
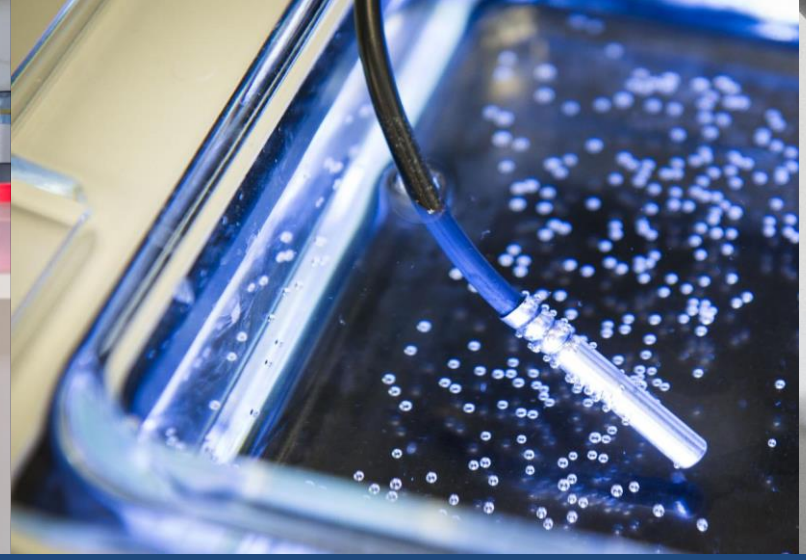
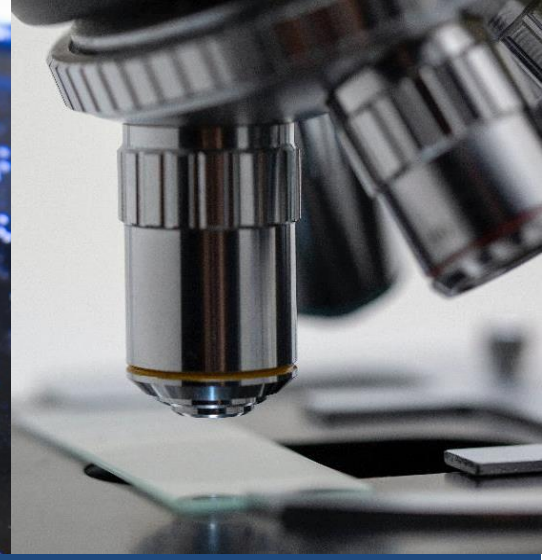

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EXCELENCIA SEVERO OCHOA 2022 - 2026

AGENCIA ESTATAL DE INVESTIGACIÓN

Session 1: The challenges of dose optimization

Project Optimus – FDA: how will this affect clinical trials and drug development?

Clinical trialist' perspective

Disclosures

- Research: Novartis / Roche / Thermo Fisher / AstraZeneca / Taiho / BeiGene / Janssen
- Consultant/Advisor: Roche/Genentech - F.Hoffmann/La Roche - Ellipses Pharma - Neomed Therapeutics1 Inc - Boehringer Ingelheim - Janssen Global Services – SeaGen – Alkermes – Thermo Fisher - Bristol-Mayers Squibb – MabDiscovery – Anaveon – F-Star Therapeutics – Hengrui - Sanofi
- Speakers Bureau: Merck Sharp & Dohme / Roche / Thermo Fisher / Lilly / Novartis, Seagen
- Clinical Trials PI (Institutional): Adaptimmune LLC - Affimed Gmbh - Amgen SA – Anaveon AG – AstraZeneca AB – Bicycletx Ltd – BioInvent International AB – Biontech SE - Biontech Small Molecules Gmbh – Boehringer Ingelhem International Gmbh - Catalym Gmbh - Cyclacel Biopharmaceuticals – Cytovation AS - Cytomx - F.Hoffmann La Roche Ltd – F-Star Beta Limited - Genentech Inc - Genmab B.V. – Hifibio Therapeutics - Hutchison Medipharma Limited – Icon - Imcheck Therapeutics – Immunocore Ltd - Incyte Corporation – Incyte Europe Sàrl - Janssen-Cilag International NV - Janssen-Cilag SA – Laboratorios Servier SL - Medimmune Llc – Merck & Co, Inc – Merck Kgga - Novartis Farmacéutica, S.A – Peptomyc – Pfizer Slu – Relay Therapeutics – Replimmune - Ribon Therapeutics – Ryvu Therapeutics SA – Seattle Genetics Inc – Sotio as – Sqz Biotechnologies - Symphogen A/S – Taiho Pharma Usa Inc – T-Knife Gmbh

