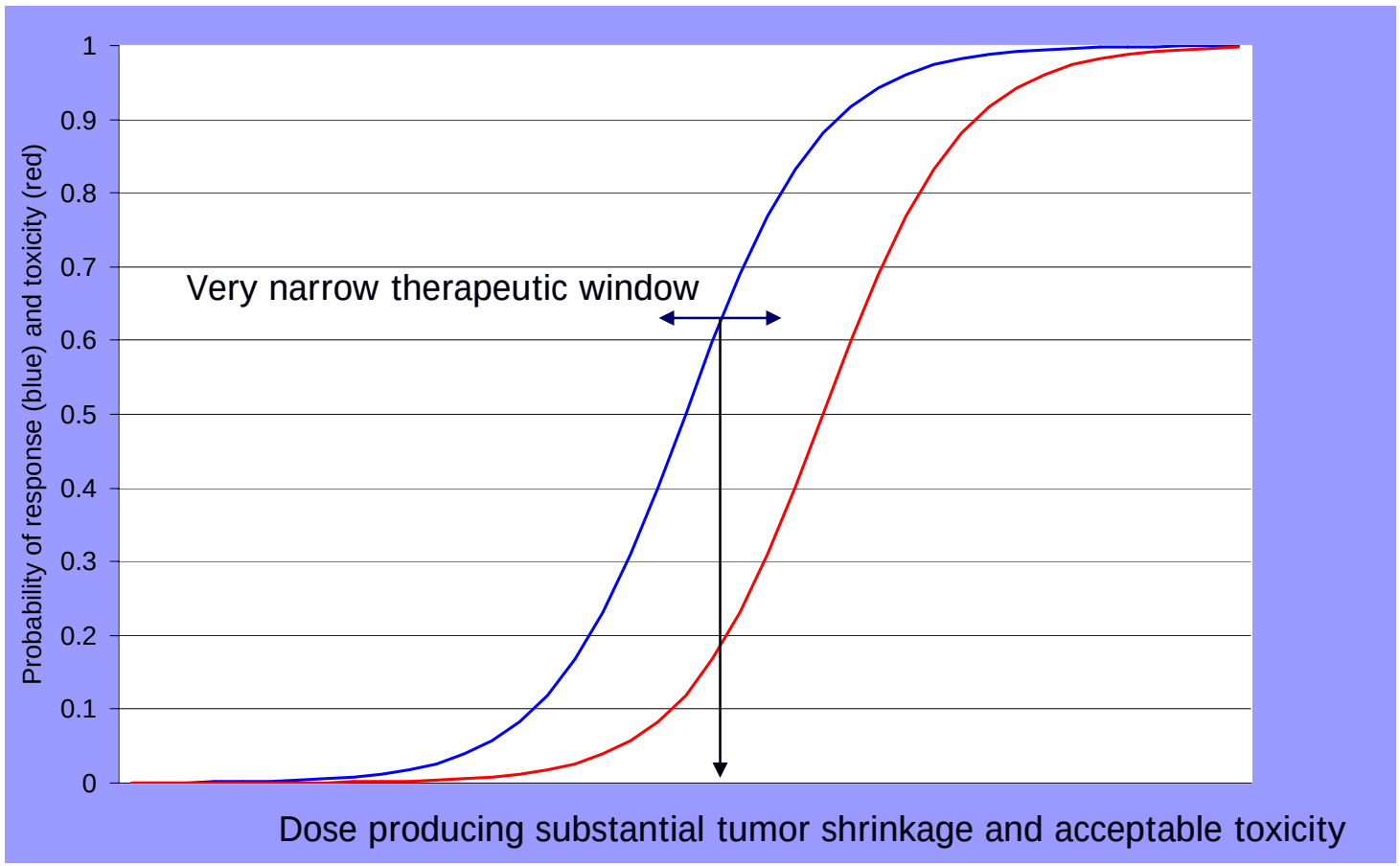
Phase I trials in oncology are carried out *in patients* with the following objectives:

- *Statistical* – Reliable identification of the highest dose that is safe enough to be used in phase II trials
- *Clinical* - Treatment of small cohorts of patients who have failed all standard therapies
- *Ethical* - Treatment of patients who might benefit from new drug at doses that are close to therapeutic

