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

Oncology Phase 1 trial design conduct: Time for a change? Novel MDICT Guidelines

Dr Sophie Postel-Vinay, MD-PhD

Clinician Scientist

Gustave Roussy DITEP – U981 INSERM ERC StG

Phases Précoces en Oncologie

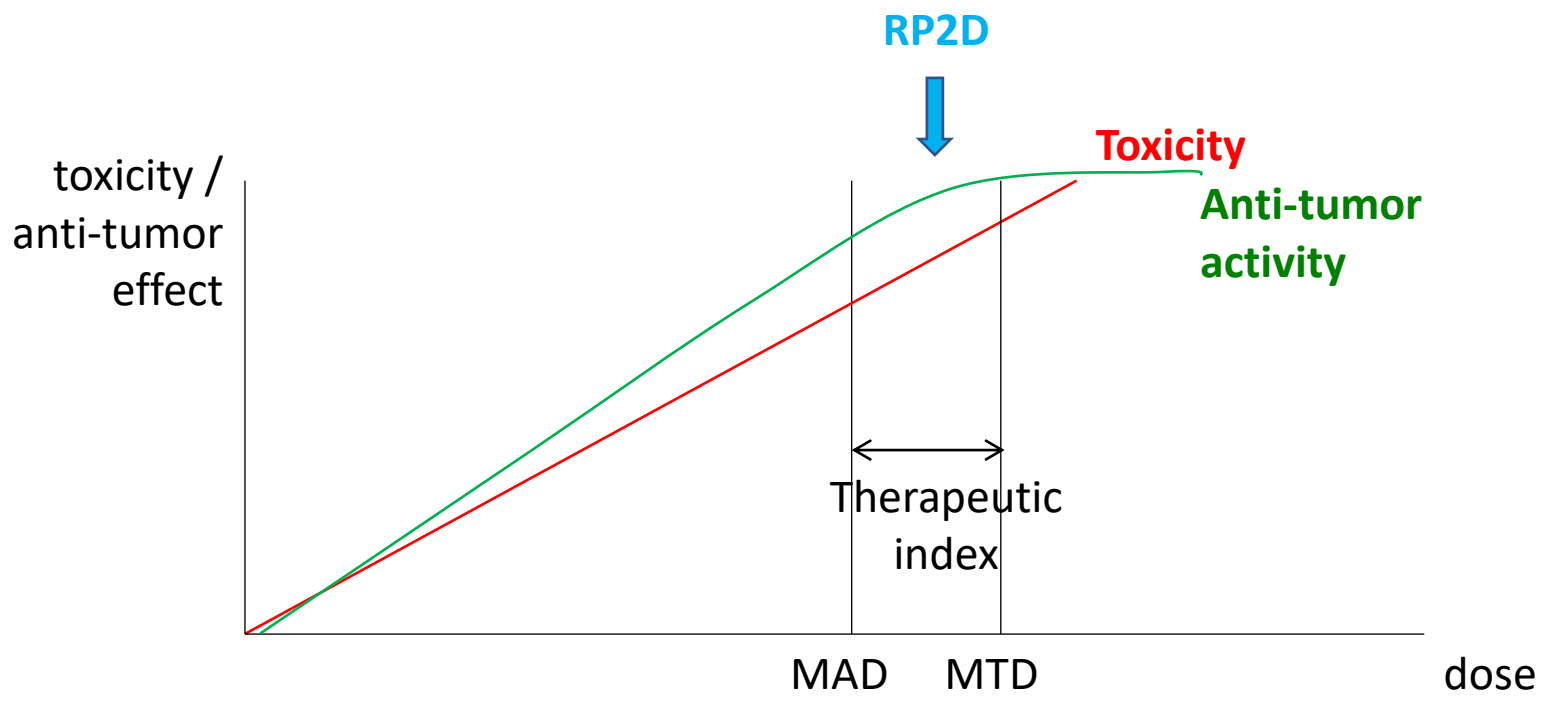
30 Novembre 2023

Conventional chemotherapy

Characteristics

- Administration **limited** in time
- **Early** toxicities
- **Linear** dose-toxicity / dose-efficacy relationship

