# Clinical Trial Designs to Expedite Drug Development in Oncology

**Rajeshwari (Raji) Sridhara, Ph.D.**

Director, Division of Biometrics V, OB, FDA

**NCPF Workshop December 13, 2016**

# Adaptive Designs

- Allows for planned design modifications
- Modifications based on data accrued in the trial up to the interim time
- Unblinded or blinded interim results
- Control probability of false positive rate for multiple options
- Control operational bias
- Assumes independent increments of information

# Definition of Adaptive Design

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 (interim data) from subjects in the study

# Types of ADs

- Exploratory:
  - Less restrictive
  - Explore without adjusting for multiple looks, multiple adaptations to generate hypothesis to be tested
- Hypotheses Testing or Confirmatory:
  - Adequate and well controlled (A & WC) studies
  - Pre-planned, type I error rate (false positive rate) well controlled
  - Decision rules specified for each adaptation

# Group Sequential and Bayesian Designs

Group Sequential Designs

- During the conduct of the study, data are analyzed and reviewed at periodic intervals
  - Correlated increments of information
- Using interim estimates of treatment effect
  - Decide whether to continue or stop the trial
  - If continuing, decide on any modifications to sampling scheme

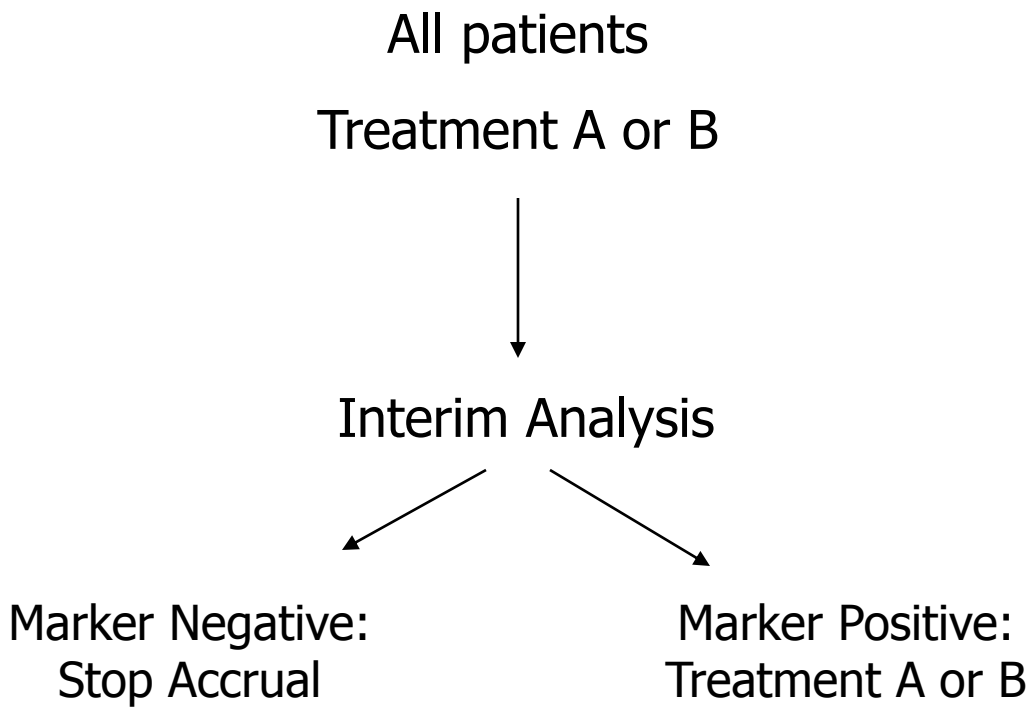
Bayesian Designs

- In the Bayesian paradigm, the parameter measuring treatment effect is regarded as a random variable
- Bayesian inference is based on the posterior distribution (Bayes' Rule – updated based on observed data)

# Enrichment Designs

- Enrich the study population
- Enrichment by prognostic marker → Examples: high risk population (where events will occur in short time) third-line setting; triple negative metastatic breast cancer; specific histology – mantle cell lymphoma
- Enrichment by predictive marker → Examples: Herceptin for Her2+ breast cancer; Zelboraf for melanoma with BRAF mutation.

