Go/ No-Go Decision-Making in Early Phase Development

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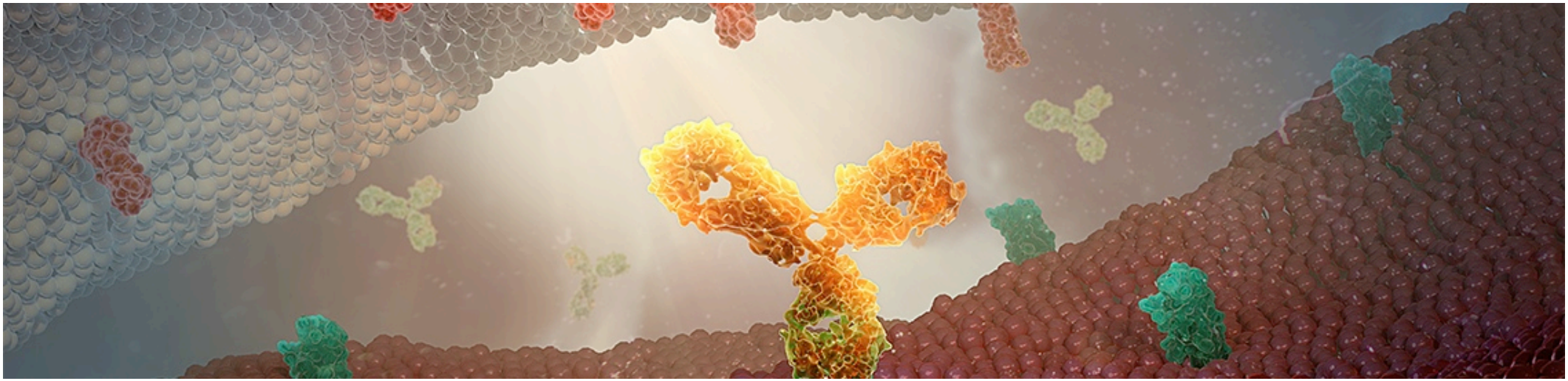


Drug Development Process

- Overall aim to create medicines that are effective and safe, providing clinical meaningful benefit with an appropriate benefit-risk ratio
- Highly innovative, cost-intense, cross-functional effort conducted within a continuously evolving regulatory framework in a highly competitive environment
- Iterative process spanning over years with defined decision gates
- Sponsors/ development teams aim to make optimal choices between several alternatives at multiple time points based on available internal and external evidence, also anticipating changes in the therapeutic landscape
- Sponsors have to make timely decisions at different levels, i.e. development team and portfolio level, at multiple time points based on accumulating internal and external evidence

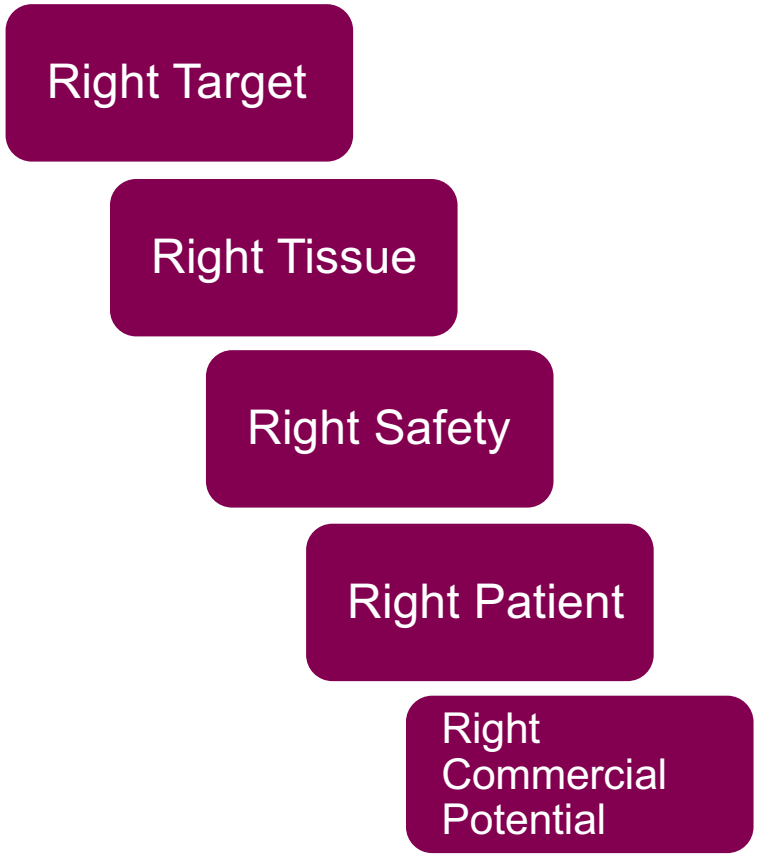
Principles of Decision Making – *"Right" or "Good"* Decision

