

Adaptive Oncology Clinical Trials : Real Life applications

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Outline

- Background
 - Definition
 - Common adaptations
 - Rules of Adaptations (Pharma adaptive group)
- Real life examples
 - Dose escalation using Bayesian TITE-CRM
 - ISPY -2 for using biomarkers in phase II for efficacy in breast cancer
 - Within patient dose treatment adaptation in Pediatric Brain tumor patients

What is an Adaptive Design?

- Many names that could be associated with it:
 - Novel, flexible, multi-stage, response driven, dynamic, sequential, self designing
- An adaptive design should be adaptive by "design" not an *ad hoc* change of the trial conduct and analysis
- Adaptation is a prospective design feature, not a remedy for poor planning
- In general it is a pre-specified modification in the design or statistical procedures of an on-going trial depending on the data generated from the trial.

What is an Adaptive Design?

- FDA Draft Guidance (2010): “An adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.”
- The Purpose is to make trial efficient, flexible and fast without undermining trial **validity and integrity**.
- Prospective here means that the adaptation was planned (and details specified) before data were examined in an unblinded manner by any personnel involved in planning the revision.
- Study design aspects that are revised based on information obtained entirely from sources outside the study are not considered adaptive design

Validity and integrity of the study

Validity :

- providing correct statistical inference (such as adjusted p-values, unbiased estimates and adjusted confidence intervals, etc.)
- assuring consistency between different stages of the study
- minimizing operational bias

Integrity :

- providing convincing results to a broader scientific community
- preplanning, as much as possible, based on intended adaptations
- maintaining confidentiality of data

Adaptive types classification

Method/design-based :

- *Based on adaptation method used*

Rule-based:

- Four rule-based :
allocation, sampling, stopping, decision

Some Common Adaptations methods-1

- Hypotheses/objectives (Non-inferiority → superiority or from primary to secondary endpoint)-before data lock/unblinding
- Primary outcome variable (Variable, timing, composite components)
- Eligibility criteria
- Adaptive dose-finding- early phase (minimum effective dose, MTL)
- Enrichment and/or Biomarker (Subgroup, response of biomarkers associated with disease)
- Statistical analysis plan

Common Adaptation methods-2

- Group sequential
- Drop-the-loser (or dose level or add a new treatment in phase II)
- Adaptive randomization (include allocation probabilities)
- Adaptive treatment-switching: for safety or efficacy
- Adaptive seamless (use of data before and after adaptation transition from phase II to III without pause)
- Multiple adaptive: combination of any above methods

Adaptive Rules-Based Types

Four adaptive rules-based types:

- **Allocation Rule:** How the subjects will be allocated to the study arms (response-adaptive randomization and Covariate adaptive allocation).
- **Sampling rule:** How many subjects will be sampled at the next stage (sample size re-estimation, and drop the loser design).
- **Stopping Rule:** When to stop the trial (group sequential design, adaptive treatment switching design)
- **Decision Rule:** Other designs (Hypothesis adaptive, primary endpoint change, statistical method, or patient population).
- next, Let us look at some details of the four rules

Allocation Rules

How the subjects will be allocated to the study arms (response-adaptive randomization and Covariate adaptive allocation).

- Static AR:
 - Randomization to balance baseline prognostic factors. It uses allocation probabilities with or without Stratification.
- Dynamic AR:
 - Response-adaptive randomization uses interim data to unbalance the allocation probabilities in favor of the “better” treatment(s)
 - Allocation can be based on posterior probabilities (Bayesian).

Sampling Rules

- Sample size re-estimation (SSR)
 - Blinded SSR or Unblinded SSR based on estimate of nuisance parameter
- Traditional Group Sequential Designs
 - Sample sizes per are known in advance and fixed.
- Error Spending Approach
 - Variable sample sizes per stage (but do not depend on observations)
- Sequentially Planned Decision Procedures
 - Future stage sample size depends on the current value of test statistic
- Flexible SSR uses also the estimated treatment effect

