Cancer, Drug Development and Regulation: A Brief Introduction

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• These slides represent my own perspective and do not necessarily reflect the official policy of the U.S. FDA or Office of Hematology and Oncology Products

• I have no financial relationships to disclose
Outline:

• **Introduction to Cancer and its Treatment**

• **FDA and the Review of Oncology Drugs**

• **Regulatory framework for drug approval and the History of Oncology Efficacy Endpoints**

• **The Renewed Importance of Response Rate and PRO**
The World of Oncology

**History**, Facts, Fear, Fiction and Hope

- Great resource for an introduction to the history of cancer and its treatment (oncology)
- Written in a very readable format
- Highly recommended!*
The World of Oncology
History, Facts, Fear, Fiction and Hope

• Facts
  – Lifetime Risk of Developing Cancer in U.S.
    • 44% for men, 38% for women (Jemal, 2011)
  – 11.7 million Americans in 2007 were alive with a current or past history of Cancer, 1.6 million new cancer cases expected in 2011
  – 572,000 cancer-related deaths in 2011
  – Cancer is the leading cause of death in the U.S. for those less than 85 years old

From the American Cancer Society: www.cancer.org
• **What is Cancer?**
  – Uncontrolled cell growth

**Homeostasis = Balance**

- Cell Death
- Cell Birth

**Multiple growth and suppression pathways which are normally balanced**

**Loss of Balance = Cancer**

- Loss of suppression
- Overactivation of growth
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History, Facts, Fear, Fiction and Hope

• “You’ve got Cancer”…

• No two cancers are alike!
  – What organ (histology)?
    • Prostate is not Leukemia.
    • Chronic Myelogenous Leukemia is not Acute Myelogenous Leukemia
  – What stage?
    • Local solid tumors can be cured with surgery or radiation.
    • Most metastatic solid tumors remain incurable
  – What genetics?!
    • BRAF+ melanoma, ALK+ lung cancer, etc.
The battle against cancer is waged at all stages of its natural history.
Systemic Therapies General Terminology:
What is your Goal? For Localized Cancer, When do you give it?

Stage of Cancer
- Localized (amenable to surgery or radiation)
  - Neoadjuvant
    Shrink it, then cut it.
  - Adjuvant
    Cut it out, mop up anything left over.

- Metastatic
  Widely spread
  Not amenable to surgery or radiation
  - Curative
    - Choriocarcinoma
    - Leukemias
    - Testicular Cancer
    - Lymphomas
  - Palliative
    - Prolong or improve life with cancer

Curative chemotherapy generally stopped after a certain period of time
Palliative chemotherapy usually continued until progression or unacceptable toxicities
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History, Facts, Fear, Fiction and Hope

• Types of Systemic Cancer Therapy
  – Cytotoxic “Chemotherapy”:
    • Farber – Late 1940s Antifolates and Pediatric ALL
    • Kills rapidly dividing cells
    • Non-specific: Normal cells that rapidly divide are affected (hair, oral and GI mucosa, bone marrow)
    • An example would be chemotherapy after Breast Cancer Surgery (AC-T) among many others
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History, Facts, Fear, Fiction and Hope

• Types of Systemic Cancer Therapy
  – “Hormonal Therapy”
    • Used for cancers that may grow faster when exposed to hormones like estrogen (breast cancer) or testosterone (prostate cancer)
    • Much different toxicity profile than traditional cytotoxic chemotherapy (hot flashes, bone loss, blood clots)
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History, Facts, Fear, Fiction and Hope

• Types of Systemic Cancer Therapy
  – “Immunotherapy”
    • Intended to stimulate your body’s immune system to recognize and help control the cancer
    • Vaccines, Immune Modulators, Cellular Therapies (e.g. CAR-T)
    • Toxicity profile can be very mild (vaccines) to very serious (Ipilimumab – severe colitis)
The World of Oncology
History, Facts, Fear, Fiction and Hope

