

CompuSyn Report

Examples

B. Drug Combination *in Animals*: Sample CompuSyn Report

“Drug Combination in Vivo Using CI Method: Taxotere and T607 against Colon Carcinoma HCT-116 Xenograft Tumor in Nude Mice”

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Synergy 3: 15-30, 2016 [For details and Discussions, see original article]

[The author’s notes are added in the shaded areas on right-side-margin of the CompuSyn Report]

CompuSyn Report

The analysis usually takes about 1 sec. Printing may take about 1 min.

The report contents depend on the selections at the “Generate Report” command in the menu.

Do not use “polygonogram” since it is for ≥ 3 drug combos

Experiment Name:

T-607 + Taxotere, Day 35 (Anti-HCT-116 Xenograft)

Date:

4/20/2016

Remove “” in front of *.cse when give file name for saving*

File Name:

C:\Users\TingChaoChou\Desktop\T6+TXT.Day35.HCT116..cse ←

Description Combination of T607 + Taxotere (5:1) in nude mice bearing human colon carcinoma HCT-116 xenograft tumor.
Based on anti-tumor data On Day 35.

Drug: T-607 (T607) [mg/Kg]

Drug: Taxotere (TXT) [mg/Kg] *Can be different units. 5 mg/Kg:1 mg/Kg in this case.*

Drug Combo: T-607 + Taxotere (T6+TXT) (T607+TXT [5:1])

Data for Drug: T607 [mg/Kg] *Data points usually from the average Fa values of duplicate or triplicate assays*

Dose Effect

15.0	0.2333
25.0	0.3506
30.0	0.4812

Design Dose Range. It's better and more appropriate to set some doses above Dm, and some doses below Dm value, which is feasible to be obtained in vitro experiments either from the preliminary data or from published literature, however, it's sometimes difficult to achieve this goal in vivo experiments based on the advocacy of econo-green bio-research (e.g. here Dm=34.011 mg/Kg).

3 data points entered.

X-int: 1.53163

*Do not enter fa <0.01 or Fa >0.99, unless the assay is very accurate
If enter fa=0 or fa=1, the computer will crash.*

Y-int: -2.3017 +/- 0.52135

m: 1.50276 +/- 0.38437

The "slope" of the median-effect (ME) plot, the dynamic order, or the "shape" of dose-effect curve; m=1, >1 and <1 indicate hyperbolic, sigmoidal and flate sigmoidal shape, respectively.

Dm: 34.0114

*Dm: The median effect dose, in this case it is IC 50 value, which indicate "potency".
The value can be obtained from the X-intercept of the ME-plot*

r: 0.96881

*r: The linear correlation coefficient of the ME-plot. It signifies the "conformity" of the data with the mass-action law;
an indication of how good are the data, when r=1, it is perfect; For in vitro experiment, usually r>0.95 are considered good or acceptable.*

Data for Drug: TXT [mg/Kg]

Dose Effect

3.0	0.5317
5.0	0.7424
7.0	0.8706

3 data points entered.

X-int: 0.45828

Here, D1 and D2 have the same number of 3 doses (concentrations), which is not necessary. Not the same number is OK as long as they provide m1, (Dm)1, m2, and (Dm)2 values from the dose-effect curves.

Y-int: -0.9521 +/- 0.13103

m: 2.07743 +/- 0.18976

Dm: 2.87266

The m1, (Dm)1 as well as m2, (Dm)2 are absolute requirements for determining synergism or antagonism or additive effect since they are required for the calculation of the CI value

r: 0.99585

Data for Drug Combo: T607+TXT (T607+TXT [5:1])

Dose A	Effect
15.0+	0.6595
25.0+	0.8601
30.0+	0.9438
35.0+	0.9565

In this case 5:1 means T607 15 mg/Kg + TXT 3 mg/Kg, etc

[NOTES]

Recommend to make a 1:1 mixture, and serial dilution them; Do not do more than 2-fold or 3-fold serial dilutions, otherwise the dose-range would be too large for the accurate measurements of effects.

4 data points entered.