Stopping Rules

- Early Stopping based on Boundary Crossing
 - Superiority
 - Harm
 - Futility
- Stochastic Curtailment
 - Conditional power
 - Predictive power
- Bayesian Stopping Rules
 - Based on posterior probabilities of hypotheses
 - Complemented by making predictions of the possible consequences of continuing

Decision Rules

- Changing the test statistics
 - Adaptive scores in trend test or under non proportional hazards
 - Adaptive weight in location-scale test
 - Including a covariate that shows variance reduction
- Redesigning multiple endpoints
 - Changing their pre-assigned hierarchical order in multiple testing
 - Updating their correlation in reverse multiplicity situation
- Switching from superiority to non-inferiority
- Changing the hierarchical order of hypotheses
- Changing the patient population
 - going forward either with the full population or with a pre-specified subpopulation

Real Life Examples

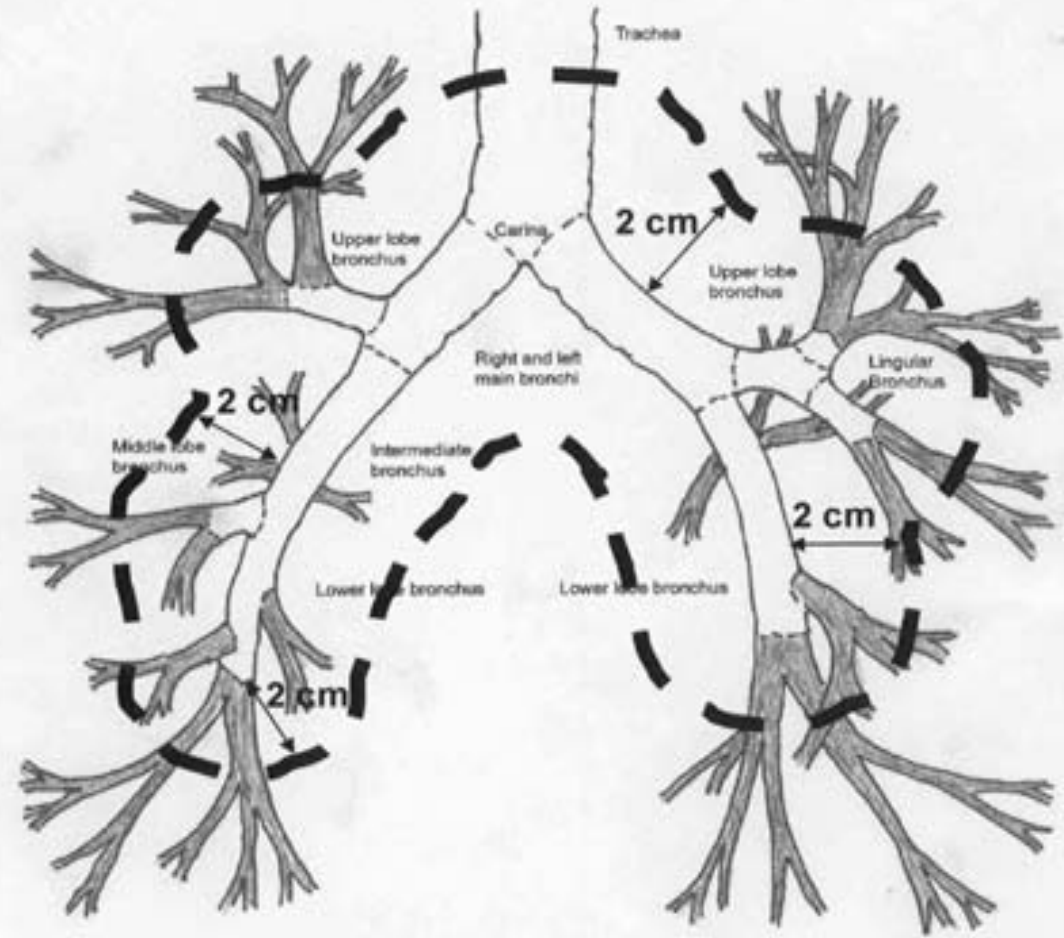
- **RTOG 813**: Seamless Phase I/II Study of Stereotactic Lung Radiotherapy for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) Medically Inoperable Patients.
- **I-SPY 2**: Neoadjuvant and personalized adaptive Novel agents to Breast Cancer
- *Radio-chemo-immunotherapy using the IDO-inhibitor indoximod for children with **progressive brain tumors***