- Decision challenge: future outcome of a decision *("good/ bad")* is not known
  - Build on science/ data – acknowledge uncertainty – apply good judgement
- Clear link between scientific question – method – results – decision & action
- Good decision is an informed choice, made in a transparent & consistent way, based on valid (but incomplete) data and applying judgement
- In clinical development, a good decision can be moving forward or terminating a program
- Decision-making frameworks guide good - decision - making

Good-Decision Making …

… continuing challenge for mankind …

Five-dimensional Framework on R&D Productivity at AstraZeneca



- 5Rs capture key technical dimensions and support teams to make optimal decisions at the right stage
- Allow teams to identify critical areas of risk that need to be addressed during development
- Provide a more objective assessment of a project within project team and with decision boards
- Facilitate open and constructive discussion of data, assumptions and risks
- Supports scientific quality, consistency, smart risk-taking, and good decision making
- Across organisations, quantitative Go/NoGo frameworks are an important element

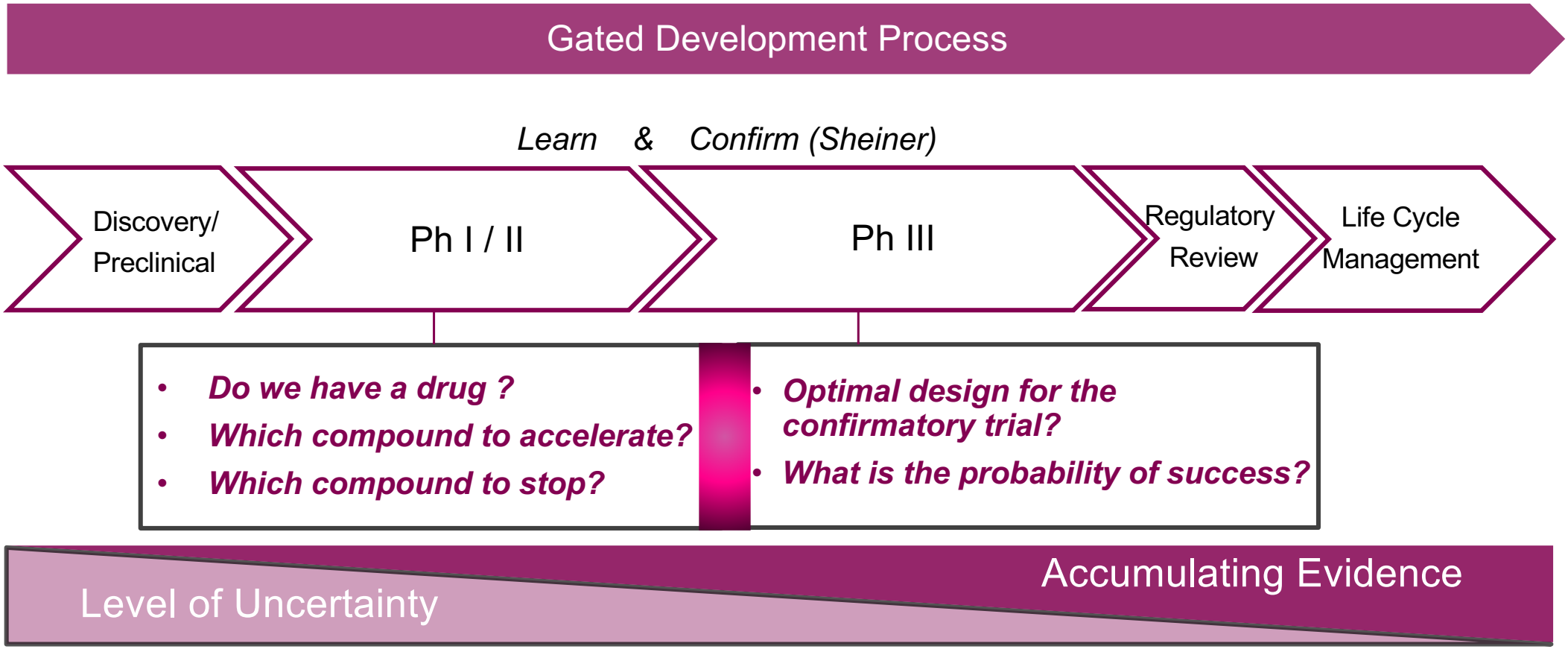
Builds on shared culture and mindset

Cook et. al. Nat Rev Drug Discovery 2014; Morgan et. al. Nat Rev Drug Discovery 2018