# Adaptive Enrichment Design



# Master Protocols

- One overarching protocol that includes one or more of the following:
  - Multiple diseases
  - Multiple treatments
  - Multiple molecular markers
- Other names:
  - Platform Trials
  - Umbrella Trials
  - Basket Trials

# Characteristics of a Master Protocol

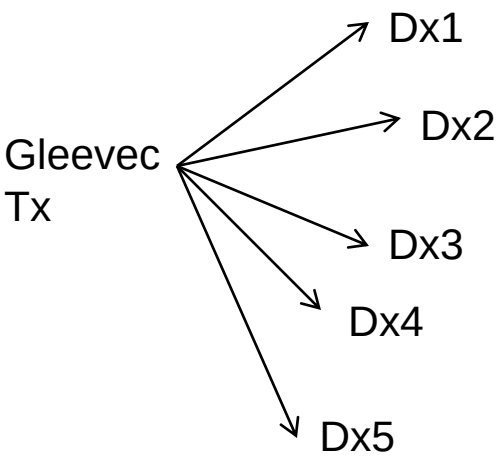
- One Protocol
- Central governance structure
- Central IRB
- Central DMC
- Central Independent review committee
- Central repository of data and specimens

- Study multiple drugs
  - Targeting more than one marker
  - More than one drug for one marker
- Study multiple markers
  - Overlapping expression of markers
- Leverage common control group(s)
- Flexibility to add/remove agents

# Non-Comparative Studies

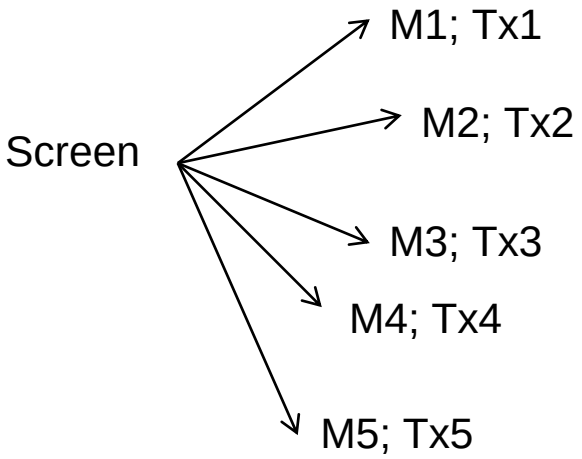
**Imatinib**

Considered as registration study with multiple cohorts of diseases with a common molecular biomarker (earlier approvals with proven efficacy and safety profile)




**NCI MATCH Trial**

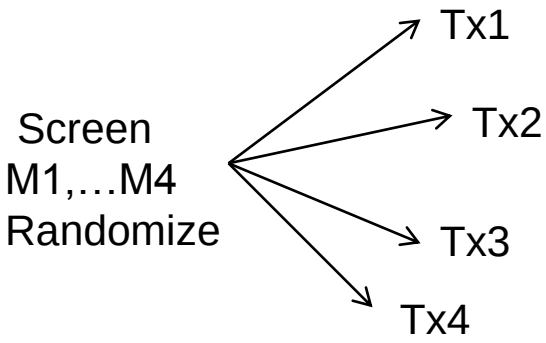
Exploratory study; Not defined by histology, multiple molecular markers, multiple treatments