Example #1: RTOG 0813

Seamless Phase I/II Study of Stereotactic Lung Radiotherapy for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) Medically Inoperable Patients

Patient Population

- Patients with stage T1-2, N0, M0, non-small cell lung cancer, tumor size ≤ 5 cm, who are not candidates for a complete surgical resection in the opinion of a thoracic surgeon;
 - (primary tumor T1-T2 with no regional lymph node and no distant Metastasis)
- only patients with tumors within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura.



— — — — Defines zone of the proximal bronchial tree

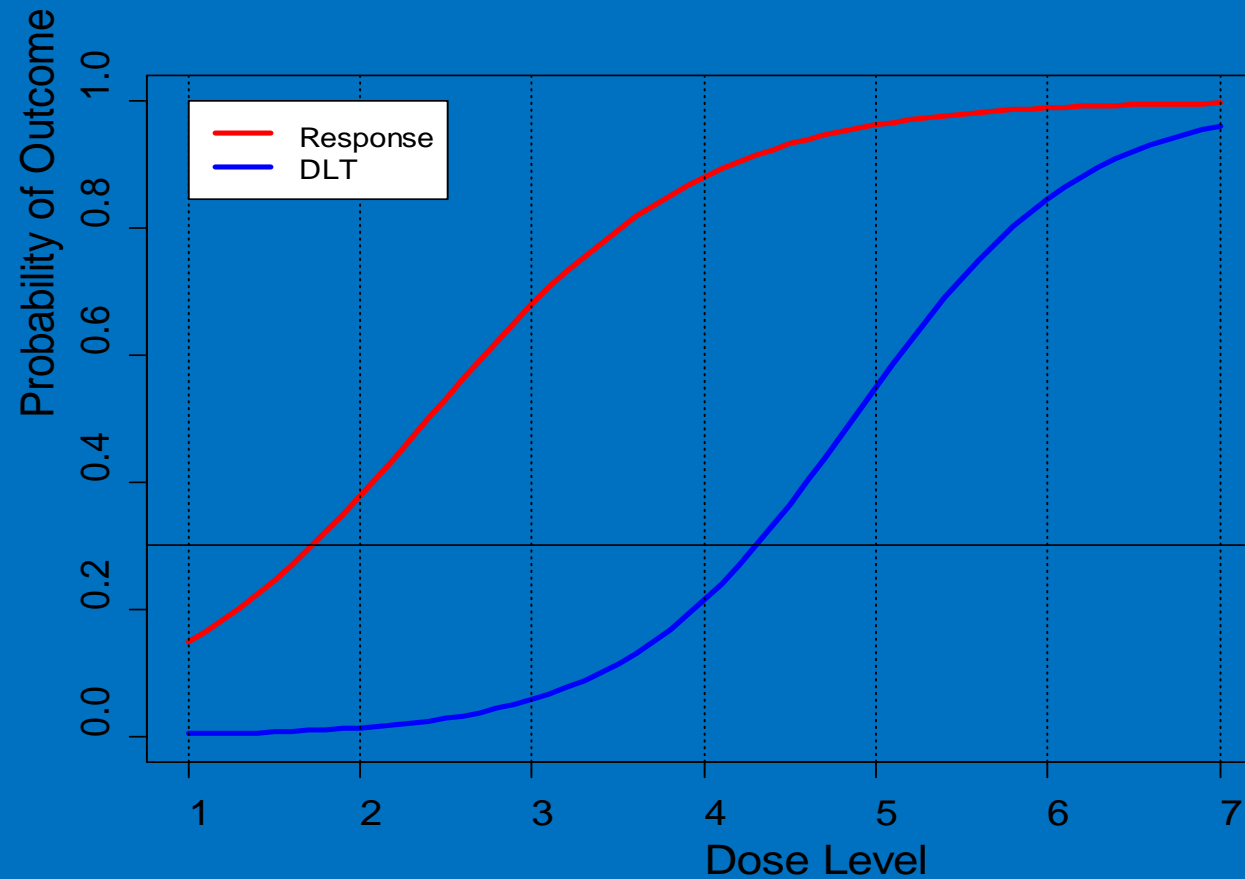
Stereotactic Body Radiation Therapy (SBRT)

