How Can Pharmaceutical Companies Facilitate Global Collaboration in Phase 1 Cancer Drug Development in Asia?

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Disclosures

• Employee and stockholder: Johnson & Johnson

• I will not discuss any off label use of any drug or product

• I will describe a Phase 1/2a clinical trial of an experimental oncology therapeutic

• These are my own personal opinions on drug development and do not represent any official company positions
Warning!! This is an Industry Perspective!

Welcome to a view from the "Dark Side"!
Overview

• Historical Approach to ED in Asia: The AP Drug Lag
• Current Vision: Coordinated Global/AP ED strategies
• Why Conduct Early Development Studies in the AP Region?
• Example: FGFRi Phase 1/2a Trial
• AP Early Development Pharma Industry Challenges
• How Can Pharma Facilitate This Effort?
Historical Approach to AP Drug Development

-- Modified from Ken Kobayashi, MD
Historical Approach

• The **Drug Lag**: delayed approval of drugs in AP region
  – Median drug lag in Japan is ~3 years (Ueno, Clin Pharm Ther 2014)
  – Major cause is new drug applications being “submitted later than those submitted in other regions” (Honig, Clin Pharmacol Ther 2014)
  – Delayed initiation of clinical programs in Asia is common

• Keys to **shortening the drug lag** (Ueno, CPT 2014)
  – Inclusion of **AP patients in global** clinical registration trials
  – Consideration of an **AP regional development strategy as early as possible**

• **AP participation in global registration** trials is growing
  – Drug lag may be shortening: **Nivolumab** first world-wide approval in Japan in July 2014!
Why Conduct Early Development Studies in the AP Region?

• Provide rapid access to transformational therapeutics to **57% of the world’s** population

• **Access strong regional scientific expertise**
  – Japan, China, Hong Kong, Taiwan, Korea, Singapore, Australia/NZ, and others

• Gain a better understanding of **large and growing markets**
  – China, Japan, Korea, and others

• **Recommended Phase 2 doses for oncology drugs may differ**
  – Japan vs. US dose differences noted in 73 of 190 (38%) approved drugs (Arnold Clin Pharmacol Ther 2014)
  – Unique Asian pharmacogenomic profiles
  – Different social and cultural tolerance limits for drug-related toxicities
Why Conduct Early Development Studies in the AP Region?

• Accelerate the impact on unmet medical needs in key AP tumor types
  – Adenocarcinoma of the Lung
  – Gastric/Esophageal cancer
  – Hepatocellular cancer
  – Nasopharyngeal cancer

• Foster a global oncology drug development perspective
  – Broaden thinking about global indications and opportunities
Current Vision: Coordinated AP Early Development Programs

• Coordinated early clinical development
  – Selective AP participation in oncology early development programs
  – AP regional strategy teams choose from Global R&D projects

• Example
  – Preclinical translational studies initiated in AP region to evaluate potential
  – Staggered or parallel AP Phase 1 studies conducted simultaneously with Global studies
  – Rapid advancement to Phase 2 proof of concept studies in key AP tumor types (Lung, liver, gastric cancers)

• Goals
  – Contribute to clinical programs in indications of global interest
  – Address unmet medical needs in AP region with the potential for global application
First in Human Study of JNJ-42756493, A Potent Pan Fibroblast Growth Factor Receptor (FGFR) Inhibitor, in Patients with Advanced Solid Tumors

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-- Presented at AACR 2014
JNJ-42756493 FGFR Inhibitor in Ph 1 Trials

- JNJ-42756493 is a highly potent FGFR 1, 2, 3 and 4 inhibitor that was designed using structure based drug approach coupled to a fragment based approach
- JNJ-42756493 is a selective FGFR inhibitor

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--- Presented at AACR 2014
JNJ-42756493 Global FIH Phase 1/2 Study

**Part 1**

- Alternative schedule
- MAD
- RP2D
- 12 mg
- 9 mg
- 6 mg
- 4 mg
- 2 mg
- 0.5 mg

3 +3 Dose Escalation

**Part 2**

- Biopsy Cohort
- PD Cohort, N = 10–20

**Part 3**

- A = Sq Cell Ca Lung
- B = Small Cell Lung Ca
- C = Breast Ca
- D = Solid Tumors