X-int: 1.16874

Y-int: -3.4421 +/- 0.56600

m: 2.94516 +/- 0.38128

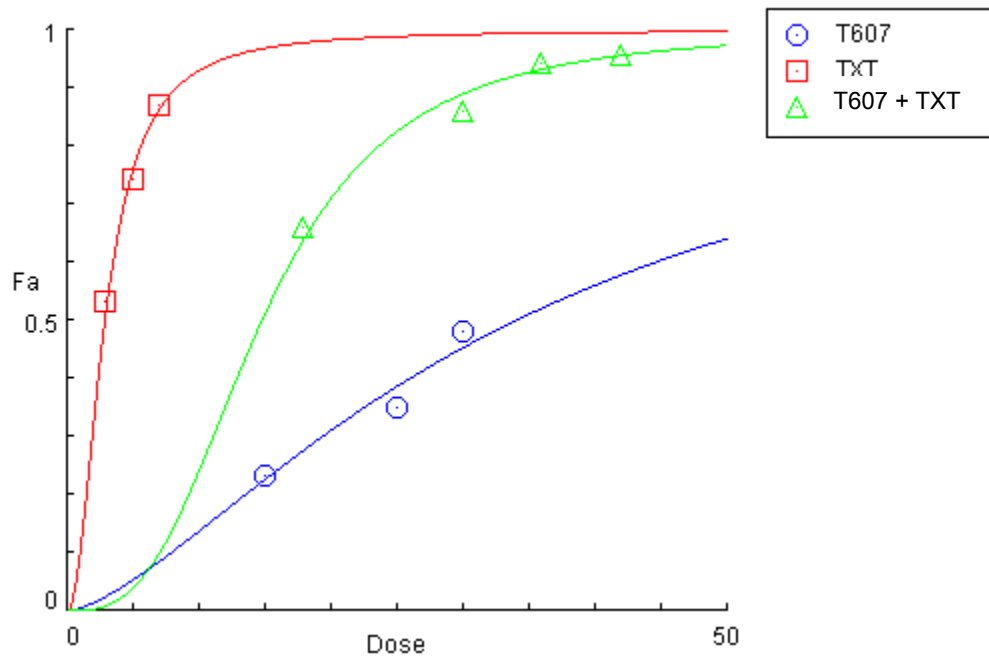
Dm: 14.7481

r: 0.98365

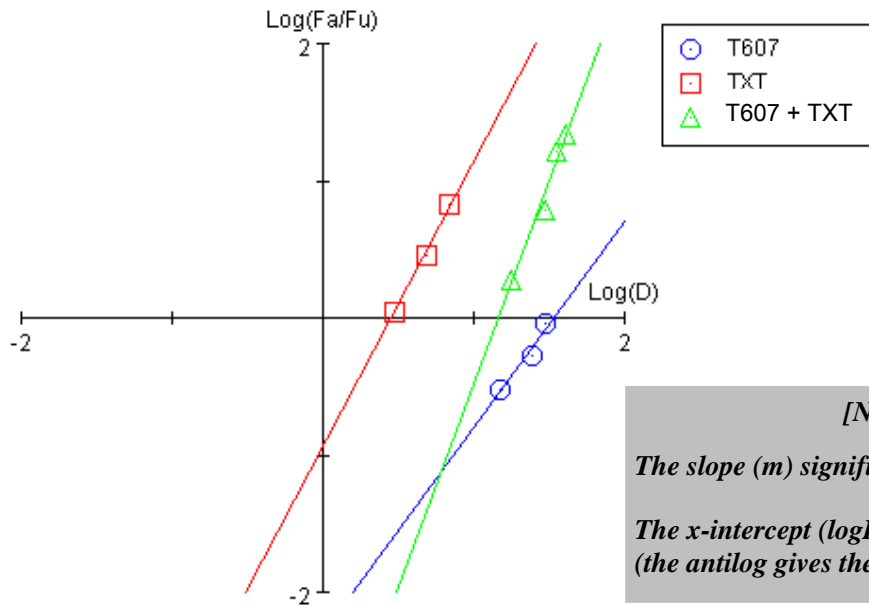
The constant ratio combination allows computerized simulation of dose-effect curves, Fa-CI effect, Fa-DRI Plot, and isobologram based on the $m_{1,2}$ and $(Dm)_{1,2}$ values.

When combinations are at non-constant ratios, each "data point" has a ratio, the CI and DRI value can still be calculated, but automated computer simulation can't be carried out; therefore, the acquired conclusions are limited.

