Statistical Impact of Incomplete Patient Follow-Up

Oishi Symposium

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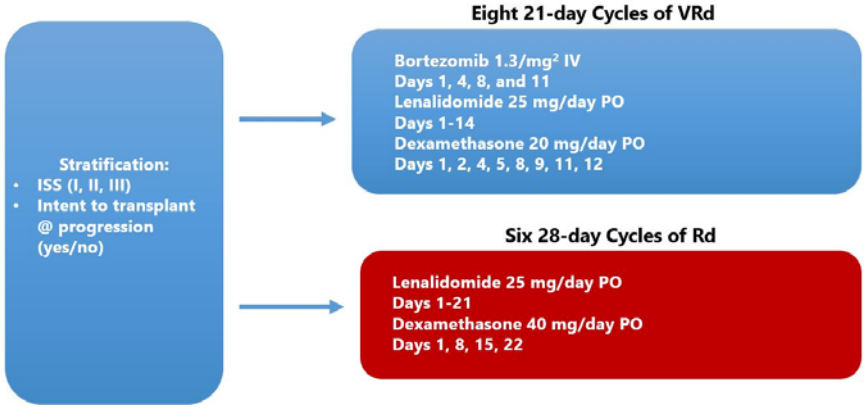
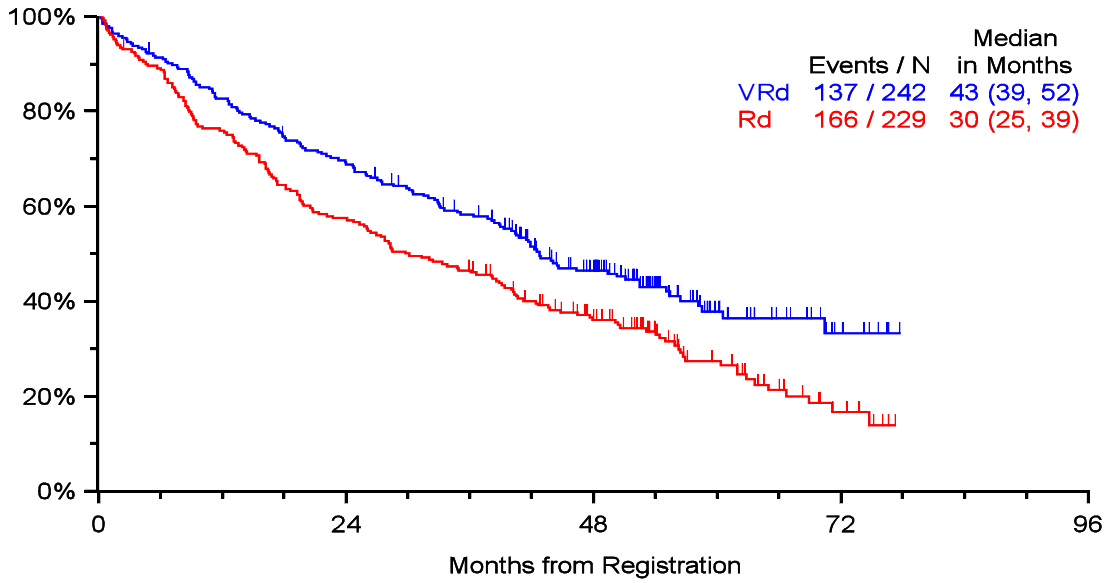
Outline

- Result: S0777 - Impact of high quality data and follow-up
- Statistical designs assume no (or minimal) missing data
- Important case of loss to follow-up, unequal consent withdrawal
- Assessing differences between arms
- Study impact of loss to follow-up in real hypothetical scenarios
- Conclusions

SWOG Myeloma Study S0777 Presented in Oishi Symposium Fall 2017. Key role of the CRAs in achieving high quality follow-up data and results





HR = 0.712 (0.560, 0.906)*

Stratified Log-rank P value = 0.0018 (one sided)

Strong Result Because of Best Science and Data

Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial

Brian G M Durie, Antje Hoering, Muneer H Abidi, S Vincent Rajkumar, Joshua Epstein, Stephen P Kahanic, Mohan Thakuri, Christopher M Reynolds, Rachael Sexton, Robert Z Orlowski, Bart Barlogie, Angela Dispenzieri

Summary

Background Lenalidomide plus dexamethasone is a reference treatment for patients with newly d
The combination of the proteasome inhibitor bortezomib with lenalidomide and dexamet
significant efficacy in the setting of newly diagnosed myeloma. We aimed to study wheth
bortezomib to lenalidomide and dexamethasone would improve progression-free survival
response rates in patients with previously untreated multiple myeloma who were not plan
autologous stem-cell transplant.