- Increasing RT dose may help but often fail to reach the tumor.
- SBRT is a technique that allows delivery of high doses of Radiation by multiple co-planar and non-coplanar beams & guided by a set of coordinates (stereotactic)
- It is borrowed from experience gained from brain RT.
- It requires precise definition of the target, assessment of target motion, planned volume, and daily high quality set-up verification prior to each treatment

Primary Study Objectives

- Phase I Portion To determine the maximum tolerated dose (MTD) of SBRT for centrally-located NSCLC and the efficacy of that dose in patients who are not operative candidates *
- Phase II Portion : To estimate the primary tumor control rate at the MTD of SBRT
- We will focus on Phase I part

Efficacy & Toxicity Both Increase With Dose



DLT = dose-limiting
toxicity

Dose Escalation & Patient Assignments

- Several methods, for example:
 - 1. The classic 3+3 method
 - 2. Continual Reassessment method (CRM)
 - 3. Time-To-Event CRM (TITE-CRM) * (modification of CRM)

CRM: Bayesian Adaptive Design

- Dose for next patient is determined based on toxicity responses of all patients previously treated
- Based on statistical model
- After each cohort of pts, posterior distribution is updated to give model prediction of optimal dose for a given level of toxicity (DLT rate)
- Find dose most consistent with desired DLT rate
- Modifications have been both Bayesian and non-Bayesian.

Statistical Models for CRM

Let the toxicity response be $x_j \sim \text{Binomial}(n_j, p_j)$ for doses $j = 1, \dots, J$. The following models are commonly used with CRM:

Hyperbolic Tangent $p_j = \left(\frac{\tanh(x_j) + 1}{2} \right)^\alpha$

Logistic: $\log\left(\frac{p_j}{1-p_j}\right) = b + \alpha x_j$

Power: $p_j = (x_j)^\alpha$

Prior for α : Unit Exponential, Uniform, Gamma, etc.

CRM Steps

1. Start with a prior estimate of $\text{Pr}(\text{DLT})$ for each dose level.
2. Select a mathematical model to describe the relationship between dose and $\text{Pr}(\text{DLT})$.
3. Describe uncertainty of the model by a prior distribution
4. After each patient, update the model, and estimate the probability of toxicity for each dose level.
5. Treat next patient at the dose whose estimate is closest to some pre-specified target (say, 20%).
6. Stop when a maximum sample size is reached.

Issues With 3+3 Cohort and CRM

- Must be closed to accrual while cohorts are observed
- Toxicities of interest may occur late, resulting in a long time interval before escalating or de-escalating the dose
- Long time interval leads to difficulty in recruitment and management.

Long-Term Toxicities?

- Toxicities for RTOG 0813 may happen > one year later.
- CRM and 3+3 algorithm take a long time to accrue, even with rapid accrual
- Investigators may be interested in toxicities over one or two years
- For study with 15 pts and 1 year follow-up, 3 pts at a time requires 5 years
- Need an alternative: one answer is TITE-CRM

Time-to-Event CRM (TITE-CRM)

- Modifies CRM by weighting to account for proportion of the observation period that each currently enrolled patient has been observed.
- No extra assumptions in final analysis beyond those made by CRM;
- Extra assumptions invoked for early dose-escalation;
- Like CRM, is model-based, thus very flexible.

Investigator Defined Components

- The target toxicity probability $p^* \in (0,1)$
- The fixed number of subjects, n , to be evaluated
- Length of observation time.
- The set of K doses to be administered over the course of the study, $\{d_1, \dots, d_k\}$
- Dose level to assign to first Pt+ rules/restrictions
- Initial estimates for the probability of dose limiting toxicity for each of the k -th dose levels $\{\hat{p}_{01}, \dots, \hat{p}_{0k}\}$

RTOG 0813 SBRT Dose Schema

Dose Level	Level 1	Level 2	Level 3	Level 4	Level 5 (*)	Level 6	Level 7	Level 8	Level 9
Dose/Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	10 Gy	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40Gy	42.5 Gy	45 GY	47.5 Gy	50 Gy	52.5 Gy	55 Gy	57.5 Gy	60 Gy

- †Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.

