The P-4 NSABP Trial: NCAB Subcommittee Recommendations

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Prior NCI-Sponsored Breast Cancer Prevention Trials

- P-1: Tam vs Placebo. 13,388 women, Gail Risk 1.67 or higher.
- 49% reduction in invasive breast cancer over 5 yrs (3.3% vs. 1.7%)
- 2.9/ 100 subject had serious adverse events in Tam group vs 1.5 in control (DVT, PE, stroke, endo ca)
- Cost: $64.5 (yrs 1991-2004)
- Tam approved for prevention, clinical use modest

P-2 (STAR) Trial: Tam vs. Raxolifene

- 19,747 subjects randomized, 1999-2004
- Equal reduction of invasive breast cancer, but raloxifene less effective in reducing DCIS
- Raloxifene had fewer serious adverse effects (1/3 fewer endo cancers, thrombotic episodes)
- Cost: $129.5M to date
- Clinical use of raloxifene low, NDA to be filed

P-4: Major Concern

- If positive, will AI's change the practice of preventive oncology?

  - Toxicity have discouraged use of tamoxifen and raloxifene

  - Lack of a placebo control in P-4 will make it difficult to assess toxicity of AI: bone and cardiac effects

  - No effect of SERMS on survival. AI effect will take years to assess.

Additional Concern: Is P-4 a Registration Trial?

- Letrozole goes off patent in 2011. Novartis would file for prevention indication if study is positive, but would not invest in marketing
- Position of FDA on trial design is uncertain. Is evaluation of toxicity adequate? How long it will be necessary to monitor subjects?

Additional Concern: P-4 Trial Cost

- Initial cost of trial (5 yrs) will be $55M
- Follow-up will be an additional 5-10 yrs, with an additional cost of $80 M or more

Expert Panel: Biomarker for Risk Is Highest Priority for Breast Prevention Trials

- All participants recognize the need to narrow the circle of “high risk” patients, in order to improve the risk/benefit ratio
- NSABP must assure the sharing of blood, tissues, and data (as necessary) to outside investigators through a transparent process

Recommendations of the NCAB Subcommittee

- While P-4 is a well-designed, interesting, and relevant clinical trial, even if positive, it is unlikely to change the practice of preventive oncology. In view of the cost of the trial, the patent status of letrazole, and the need for expanded research on biomarkers for risk, we can not offer strong endorsement of its funding.