Dose Expansion Cohort N = 24/cohort

**Part 2 & 3 FGFR amp/mut/translocation**

- Primary Objectives: Safety and RP2D, Clinical activity in select cohorts
- Secondary Objectives: PK and PD for JNJ-42756493

-- Presented at AACR 2014
JNJ’493 Data Highlights from Dose Escalation

Pharmacokinetics

PD Serum Biomarkers: Phosphate Percent Change from Baseline to Cycle 1 D8

-- Presented at AACR 2014
Metastatic Bladder Cancer with Partial Response at 9 mg
(-38% decrease)

Tumor tissue positive for FGFR3-TACC3 translocation

-- Presented at AACR 2014
Clinical Activity of JNJ-42756493 in Patients with FGFR Aberrations Treated at ≥ 6mg Dose

1 – Intrahepatic Cholangiocarcinoma: FGFR2-CCDC6 fusion
2 – Breast Cancer: FGF3/4 amp
3 – Adrenal Carcinoma: FGFR3-TAC3/FGFR2-CCDC6 fusion
4 – NSCLC: FGFR1 amp
5 – Breast cancer: FGFR1 amp
6 – NSCLC: FGF6/23 amp
7 – Urothelial CA: FGFR3-TACC3 fusion
8 – GBM: FGFR3-TACC3 fusion
9 – Urothelial CA: FGFR2-BICC1 fusion

*Ongoing

--- Presented at ASCO 2014
JNJ493 FGFR Inhibitor: Global Early Development!

Global

EU/US Phase 1

AP

China Ph 1/2a

Japan/AP Ph 1/2a

Pre-POC Trials in the Asia-Pacific Region!
AP Early Development Pharma Industry Challenges

- Establish and sustain a strong and stable AP R&D presence (Japan, China and elsewhere)
  - Build **clinical research expertise** beyond Phase 3
    - Enhance experience in oncology Phase 1 trials
  - Build **translational science** expertise
    - Preclinical investigations to support indications of regional interest
    - Example: Molecular profiling on local tissue specimens
  - Establish AP translational and clinical **research collaborations and networks**

- Build **AP Regional strategic teams** that work across countries
  - Global >> AP Regional >> Country organizations
  - History of autonomous R&D activities in AP countries
AP Early Development Pharma Industry Challenges

- Promote **strong mutual respect** and good lines of **communication**
  - Execute integrated strategies that create value for the AP regional and global portfolios
  - Provide insight and feedback on clinical data interpretation

- Cultivate an **ED culture**: calculated risk-taking and considered risk management

- AP Countries are **scientifically and economically diverse**

- **Regulatory** environment can be unpredictable

- **Restrictions on specimen shipping** can impact biomarker screening strategies
AP Early Development Pharma
Industry Challenges

• Personnel challenges
  – Build and **sustain** a **diverse and expert professional workforce**
  – **High turnover** of individuals
  – Invest regional teams with an **appropriate independence**

• Must proactively address key issues
  – Cultural **differences in defining dose limiting toxicities**
  – Regional **differences in disease management** and standards of care
  – Unexpected **safety findings**
  – Population specific **differences in drug pharmacokinetics**
  – Possible racial or ethnic **differences in dosing**
  
  • Is the “**One World-One Dose**” concept outdated?

--- Adapted from Ken Kobayashi, MD
How Can Pharma Facilitate This Effort?

- **Commit** to early drug development in the region

- **Build** **experienced AP teams**
  - Collaborate with dedicated Phase 1 and Ph 2 centers
  - Establish translational research networks

- **Strive for** **two way integration** of discovery and development
  - Not a one way flow of drugs to Asia
  - AP can lead translational/Phase 1 programs that expand globally
The Future Approach to AP Drug Development
And we cannot allow our key messages to be...
Remember! Oncology Drug Development…

is a Global Enterprise!
Thank You!