Basel Biometrics Society seminar
Basel, 26th June 2018

BBS Seminar:
RCTs, personalized medicine, and surrogacy
Date: Tuesday, June 26, 2018, 15:30-17.45
Venue: Auditorium Building 71, Roche Campus, Grenzacherstrasse, Basel

A statistical approach for personalized medicine and benefit / risk assessment

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San Francisco, CA

IDDI
ADDING VALUE TO CLINICAL DATA

TRIAL DESIGN - RANDOMIZATION -
DATA MANAGEMENT - BIOSTATISTICS

universiteit hasselt

Limitations of current analyses of clinical trials

- A single (« primary ») endpoint drives decision-making
- Composite endpoints consider time to *first* event, instead of time to *most relevant* endpoint
- « Secondary » endpoints are analyzed descriptively
- Safety is informally balanced against efficacy, resulting in debatable risk / benefit analyses
- Patient preferences are not formally taken into account

OXALIPLATIN IN COLORECTAL CANCER

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

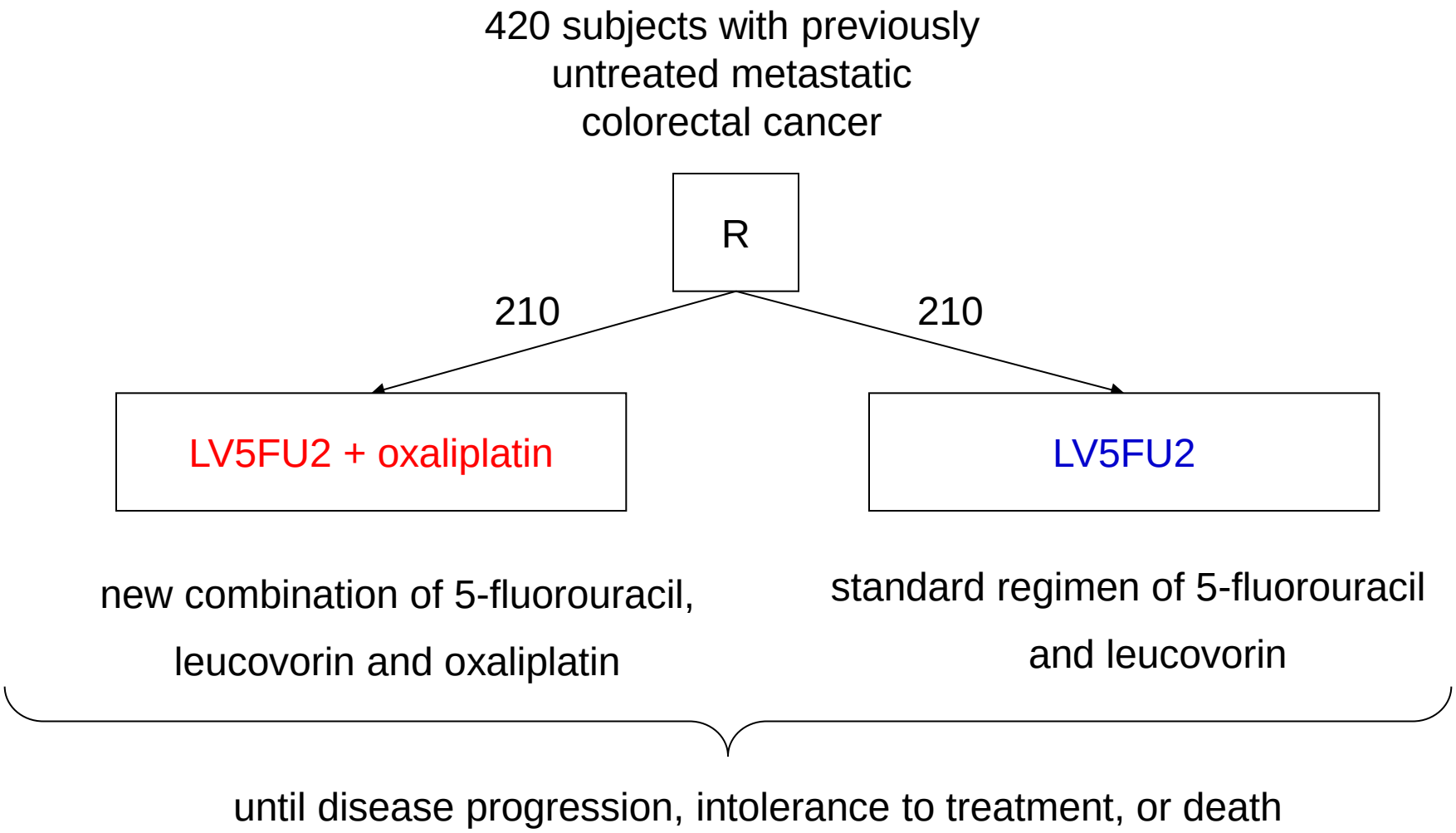
Leucovorin and Fluorouracil With or Without Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer

By A. de Gramont, A. Figer, M. Seymour, M. Homerin, A. Hmissi, J. Cassidy, C. Boni, H. Cortes-Funes, A. Cervantes, G. Freyer, D. Papamichael, N. Le Bail, C. Louvet, D. Hendler, F. de Braud, C. Wilson, F. Morvan, and A. Bonetti