Outline

- The goal
- The problems (some)
- OBD instead of RP2D (based on MTD/TD)
- Potential clinical trial design opportunities
- Take home messages

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The goal

- To best characterize the optimal biological, efficacious, less toxic and more convenient schedule and dose in the early drug development period before going to a registrational study (usually phase III)
- To decrease the period of drug approval without taking wrong decissions
- To benefit the wider population ASAP
- Does one size fit all?
- (Does one drug development model fit for all drugs?)

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The problems (some)

- Toxicities: acute vs late onset vs chronic toxicities (i.e. regorafenib)
- Tumor setting:
  - Early stage (adjuvant/neoadjuvant) vs late stage: different tumor burden
  - Different tumor types (i.e. regorafenib in GIST vs mCRC)
  - Different molecular profiles (imatinib in GIST in exon 9 vs exon 11 KIT mutation)
- Big protein molecules (i.e. antibodies) vs small molecules (i.e. kinase inhibitors)
- Specific inhibitors (one aberrated protein/gene) vs multiple targets (i.e. promiscuous kinase inhibitors)
- Correlation or no correlation between dose and PK/PD effects (i.e. adagrasib/sotorasib)
- Definition of OBD (based on efficacy/toxicity) vs optimal & more convenient biological dose (based on efficacy/toxicity and convenience)

The problems (some)

Drugs requiring a tailored drug-development plan

	Small molecules			Proteins (large molecules)		
Class of Drugs	Mutant and isoform selective agents	Kinase family selective agents	Multi-kinase inhibitor agents	Targeted monoclonal antibodies	Immune checkpoint inhibitors	ADCs
Examples	Sotorasib	Erdafitinib	Lenvatinib Regorafenib	Bevacizumab Cetuximab	Pembrolizumab	Gemtuzumab ozogamycin
Off target effects	Minimal	Moderate	High	Moderate	Moderate (umpredictable)	Moderate (umpredictable)
Relevance of preclinical data	Highly relevant	Highly relevant	Highly relevant	Highly relevant	Hard to extrapolate to humans	Highly relevant
Therapeutic window	Wide	Moderate	Narrow	Wide/Moderate	Unclear	Moderate
Target population	Highly selected	Selected	Selected/ Less selected	Selected/ Less selected	Not clear	Selected

Modified from Araujo D et al (MDICT), Ann Oncol 2022

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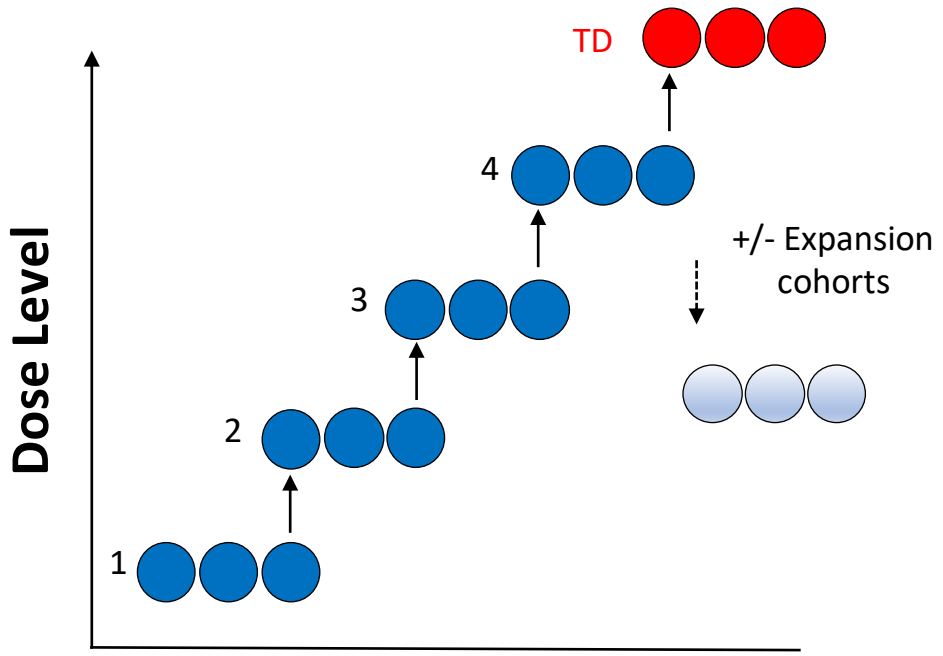
Classical Drug Development Path

