

CDDF Multi-Stakeholder Workshop

Dose optimization in oncology drug development

3 – 4 April 2023, HYBRID WORKSHOP – Amsterdam (NL)



CDDF MULTI-STAKEHOLDER WORKSHOP

Dose optimization in early
oncology drug development

3 - 4 April 2023
AMSTERDAM (NL)



Program Committee, Speakers and Panelists



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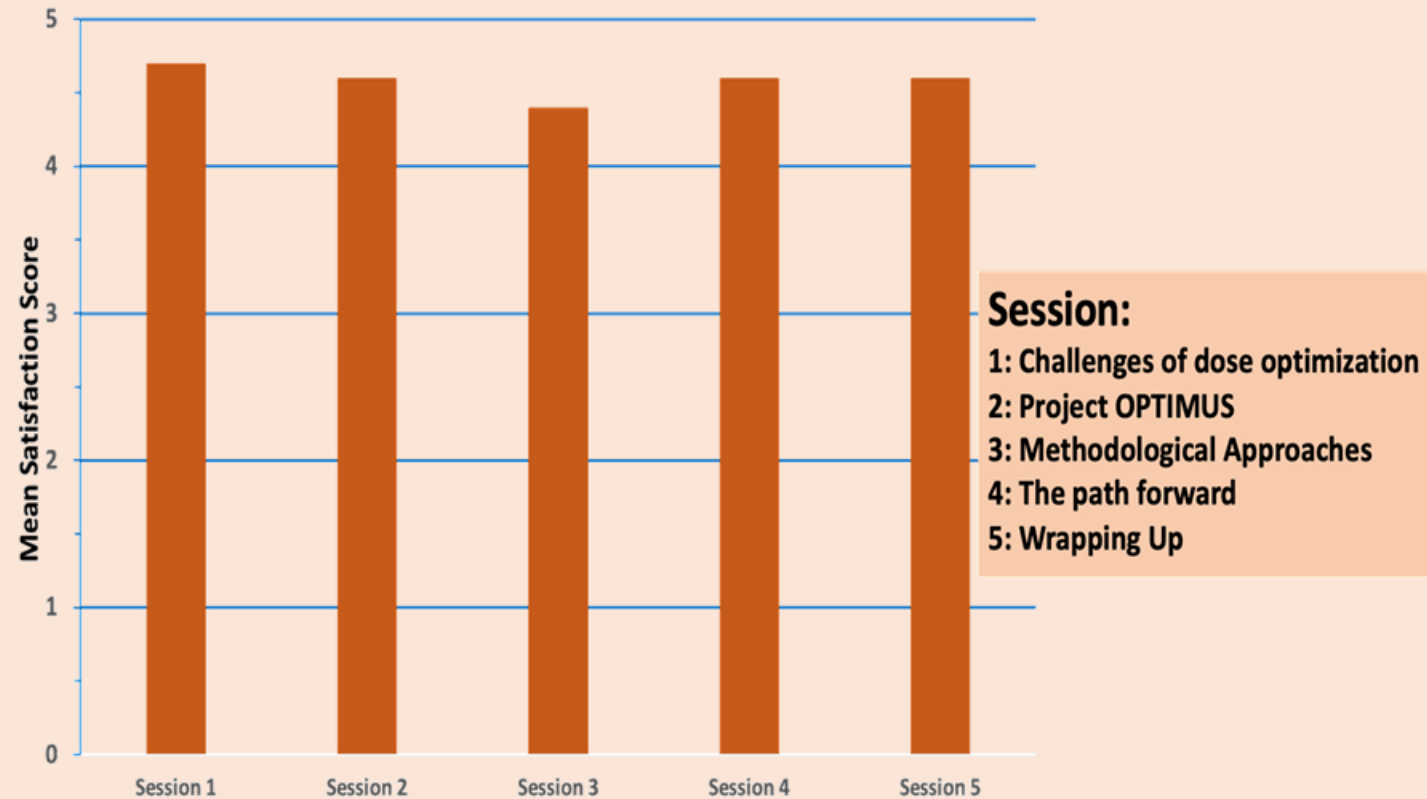
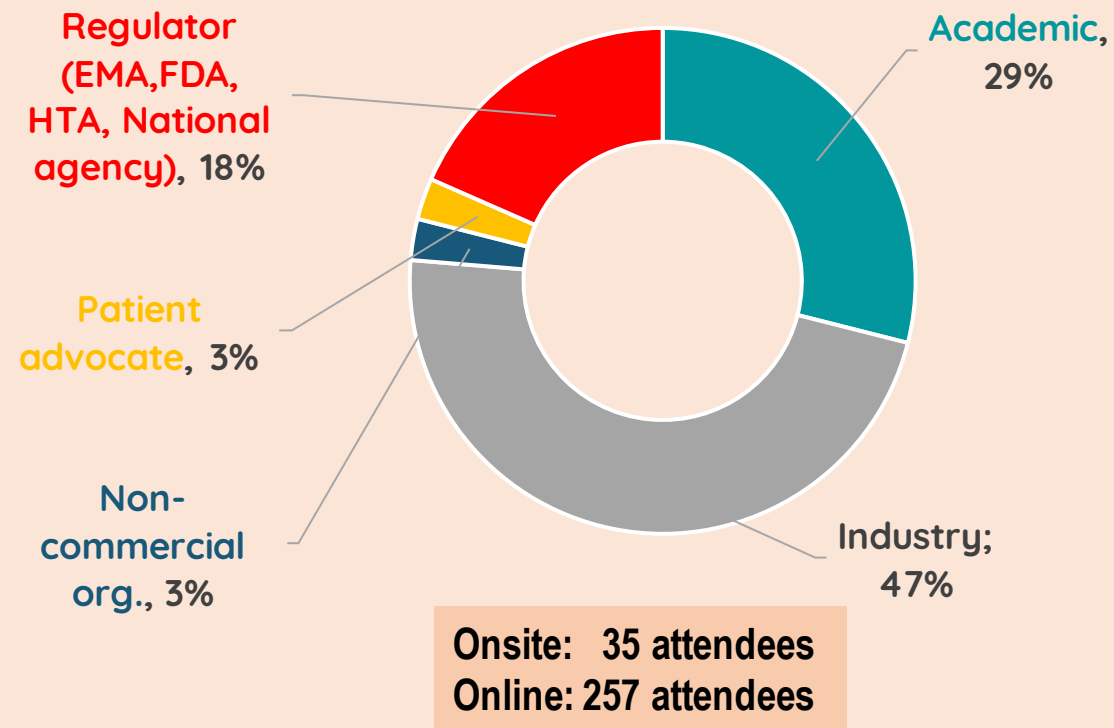