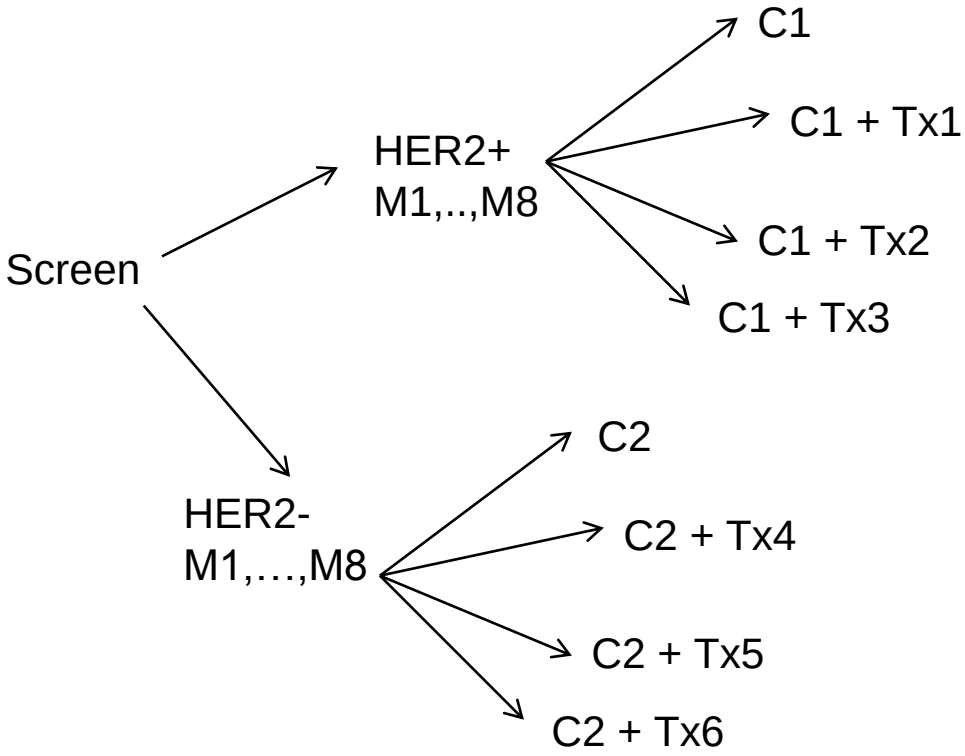

Tx = Treatment; Dx = Disease; M = Marker; P = Pathway

# Exploratory Comparative Studies

**BATTLE 1**
Advanced NSCLC




**ISPY 2**
Early Breast Cancer




Bayesian Response-adaptive randomization in both studies

# Phase 1/2 Expansion Cohort Studies

- Start with a dose escalation study in all solid tumors or hematological malignancies
- Amend protocol to start expansion cohorts in specific diseases, with different dosing regimens, single arm and randomized studies
- Central Governance

Things to consider:

- Pre-specified starting and stopping criteria and maximum sample size needed
- Patient protection – exposing patients to unknown safety risk
- Data tracking, Data dissemination, IRB involvement, etc.

