Pitfalls in Oncology Drug Development

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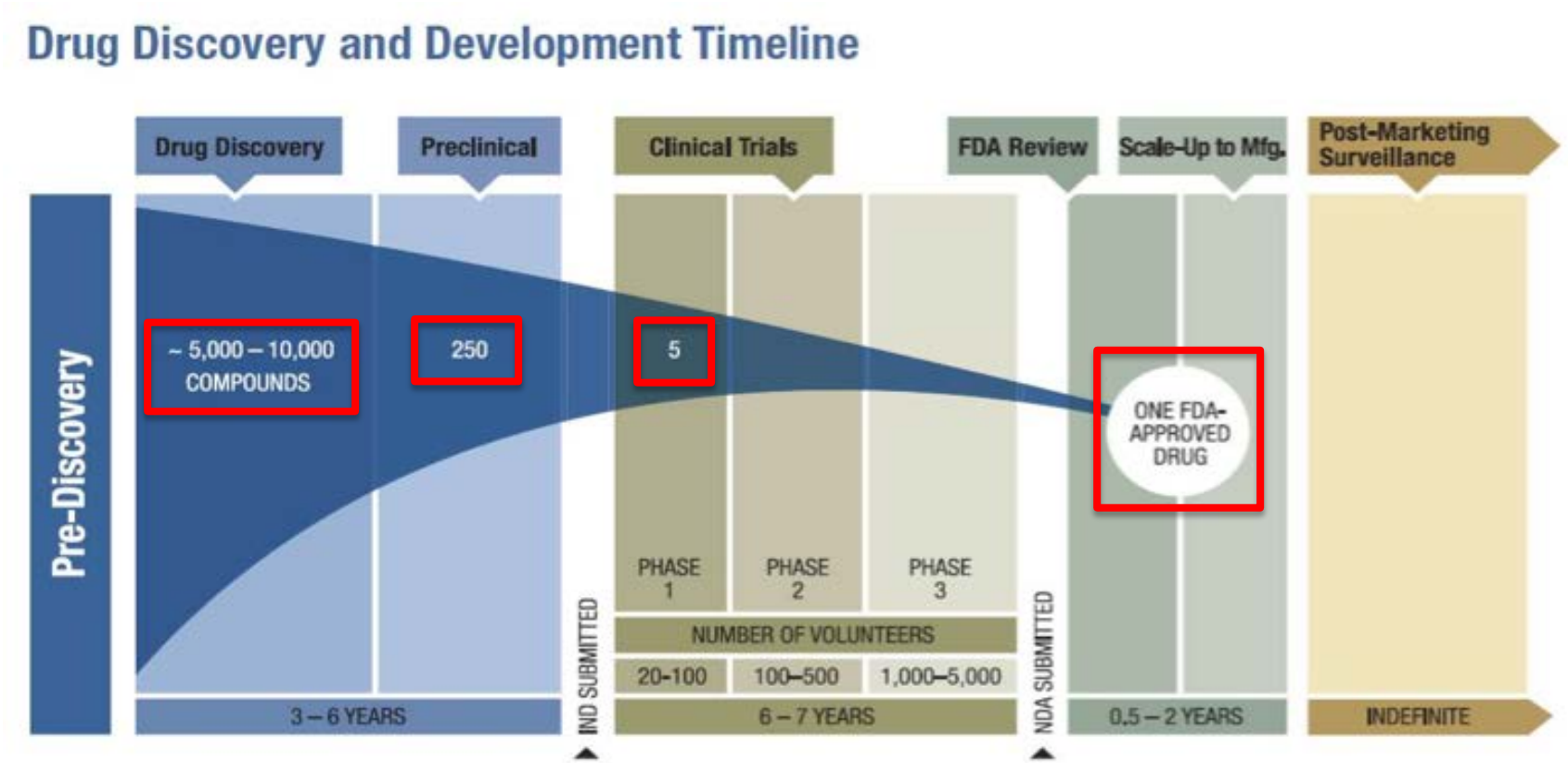
Disclosure Information

- I have no financial relationships to disclose
- I will not be discussing off-label or investigational use of named products in my presentation

Drug Activity vs Clinical Benefit



American Association of Cancer Research, 2011 Cancer Progress Report

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**
✓	**Risk:Benefit is patient and drug specific**

Common Errors in Developing Oncology Drugs

- Drug activity vs. Clinical benefit
- Dose Optimization
- Relevance to U.S. population
- Trial design

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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

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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