Quantitative Decision Making – Evidence Based Frameworks

- Apply quantitative statistical methods to inform decision-making
- Build on available evidence, i.e. trial data, competitor data, expert judgement, characterize uncertainty (probability) and link potential outcomes with a decision
- Areas for quantitative decision-making in clinical development include
    - Go/ no go Decision-Making
    - Probability of Success/ Clinical Assurance
    - Quantitative Benefit-Risk frameworks
- When applied during planning these frameworks make assumptions and underlying subjectivity visible and enable faster decision-making after results become available

Early & Late Phase Development – Different Questions to Answer



Lalonde et. al. Clin Pharm & Ther 2007; Sheiner Clin Pharm Ther 1997; Sabin et. al. Stat Biopharm Res 2014

Go/ NoGo Decision Framework in Early Phase Oncology at AstraZeneca

- Candidate-rich early phase portfolio requires focus on good decision-making at the point of investment decisions
- Use of a consistent approach to quantitative decision making for all early phase investment decisions, based on adaptation of a method initially proposed by Lalonde
- Key considerations:
  - Studies are designed with the decision in mind
  - Once results are available they are interpreted against the pre-agreed decision framework, so clear decisions can be made quickly
  - Framework focuses on one outcome, e.g. efficacy, pharmacodynamic markers, however multiple outcomes can be considered

Lalonde et. al. Clin Pharm & Ther 2007; Frewer et. al. Pharmceut Statist 2016

Go/ NoGo Decision Framework

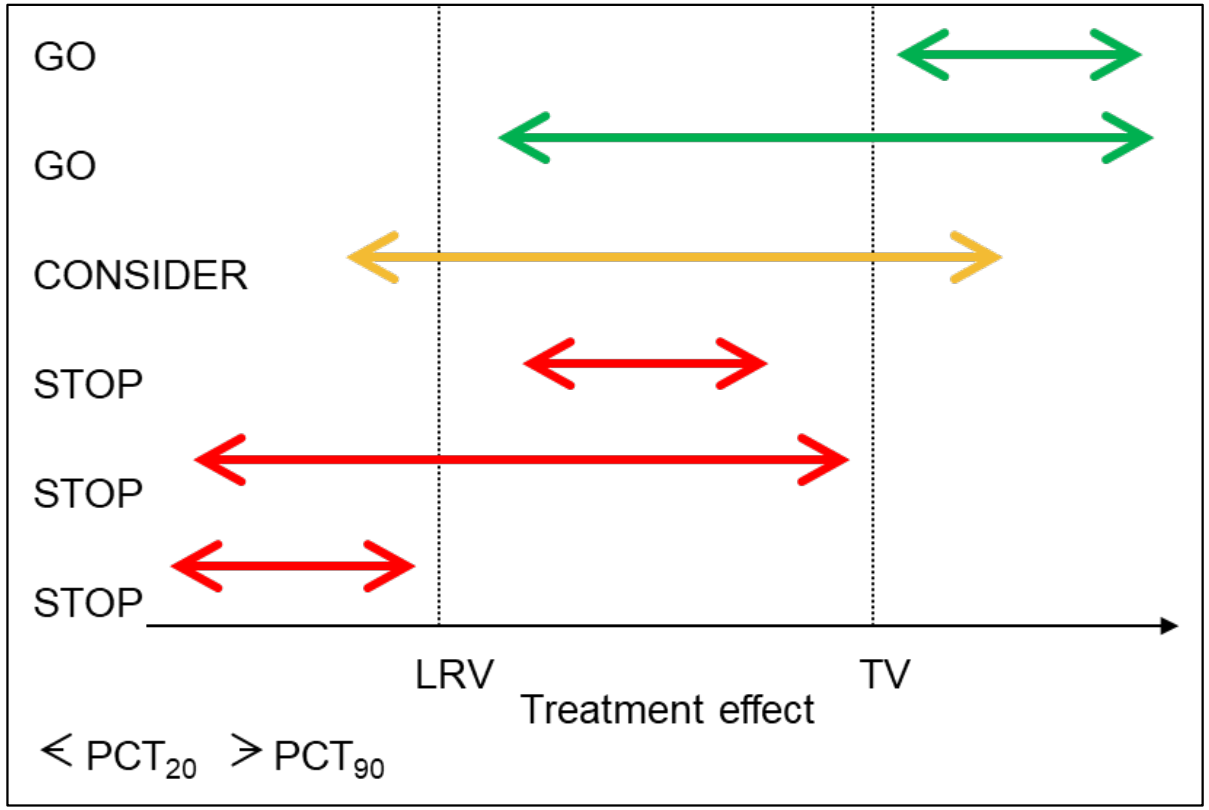
Three outcome decisions

Input parameters

Target Value (TV)	Desired level of performance
Lower Reference Value (LRV)	Minimal level of performance
False Stop Risk	Risk of a “Stop” decision if the truth is better than the TV (typically 10%)
False Go Risk	Risk of “Go” decision if the truth is at worse than the LRV (typically 20%)