Ref: Eisenhauer et al, *J Clin Oncol* **18**:684 (2000)

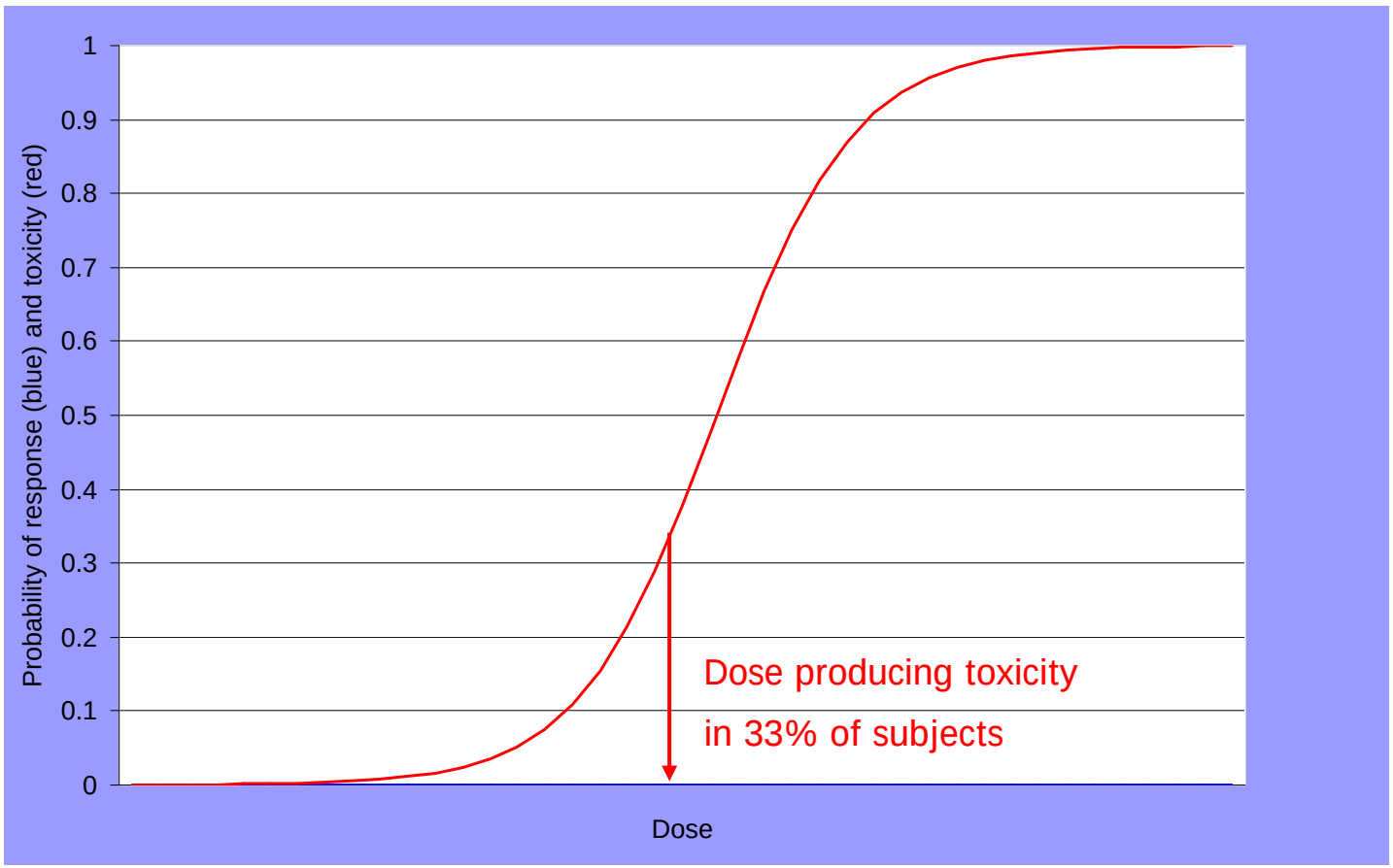
Phase I trials of cytotoxic drugs

Parallel dose-effect curves for efficacy and toxicity, with efficacious doses only slightly lower than toxic doses



Phase I trials of cytotoxic drugs

The purpose of a phase I trial is to determine the maximum tolerated dose, i.e. the dose at which a given percentage of subjects experience toxicity (which is a surrogate for activity).



