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Bayesian Continual Reassessment Method for Dual-Agent Incorporating Binary Toxicity and Binary Efficacy Outcomes

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Session: **Trial Design and Decision-Making of Early Oncology Development in the Era of Immune-Oncology**
ASA Biopharmaceutical Section Regulatory-Industry Workshop
25-27 September 2019

Disclosure

- This presentation was sponsored by AbbVie. AbbVie contributed to the design, research, and interpretation of data, writing, reviewing, and approving the publication.
- Bo Tong, Wijith Munasinghe, and Dave Hoffman are employees of AbbVie Inc.

Outline

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Motivation/Statistical Considerations

- With targeted and/or immunotherapy dual agents, finding best dose combination/s (BDC) is/are generally required than finding maximum tolerated dose combination (MTDC)
- Utilize dual-agent Bayesian continual reassessment method (2D-BCRM) framework for both binary toxicity outcomes and binary anti-tumor activity outcomes
- Account for potential uncertainty in the corresponding posterior distributions
- Incorporate potential trade-off between two endpoints via utility score

Details of the Method: Dual Agent Dose-Toxicity Relationship

- Let Agent 1 dose levels be denoted by d_{1k}, where $k = 1,2,\ldots,K$ and Agent 2 dose levels be denoted by d_{2l}, where $l = 1,2,\ldots,L$.
- Let $\left(odds_{DC_{kl}}\right)^T$ be the odds of observing a DLT at dose combination DC_{kl} where $k = 1,2,\ldots,K$ and $l = 1,2,\ldots,L$. The dual agent dose-toxicity relationship will be described by the model:

$$\left(odds_{DC_{kl}}\right)^T$$

$$= \left[\left(odds_{d_{1k}}\right)^T + \left(odds_{d_{2l}}\right)^T + \left(odds_{d_{1k}}\right)^T\left(odds_{d_{2l}}\right)^T\right] exp\left(\eta^T \frac{d_{1k}}{d_1^*}\frac{d_{2l}}{d_2^*}\right)$$

Details of the Method: Dual Agent Dose-Toxicity Relationship (Cont.)

- Where $\left(odds_{d_{NM}}\right)^T = \alpha_N^T \left(\frac{d_{NM}}{d_N^*}\right)^{\beta_N^T}$ for $N = 1, 2; M = k, l$ and η^T is the interaction parameter.
- Interaction allows agonism and antagonism between two agents
- Additionally, η^T represents the log-odds ratio between the interaction and no interaction model for DC
- d_N^* represents an arbitrary reference dose
- α_N^T represents the odds of a DLT at the reference dose d_N^* , and β_N^T represents the increase in the log-odds of a DLT for a unit increase in log-dose.

Details of the Method: Dual Agent Dose-Efficacy Relationship

- A similar model will be utilized to describe the dual agent dose-binary efficacy outcome relationship and it will be fitted separately from dose-toxicity model. The superscript T in dose-toxicity model parameters is replaced by E in this setting.

Details of the Method: Selecting Priors and Prior Elicitation

- The dual agent dose-toxicity relationship model parameters are assumed to follow following distributions:

$$(\log(\alpha_N^T), \log(\beta_N^T)) \sim BVN\left(\mu_{\alpha_N^T}, \mu_{\beta_N^T}, \sigma_{\alpha_N^T}, \sigma_{\beta_N^T}, \rho_N^T\right) \text{ for N} = 1, 2 \text{ and}$$

$$\eta^T \sim N\left(m_{\eta^T}, s_{\eta^T}^2\right)$$

- Where m_{η^T}, $\mu_{\alpha_N^T}$ and $\mu_{\beta_N^T}$ represent the population means of $\eta^T, \log(\alpha_N^T)$ and $\log(\beta_N^T)$ respectively, s_{η^T}, $\sigma_{\alpha_N^T}$ and $\sigma_{\beta_N^T}$ represent the population standard deviations of η^T, $\log(\alpha_N^T)$ and $\log(\beta_N^T)$ respectively, and ρ_N^T represents the population correlation coefficient between $\log(\alpha_N^T)$ and $\log(\beta_N^T)$.

