U.S. FOOD & DRUG ADMINISTRATION

Statistical Considerations in Designing Clinical Trials Evaluating IO Products

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Regulatory Considerations

- "…Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling…" (Section 505(d) FD&C Act of 1962 as amended)
- Single study – consistency among different endpoints

Traditional Endpoints

- Objective Response Rate based on RECIST criteria
- Progression-Free Survival – Time from randomization to disease progression (based on RECIST criteria) or death whichever occurs first
- Overall survival – Time from randomization to death
- Patient reported outcome (PRO) – improvement or time to deterioration

Effect of Immuno-oncology Product

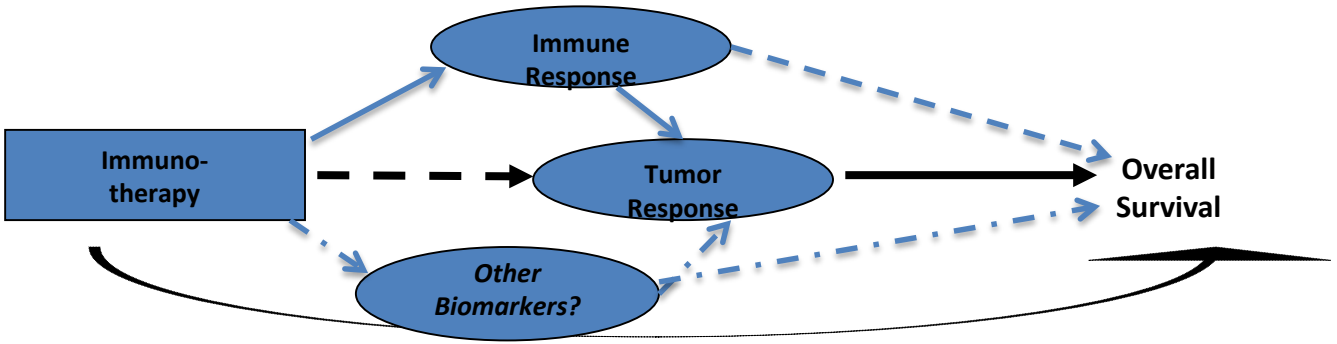
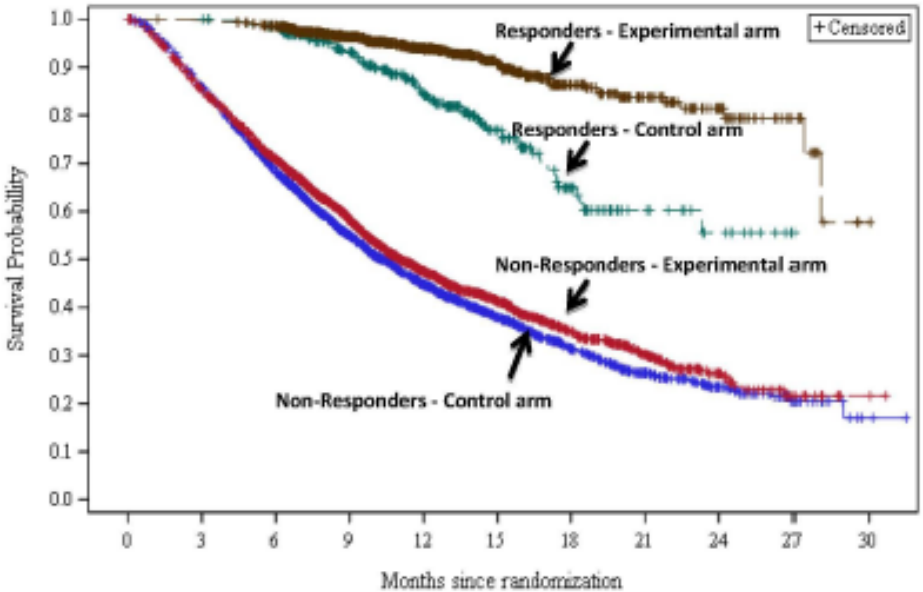


Figure 1: Patient-level Responder analysis results for OS and PFS

(A) OS



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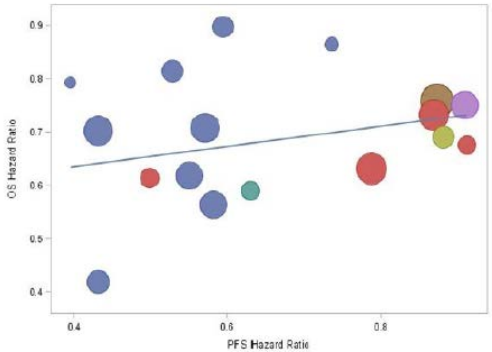
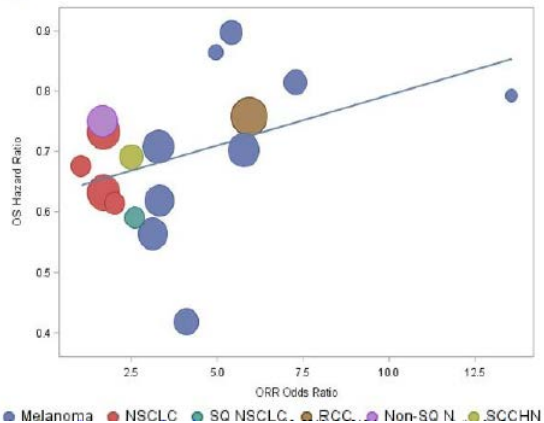
(A) OS vs. PFS (using 20% per RECIST criteria)



