FDA Approvals in Multiple Myeloma

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Outline of Presentation

- Regulatory basis for marketing authorization (New drug approval)
- Types of approval
- Drugs approved for multiple myeloma
- Study designs and endpoints supporting drug approval

Federal Law - Drug Approval

- Safety (FD&C Act 1938)
- Efficacy - Substantial evidence (1962)
  - K-H amendments
  - “Adequate and well-controlled investigations”
- Labeling - from the studies to
  - Define an appropriate patient population for treatment with the drug
  - Provide adequate information for safe and effective use of the drug
- Similar requirements for biologicals

How Many Trials?

- Usually more than one trial is expected

  Substantial evidence: "Adequate and well-controlled investigations"

- Sometimes a single trial may suffice
  - FDAMA (1997) single trial plus other supportive evidence
  - 1998 FDA Effectiveness Guidance:
    - Large and multicenter trial
    - Statistically strong evidence
    - Demonstrates an important clinical benefit
    - Results so persuasive - additional trials not ethical

Requirements for NDA Approval

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies
- FDA examines the evidence in the context of the disease state, available therapy, study design, endpoints selected, and strength of the evidence

NDA - Efficacy Requirements

- Regular (full) approval - demonstrate
  - Clinical benefit or effect on established surrogate
- Accelerated Approval
  - Uses a surrogate endpoint reasonably likely to predict clinical benefit
  - Requires subsequent confirmation of benefit

Surrogates That May Support Regular Approval

- Disease-free survival (DFS) - selected settings
- Progression-free survival (PFS) – selected settings
- Complete response rate with duration in some settings (e.g., acute leukemia, when the alternative is rapid decline)
- Partial response rates in some settings

Magnitude and duration of effect

Discuss with us in advance

Efficacy Endpoints Commonly Used for Regular Approval

Improvements in:

- Overall Survival
- Time to recurrence / Disease-free survival (commonly used in adjuvant studies)
- Time to progression / PFS (selected)
- Palliation (objective response with PRO-reduction in tumor-related symptoms)

Accelerated Approval Regulatory Basis

- For serious or life-threatening diseases
- Where the drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit

Accelerated Approval requirements

- Subject to the requirement that the applicant verify and describe clinical benefit
- Post-marketing studies would usually be underway at time of approval
- The applicant shall carry out such studies with due diligence

Accelerated Approval (AA)

- AA study designs used to demonstrate benefit over available therapy
  - In refractory settings: single arm trials
  - In available therapy settings: comparative trials
- Post-approval confirmation of benefit
  - Related (e.g. less refractory) population
  - Could use same trial/population (HIV example) with subsequent clinical benefit endpoint

Evidence Required for Accelerated Approval

- Substantial evidence from well controlled clinical trials regarding a surrogate endpoint
- NOT: Borderline evidence regarding a clinical benefit endpoint

Convincing Magnitude and Duration of effect

Choice of Endpoints – Response Rate or Time to Event?

- Objective Response - treatment is responsible for the effect of tumor reduction
  - Responders are a subgroup!
  - Magnitude and duration
  - Not minimal response or stable disease
  - Primarily of interest in single-arm studies

Choice of Endpoints – Response Rate or Time to Event?

- In contrast, survival, TTP, and PFS encompass effects of the natural history PLUS treatment effect AND express the effect on the entire study arm population
  - Cannot evaluate time to event results in single-arm studies

What Is a Response?

- Assessment method?
  - Prospective definitions
    - working group criteria generally acceptable
    - consensus or evidence-based
  - Timing and frequency of evaluations
  - Radiographic or clinical or both
  - Independent blinded review of measurements?
- Quality of response
  - Numbers of CRs *vs.* PRs
  - Durability of responses
  - Associated evidence of symptom improvement?

‘Older’ Molecular Entities - Approved Prior to 2003

- Carmustine - palliative treatment in combination with prednisone
- Melphalan - palliative treatment
- Both approvals based on:
  - Response rates from case series and testimonials

New Molecular Entities Approved for Myeloma - Current Status

- Velcade – Regular approval
  - after 1 prior therapy
- Thalidomide – Accelerated approval
  - newly diagnosed
- Lenalidomide – Regular approval
  - after 1 prior therapy

Velcade (bortezomib)

- 2003 - Accelerated Approval
  - Based on two multicenter, single arm studies
  - Patients with MM whose disease had relapsed after at least 2 prior therapies (median 6 prior Rx)
  - Primary endpoint: CR+PR EBMT criteria
  - Independent analysis of response data
  - Response rate 28%
  - Median duration of response: 12 months

Velcade

- 2005 - Regular approval
  - Demonstration of improvement in time-to-progression (TTP) and overall survival
  - Large, international, randomized, open-label study in patients who had received at least one prior therapy for myeloma (N = 669)
  - Velcade versus Dexamethasone
  - TTP primary endpoint (EBMT progression)
    - HR=0.55
    - median TTP 6.2 vs. 3.5 months
  - OS (HR=0.57; P <0.05)

Revlimid (lenalidomide)

- Regular approval
  - 2 multicenter, randomized, placebo-controlled trials (N = 341 and 351)
  - At least 1 prior therapy for myeloma

Lenalidomide plus dexamethasone

versus

placebo plus dexamethasone

Revlimid (lenalidomide)

- Regular approval
  - Primary endpoint: TTP
  - EBMT criteria for progression
  - Independent review of progression
  - TTP HR=0.36 and 0.39; P < 0.0001
  - Median TTP: (1) 9+ months vs. 5 months
    (2) not reached vs. 5 months

Thalidomide

- Accelerated Approval
  - Primary endpoint - response rate using serum/urine protein assays
  - Randomized trial - cooperative group setting

    Thalidomide + Dexamethasone

    versus

    Dexamethasone alone
  - N = 207
  - Response rate: 52% (DT) vs. 36% (D)

Conclusions

- Accelerated Approval
  - Convincing response rate and duration
  - Single-arm study design plausible if in a setting of no available therapy
- Regular approval
  - OS
  - TTP / PFS of sufficient magnitude
  - Usually, when there is available therapy, a comparator study design to demonstrate superiority

The FDA mission is not a new idea!

"The aim ... is not simply to accept the statements of others, but to investigate the causes that are at work in nature."

Albertus Magnus, *de Mineralibus circa 1250 a.d.*