



# Do we know enough about drug exposure?

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- All opinions expressed in this presentation are my personal views, and do not reflect the views or opinions of Novartis.
- References are mentioned in last slide.



- Introduction
- Single dose study
- Multiple dose study
  - Limited doses
  - Multiple doses
- Exposure in cycle
- Dose escalation
- Combination study
- Cancer study



- Dose: recommended amount of drug/medicine
- Type of Dosing
  - Fixed
    - eg: 500 mg, 200 mg
  - Variable
    - BSA eg: 5mg/m<sup>2</sup>
    - Weight eg: 5mg/kg



- Drug Exposure can impact the safety and efficacy of investigational drug
- Mainly Duration of exposure, Planned dose, Actual dose, Actual/Planned dose intensity and relative dose intensity
- Duration of exposure: total duration in which drug is administered to subject/patient
- Duration of treatment: Total duration of exposure which does not includes the periods of temporary interruption of the study treatment for any reason.



- Cumulative Dose: Total dose given during the study treatment exposure.
- Average daily dose: Dose taken per day
- Dose Intensity: Dose intensity is a function of dose and frequency of administration. It is defined as the amount of drug delivered per unit of time.
  - Actual Dose Intensity – Actual dose over real treatment duration
  - Planned Dose Intensity – Planned dose over total duration.
  - Relative Dose Intensity – is the ratio of Actual Dose Intensity and Planned Dose Intensity, expressed as a percentage.



# SINGLE DOSE STUDY

# Table for Single Dose Study



## Summary of dose administration

### Population set

	Treatment A	Treatment B	Treatment C	All Patient
	N=XX	N=XX	N=XX	N=XX
Study Drug	n(%)	n(%)	n(%)	n(%)
Xxxxxx(Unit)	XX(xx.xx)	XX(xx.xx)	XX(xx.xx)	XX(xx.xx)



# Listing for Single Dose Study



## Dose Administration

### Population set

Country/ Center/ Subject	Age/ Sex/ Race	Visit	Study Drug	Date of Dosing	Time of Dosing (hh:mm)	Total Dose (unit)
AA/001	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234
AA/002	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234
AA/003	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234
AA/004	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234
AA/005	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234
AA/006	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234
AA/007	XX/M/AA	Day 1	Xxxxxx	01JAN12	00:00	1234



# MULTIPLE DOSE STUDIES

**WITH LIMITED NUMBER OF DOSES**

# Ideal Situation



## Summary of dose administration, by treatment sequence

### Population set

	A-D-B-C	B-A-C-D	All Subject
	N = 13	N = 13	N = 26
Treatment	n(%)	n(%)	n(%)
A	13(100%)	13(100%)	26(100%)
B	13(100%)	13(100%)	26(100%)
C	13(100%)	13(100%)	26(100%)
D	13(100%)	13(100%)	26(100%)



## Summary of dose administration, by treatment sequence

### Population set

	A-D-B-C	B-A-C-D	All Subject
	N = 13	N = 13	N = 26
Treatment	n(%)	n(%)	n(%)
A	13(100%)	11(84.6%)	24(92.3%)
B	11(84.6%)	13(100%)	24(92.3%)
C	9 (69.2%)	10(76.9%)	19(73.1%)
D	11(84.6%)	9 (69.2%)	20(76.9%)



