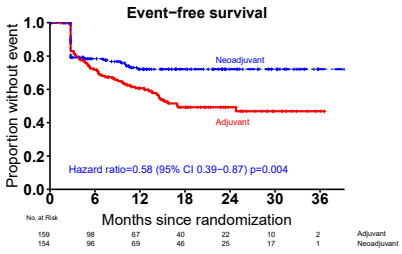
Scientific Impact of the CRA

Michael LeBlanc

1

S1801 A Phase II Randomized Study of Adjuvant versus Neoadjuvant Pembrolizumab for Clinically Detectable Stage III-IV High-risk Melanoma



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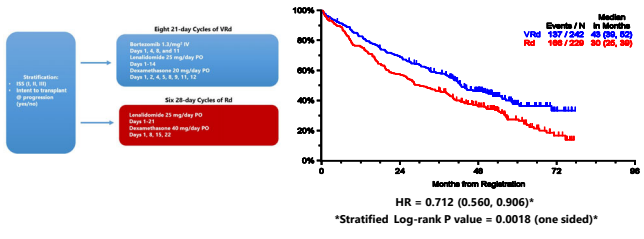
SWOG Myeloma Study S0777

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)

3

Stages of Treatment Testing

- Phase I
  - The safe dose range, side effects, early activity.
- Phase II
  - Sufficient promise for further testing, more side effect assessment, refinement of dose, evidence of disease subtypes with most promise and feasibility.
  - Some design examples: single arm 2-stage, single arm pilot, multi-arm randomized (screening or selection).
- Phase III
  - Formal comparison of new treatment to standard treatment.

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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

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Variability and Bias

- What are they and how do they arise?
- What problems do they cause?
- How can they be prevented or reduced?

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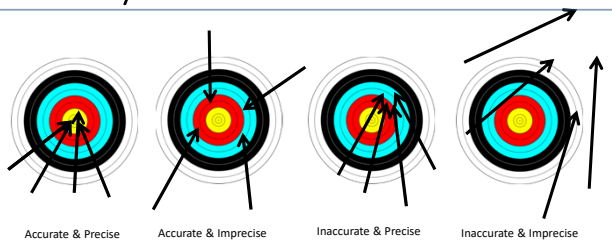
6

Variability and Bias



7

How do we control variability?

- Eligibility criteria

  Example: Results of studies which allow only patients with local disease and performance status 0-1 will be less variable than those from studies allowing any stage and any performance status.

8

How do we control variability? (cont.)

- Sample size

  Larger numbers of patients lead to reduced variability.

9

The CRA's Role in Reducing Variability

- Verification of eligibility
- Avoidance of deviations from protocol treatment plans
- Submission of complete and timely data

10

Bias

- 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.

11

Bias

- Example

  If a study of a treatment intended for patients with local disease includes a number of patients with more advanced disease, the treatment's efficacy may be underestimated.

12

Bias

- Solution
  Ensure adherence to eligibility criteria

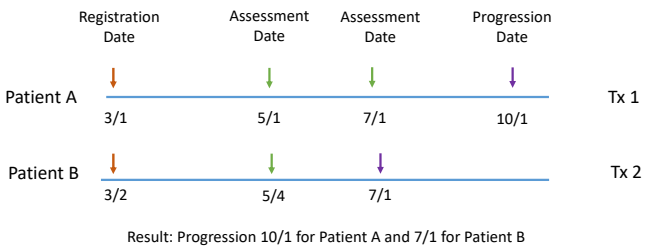
13

Bias

- Example
  If patients in an adjuvant therapy arm of a comparative study are followed more closely than those in an observation arm, the benefit of the adjuvant therapy may be underestimated.

14

Illustration of Impact Lost to Follow-up



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

15

Illustration of Impact Lost to Follow-up

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

16

Bias

- Solution
  - Ensure adherence to protocol requirements for follow-up examinations
- Schedule
  - Have patients return for evaluation according to protocol schedule
- Tests
  - Have all required tests performed at each evaluation

17

The CRA's Role in Controlling Bias

- Verification of eligibility
- Adherence to protocol follow-up requirements

18

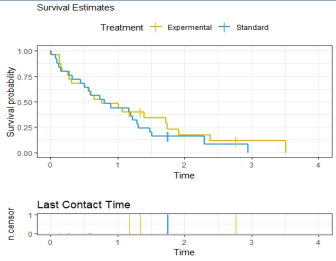
Variability and Bias in Survival Data

- Survival - how long patients live after entering a study - is often the most important outcome we study
- Incomplete data increases both variability and potentially bias in studies of survival

