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


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AN
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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**

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

Common Errors in Developing Oncology Drugs

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

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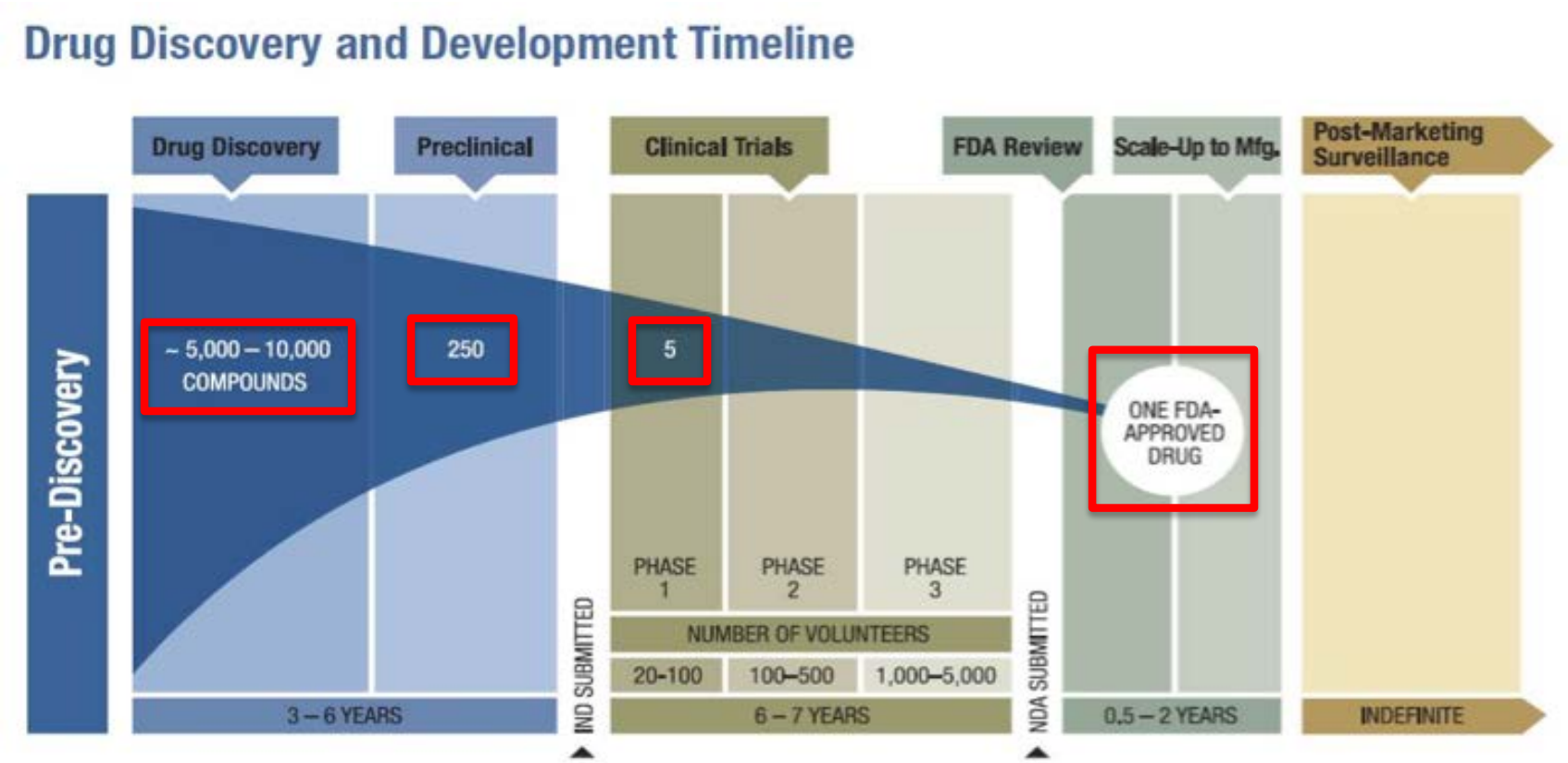
Drug Activity vs Clinical Benefit

