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Challenges, Opportunities and Ethical Considerations of Early Phase Oncology Trials

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Disclosures | COIs – H Loong

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My Role as a Clinical Trialist …

"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

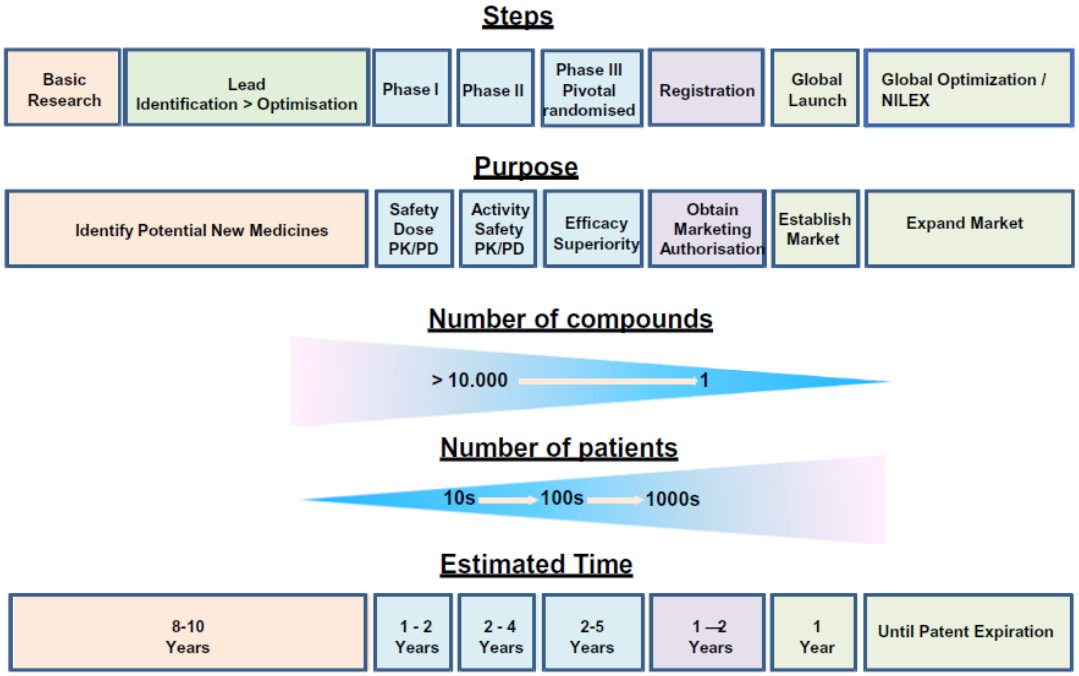

Fig. 1. Oncology Drug Development: The Traditional Rocket Model.

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

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

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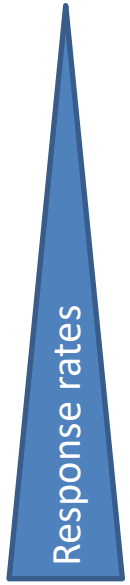
How have oncology phase 1 trials performed over the years?

Response Rates of Phase 1 Trials

Table 1 | **Response rates observed in selected oncology phase I trials**

Series	Period covered	Trials included (*n*)	Patients (*n*)	Agents tested (*n*)	ORR	Grade 5 AEs at least possibly related to drug	Ref.
Estey et al. (1986)	1974–1982	187	NR	54	4.2%	NR	13
Decoster et al. (1990)	1972–1987	211	6,639	87	4.5%	0.5%	14
Horstmann et al. (2005)	1991–2002	460	11,935	NR	10.6%	0.49%;	15
Roberts et al. (2004)	1991–2002	213	6,474	149	3.8%	0.54%	16
Schwaederle et al. (2016)	2011–2013	Biomarker-driven trials of targeted agents: 57	Biomarker-driven trials: 2,655	NR	31.1% (42% in the case of genomic biomarkers)	1.9%	17
		Non-biomarker-driven trials of targeted agents: *n* = 177	Non-biomarker-driven trials: *n* = 10,548		5.1%	NR	
		Non-biomarker-driven trials of cytotoxic agents: *n* = 116			Non-biomarker-driven trials of cytotoxic agents: 4.7%	Non-biomarker-driven trials of cytotoxic agents: 2.2%	
Waligora et al. (2018)	2004–2015	170	4,604	NR	10.29%	2.09%	18
Chakiba et al. (2018)	2014–2015	224	NR	224	19.8%	NR	19