Hillary Stires



Weirong Wang

Participants & Feedback



Workshop overview

Monday, 3 April

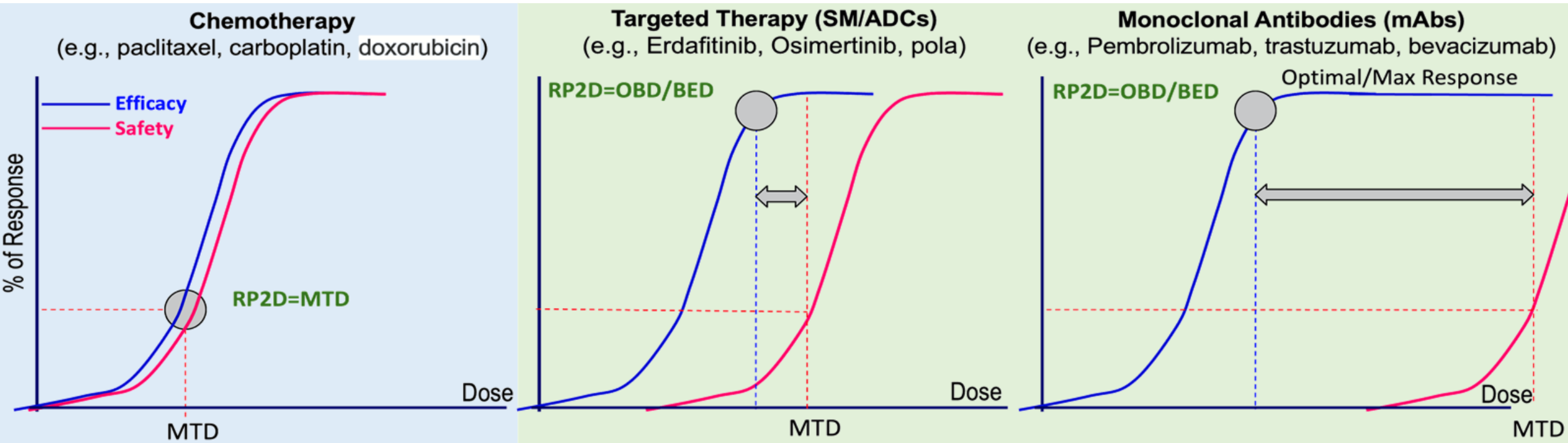
- 13:00 – 15:20 **Session 1:** The challenges of dose optimization
- 15:50 – 16:50 **Session 2:** Project Optimus and other regulatory initiatives
- 16:50 – 18:00 **Session 3:** Dose optimization - methodological approaches