Classical design

- Initial low dose extrapolated from animal data (e.g. 1/10 LD_{10} in mice)
- Doses are increased according to a "modified Fibonacci series" (1, 2, 3.3, 5, 7, 9, 12, ...) for which dose increments are decreasing (100%, 66%, 50%, 40%, 33%, 33%, ...)
- Maximum Tolerated Dose (MTD) is dose for which a given proportion of patients (e.g. 33%) experience Dose Limiting Toxicity (DLT)

Classical design

- Dose-limiting toxicities (DLT) are usually pre-defined adverse events (depending on the mode of action of the drug) of grade 3 or 4 severity

Scale	NCI/CTC*
none	0
mild	1
moderate	2
severe	3
life-threatening	4

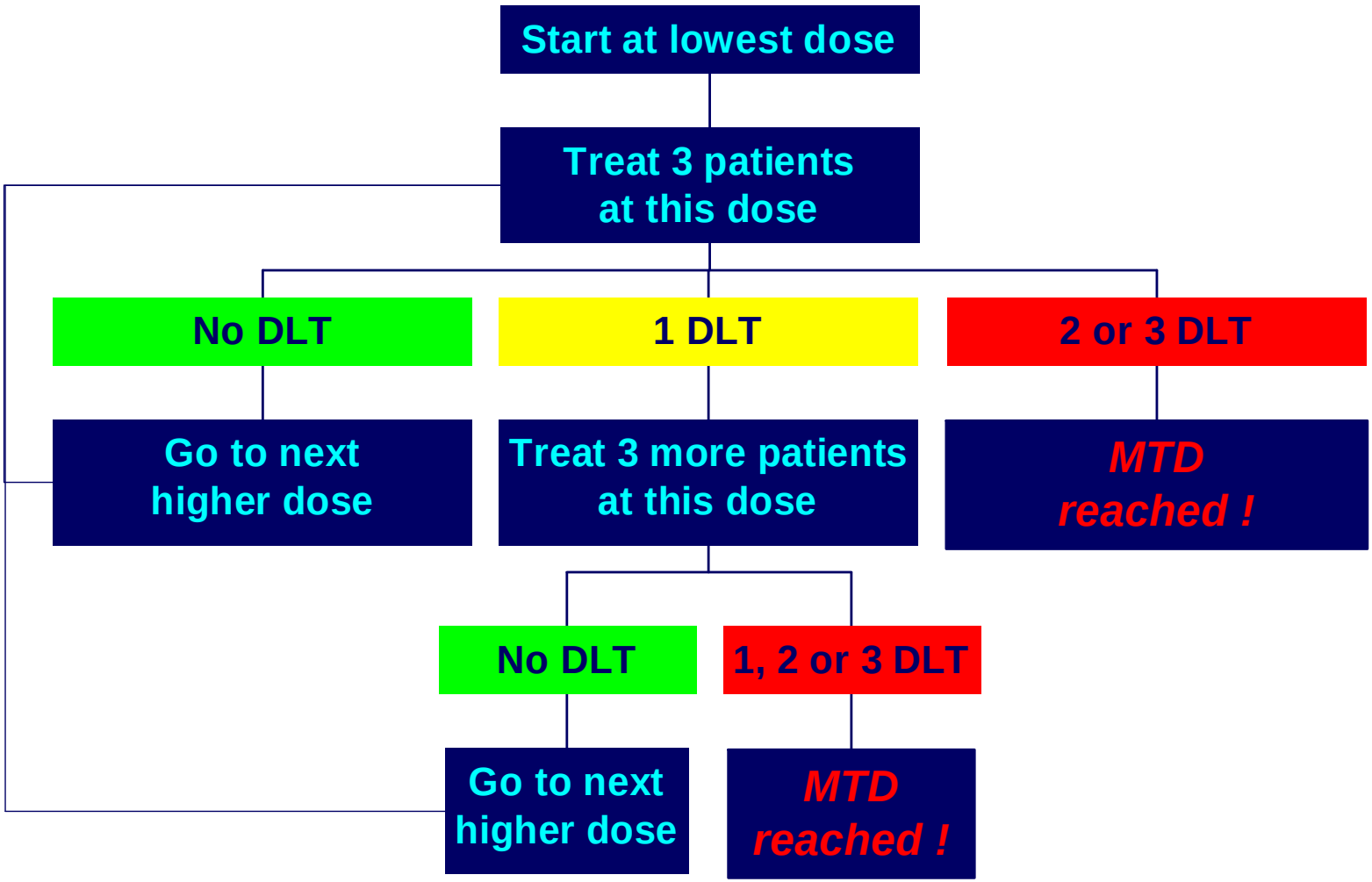
* National Cancer Institute Common Toxicity Criteria

