Pitfalls in Oncology Drug Development

Nicholas Richardson DO, MPH
Pediatric Oncologist
FDA

Challenges in Oncology Drug Development and Review

- Oncology drugs are developed for life-threatening diseases

✓	**Balance patient access and adequately studying drug**
✓	**Small patient samples and short drug exposure**
✓	**Severe toxicity may be deemed acceptable**
✓	**Indications span a wide spectrum** **Prevention – Cure**
✓	**Benefit:Risk is patient and drug specific**

Common Errors in Developing Oncology Drugs

- Drug activity vs. clinical benefit
- Dose optimization
- Relevance to U.S. population
- Patient-reported outcomes
- Trial design pitfalls

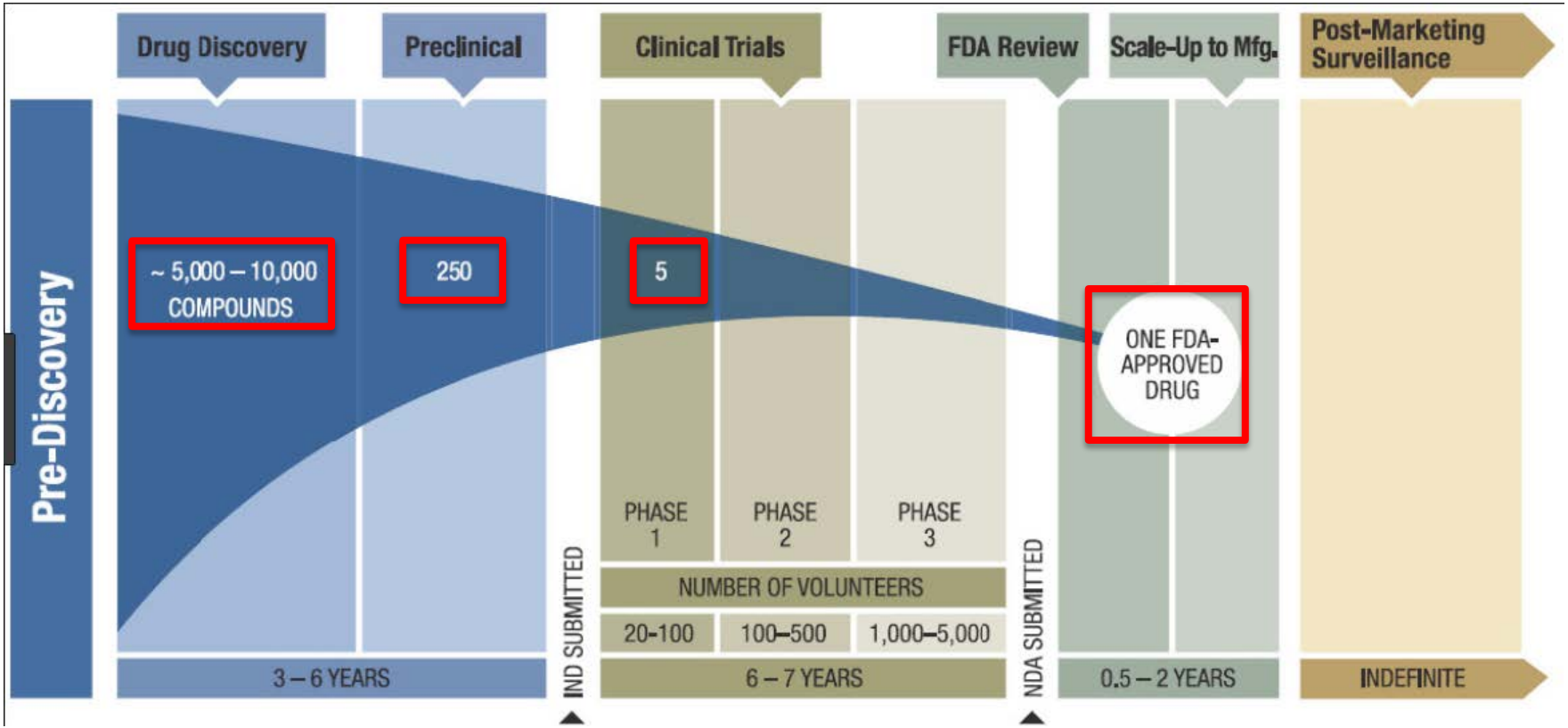
Common Errors in Developing Oncology Drugs

