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## PANEL THREE: THE BLURRING OF PHASE 1,2, & 3 TRIALS IN ONCOLOGY

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# Regulatory Perspective on Seamless Drug Development

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# Disclosures

- No conflicts of interest to disclose.
- This presentation contains statements that are my own views and may not represent the official position of the Office of Hematology & Oncology Products.



# Then and Now

- Oncology drug development has historically passed through 3 discrete steps:
  - Phase 1: MTD, DLTs, preliminary efficacy
  - Phase 2: Efficacy assessment for “go/no-go”
  - Phase 3: RCTs designed to provide adequate efficacy/safety data support drug approval
- Distinct phases have become blurred both in theory and in practice.



# What Has Driven the Change?

- Scientific advances resulting in more effective drugs or “right drug/right patient”
- Focus on pathways more than tissue of origin
- Desire for greater efficiency in drug development
  - Avoid delays inherent in discrete phase development
  - Industry, clinician, and patient factors



# OHOP Experience

- More than 3 dozen commercial INDs with active first-in-human/phase 1 trials enrolling > 100 pts
  - Many have hundreds to >1200 patients
  - Up to 14 expansion cohorts
  - Expansion cohorts from 10-180 patients/cohorts
  - Sample size often not pre-specified or justified
  - More than a third are anti-PD-1/PD-L1 agents



# OHOP Experience

- Stated objectives/endpoints/eligibility criteria/informed consent consistent with usual phase 1 trials, but sample size/nature of data collected/actual goals are not!
- Nature of expansion cohorts in these trials
  - Dose/schedule refinement
  - Variety of of tumor types
  - Variety of molecularly-defined subsets
  - Other drug combinations





# Questions We Consider

- Are patient protections adequate?
  - Eligibility criteria
  - Informed consent
- Is there rationale for tumor types being included?
- Does trial have clear goals and an adequate design/SAP?
- Do questions being asked justify size of the trial?
- Is there a defined end (futility & efficacy) to trial?



# Regulatory Discussion Points

- Entire drug development program may occur within a single first-in-human protocol
  - Implications for meetings between FDA & companies
  - Oversight by relevant disease experts/division within OHOP
  - Size and quality of safety database
  - Adequacy of data to support global regulatory approvals
- Should these types of protocols be reserved for drugs with breakthrough therapy designation?
- What level of independent oversight is needed?



# Breakthrough Therapy Designation

- FOCR/Brookings Annual Meeting November 2011
  - FDA Safety & Innovation Act (FDASIA) passed July 2012
  - 1<sup>st</sup> breakthrough designation granted Jan 2013
- Breakthrough Therapy Designation essential points:
  - Granted for drugs intended to treat a serious condition where preliminary clinical evidence indicates substantial improvement on clinically significant endpoint over available therapy
  - Offers all-hands-on-deck approach with all disciplines of FDA including multiple informal/formal meetings
  - Provides a proactive approach to challenge of manufacturing readiness with a compressed development timeline



# Breakthrough Therapy Designation

- CDER experience
  - Approximately 100 BTM requests to CDER per year
  - Approximately 1/3 of requests granted
  - Approximately 1/2 of current BTMs are for oncology indications
- OHOP experience
  - 43 BTM requests granted
  - 15 approvals of new or supplemental indications for BTM drugs
  - No BTMs rescinded



# Need for Independent Oversight

- Independent oversight needed for trials of sufficient size/score to support regulatory approval
  - Ensure standard patient protections
  - Provide scheduled “pauses” to review and respond to the data observed thus far in development program
  - Improve transparency/reduce bias in decision-making
  - Ensure appropriate statistical rigor



# Conclusions

- FDA shares the sense of urgency to make effective new therapies widely available to oncology patients.
- New nomenclature & processes are needed.
- We have obligations to current & future cancer patients:
  - Provide adequate protections for trial participants
  - Characterize efficacy/safety of new anti-cancer agents to ensure
    - Amount/quality of data collected are sufficient to support a regulatory or payer decision
    - Clinicians can appropriately counsel patients
    - Patients can make an informed choice whether to take a drug



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# **Case Study - Pembrolizumab**

