# FDA Oncology Drug Development Overview Past to Present

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# Disclosures

- I have no conflicts of interest to disclose

# Abbreviations

- HNSTD-highest non-severely toxic dose
- STD10-severely toxic dose in 10% of animals
- MOA-mechanism of action
- POC-proof of concept
- MABEL-minimally anticipated biological effect level
- CBER-Center for Biologics Evaluation and Research
- CDER-Center for Drug Evaluation and Research
- ICH-International Council on Harmonization

# Historical Perspective – Selective Events

- Aug 5 1937 – NCI established with the signing of the National Cancer Act by President Roosevelt
- 1955 – Cooperative Groups established
- Oct 1971 – Ft Detrick bioweapons lab converted to cancer research facility
- Dec 1971 – President Nixon signs the National Cancer Act
  - War on Cancer declared
  - Gives NCI a “bypass budget”
  - Cancer research centers established
- 1986 – first Consortium Cancer Center established among 3 Historically Black MCs

# NCI Nonclinical Evaluation

- Prieur et al. (1973) provide a detail description of the protocols to be used by NCI
- The toxicological evaluation may result in the following:
  - The anticipated toxicological effect may show up in humans
  - The expected effect may show up in man at a higher or lower dose
  - The toxic effect may show up in a different order than in animals
  - The toxic effect may not show up in humans
- Starting dose was 1/3 the toxic dose low (TDL) in the most sensitive species (dog or monkey)

# NCI Toxicology Protocol 1972 - 1980

## Preclinical Studies for Oncology Drugs

- Single dose toxicology in dogs
- Daily x 5 toxicology in dogs
- Daily x 5 toxicology in monkeys
- Daily x 5 every 14 days x 3 cycles toxicology in dogs
- Schedule dependency in dogs – one of the following
  - 48 hr iv infusion for weekly for 6 weeks
  - 6 hr infusion for 42 hr for 6 weeks
  - Once/week for 6 weeks
  - Daily for 10 days
- Single dose lethality study in mice

From Lowe and Davis (1987)

# Historical Perspective - 1980s and Beyond

- Recognition in late 1970s that the paradigm needed to be modified
- Oncology Advisory Committee meetings in July and Oct, 1979
- Based on discussions, the NCI recommendation for nonclinical protocols to initiate an IND
  - Mice: LD10, LD50, LD90 on Dx1 and Dx5 schedules
  - Dogs: Dx1 and Dx5
    - $1/10^{th}$ LD10 in mice
    - Dose that produces overt toxicity

Lowe and Davis (1987)