Examples of NCI/CTC toxicity grades

Grade	0	1	2	3	4
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L	≥2.0 - < 3.0 x 10^9 /L	≥1.0 - < 2.0 x 10^9 /L	< 1.0 x 10^9 /L
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> 1 - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Stomatitis / pharyngitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation

WNL = Within Normal Limits; ULN = Upper Limit of Normal

Classical design



Continual reassessment method (CRM)

In the CRM, the dose given to the next patient is based on an assumed dose-effect relationship for dose-limiting toxicities.

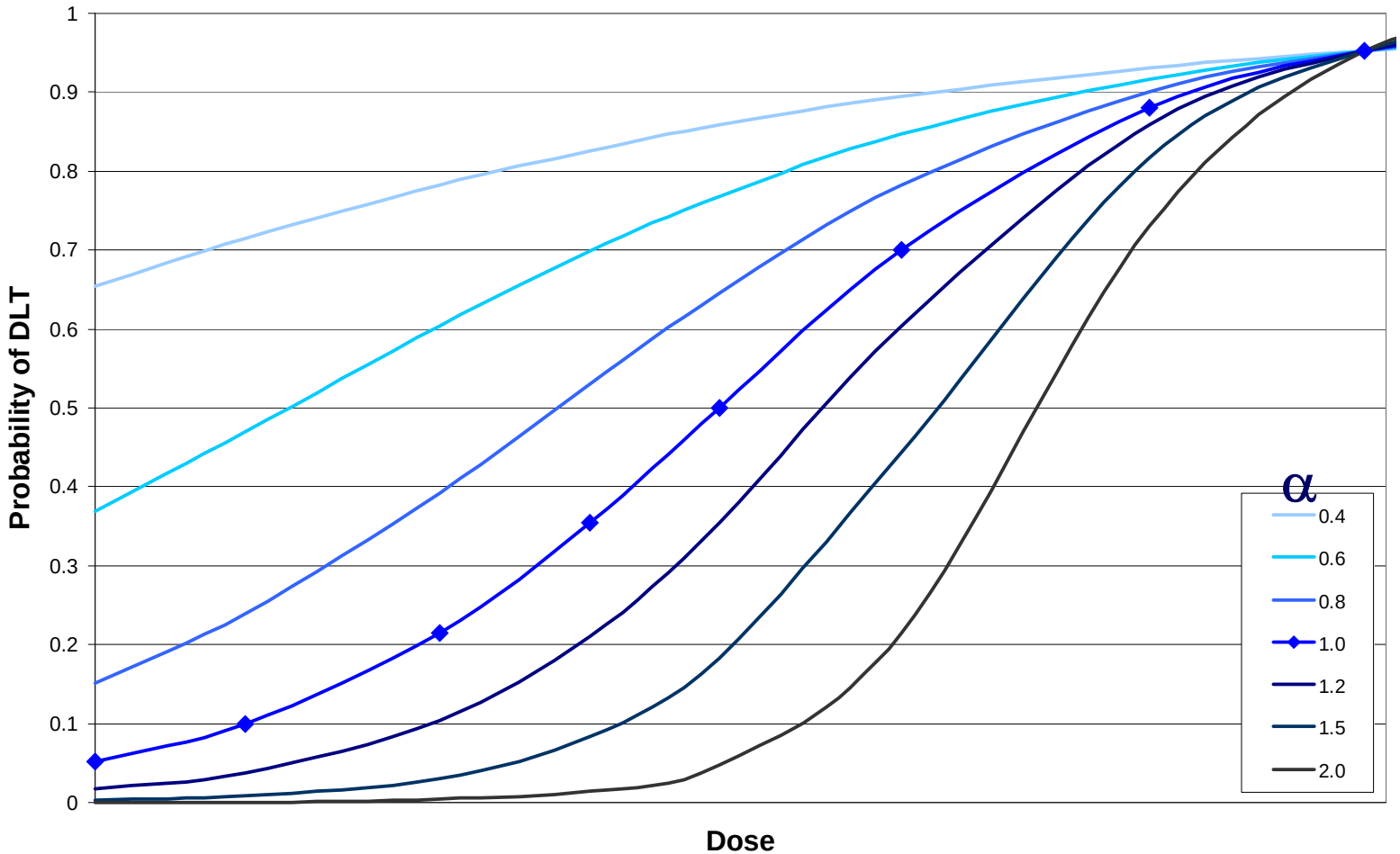
The idea is to assume some initial (one parameter) relationship and to reassess this relationship in the light of the toxicities (DLT) observed in successive patients

