The "Net Benefit" and the correlation between benefits and harms

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June 28, 2021

Problem

Benefit / risk assessments use *marginal* estimates that do not account for the correlation between the outcomes (benefits / risks)

Positive correlation

Example: skin rash in patients with EGFR-mutated advanced lung cancer receiving inhibitors of EGFR

No correlation

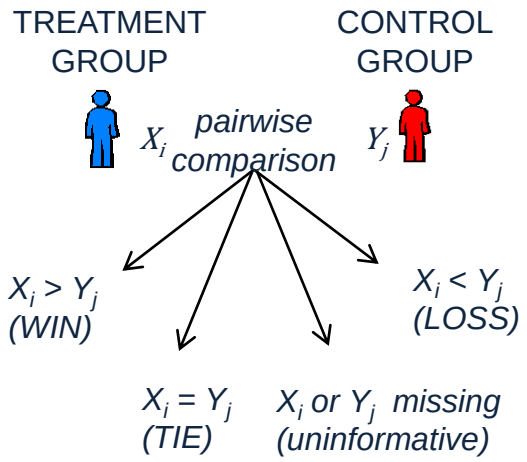
Example: cardiac toxicity in frail patients with advanced breast receiving anthracyclines

Negative correlation

Example: toxicities leading to treatment stop in enzyme-deficient patients with advanced colorectal cancer receiving irinotecan

Ref: Buyse et al. J Clin Epidemiol 2021

Pairwise Comparisons



WINS $X_i > Y_j$

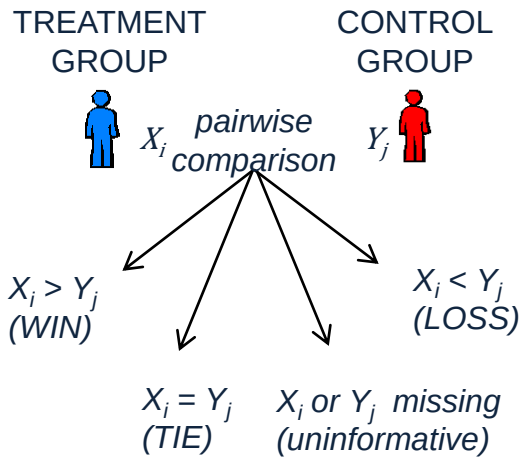
LOSSES $X_i < Y_j$

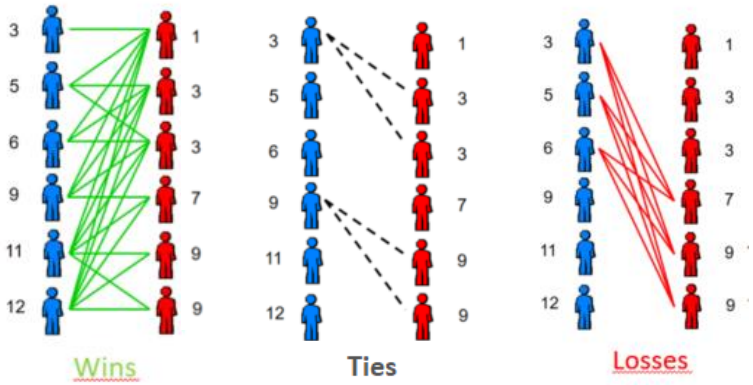
TIES $X_i = Y_j$

(UNINFORMATIVE)