- Drug activity vs. clinical benefit
- Dose optimization
- Relevance to U.S. population
- Patient-reported outcomes
- Trial design pitfalls

Drug Activity vs Clinical Benefit

- Activity: reflects biologic effect
- Clinical benefit: reflects clinical effect that is meaningful for a patient
- Failure to distinguish between activity and clinical benefit may waste resources

Drug Activity vs Clinical Benefit



American Association of Cancer Research, 2011 Cancer Progress Report

Common Errors in Developing Oncology Drugs

- Drug activity vs. clinical benefit
- Dose optimization
- Relevance to U.S. population
- Patient-reported outcomes
- Trial design pitfalls

Dose Optimization

- Maximum tolerated dose (MTD) historically chosen as the dose for Phase 2 and 3 trials

- May not be appropriate for non-cytotoxic therapies
  - Targeted therapies
  - Chronic administration
  - Goal of treatment


Do we have the right dose at the time of approval?

Common Errors in Developing Oncology Drugs

- Drug activity vs. clinical benefit
- Dose optimization
- Relevance to U.S. population
- Patient-reported outcomes
- Trial design pitfalls

Question

Can trials conducted outside of the United States be used to support U.S. regulatory approval?

A. Yes

B. No

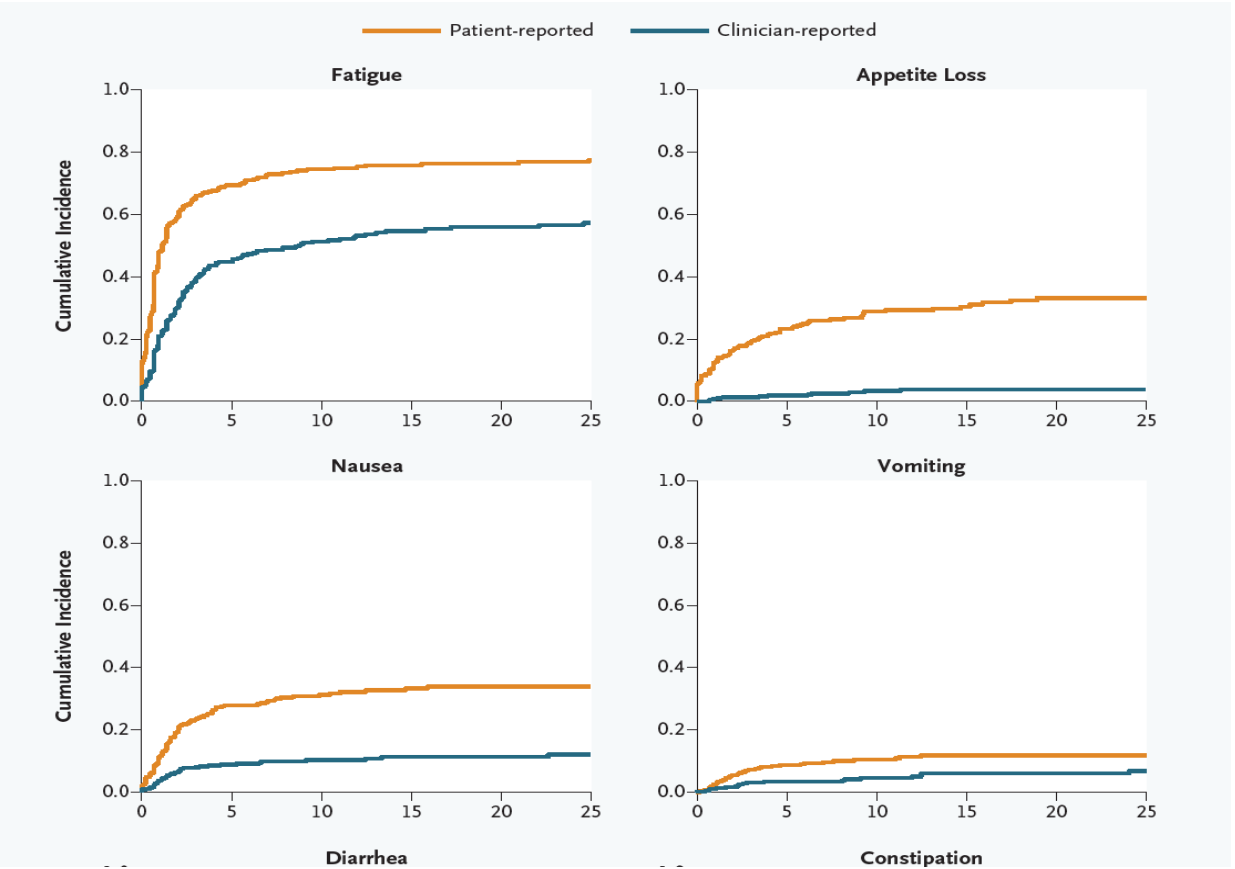
Relevance to the U.S. Population

- Yes, trials to support U.S. regulatory approval may be conducted outside of the U.S. but should be relevant to a U.S. population
  - Relevant patient population
  - Relevant treatment arms
  - Appropriate endpoint
  - Context of available therapy

