BEVACIZUMAB (AVASTIN®) AND
THE ACCELERATED APPROVAL PROCESS:
A STICKY SITUATION?

Pharmacotherapy Rounds
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Learning objectives:
1. Outline the Food and Drug Administration (FDA) accelerated approval process for oncology agents
2. Interpret the various end-points used in oncology-related clinical research
3. Analyze the current debate surrounding the accelerated approval process for oncology agents
4. Assess the current status of bevacizumab (Avastin®) as it relates to the FDA accelerated approval process
I. The Food and Drug Administration (FDA) Drug Review Process
   A. Drug review process (see Table 1)

Table 1. The Drug Development Process

<table>
<thead>
<tr>
<th>Preclinical Phase</th>
<th>Clinical Phase</th>
<th>Approval Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology studies</td>
<td>Investigational New Drug (IND) application filed</td>
<td>Phase I</td>
</tr>
<tr>
<td>Time (Non-oncology)</td>
<td></td>
<td>6.3 years</td>
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<td></td>
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<td>8.1 years</td>
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<tr>
<td>Time (Oncology)</td>
<td></td>
<td>7.8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.1 years</td>
</tr>
</tbody>
</table>

i. Purpose of the review process
   1. Establish the safety and efficacy of medications
      a. Survival
      b. Quality of life
      c. Toxicity

   ii. Costs associated with non-oncologic drug approval
      1. Estimated at least $500 million
      2. Forty percent increase between 1996 and 2001

B. Historic legislation
   i. 1938 Federal Food, Drug and Cosmetic (FD&C) Act
      1. Established drug safety requirement
   ii. 1962 FD&C Act Amendment
      1. Established need for efficacy through “substantive” evidence
         a. Clinical outcomes
            i. Survival
            ii. Function
            iii. Symptomatic improvement
   iii. 1983 Orphan Drug Act
      1. Increased incentives for research in diseases affecting less than 200,000 persons
         a. Advanced counseling
         b. Fifty percent tax break on trial expenditures
         c. Seven year market exclusivity
   iv. 1992 Prescription Drug User Fee Act
      1. Established two review processes for NDAs
         a. Priority review: completed within six months
         b. Standard review: completed within 10 months
v. **1992 Accelerated Approval Regulation**\(^5,7\)
   1. Implemented largely because of Human Immunodeficiency Virus (HIV)/Autoimmune Immune Deficiency Syndrome (AIDS): four of the six approved agents for HIV/AIDS
 vi. **1996 Accelerated approval regulations expanded to oncology agents**\(^5,6\)
   1. Initiated by the U.S. Office of the President
      a. Docetaxel-first drug approved under accelerated approval
 vii. **1997 FDA Modernization Act**\(^5,6\)
    1. Requires two well-controlled studies to establish efficacy
    2. One trial may be appropriate to establish efficacy in select circumstances
 viii. **2003 Oncologic Drugs Advisory Committee (ODAC) established**\(^5,6\)
    1. Reviews agents that have not completed phase IV confirmatory trials
 ix. **2005 ODAC meets to discuss failure to complete confirmatory studies**\(^6\)
    1. Interim analysis of phase III studies as basis of accelerated approval
 x. **2007 Legislation passed allowing for imposition of fines**
    1. Up to $10 million for failure to conduct confirmatory studies\(^6\)

II. **The FDA Drug Review Process in Oncology**

A. **Background**
   i. Definitions (see Table 2)

Table 2. Established FDA Regulatory Processes\(^5,8\)

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Regular Approval</th>
<th>Fast Track</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requirements</strong></td>
<td>• Submission of NDA&lt;br&gt;• Use of established study end points&lt;br&gt;• Two well-designed, multi-center studies</td>
<td>• Serious illnesses&lt;br&gt;• Unmet medical needs&lt;br&gt;• First in-class drug</td>
<td>• Serious/life threatening illnesses&lt;br&gt;• Requires confirmatory phase IV trials</td>
<td>• Unmet medical needs&lt;br&gt;• Requires manufacturer submission</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>• Full approval granted</td>
<td>• FDA contact throughout process&lt;br&gt;• “Rolling review”&lt;br&gt;• Allows for one adequate trial to establish efficacy</td>
<td>• Provisional approval&lt;br&gt;• Use of surrogate endpoints (e.g., tumor shrinkage)</td>
<td>• Review completed in 6 vs. 10 months</td>
</tr>
</tbody>
</table>

