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항암제 1상 통계분석

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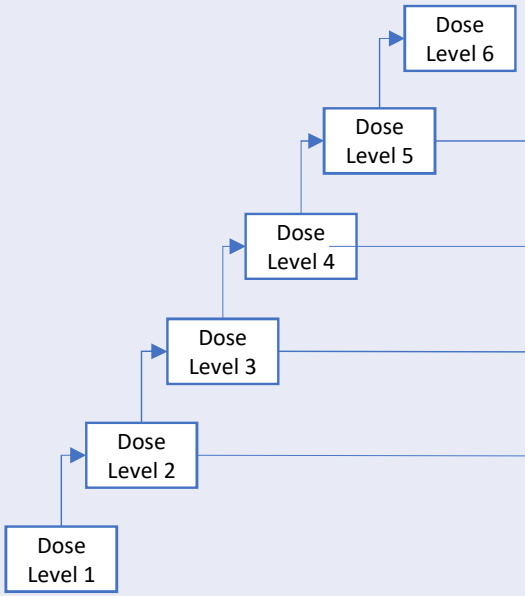
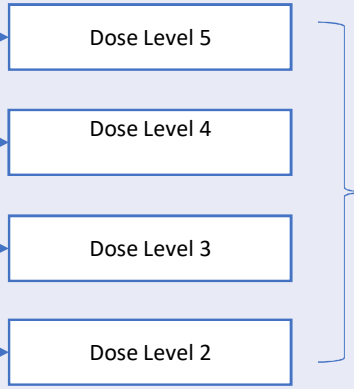
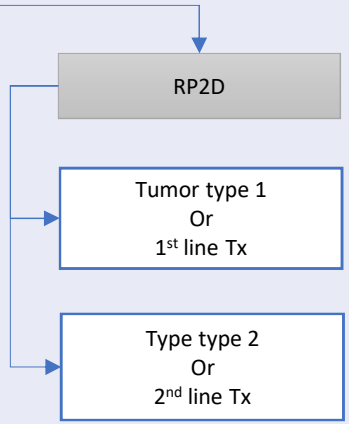
목차

초기 항암제 임상시험 설계

- **Phase I study design to find MTD**
  - Rule based design: 3+3, up and down, accelerated titration, etc
  - Model based / assisted design: (m)CRM, BOIN, mTPI, EWOC, etc
- **Overall design frame**
  - Single stage: MTD & RP2D
  - Multiple stage
    - Phase I with Part A, Part B
      - MTD + preliminary efficacy (by biomarker/treatment regimen)
    - Phase I+IIa
      - IIa to confirm the efficacy of IP with single arm
        - Simon's two stage design
      - IIa in form of basket trial with several tumor types/disease.
    - Integrated analysis

Overall Design Frame - Example

Phase I(a)	Phase I(b)	Phase IIa
Dose Escalation (Mono Tx)	Dose Expansion (biomarker +, combination Tx)	Dose Extension (1st/2nd Tx or Other tumor type)
		
• MTD	• MTD, RP2D for target treatment • Preliminary efficacy	• Preliminary efficacy for target disease • Decision rule to confirm the efficacy - Eg) Simon 2 stage design. other efficacy rule for single stage.

Study Endpoints

- MTD – Primary for phase I
- **Efficacy endpoints**
  - Objective response rate (ORR)
  - Disease control rate (DCR)
  - Duration of response (DoR)
  - Progression free survival (PFS)
  - Time to progression (TTP)
  - Disease free survival (DFS)
  - Overall survival (OS)
- Safety endpoints
  - AE, SAE, AESI, Hematotoxicity, ECG, etc.
- Biomarkers
- PK/PD

Efficacy endpoints

- **Response Rate**
  - for Phase I,III(secondary) or IIa (primary)
  - Objective Response Rate (ORR)
  - Disease Control Rate (DCR) or Clinical Benefit Rate (CBR)
- **Time to event**
  - for phase II(a,b) or III (primary or secondary)
  - Progression Free Survival (PFS)
  - Time to Progression (TTP)
  - Disease Free Survival (DFS)
  - Duration of Response (DoR)
  - Overall Survival (OS)

Definition of Efficacy Endpoints - Response

Endpoint	Definition	Characteristics
Objective Response Rate (ORR)	The proportion of pts with tumor size reduction of a predefined amount and for a minimum time period. - CR + PR	• Direct measure of drug antitumor activity
Disease Control Rate (DCR)	Percentage of patients whose disease shrinks or remains stable over a certain time period. - CR+PR+SD	• Useful to measure the efficacy of therapies that have tumoristatic effects rather than tumoricidal effects.
Complete Response (CR)	No detectable evidence of tumor	• A clinical endpoint for TA in hematologic malignancies(acute leukemia) • Pathologic CR(pCR) - A surrogate endpoint for AA in early high-risk breast cancer.

Ref.) UF FDA(2018 Dec), Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Decision of Tumor Response

[RECIST V1.1, Korean version]

표 1. Time Point Response – 표적 (비- 표적 병변이 있거나 없음) 병변

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD

표 2. Time Point Response –비-표적 병변

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Best Overall Response(BOR)

- **RECIST V1.1**
- **Best overall response**
  - Response is **primary** endpoint => confirmation is required (confirmed BOR).
    - e.g., phase II single agent trial (non-randomized)
  - Response is **secondary** endpoint => confirmation is not required (unconfirmed BOR).
    - e.g., randomized trial with stable disease or progression endpoints (e.g., PFS)
    - may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

- **Unconfirmed BOR (uBOR)**
  - the best response recorded from the start of the study treatment until the end of treatment
  - e.g., PR-CR-SD-PD: uBOR=CR

- **Confirmed BOR (cBOR)**
  - CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later)
  - e.g., CR-PR-PR(>4wks)-PD: cBOR=PR