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



1970-80s – <5%

1990s - ~ 11%

Contemporary ~ 20% (biomarker driven even higher ~ 42%)

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

Adashek et al. Nature Reviews Clinical Oncology 2019

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 Solomon[1], **Herbert Loong[2]**, Yvonne Summers[3], Zachary M Thomas[4], Pearl French[4], Boris Kin Lin[4], Andreas Sashegyi[4], Jurgen Wolf[5], James Chih-Hsin Yang[6], Alexander Drilon[7]

[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

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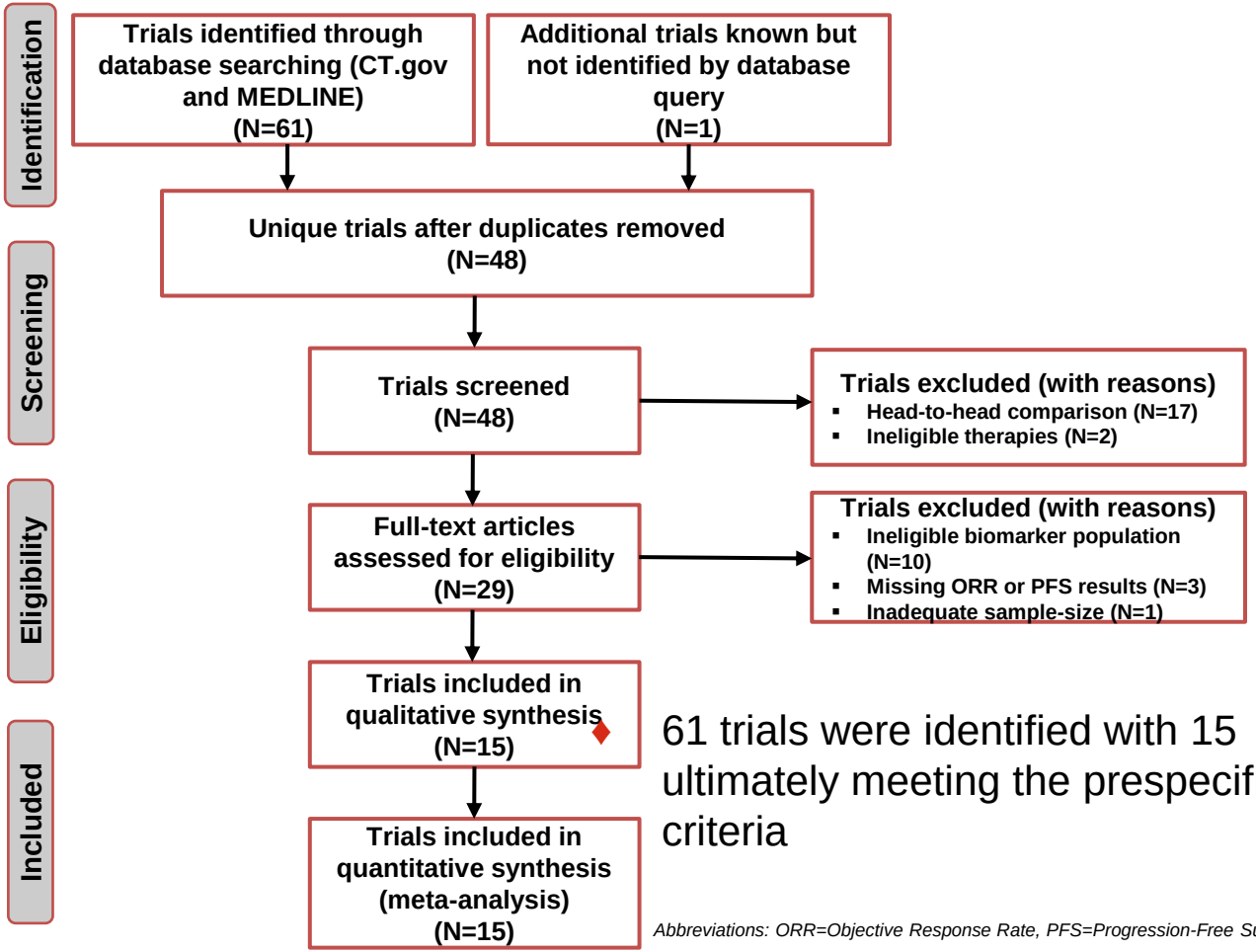
Solomon BJ, Loong HH … Drilon A | Journal of Clinical Oncology 2020 38:15_suppl, 3588-3588

