Mylotarg®
(gemtuzumab ozogamicin)

Wyeth Pharmaceuticals
Oncologic Drugs Advisory Committee
13 March 2003
Mylotarg®
(gemtuzumab ozogamicin)

Matthew L. Sherman, MD
Assistant Vice President
Therapeutic Area Director, Oncology
Clinical Research & Development

Wyeth
Agenda

- Introduction and Regulatory History
- Post-approval Commitment
- Post-marketing Safety Surveillance
- Prospective Observational Study
- Conclusions
Introduction

- **Indication**
  - Mylotarg is indicated for patients with CD33 positive AML in first relapse who are ≥ 60 years of age and not candidates for other cytotoxic chemotherapy

- **Mechanism of Action**
  - Antibody-targeted chemotherapy
  - Binds CD33 cell surface antigen on myeloid cells
  - Internalization and release of highly potent antitumor enediyne calicheamicin
  - Spares pluripotent stem cell and allows regeneration of normal blood cells following therapy
Regulatory History

- November 24, 1999 Orphan Drug Designation
  - AML incidence in US population ~10,000 per year (NCI/SEER)

- May 17, 2000 Accelerated Approval
  - Pivotal studies: Three ongoing Phase 2 open-label studies (n = 142 patients)
  - Endpoint for approval: Response rate

- Current
  - Pivotal Phase 2 studies completed (n = 277 patients)
  - Post-approval commitment for full approval
Post-Approval Commitment

Use of Mylotarg in combination with induction chemotherapy for the treatment of first-line patients with *de novo* AML
## Post-Approval Commitment

<table>
<thead>
<tr>
<th>Indication</th>
<th>Accelerated Approval</th>
<th>Full Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed AML</td>
<td>de novo AML</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Single agent</th>
<th>Combination</th>
</tr>
</thead>
</table>

| Dose                | 9 mg/m² days 1,15    | 6 mg/m² day 4       |

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Response rate (CR, CRp)</th>
<th>Survival</th>
</tr>
</thead>
</table>

| Timeframe           | Ph 1: 2 years           | Ph 1/2: 2.5 years   |
|                     | Ph 2: 2.5 years         | Ph 3: 7.5 years     |
Phase 1/2 Combination Studies

- Pilot dose-escalation studies to establish safety and MTD of Mylotarg in combination with standard chemotherapy

- **Study 205**
  - Patients $\geq 60$ years of age
  - Mylotarg and cytarabine
  - First patient enrolled: August 2000; last patient visit: April 2003

- **Study 206**
  - Patients 18 to 60 years of age
  - Mylotarg and daunorubicin + cytarabine
  - First patient enrolled: October 2000; last patient visit: April 2003
## Phase 1/2 Combination Studies

<table>
<thead>
<tr>
<th></th>
<th>Study 205</th>
<th>Study 206</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mylotarg</td>
<td>Mylotarg</td>
</tr>
<tr>
<td></td>
<td>Cytarabine</td>
<td>Cytarabine</td>
</tr>
<tr>
<td>Part 1 Dose-escalating</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Part 2 Expanded cohort</td>
<td>17</td>
<td>49</td>
</tr>
<tr>
<td>Total Patients</td>
<td>38</td>
<td>71</td>
</tr>
</tbody>
</table>
Establishing the MTD

- **Study 205**
  - Mylotarg 6 and 4 mg/m² IV day 1 and 8
  - Cytarabine 100 mg/m² CIVI days 1 to 7

- **Study 206**
  - Mylotarg 6 mg/m² IV day 4
  - Daunorubicin 45 mg/m² IV days 1, 2, 3
  - Cytarabine 100 mg/m² CIVI days 1 to 7
Study 206 Preliminary Data
Part 1 and 2 *de novo* Patients

<table>
<thead>
<tr>
<th></th>
<th>Response rate</th>
<th>RFS</th>
</tr>
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<tbody>
<tr>
<td>Part 1 patients (n=8)</td>
<td>7 (88%)</td>
<td>17.3 mo</td>
</tr>
<tr>
<td>Part 2 patients (n=43)</td>
<td>36* (83%)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

1 CRp
ASH 2002
Proposed Phase 3 Study

- **Study 301 (SWOG S0106)**
  - Phase 3, randomized, controlled trial of Mylotarg in combination with standard induction chemotherapy in de novo AML
  - Comparison of daunorubicin/cytarabine “3 and 7” chemotherapy ± Mylotarg
  - Primary endpoint: Survival

- **Status**
  - Submitted for Special Protocol Assessment
  - Southwest Oncology Group (SWOG), Dr. Frederick Appelbaum, Chair of Leukemia Subcommittee
  - Target 684 patients, 160 patients/year: 4.5 years to accrue
  - Anticipated time to complete study: 7.5 years
Study Challenges

- Uncommon disease

- Treatment typically at major medical centers and universities therefore a need for cooperative group involvement
  - SWOG accepted our request to participate in study
  - CALGB, ECOG, EORTC, GIMEMA cooperative groups had prior commitments
Post-marketing Safety Surveillance

Hepatotoxicity

- Clinical trial experience
  - Liver function test abnormalities: mild to moderate in severity; generally reversible
  - Severe hepatotoxicity including veno-occlusive disease (VOD): Low incidence rate reported

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<th>VOD, n (%)</th>
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<td>3 (2.1)</td>
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<td>Completed Registration Trial (n = 277)</td>
<td>7 (2.5)</td>
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Post-marketing Safety Surveillance
Hepatotoxicity

• Post-marketing experience
  ‣ Grade 3 and 4 hepatotoxicity and VOD reported at higher than expected rate

| VOD, n (%) | Giles FJ, et al. (n = 119) | 14 (12) |

Cancer 2001; 92: 406-413
Post-marketing Safety Initiatives

- Label changes implemented to strengthen warnings
- Developed and initiated a Prospective Observational Study
- Study rationale
  - Assess the safety of Mylotarg when used in routine practice
Prospective Observational Study

- Status
  - Patient enrollment ongoing
  - 57 sites have been activated with IRB approval
  - 11 additional sites under recruitment
  - 101 patients consented and enrolled
  - ~90 patients have received Mylotarg
# Incidence of VOD

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</tr>
<tr>
<td>Prospective Observational Study† (n = 90)</td>
<td>4 (4.4)</td>
</tr>
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</table>

* Cancer 2001; 92: 406-413
† as of February 28, 2003
Prospective Observational Study

- **Challenges**
  - Site recruitment is difficult
  - Contacted >200 sites to participate
    - ~1/3 no response
    - ~1/3 would not participate
    - ~1/3 would participate
  - Patient recruitment is difficult in small patient population
    - Even major centers only treat limited AML patients per year
Conclusions

- Patient recruitment and study completion have been appropriate for this patient population
- FDA approval of Mylotarg under Subpart H provided older AML patients in first relapse with a meaningful treatment option for an unmet medical need
- Wyeth is committed to completing the post-approval obligation
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