Methods In this randomised, open-label, phase 3 trial, we recruited patients with newly diagnosed
aged 18 years and older from participating Southwest Oncology Group (SWOG) and National Cli

And regulatory impact

NEWS RELEASE

Celgene Receives CHMP Positive Opinions for Both REVLIMID® (lenalidomide) and IMNOVID® (pomalidomide)-Based Triplet Combination Regimens for Patients with Multiple Myeloma

3/29/2019

The CHMP adopted two positive opinions recommending European Commission approval of:

Statistical Design of S0777

- The sample size was based on the assumption of an eligible patient accrual rate of 110 patients per year (440 eligible patients over 4 years), a median progression-free(PFS) survival of about 3 years in the control group, exponential distribution of progression-free survival, and roughly 2.5 years of additional follow-up

- The study was designed to detect a hazard ratio of 1.5, with approximately 87% power and an overall study alpha of 0.05

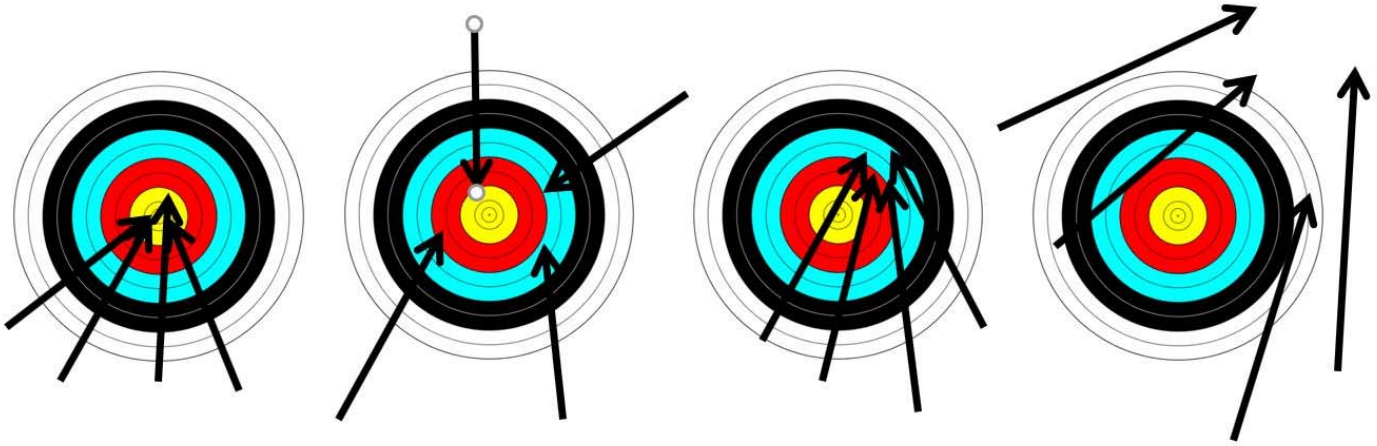
- Conclusions depend on complete patient follow-up (on both arms)

Critical Elements in Evaluating Therapeutic Interventions

- Biological Activity
- Safety/Toxicity
- Clinical Efficacy
  - Clinical Response
  - Patient Reported Outcomes
  - Disease recurrence or progression
  - Survival
- Other long-term data
  - Long term adverse events and related malignancies

