Challenges of clinical research. Risk of extinction?

introduction

(Clinical perspective)

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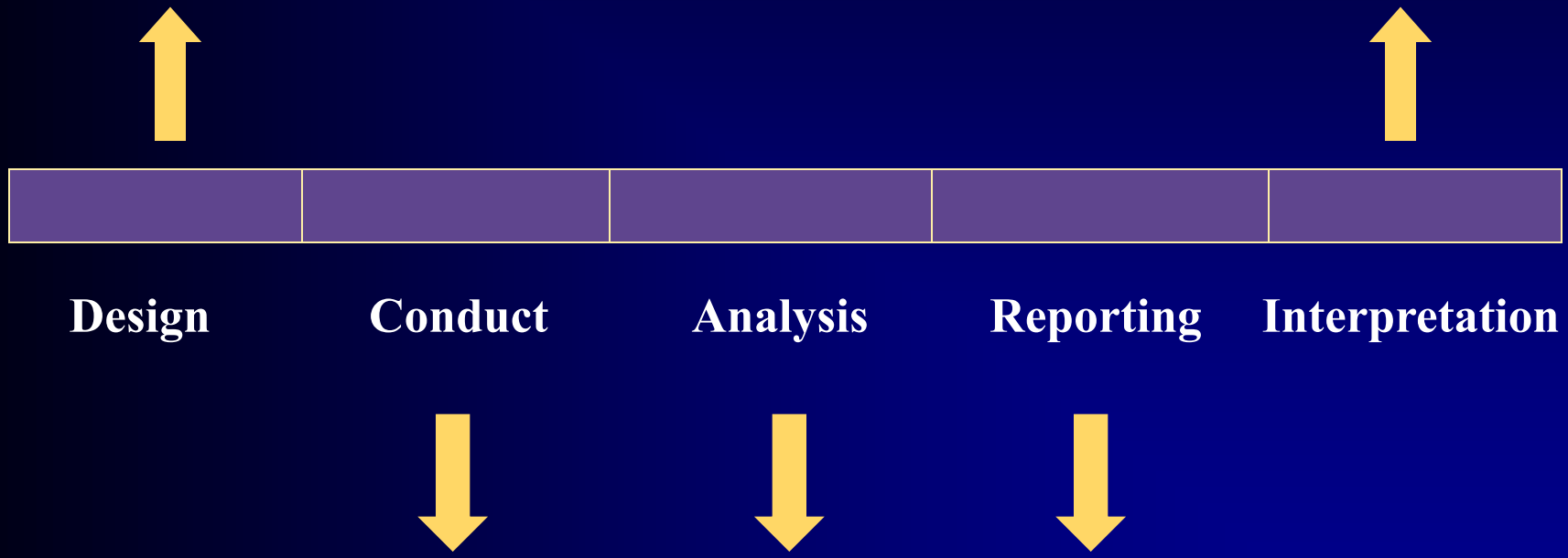
Clinical trials: the 5 phases and their actors

