PLÉNIÈRE

Méthodologie des essais cliniques : vers une optimisation de la recherche de dose, comment les phases précoces s'adaptent aux nouvelles réglementations ?

Débat animé par : Fabrice Barlesi et David Pérol

Avec la participation de : Olivier Mir, Xavier Paoletti, Sophie Postel-Vinay

30 novembre 2023

Dose finding methods for early phase trials

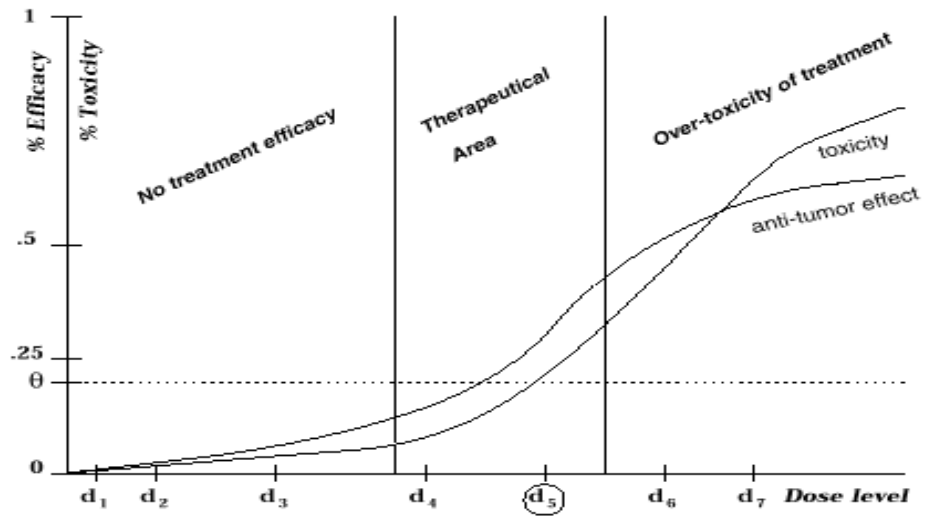
Xavier Paoletti

Curie / UVSQ-Paris Saclay / INSERM
U900 *Statistics for personalized Medicine*

ENSEMBLE, PRENONS LE
CANCER DE VITESSE

institut Curie

Phase I: A revolution at the era of immune checkpoint blockers



- A narrow therapeutic index: Still a paradigm?
- To find the MTD? Still the primary objective?
- To enroll between 15 et 25 patients at 6 to 8 dose levels?

Lancet Oncol 2022 Dec;23(12):1558-1570.

Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study

Funda Meric-Bernstam et al.

- « In Part 1 (n=46), no dose-limiting toxicities were detected and the **maximum tolerated dose was not reached**. »
- n=22 for biliary tract cancer; n=28 for colorectal cancer; and n=36 for other HER2-expressing or *HER2*-amplified cancers excluding breast or gastro-oesophageal cancers;
  total n=86
- In part 2, **31 (37%; 95% CI 27·0–48·7)** of 83 evaluable patients had a confirmed objective response

