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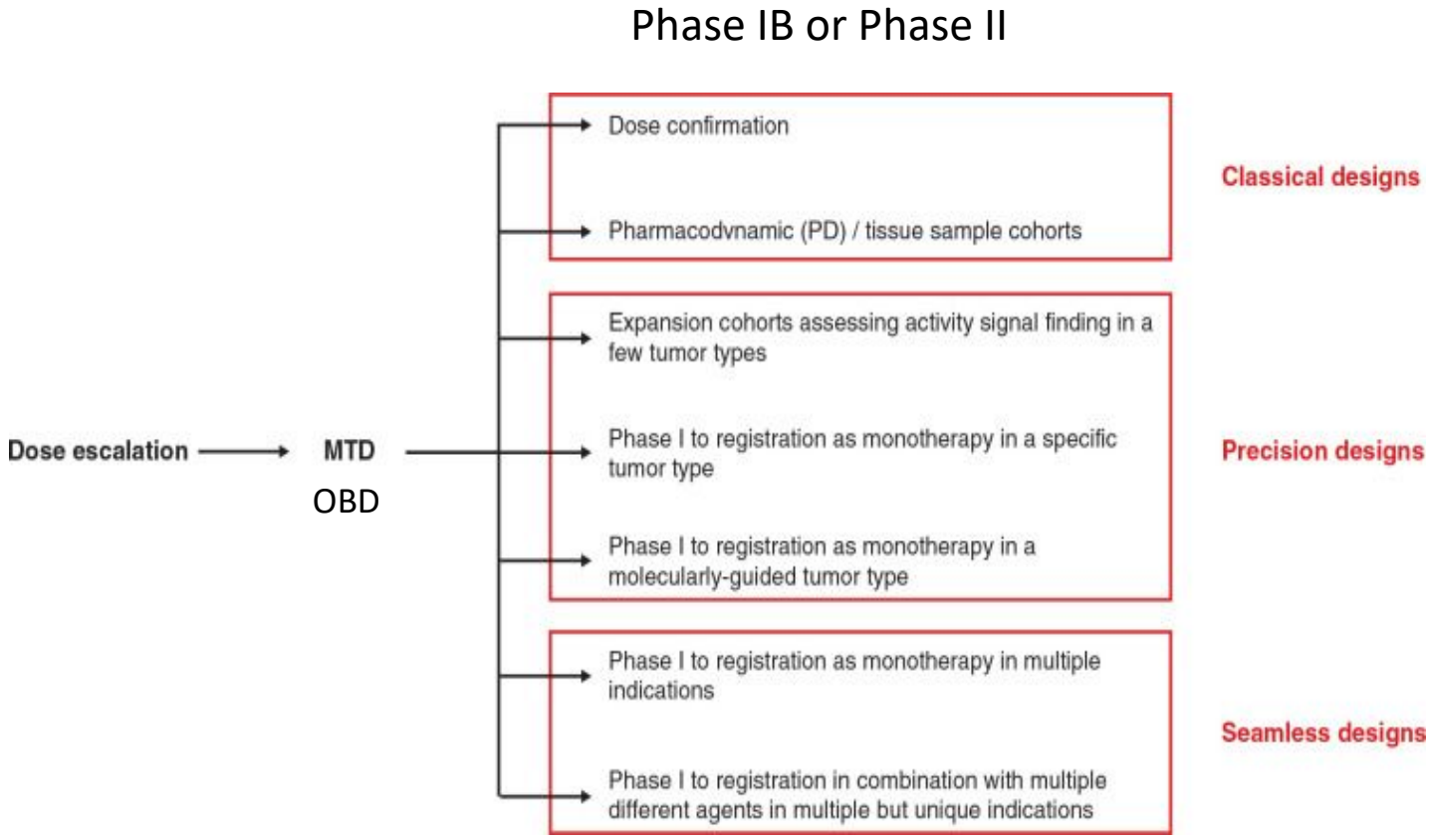
Opening Remark

