Table of effects in benefit-risk assessments

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Disclaimer

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What is expected from a regulatory agency?

Table of effects in benefit-risk assessments

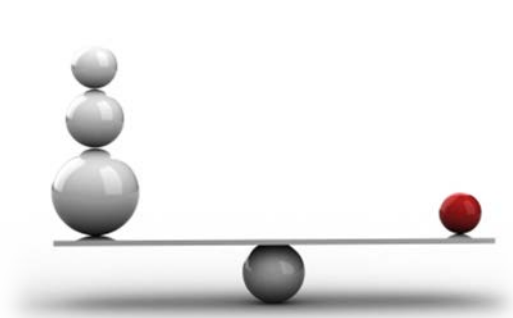
*A fair regulatory process requires "**accountability for reasonableness**", i.e., publicity about the reasons and rationales that play a part in decisions*

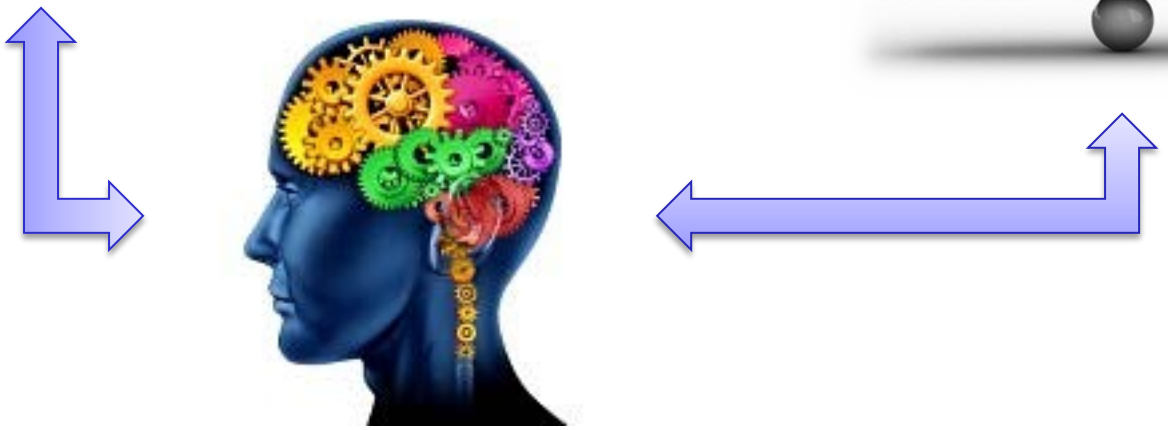
Daniels N. Accountability for reasonableness. BMJ. 2000;321(7272):1300-1

Table 1. Effects Table for low-dose unfractionated heparine vs enoxaparin for the prevention of DVT following major trauma.

Effect	Short Description	Unit	Heparine	Enoxapa-rine	Uncertainties/ Strength of evidence	References
Favourable Effects						
Prox. DVT	Incidence of proximal-deep vein thrombosis (95%CI)	%	14.5 (9.3-21.6)	6.0 (2.8-11.2)	SE: statistically significant RD -8.5 (-1.2 - -15.7), RR 0.42 (0.19-0.92) p = 0.024 U: single center, 2x171 patients randomized, 30 cases of failed venography, one case of PE.	J. of Clin. Epidemiol 57 (2004) 795-803, table 1
Dist. DVT	Incidence of distal deep vein thrombosis (95%CI)	%	29.4 (22.0-38.3)	24.9 (18.4-33.4)	SE: statistically non-significant RD -4.6 (-15.3 - 6.0), RR 0.84 (0.57-1.25) p = 0.399	
Unfavourable Effects						
Maj. Bleed.	Incidence of major bleedings (95%CI)	%	0.5 (0.0-2.6)	3.6 (1.3-7.7)	SE: statistically nonsignificant RD 3.1 (-0.5 -6.8), RR 5.3 (.62-44.5) p = 0.085 U: although not statistically significant substantial difference.	

Abbreviations: Prox=proximal, DVT=Deep venous thrombosis, 95%CI=95% confidence interval, SE=strength of evidence, U=uncertainties, PE=pulmonary embolism.





Background

Table of effects in benefit-risk assessments

March 2008 CHMP: Reflection paper on benefit-risk assessment methods with two main recommendations to improve consistency, transparency and communication of B/R :

- Revise the benefit-risk balance section of the CHMP Assessment Report template

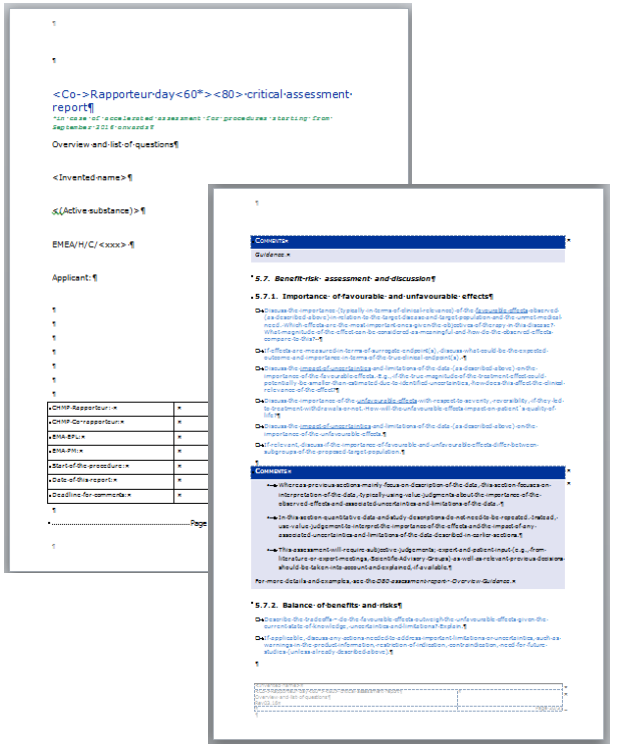
- Introduce research methodologies of benefit-risk balance
  - Involve experts, assessors, and specialists in Decision Theory
  - Switch from “implicit” to “explicit” decision making