Dose-Effect Curve



Median-Effect Plot



CI Data for Drug Combo: T607+TXT (T607+TXT [5:1])

Fa	CI Value	Total Dose
0.05	2.24250	5.42683
0.1	1.90798	6.99409
0.15	1.73028	8.18371
0.2	1.60929	9.21110
0.25	1.51684	10.1562
0.3	1.44118	11.0609
0.35	1.37630	11.9523
0.4	1.31870	12.8512
0.45	1.26613	13.7767
0.5	1.21701	14.7481
0.55	1.17012	15.7880
0.6	1.12446	16.9249
0.65	1.07907	18.1978
0.7	1.03293	19.6643
0.75	0.98481	21.4160

[NOTES]
 CI < 1, = 1, and > 1 indicates synergism, additive effect and antagonism, respectively.
 This is Fa-CI table with Fa increment of 0.05.
 At fa > 0.75 showed synergistic effect (CI < 1).
 For anti-cancer agents, synergism (CI < 1) at high dose (high effect) is more relevant to the therapy than the CI values at low dose (low effect).

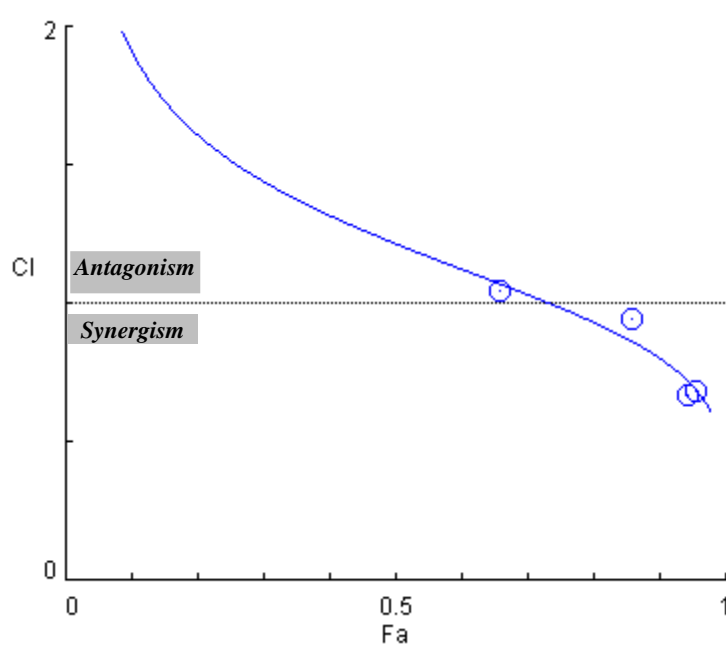
0.8	0.93293	23.6134
0.85	0.87437	26.5779
0.9	0.80314	31.0985
0.95	0.70198	40.0797
0.97	0.63903	48.0091

CI values for actual experimental points:

Total Dose	Fa	CI Value
18.0	0.6595	1.04376
30.0	0.8601	0.94565
36.0	0.9438	0.67216
42.0	0.9565	0.68207

→ *The CI values for each individual combination data point without a simulation*

Combination Index Plot

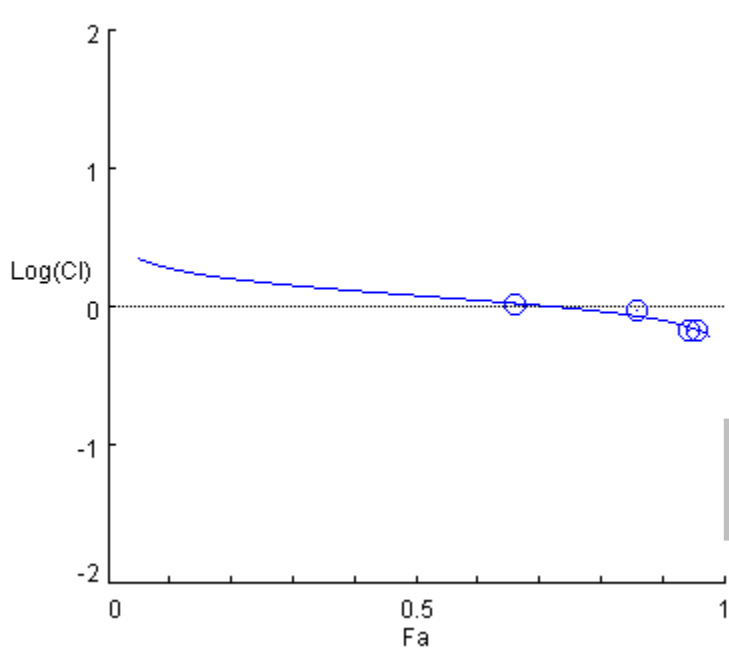


[NOTES]