Best Overall Response(BOR)

- **uBOR, cBOR 결정을 위한 순서를 SAP에 기재되어야 함**
  - OR category with target and non-target lesions: CR, PR, SD, PD, NE
  - OR category with non-target lesions only: CR, Non-CR/non-PD, PD, NE
  - 모든 category 통합하는 경우: CR, PR, SD, Non-CR/non-PD, PD, NE
  - Non-CR/non-PD를 SD에 포함한 경우: CR, PR, SD, PD, NE

- **SD minimum duration**
  - SD minimum duration = date of response result – 1st IP admin. date(or RDZ date)
  - Prespecified in the protocol (in general not less than 6–8 weeks)
  - Applied to both uBOR and cBOR
  - If not meet the SD criteria(eg., 7 weeks), BOR depends on the subsequent assessments
    - Eg., SD-PD (5wks): BOR=PD
      SD-PD (9wks): BOR=SD
      SD-NE(4wks): BOR=NE

Best Overall Response using RECIST1.1

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

1) (CR이 맞는 경우) 첫 복용일부터 첫 CR까지의 기간이 SD minimum duration을 만족하면, **cBOR = SD**.
2) (CR이 맞는 경우) SD minimum duration 불만족하면, **cBOR = PD**.
3) (CR이 아닌 경우) 작은 병변이 PR 판정된 스캔에서 연속으로 계속 존재하는 경우, 최초 CR을 PR로 변경하고 **cBOR = PR**.

Example – Definition of Confirmed Response

- **Best Overall Response (BOR)**
  - The BOR categories (CR, PR, SD (including non-CR/non-PD), PD, NE, Unknown) will be derived based upon time point tumor responses during the study as assessed by ICR as well as the investigator.
  - BOR of **SD must occur at least 5 weeks** (6weeks minus the 7-day visit window) **after the first dose of IP**.
  - If a patient has non-CR/non-PD, the category will be grouped as SD.

  - A patient's BOR will be determined:
    - **CR**: At least one visit response of CR **confirmed** by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.
    - **PR**: At least one visit response of PR **confirmed** by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.
    - **SD**: Stable disease recorded at least 35 days after start of treatment.
    - **PD**: Progression or death in the absence of CR/PR or SD.
    - **NE**: no evidence of CR/PR or SD or PD or death

Example – Programming Specification for cBOR

Scenario-ID	Assessment at The Current Time Point (TP0)	Assessment at The First Subsequent Time Point (TP1)	Assessment at The Second Subsequent Time Point (TP2)	The Current Assessment Is Eligible for BOR Derivation (Y/N) with The Condition?	Derived Assessment with The Condition: Meeting SD Criteria at TP0
CR1	CR	CR	CR	Y, if nxt1dy >= 28 or nxt2dy >= 28	
CR12	CR	CR	CR	N, if nxt1dy < 28 and nxt2dy < 28	SD, if crit1fl='Y'
CR13	CR	CR	CR	N, if nxt1dy < 28 and nxt2dy < 28	NE, if crit1fl=''
CR2	CR	CR		Y, if nxt1dy >= 28	
CR22	CR	CR		N, if nxt1dy < 28	SD, if crit1fl='Y'
CR23	CR	CR		N, if nxt1dy < 28	NE, if crit1fl=''
CR3	CR	NE	CR	Y, if nxt2dy >= 28	
CR32	CR	NE	CR	N, if nxt2dy < 28	SD, if crit1fl='Y'
CR33	CR	NE	CR	N, if nxt2dy < 28	NE, if crit1fl =''
CR4	CR	NE	PR/SD	N	SD, if crit1fl='Y'
CR42	CR	NE	PR/SD	N	PD, if crit1fl=''
CR5	CR	PR/SD		N	SD, if crit1fl='Y'
CR52	CR	PR/SD		N	PD, if crit1fl=''
CR6	CR			N	SD, if crit1fl='Y'
CR62	CR			N	NE, if crit1fl=''

- Nxt*n*dy: number of days from the current time point overall response evaluation to the n^{th} subsequent time point overall response evaluation;
- Crit1fl: For the meeting of SD criteria, CRIT1FL='Y' if RS.RSDT-TRTSDT (RANDDT) +1 >= 49.

Ref.) PharmaSUG 2020 - Simplifying the Derivation of Best Overall Response per RECIST 1.1 and iRECIST in Solid Tumor Clinical Studies; Xiangchen (Bob) Cui, and Sri Pavan Vemuri

Example – uBOR or cBOR Decision

Best Overall Responses:

Example 1

	Subject ID	Visit	Study Day	Parameter Name	Analysis Value, Character
1	001	Week 8	56	Overall Response	SD
2	001	Week 16	112	Overall Response	PR
3	001	Week 24	168	Overall Response	PR
4	001	Week 32	224	Overall Response	PR
5	001	Week 40	280	Overall Response	CR

1. **Unconfirmed BOR is CR.**
2. **Confirmed BOR is PR**, because there are two consequent PR observation with >= 28 days in between and there is no record available to confirm CR.

Example 2

	Subject ID	Visit	Study Day	Parameter Name	Analysis Value, Character
1	002	Week 8	56	Overall Response	PR
2	002	Week 16	112	Overall Response	NE
3	002	Week 24	168	Overall Response	PD

1. **Unconfirmed BOR is PR.**
2. **Confirmed BOR is SD**, because first PR assessment has met min criteria for SD duration.

Example 3

	Subject ID	Visit	Study Day	Parameter Name	Analysis Value, Character
1	003	Unscheduled Visit	30	Overall Response	CR
2	003	Week 8	56	Overall Response	PR

1. **Unconfirmed BOR is CR.**
2. **Confirmed BOR is SD**, because only two responses are available with 26 days in between, but the second PR assessment has met min criteria for SD duration.

