Taiwan CDE’s Experience to Review MRCT Results

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Disclaimer

• This presentation was not officially cleared, and the views offered here do not necessarily represent the official positions at MOHW, including TFDA.
Outline

• New Drug Review Process in Taiwan

• NDA Approval Based on E17 Concept

• Conclusion
Outline

• New Drug Review Process in Taiwan
  – Two key steps: BSE & NDA
  – Compatible with E17 principles

• NDA Approval Based on E17 Concept

• Conclusion
Integrate BSE & NDA review

**BSE:Q1**
- Any clinical relevant difference within East Asians/ East Asia
- If not, then
  - pool East Asians as a subpopulation
  - pool East Asia as a region

**BSE:Q2**
- Any clinical relevant difference between
  - East Asians & Non-East Asians
  - East Asia & Non-East Asia?
  - If not, then the results of overall trial population can apply to Taiwanese

**NDA**
- Is the B/R reasonable to the overall trial population?
- If we can’t do the pooling or there is difference between East & West, then the results of overall trial population may not apply to Taiwanese → bridging study/restriction of indication/RMP may be needed (depends on what kind of gap)
How to do BSE (1)

• For the drug/disease being evaluated

Any clinical relevant difference in intrinsic/extrinsic factors within East Asians/ East Asia?
– Can we pool East Asians as a subpopulation?
– Can we pool East Asia as a region?
BSE Q1: Pooling?

East Asia

China, Japan, Korea, Singapore, Taiwan, Thailand, Vietnam, …etc

Similar intrinsic/extrinsic factors relevant to the disease/drug?

If yes, then do pooled subpopulation analysis

If yes, then do pooled region analysis
## Ethnic Factors Defined in ICH E5

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXTRINSIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Environmental</td>
</tr>
<tr>
<td>Gender</td>
<td>Culture</td>
</tr>
<tr>
<td>Height</td>
<td>Socioeconomic factors</td>
</tr>
<tr>
<td>Bodyweight</td>
<td>Educational status</td>
</tr>
<tr>
<td>Liver</td>
<td>Language</td>
</tr>
<tr>
<td>ADME</td>
<td>Medical practice</td>
</tr>
<tr>
<td>Receptor sensitivity</td>
<td>Disease definition/Diagnostic</td>
</tr>
<tr>
<td>Race</td>
<td>Therapeutic approach</td>
</tr>
<tr>
<td>Genetic polymorphism of the drug metabolism</td>
<td>Drug compliance</td>
</tr>
<tr>
<td>Genetic diseases</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Food habits</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Regulatory practice/GCP</td>
</tr>
<tr>
<td></td>
<td>Methodology/Endpoints</td>
</tr>
</tbody>
</table>

**Physiological and pathological conditions**
- Age
  - (children-elderly)
- Liver
- Kidney
- Cardiovascular functions
- ADME
- Receptor sensitivity
- Genetic polymorphism of the drug metabolism
- Genetic diseases
- Diseases
- Environmental
  - Climate
  - Sunlight
  - Pollution
  - Culture
  - Socioeconomic factors
  - Educational status
  - Language
  - Medical practice
  - Disease definition/Diagnostic
  - Therapeutic approach
  - Drug compliance
  - Smoking
  - Alcohol
  - Food habits
  - Stress
  - Regulatory practice/GCP
  - Methodology/Endpoints
How to do BSE (2)

• For the drug/disease being evaluated

If we can do the pooling, ie
  - pool East Asia as a region
  - pool East Asians as a subpopulation
then go to Q2
How to do BSE (2)

- For the drug/disease being evaluated
  
  if we can do the pooling, ie
  - pool East Asia as a region
  - pool East Asians as a subpopulation
  then go to Q2

Compare
- PK profiles between East Asians & Non-East Asians
- Clinical efficacy/safety between
  - East Asians & Non-East Asians
  - East Asia & Non-East Asia
- To see if the results of overall trial population can apply to East Asians/East Asia (Taiwan)
Outline

• New Drug Review Process in Taiwan

• NDA Approval Based on E17 Concept
  – Onivyde (Liposomal irinotecan)

• Conclusion
### Example: Onivyde

<table>
<thead>
<tr>
<th>Onivyde</th>
<th>Approved in Taiwan</th>
<th>Classification of Onivyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal irinotecan</td>
<td>Irinotecan</td>
<td></td>
</tr>
</tbody>
</table>
Onivyde: NAPOLI-1

- R, open, three arm study
- Metastatic pancreatic adenocarcinoma with documented disease progression after gemcitabine or gemcitabine-based therapy