Example: KEYNOTE 001 pembrolizumab study

# Keynote-001: Phase I Trial of Patients with Advanced Solid Tumors (N=1255)

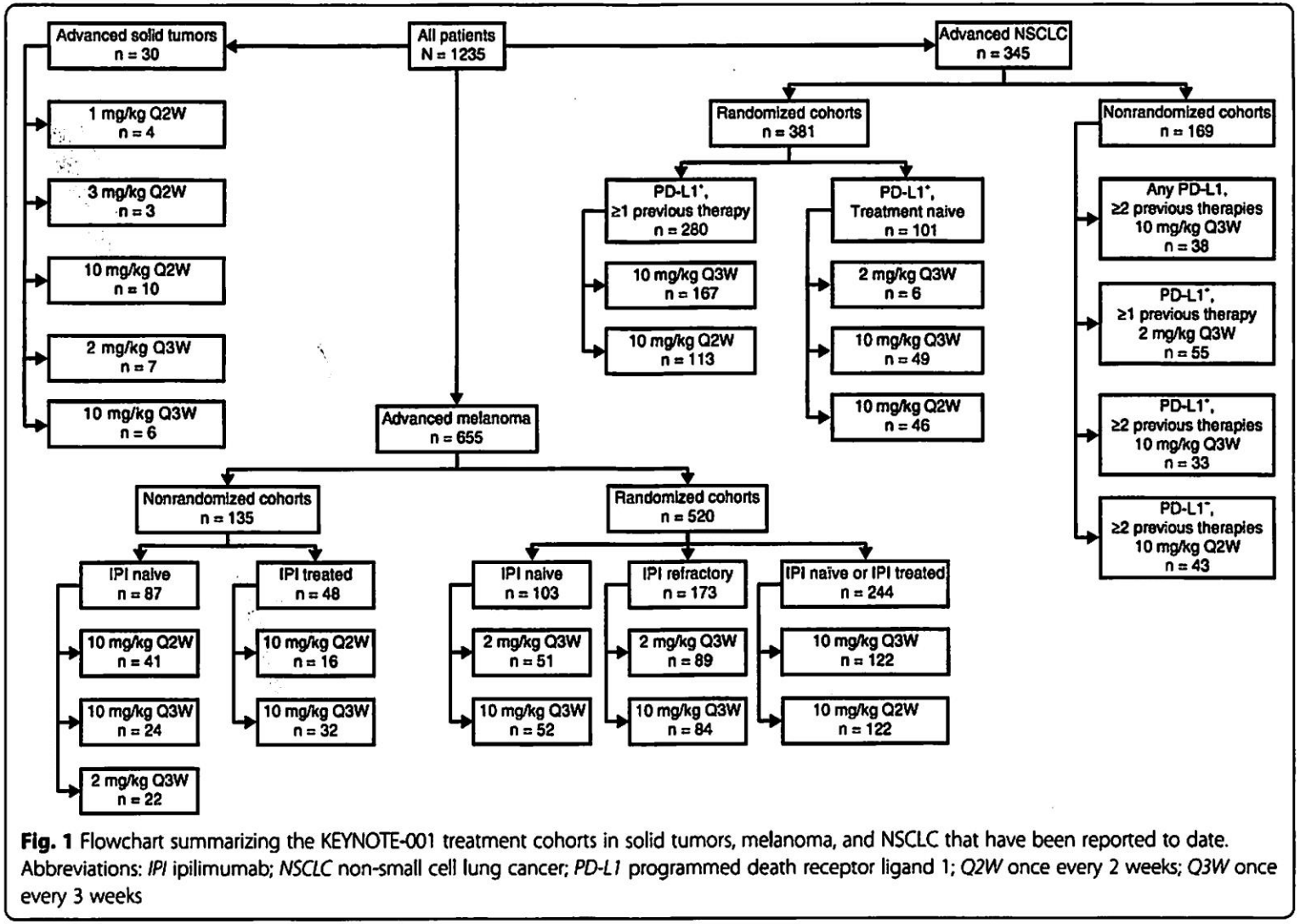



**Fig. 1** Flowchart summarizing the KEYNOTE-001 treatment cohorts in solid tumors, melanoma, and NSCLC that have been reported to date. Abbreviations: *IPI* ipilimumab; *NSCLC* non-small cell lung cancer; *PD-L1* programmed death receptor ligand 1; *Q2W* once every 2 weeks; *Q3W* once every 3 weeks

Khoja et.al., J of Immuno Therapy of cancer 2015

# Clinical Trial with Common Control

- Several treatments (T1, T2,…)compared to the same common control (C) in a given disease setting
- Compare each treatment with the control (T1 *vs.* C, T2 *vs.* C, etc.
- No comparison between treatments
- Equal randomization to treatments (1:1:1… randomization - C:T1:T2:….)

# Hypothetical Example to Illustrate Gain with Common Control

| **To detect HR = 0.5 with respect to OS** | **Median ~ 6 months with C** |
|---|---|
| **Two independent RCTs (T1:C and T2:C)** | 176 events<br>336 subjects |
| **Common Control Design (T1:T2:C)** | 124 events (↓30%)<br>216 subjects (↓36%) |

# Resources can be saved!

- 5 concurrent currently ongoing studies in advanced RCC
- In each of the 5 studies control arm is Sunitinib:
  - Checkmate 214: Ipi + Nivo →Nivo vs. Sunitinib
  - Keynote 426: Pembro + Axitinib vs. Sunitinib
  - Javelin Renal 001: Avelumab + Axitinib vs. Sunitinib
  - NCT02420821: Atezo + Bev vs. Sunitinib
  - NCT02811861: Lenvatinib + everolimus vs. Lenvatinib + pembro vs. Sunitinib
- Could have saved precious patient resource in one study with a common control!