NDA = new drug application
B. Need for rapid approval of agents
   i. Estimated 2008 Surveillance, Epidemiology, and End Result (SEER) cancer incidence rates (455.7 per 100,000 population per year) (see Figure 1)

Figure 1. Cancer Incidence Rates by State (2008)^9

ii. Cancer causes 568,668 deaths second only to heart disease^10
   1. Approved medications in heart disease have outnumbered those in oncology (see Figure 2)

Figure 2. Number of Approved Agents (per decade)^11
iii. Demand for new agents targeting tumor pathways
   1. Fastest growing therapeutic class\textsuperscript{2}
   2. Currently over 700 drugs in development\textsuperscript{11}

C. Obstacles surrounding approval of oncologic agents
   i. Difficulty recruiting patients for clinical studies
   ii. Cost associated with oncology agent development
      1. Research and development costs estimated to be 20% higher ($1,042 million)\textsuperscript{4}
   iii. Poor attrition rates between phases
      1. Phase III FDA approval probabilities vary, 57.1% for oncologic agents vs. 68.4% for non-oncologic agents\textsuperscript{2}

D. Advantages of accelerated approval
   i. Decreased time to market
   ii. Decreases number of patients needed to complete clinical studies
   iii. Increases probability of approval of new molecular entities
   iv. Allow use of surrogate endpoints (see Appendix 1)\textsuperscript{12}

III. Impact of Accelerated Approval Process on Oncology Drug Development

A. Medication approval (see Appendix 2)
   i. From 1996 to 2010, 35 agents with 47 indications received accelerated approval\textsuperscript{5-7,13}
      1. National Comprehensive Cancer Network (NCCN) guidelines list 63% of agents as first line\textsuperscript{6}

B. Time to approval
   i. Time from IND submission to FDA approval\textsuperscript{6,13}
      1. 6.1 years (3.1 to 12.4 years) vs. 7.2 years (3.0 to 33.4 years) for accelerated approval and regular approval, respectively

C. Proportion of oncology medications undergoing accelerated approval (see Figure 3)

**Figure 3. Oncology Medication Approvals**\textsuperscript{6}
IV. **Bevacizumab (Avastin®)**  
A. **Background**  
   i. **Mechanism of action**\(^{14}\)  
      1. Recombinant humanized monoclonal immunoglobulin gamma (IgG) antibody  
      2. Inhibits the activity of vascular endothelial growth factor (VEGF) alpha  
         a. Prevents interaction with endothelial cell receptors  
         b. Inhibits cell proliferation and new blood vessel formation  
         c. Reduces microvascular growth of tumors  
   ii. **Adverse effects**\(^{14}\)  
      1. Black Box warnings  
         a. Gastrointestinal perforation (0.3% to 2.4%)  
         b. Delayed wound healing  
         c. Hemorrhage (severe, 1.2% to 4.6%)  
      2. Warnings/precautions  
         a. Non-gastrointestinal fistula formation (<0.6%)  
         b. Thromboembolic events (2.4%)  
         c. Reversible posterior leukoencephalopathy (<0.1%)  
         d. Proteinuria (4% to 36%)  
         e. Ovarian failure (34%)  
         f. Heart failure (1% to 4%)  
         g. Hypertension (5% to 18%)  
      3. **Common adverse effects (>10%)**  
         a. Hypertension, fatigue, headache, gastrointestinal effects  
   iii. **Therapeutic indications**\(^{14}\)  
      1. Metastatic colorectal cancer with fluorouracil/leucovorin (5-FU/LV) regimens  
      2. Non-small cell lung cancer with carboplatin/paclitaxel (first line)  
      3. Glioblastoma in patients with progressive disease  
      4. Metastatic renal cell cancer with interferon alpha  
   5. **Metastatic breast cancer (until 2011)**  
      a. Human epidermal growth factor receptor-2 (HER-2) negative (-) patients  
   iv. **Cost of therapy**  
      1. $8,000 per month\(^{15}\)  
B. **Bevacizumab in metastatic breast cancer**  
   i. **Early phase studies**  
      1. Improvement in patient response when added to chemotherapy\(^{16}\)  
   ii. **Progression free survival (PFS)**  
      1. Used in place of overall survival\(^{17-19}\)  
         a. Minimize effect of subsequent therapies  
         b. Shorter follow-up
Study #1. (Eastern Cooperative Oncology Group 2100 (E2100)\textsuperscript{16}