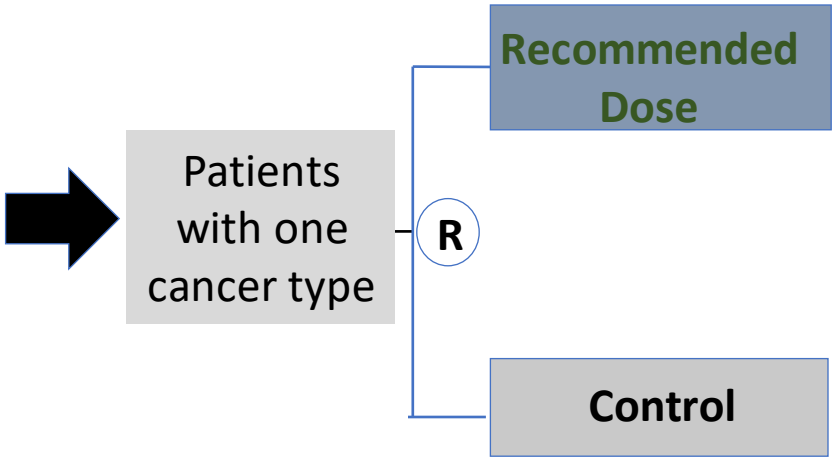
Dose Escalation Phase I study



Usually patients with multiple cancer types, fit, good PS

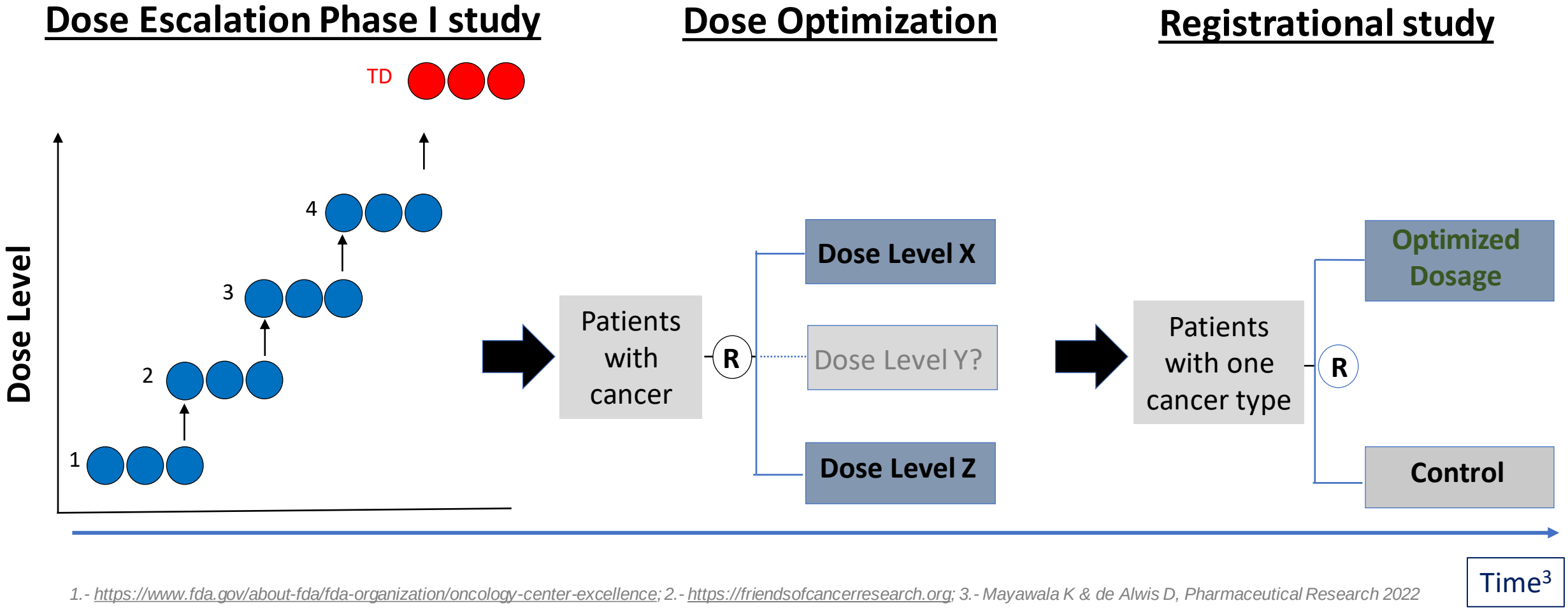
- Few patients at each cohort
- Short observation period for DLTs
- Based on DLTs, but not other safety