Ref: Buyse. Stat Med 2010

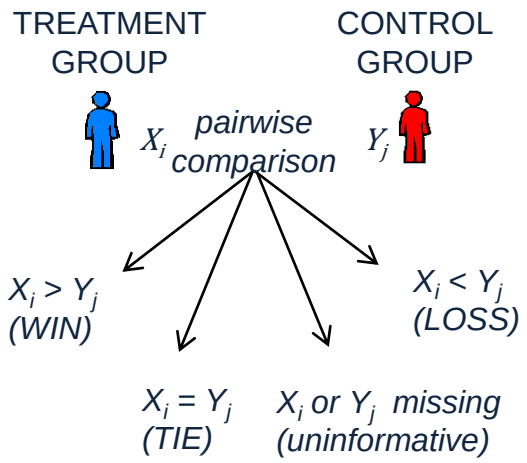
All Pairwise Comparisons





Ref: Buyse. Stat Med 2010

Net Benefit



$$Net\ Benefit = \frac{\#Wins}{\#Pairs} - \frac{\#Losses}{\#Pairs}$$

$$= 2\theta - 1$$

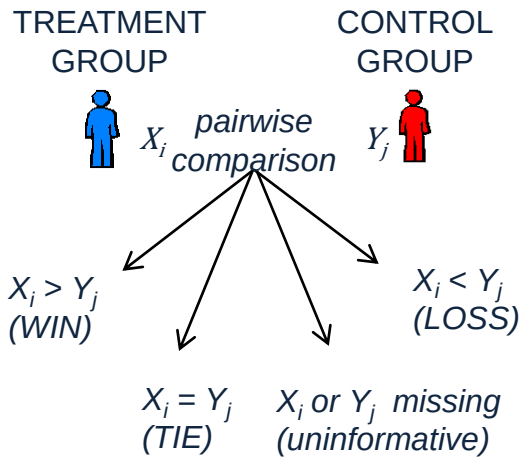
where θ is the « probabilistic index »

$$-1 < Net\ Benefit < 1$$

$Net\ Benefit$: probability that a random patient receiving Treatment does better than a random patient receiving Control, minus the probability of the opposite situation

Ref: Buyse. Stat Med 2010

Win Ratio

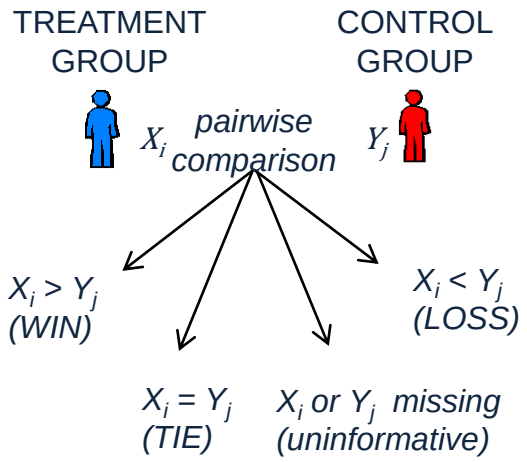


$$Win\ Ratio = \frac{\#Wins}{\#Losses}$$

$$0 < Win\ Ratio < \infty$$

Ref: Pocock et al. Eur Heart J 2012

Win Odds



$$Win\ Odds = \frac{\#Wins + \#Ties/2}{\#Losses + \#Ties/2}$$

$$= \frac{\theta}{1-\theta}$$

$$0 < Win\ Odds < \infty$$

Ref: Brunner et al. Stat Med 2021

The Net Benefit is a U-statistic

$X_i \ (i = 1, \dots, m)$

$Y_j \ (j = 1, \dots, n)$

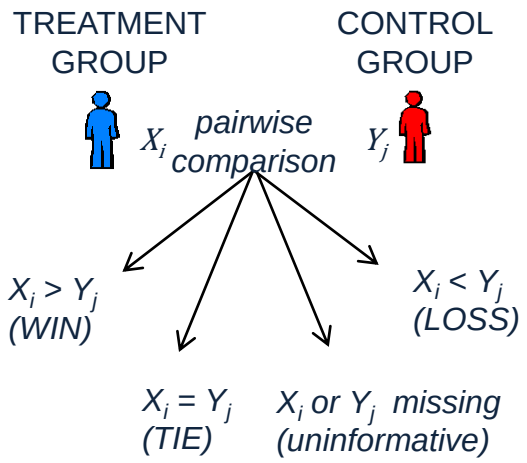
$$u_{ij} = \begin{cases} +1 \ if \ (X_i, Y_j) \ pair \ is \ a \ win \\ -1 \ if \ (X_i, Y_j) \ pair \ is \ a \ loss \\ 0 \ otherwise \end{cases}$$

$$U = \frac{1}{mn} \sum_{i=1}^{m} \sum_{j=1}^{n} u_{ij}$$

U, the Net Benefit, is unbiased and efficient in situations of practical interest