Pembrolizumab Phase I Study

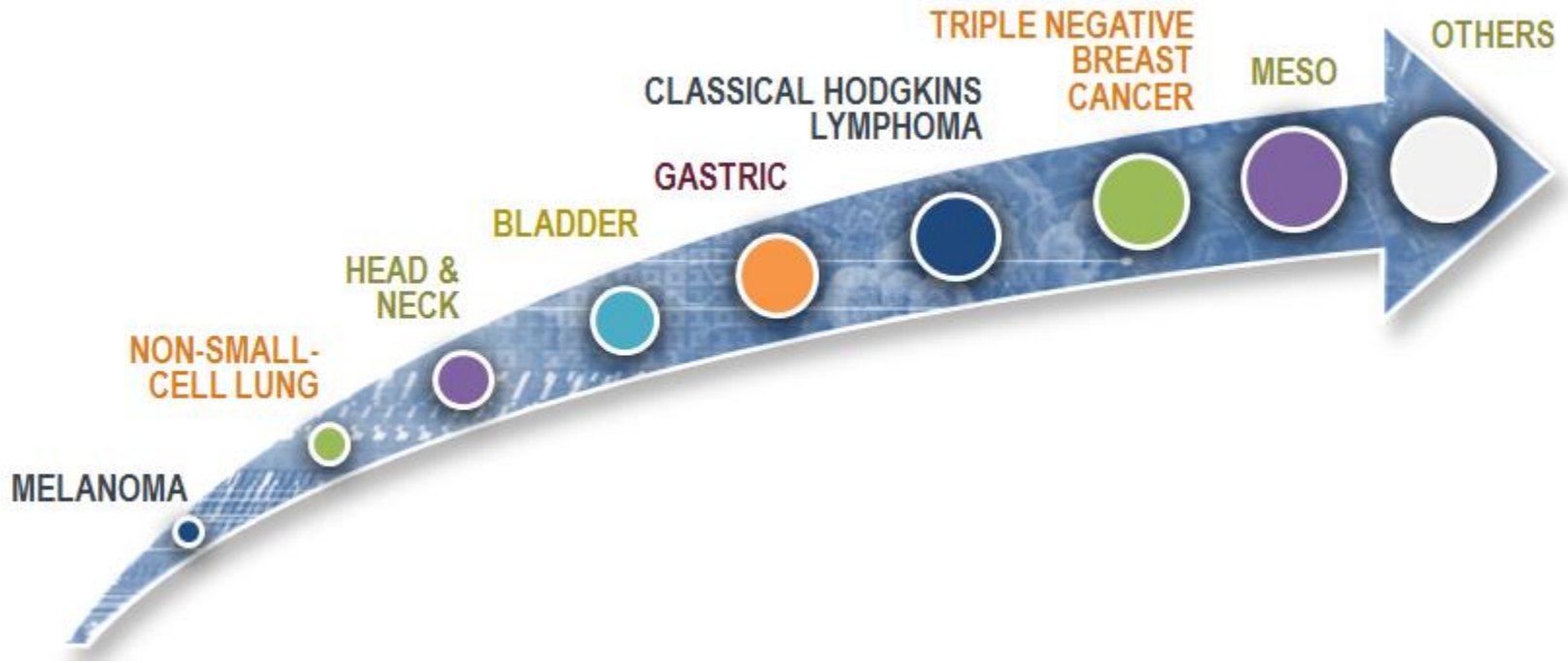
NCT01295827

PN-001, Phase I study, began in 2011

Initially a 32 patient study

Actually enrolled over 1260 patients

Became basis for FDA Breakthrough designation in melanoma + lung cancer



By courtesy of Pr J-C Soria

Statistical methods in phase I trial: from dose finding to toxicity monitoring?

- 3+3 method less and less used (but still quite common)
- An approach to screen dose levels
- But
  - Who is convinced by n=3 or n=6 patients?
  - Very conservative!
    $\Rightarrow$ too many patients at too low dose levels
  - Not flexible. Hard to deal with:
    - extra patients
    - late toxicity or reassessment of toxicity
    - Different acceptable risks of tox

