dECiDe: A dual target method for setting Go no Go criteria

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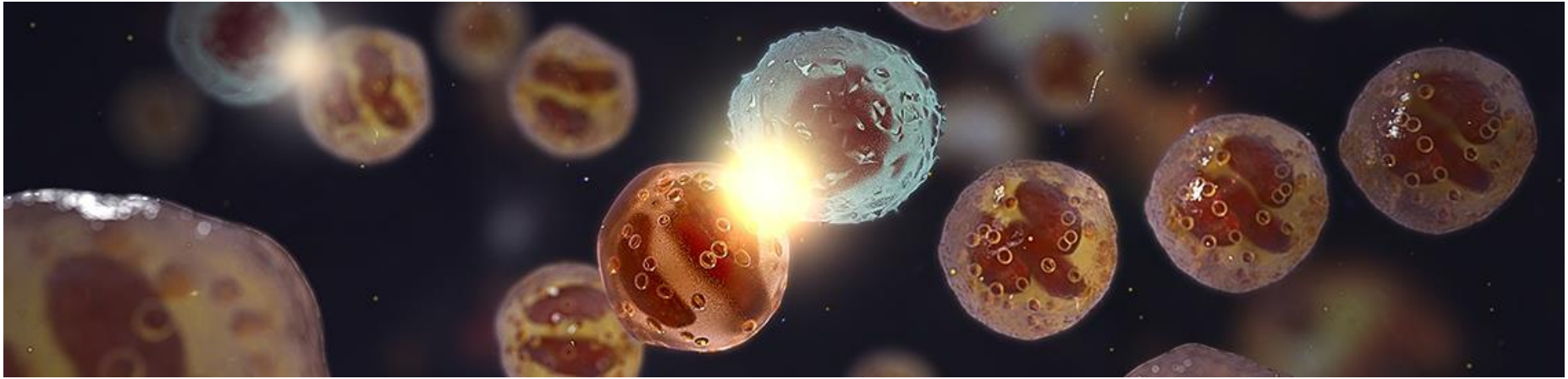


GNGs minimize time spent deciding

1. **Drug development time consuming and expensive.**
2. **Time is money so we need:**
    - Shorter development programs
    - More chances to make earlier decisions (to accelerate or stop)
    - More efficient processes to interpret data and make decisions

One approach: Frontload data interpretation as much as possible

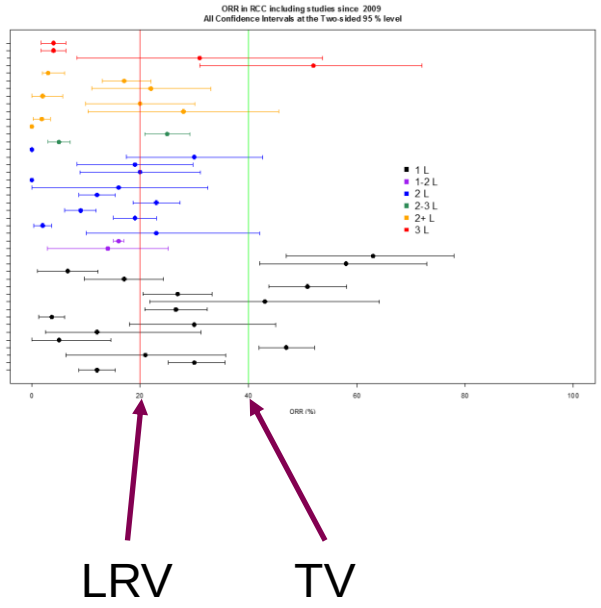
- Establish decision criteria during the design Phase
- Adoption of standardized method and presentation supports success

Decision criteria relate data to competition

Targets are set using competitive information either based on published results or established Target Product Profiles (Evidence based target setting)

Lower reference value (LRV) – The LRV is the smallest clinically meaningful treatment effect

Target value (TV) - desired effect to potentially establish the compound as the treatment of choice