Ref: Verbeeck et al. SMMR 2021

GENERALIZATIONS
1 - Thresholds of Clinical Relevance



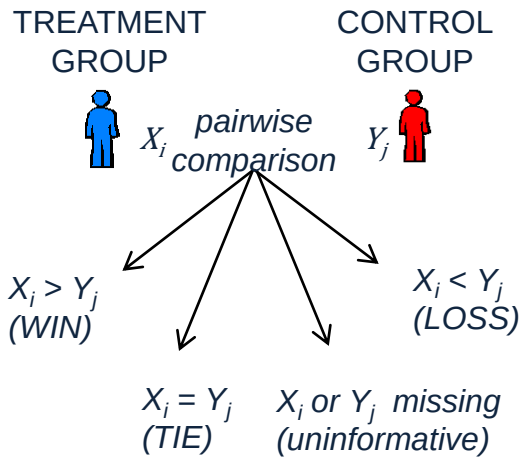
WINS $X_i - Yj > \tau$

LOSSES $X_i - Y_j < -\tau$

TIES $|X_i - Y_j| < \tau$

Ref: Buyse. Stat Med 2010

GENERALIZATIONS
2 – Outcomes of Any Type



$\succ$ *denotes « better outcome »*

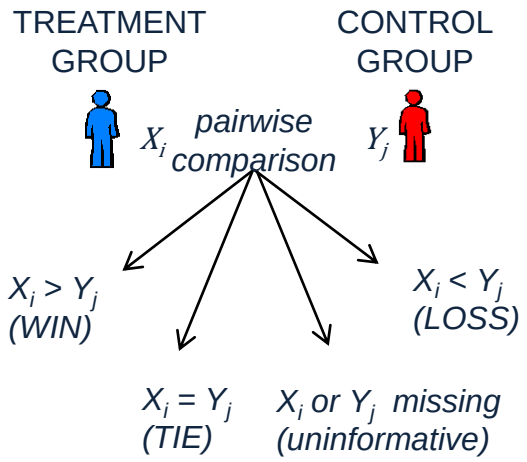
$\prec$ *denotes « worse outcome »*

WINS $X_i \succ Y_j$

LOSSES $X_i \prec Y_j$

Ref: Buyse. Stat Med 2010

GENERALIZATIONS
3 – Multiple Prioritized Outcomes



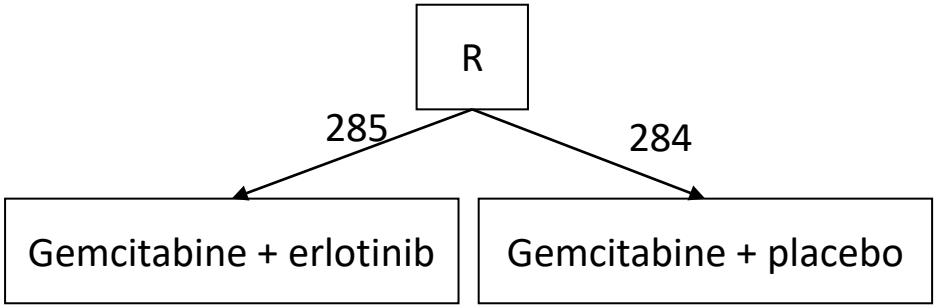
Prioritized outcome 1	Prioritized outcome 2	Pairwise comparison
win	ignored	win
loss	ignored	loss
uninformative or tie	win	win
uninformative or tie	loss	loss
uninformative or tie	tie	tie
uninformative or tie	uninformative	uninformative

Ref: Finkelstein and Schoenfeld Stat Med 1999; Wittkowski et al. Stat Med 2004; Buyse Stat Med 2010