Details of the Method: Selecting Priors and Prior Elicitation (Cont.)

- The dual agent dose-efficacy relationship model parameters are assumed to follow similar distributions. The superscript T in dose-toxicity model prior parameters is replaced by E in this setting.
- The prior distributions for η^T, $\log(\alpha_N^T)$ and $\log(\beta_N^T)$ is elicited from preclinical data from dual-agent program and clinical data from single-agent program. Additionally, large uncertainty for the probabilities of a DLT at each DC is considered.
- Similarly, the prior distributions for η^E, $\log(\alpha_N^E)$ and $\log(\beta_N^E)$ is elicited considering possible synergy or antagonism between agents

Details of the Method: Quantities of Interest based on Posterior

- Based on the posterior distribution of the model parameters for each dual-agent model, the following quantities will be calculated for each DC_{kl}:
  - $E(p^T_{DC_{kl}})$: Posterior mean DLT rate
  - $P\left(p^T_{DC_{kl}} \geq \omega_2\right)$: Posterior probability that the DLT rate ≥ ω_2 (i.e., *excessive toxicity*)
  - $P\left(\omega_1 \leq p^T_{DC_{kl}} < \omega_2\right)$: Posterior probability that ω_1 ≤ DLT rate < ω_2 (i.e., *target interval toxicity*)
  - $E(p^E_{DC_{kl}})$: Posterior mean response rate
  - $max\left[E(p^E_{DC_{kl}})\right] - \tau$: Clinically significant difference in posterior mean response rate from its maximum value, where $\tau \in (0, 1)$ is indifference limit.

Dose Escalation Process: Dose Recommendations

- Starting DC can be based on pre-clinical and/or historical data
- Each cohort will enroll at least three DLT evaluable subjects
- After at least three subjects become DLT evaluable, the dual-agent dose-toxicity and dose-efficacy models will be updated. The recommended DCs for the subsequent cohort of subjects will be the DC_{kl} which satisfies all the steps described in next two slides
- The process will continue until the BDCs is declared and/or a stopping rule is triggered

Dose Escalation Process: Dose Recommendations (Cont.)

- **Step 1** – Find an admissible DCs that satisfy all the following criteria based on the dual-agent dose-toxicity model posterior quantities
  - $E(p^T_{DC_{kl}})$≤δ (i.e., posterior mean DLT rate ≤δ)
  - $P\left(p^T_{DC_{kl}} \geq \omega_2\right)$ ≤γ (i.e., ≤γ posterior probability that DLT rate is ≥ ω_2)
  - ≤*Y*-fold increase in one direction of either agent

Dose Escalation Process: Dose Recommendations (Cont.)

- **Step 2** – For admissible DCs from Step 1, identify DCs satisfying the criteria $E(p^E_{DC_{kl}}) \geq \{max\left[E(p^E_{DC_{kl}})\right] - \tau\}$ based on the dual-agent dose-efficacy model posterior quantities. Here,τ can be considered clinically significant difference due to small cohort size and variability in response rate. Then select the recommended DC as follows:
  - If all DCs from Step 2 are not utilized before OR all of them are utilized before then select DC based on efficacy-toxicity trade off score (utility score) $max\{\left[E\left(p^E_{DC_{kl}}\right)\right] - \left[\theta * E\left(p^T_{DC_{kl}}\right)\right]\}$. Here θ can be a value considering higher efficacy/acceptable toxicity and acceptable efficacy/lower toxicity scenarios with positive utility score.
  - If some DCs from Step 2 are utilized before then those DCs are not candidates for selection. Select DC with maximum utility score from the remaining DCs