- Dose selection: driven by **safety**, efficacy, and PK

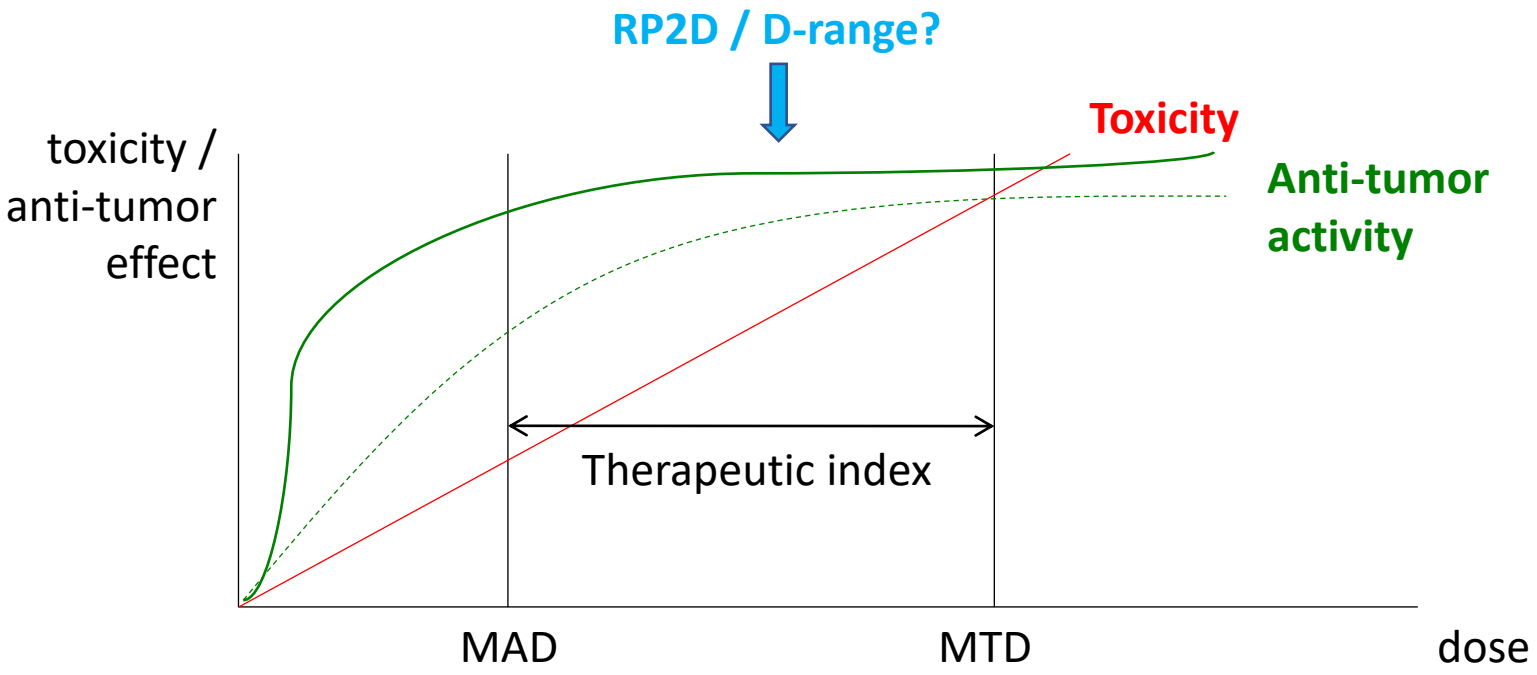


MTA & Antibody-based therapies

Novel characteristics

- **Chronic** administration
- **Late** toxicities (>50% G3 after DLT period)
- **No linear** dose-toxicity / dose-efficacy relationship
- **MTD** not always reached

- **Dose selection**: driven by safety, efficacy, and PK
- **Proof of biological effect** : **efficacy** and **PD**



Postel-Vinay , JCO 2013; Postel-Vinay EJC 2014; Postel-Vinay, Ann Oncol 2016

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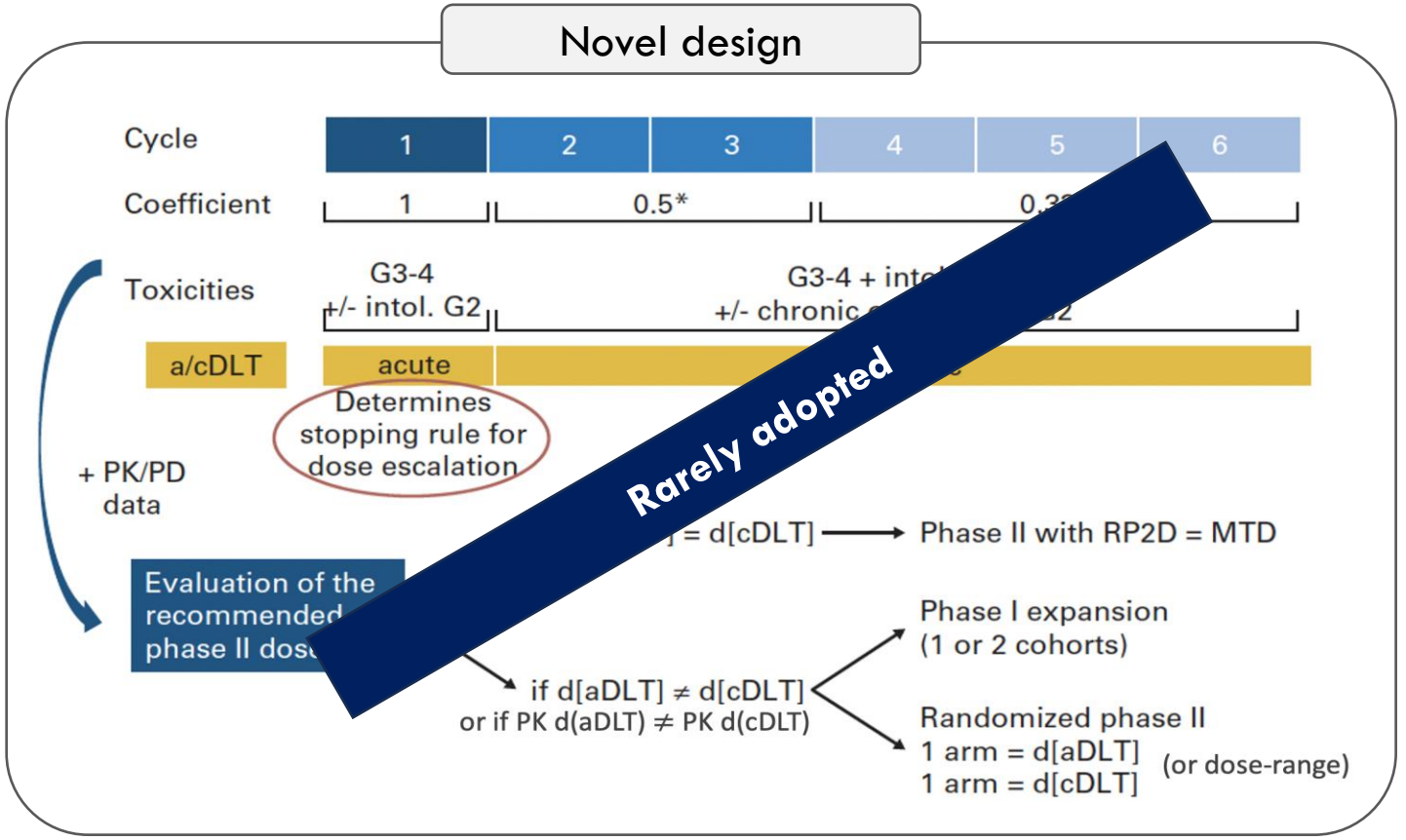


Postel-Vinay , JCO 2011; Postel-Vinay EJC 2012; Postel-Vinay, Ann Oncol 2016

Pressurising need to revisit drug development methodology

The Drug-Dosing Conundrum in Oncology — When Less Is More

Mirat Shah, M.D., Atiqur Rahman, Ph.D., Marc R. Theoret, M.D., and Richard Pazdur, M.D.

