



A new measure of treatment benefit in randomized clinical trials

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Outline

- Oxaliplatin in advanced colorectal cancer
- Problems with the oxaliplatin example
- Another approach...
- ... and a new measure of treatment benefit
- Re-analysis of the oxaliplatin example
- Conclusions

OXALIPLATIN IN COLORECTAL CANCER

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. © 2000 by American Society of Clinical Oncology.

Advanced colorectal cancer

420 subjects with previously
untreated metastatic
colorectal cancer

R

210

210

LV5FU2 + oxaliplatin

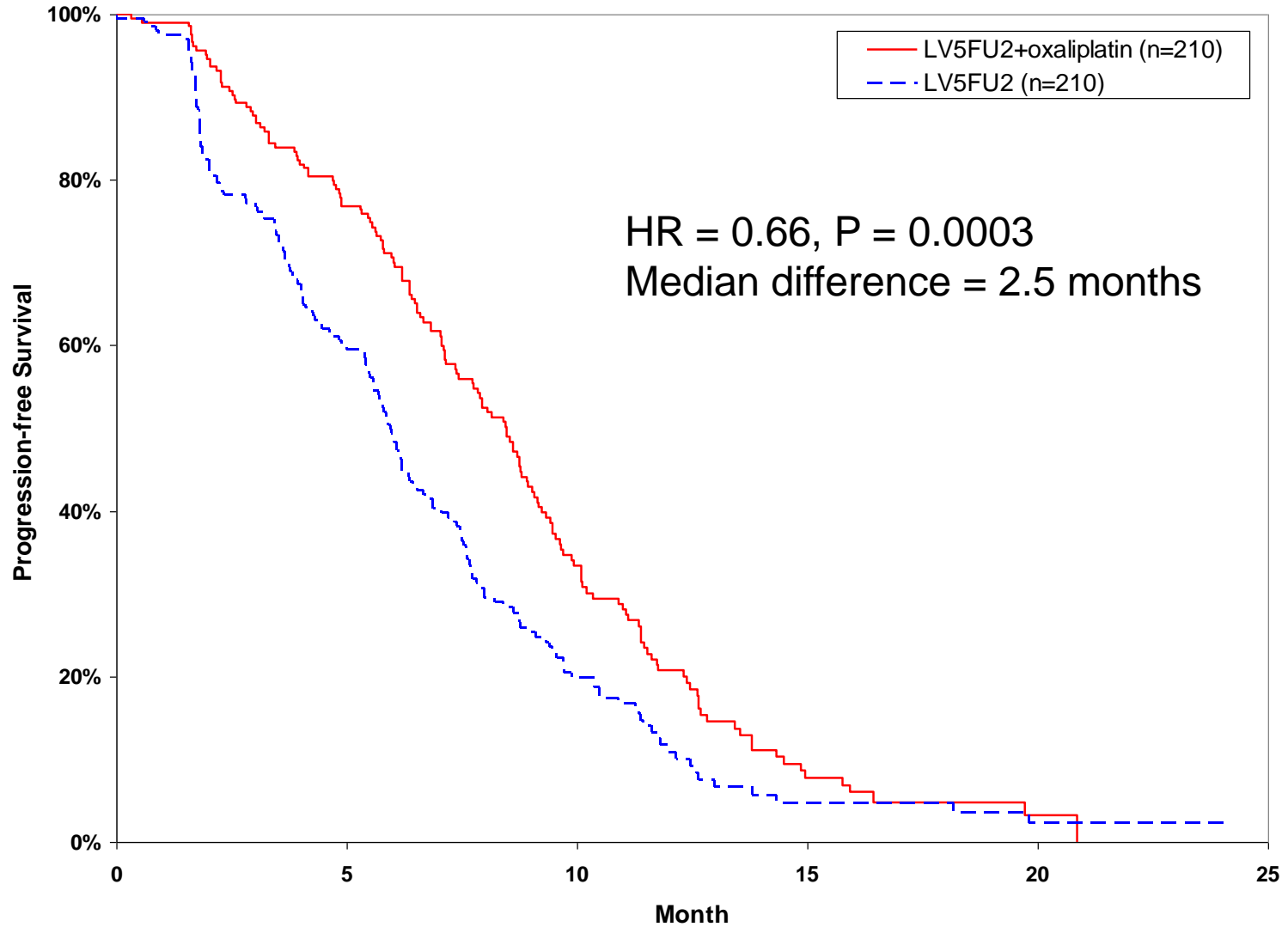
LV5FU2

new combination of 5-fluorouracil,
leucovorin and oxaliplatin

standard regimen of 5-fluorouracil
and leucovorin

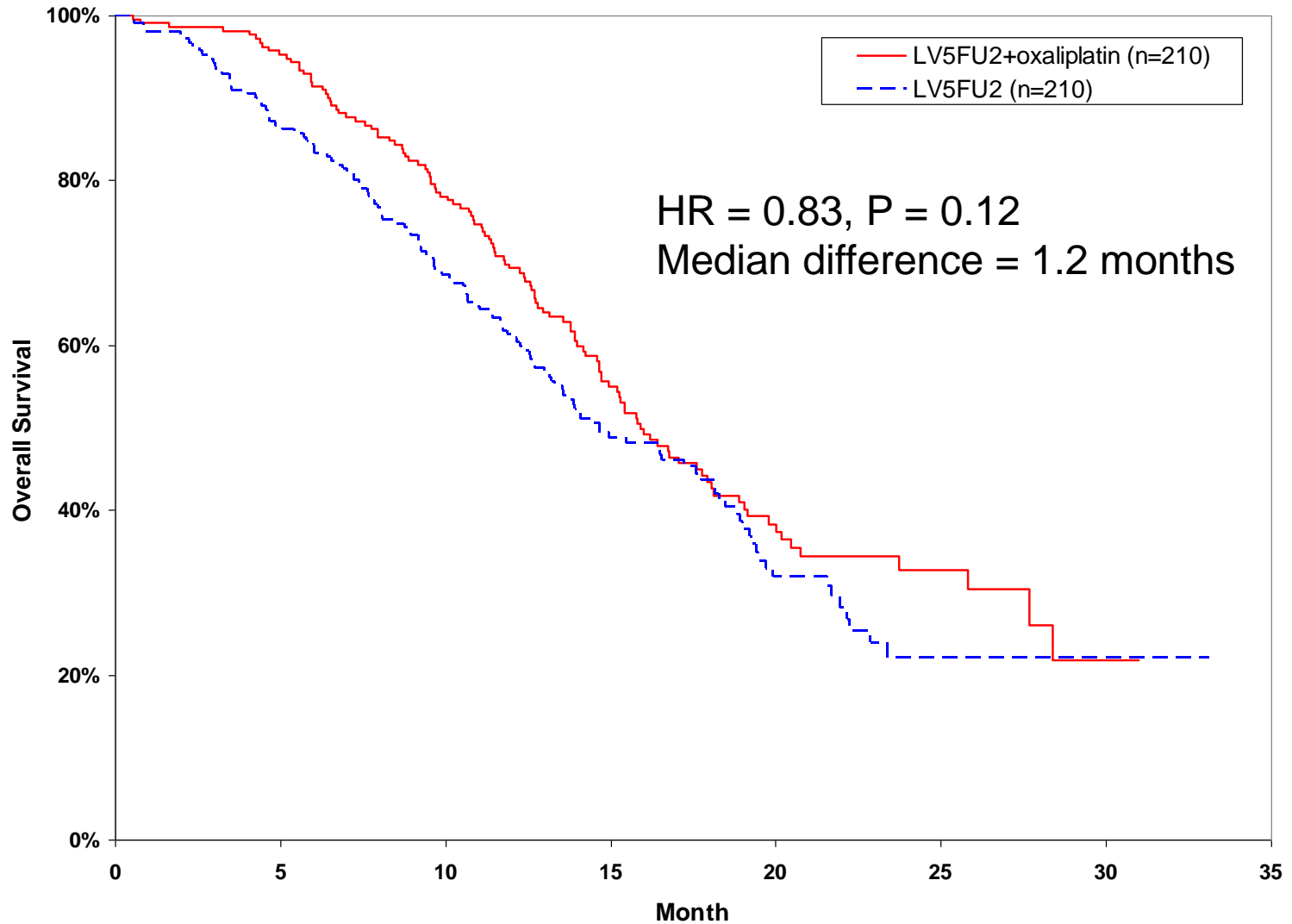
until disease progression, intolerance to treatment, or death

Progression-free survival



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

Survival



Approval of oxaliplatin

Oxaliplatin was approved for metastatic colorectal cancer

- by AFSSAPS in France in 1996
- by EMEA in Europe in 1999
- by FDA in the US in 2002

It is currently a key chemotherapeutic agent for the treatment of both resectable and advanced colorectal tumors

PROBLEMS WITH TRADITIONAL ANALYSIS?

Problems?

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

Problems?