Dose Escalation Process: Stopping Rules

- Stop for sufficient evidence of clinical benefit and the BDC declared if either of the following criteria is satisfied:
  - The recommended DC is DC_{kl} with at least *n* subjects previously allocated and $P\left(\omega_1 \leq p^T_{DC_{kl}} < \omega_2\right) \geq \phi$ and has highest utility score along with satisfying the criteria in step 1.
  - The recommended DC is the highest DC to be explored (DC_{KL}) with at least *n* subjects previously allocated

- Stop for excessive toxicity if at least *X* DLTs have been observed across all cohorts and $P\left(p^T_{DC_{11}} \geq \omega_2\right) > \gamma$ (i.e., the lowest DC has >γ posterior probability that DLT rate is ≥ ω_2)

Performance Characteristics

- Simulations were performed under different dose-toxicity and dose-efficacy scenarios. They represent a wide range for the location of the true BDCs as well as varying shapes for the true dose-toxicity curve and dose-efficacy curve. For comparison, dual-agent CRM for binary toxicity outcome was performed.
- For simplicity, the following conventions were implemented:
  - Each cohort consisted of exactly 3 subjects
  - Only the available DCs were explored and the recommended DC was allocated to all cohorts (i.e., no intermediate DCs allocated)
  - The maximum trial size was 36 subjects

Performance Characteristics (Cont.)

- For dual-agent dose-toxicity model and dose-efficacy model the reference dose is highest available dose for each agent
- Θ=33%, ϕ=35%, γ=25%, δ=30%, ω_1=25%, ω_2=35%, τ=10%, n=6, K=4, L=4, X=4, Y=2

- The simulated trials were summarized to obtain the following operating characteristics of the design under each scenario:
  - BDC selection percentage (% of trials which select each DC as the BDC including no BDC selection)
  - Average number of subjects allocated per DC

DLT Probability and Response Probability Prior Model Parameters

Parameters	$(\mu_{\alpha_N}, \mu_{\beta_N})$	$(\sigma_{\alpha_N}, \sigma_{\beta_N})$	ρ_N	m_η	s_η
$\log(\alpha_1^T), \log(\beta_1^T)$	(-1.95, -0.73)	(1.19, 0.45)	0	NA	NA
$\log(\alpha_2^T), \log(\beta_2^T)$	(-1.95, -0.58)	(1.19, 0.45)	0	NA	NA
η^T	NA	NA	NA	0.1	2.0
$\log(\alpha_1^E), \log(\beta_1^E)$	(-0.85, 0.98)	(1.28, 1.98)	0	NA	NA
$\log(\alpha_2^E), \log(\beta_2^E)$	(-0.30, 0.40)	(1.79, 1.98)	0	NA	NA
η^E	NA	NA	NA	0.5	0.96