NEJM 2021

Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*

Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Small-molecule drugs			
Ceritinib (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel (Jevtana)	25 mg/m^2 IV every 3 wk (TROPIC)	20 mg/m^2 IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody–drug conjugates			
Gemtuzumab ozogamicin (Mylotarg)	9 mg/m^2 IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m^2 IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

ESMO TAT

PARIS 2022

Pressurising need to revisit drug development methodology

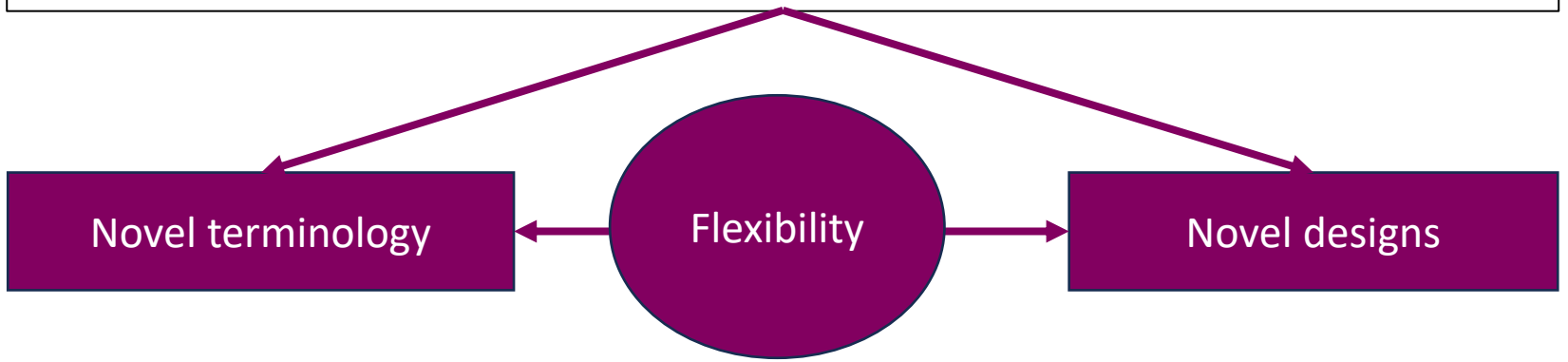
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

Oncology phase I trial design and conduct: time for a change - MDICT Guidelines 2022

D. Araujo[1†], A. Greystoke[2†], S. Bates[3], A. Bayle[4], E. Calvo[5], L. Castelo-Branco[6], J. de Bono[7,8], A. Drilon[9], E. Garralda[10], P. Ivy[11], O. Kholmanskikh[12,13], I. Melero[14], G. Pentheroudakis[6], J. Petrie[15], R. Plummer[2], S. Ponce[4], S. Postel-Vinay[4], L. Siu[16], A. Spreafico[16], A. Stathis[17], N. Steeghs[18], C. Yap[7], T. A. Yap[19], M. Ratain[20] & L. Seymour[15*]



ESMO TAT

PARIS 2022

For which drugs?

	Mutant and isoform-selective agents	Kinase family selective agents	Multi-kinase inhibitor agents	Immune checkpoint inhibitors
Example	Sotorasib	Erdafitinib	Lenvatinib	Pembrolizumab
Off-target effects*	Minimal	Moderate	High	Moderate (however, unpredictable magnitude of effect)
Relevance of preclinical data	Highly relevant	Highly relevant	Highly relevant	May be hard to extrapolate to humans
Therapeutic window	Wide	Moderate	Narrow	Unclear
Target population	Highly selected	Selected	Not clear	Not clear

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Dose Optimization of Sotorasib: Is the US Food and Drug Administration Sending a Message?

Mark J. Ratain, MD[1,2]; Ian F. Tannock, MD, PhD, DSc[2,3]; and Allen S. Lichter, MD[2]

Low-Dose Immunotherapy in Head and Neck Cancer: A Randomized Study

Vijay Maruti Patil, MBBS, MD, DM[1]; Vanita Noronha, MBBS, MD, DM[1]; Nandini Menon, MBBS, MD, DNB[1];

New terminology for endpoints

Existing term		Suggested new term		Rationale
Term	*Abbreviation*	**Term**	*Abbreviation*	

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Existing term		Suggested new term		Rationale
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Dose limiting toxicity	*DLT*	**Treatment limiting toxicity**	*TLT*	**Chronic** or **incremental** toxicity
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Recommended phase 2 dose	*RP2D*	**Recommended dosage**	*RD*	For later phase trials (such as phase 3 or combination studies)

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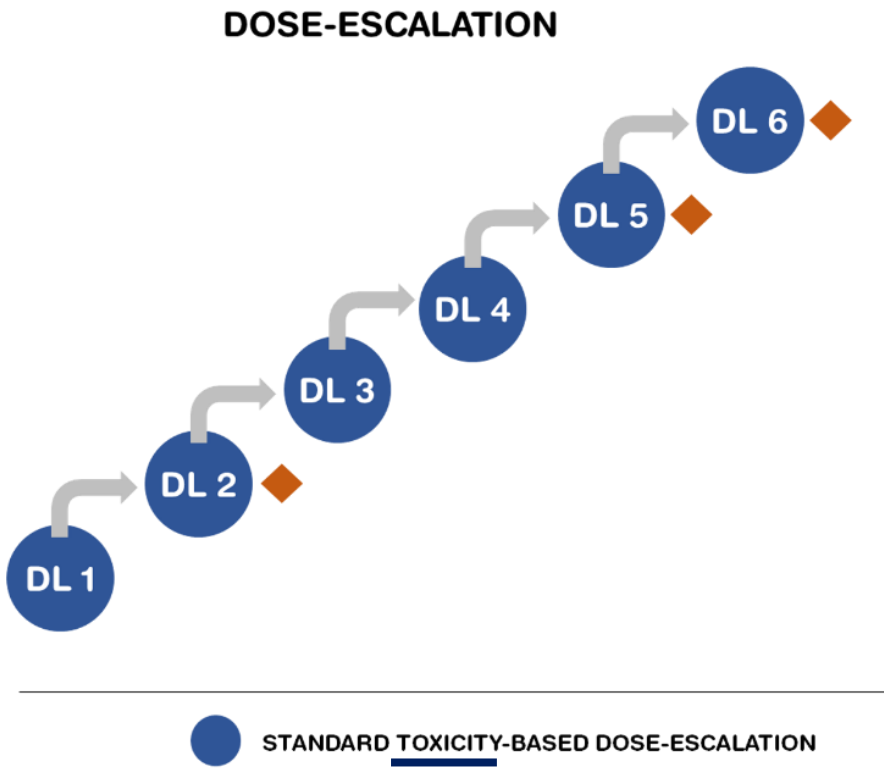
Phase 1		**Dosage escalation study**		To define a RDR +/- dose confirmation
Consider a phase 1 study with expansion cohorts or a separate phase 2 study		**Dosage ranging / dosage confirmation study**		Will define a **RD**, typically by randomizing between 2 or more dosages Sometimes separately defined for different patients (e.g., genetic aberrations, tumor sites, …)