2009 Start Benefit-risk methodology project

The New Benefit-Risk Assessment Template

Table of effects in benefit-risk assessments

- Therapeutic context
- Favourable effects
- Uncertainties and limitations
- Unfavourable effects
- Uncertainties and limitations
- Effects Table
- Benefit-risk assessment and discussion
  - Importance of effects
  - Benefit-risk balance
  - Additional considerations
- Conclusions



The Effects table

- An effects table is a useful qualitative tool for displaying a concise summary of the key benefits and risks of a new product (single or multiple doses) compared to either placebo or an existing product
- It displays all important favourable and unfavourable effects including all uncertainties and limitations that may affect their clinical interpretation

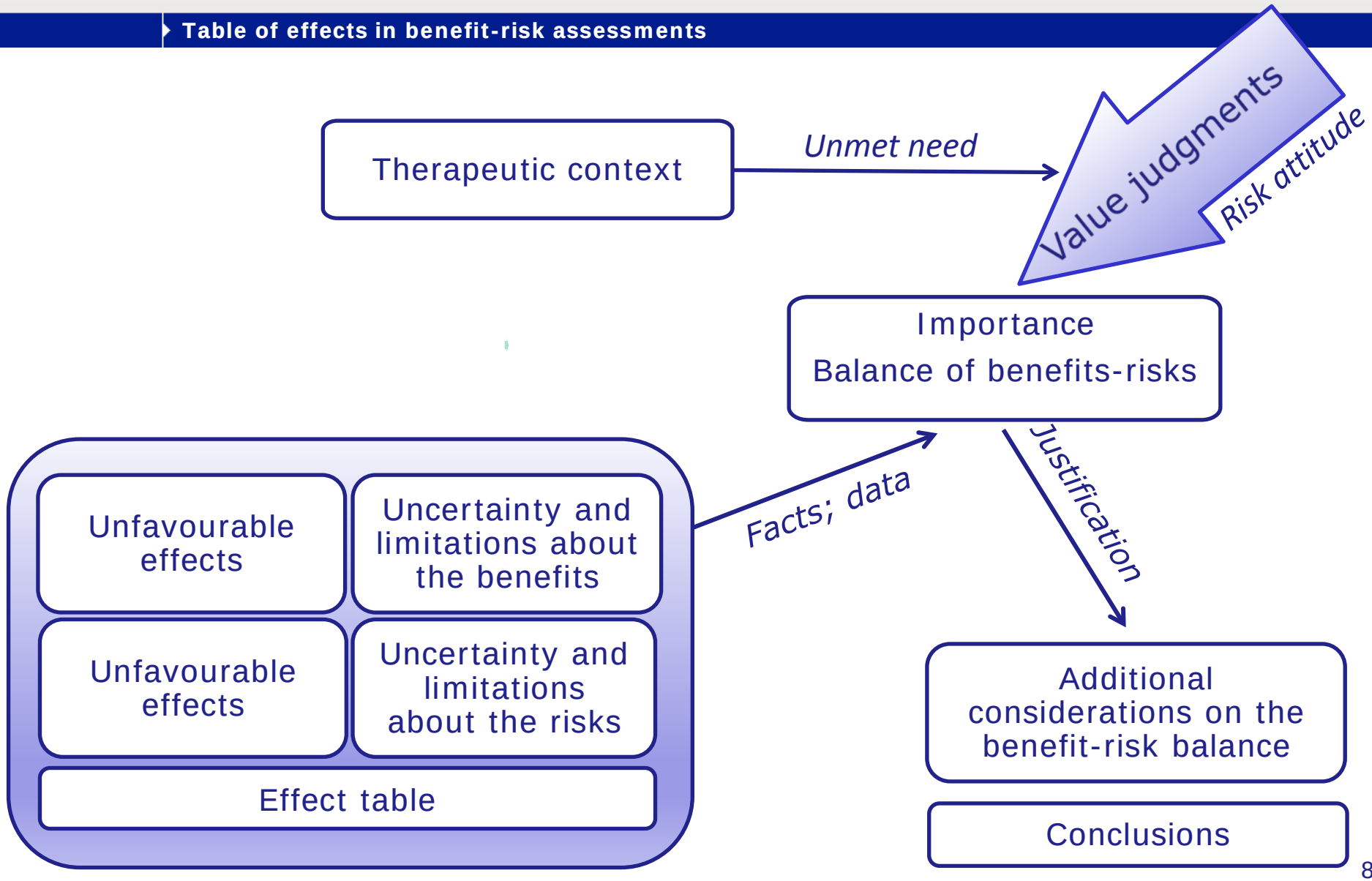
Effects table example

Table of effects in benefit-risk assessments

	Effect	Short Description	Unit	Placebo	Vandetanib	Uncertainties / Strength of evidence	References
Favourable	PFS	From randomization to progression or death (blinded independent review)	%	51.0 (41.4-60.1)	31.6 (26.0-37.9)	HR 0.45 (0.31, 0.6) Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Months	19.3	30.5	Log rank P-value (2-sided) p<.0001	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13.0 (7.8-21.0)	45.0 (38.7-51.5)	RR 3.5 (2.0-5.9) Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy? No clear effect on PRO/QoL (missing data) 9)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4 (1)	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0 (0.6-7.0)	10.8 (7.4-15.5)	RR 3.5 (2.0, 5,9) Duration of follow up is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4) Restrict to symptomatic and aggressive disease (see SmPC 4.1). Explore lower dose (see See Table 20. Summary of the RMP)
	QTc related events Grade 3-4 (1)	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0 (0.2-5.5)	13.4 (9.6-18.4)	RR 13.0 (1.8-94.0) Risk of developing further major cardiac SAEs including Torsades de pointe?	
	Infections Grade 3-4 (1)	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4 (27.3-45.8)	49.8 (43.4-56.2)	RR 1.4 (1.0, 1.9)	

Benefit-risk assessment Template

Table of effects in benefit-risk assessments



Effects table pros and cons

Table of effects in benefit-risk assessments

Pros

- It drives alignment on key benefits and risks
- It clarifies the way to measure and/or present key benefits and risks
- It's an efficient tool to aid communication
- It permits an opportunity to rank key benefits and risks
- It can be used to look for consistency of the benefit-risk ratio across subgroups
- It will facilitate internal governance reviews
- It may help in payer discussions

Cons

- Risk of focusing on table and missing the totality of evidence
- Risk of oversimplification