Ref.) PhUSE EU Connect 2018 , Paper AS04 ; Step by Step Guide to Efficacy Analysis in Solid Tumors Oncology Clinical Trials; Anastasiia Tiurdo

Example – ADORS domain

USUBJID	TRTP	PARAM	PARAMTYP	AVIVIT	ADT	AVALC	RESEQ
001	DRUG	Overall Response		Cycle 1	2017-01-01	CR	1
001	DRUG	Overall Response		Cycle 2	2017-04-01	SD	4
001	DRUG	Overall Response		Cycle 3	2017-07-01	SD	7
001	DRUG	Overall Response		Cycle 4	2017-10-01	PR	10
001	DRUG	Overall Response		Cycle 5	2018-01-01	PD	13
001	DRUG	cBOR	DERIVED	End of Study		SD	
001	DRUG	uBOR	DERIVED	End of Study		CR	
001	DRUG	ORR	DERIVED	End of Study		N	

Definition of Efficacy Endpoints – Time to Event

Endpoint	Definition	Characteristics
Progression-Free Survival (PFS)	The time from RDZ until objective tumor progression or **death** whichever occurs first.	A better correlate to OS
Time to Progression (TTP)	The time from RDZ until objective tumor progression	Death as censored.
Time-to Treatment Failure	Time from randomization* to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death	• Useful in settings in which toxicity is potentially as serious as disease progression (eg, allogeneic stem cell transplant) • Does not adequately distinguish efficacy from other variables, such as toxicity
Time-to Next Treatment	Time from end of primary treatment to institution of next therapy	• For incurable diseases, may provide an endpoint meaningful to patients • Not commonly used as a primary endpoint • Subject to variability in practice patterns
Duration of Response	Time from documentation of tumor response to disease progression	• Effect is attributable directly to the drug, not the natural history of the disease • Not a comprehensive measure of drug activity

Source: UF FDA(2018 Dec), Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Definition of Efficacy Endpoints – Time to Event

Endpoint	Definition	Characteristics
Overall Survival (OS)	The time from randomization until death from any cause	Measured in the ITT population
Disease-Free Survival (DFS)	The time from RDZ until disease recurrence or death from any cause	•Adjuvant setting **AFTER** surgery or Rx. •Can be used in situations where survival may be prolonged, OS impractical. •Adj. breast cancer hormonal Tx. Adj. colon cancer, Adj. cytotoxic breast cancer Tx.
Event-Free Survival (EFS)	The time from RDZ to any of the following events: PD that precludes surgery, Local or distant recurrence, Death due to any cause. (Tx fail due to any cause)	Neoajd. setting RDZ **BEFORE** surgery. Neoadj. breast cancer before surgery

Source: UF FDA(2018 Dec), Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Definition of PFS

- **Progression free survival (PFS)**
  - defined as the time from **the first dose of the investigational product to progression of disease (PD) or death**.
  - A subject with no progression of disease (PD) or death event will be censored at the last evaluable tumor assessment time.
  - A subject with no tumor assessment after baseline will be censored at the first dose of the investigational product +1 day.

> **Status** = 0 (event), if PD or death from any cause
> = 1 (censored), if no PD or alive until last survival f/u

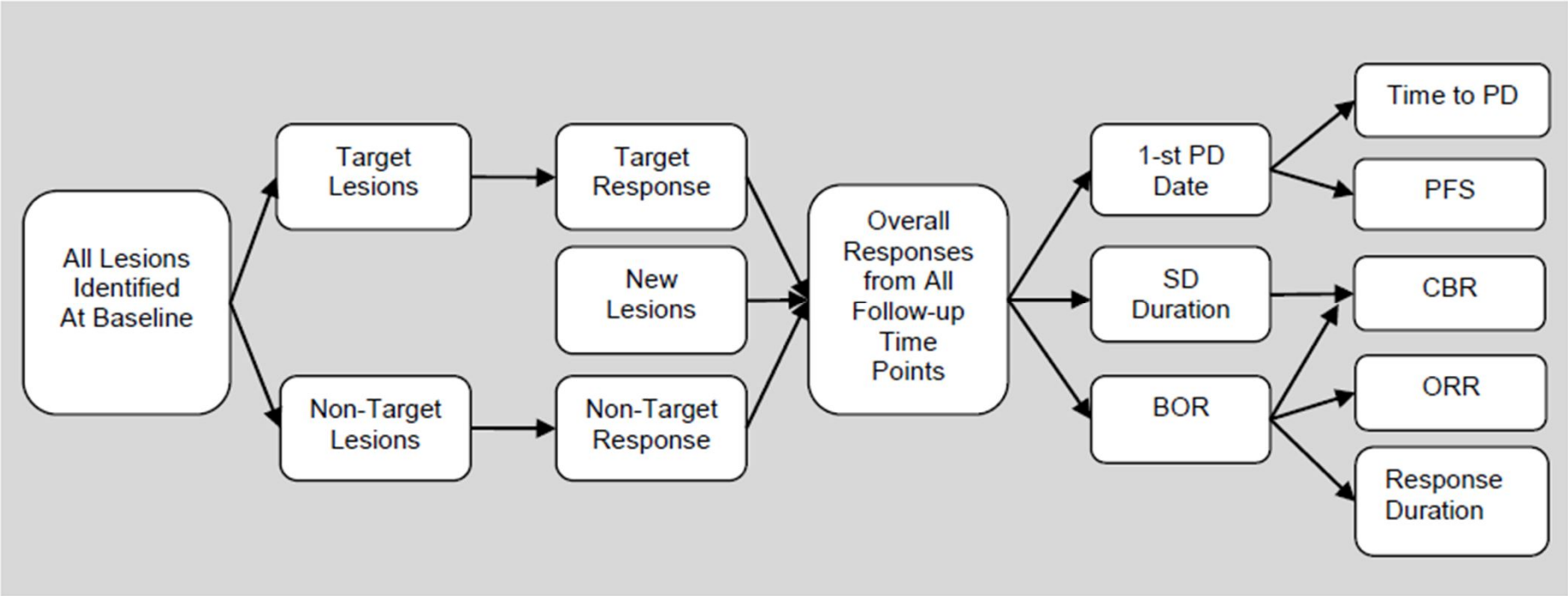
  - **Duration (days)**
    - (Date of Event or Censoring, whichever occurred first)– (Date of the first dose of the investigational product)+ 1