Criteria are set using company tolerances and planning assumptions

1. **Acceptable risk that the truth is better than the TV given a stop decision is made: AR_TV**
   - Similar to False STOP error
2. **The desired confidence that the truth is better than the LRV given a go decision is made: DC_LRV**
   - Similar to 1 - False GO error

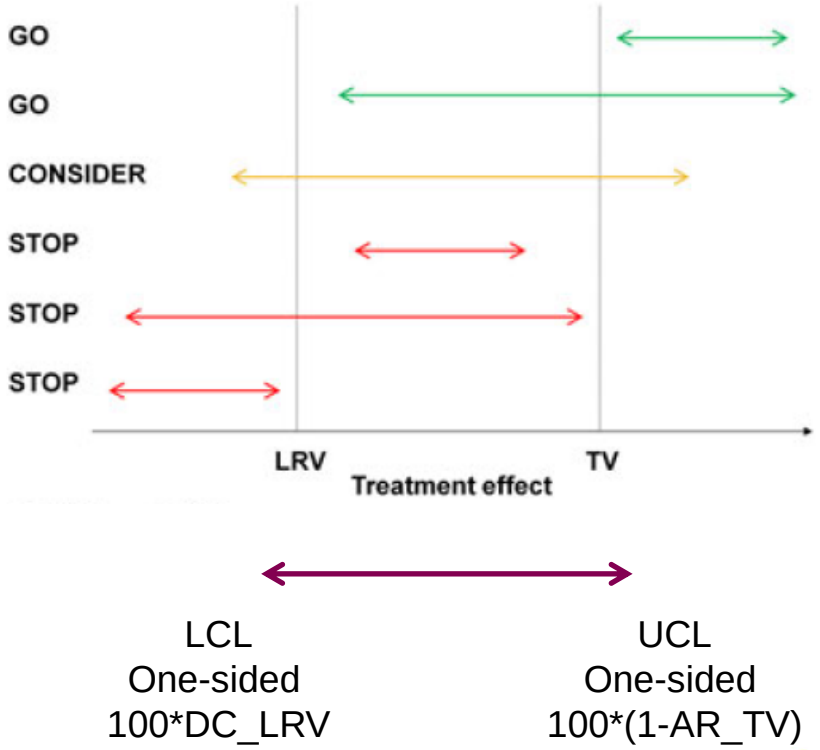
3. **Sample size and variability are also required**

Results interpretation is clear

1. **An unbalanced CI for the treatment effect can be used to compare against the targets**

2. **Alternatively, the decision criteria can be used directly comparing the treatment effect to the GO / No GO cirteria***

3. *** Assumes planning assumptions not grossly violated. Otherwise criteria should be recalculated.**



More decisive trials are better

1. **A decisive results are GO or STOP.**
2. **A CONSIDER result can be observed.**
3. **Decisive trials minimize chance of CONSIDER.**