- Increased workload for assessors
- Difficult to have a good ET for large and complex applications

Compliance with template guidance (B-R balance)

Table of effects in benefit-risk assessments

Item(s)	Score
BR Balance Items	.55
Importance	.64
• Important benefits identified?	.94
✓ Explicit value judgements?	.45
• Important risks identified?	.87
✓ Explicit value judgements?	.29
Benefit risk balance	.37
• Value function?	.07
• Benefits and risks trade-offs?	.66
Discussion	.29
• Effect of uncertainties?	.48
• Different stakeholders?	.11

Compliance with template guidance (B-R balance)

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Discussion	**.29**
• **Effect of uncertainties?**	**.48**
• **Different stakeholders?**	**.11**

0=Not covered
1=Partly covered
2=Fully covered

B/R balance, intuitive assessment

Table of effects in benefit-risk assessments

Effect	Short description	Unit	Treatment	Control
Favourable effects				
Progression free survival	Proportion of patients who have a time to progression of at least 12 months	%	70%	50%
Unfavourable effects				
Severe toxicity	Proportion of patients who experience severe or life-threatening side-effects	%	85%	45%

Intuitive vs explicit assessment

- **Intuitive assessment:** preferences for different treatment outcomes remain implicit and undocumented
- **Explicit assessment:** the conclusion regarding the B/R balance is derived from a set of qualitative or quantitative preference statements elicited from the decision maker

B/R balance, intuitive assessment

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Conclusion

The increase in PFS from 50% to 70% is clinically relevant and outweighs the increase in severe toxicity. Therefore, the B/R balance of the new treatment is positive.

B/R balance, explicit assessment

Elicited preference statement:

Starting from a value of 50%, the smallest increase in PFS that would be required to offset an increase in severe toxicity from 45% to 85% is 15% (i.e., an increase from 50% to 65%).

Conclusion:
The increase in PFS with the new treatment exceeds the minimum required benefit of 15%. Therefore, the B/R balance of the new treatment is positive.

Explicit assessment (cont)

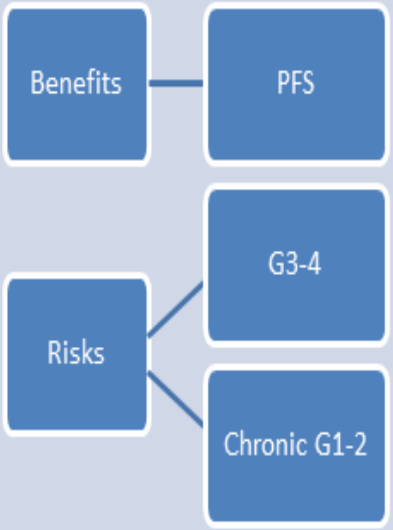
- Myeloma patients from the Myeloma UK patient organisation were invited to complete a multi-criteria decision analysis comprising the following three attributes: (i) progression-free survival, (ii) moderate but chronic toxicity, and (iii) severe toxicity.
- A total of 560 participants completed the questionnaire.
  - Overall context of the survey was discussed in a focus group
  - First version of the online questionnaire was developed and pre-tested in a second group of myeloma patients;
  - Revised version of the questionnaire was developed.

