CARDIAC SAFETY RESEARCH CONSORTIUM

CSRC Meeting
&
CSRC Think Tank: Detection, Assessment and Risk Mitigation of Cardiac Safety Signals in Oncology Drug Development

FDA White Oak
10903 New Hampshire Avenue
Silver Spring, MD 20993
October 24th -25th, 2017

October 24th Day 1

1:15pm-2:30pm Session I: Update on CSRC Activities

- Executive Committee- **Ignacio Rodriguez, MD** (Roche)
- Inter-organization Partnership Liaison Committee **Rick Turner, PhD, DSc** (Quintiles)
- Scientific Oversight Committee **Mary Jane Geiger, MD, PhD** (Icon)
- Scientific Programs Committee- **Jonathan Seltzer, MD, MBA, MA** (ACI Clinical)
- ECG Database Committee **Cindy Green, PhD** (Duke Clinical Research)
- White Paper Writing Committee **Thomas Todaro, MD, JD** (Medpace)
- Membership Committe**e Theressa Wright, MD** (Eli Lilly)

Discussion: New ideas and Suggestions for 2018

2:30-3:00: Regulatory Science: FDA Paths Forward- Mitchell Krucoff, MD (Duke Clinical Research Institute)

3:00pm-5:00 pm Session II: Hot Topic- A new FDA Pilot Program for providing pre-market "real time" safety data: Implications for Monitoring CV safety in Oncology Trials in Real Time

- Risk: Benefit evaluation of cardiac toxicity in Oncology Drug approvals **Bindu Kanapuru, MD** (FDA)
- Best practices for CV safety monitoring
    - Investigator- **Susan Dent, MD** (Ottawa University)
    - Sponsor
    - Regulator

Discussion: Impact of availability of real time data on CV monitoring. What are the possibilities of pre-market 'real time' data for detection/mitigation of CV safety issues? What are limitations (e.g. potential false positives, false negatives)? What process/education changes need to be made to accommodate real time information? Should CSRC actively pursue developing best practices in this area?

October 25th Day 2

8:00am- 8:10am CSRC Welcome & Goals of the Think Tank

8:10am-9:40 Session I: Translational Medicine and Non-clinical signals of potential cardiac toxicity
What is the current state of non-clinical testing for CV safety? How does evaluation of oncology compounds in Phase 1/1st-in-human oncology studies differ from other compounds? How does mechanism of action and metabolic profile effect evaluation of nonclinical signals?

- An Overview of Translational Medicine in Cardio-Oncology **Luana Pesco Koplowitz, MD, PhD** (Ducks Flats Pharma)(10mins)
- Cardiovascular Oncology: Do We Need Plumbers, Electricians, or Strength Trainers? **Gary Gintant, PhD** (Abbvie)(10mins)
- Preclinical Assessment of Potential Small Molecule Kinase Inhibitor-Induced Cardiac Toxicity: Past, Present, and Future **Baichun Yang, PhD** (FDA)(10mins)
- Induced Pluripotent stem Cells for Cardiac Safety Assessment and Precision Medicine: Regulatory Research at FDA **Ksenia Blinova, PhD** (FDA)(10mins)
- Personalized Assessments of Drug-Induced Cardiac Toxicities
- Discovery Phase Counterscreening for Functional Cardiotoxicity **Mathew Brock, PhD** (Genentech)(10mins)

Discussion: **How can we characterize cardiac risk more precisely and earlier?**

9:40am-10:00am Break

10:00am-12:00pm Session II: Specific CV issues in Oncology Development
For specific areas such as HTN, LV dysfunction, pro-arrhythmia: What are the differences in the oncology population compared to a reference population? Why can't we extrapolate from non-oncology population? What is the burden on cardiologists in evaluation of potential cardiac safety signals?

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- What are the cardiovascular toxicities germane to oncology drug development? **Javid Moslehi, MD** (Vanderbilt University)(10mins)
- What patient CV risk factors should be excluded from what types of oncologic agents **Anthony Yu, MD** (Memorial Sloan Kettering)(10mins)
- Redefining cardiac eligibility thresholds in oncology trials **Ana Barac MD, PhD** (Georgetown University/Medstar Health) (10 mins)
- Who should be responsible for cardiac safety design in oncology drug development? Oncologist, cardiologist, pharmacologist etc. How does a clinical and research cardiologist efficiently integrate him/herself into cancer therapy development at an early stage?

Discussion: How can cardiologists improve evaluation of potential cardiac signals? Are there assumptions we should avoid that would retard our understanding of toxicities in the oncology population?

12:00pm-12:30pm Lunch

12:30pm-2:30pm Session III: Assessment of CV signals
What areas of study design for Phase 2 and Phase 3 oncology studies need to be addressed in order to ensure that CV signals are detected? Are there standard data fields/CRFs that should be completed for suspected CV signals? In what situation will suspected events require adjudication? Do they need to be characterized differently in the oncology population? What is needed for safety reporting?

- Oncology Study design for assessment of CV safety endpoints
  - Design considerations for Cardio-oncology studies **Boaz Mendzelevski, MD** (Cardiac Safety Consultants)(12mins)
- Utilization of biomarkers for CV safety assessments
  - Serial assessments of serum biomarkers and when they might be considered. **Alan Jaffe, MD** (Mayo Clinic)(10mins)
  - Cardiovascular imaging endpoints in oncology clinical trials **Bonnie Ky, MD** (University of Pennsylvania)(10min)
- Practical considerations for CV safety monitoring
  - Strengths and weaknesses of standardized collection of cardiovascular risk data at baseline and MedDRA coding **Anupam Agarwal, MD, MPH** (Zogenix)(10mins)
  - Standard approaches to AE reporting **Jonathan Deutsch, MD** (Bristol-Myers Squibb)(10min)
  - Should suspected CV events be adjudicated **Jonathan Seltzer, MD, MBA, MA** (ACI Clinical)(5mins)

Discussion: **What is the proper role of a cardiologist in oncology clinical trials? When is cardiac expertise needed at the site? When is cardiac expertise needed in evaluation of signals? Is there a need for a more precise characterization of cardiac events in the oncology population?**

2:30pm-3:10pm Session IV: Balancing CV risk vs benefit in Oncology Drug Development
What are the patient and compound features that should be evaluated in determination of risk vs. benefit? What are the particular issues with respect to CV health/toxicity? How do we weigh these factors? Is there a common framework from which we can work to evaluate the value equation?

Panel Discussion: Regulatory, Industry, Patient, Academia, Payer

- **Laleh Amiri-Kordestani, MD** (FDA)
- **Richard Steingart MD,** (Memorial Sloan Kettering)

3:10pm- 3:30pm Wrap-up & Next Steps