Simple approaches for portfolio quantitative decision-making

18 June 2024 – PSI conference

Gaëlle Saint-Hilary (Saryga)
Hugo Hadjur (Saryga)
Jean-François Collin (Ceva)
Véronique Robert (Daiichi-Sankyo Oncology)

SARYGA
STATISTICS & METHODOLOGY

Outline

- Introduction
- Probability of success and Net Present Value
- Prediction of Marketing Authorizations over time

Without financial considerations

- Portfolio risk-value profile
- Discussion

SARYGA
STATISTICS & METHODOLOGY

Introduction

Quantitative Decision-Making is increasingly used in the pharma industry

- Many questions → many methods
- **Evidence-based** methods
- Statistical methods permit to incorporate **uncertainties**
- **Subjectivity** can be incorporated (but should also be challenged)

SARYGA
STATISTICS & METHODOLOGY

Decisions at different levels in drug development

Study level

- Choice of the dose range, therapeutic scheme, ….
- Population, design (sample size, control arms, duration)
- Stop/continue at interim analyses
- Operational aspects (recruitment projections, number of events, ….)

Development level

- Strategy: indication, population, number of studies, timing of the studies
- Go/No Go at strategic milestones
- Due diligences
- Global project value assessment

Portfolio level

- Strategy: Go/No Go and selection of development projects
- Financial resource allocation
- Return-On-Investment evaluation

SARYGA
STATISTICS & METHODOLOGY

Outline

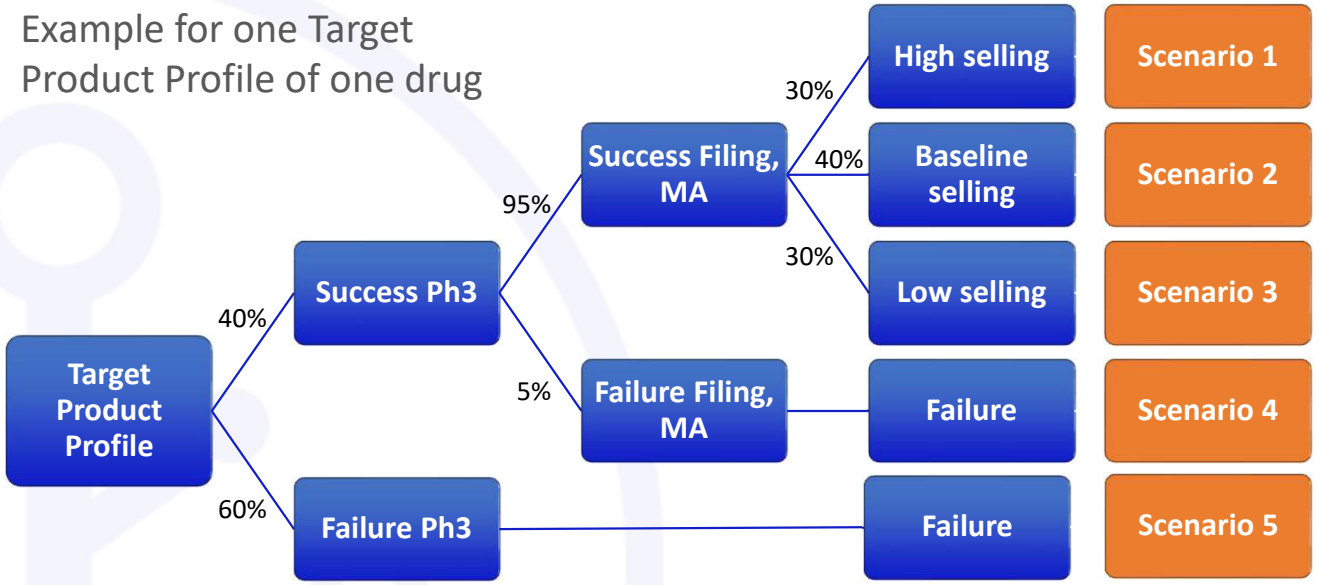
- Introduction
- **Probability of success and Net Present Value**
- Prediction of Marketing Authorizations over time
- Portfolio risk-value profile
- Discussion

Without financial considerations

SARYGA
STATISTICS & METHODOLOGY

Net Present Value (NPV)

Example for one Target Product Profile of one drug



	Probability	NPV (M€)	Probability x NPV
Scenario 1	11.4%	30	3.42
Scenario 2	15.2%	25	3.8
Scenario 3	11.4%	20	2.28
Scenario 4	2%	-10	-0.2
Scenario 5	60%	-8	-4.8

eNPV = 4.5 M€

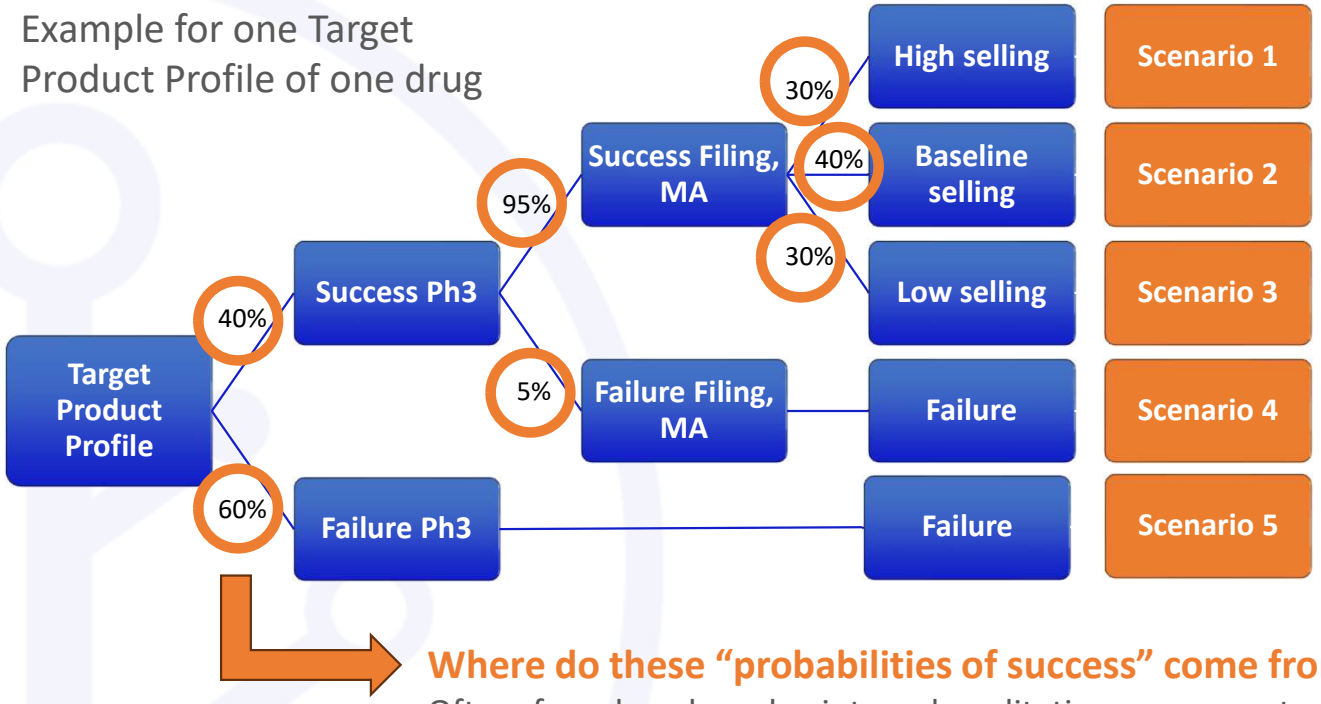
(= 3.42 + 3.8 + 2.28 – 0.2 – 4.8)