Stated Preferences for multiple myeloma: Methods

Table of effects in benefit-risk assessments

1. Design

Model



2. Elicit

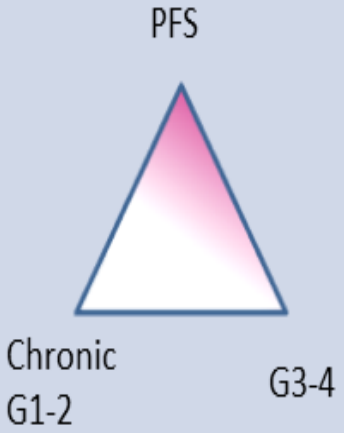
Ordinal ranking

1. PFS (50%→90%)
2. G3-4 (80%→20%)
3. Chronic G1-2 (85%→45%)

Choice matching

3. Analyse

Weights

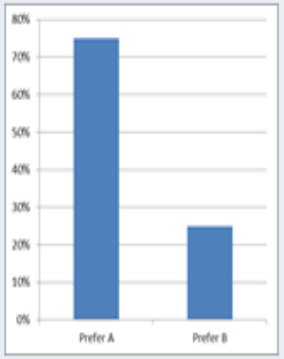


4. Apply

Clinical data

Attribute	A	B
PFS	66%	59%
G3-4	60%	53%
Chronic G1-2	71%	69%

Acceptability of treatments



D. Postmus *et al*. *The Oncologist 2017*. Individual trade-offs between possible benefits and risks of cancer treatments: Results from a stated preference study with multiple myeloma patients.

Example: new treatment for multiple myeloma

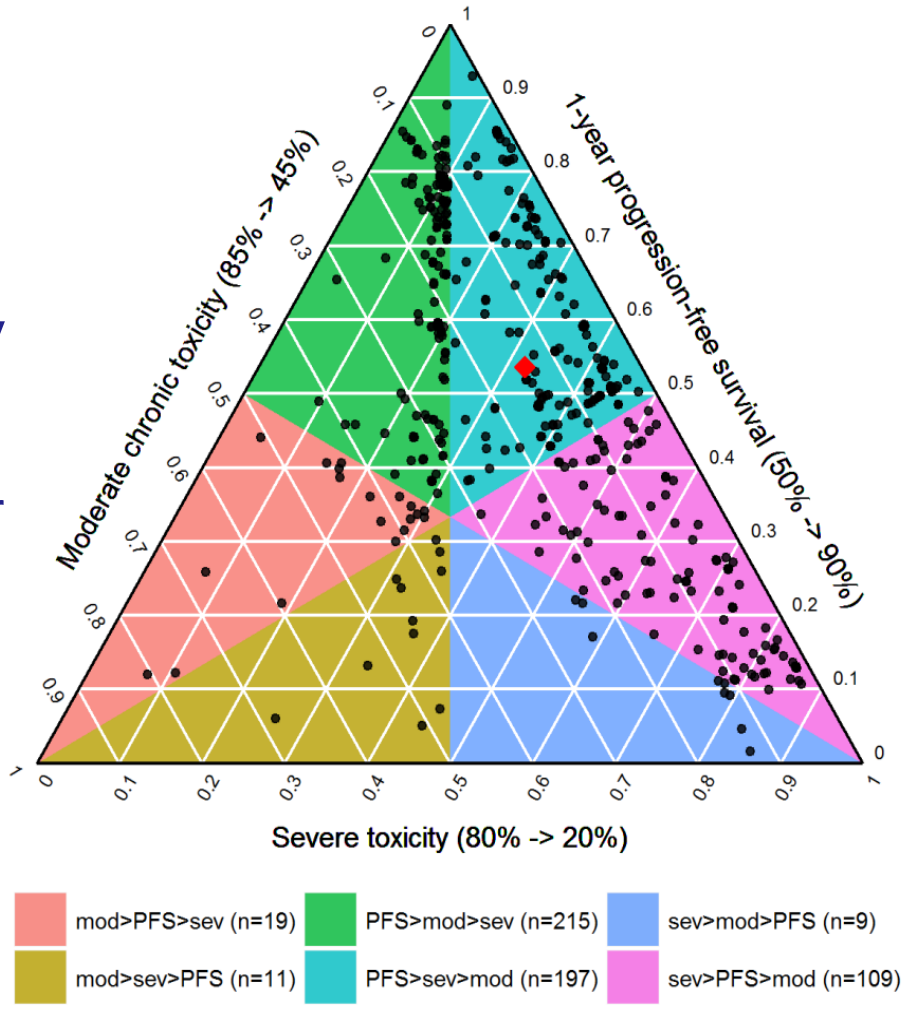
Table of effects in benefit-risk assessments

Effect	Short description	Unit	Treatment	Control
Favourable effects				
Progression free survival	Proportion of patients who have a time to progression free survival of at least 12 months	%	90%	50%
Unfavourable effects				
Severe toxicity	Proportion of patients who experience severe or life-threatening side-effects	%	85%	45%
Moderate but chronic toxicity	Probability of experiencing mild to moderate side-effects for two months or longer	%	80%	20%

Survey with 560 myeloma patients from the cancer charity Myeloma UK

Table of effects in benefit-risk assessments

- The average weight given to PFS was 0.54, followed by 0.32 for G3-4 toxicity, and 0.14 for G1-2 chronic toxicity
- Considerable heterogeneity
- Severe toxicity ranked higher among younger, working, and looking after dependent family members and who had more frequently experienced severe toxicity