2021.06.02

A revolutionary change in early clinical designs



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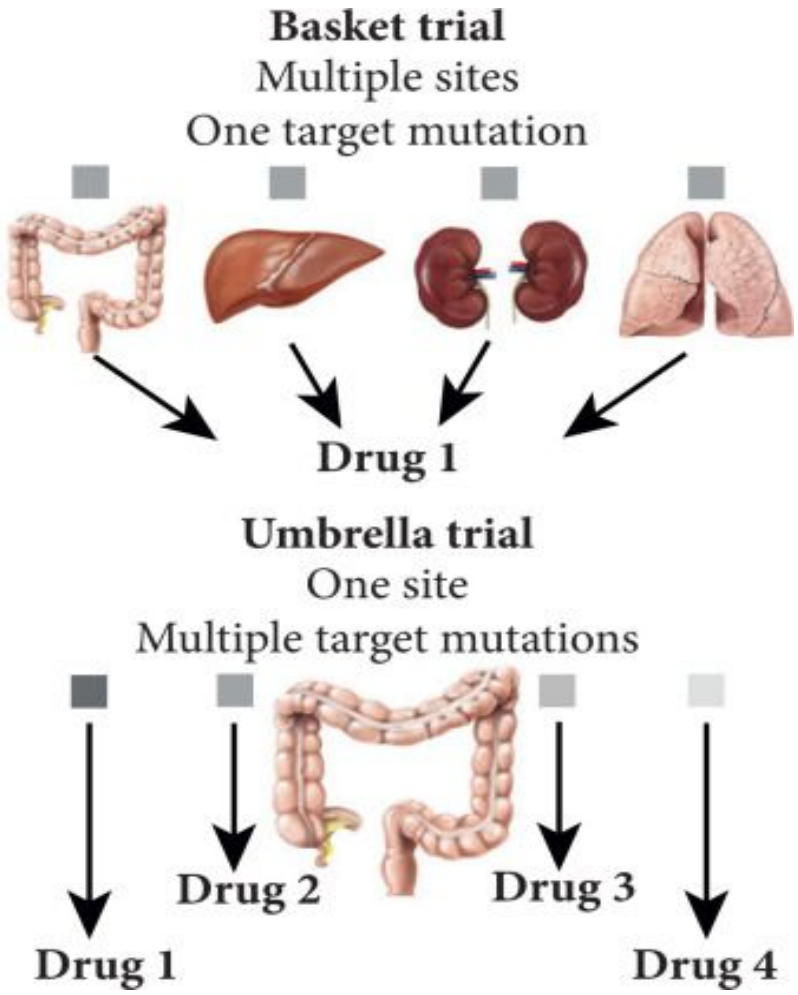
Precision Designs: Basket and Umbrella Designs



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PhAT: A biomarker driven roadmap

1. Defining the right patient population
2. Describing the NME pharmacokinetic characteristics
3. Determining the NME PD biomarkers such as target engagement, key pathway modulation and biological effect
4. Discovering intermediate biomarkers of response
5. Assess tumor response at the end of treatment
6. Learning how to overcome tumor resistance paradigms

P1 for Seamless designs

- Higher doses of may not induce a higher immunological effects because of plateau.
- AEs are typically non-dose related and their time frame can prolong itself.
- The goal is to locate OBD (Optimal Biological/Immunological Dose), not MTD.

	Historical Designs	Seamless Designs
Recommended D.	MTD	OID
Study Goals	DLT Dose-finding studies	TLT Dose-ranging studies
AEs	Dose related	Non-dose related
Study size	Small	Can be large

Types of Cancer Treatment

- Surgery
- Radiation Therapy
- Chemotherapy
- Immunotheraphy
- Targeted Therapy
- Hormone Therapy
- Stem Cell Transplant
- Biomarker Testing for Cancer Treatment

Route of Administration

- Oral
- Intravenous (IV)
- Injection
- Intrathecal
- Intraperitoneal (IP)
- Intra-arterial (IA)
- Topical

Types of immunotherapy

- Immune checkpoint inhibitors
- T-cell transfer therapy
- Monoclonal antibodies
- Treatment vaccines
- Immune system modulators

Targeted Therapy

- **Small-molecule drugs**
- **Monoclonal antibodies**

Hormone Therapy

- Hormone therapy falls into two broad groups, those that block the body's ability to produce hormones and those that interfere with how hormones behave in the body.