Variability and Bias in Survival Data

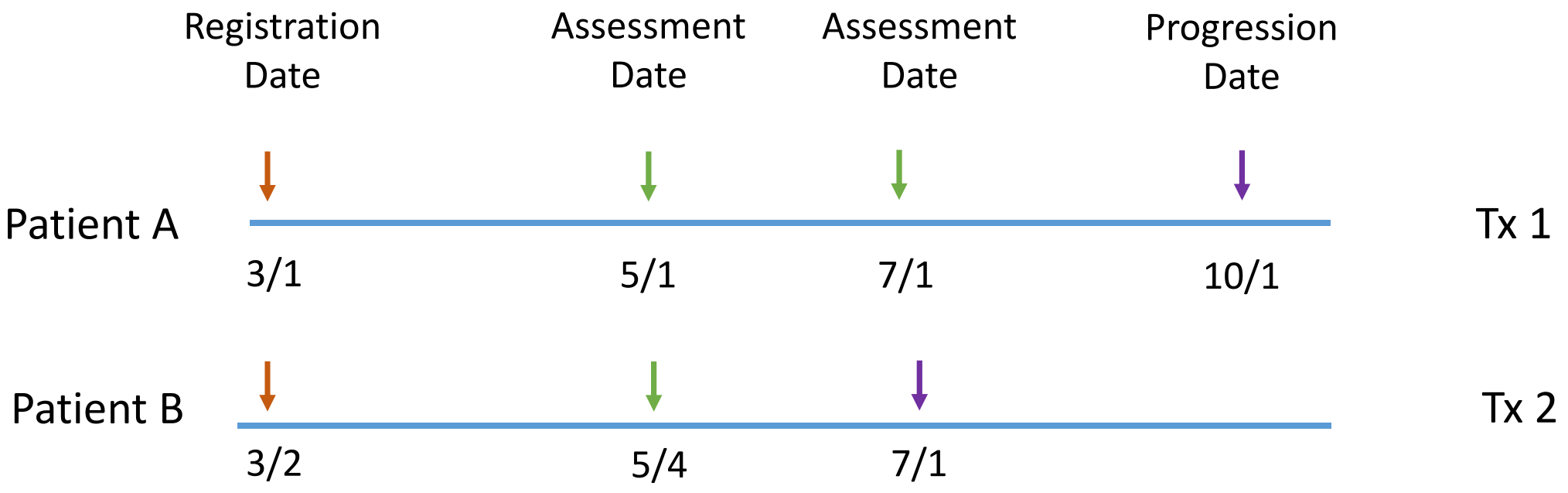
- Survival (or disease-free survival) how long patients live (disease-free) after entering a study -- is often the most important outcome we study
- Lost follow-up data increases both variability and bias in studies of survival



Bias and Missing Follow-up Patient Data

- A tendency for a statistical result to differ on average from the true state of affairs, often due to flaws in the design or conduct of a study
- Lost to follow-up, can introduce bias because the reason for the loss, or consent withdrawal “MAY” be related to the underlying patient health status
- A lost patient maybe doing worse (or better) than a comparable patient with complete data
- Worse yet – we don’t know the nature of the bias
- Leads to either incorrect or less impactful statistical results