Model Used In The Trial

- The Weighted Dose-Toxicity Model Doses was allocated to patients by means of TITE-CRM Phase I.
- A logistic dose-toxicity model was used
- The prior distribution of the dose-toxicity parameter α is Gaussian $N(1, 0.3)$ which is based upon experience with other trials using this model.
- $\alpha=1.0$ represents the initial assumption about the toxicity of treatment

Use of Weights: Partial Patient Contribution

- Weight function $\omega(u) = u/12$ as a uniform distribution over 12 months.
- A) Patients who have enrolled in this trial but have not experienced a DLT have a weight equal to the proportion of the 12 months observation period they have completed.
- B) Patients who have experienced a DLT before 12 months from the start of SBRT or complete protocol treatment without a DLT have a full weight, 1.

Assignment Of Doses

- The 1st patient will be treated at dose Level 5 (10 Gy).
- A subsequent pt presents for enrollment, the expected value of α , conditioned on the prior distribution and the weighted data will be calculated, from which the expected probability of a DLT at each dose level will be estimated
- The patient will be assigned to the highest dose level with an expected probability of a DLT \leq the target rate of 0.20.

Assignment Of Doses- cont.

Escalation conditions:

- Dose may only increase one level between consecutive patients;
- Dose may decrease any number of levels between consecutive patients;
- A patient may not be assigned to a next higher dose level unless there is at least 1 year of cumulative observation at the current dose level.

Verifications And Assessments Of The Model

- Monte Carlo simulation was used to assess the operating characteristics of this trial with respect to each of these metrics in turn.
- Three simulations were performed for the true dose-conditional probability of toxicity.
 - Scenario 1 (DLT_{td}) is the initial trial design for true dose-conditional probability of toxicity.
 - Scenario 2 (DLT₊) is approximately twice as toxic as assumed by the trial design.
 - Scenario 3 is more than twice as toxic as the trial design, with rapidly increasing toxicity at dose Levels 7 and higher (DLT₊₊).
- A sample size of 75 patients was determined to have acceptable probability of correctly selecting a dose with acceptable toxicity and enough patients treated about the target dose for characterization of the efficacy endpoints, while being feasible for completion of accrual within 4 years.

Toxicity prob. Simulation Assumptions Used to Determine Operating Characteristics

Dose Level	SBRT Fr dose (Gy)	Probability Of Toxicity			
		Design (P0)	DLT -trial design	DLT+	DLT++
1	08.0	0.01	0.01	0.02	0.02
2	08.5	0.02	0.02	0.04	0.05
3	09.0	0.04	0.04	0.06	0.08
4	09.5	0.05	0.05	0.10	0.13
5	10.0	0.08	0.08	0.15	0.18
6	10.5	0.10	0.10	0.20	0.30
7	11.9	0.14	0.14	0.30	0.40
8	11.5	0.17	0.17	0.35	0.60
9	12.0	0.20	0.20	0.40	0.80

Things To Consider

- TITE-CRM required a well trained statistician available all time (or a backup statistician) to help determine the dose for the incoming patient based on the information from all previous patients.
- Need to explain to investigators and work with them on the assumptions.
- It is an efficient method for the late toxicity.
- Seamless Phase I/II was a good design for this study and should be considered for similar studies.