$R^2 \approx 0.13$

(B) OS vs. ORR



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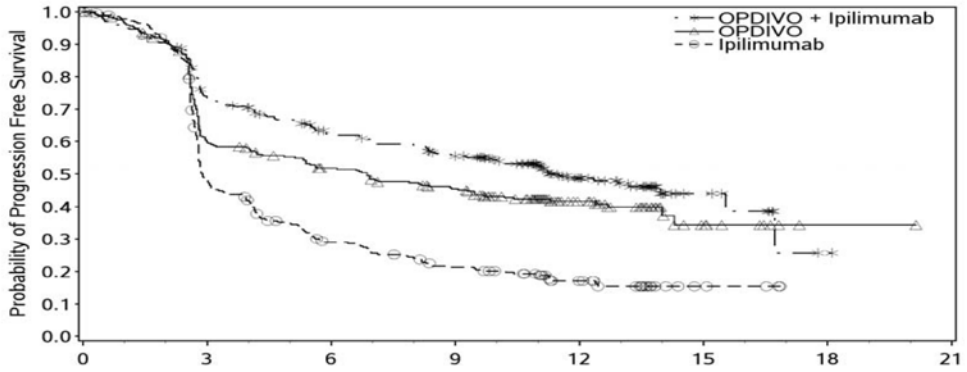
Examples of Non-proportionality: Nivolumab, CA209067 Trial - PFS



Number of Subjects at Risk							
OPDIVO + Ipilimumab							
314	219	173	151	65	11	1	0
OPDIVO							
316	177	147	124	50	9	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

Combination Strategies – Key Questions

- Which IO?: Cytokines, Checkpoint inhibitors, Cell-based therapies, Vaccines, or Others
  - Most of our recent experience is in checkpoint inhibitors
- Sequential or simultaneous administration?
- What added treatment effect is considered clinically meaningful? How much of added toxicity is acceptable?

Combination Strategies – Key Questions

Which Combination?:

- New IO + Chemotherapy, New IO + Targeted therapy, New IO + Chemotherapy + Targeted therapy, New IO + Approved IO, New IO + New IO
- The selection endpoint and length of follow-up depends on the combination to be evaluated

Combination Strategies – Key Questions

Which Population?: All Comers, Histology specific, site specific, or Enriched population – Biomarker directed therapy (example: MSI-H)

- Biomarker considerations
  - Threshold
  - Impact of miss-specification
  - Standardized measurement using validated assay

Combination Strategies – Key Questions

Which Endpoint?:

- Objective Response Rate based on RECIST criteria or modified or another criteria
- Progression-Free Survival – based on RECIST criteria or another criteria
- Overall survival
- Patient reported outcome or clinical outcome assessment
- Other endpoints such as circulating tumor cells and biomarker based endpoints

Traditional Paradigm of Drug Development

- Phase I Dose-finding study
- Phase II Activity finding study
- Phase III Treatment effect (benefit and risk) assessing study

This paradigm of drug development may not be efficient or optimal in some cases.

Phase I Study

- Should we use MTD based on DLT?
  - Both algorithmic (eg: 3+3) and model-based designs (eg: CRM) are based on reaching DLT
  - Depends – if IO is combined with chemo or it is IO + IO
  - How should DLT or some other threshold be defined?
  - Toxicity – additive, synergistic or independent?; can we use animal models?
  - How to evaluate long-term toxicity – toxicity beyond 1st cycle?
  - Optimal length of follow-up?
- Hold dose of one product and increase the other or simultaneously change, or use factorial design

Phase II Study

- Single arm study
  - Phase I study only with the new IO
  - Phase II single arm study with combination therapy
  - Or Factorial Design
- Randomized study (monotherapy compared to combination)
  - Three arm study, eg., IO_1 vs. IO_2 vs. IO_1 + IO_2
  - This can help decide if 3 arm study is needed in Phase 3 study
- Length of follow-up – sufficient to capture adequate duration of response

Phase III Study

- Randomized controlled study
- Isolation of effect for each component
  - Depends on the accumulated data
  - Novel –novel combinations
  - Selection of control treatment
- Enrichment Design (enriched population)
  - Adaptive enrichment design
- Master protocols/umbrella trials/platform trials
  - Unique opportunity to study multiple treatments efficiently

Enrichment Strategy

- PD-L1 expression 1%, 5% , 10% or 50%?
- No standard assay or threshold
- Other biomarkers? TMB?
- Unanswered: *Is there a subgroup of patients who benefit more than others, contribute to the plateau at the end of the survival curve*

Things to Consider

- What should be the primary endpoint?
  - OS directly measures clinical benefit. But may not be feasible – example in first-line treatment.
  - PFS and ORR – RECIST criteria or modified criteria. Control treatment or combination may include non-IO therapy
  - Any other intermediate endpoint that can reliably measured that has clinical relevance
- Length of follow-up
  - Toxicities different from chemotherapy
  - Beyond treatment follow-up
- Analyses methods
  - Delayed separation of survival curves (Non-proportional hazards)
  - Planned subgroup analyses

Summary

- Selection of combinations based on pre-clinical and early clinical data
- Efficient trial design in each Phase of development that can answer the main research question or objective
- Selection of outcome measurements that will provide information to test the research hypothesis specific to each Phase of development
- Analyses methods that fits the data