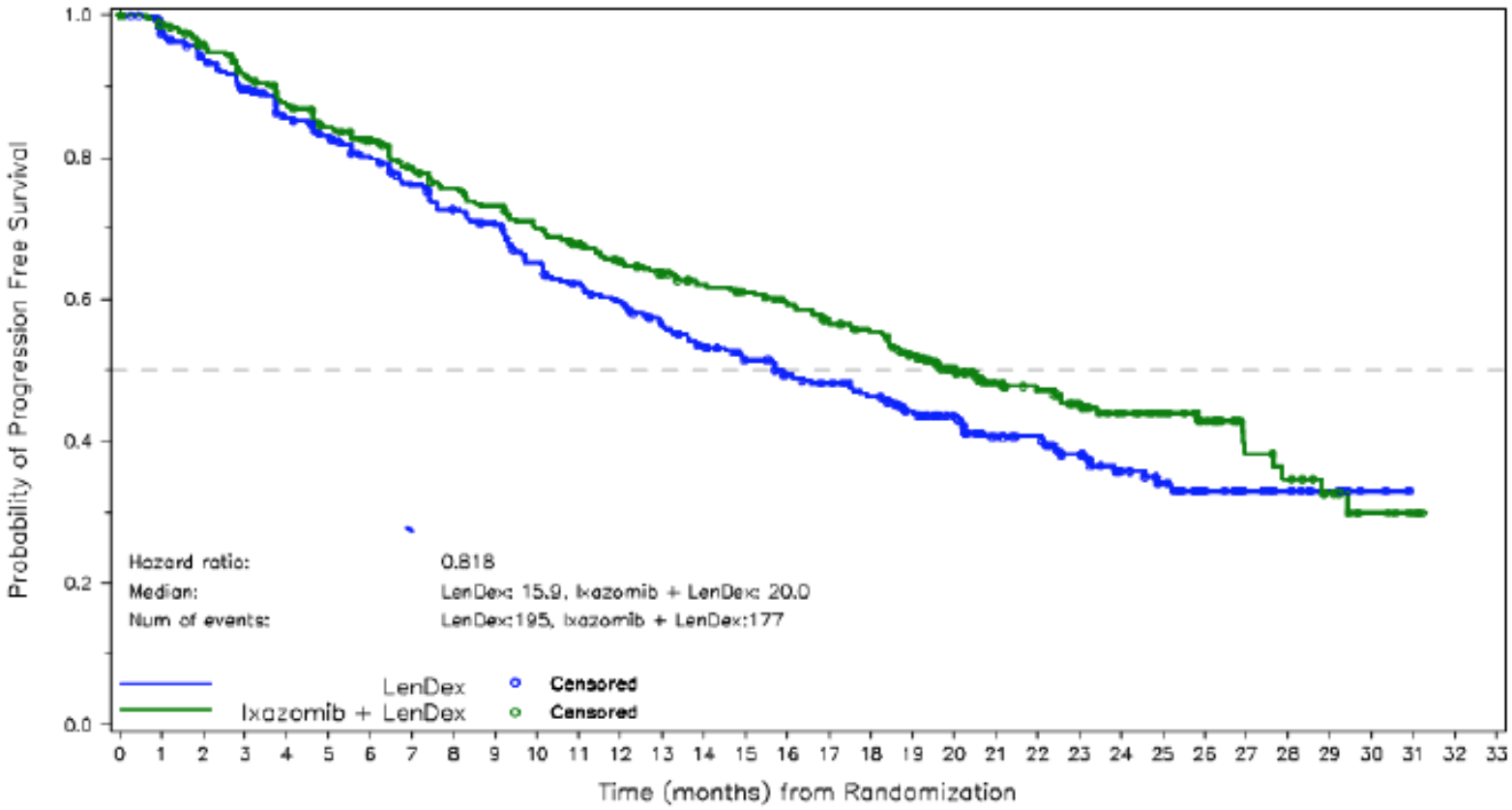


D. Postmus *et al*. The Oncologist 2017

Applied to the recently approved oral proteasome inhibitor ixazomibc

Table of effects in benefit-risk assessments

Figure 4 Kaplan-Meier Plot of Progression-Free Survival (IRC Assessments)—ITT



Number of Patients at Risk

LenDex	362	340	325	307	287	275	262	246	232	225	206	195	186	172	160	147	136	131	123	107	94	75	66	55	43	35	22	15	12	6	2	0	0	0
Ixazomib + LenDex	360	343	330	312	298	282	272	255	244	236	225	216	203	194	184	178	170	162	155	138	115	90	81	71	61	50	37	24	20	14	7	4	0	0

Applied to the recently approved oral proteasome inhibitor ixazomibc

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Unfavourable effects				
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Moderate but chronic toxicity	Probability of experiencing mild to moderate side-effects for two months or longer	%	60%	53%

Is the B/R balance of the new treatment positive or negative?

Importance of the effects Ranking – Trade-offs

Table of effects in benefit-risk assessments

Imagine that you are on a treatment that has all of the following effects
Probability of surviving 12 months = 50 %
Probability of experiencing severe side effects = 80%
Probability of experiencing of moderate side effects = 45%
You are given the opportunity to upgrade the performance of treatment on one of these outcomes.

Which of the following options would you prefer?