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

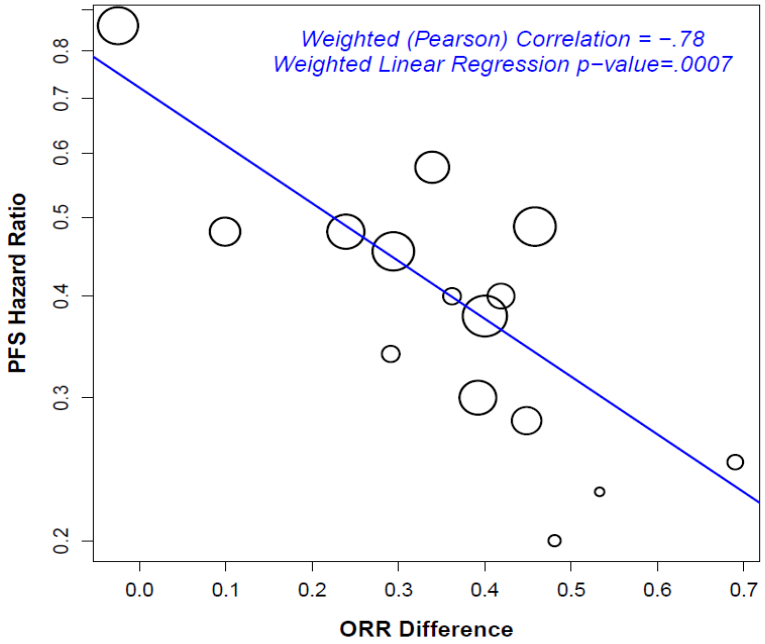
Solomon BJ, Loong HH … Drilon A | Journal of Clinical Oncology 2020 38:15_suppl, 3588-3588