CRM: principle

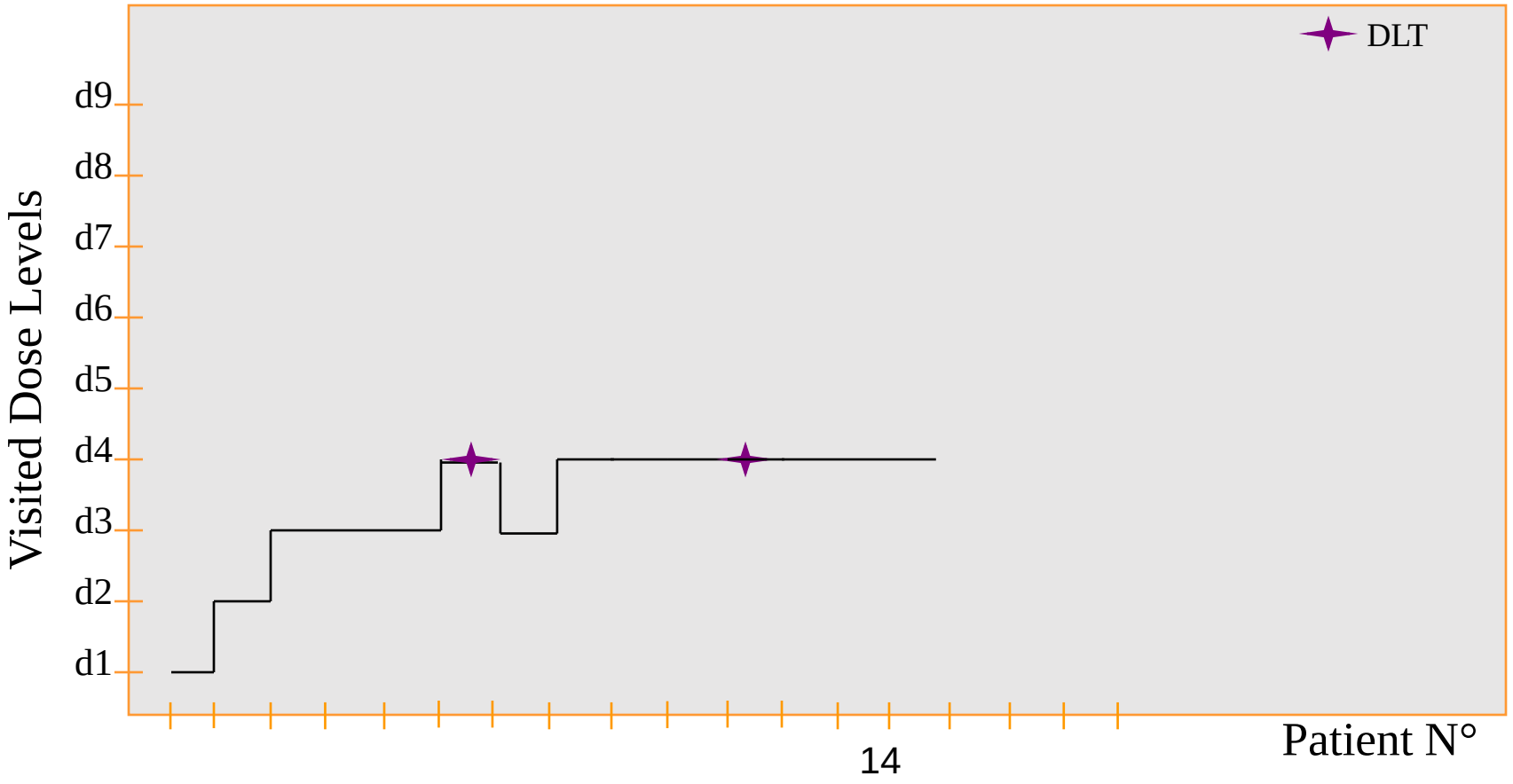
- Basic idea is to allocate every patient at the current best estimate of the MTD.

- Model guided:
  - Fit a model of the dose-toxicity curve on ALL the previous data
  - Estimate the probabilities of DLT at each dose

  $\Rightarrow$ Next dose = dose whose estimate is closest to the target 20%
  (best current estimate of the MTD)
  - Treat the next patient at the recommended dose

O'Quigley (Biometrics 1990, 1996)