Ref: O'Quigley et al, *Biometrics* **46**:33 (1990)

Continual reassessment method (CRM)

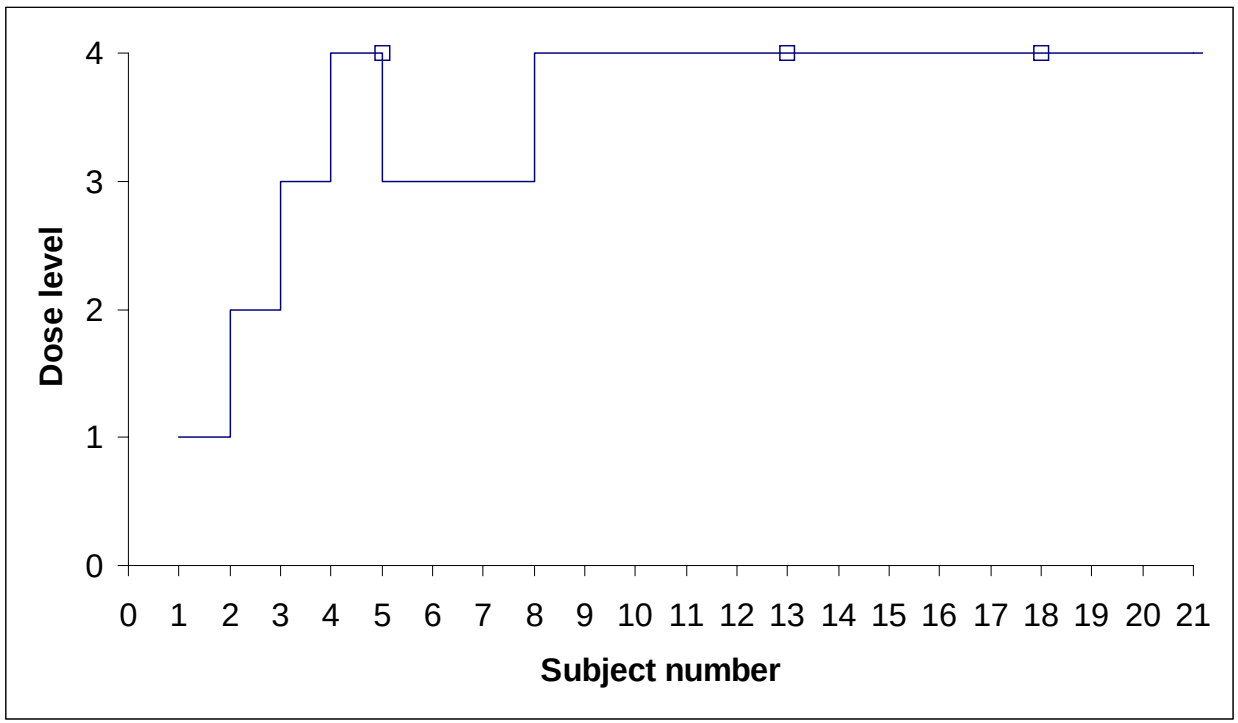
A model is chosen to describe the dose-response relationship

e.g. $P_i = \exp(3+\alpha d_i)/[1+\exp(3+\alpha d_i)]$



Continual reassessment method (CRM)

Example of a dose escalation using the CRM, constrained to start at dose level 1 and increase by only 1 dose level at a time. The target dose is level 4. Patients with a DLT are indicated by an open square.