## **Keynote 001**

Eric H. Rubin, MD

Merck Research Laboratories

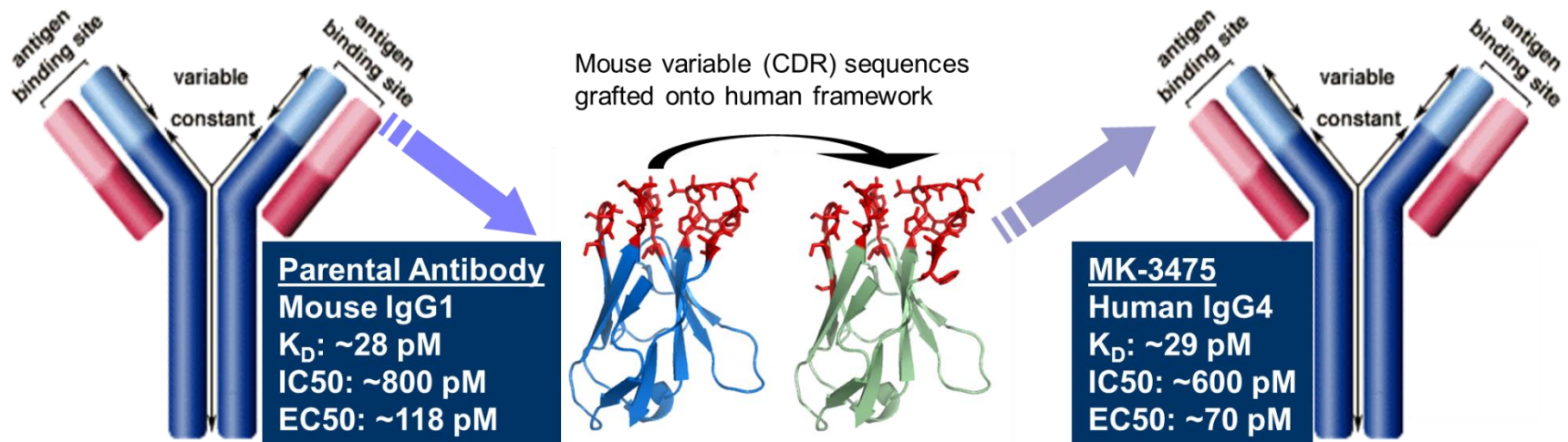
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# Pembrolizumab (MK-3475) product characteristics

- Potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype



- Blocks interaction between programmed death (PD) -1 and its ligands, PD-L1 and PD-L2 => enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection

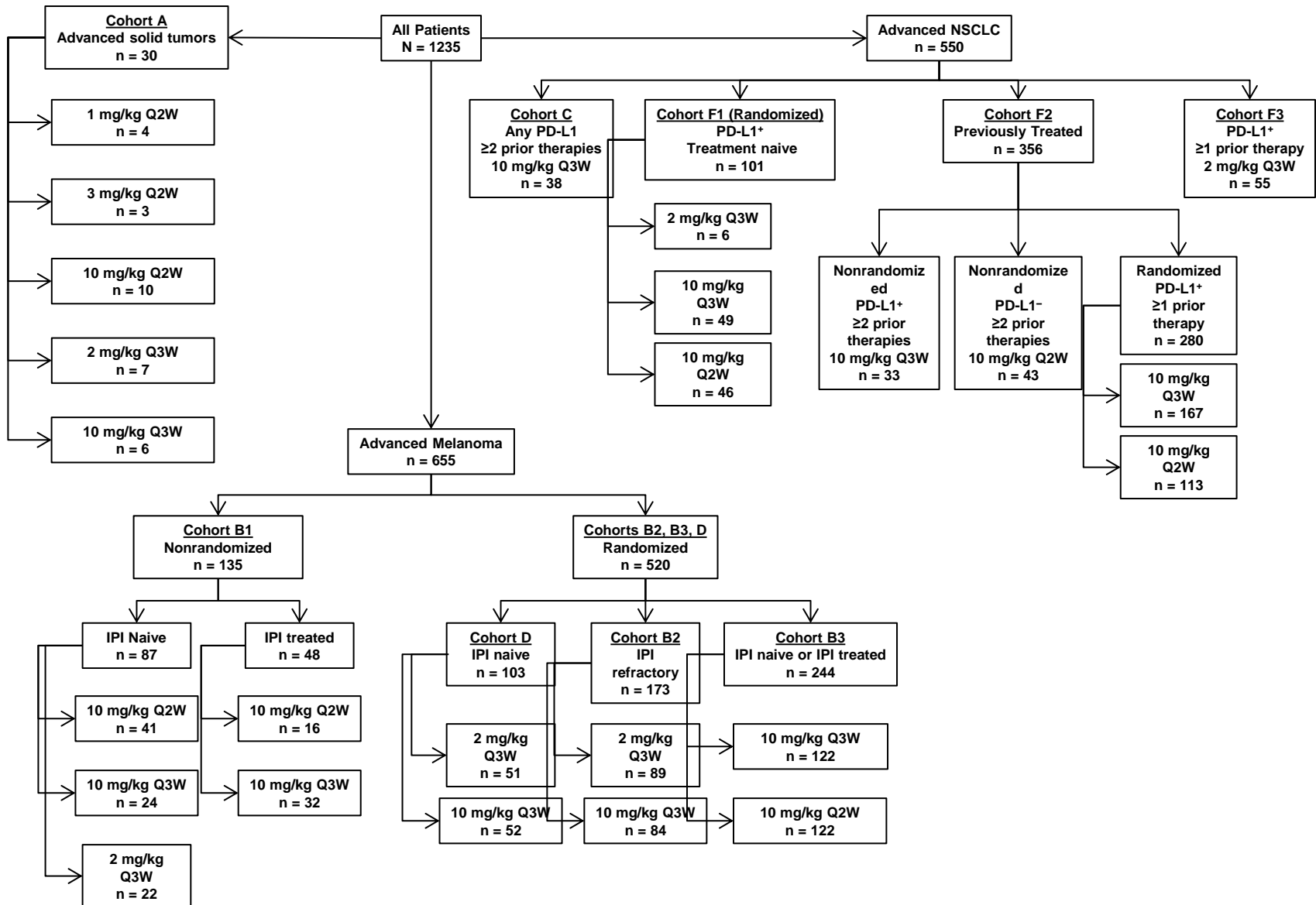
# Initiation of MK-3475 Clinical Program

- Preclinical data suggested that MK-3475 would have anti-tumor activity in multiple cancers
- US IND was opened on Jan 7, 2011
  - *A Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas and Melanoma (Protocol 001)*
    - Initial intent was to define DLT, characterize PK, and establish proof of concept
    - 3+3 dose escalation with expansion cohort in melanoma, estimated sample size 32

# History of Pembrolizumab P001 Study

- Striking responses observed in initial melanoma patients enrolled in dose escalation cohort
  - Led to increase in expansion cohort sample size to 60, including ipi-naïve and ipi-treated patients
  - 97% power to exclude null hypothesis of 10% ORR and 30% DCR in ipi-naïve patients, with alternative hypothesis of 30% ORR or 55% DCR (Hochberg), one-sided  $p=0.05$
  - Included interim futility analysis after evaluation of 11 ipi-naïve patients
- Added 35 patient cohort of previously treated NSCLC patients based on suggestion of potential for efficacy in this population
  - 80% power to exclude null hypothesis of 9% ORR with alternative hypothesis of 22%, one-sided  $p=0.10$
- Given preliminary evidence of activity in ipi-treated patients, **applied for BT designation** and added 40 patient ipi-refractory cohort to evaluate efficacy in a strictly defined population with high unmet need
  - 98% power to exclude null hypothesis of 5% ORR, with alternative hypothesis of 25%, one-sided  $p=0.05$
- Randomized cohorts in melanoma ( $n=520$ ) and NSCLC ( $n=381$ ) added to investigate dose (2 mg/kg vs 10 mg/kg Q3W and 10 mg/kg Q3W vs 10 mg/kg Q2W) and to provide training and validation sets for PD-L1 expression test in NSCLC patients
  - All with pre-specified statistical hypotheses
- Ultimately 1235 patients treated, with enrollment completed in July 2014