Common Errors in Developing Oncology Drugs

- Drug activity vs. clinical benefit
- Dose optimization
- Relevance to U.S. population
- Patient-reported outcomes
- Trial design pitfalls

Patient-Reported Outcomes (PRO)



- Clinicians underreport patient symptoms.

- Patient-reported symptoms demonstrate better correlation than clinician-reported symptoms with disease status.

Basch E., NEJM 2010.

PRO Example

How Strong Is Your Pain?

People agree that the following 5 words represent pain of increasingly intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. **Which word describes your pain right now?** _____

Challenges with PROs

- PROs have many challenges
  - Reliability (test-retest)?
  - Content validity (developed with patient/parent input)?
  - Appropriate recall period?
  - Appropriate language translations?
  - Ability to detect change over time in response to an intervention?
  - Clinically meaningful score changes?

Common Errors in Developing Oncology Drugs

- Drug activity vs. clinical benefit
- Dose optimization
- Relevance to U.S. population
- Patient-reported outcomes
- Trial design pitfalls

Trial Design Case

Scenario

- 2 drugs
  - **Drug X (Your drug)**
  - **Drug Y (Competitor)**

- Biologic rationale to combine the drugs

- You're asked to design the Phase 3 trial of your company's drug to support potential FDA approval

Trial Design Case

- Your company makes Drug X
- Which design do you choose? Why?

Choice A

Drug X + Drug Y
vs.
Drug Y

Choice B

Drug X + Drug Y
vs.
Drug X

Trial Design Case

- The purpose is to isolate the treatment effect for your drug (Drug X)