Overall design



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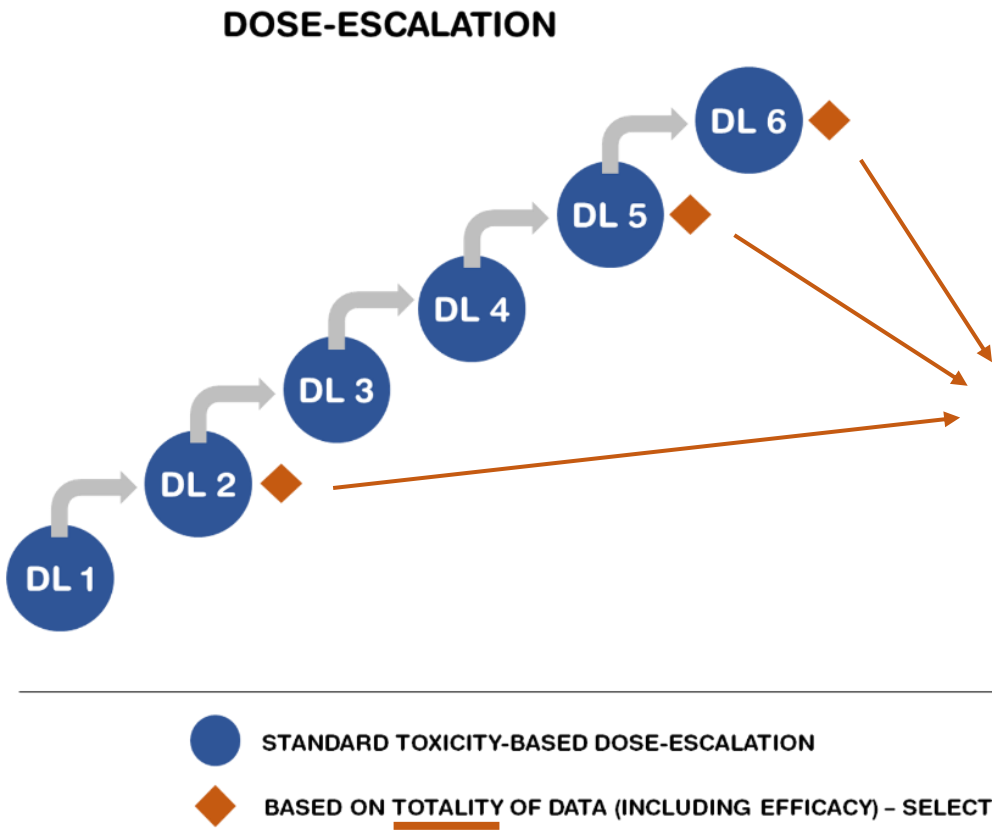

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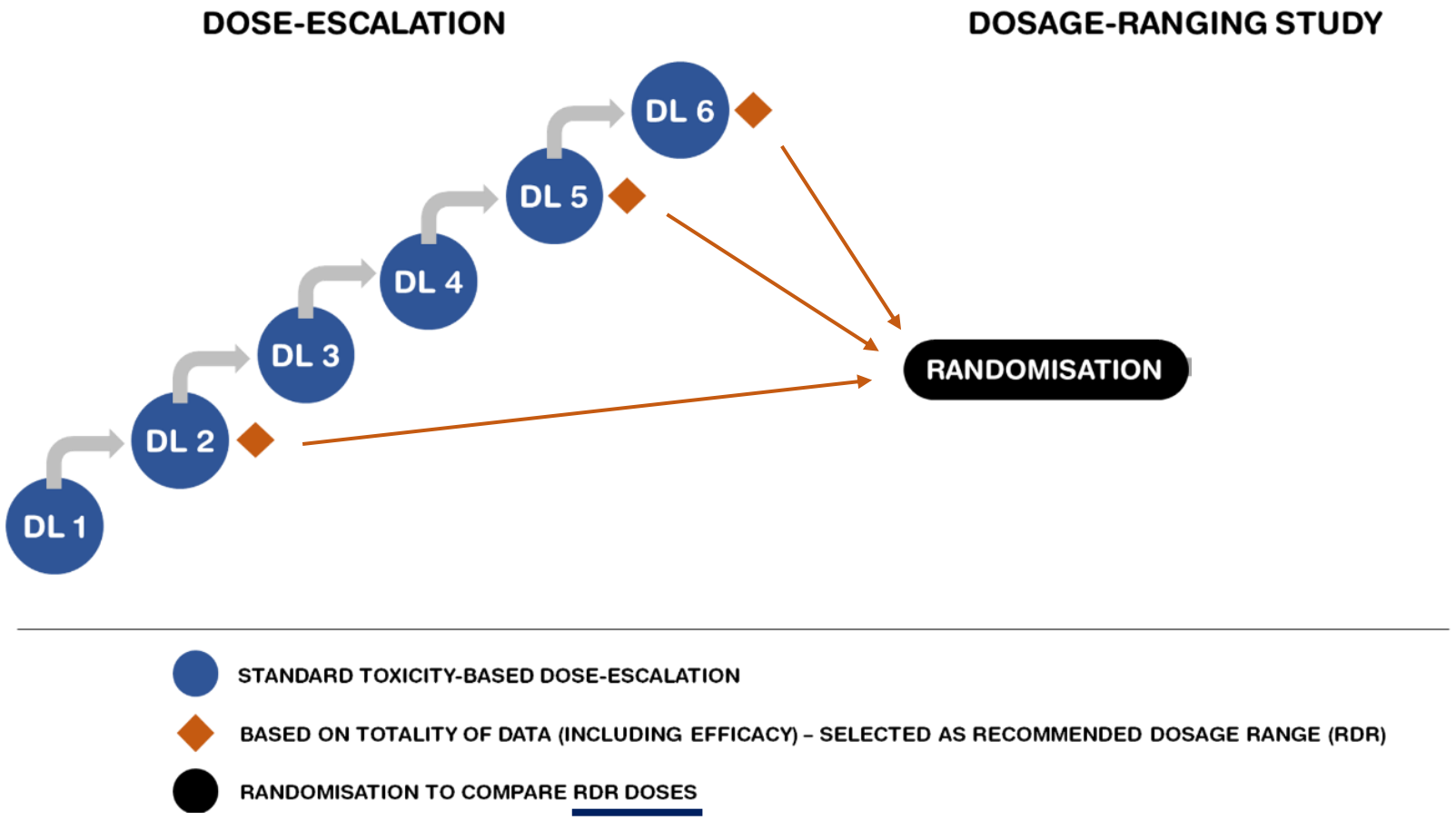