Among 4 combination data points 3 of them are on the synergy side ($CI < 1$), the other 1 point is nearly additive

The simulation at low f_a showed substantial antagonism. This is of less concern since CI values for synergism is 0-1, and for antagonism is 1- ∞ ; low f_a is less relevant to therapy than high f_a (i.e. Killing cancer cells in small fraction is not useful in cancer therapy)

Logarithmic Combination Index Plot



Antagonism
 Additive effect
 Synergism

The logarithmic scale for CI values is to condense the graph so if there are out of scale data point can be shown

DRI Data for Drug Combo: T607+TXT (T607+TXT [5:1])

Fa	Dose T607	Dose TXT	DRI T607	DRI TXT
0.05	4.79390	0.69621	1.06004	0.76974
0.1	7.88192	0.99758	1.35233	0.85579
0.15	10.7233	1.24641	1.57239	0.91382
0.2	13.5204	1.47392	1.76140	0.96009
0.25	16.3730	1.69284	1.93453	1.00008
0.3	19.3534	1.91053	2.09965	1.03636
0.35	22.5281	2.13242	2.26180	1.07046
0.4	25.9685	2.36331	2.42484	1.10338
0.45	29.7599	2.60815	2.59220	1.13590
0.5	34.0114	2.87266	2.76739	1.16869
0.55	38.8704	3.16399	2.95443	1.20243
0.6	44.5455	3.49179	3.15834	1.23787
0.65	51.3483	3.86987	3.38601	1.27594
0.7	59.7712	4.31932	3.64750	1.31792
0.75	70.6515	4.87476	3.95882	1.36574
0.8	85.5581	5.59879	4.34794	1.42261
0.85	107.875	6.62078	4.87059	1.49465
0.9	146.764	8.27222	5.66317	1.59600
0.95	241.302	11.8531	7.22468	1.77442
0.97	343.724	15.3100	8.59148	1.91339

DRI >1 and <1 indicate favorable and not favorable dose-reduction; DRI=1 indicates no dose-reduction

This is Fa-DRI table with fa increment of 0.05

At 50% inhibition, it requires 34.0114 mg/Kg of T607, and requires 2.87266 mg/Kg of TXT

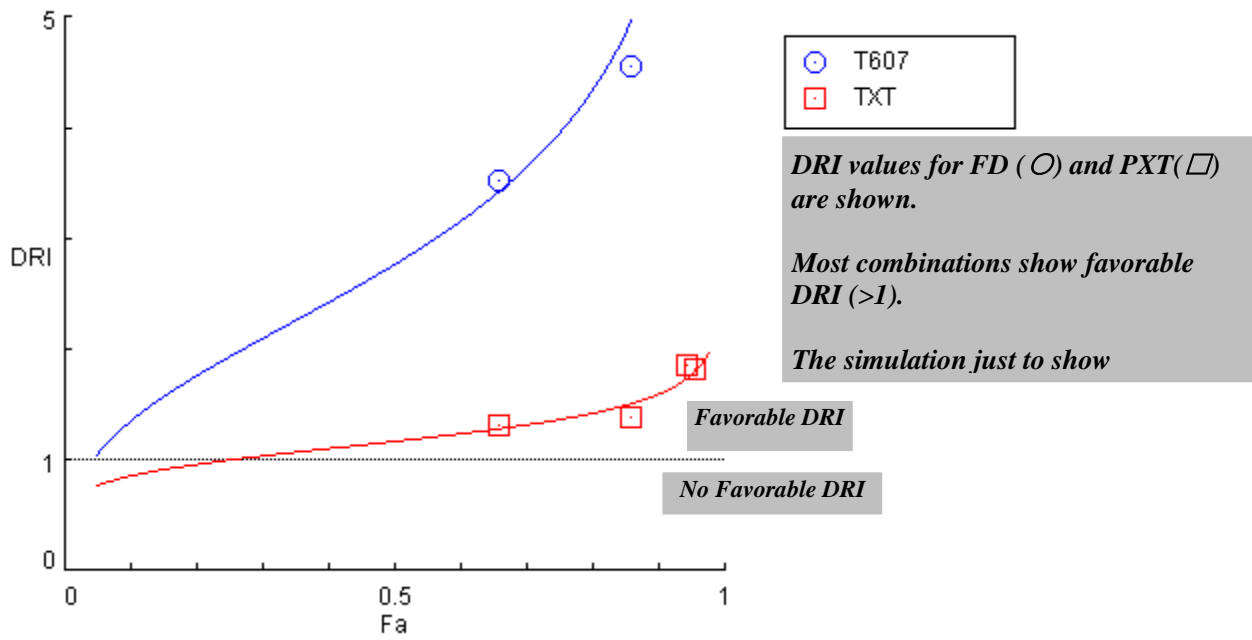
However, it requires 2.76739-fold less T607 plus 1.16869-fold less TXT to achieve the same 50% inhibition (i.e., 12.290 mg/Kg T607 +2.458 mg/Kg TXT) (5:1 combination)

