Challenges, Opportunities and Ethical Considerations of Early Phase Oncology Trials

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## Disclosures | COIs – H Loong

<table>
<thead>
<tr>
<th>Advisory:</th>
<th>Boehringer-Ingelheim, Celgene, Eli-Lilly, Illumina, Novartis, Merck Sereno, Takeda, George Clinical</th>
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<tr>
<td>Speakers’ Bureau:</td>
<td>AbbVie, Bayer, Eisai, Eli-Lilly, Guardant Health, Novartis</td>
</tr>
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</tr>
</tbody>
</table>
As an early phase drug developer, my interest is to interrogate a candidate drug recently developed in the laboratory, through the hoops and hurdles of clinical trials and potentially improving the standard of care of patients
Oncology Drug Development: The Traditional Model

**Steps**
- Basic Research
- Lead Identification > Optimisation
- Phase I
- Phase II
- Phase III Pivotal Randomised
- Registration
- Global Launch
- Global Optimization / NILEX

**Purpose**
- Identify Potential New Medicines
- Safety Dose PK/PD
- Activity Safety PK/PD
- Efficacy Superiority
- Obtain Marketing Authorisation
- Establish Market
- Expand Market

**Number of compounds**
- > 10,000
- 1

**Number of patients**
- 10s
- 100s
- 1000s

**Estimated Time**
- 8-10 Years
- 1 - 2 Years
- 2 - 4 Years
- 2 - 5 Years
- 1 - 2 Years
- 1 Year
- Until Patent Expiration

- High attrition rate
- Large number of patients
- Long development time

Fig. 1. Oncology Drug Development: The Traditional Rocket Model.
Evolving Roles of Phase 1 Oncology Trials

Traditional

• “Toxicity trials”

• Traditionally all-comers

• Determine recommended phase 2 dose and schedule

• Aim to elucidate adverse events and pharmacokinetic profiles with limited or no therapeutic intent

Recent

• Determination of safety remains paramount importance

• Increase availability of molecularly targeted agents w/ biomarkers → refine patients’ selection

• Phase 1b trials in combination with existing (approved) agents

• Majority of phase 1 trials now have therapeutic aims, even in FIH settings
How have oncology phase 1 trials performed over the years?
Response Rates of Phase 1 Trials

As comparison, ORRs of approved oncology drugs as monotherapy are often >20%

<table>
<thead>
<tr>
<th>Series</th>
<th>Period covered</th>
<th>Trials included (n)</th>
<th>Patients (n)</th>
<th>Agents tested (n)</th>
<th>ORR</th>
<th>Grade 5 AEs at least possibly related to drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estey et al. (1986)</td>
<td>1974–1982</td>
<td>187</td>
<td>NR</td>
<td>54</td>
<td>4.2%</td>
<td>NR</td>
<td>13</td>
</tr>
<tr>
<td>Decoster et al. (1990)</td>
<td>1972–1987</td>
<td>211</td>
<td>6,639</td>
<td>87</td>
<td>4.5%</td>
<td>0.5%</td>
<td>14</td>
</tr>
<tr>
<td>Horstmann et al. (2005)</td>
<td>1991–2002</td>
<td>460</td>
<td>11,935</td>
<td>NR</td>
<td>10.6%</td>
<td>0.49%;</td>
<td>15</td>
</tr>
<tr>
<td>Roberts et al. (2004)</td>
<td>1991–2002</td>
<td>213</td>
<td>6,474</td>
<td>149</td>
<td>3.8%</td>
<td>0.54%</td>
<td>16</td>
</tr>
<tr>
<td>Schwaederle et al. (2016)</td>
<td>2011–2013</td>
<td></td>
<td>Biomarker-driven trials: 2,655</td>
<td>NR</td>
<td>31.1% (42% in the case of genomic biomarkers)</td>
<td>1.9%</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-biomarker-driven trials: n = 177</td>
<td>Non-biomarker-driven trials: n = 10,548</td>
<td>5.1%</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-biomarker-driven trials of cytotoxic agents: n = 116</td>
<td>Non-biomarker-driven trials of cytotoxic agents: 4.7%</td>
<td>2.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; NR, not reported; ORR, overall response rate

1970-80s – <5%
1990s - ~ 11%
Contemporary ~ 20%
(biomarker driven even higher ~ 42%)
Do we know whether improvement in ORR is associated with improvement in survival?