# MULTIPLE DOSE STUDIES WITH LARGE NUMBER OF DOSES

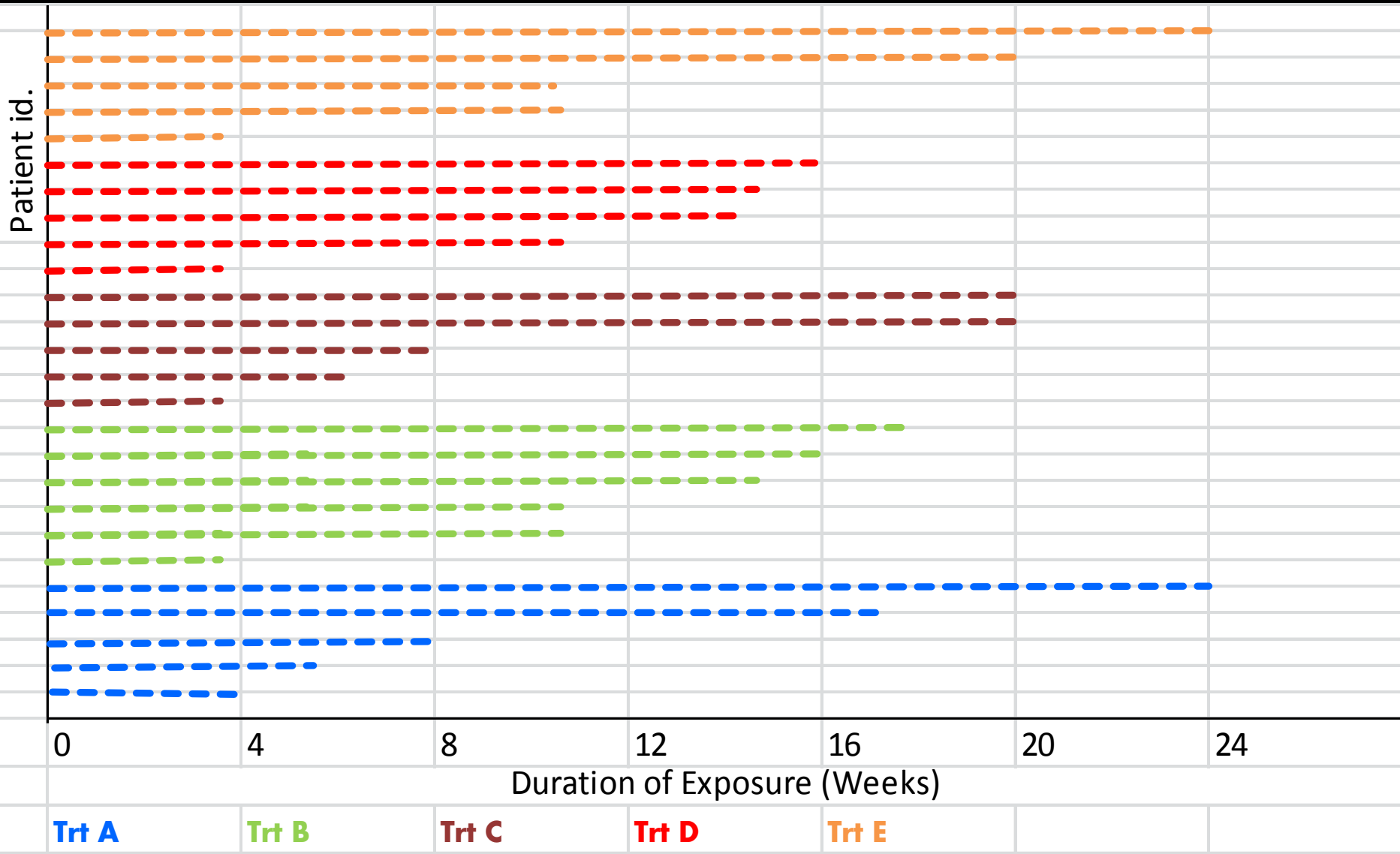


### Duration of exposure to study drug, by treatment

#### Population set

Duration of exposure (weeks)	Treatment A N = 11	Treatment B N = 15	Treatment C N = 23	All Patients N = 49
< 4	0(0.0)	1(6.7)	3(13.0)	4(8.2)
4 - <8	1(9.1)	1(6.7)	2(8.7)	4(8.2)
8 - <12	0(0.0)	1(6.7)	2(8.7)	3(6.1)
12 - <18	0(0.0)	2(13.3)	5(21.7)	7(14.3)
18 - < 24	5(45.5)	1(6.7)	6(26.1)	12(24.5))
> = 24	5(45.5)	9(60.0)	5(21.7)	19(38.8)
n	11	15	23	49
Mean	22.2	19.0	15.9	18.3
SD	5.72	7.98	8.25	7.94
Median	23.9	24.0	17.0	23.7
Range (min: max)	5 : 27	1 : 25	2 : 26	1 : 27

# Duration of Exposure





# DURATION OF EXPOSURE IN “CYCLE”





## Duration of exposure to study drug in cycle by treatment group

### Population set

Number of Patient completed	Treatment A N = xx	Treatment A N = xx	All Patients N = xx
Cycle 1	XX(xx.x%)	XX(xx.x%)	XX(xx.x%)
Cycle 2	XX(xx.x%)	XX(xx.x%)	XX(xx.x%)
Cycle n	XX(xx.x%)	XX(xx.x%)	XX(xx.x%)
Exposure (Cycle)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Range (Min : Max)	xx : xx	xx : xx	xx : xx