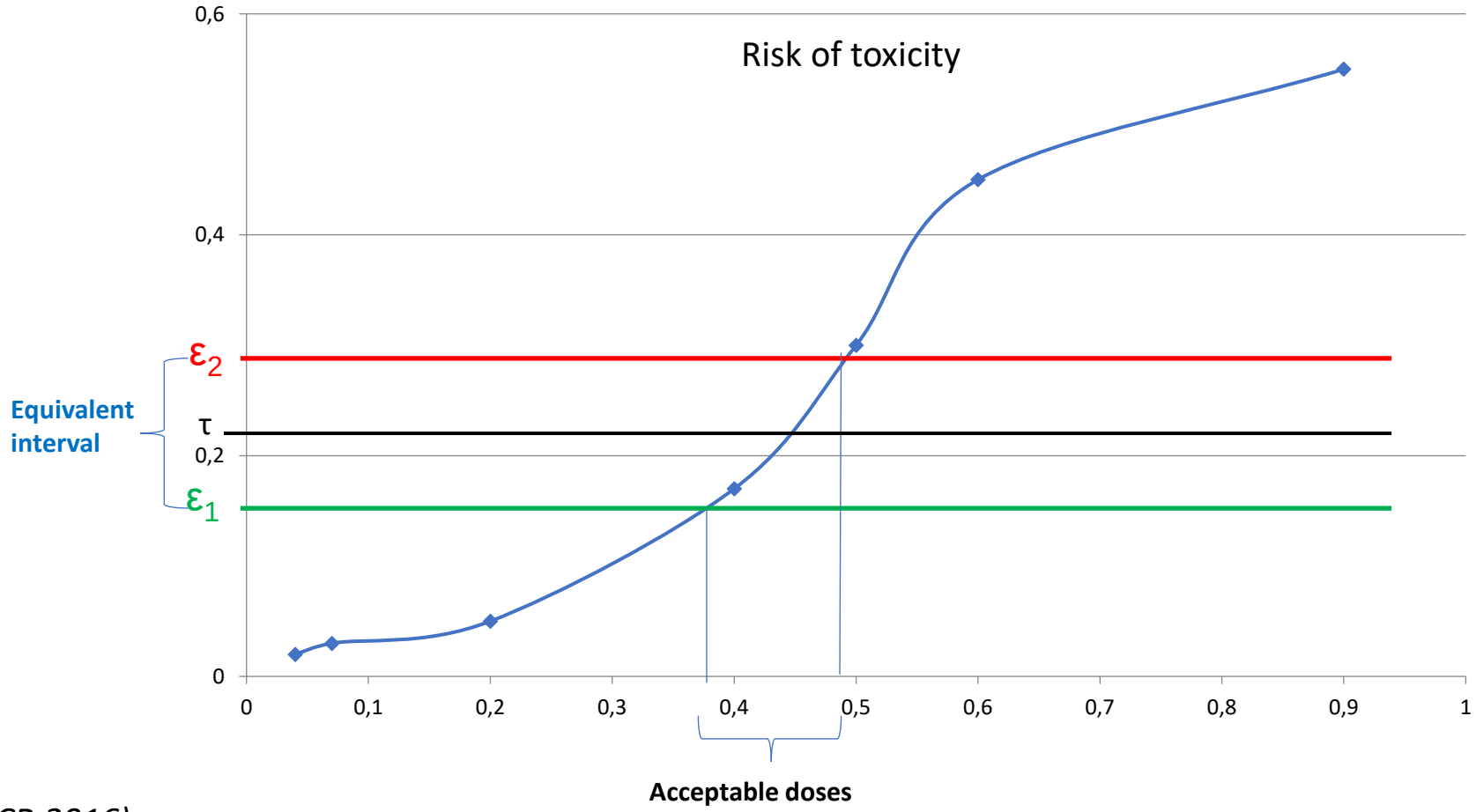
CRM: Example



Paoletti (Annals of Onco 2015)

Bayesian Optimal Interval (BOIN)

1. Define the MTD as an <u>interval</u> of “acceptable” risk of DLT around the target τ : (ε_1, ε_2)



Yuan (CCR 2016)

Bayesian Optimal Interval (BOIN)