Is this true in the era of molecular targeted therapies?
Correlation between treatment effects on overall response rate and progression-free survival/overall survival in comparative trials involving targeted therapies in molecularly enriched populations

- BJ Solomon¹, Herbert Loong², Yvonne Summers³, Zachary M Thomas⁴, Pearl French⁴, Boris Kin Lin⁴, Andreas Sashegyi⁴, Jurgen Wolf⁵, James Chih-Hsin Yang⁶, Alexander Drilon⁷

¹ Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; ² Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR; ³ The Christie Hospital, Manchester, UK; ⁴ Eli Lilly and Company, Indianapolis, Indiana, USA; ⁵ Centrum für Integrierte Onkologie (CIO), Universitätsklinikum Köln, Cologne, Germany; ⁶ Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; ⁷ Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA
Inclusion Criteria:

- Phase 3 clinical trials
- Targeted agents in experimental arm, conventional treatment (non-targeted) in control arm
- Study conducted in molecularly enriched population
- Availability of ORR and PFS data at minimum

61 trials were identified with 15 ultimately meeting the prespecified criteria

Abbreviations: ORR=Objective Response Rate, PFS=Progression-Free Survival
# Results

<table>
<thead>
<tr>
<th>Trial ID (NCT Number)</th>
<th>Experimental Arm Therapy</th>
<th>Control Arm Therapy</th>
<th>Experimental Arm N</th>
<th>Control Arm N</th>
<th>Experimental Arm ORR</th>
<th>Control Arm ORR</th>
<th>Experimental Arm mPFS (mos)</th>
<th>Control Arm mPFS (mos)</th>
<th>PFS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00949650</td>
<td>afatinib</td>
<td>pemetrexed/cisplatin</td>
<td>230</td>
<td>115</td>
<td>0.56</td>
<td>0.23</td>
<td>11.2</td>
<td>6.9</td>
<td>0.58</td>
</tr>
<tr>
<td>NCT01154140</td>
<td>crizotinib</td>
<td>pemetrexed/platinum</td>
<td>172</td>
<td>171</td>
<td>0.74</td>
<td>0.45</td>
<td>10.9</td>
<td>7.0</td>
<td>0.45</td>
</tr>
<tr>
<td>NCT02604342</td>
<td>alectinib</td>
<td>pemetrexed or docetaxel</td>
<td>79</td>
<td>40</td>
<td>0.51</td>
<td>0.02</td>
<td>10.9</td>
<td>1.4</td>
<td>0.20</td>
</tr>
<tr>
<td>NCT01639001</td>
<td>crizotinib</td>
<td>pemetrexed/platinum</td>
<td>104</td>
<td>103</td>
<td>0.87</td>
<td>0.46</td>
<td>11.1</td>
<td>6.8</td>
<td>0.40</td>
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<tr>
<td>NCT00932893</td>
<td>crizotinib</td>
<td>pemetrexed or docetaxel</td>
<td>173</td>
<td>174</td>
<td>0.65</td>
<td>0.20</td>
<td>7.7</td>
<td>3.0</td>
<td>0.49</td>
</tr>
<tr>
<td>NCT01121393</td>
<td>afatinib</td>
<td>gemcitabine/cisplatin</td>
<td>242</td>
<td>122</td>
<td>0.68</td>
<td>0.23</td>
<td>11.0</td>
<td>5.6</td>
<td>0.28</td>
</tr>
<tr>
<td>NCT01544179</td>
<td>gefitinib/pemetrexed/cisplatin</td>
<td>placebo/pemetrexed/cisplatin</td>
<td>133</td>
<td>132</td>
<td>0.32</td>
<td>0.34</td>
<td>5.4</td>
<td>4.6</td>
<td>0.86</td>
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<tr>
<td>NCT01227889</td>
<td>dabrafenib</td>
<td>dacarbazine</td>
<td>187</td>
<td>63</td>
<td>0.6</td>
<td>0.24</td>
<td>6.9</td>
<td>2.7</td>
<td>0.40</td>
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<tr>
<td>NCT02151981</td>
<td>osimertinib</td>
<td>pemetrexed/platinum</td>
<td>279</td>
<td>140</td>
<td>0.71</td>
<td>0.31</td>
<td>10.1</td>
<td>4.4</td>
<td>0.30</td>
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<tr>
<td>STI571 (IRIS)*</td>
<td>imatinib</td>
<td>interferon/cytarabine</td>
<td>534</td>
<td>313</td>
<td>0.97</td>
<td>0.57</td>
<td>NR</td>
<td>NR</td>
<td>0.38</td>
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<tr>
<td>NCT00322452</td>
<td>gefitinib</td>
<td>carboplatin/paclitaxel</td>
<td>132</td>
<td>129</td>
<td>0.71</td>
<td>0.47</td>
<td>NR</td>
<td>NR</td>
<td>0.48</td>
</tr>
<tr>
<td>NCT01342965</td>
<td>erlotinib</td>
<td>gemcitabine/cisplatin</td>
<td>110</td>
<td>107</td>
<td>0.63</td>
<td>0.34</td>
<td>11.0</td>
<td>5.5</td>
<td>0.34</td>
</tr>
<tr>
<td>NCT02959749</td>
<td>osimertinib</td>
<td>docetaxel/bevacizumab</td>
<td>74</td>
<td>73</td>
<td>0.62</td>
<td>0.08</td>
<td>10.2</td>
<td>3.0</td>
<td>0.23</td>
</tr>
<tr>
<td>NCT00883779</td>
<td>erlotinib/gemcitabine/platinum</td>
<td>gemcitabine/platinum</td>
<td>49</td>
<td>48</td>
<td>0.84</td>
<td>0.15</td>
<td>16.8</td>
<td>6.9</td>
<td>0.25</td>
</tr>
<tr>
<td>NCT01000025</td>
<td>dacomitinib</td>
<td>placebo</td>
<td>114</td>
<td>68</td>
<td>0.11</td>
<td>0.01</td>
<td>3.52</td>
<td>1.0</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Abbreviations: mos=Months, NCT=National Clinical Trial, ORR=Objective Response Rate, PFS=Progression-Free Survival, mPFS=median Progression-free Survival, HR= Hazard Ratio*
Linear relationship of the log PFS hazard ratio with ORR difference and log ORR odds ratio

