Regulatory Considerations in Oncology Trials in China

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Disclaimer

• The views and opinions provided are those of the speaker and do not reflect those of Sanofi
Outline

• Overview of China Drug Registration System

• Regulatory Opportunities/Challenges in Oncology Trials

• Regulatory Considerations in Oncology Clinical Development

• Conclusion
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China’s Drug Administration & Registration System

Drug Approval Process

- Review of dossier for content and format acceptance
- Technical evaluation
- Administrative approval

Laws and Regulations For Drug Registration

- China’s Drug Administration Law (2001)
- GCP, GMP and GLP (1998)
- Drug Registration Regulation (2007)
### Regulation Requirements for Registration
**Clinical Trial including Oncology Drugs**

<table>
<thead>
<tr>
<th>Chemical Drug</th>
<th>Biological Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No market authorization in any country, the minimal cases required (trial group) are as follows</td>
<td>• No matter oversea market authorization available or not, the minimal cases required (trial group) are as follows</td>
</tr>
<tr>
<td>– Phase I: 20-30</td>
<td>– Phase I: 20</td>
</tr>
<tr>
<td>– Phase II: 100</td>
<td>– Phase II: 100</td>
</tr>
<tr>
<td>– Phase III: 300</td>
<td>– Phase III: 300</td>
</tr>
<tr>
<td>• Oversea market authorization available</td>
<td>• CTA approval</td>
</tr>
<tr>
<td>– PK</td>
<td>– ~ 15 months</td>
</tr>
<tr>
<td>– Randomization trial: 100 pairs</td>
<td>– NDA-like CTA package</td>
</tr>
<tr>
<td>– Adequacy of foreign clinical trial data</td>
<td>– QT test is required</td>
</tr>
<tr>
<td>• CTA approval</td>
<td></td>
</tr>
<tr>
<td>– ~ 10 months</td>
<td></td>
</tr>
<tr>
<td>– NDA-like CTA package</td>
<td></td>
</tr>
</tbody>
</table>
Policy and Regulations for Oncology Drugs

- No policies/regulations specific for Oncology Drugs
- Several Technical guidance for anticancer agents are available or in the development (similar with those of FDA)
- Special Review and Approval Procedure (SRAP) applies to Oncology Drugs (2009)
  - Review time is shortened (~ 80 days)
  - Consultation meeting could be applied before CTA/NDA
  - Binding agreement between SFDA and Sponsor for development
Some Rules agreed by SFDA for Oncology Clinical Trial Design and Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Non-Oncology Drugs</th>
<th>Oncology Drugs *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal studies</td>
<td>At least 2 well-controlled studies</td>
<td>Usually 1 study</td>
</tr>
<tr>
<td>Sample size</td>
<td>1,000 ~ 5,000 pts</td>
<td>100 ~ 800 pts</td>
</tr>
<tr>
<td>Study design</td>
<td>Placebo control, double blinded needed, e.g., CNS, CVS, Diabetes drugs</td>
<td>Usually active control, Open-label</td>
</tr>
<tr>
<td>Statistical Consideration</td>
<td>Higher statistical significance (P value 0.001)</td>
<td>Relatively low statistical significance (P value 0.03~0.05)</td>
</tr>
</tbody>
</table>

* Flexibility exists, driven by the benefit/risk ratio
Basic Factors for China NDA for Oncology Drugs

• High unmet medical needs in China?
  – Is it unique? E.g., NPC, esophageal cancer?

• Significant clinical benefit has been demonstrated by available data?

• Safety profile is acceptable, well controlled or predictable?

• Adequate Asian data?

• Ethical difference?

• Effective risk control plan?

• Difficulty in study operation? eg: rare disease, low incidence

Source: Chen Xiaoyuan, Clinicaltiral 2009
Chenxiaoyuan, Journal of China Prescription Drug, No.95
NPC: Nasopharyngeal Cancer
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Regulatory Opportunities

• Global/regional trials remain to be the backbone for oncology drug registration in China

• Focus on the China specific tumor types may increase the successful rate
  – The following Sorafenib ① and Eloxatin Story ② will tell you more…..