Censoring Rule for Time to Event (PFS)

Status	Event or censoring date	Result
• Subjects for whom diagnostic imaging was missed at baseline.	Date of starting the study treatment (or the randomization)	Censoring
• Subjects for whom evaluable diagnostic imaging has not been performed and who are alive	Date of starting the study treatment(or the randomization)	Censoring
• Subjects who received subsequent anti-cancer therapy before he/she died or were assessed as having PD	Date when the last evaluable diagnostic imaging was performed before starting subsequent anti-cancer therapy	Censoring
• Subjects for whom the outcome follow-up was ended before death or assessment as PD	Date when the last evaluable diagnostic imaging was performed before the end of the outcome follow-up	Censoring
• Subjects who are alive and have not been assessed as having PD	Date when the last evaluable diagnostic imaging was performed	Censoring
• Subjects who died or have been assessed as having PD	Date of death or date when the first diagnostic imaging to provide assessment as PD was performed, whichever comes first	Event
• Subjects who died before initial evaluable diagnostic imaging	Date of death	Event

*** Apply image examination date, not the evaluation date**

Endpoint Decision Pathway



Ref.) PhUSE EU Connect 2018 , Paper AS04 ; Step by Step Guide to Efficacy Analysis in Solid Tumors Oncology Clinical Trials; Anastasiia Tiurdo

Statistical Analysis Method

Variables	Analysis method	Missing data	Graph
ORR/DCR	• Summary statistics (N, %) • Exact CI	• Response decision rule	• Bar chart • Swimmer's plot • Spider plot • Waterfall plot
PFS/TTP/DFS/ DoR/OS	• Summary statistics • Median and CI • Kaplan-Meier method • Log Rank test • Cox regression	• Censoring rule	• Kaplan-Meier plot • Forest plot with HR and CI

Analysis population - Example

- **FAS / PP / (Efficacy, PK, DLT) Evaluable set**
  - FAS: subjects who take at least IP once and have at least one efficacy evaluation(?).
- **Dose Evaluation Phase:**
  - **DLT-evaluable Subjects**: All subjects who completed the DLT evaluation period
  - **Enrolled Subjects**: All subjects who signed an informed consent form and were registered into the IVRS during the Dose Evaluation Phase
  - **Treated Subjects**: All subjects who received at least one dose of any study medication during the Dose Evaluation Phase
- **Dose Expansion Phase:**
  - **Enrolled Subjects**: All subjects who signed an informed consent form and were registered into the IVRS during the Dose Expansion Phase.
  - **Treated Subjects**: All subjects who were allocated to a unique cohort during the Dose Expansion Phase and were treated
- **Other populations**
  - **PK Evaluable Subjects**: All subjects who received at least one dose of study medication and have available serum concentration data during the Dose Evaluation Phase.
  - **Biomarker Evaluable Subjects**: All subjects who received at least one dose of study medication and have baseline and at least one post-baseline biomarker assessment during the Dose Evaluation Phase.

Example-Statistical Analysis Methods

- **Objective Response Rate**
  - BOR will be summarized by response category and ORR will be computed along with an **exact 90% CI**
  - ORR figure by dose level
  - The primary population for estimating the ORR will be the Efficacy Evaluable population.
- **Disease Control Rate**
  - Analyses on disease control rate will be similar to the ones conducted on the ORR.
- **Duration of Objective Response**
  - Duration of response will be estimated using KM methodology for subjects who achieve PR or CR.
  - Median values along with two-sided 95% CIs will be calculated.
  - For the responders only, the time course of the following events of interest will graphically be displayed **(swimmers plot)**: tumor response, progression, last dose received and death.