1. Define the MTD as an <u>interval</u> of "acceptable" risk of DLT around the target τ : (ε_1, ε_2)

Recommended:

$\tau = 0.25$

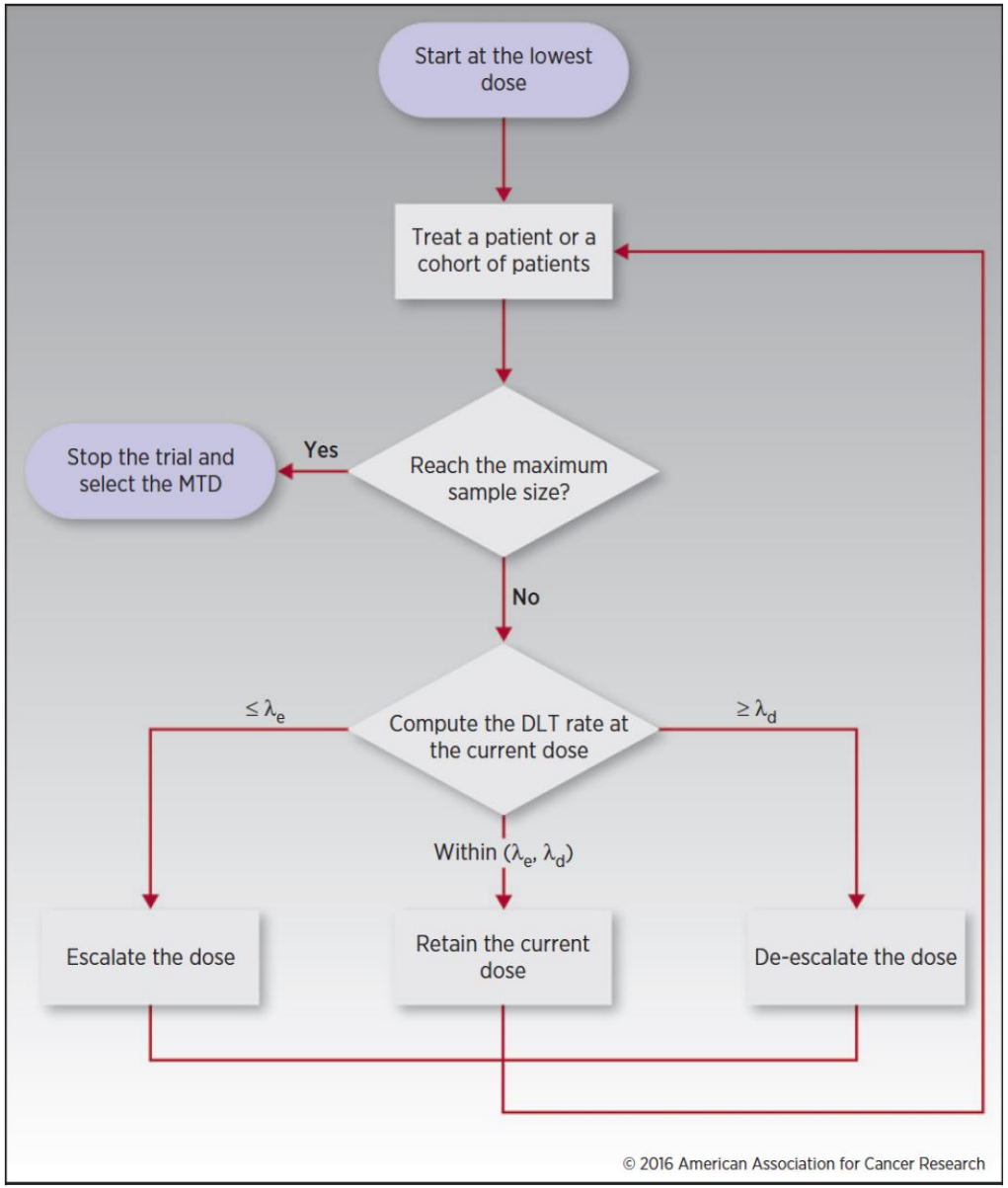
$\varepsilon_1 = 0.25 - 0.10 = 0.15$ (underdosing)