The LRV and TV needed to be evidence based and scientifically justified, eg evidence from literature review, data from other compounds in the same area, medical opinion

Visualisation of the Framework



Go if : $PCT_{20} > LRV$ and $PCT_{90} > TV$

Consider if : $PCT_{20} \leq LRV$ and $PCT_{90} > TV$

Stop if : $PCT_{90} \leq TV$

where PCT_x denotes the x-th percentile of P (Δ)

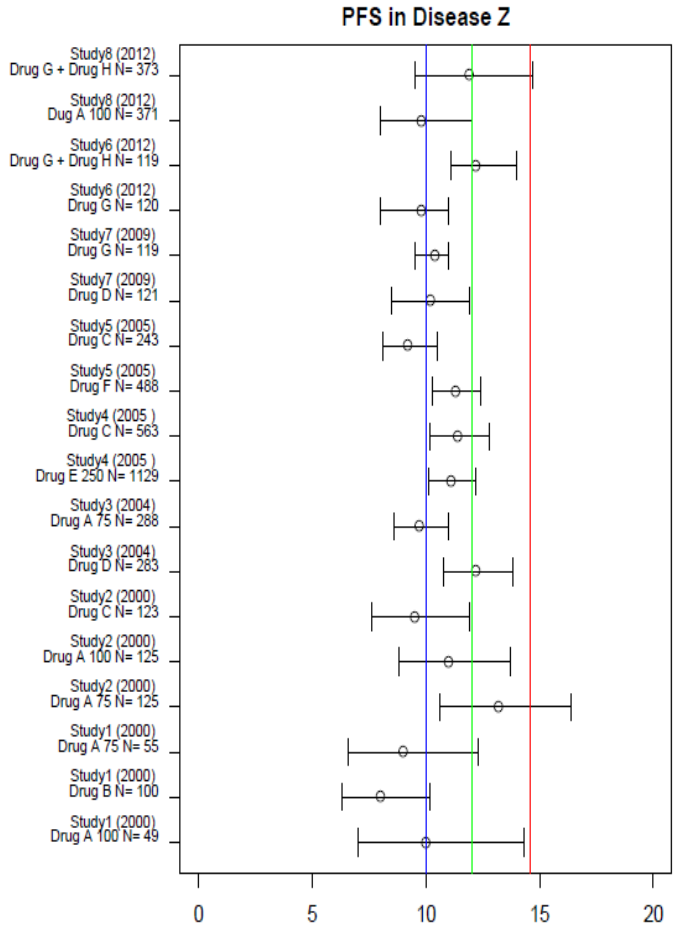
For the outcome 'Consider' additional information to be taken into consideration can be specified

The probability for 'Consider' should not exceed 30% as a standard

Example #1

- Randomized phase-2 study investigating drug ABC versus treatment standard
- Primary endpoint PFS
- The Target Product Profile included the following specifications
  - Base case: median PFS 10 vs. 14.6 mths (HR 0.68) → ***TV***
  - Downside case: median PFS 10 vs. 12 mths (HR 0.83) → ***LRV***

Evidence Base the Target Value and the Lower Reference Value



Target Product Profile (TPP)

Indication	Disease Z			
Claim/Description		**Standard Of Care**	**Min**	**Base**
Efficacy	**ORR**	X%	X%	X%
	Median PFS	10 mo	12 mo (HR 0.83)	14.6 mo (HR 0.68)
	Median OS	X mo	No detriment	Positive trend
Safety				