- ORR effect size (both the ORR difference and log odds ratio) and the log PFS hazard ratio were strongly correlated (-0.78, p-value = 0.0007)
- No significant correlation was found between ORR and OS – likely due to subsequent therapies
**‘Germline Issues’ of phase 1 trials**

<table>
<thead>
<tr>
<th>Description</th>
<th>Issues</th>
<th>How to rectify?</th>
</tr>
</thead>
</table>
| Invariably single-arm studies      | • Statistical framework based on accuracy of performance of historical controls – are these contemporary enough? | • Require updated data on performance of ‘standard-of-care’  
• Clear biological rationale for MTAs |
| Invariably open-labelled studies    | • Investigators’ bias on assessment of response and toxicities          | • BICR of imaging if feasible                       |
| Initial patients treated at lower dose levels | • Possible sub-therapeutic dosing in initial cohorts  
  • Although typically in MTA trials, higher dose levels are not associated with higher RR | • Accelerated dose titration  
• Allowance of intra-patient dose modification/escalation |
| Selected patients at selected centres | • Typically patients of good PS recruited in phase 1 trials – does this necessary recapitulate in community patients?  
• Patients treated at expert centres | • Widening of inclusion criteria to allow for lower PS during expansion phase |
Phase 1 oncology trials are now considered therapeutic trials

- **Survival**: An 18–38% increase in ORR might predict increased OS
- **Safety**: Low toxic death rate of ~0.5–2.0%
- **Response rates**: ORRs of ~20% have been reported in contemporary phase I trials
- **Biomarkers**: Genomic marker-driven approaches correlate with ORRs of ~40%
- **Dosing**: High doses might not always be preferable with targeted and immunotherapeutic agents

By virtue of good ORR
Direct from Phase 1 to registration

Efficacy and superiority to be embedded in phase 1

Steps

Basic Research | Lead Identification > Optimisation | Phase I | Registration | Global Launch | Global Optimization / NILEX

Purpose

Identify Potential New Medicines | Safety Dose PK/PD | Obtain Marketing Authorisation | Establish Market | Expand Market

Need to be more efficient in choosing compounds for testing with clear scientific rationale

Increase number of pts required for earlier phase trials ...