- **Types of Systemic Cancer Therapy**
  - **“Targeted Therapy”**
    - Small molecules or antibodies used to target cellular pathways identified by in vitro diagnostic tests
    - Drugs such as Tarceva (erlotinib), Herceptin (traztuzumab), Gleevec (imatinib)
    - Toxicities unique to the mechanism of action, but as a whole better tolerated than cytotoxic chemotherapy
    - Unfortunately, cancers become resistant due to mutations in other pathways
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History, Facts, Fear, Fiction and Hope

• What is the first thing that comes to mind when you hear the word cancer?
  – Fear
  – Death
  – Chemotherapy
    • Baldness, Vomiting
  – Wasting, thin, pale
  – Sadness, grief, loss

• Fear is a strong emotion and can hamper ones ability to make well-informed decisions…
The World of Oncology

History, Facts, Fear, Fiction and Hope

Don’t Believe the Hype! Reliable websites for Cancer-Related Information can help you Dispel Myths:

• Federal Government Sites
  – National Cancer Institute
    • www.cancer.gov
  – Food and Drug Administration
    • www.fda.gov

• Large University Sites

• Established Health Organization Sites
  – American Cancer Society
    • www.cancer.org
  – American Society of Clinical Oncologists
    • www.cancer.net
The World of Oncology
History, Facts, Fiction, Fear and Hope

- Prevention
- Smoking Cessation
- Early Detection
- Supportive Care
- New Therapies

Jemal, *Cancer* (2011)
Outline:

- Introduction to Cancer and its Treatment

- **FDA and the Review of Oncology Drugs**

- Regulatory framework for drug approval and the History of Oncology Efficacy Endpoints

- The Renewed Importance of Response Rate and PRO
FDA Office of Hematology and Oncology

- Located in Silver Spring Maryland

- Almost 200 employees including medical oncologists and other physicians, nurse practitioners, pharmacologists, toxicologists and support staff.

- Work very closely with other centers, divisions and offices with an array of scientists including biostatistics, chemists, physicists, and others throughout the FDA
Key FDA Centers in Heme/Onc Development

Center for Drug Evaluation and Research (CDER)
• Drugs and Antibodies.
• Office of Hematology and Oncology Products

Center for Biologics Evaluation and Research (CBER)
• Cellular and Gene Therapies, Vaccines.

Center for Devices and Radiologic Health (CDRH)
• Devices, In Vitro Diagnostics, Diagnostic and Therapeutic Radiologics.
FDA Mission:

• FDA is responsible for:
  – Assurance of the Safety, Efficacy and Security of:
    • Drug and Biological products
    • Medical Devices
    • Food supply
    • Cosmetics
    • Radiation products
  – Accounts for 25 cents of every dollar spent by Americans…

• FDA does not take into account cost or payment issues

• FDA does not regulate “practice of medicine”
Office of Hematology and Oncology

- Disease-specific structure akin to current academic models:

  **Oncology Office**

  - **Div of Oncology Products 1**
    - Breast Cancer
    - Gynecologic Cancer
    - GU Malignancies
  
  - **Div of Oncology Products 2**
    - Thoracic - Head and Neck
    - Gastrointestinal
    - Melanoma-Sarcoma
    - Pediatric-Neuroendocrine-Rare Tumors
  
  - **Div of Hematology Products**
    - Benign Heme
    - Lymphomas
    - Leukemias
    - Transplant
  
  - **Div of Hematology and Oncology Toxicology**
    - Toxicologists supporting each clinical division
We Review CANCER Drugs

• Severe and Life Threatening Diseases
• Large Public Interest
• Different Risk Tolerance for Side Effects
• Very Emotional and Active Advocacy Groups
• Very Active area of Biomedical Research
• Many New Drugs in the Pipeline
Striking the Balance

Flexible, Efficient, Interactive

CERTAINTY
DATA
Regulatory BURDEN

Consistent, Thorough, Independent

“Too Cautious!
Stifling Innovation!
Reduce regulatory burden!”

“Too Cautious!
Stifling Innovation!
Reduce regulatory burden!”

