Dose expansions cohorts

Alexia Iasonos

Why have Phase I trials become so complicated?

Simplest case	More Complex cases
• Single agent • Single schedule • MTD • 5-6 levels • N=20-25	• Combination agents • 2 schedules • MTD (1 or >1) • OBD • multiple disease groups • DLT definition (onset, attribution AE) • starting dose relative to MTD • N=50 – 60 dose escalation • >120 (25-40 per cohort)

Need to use efficient designs

Is the drug safe and at which dose? Which patient population and which drug/regimen to prioritirize?

- Success with single agent targeted therapies
- Develop resistance because of multiple genetic alterations and advanced metastatic disease
- Regimens with 1 or more targeted agent
- Many single agents/ combination regimens in the pipeline. Competing Resources

- Minimize number of patients and trial duration

Dose expansion Cohorts

Aim:

further evaluate safety

and to

obtain preliminary evidence of efficacy

multiple disease specific or histology specific cohorts

Does the drug work and

in which disease type?

Homogeneous or heterogeneous patient population

– Dose escalation : solid tumors

- Same MTD applies to several disease populations

– Dose expansion: disease specific

biomarker specific (biopsy required)

5 disease groups of 20 pts each = 100 pts

Dose Expansion Cohorts

Is the design appropriate to answer the study's objective?

Iasonos, O'Quigley JCO 2013
Iasonos A, O'Quigley J. Nat Rev Clin Oncol. 2015

Phase I/ II

Phase I
Safety
alone

Dose
Expansion
Cohorts

Phase II
Establish some
prespecified level
of efficacy

Efficacy assessment

Projections from these data

False + and False –

How many pts are needed?

Is 1/10 enough?

Phase 1b:biomarker +/
Enriched population

Dose escalation → Dose Expansion → Phase II or III

Clinical Aims:
- Evaluate Safety
- Establish the MTD

Dose selection and dose elimination for the dose expansion phase

Clinical Aims:
- Further evaluate safety
- Obtain preliminary evidence for efficacy
- Perform correlative, PK,PD studies

Accurate and Precise RP2D →

Aims:
Establish Efficacy; selected population

Iasonos, O'Quigley JCO 2013

Dose expansion Cohorts

- Endpoint: safety and efficacy
- Patient population: multiple disease specific or histology specific cohorts
- Does the drug work and in which disease type?

Example: Safety of anti PD-1 antibody

(Topalian SL et al N Engl J Med. 28;366(26):2443-54.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Topalian SL et al

RESULTS

A total of 296 patients received treatment through February 24, 2012. Grade 3 or 4 drug-related adverse events occurred in 14% of patients; there were three deaths from pulmonary toxicity. No maximum tolerated dose was defined. Adverse events consistent with immune-related causes were observed. Among 236 patients in whom response could be evaluated, objective responses (complete or partial responses) were observed in those with non–small-cell lung cancer, melanoma, or renal-cell cancer. Cumulative response rates (all doses) were 18% among patients with non–small-cell lung cancer (14 of 76 patients), 28% among patients with melanoma (26 of 94 patients), and 27% among patients with renal-cell cancer (9 of 33 patients). Responses were durable; 20 of 31 responses lasted 1 year or more in patients with 1 year or more of follow-up. To assess the role of intratumoral PD-1 ligand (PD-L1) expression in the modulation of the PD-1–PD-L1 pathway, immunohistochemical analysis was performed on pretreatment tumor specimens obtained from 42 patients. Of 17 patients with PD-L1–negative tumors, none had an objective response; 9 of 25 patients (36%) with PD-L1–positive tumors had an objective response ($P=0.006$).