1. The two endpoints (OS and PFS) are analyzed separately. One endpoint (PFS) suggests statistically significant benefit, the other (OS) does not. On balance, do we claim treatment to be better?
2. Neither endpoint is perfect:
 - PFS is not confounded by other treatments, is less affected by unrelated causes of death, and has more events
 - OS is clinically most relevant and is measured without bias or error
3. **The PFS ignores the time between progression and death.** The time to first event ignores subsequent events. Thus, LV5FU2 + oxaliplatin might prolong the PFS of some patients, but shorten their remaining survival afterwards.

Problems?

4. Traditional methods of analysis cannot differentiate between a modest benefit in all patients and a large benefit in some patients.

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5. The benefit of treatment is expressed through a relative reduction in risk. This measure of treatment effect does not reflect absolute benefits, which vary with baseline risk.

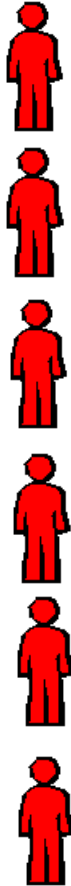
A DIFFERENT APPROACH

A new method of analysis...

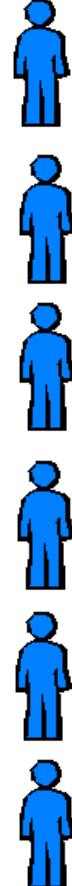
Pairwise comparisons:

Compare every patient in the treated group with every patient in the control group by forming « all pairwise comparisons »

TREATMENT
GROUP

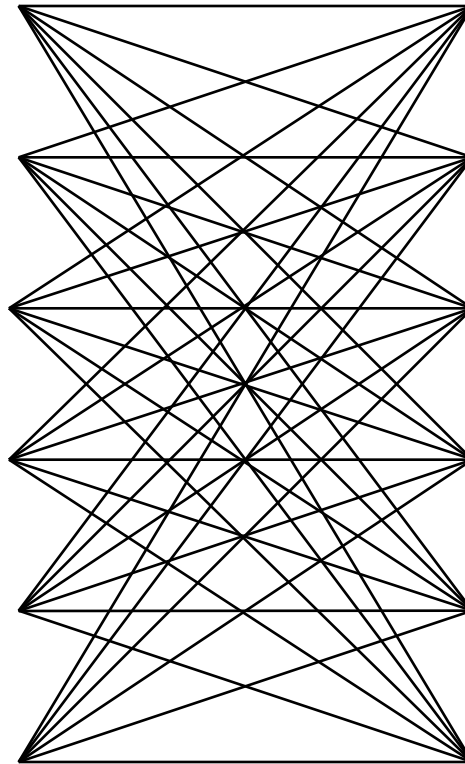
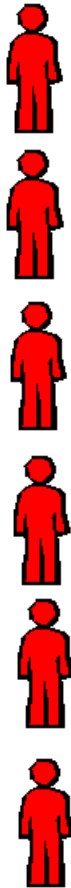