# P001 Treatment Cohorts



# Benefits of Large Cohorts Approach

- Efficiently address multiple hypotheses with appropriate type 1 error control
  - Population, dose, and biomarker development
- Aligned with single-arm trial design as one of the accepted approaches to seeking accelerated approval
- Can be performed with sufficient rigor to support regulatory filings (e.g. central independent review of efficacy)
- Accelerates development and approval for drugs that are transformative in nature based on early and strong efficacy signals
  - Avoids multiple trials replicating the initial findings
  - Makes transformative therapies available to patients at earliest opportunity, particularly where effective therapies do not exist

# Challenges of Large Cohorts Approach

- Operational burden on sites and sponsor due to rapid accrual in multiple separate cohorts
- Multiple amendments generate protocol complexity and potential adherence issues
- Complexity of analysis and interpretation of data supporting multiple hypotheses tested simultaneously rather than sequentially
  - E.g. dose hypotheses evaluated in NSCLC simultaneously with melanoma, rather than waiting for melanoma data
  - Must ensure statistical rigor
- Multiple database locks during an ongoing study
  - Programming challenges to “isolate” one cohort for submission purposes

# Key to Success and Lessons Learned

- Strong science and frequent Interactions with FDA
  - Established good lines of communication
    - Helped to resolve any issues quickly
  - Requested all available PDUFA meetings (Application orientation, Mid-cycle, Late-cycle) to ensure alignment on content, and address any problems with datasets or other issues impeding review
    - Merck had formal CMC-focused meetings with the FDA routinely, every 2-3 months: 5 in total with informal teleconferences
- Commitment from both FDA and Sponsor to deliver the product to patients as quickly as possible

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STATISTICAL CONSIDERATIONS FOR LARGE EXPANSION  
COHORTS

ELIZABETH GARRETT-MAYER, PhD  
MEDICAL UNIVERSITY OF SOUTH CAROLINA



# Disclosure Information

- I have no financial conflicts to disclose
- I will not discuss off label use and/or investigational use in my presentation



# Statistical Issues: Validity

- “What makes clinical research ethical” (Emanuel et al., JAMA, 2000)
- The second (of seven) principles:
  - “**Scientific validity**-- the research must be methodologically rigorous”
  - For a clinical research protocol to be ethical, the methods must be valid and practically feasible
  - The research must:
    - have a clear scientific objective;
    - be designed using accepted principles, methods, and reliable practices
    - Have sufficient power to definitively test the objective
    - Offer a plausible data analysis plan
- Standards have consistently insisted on ***valid study designs***



# Old paradigm:

## Classic Phase Ia, Ib or I/II

- Objectives are consistent with design
- Outcome variables are defined; the primary outcome is identified
- Power/sample size calculations are included to justify design and ability to reach meaningful conclusions.
  - Dose finding has historically had loose expectation for sample size. Approximately 3-6 times the number of doses was common.
  - Expansion cohorts of 20+ are “phase II” sized and warrant justification via a clearly stated objective, analysis plan, and sample size justification.
- A predefined analysis plan is described in detail.
- ***“Adaptive” designs provide detailed explanations of how/when adaptations occur and operating characteristics are stated.***



# New paradigm

- Primary objective addresses dose finding with a small number of patients.
- Open-ended secondary objectives address large (100-1000 patient) expansions
  - Endpoints often not defined
  - “Adaptive” designs with no clear idea of how decisions will be made.
- Overall, a lack of details.
- *Can we approve studies when we cannot assess the scientific validity?*
- *How can we be assured patients are protected?*



# We are seeing these problems at different points in the development process

1. A small study morphs into a large study.
  - Breakthrough designation?
  - Cohorts are added without appropriate updates to the objectives, design, analysis and sample size justification sections. And, the informed consent (as the objective may have changed)
2. New phase I trials are mimicking the “final” designs from the pembrolizumab and nivolumab studies.
  - Protocol version 1 proposes hundreds of patients with most of them in expansion cohorts.
  - Very open-ended
  - Lacking important design, sample size and monitoring considerations from the very beginning.