Tuesday, 4 April

- 10:30 – 12:15 **Session 4:** Dose optimization - Options for the path forward
- 12:15 – 13:30 **Session 5:** Panel discussion

Why do we need Dose Optimization?

- Historical paradigm developed for cytotoxic anticancer agents:
 - Determine MTD, reduce dose in individual patients
 - Optimize dose intensity, rather than therapeutic index or efficacy
- Optimal biological doses for molecular targeted or immunotherapeutic agents are often significantly lower than the MTD because of differences in mode of action



RP2D: Recommend Phase 2 Dose; MTD: Maximal tolerated dose; OBD: optimal biological dose; BED: biological effective dose

Figure modified from Chunze Li: Oncology Dose Optimization – how to optimize the trade-offs, CDDF Workshop Dose Optimization, April 2023

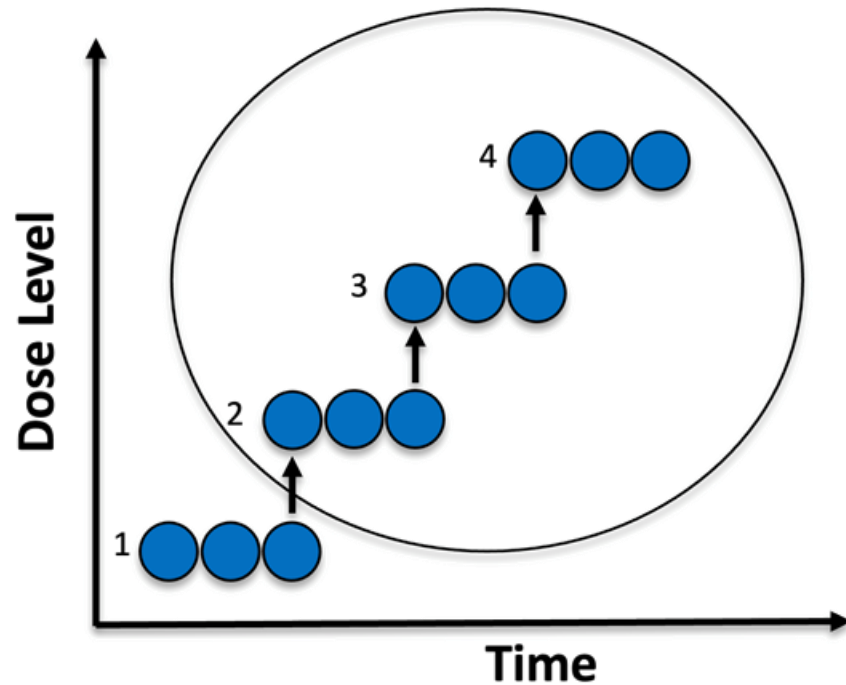
Consequences of Not Optimizing Dosage Before Approval



- Drug is poorly-tolerated at the approved recommended dosage
 - Patients may stop taking a potentially efficacious drug
 - Patients choose to try a different drug
- It takes a long time to evaluate alternative dosages following approval
 - Patients may not want to participate in trial if commercially available
 - Disease area moves on to other treatments
- Drug does not make it to market or must be withdrawn from the market