CONTROL
GROUP



TREATMENT
GROUP

CONTROL
GROUP



ALL PAIRWISE COMPARISONS
(36)

TREATMENT
GROUP

CONTROL
GROUP

Survival
times

Survival
times

3



1

5+



3

6



3

9+



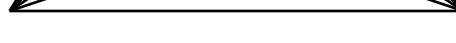
7+

11+



9

12



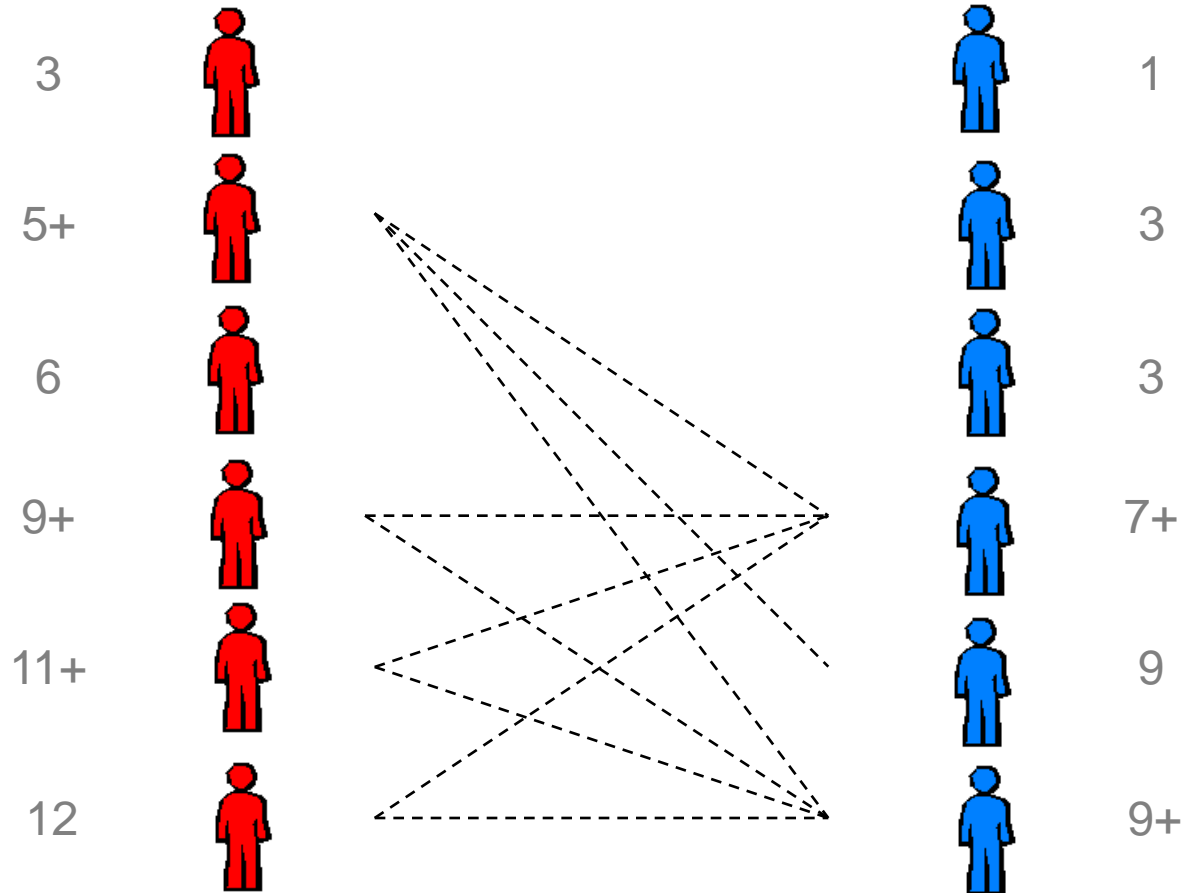
9+

ALL PAIRWISE COMPARISONS

(36)