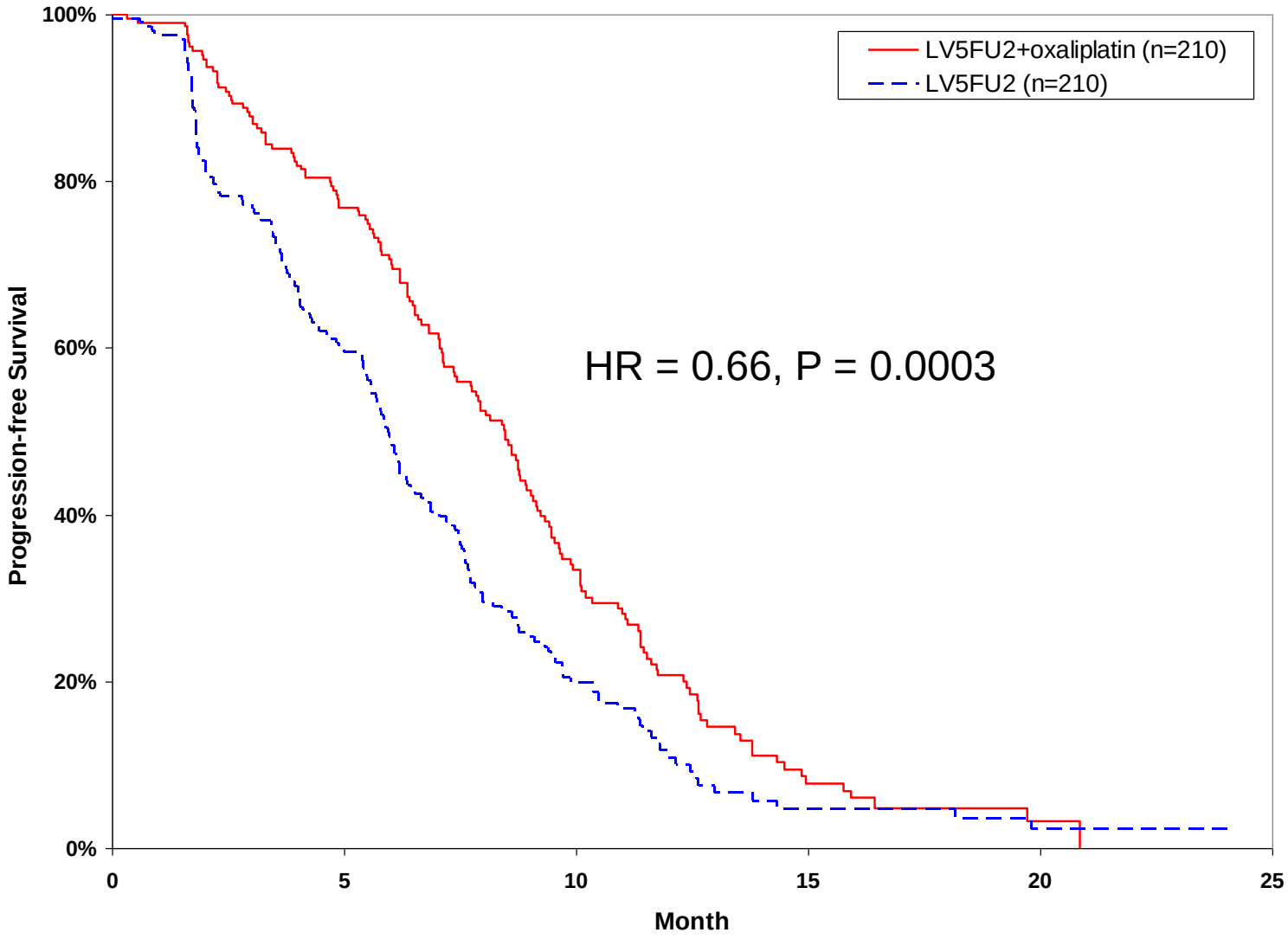
Conclusion: **The LV5FU2-oxaliplatin combination seems beneficial as first-line therapy in advanced colorectal cancer, demonstrating a prolonged progression-free survival with acceptable tolerability and maintenance of QoL.**

J Clin Oncol 18:2938-2947.

Advanced colorectal cancer

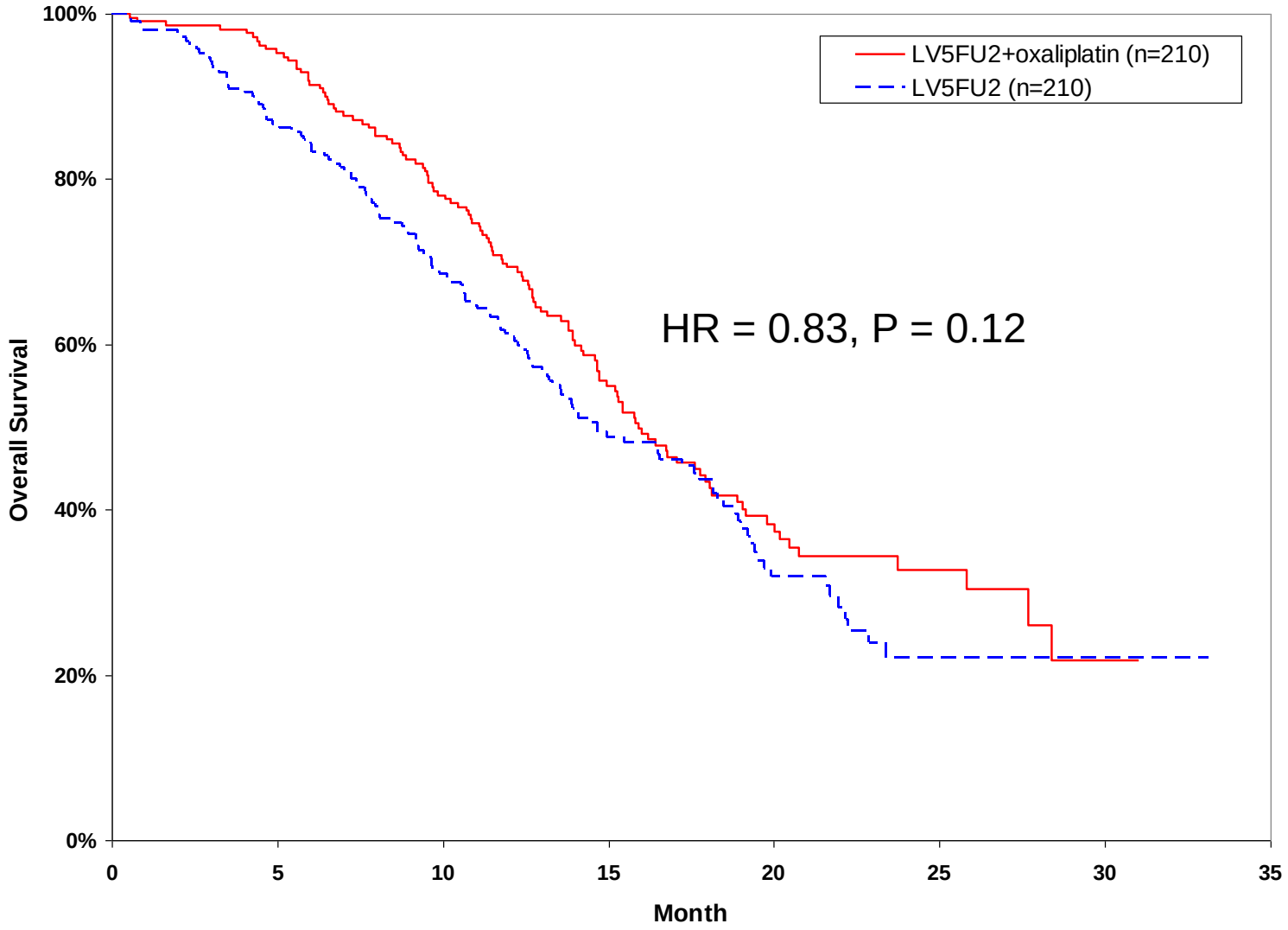


Progression-free survival



Ref: de Gramont et al, J Clin Oncol 18:2938, 2000.