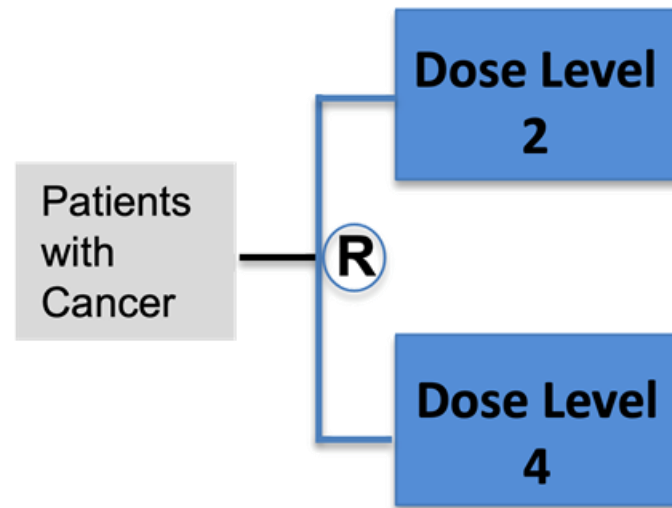
Updated Dosage Selection Strategy

Dose Escalation



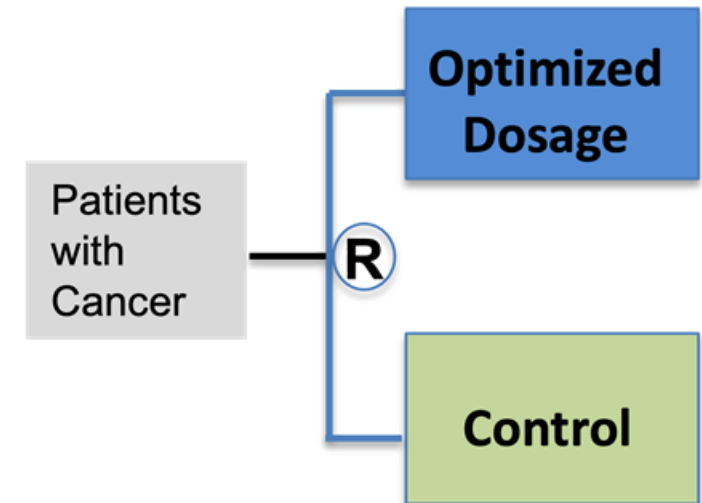
Select Dosage for
Further
Exploration

Dosage Optimization



Evaluate Several
Dosages

Comparison to Standard-of-Care



Comparison to
Standard-of-Care

Industry Perspective: Challenges & Opportunities

COMPLEXITY of Study Designs

- Randomised dose-response trials
- Model-based systems integrating later data
- Adaptive designs with interim analyses
- ORR/DoR may not be adequate endpoints

OPPORTUNITIES

- Development of PK/PD models may increase early-stage success rates
- New stat methods may reduce study sizes
- Optimised dosing may increase late-stage success rates