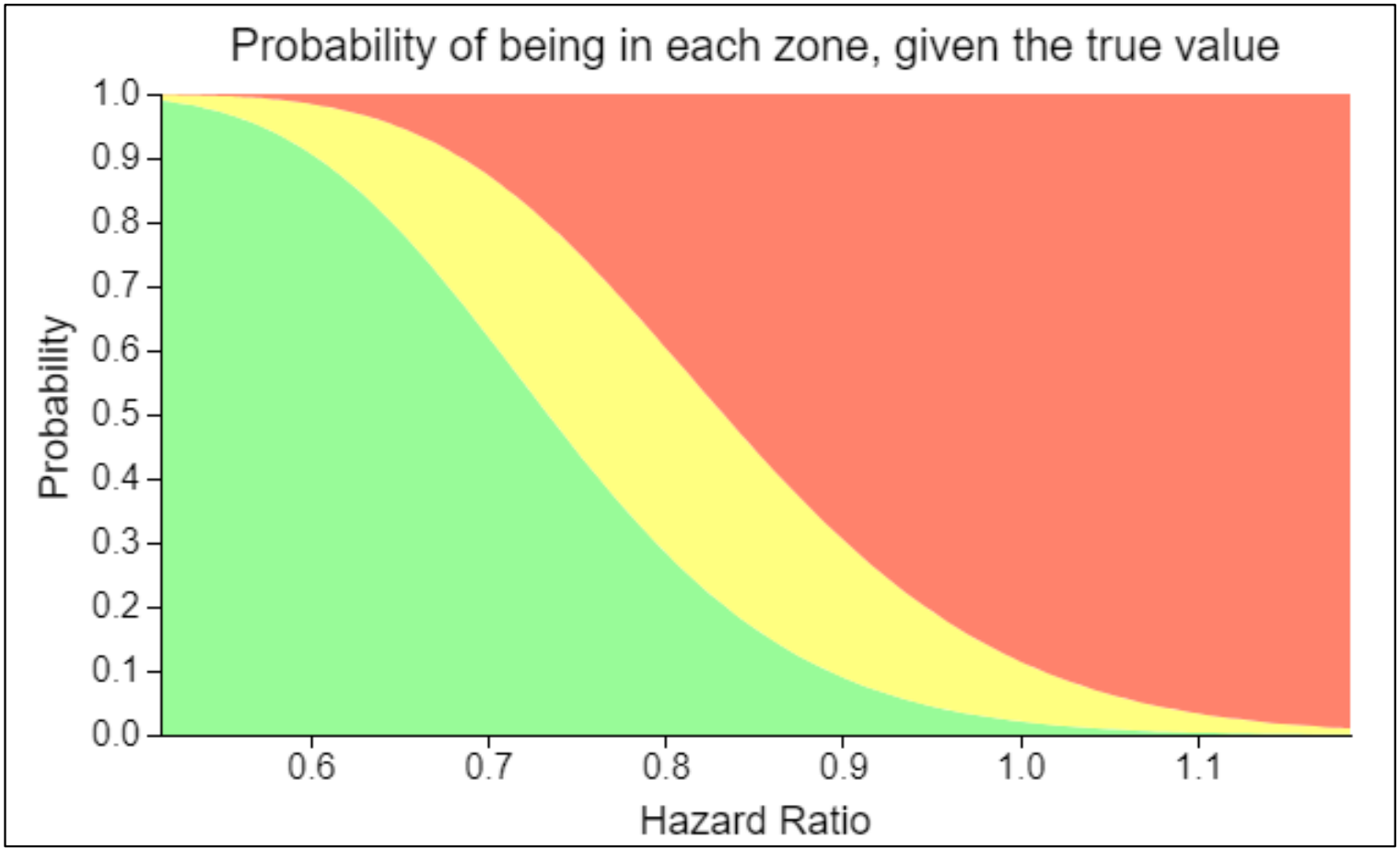
Operating Characteristics

- Enable evaluation of whether the framework is robust and will enable clear decisions or if the chance of being in the consider zone is too high
- What defines acceptable operating characteristics is open to interpretation; it depends not just on the risk but also other factors, length of time to obtain a decision