Survival



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PROBLEMS?

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   PFS reached statistical significance, OS did not

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   - PFS not confounded by further line treatments, less affected by non cancer deaths, and has more events
   - OS clinically most relevant and measured without bias or error

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   PFS reached statistical significance, OS did not

2. Neither endpoint is perfect:
   - PFS not confounded by other treatments, less affected by non cancer deaths, and has more events
   - OS clinically most relevant and measured without bias or error

3. PFS ignores the time between progression and death.
   The time to first event ignores subsequent events. LV5FU2 + oxaliplatin might prolong PFS, but shorten OS afterwards.

A DIFFERENT APPROACH

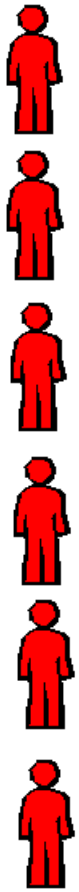
A new method of analysis…

Generalized pairwise comparisons:

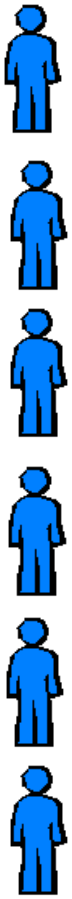
- Compare every patient in the treated group with every patient in the control group
- each pair may favor treatment, control, or neither in terms of several prioritized outcomes (OS first priority, TTP second)
- This approach naturally leads to the « net treatment effect »

Ref: Buyse, Stat Med 29:3245, 2010.

