Regulatory Recommendations for Nonclinical Studies of Anticancer Pharmaceuticals

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What is the Issue?

• Cardiovascular toxicity of pharmaceuticals are not always predicted by in vitro and animal safety studies
  – If nonclinical studies do not inform appropriate monitoring in clinical trials, then mechanism, severity, incidence and long-term impact on the patient not characterized prior to regulatory approval
  – Mitigation or treatment strategies for cardiovascular toxicities often not explored during drug development
  – May not screen for potential of known cardiovascular toxicity in next generation products
Goals of this Session

• Discuss in vitro and in vivo nonclinical models to assess cardiovascular toxicity
  – Utility to identify the level of potential risk or elucidate mechanism
  – Cases when additional nonclinical cardiovascular safety studies may be warranted and timing of when they should be conducted (e.g., up front IND-enabling or after toxicity is observed in patients)
Regulatory Guidances for Nonclinical Cardiovascular Safety Studies

• ICH M3(R2)
  – Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals

• ICH S6(R1)
  – Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals

• ICH S9
  – Nonclinical evaluation for anticancer pharmaceuticals

• ICH S7(A) and ICH S7(B)
  – Safety pharmacology studies for human pharmaceuticals
ICH S9: Nonclinical Evaluation of Anticancer Pharmaceuticals

- Pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies
- Provide recommendations on type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals
- Includes both small molecule and biotechnology-derived pharmaceuticals (although S6 is generally referenced)
- “This guidance aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects...”
ICH S9: Nonclinical Data to Assess Potential for Cardiovascular Toxicity

• In general, 28-day repeat-dose toxicity studies in 2 species (rodent and non-rodent) with similar route and schedule can support Phase 1 and 2 clinical trials with continuous dosing
  – Clinical chemistry (e.g., creatine kinase, aspartate transaminase, lactate dehydrogenase, troponin)
  – Organ weights (heart)
  – Histopathology (heart)
  – ECG in non-rodent
• hERG assay (not always included)
ICH S7A: Safety Pharmacology Studies

• Definition:
  – studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above

• Objectives:
  – to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety
  – to evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies
  – to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected
ICH S7A and ICH S7B

• Detection of pro-arrhythmic risks much better as a result of additional testing and monitoring
  – Nonclinical: hERG assay, Purkinje fiber assays, intact heart, animal CV safety pharmacology studies (ICH-S7A and ICH-S7B Guidances)
  – Clinical: Human ECGs and thorough QT/QTc studies (ICH-E14 Guidance)

• Failure to prevent or anticipate cardiovascular risk in humans continues to occur, particularly with pharmaceuticals that do not specifically interfere with cardiac ion channels
ICH S9: Safety Pharmacology

- Safety pharmacology includes an assessment of the effect on cardiovascular system
  - Could be included in general toxicology studies
  - Detailed clinical observations following dosing and appropriate electrocardiographic measurements in nonrodents are generally considered sufficient
  - Conducting stand-alone safety pharmacology studies not warranted

- In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials, appropriate safety pharmacology studies described in ICH S7A and/or S7B should be considered.
SOME DIFFERENCES BETWEEN ICH S9 AND ICH M3(R2) ...
### ICH S9 vs. ICH M3(R2): Studies and Timing

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
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<tr>
<td><strong>Studies</strong></td>
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<tr>
<td>Safety Pharmacology parameters can be incorporated into general toxicology studies</td>
<td>Core battery of Safety Pharmacology studies (ICH S7A and S7B)</td>
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## ICH S9 vs. ICH M3(R2): Studies and Timing

### General Toxicology – Clinical Development

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<td>28 day repeat dose toxicity studies (rodent and non-rodent)</td>
<td>Repeat dose toxicity studies (rodent (r) and non-rodent (n)) similar to clinical trial duration (i.e., ≤ 2 week trial = 2 week studies; 2 week – 6 month trial = same duration for studies; &gt; 6 month trial = 6 (r) and 9 (n)* month studies)</td>
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<td><strong>Timing</strong></td>
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<td>support single through continuous dosing (if patient benefits)</td>
<td>prior to conducting clinical trials</td>
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* 6 month studies in non-rodents may be acceptable (e.g., treatment of cancer recurrence, short life expectancy, etc.)
## ICH S9 vs. ICH M3(R2): Studies and Timing

### General Toxicology – Marketing

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<td>3 month repeat dose toxicity studies (rodent (r) and non-rodent (n))</td>
<td>prior to Phase 3; marketing</td>
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Why has Cardiovascular Toxicity Persisted in Oncology Drug Development?

• Risk-Benefit evaluation
  – Patients and healthcare providers are willing to accept a certain level of toxicity and risk
  – Need for better pharmaceuticals to treat patients with various cancers

• Cardiovascular toxicity may not always be separated from anti-tumor activity
  – Not always traditional “off-target” effects
  – Cardiovascular toxicities may be related to the primary mechanism of action
Oncology Treatment is Changing

• Multiple therapies approved for some indications
  – Need for treatments with better activity and better safety profile

• Patients with certain diseases have improved outcomes and longer life expectancies (e.g., CML)
  – Long-term impact on cardiovascular system

• Evaluation of therapies in first- or second-line setting, patients with newly diagnosed (and potentially curable) disease, etc.
Room for Improvement?
Focused Nonclinical Studies to Assess Cardiovascular Safety of Oncology Drugs

• Development of better models may improve screening of candidate drugs for potential cardiotoxicity and mechanistic characterization
• Are additional studies warranted based on findings in nonclinical or clinical studies?
• Is there potential to impact clinical development or use?
  – Better predict potential level of risk for cardiovascular toxicity
  – Identify appropriate clinical monitoring
  – Identify patients with relevant risk factors
  – Mitigate cardiovascular toxicity in patients

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