Registrational study



Time

Updated Dosage Selection Strategy FDA Optimus



1.- https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence; 2.- https://friendsofcancerresearch.org; 3.- Mayawala K & de Alwis D, Pharmaceutical Research 2022

How to improve Dosage Optimization

- Evaluate safety beyond DLT
- Consider the totality of the data: Pk,PD, efficacy, safety and tolerability at each step
- Characterize dosage and exposure relationships for efficacy and toxicity.
- Identify a target dosage range early and then further evaluate several dosages (ideally in a randomized trial)

Challenges

- **The MTD Paradigm- The higher the dose the higher the efficacy.**
  - Educating all stakeholders
  - IC needs to document clearly the reasoning for various dosings
  - Trial design aspects such as treatment crossovers and interim analysis

- **Perception it is too time consuming**
  - Understand ill optimized dose can negatively impact the ability to document the true Benefit of a Drug
  - Communication with regulatory agencies- need for efficiency.
  - Comprehensive dose selection may support a more seamless updates to the drugs post approval
  - Earlier understanding of dosage- and exposure- response allows for more rapid development of new therapies (combination regimens, new dosing regimens, new formulations)

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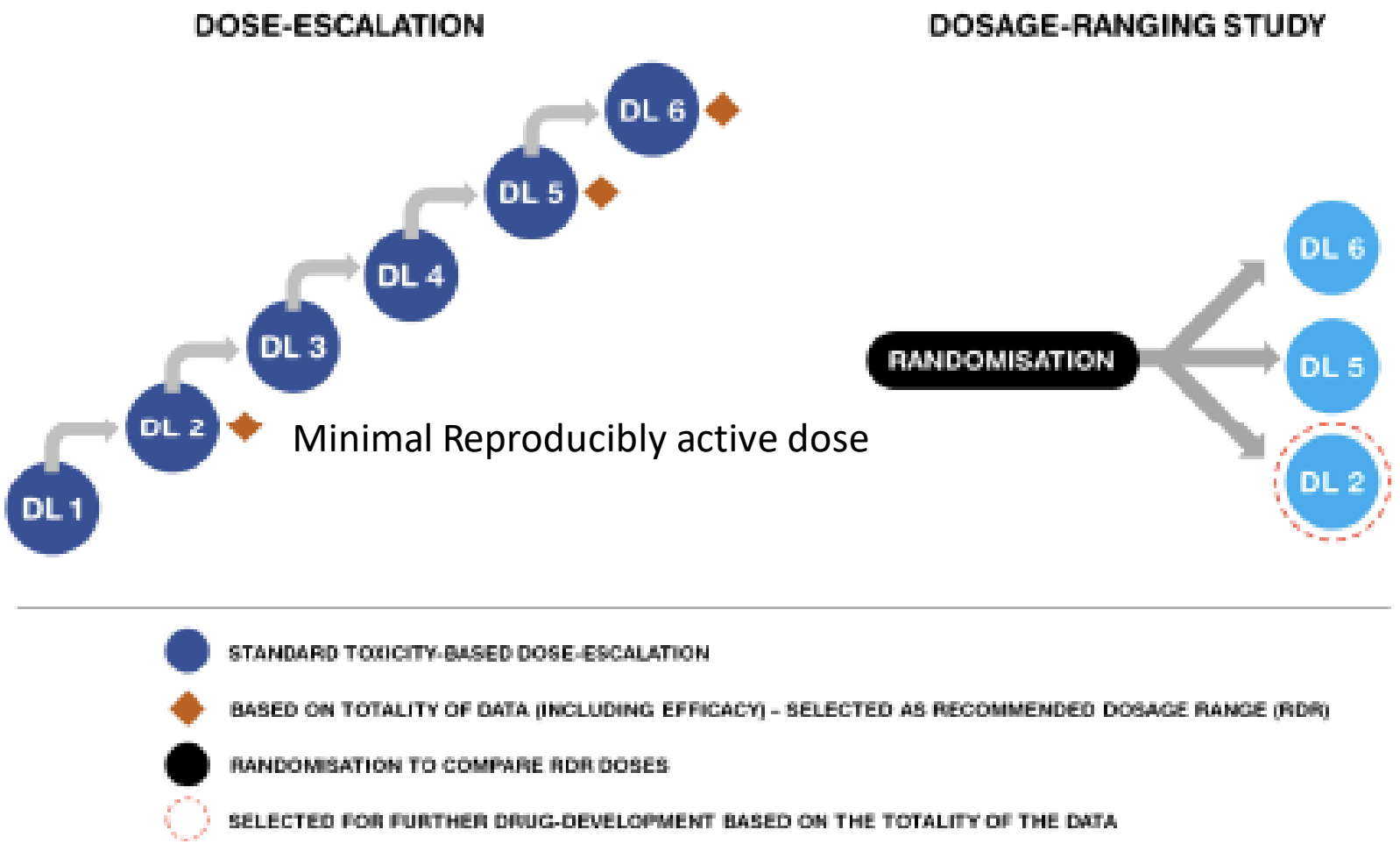
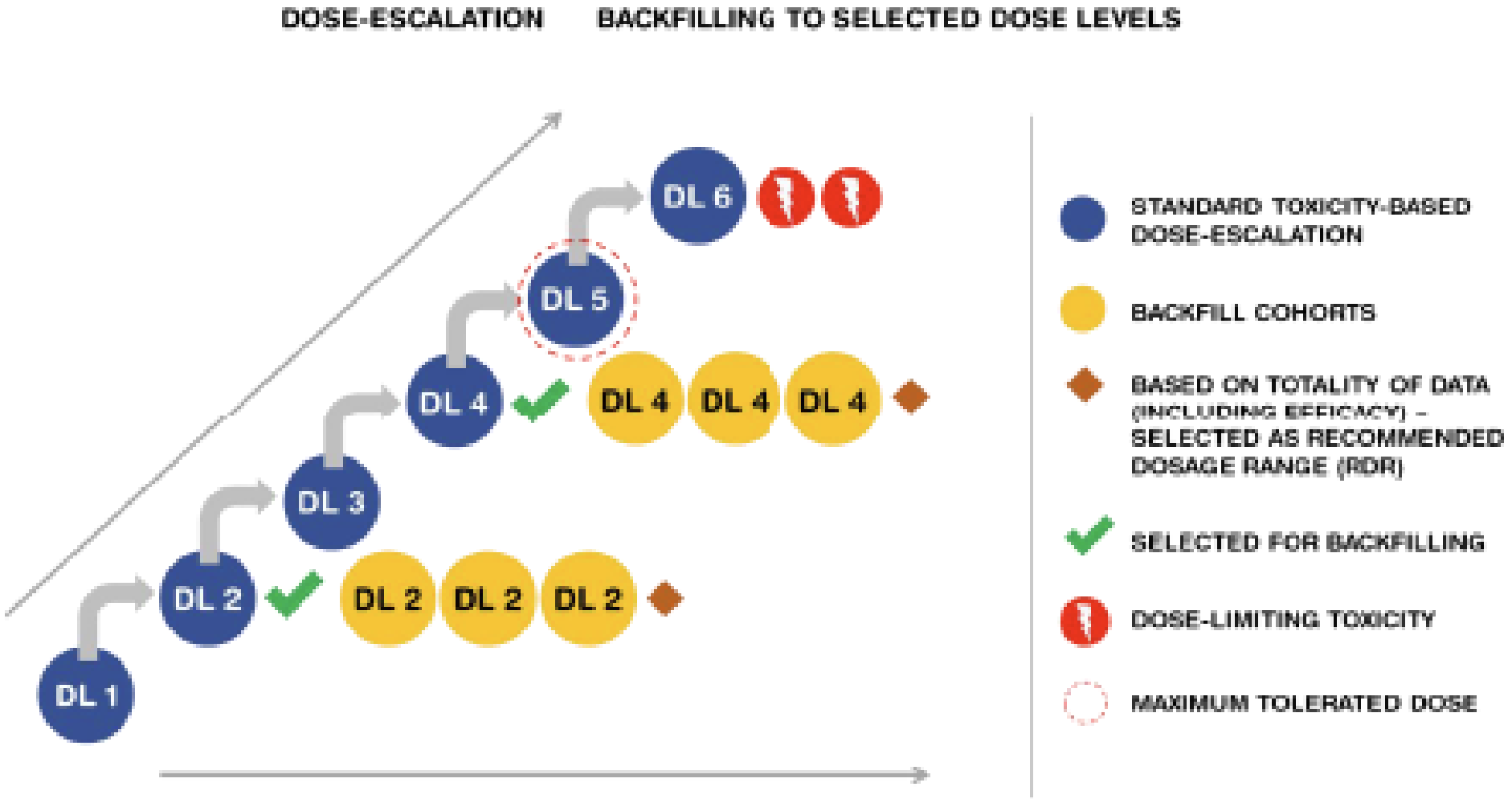
Proposed new model for drug development (I)



