# Challenges in Accelerating the Drug Development Paradigm in Oncology

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# Changes in Drug Development

- Two dominant therapeutic directions
  - Targeted (molecularly specified) agents
    - Small molecules, monoclonal antibodies
  - Immunotherapeutics
    - Multiple agents, targets, approaches
- "Seamless" drug development
  - Evolution of the continuous phase I trial

# Seamless Drug Development

- Blurring of phases of trials/removal of later phase trials
  - Bendamustine, crizotinib, osimertinib
- Pembrolizumab
  - Phase I initiated 2011
  - Early activity signals led to rapid expansion of cohorts
  - Total phase I population = 1200 patients
  - Led to approval in 2 diseases and a companion diagnostic
- More efficient enrollment, lower total sample size in development

Prowell TM, Theoret MR, Pazdur R. N Engl J Med 2016;374:2001-3.

# Seamless Drug Development

- Design concerns emerge

**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?

Prowell TM, Theoret MR, Pazdur R. N Engl J Med 2016;374:2001-3.

# Seamless Drug Development – Mind the Gap(s)

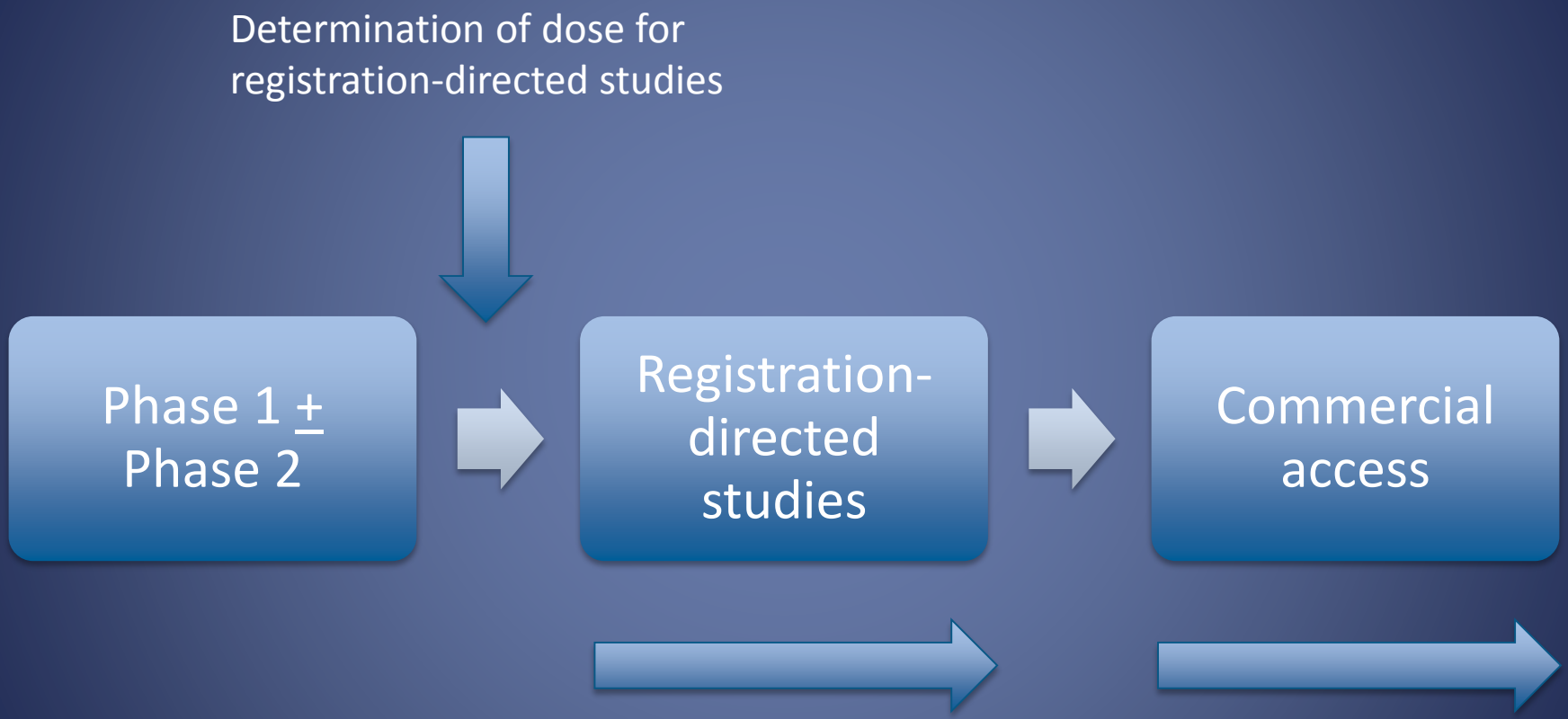
- Decreased trial population
- Rapid acceleration of dose derivation and adoption for licensing trials
- Clinical pharmacology studies