Example – Mock Table of OR

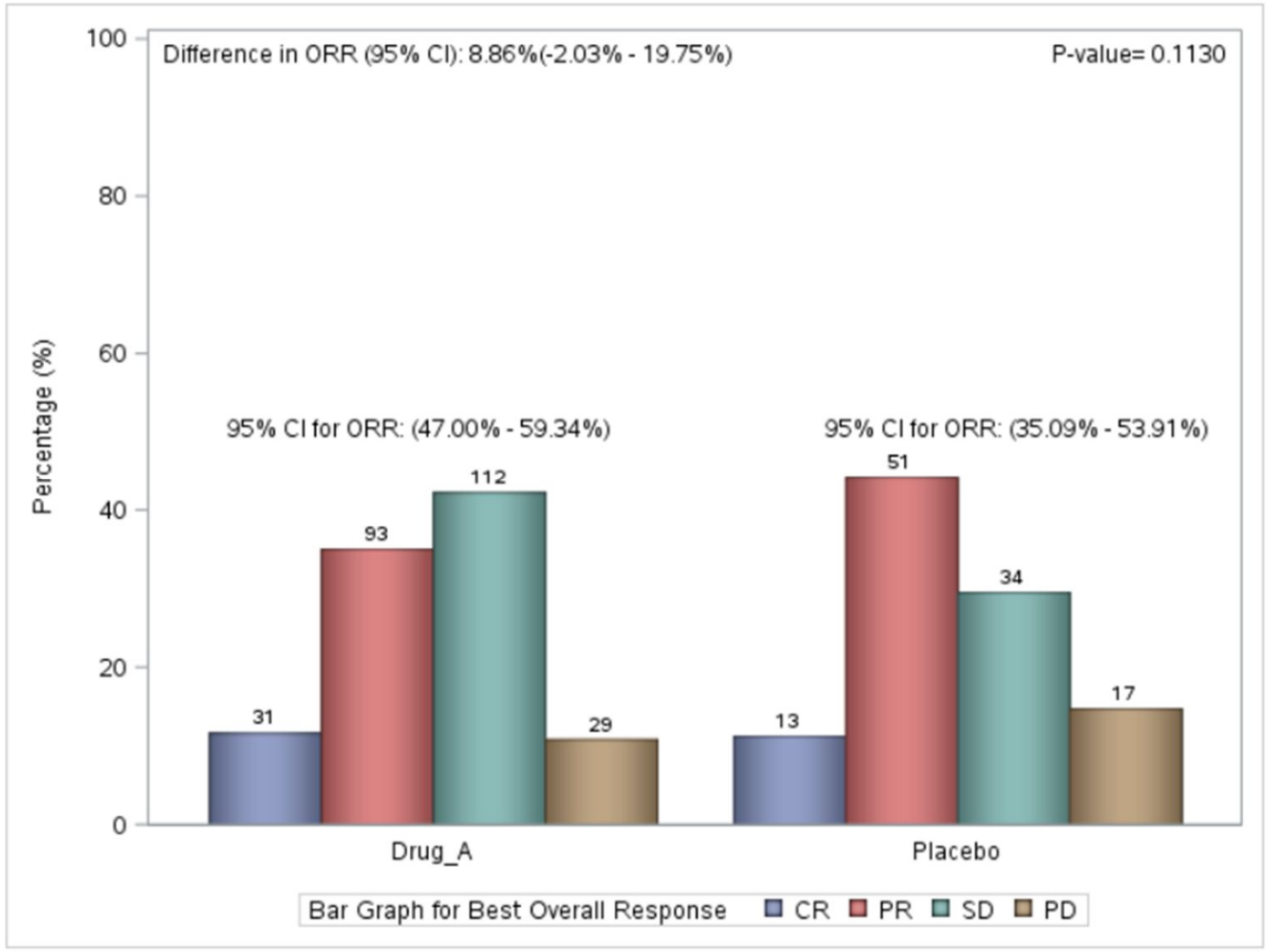
Sponsor: ABC Corporation
Protocol no.: AB-01234

Table 16.5.4.13
Overall Response by Investigator
Evaluable for Response Population

