Data Safety Monitoring Plan

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Practice vs. Research

- Practice
  - To provide diagnosis, preventive treatment or therapy
  - Interventions designed solely to enhance the well-being of the patient/client
  - Reasonable expectation of successful outcome
- Research
  - Activities designed to contribute to generalizable knowledge
  - To test a hypothesis and draw conclusions
  - Not necessarily provide direct benefit

- "임상시험(Clinical Trial/Study)"이라 함은 임상시험용의약품의 안전성과 유효성을 증명할 목적으로, 해당 약물의 약동 · 약력 · 약리 · 임상적 효과를 확인하고 이상반응을 조사하기 위하여 사람을 대상으로 실시하는 시험 또는 연구를 말한다.

KGCP 제2조(정의)1항

What Is Data and Safety Monitoring (DSM)?

Definition of DSM

" Data and safety monitoring is any process during a clinical trial that involves review of accumulated outcome data for groups of patients to determine if any of the treatment procedures should be altered or stopped."

(Meinert 1986)

Goals of DSM

- Protecting safety of human research subjects, while also …
- Ensuring and maintaining scientific integrity or research
- This includes protecting against intentional or unintentional bias by people who carry out, pay for, or otherwise benefit from the research

How Are Goals Achieved?

As opposed to pre-study or continuing reviews done by the IRB, Data and Safety Monitoring:

- Analyzes cumulative data at strategic points while the trial is going on
- Might un-blind data if necessary to uncover emerging safety or ethical risks
- Evaluates emerging patterns for statistical significance

What Is a DSMP?

- A Data and Safety Monitoring Plan (DSMP) is a comprehensive system to ensure complete but efficient oversight and monitoring of safe and ethical conduct of a particular clinical investigation
- The DSMP ensures safety of human subjects as well as validity and integrity of trial conduct and outcomes

Key Elements of DSMP

- How will progress and safety be monitored? Who and When?
- How will adverse and unanticipated events be reported as required by regulations?
- How will data accuracy and protocol compliance be maintained?
- What are the "stopping rules", and how will any modification, suspension or termination of the trial be reported?
- If this is a multi-center trial, what is the planned process for communicating important information among all sites to protect safety of all subjects?

What Do We Mean by "Stopping Rules"?

- Any guideline that is established for the specific purpose of forcing a revision of the study protocol, based on review of events that occur during the conduct of the study.
- A trial might be stopped based on strong early evidence of safety problems, efficacy (success) or futility (failure)?

When Is a DSMP Necessary?

- The FDA and NIH agree that all trials with greater than minimal risk should have a DSMP.
- The plan should fit the risk level and other characteristics of the particular trial.
- It can be as simple as the investigator annually submitting safety data to the IRB, or as complex as having a full, independent Data Monitoring Committee (DMC) along with other kinds of internal monitors.

DSMPs for Higher-Risk Trials

- Trials with large populations, vulnerable subjects, or high-risk treatments probably require external, independent monitoring in addition to internal monitoring.
- The sponsor might call on external monitoring experts to advise of safety factors in the protocol, the DSMP, or the statistical analysis plan (SAP) related to interim review of data.

DSMPs for Higher-Risk Trials

The sponsor might ask external experts to monitor periodically:

- Accrual and disposition of subjects – overall, and by site and study arm
- Quality and timeliness of data reporting
- Agreement between site-level evaluations and centralized (sponsor) review
- External events that might affect the trial

Acronyms

- DMC – Data Monitoring Committee
- SMC – Safety Monitoring Committee

You may hear another term that means the same thing as DMC:

- DSMB – Data and Safety Monitoring Board

Because DSMB sounds like DSMP, the two can be easily confused, so DMC may be preferable.