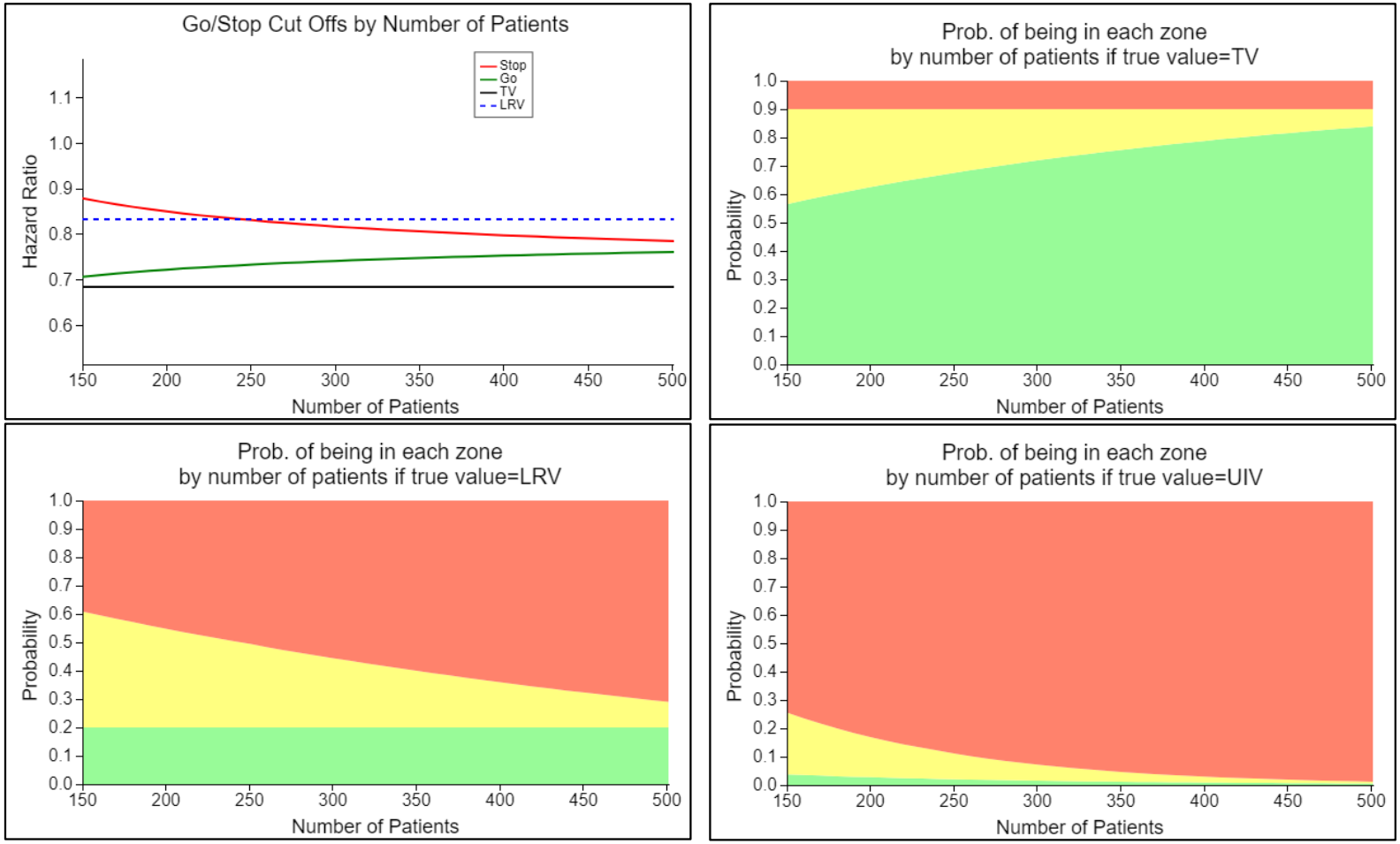
True effect	**Operating characteristics for a range of true effects assuming a false go risk of 20% and a false stop risk of 10% and 126 events (180 patients)**			**Operating characteristics for a range of true effects assuming a false go risk of 20% and a false stop risk of 10% and 173 events (248 patients)**		
	Probability of Making each Decision for a given True Effect			Probability of Making each Decision for a given True Effect		
	Go	Consider	Stop	Go	Consider	Stop
Good (TV; HR=0.68)	60.2%	29.8%	10.0%	67.3%	22.7%	10.0%
Reasonable (LRV; HR=0.83)	20.0%	37.2%	42.8%	20.0%	29.7%	50.3%
Minimal Effect (1/4 TV HR=0.90)	10.5%	30.4%	59.2%	9.3%	21.9%	68.8%
No Effect (HR=1)	3.1%	16.9%	80.0%	2.1%	9.3%	88.6%