<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine the safety and efficacy of bevacizumab in combination with paclitaxel for patients with metastatic breast cancer</th>
</tr>
</thead>
</table>
| Methods   | **Study design:** phase III, randomized, open label, prospective study, 2001 to 2004  
**Population:** histologic and cytological confirmed metastatic breast cancer without prior cytotoxic treatment for metastatic disease  
**Intervention:**  
  - Paclitaxel 90 mg/m\(^2\) days 1, 8, 15 + bevacizumab 10 mg/kg days 1, 15, every 28 days  
**Control group:**  
  - Paclitaxel 90 mg/m\(^2\) days 1, 8, 15, every 28 days  
**Primary outcome:**  
  - PFS as determined by RECIST criteria (measurable disease) or development of new lesions or progression of existing lesions (non-measurable)  
  - Assessments completed every 12 weeks  
**Secondary outcomes:**  
  - Toxicity  
  - OS  
**Statistical analysis:**  
  - Baseline values: Fisher’s exact test  
  - Primary outcome: Kaplan Meier analysis; Cox-proportional hazards for stratified data (prior adjuvant therapy, disease-free interval) |
| Results   | **Paclitaxel with bevacizumab:** 347 patients; 238 (68.6%) with measurable disease  
**Paclitaxel alone:** 326 patients; 254 (77.9%) with measurable disease  
**Primary outcome:**  
  - Paclitaxel with bevacizumab significantly prolonged PFS (11.8 months) vs. paclitaxel alone (5.9 months); (p<0.001)  
**Secondary outcomes:**  
  - Toxicity: increased frequency of hypertension, cerebrovascular ischemia, and grade 3/4 neuropathy (23.6% vs. 17.6%) and fatigue (8.5% vs. 4.9%) with combination therapy  
  - OS: median survival similar between groups (26.7 months vs. 25.2 months; p=0.16) |
| Study critique | **Strengths:**  
  - Use of control group  
  - Multivariate analysis to account for baseline imbalances  
  - Secondary analysis of progression intervals to investigate potential influence of investigator bias  
**Limitations:**  
  - Open-label design in study with PFS as endpoint  
  - Small patient population  
  - Disproportionate number of patients with measurable disease favoring paclitaxel only arm  
  - Large proportion of patients discontinuing paclitaxel prior to progression |
| Reviewer’s Conclusion | Bevacizumab in combination with paclitaxel improves PFS compared to single agent therapy with limited toxicity; however, the study design limits the interpretation of the benefit vs. risk |

PFS = progression free survival; RECIST = response evaluation criteria for solid tumors; OS = overall survival
C. Effect of E2100 study
   i. Bevacizumab receives approval in February 2008 for HER-2 (-) metastatic breast cancer\textsuperscript{20}
   ii. Recommendations for use
       1. Indicated in HER-2 (-) metastatic breast cancer patients
           a. Combination with paclitaxel
           b. Patients not progressing on prior anthracycline/taxane therapy
       2. NCCN guidelines\textsuperscript{21}
           a. Grade 2A recommendation
       3. One of the four largest selling agents in 2006\textsuperscript{2}
           a. Accounted for $3.1 million in annual sales (2010)\textsuperscript{15}
           b. Breast cancer sales approximated $750 million (2010)\textsuperscript{15}
   iii. Pharmacoeconomic studies based on E2100
       1. Approximately $88,000 for 11.3 months\textsuperscript{15}
       2. Approximately $200,000 per year of PFS\textsuperscript{22}
           a. Cost-effectiveness ratio of $745,000 per quality-adjusted life-years
   iv. Use of PFS as surrogate endpoint in metastatic breast cancer
       1. OS historically used as primary clinical outcome\textsuperscript{18}
       2. PFS increasingly used as surrogate endpoint
           a. Shorter follow-up
           b. Eliminates confounding influence of subsequent treatments
       3. Correlation between PFS and OS\textsuperscript{17,19}
           a. Only 22.5% of tumor assessment trials have demonstrated OS benefit
           b. Rank correlation coefficient estimated at 0.68 (moderately associated)
D. Follow-up to E2100
   i. Confirmatory studies needed to achieve full FDA approval
      1. Two phase III studies planned during initial FDA review
         a. AVADO (completed prior to initial approval)
         b. RIBBON-1 (anticipated completion within one year of approval)
**Study #2. (AVADO)**