Benefit/Risk Analyses

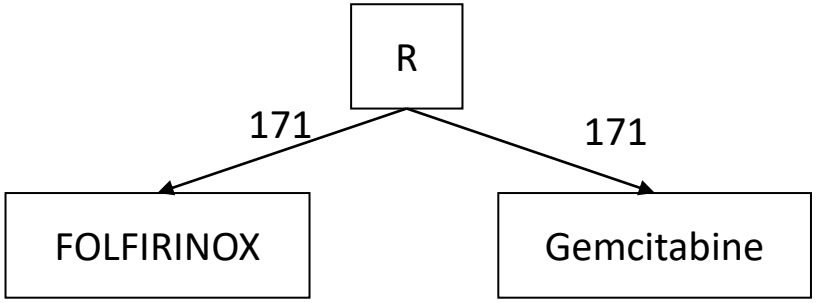
Erlotinib

569 advanced pancreatic cancers



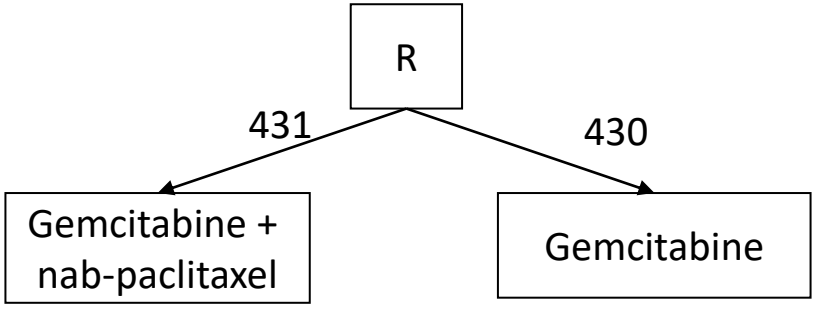
FOLFORINOX

342 advanced pancreatic cancers



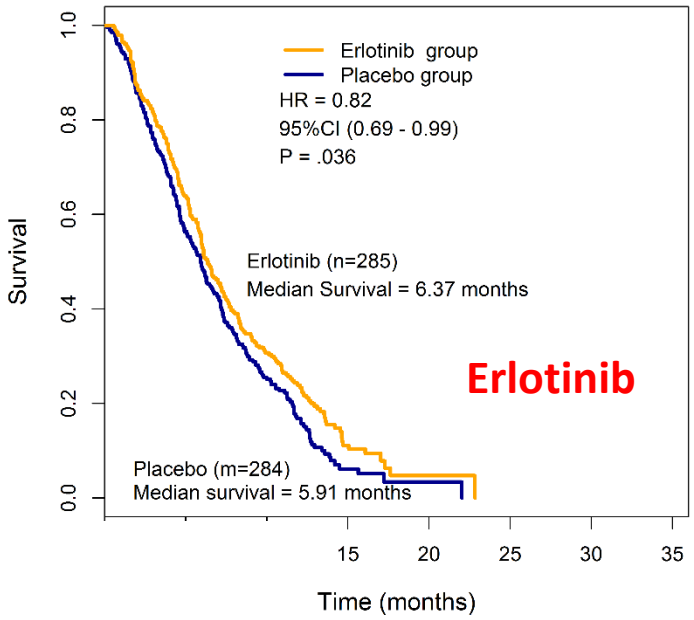
Nab-Paclitaxel

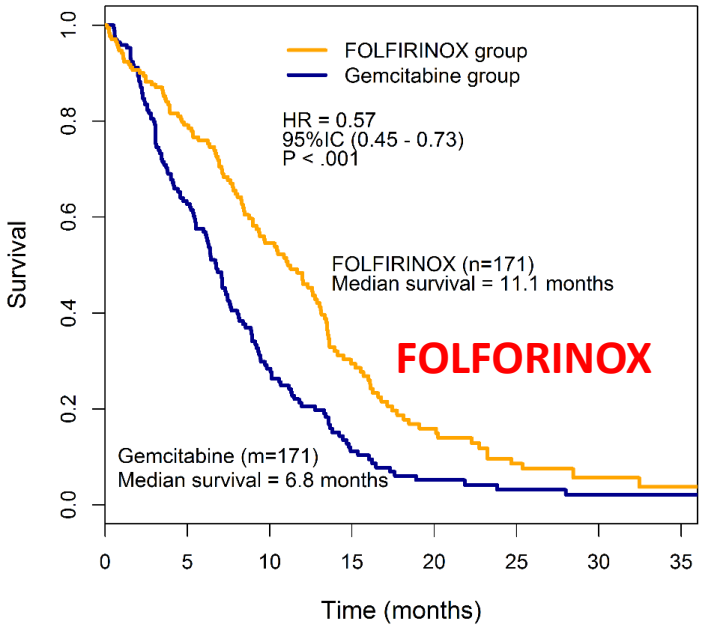
861 advanced pancreatic cancers

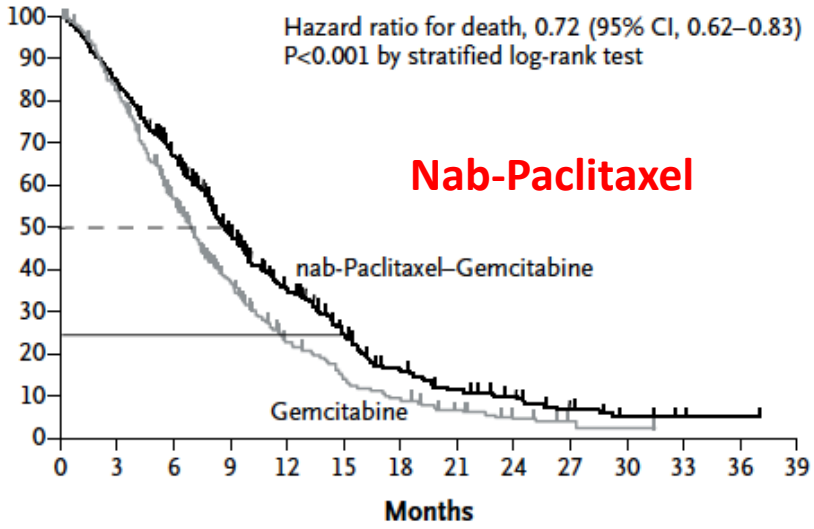


Refs: Moore et al. JCO 2007; Conroy et al. NEJM 2011; Von Hoff et al. NEJM 2013