Number of compounds

> 10,000

1

... invariably decrease number of pts treated with ‘less optimal’ SoC

Number of patients

10s

100s

1000s

Estimated Time

8-10 Years

1 Year

Until Patent Expiration

1 – 2 Years

Ultimately shorten timeframe

Adapted from Verweij, Hendricks & Zwierzina Cancer Treatment Reviews 2019
What is the situation in Asia?
Improving Asian Access to Early Phase Clinical Trials

Why do Oncology Phase 1 Trials in Asia?

- Different epidemiology of cancer in Asia countries from Western population
- Possible difference in drug tolerance, metabolism, pharmacogenomic profiles in Asians
- Large population of patients
- Huge market share
- Requirement of local clinical trial data for drug approval in some jurisdictions
Enhancing collaborations
- “AsiaOne” – Asian Phase 1 Consortium

“Robust Asian Early Phase 1 Consortium”

PHASE ONE  ASIA ONE Since Dec 2016

Key Top Phase 1 Sites Collaboration Across HK, JP, KR, SIN and TW

Allied Dedicated Phase 1 Investigators across Pan-Asia

Hong Kong

Chinese University of Hong Kong

Japan

National Cancer Centre Hospital

Korea

Seoul National University Hospital

Singapore

National Cancer Centre Singapore

Taiwan

National Taiwan University Hospital

Dr. Loong Ho Fung Herbert
Dr. Noboru Yamamoto
Dr. Chia-Chi (Josh) Lin

Dr. Yung-Jue Bang

Dr. Daniel SW Tan

National Cancer Centre Singapore

SingHealth

Faculty of Medicine

The Chinese University of Hong Kong

Asian Oncology Early Phase 1 Consortium
2nd CUHK Masterclass in Early Phase Clinical Cancer Research

Date: 9th November 2018 (Friday)
Time: 13:00 – 18:00
Venue: Seminar Room 1 (next to Li Ping Medical Library), 2/F Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong

Agenda

13:00 – 13:05 Welcome and Introductions
Prof. Birgitta Ma
Medical Director (Oncology), Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong

13:05 – 13:40 Approaching Translational Research as a Clinician Investigator
Dr. Daniel Tan
Senior Consultant, National Cancer Centre Singapore

Dr. Toshio Shimizu
Head of Physicians, Early Phase 1 Drug Development Unit, National Cancer Center Japan

14:15 – 15:15 Tour at PICTC with Light Refreshments

15:15 – 15:50 The Promise and Problems of Phase Ib Trials
Dr. Chieh-Chi (Josh) Lin
Director of Phase 1 Center, National Taiwan University Hospital, Taiwan

15:50 – 16:25 Role of Specific Clinical Trial Endpoints and Implications on Drug Approval – The Canadian Example
Dr. Andrea Fung
Medical Oncology Resident, University of Calgary, Alberta, Canada

16:25 – 16:45 Coffee Break

16:45 – 17:45 Case Scenario – Practical Considerations of Developing IO-IO Combinations
Led by Prof. Lillian Sun
BMO Chair in Precision Genomics
Professor, University of Toronto

17:45 – 18:00 Wrap Up and Closing Remarks
Dr. Herbert Loong
Deputy Medical Director (Oncology), Phase I Clinical Trial Centre, The Chinese University of Hong Kong
Challenges & Opportunities for Drug Development in Asia

- Geographical and ethnic diversities
- Healthcare disparities
- Regulatory hurdles & approval timelines
- Early phase trial infrastructures

Impact of COVID19 on Oncology Phase 1 Trials in Asia

Abstract

Aim: The significance and prioritization of early phase oncology trial continuation during a global pandemic is unknown. This study reported the outcomes, multiple challenges, and broad recommendations associated with the impact of the novel coronavirus disease 2019 (COVID-19) on oncology early phase 1 trials and drug development in Asia—based on the experiences and perspectives of the Asian Oncology Early Phase 1 Consortium.