Illustration of Impact Lost to Follow-up



Result: Progression 10/1 for Patient A and 7/1 for Patient B

Illustration of Impact Lost to Follow-up

Result: Progression 10/1 for Patient A and no progression for Patient B

SWOG Monitors Lost to Follow-up and Consent Withdrawals

Treatment Summary

Registrations ending April 2, 2019; Data as of April 2, 2019

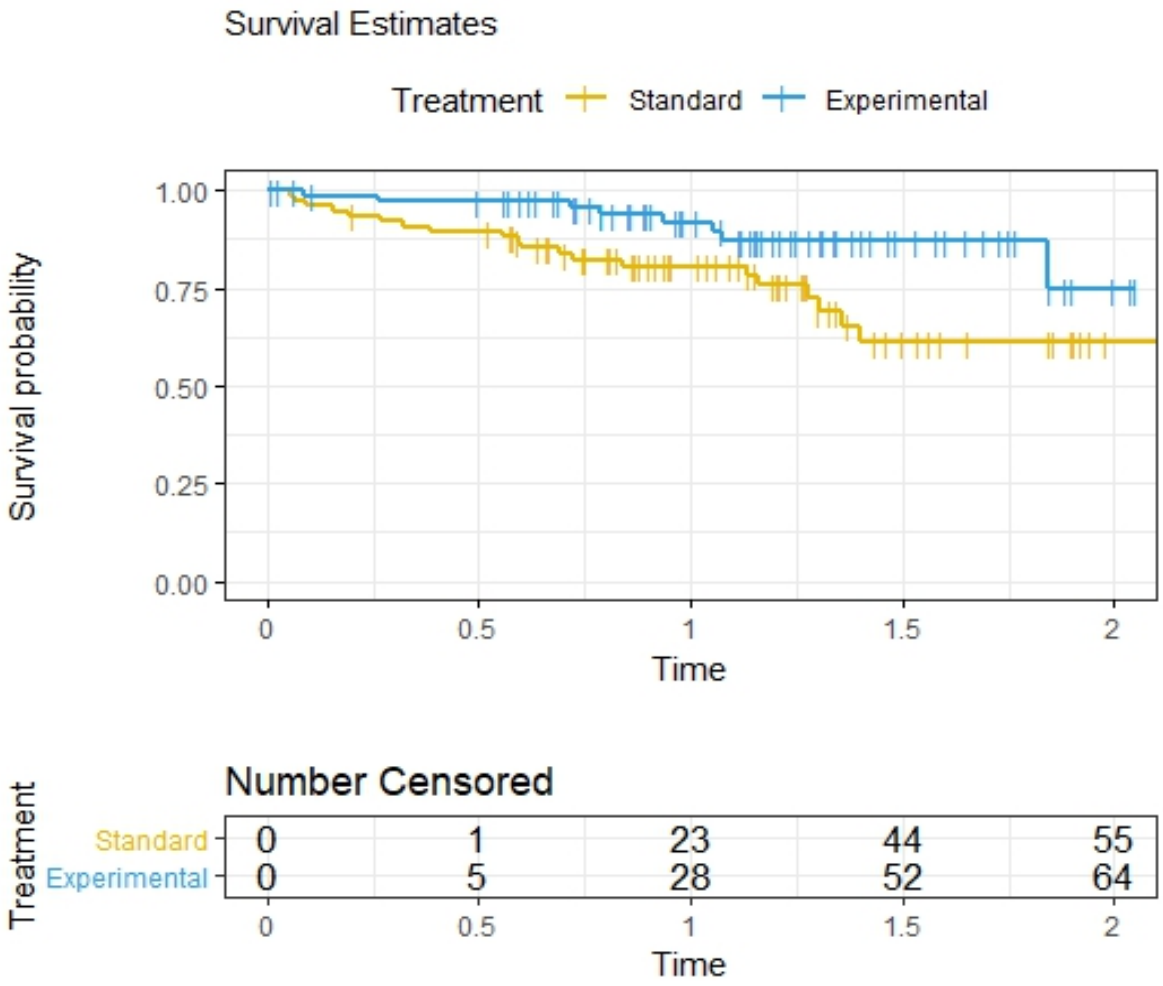
	TOTAL	Treatment X	Treatment Y
NUMBER ON PROTOCOL TREATMENT	59	33	26
NUMBER OFF PROTOCOL TREATMENT	242	128	136
REASON OFF TREATMENT			
Adverse Event or side effects	45	20	25
Refusal unrelated to adverse event	21	8	13
Progression/relapse	157	81	76
Death	0	0	0
Other - not protocol specified	13	6	7
Reason under review	3	2	1
MAJOR PROTOCOL DEVIATIONS	19	11	8
LOST TO FOLLOW-UP	0	0	6
CONSENT WITHDRAWAL AFTER TREATMENT INITIATION	53	21	32

The Data Safety Monitoring Committee sees these data by Treatment Arm

Study SXXXX (actively accruing)

- Study accrued 1/3 patients
- Survival curves look promising
- A Phase II analysis of data yields significant result

  p-value=.01 (one-sided)