- 1:1:1 randomization to
  - Onivyde monotherapy (120mg/m²)
  - Onivyde (80mg/m²) + 5FU + LV
  - 5FU+LV

- Stratify by
  - ethnicity (White vs East Asians vs others)
  - KPS (70-80 vs 90-100)
  - Baseline albumin (≥ 4 g/dL vs. 3.0-3.9 g/dL)

- Conducted in Europe, US, South Korea and Taiwan

Onivyde TFDA label, US FDA label
Lancet 2016; 387:545
## East Asia: South Korea & Taiwan

<table>
<thead>
<tr>
<th></th>
<th>Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)</th>
<th>Fluorouracil and folinic acid combination therapy control (n=119)</th>
<th>Nanoliposomal irinotecan monotherapy (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>69 (59%)</td>
<td>67 (56%)</td>
<td>87 (58%)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>48 (41%)</td>
<td>52 (44%)</td>
<td>64 (42%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>63 (57-70)</td>
<td>62 (55-69)</td>
<td>65 (58-70)</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asian</td>
<td>34 (29%)</td>
<td>36 (30%)</td>
<td>52 (34%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4 (3%)</td>
<td>3 (3%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>White</td>
<td>72 (62%)</td>
<td>76 (64%)</td>
<td>89 (59%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (6%)</td>
<td>4 (3%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>34 (29%)</td>
<td>35 (29%)</td>
<td>50 (33%)</td>
</tr>
<tr>
<td>Europe</td>
<td>47 (40%)</td>
<td>49 (41%)</td>
<td>54 (36%)</td>
</tr>
<tr>
<td>North America</td>
<td>19 (16%)</td>
<td>19 (16%)</td>
<td>26 (17%)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (15%)</td>
<td>16 (13%)</td>
<td>21 (14%)</td>
</tr>
</tbody>
</table>
Primary endpoint: OS

Lancet 2016; 387:545
Nanoliposomal irinotecan plus fluorouracil and folinic acid

<table>
<thead>
<tr>
<th>Ethnic origin</th>
<th>Events/patients (n/N)</th>
<th>Fluorouracil and folinic acid</th>
<th>Events/patients (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>45/75</td>
<td>53/75</td>
<td></td>
</tr>
<tr>
<td>East Asian</td>
<td>23/34</td>
<td>25/36</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7/8</td>
<td>2/8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Events/patients (n/N)</th>
<th>Hazard ratio for death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>14/19</td>
<td>0.62 (0.41-0.92)</td>
</tr>
<tr>
<td>Asia</td>
<td>23/34</td>
<td>0.49 (0.27-0.90)</td>
</tr>
<tr>
<td>Europe</td>
<td>28/47</td>
<td>3.27 (0.67-15.84)</td>
</tr>
<tr>
<td>Other</td>
<td>10/17</td>
<td>0.51 (0.28-0.93)</td>
</tr>
</tbody>
</table>

Lancet 2016; 387:545
East Asians Safety

• Overall, the safety profile of East Asians was comparable to that of White patients, except

<table>
<thead>
<tr>
<th></th>
<th>East Asians</th>
<th>White patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 neutropenia</td>
<td>55%</td>
<td>18%</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis</td>
<td>6%</td>
<td>1%</td>
</tr>
</tbody>
</table>

• these AEs are manageable, B/R still positive
BSE & NDA review of Onivyde

BSE:Q1
• Pooling?
  • Yes, we can pool Korean & Taiwanese as a subpopulation

BSE:Q2
• East vs West?
  • Similar PK profiles between East Asians & Non-East Asians
  • Similar clinical efficacy/safety between East Asians & Non-East Asian
  • Results of overall trial population can apply to Taiwanese

NDA
• Is the B/R reasonable to the overall trial population?
  • Yes
  → Onivyde was approved by TFDA in Oct 2015
Globally First Approval in Taiwan

- ONIVYDE is indicated, in combination with 5-fluorouracil and leucovorin, for the treatment of patients with metastatic pancreatic adenocarcinoma following gemcitabine-based therapy
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Conclusion

• In designing MRCT
  – Prospectively consider the potential impact of extrinsic and intrinsic factors on the product and development program

• Recruit Asians as early as possible during drug development process

• More Asian data will enable the evaluation of the impact of intrinsic/extrinsic factors
Conclusion

• More cooperation between regulatory authorities

• More interaction between regulatory authorities and sponsors
  – early consultation is encouraged
THANK YOU FOR YOUR ATTENTION