• SRAP could be considered to shorten the review time and enhance the communication with SFDA
  – By the end of 2010, 28 drugs got SRAP, and > 50% are oncology drugs
    ( 10 chemical drugs, and 5 biologics )
SFDA granted 114 CTA approval for Oncology Global/Regional trials from 2005 to 2010.6

**Phase Distribution**

- Phase I: 2
- Phase II: 27
- Phase III: 82
- Phase IV: 3

**Indication Distribution**

- Lung Cancer: 29
- Breast Cancer: 16
- Hematological Malignancy: 17
- Liver Cancer: 11
- Renal Cancer: 9
- Gastric Cancer: 7
- Colorectal Cancer: 3
- Others: 1

Regional Trial helps Sorafenib got China NDA just 8 months after US approval while usually it take years…

- **Drug lag for selected oncology drugs**
  - Avastin 1st line mCRC: US 2004 vs China 2010 (~6Yrs)
  - Faslodex 2nd line Breast Cancer: US 2002 vs China 2010 (~8Yrs)
  - Alimta 2nd line NSCLC: US 2004 vs China 2010 (~6Yrs)
  - Taxotere 1st line Prostate Cancer: US 2004 vs China 2009 (~5Yrs)

- **The story of Sorafenib in China…**

<table>
<thead>
<tr>
<th></th>
<th>SHARP¹</th>
<th>Oriental²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>US, EU</td>
<td>China, Taiwan and Korea</td>
</tr>
<tr>
<td>Patient No.</td>
<td>602</td>
<td>226</td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Primary Endpoints</td>
<td>OS</td>
<td>No predefined</td>
</tr>
</tbody>
</table>

② Eloxatin might be the 1st cytotoxic drug approved for advance HCC in China (EACH study)

- **Background**
  - Eloxatin is well recognized in CRC worldwide
  - HCC is the key indication in Asia Pacific
  - A phase II study showed promising data in advanced HCC with mOS > 12 months

- **Development Plan**
  - A regional study was conducted in China, Korea, Thailand and Taiwan
  - 370 pts enrolled from Mar 07 to Jun 09, 260 pts from China
  - The Chinese data reached the statistical significance and the study results have been presented in ASCO 2010

- **EACH data have now been incorporated in the most recent MOH guideline, and Eloxatin (FOLFOX4) has the potential to be the first cytotoxic drug approved in advanced HCC in China and other AP countries/regions**
EACH study results presented in ASCO 2010

Phase III study of oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX4) versus doxorubicin as palliative systemic chemotherapy in advanced HCC in Asian patients.

Attend this session at the ASCO Annual Meeting!
Session: Gastrointestinal

Author(s): S. Qin, Y. Bai, S. Ye, J. Fan, H. Lim, J. Y. Cho, C. Thongprasert, Y. Chao, K. Rai, Y. Sun; The 81 Hospital of the Chinese People’s Liberation Army, Nanjing, China; Helongjiang Provincial Cancer Hospital, Harbin, China.
Each data incorporated in the MOH 2011 guideline for the therapy of advanced HCC
Key points for using global/regional trials for China Registration

- PK / Phase I study needs to be planned in China, in parallel with the global Phase III study

- Chinese patient number in the global/regional studies meets the requirements for local registration clinical trial (100 CN pairs) or ≥ 15% Chinese population is recommended in global study

- The parallel regional trial involves ≥ 3 countries including China, but it needs company commitment to a second trial before pivotal study shows positive signal (Investment at risk).

- For biological product, more patient number may be needed, and the rationale for waiving Phase II is necessary / mandatory.
Key challenges and how to address....

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lengthy CTA approval time</td>
<td>• Submit CTA early for global/regional trials</td>
</tr>
<tr>
<td>• No separation in IND and NDA</td>
<td>• Encourage IND and NDA separation</td>
</tr>
<tr>
<td>• No binding between IND and NDA</td>
<td>• Take the chance of SRAP to enhance the binding between IND and NDA</td>
</tr>
<tr>
<td>• High registration bar for biologics</td>
<td>• Target China Specific tumor types (high incidence) e.g., HCC, NPC to increase the regulatory success as it targets the unmet medical needs, especially for biologics</td>
</tr>
<tr>
<td>• No regulations or guidelines for rare diseases/orphan drugs/early development</td>
<td>• Press the government for orphan drug/early development legislation</td>
</tr>
</tbody>
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Oncology Drug Development: Dynamic & Evolving

- The paradigm for oncology drug development is changing rapidly
- There is an unprecedented number of anti-cancer therapies in development and standard of care changes quickly
- The complexity of information concerning tumor genetics and signaling pathways is growing and brings greater opportunities for personalized medicine
Regulatory Considerations in Study Design