The clinical investigators and the statisticians



The patients and an army of people

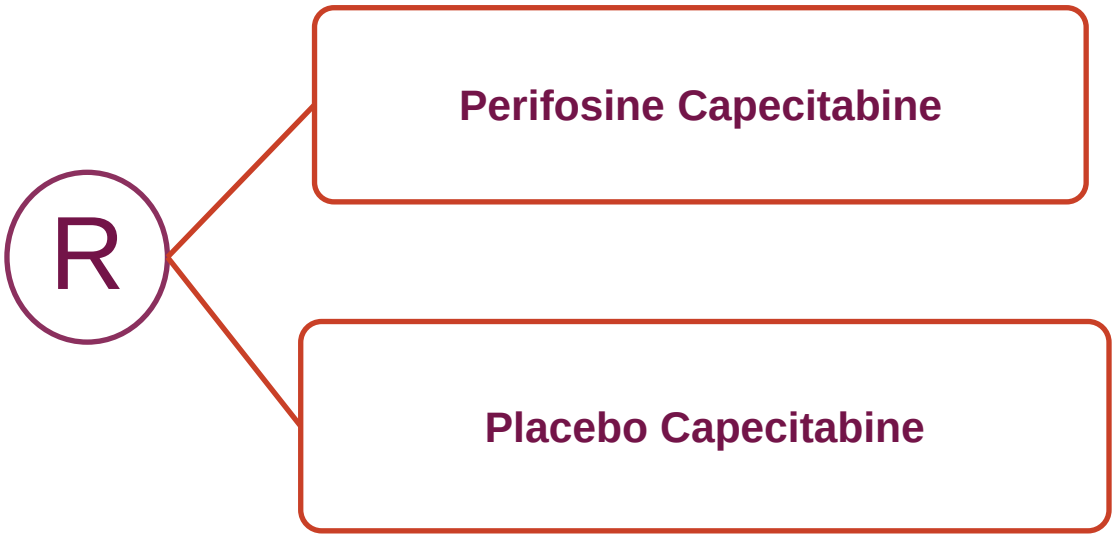
Clinical trials: the challenges

What we want from clinical research

1. New
2. True
3. Relevant

- Selection for phase I
- go-no-go from phase 2 to 3

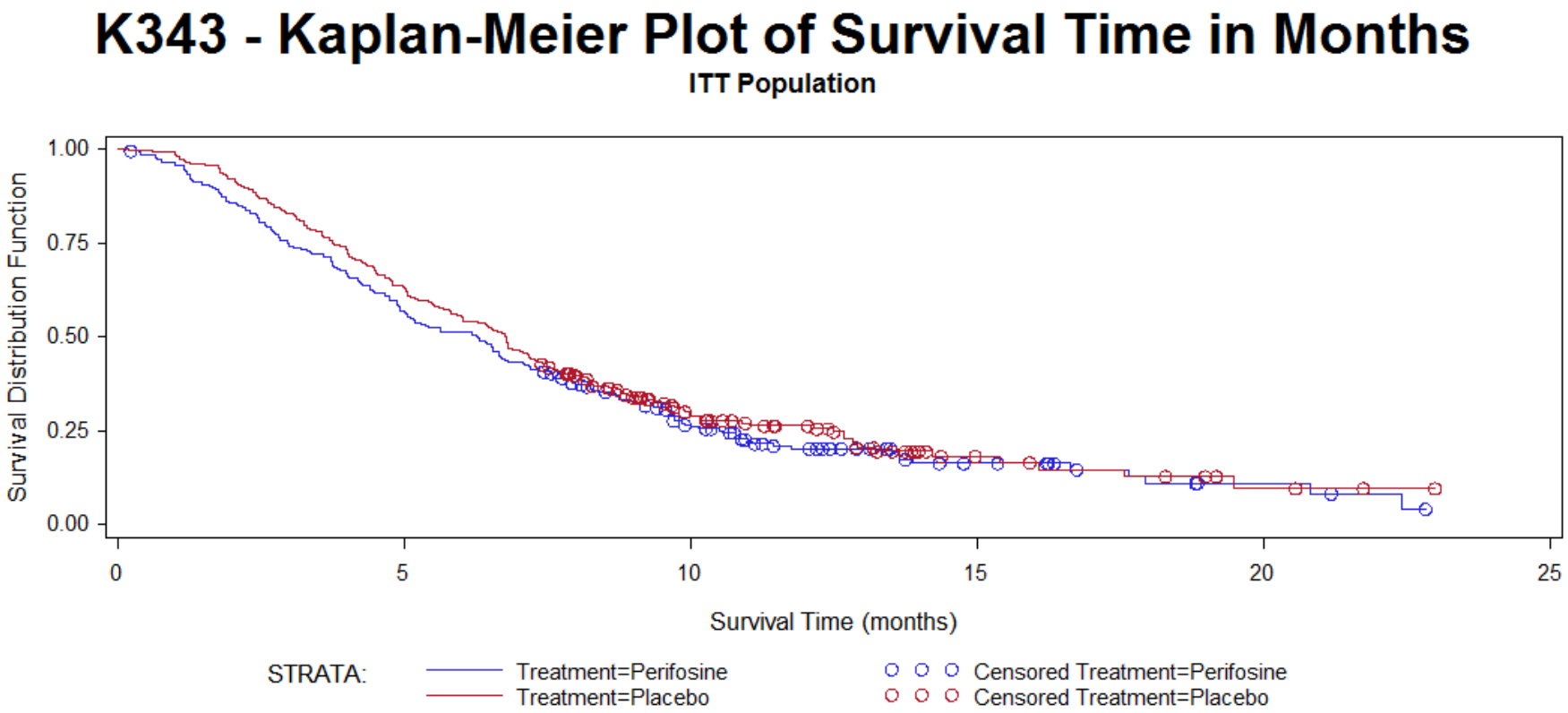
Randomized Phase II