## Example: Novel immune checkpoint inhibitor study

- “Phase I study”
- Dose finding: 3+3 design with 20-30 patients
- Expansion cohorts:
  - Up to 8 disease subtypes (6 subtypes not yet defined)
  - 20 patients per cohort
  - Based on emerging data, expansion cohorts may enroll up to 60 patients
  - 8 x 60: as many as 480 patients in expansions
- Monitoring:
  - *Reporting* of adverse events is described
  - No *monitoring* of adverse of events is mentioned
- Interim analyses:
  - “No interim analysis is planned.”



## Example: Novel immune checkpoint inhibitor study

- Questions for sponsor and responses:
  - Who decides? Based on what information?
    - “The Sponsor will make internal assessment based on observed efficacy results from the initial 20 subjects as well as efficacy results of [standard of care] at the time for each individual tumor type to make the decision whether to expand to 60 subjects. **Since it's not based on one single efficacy endpoint and we need the flexibility to look at totality of efficacy data, we choose not to formally put decision criteria in the protocol.**”
  - Safety monitoring?
    - No response from company regarding monitoring





# Statistical Issues

- Lack of clarity of designs
    - No justification for sample sizes
    - Endpoints are poorly or simply not defined
  - Lack of monitoring and oversight
    - No or weak monitoring plans
    - No early stopping rules for toxicity issues in expansions
    - No peer review for endorsement of cohorts to enroll or expansion size
- ⇒ Decisions for modifications or adaptations are left entirely to the sponsor.
- ⇒ Obvious conflict and lack of ‘independent’ oversight and pre-defined criteria for decision-making
- ⇒ **These raise ethical issues regarding the safety of patients and whether or not these trials yield “good science.”**





# New “paradigm”?

- Cannot have a separate set of rules for novel agents of a particular class.
  - How can we require other trials to adhere to the same scientific standards if we do not require rigorous protocols for these trials?
- Not all agents will have the same successes as the “breakthrough” approvals of nivolumab and pembrolizumab
- Studies cannot be designed to presume success: studies need to be designed to protect patients from failures.



## How to keep the statisticians happy as the paradigm evolves?

1. Objectives should comprehensively cover the true intention(s) of the study
2. The design should reflect the primary objectives.
3. *At least* one of the following:
  - Statistically based justification for design;
    - Clearly defined endpoints
    - Futility stopping rules
    - Justification of sample size including interim looks
  - Independent monitoring
    - Safety monitoring
    - Decision-making panel for approval of opening, continuation and closure of expansions



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AMAN BUZDAR, MD  
M.D. ANDERSON CANCER CENTER

Simple futility rule in phase II: stop if no responses in 14 patients.


This rule is from Gehan (1961, J Chron Dis). It is based on ruling out a 20% response rate.

In phase I setting, a more reasonable threshold response rate would be 10%.

Stopping if we see no responses in 29 patients, can rule out a 10% response rate.

Note: the higher the response rate threshold, the fewer consecutive patients without response are needed to rule out the response rate.

Thus, if we redefine success to include stable disease as is common in phase I, then the threshold probability will be increased and thus fewer patients are needed to assess futility using Gehan's approach. Only 9 patients are needed to rule out a 30% success rate.




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2015-0732  
October 2, 2015  
Abstract - Page 19

 In Phase 1b, approximately 30 patients will be enrolled per cohort. Enrollment will be open for all cohorts in parallel and will continue until the enrollment target is reached. Once a cohort is filled, further enrollment will be restricted to the cohort(s) that have not been filled. A total of approximately 240 patients will be enrolled in the Phase 1b arm of the study.

- Cohort 1b1: NSCLC (Second/third line, anti-PD-1 pathway targeting drug-naive)
- Cohort 1b2: NSCLC (De novo or acquired resistance to anti-PD-1 targeting drug)
- Cohort 1b3: Melanoma (Previously untreated)
- Cohort 1b4: Melanoma (De novo or acquire resistance to anti-PD-1 targeting drug)
- Cohort 1b5: SCCHN (Second line)
- Cohort 1b6: Pancreatic Cancer (Second line)
- Cohort 1b7: Colorectal Cancer (Third line)
- Cohort 1b8: GBM (Second line)

**Objective** response rate is the primary efficacy variable for the Phase 1b portion of the study. With approximately 30 patients in each disease type, the 95% confidence interval half-width for the corresponding response rate would be within 18%.