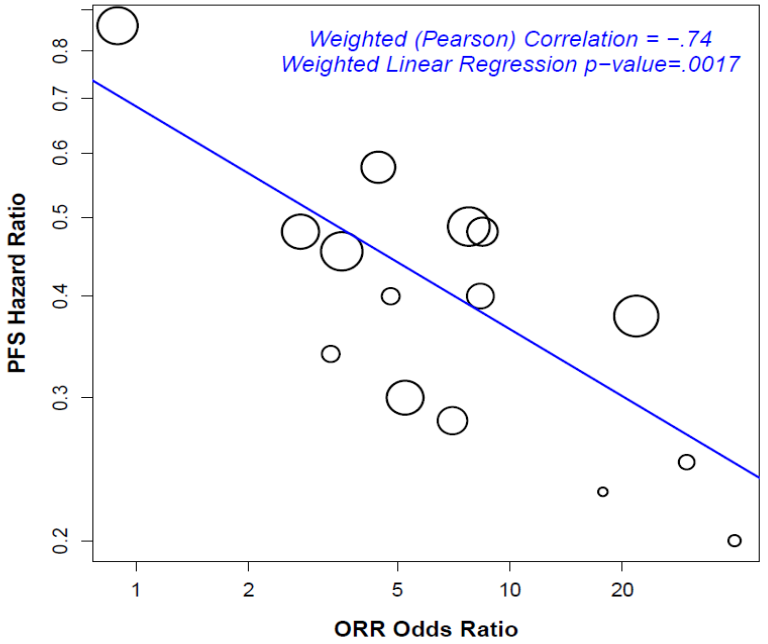
Results

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

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



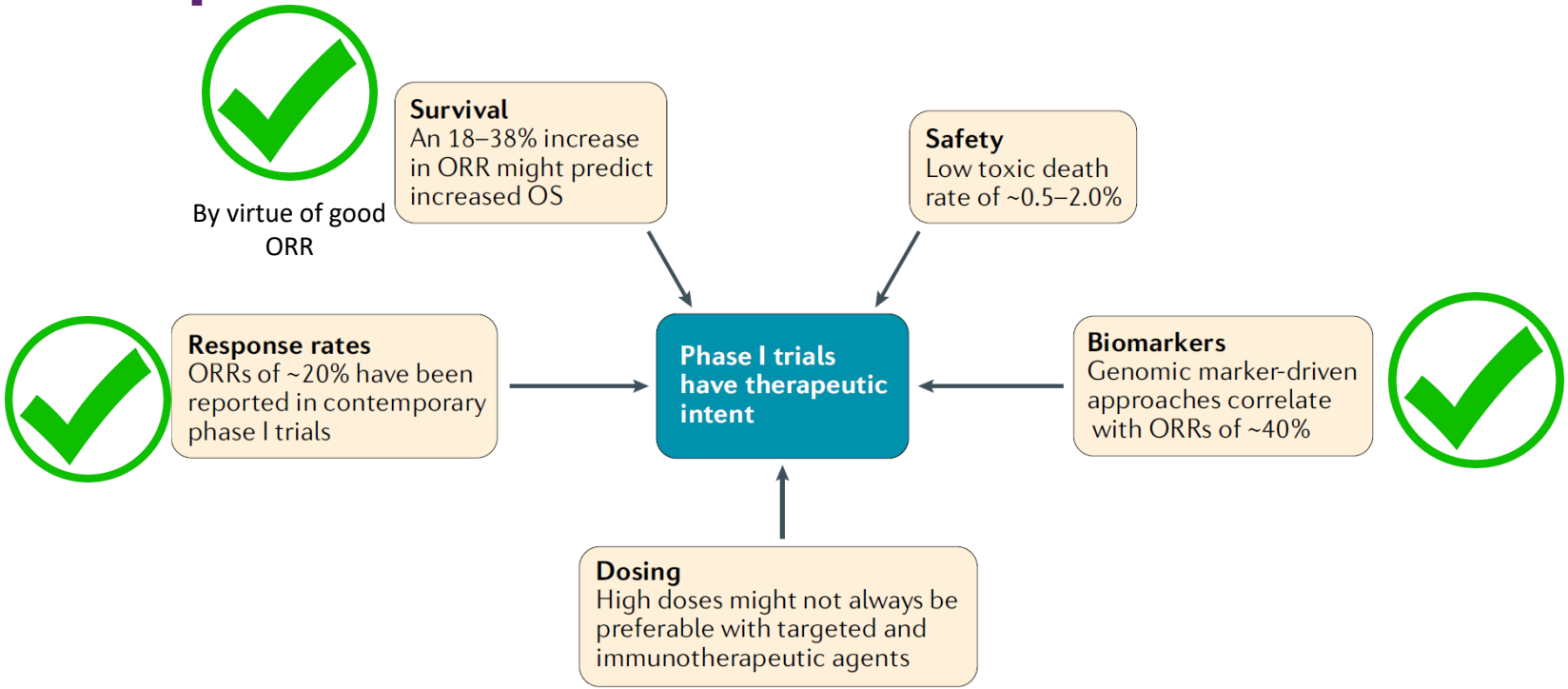


- ORR effect size (both the ORR difference and log odds ratio) and the log PFS hazard ratio were strongly correlated (-.78, p-value = .0007)
- No significant correlation was found between ORR and OS – likely due to subsequent therapies

‘Germline Issues’ of phase 1 trials

Description	Issues	How to rectify?
• 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



Adapted from Adashek et al. Nature Reviews Clinical Oncology 2019

Steps

Basic Research	Lead Identification > Optimisation	Phase I	Direct from Phase 1 to registration	Registration	Global Launch	Global Optimization / NILEX