Prior Distribution of DLT Probability and Response Probability

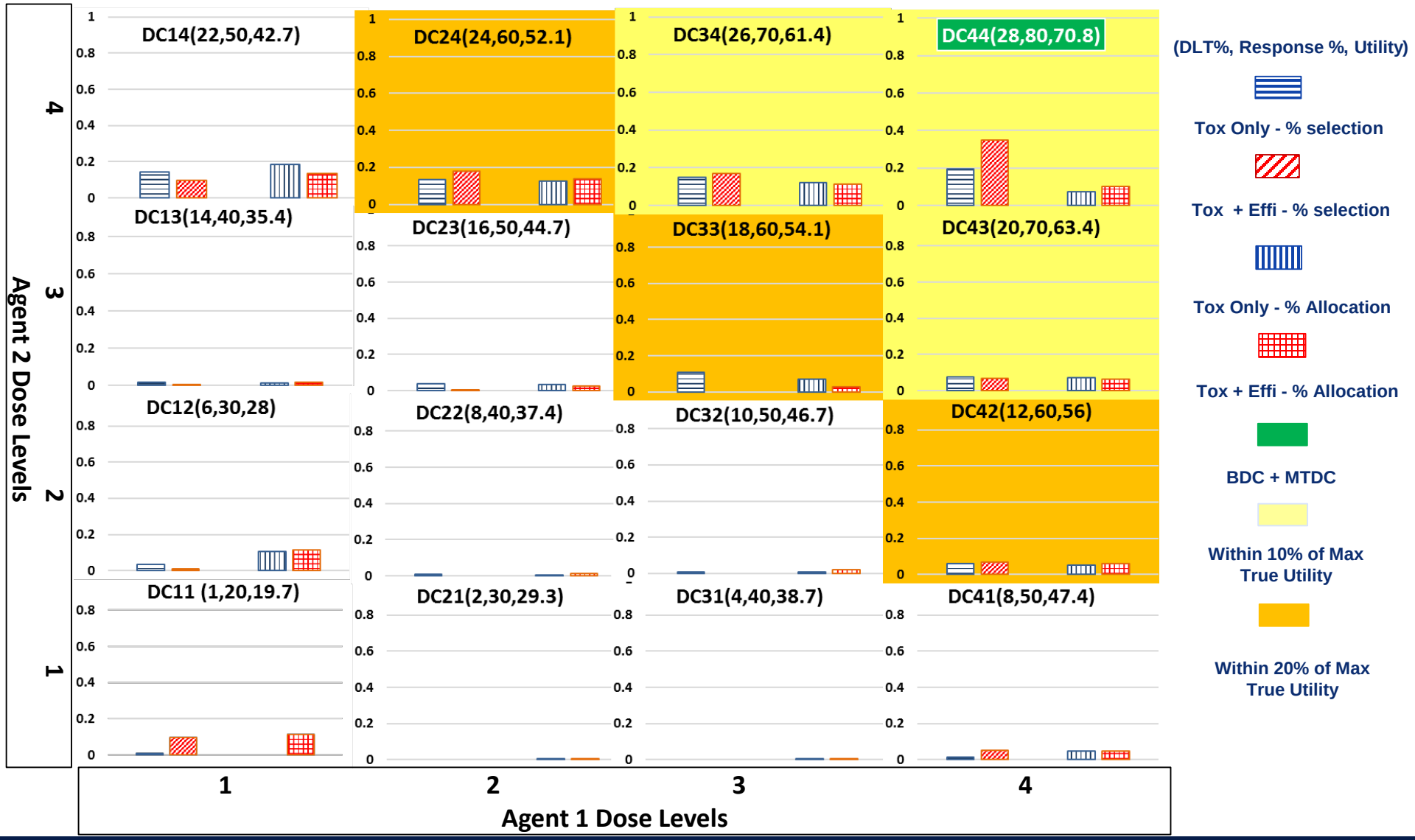
Agent 2 Dose Levels					
	4	0.203 (.065,.499)	0.232 (.064,.581)	0.254 (.056,.673)	0.275 (.045,.758)
	3	0.166 (.054,.412)	0.192 (.063,.473)	0.213 (.065,.523)	0.231 (.065,.575)
	2	0.138 (.044,.365)	0.164 (.054,.411)	0.183 (.061,.449)	0.199 (.065,.484)
	1	0.117 (.036,.325)	0.142 (.045,.373)	0.161 (.052,.409)	0.176 (.058,.439)
		1	2	3	4
		Agent 1 Dose Levels			

Prior Distribution of DLT Probability at Each Dose Combinations: Median (10, 90 percentiles)