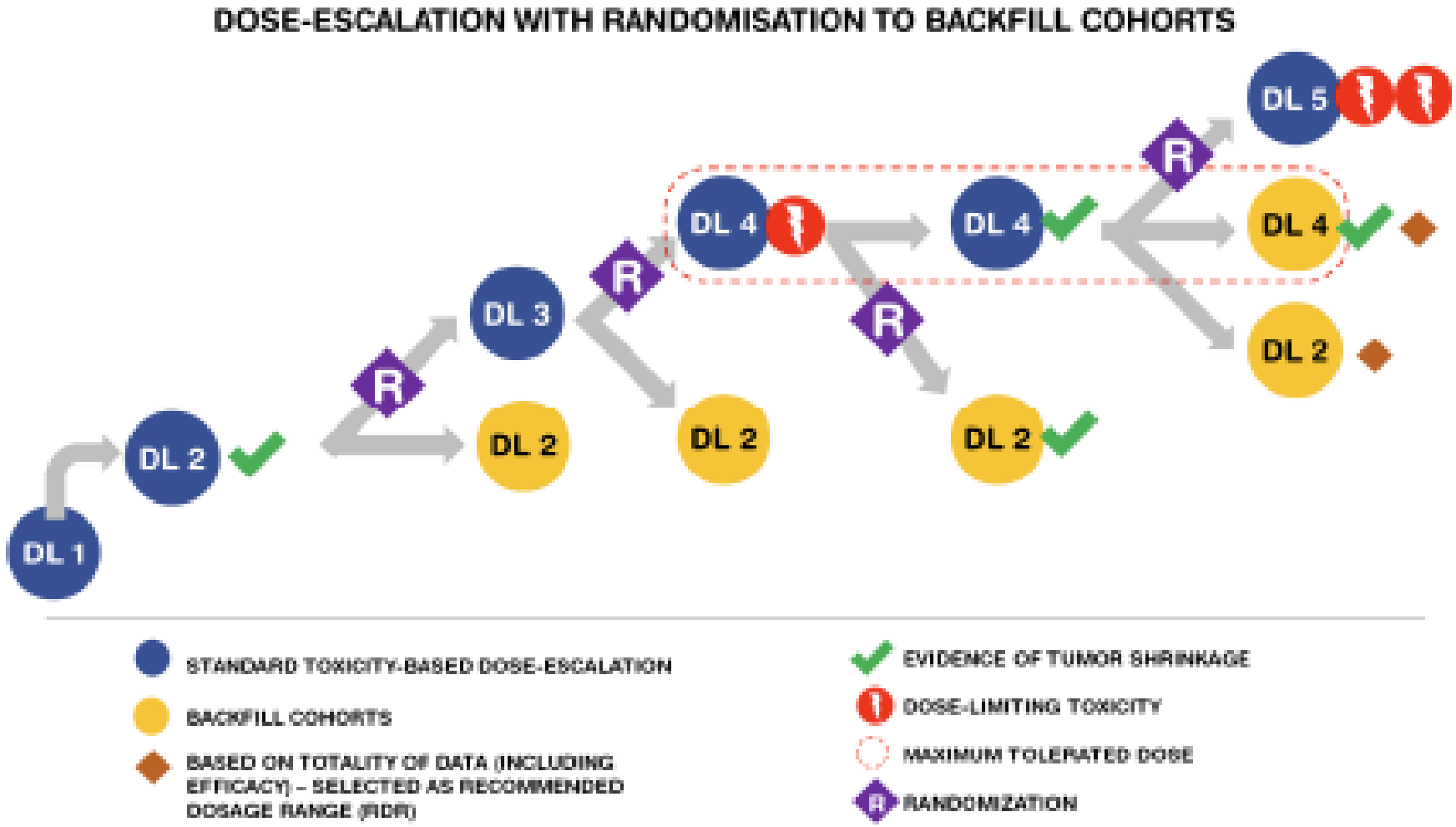
Araujo D et al (MDICT), Ann Oncol 2022

Proposed new model for drug development (II)



Araujo D et al (MDICT), Ann Oncol 2022