Purpose

Identify Potential New Medicines	Safety Dose PK/PD	Efficacy and superiority to be embedded in phase 1	Obtain Marketing Authorisation	Establish Market	Expand Market

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

Number of compounds

> 10.000 → 1

… invariably decrease number of pts treated with 'less optimal' SoC

Increase number of pts required for earlier phase trials …

Number of patients

10s → 100s → 1000s

Estimated Time

8-10 Years	1	Ultimately shorten timeframe	1 –2 Years	1 Year	Until Patent Expiration

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

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FACULTY OF MEDICINE

PHASE 1 CLINICAL TRIAL CENTRE

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. Brigette 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
13:40 – 14:15	**Practical Issues and Considerations for Conducting Global First-in-Human Phase 1 Trials** Dr. Toshio Shimizu Head of Physicians, Early Phase 1 Drug Development Unit, National Cancer Center Japan
14:15 – 15:15	**Tour at P1CTC with Light Refreshments**
15:15 – 15:50	**The Promise and Problems of Phase 1b Trials** Dr. Chia-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 Siu 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 1 Clinical Trial Centre, The Chinese University of Hong Kong

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Challenges & Opportunities for Drug Development in Asia

eview Article

hallenges and insights of early phase oncology drug evelopment in the Asia-Pacific region

erbert H. Loong[1,2,3], Daniel S. W. Tan[4], Toshio Shimizu[5]

partment of Clinical Oncology, [1]Phase 1 Clinical Trial Centre, [2]State Key Laboratory in Translational Oncology Research, The Chinese versity of Hong Kong, Hong Kong, China; [3]National Cancer Centre Singapore, Singapore; [4]National Cancer Center Hospital, Tokyo, Japan

ntributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All hors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) al approval of manuscript: All authors.

rrespondence to: Dr. Herbert H. Loong. Clinical Assistant Professor, Department of Clinical Oncology, The Chinese University of Hong Kong, ace of Wales Hospital, 30-32 Ngan Shing Street, Shatin, NT, Hong Kong, China. Email: h_loong@clo.cuhk.edu.hk.

Abstract: Early phase clinical trials form the very foundation of a drug's clinical development. Traditionally, these trials were focused exclusively on dose optimization and toxicities with a broad aim across tumour types in the hope of achieving a signal of response. No real efforts were made to pair patients with best therapies. Moreover, early phase clinical trials have traditionally been performed in Western populations. Asia is the world's largest continent in terms of population size, and is rich in ethnic, cultural and socio-economic diversities. There are also distinct regulatory and methods of healthcare provision between countries within the region. These qualities form a 'double-edge sword' when it comes to drug development. However, the rapidly growing population which inevitability leads to increasing patients' numbers, coupled with improving economies and accessibility to quality healthcare put Asia in a prime position to play a more dominant role in early phase oncology drug development. At the same time, there is also increasing recognition of differences in disease epidemiology between different geographical regions, as well as potential pharmacogenomic differences between ethnicities. In this review article, the challenges faced, and opportunities foreseen for early phase oncology drug development in Asia will be discussed and illustrated with practical examples of international collaborations formed in recent years.

Keywords: Drug development; experimental therapeutics; phase 1 clinical trials; investigational new drugs (INDs); Asia

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View this article at: http://dx.doi.org/10.21037/cco.2019.06.02

troduction

e advent of globalization has led to significant changes the biomedical field over the past two decades. ditionally, phase 1 clinical trials or First-in-Human H) trials are the first step in clinical drug development d are primarily designed to evaluate the safety of new nts and the recommended dose for further definitive ting in a small group of participants. This may have been undirected approach involving patients of various types cancer. The commonality between subjects participating ough such an approach is that they commonly had a reasonable performance status, adequate haematological and biochemical reserves, and have exhausted otherwise approved treatments for their condition. Whilst taking such a broad-based approach in terms of patients' recruitment may potentially increase the rapidity of subjects' recruitment as it casts a wider net for eligible patients and determination of a recommended phase 2 dose for further testing, it does not reliably provide any efficacy information. This limitation has become more apparent in the era of advanced genomics and targeted therapies, whereby many a times improved efficacy of a therapy is not necessarily guaranteed by a higher or near toxic dose, but rather by interfering with

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

Loong HH, Tan DSW, Shimizu T. Challenges and insights of early phase o ncology drug development in the Asia-Pacific region. Chinese Clinical O ncology. 2019;8(3).