$\varepsilon_2 = 0.25 + 0.10 = 0.35$ (overdosing)

➔ Defines the boundaries, λ_e and λ_d for (de)-escalating levels

Target toxicity rate τ						
Boundaries	0.15	0.20	0.25	0.3	0.35	0.40
λ_e	0.12	0.16	0.20	0.24	0.28	0.32
λ_d	0.18	0.24	0.30	0.36	0.42	0.48

Bayesian Optimal Interval (BOIN)



Yuan (CCR 2016)

Spaning from phase I to phase IIa: the expansion cohort

- Objective:

  To document <u>preliminary sign of activity</u>

- Then
  - **Compute sample size to control error rates**

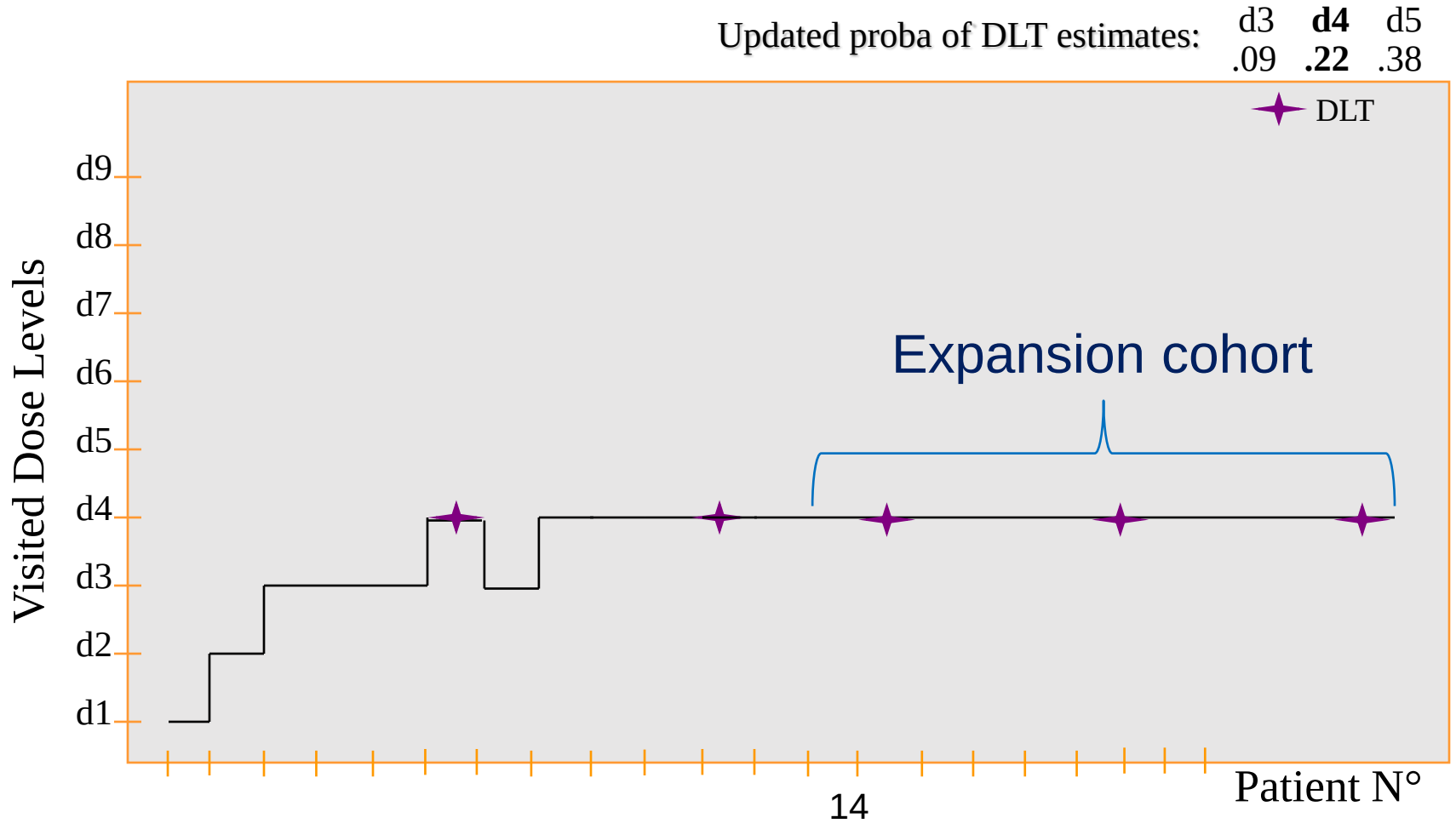
    (as a first step of a phase II design)
    - For instance 15 patients

