Conference on Clinical Cancer Research

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Re-evaluating Criteria for Accelerated Approval
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Richard L. Schilsky, M.D.
University of Chicago Comprehensive Cancer Center
Accelerated Approval

- Allows a drug to be granted conditional approval using a surrogate endpoint reasonably likely to predict clinical benefit
- Requires further well-controlled studies to verify and describe the clinical benefit
  - Converted to “regular approval” if clinical benefit confirmed
  - Withdrawn from the market if not confirmed
Successful Track Record

AA pathway has provided early access to clinically meaningful cancer therapies

• 47 new oncology indications, 35 new products
  – 1993- July, 2010*

• 26 oncology indications have confirmed clinical benefit in post-marketing trials
  – Available an average of 4.7 years before verification of clinical benefit

* Johnson, et al. JNCI, 2011
Eligibility for Accelerated Approval

• Treat serious or life-threatening disease

• Provide meaningful therapeutic benefit over available therapies
  – Must fill an unmet medical need (although “unmet need” not clearly defined)

• Demonstrate activity using a surrogate endpoint reasonably likely to predict clinical benefit. RR and PFS used most often.
Two Approaches to AA in Oncology

• In settings with no approved treatment options
  – Example- refractory disease
  – Often in single arm trials utilizing historical controls

• In settings with approved treatment options
  – Earlier disease settings
  – Must demonstrate superiority in comparator trial
    • Efficacy (using a surrogate endpoint)
    • Tolerability
    • Practical benefit
Barriers to Utilization of the Accelerated Approval Pathway

• Increasing number of available therapies pushing developers to pursue AA in heavily pre-treated patients to fulfill an “unmet need”

• Lack of qualified surrogate endpoints for AA

• Lack of clarity early in development regarding circumstances in which a new product will qualify for accelerated approval
Charge to this Panel

• Identify ways to promote the use of accelerated approval in earlier disease settings

• Focus on three issues:
  – Propose broadening definition of “unmet medical need” and refining definition of “available therapy”
  – Describe the evidence required for qualification of a new surrogate endpoint suitable for AA
  – Propose structured process for sponsors and FDA to follow regarding AA
Despite the Availability of New Therapies, Unmet Need Still Exists

- Most available cancer drug therapies are not curative, have limited survival benefit, and cause significant toxicities
- “Unmet need” exists in any non-curative setting
- Need for mechanistic diversity
  - Provides physicians with more options depending on patient need
  - Fosters development of combination regimens
Vemurafenib Tumor Response

Vemurafenib Impact on Overall Survival

“Available Therapy” Should be Defined in a Biological Context for Targeted Agents

• If an investigational agent targets a specific pathway and will be labeled for use in a selected patient population, the only drugs that should be considered “available therapy” are those that target the same pathway –this recognizes our understanding of cancer as a genetic disease

• If a new drug targets a previously untargeted pathway then there is no “available therapy”

• New agents should demonstrate comparable activity to existing therapies for AA, but not necessarily superiority
Speakers

- Richard L. Schilsky, M.D., U. of Chicago
- Wyndham H. Wilson, M.D., NCI
- David P. Schenkein, M.D., Agios Pharmaceuticals
- Cheryl L. Jernigan, Susan G. Komen
- Janet Woodcock, M.D., FDA
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Wyndham H. Wilson
National Cancer Institute
Surrogate Endpoints

• An indirect measurement of clinical benefit
  – Direct measure: Survival (OS)- **Gold Standard**
  – Direct measure: Quality of life (QOL)

• Surrogate allows early measurement
  – Overall response rate
  – Progression free survival

• Surrogate may be the only possible endpoint
  – Randomized studies needed for OS and QOL
  – Randomized studies with crossover (planned or not)
  – Neoadjuvant response of breast cancer
Surrogate Endpoints

• Accelerated approval
  – Surrogate must be reasonably likely to predict clinical benefit
  – Some validation/qualification (validated-robust statistical methods)-may not be generalizable

• Accepted surrogate endpoints for AA
  – Response rate (overall or complete)
  – Progression free survival
  – Disease free survival
  – All setting specific and considering the totality of evidence
Need for New Surrogate Endpoints

• Limitations of ORR and PFS
  – Based on anatomical imaging
  – Flawed response criteria (RECIST or Cheson)
  – Subject to reader variation and staging times
  – Not feasible or poorly correlated or qualified with clinical outcome
Surrogate Endpoint and Biomarkers