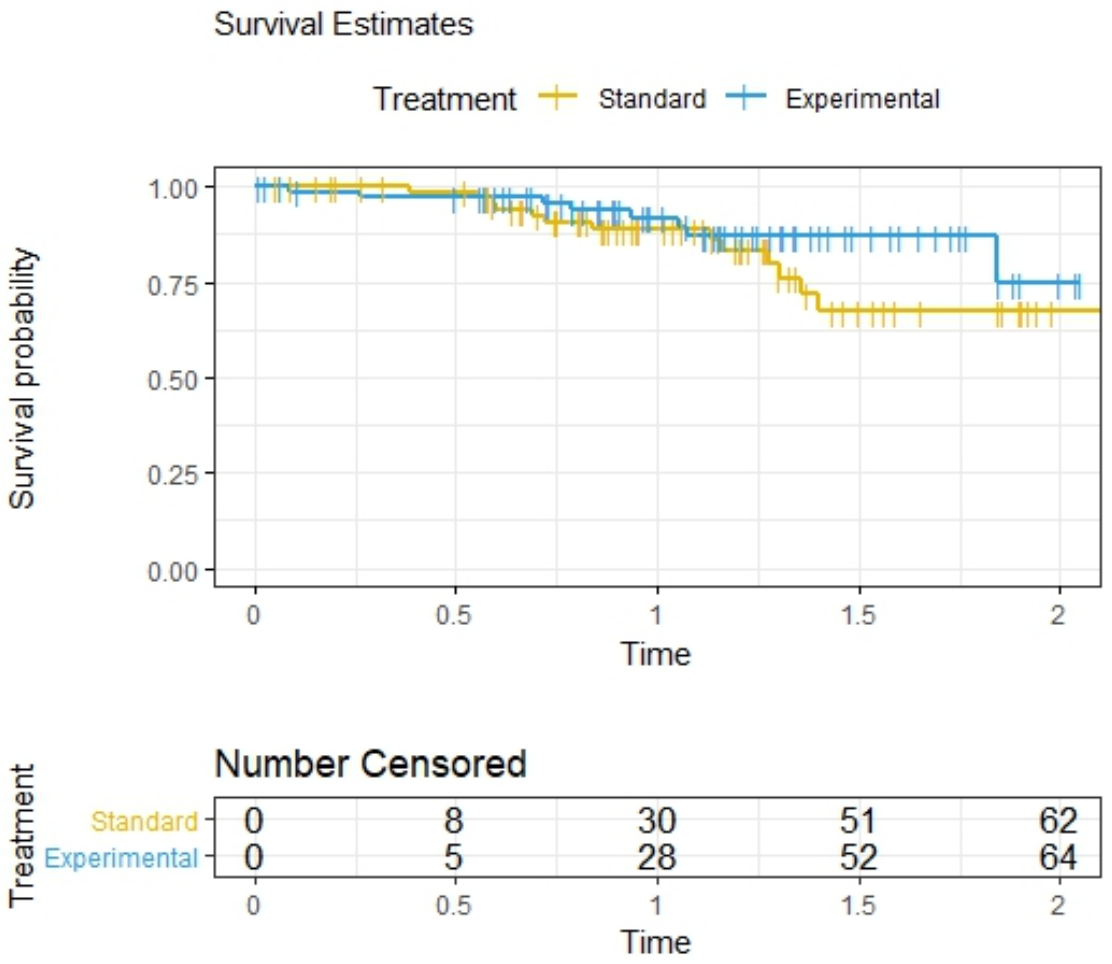


SWOG CANCER RESEARCH NETWORK

Study SXXXX (actively accruing)

- Study accrued 1/3 patients
- But now assume there is differential lost to follow
- 6 patients on Standard arm, 0 on Experimental arm lost
- Conclusion: early results not very promising
- If a Phase II/III study maybe close study for accrual

p =.12 (one-sided)