HR, hazard ratio; TV, target value; LRV, lower reference value

Graphical Displays of Operating Characteristics

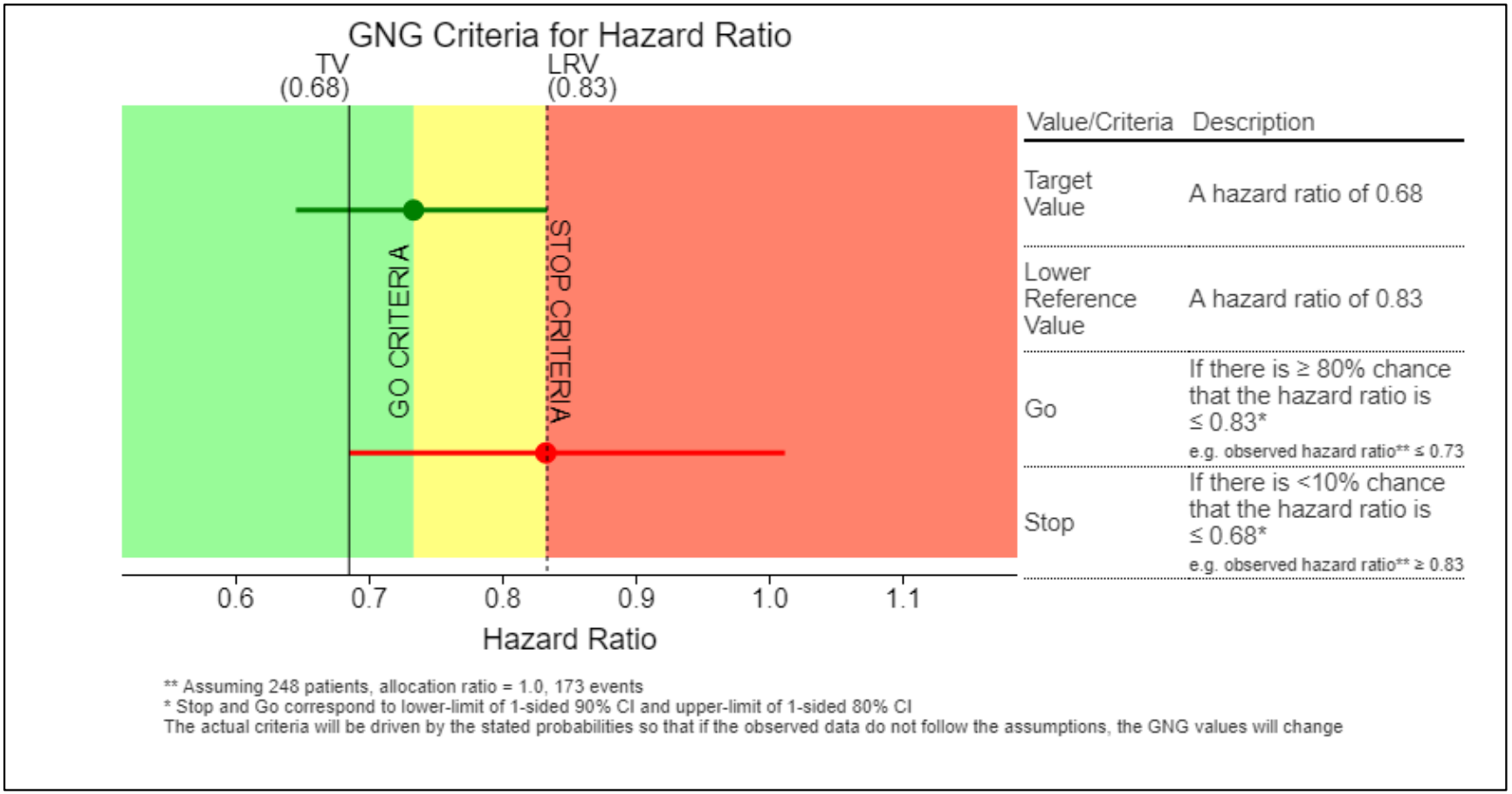


Operating Characteristics by Sample Size



Assumes data maturity of 70%, e.g. 150 patients have 105 events and 500 patients have 350 events, UIV=1

Decision Plot

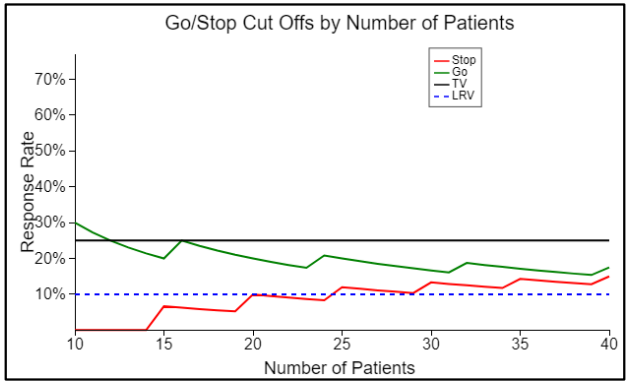


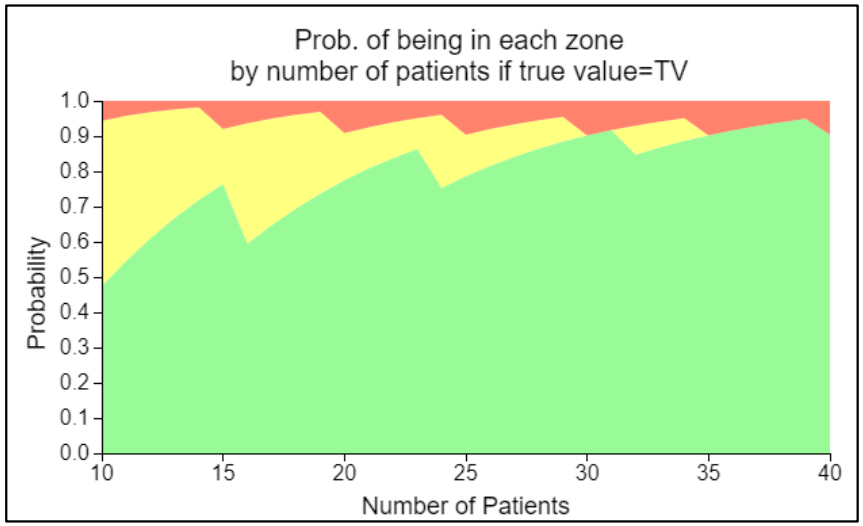
The sample size had been calculated to detect a Hazard Ratio=0.685 assuming 80% power and a 1-sided alpha=0.05