# Oral Agents – New Molecular Entities

| 2006 – 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|
| Dasatinib | Abiraterone | Axitinib | Afatinib | Ceritinib |
| Everolimus | Crizotinib | Bosutinib | Dabrafenib | Idelalisib |
| Lapatinib | Vandetanib | Cabozantinib | Ibrutinib | Olaparib |
| Nilotinib | Vemurafenib | Enzalutamide | Pomalidomide | Trametinib |
| Pazopanib | | Regorafenib | | |
| Sunitinib | | Vismodegib | | |

| 2015 | | 2016 |
|---|---|---|
| Alectinib | Panobinostat | Venetoclax |
| Cobimetinib | Sonidegib | |
| Ixazomib | Trifluridine/tipiracil | |
| Lenvatinib | | |
| Osimertinib | | |
| Palbociclib | | |

# Dose Finding



# Process of Dose Finding

- Preclinical toxicity data
- Formulation
  - Optimization of dissolution, pH dependence
    - Increasing need for acidic GI environment
- Phase 1 dose derivation
  - Oral more fixed than IV therapies
  - Food effects ignored early or require fasting
  - Aimed at the maximum tolerated dose (MTD) in the first cycle
- MTD often the only dose evaluated in phase 2 and beyond
- Trials define dose for a population, individual dose adjustment is empiric