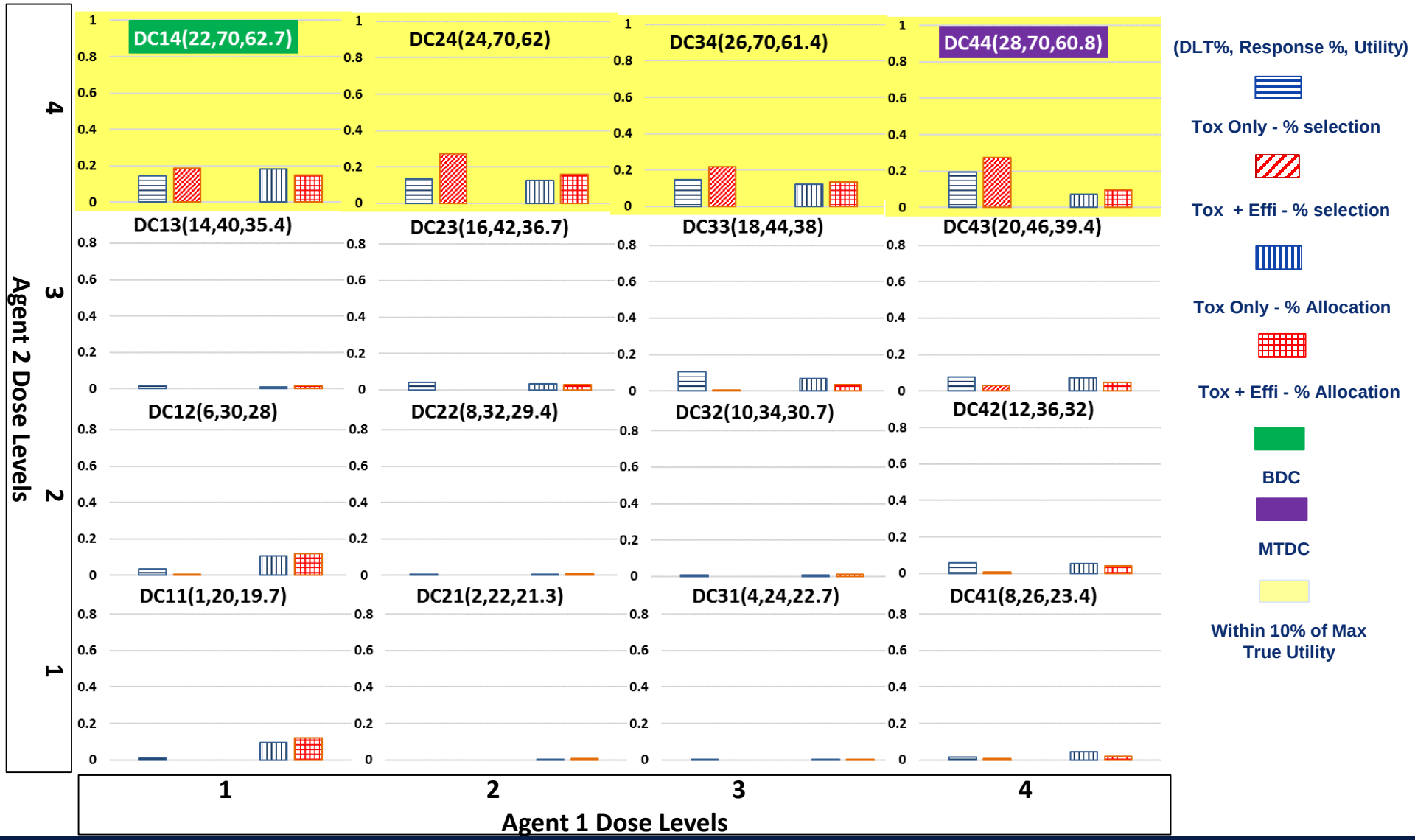
Prior Distribution of Response Probability at Each Dose Combinations: Median (10, 90 percentiles)

Agent 2 Dose Levels					
	4	0.505 (.104,.903)	0.536 (.118,.913)	0.597 (.145,.932)	0.780 (.304,.973)
	3	0.308 (.016,.833)	0.341 (.022,.847)	0.406 (.038,.874)	0.649 (.206,.941)
	2	0.212 (.002,.779)	0.243 (.004,.795)	0.304 (.012,.825)	0.562 (.169,.906)
	1	0.139 (0,.716)	0.167 (0,.733)	0.223 (.003,.764)	0.481 (.139,.863)
		1	2	3	4
		Agent 1 Dose Levels			