KGCP

- “모니터링(Monitoring)이란 임상시험 진행 과정을 감독하고, 해당 임상시험이 계획서, 표준작업지침서, 임상시험관리기준 및 관련규정에 따라 실시 · 기록되는지 여부를 검토 · 확인하는 활동을 말한다.
- “자료모니터링위원회(Independent Data-Monitoring Committee, IDMC)란 주기적으로 임상시험의 진행 상황, 안전성 관련 자료, 중요한 유효성 결과 변수를 평가하고, 해당 임상시험의 계속 진행, 변경 또는 중지를 의뢰자에게 권고하는 독립된 위원회를 말하며, 의뢰자에 의해 조직될 수 있다. (KGCP 제2조 정의)

Data Monitoring Committee (DMC)

- A formal, independent advisory committee, usually 3 to 5 members, with appropriate expertise to periodically review accumulating trial data
- Has authority to perform interim un-blinded review if necessary to identify and address an emerging safety or ethical risk
- Because of administrative costs and risks associated with early un-blinding of data, DMCs are NOT necessary or recommended for most trials.

How Can Independent Monitoring Benefit the Sponsor?

- Safety is a positive social value (but has costs).
- When interim results are not known to sponsor, proposed changes to a trial in progresses are less likely to be biased, and thus more credible.
- In blinded trial, independent monitoring may shield sponsor from "securities issues".
- May satisfy conditions imposed by regulatory bodies (KFDA, IRB)

Sponsor Responsibilities

- Appointing the DMC chair
- Establishing procedures to assess potential COI of members
- Ensuring the confidentiality of the interim data analyses
- Establishing or approving DMC SOPs – meeting schedule, reporting
- Submission to KFDA of all DMC meeting records and interim reports
- Notifying KFDA and responsible IRBs of any recommendations or requests made by the DMC regarding the safety of the participants
- Consulting with KFDA before accessing interim data, terminating the study or modifying the protocol (could affect the validity of the study)

Regulatory and Ethical Considerations

Regulations Address IRBs…

- KFDA says IRBs must make sure protocols include "adequate provisions" for monitoring data to ensure safety of subjects.
- AAHRPP holds IRBs accountable for reviewing the DSMP and determining if it provides "adequate" protection for subjects.

What Regulations Govern DSM?

- 임상시험에서는 특히 면밀하게 피험자를 모니터링해야 하고, 만일 피험자에게 부당한 위협이 가해지는 것으로 판단된 경우 즉시 이들에 대한 임상시험을 중지시켜야 한다. (KGCP 제17조 피험자동의)
- 의뢰자는 안전성 관련 자료와 중요한 유효성 결과변수를 포함한 임상시험의 진행 정도를 주기적으로 평가하여, 해당 임상시험의 계속 진행, 변경 또는 중지에 대한 자문을 얻기 위해 독립적인 자료모니터링위원회(Independent Data Monitoring Committee, IDMC)를 설치할 수 있으며, 이러한 자료모니터링위원회는 문서화된 표준작업지침서를 보유하고, 회의록을 문서화하여 이를 유지하여야 한다. (KGCP 제27조 임상시험의 관리)

ICH GCP

- 5.5.1 “The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial report.”
- 5.5.2 “The sponsor may consider establishing an IDMC to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.”

Formation of DMC

- Ideally, the Committee should be formed before the protocol is finalized and approved.
- If the Committee is formed after approval of protocol, it should be established and oriented to the trial before any subjects are enrolled and treated.
- The scope of the Committee's assignment from the sponsor, and the responsibilities of the Committee and sponsor to one another in carrying out monitoring activities, are set out in a written document called a charter.

When Is a DMC Necessary?

Subject Safety

- Is mortality or major morbidity an end point?
- Would positive or negative results during the study require termination for ethical reasons?
- Is there little knowledge regarding the safety of the intervention or is there knowledge of safety concerns (potential toxicity)?
- Is the targeted study population fragile, e.g., elderly, children, pregnant women, where there may be an increased risk?
- Is the study a large, multi-center trial, with a long duration, where subjects would not be as easily identified in single-center studies with shorter durations?

When Is a DMC Necessary?

Practicality

- Is the study a short-term trial where a DMC would not have adequate time to respond?
- If the study is a short-term trial where subject safety is a concern, are there mechanisms in place where a DMC would be notified quickly of unexpected events/results?

Scientific Validity

- Is the study of long duration in which changes in the understanding of the disease progress, the target population or new treatment discoveries would warrant changes to the trial as it progresses?