TREATMENT
GROUP

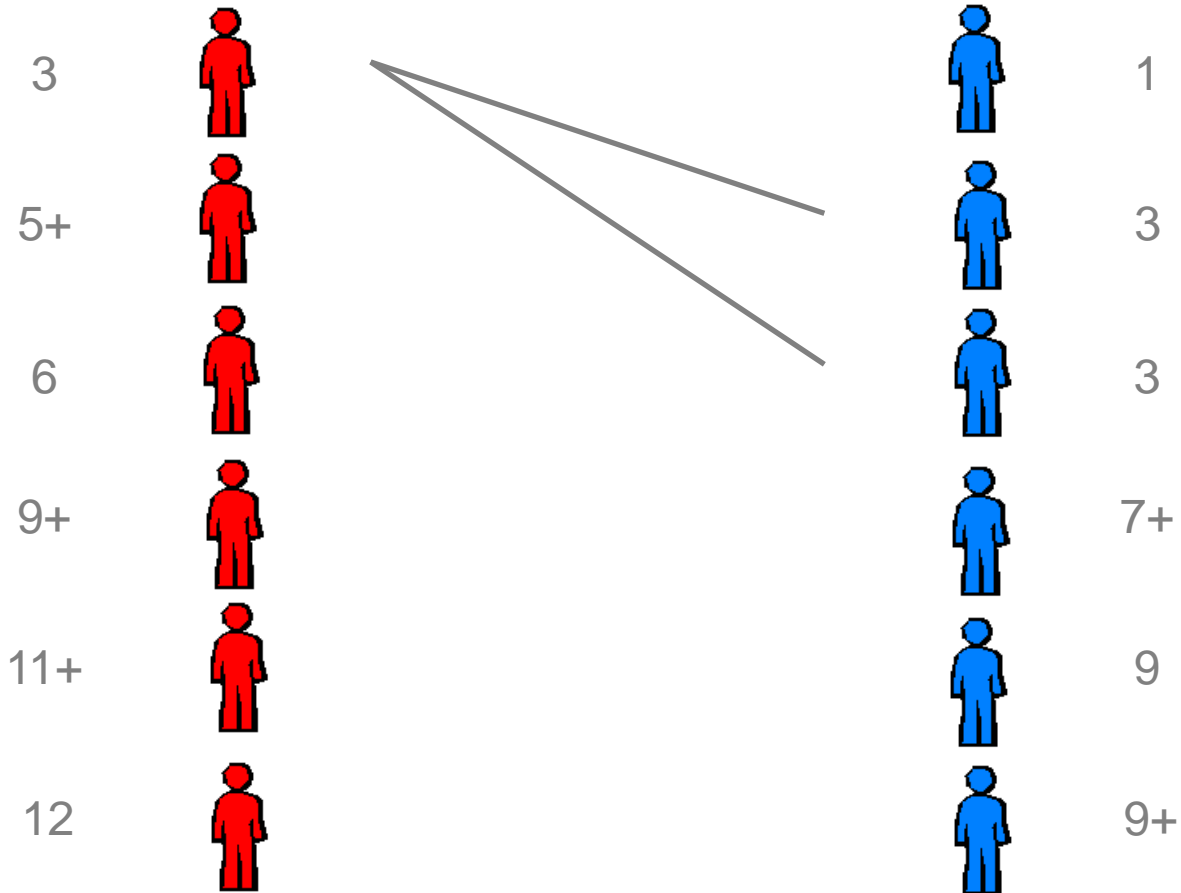
CONTROL
GROUP



UNINFORMATIVE PAIRS
(9 PAIRS)

TREATMENT
GROUP

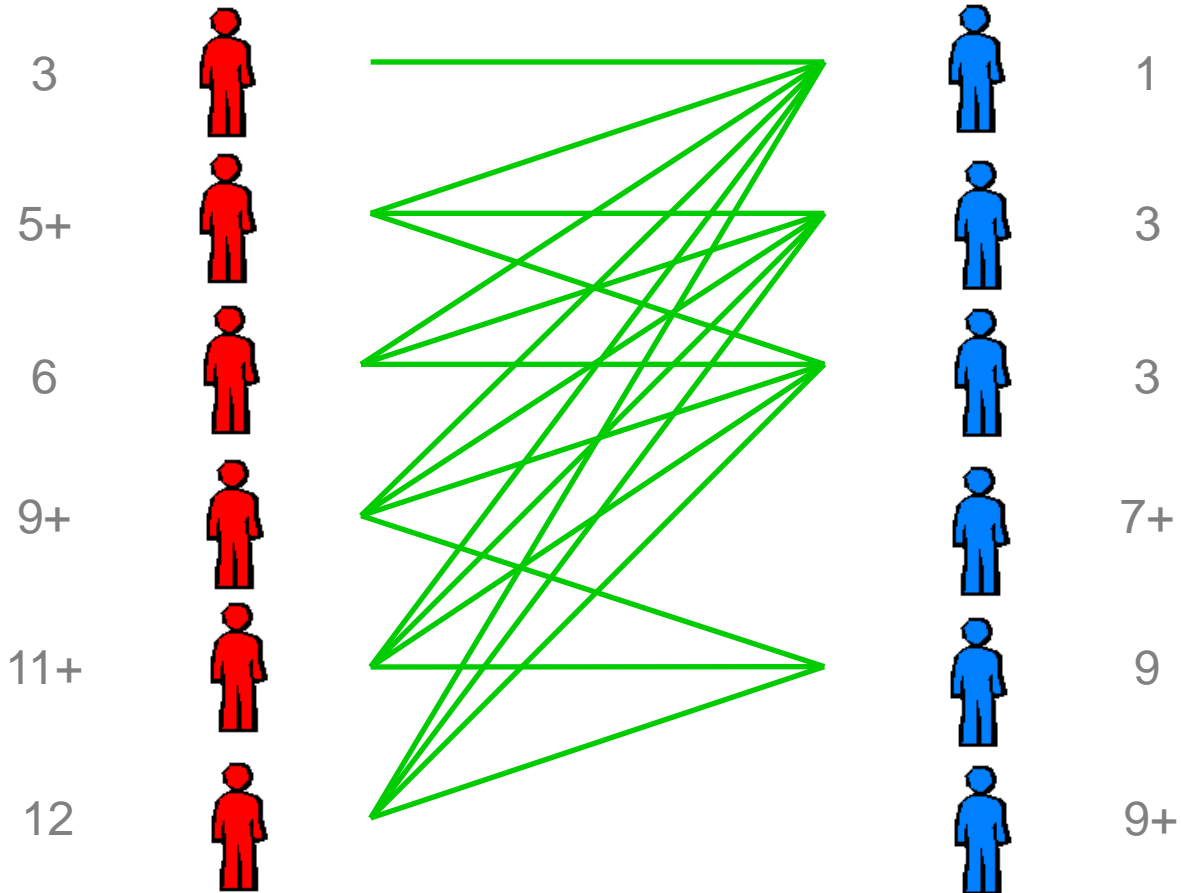
CONTROL
GROUP



TIES
(2 PAIRS)