TREATMENT GROUP

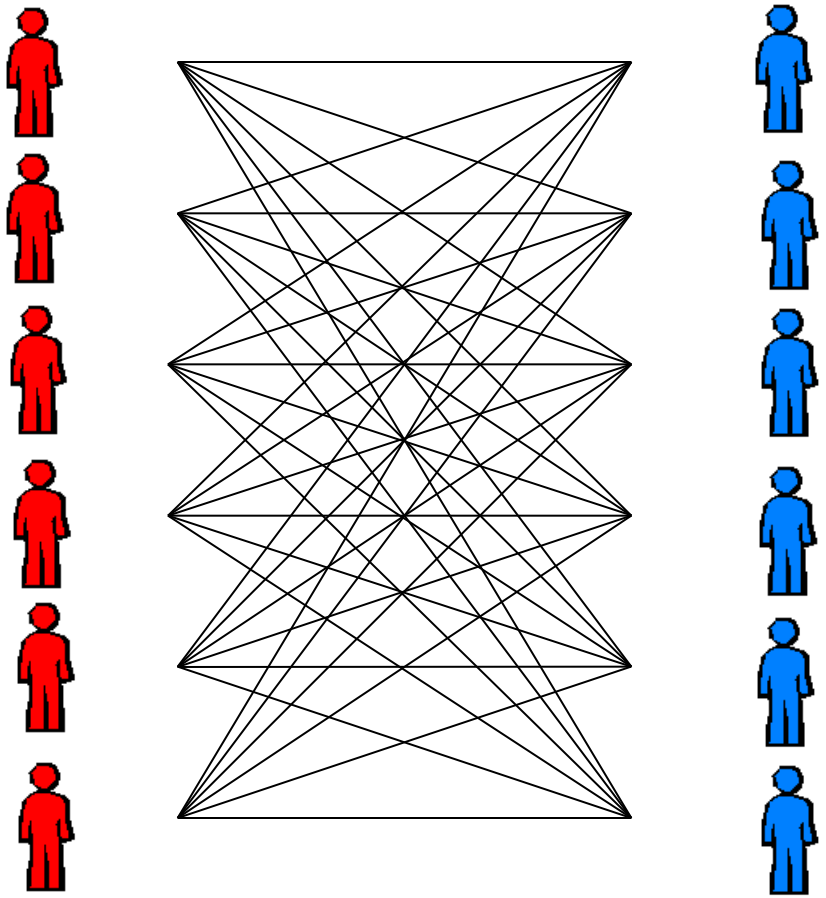


CONTROL GROUP

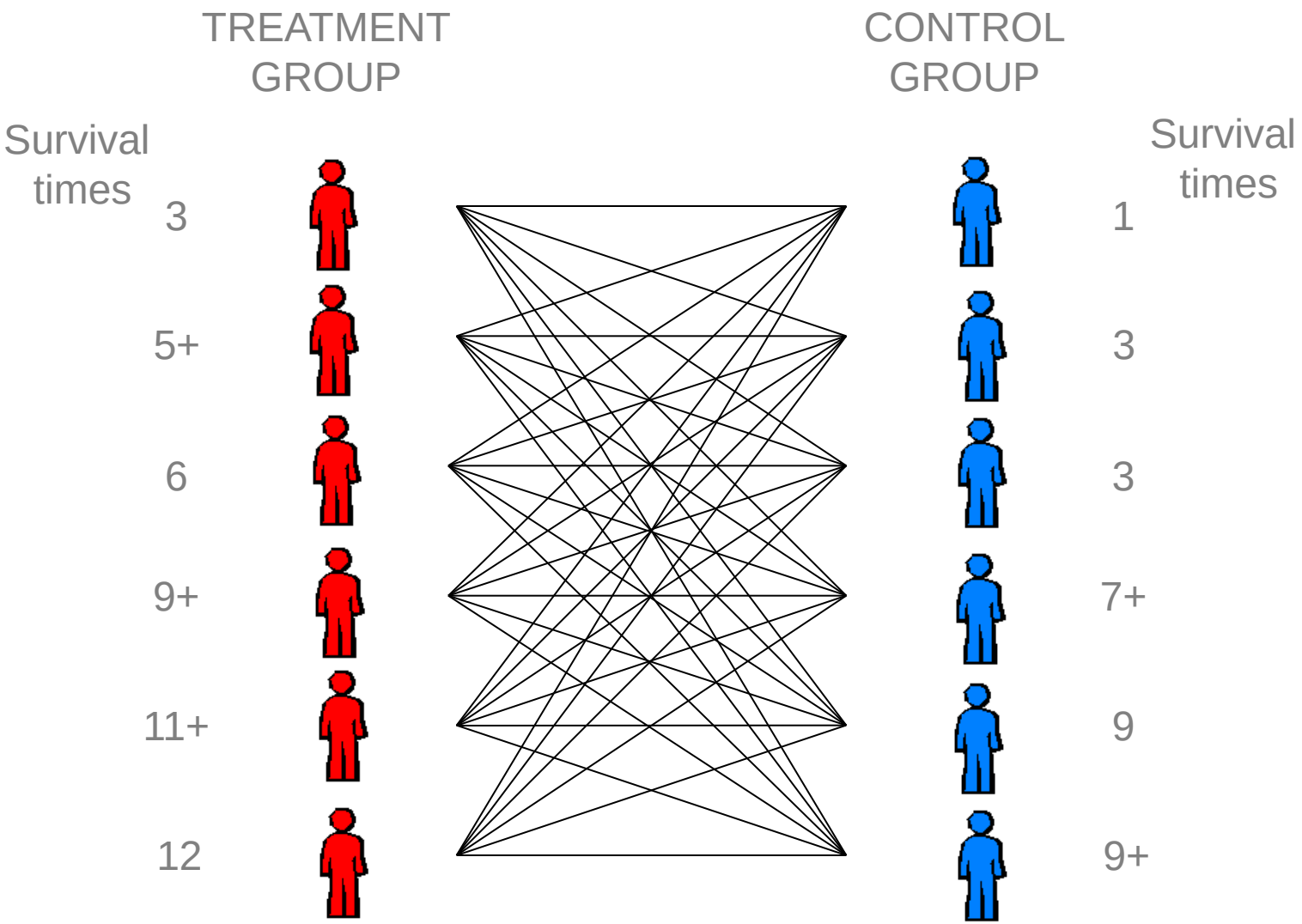


TREATMENT GROUP

CONTROL GROUP



ALL PAIRWISE COMPARISONS
(36)