<table>
<thead>
<tr>
<th>Study Critique</th>
<th>Strengths:</th>
<th>Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>- Study design: phase III, randomized, blinded, placebo controlled study, 2006 to 2007</td>
<td>- Investigators assessed RECIST criteria in study</td>
</tr>
<tr>
<td></td>
<td>- Population: women with histologic or cytological confirmed, HER-2(-) locally recurrent or metastatic breast cancer</td>
<td>- Large early discontinuation rate of docetaxel (68% placebo, 49% to 52% combination)</td>
</tr>
</tbody>
</table>
|                | - Interventions:  
|                | o Docetaxel 100 mg/m$^2$ day 1 + bevacizumab 7.5 mg/kg day 1, every 21 days  
|                | o Docetaxel 100 mg/m$^2$ day 1 + bevacizumab 15 mg/kg day 1, every 21 days  
|                | o Control group:  
|                | o Docetaxel 100 mg/m$^2$ day 1 + placebo, every 21 days  
|                | - Primary outcome:  
|                | o PFS as determined by RECIST criteria (measurable disease) or appearance of new lesions or symptomatic deterioration (non-measurable disease)  
|                | o Assessments performed every 9 weeks until week 36, then every 12 weeks  
|                | - Secondary outcome:  
|                | o OS  
|                | o Safety  
|                | - Statistical analysis:  
|                | o Baseline values: chi-square  
|                | o Primary outcome: Kaplan Meier analysis; log rank test (unstratified comparison)  
|                | o Secondary outcome: Kaplan Meier  
| **Results**    | - Study included 736 patients; 241 docetaxel + placebo, 248 docetaxel + bevacizumab 7.5 mg, 247 docetaxel + bevacizumab 15 mg  
|                | - Primary outcome:  
|                | o Docetaxel + placebo: median PFS 8.1 months  
|                | o Bevacizumab 7.5 mg/kg + docetaxel: median PFS 9 months (p=0.045),  
|                | o Bevacizumab 15 mg/kg + docetaxel: median PFS 10 months (p<0.001)  
|                | - Secondary outcome:  
|                | o OS: similar in all three groups (approximately 31 months)  
|                | o Safety: increased risk of bleeding (19% vs. 49.4%) and hypertension (10% vs. 21.9%) with bevacizumab 15 mg/kg  
| **Reviewer’s Conclusion** | - Bevacizumab at a dose equivalent to 5 mg/kg per week statistically improves PFS when combined with docetaxel therapy  
|                | - The combination’s increased toxicity and limited clinical improvement should raise questions surrounding the treatment’s benefits and risks  

PFS = progression free survival; RECIST = response evaluation criteria in solid tumors; OS = overall survival
Study #3. (RIBBON-1)\textsuperscript{24}

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the efficacy and safety of bevacizumab for metastatic breast cancer in combination with standard chemotherapeutic regimens</th>
</tr>
</thead>
</table>
| Methods   | • **Study design:** phase III, multi-center, randomized, placebo-controlled study, 2005 to 2007  
            • **Population:** patients 18 years of age or older with HER-2 (-), locally recurrent or metastatic breast cancer untreated with prior chemotherapy  
            • **Interventions** (assigned prior to randomization):  
              - Capecitabine 1,000 mg/m\(^2\) BID days 1 to 14 + bevacizumab 15 mg/kg, every 21 days  
              - Taxane/anthracycline + bevacizumab 15 mg/kg  
                - Docetaxel 75 to 100 mg/m\(^2\) every 21 days  
                - Nab-paclitaxel 260 mg/m\(^2\) every 21 days  
                - Epirubicin 500 mg/m\(^2\), fluorouracil 500 mg/m\(^2\), cyclophosphamide 500 mg/m\(^2\) every 21 days  
                - Doxorubicin 50 to 60 mg/m\(^2\), cyclophosphamide 500 to 600 mg/m\(^2\) every 21 days  
              - Epirubicin 500 mg/m\(^2\), cyclophosphamide 500 to 600 mg/m\(^2\) every 21 days  
            • **Control group:**  
              - Capecitabine 1,000 mg/m\(^2\) BID days 1 to 14 + placebo, every 21 days  
              - Taxane/anthracycline:  
                - Docetaxel 75 to 100 mg/m\(^2\) every 21 days  
                - Nab-paclitaxel 260 mg/m\(^2\) every 21 days  
                - Epirubicin 500 mg/m\(^2\), fluorouracil 500 mg/m\(^2\), cyclophosphamide 500 mg/m\(^2\) every 21 days  
                - Doxorubicin 50 to 60 mg/m\(^2\), cyclophosphamide 500 to 600 mg/m\(^2\) every 21 days  
              - Epirubicin 500 mg/m\(^2\), cyclophosphamide 500 to 600 mg/m\(^2\) every 21 days  
            • **Primary outcome:**  
              - PFS as determined by RECIST criteria (measurable disease) or appearance of new lesions or symptomatic deterioration (non-measurable disease)  
              - Assessments performed every nine weeks  
            • **Secondary outcomes:**  
              - OS  
              - PFS by independent review committee  
              - Safety  
            • **Statistical analysis:**  
              - Primary outcome: Kaplan Meier with Cox proportional hazards model  
              - Secondary outcome:  
                - Response rates: Mantel-Haenszel chi-square  
                - Time to event analysis: stratified log-rank |

