

Evaluating Evidence of Clinical Benefit

Steven Hirschfeld, MD PhD
Eunice Kennedy Shriver National
Institute of Child Health and
Human Development
Bethesda, MD



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General Principles

- Data is obtained and assessed without bias
- Assessment techniques are qualified and validated
- Outcomes are interpretable in context
- Outcomes are consistent with regard to effect, magnitude, duration and population
- Development program continues to refine results for outcomes of interest and minimize uncertainty

Overlapping Outcome Variables

Development Plan Sequence



	Study 1	Study 2	Study 3	Study 4
Study	1	2	3	4
Outcomes				
				
				
				
 CI				

General Principles

- For therapeutic interventions, the risks must be commensurate with the benefit
- Evaluation is based on the totality of evidence seeking consistency and persuasiveness
 - Not dependent upon a single study and a single test on a single outcome

Immunotherapy & Metabolic Therapy Comparison

Immunotherapy

- Manufacturing is completed *in vivo* with multiple downstream processes
- Dosing precision challenging to monitor
- Generally multiple cellular targets
- Time clock dependent upon cell signaling, replication and differentiation = weeks to months

Metabolic Therapy

- Manufacturing essentially complete *ex vivo* with perhaps enzymatic modification to achieve activity
- Dosing precision generally monitored by pharmacokinetics
- Generally one molecular target
- Time clock dependent upon metabolic rate = minutes to days

Empirical observations

- Immunotherapies require weeks to months to manifest effect
 - Examples include time to achieve protective immunity for prophylactic vaccines
 - delayed clinical and biological response for therapeutic vaccines
- Outcome measures and criteria that are informative for short term activity as conventionally used for metabolic inhibitors may not apply for immunotherapies

Indices of effect

- Reference, but not formal statistical comparison, to robust historic data
 - Robust historic data is based on oversampling, outcome of clinical interest, formal meta analysis, and relatively narrow confidence intervals around predictable effect
- Exposure responsiveness
 - Biological and clinical effects reflect a correlation with the extent of exposure

Development Plan for Ipilimumab

- Robust historic analysis
 - Clinical informative outcomes of median and one year overall survival
 - Favorable comparison
 - Lacking formal assessment of patient performance status or other index of condition
- Dose responsiveness
 - Documented across physiologic and clinical outcomes

Redefining Paradigms

- Systematic effort to adapt and develop outcome measures that are informative for biological effect and clinical benefit
- Response outcomes may be best used for development plan decision making
- Response outcomes are not robust for predicting clinical outcome
- Association between response and clinical benefit such as progression free survival or overall survival may not reflect causal pathway

Outcome Proposal

- Formal study assessments are not scored until a sufficient time (perhaps several months) for immunotherapies
- Patient monitoring is based on standard of care with major criteria associated with deterioration of clinical condition as a trigger for intervention
- Serial assessment of informative disease specific criteria for patient status
- Imaging and biochemical assessments should not be used during the first 4 months for individual patient decision making if the clinical condition is not deteriorating, particularly in context of no available life prolonging therapy
- Focus on overall survival and patient performance status

Context Proposal

- If diseases can be grouped based on median overall survival, then those with the shortest duration (advanced pancreatic cancer, recurrent or refractory metastatic ovarian cancer, etc.) may not be good candidates for immunotherapies
- Focus on diseases with intermediate (1.5 to 3 year) overall survival
- Investigate in setting of combination with antimetabolic therapy