## Duration of exposure to study drug by cycle and treatment group

### Population set

Treatment A (N =xx)	Cumulative Dose (mg)	Dose intensity (mg)	Relative dose intensity (%)
<b>Cycle 1</b>			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Range (Min : Max)	xx : xx	xx : xx	xx : xx
<b>Cycle n</b>			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Range (Min : Max)	xx : xx	xx : xx	xx : xx

# DOSE ESCALATION



### Shift table of adjustment in dose by dose cohort

#### Population set

		-----Minimum Actual dose category-----				
		--				
Planned dose category	Number of patients	>=4mg/kg n(%)	3 - <4mg/kg n(%)	2 - <3mg/kg n(%)	1 - <2mg/kg n(%)	0 - <1mg/kg n(%)
>=4 mg/kg	50	0(0.0)	14(28.0)	34(68.0)	2(4.0)	0(0.0)
3 - <4 mg/kg	4	0(0.0)	0(0.0)	0(0.0)	2(50.0)	2(50.0)
2 - <3 mg/kg	34	0(0.0)	0(0.0)	11(32.4)	23(67.6)	0(0.0)
1 - <2 mg/kg	1	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)
0 - <1 mg/kg	0	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

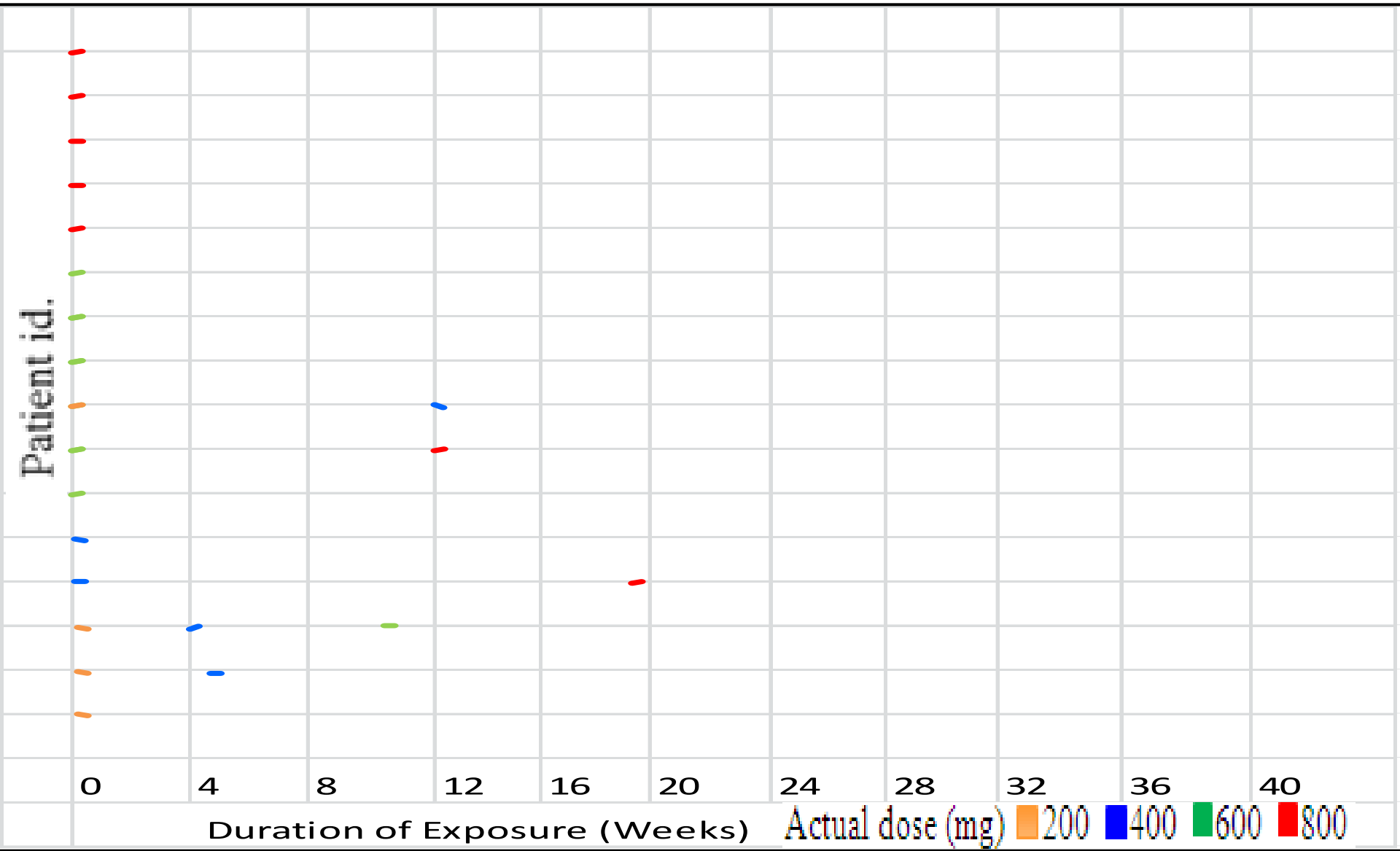
# Intra-patient dose escalation



**Shift table of adjustment in dose by dose cohort**

**Population set**

		-----Max dose category-----				
Actual dose category	Number of patients	0 - <1mg/kg n(%)	1 - <2mg/kg n(%)	2 - <3mg/kg n(%)	3 - <4mg/kg n(%)	>=4mg/kg n(%)
0 - <1 mg/kg	50	0(0.0)	34(68.0)	14(28.0)	2(4.0)	0(0.0)
1 - <2 mg/kg	4	0(0.0)	2(50.0)	2(50.0)	0(0.0)	0(0.0)
2 - <3 mg/kg	34	0(0.0)	0(0.0)	11(32.4)	23(67.6)	0(0.0)
3 - <4 mg/kg	0	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=4 mg/kg	0	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)



# CORE AND EXTENSION



Exposure by treatment			
Population set			
	-----Core-----		-----Extension-----
	Treatment A N = xxx	Treatment B N = xxx	Treatment A N = xxx
Duration of exposure			
Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
Median	xx.x	xx.x	xx.x
Range (Min : Max)	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x
Cumulative dose			
Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
Median	xx.x	xx.x	xx.x
Range (Min : Max)	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x
Average daily dose			
Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
Median	xx.x	xx.x	xx.x
Range (Min : Max)	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x



# COMBINATION DRUG STUDY

# Combinational drug therapy



Duration of Exposure to study treatment (Population set)						
	Study Drug		Combination A		Combination B	
	Treat. A	Treat. B	Treat. A	Treat. B	Treat. A	Treat. B
Total number of patient received component	xx	xx	xx	xx	xx	xx
Exposure categories (unit)						
<1	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
1- <2	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
2- <3	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
3- <4	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
>=4	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Cumulative Exposure (unit)						
> = 1	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
> = 2	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
> = 3	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Exposure (unit)						
Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Range (Min : Max)	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x	xx.x : xx.x

# CANCER STUDIES



**Cumulative dose and relative dose intensity of study drug, by treatment  
(population set )**

	<b>Statistic</b>	<b>TRT A N = X</b>	<b>TRT B N = X</b>	<b>TRTC N = X</b>	<b>All Patient N = X</b>
<b>Cumulative intended dose (unit)</b>	<b>n</b>	<b>x</b>	<b>x</b>	<b>x</b>	<b>x</b>
	<b>Mean (SD)</b>	<b>xx.x(x.xx)</b>	<b>xx.x(x.xx)</b>	<b>xx.x(x.xx)</b>	<b>xx.x(x.xx)</b>
	<b>Median</b>	<b>xx.x</b>	<b>xx.x</b>	<b>xx.x</b>	<b>xx.x</b>
	<b>Range (Min : Max)</b>	<b>xx.x: xx.x</b>	<b>xx.x : xx.x</b>	<b>xx.x : xx.x</b>	<b>xx.x : xx.x</b>
<b>Relative dose Intensity (%)</b>	<b>n</b>	<b>x</b>	<b>x</b>	<b>x</b>	<b>x</b>
	<b>Mean (SD)</b>	<b>xx.x(x.xx)</b>	<b>xx.x(x.xx)</b>	<b>xx.x(x.xx)</b>	<b>xx.x(x.xx)</b>
	<b>Median</b>	<b>xx.x</b>	<b>xx.x</b>	<b>xx.x</b>	<b>xx.x</b>
	<b>Range (Min : Max)</b>	<b>xx.x: xx.x</b>	<b>xx.x : xx.x</b>	<b>xx.x : xx.x</b>	<b>xx.x : xx.x</b>

Actual dose, Planned dose, Actual Intensity, Planned dose intensity can be included in the table