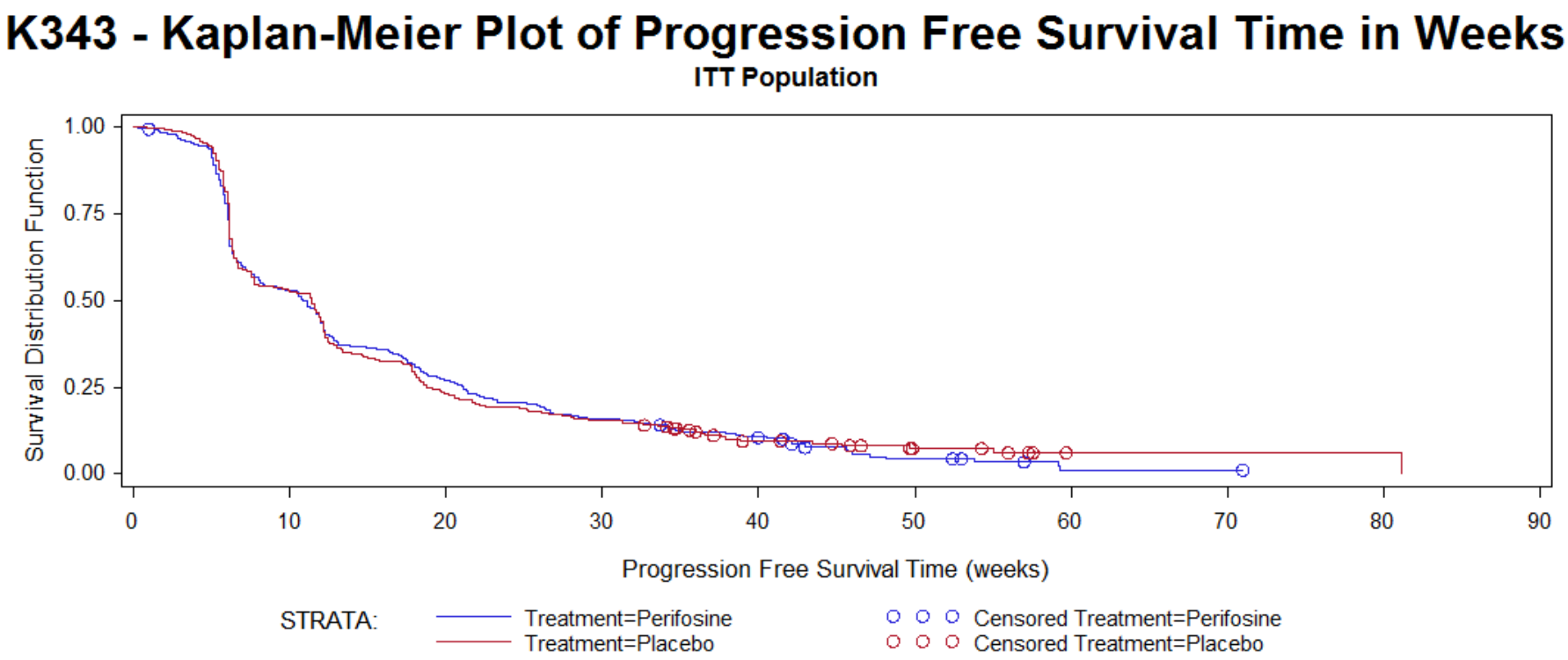
Median PFS	6 vs 2.5 mo	HR: 0.25 (0.1-0.5)
Median OS	17.7 vs 6.7 mo	HR 0.37 (0.2-0.7)

Bendell JCO 2011

Overall Survival – All Patients



Progression Free Survival – All Patients



Duration of PFS (weeks) = (date of progression or death due to any case – randomization date + 1)/7.