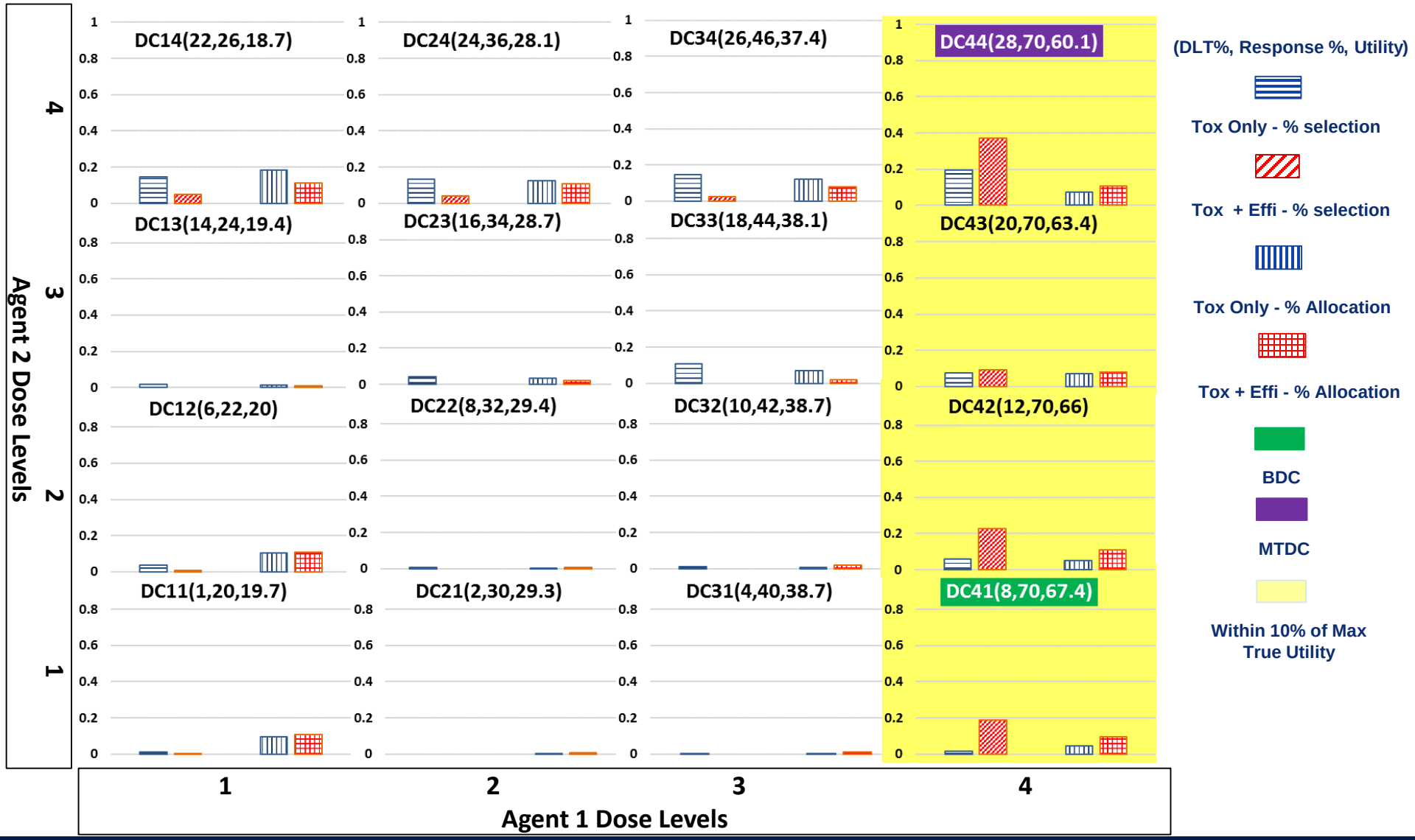
Scenario 1: All available DCs are safe and efficacy slightly increases as either agent dose increases