Cancer Chemother Pharmacol (1998) 41: 173–185



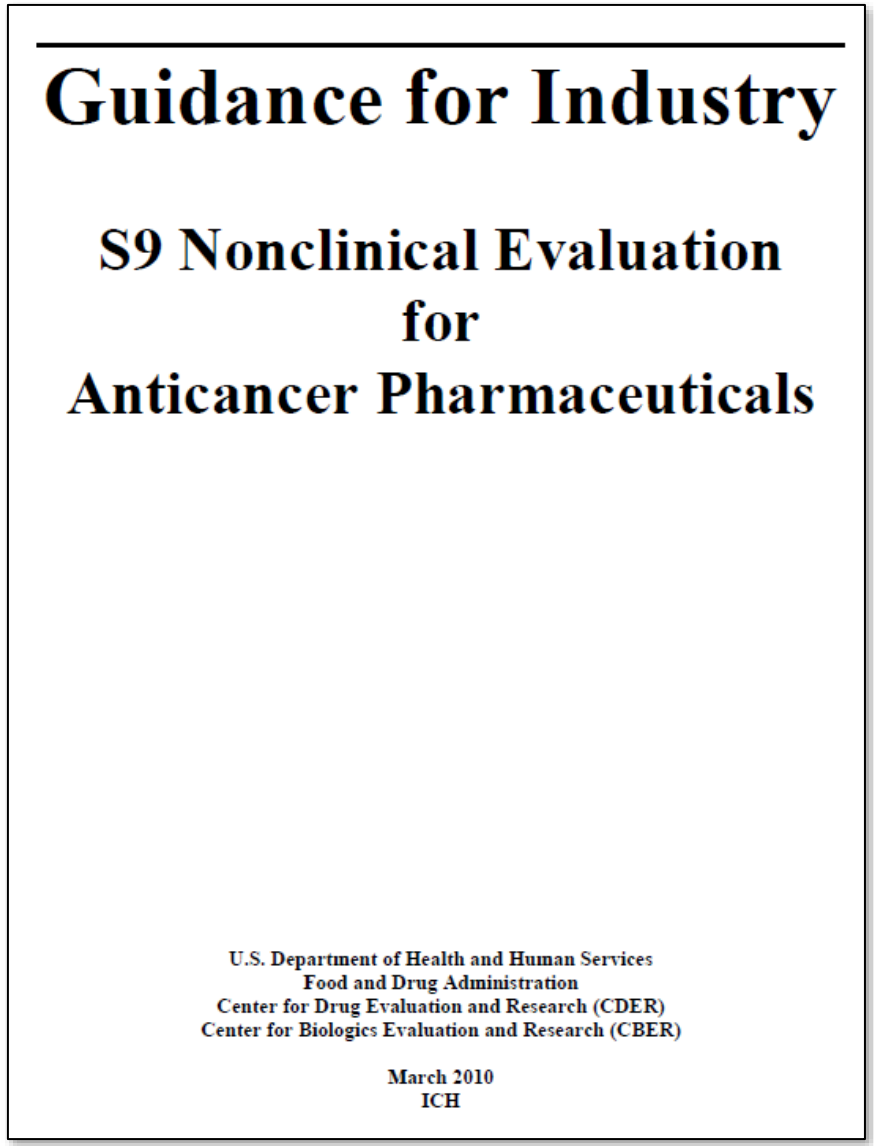
ORIGINAL ARTICLE

Joseph J. DeGeorge · Chang-Ho Ahn
Paul A. Andrews · Margaret E. Brower
Diana W. Giorgio · M. Anwar Goheer
Doo Y. Lee-Ham · W. David McGuinn
Wendelyn Schmidt · C. Joseph Sun
Satish C. Tripathi

# Regulatory considerations for preclinical development of anticancer drugs

# Goals of a FIH Nonclinical Program

- Identify the pharmacologic properties of a pharmaceutical
- Estimate a safe initial dose level for the first human study
- Understand the toxicological profile of a pharmaceutical to help identify safety parameters for clinical monitoring
  - e.g., identification of target organs, exposure-response relationships and reversibility




https://www.fda.gov/media/73161/download

# Recommendations for Anticancer Pharmaceuticals

- The ICH S9 Guidance for Industry explains the basic recommendations for the development of anticancer pharmaceuticals
  - To initiate clinical trials for anti-cancer therapeutics you typically need 28-day toxicology studies in 2 species
  - For biologics, as discussed in ICH S6 and its addendum a single pharmacologically relevant species is often acceptable
  - These studies are the primary data used to determine the acceptability of the proposed starting dose for first-in-human trials
- ICH S9 Q&A further informs on pharmaceutical development

# Nonclinical Studies to Support Phase I Trials in Patients

- Pharmacology/ proof of principle
- Toxicology
  - Rodent study that identifies the $STD_{10}$ , usually based on a body surface area
  - Nonrodent study that confirms non-life threatening doses have been identified
  - Histopathology
- Consider relevance of nonclinical model

# Nonclinical Studies to Support Product Development

- Pharmacodynamics/Pharmacology
- Pharmacokinetics
- Safety pharmacology
- Toxicology
- Genetic toxicity
- Reproductive toxicity
- Carcinogenicity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