# Comparison of Dynamic Treatment Regimes

Example: US Intergroup study of R-CHOP vs. CHOP

A two-stage random assignment:

1st stage: Induction R-CHOP vs. CHOP

2nd stage: Maintenance R vs. Observation in patients who achieve CR/PR with induction treatment

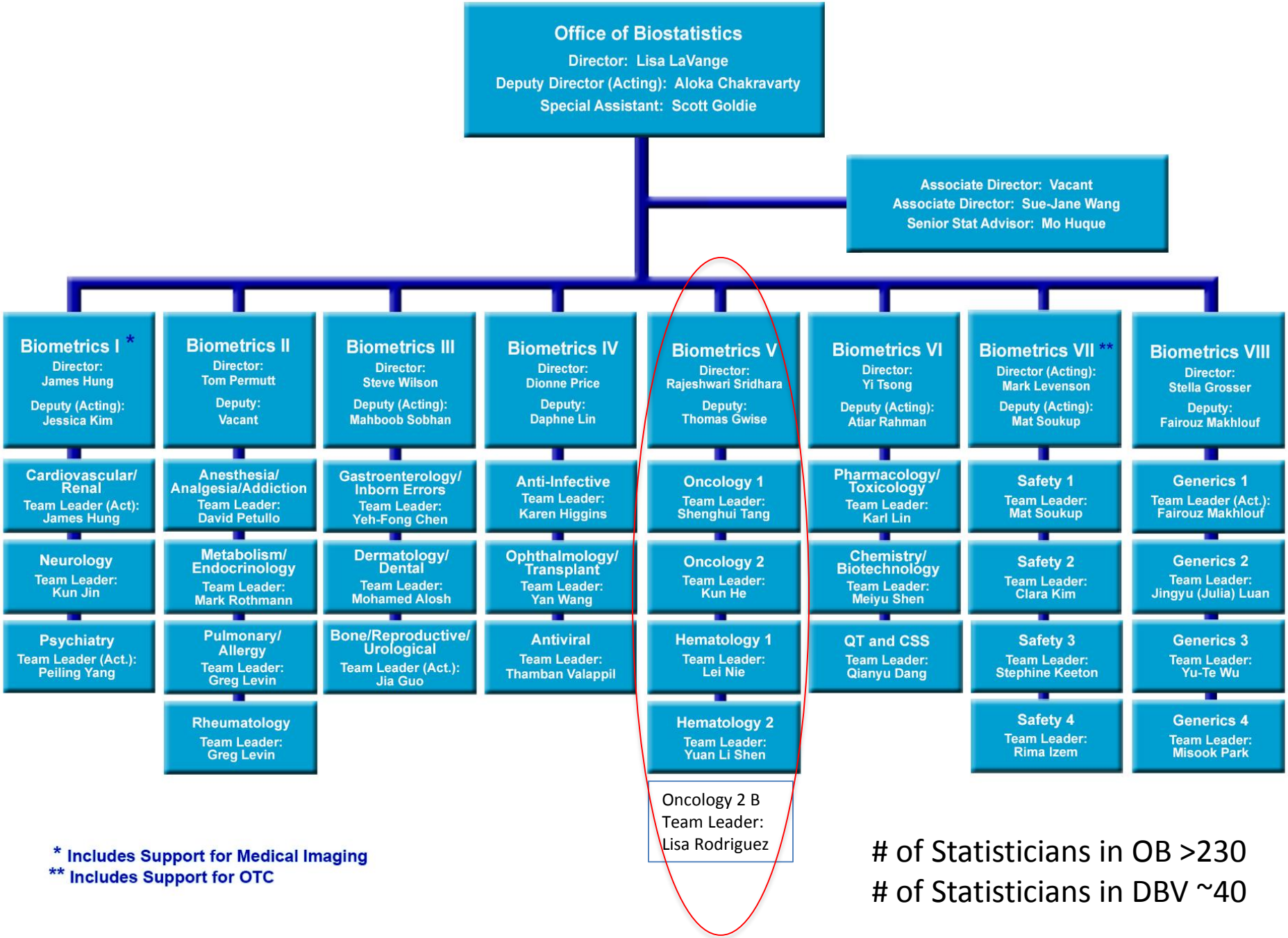
Primary Endpoint: Failure-free survival (failure: relapse, non-protocol treatment or death)