“Toxic deaths!
Delayed safety findings!
FDA asleep at the Wheel”

Consistent, Thorough, Independent
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Safety and Efficacy Requirements:
Drugs (FD&C Act) and Biologics (PHS Act)

• FD&C Act “Safe and Effective”
  – Adequate and well-controlled investigations (typically 2 or more trials)
  – Experts qualified to evaluate the effectiveness of the drug
  – Reach a conclusion that the drug will have the effect it purports

• PHS Act “Safe Pure and Potent”
  – FDA Modernization Act – Minimize differences in review and approval between drugs and biologics

• For all intents and purposes, Safety and Efficacy of Drugs and Biologics use a similar evidentiary framework
U.S. Approval Pathways for Drugs and Biologics

• Traditional Approval or Accelerated Approval

Which pathway one uses relates to the **Primary Endpoint** selected…
Traditional ("Regular") Approval

• Traditional approval requires
  – Substantial evidence of Safety and Efficacy
  – Well-controlled clinical trials (usually 2 or more)
  – based on prolongation of life, a better life or an established surrogate for either of the above

• No comparative efficacy for Traditional Approval
  – As safe and effective as existing therapies, allowing for non-inferiority designs
Accelerated Approval

- ALSO requires **Substantial Evidence of Safety and Efficacy**

- “Provide meaningful therapeutic benefit… over existing therapies”

- *Can be based on a* “Surrogate endpoint… reasonably likely… to predict clinical benefit”

- But are “Subject to the requirement that the applicant study the drug further”

- **Post-Marketing Clinical Trials are Required**
  - Should usually be underway at the time of accelerated approval
  - Applicant should carry out studies with due diligence
Accelerated Approval

- **Benefits:**
  - Use of an unestablished surrogate endpoint
  - Usually provides for earlier events and smaller, quicker trials

- **Risks:**
  - Must demonstrate product is better than existing therapy (unlike traditional approval, there is an implied comparative efficacy requirement here)
  - Must complete post-marketing trials and confirm meaningful clinical benefit

- **10% of Accelerated Approvals in oncology have been withdrawn** for failure to confirm a benefit
  - NOT a failure of the accelerated approval program
  - We expect a small percentage of products to fail to verify this benefit
  - This is the anticipated tradeoff for earlier availability of promising anti-cancer agents.
The greater uncertainty that exists that the endpoint measures direct clinical benefit, the more data that will be required to support approval:

- Large magnitude of effect
- Internal consistency via key secondary endpoints
- Randomized Data
- Supporting Clinical Trials
- Confirmatory Post-Marketing Trials (Accelerated Approval)
• A perspective on the strength of an efficacy endpoint result in pivotal trials...
Oncology Efficacy Endpoints

• We are fortunate in that we can “see” our disease.

• Objective surrogate endpoints in oncology based on Radiographic Tumor Measurement
  – ORR: Objective Response Rate
  – TTP: Time to Progression
  – PFS: Progression Free Survival
Common Oncology Endpoints
Radiographic Endpoints and Survival

- Response Rate (ORR)
- Progression (TTP, PFS)
- Morbidity (SRE)
- Death (OS)

Tumor Size / Burden

Weeks  Months  Years

Time to reach these endpoints
Less Common Oncology Endpoints
Morbidity or Symptoms

Symptom Palliation (PRO)
Response Rate (ORR)
Time to Symptom Progression (PRO)
Progression (TTP, PFS)
Morbidity (SRE)
Death (OS)

Tumor Size / Burden

Weeks Months Years

Time to reach these endpoints
Infrequent Oncology Endpoints
Functional Measures

- Functional Improvement
- Symptom Palliation (PRO)
- Response Rate (ORR)
- Time to Deterioration of Function
- Time to Symptom Progression (PRO)
- Progression (TTP, PFS)
- Morbidity (SRE)
- Death (OS)

Tumor Size / Burden

Weeks
Months
Years

Time to reach these endpoints
Strength of Efficacy Endpoint Results:

• **What** is being Measured? *(Endpoint Selection)*
  – Measures of Direct Benefit (Feels/Functions/Survives) are preferred over a radiographic surrogate of tumor control and may be used for “Traditional Approval”

• **How** accurately is it being measured? *(Measurement Characteristics)*
  – How certain can we be regarding the result and magnitude?
  – Susceptibility to Bias
    • The more interpretation required for an event, the more susceptible it is to bias.
  – Accuracy of the Timing of the Event (When did the event Occur?)
    • Only as good as the frequency of assessments