NPV = diff between present value of future returns and amount of future investment
eNPV = expected NPV (averaged over probabilities of scenarios)
Portfolio NPV = sum of all Project's NPV

SARYGA
STATISTICS & METHODOLOGY

Net Present Value (NPV)

Example for one Target Product Profile of one drug



	Probability	NPV (M€)	Probability x NPV
Scenario 1	11.4%	30	3.42
Scenario 2	15.2%	25	3.8
Scenario 3	11.4%	20	2.28
Scenario 4	2%	-10	-0.2
Scenario 5	60%	-8	-4.8

eNPV = 4.5 M€

(= 3.42 + 3.8 + 2.28 – 0.2 – 4.8)

Where do these "probabilities of success" come from?

Often: from benchmark + internal qualitative assessment

NPV = diff between present value of future returns and amount of future investment

eNPV = expected NPV (averaged over probabilities of scenarios)

Portfolio NPV = sum of all Project's NPV

SARYGA
STATISTICS & METHODOLOGY

Probability of Success

- In the past, Probabilities of Success used to be based on **industry benchmark and subjective assessment** only
  - Usually provide limited (and sometimes unreliable) information

- More and more, **"evidence-based" Probabilities of Success** are calculated by statisticia
  - Based on **prior knowledge** rather than on questionable hypotheses
  - Expert elicitation and industry benchmark could be combined with prior data
  - PoS are updated with the accumulation of knowledge from trial to trial
  - The scenarios (= definitions of success) should be agreed with the project team

A New Comprehensive Approach to Assess the Probability of Success of Development Programs Before Pivotal Trials

Programs Before Pivotal Trials

Lisa V. Hampson[1,*], Björn Holzhauer[1], Björn Bornkamp[1], Joseph Kahn[2], Markus R. Lange[1], Wen-Lin Luo[2], Pritibha Singh[1], Steffen Ballerstedt[1] and Giovanni Della Cioppa[3]

Hampson's approach to PoS calculation is certainly the most achieved and complete one in the pharma industry…

… but necessitates a substantial amount of resources

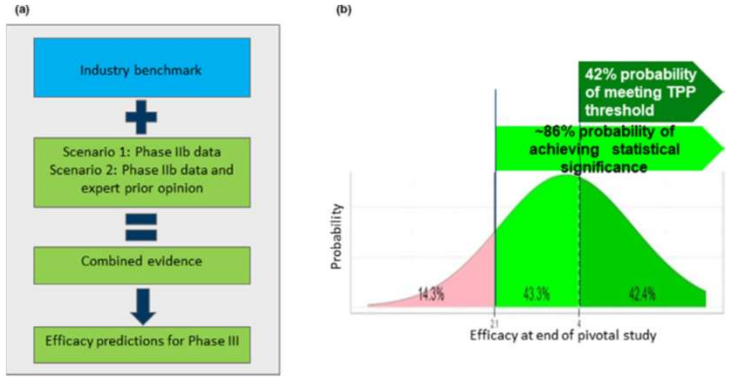
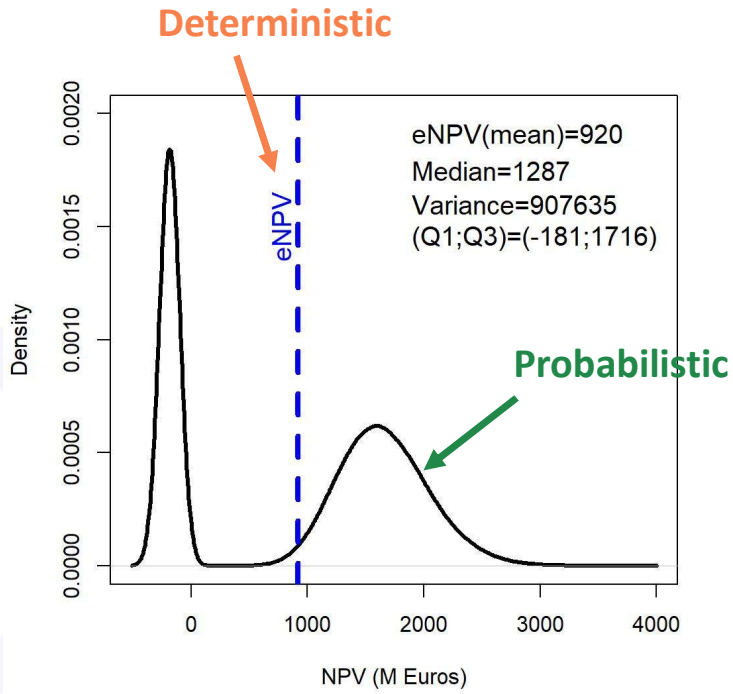


Figure 2 (**a**) A schematic of the Bayesian approach used to calculate the probability of efficacy success in phase III. (**b**) An example of how we can use simulation to assess the probability of observing different phase III outcomes. TPP, Target Product Profile. [Colour figure can be viewed at wileyonlinelibrary.com]

SARYGA
STATISTICS & METHODOLOGY

Net Present Value (NPV)



Two-peaked NPV distribution and associated descriptive metrics for one fictive project

eNPV = 920 M€

But $Prob(NPV \in [eNPV - 10\%; eNPV + 10\%]) = 2\%$!

