Overview of oncology clinical trial in Korea: Case study in gastric cancer

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Oncology R&D, GlaxoSmithKline
• I am an employee of GlaxoSmithKline.
• My presentation today includes my experience in academia and industries including sanofi-aventis and GlaxoSmithKline.
• The content and opinion of the presentation is not from official point of view in GSK.
2007-2012 Market Prognosis – with 12% CAGR

- Growth drivers: Oncology, Anti-thrombosis market
- Value drivers: CV, Anti-infective, Metabolism, CNS


* Markets included: Argentina, Brazil, China, Columbia, Hong Kong, India, Indonesia, Korea, Malaysia, Mexico, Philippines, Singapore, Taiwan, Thailand, and Venezuela
What challenges and opportunities global companies face at in oncology development?

- Challenges in oncology development
  - Competition
  - Cost – Speed(productivity/efficiency)/Quality
  - Ethnic difference with regulatory requirement (Japan, China, Taiwan, Korea)

- Opportunities
  - Cancers in high incidence – breast cancer, CRC, prostate cancer
  - Cancers in special interest – region, pathogenesis
    - Gastric cancer, HCC, adenocarcinoma of lung (EGFR)
  - Unmet needs – rare cancers
  - Centers, investigators qualified, highly motivated
Regionally common cancers

These 9 cancer types account for 58 - 70% of all cancers within AP, Japan, China
- Especially HCC, gastric, H&N, lung, cervical

In contrast, they account for <43% within US and EU5
Female cancer incidence distribution 2007

[US] [Korea]

Breast
Lung
CRC
Uterine corpus
NHL
Melanoma
Thyroid
Kidney

30 20 10 0 10 20 30

% American Cancer Society 2007 Cancer Fact & Figures
Korea cancer registry annual report 2007
Overall Oncology Clinical Trials – Environment in Korea

- **Market** – 2 digit growth
- **Investigators and Infrastructure**
  - Highly motivated
  - Collaborative study group – Korean Cancer Study Group
  - Trial experience in multinational trials as a part; Global PIs;
    Proposal of global trials and conduction, (being) utilized as pivotal
    trials for registration
  - The number of centers – 6-7 top centers recruits > 80-90% of
    subjects
  - High quality/performance of IRB, coordinators, CTC
- **Regulatory environment**
  - Improving fast
KCSG: Organization as a cooperative group

- History
  - Established in 1998
  - 2002: Development of Standard Chemotherapeutic Guidelines with HIRA
  - 2005: Central IRB review
  - 2006: Data Management Center: 6 staffs including 2 CRC
- Members: Over 400 from 89 institutes or hospitals in Korea – mainly medical oncologists
- other health care professionals participating in approved oncology training programs; fellows, residents, oncology nurses
- Homogenous, well trained, highly motivated network group
- Home page: www.kcsg.org
KCSG: Disease subcommittee

- Gastric cancer subcommittee
- Colorectal cancer subcommittee
- Lung cancer subcommittee
- Breast cancer subcommittee
- Lymphoma subcommittee
- Head and Neck cancer subcommittee
- Hepato-biliary cancer subcommittee
- Supportive care subcommittee
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<td>St. petersburg</td>
<td>280 0.34%</td>
<td>Indianapolis</td>
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</tbody>
</table>

Source: www.clinicaltrials.gov, as of Dec 31, 2009, by the number of centers, analyzed by KoNECT.
Multinational study TA distribution in Korea, 08-09

2009 KFDA Data
Oncology trial status in Korea

2009 KFDA Data

2009 KFDA Data
Trial status by cancer type (‘08-09)

2009 KFDA Data

- **NSCLC**
  - 2008: 19
  - 2009: 11

- **Breast**
  - 2008: 10
  - 2009: 19

- **Gastric**
  - 2008: 9
  - 2009: 12

- **Liver**
  - 2008: 8
  - 2009: 12

- **Unspecified/Solid**
  - 2008: 11
  - 2009: 7

- **Prostate**
  - 2008: 9
  - 2009: 2

- **Ovarian**
  - 2008: 1
  - 2009: 4

- **Mesothelioma**
  - 2008: 0
  - 2009: 3
Number of industry sponsored oncology trials by cancer type

Clinical trial magnifier 2009
Clinicaltrials.gov (Oct 2005 – Jul 2009, interventional studies only)
Number of GSK oncology studies by phase

GSK data (2005-2009)
Case Study 1: CLASSIC

- Adjuvant CapeOx vs Observation after gastric cancer surgery

- History
  - 2004 PI proposed the concept to the sponsors
  - Phase III Open Label Randomized Multinational multicenter trial
  - 2005 IND in Korea, China, and Taiwan
  - 2006 FSFV
Case Study 1: CLASSIC