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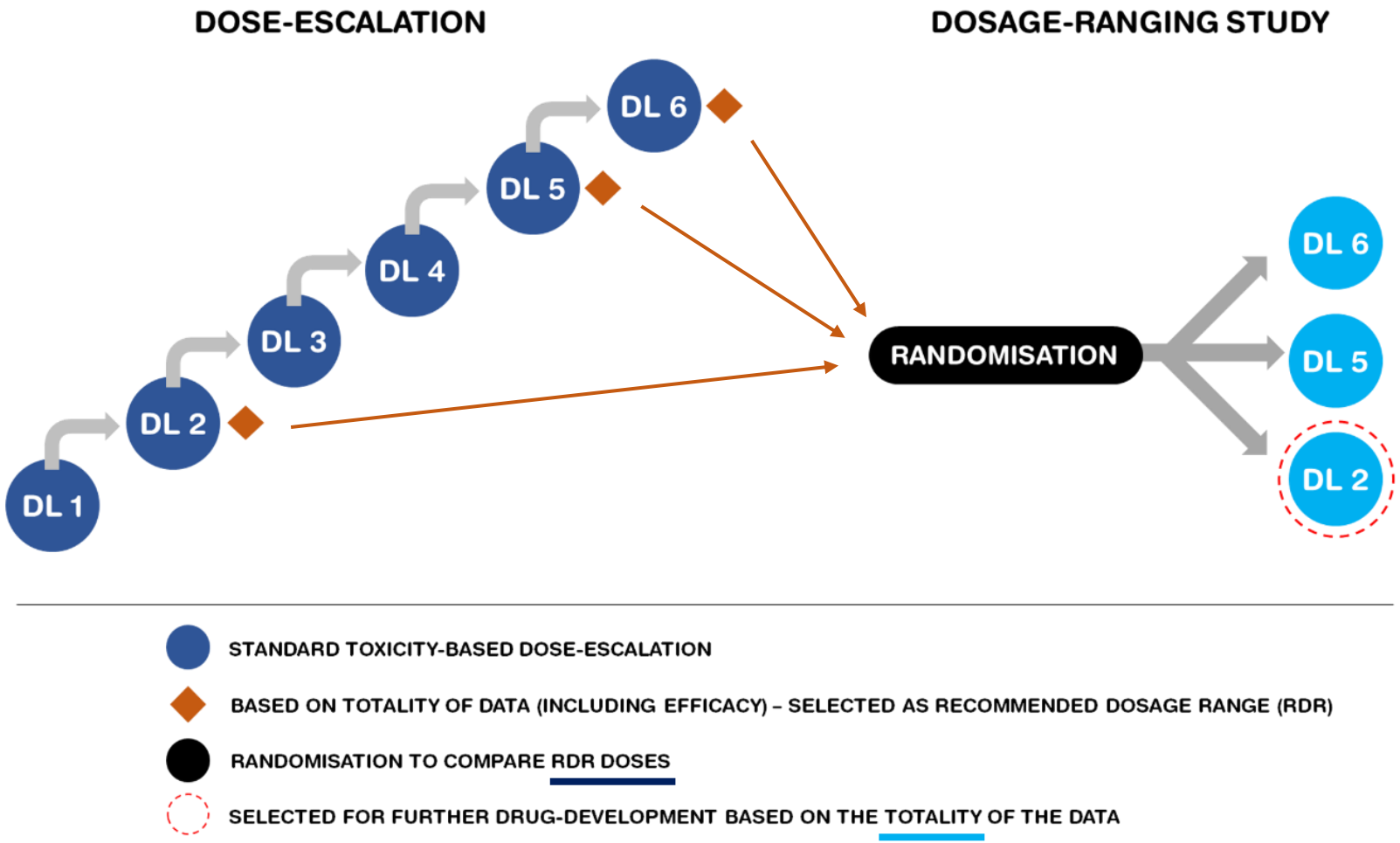