- Biomarker: Objectively measured indicator of normal, pathogenic or pharmacologic response to a therapeutic intervention
- Prognostic biomarker: Predicts disease course irrespective of treatment
- Predictive biomarker: Predicts likely response to a specific treatment
Qualification of a Surrogate Endpoint

- Standardized definition
- Statistically robust correlation between surrogate endpoint and clinically meaningful outcome
- Large, prospective trials to validate the surrogate endpoint
- Prospective studies to determine context-dependent utility of surrogate endpoint
Recent example- pathologic complete response in localized breast cancer

- pCR-No invasive cancer in resected breast tissue following systemic neoadjuvant therapy
- Meta-analysis of 14 randomized trials: pCR may predict DFS and OS
- Neoadjuvant Herceptin Trial- randomized trial: doubling pCR needed to predict a significant difference in DFS
- Ongoing prospective trials hoped to clarify in which subtypes of early breast cancer pCR is most likely to predict benefit
Potential Imaging Surrogate- FDG-PET

- Exploits differential uptake of glucose by normal and malignant cells
- Measure of tumor metabolism can be measured earlier than tumor regression
  - Most useful for durable response
- Studies suggest correlation with clinical outcomes
- Validation studies ongoing in lung cancer and non-Hodgkin’s lymphoma
Biomarker Surrogate- Circulating prostate cancer cells

- Quantitative assay
- Sensitive measure of tumor response beyond radiographic
- Validation necessary for clinical benefit
  - Is it prognostic/predictive
  - Correlate with OS or QOL?
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Re-evaluating Criteria for Accelerated Approval

David P. Schenkein, M.D.
Agios Pharmaceuticals
Lack of Predictability

• There is no formal process for designating a product for development through the accelerated approval pathway
• Regulatory uncertainty cited as one of the primary reasons for the decline in venture funding of new start-ups
• Decision to pursue accelerated approval often an afterthought or a “review issue”, rather than a goal throughout development
• Many sponsors wary of pursuing accelerated approval due to concern over RTF- currently no real incentive to pursue novel trial design and/or surrogate markers.
Proposal for a Structured AA Process

• Sponsors and FDA meet early and agree that a drug will be developed by:
  – “Adaptive Clinical Development Plan” with possibility for accelerated approval if certain results are generated
  – Or- utilize full approval process
  – Formalize process with application, set review time and minutes
Adaptive Clinical Development Plan

• Decision to pursue accelerated approval should include:
  – Agreement that unmet need exists in the patient population being studied
  – Agreement on surrogate endpoint to be assessed
  – Agreement on trial design
  – Agreement on magnitude of benefit needed for AA
  – Agreement on post-marketing commitments
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Re-evaluating Criteria for Accelerated Approval

Cheryl L. Jernigan
Susan G. Komen for the Cure
Critical Issues from a Patient Perspective

• No Cure => “Unmet medical need”
  – True for metastatic disease, but also for early stage cancers
  – Consider cancer subtypes => Different genetic drivers
  – Need for additional treatment options to choose from
    • Less toxic therapies
    • Combination therapies to overcome drug resistance
    • Companion diagnostics needed
Critical Issues from a Patient Perspective

• New **surrogate endpoints** are needed
  – Their utility depends on the context – consider cancer subtypes
  – How do we encourage their development and qualification?
Critical Issues from a Patient Perspective

• Structured process ➔ Patient-focused
  – FDA and Sponsors ➔ Talk sooner, talk often
  – **Timely** post-approval trials to confirm (or not!) clinical benefit
    • Timely confirmatory trials – a critical part of a comprehensive drug development strategy
    • Appropriate carrots and sticks to ensure due diligence
    • Patient-reported outcomes also a key component
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Re-evaluating Criteria for Accelerated Approval

Janet Woodcock, M.D.
US Food and Drug Administration
Comments on Proposals

• Consider re-defining “available therapy” in context of targeted therapy
  – Drugs not targeted to that mechanism would not be considered “available therapy”
  – Rational if drug will only be targeted to that subgroup, in patients who lack curative therapies

• Consider re-defining “unmet medical need” in cancer
  – Where current therapy not curative
  – Clear need exists for advances in treatment
Comments on Proposals

• Standard for accelerated approval:
  – Proposal: accept new mechanism as “providing meaningful clinical benefit over existing therapy” when indication is targeted towards mechanism
  – Assume randomized trial vs existing therapy in the subset; What outcome would be acceptable?
  – When would non-randomized trial be acceptable?

• Process proposal
  – Up front agreement on potential AA
  – Work intensive for FDA but may actually save effort overall
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