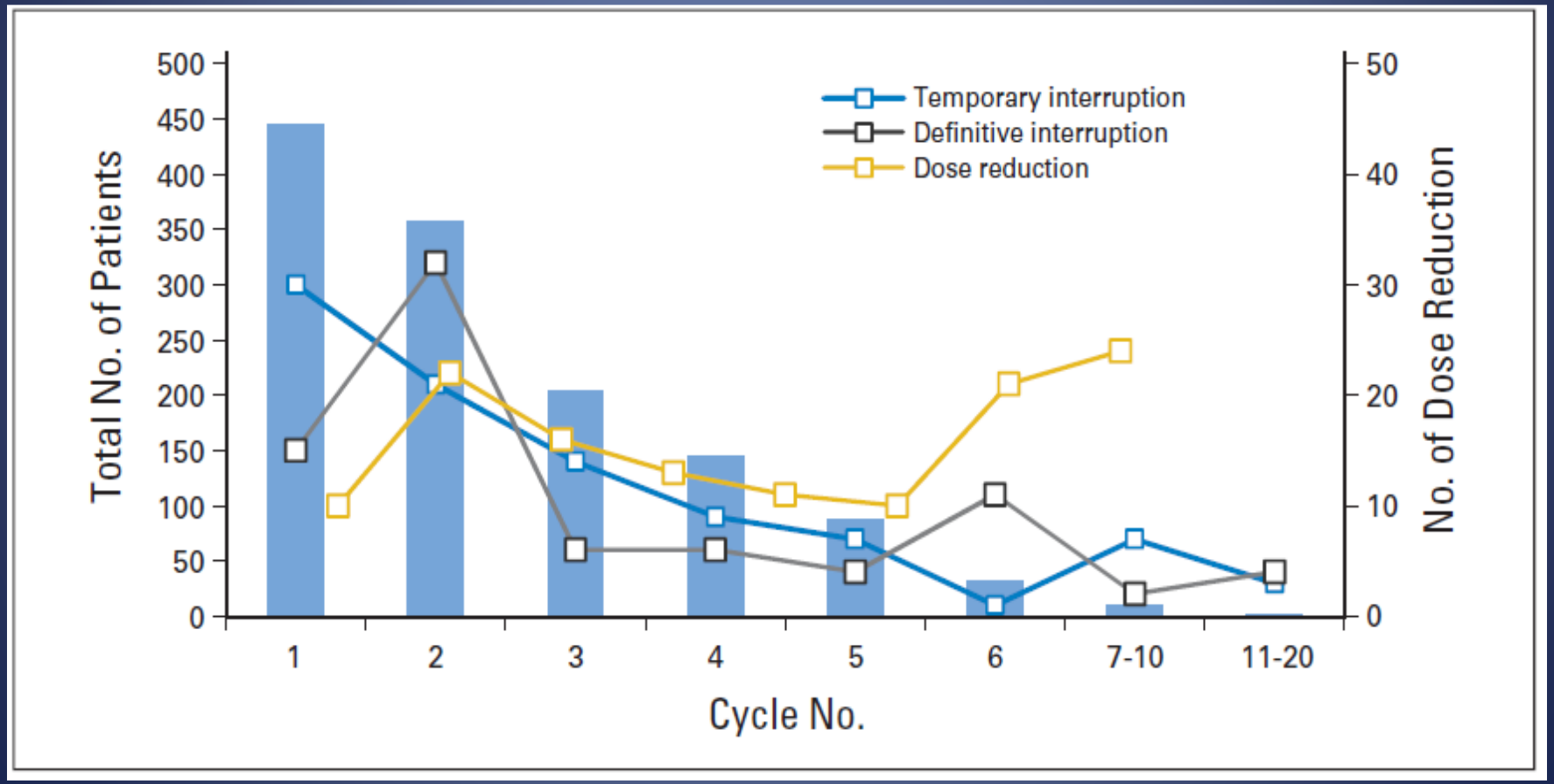
# Limitations to the Current Approach

- Dose-exposure-effect relationships are rarely well defined a priori
- High rates of dose reductions in subsequent trials
- Fails to identify patients who may benefit from lower and higher doses
- Targeted agents – the optimal biologic dose (OBD) may not = MTD

# Limitations to the Current Approach

- Chronic therapy-limiting adverse events may not be incorporated in dose decisions
- Application of MTD to subsequent combinations, populations questionable
- Multiple schedules are rarely explored in a comparative fashion
  - Continuous dosing of oral agents for activity not necessarily needed