• **How Much** effect on the endpoint is observed? *(Magnitude of Effect)*
  – Large effects seen in trial results can mitigate some of the uncertainty associated with an endpoint and how it is measured.
  – Even accurately measured endpoints like overall survival can still be of insufficient magnitude to be considered clinically meaningful benefit. (a 7 day survival benefit)
“What” you are measuring: Categories of Efficacy Endpoints

- **Direct Measure** of Clinical Benefit
  - Directly measures how a patient “feels, functions or survives”
    - Overall Survival
    - Measures of symptoms or function
      - Patient Reported Outcomes

- **Surrogate Endpoints** intend to PREDICT clinical benefit
  - Surrogate endpoints do not measure benefit in and of themselves
  - Surrogate endpoints in oncology are commonly radiographic findings
    - Tumor shrinkage (response rate by CT scan)
    - Time to Progression (time to tumor growth by CT scan)

Given a large enough magnitude, objective measurement of tumor control (PFS and even very high rates of durable Responses) could be considered acceptable for TRADITIONAL APPROVAL.
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Endpoint Interpretation:
How Much Investigator Interpretation is Required?

Unformed Figure, Jackson Pollock
American Gothic, Grant Wood
How is the endpoint measured:

• How much interpretation is required?
  – More interpretation = more risk for bias / variability

  **High**
  - EBRT in SRE composite: Investigator interpretation that pain is of sufficient magnitude and focal enough that patient needs EBRT… (significant interpretation required… more risk for bias)
  - rPFS (PCWG-2): Interpret two new lesions on a bone scan
  - PFS: Interpret target lesion increases by 20%

  **Low**
  - Survival: No interpretation required

• How accurate is the timing of the event?
  – Timing of the event affects magnitude of benefit in time to event analysis
  – For PFS, frequency of assessments important
Direct Measures of Efficacy: Overall Survival - Gold Standard

• Strengths:
  – Direct measure of benefit
  – Least prone to bias, no interpretation of the event (death yes or no)
  – Event timing (date of death) typically known to the day
  – Includes information regarding safety
    • Deaths due to drug toxicity are part of the endpoint

• Limitations
  – Last Event in a Disease’s Natural History = Longer and Larger Trial
  – Requires randomized controlled trial
    • Comparison with historical control limited (differing populations, differing standards of care, etc.)
  – May be confounded by cross-over (depending on magnitude of effect) and subsequent therapies if given unequally between arms

* Meaningful Clinical benefit of a survival advantage is still based on toxicity of drug and magnitude of OS result
Surrogates Endpoints: Radiographic Evidence of Anti-Tumor Effect

- **Response Rate (RR)**
  - Shrinking a tumor
  - *Critically important: tumor location, number of CRs, duration of response*

- **Time to Progression (TTP), Progression Free Survival (PFS)**
  - Time from Randomization to Growth of Tumor past predefined threshold
  - PFS counts death as a progression event and is preferred

- **Radiographic Endpoints Strengths**
  - Earlier events than survival = smaller, shorter trial
  - Radiographs can be captured and stored to verify the event
  - Not confounded by cross over or subsequent therapies (Event occurs prior to crossover)

- **Radiographic Endpoints Limitations**
  - Uncertainty regarding Clinical Benefit: Will a given change in an asymptomatic radiographic finding predict true clinical benefit?
  - Missing, incomplete, infrequent or uneven assessments
  - Difficult to measure disease (ill-defined lesions), Bone metastases, peritoneal carcinomatosis
Strength of Efficacy Endpoint Results:

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• Resurgence of Response Rate and PRO
FDA Historical Perspective: Oncology Efficacy Endpoints

- 1970s: A Setting of Limited Available Therapies
  - Tumor shrinkage (response rate) was accepted as a primary efficacy endpoint for regular approval

- 1980s: A change in this interpretation occurred:
  - 10-20% of patients with asymptomatic radiographic tumor shrinkage may not translate into an improvement in overall outcome (particularly given the toxicity of the agents being evaluated).

