Mylotarg®
(gemtuzumab ozogamicin)

Wyeth Pharmaceuticals
Oncologic Drugs Advisory Committee
13 March 2003

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(gemtuzumab ozogamicin)

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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**

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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

	Accelerated Approval	Full Approval
Indication	Relapsed AML	de novo AML
Schedule	Single agent	Combination
Dose	9 mg/m^2 days 1,15	6 mg/m^2 day 4
Endpoints	Response rate (CR, CRp)	Survival
Timeframe	Ph 1: 2 years Ph 2: 2.5 years	Ph 1/2: 2.5 years Ph 3: 7.5 years

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Phase 1/2 Combination Studies

- **Pilot dose-escalation studies to establish safety and MTD of Mylotarg in combination with standard chemotherapy**
- **Study 205**
  - **Patients ³ 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

	Study 205 Mylotarg Cytarabine	Study 206 Mylotarg Cytarabine Daunorubicin
Part 1 Dose-escalating	21	22
Part 2 Expanded cohort	17	49
Total Patients	38	71

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Establishing the MTD

- **Study 205**
  - **Mylotarg 6 and 4 mg/m^2 IV day 1 and 8**
  - **Cytarabine 100 mg/m^2 CIVI days 1 to 7**
- **Study 206**
  - **Mylotarg 6 mg/m^2 IV day 4**
  - **Daunorubicin 45 mg/m^2 IV days 1, 2 , 3**
  - **Cytarabine 100 mg/m^2 CIVI days 1 to 7**

Study 206 Preliminary Data
Part 1 and 2 *de novo* Patients

	Response rate	RFS
Part 1 patients (n=8)	7 (88%)	17.3 mo
Part 2 patients (n=43)	36* (83%)	n/a

1 CRp

ASH 2002

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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**

Study	VOD, n (%)
NDA Submission (n = 142)	3 (2.1)
Completed Registration Trial (n = 277)	7 (2.5)

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

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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

Study	VOD, n (%)
NDA Submission (n = 142)	3 (2.1)
Completed Registration Trial (n = 277)	7 (2.5)
Giles FJ, et al. (n = 119)*	14 (12)
Prospective Observational Study† (n = 90)	4 (4.4)

* Cancer 2001; 92: 406-413

† as of February 28, 2003

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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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