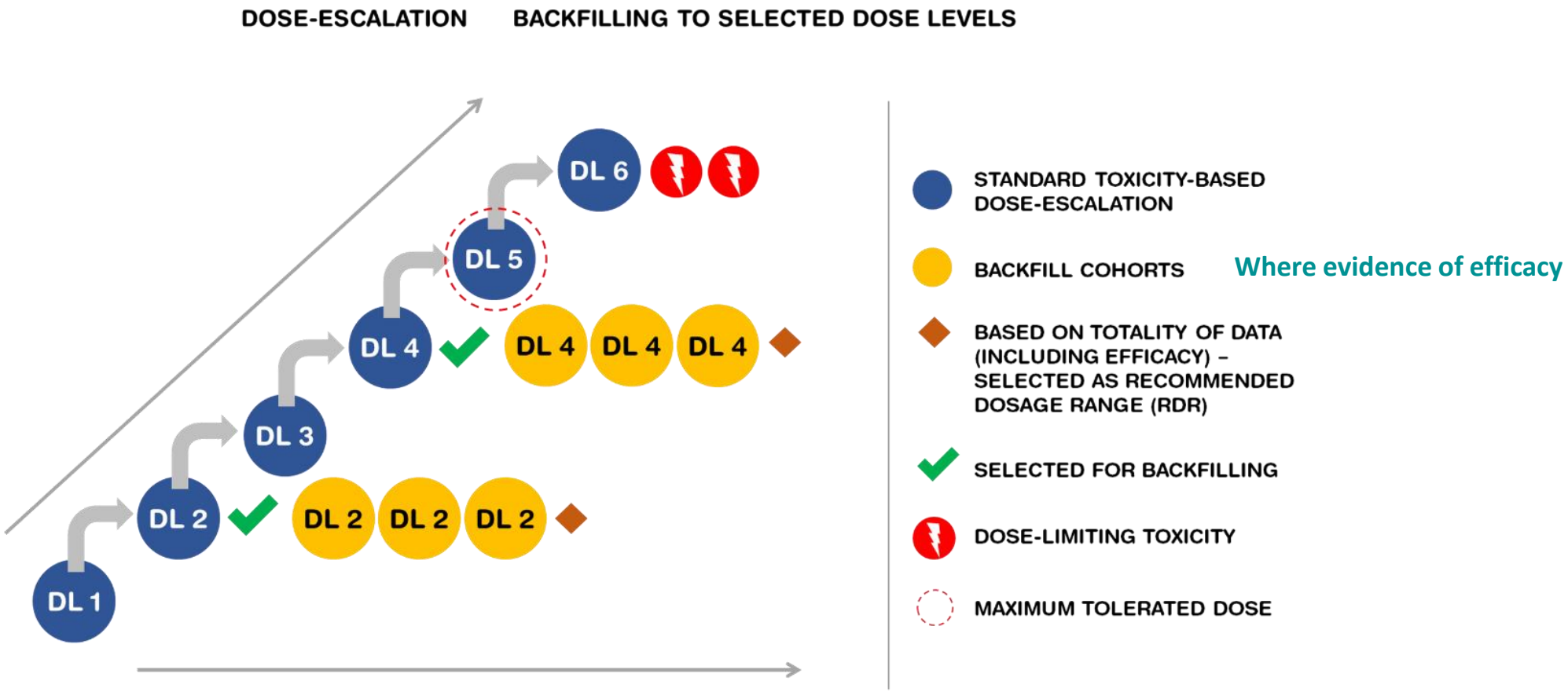
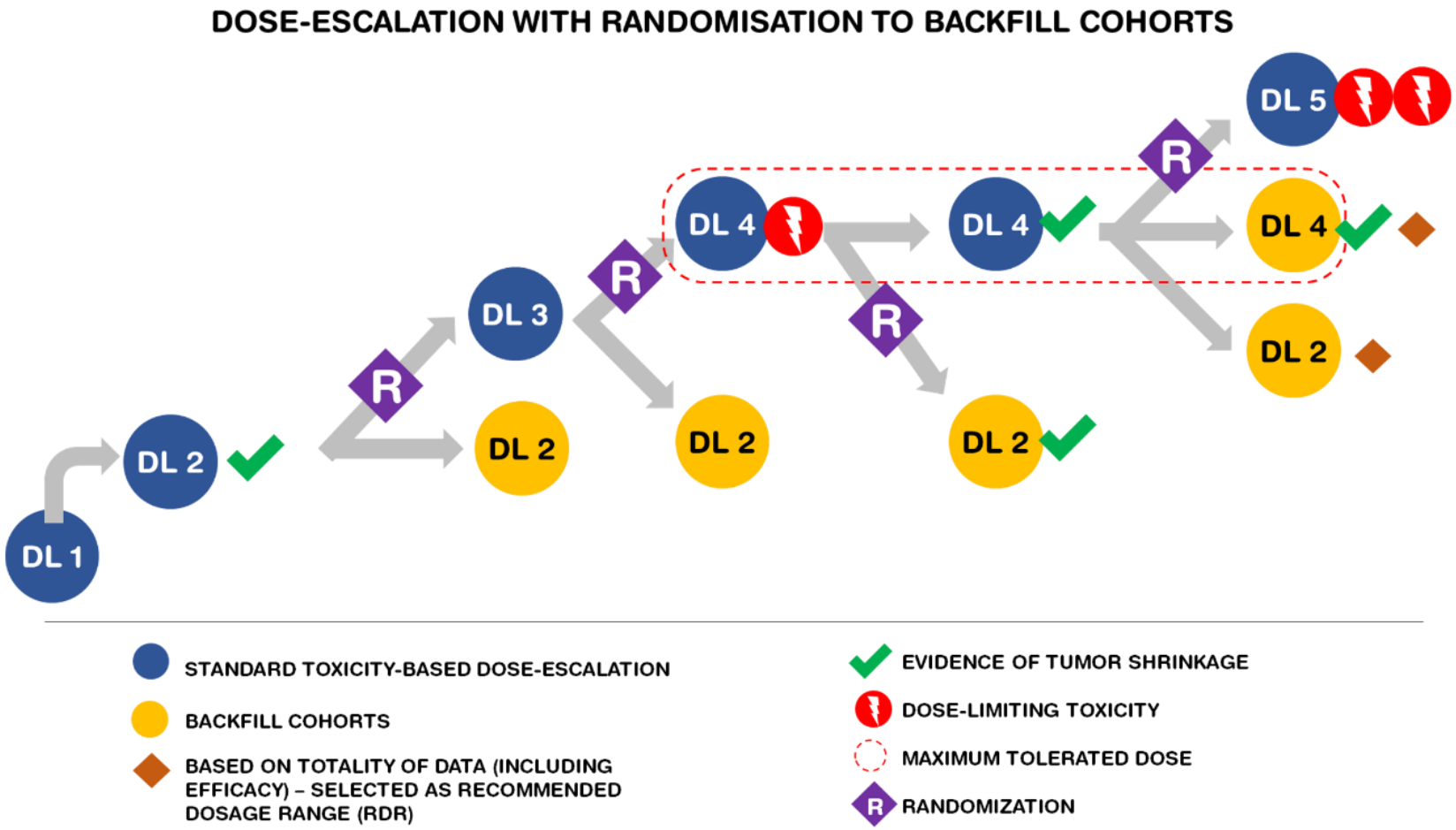