Proposed new model for drug development (III)



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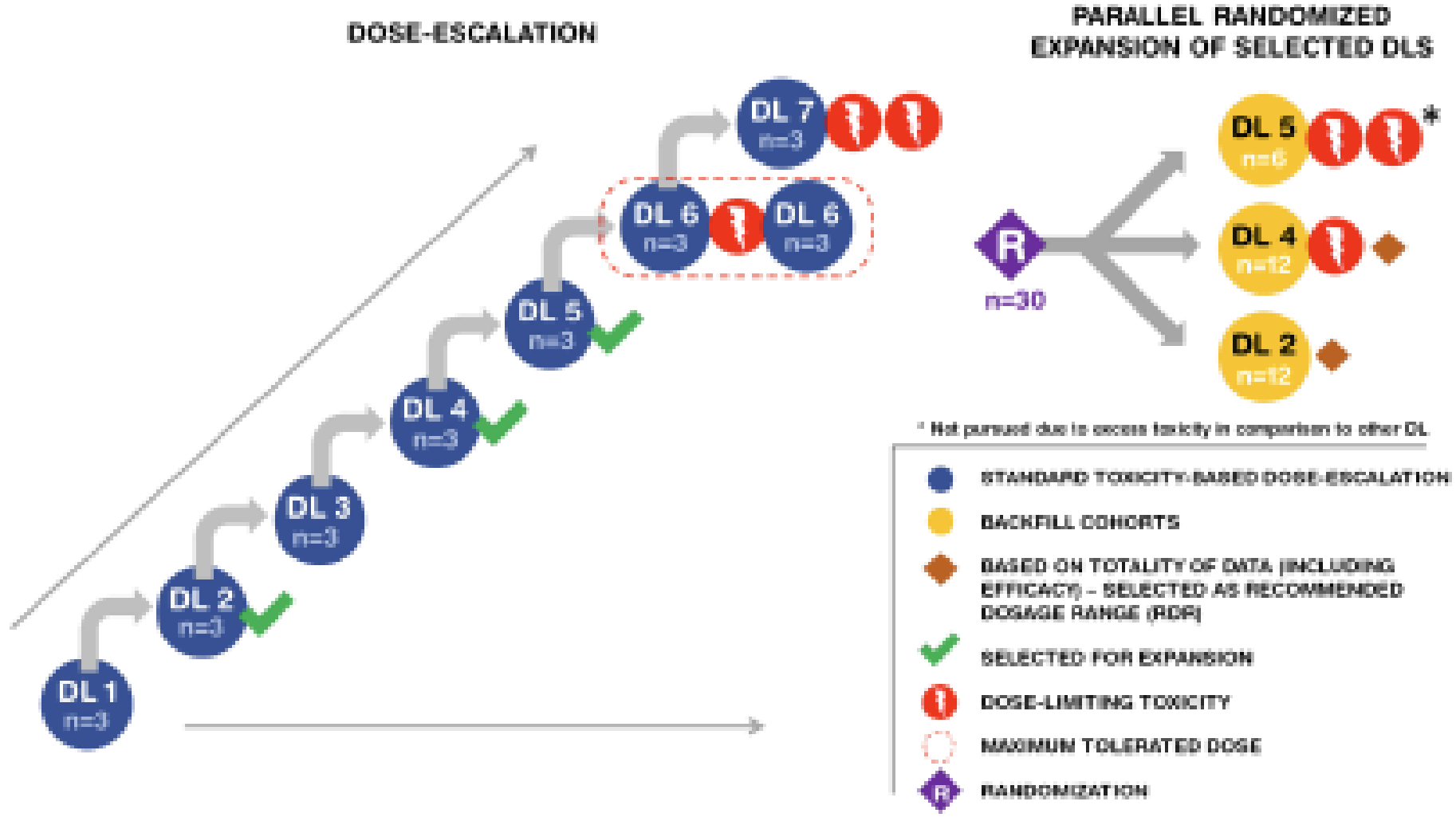
Proposed new model for drug development (IV)