Stem Cell Therapy

- Autologous, which means the stem cells come from the patient
- Allogeneic, which means the stem cells come from someone else. The donor may be a blood relative but can also be someone who is not related.
- Syngeneic, which means the stem cells come from the identical twin, if there is one.

Biomarker Testing for Cancer Treatment

- Biomarker tests can help you and your doctor select a cancer treatment for you. Some cancer treatments, including targeted therapies and immunotherapies, may only work for people whose cancers have certain biomarkers.
- For example, people with cancer that has certain genetic changes in the *EGFR* gene can get treatments that targets those changes, called EGFR inhibitor. In this case, biomarker testing can find out whether someone's cancer has an EGFR gene change that can be treated with an EGFR inhibitor.

Biomarker Testing for Cancer Treatment

- Biomarker test는 항암치료 선택에 보조수단으로 쓰인다. 대부분 biomarker는 genetic marker와 관계되어 있지만 biomarker에 따라서 protein 또는 다른 marker를 찾는데 응용된다.
- Biomarker에 따라서 한가지 biomarker를 하거나 여러 biomarker를 동시에 test 하기도 하는데 multigene tests 또는 panel tests라고 한다. 예를 들어 Oncotype DX test는 주어진 유방암환자에게서 chemotherapy의 효과를 예측할 수 있는 21개의 유전자 test를 한다.
- Biomarker에 따라서 Melanoma와 같은 특정한 암 환자에게 적용되는 test도 있고 많은 cancer type에서 공통되게 발견되는 biomarker들을 test한다.

First-in-Human Phase 1 Studies in Oncology

- 항암 1상 임상시험은 건강인 보다는 환자를 대상으로 한다는 점에서 여타 의약품 임상시험과 다르다.
- Targeted drug의 임상시험 에서는 환자군이 좀더 정밀하게 정의되며 효율적인 참가 자격이 요구된다. 임상시험의 목표가 MTD (maximum tolerated dose)에서 RPTD (Recommended Phase 2 Dose)로 바뀌었다.
- Biological doses의 定義, 대리변수(surrogate maker) 분석을 위한 fresh tumor tissue 수집, infusion 과정에서 발생할 수 있는 MAB (monoclonal antibodies) 반작용 등을 고려하여 FIH (first-in-human) study를 하는 挑戰이 있다.

항암1상 임상시험은 변화를 요구한다. 변화하는 1상 임상시험의 복잡한 항암 의약품 개발과정이 의료진의 항암연구 교과과정의 중요한 부분이 되어야 한다.

References

https://www.cancer.gov/about-cancer/treatment/types

https://www.researchgate.net/publication/254285428_First-in-Human_Phase_1_Studies_in_Oncology_The_New_Challenge_for_Investigative_Sites

https://www.annalsofoncology.org/article/S0923-7534(19)45984-X/fulltext

LSK's Experience in Oncology Trials

Indication	총합계
Acute Lymphoblastic Leukemia	1
Acute Myelogenous Leukemia	4
Bone Metastasis	1
Brain Cancer	4
Breast cancer	23
Cancer	5
Cervical intraepithelial neoplasia III(CIN3)	1
Cervix cancer	1
Childhood cancer	1
Chronic Lymphoblastic Leukemia	1
Chronic Myelogenous Leukemia	4
Colorectal Cancer	11
Diffuse large B-cell lymphoma	1
DLBCL(Diffuse Large B-cell Lymphoma)	1
EBV(+) lymphoma	2
Gastric cancer	13
Glioblastoma	2
Hematologic Malignancy	2
Hepatocellular carcinoma(HCC)	17
Hepatoma	1
Improvement of Fatigue	1
Lung cancer	4
Melanoma	1
Metastasis Colorectal cancer	1