4. **Trials with lower P(CONSIDER|TV or LRV) are better.**

5. **How low?**
   - Company tolerances
   - May also vary due to circumstances

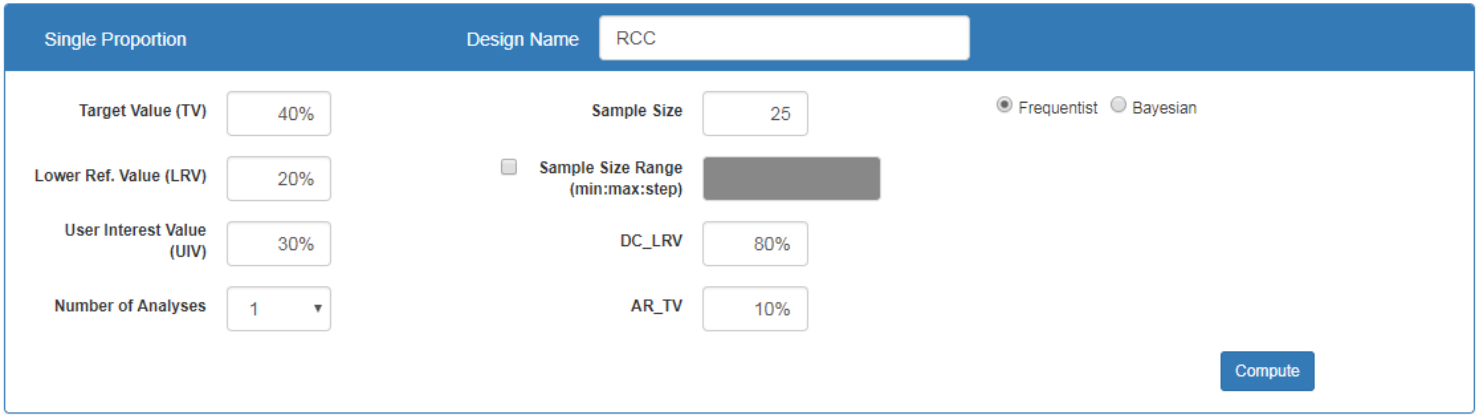
6. **A CONSIDER result can also be managed.**

dECiDe makes calculating GNG criteria easy

1. **dECiDe**
   - Software developed in partnership with AZ and Cytel
   - Implements the method described

2. **Suppose we have a real trial:**
   - Early oncology trial in RCC (Phase IIa single arm in ORR)
   - Dose expansion following an all solids dose finding trial
   - LRV = 20%, TV = 40%
   - AR_TV = 10%, DC_LRV = 80%
   - N=25

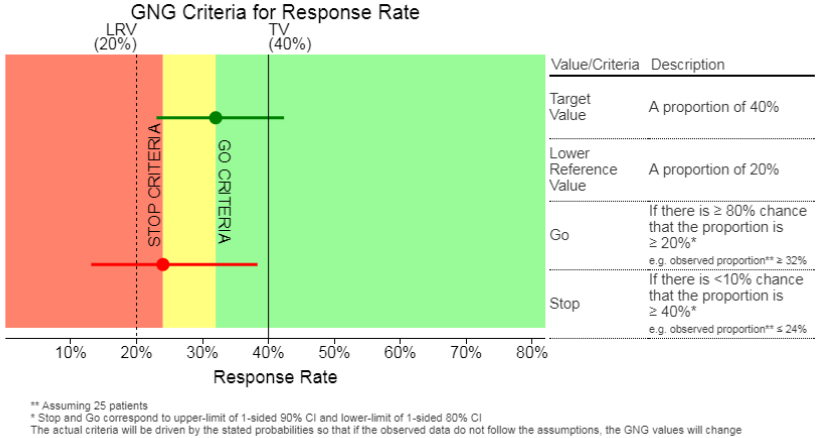
We enter the information…



1. TV, LRV, Sample size, DC_LRV and AR_TV are entered as mentioned.
2. No interims are considered for the moment
3. Not requesting information over a range of Ns yet
4. Staying within the Frequentist framework

dECiDe tells us…

1. **Decision criteria:**
   - Based on unbalanced CIs
   - STOP if ≤ 6/25 respond
   - CONSIDER if 7/25 respond
   - GO if ≥ 8/25 respond



2. **Chance of CONSIDER (Amber) given either TV or LRV is less than 20%**

Prob of GAR given the true value

True Value	Green	Amber	Red	G or A	R or A
TV (40%)	85%	8%	7%	93%	15%
LRV (20%)	11%	11%	78%	22%	89%
UIV (30%)	49%	17%	34%	66%	51%