DRI values calculated at experimental points

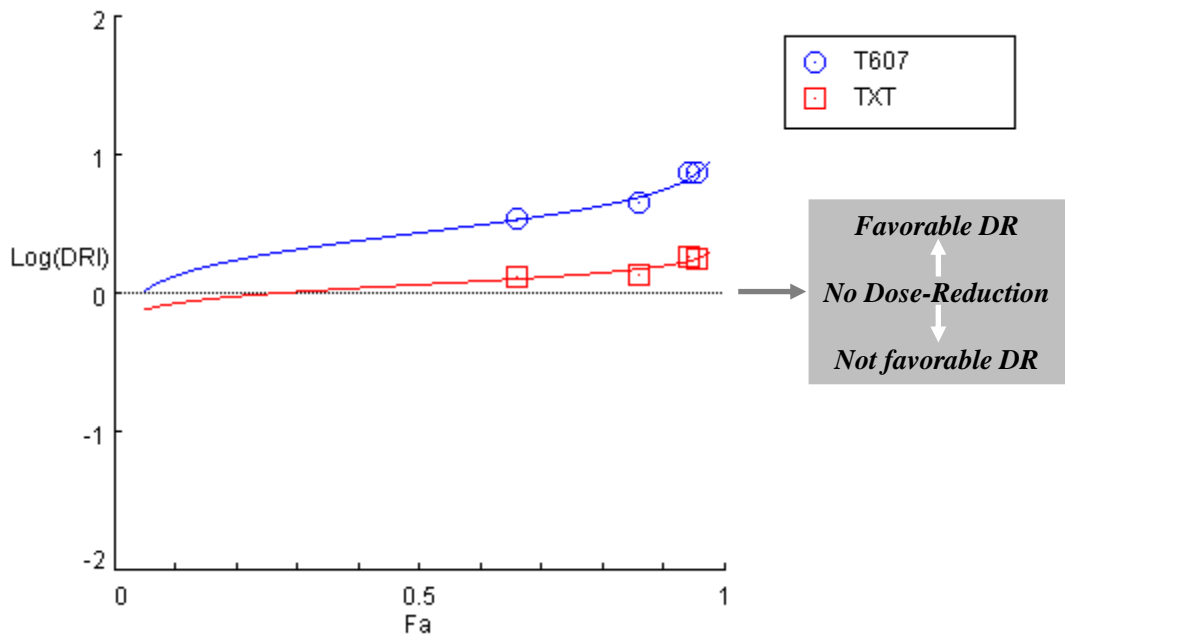
Fa	Dose T607	Dose TXT	DRI T607	DRI TXT
0.6595	52.8046	3.94896	3.52031	1.31632
0.8601	113.889	6.88575	4.55554	1.37715
0.9438	222.273	11.1693	7.40911	1.86154
0.9565	265.937	12.7165	7.59819	1.81665