Indication	총합계
Metastatic Breast Cancer(mBC)	1
Multiple Myeloma	6
Myelodysplastic syndrome (MDS)	1
Neutropenia	6
Non-Hodgkin's Lymphoma	1
NSCLC	31
Ovarian cancer	1
Pancreatic Cancer	7
Peripheral T cell Lymphoma	1
Ph+Chronic myelogenous Leukemia	1
Prostate cancer	7
Renal cell carcinoma	7
Sarcoma	1
Solid Cancer	27
Therapeutic Vaccine(HPV)	1
Thymic epithelial tumour(흉선상피종양)	1
TNBC(Triple Negative Breast Cancer)	2
Urothelial Cell Cancer(UCC)/Renal Cell Cancer(RCC)	2
antiemesis drugs	2
UK	4
총합계	**213**

Oncology Experience – Oncology Clinical Trial Experience (Early Phase)

Oncology Indication	I	I(FE)	I/II	I/IIa	Ib	Ib/IIa	IIT(I)	총합계
Acute Myelogenous Leukemia	2							2
Brain Cancer						1		1
Breast cancer	3							3
Cervix cancer			1					1
Childhood cancer	1							1
Colorectal Cancer						1		1
Diffuse large B-cell lymphoma	1							1
EBV(+) lymphoma	1							1
Gastric cancer					1			1
Glioblastoma						1		1
Hematologic Malignancy	1							1
Hepatocellular carcinoma(HCC)						1		1
Metastasis Colorectal cancer	1							1
Multiple Myeloma					1			1
Neutropenia	3							3
NSCLC	4	1	3	1	1			10
Ovarian cancer	1							1
Pancreatic cancer			1	1				2
Prostate cancer	1							1
Solid Cancer	19		2	1	2		1	25
TNBC(Triple Negative Breast Cancer)				1		1		2
UK	1							1
총합계	**39**	**1**	**7**	**4**	**5**	**5**	**1**	**62**

Oncology Experience – PD1/PDL-1/CTLA4 target indications for approved drugs

Year	Product type	Indication	Study Phase	No. of Subjects	No. of sites	Service scope	Study Global/Local
2021	anti-PD-L1 Ab(Durvalumab) Combination trial	Urothelial Cell Cancer(UCC)/ Renal Cell Cancer(RCC)	II	48	2 (USA)	Data Management	Global Project
2019	anti-PD-L1 IgG1 type monoclonal antibody	cancer	IIT(II)	50	1 (Korea)	Pharmacovigilance	Local Project
2018	anti-PD-1 Ab (Pembrolizumab) Combination Trial	TNBC(Triple Negative Breast Cancer)	Ib/IIa	83	12 (Korea)	Clinical Operation Data Management Statistics Medical Writing Project Management	Local Project
2014	anti-PD-1 Ab (Nivolumab) Combination Trial	NSCLC	I	18	5 (Korea)	IND Submission Clinical Operation Data Management Statistics Medical Writing (CSR) Project Management	Global Sponsor
2014	anti-PD-1 Ab (Nivolumab) Combination Trial	NSCLC	II	104	10 (Korea)	IND Submission Clinical Operation Data Management Statistics Medical Writing Project Management	Global Sponsor

FIH Case Study – Australia and South Korea Enrollment and Timeline

Protocol Title	XXXX phase 1 FIH study for advanced cancer patients				
Number of Patients	Part A 40, part B 60 (30 advanced/metastatic gastic cancer patients, 30 NSCLC patients)				
Design	Part A : Maximum tolerance dose estimation (multi-centre, open, dose escalation study), PK, PD, administered 1 or 2 times/day				
	Part B : Extension study based on suggested dose from Part A, identifying PK variables and/or PD biomarker from advanced gastric cancer or advanced NSCLC.				
IND Submission	2010-10-18 (Initial submission)				
Sites	Enrollment/Dosed Status: Part A*	Enrollment/Dosed Status: Part B	IRB Submission Date	IRB Approval Date	SIV Date
Center 1(South Korea	5	19	2010-11-17	2010-12-13	2011-03-07
Center 2(South Korea)	5	21	2010-11-11	2010-12-03	2011-02-11
Center 3(South Korea)	6	11	2010-11-08	2010-11-24	2011-02-14
Center 4(Australia)	8	3	UK	UK	2010-12-02
Center 5(Australia)	12	4	UK	UK	2010-11-22