TREATMENT
GROUP

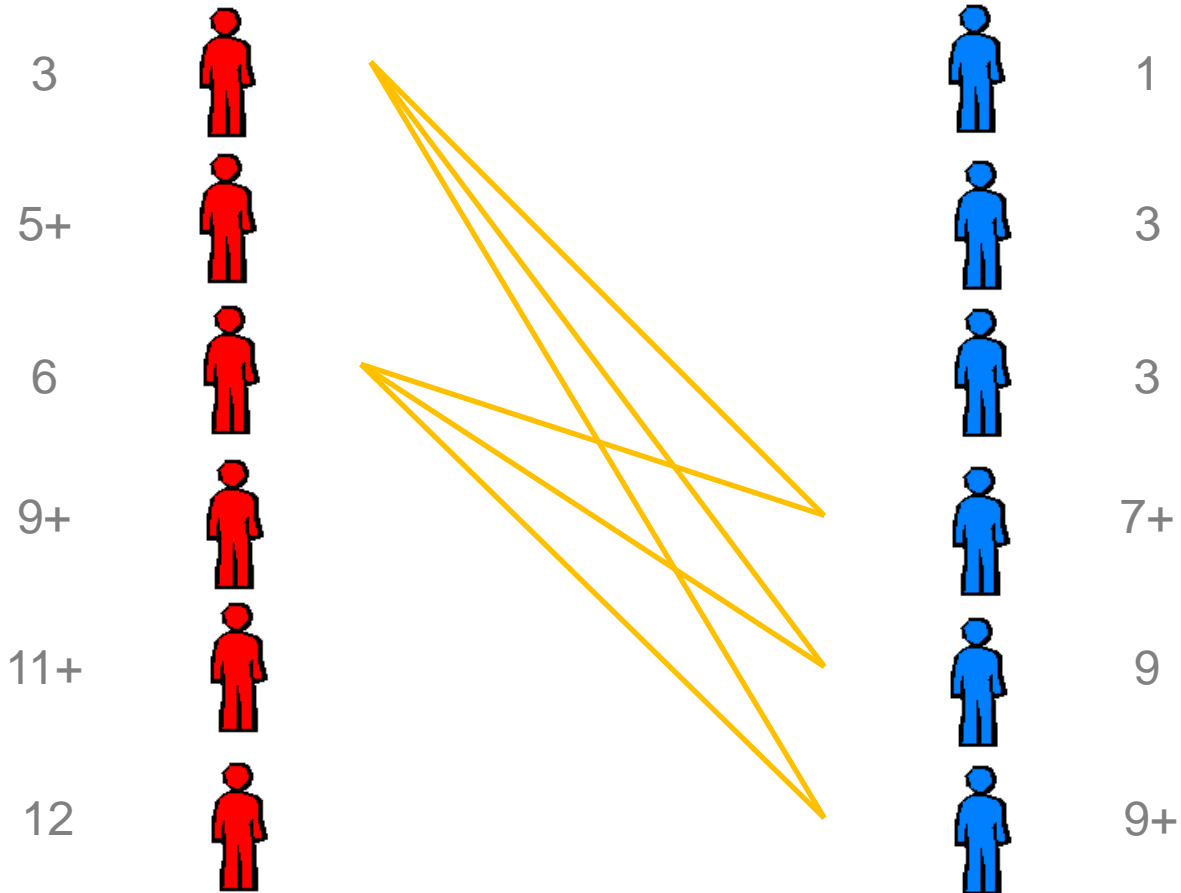
CONTROL
GROUP



**TREATMENT BETTER
(19 PAIRS)**

TREATMENT
GROUP

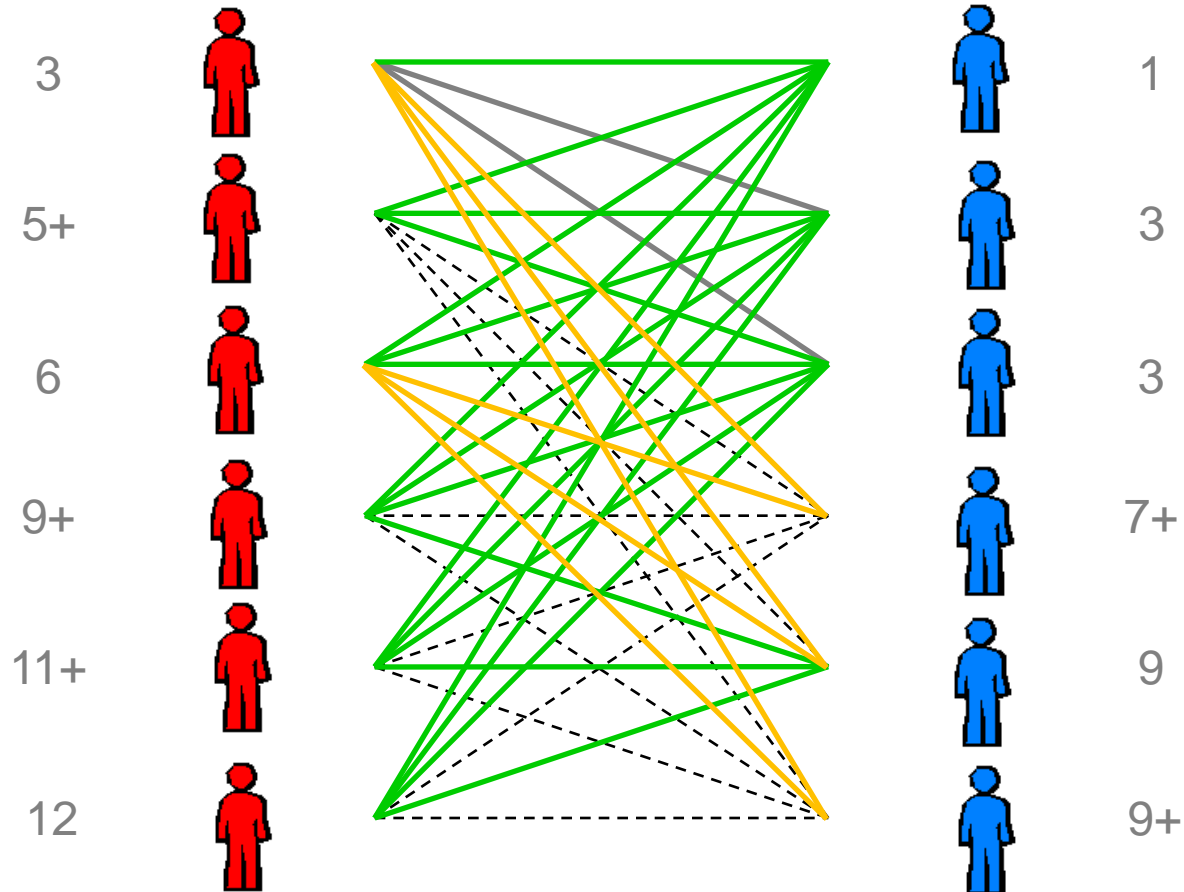
CONTROL
GROUP



**STANDARD BETTER
(6 PAIRS)**

TREATMENT
GROUP

CONTROL
GROUP



9 UNINFORMATIVE PAIRS
+ 2 PAIRS FAVORING NEITHER
+ 19 PAIRS FAVORING TREATMENT
+ 6 PAIRS FAVORING STANDARD

Pairwise comparisons

Define U_{ij}

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

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

This U -statistic generalizes the Wilcoxon-Mann-Whitney test statistic (for complete data) or the Gehan-Wilcoxon test statistic (for censored data). It is simply the difference between the proportion of favorable pairs and the proportion of unfavorable pairs.

A NEW MEASURE OF TREATMENT BENEFIT

A general measure of treatment effect

The difference between the proportion of favorable pairs and the proportion of unfavorable pairs is a direct estimate of the treatment benefit, which we denote Δ and call the « *proportion in favor of treatment* ».

Let f be the proportion of informative pairs, then

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

where λ is the hazard ratio.

Generalized pairwise comparisons

Pairwise comparisons can be generalized to successive thresholds of a continuous (or time to event) variable:

| Priority | Outcome of interest: time to death with pairwise difference |
|----------|---|
| 1 | ≥ 12 months |
| 2 | ≥ 6 months but < 12 months |
| 3 | < 6 months |

Generalized pairwise comparisons

Pairwise comparisons can be generalized further to several prioritized outcomes defined by different variables:

| Priority | Outcome of interest: |
|----------|--|
| 1 | Time to death from any cause |
| 2 | Time to objective progression of disease |

RE-ANALYSIS OF COLORECTAL TRIAL

Oxaliplatin benefits - progression-free survival

GENERALIZED PAIRWISE COMPARISONS (44,100 pairs)

| Difference in PFS (months) | Δ (%) | Cumulative Δ (%) | P-value * |
|-------------------------------|--------------|----------------------------|-----------|
| ≥ 12 | 1.5 | 1.5 | 0.09 |
| 6 -12 | 10.1 | 11.6 | <0.0001 |
| < 6 | 12.6 | 24.2 | <0.0001 |