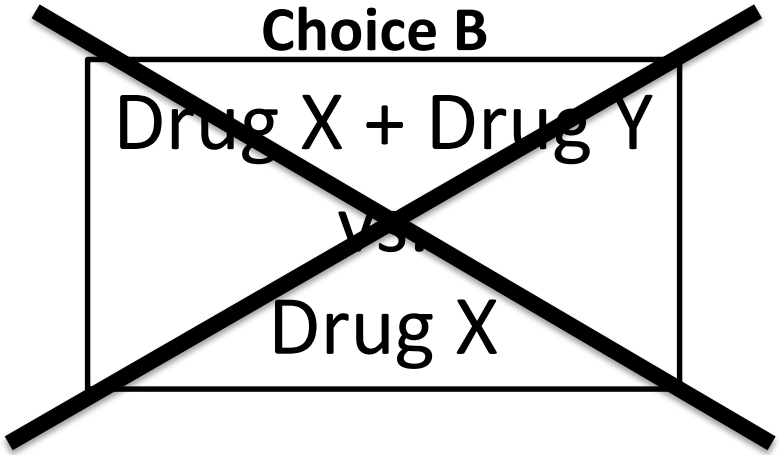
Choice A

Drug X + Drug Y

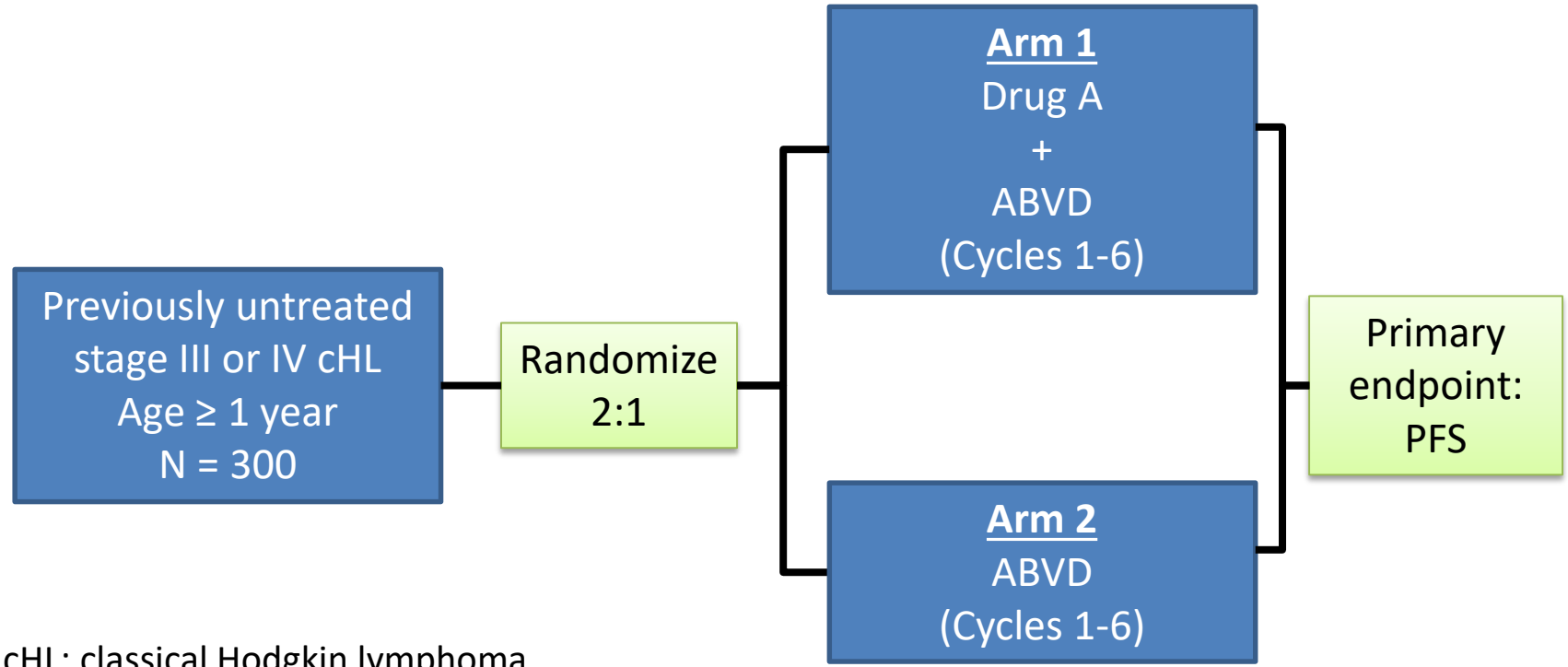
vs.

Drug Y

Choice B



Trial Design & Patient Resources



cHL: classical Hodgkin lymphoma
ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine
PFS: Progression-free survival

Failure to Distinguish Between Statistical and Clinical Significance

"In a press release, Company X announced today the results of a phase 3 trial showing that Drug X significantly reduces the risk of cancer progression or death in pediatric patients with relapsed osteosarcoma (p=0.00001)."

Statistical vs. Clinical Significance

Improvement in PFS	p-value
2 weeks	0.00001
2 months	0.00001
2 years	0.00001

PFS: Progression-free survival

Closing Remarks

- Moderate mid- to late-stage error/failure rate for oncology drugs that can be improved
- Advocates can play a big role
- Frequent consultation with FDA
- Clinical benefit-risk is essential

Acknowledgements

- Tatiana Prowell
- Virginia Kwitkowski
- Paul Kluetz
- Oncology Center of Excellence


FDA
U.S. FOOD & DRUG
ADMINISTRATION