Example 2: Neoadjuvant And Personalized Adaptive Novel Agents To Breast Cancer (ISPY-2)

ISPY-2 Objectives

- Started in 2010 intended to speed up the process of finding effective drugs for a specific breast cancer subtypes
- Employ Adaptive design to test new agents among smaller groups identified as likely candidates for the therapy through detailed screening
- Compare efficacy of novel drug in combination with standard chemotherapy Vs. Standard therapy alone, in terms of **probability of pathologic complete response (pCR)** for each biomarker signature established at trial entry
- Identify improved treatment regimens for subsets on basis of biomarker signature of their disease.
- What changes these drugs make on tumor biomarkers and MRIs

Study Population

- 18 YO+ (adult+senior) females newly diagnosed with stage II or III breast C with
- No prior cytotoxic regimens
- Willing to undergo core biopsy of primary breast lesion to assess baseline biomarkers (≥ 2.5 cm).
- Clinically or radiologically measurable disease in the breast after diagnostic biopsy
- Have a biomarker profile indicating a high risk of recurrence with standard treatment, based on:
 - ER/PR status (Estrogen /Progesterone Receptors)
 - HER2 status
 - MammaPrint results

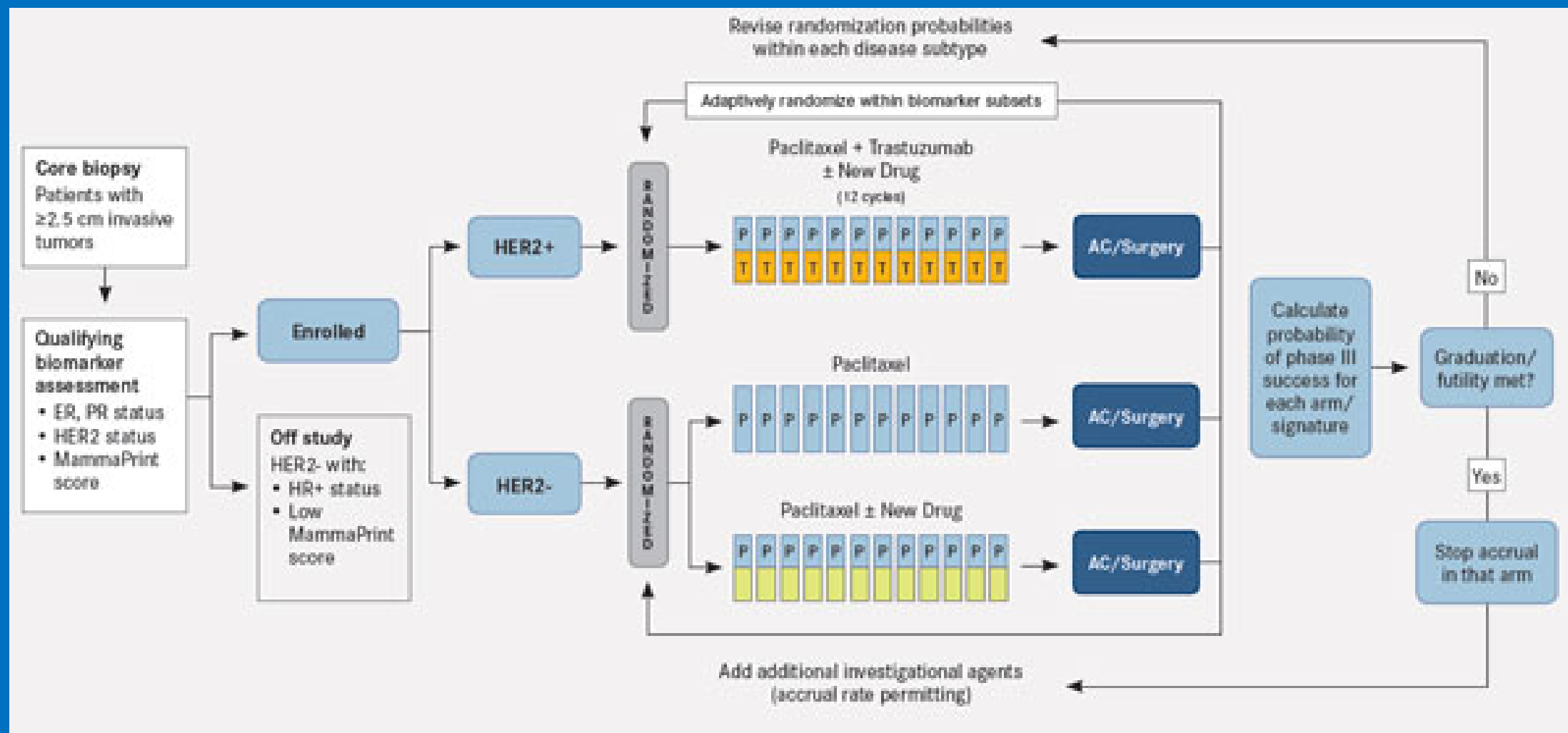
Two Step Informed Consent Process

- Screening
 - Provides general description of I-SPY 2
 - Provides specific information about eligibility requirements and screening procedure
 - Does *not* provide specific information about drugs
 - Requests patient's agreement to be screened
- Treatment
 - Follows patient randomization
 - Provides detailed description of I-SPY 2
 - Requests patient's agreement to be treated in I-SPY 2

Standard Treatment During I-SPY 2

- Chemotherapy is given prior to surgery (neoadjuvant treatment).
- Standard chemotherapy includes Taxol, AC, and Herceptin (if HER2+).
- Surgery takes place approximately 6 months after the first treatment.
- Hormonal treatment and/or radiation therapy is given after surgery to patients, if indicated.

I-SPY 2 design process



New Drug Criteria

- Criteria for drug inclusion:
 - Evidence of potential efficacy from preclinical/clinical studies
 - Found safe in at least 1 Phase I with taxane (or taxane & trastuzumab combination in patients with HER-2 positive tumors).
- Criteria for Graduation:
 - Meet threshold of 85% of predicted probability of success in phase III trial of at least 300 patients.
 - Double the log odds of achieving pathologic complete response.

Active Clinical Investigations

Agent/Regimen	Target (s)	Company
Trebananib (AMG 386) ± trastuzumab (Herceptin)	Angiopoietin 1/2-neutralizing peptibody + HER2-targeting agent	Amgen
Ganitumab (AMG 479) + metformin	Insulin-like growth factor 1 receptor inhibitor + anti hyperglycemic agent	Amgen
MK-2206 ± trastuzumab	Akt inhibitor + HER2-targeting agent	Merck
Pertuzumab (Perjeta) + trastuzumab	HER2-targeting agents	Genentech
Pertuzumab + T-DM1 (Kadcyla)	HER2-targeting agents	Genentech
Graduated Agents		
Veliparib (ABT-888) + carboplatin	PARP inhibitor with platinum compound	AbbVie
Neratinib	Pan-ErbB inhibitor	Puma Biotechnology

ISPY-2 Adaptations

- Regimens that show high Bayesian predictive prob. of being more effective than Standard Trt will graduate to the trial with their corresponding biomarker signature(s).
- Drugs graduate along with biomarker signature in which they demonstrate success, therefore subsequent Phase III trials can be much smaller and more precise.
- Regimens will be dropped if low probability of improved efficacy with any biomarker signature(s).
- New drugs will enter as those that have undergone testing complete their evaluation.

***Example 3: Radio-Chemo-Immunotherapy
Using The IDO-inhibitor Indoximod For
Children With Progressive Brain Tumors***

***Within patient treatment adjustment
Georgia Cancer Center***

Can Combined Radio-Chemo-Immunotherapy Improve Efficacy With Lower Toxicity?

- Pediatric brain tumors are ~70% curable
- In the relapse setting, conventional therapy is either not effective, or works for some cases but is too toxic
 - Relapsed glioblastoma
 - Radiation - unclear benefit
 - Chemotherapy - does not work
 - Relapsed medulloblastoma
 - Many patients have already failed tandem autologous transplant
 - Relapsed ependymoma
 - Full dose radiation - works but too toxic for 80% of cases
 - Lower dose radiation - doesn't work
 - Chemotherapy - doesn't work

Hypothesis

Radio-immunotherapy using IDO-blockade may act as a one-time endogenous vaccine to activate native immunity

... but must be followed by

Cyclic chemo-immunotherapy to achieve sustained responses and late responses.

Resulting anti-tumor immunity may allow less intense conventional therapy to be effective.