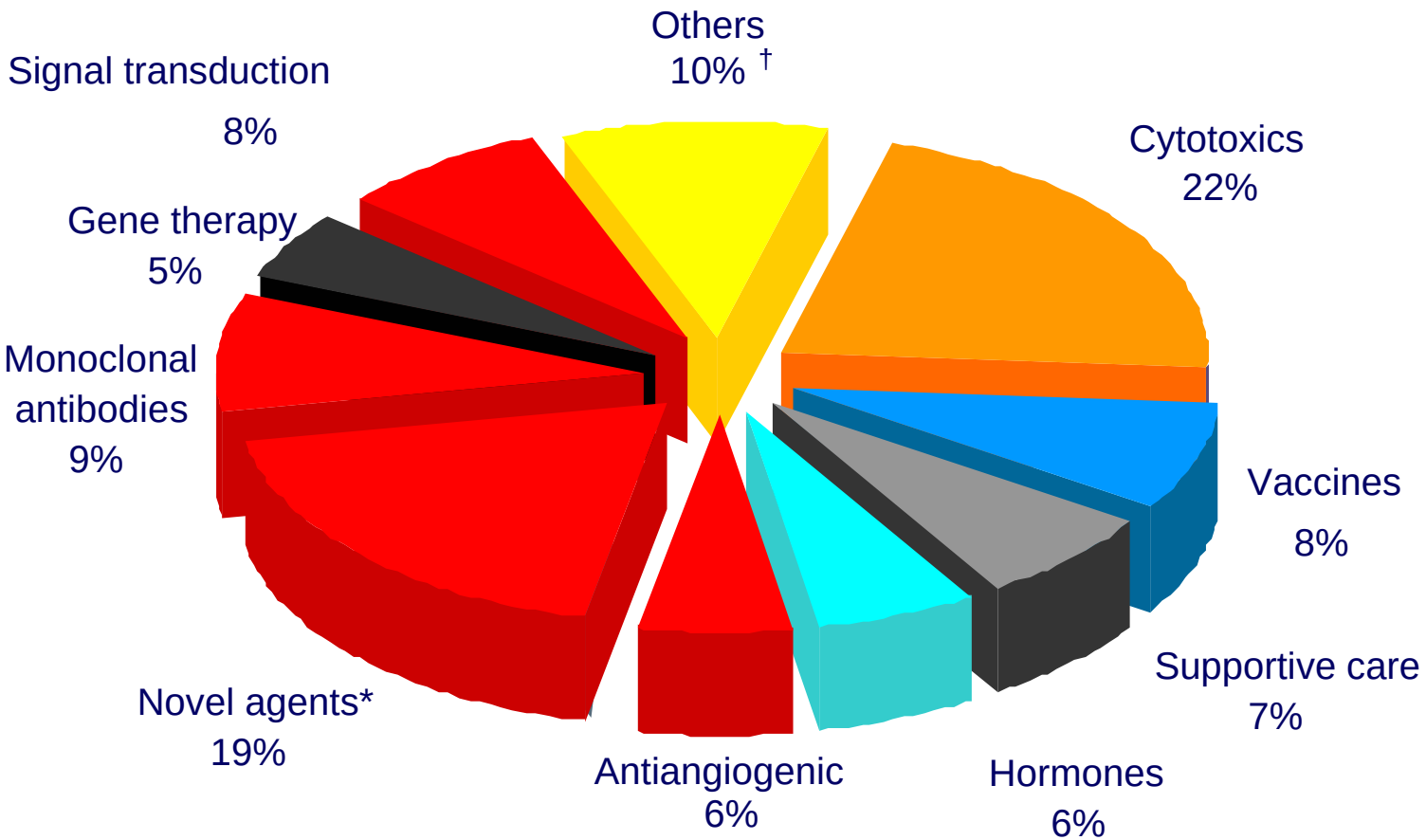
Phase I trials in oncology

A distinction must be made between agents that produce acute toxicity (cytotoxics) and agents that do not (cytostatics).

For cytotoxics, phase I trials aim at determining the Maximal Tolerated Dose (MTD). For cytostatics, phase I trials aim at determining the Optimal Biological Dose (OBD).

The most promising new agents in oncology are not traditional cytotoxics, but targeted therapies, therapeutic vaccines, immunotherapies, etc.