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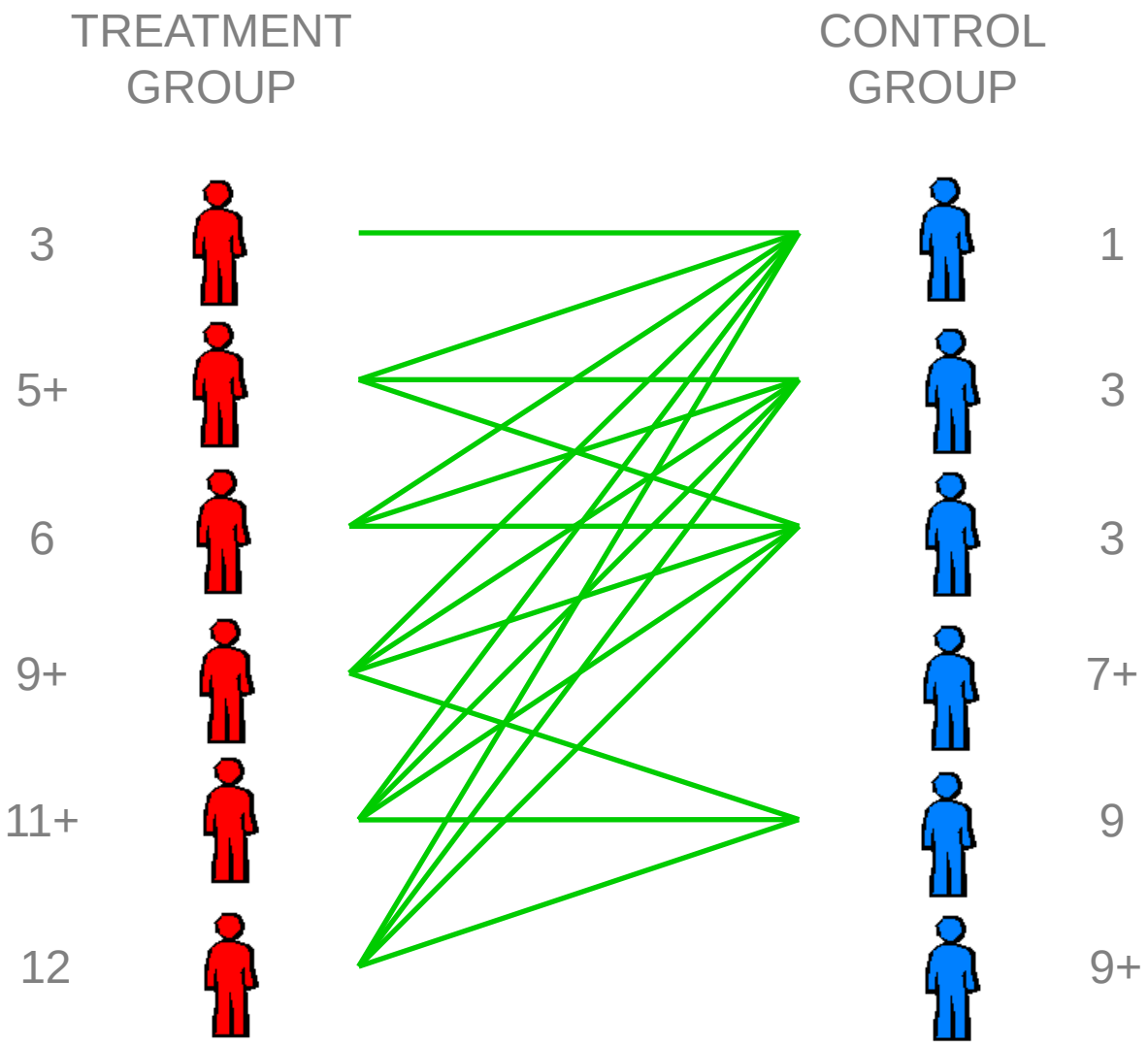