"Probabilistic" way to describe the NPV:

$Prob(NPV > 0\ M€) = 60\%$ "min value"
$Prob(NPV > 1000\ M€) = 58\%$ "target value 1"
$Prob(NPV > 2000\ M€) = 11\%$ "target value 2"

SARYGA
STATISTICS & METHODOLOGY

Outline

- Introduction
- Probability of success and Net Present Value
- **Prediction of Marketing Authorizations over time** *Without financial considerations*
- Portfolio risk-value profile
- Discussion

SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time

- Objective: estimate the probability to reach a target number of Marketing Authorizations (MAs) over time

- Fictive example
  - Portfolio of 76 projects in 4 therapeutic areas (Oncology, Neurology, Immunology, Cardiology)

SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time
Method: simulation of 100 000 portfolios

Data

Project	TA	Date MA	Prob MA
A001	Immuno	2025-03	72%
B002	Neuro	2030-10	81%
…	…		…
C003	Cardio	2029-05	72%
…	…		…
D004	Onco	2027-01	81%
…	…		…

Simulated data in N+5

Simulation 1		
Project	**TA**	**MA Yes / No**
A001	Immuno	No
B002	Neuro	Yes
…	…	…
C003	Cardio	Yes
…	…	…
D004	Onco	No
Total		**11**

72% chances to have a Yes
28% chances to have a No

Total number of MA for this simulated portfolio

MA = Marketing Authorization

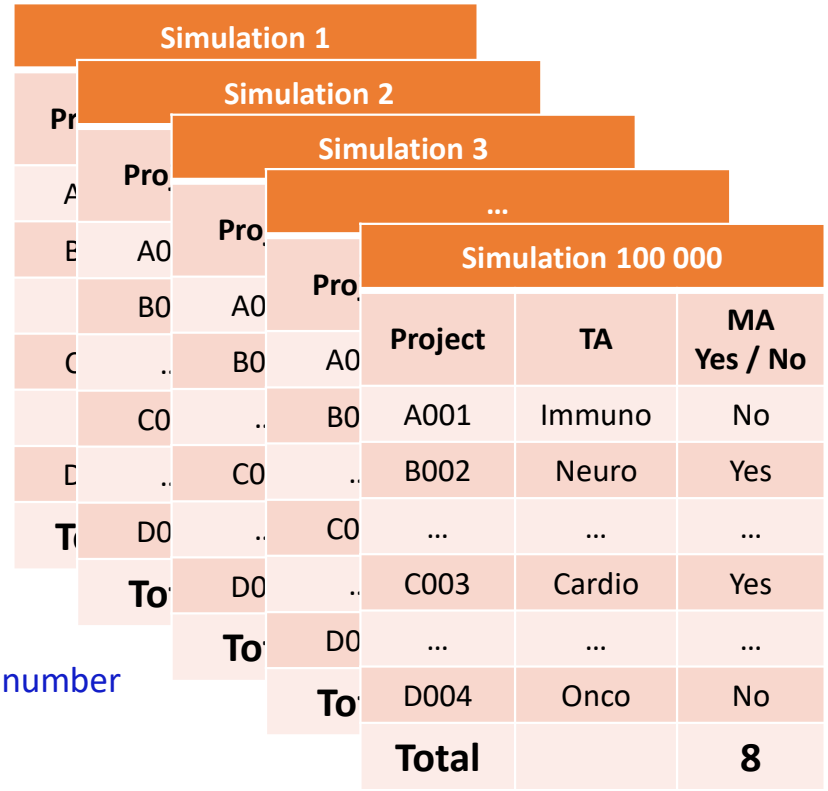
SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time
Method: simulation of 100 000 portfolios

Data

Project	TA	Date MA	Prob MA
A001	Immuno	2025-03	72%
B002	Neuro	2030-10	81%
…	…		…
C003	Cardio	2029-05	72%
…	…		…
D004	Onco	2027-01	81%
…	…		…

Simulated data in N+5



Simulations: permit to assess the variability of the number of MAs (uncertainty)

→ **Descriptive statistics on the number of MAs**:

- Mean, Median, Variance, Confidence Intervals…
- Prob(≥ x MAs) at different time points

MA = Marketing Authorization

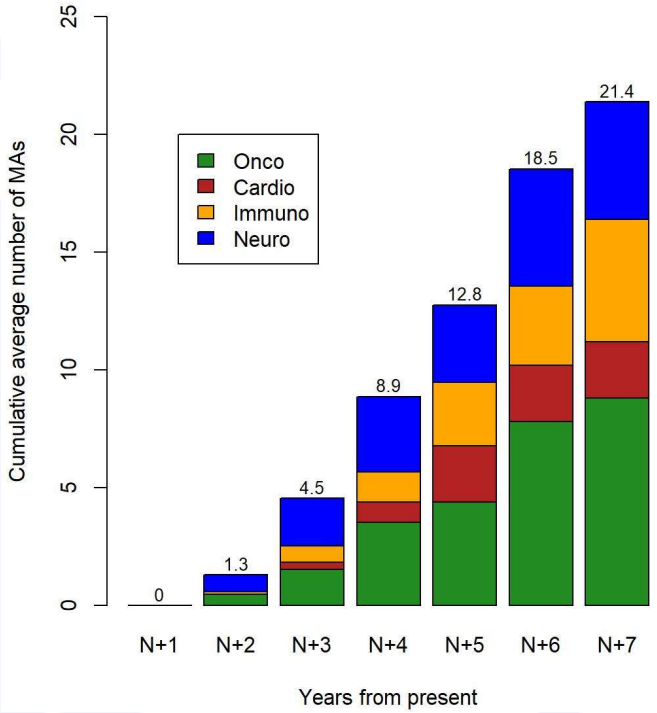
SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time