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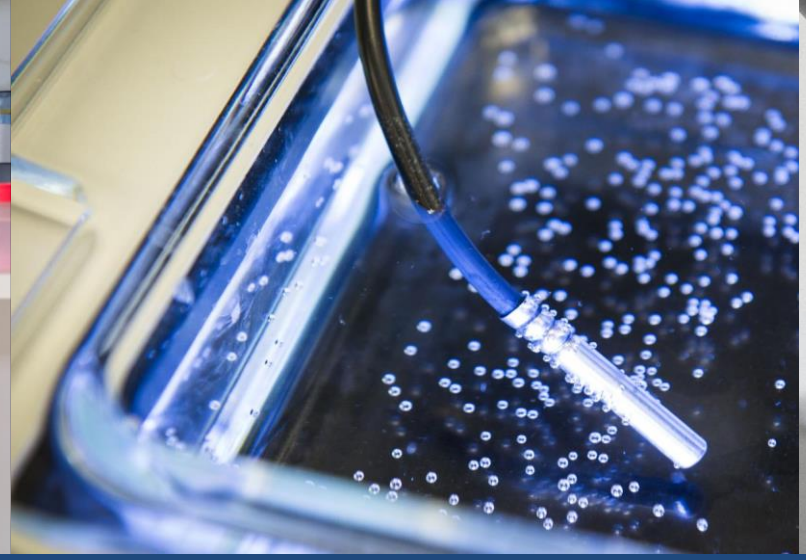
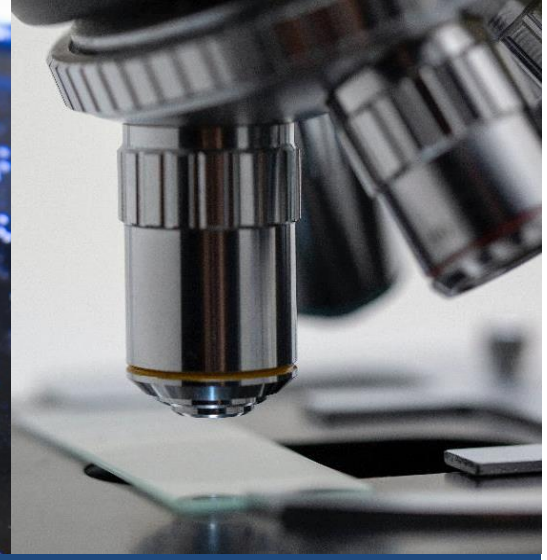
Take home messages

- Regulators (& all stakeholders) are challenging the paradigm that assumes that “more is better”
- Patient-focused drug development is not only an idea. It will happen, and the early drug development field is not an exception, actually is the piece to start
- Instead of choosing a single RP2D we will be asked to provide a range of doses to be further explored in more advanced phases
- Toxicity, pk parameters and clinical efficacy will still be used, but pharmacodynamic markers, PROs, PK/PD models, and even costs will be part of the consideration
- The question is whether this concept should apply to all types of drugs

Thank you

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