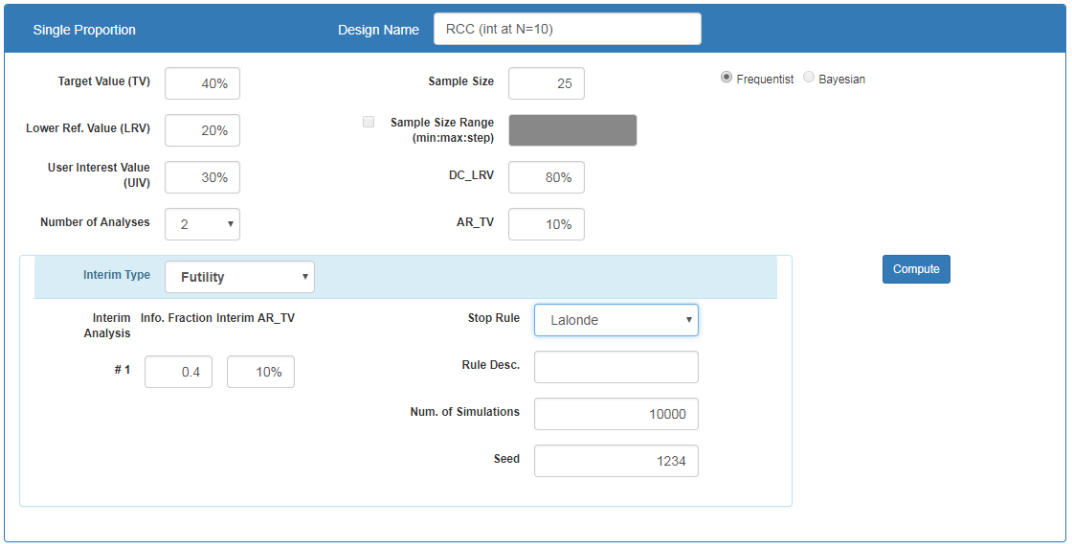
Sum of the probabilities may not be 100% due to rounding for display

We can make an earlier decision.

1. **What if we want to be able to stop for futility?**

2. **We use the same information (TV, LRV, etc.)**

3. **We just add an interim following 40% information (N=10)**



dECiDe adds this information:

1. **Our interim stop rule:**
   - Stop after N = 10 if no more than 1 patient responds.

2. **Adding the interim doesn't add much risk of stopping**
   - ~4 points under the UIV

3. **Expected N under range of true values**

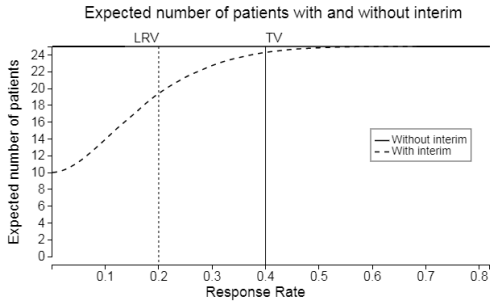
Interim Design

Analysis	Info. Fraction	Interim Sample Size	Stop Rule Type	Interim AR_TV	Stop Count	Stop Boundary
#1	0.4	10	Lalonde	10%	1	10%