PFS = progression free survival; RECIST = response evaluation criteria in solid tumors; OS = overall survival
### Results

- Study included 1,237 patients (615 capecitabine vs. 622 taxane/anthracycline)
- **Primary outcome:**
  - Capecitabine: median PFS increased from 5.7 months to 8.6 months in favor of combination therapy (hazard ratio (HR), 0.69; 95% confidence interval (CI), 0.56-0.84)
  - Taxane/anthracycline: median PFS increased from 8.0 months to 9.2 months in favor of combination therapy (HR, 0.64; 95% CI, 0.52-0.80)
- **Secondary outcomes:**
  - OS:
    - Capecitabine vs. capecitabine + bevacizumab: no difference (HR, 0.85; 95% CI, 0.63-1.14)
    - Taxane/anthracycline vs. taxane/anthracycline + bevacizumab: no difference noted (HR, 1.03; 95% CI, 0.77-1.38)
  - Independent review PFS:
    - Capecitabine vs. capecitabine + bevacizumab: median PFS increased from 6.2 months to 9.8 months (HR, 0.68; 95% CI, 0.54-0.86)
    - Taxane/anthracycline vs. taxane/anthracycline + bevacizumab: median PFS increased 8.3 months to 10.7 months (HR, 0.77; 95% CI, 0.60-0.99)
  - Safety: incidence of grade 3/4 events higher in bevacizumab arms vs. control arms
    - Increased frequency of hypertension (1% vs. 10%) and proteinuria (0% vs. 2.8%)
    - Increased risk of bleeding events (0% vs. 5.4%) and febrile neutropenia (2% vs. 8.4%) in taxane combination

### Study critique

<table>
<thead>
<tr>
<th><strong>Strengths:</strong></th>
<th><strong>Limitations:</strong></th>
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<tbody>
<tr>
<td>- Large sample size</td>
<td>- Use of nab-paclitaxel vs. standard paclitaxel</td>
</tr>
<tr>
<td>- Double-blind, placebo-controlled</td>
<td>- Chemotherapeutic regimen selected prior to randomization to placebo or bevacizumab</td>
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<td>- Over 80% of patients enrolled with measurable disease</td>
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<tr>
<td>- PFS assessed by independent review committee</td>
<td></td>
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<tr>
<td>- Chemotherapeutic regimens assessed</td>
<td></td>
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<td>- Comparable dose intensity between cohorts</td>
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### Reviewer’s Conclusion

- Bevacizumab statistically improved PFS when compared to non-bevacizumab regimens; however, the clinical benefit is less when compared to the original E2100 study
- The study addresses the limitations of prior studies increasing the validity of the results

PFS = progression free survival; RECIST = response evaluation criteria in solid tumors; OS = overall survival
Table 3. Summary of Study Comparisons^23-26

<table>
<thead>
<tr>
<th>Study Design</th>
<th>E2100</th>
<th>AVADO</th>
<th>RIBBON-1</th>
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</thead>
<tbody>
<tr>
<td>FDA approved dosage or equivalent</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>First line therapy</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Blinded study</td>
<td></td>
<td>✔️</td>
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<tr>
<td>Independent reviewer</td>
<td></td>
<td>✔️</td>
<td></td>
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<tr>
<td>Primary end point</td>
<td>PFS</td>
<td>PFS</td>
<td>PFS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>E2100</th>
<th>AVADO</th>
<th>RIBBON-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent patients with measurable disease</td>
<td>73%</td>
<td>83.4%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Primary end point (median PFS in months)</td>
<td>5.9 vs. 11.8</td>
<td>8.1 vs. 10</td>
<td>5.7 vs. 8.6 (cape) 8.0 vs. 9.2 (tax/anthra)</td>
</tr>
<tr>
<td>Any AE ≥ grade 3</td>
<td>25.4% vs. 41.4%</td>
<td>31.2% vs. 37.5%</td>
<td>24% vs. 40.1%</td>
</tr>
</tbody>
</table>