Size or confidence?....both !

- **Delta for deciding GO - NO GO to phase III (signal generating trials)**

very large

is this sufficient to go ?

no, must also be sufficiently sure

What we want from clinical research

1. New
2. True
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- Selection for phase I
- go-no-go from phase 2 to 3
- delta

The challenge of the delta in phase III trials : 3 problems

1. HR vs absolute delta
2. low target HR in trial design
3. target HR in trial design vs p value in trial analysis and interpretation.

PROBLEM 2. ‘ LOW PROFILE’

Typical phase III trial design in advanced cancer (PFS 6 mo)

- **Delta 25% i.e. HR**
- **Median delt .8 mo**
- **Pow %**
- **800**
- **Cost = 10**

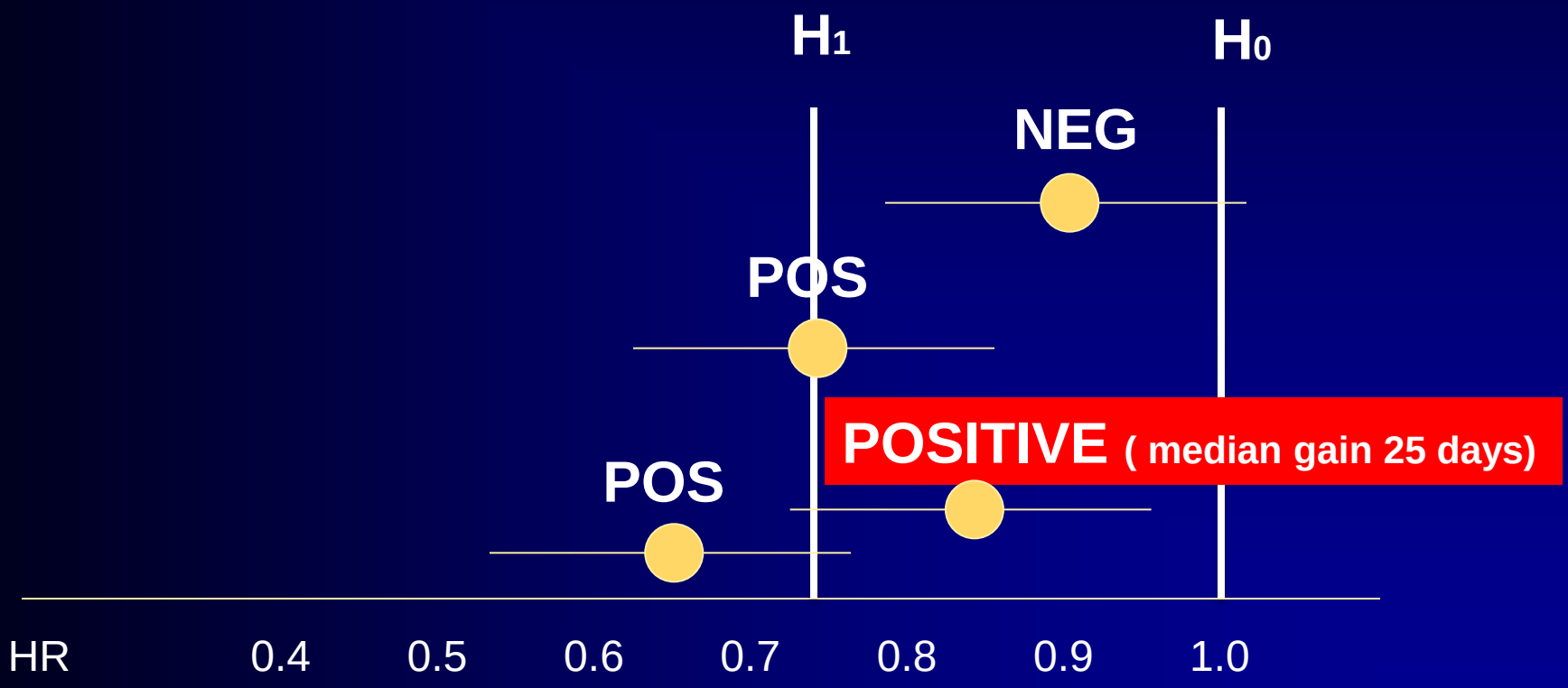
If we get this , is this really clinically worthwhile?