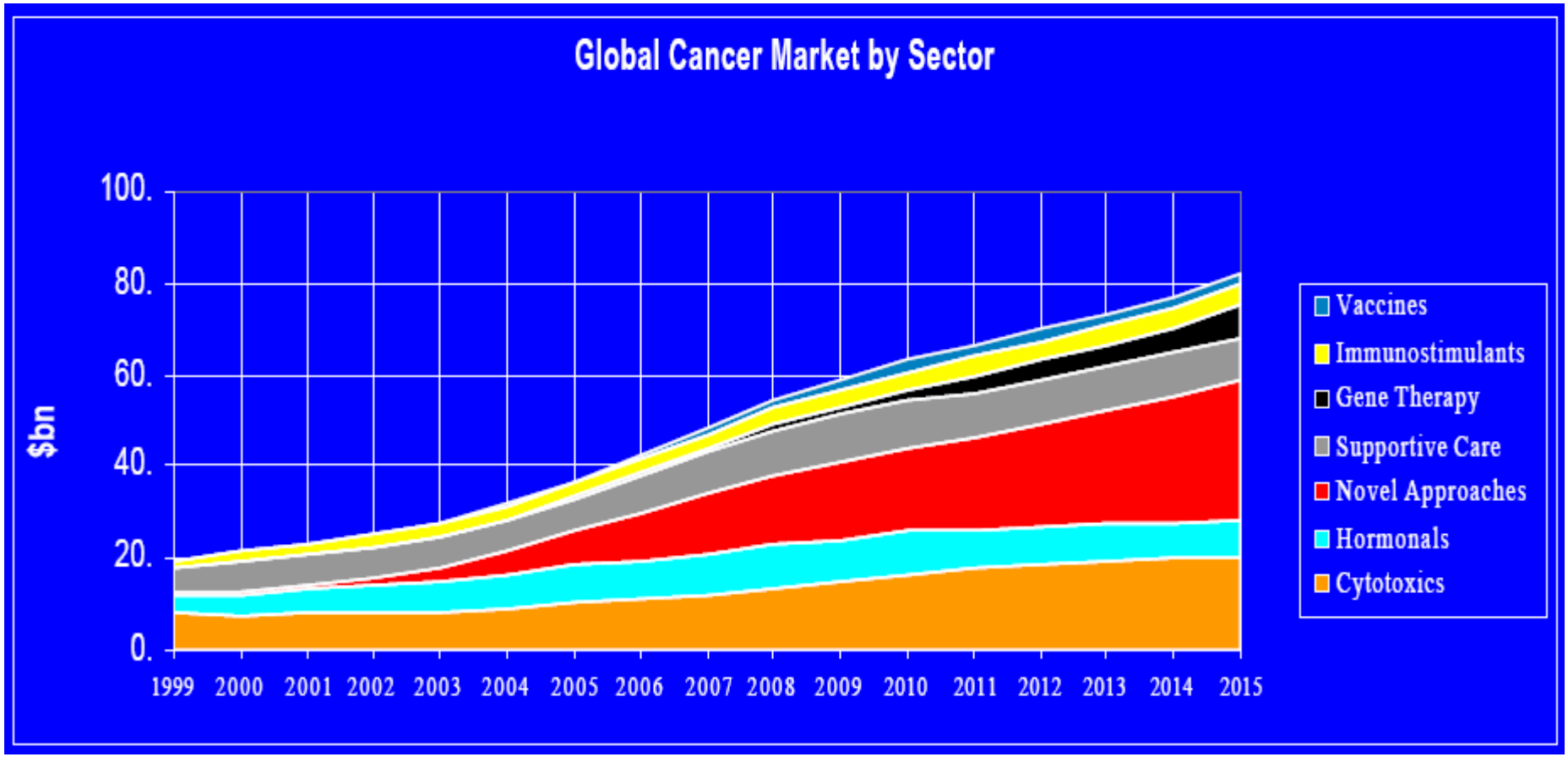
Oncology Drugs in Development
Preclinical to Phase III (n = 374)