Specific recommendations & designs (1)



Where evidence of efficacy

Specific recommendations & designs (2)



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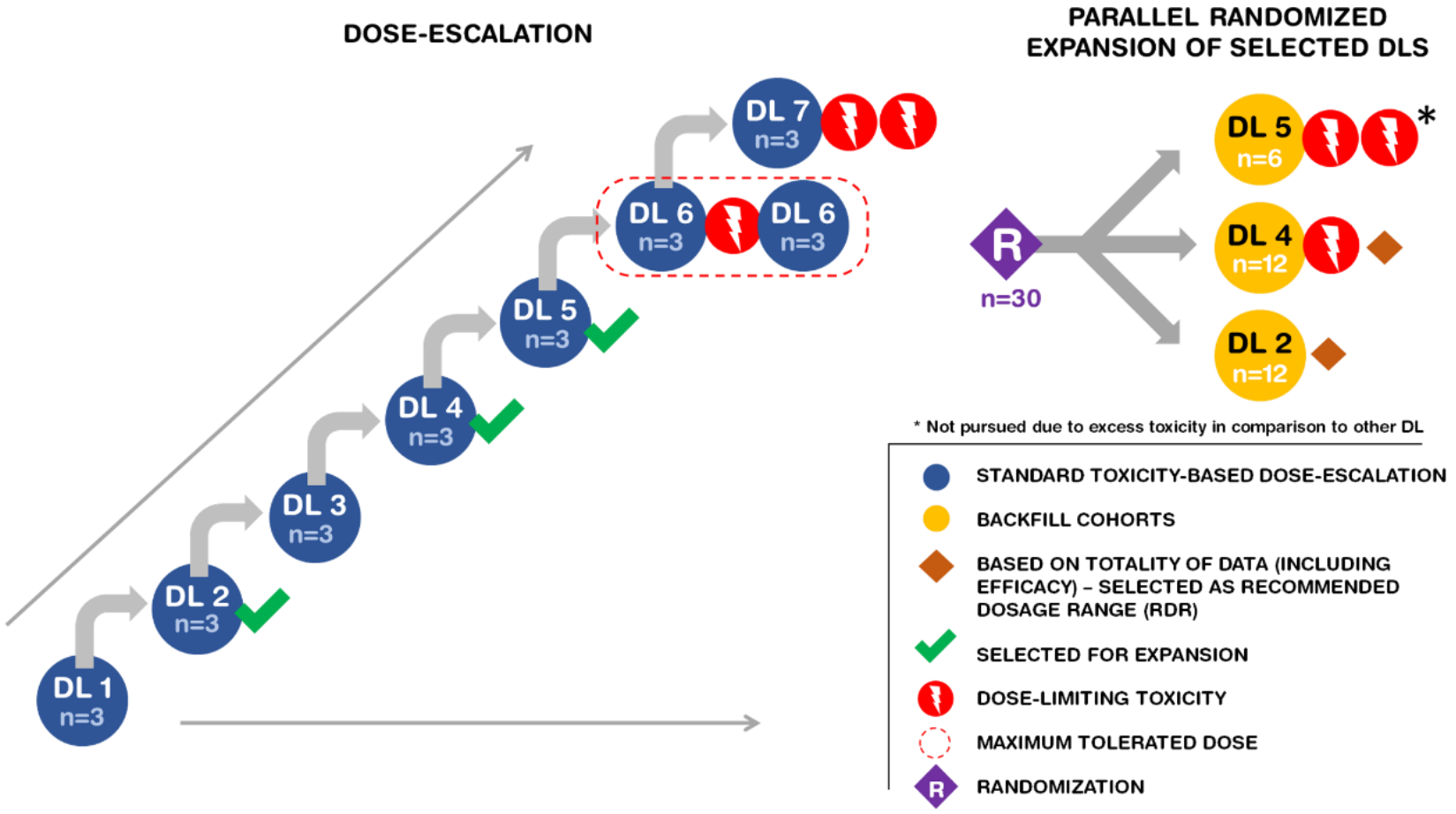