- 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

Drug Activity vs Clinical Benefit



American Association of Cancer Research, 2011 Cancer Progress Report

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Dose Optimization

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

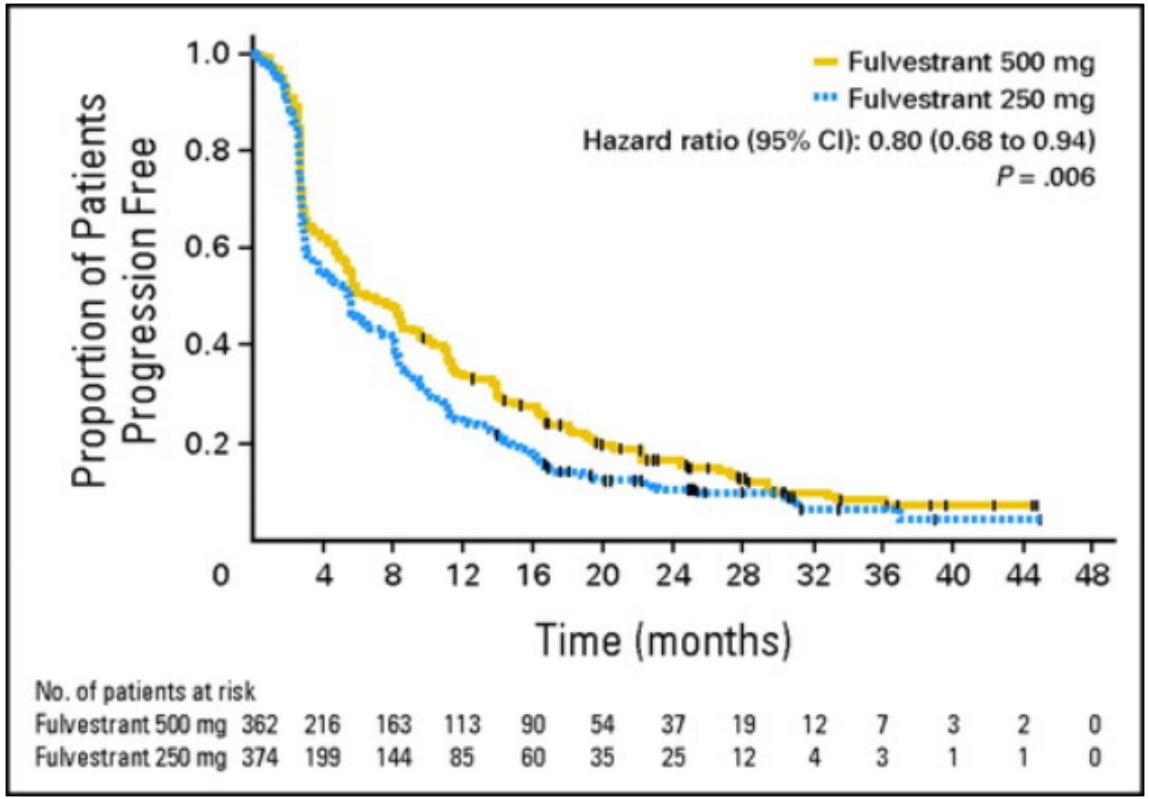
- May not be appropriate for non-cytotoxic therapies
  - Targeted therapies
  - Chronic administration
  - Goal of treatment

Dose Optimization Example

- 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:
  - 250mg IM monthly
  - 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.Ibrutinib	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

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Trial Design Case #1

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 #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)

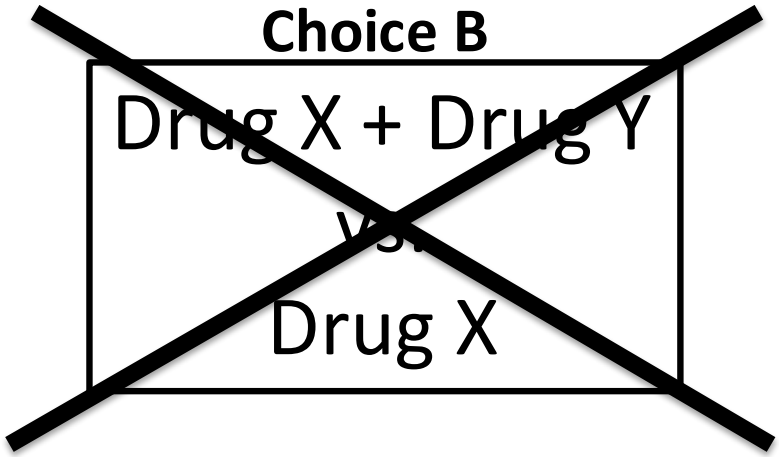
Choice A

Drug X + Drug Y

vs.