Benefit : Longer OS

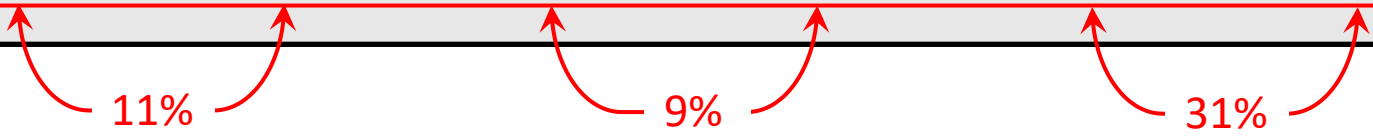






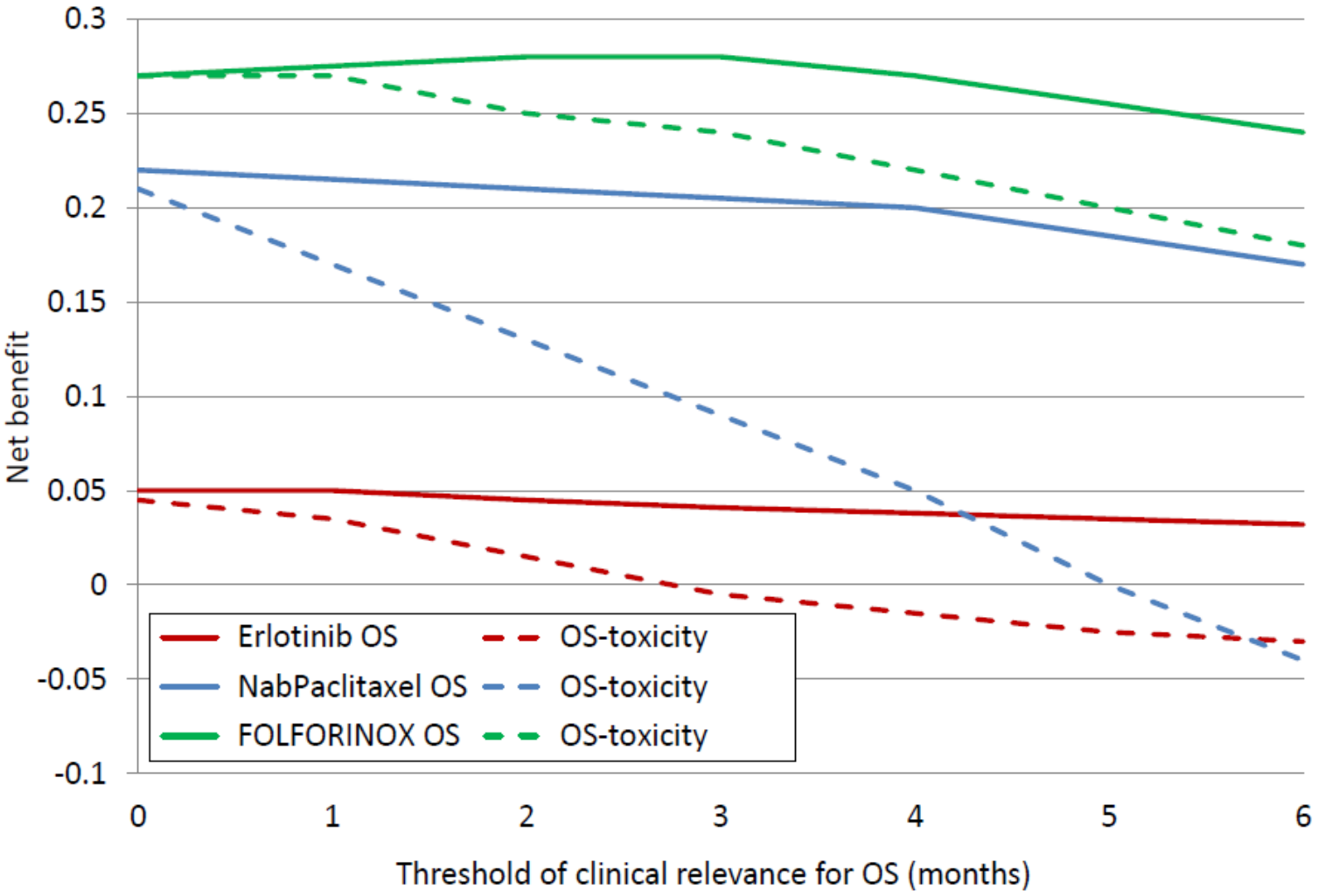
Risk : Severe Toxicity

	Erlotinib		FOLFORINOX		Nab-Paclitaxel	
Worst Toxicity	Erlotonib	Gem	FOLFORINOX	Gem	Gem+NabP	Gem
None	10%	23%	4%	1%	9%	22%
Grade 1-2	59%	57%	27%	39%	36%	54%
Grade 3-5	31%	20%	69%	60%	55%	24%



Refs: Péron et al. BJC 2015; Péron et al. Oncotarget 2016; Péron et al. Pancreas 2019

Clinical Thresholds for OS



Ref: Buyse & Péron, In: Piantadosi & Meinert (eds.), Principles and Practice of Clinical Trials, 2021

Conclusions

The Net Benefit, estimated with Generalized Pairwise Comparisons

- is flexible
- can incorporate multiple prioritized outcomes
- can incorporate thresholds of clinical relevance
- provides a mathematically correct benefit / risk assessment
- is meaningful to patients

Selected References

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