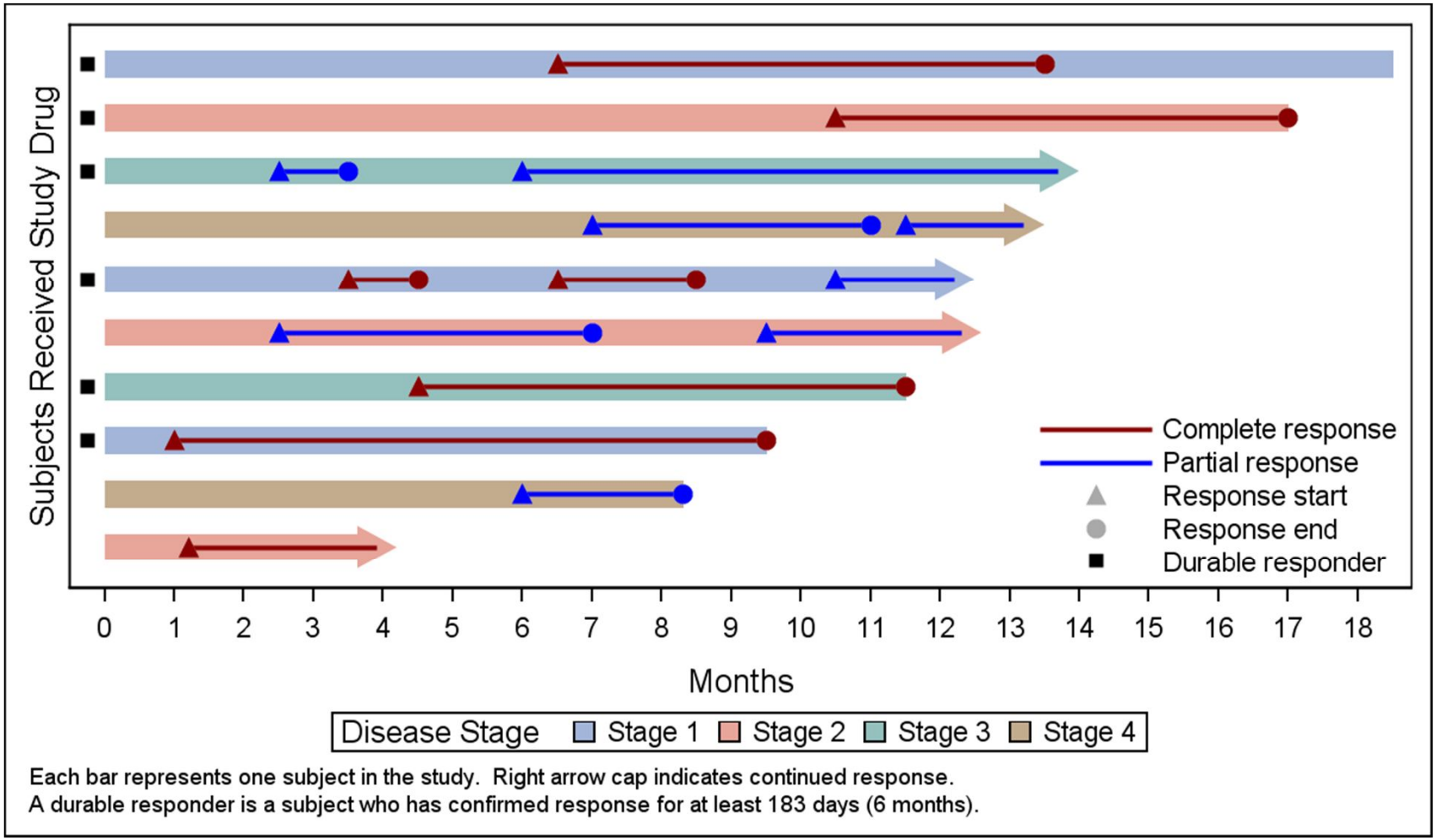
Page 1 of 2

	ABC001 10mg (N=xx)	ABC001 20mg (N=xx)	ABC001 40mg (N=xx)	ABC001 80mg (N=xx)	ABC001 160mg (N=xx)	Total (N=xx)
Unconfirmed best overall response, n(%)						
Complete Response (CR)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Partial Response (PR)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Stable Disease (SD)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Progressive Disease (PD)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Not Evaluable (NE)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Not Applicable (NA)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Objective response rate (unconfirmed CR + unconfirmed PR)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
95% Confidence Interval	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]
Confirmed best overall response, n(%)						
Complete Response (CR)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Partial Response (PR)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Stable Disease (SD)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Progressive Disease (PD)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Not Evaluable (NE)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Not Applicable (NA)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Objective response rate (confirmed CR + confirmed PR)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
95% Confidence Interval	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]
Disease control rate (DCR, confirmed CR+ confirmed PR + confirmed SD)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
95% Confidence Interval	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]	[xx.x, xx.x]

