FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Conference on Clinical Cancer Research

Supported by:

ASCO American Society of Clinical Oncology

Susan G. Komen for the Cure

AACR Centennial 1907 – 2007 American Association for Cancer Research

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Re-evaluating Criteria for Accelerated Approval

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Re-evaluating Criteria for Accelerated Approval

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  - Withdrawn from the market if not confirmed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

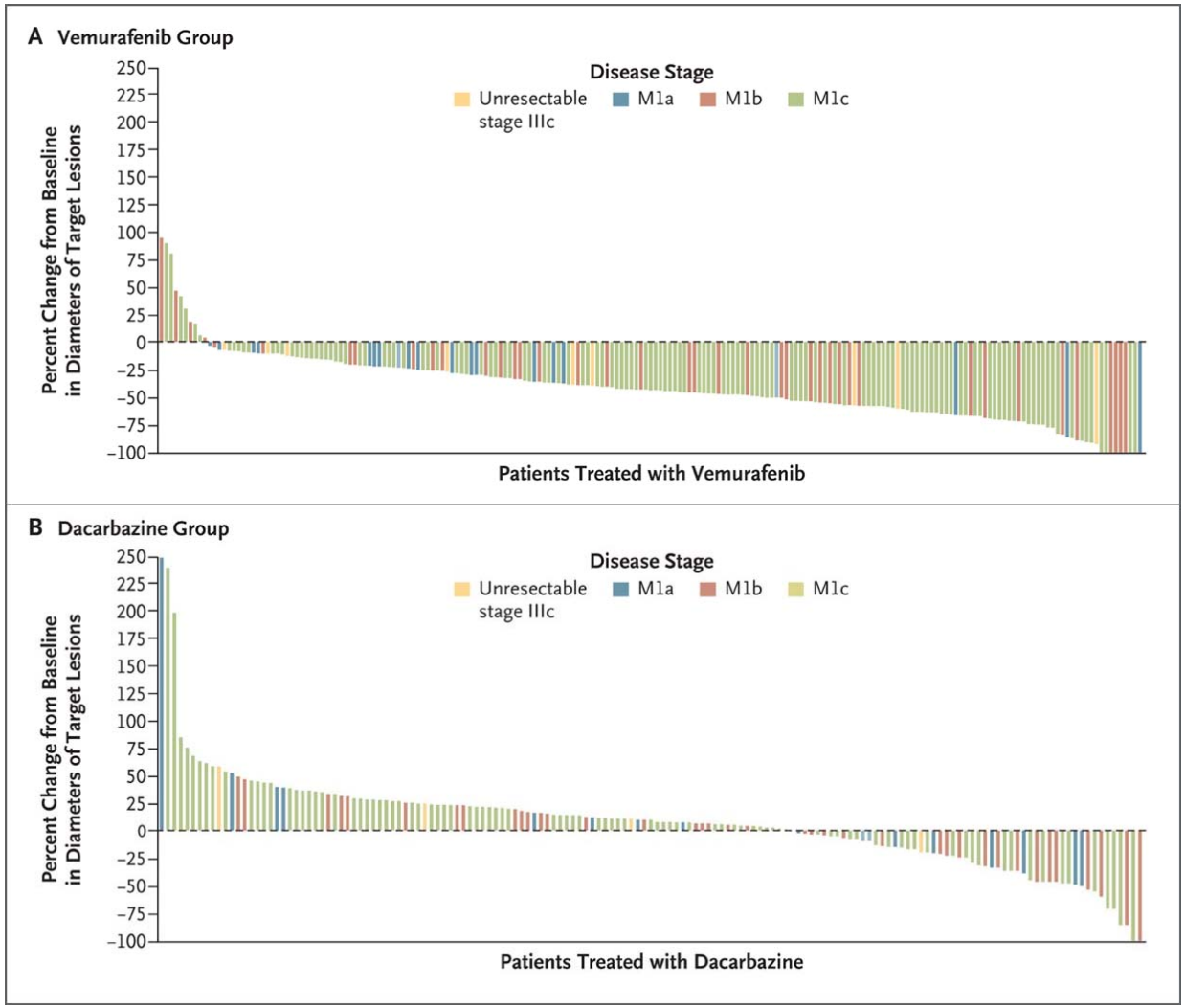
Charge to this Panel

- 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

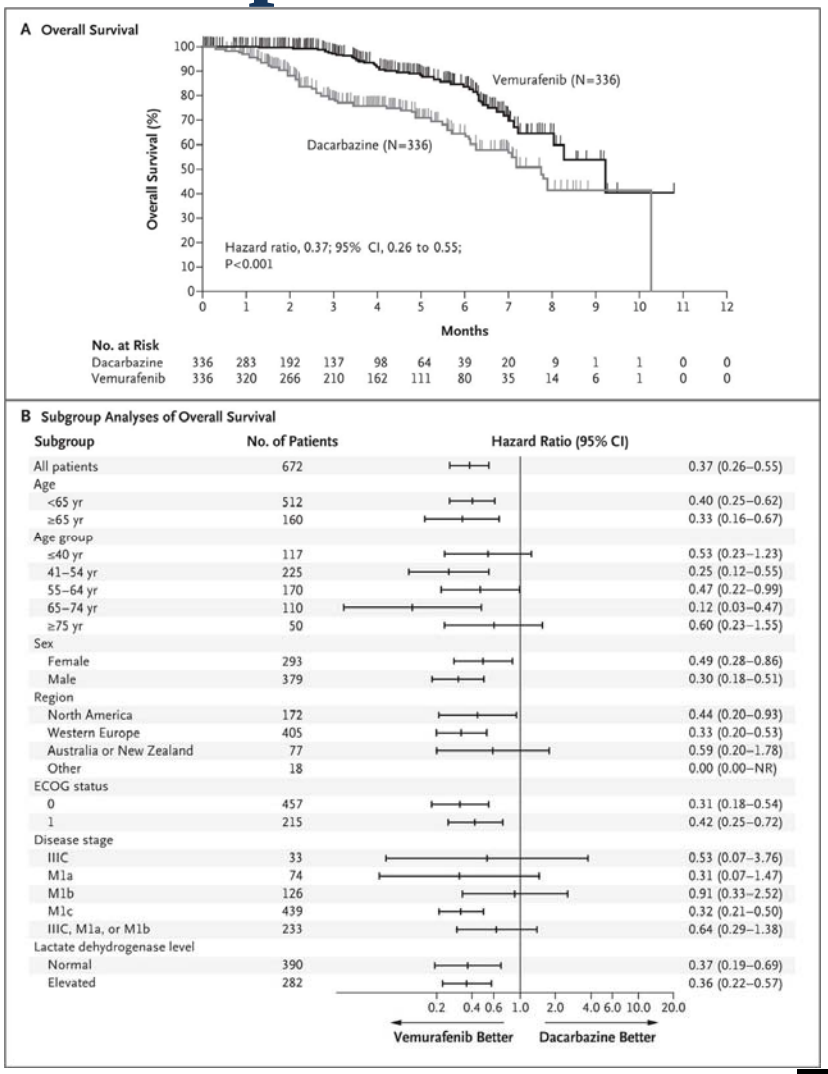
Vemurafenib Tumor Response



Chapman PB et al. N Engl J Med 2011;364:2507-2516

The NEW ENGLAND JOURNAL of MEDICINE

Vemurafenib Impact on Overall Survival



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"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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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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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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