Fictive example: results

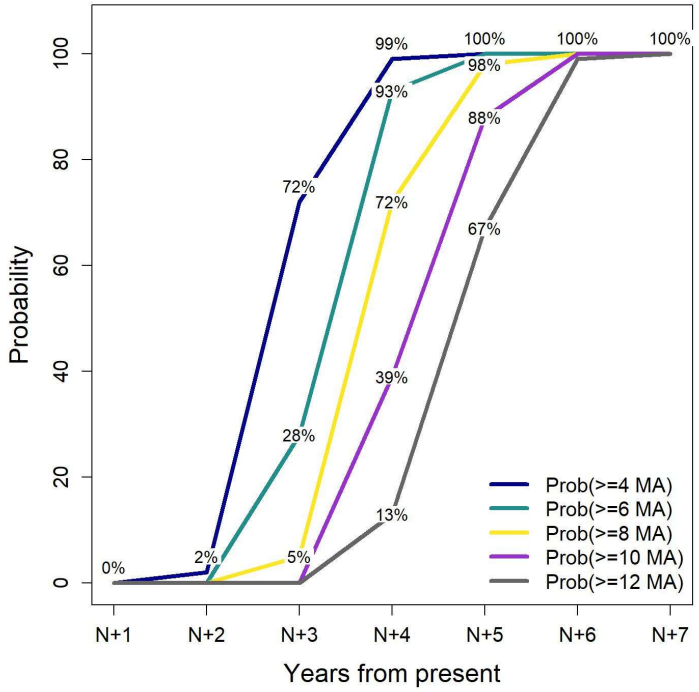
Portfolio: 76 projects

Deterministic



Cumulative average number of marketing authorisations per year

Probabilistic



Prediction of the number of marketing authorisations over time

MA = Marketing Authorization

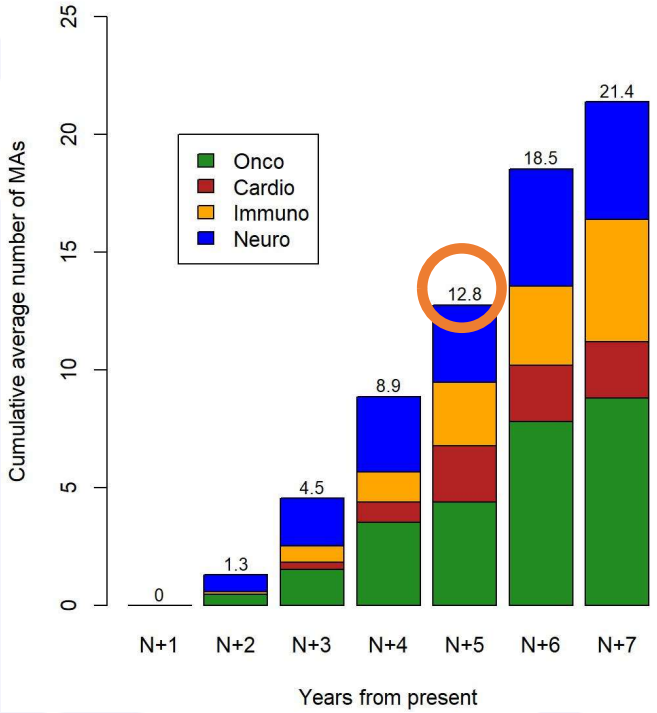
SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time

Fictive example: results

Portfolio: 76 projects

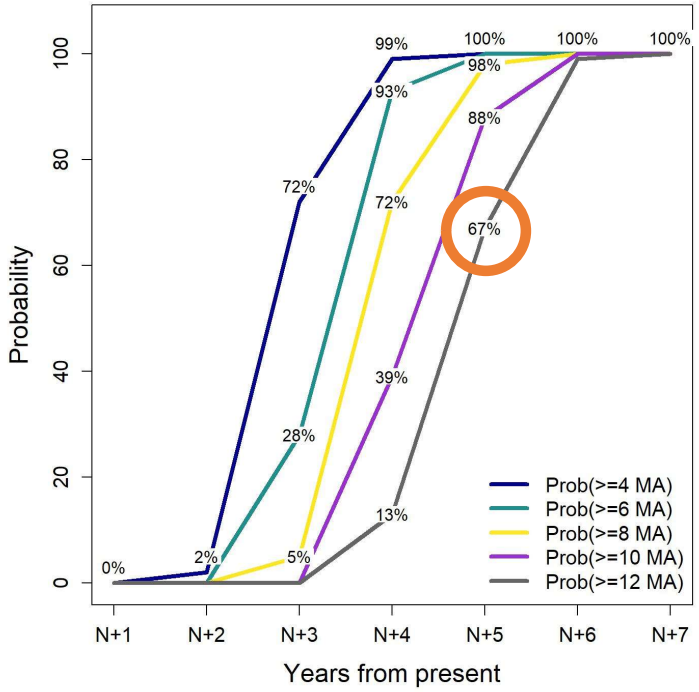
Deterministic



Cumulative average number of marketing authorisations per year

Within 5 years
Average number of MA = 12.8
< 67% chance to reach it!

Probabilistic



Prediction of the number of marketing authorisations over time

MA = Marketing Authorization

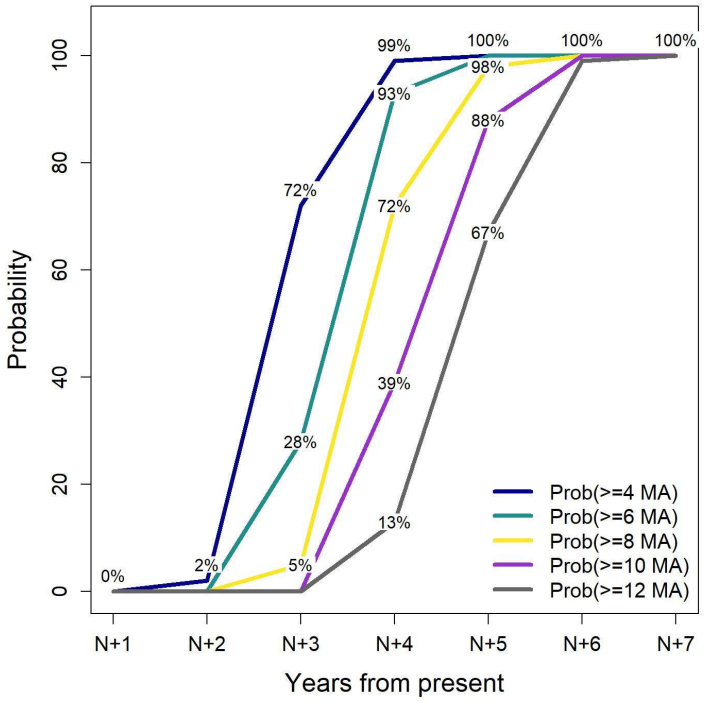
SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time