Graphical Analysis – Bar chart

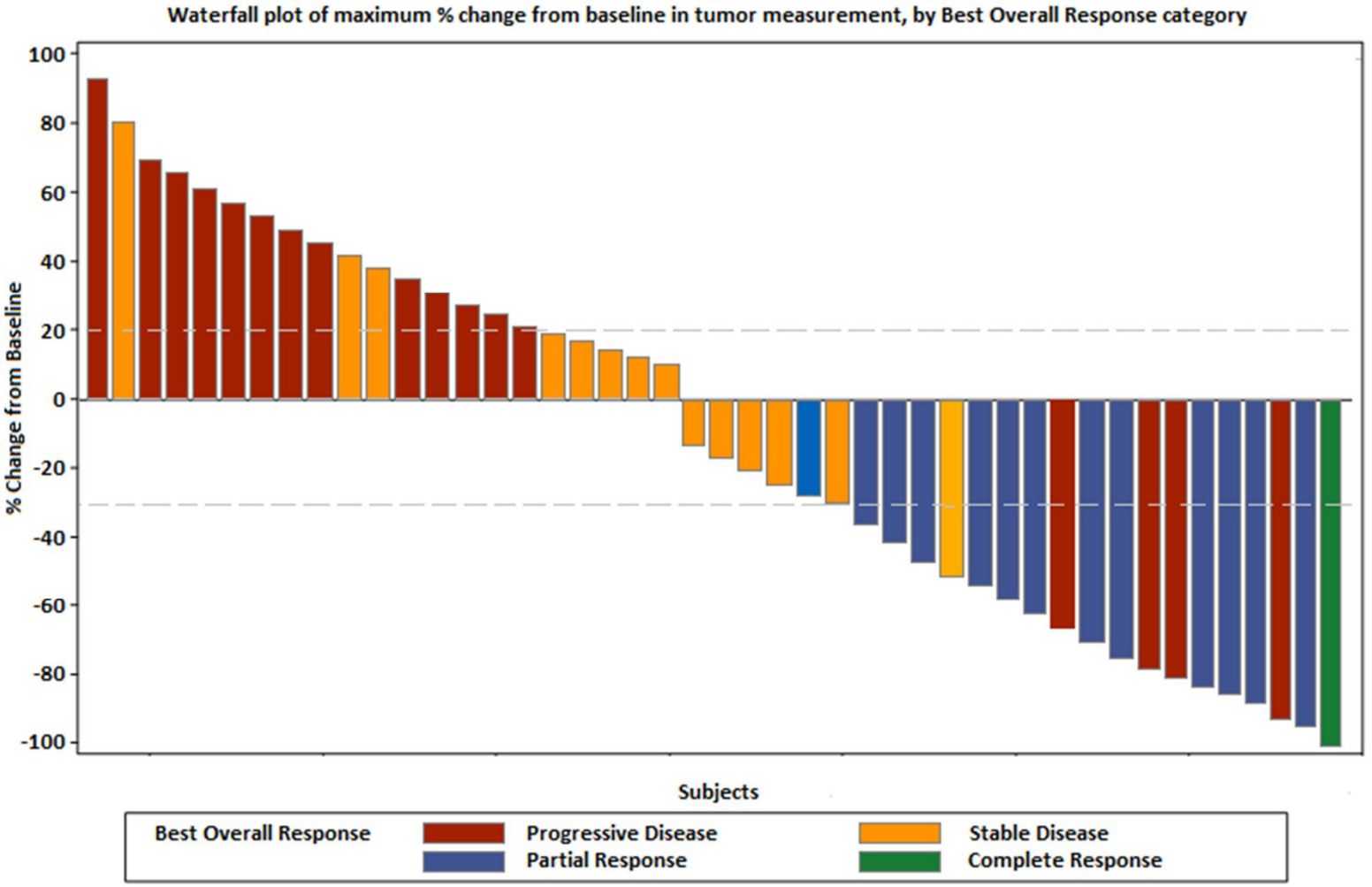


Graphical Analysis – Swimmer plot



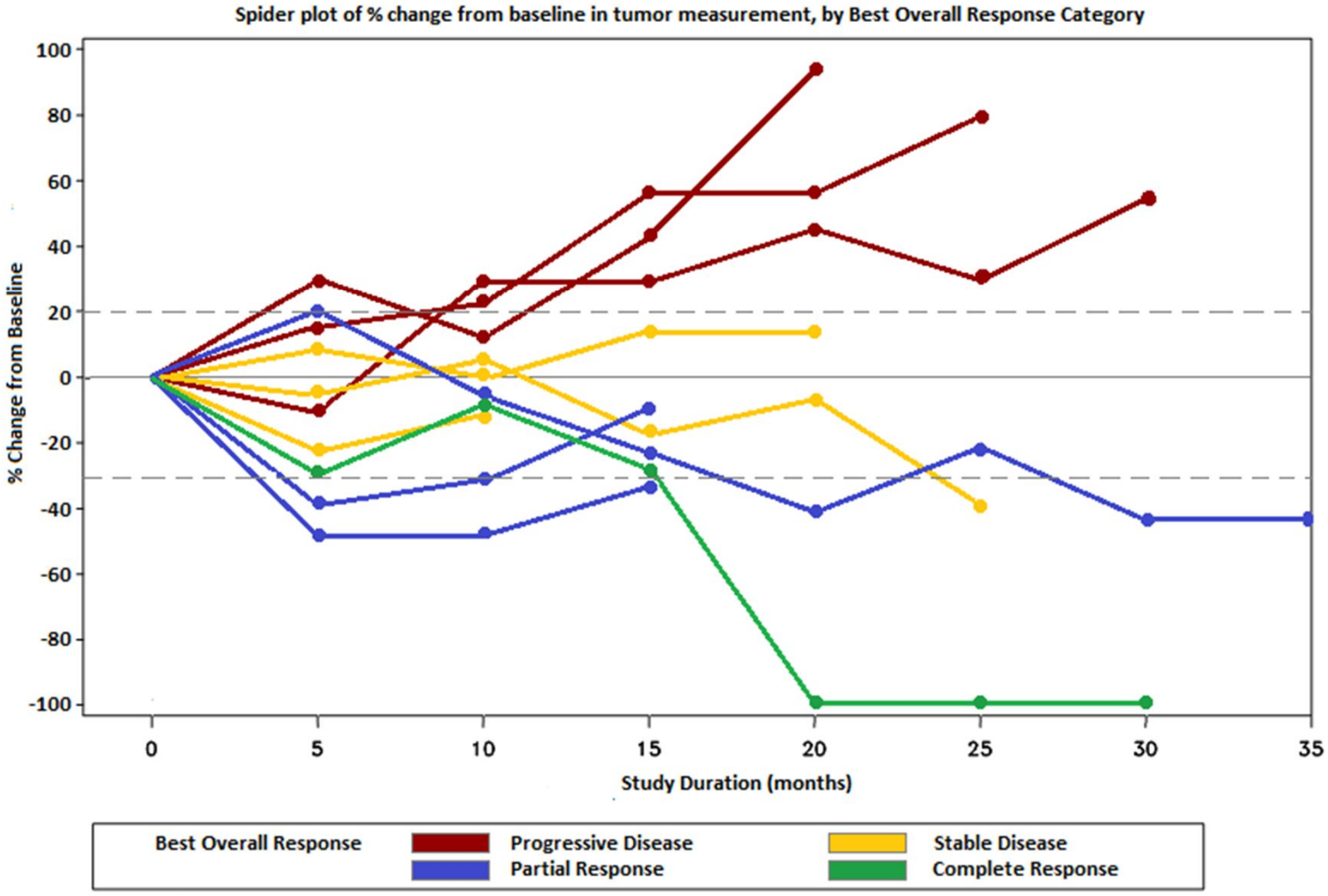
Ref.) https://blogs.sas.com/content/graphicallyspeaking/2014/06/22/swimmer-plot/#prettyPhoto

Graphical Analysis – Waterfall plot



Ref.) PharmaSUG China 2019 - Paper DV-085; Visualization of efficacy endpoints in oncology clinical trials; Shilpakala Vasudevan