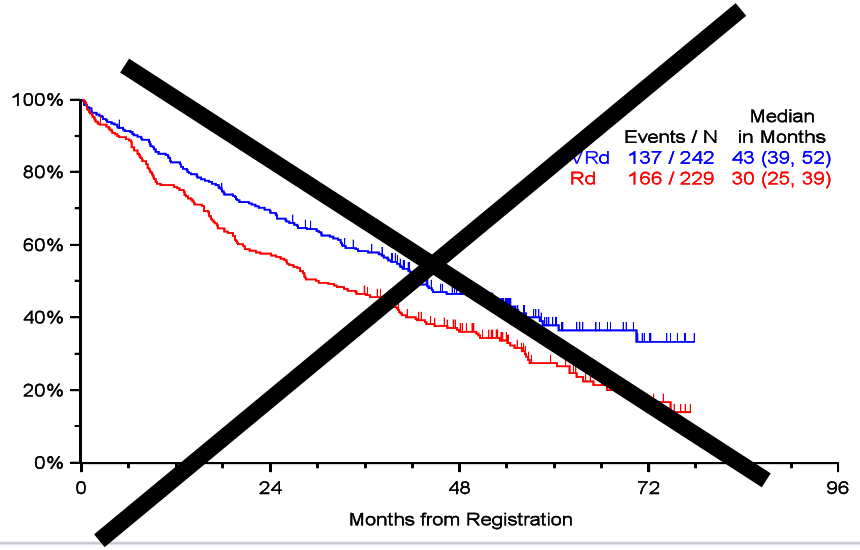


Myeloma Study S0777

- Differential Drop Out
- Interim analysis did not show sufficient activity

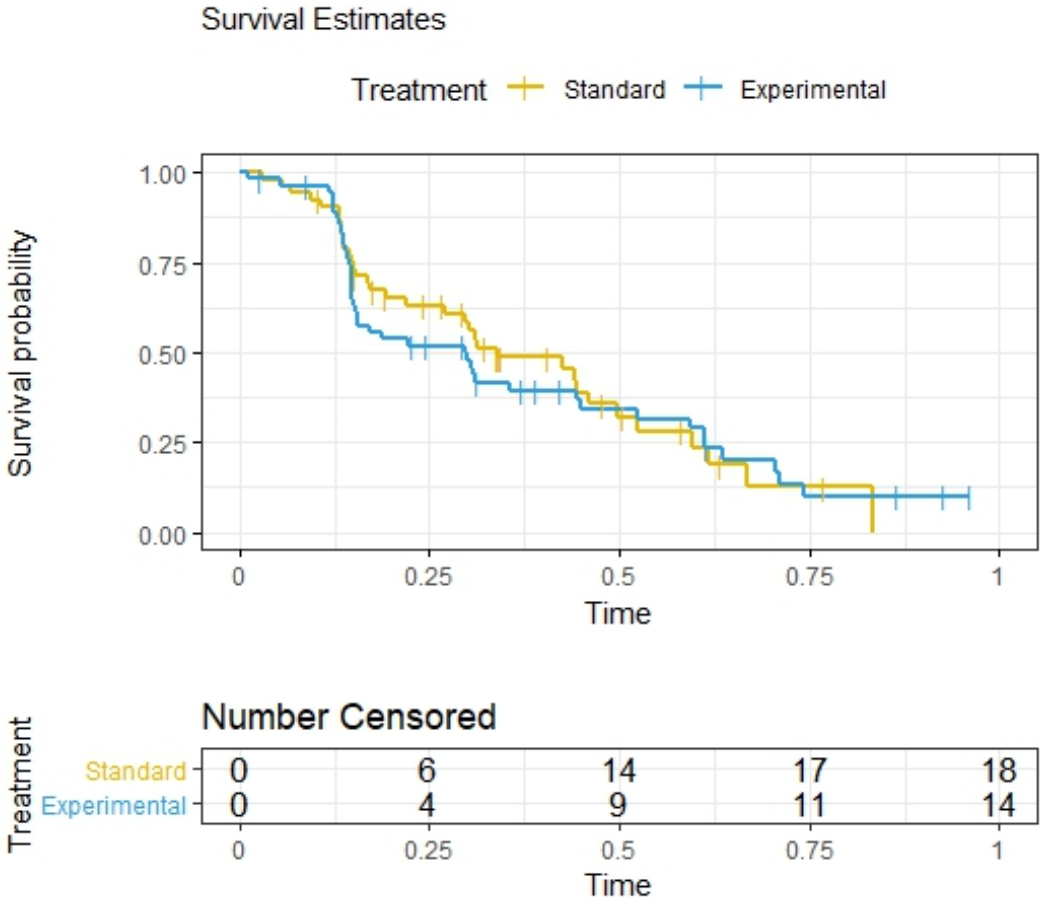
Assuming a design with early look this study
Potentially would have closed early