      if no clinical responses ➔ 95% chance that activity <20%
    - Use all patients treated at the RPIID with the selected disease
  - Use the CRM (or BOIN) to update the estimate of the toxicity

    ➔ control for safety

Manji et al. (JCO 2013), Iasonos (JCO 2014)

From dose finding to toxicity monitoring



« To document preliminary sign of activity »

- ORR doubled in phase I trials
  10% to 18%
  but not in single agent trials
  ORR <5%
- ORR cannot be compared across doses
- Why not using more sensistive endpoints?
  - cDNA
  - CTC

➔ Investigate the **dose activity** curve

Lancet. 2022 August 13; 400(10351): 512–521. doi:10.1016/S0140-6736(22)01390-3.

Evolving Landscape of Early Drug Development in Solid Tumors: Analysis of National Cancer Institute Sponsored Phase 1 Trials

Dai Chihara, MD[1,2], Ruitao Lin, PhD[3], Prof. Christopher R. Flowers, MD[1], Shanda R. Finnigan, MPH[4], Lisa M. Cordes, Pharm.D[5], Yoko Fukuda, MD[4], Erich P. Huang, PhD[6], Larry V. Rubinstein, PhD[6], Loretta J. Nastoupil, MD[1], S. Percy Ivy, MD[4], James H. Doroshow, MD[4], Naoko Takebe, MD[4]

Sample sizes and equipoise…

Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial Sagar Lonial et al. Lancet Heamatology (2022)

- We conducted a multicohort, open-label, phase 1/2 trial (CC-220-MM-001) at 42 treatment centres in Europe, Canada, and the USA.
- 197 were treated with iberdomide plus dexamethasone (90 patients in the dose-escalation cohort and 107 in the dose-expansion cohort)

- Ready to randomize now?

Introducing randomization in expansion cohorts

- Randomize the first patient…

  At least as soon as you as you have the first responses
- Randomized Phase II are more informative than single arm trials
  Phase I/II should be randomized

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nature communications

Article

https://doi.org/10.1038/s41467-023-42744-y

Paclitaxel plus carboplatin and durvalumab with or without oleclumab for women with previously untreated locally advanced or metastatic triple-negative breast cancer: the randomized SYNERGY phase I/II trial

- The phase I part included 6 patients
- In the phase II part, 127 women were randomized 1:1

- Keep on montoring toxic side events
- Investigate cumulative toxicity

Introducing randomization in phase I?

nature medicine

Article

https://doi.org/10.1038/s41591-022-02141-2

Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial

Received: 29 March 2022

Ingo K. Mellinghoff[1,14] ✉, Min Lu[2,12,14], Patrick Y. Wen[3], Jennie W. Taylor[4],

Phase I clinical trials

- An important step
- That should cleary be designed for activity assessment
- With the ambition to select
  - A right dose
  - With a promising activity on short-term endpoint
  - In a promising population