REDUCED SPEED

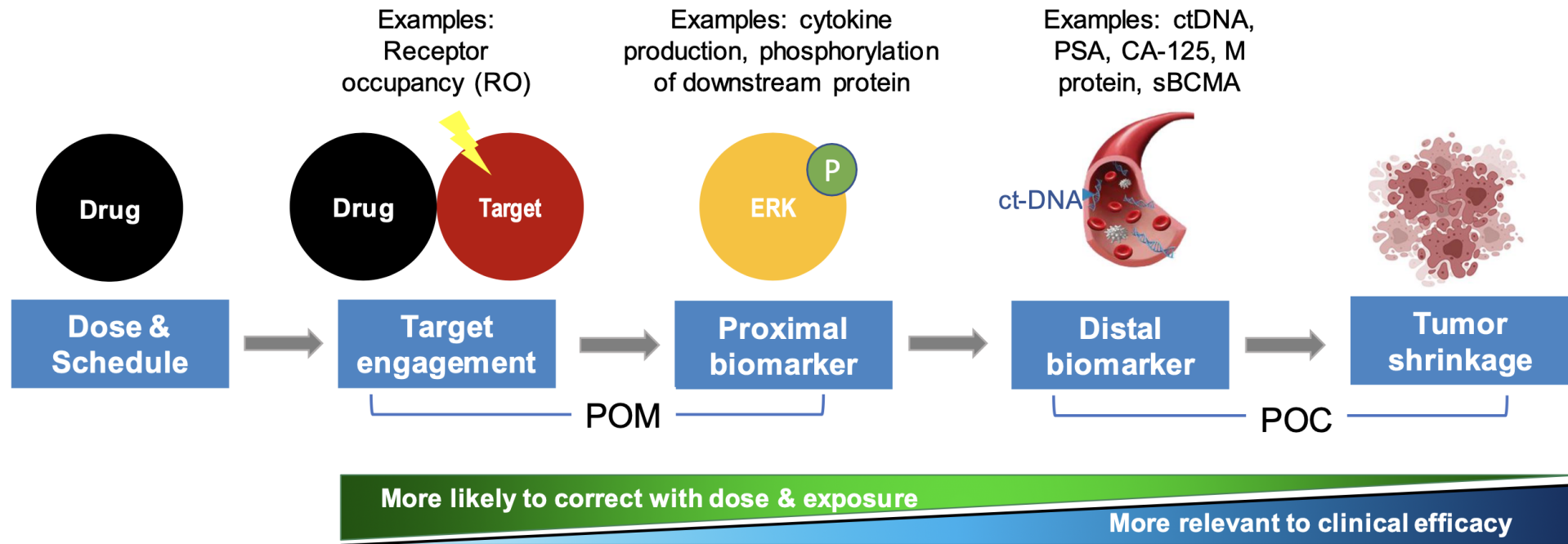
- Overall duration is likely to increase
- Increased intervals between dose cohorts
- Real-time PK/PD data needed
- Timing of expansion cohorts
- Fast-track program may be delayed

INCREASED COST

- Significant hurdle for smaller biotech
- Funding difficulties in context of other developments (e.g. IRA)

Industry Perspective: The Path Forward

Clinically Relevant PD Biomarkers Important to support the Dose Optimization, but Unlikely to be useful in Isolation



The selection of the relevant marker(s) for exposure-response (E-R) characterization is driven by the available **preclinical data**, drug MoA, and the biomarker(s) characterization, variability, dynamics, covariates etc.

Industry Perspective: The Path Forward

Strategic Context

disease specific need for efficacy and patient tolerance/experience, CMC feasibility, unmet medical need, speed & competition

Innovative/adaptive Study Design

- Backfill cohorts
- Multiple dose expansion cohorts
- Randomized dose finding
- adaptive study with registration potential
- WoO Biomarker study
- Collect robust clinical data across multiple doses, especially when benefit-risk is not clear across doses

Full Spectrum of Data & knowledge

- Preclinical & translational evidence
- PK (linearity, t1/2)
- PD biomarkers (MOA markers, IL-6, ct-DNA, MRD, tumor size)
- Pharmacology (RO)
- Safety (Cumulative Tox)
- Efficacy
- PRO (QoL, patient experiences)
- Competitor's data
- Platform data
- Disease biology

Predictive modeling (MiDD)

- Dose/exposure response analysis & PKPD (e.g., PK-biomarker, PK-TGI, translational PKPD, QSP) to provide quantitative evidence of dose selection
- Statistical & AI/ML modeling (e.g., multivariate) to understand patient heterogeneity across doses