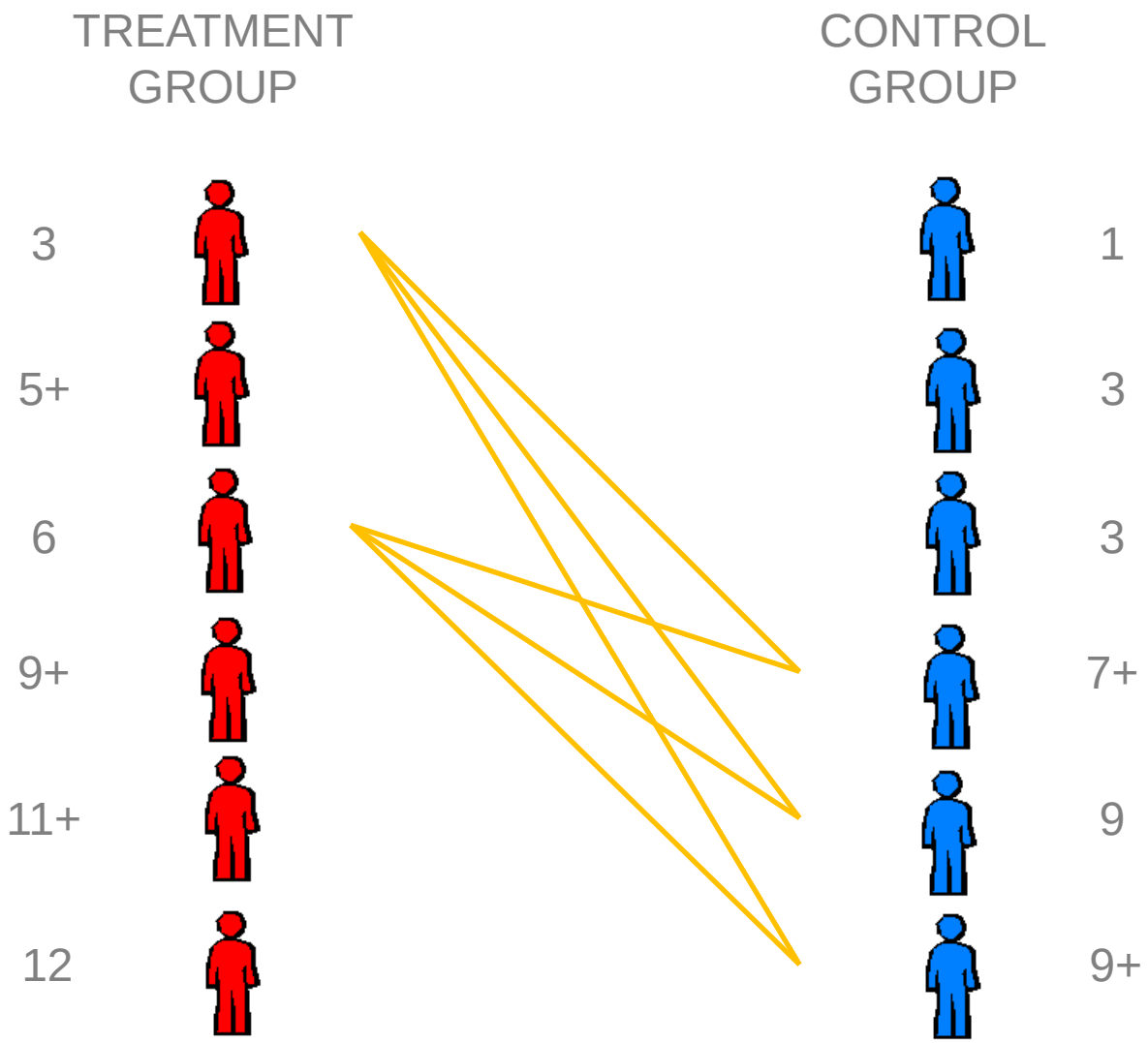
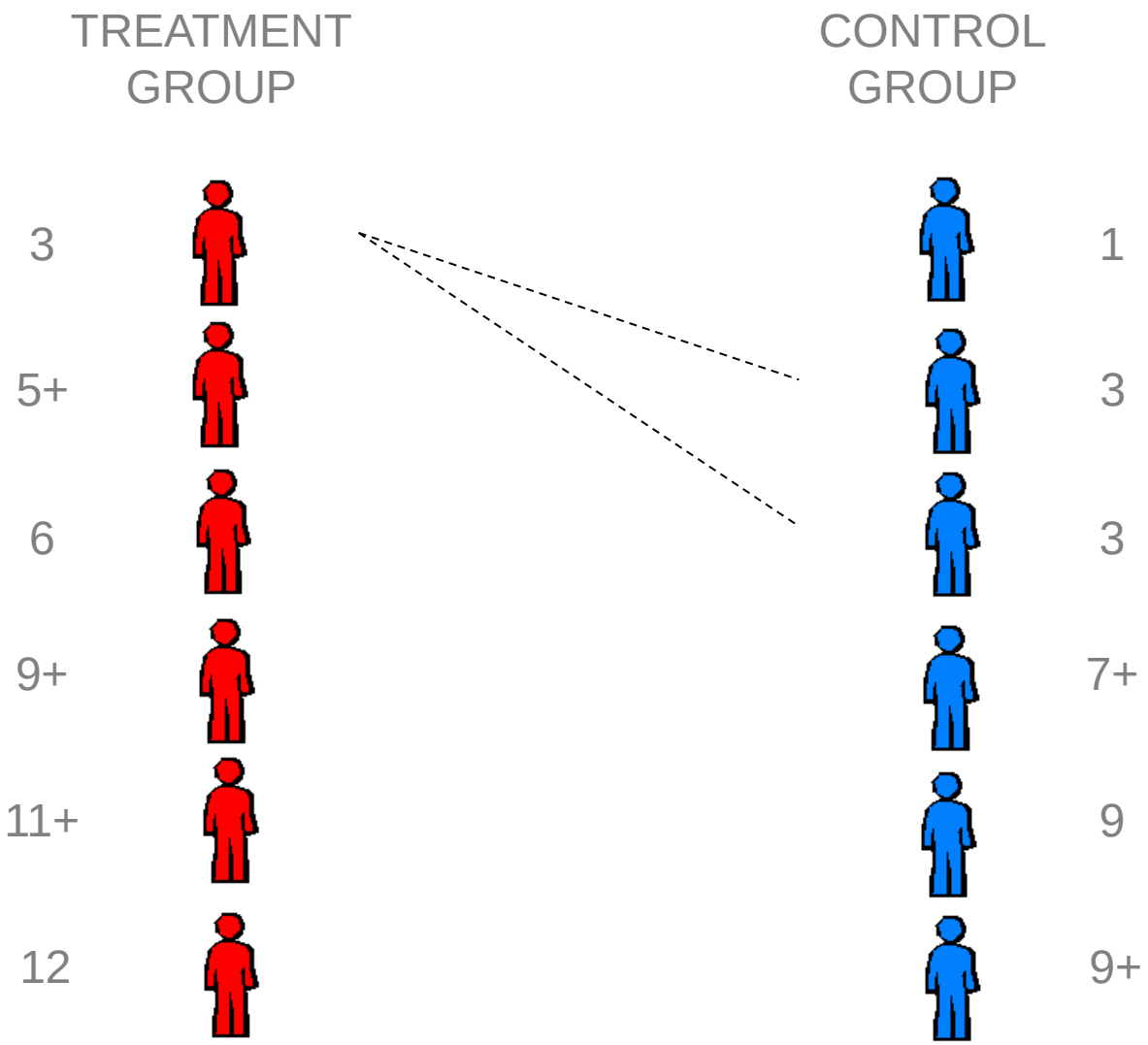
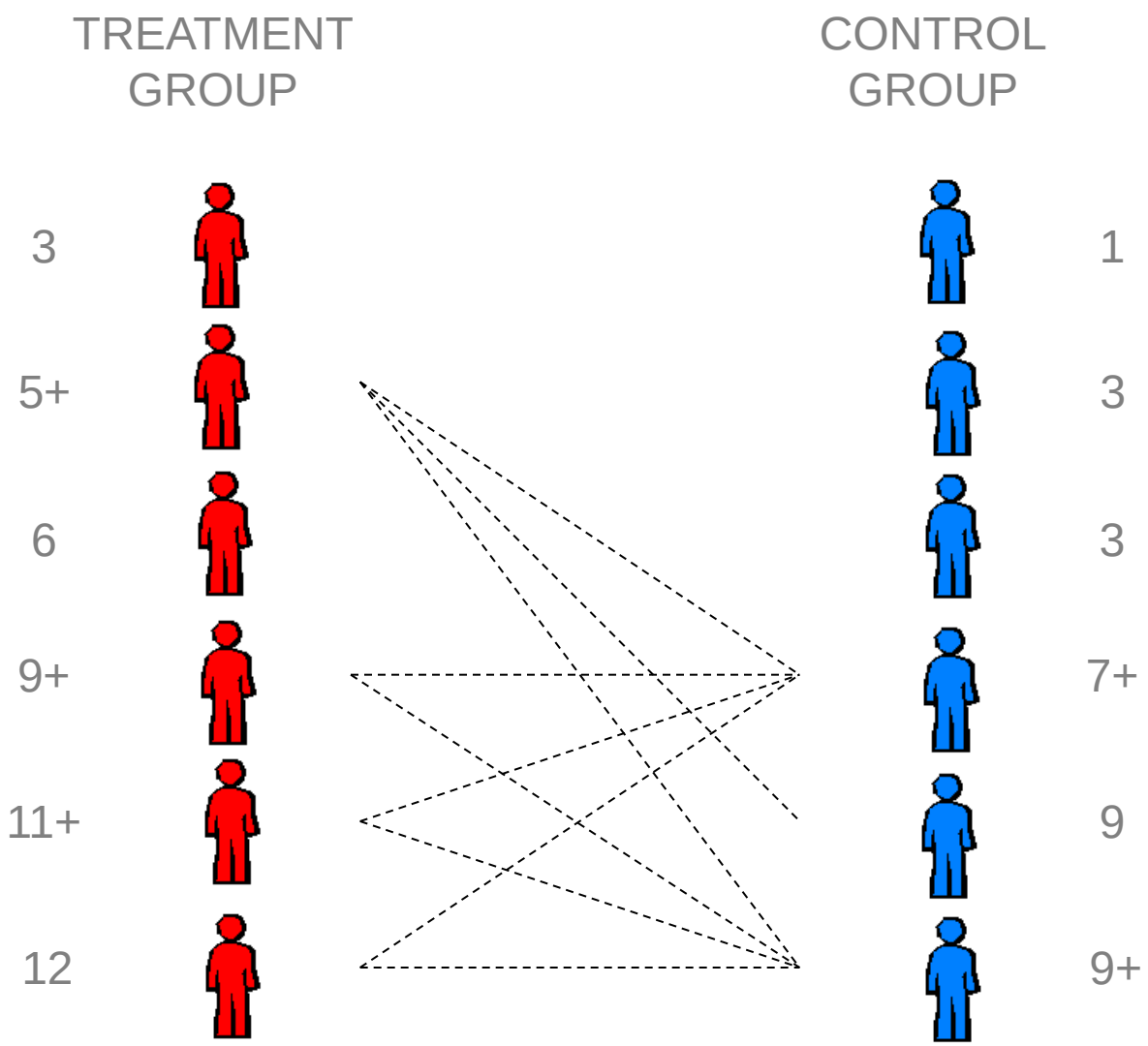