* Includes antisense, peptides, oligonucleotides

† Includes immunomodulators, radiosensitizers, chemoprevention

Source: PhRMA, New Medicines in Development for Cancer

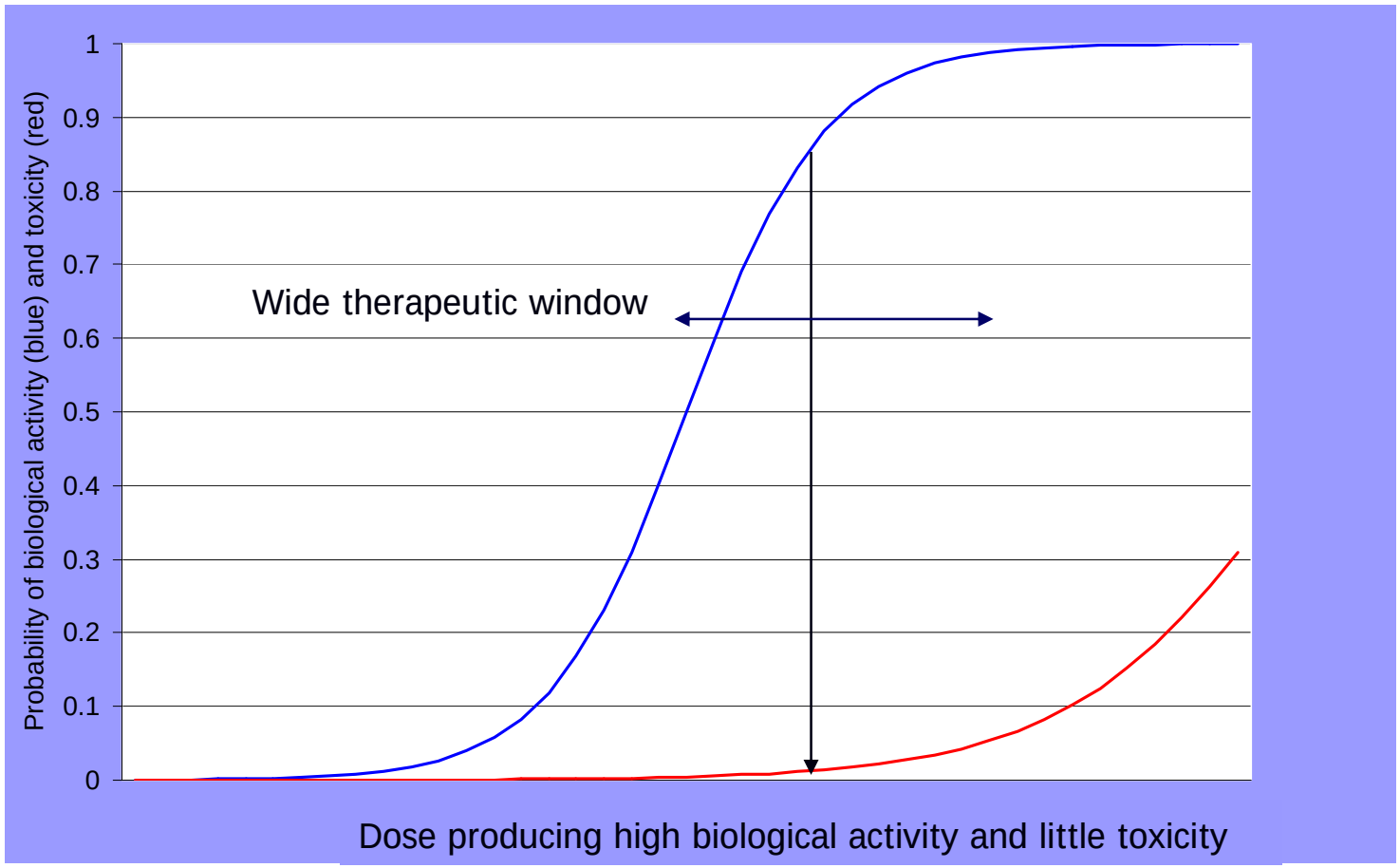


The main drivers of the growth are:

- increase in patient numbers (ageing population)
- early intervention
- use of biologically targeted therapies

Phase I trials of cytostatics

Dose-effect curve much flatter for toxicity than for efficacy, with efficacious doses sub-toxic



Phase I trials of cytostatics

	Cytotoxics	Targeted agents
Objective	MTD	OBD
Patients	All	Target-bearing
Endpoint	Toxicity	Inhibition of target
Design	Dose escalation in small cohorts	Guided-dose escalations