• Study Endpoints ①

• Study Comparator ②

• Target Population (biomarker) ③

• Sample Size ④
**Study Endpoints in Oncology Trials**

<table>
<thead>
<tr>
<th>Overall Survival (OS)</th>
<th>Time interval between randomization to the death due to any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global, gold standard</td>
</tr>
<tr>
<td></td>
<td>Accurate for event and date, not subject to investigator bias</td>
</tr>
<tr>
<td></td>
<td>Requires larger sample size and longer follow-up</td>
</tr>
<tr>
<td></td>
<td>Crossover and secondary therapy may obscure the results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression Free Survival (PFS):</th>
<th>Time interval between randomization to disease progression or death due to any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shorter follow-up</td>
</tr>
<tr>
<td></td>
<td>Results not obscured by secondary therapy</td>
</tr>
<tr>
<td></td>
<td>Potential for bias due to sensitivity to timing of the assessment</td>
</tr>
<tr>
<td></td>
<td>Regulatory acceptability is in part dependent upon tumor type</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to Progression (TTP):</th>
<th>Time interval between randomization to disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acceptable only if demonstrated to be a reliable surrogate for clinical benefit</td>
</tr>
<tr>
<td></td>
<td>Most applicable to cytostatic agents, does not require tumor size reductions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall Response Rate (ORR):</th>
<th>The proportion of patients with objective response relative to the total number of patients in relevant analysis population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reliability of response rate to predict survival varies by tumor type</td>
</tr>
</tbody>
</table>

| Others | Quality of Life (QOL)/ Patient Reported Outcomes (PRO) |
Key Considerations for Endpoints Selection

• Overall Survival remains to be the gold standard, even in the shift to the personalized medicine

• Other endpoints such as PFS could be considered case by case but controversy remains
  – Avastin-breast cancer

• Strongly recommend to use “Central Review” for less objective endpoints, eg: PFS, TTP, ORR to reduce the bias

• The relationship between tumor markers and clinical benefit has not been established, thus tumor markers is not accepted as an independent endpoint for efficacy assessment
  – PSA- prostate cancer, CA 125- ovarian cancer
② Selection of the Comparator

- Usually, the standard of care is selected as Control

- Only drugs that have been approved in China can be selected as control, either with IDL or DPP
  - New drugs that have been approved outside of China but are not available in China (e.g., due to “drug lag”) are also reviewed as investigational drug in trials.

- Placebo could be used as control if scientifically feasible and ethically appropriate
  - The existing therapies are minimally effective or have serious adverse events; or in the absence of effective therapy.
  - Full disclosure to the patients
  - Assurance that participants randomly assigned to placebo are not substantially more likely than those in active treatment groups to die, suffer irreversible morbidity, disability, or other substantial harms etc.
Selection of the Targeted Population

- Biomarkers are the key to the realization of Personalized Medicine
  - The right drug at the dose for the right patients at the right time

- Targeting therapy at patients most likely to benefit
  - Enrollment of “all comers” may result in a negative study if therapy is only active in Biomarker+ population
  - Patients not likely to benefit will be exposed to toxicity of investigational therapy

- Need novel study design to support
  - Adaptive study design in biomarker + vs biomarker - groups

Image Courtesy: Erasmus MC at University Medical Center Rotterdam
Successful Stories

• HER-2/NEU and Herceptin
• EGFR mutation and Iressa
• K-ras and anti-EGFR
• Brc Abl and Gleevec
• ALK and Crizotinib
• RAF and Vemurafenib
• .....
Sample Size

- **Full development for new drugs**
  - In line with the regulatory requirements for different phases
  - Pivotal studies should demonstrate the statistically significance based on the study design eg: superiority or non-inferiority design

- **Local development for imported drugs**
  - In line with the regulatory requirements for the registration study (eg: ~100 pairs)
  - Need to demonstrate the treatment trend in the registration trials, better if could also show statistical significance
  - There is some negotiation room for the sample size for the rare oncology diseases/orphan drugs
Regulatory Considerations for Study Implementation

• For registration, the clinical trial can only be performed in SFDA approved sites
  – By Nov 2010, there are 112 oncology sites in Mainland China.
  – HK data could also support the China registration if the study is also performed in SFDA approved sites
    • Princes of Wales
    • Queen Mary

• Different treatment philosophy may affect the study compliance
  – Chinese investigators seem to be more flexible in terms of the dose and regimen
  – Role of traditional Chinese Medicine and other herbal medicine

• Tumor samples could not be shipped outside of China for genomic testing
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Conclusion

• Chinese regulatory system for oncology drugs/trials is evolving although with challenges.

• The rising bar for new drug approval calls for the understanding of regulatory requirements in the design and implementation of oncology trials in China.

• There is a huge need to develop regulations/guidelines for orphan drugs/early development for Oncology drugs in China.