TREATMENT GROUP
CONTROL GROUP
3
5+
6
9+
11+
12
1
3
3
7+
9
9+
TREATMENT BETTER
(19 PAIRS)

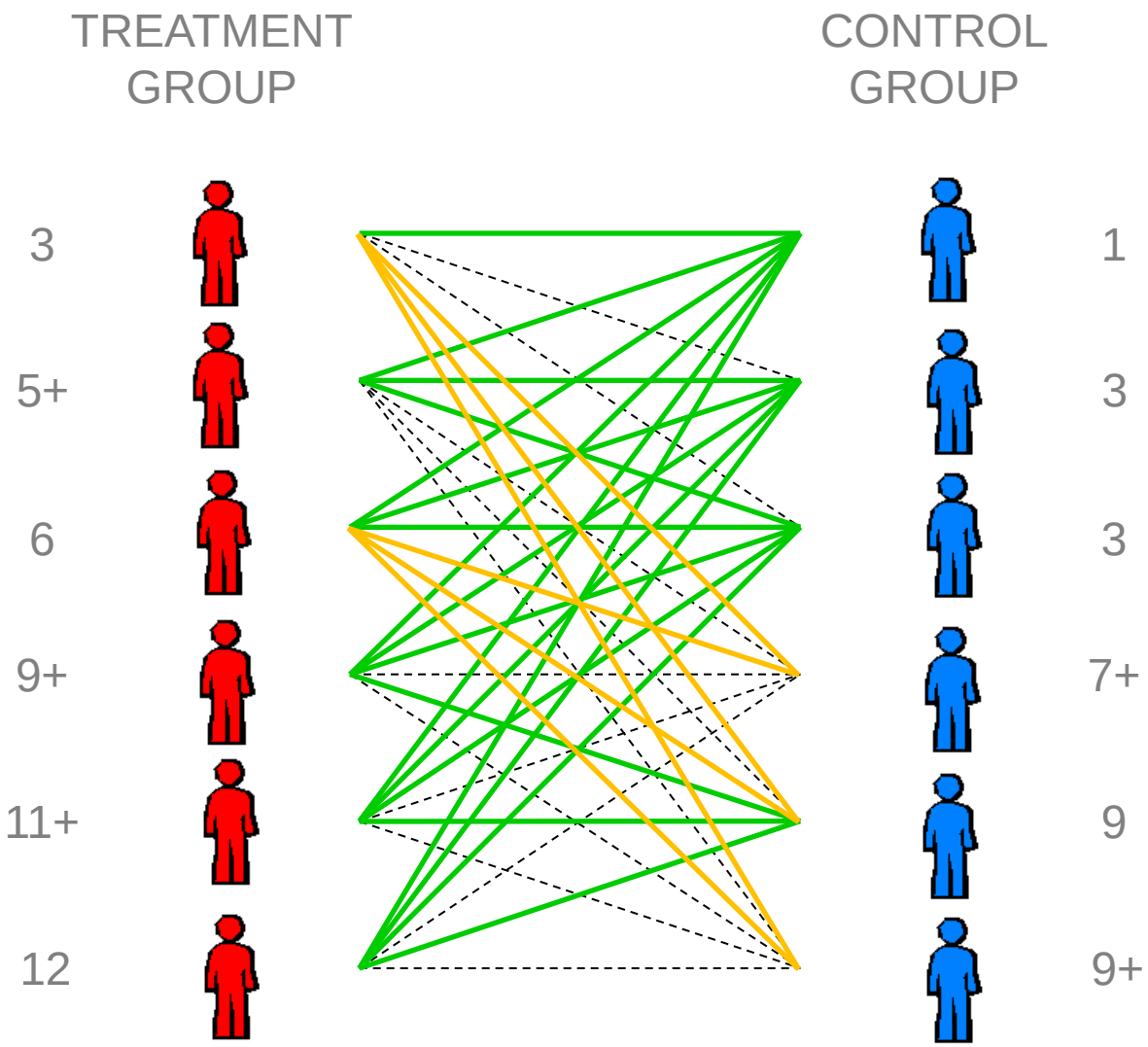

TREATMENT GROUP
CONTROL GROUP
3
5+
6
9+
11+
12
1
3
3
7+
9
9+
CONTROL BETTER
(6 PAIRS)



UNINFORMATIVE PAIRS:
TIES
(2 PAIRS)



UNINFORMATIVE PAIRS:
CENSORING
(9 PAIRS)



19 PAIRS FAVOR TREATMENT

6 PAIRS FAVOR CONTROL

11 PAIRS ARE UNINFORMATIVE

A general measure of treatment effect

Consider a generalization of the Wilcoxon-Mann-Whitney *U*-statistic

$$U_{ij} = \begin{cases} +1 & \text{if } (X_i, Y_j) \text{ pair is favorable} \\ -1 & \text{if } (X_i, Y_j) \text{ pair is unfavorable} \\ 0 & \text{otherwise} \end{cases}$$

$$U = \frac{1}{m \cdot n} \sum_{i=1}^{n} \sum_{j=1}^{m} U_{ij}$$

U is the difference between the proportion of favorable pairs and the proportion of unfavorable pairs. We call this general measure of treatment effect the « net benefit » (Δ).

Pocock *et al.* proposed a similar (relative) measure of treatment effect called the « win ratio ».

Ref: Buyse, Stat Med 29:3245, 2010; Pocock et al. Eur Heart J 33:176, 2012.

Net benefit (Δ)

For a binary variable, Δ is equal to the difference in proportions

$$\Delta = p_T - p_C$$

For a continuous variable , Δ is related to the effect size d

$$\Delta = 2 \cdot \phi\left(d/\sqrt{2}\right) - 1$$

For a time-to-event variable, Δ is related to the hazard ratio λ and the proportion of informative pairs f

$$\Delta = f \cdot \frac{1-\lambda}{1+\lambda}$$

Refs: Moser and McCann, Clinical Trials 5:248, 2008; Buyse, Clinical Trials 5:641, 2008.

Net benefit (Δ)

Δ is a linear transformation of Harrell's c-index (or probabilistic index)

$$U = \Delta = 2 \cdot P(X > Y) - 1$$

Situation	$P(X > Y)$	Δ
T uniformly worse than C	0	-1
T no different from C	0.5	0
T uniformly better than C	1	$+1$