DRI values of each drug at each combination data point

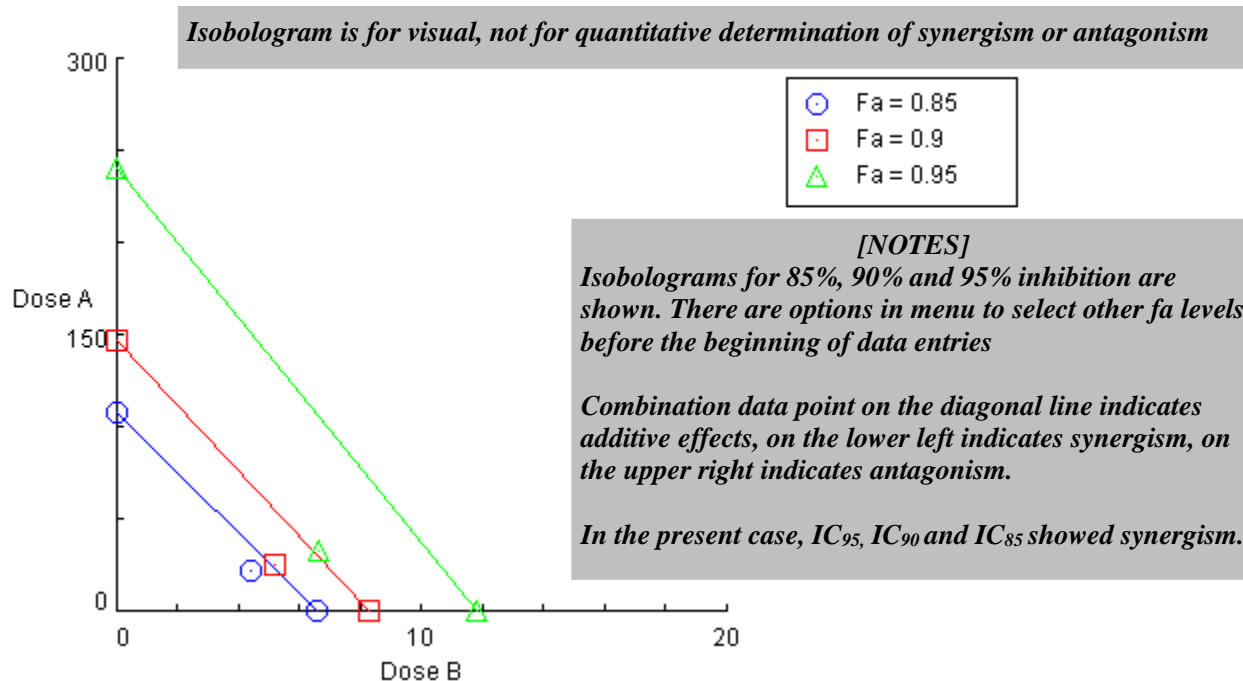
DRI Plot for Combo: T607+TXT (T607+TXT [5:1])



Log (DRI) Plot for Combo: T6+TXT (T607+TXT [5:1])



Isobologram for Combo: T607+TXT (T607+TXT [5:1])



Summary Table

Experiment Name: T-607 + Taxotere Day35 (Anti-HCT-116 Xenograft)

Date: 4/20/2016

File Name: C:\Users\TingChaoChou\Desktop\T6+TXT.Day35.HCT116..cse

Description: Combination of T607 + Taxotere (5:1) in nude mice bearing human colon carcinoma HCT-116 xenograft tumor. Based on anti-tumor data on Day 35.

Drug: T-607 (T607) [mg/Kg]

Drug: Taxotere (TXT) [mg/Kg]

Drug Combo: T-607 + Taxotere (T6+TXT) (T607+TXT [5:1])

Drug/Combo	Dm	m	r
T607	34.0114	1.50276	0.96881
TXT	2.87266	2.07743	0.99585
T6+TXT	14.7481	2.94516	0.98365

CI values at:

Combo	ED50	ED75	ED90	ED95
T6+TXT	1.21701	0.98481	0.80314	0.70198

Data for Fa = 0.5

Drug/Combo	CI value	Dose T607	Dose TXT
T607		34.0114	
TXT			2.87266
T6+TXT	1.21701	12.2901	2.45801

These data are illustrated for the ED₅₀-Isobologram at Fa=0.5

*For DRI at fa=0.5
for T607=34.0114/12.2901=2.7674
for TXT=2.87266/2.45801=1.1687*

Data for Fa = 0.75

Drug/Combo	CI value	Dose T607	Dose TXT
T607		70.6515	
TXT			4.87476
T6+TXT	0.98481	17.8466	3.56933

For ED₇₅-isobologram

Data for Fa = 0.9

Drug/Combo	CI value	Dose T607	Dose TXT
T607		146.764	
TXT			8.27222
T6+TXT	0.80314	25.9154	5.18308

For ED₉₀-isobologram

Data for Fa = 0.95

Drug/Combo	CI value	Dose T607	Dose TXT
T607		241.302	
TXT			11.8531
T6+TXT	0.70198	33.3997	6.67995

Synergy (CI<1) at high effect levels (e.g., at fa>0.90) is more relevant to anticancer therapeutic effect than the CI at low effect levels (e.g., at fa <0.3)

Data for Fa = 0.97

Drug/Combo	CI value	Dose T607	Dose TXT
T607		343.724	
TXT			15.3100
T6+TXT	0.63903	40.0075	8.00151