19

Estimated Survival

Study design: accrued over 3 years + 1 year of follow-up

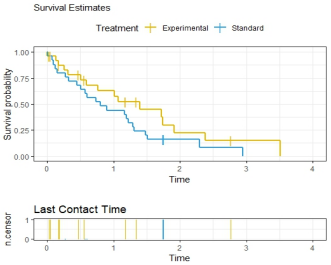


Correct conclusion: new treatment does not help survival outcome

20

Estimated Survival

Some Patients lost to follow-up on one arm



Incorrect conclusion: new treatment helps survival outcome

21

What We Need

- Complete and timely submission of accurate
- Thorough documentation of all eligibility criteria

22

What We Need, cont.

- Complete description of all treatment received, whether according to protocol or not
- Complete description of objective status and toxicities at every evaluation

23

Effect of Non-dropout or Non-adherence on Sample Size

New sample size = sample size ÷ $(1\text{-}r)^2$

Non-adherence Rate	Sample Size (Example)
0%	100
10%	123
20%	156
30%	204
40%	278

24

High quality data are essential for good studies.

Your efforts are essential for high quality data.

25

WHY IS IT ALWAYS CRITICAL?

Trial Monitoring

- Accrual monitoring (Stats, SC)
- Adverse event monitoring
  - SC, Stats, AE coordinator
  - CTEP-AERS reporting
  - Monthly reports (AE and dose summaries)
- Interim Analyses
- Data and Safety Monitoring Committee (DSMC)

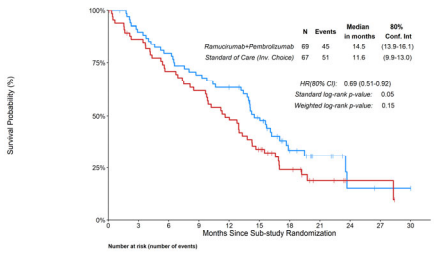
26

SWOG Data Safety Monitoring Committee

- Evaluation of interim results (endpoints, safety)
- Recommendations on when to stop accrual, when to report early results
- Evaluate data requests from disease committee leadership for planning purposes
- NEED HIGH QUALITY CURRENT DATA TO MAKE CRITICAL RECOMMENDATIONS

27

S1800A: LungMAP - Overall survival



Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

Subgroup analyses:

- HRs do not vary by PD-L1
- Pronounced benefit in SCC/mixed histology
- Benefit seen with PS 0 and 1
- Co-mutations did not affect OS improvement

Reckamp KL et al ASCO 2022; J Clin Oncol 2022

SWOG LUNG-MAP

28

S2302 Treatment/Schema

A PROSPECTIVE RANDOMIZED STUDY OF RAMUCIRUMAB (NSC 749128) PLUS PEMBROLIZUMAB (MK-3475; NSC 776864) VERSUS STANDARD OF CARE FOR PARTICIPANTS PREVIOUSLY TREATED WITH IMMUNOTHERAPY FOR STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER

Randomization

ARM A
Standard of Care (SoC)*

Stratified by:
Zubrod PS (0/1 v 2)
Most recent therapy ICI (yes v no)

ARM B
Ramucirumab
+
Pembrolizumab

*SoC treatment is to be determined by the treating investigator and participant. It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a "systemic therapy for advanced or metastatic disease-subsequent."

Primary endpoint: OS

N= 700 patients

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29

Pragmatic Considerations

— Minimum Data Collection

Baseline:
- **S2302 Vital Status Form**
- **S2302 Onstudy Forms**
- **S2302 Eligibility Criteria Form**

On Treament:
- **S2302 Vital Status Form**
- **S2302 Adverse Event Form**

✖ No Cycle based Treatment Form: dose intensity, dose modification
No Disease Assessment Form (BTA, FUTA)

Off Treatment:
- **S2302 Vital Status Form**
- **S2302 Treatment Summary Form**

Follow Up:
- **S2302 Vital Status Form**
- **Late Adverse Events**

✖ No Detailed Follow Up form, only live status

Death:
- **S2302 Notice of Death**

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High quality and timely data are essential for good studies.

Your efforts are essential for high quality data.

31

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32