



Issues in Cancer Drug Development of the Future

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Agenda: Scientific Issues

- n Why improve the quality of cancer clinical trials?
- n Modernizing the science:
 - n Phase 0 through 2 trials
 - n Use of imaging and other biomarkers
 - n Use of modeling and simulation
 - n Efficacy trials
 - n Use of composite endpoints



Agenda: Regulatory Issues

- n Investigational drug-investigational diagnostic co-development
- n Combining several investigational agents in a single development program
- n Use of surrogate endpoints
- n Use of adaptive trial designs



Why Do Cancer Clinical Trials Need to be Improved?

- n Average success rate for all therapeutic areas: 11%
- n Major disease area success rates:
 - n cardiovascular: 20%
 - n arthritis: 17%
 - n infectious disease: 16%
- n Oncology drugs: 5%

From Kola and Landis. **Nature Reviews Drug
Discovery** 3: 711, 2004

Success rate=from first in human to registration



Modernizing the Science

- n Most experts in drug development agree that better evaluation of candidates, earlier in the process, will increase the success rate and and decrease the amount of residual uncertainty
- n This means modifying the traditional oncology drug trial process



Modernizing: Early Trials

- n Phase 0: proof-of-mechanism
 - n Concept is iterative development between laboratory and clinic
 - n Evaluate key parameters in most relevant species
- n Phase 1: increase use of biomarkers, pharmacokinetic analyses
- n Phase 2:
 - n Better dosing: adaptive dose finding trials (results analyzed collectively)
 - n End-of-phase 2a FDA pilot: use all knowledge to date on drug and develop model of drug effect, simulate next set of trials



Modernizing: Efficacy Trials

n Use of biomarkers

- n Many uses: select patients, select dose, monitor response, modify therapy
- n Biomarker should have good analytical validity if used in this way
- n Surrogate endpoints—regulatory issue

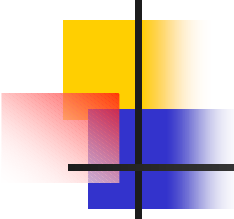
n Use of Composite Endpoints

- n Use of several outcome measures in one composite is accepted in many indications: cardiovascular, arthritis, psychiatric
- n Need to establish validity of composite



Regulatory: Investigational drug- ivg. diagnostic co-development

- n Can utilize same trial(s) to determine of drug and clinical utility of diagnostic
- n Drug needs normal safety workup
- n Diagnostic needs to have established analytical validity
- n Need to establish that test contributes some information
- n FDA to issue new concept paper ?next month



Regulatory: combining several investigational agents in a single development program

- n Not traditionally done but recognize may be needed for targeted RX
- n Three issues
- n Commercial considerations: can the companies work together?
- n Safety:
 - n Need some idea of toxicity profile of single agents
 - n Profile together will emerge from combination trials
- n Efficacy
 - n Need demonstration that each agent makes a contribution to the clinical effect



Use of Surrogate Endpoints

- n More complex than debate would let on, particularly in oncology
- n Confused with use of biomarkers for other purposes in trials
- n Many “surrogates” used now in oncology trials, e.g., RECIST
- n Refinement of these measures, e.g., using functional imaging, is not a hugely complex endeavor
- n For purposes of drug development, good reliable response measures (to increase ultimate success rate) combined with outcome trials, where outcomes don't take that long to occur, are reasonable



Use of Surrogate Endpoints

- n Field would benefit from rigorous identification of candidate surrogates and analysis of pathway to qualification
- n Where qualification feasible, could be carried out by consortium (e.g., critical path project)
- n Prevention is the area with the greatest challenges



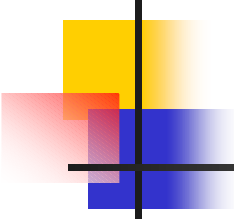
Use of Adaptive Trial Designs

- n Carefully thought through and executed designs that preserve both statistical rigor and trial integrity are accepted by the regulators
- n Industry very cautious
 - n Adaptive design involves some loss of direct control of the trial
 - n One path forward is to start using for dose finding and other lower risk areas
 - n Government trials could be the innovators



Additional Aspects of Trial Quality

- n Mechanics of trial conduct and execution—across all disease areas—are extremely suboptimal
- n FDA-DIA workshop (NCI and many academic and industrial participants)
 - n Urgent need for standardization of all aspects of trial design and execution
 - n Form public-private partnership to drive these changes
 - n FDA “BiMo” Initiative: Modernize FDA regulation



Societal Issues: Quality of Cancer Clinical Trials

- n Purpose of trials:
 - n develop evidence so that beneficial products will save lives and improve health
 - n provide access to investigational products
 - n support regulatory approval
 - n advance scientific knowledge
- n Are cancer product development programs meeting these purposes?



Definition of Quality

- n Quality= meeting needs of customers
- n Patients and prescribers are the ultimate customers
- n Regulatory agencies are “surrogates” for the customer
- n Quality issues raised in this session beyond the scientific problems



Summary

- n Better science in the early phases of cancer clinical trials would improve quality, increase the amount of information, and raise the probability of success in efficacy trials
- n Late stage trials in cancer could be confirmatory and incorporate evaluation of a wider target population



Summary

- n Quality of cancer trials also includes quality and efficiency of execution—something that needs improvement
- n Must keep in mind the purpose of the clinical trial enterprise—saving lives and improving the health of population