PD1 study – Design
Phase I protocol – 5 amendments

- Dose escalation: 3+3: Doses 1, 3, 10 mg/kg
- Dose expansion: 5 cohorts,16 pts(n=80) at 10mg for melanoma+RCC, NSCL, Prostate, Colorectal.
- Cohorts of 16pts randomly assigned at:
  - 1 and 3mg melanoma then randomly at 0.1, 0.3, 1 mg (RR 19-41%)
  - 1, 3, 10 mg randomly for Lung (RR: 6%, 32%, 18%)
  - 1.0 mg for RCC (RR: 24%); 10mg for RCC (RR=31%)
  - 14 expansions cohorts; 7 DEC up to amendment 4
- Safety stopping rules: DLT ≥ 33% across all 5 indications or from first 6 pts within an indication

Grey Area – Discovery

- a chance you miss an effective drug (false -)
- a chance you erroneously take an ineffective drug forward (false + = type I error)

- Tradeoff between False + versus (>) False –

- Small sample size

- Inconclusive / need more patients

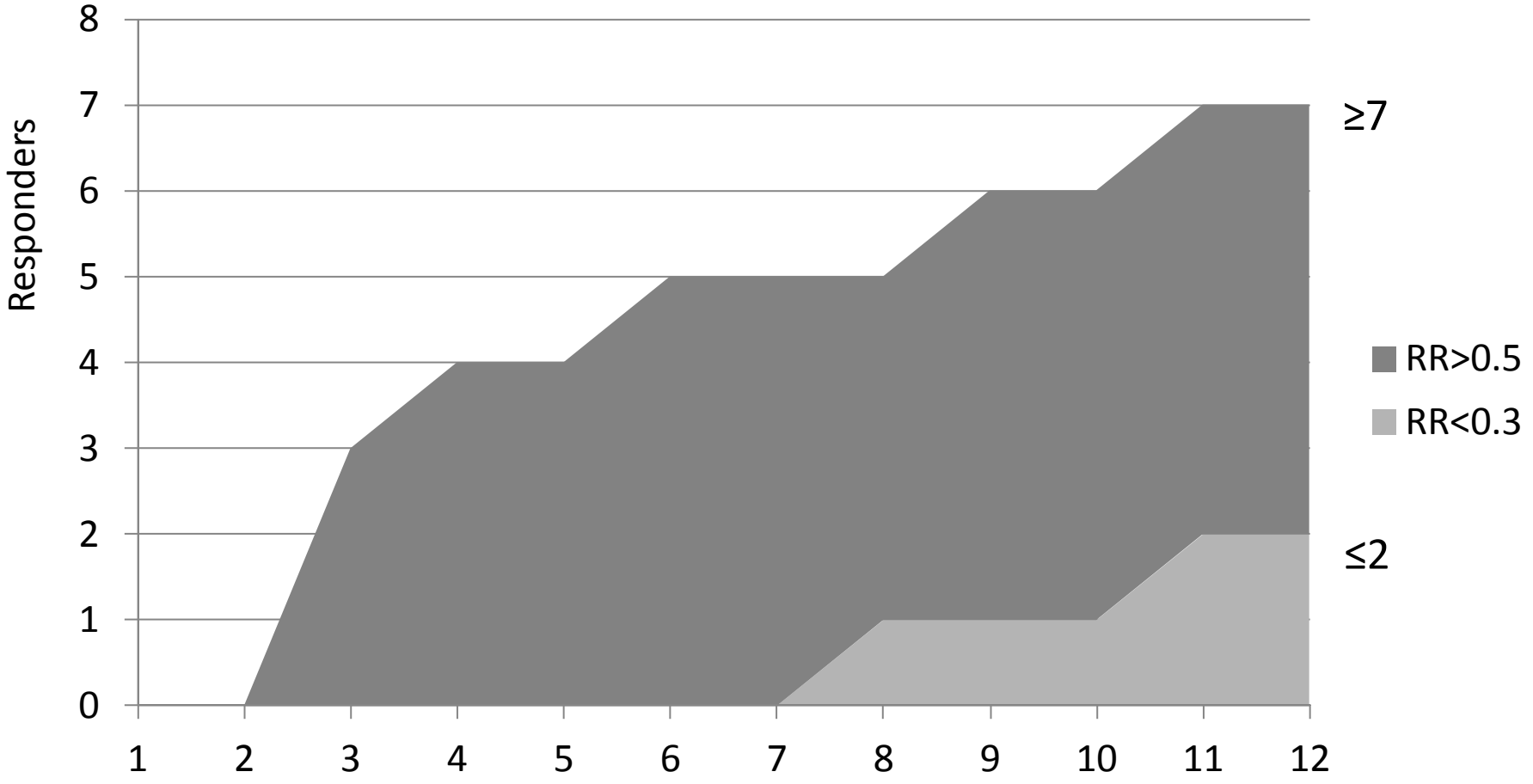
Compromise

- With a small sample size there is a chance you miss an effective drug (false -) and a chance you erroneously take a drug forward (false +)