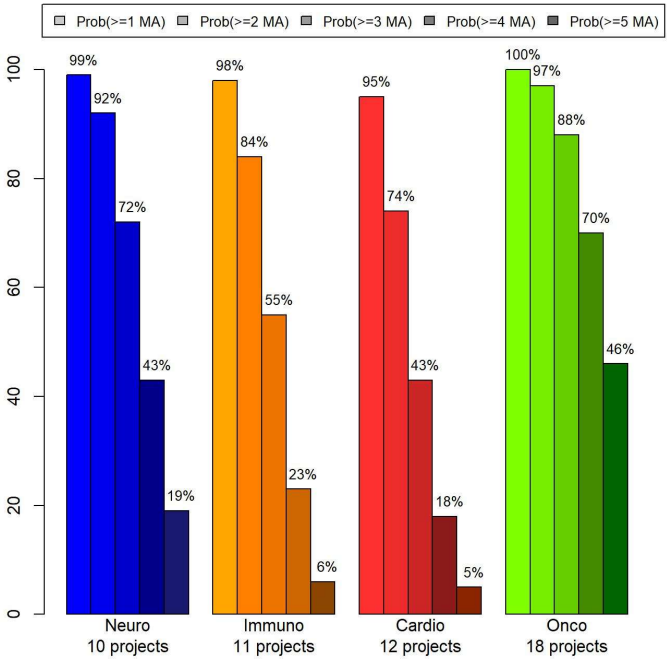
Fictive example: results

Portfolio: 76 projects

All 76 projects, over time



By therapeutic area, in N+5



MA = Marketing Authorization

SARYGA
STATISTICS & METHODOLOGY

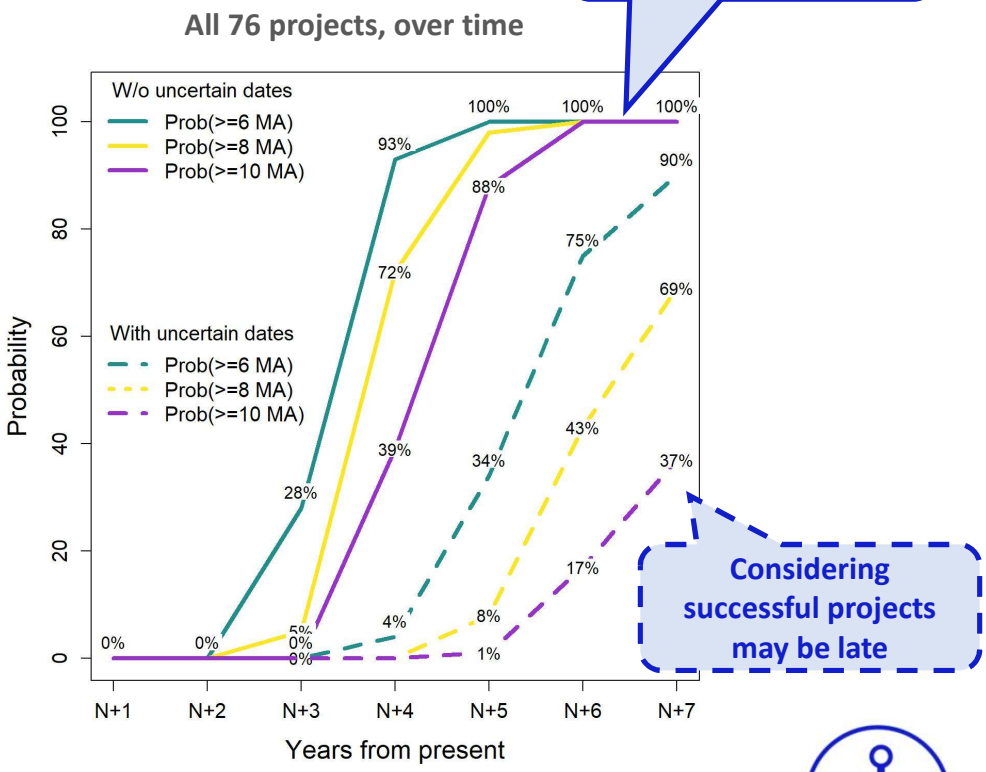
Prediction of the number of Marketing Authorizations over time

Fictive example: results

Portfolio: 76 projects

Data, with uncertain MA dates

Project	TA	Target date MA	Prob On Time	Prob 1y late	Prob 2y late	Prob MA
A001	Immuno	2025-03	90%	10%	0%	72%
B002	Neuro	2030-10	70%	20%	10%	81%
…	…					…
C003	Cardio	2029-05	30%	40%	30%	72%
…	…					…
D004	Onco	2027-01	50%	25%	25%	81%
…	…					…



Considering all successful projects will be on time

Considering successful projects may be late

MA = Marketing Authorization

SARYGA
STATISTICS & METHODOLOGY

Prediction of the number of Marketing Authorizations over time

- Permits to **identify potential weaknesses**, by therapeutic area and overall, and to **trigger action plans** (licensing-in, partnerships)

- Increasingly used in the Pharma industry

- **Simple approach**
  - Monte-Carlo simulations (no complex model)
  - No need for a large amount of data (only time of MA and probability of MA for each project in the portfolio)

- Same predictions are possible for other milestones, other criteria (e.g. turnover over time)

SARYGA
STATISTICS & METHODOLOGY

Outline

- Introduction
- Probability of success and Net Present Value
- Prediction of Marketing Authorizations over time

Without financial considerations

- **Portfolio risk-value profile**
- Discussion

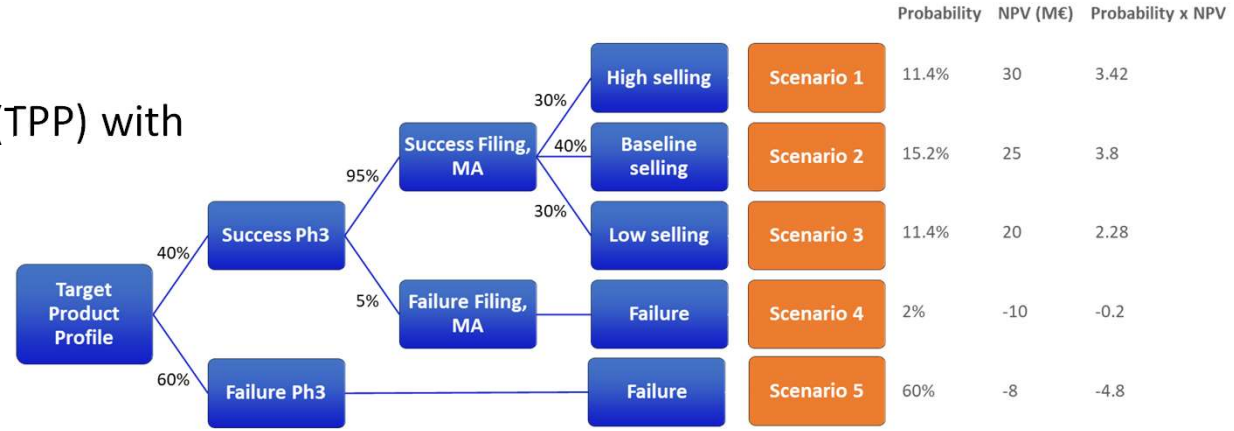
SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