DMC Responsibilities

- Safety monitoring
- Monitoring for effectiveness
- Monitoring study conduct
- Monitoring external data
- Making recommendations
- Maintenance of records

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study of Pemetrexed Plus Carboplatin Compared With Etoposide Plus Carboplatin in Chemotherapy-Naive Patients With Extensive-Stage Small-Cell Lung Cancer

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Submitted March 24, 2009; accepted May 5, 2009; published online ahead of print at www.jco.org on August 3, 2009.

Supported by Eli Lilly, Indianapolis, IN.

Presented in part as an oral presentation at the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL, and the 8th Annual Targeted Therapies for the Treatment of Lung Cancer Meeting, February 20-23, 2008, Santa Monica, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of the article.

Clinical Trials repository link available on JCO.org.

ABSTRACT

Purpose

Following a phase II trial in which pemetrexed-platinum demonstrated similar activity to that of historical etoposide-platinum controls, a phase III study was conducted to compare pemetrexed-carboplatin with etoposide-carboplatin for the treatment of extensive-stage small-cell lung cancer (ES-SCLC).

Patients and Methods

Chemotherapy-naive patients with ES-SCLC and an Eastern Cooperative Oncology Group performance status of zero to 2 were randomly assigned to receive pemetrexed-carboplatin (pemetrexed 500 mg/m^2 on day 1; carboplatin at area under the serum concentration-time curve [AUC] 5 on day 1) or etoposide-carboplatin (etoposide 100 mg/m^2 on days 1 through 3; carboplatin AUC 5 on day 1) every 3 weeks for up to six cycles. The primary objective of the study was noninferiority of pemetrexed-carboplatin overall survival with a 15% margin.

Results

Accrual was terminated with 908 of 1,820 patients enrolled after results of a planned interim analysis. In the final analysis, pemetrexed-carboplatin was inferior to etoposide-carboplatin for overall survival (median, 8.1 *v* 10.6 months; hazard ratio [HR], 1.56; 95% CI, 1.27 to 1.92; log-rank $P < .01$) and progression-free survival (median, 3.8 *v* 5.4 months; HR, 1.85; 95% CI, 1.58 to 2.17; log-rank $P < .01$). Objective response rates were also significantly lower for pemetrexed-carboplatin (31% *v* 52%; $P < .001$). Pemetrexed-carboplatin had lower grade 3 to 4 neutropenia, febrile neutropenia, and leukopenia than etoposide-carboplatin; grade 3 to 4 thrombocytopenia was comparable between arms and anemia was higher in the pemetrexed-carboplatin arm.

Conclusion

Pemetrexed-carboplatin is inferior for the treatment of ES-SCLC. Planned translational research and pharmacogenomic analyses of tumor and blood samples may help explain the study results and provide insight into new treatment strategies.

