Clinical Trials of Radiation-Drug Combinations: The FDA’s Perspective

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Disclosures

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

• Regulatory landscape of RT-drug combinations
• Approval Pathways
  – Regular Approval vs. Accelerated Approval
• Examples of drugs approved with radiation
• When do you need an IND?
Outline

• Regulatory landscape of RT-drug combinations

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• Examples of drugs approved with radiation

• When do you need an IND?
How many indications with radiation? Zero 😞
Outline

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• When do you need an IND?
Clinical Considerations

• Must demonstrate **efficacy** with **acceptable safety** in adequate, well-controlled trials.

• Appropriate endpoints apply to specific disease sites and stages.

• Efficacy
  – Survival
  – PFS/DFS
  – ORR
  – Improved physical function or symptoms (PROs)
Goal of FDA Review

Efficacy  Safety  Disease

Patient Population  “State of Science”  Available Therapies

Does the drug/biologic provide meaningful clinical benefit?
Two Approval Pathways

- Traditional
- Accelerated

Pathway relates to the primary endpoint selected
Traditional ("Regular") Approval

• Substantial evidence of safety and efficacy
• Well-controlled clinical trials
• Based on prolongation of life, a better life, or an established surrogate of either of the above
• No comparative efficacy for Traditional Approval
  – As safe and effective as existing therapies, allowing for non-inferiority designs
Accelerated Approval

• Substantial evidence of safety and efficacy
• Provide meaningful clinical benefit over existing therapies
• Can be based on
  – “Surrogate endpoint... reasonably likely... to predict clinical benefit”
  – “Clinical endpoint other than survival or irreversible morbidity”
• Post-marketing clinical trials are required
  – Should usually be underway at the time of accelerated approval
  – Applicant should carry out studies with due diligence
Efficacy Endpoints and Approval Pathways

The greater uncertainty that exists that the endpoint measures direct clinical benefit, the more data that will be required to support approval.

Surrogate Endpoints
- RESPONSE RATE

Direct Clinical Benefit Endpoints:
- OVERALL SURVIVAL
- PRO
- DFS
- PFS

Lower Certainty
ACCELERATED APPROVAL

Certainty of Measuring / Predicting Direct Clinical Benefit

Higher Certainty
TRADITIONAL APPROVAL
## Two Approval Pathways for Drugs and Biologics in the U.S.

<table>
<thead>
<tr>
<th></th>
<th>Accelerated Approval</th>
<th>Regular Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diseases</strong></td>
<td>Serious/life-threatening</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Surrogate endpoint†</td>
<td>Direct clinical benefit</td>
</tr>
<tr>
<td><strong>Improved Efficacy Over Available Therapy</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Confirmatory Trial Required</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

†Accelerated approval uses a surrogate endpoint reasonably likely to predict clinical benefit.
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Cetuximab (2006)

• Indication: Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy

• Primary outcome measure was **locoregional control** (not OS!)

<table>
<thead>
<tr>
<th></th>
<th>Cetux + RT (n=211)</th>
<th>RT (n=213)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Locoregional Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>24.4</td>
<td>14.9</td>
<td>0.68 (0.52-0.89)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>49.0</td>
<td>29.3</td>
<td>0.74 (0.57-0.97)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Amifostine (1999)

• Indication: to reduce incidence of moderate to severe xerostomia in patients undergoing post-op RT for head and neck cancer, where the radiation port includes a substantial portion of the parotid gland

• Phase III randomized trial with RT +/- amifostine (n=315)

• Co-primary endpoints included incidence of
  – Grade ≥ 2 acute xerostomia
  – Grade ≥ 2 late xerostomia
  – Grade ≥ 3 acute mucositis
Past Success: Amifostine (1999)

**Incidence of Grade 2 or higher xerostomia**

<table>
<thead>
<tr>
<th></th>
<th>Amifostine + RT</th>
<th>RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≤ 90 days)</td>
<td>24.4</td>
<td>14.9</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9-12 months)</td>
<td>49.0</td>
<td>29.3</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- Additional supportive data
  - Improvement in saliva collection and production at 1 year post-RT
  - Supportive PROs
- Locoregional control, DFS, and OS were comparable
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What is an IND?

• Investigational New Drug Application
• Request for authorization from the FDA to administer an investigational drug or biologic product to humans
When do I need an IND?

- When does your trial qualify for an IND Exemption?
  - Drug is lawfully marketed in the US
  - Does not involve a route of administration, dose, patient population, or other factor that increases patient risk
  - Results are not intended to be reported to FDA in support of a new indication.
  - Investigation is not intended to support a significant change in the advertising of the drug
Guidance for Clinical Investigators, Sponsors, and IRBs

Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Food Safety and Applied Nutrition (CFSAN)

September 2013
Clinical/Medical
Summary

• Very few drugs are currently approved for the use with radiation therapy

• Two approval pathways – Accelerated vs. Regular

• IND is needed when you want to expand an indication for a drug (have to talk to Sponsor)
Thank you

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