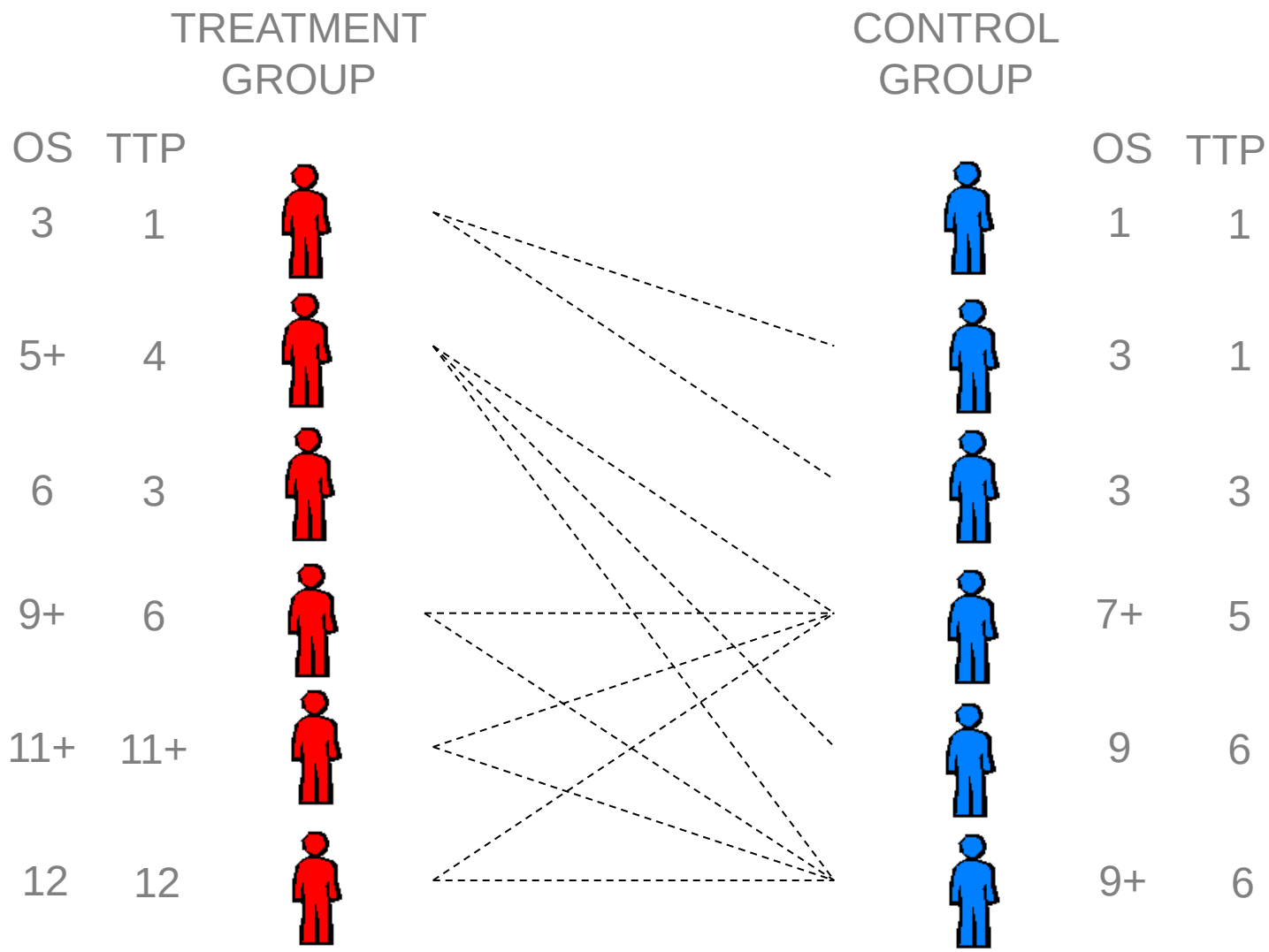
BACK TO OXALIPLATIN IN COLORECTAL TRIAL

Prioritized outcomes

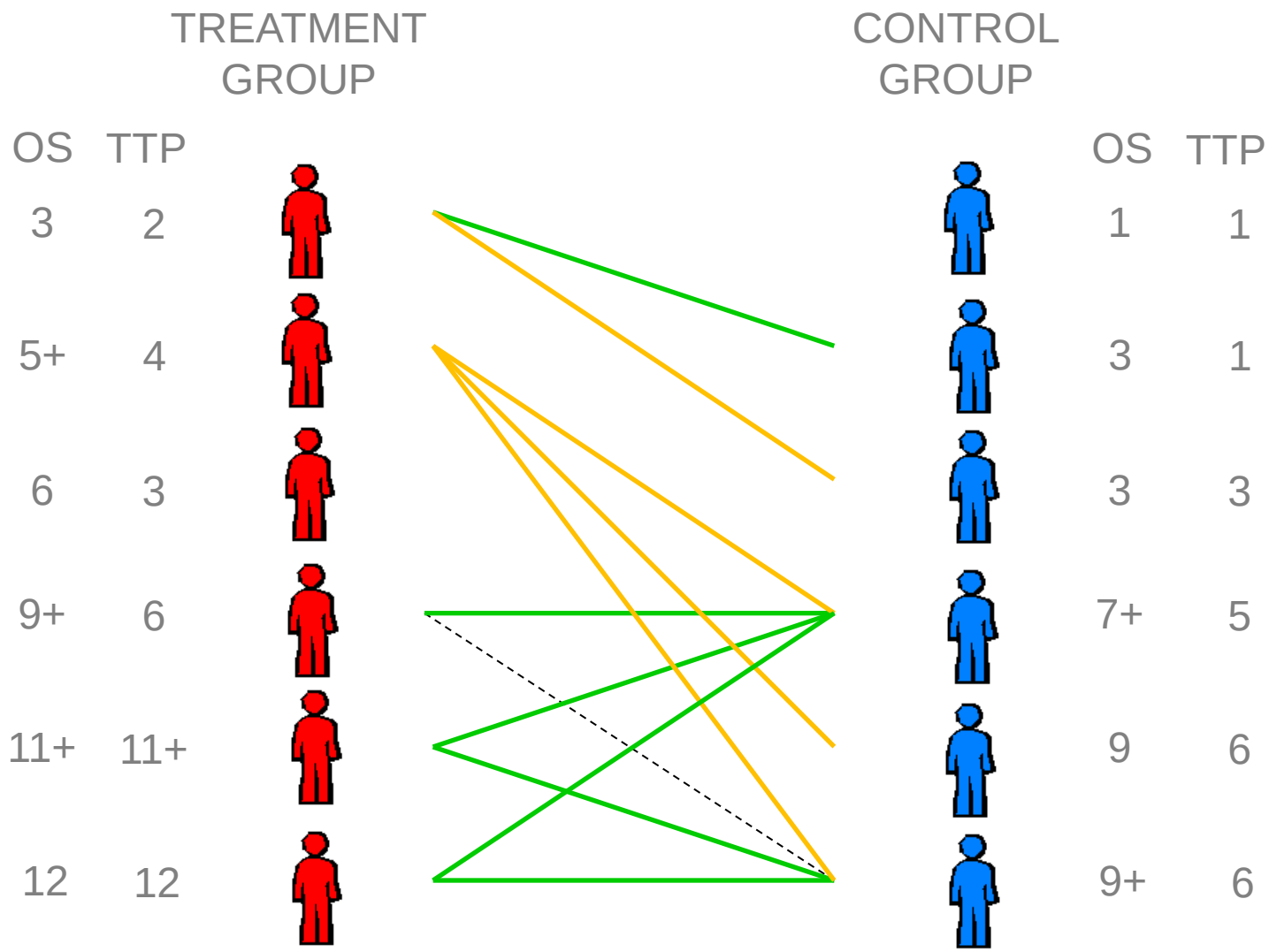
Priority	Outcome	Threshold of clinical relevance
1	OS	12 months
2	OS	6 months
3	OS	0 month

Prioritized outcomes

Priority	Outcome	Description
1	OS	Time to death from any cause
2	TTP	Time to progression of disease



11 UNINFORMATIVE PAIRS



1 UNINFORMATIVE PAIR

Prioritized outcomes

GENERALIZED PAIRWISE COMPARISONS
(210 × 210 = 44,100 pairs)

Difference in	Oxliplatin better	Standard better	Δ	Cumulative Δ	*P*-value *
OS	42.6%	32.5%	10.1%	10.1%	0.050
TTP	9.1%	4.4%	4.7%	14.8%	0.0054

* *Unadjusted for multiplicity*

CONCLUSIONS

- Generalized pairwise comparisons provide a versatile and powerful analysis method when multiple prioritized outcomes are of interest.

- The net benefit (Δ) is a measure of overall treatment effect (benefit / risk) that has direct clinical meaning.

- The priority of outcomes can be patient-dependent.

References

Buyse M. Reformulating the hazard ratio to enhance communication with clinical investigators. *Clin Trials* 5: 641-2, 2008.

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Péron J, Roy P, Conroy T, Desseigne F, Ychou M, Gourgou-Bourgade S, Stanbury T, Roche L, Ozenne B, Buyse M. An assessment of the benefit-risk balance of FOLFORINOX in metastatic pancreatic adenocarcinoma. Oncotarget 7:82953-60, 2017.