Dose Optimization Example

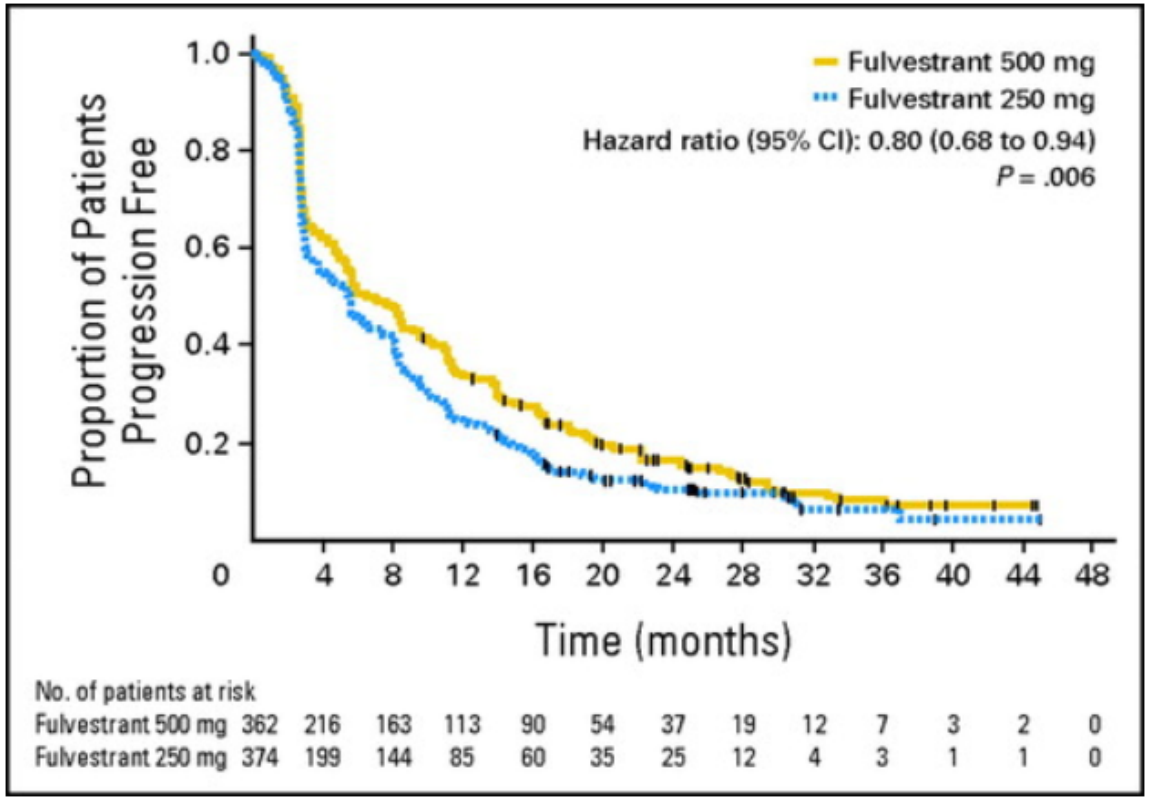
- Fulvestrant - Initial U.S. approval in **2002** at 250mg IM monthly

- Based on non-inferiority versus anastrozole in 2 clinical trials

- Regulators requested post-marketing trial comparing approved dose/schedule to a higher dose with a loading dose

Dose Optimization Example

- Trial compared:
  - Fulvestrant 250mg IM monthly
  - Fulvestrant 500mg IM on Day 1, Day 14, and Day 28 and monthly thereafter
- Improved PFS and no greater toxicity
- Label updated in **2010**



IM: Intramuscular; PFS: Progression-free survival

Di Leo, A., et al. J Clin Oncol, 2010. **28**(30).