Adjuvant CapeOx vs observation after gastric cancer surgery

• Roll out and performance
  – 2006 FSFV
  – 2009 accrual finished (n=1024, >300 subjects/yr from 3 countries, >800 subjects from Korea)
  – Korean proposal to China and Taiwan
  – Collaboration with medical and surgical oncology
  – Workshop for D2 dissection for 3 countries
  – Clinical endpoint: 3 year DFS, correlative science through meta-analysis to prove 3 yr DFS correlated with 5 yr OS in GC
• Standard of care in operable gastric cancer in 2005
  – Surgery: D2 standard, but still variation in different centers in Korea, China and Taiwan
  – Adjuvant chemotherapy in Korea, China and Taiwan – empirical, no Category 1 evidence
  – US: Intergroup study with concurrent chemoradiotherapy due to inadequate surgery for D2

→ D2 workshop between surgeons in 3 countries
Clinical Endpoint in Adjuvant Chemotherapy Trial

- Golden standard: 5 year Overall Survival
- 2005: Sargent et al. “3 year disease free survival is correlated to 5 year overall survival in operable colorectal cancer”
- Gastric cancer adjuvant trial – No evidence on the concept
  - Correlative science through meta-analysis to prove 3 yr DFS correlated with 5 yr OS in GC
Case study 2. Exploratory oncology trials to move to clinical development

- Phase II XP done by investigator as an investigator initiated trial
  - XP vs FP phase III (ML17032)
  - EU labeling for Xeloda in advanced gastric cancer

- CapeOx phase II in advanced GC
  - CapeOx vs placebo phase III in adjuvant setting in GC (Xeloda, Eloxatin)
XP vs. FP in advanced gastric cancer: trial conduct

- Patients with previously untreated AGC
  1:1 randomized to XP or FP
    - (neo)adjuvant treatment completed at least 6 months prior
- Patients treated until disease progression or unacceptable toxicities
- From April 2003 to January 2005, 316 patients were enrolled in 42 centers across 12 countries
  - regions: Asia, Europe, South America
  - main recruiting countries: Korea, China, Russia
  - randomization stratified by country

Kang 2006 ASCO
### Korea as a Major Player in Multinational Trials in Regionally Common Cancers

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<tr>
<th>Title</th>
<th>No. Pts</th>
<th>Status</th>
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<tbody>
<tr>
<td>Roche/KCSG (Korean PI proposal) FP vs XP, multinational Phase III</td>
<td>316 (80)</td>
<td>Completed, Indication of Xeloda in gastric cancer in EMEA</td>
</tr>
<tr>
<td>Roche/Sanofi-Aventis (Korean PI proposal) CLASSIC: Adjuvant CapeOx vs</td>
<td>1024 (&gt;800)</td>
<td>Enrollment completed after gastric cancer surgery</td>
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<tr>
<td>Astra-Zeneca/KCSG (Korean PI proposal) Gefitinib vs Docetaxel after</td>
<td>316 (162)</td>
<td>Enrollment completed</td>
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<tr>
<td>failure with platinum based chemoTx in adenocarcinoma of lung,</td>
<td></td>
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<tr>
<td>multinational Phase III</td>
<td></td>
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<tr>
<td>Roche (Korean PI – Global PI) – 22 countries ToGA: F/XP +/- Trastuzumab in HER2 (+) advanced gastric or GE junctional cancer</td>
<td>584 (116)</td>
<td>Completed Indication of Herceptin in EMEA/Korea in GC</td>
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<tr>
<td>GSK (Korean PI – one of 4 Global Pls) – 23 countries CapeOx +/-</td>
<td>221 (54) ( /445 )</td>
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<td>Lapatinib in HER2 (+) advanced esophageal, gastric or GE junctional</td>
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To be improved

• Early phase trials
  – Ethnic concern in East Asian patients – involvement of Asian population in early stage involvement is essential.
• Regulatory approval process
• Reimbursement environment
Approved industry sponsored oncology trials by development phase

Data generated from KFDA, ez drug
Number of trials for industry sponsored trials in oncology

Clinical trial magnifier 2009
Clinicaltrials.gov (Oct 2005 – Jul 2009, interventional studies only)
Speed: Site Activation Time

Source: Parexel data

- **Korea**: 18 wk
- **Taiwan**: 18 wk
- **Hong Kong**: 22 wk
- **Singapore**: 16 wk
- **Malaysia**: 20 wk
- **Thailand**: 26 wk

**Legend**
- Preparation
- Import
- HA/EC parallel
- EC
- Import
- Contract/Logistics/SIV

**Abbreviations**
- HA: Health Authority
- EC: Ethical Committee
- SIV: Site Initiation Visit

Source: Parexel data
In global anti-cancer drug development, Korea has played important roles in regionally common diseases – as in Gastric Cancer trials

- Generation of exploratory data, lead to concept of phase III
- Has contributed to generating a novel clinical endpoint (3 year DFS)
- Playing an active role for roll-out of pivotal trials, embarking development of indication
- Subsequently, successful in registration of indication

More active and planned involvement in early phase trials including FTIH and ethnic study will make more solid background for the regional studies.

Regional initiatives and collaborative effort on early involvement in new drug development in East Asian countries will facilitate the improvement of cancer care for the regionally common diseases.