Pitfalls in Oncology Drug Development

Vishal Bhatnagar, MD
Acting Associate Director for Patient Outcomes
Oncology Center of Excellence
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
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
Common Errors in Developing Oncology Drugs

• Drug activity vs. Clinical benefit
• Dose Optimization
• Relevance to U.S. population
• Trial design
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
Common Errors in Developing Oncology Drugs

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

# New Molecular Entities with Dose-Related Postmarketing Studies

<table>
<thead>
<tr>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11. Regorafenib</td>
<td></td>
<td></td>
<td>11. Osimertinib</td>
</tr>
<tr>
<td></td>
<td>12. Omacetaxine</td>
<td></td>
<td></td>
<td>12. Daratumumab</td>
</tr>
<tr>
<td></td>
<td>13. Cabozantinib</td>
<td></td>
<td></td>
<td>13. Ixazomib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15. Elotuzumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16. Alectinib</td>
</tr>
</tbody>
</table>
Common Errors in Developing Oncology Drugs

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

<table>
<thead>
<tr>
<th>Key Comparison</th>
<th>Chronic Lymphocytic Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Trial (N = 89)</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>36%</td>
</tr>
<tr>
<td>Charlson Score &gt;3</td>
<td>24%</td>
</tr>
<tr>
<td>Treatment Duration Median</td>
<td>16 months</td>
</tr>
<tr>
<td>Overall Survival by 6 months</td>
<td>94%</td>
</tr>
</tbody>
</table>

**RW vs CT: HR 1.40 (CI: 0.93, 2.11)**

**Source:** Adapted from Bird ST et al. Blood 2018

**Abbreviations:** CI: 95% Confidence interval, CT: Clinical trial, HR: Hazard ratio, RW: Real world
Common Errors in Developing Oncology Drugs

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

Choice A

Drug X + Drug Y

VS.

Drug Y

Choice B

Drug X + Drug Y

VS.

Drug X

Choice B is not recommended.
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
Acknowledgements

• Tatiana Prowell
• Aviva Krauss
• Virginia Kwitkowski
• Nicholas Richardson
• Paul Kluetz
• Rick Pazdur
• Oncology Center of Excellence