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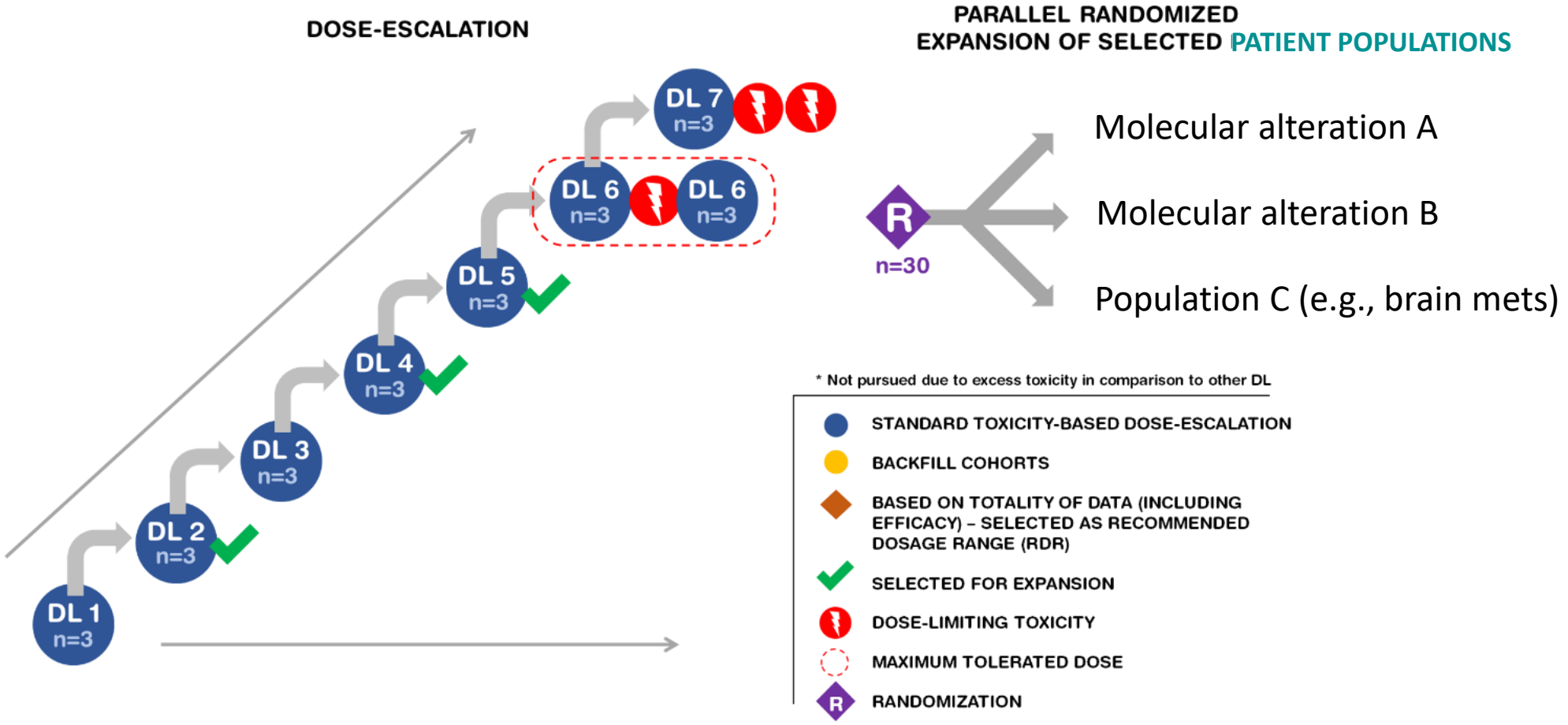

Other considerations

Intra-patient dose-escalation

- Cleared DLT period for several cycles
- **Stable** disease but no shrinkage
- No activity seen at that dose level
- **Higher dose tolerable**

Broaden eligibility criteria

- Specific patient population
- Backfill

Serial tumor biopsies

- 72 trials
  -> 12 significant BM results
  -> 5 subsequently cited in PII/III trials

Sweis, JCO 2015

Salawu, JCO 2021

Levit, ASCO Guidelines, JCO 2019

-> Favor

- **Liquid biopsies**
- **Molecular imaging**

Cescon, Nat Cancer 2020

Take home message – key points

Trial development	Robust non-clinical package including PER, PK, PD, biomarkers etc.
	Assemble expert team including statistics, pharmacology etc.
	Consult early with health authorities
	Flexible and **adaptive** design to minimize holds
	Define TLT and how RDR will be decided

level, MTD – maximal tolerated dose, IPDE – intrapatient dose escalation, PD, disease progression, MRAD - minimally reproducibly active dose

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	Consider randomization to improve efficiency by **backfilling** DLs, investigate food effect
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	Allow IPDE to tolerable DLs (prior to disease progression except under select circumstances)
	Choose **real world** eligibility criteria (including for example stable CNS metastases)
	Oral drugs should be dosed with food, and food effect formally examined by randomization after cycle 1

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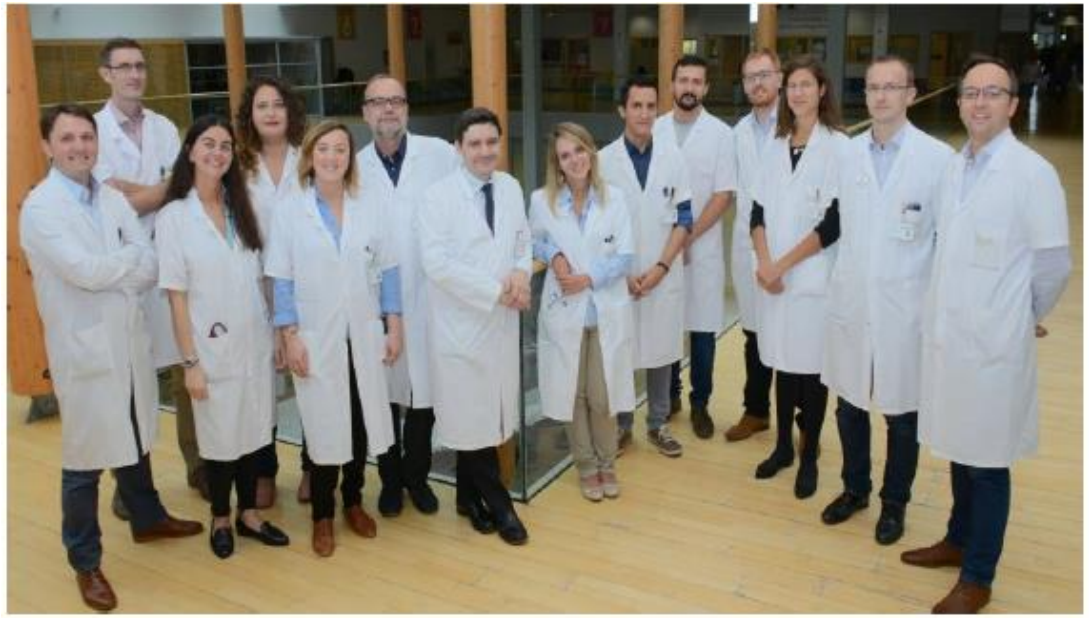
Formulating the RDR	Use all available data – PK and PD results available quickly
	Define at least 2 dosages which must include the **MRAD** and an effective dose approximating the **MTD**; preferably include an intermediate dosage as well
	Recognize that **special populations** may need **different RDR/RD** (sanctuary sites, alterations with potentially variable sensitivity)

PER – predicted effective dose range, PK – pharmacokinetics, PD – pharmacodynamic, TLT – treatment limiting toxicity, RDR – recommended dosage range, PRO – patient related outcomes. DL – dose level, MTD – maximal tolerated dose, IPDE – intrapatient dose escalation, PD, disease progression, MRAD - minimally reproducibly active dose

Take home message – Summary

Acknowledgements



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