FDA = Food and Drug Administration; PFS = progression free survival; cape = capecitabine; tax/anthrax = taxane/anthracycline; AE = adverse event

E. Current events

i. Recent concerns regarding the use of bevacizumab in breast cancer
   1. FDA^27
      a. December 2010, FDA Center’s for Drug Evaluation and ODAC voted 12 to 1 revoking bevacizumab’s approval in metastatic breast cancer
      b. January 2011, Genentech, Inc. requests public hearing to appeal decision
      c. February 2011, FDA grants two day appeal hearing to Genentech, Inc.
      d. June 2011, ODAC voted six to zero in favor of withdrawing breast cancer indication
      e. November 18, 2011 FDA commissioner revoked bevacizumab’s indication in breast cancer
   2. European Medicines Agency
      a. Bevacizumab may be used in metastatic breast cancer, only with paclitaxel^25
   ii. Current guideline recommendations
      1. NCCN guidelines^28
         a. Continued recommendation for use with paclitaxel (grade 2A)
   iii. Centers for Medicare and Medicaid position regarding reimbursement^15-29
         a. “The drug will still be on the market, doctors will still be prescribing it, and we will continue to pay for it” –Don McLeod Centers for Medicare and Medicaid spokesman
V. Controversy Surrounding the Accelerated Drug Approval Process: Revisited

A. Does the accelerated approval process speed up drug availability?
   i. Time from IND application to approval

Table 4. Studies Evaluating Drug Approval Time\textsuperscript{6,13}

<table>
<thead>
<tr>
<th>Study</th>
<th>Richey et al.*</th>
<th>Lanthier et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective review</td>
<td>Retrospective review</td>
</tr>
<tr>
<td>Time Period</td>
<td>1995 to 2008</td>
<td>1995 to 2008</td>
</tr>
<tr>
<td>Number of Agents</td>
<td>51 agents</td>
<td>51 agents</td>
</tr>
<tr>
<td>Development Time (years)</td>
<td>Regular: 7.2</td>
<td>Regular: 7.1 (3.0 to 33.4)</td>
</tr>
<tr>
<td></td>
<td>Accelerated: 7.3</td>
<td>Accelerated: 6.1 (3.1 to 12.4)</td>
</tr>
</tbody>
</table>

* Limitations: classification inaccuracies, failure to obtain 25% of investigational new drug applications

B. Are trials conducted under the accelerated approval process appropriate?
   i. Of the 47 approvals, 28 (59.6%) were based on single arm studies (1992 to 2010)\textsuperscript{7}
      1. One medication received first line approval from single arm studies- imatinib (Gleevec\textsuperscript{8})\textsuperscript{7}
   ii. Since 2005, half of accelerated approvals were based on randomized trials

C. Does accelerated approval delay completion of post-approval studies needed to confirm clinical outcomes?
   i. Of the 35 oncology products granted accelerated approval, 14 have not completed confirmatory analysis\textsuperscript{5}
      1. Twenty-six of 47 (55.3%) indications approved under accelerated approval between have been confirmed (1992 to 2010)
         a. Median time to conversion, 3.9 years (0.8 years to 12.6 years)

D. Are medications approved under the accelerated approval process safe and effective?
   i. Safety
      1. Four (21%) black boxed warnings added to agents undergoing accelerated approval (1995 to 2008)\textsuperscript{6}
         a. Warnings added more than two years following approval
         b. Three warnings added to agents undergoing regular approval
   ii. Efficacy
      1. Only three medications have been withdrawn from market\textsuperscript{6}
         a. Withdrawn agents are currently being evaluated for use in select patients
VI. Conclusions

A. The FDA accelerated approval process, originally implemented for oncologic agents in 1996, is aimed at shortening the time to approval of novel agents for diseases with unmet medical needs

B. The FDA accelerated approval process has raised several questions concerning the safety, efficacy, and timeliness of approved agents

C. Thirty-five of all oncologic agents approved from 1996 to 2010 were approved under the FDA accelerated approval program

D. The accelerated approval process has demonstrated an ability to shorten the time needed for approval

E. Only three medications, including bevacizumab, have been withdrawn from the market following lack of efficacy data during confirmatory trials

F. Despite concerns over safety and efficacy, the accelerated approval process has been efficient in achieving its’ goal of producing quality agents and in ensuring these agents are effective
### VII. Appendices