Be more corageous : raise the bar

PROBLEM 3: INCONSISTENCY

Define target delta……..target delta is ignored and...
p value becomes the focus…

Problem 3 : INCONSISTENCY



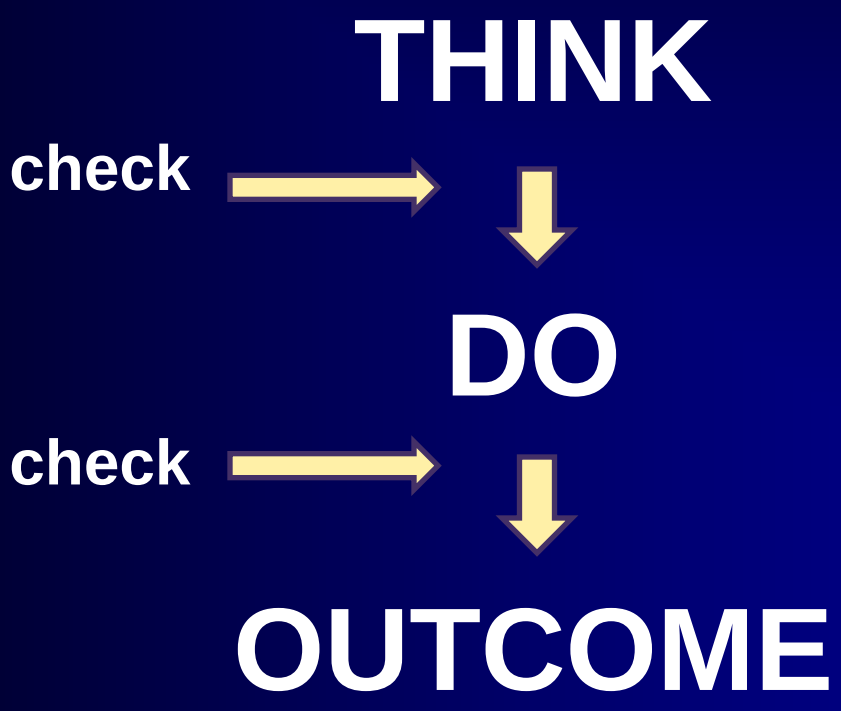
‘Statistically positive’ trials with deltas lower than those pre-specified in the protocol

AUTHOR	DRUG	TUMOR	predefined HR	reported HR	p value
Johnstone 09	lapatinib	breast	0.64	0.71	0.019
Jonker 07	cetuximab	colon	0.74	0.77	0.001
Moore 07	erlotinib	pancreas	0.75	0.82	0.038
Llovet 08	sorafenib	liver	0.6	0.69	0.001
Escudier 07	sorafenib	renal	0.67	0.72	0.02

modified from Ocana A. JNCI,2011

Clinical trials: the challenges

Introduction to the practical challenges → risk of extinction ?



Introduction to the practical challenges → risk of extinction ?

Introduction to the practical challenges → risk of extinction ?

1. Informed consent
2. Responsabilities of the institutions and of the PI
3. The jungle of the ‘committees’ : EC, IRB, SC, IDMC, etc
4. Too many others….leading to a wave of patient/families/colleagues uprising against a complexity that ultimately appear as barrier to pts and doctors participation to trials.
5. The ‘panda’ phoenomenon