- Ideally, measurement, should reflect Direct Clinical Benefit
  - How one “Feels, Functions or Survives”
  - A move away from ORR for traditional approval and a focus on Overall Survival
And then this started to happen...

Complete hematologic response in 53 of 54 patients with IFN refractory chronic phase CML...

“Our results…demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in human cancer.”
Unprecedented Response Rates

- Enriched populations
- Strong basic science

ALK+ NSCLC: ORR 61%
EGFR-Mut+ NSCLC: ORR 61%
CD30+ Hodgkins: ORR 75%

Crizotinib: Phase 1
Camidge et al Lancet Oncol 2012

Afatinib: LUX-LUNG-2
Yang et al Lancet Oncol 2012

Brentuximab Vedotin: Phase 2
Younes et al JCO 2012
Looking Closer at ORR

- There are multiple variables in “Response Rate”
  - Location of Tumor
  - # of Complete Responses
  - Duration of Responses
  - What was initial tumor burden?
  - How many patients tumor reduced, but <30%?
    - Not currently captured in RECIST ORR
    - These patients may derive benefit if activity/stability of long duration depending on toxicity of the treatment
    - Value of the waterfall plot
A Tale of Two Responses

• Shrinkage of a likely asymptomatic pelvic lymph node may or may not predict an improvement in patient symptoms or survival...
Where are the tumors that are responding?
When “Response Rate” may be considered Direct Clinical Benefit…

• Near complete responses of disfiguring or fungating skin lesions are a different context:
• Traditional approval granted based on clinical response rate (and duration), the cosmetic improvement and the high likelihood of tumor related symptomatic relief

**Vismodegib Response.**
*Von Hoff et al., NEJM, 2009; 361: 1164-72*

**Depsipeptide Response.**
*Piekarz et al., JCO, 2009; 27: 5410-5417*
Clinical Equipoise:
- When there is general uncertainty in the expert medical community on whether a treatment is effective

- Important for ethical conduct of randomized trials AND can effect feasibility
- What is ORR improvement over existing therapies where equipoise is lost?

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Arm A N=151</th>
<th>Arm B N=156</th>
<th>Arm C N=152</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>2 (1%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0002 for Arm A vs. Arm C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.2-4.6%</td>
<td>4.6-14.2%</td>
<td></td>
</tr>
</tbody>
</table>

FDA Review: Oxaliplatin in Colorectal Cancer
- 9% ORR, all partial responses with added toxicity over the chemo backbone...

FDA Review: Crizotinib for Non-Small Cell Lung Cancer
- 50-61% ORR, median duration of over 10 months with deep responses and favorable toxicity when compared with chemotherapy doublet...
Strengths and Limitations of ORR

• **Strengths:**
  – **Allows for use of single arm trials**
    • Tumor shrinkage unlikely due to anything other than the therapy being studied…
  – Early event = faster trials, less patients
  – Objective and verifiable with archived scans

• **Weaknesses:**
  – Not a direct measure of clinical benefit
  – Much inferior to a randomized trial with respect to safety
  – If in an enriched population, historic control unclear
Very high durable ORR is a good problem to have!
But there are some Unique Regulatory Issues

• How do unprecedented high ORR fit into our current approval paradigm?

• At what point is a randomized trial with a control arm unnecessary?

• Regardless of approval pathway, trials using ORR will be smaller and there will still be important questions to answer in the post-marketing trial setting
  – Verification of the initial ORR magnitude and duration
  – Multiple dose study to optimize dose
  – Additional safety data
  – Dedicated PRO study in symptomatic patients?
• Switching gears:

• In addition to looking at ORR in new ways, patient reported outcomes (PRO) has received a lot more attention.
Increasing Focus on PRO

• FDASIA – Patient-Focused Drug Development
• In 2014 PRO front and center at meetings:
  – AAADV Plenary Session on PRO in Oncology
  – Two Brooking’s Meetings on PRO
    • High level Office of New Drugs Leadership across Therapeutic areas
  – AACR Turning the Tide Against Cancer
Challenges for PRO unique to Oncology

- Asymptomatic / minimally symptomatic populations
- Open Label Trials
- Single Arm Trials
- Missing Data

- Most Pivotal Trials have included large HrQOL instruments
  - FACT, QLQ-C30, EQ-5D
  - Can this data help us understand the impact of the above limitations?
  - How can we most effectively capture the patient perspective?
  - Is this sort of data suitable for labeling? How would we best label it?
  - What are the marketing implications in the U.S.?
What questions can PRO answer?