- Inconclusive / grey area / need more patients

RR >50%, RR≤30%

False -=15% False +=20%



Iasonos A, O'Quigley J.
2016 SBR; 2016 Stats Med

SPRT: Simple Hypotheses, O'Quigley et al 2001

$$H_0 : Q(d_i) = q_0 \text{ against } H_1 : Q(d_i) = q_1,$$

- Based on observed efficacy rates (binomial likelihood)

$$T_O(d_i) = r_i(j) \log\left(\frac{q_1(1-q_0)}{q_0(1-q_1)}\right) + j * \log \frac{(1-q_1)}{(1-q_0)}$$

$$\log(\text{Type II}/(1-\text{Type I})) < T_O(d_i) < \log((1-\text{Type II})/\text{Type I}).$$

$T_O(d_i) < \log(\text{Type II}/(1-\text{Type I}))$ H0

$T_O(d_i) > \log((1-\text{Type II})/\text{Type I})$ H1

Composite Hypotheses

$H_0 : Q(d_i) \leq q_0 \quad Q(d_i) \geq q_1$

$H_0 : b \geq b_0$ against $H_1 : b \leq b_1 \qquad \phi(d_i, b) = \beta_i^b$

lefine the region B_0 to be (b_0, ∞) and similarly under H_1 the region B_1 is $(0, b_1)$.

- SPRT using model based efficacy rates

$$T_1(d_i) = \frac{\int_{B_1} \prod_{l=1}^{j^*} \beta_i^{bv_l}(1-\beta_i^b)^{(1-v_l)} g(b)\, db}{\int_{B_0} \prod_{l=1}^{j^*} \beta_i^{bv_l}(1-\beta_i^b)^{(1-v_l)} g(b)\, db}$$

Iasonos A, O'Quigley J.
2016 SBR;
2016 Stats Med

Need for a formal evaluation of dose expansion cohorts

Iasonos A et al JCO 2013
Manji A et al. JCO, 2013
Dahlberg S et al. JNCI 2014

- Design needs to be consistent with DEC aims
- Sequentially monitoring safety and/or efficacy
- Efficient use of dose expansion data to answer the primary and secondary aims
  - Take 2 dose levels in the dose expansion; randomize
  - RP2D is based on highest efficacy provided is safe

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Seamless Oncology-Drug Development

T Prowell, M R. Theoret, R Pazdur, April 2016

Questions Regarding the Design of Large First-in-Human Cancer Trials.

- Is there a compelling rationale for including multiple expansion cohorts?
- **Is the sample-size range consistent with the stated objectives and end points?**
- **Is there an appropriate statistical analysis plan for all stated end points?**
- Are the eligibility criteria appropriately tailored to the expansion cohorts?
- Is there a defined end to the trial, in terms of both efficacy and futility?
- Is there a system in place to communicate with all investigators in a timely fashion?
- Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
- If the trial may be used for regulatory approval, is there an independent oversight committee?
- If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

2016 NEJM editorial by the FDA; Prowell, Theoret, Pazdur

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Extend established work to different schedules and groups

- Two Schedules/routes of administration
  - one schedule is less toxic than the other for example in once vs twice daily dosage
  - Unknown how the schedules are related in terms of higher toxicity

- Two patient populations:
  - heavily vs non heavily pretreated patients
  - Pediatrics and adult patients

Specialized expertise

- Funding agencies, sponsors, statistical journals need to be on the same page
- "All safety and efficacy outcomes are dichotomous which does not seem realistic"

  Dose limiting toxicity (NCI CTCAE version 4)

  Response Rate or Clinical Benefit (RECIST)
- "scientific basis to bind several cohorts in one study"; basket trials leading to drug approvals

What should a design be able to achieve?

- Answer scientific question
  - find the MTD or OBD
  - evaluate safety - DLTs
- Ethical
  - safe
  - optimal, efficient (how to get to the answer)
  - patient allocation: over dose, under dose,
  - minimum sample size and trial duration