Probability of overall decision with (without) interim

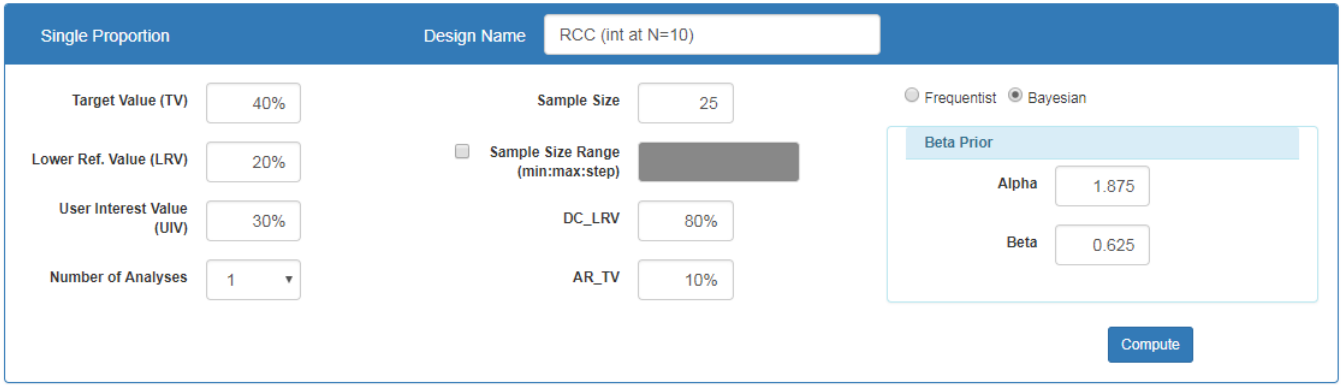
True Value	Interim?	Red	Amber	Green	G or A	Sample Size
TV (40%)	With	10%	7%	83%	90%	24.29
TV (40%)	(Without)	(7%)	(8%)	(85%)	(93%)	(25)
LRV (20%)	With	79%	10%	11%	21%	19.42
LRV (20%)	(Without)	(78%)	(11%)	(11%)	(22%)	(25)
UIV (30%)	With	38%	15%	47%	62%	22.74
UIV (30%)	(Without)	(34%)	(17%)	(49%)	(66%)	(25)

Sum of the probabilities may not be 100% due to rounding for display



What if we were lucky in the dose escalation phase?

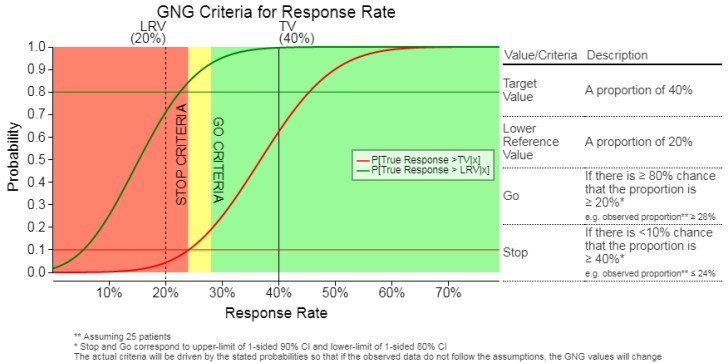
1. **Suppose:**
   - 4 patients in the all solids expansion were RCC
   - Same Line of therapy
   - All at dose to be studied
   - 3 of these patients responded
2. **We can incorporate this prior information:**



Beta parameters are adjusted outside so that they are no more than 10% of overall planned N

dECiDe now tells us…

1. **Decision criteria:**
   - Based on posterior probabilities
   - STOP if ≤ 6/25 (24%)
   - GO if ≥ 7/25 (28%)



2. **Chance of CONSIDER (Amber) given either TV or LRV is less than 20%**
   - Specifically 0%
   - Likely due to the effect of the prior information.

Prob of GAR given the true value

True Value	Green	Amber	Red	G or A	R or A
TV (40%)	93%	0%	7%	93%	7%
LRV (20%)	22%	0%	78%	22%	78%
UIV (30%)	66%	0%	34%	66%	34%

Sum of the probabilities may not be 100% due to rounding for display

Next steps

1. **dECiDe covers the beginning methods to address univariate problems in setting decision criteria.**
   - We continue to consider the needs of the variety of drug development programs.
   - We will continue to work with Cytel to improve dECiDe through the inclusion of new methods in the software.

References and contact info

1. **Chuang-Stein, C., et al. "A Quantitative Approach for Making Go/No-Go Decisions in Drug Development".** Drug Information Journal **2011** 45: 187. DOI: 10.1177/00928615110450021 3
2. **Frewer, P., et al**. **"Decision-making in early clinical drug development"**. Pharmaceut. Statist. **2016**, 15 255–263. DOI: 10.1002/pst.1746.
3. **Lalonde, R.L., et al. "Model-Based Drug Development"**. Clin Pharm Ther **2007**;82:21-32. doi:10.1038/sj.clpt.6100235.

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Thank you

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