Objective and Data

- **Objective: simulate the financial sustainability of the portfolio and compare different portfolios**
  - Calculate the probabilities to have **Portfolio Net Present Value (NPV) > pre-specified targets**

- **Data for each project:**
  - One or several Target Product Profiles (TPP) with
    - Probability of selection
  - For each TPP, several scenarios with
    - Probability of occurrence
    - NPV



NPV = diff between present value of future returns and amount of future investment

Portfolio NPV = sum of all Project's NPV

SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

Method: simulation of 100 000 portfolios

Data

Project	TPP	Prob TPP	Scena -rio	Prob scenario	NPV (M€)
A001	1	100%	1	18%	27
A001	1	100%	2	36%	26
…	…	…	…	…	…
B002	2	20%	3	14%	-20
…	…	…	…	…	…
E005	1	100%	1	73%	104
…	…	…	…	…	…

Simulated portfolios

Simulation 1			
Project	TPP	Scena-rio	NPV (M€)
A001	1	1	27
B002	2	3	-20
…	…	…	…
E005	1	5	-14.7
…	…	…	…
F006	1	1	104
Total			**413**

Random simulation 18% chances to have an NPV=27 M€ for Project A001

Portfolio NPV = sum of all Project's NPV

SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

Method: simulation of 100 000 portfolios

Data

Project	TPP	Prob TPP	Scena -rio	Prob scenario	NPV (M€)
A001	1	100%	1	18%	27
A001	1	100%	2	36%	26
…	…	…	…	…	…
B002	2	20%	3	14%	-20
…	…	…	…	…	…
E005	1	100%	1	73%	104
…	…	…	…	…	…

Simulated portfolios

Simulation 1

Simulation 2

Simulation 3

…

Simulation 100 000

Project	TPP	Scena-rio	NPV (M€)
A001	1	2	26
B002	2	3	-20
…	…	…	…
E005	1	5	-14.7
…	…	…	…
F006	1	1	104
Total			**543**

Simulations: permit to assess the variability of the Portfolio NPV (uncertainty)

→ **Descriptive statistics on the Portfolio NPV**:

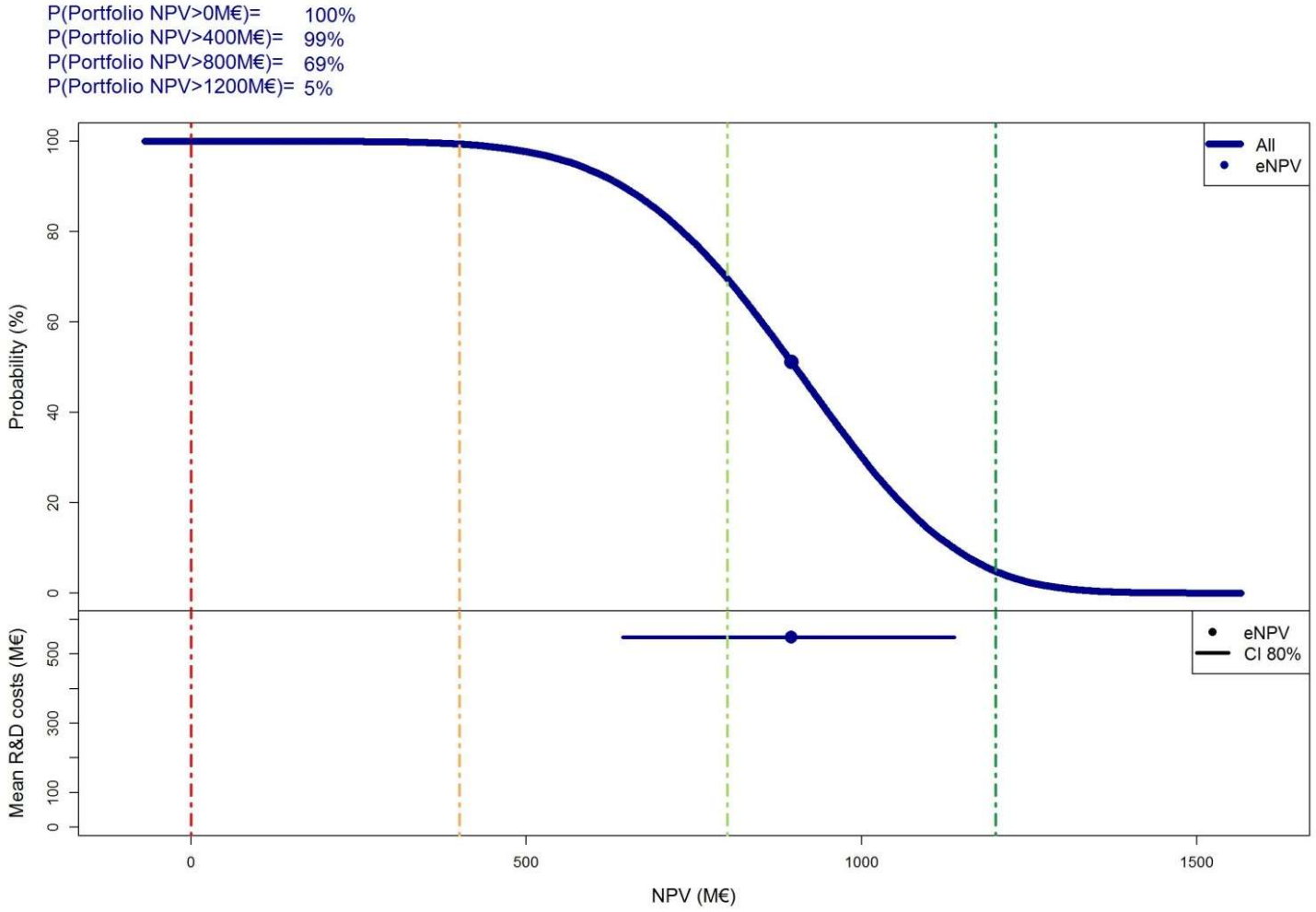
- Mean (=eNPV), Median, Variance, Confidence Intervals…
- Prob(Portfolio NPV > target)

SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

Fictive example: results for all projects

(% obtained in 100 000 simulated realizations of the portfolio)

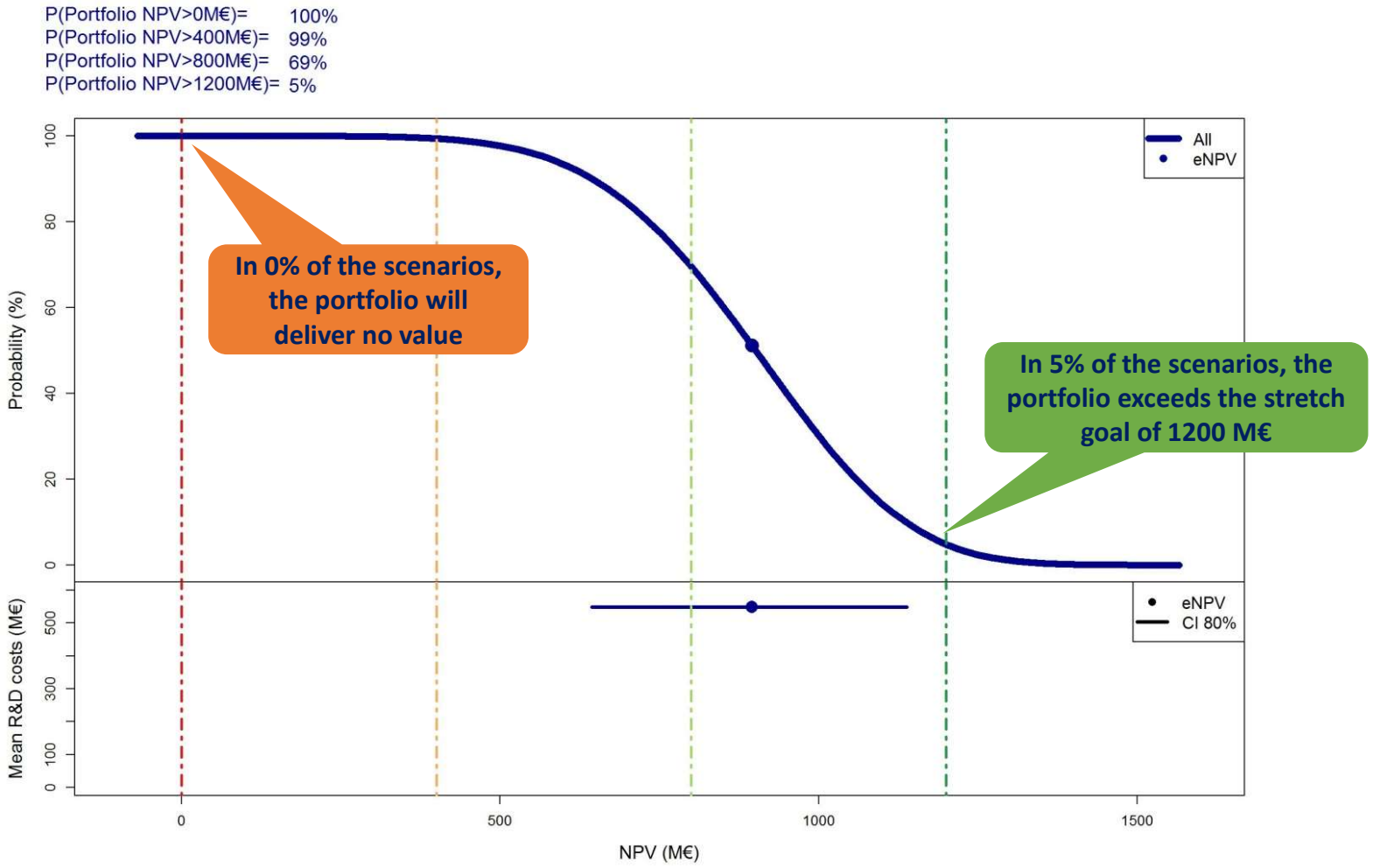


SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

Fictive example: results for all projects

(% obtained in 100 000 simulated realizations of the portfolio)