A Global Gastric Cancer Experience

Global Project Management by LSK Global PS as Lead CRO (2016~2019.05 **DBL**)

Global Project Example

Category	Content
Therapeutic area	Oncology
Study type	Double-blind Ph3 Clinical Trial
Locations	Total 12 Countries, 95 Sites
Number of Subject	460
Status	Recruitment Completed
Vendors	Regional CROs : Japan, Taiwan, EU/US
	Central Imaging, Central PK/PD
	Safety Committee (IDMC), PV system
	EDC, CTMS, eTMF
	Medical Monitor, Quality Consultant

Total 12 Countries, 95 sites

Europe 8	
France	Germany
Ukraine	Poland
Italy	UK
Romania	Russia

Asia-Pacific 3
Korea
Taiwan
Japan

A Global Pivotal Oncology Study by LSK

	LSKG , Korea	Global CRO, EU & US	Local CRO, Japan	Local CRO, Taiwan
# of Sites	**22**	**50**	**15**	**8**
Site Feasibility Completion	13-Sep-16	30-Oct-16	15-Dec-16	13-Sep-16
Regulatory Submissions	07-Dec-16	Dec 2016 – May 2017	07-Dec-16	16-Dec-16
Regulatory Approvals	06-Jan-17	US : 26-May-2017 EU Region : 10-Apr-18 (last)	06-Jan-17	16-Feb-17
Site Initiation Visit	24-Feb-17	US: 04 May 2017 EU Region : 13 Oct 2017 (first)	28-Mar-17	05-May-17
First Patient Screening	08-Mar-17	US : 01-Sep-17 EU Region : 11-Dec-17	05-Apr-17	03-Aug-17
First Patient In	14-Mar-17	US : 02-Jan-18 EU Region : 19-Dec-17	13-Apr-17	23-Aug-17
Subjects Enrolled	**214**	**150**	**59**	**37**
CRO Cost	**$9.5M***	**$10.4M**	**$4.6M**	**$0.6M**
Per patient CRO Cost	**$44,381***	**$69,005**	**$77,527**	**$17,307**

*: Including DM/STAT/Global PM/Global PV/MW etc. If limited to just patient management and RA support, the cost could have been lowered by 1/3 to $30,000.

Symposium 일정

9:30	9:45	0:15	Opening	이영작 대표 LSK Global PS
9:45	10:35	0:50	항암제 1상 임상시험 설계 전반	안철우 교수 UT Southwestern Medical Center
10:35	11:00	0:25	Q&A / 휴식	
11:00	11:50	0:50	Bayesian Optimal Interval (BOIN) Design	길시연 팀장 LSK Global PS
11:50	12:10	0:20	Q&A / 휴식	
12:10	13:00	0:50	Model-based, Model-assisted Designs for Early Phase Clinical Study: CRM, mTPI, Keyboard Design etc.	이정복 교수 서울아산병원
13:00	14:00	1:00	점심식사	
14:00	14:30	0:30	항암제 초기 임상에서 Effective Dose 결정 시 고려사항	나현희 상무 LSK Global PS
14:30	14:50	0:20	Q&A / 휴식	
14:50	15:40	0:50	PV in Phase I Oncology Study	이정민 상무 LSK Global PS
15:40	16:00	0:20	Q&A / 휴식	
16:00	16:50	0:50	항암제 1상 통계분석 사례	박병관 상무 LSK Global PS
16:50	17:00	0:10	Q&A	

감사합니다.