# Late Toxicities with Targeted Agents



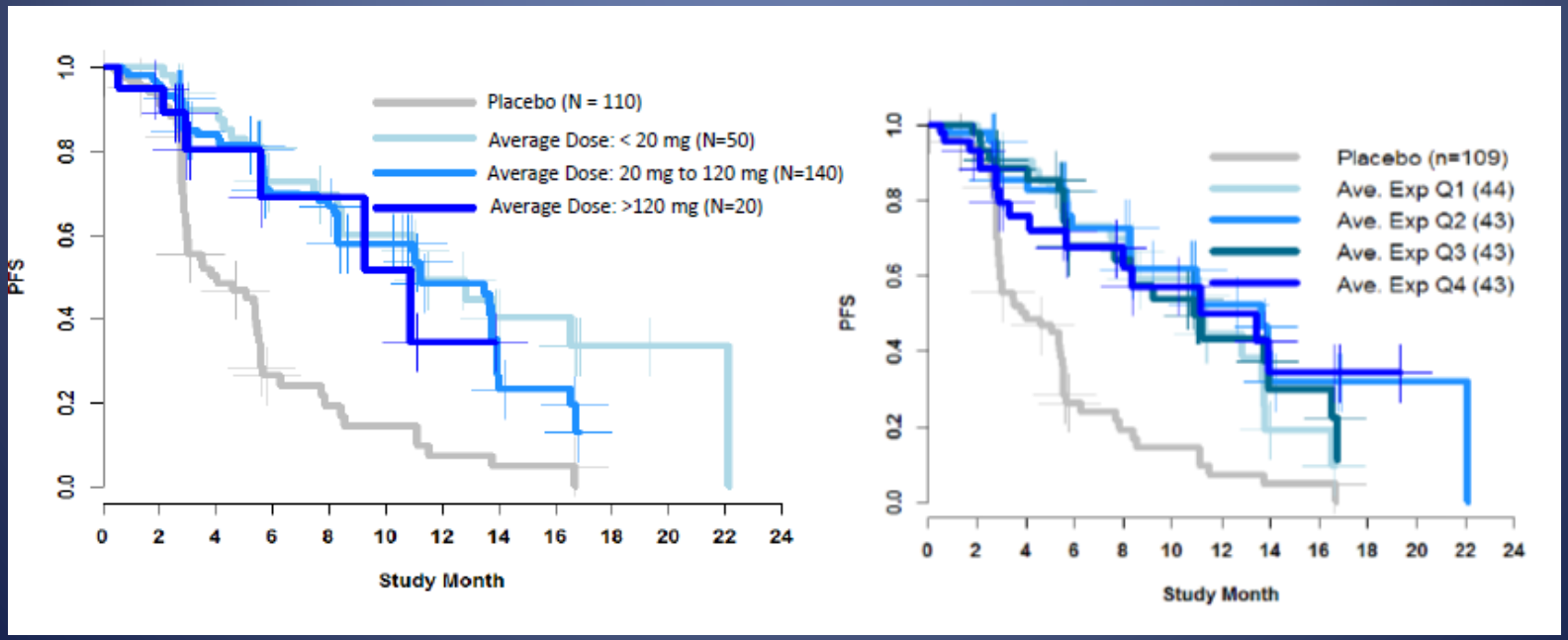

Postel-Vinay S, et al. J Clin Oncol 2011;29:1728-1735.

# Case Study #1

- Drug X is a multi-kinase inhibitor
- FDA approved dose = MTD from single agent phase 1 trial
- In phase 3, 86.4% required at least one dose modification (interruption, reduction, discontinuation)
  - 2 dose reductions allowed (70% and 40% of starting dose)

# Case Study #1

- PK/PD
  - High fat meal increases AUC by 57%
  - $T_{1/2}$ = 55 hours
    - Accumulates 5-fold at 21 days
  - Efficacy: No relationship between exposure (AUC) and PFS
  - Safety: Increased exposure = decreased time to first dose modification, increased QTc
- Post-marketing requirement to study lower doses



# Case Study #2

- Drug Y is another multikinase inhibitor
- Dose – 4 tablets daily
- PK
  - Parent $t_{1/2}$ = 14-58 hr, M2 metabolite = 14-32 hr, M5 metabolite = 32-70 hr
  - Different formulation in clinical trials versus marketed one
    - Higher M2 and M5 exposure
  - Undergoes enterohepatic cycling (3 peaks at 4, 8, and 24 hours)
  - Parent and metabolites highly albumin-bound (99.5%)
  - M2 and M5 exposure higher in those > 65 years and in women
  - High fat meal increases parent AUC by 48%

# Case Study #2

- Dose interruptions in 61%, 38% reduced due to AEs
- Two post-marketing pharmacology commitments
- Three post-marketing trials (CYP probe trial after repeated dosing, QT prolongation study, and renal impairment)
- Intrapatient variability for metabolites = 46% and 64%
- FDA clin pharm review – “A population PK analysis has not been completed, therefore covariates contributing to variability are unknown”