**Appendix 1. Surrogate Markers Commonly Used in Oncology Studies**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Definition</th>
<th>Trial Design</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>• Proportion of patients achieving a complete and sustained reduction in tumor size</td>
<td>• Single arm vs. RCT&lt;br&gt;• Commonly used in hematologic malignancy studies&lt;br&gt;• Blinding preferred</td>
<td>• Assessable in single arm studies&lt;br&gt;• Durable response can represent clinical benefit&lt;br&gt;• Shorter follow-up&lt;br&gt;• Small sample size adequate</td>
<td>• Not a direct measure of survival benefit&lt;br&gt;• Non-comprehensive measure of drug benefit&lt;br&gt;• Potential only small subset will benefit</td>
</tr>
<tr>
<td>Disease-Free Survival (DFS)</td>
<td>• Time from randomization to disease recurrence or death from any cause</td>
<td>• RCT&lt;br&gt;• Used when prolonged survival is expected&lt;br&gt;• Blinding preferred</td>
<td>• Smaller sample size adequate&lt;br&gt;• Shorter follow-up</td>
<td>• Not fully validated as survival surrogate&lt;br&gt;• Subject to bias in open label design&lt;br&gt;• Dependent on frequency/timing assessments&lt;br&gt;• Variable definitions</td>
</tr>
<tr>
<td>Objective Response Rate (ORR)</td>
<td>• Proportion of patients achieving sustained reduction in tumor size</td>
<td>• Single arm vs. RCT&lt;br&gt;• Used in refractory settings&lt;br&gt;• Blinding preferred</td>
<td>• Assessable in single arm studies&lt;br&gt;• Shorter follow-up&lt;br&gt;• Smaller sample size adequate&lt;br&gt;• Outcome attributed to drug</td>
<td>• Not a direct measure of survival&lt;br&gt;• Dependent on radiographic interpretation&lt;br&gt;• Only subset of patients may benefit&lt;br&gt;• Not comprehensive measure of drug activity&lt;br&gt;• Stable disease not included</td>
</tr>
<tr>
<td>Progression-Free Survival (PFS)</td>
<td>• Time from randomization to tumor progression or death</td>
<td>• RCT&lt;br&gt;• Double blinding necessary to minimize bias</td>
<td>• Better predictor of stable disease&lt;br&gt;• Not affected by future treatment&lt;br&gt;• Shorter follow-up&lt;br&gt;• Smaller sample size</td>
<td>• Dependent on radiographic assessment&lt;br&gt;• Dependent on frequency/timing of assessments&lt;br&gt;• Not validated as surrogate for overall survival&lt;br&gt;• Missing data affects interpretation of results</td>
</tr>
<tr>
<td>Time to Progression (TTP)</td>
<td>• Time from randomization to tumor progression</td>
<td>• RCT&lt;br&gt;• Blinding necessary to minimize bias&lt;br&gt;• Primary endpoint when death is not related to cancer</td>
<td>• Better predictor of stable disease&lt;br&gt;• Not affected by future treatment</td>
<td>• Dependent on radiographic assessment&lt;br&gt;• Dependent on frequency/timing of assessments</td>
</tr>
<tr>
<td>Time to Treatment Failure (TTF)</td>
<td>• Composite endpoint from randomization to discontinuation of therapy (all cause)</td>
<td>• Single arm</td>
<td>• Unable to distinguish efficacy from other variables (e.g., toxicity)</td>
<td>• Not recommend by FDA</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial
### Appendix 2. Oncology Medications Receiving FDA Accelerated Approval (1996-2010)\(^5\)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Study Design</th>
<th>Study Endpoint</th>
<th>Current Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath(^®))</td>
<td>Chronic lymphocytic leukemia</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Amifosine (Ethyol(^®))</td>
<td>Cisplatin associated renal toxicity</td>
<td>Single arm</td>
<td>CrCl</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Anastrozole (Arimidex(^®))</td>
<td>Adjuvant treatment in ER(+) breast cancer</td>
<td>RT</td>
<td>DFS</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Bevacizumab (Avastin(^®))</td>
<td>HER-2 (-) metastatic breast cancer</td>
<td>RT</td>
<td>PFS</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Bicalutamide (Casodex(^®))</td>
<td>Prostate Cancer</td>
<td>RT</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Bortezomib (Velcade(^®))</td>
<td>Multiple myeloma</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Capecitabine (Xeloda(^®))</td>
<td>Breast cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Celecoxib (Celebrex(^®))</td>
<td>Reduction in polyps in familial adenomatous polyposis</td>
<td>RT</td>
<td>Incidence Rate</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Cetuximab (Erbitux(^®))</td>
<td>EGFR expressing metastatic colorectal cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Cladribine (Clolar(^®))</td>
<td>Acute lymphocytic leukemia</td>
<td>Single arm</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Dasatinib (Sprycel(^®))</td>
<td>Philadelphia (+) CML</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Denileukin (Ontak(^®))</td>
<td>Cutaneous T-cell lymphoma</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Dexrazoxane (Zinconar(^®))</td>
<td>Cardiac Protection</td>
<td>RT</td>
<td>TTP (cardiomyopathy)</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Docetaxel (Taxotere(^®))</td>
<td>Breast Cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Eltrombopag (Promacta(^®))</td>
<td>Refractory ITP</td>
<td>RT</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Fludarabine (Oforta(^®))</td>
<td>Chronic lymphocytic leukemia</td>
<td>Single arm</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Gefitinib (Iressa(^®))</td>
<td>Non-small cell lung cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin (Mylotarg(^®))</td>
<td>Acute myelogenous leukemia</td>
<td>Single arm</td>
<td>ORR</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Ibrutinomab (Zevalin(^®))</td>
<td>Relapsed/refractory follicular lymphoma</td>
<td>RT</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Imatinib (Gleevec(^®))</td>
<td>Philadelphia (+) CML</td>
<td>RT</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Irinotecan (Camptosar(^®))</td>
<td>Metastatic colorectal cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
</tbody>
</table>