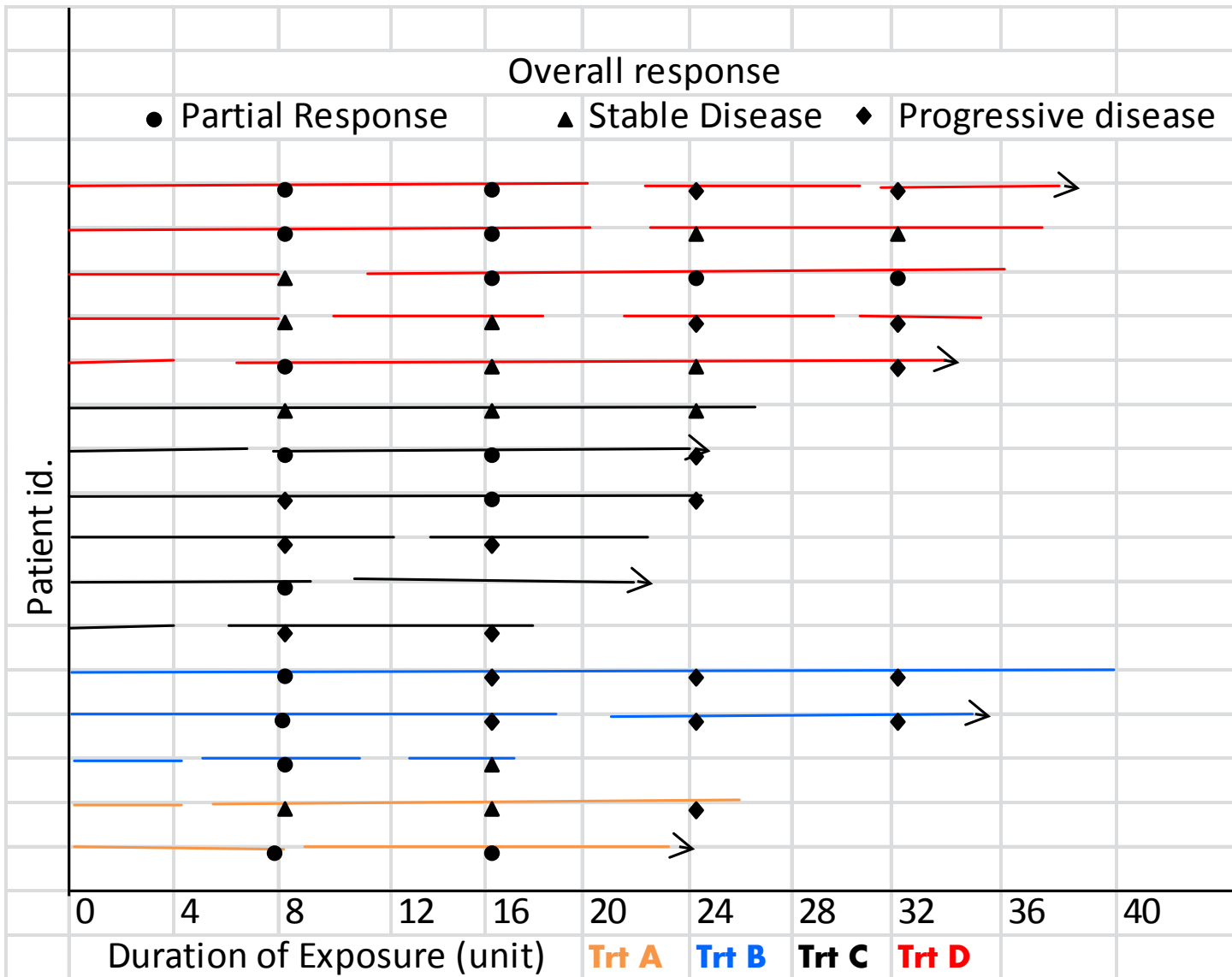


## Compliance to study drug during by treatment (Population set)

Compliance (%)	TRT A N = X	TRT B N = X	TRT C N = X	All Patient N = X
< 70	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
> = 70 - < 80	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
> = 80 - < 90	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
> = 90 - < =100	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
> 100	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
n	x	x	x	x
Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Range (Min : Max)	xx.x: xx.x	xx.x: xx.x	xx.x: xx.x	xx.x: xx.x

# DURATION OF EXPOSURE AND RECIST

# Duration of exposure and overall response



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- ICH E3
- K. Itoh, T. Ohtsu, et.al. Dose-escalation study of CHOP with or without prophylactic G-CSF in aggressive non-Hodgkin's lymphoma. *Annals of Oncology* 11: 1241-1247, 2000.
- Xiaoqiang Wang, Counting Drug Exposure in SAS® with Interval Graph Modeling. *NESUG* 2010.
- B. H. Ch. Stricker, T. Stijnen. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. *Eur J Epidemiol* (2010) 25:245–251

**THANK YOU**