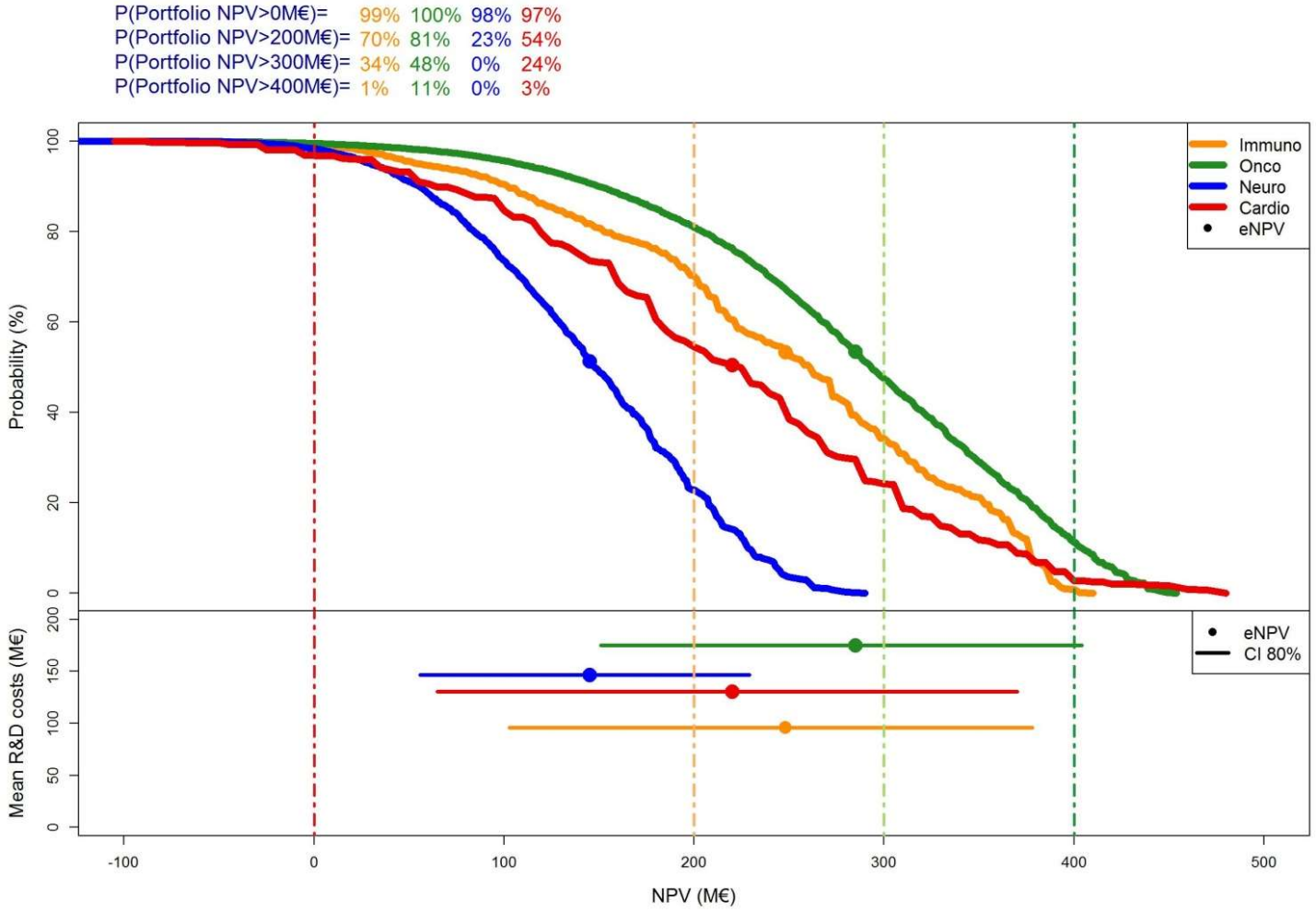


SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

Fictive example: results by therapeutic area

(% obtained in 100 000 simulated realizations of the portfolio)



SARYGA
STATISTICS & METHODOLOGY

Portfolio risk-value profile

- Permits to **identify potential weaknesses**, by therapeutic area and overall, and to **trigger action plans** (licensing-in, partnerships)

- **Relatively simple approach**
  - Monte-Carlo simulations (no complex model)
  - No need for a large amount of data

- **Warning**: ideally, all NPVs should be calculated at the same time, just before the analysis – may be difficult to achieve in practice…

SARYGA
STATISTICS & METHODOLOGY

Outline

- Introduction
- Probability of success and Net Present Value
- Prediction of Marketing Authorizations over time

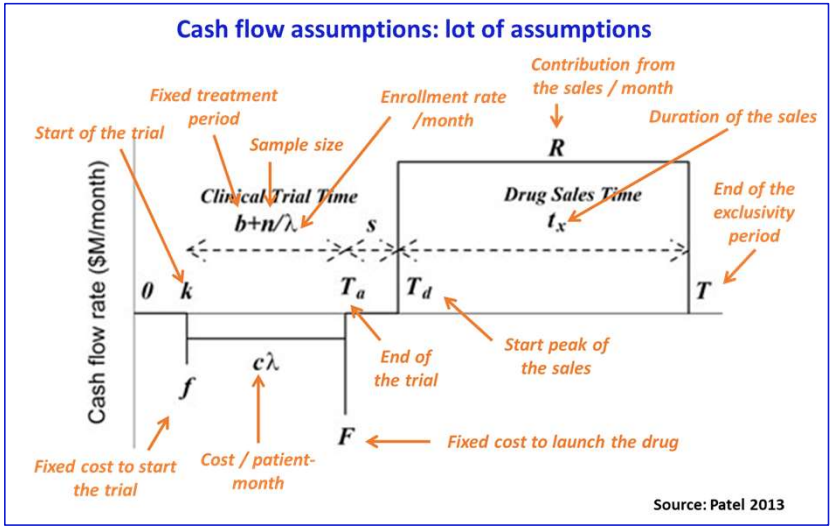
Without financial considerations

- Portfolio risk-value profile
- **Discussion**

SARYGA
STATISTICS & METHODOLOGY

A more sophisticated method: portfolio optimization

- Maximizes the **value of a portfolio** under a **global budget constraint**
  - Better than optimizing each drug separately
  - Optimizes the variables that have the greatest impact on the costs: sample size and timing
- **Complexity**
  - Lots of data as input
  - Lot of assumptions: high level of uncertainty
    → importance of sensitivity analyses
  - Challenging communication with governance boards
- Focus on the **financial** value of the portfolio
  - Lack of clinical considerations?



- Need knowledge of experts from different teams (statistics, finance, strategy, regulatory affairs…)

SARYGA
STATISTICS & METHODOLOGY

Conclusion

- Quantitative Decision-Making is increasingly used in the pharma industry
  - Many questions → many methods
  - Evidence-based methods avoid relying on questionable assumptions
  - Subjectivity can be incorporated but should also be challenged
  - Statistical methods permit to incorporate uncertainties
- Quantitative tools are intended to support but not to replace the human decision-making process for strategic decisions
- Importance of sensitivity analyses
- Statisticians are the right person to initiate and drive the discussions around quantitative decision making
  - Interactions between statisticians and multi-disciplinary teams

SARYGA
STATISTICS & METHODOLOGY

Main references

- Hampson LV, Bornkamp B, Holzhauer B, et al. Improving the assessment of the probability of success in late stage drug development. Pharmaceutical Statistics. 2022; 21(2): 439-459. doi:10.1002/pst.2179
- Hampson, L.V., Holzhauer, B., Bornkamp, B., Kahn, J., Lange, M.R., Luo, W.-L., Singh, P., Ballerstedt, S. and Cioppa, G.D. (2022), A New Comprehensive Approach to Assess the Probability of Success of Development Programs Before Pivotal Trials. Clin Pharmacol Ther, 111: 1050-1060. https://doi.org/10.1002/cpt.2488
- Antonijevic Z. Optimization of Pharmaceutical R&D Programs and Portfolios. Springer International Publishing Switzerland, 2015.
- Thunecke M and Elze C. Commentary. Risk Profiles of Corporate Portfolio Strategies – A Perspective for the Pharmaceutical Executive, 2014. https://catenion.com/wp-content/uploads/2021/11/Catenion-Commentary-Risk-Profiles_20142.pdf
- Patel NR, Ankolekar S, Antonijevic Z and Rajicic N (2013), A mathematical model for maximizing the value of phase 3 drug development portfolios incorporating budget constraints and risk. Statist. Med., 32: 1763-1777. doi:10.1002/sim.5731
- Wiklund S-J, Thorn K, Götte H, Hacquoil K, Saint-Hilary G and Carlton A. Going beyond probability of success: Opportunities for statisticians to influence quantitative decision-making at the portfolio level. Pharmaceutical Statistics. 2024; 1-10. doi:10.1002/pst.2361

SARYGA
STATISTICS & METHODOLOGY