Methods: Between March and April 2020 during the initial period of lockdown, the impact of COVID-19 on oncology phase 1 sites in five Asian countries—China (Hong Kong), Japan, South Korea, Taiwan, and Singapore—was retrospectively analyzed.

Results: There was no trial termination or treatment discontinuation in all five countries. Although the main concern was new patient enrollment being placed on hold, which was based on pharmacological and a patient's decision making, the situation varied per site. Most sites had no restrictions in place that would limit their ability to fully comply with the requirements of conducting the early phase studies. The number of protocol deviations during the pandemic was largely dependent on her domestic transportation status during the lockdown rather than the ability of the clinical trial centers. Conclusions: Determining the risk to benefit ratio of patients with cancer who are enrolled in early phase 1 clinical trials under the unusual circumstances of a global pandemic is needed.

TABLE 2 Details of new patient enrollment being placed on hold owing to COVID-19 across five phase 1 centers in Asia during the initial period of pandemic

<table>
<thead>
<tr>
<th>Country</th>
<th>China (Hong Kong)</th>
<th>Japan</th>
<th>South Korea</th>
<th>Singapore</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n = 1</td>
<td>n = 10</td>
<td>n = 5</td>
<td>n = 19</td>
<td>n = 4</td>
</tr>
<tr>
<td>Sponsors’ decision</td>
<td>1/1 (100%)</td>
<td>10/10 (100%)</td>
<td>5/5 (100%)</td>
<td>1/19 (5.2%)</td>
<td>0/4 (100%)</td>
</tr>
<tr>
<td>Site/institute policy</td>
<td>0/1 (10%)</td>
<td>0/10 (0%)</td>
<td>0/5 (0%)</td>
<td>18/19 (94.7%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Government statement</td>
<td>0/1 (0%)</td>
<td>0/10 (0%)</td>
<td>0/5 (0%)</td>
<td>0/19 (0%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Delay of study material shipment</td>
<td>0/1 (0%)</td>
<td>0/10 (0%)</td>
<td>0/5 (0%)</td>
<td>0/19 (0%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>0/1 (0%)</td>
<td>0/10 (0%)</td>
<td>0/5 (0%)</td>
<td>0/19 (0%)</td>
<td>0/4 (0%)</td>
</tr>
</tbody>
</table>
What’s next?

- Achieving regulatory approval is not the endgame – getting drug to patients is!
- As investigators / clinical trialists, how can we improve patients’ accessibility to therapeutic options?

Access to improved therapeutics for patients can only be achieved through:

1. Improved access to clinical trials
2. Enhanced identification of patients with actionable tumours
3. Encourage adoption of new health technologies
Asia Pacific Oncology Drug Development Consortium (APODDC)

Scientific Committee:
- Joanne Chiu (Hong Kong)
- Tira Tan (Singapore)
- Valerie Hong (Singapore)
- David Tan (Singapore)
- Bhumsuk Keam (South Korea)
- Thanynanan Regungwetwattana (Thailand)
- Naiyarat Pasongsook (Thailand)
- Chia-Chi (Josh) Lin (Taiwan)
- Pei Jye Woon (Malaysia)
- Ben Tran (Australia)
- Daphne Day (Australia)
- Amy Prawira (Australia)

Executive Committee:
- Herbert Loong (Hong Kong)
- Daniel Tan (Singapore)
- Toshio Shimizu (Japan)
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- Naiyarat Pasongsook (Thailand)
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- Pei Jye Woon (Malaysia)
- Ben Tran (Australia)
- Daphne Day (Australia)
- Amy Prawira (Australia)

Kick off meeting on 31 March 2021!
Conclusions

• In the era of molecular genomics, targeted therapies & smarter clinical trial designs have put early phase clinical trials in the forefront of efficacy testing and regulatory approval

• This is especially true in matched molecular subsets, as evidenced by histologic-agnostic and line-agnostic approvals of recent agents

• Drug development is not only about obtaining regulatory approval, but rather it is a holistic approach of getting effective therapies to patients.

• Our roles as investigators are to expedite this process through (i) conducting well designed and meaningful clinical trials; (ii) international collaborations; (iii) framing the perceived improved efficacy seen in trials to real life practice through discussions and studies with health authorities.
Sky-Diving 33 y.o. RET+ NSCLC patient