* *Significance level, adjusted for multiplicity = 0.022*

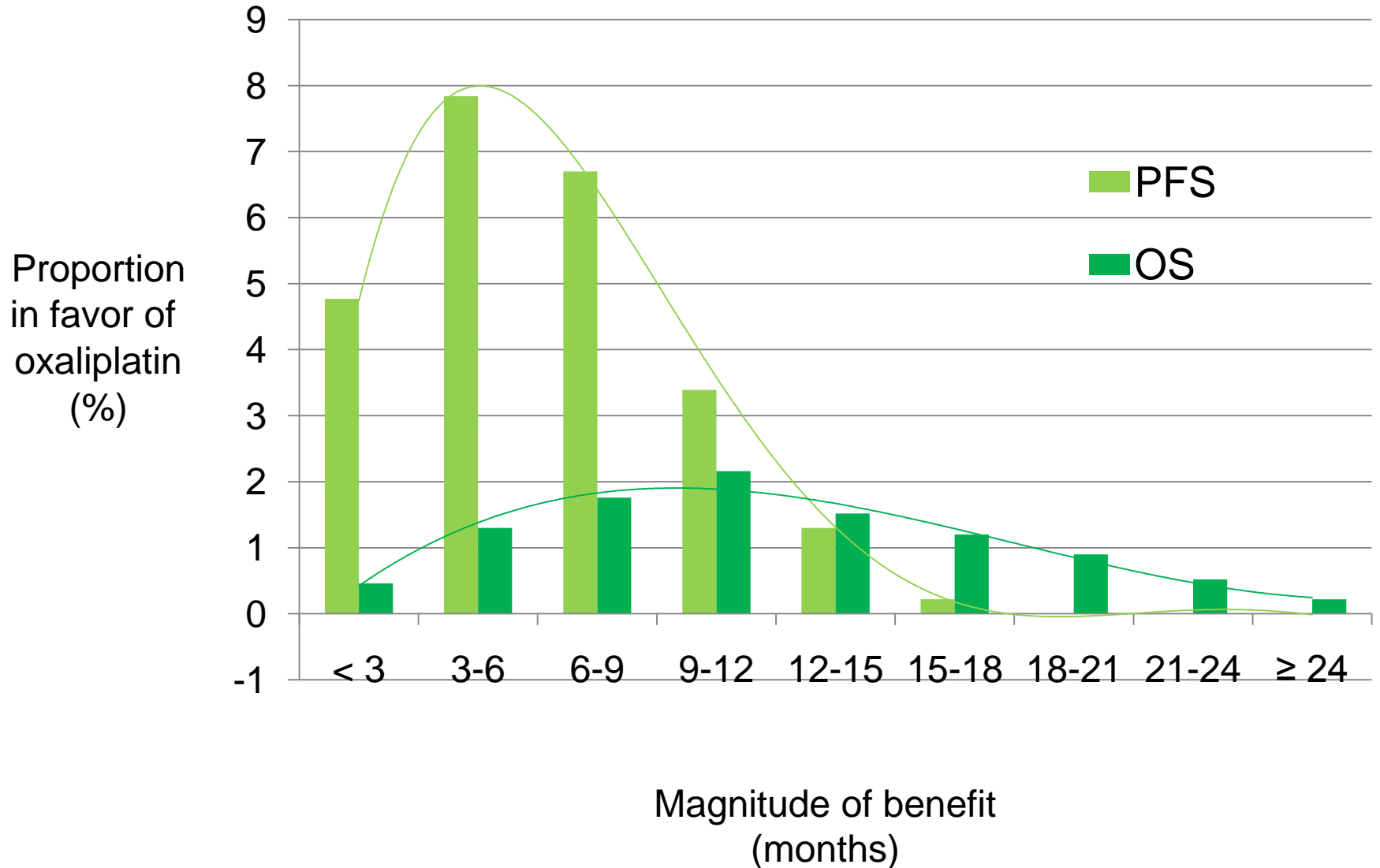
Oxaliplatin benefits - overall survival

GENERALIZED PAIRWISE COMPARISONS (44,100 pairs)

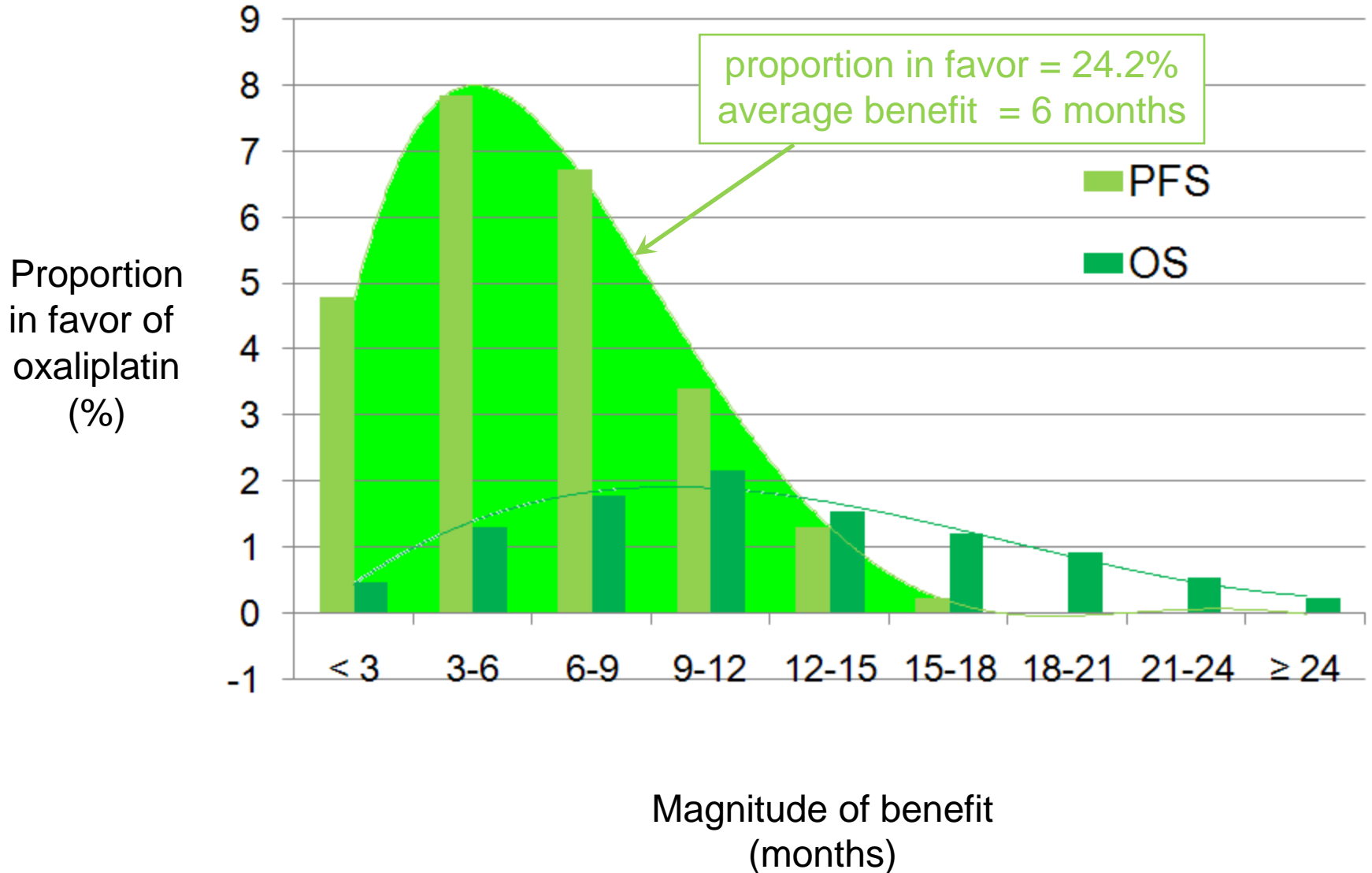
| Difference in survival (months) | Δ (%) | Cumulative Δ (%) | P-value * |
|------------------------------------|--------------|----------------------------|-----------|
| ≥ 12 | 4.4 | 4.4 | 0.043 |
| 6 -12 | 3.9 | 8.3 | 0.038 |
| < 6 | 1.8 | 10.1 | 0.050 |