Graphical Analysis –Spider plot



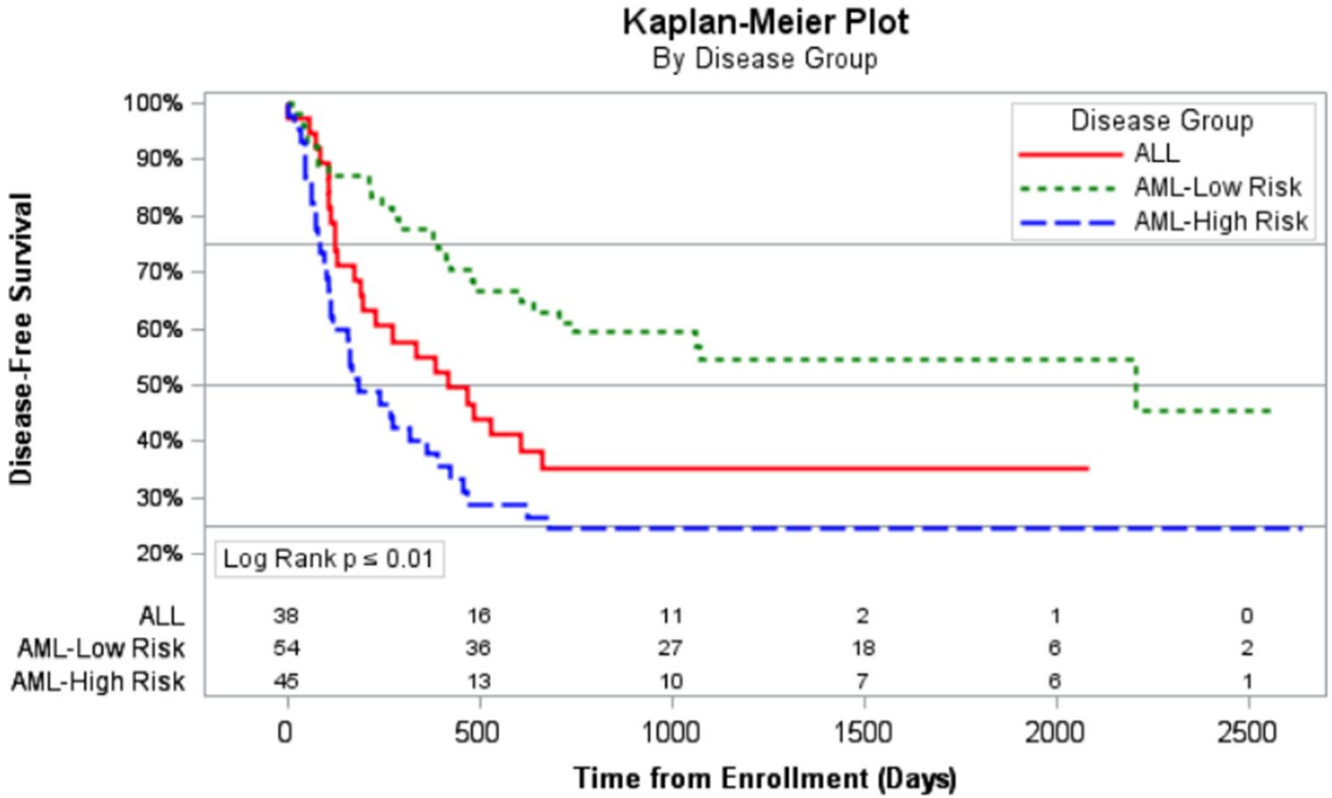
Ref.) PharmaSUG China 2019 - Paper DV-085; Visualization of efficacy endpoints in oncology clinical trials; Shilpakala Vasudevan

Example-Statistical Analysis Methods

- **Overall Survival**
  - OS will be estimated using KM methodology. Median values along with two-sided 95% CIs will be calculated.
  - KM based OS rates at 3, 6, 9, 12, 18, and 24 months will be estimated and associated two-sided 95% CIs will be provided.

- **Progression-free Survival**
  - PFS will be estimated using Kaplan-Meier(KM) methodology.
  - Median values along with two-sided 95% CIs will be calculated.
  - KM based PFS rates at 3, 6, 9, 12, and 18 months will be estimated and associated two-sided 95% CIs will be provided.
  - The following information will also be summarized:
    - Number and type of events
    - Number of subjects censored on first dosing date
      - number with no baseline tumor assessment and no death, number with no on-study tumor assessment and no death
    - Number of subjects censored on date of last tumor assessment on-study
      - number received subsequent anti-cancer therapy, still on-treatment, in follow-up, off study [lost to follow-up, withdraw consent, other].

Graphical Analysis – KM Plot



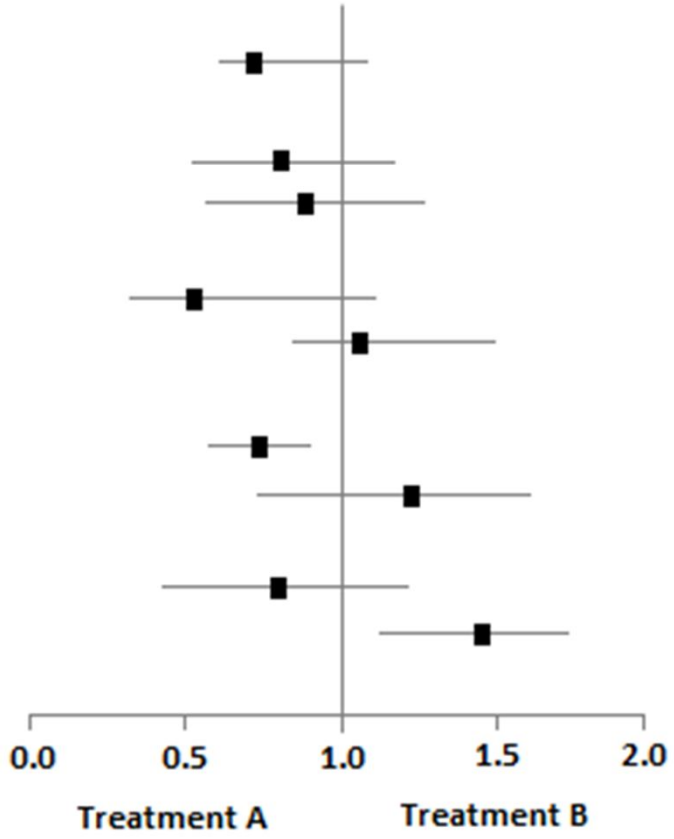
	Subjects	Event	Censored	Median Survival	95% CL	
ALL	38	24	14	418	192	.
AML-Low Risk	54	25	29	2204	641	.
AML-High Risk	45	34	11	183	113	390

Ref.) https://proceedings.wuss.org/2019/167_Final_Paper_PDF.pdf

Graphical Analysis – Forest plot

Forest plot of Progression-Free Survival analysis, by subgroup

Subgroup	Number of Subjects (Treatment A)	Number of Subjects (Treatment B)
Overall	100	100
Age		
<65	45	50
>=65	55	50
Gender		
Male	62	65
Female	38	35
ECOG Performance Status		
0	57	55
>1	43	45
Measurable disease		
Measurable	79	72
Non-measurable	21	28



감사합니다.