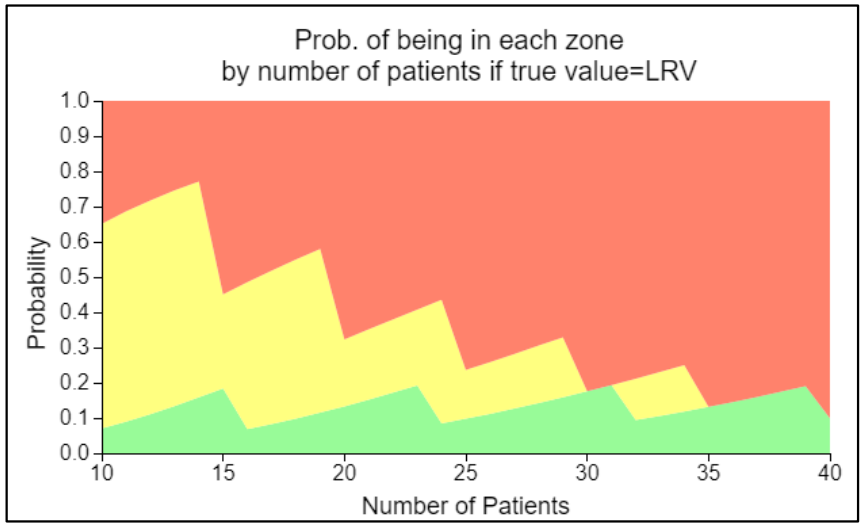
Example #2

- Expansion cohort in a phase 1/2a study
- Primary endpoint overall response rate (ORR)
- The development team decided after review of available evidence on the following TV and LRV
  - LRV: ORR 10%
  - TV: ORR 25%

Operating Characteristics by Sample Size: TV=25%, LRV=10%







Operating Characteristics by Sample Size: TV=25%, LRV=10%

Sample Size	Truth =TV (25%)			Truth =LRV (10%)		
	Go	Consider	Stop	Go	Consider	Stop
12	61%	36%	3%	11%	61%	28%
13	67%	31%	2%	13%	61%	25%
14	72%	26%	2%	16%	61%	23%
15	76%	16%	8%	18%	27%	55%
16	59.5%	34%	6%	7%	42%	51%
17	65%	30%	5%	8%	44%	48%
18	69%	27%	4%	10%	45%	45%
19	74%	23%	3%	11%	46%	42%
20	77%	13%	9%	13%	19%	68%
21	81%	12%	7%	15%	20%	65%
22	84%	10%	6%	17%	21%	62%
23	86%	9%	5%	19%	22%	59%
24	75%	21%	4%	9%	35%	56%
25	79%	12%	10%	10%	14%	76%

Highlighted cells are where the probability of a Go | TV is ≥60% and the probability a Stop | LRV is ≥50% (i.e. the consider zone probabilities are ~≤30%)

Interim Analyses

- The decision framework can also be used to set interim decision criteria. In general, interim analyses in early phase studies fall into two categories:

- Adaptive designs, where internal changes are made to the trial
  - Futility analyses – the current trial is stopped early if it is unlikely to be successful

- Non-adaptive designs, where changes are made externally to the trial
  - Administrative analyses – other project activities are accelerated (or decelerated) on the basis of interim data from the current trial, but the current trial is not changed, i.e. initiation of additional manufacturing runs, preparations for subsequent trials as per clinical development plan

Go/ NoGo Decision Making Experiences at AstraZeneca

- This decision framework has been used at AZ since 2013; the framework is embedded into AstraZeneca's R&D 5R-Framework
- Decision frameworks are now produced routinely within the teams as part of the design of all studies/ clinical development plans; teams are trained on its principles
- Governance approves the decision framework prospectively at the time of an investment decision
- Templates are in place for the statisticians to display the information in a consistent way across all projects in early oncology
- Decisions made are based on trial data against the previously agreed decision framework; decision consider totality of the data
- The statistician has a key role and partners with the medical function to develop the criteria; statistician can be the "team's conscience"

Conclusion

- Decision-making in drug development is a cross-functional effort
- Quantitative decision-making provides a transparent and consistent approach to define go/ no-go criteria, this includes the supporting evidence and underlying assumptions
- It requires from all team member general understanding of principles for good decision-making and a mindset embracing constructive debate
- Quantitative-decision-making should start when planning a study
- Teams should be clear on the question they aim to address and the action that is related to each of the three outcomes
- The statistician has a key role to guide the cross-functional team. The statistician and the physician/ clinical scientist work closely together to develop the criteria
- Quantitative decision-frameworks provide decision recommendations, the final decision has to be made considering the totality of the data