J Clin Oncol 27:4787-4792. © 2009 by American Society of Clinical Oncology

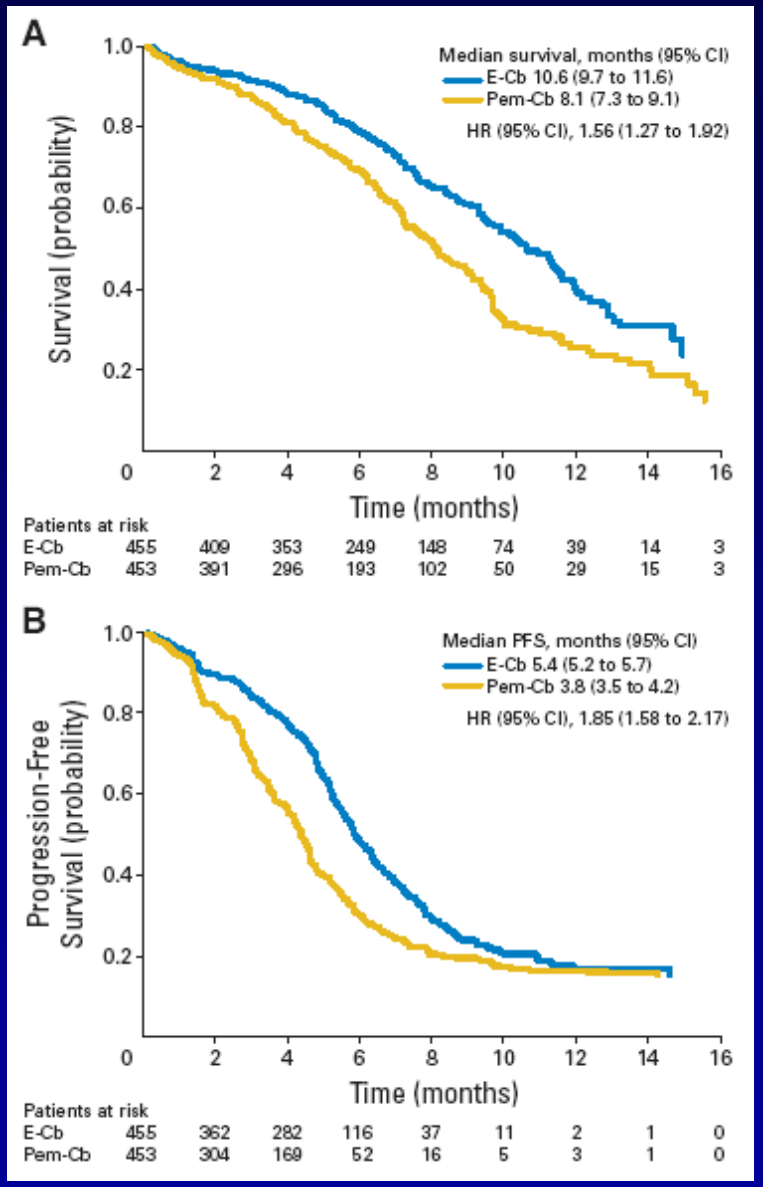
Statistical Analyses

A planned interim futility analysis conducted by an independent data monitoring committee was to be performed after approximately 700 patients were enrolled. The trial was to be stopped for futility if the PFS for pemetrexed-carboplatin was inferior to etoposide-carboplatin, with inferiority concluded if the lower limit of the 90% CI of the PFS hazard ratio (HR) of pemetrexed-carboplatin over etoposide-carboplatin was more than 1.0.

Using a noninferiority design, the primary analysis was to compare OS between the two treatment arms using the fixed margin method after approximately 1,270 deaths. Assuming that HR = 1.0, and with a plan to enroll 1,820 patients, the analysis provided an 83% power to reject the null hypothesis (H_0). The H_0 assumed that etoposide-carboplatin would provide a ≥ 15% reduction in the risk of death over pemetrexed-carboplatin, corresponding to a fixed margin of 1.176. Using the Cox model,[14] with baseline covariates and a two-tailed 95% CI for the HR, rejection of the H_0 occurred if the 95% CI of the OS HR was less than 1.176.