- ☒ Increasing probability of surviving 12 months from 50% to 90%
- ☐ Decreasing probability of experiencing severe side effects from 80% to 20%
- ☐ Decreasing probability of experiencing moderate side effects from 85% to 45%

Consider the following treatments:

Treatment 1:
Probability of surviving the first 12 months = 50%
Probability of severe effects = 20%

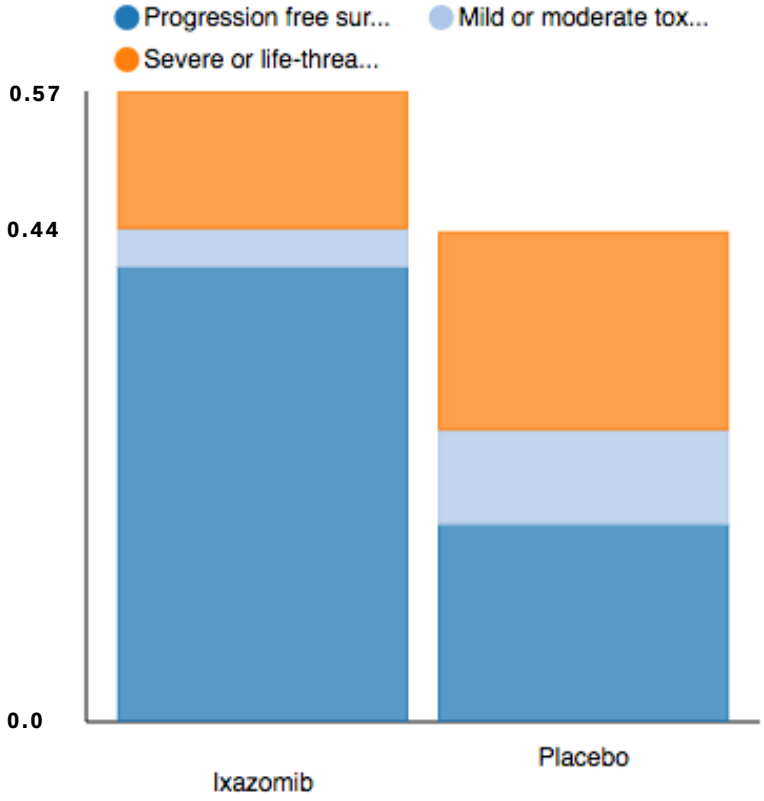
Treatment 2:
Probability of surviving the first 12 months = 60%
Probability of severe effects = 80%

Which of the treatments would you prefer?

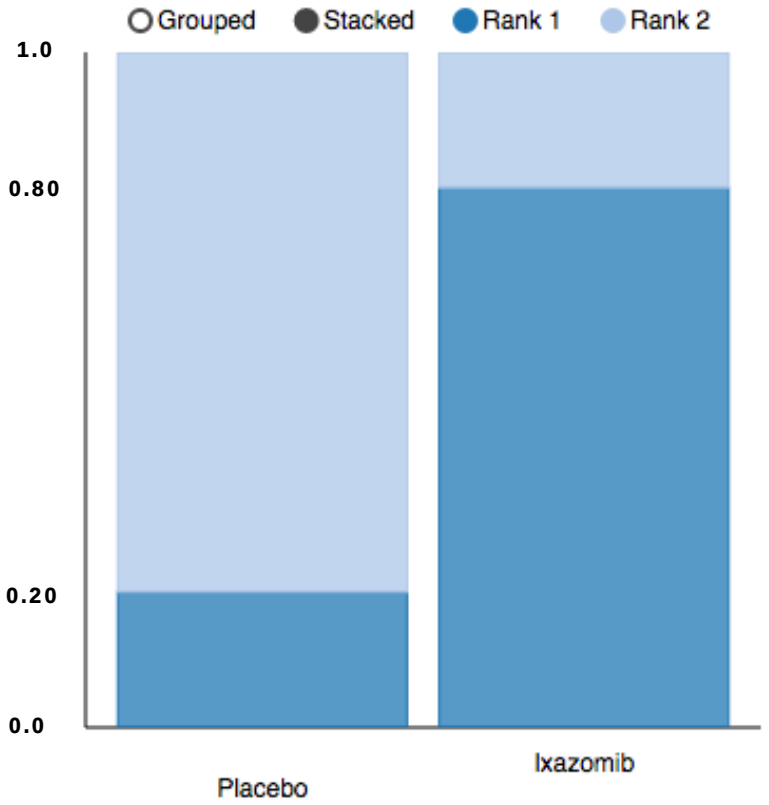
- ☐ Treatment 1
- ☒ Treatment 2
- ☐ Both treatments are equally desirable