* *Significance level, adjusted for multiplicity = 0.022*

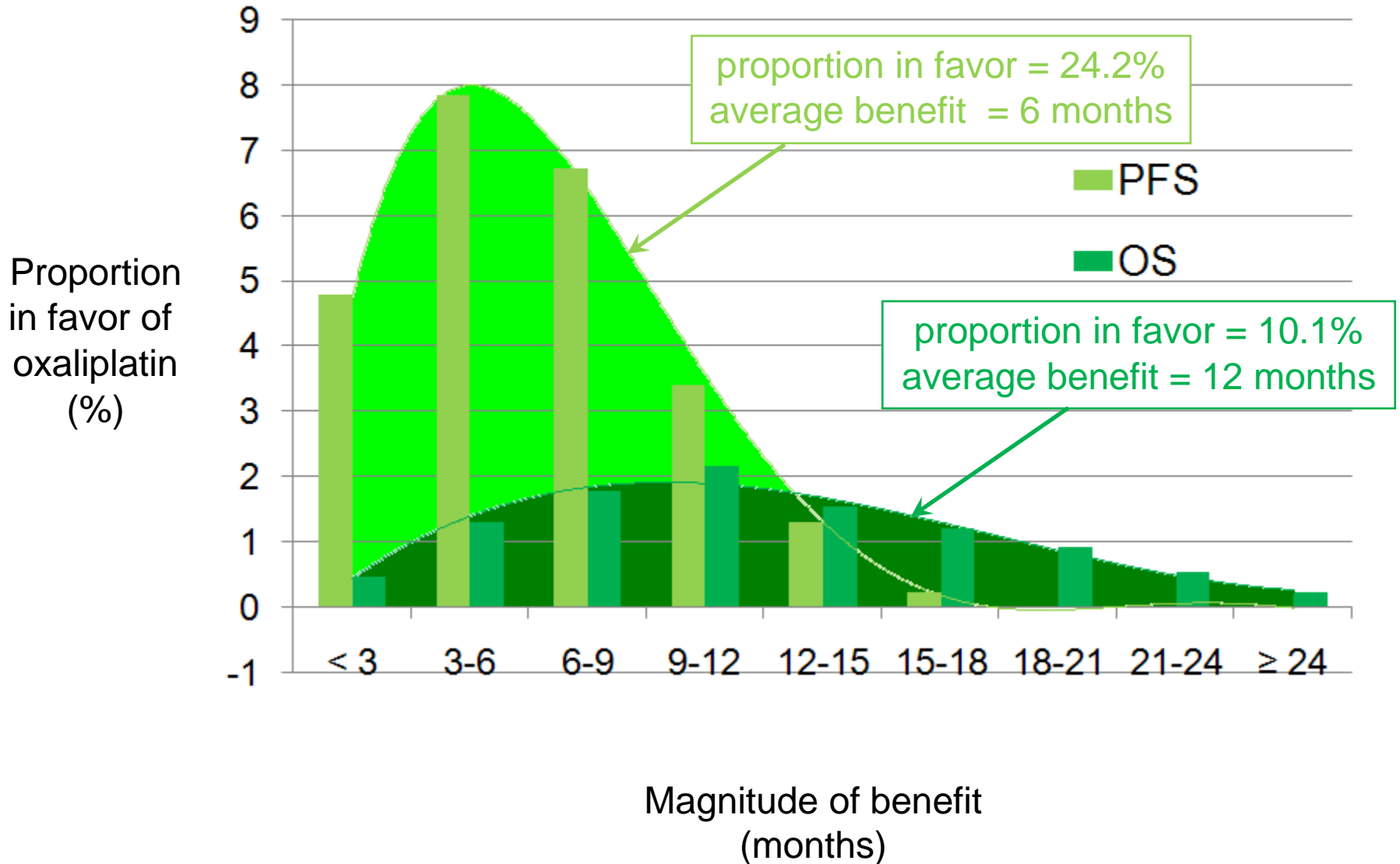
Oxaliplatin benefits – PFS and OS



Oxaliplatin benefits – PFS and OS



Oxaliplatin benefits – PFS and OS



Oxaliplatin benefits for time to death or progression

GENERALIZED PAIRWISE COMPARISONS (44,100 pairs)

| Difference in | Δ (%) | Cumulative Δ (%) | P-value * |
|------------------------|--------------|----------------------------|-----------|
| time to death | 10.1 | 10.1 | 0.050 |
| time to progression | 4.7 | 14.8 | 0.0054 |

* *Significance level, adjusted for multiplicity = 0.0296*

CONCLUSIONS

Generalized pairwise comparisons shed a very different light on these data:

- The proportion in favor of oxaliplatin is twice as large for PFS (24.2%) as for OS (10.1%)
- The average magnitude of the benefit is twice as large for OS (12 months) as for PFS (6 months)

These measures of treatment benefits may usefully complement survival curves for clinical decision making.