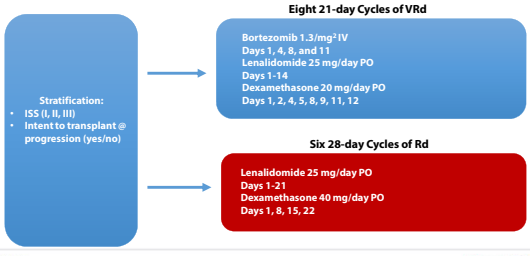
Scientific Impact of the CRA

Michael LeBlanc

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".

EXAMPLE: SWOG S0777 Study Design



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

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Summary

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

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

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See Comment page 480

Cedars-Sinai Samuel Oschin Cancer Center, Los Angeles, CA, USA (Prof B G M Durie MD); Cancer Research and

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:

- REVLIMID in combination with bortezomib and dexamethasone (RVd) in adult patients with previously untreated multiple myeloma who are not eligible
- IMNOVID in combination with bortezomib and de myeloma, who have received at least one prior tr

SUMMIT, N.J.--(BUSINESS WIRE)-- Celgene Corporation Medicines Agency's (EMA) Committee for Medicinal Pro for two triplet regimens based on Celgene's proprietary (pomalidomide).

The CHMP positive opinion for REVLIMID was based on the data from SWOG S0777, a phase 3 trial evaluating the triplet combination of REVLIMID, bortezomib and dexamethasone (RVd) in adult patients with previously untreated multiple myeloma, without an intent for immediate autologous stem cell transplant (ASCT).1 Results from SWOG S0777 showed statistically significant progression-free (PFS) and overall survival improvements in patients treated with RVd compared to those treated with REVLIMID and dexamethasone alone (Rd). The choice of treatment in a first-line therapy setting is important2 as patients progressively become less responsive to therapy and experience shorter periods of remission at later lines of treatment.3

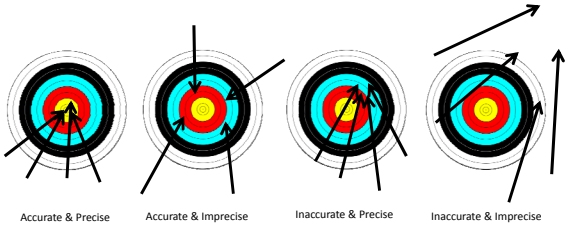
Critical Elements in Evaluating Therapeutic Interventions

- Biological Activity
- Safety/Toxicity
- Clinical Efficacy
  - Response, Survival
  - Patient Reported Outcomes

Variability and Bias

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

Bias and Variation



Accurate & Precise | Accurate & Imprecise | Inaccurate & Precise | Inaccurate & Imprecise

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.

How do we control variability? (cont.)

- Sample size
  Larger numbers of patients lead to reduced variability.

The CRA's Role in Reducing Variability

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

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.

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.

Bias

- Solution
  Ensure adherence to eligibility criteria

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.

Illustration of Bias

- Results with Complete Follow-up
  - NED 3/1/16
  - Asymptomatic Bone Lesions 5/1/16
  - Tumor Recurrence 7/1/16
  - Death, Cause Unknown 9/1/16
  - Progression Date 5/1/16

Illustration of Bias

- Effect of Missing Follow-up #1
  - NED 3/1/16
  - Bone Scan Not Done 5/1/16
  - Tumor Recurrence 7/1/16
  - Death, Cause Unknown 9/1/16
  - Progression Date 7/1

Illustration of Bias

- Effect of Missing Follow-ups #1 and #2
  - NED 3/1/16
  - Bone Scan Not Done 5/1/16
  - Exam Postponed 7/1/16
  - Death, Cause Unknown 9/1/16
  - Progression Date None!

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

The CRA's Role in Controlling Bias

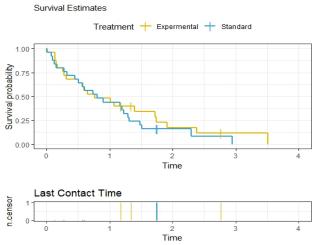
- Verification of eligibility
- Adherence to protocol follow-up requirements

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 bias in studies of survival

Estimated Survival

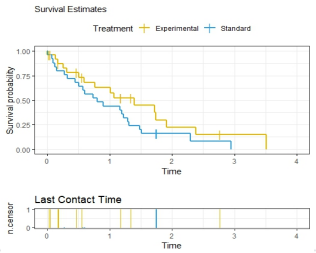
Study design: accrued over 3 years + 1 year of follow-up



Correct conclusion: new treatment does help survival outcome

Estimated Survival

Some Patients lost to follow-up on one arm



Incorrect conclusion: new treatment helps survival outcome

What We Need

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

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

SWOG

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

SWOG

High quality data are essential for good studies.

Your efforts are essential for high quality data.

SWOG

WHY IS IT ALWAYS CRITICAL?

Trial Monitoring

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

SWOG Data Safety Monitoring Committee

- Evaluation of interim results (endpoints, safety)
- Approval of major design changes
- Decisions 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 DECISIONS

High quality data are essential for good studies.

Your efforts are essential for high quality data.


SWOG
CANCER
RESEARCH
NETWORK