Impact of COVID19 on Oncology Phase 1 Trials in Asia

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DOI: 10.1111/ajco.13510

ORIGINAL ARTICLE

WILEY

Overcoming the impact of the COVID-19 pandemic on oncology early phase trials and drug development in Asia—Experiences and perspectives of the Asian Oncology Early Phase 1 Consortium

Toshio Shimizu[1] | Dong-Wan Kim[2] | Herbert H. Loong[3,4] | Chia-Chi Lin[5] | Matthew CH Ng[6] | Noboru Yamamoto[1] | Brigette Ma[3,4] | Daniel SW Tan[6]

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Email: toshimi@ncc.go.jp

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 on drug development in Asia—based on the experiences and perspectives of Asian oncology phase 1 centers.

Methods: Between March and April 2020 during the initial period of outbreak, the impact of COVID-19 across 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 most common impact was new patient enrollment being placed on hold, which was based on pharmaceutical sponsors' 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 domestic transportation status during the outbreak rather than the ability of the clinical trial centers.

Conclusion: Determining the risk to benefits ratio of patients with cancer who are enrolled in early phase 1 clinical trials under the unusual circumstances of a global

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

	China (Hong Kong)	Japan	South Korea	Singapore	Taiwan
Impacted trials	n = 1	n = 10	n = 5	n = 19	n = 4
Sponsors' decision	1/1 (100%)	10/10 (100%)	5/5 (100%)	1/19 (5.2%)	4/4 (100%)
Site/institute policy	0/1 (0%)	0/10 (0%)	0/5 (0%)	18/19 (94.7%)	0/4 (0%)
Government statement	0/1 (0%)	0/10 (0%)	0/5 (0%)	0/19 (0%)	0/4(0%)
Delay of study material shipment	0/1 (0%)	0/10 (0%)	0/5 (0%)	0/19 (0%)	0/4(0%)
Other	0/1 (0%)	0/10 (0%)	0/5 (0%)	0/19 (0%)	0/4(0%)

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Shimizu et al. APJCO 2020

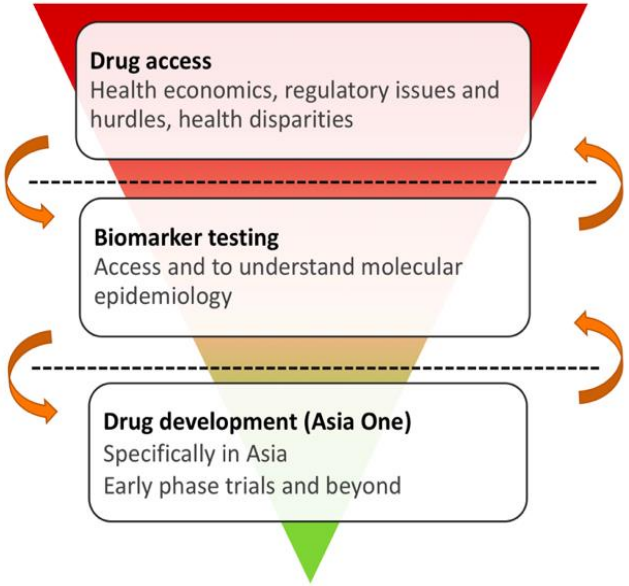
What's next?

- 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)

Executive Committee:

- Herbert Loong (Hong Kong)
- Daniel Tan (Singapore)
- Toshio Shimizu (Japan)

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)

Asia Pacific Oncology Drug Development Consortium (APODDC)

Kick off meeting on 31 March 2021!

mittee:

Kong)

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an (South Korea)

ynanan Regungwetwattana (Thailand)

- Naiyarat Pasongsook (Thailand)
- Chia-Chi (Josh) Lin (Taiwan)
- Pei Jye Woon (Malaysia)
- Ben Tran (Australia)
- Daphne Day (Australia)
- Amy Prawira (Australia)

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

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