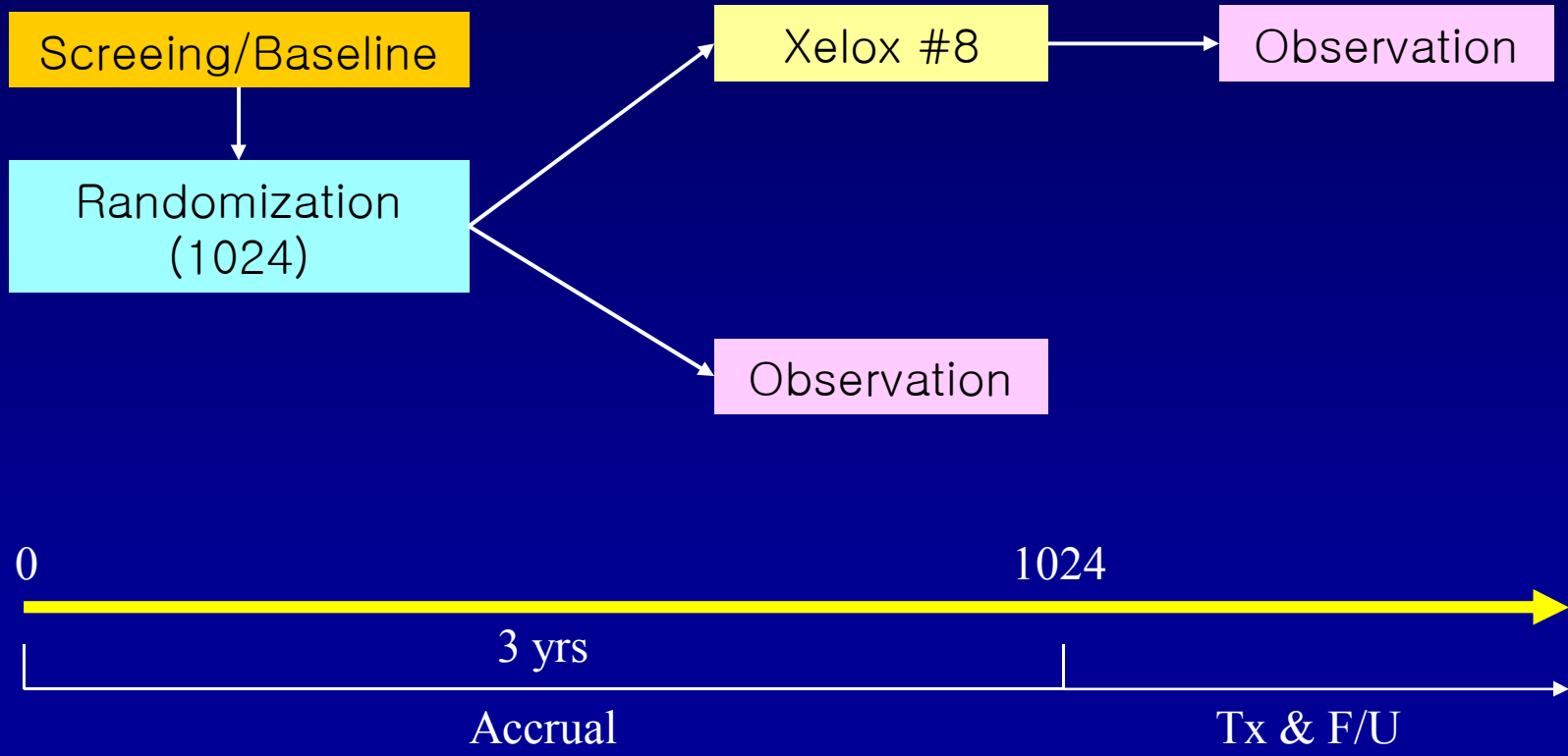
RESULTS

The planned interim analysis completed in December 2007 included 733 randomly assigned patients. At the interim analysis, PFS was significantly lower on the pemetrexed-carboplatin arm (HR, 1.79; 90% CI, 1.49 to 2.15) indicating futility, and study enrollment was closed. While the interim data were being analyzed and before study closure, an additional 175 patients were randomly assigned for a total of 908 patients. Patients were followed after trial closure until August 2008. The median follow-up time for all patients was 6.0 months.



"CLASSIC" Study

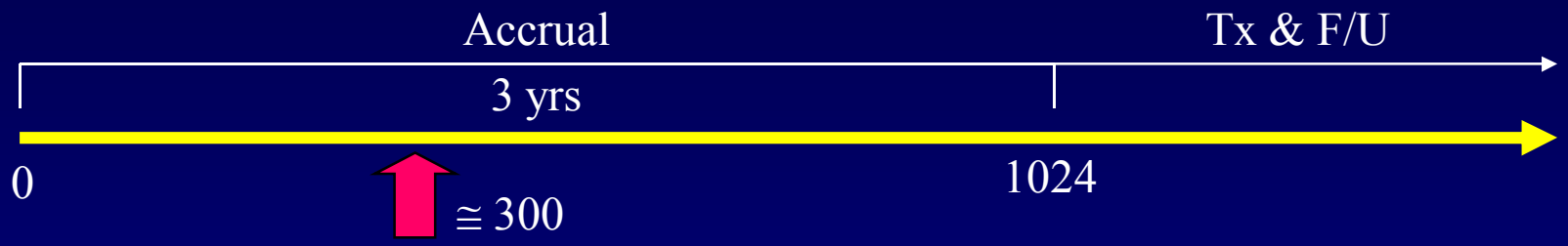
- Stage II, IIIa, 및 IIIb 위암환자에서 수술 후 카페시타빈/옥살리플라틴 (XELOX) 보조 항암화학요법과 수술단독을 비교하는 제 3상 임상시험