• **Efficacy:** Does the drug improve disease related symptoms or functional deficits?
  – Pain, Total Symptom Score, Performance related outcomes
  – More conducive to formal statistical analysis and claims of treatment benefit

• **Tolerance:** How do patients feel while on therapy?
  – Tolerance/ Symptoms / “Quality of Life”
  – Like AE data, more descriptive in nature
  – Much harder to quantify and statistically test
    • What is the numerical difference that a patient can discriminate?
PRO as an Efficacy Endpoint

• Strengths:
  – Like OS, can be a **direct measure of clinical benefit if it accurately measures how a patient feels or functions**

• Limitations
  – What you are measuring is strong, but **how you are measuring it is the challenge.**
    • Validation of PRO instrument is required and can be challenging
    • Missing data and unblinding can make interpretation difficult

• PRO data has lead to U.S. approval, however
  – Early consultation with the FDA Study Endpoints and Labeling Development team (SEALD) is recommended.
  – Careful attention to the FDA PRO Guidance is critical.

PRO- Patient Reported Outcomes: Successful Contemporary Example

- **Ruxolitinib (Jakafi™) for myelofibrosis**
  - Primary endpoint: Radiographic Surrogate Endpoint
    - Reduction in spleen size by (MRI) (Splenic Response Rate)
  - Key secondary endpoint: PRO **Total Symptom Score**
    - Abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety

- **Is shrinking a patient’s spleen clinical benefit?** The total symptom score was very helpful in correlating the anti-tumor effect with improvements in how patients were feeling (symptoms) and Jakafi™ was granted traditional approval.
Ruxolitinib (Jakafi) Labelling

Table 8: Improvement in Total Symptom Score

<table>
<thead>
<tr>
<th></th>
<th>Jakafi (N=148)</th>
<th>Placebo (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24</td>
<td>68 (45.9)</td>
<td>8 (5.3)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Worsening of Total Symptom Score is truncated at 150%.
Narrow instruments may allow more informative labelling of the results.

This table helps prescribers understand if there was any one item driving the total score results.
Advancing PRO in Oncology

• With respect to PRO, we have received criticism that includes:
  – Inconsistent Advice
  – Less PRO in labels than Europe
  – Inflexible adherence to the 2009 PRO Guidance (“Perfect is the enemy of the Good..”)

• FDA is Addressing these Issues:
  – Implemented Oncology PRO lead reviewers in each division
  – Monthly meetings between Oncology Office and Study Endpoints and Labeling Division (SEALD)
  – Initiated multiple projects analyzing in-house PRO data
  – Active participation with multiple PRO stakeholders
Changing Landscape for Oncology Drug Development

• In vitro diagnostics identifying enriched subpopulations driven by strong genetic / biologic rationale
  • Much larger Magnitude of effect on endpoints like response rate

• Immunotherapies
  • Patients with prolonged response

• Many more available therapies
  • We will likely be seeing more head-to-head trials

• Beyond incremental benefits…combination regimens to overcome resistance and really?
  • Immunotherapy + targeted + chemotherapy?
  • Multiple pathway inhibition
  • Academic community / cooperative groups must lead this effort
In Conclusion:

• Goal of drug development is to provide substantial evidence that a product provides meaningful clinical benefit to patients

• Strength of an efficacy endpoint result: What, How and How Much
  – Endpoint selection, Measurement characteristics and Magnitude…

• Unprecedented magnitude can overcome some of the limitations of the surrogate endpoints like ORR and PFS

• Clinical Development Team: Does the disease being studied result in symptoms or functional limitations?
  – PRO can make the difference between accelerated and traditional approval
  – Early consultation with FDA for PRO is advised!

  – For information on how a drug was approved, review the FDA label and the clinical reviews at Drugs@FDA.