Applied to the recently approved oral proteasome inhibitor ixazomibc

Table of effects in benefit-risk assessments

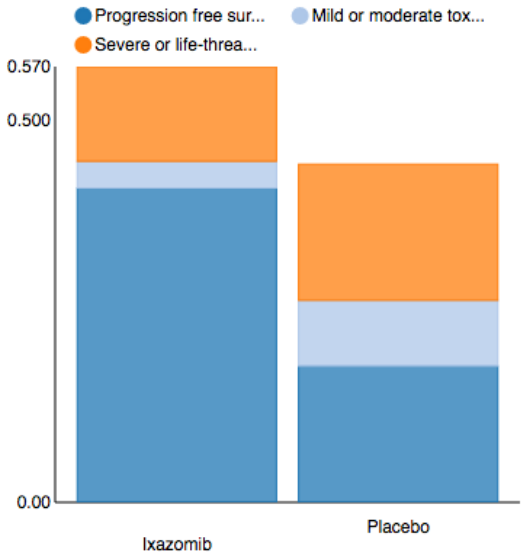


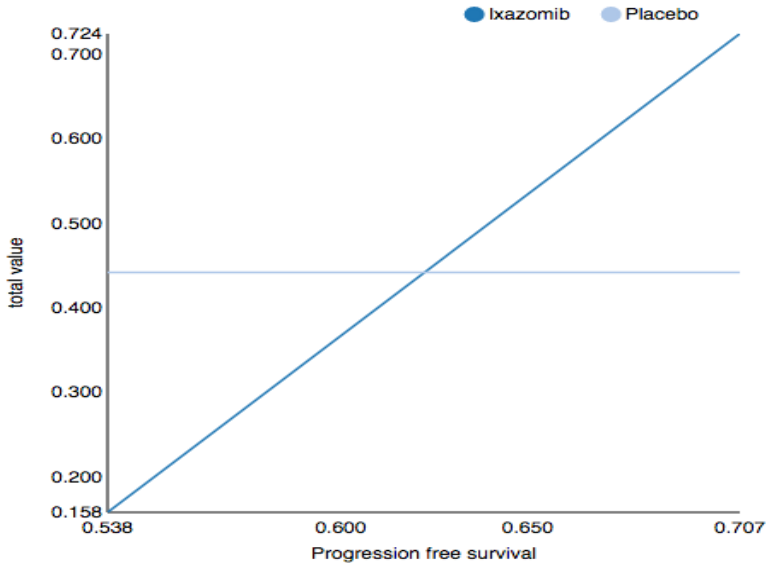
How the total value of each alternative is composed out of each value for each criterion

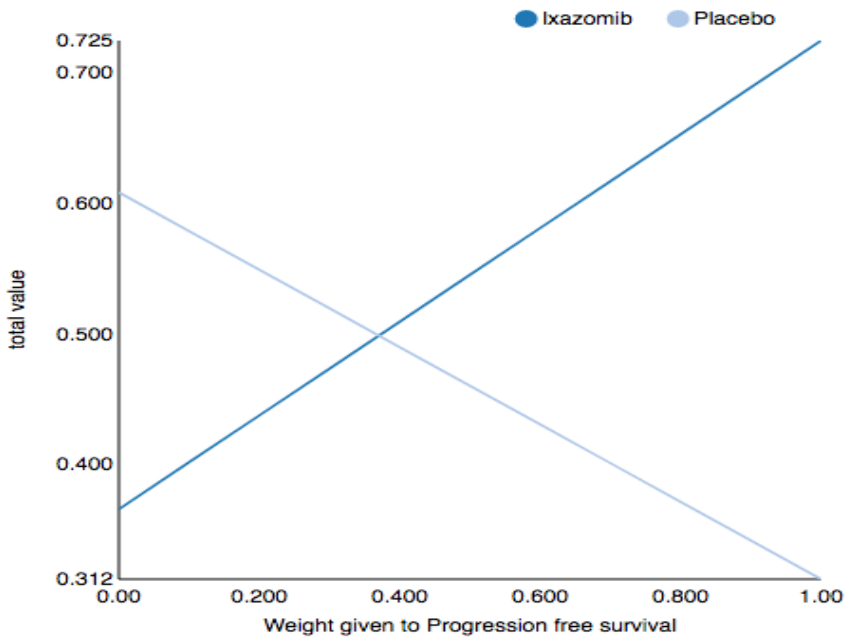


How likely each intervention is to overall be the best, worst based on the SMAA model results for the given preferences and data.

One-way sensitivity analysis







Concluding remarks (I)

Table of effects in BR assessments :

- adds transparency
- improves consistency in data presentation
- creates the possibility to make value judgements more explicit
- ensures quality of decision making

Concluding remarks (II)

- (Patient) Preference information:
  - might be helpful in regulatory decision making in situations where the balance of benefits and risks is not self-evident
  - could change the weight of benefits and risks as judged by the regulatory authorities, leading to different decisions regarding approval of medicines
  - could lead to the identification of subgroups of patients with homogeneous preferences and, as a result, to market authorization or reimbursement decisions that will be tailored to such subgroups
- Are we there, we are improving but not yet; Who, What, Why, When, Where, How, How Much?