"IDMC"

- 본 임상시험에 대한 독립적 자료모니터링위원회가 구성될 것이다.
- IDMC는 정기회의를 통해 안전성 자료를 검토할 것이며, 첫번째 검토시기는 치료군 환자 100 명이 적어도 2 주기 투여를 완료한 시점이 될 것이다. 두번째 검토는 첫번째 모니터링으로부터 6개월 후에 시행될 것이다. 이후 검토는 IDMC에 의해 결정될 것이다.
- 본 임상시험과는 독립적인 통계학자가 IDMC에 관련 표와 목록을 제공할 것이다. 안전성 자료는 인구통계학적 자료, 30일과 60일 사망률, 이상반응, 중대한 이상반응, 실험실적 이상수치가 포함된다.
- 추가적으로 중대한 이상반응 보고서 사본이 IDMC에 제공될 것이다.
- IDMC는 자료 검토 후, 임상시험의 지속, 계획서 변경의 가능성 또는 임상시험 중지 등에 대해 서면으로 권고사항을 제공할 것이다. 이에 대한 최종 결정을 의뢰자에게 있다.
- IDMC의 상세한 사항은 별도의 IDMC 관련 문서에 제공될 것이다.

Monitoring External Data



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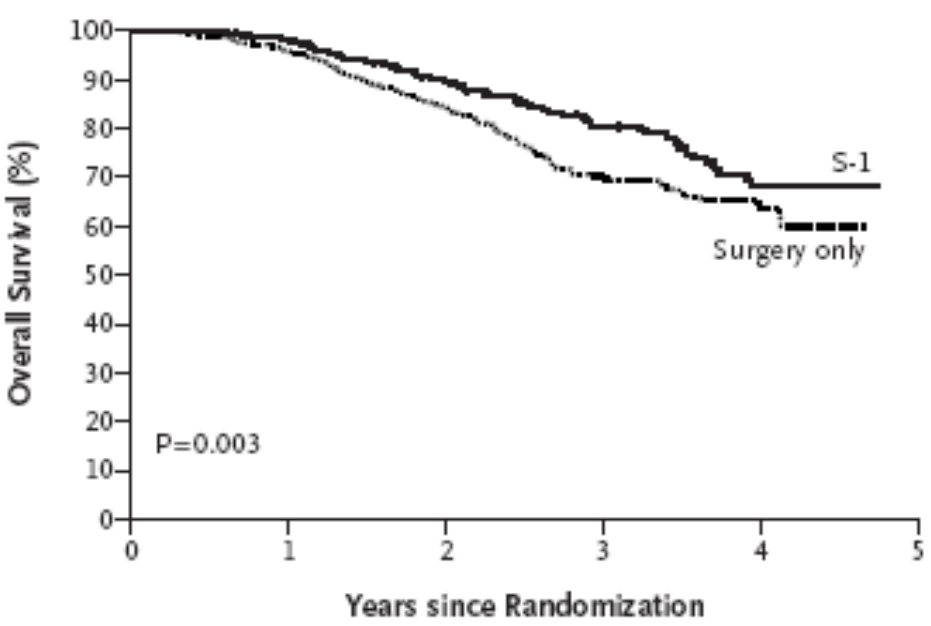