**Study Design**

MDACC will only participate in Phase 1b (dose expansion) of the study. To further characterize safety and efficacy of FPA008 in combination with nivolumab, Phase 1b will enroll up to 8 expansion cohorts in 6 advanced cancer types. Enrollment in Phase 1b will begin when an RD has been identified by the Cohort Review Committee based on overall safety, tolerability, PK, and PD (if available) data.

During enrollment of any expansion cohort, if the observed number of responses makes it unlikely to achieve a target response rate for that indication, then further recruitment to that cohort may be suspended or terminated.

All patients should return to the clinic 28 ( $\pm 7$ ) days and 100 ( $\pm 7$ ) days from their last dose of study drug to complete the End-of-Treatment Follow-up Period, irrespective of whether a

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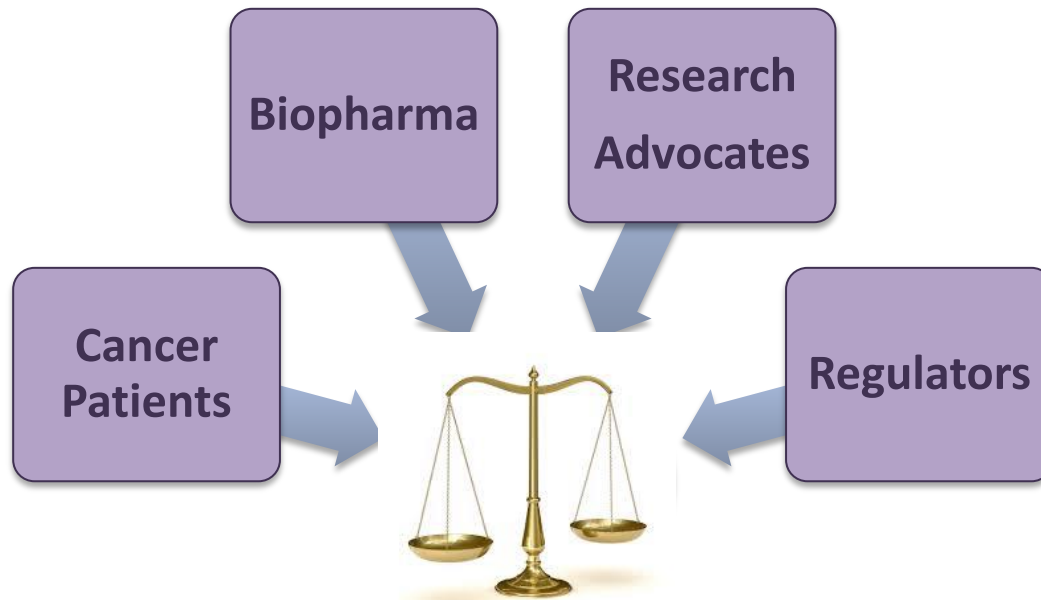
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JANE PERLMUTTER, PHD, MBA  
A PATIENT/ADVOCATE PERSPECTIVE

- Time is money
- Being first to market is huge
- Often have lots of pressure from funders

- Often “lucky” patients/survivors
- Empathize with current patients
- Understand the need for safety of future patients



- Ultimately responsible to congress and all Americans
- Tough balancing act
- Want to do the right thing
- Tend to be conservative

- Patients don't have the luxury of patience
- They need something now
- Often willing to take large risks for potential benefits

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- Review protocol prior to enrolling patients, as well as protocol amendments
- Typically responsible for many diverse trials
- Ensures research is conducted in accordance with all federal, institutional, and ethical guidelines



- Review trial data as it accumulates
- Typically responsible a single trial
- Monitor patient safety and treatment efficacy data
- Recommend early stopping due to safety concerns, futility or overwhelming benefit of investigational treatment

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# Other Things to Think About

- Continuous phase 1/2/3 trials
- Adaptive, SMART and OE-RCT designs
- Alternative designs for dose finding, especially for combination therapies
- Trials/approval/reimbursement based on biomarkers rather than organ of origin
- Increased use of “provisional” approval based on early end-points
- More effective post-marketing monitoring
- Use of single IRBs for multi-site trials



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