A weighted Cox-regression analysis was conducted – to remove the bias from analyzing only a subset of patients randomized in the second stage.

Ref: Rituxan product label Study 7; Habberman et al JCO 2006

# Comparison of Dynamic Treatment Regimes

- In practice patients are treated with sequential treatments
- The decision of the next treatment in sequence is specifically tailored to the patient
- Without re-randomization difficult to estimate treatment effect
- If the subsequent treatment is different from the first, then attribution of efficacy to a product is challenging
- Statistical methods for certain scenarios are available to determine the overall efficacy with a treatment regimen


Office of Biostatistics
Director: Lisa LaVange
Deputy Director (Acting): Aloka Chakravarty
Special Assistant: Scott Goldie
Associate Director: Vacant
Associate Director: Sue-Jane Wang
Senior Stat Advisor: Mo Huque
Biometrics I *
Director: James Hung
Deputy (Acting): Jessica Kim
Cardiovascular/ Renal
Team Leader (Act): James Hung
Neurology
Team Leader: Kun Jin
Psychiatry
Team Leader (Act.): Peiling Yang
Biometrics II
Director: Tom Permutt
Deputy: Vacant
Anesthesia/ Analgesia/Addiction
Team Leader: David Petullo
Metabolism/ Endocrinology
Team Leader: Mark Rothmann
Pulmonary/ Allergy
Team Leader: Greg Levin
Rheumatology
Team Leader: Greg Levin
Biometrics III
Director: Steve Wilson
Deputy (Acting): Mahboob Sobhan
Gastroenterology/ Inborn Errors
Team Leader: Yeh-Fong Chen
Dermatology/ Dental
Team Leader: Mohamed Alosh
Bone/Reproductive/ Urological
Team Leader (Act.): Jia Guo
Biometrics IV
Director: Dionne Price
Deputy: Daphne Lin
Anti-Infective
Team Leader: Karen Higgins
Ophthalmology/ Transplant
Team Leader: Yan Wang
Antiviral
Team Leader: Thamban Valappil
Biometrics V
Director: Rajeshwari Sridhara
Deputy: Thomas Gwise
Oncology 1
Team Leader: Shenghui Tang
Oncology 2
Team Leader: Kun He
Hematology 1
Team Leader: Lei Nie
Hematology 2
Team Leader: Yuan Li Shen
Oncology 2 B
Team Leader: Lisa Rodriguez
Biometrics VI
Director: Yi Tsong
Deputy (Acting): Atiar Rahman
Pharmacology/ Toxicology
Team Leader: Karl Lin
Chemistry/ Biotechnology
Team Leader: Meiyu Shen
QT and CSS
Team Leader: Qianyu Dang
Biometrics VII **
Director (Acting): Mark Levenson
Deputy (Acting): Mat Soukup
Safety 1
Team Leader: Mat Soukup
Safety 2
Team Leader: Clara Kim
Safety 3
Team Leader: Stephine Keeton
Safety 4
Team Leader: Rima Izem
Biometrics VIII
Director: Stella Grosser
Deputy: Fairouz Makhlouf
Generics 1
Team Leader (Act.): Fairouz Makhlouf
Generics 2
Team Leader: Jingyu (Julia) Luan
Generics 3
Team Leader: Yu-Te Wu
Generics 4
Team Leader: Misook Park
* Includes Support for Medical Imaging
** Includes Support for OTC
# of Statisticians in OB >230
# of Statisticians in DBV ~40


FDA
U.S. FOOD & DRUG
ADMINISTRATION