# Post-Approval Clinical Trial Commitments – Oral Agents

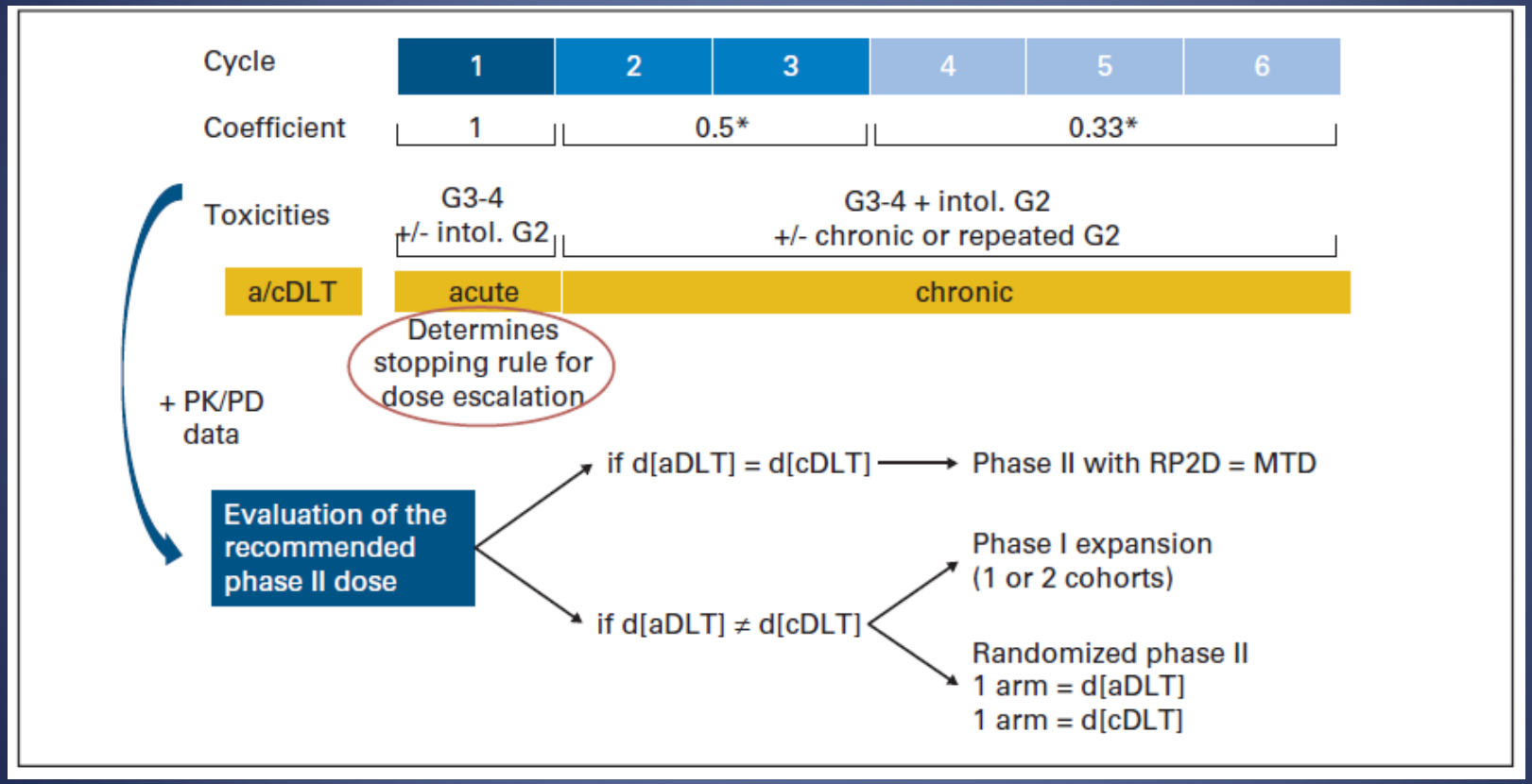
- Often clinical pharmacology studies
- Since 2011
  - 28 new approvals
    - 11 accelerated
  - 78 postmarketing requirement trials
    - 5 dose finding
    - 30 drug-drug interaction
      - CYP and gastric pH effects
    - 19 hepatic impairment, 7 renal impairment
    - 2 food effects

accessdata.fda.gov/scripts/cder/daf
clinicaltrials.gov

# Methods to Improve Dose Precision

- Precision - getting the dose right for the majority of populations
- Formulation improvement
- Earlier complete understanding of food effects and concomitant medications
- Application of physiologically based pharmacokinetic models
  - Sparse PK collection in later stage trials
- Approve multiple doses for differing populations, optimally defined by clinical variables

# Proposed Phase 2 Dose Model

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