

A Critique of the Breast Cancer Clinical Research Process

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BACKGROUND

- Part I A description of the types of clinical trials now required
- Part II Detailed proposals to improve efficiency and save lives

PART I

Types of clinical trials of new cancer agents:

1. *First, studies must be conducted in advanced disease stages to establish efficacy and maximal safe doses (Phase I and II trials).*
2. *Next follow the randomized trials, in Stage IV advanced disease. If the drug is shown to be clinically safe and effective, it must then be compared with standard treatment in a randomized trial of advanced disease.*
3. *Only if the new drug is found to be superior to standard treatment in advanced disease can it be compared with standard treatment in a randomized trial in early stage disease.*
4. *After a drug has been found effective in the adjuvant setting, it still has to be fully characterized by finding the optimum dosage, duration and combination with other therapies. This requires yet another set of randomized trials.*

PART II

Detailed proposals to improve efficiency and save lives

1. **STAGE IV: ENHANCED SPEED & SIMULTANEOUS STAGE IV STUDIES.**
 - i. **Increased efficiency** - simultaneous, multicenter randomized trials
 - ii. **No delays** - start as soon as possible after phase i & ii studies
 - iii. **Coordination** - at least four to five large randomized Stage IV trials to be completed and analyzed in meta-analysis for refined conclusion.
2. **REFINED OUTCOME ASSESSMENT OF STAGE IV RANDOMIZED TRIALS**
 - i. **Minimum response** - good responses, but no improvement of progression free survival and overall survival.

- ii. **Medium response** - good responses and improvement of progression free survival, but no benefit in overall survival.
- iii. **Maximum response** - good responses and improvement of progression free survival, but no benefit in overall survival.

nb. Only agents of the type iii. (i.e those with maximum response – 50-60% of all tested) – would qualify for the “skipping” of adjuvant trials)

3. **NEOADJUVANT TESTING OF THE NEW AGENTS - OBLIGATORY COMPONENT OF STAGE IV RANDOMIZED TRIALS.** At the completion of randomized-controlled trials in Stage IV disease, supplement the outcome information with additional data generated through a series of neoadjuvant trials involving stage II - III disease. In these trials, the new drugs are given over two to three months before the definitive surgery, while a series of needle tests secure tissue for “molecular“ responses. Those, combined with the “pathology responses” as seen from analyzing tumor at the time of mastectomy, provide the best and swiftest assessment, and monitoring, of in-vivo response of new drugs (Ragaz, Journal of Cancer, 1985). It is important to note that multiple randomized trials have shown that delaying the definitive surgery by several weeks while receiving neoadjuvant therapy is safe, without adverse impact on recurrences or relapse rates (Fisher, JCO 1989).

4. **NEW PROCESS OF CLINICAL TRIALS FOR ADJUVANT SETTING.**

Once the benefit of a new agent is documented both in stage IV and neoadjuvant disease, approve swiftly the new agent for a) routine use in the communities, and b) for a new type of studies in the adjuvant setting without the need for placebo-control randomization. In those new studies, the following features are to be considered:

- i. **Statistics.** For the selected new drugs, instead of placebo-control, use the “new study design” statistics analyzing the Concomitantly Guideline-Treated Controls (CGTC). The advantage is that a high number of new patients can be accrued and evaluated much faster.
- ii. **Registries.** These studies would require establishing uniform cancer Registries across institutions of the same region, within each Province, and eventually in the whole country. The uniform registries would collect identical prospectively controlled informatics, related to patient characteristics, their tumors and outcomes.
- iii. **Secondary outcome objectives**
Focus the new clinical adjuvant trials on secondary outcome objectives such as:
 - a. *Dose response* to obviate short-term and long-term toxicity rates;
 - b. *Duration therapy* – for example in the trastuzumab study, testing for two months versus six months versus 12 months, etc.
 - c. *Biomarkers* - identification of cohorts who benefit and those who do not. For example, use of biomarkers such as individual genes or their products (e.g. ER status, HER2/neu or topo II with a potential of restricting adjuvant chemotherapy only to “high chemotherapy responders,” or Her2/Neu, c-Myc or PTEN which can clarify the impact of trastuzumab); or more recently, the cDNA microarray applications providing a “portrait of genes” or the “genetic signature” of a given tumor – techniques where amalgamating signals of 21-80 different genes would

permit identification of cohorts who benefit and of those who do not to either a class of agents (e.g., to chemotherapy); or to individual agents (i.e., to anthracyclines).

5. INTERNATIONAL COORDINATION OF STEPS OUTLINED

Formation of a new virtual internationally-based leadership, for **S**imultaneous **P**rioritization and **E**arly evaluation of **C**oordinated of multicentre trials. (**SPEC**). This new leadership would have eventual jurisdiction to lead, execute, evaluate and eventually fund site-specific cancer studies, in coordination with multiple centres of most countries.