Integrated totality of data/evidence/practicality to support dose selection

Patient Perspectives: Safety

Toxicities

In >50% patients grade 3-5 toxicities present after the 1st cycle

Dose-reductions for toxicities grade <3 as early as in 1st cycle

Physicians frequently underestimate certain toxicities in patients

Recommendations

Dose-escalation: Base timing on cycle 1 only

Dose-increment: Consider all available information, incl. late toxicities

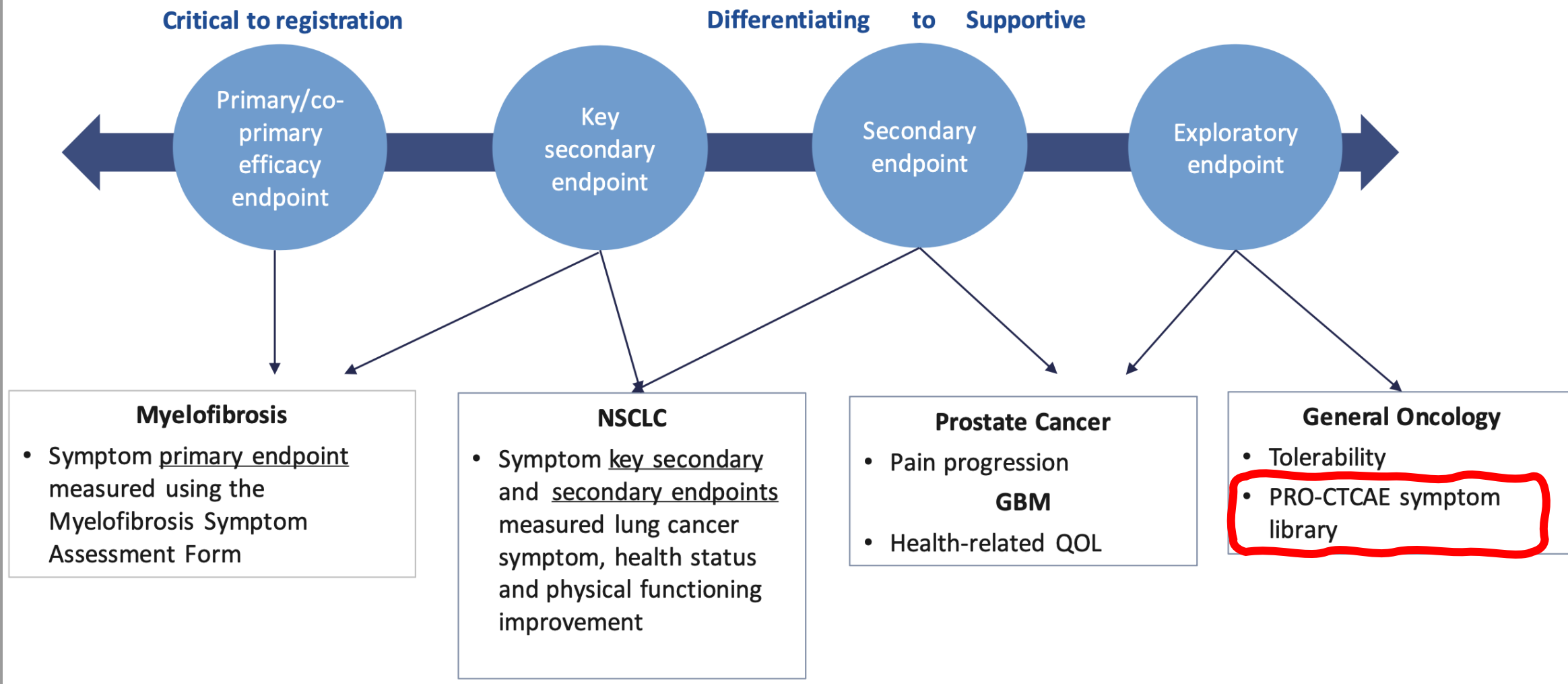
Report all toxicities comprehensively, even if not occurring during the DLT period

Recommended Dose should

- incorporate all available information,
- notably toxicities observed after C1
- be based on achieving > 75% RDI

Patient Perspectives: PROs

PRO-based endpoints can be viewed on a spectrum:



Conclusions from the Workshop

Consensus

Early dose optimization is necessary for molecular-targeted agents and immunotherapies

Regulatory Guidelines

FDA Project Optimus Draft Guidance,
EU Anti-Cancer Guideline, and more

One size will not fit all

Need to adapt dose finding strategies to MoA, tumour biology, patient population
PK/PD models can guide clinical trials and dose selections

New Methodologies

Advanced statistical analyses, Bayesian concepts, Modelling & Simulation,
Early measures of efficacy (e.g. ctDNA)

Data enrichment strategies

To underpin dose selection with data from preclinical tumour biology, *in vitro* clinical safety and efficacy across doses/regimens, and *in vivo* studies as well as PK/PD modelling and biomarker data of target engagement

Tolerability and PROs

Late (i.e. > 1st cycle) and lower grade toxicity very relevant for treatment success
Focus on Dose-Limiting Toxicity is no longer adequate
Patient-reported outcomes should be integrated as early as possible.

Many thanks for your attention!



CDDF Dose Optimization Workshop
in Amsterdam, April 2024