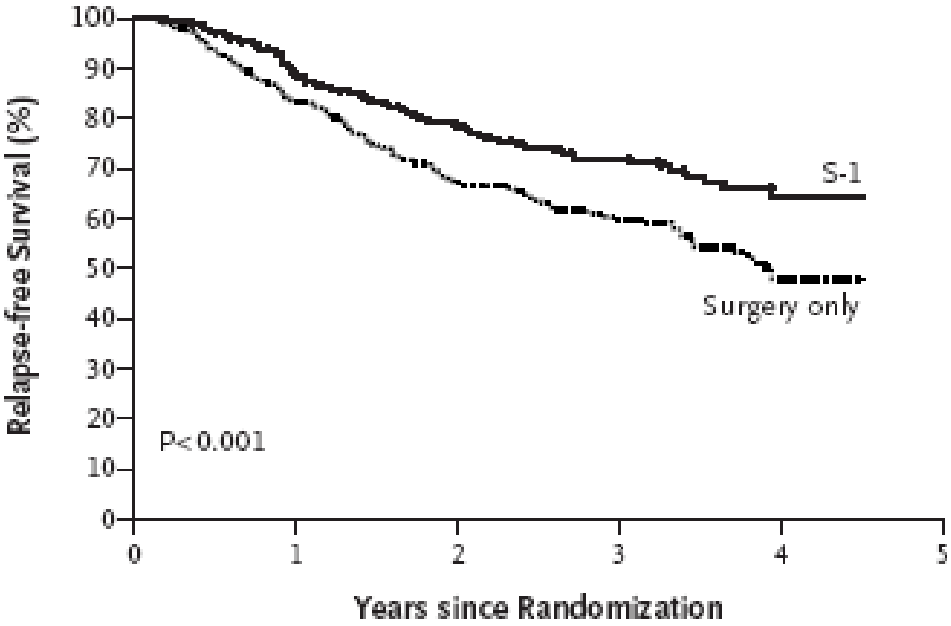

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What Ethical Challenges Might You Encounter as a DMC Member?

- If you treat patients with the condition under study, how can you make clinical recommendations that may be influenced by confidential interim results?
- How will you handle questions from colleagues and patients?
- What if a friend or family member is making a financial or personal medical decision that could be influenced by confidential interim results?

More Ethical Notes…

- Because a DMC may have access to early, un-blinded trial results, its members must maintain complete separation and independent from all other trial conduct and monitoring functions for the duration of the research!
- Members should not be authors of the clinical study report.

What Are Our Rules?

(DMC Member)

Member Responsibilities

- Commit to the entire process
- Participate in all areas of the discussion (clinical, statistical, and ethical)
- Bring out the important questions
- You will not likely do primary statistical analysis.

Types of Meetings

- Organizational meeting: approve charter
- Review meetings: open and closed sessions
- Final meeting: Committee closure process, possible sharing of Committee interpretations or insights

Organizational Meeting

- Introductions, SOPs, confidentiality
- Review protocol
- Review SMP (identify the risks & concerns)
- Review statistical analysis plan
- Review information flow diagram
- Review charter: modify and approve

Review Meetings

Open portion: discuss “public” information

- Input from study arm (investigator, sponsor, regulatory authority etc.)
- Progress and problems: recruitment, data quality, study design

Closed portion: confidential

- Un-blinded data
- Recommendation

DMC Recommendations

- Continue without change
- Modify the study (re-size, speed accrual)
- Stop the study (or part of study, such as one arm)
  - Efficacy
  - Safety
  - Futility
- Other

DMC Minutes: Open Minutes

- Audience: sponsor, investigators, IRB
- Timing: immediate release
- Contents: summary of recommendations; not to include interim or blinded results unless required to support recommendation for study closure or modification

DMC Minutes: Closed Minutes

- Audience: DMC files (but may not provided to sponsor, investigators upon study closure)
- Timing: draft circulated promptly after meeting for member correction and endorsement
- Contents: recommendations and description of supporting discussion, likely including interim or blinded results

DMC Communications

- DMC reports directly to the sponsor, and does not communicate directly with investigators or regulatory authorities (KFDA, IRB) unless sponsor gives permission
- Communications typically issue from Chair, members do not discuss outside of meetings

IRB Responsibilities

- After its initial approval of studies, the IRB is responsible for reviewing all available information both from the study site and external sources to ensure the continued acceptability of the trial.
- The IRB may take actions based on the recommendations of the DMC to the sponsor.

What Should We Do as IRB Member?

- Minimize the potential stress, discomfort and other harms.
- Guard against factors leading to undue influence.
- Provide adequate safeguards when studying vulnerable populations
- Respect subject's privacy and minimize intrusion.
- Design mechanisms to protect confidentiality of research data.

Thank you for your attention !

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