Drug Y

Choice B



Trial Design Case #2

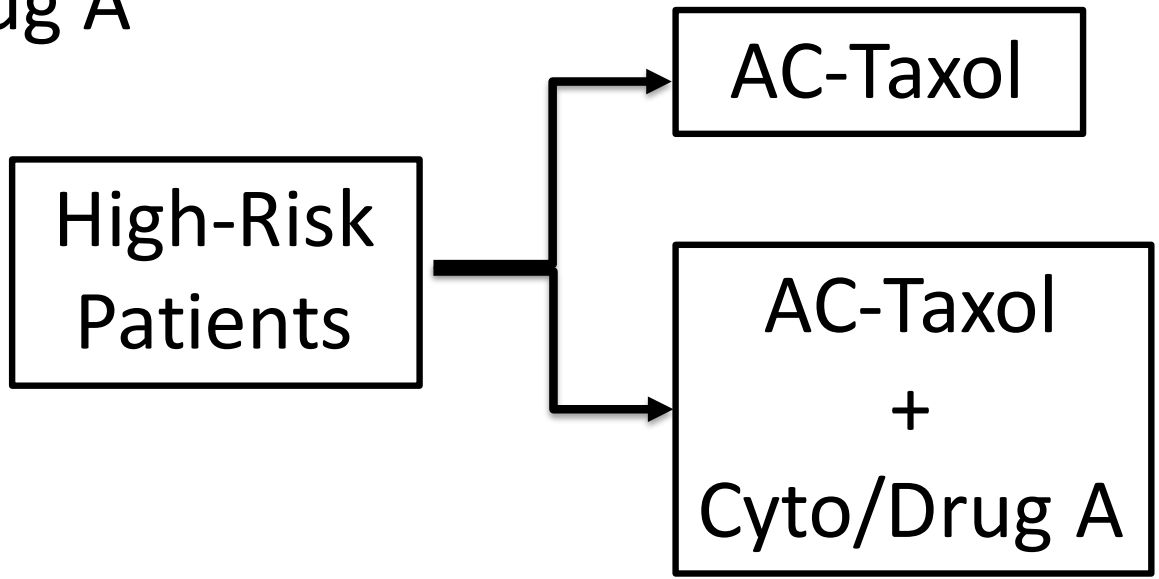
- Your company is developing a first-in-class targeted therapy (Drug A) for patients with early-stage breast cancer

- Preclinical studies suggest Drug A will work better when given with a well-known chemotherapy agent (“Cyto”) used in other solid tumors

- You’re asked to help design a Phase 3 trial to support potential FDA approval

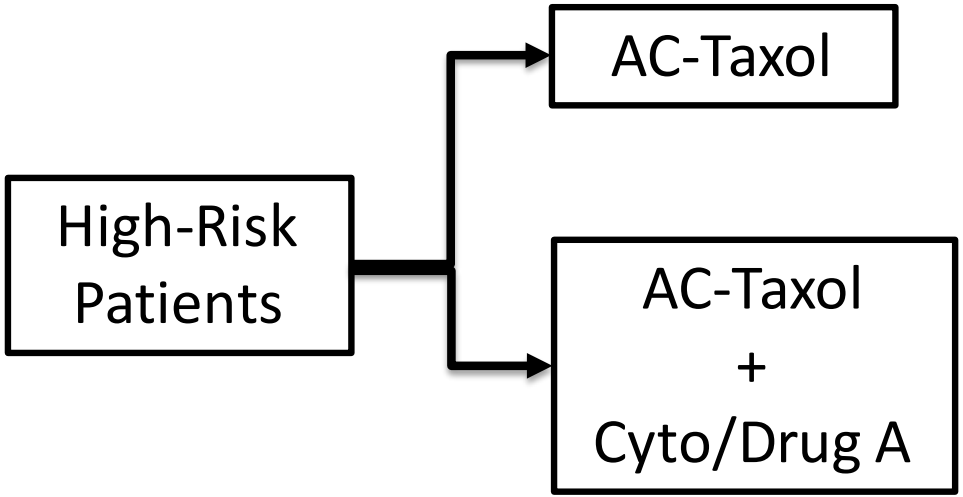
Trial Design Case #2

- You proposed the trial design below to support initial FDA approval of your company's drug – Drug A



Trial Design Case #2

- Isolate treatment effect
- Control arm
- Remove “Cyto”
- Add a 3rd treatment arm
- Solution



Trial Design Case #3

Interim Analyses

- Phase 3 trial: Cytotoxic +/- Drug B in 324 patients with advanced, refractory breast cancer

- Trial terminated after a prespecified interim analysis demonstrated a **17 week difference in time to progression** (TTP) favoring the combination arm
  - **Hazard ratio (HR) 0.49, p<0.001**
  - **No difference in overall survival (HR 0.92, p=0.72)**

- Safety
  - Diarrhea (65%)
  - Hand-foot syndrome (53%)
  - Rash (28%)
  - Decreased heart function (5%)

Trial Design Case #3

Final analysis of the same trial:

- Investigator – **6 week difference in TTP in favor of the combination**
  - **HR 0.57, p=0.0001**
  - No difference in overall survival (HR 0.89, p=0.28)

- Risk-benefit evaluation: interim vs. final

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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FDA
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