CML = chronic myelogenous leukemia; CrCl = creatinine clearance; DFS= disease free survival; EGFR= epidermal growth factor receptor; ER = estrogen receptor; FU/LV= fluorouracil/ leucovorin; GIST= gastrointestinal stromal tumor; HER-2 = human epidermal growth factor receptor 2; ITP= immune thrombocytopenia purpura; ORR= overall response rate; PFS = progression free survival; RT = randomized trial; TTP= time to progression
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Study Design</th>
<th>Study Endpoint</th>
<th>Current Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib (Tykerb®)</td>
<td>HER-2(+) metastatic breast cancer</td>
<td>RT</td>
<td>PFS</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Letrozole (Femara®)</td>
<td>Adjuvant treatment in ER(+) breast cancer</td>
<td>RT</td>
<td>DFS</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Liposomal Cytarabine (DepoCyt)</td>
<td>Lymphomatous Meningitis</td>
<td>RT</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Liposomal Doxorubicin (Doxil®)</td>
<td>Kaposis Sarcoma</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Nelahbine (Arranon®)</td>
<td>T-cell acute lymphocytic leukemia</td>
<td>Single arm</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Nilotinib (Tasigna®)</td>
<td>Philadelphia (+) CML</td>
<td>RT</td>
<td>ORR</td>
<td>Under Review</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra®)</td>
<td>Chronic lymphocytic leukemia</td>
<td>Single arm</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Oxaliplatin (Eloxatin®)</td>
<td>Metastatic colorectal cancer with FU/LV</td>
<td>RT</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Panitumumab (Vectibix®)</td>
<td>EGFR expressing metastatic colorectal cancer</td>
<td>RT</td>
<td>PFS</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Pemetrexed (Alimta®)</td>
<td>Non-small cell lung cancer</td>
<td>RT</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Pralatrexate (Folotyn®)</td>
<td>Peripheral T-cell lymphoma</td>
<td>Single arm</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
<tr>
<td>Sunitinib (Sutent®)</td>
<td>Renal cancer</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Temozolomide (Temodar®)</td>
<td>Astrocytoma</td>
<td>Single arm</td>
<td>ORR</td>
<td>Full Approval</td>
</tr>
<tr>
<td>Thalidomide (Thalomid®)</td>
<td>Multiple myeloma</td>
<td>RT</td>
<td>ORR</td>
<td>Under Review</td>
</tr>
<tr>
<td>Tositumomab (Bexxar®)</td>
<td>Follicular lymphoma (relapsed)</td>
<td>Single arm</td>
<td>ORR</td>
<td>Not Completed</td>
</tr>
</tbody>
</table>

CML = chronic myelogenous leukemia; CrCl= creatinine clearance; DFS= disease free survival; EGFR= epidermal growth factor receptor; ER = estrogen receptor; FU/LV= fluorouracil/leucovorin; GIST= gastrointestinal stromal tumor; HER-2 = human epidermal growth factor receptor 2; ITP= immune thrombocytopenia purpura; ORR= overall response rate; PFS = progression free survival; RT = randomized trial; TTP= time to progression.
References


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