Population And Treatment

- Patients 3 to 21 years of age with newly-diagnosed with brain cancer
- Uses the IDO-inhibitor drug indoximod in combination with radiation and chemotherapy for front-line treatment.
- Because of the relentlessly progressive course and grim prognosis, we introduced novel experimental indoximod immunotherapy during up-front radiotherapy.
- Indoximod blocks the indoleamine 2,3-dioxygenase (IDO) pathway, which is an endogenous immune-regulatory pathway expressed by myeloid cells in the tumor microenvironment.
- We have recently completed two separate indoximod dose-finding arms in a first-in-children

Adaptations

- Using indoximod combined with fractionated radiation (54 Gy), followed by maintenance immunotherapy with indoximod combined with conventional cyclic temozolomide chemotherapy.
- We hypothesize that indoximod-based combination radio-chemo-immunotherapy will improve outcomes (objective response rate, 12-month progression-free survival, median overall survival).
- Patients who progress are
 - allowed an additional course of radio-immunotherapy with indoximod, if appropriate to re-establish disease control,
 - and are allowed to crossover to oral metronomic cyclophosphamide plus etoposide chemo-immunotherapy with indoximod as tolerated.

Selected Readings

- FDA IND application
- FDA Guide to enrichment trials.
- FDA Guidance:
- NCI website
- I-Spytrials.org
- Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities, *Biometrics*. 56:1177-1182, 2000
- Normolle D, Lawrence T: "Designing Dose Escalation Trials with Late Onset Toxicities Using the Time-to-Event Continual Reassessment Method." *J Clin Oncol* 24: 4426-4433, 2006.
- Adjei A, Christian M, Ivy P. (2009). Novel Designs and End Points for Phase II Clinical Trials. *Clinical Cancer Research*, 15(6), 1866-1872.
- Ariel Lopez-Chavez et al. *JCO* 2015; 33:1000-1007
- Ananthakrishnan R et al. *Crit Rev Oncol Hematol*. 2013 Oct;88(1):144-53

Additional slides

Parametric Dose Toxicity Model

- The model specifies how dose level relates to the probability of dose limiting toxicity.
- Should be monotone increasing and usually consists of a single parameter.
- A common choice is to use a logistic dose toxicity
- model given by (k is an index for dose k)

$$p_k = \phi(d_k, \alpha) = \frac{e^{\beta + \alpha d_k}}{1 + e^{\beta + \alpha d_k}}$$

Finding dose for DLT

- α influences rate of change of dose-toxicity function
- has a prior distribution, $\pi(\alpha)$, Normal (1, 0.3) for prior is commonly used..
- Setting $\alpha = 1$ fits initial estimate of probability of DLT

$$\phi(d_k; \alpha = 1) = \hat{p}_{0k} \rightarrow \rightarrow d_k = \log\left(\frac{\hat{p}_{0k}}{1 - \hat{p}_{0k}}\right) - 3$$

- The operating characteristics of the trial can be evaluated and optimized using simulations

α Estimation

- With J pts enrolled, to estimate α , we have a set of doses (d_1, \dots, d_J) , toxicity outcomes (y_1, \dots, y_J) where $y_j=1$ if toxicity; and times observed (u_1, \dots, u_J) , $0 < u_j < T$
- The information about alpha is given by the likelihood:

$$L_J(\alpha) = \prod_{j=1}^J (\omega_j \phi(\mathbf{x}_j; \alpha))^{y_j} (1 - \omega_j \phi(\mathbf{x}_j; \alpha))^{1-y_j}$$

- Where weights are defined as:

$$\omega_j = \begin{cases} \frac{u_j}{T}, & \dots y_j = 0 \\ 1, & \dots y_j = 1 \end{cases}$$

- u_j is the current length of follow up for pt j

Simulations and Results

- Complete trials (2,250 for each trial scenario considered) were simulated using 3 different assumptions about the true probabilities of dose-limiting toxicity at each dose.
- Trail sizes from 30 to 120 were evaluated, as were different rates of patient accrual.
- The number of toxicities observed is relatively insensitive to the mis-specification of the hazard rate.
- A sample size of 75 patients was determined to have acceptable probability of correctly selecting a dose with acceptable toxicity and enough patients treated about the target dose for characterization of the efficacy endpoints, while being feasible for completion of accrual within 4 years.