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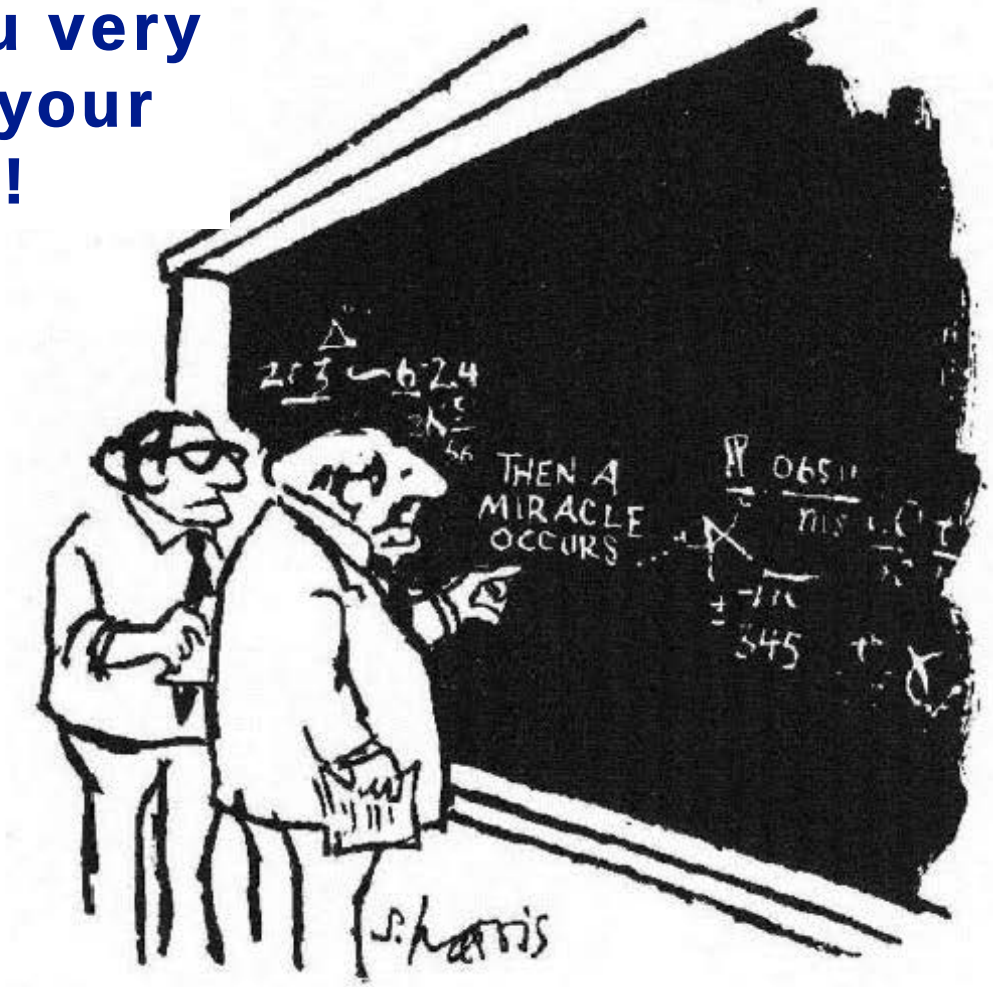
Then a Miracle Occurs

Thank you very much for your attention !



"I think you should be more explicit here in step two."


C B G
M E B

Reminder

In the mind's eye

"Subjectivity is inescapable in all phases of clinical research: planning, execution, analysis and reporting.

The ultimate subjectivity is in the interpretation of published data".

J.P. Van der Broecke NTvG 1996; 14: 220-1

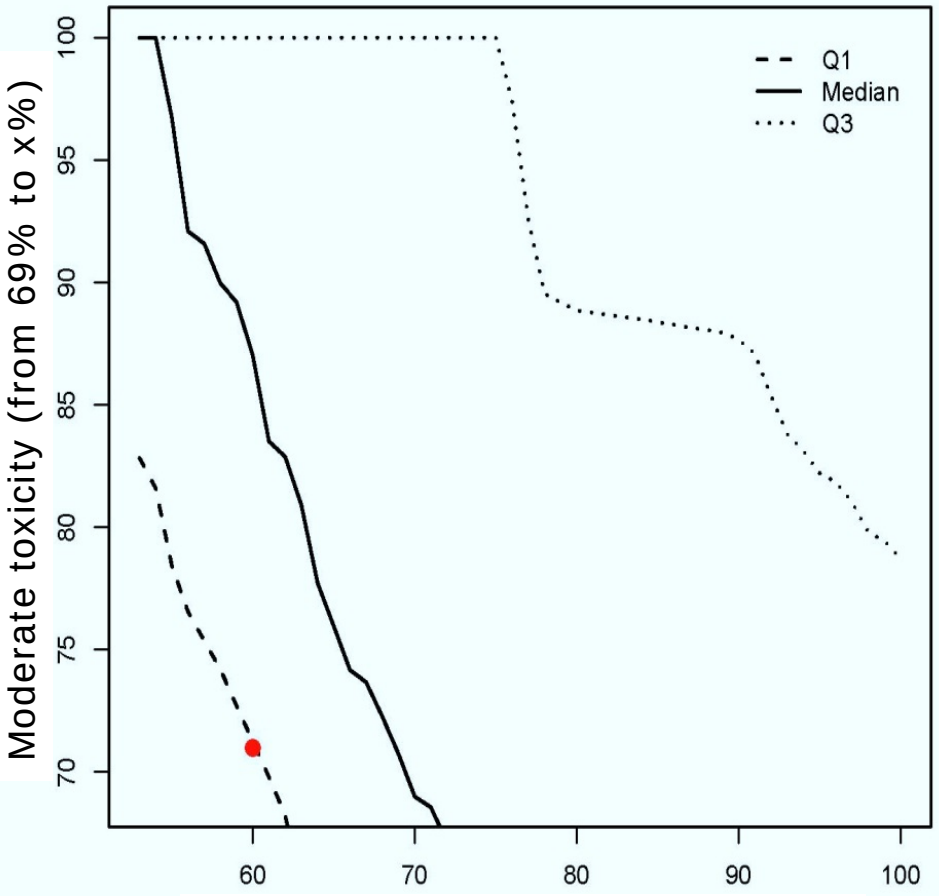
Application example

Table of effects in benefit-risk assessments

Attribute	Experi-mental	Placebo
1-yr PFS	66%	59%
G 1-2 chronic	71%	69%
G 3-4	60%	53%

SMAA: The proportion of patients ranking the experimental regimen above the placebo regimen was 76%

Max. acceptable Risk for an increase in 1-year PFS from 59% to 66%



Abbreviations: SMAA, Stochastic multi-criteria acceptability analysis.

Proportion of patients ranking ixazomib lower than the standard regimen stratified for time of diagnosis

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