No Result –Missed a Positive Result for Patients



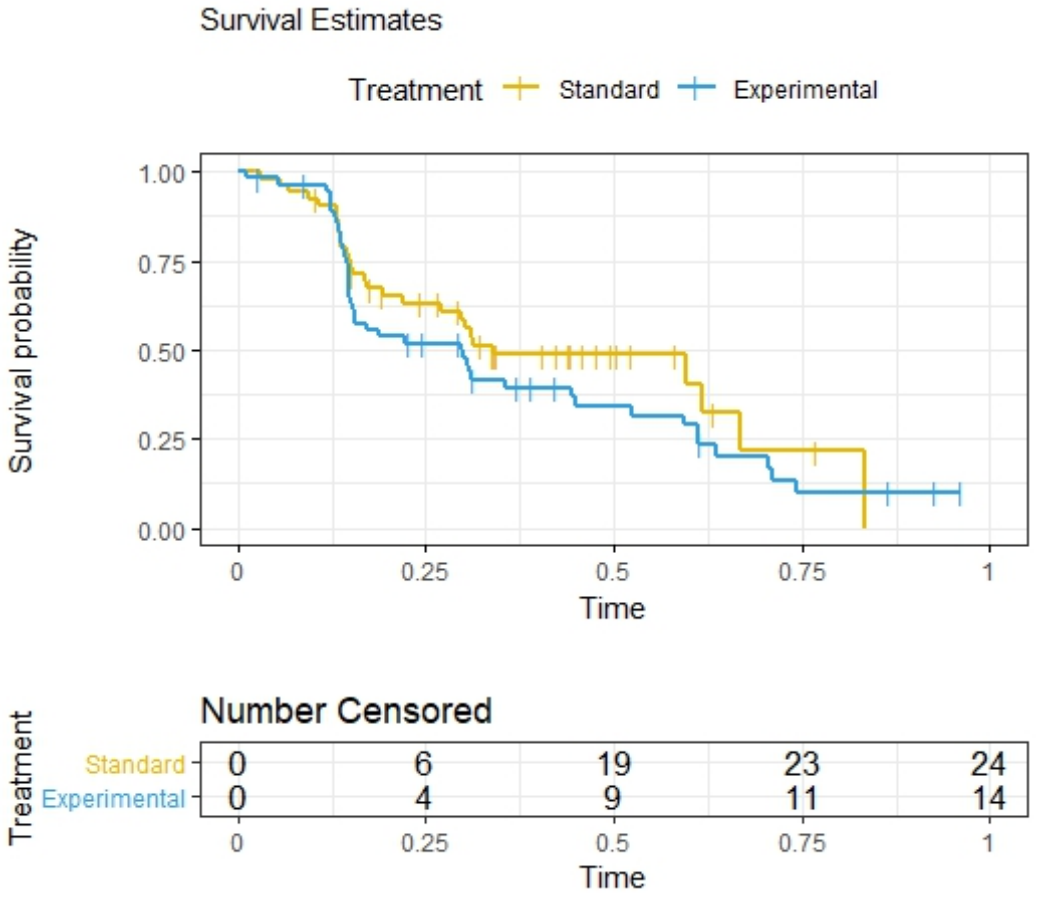
Phase II Gemcitabine, Erlotinib, and Cixutumumab vs Gemcitabine Plus Erlotinib (SWOG S0727)

- Study supported no improvement in PFS for 3 drug combination



Phase II Gemcitabine, Erlotinib, and Cixutumumab vs Gemcitabine Plus Erlotinib (SWOG S0727)

- Hypothetical differential loss to follow-up
- Could have led to conclusion of harm for experimental arm
- Significant implications for study conduct



Conclusions

- Complete patient follow-up and minimizing the impact of consent withdrawal is critical for study interpretation
- Follow-up on every patient is essential for both final statistical analysis but also for trial monitoring and decision making. Important decisions are made on small numbers of patients
- There are no statistical adjustments that correct for this issue
- Practical steps – focusing on Consent Withdrawal (Keisha Humphries)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