New Molecular Entities with Dose-Related Postmarketing Studies

2011	2012	2013	2014	2015
1.Ipilimumab	1.Glucarpidase	1.Pomalidomide	1.Ramucirumab	1.Edoxaban
2.Vandetanib	2.Axitinib	**2.Ado-trastuzumab**	2.Siltuximab	2.Palbociclib
3.Abiraterone	3.Vismodegib	**3.Radium RA-223**	**3.Ceritinib**	**3.Lenvatinib**
4.Rivaroxaban	4.Peginesatide	4.Trametinib	4.Belinostat	**4.Panobinostat**
5.Vemurafenib	5.Pertuzumab	5.Dabrafenib	**5.Idelalisib**	5.Dinutuximab
6.Brentuximab	**6.Carfilzomib**	6.Afatinib	6.Pembrolizumab	6.Sonidegib
7.Crizotinib	7.Ziv-aflibercept	7.Obinutuzumab	7.Blinatumomab	7.Trifluridine/ Tipiracil
8.Deferiprone	8.Tbo-filgrastim		8.Olaparib	8.Idarucizumab
9.Ruxolitinib	9.Enzalutamide		9.Nivolumab	9.Trabectedin
10.Asparaginase	10.Bosutinib			10.Cobimetinib
	11.Regorafenib			11.Osimertinib
	12.Omacetaxine			12.Daratumumab
	13.Cabozantinib			13.Ixazomib
	14.Ponatinib			14.Necitumumab
				15.Elotuzumab
				16.Alectinib

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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

Challenges in Oncology Drug Development

Registration trials may poorly predict real-world experience with an oncology drug

Key Comparison	Chronic Lymphocytic Leukemia	
	Clinical Trial (N = 89)	Real World (N = 294)
Age ≥ 75 years	36%	52%
Charlson Score >3	24%	52%
Treatment Duration Median	16 months	6 months
Overall Survival by 6 months	94%	86%
	RW vs CT: HR 1.40 (CI: 0.93, 2.11)	

Abbreviations: CI: 95% Confidence interval, CT: Clinical trial, HR: Hazard ratio, RW: Real world
Source: Adapted from Bird ST et al. Blood 2018

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Trial Design Case #1

Scenario

- Two drugs
  - **Drug X (Your drug)**
  - **Drug Y (Standard of care)**

- Biologic rationale to combine the drugs – your drug added onto the standard of care

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

Trial Design Case #1

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

Choice A

Drug X + Drug Y

vs.

Drug Y

Choice B

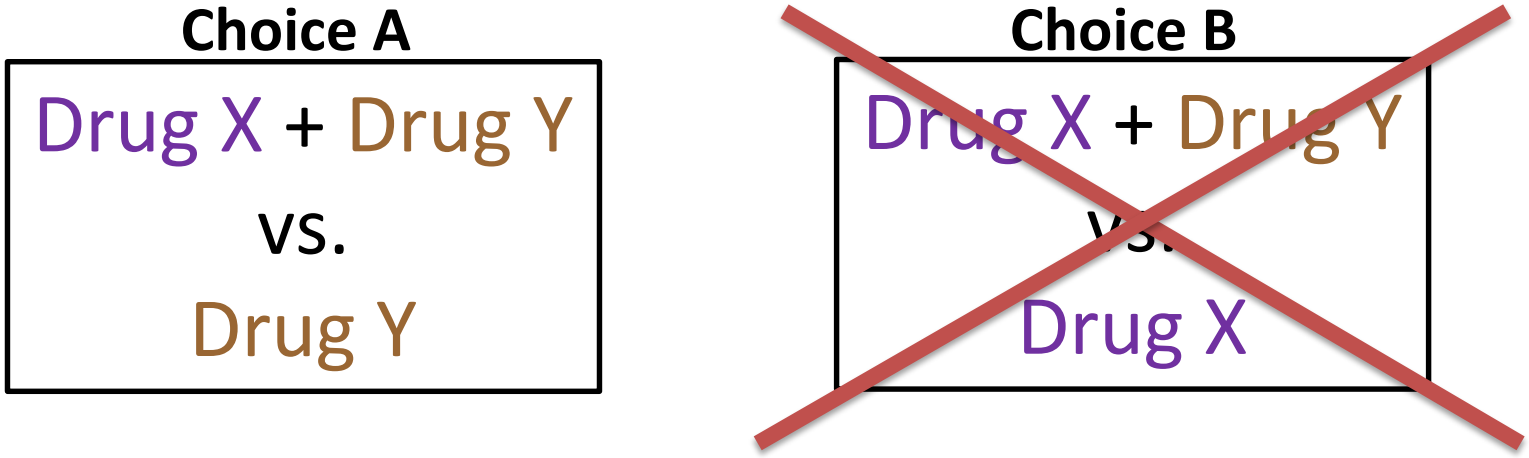
Drug X + Drug Y

vs.

Drug X

Trial Design Case #1

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



Subgroup Analyses

- Great for hypothesis generation
- Should not be used to salvage a trial a failed trial
- “It’s like shooting an arrow and then painting the bull’s-eye around it!” Richard Pazdur, MD

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 risk-benefit is essential

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