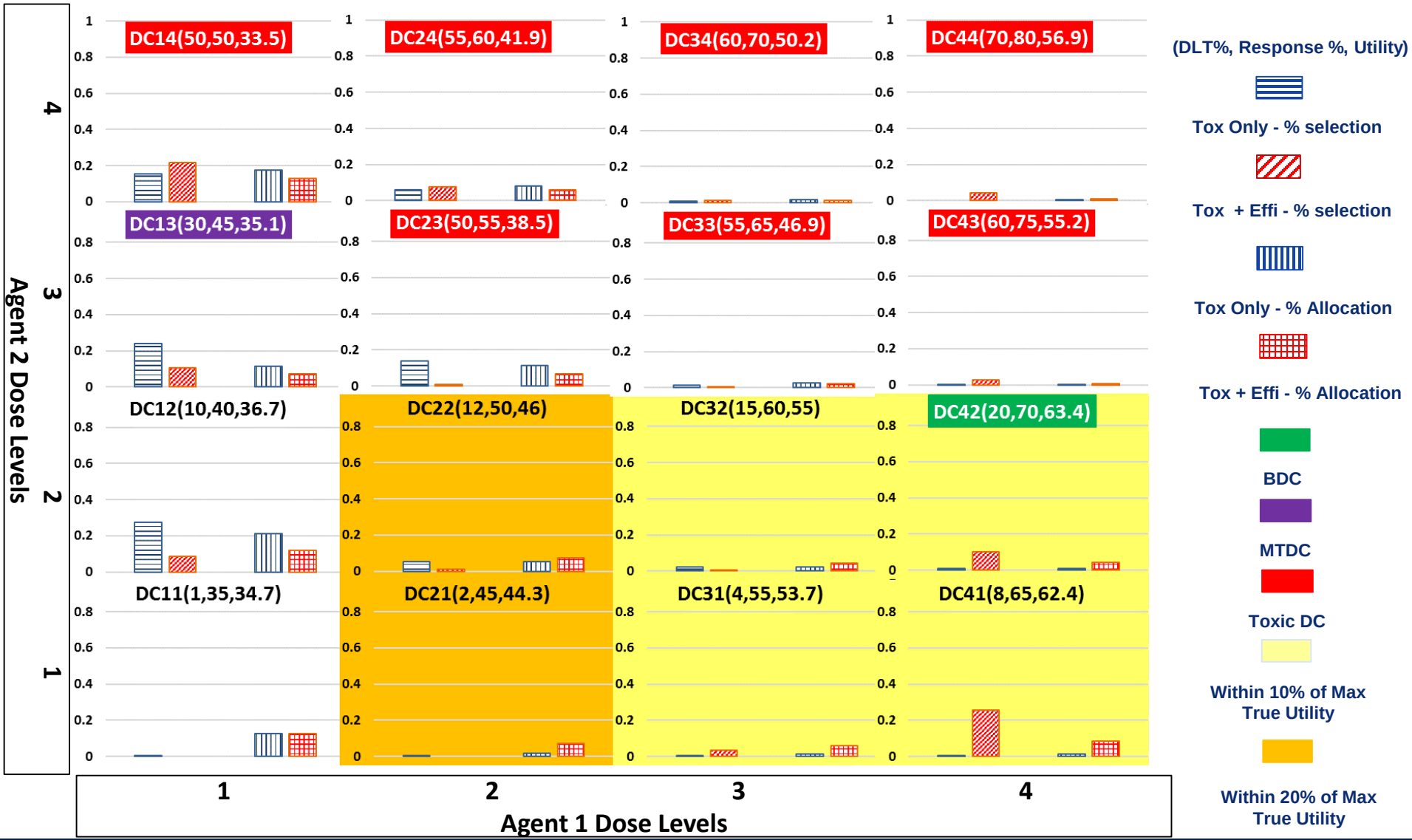
Scenario 2: All available DCs are safe and no change in efficacy after DC14 as agent 1 dose increases



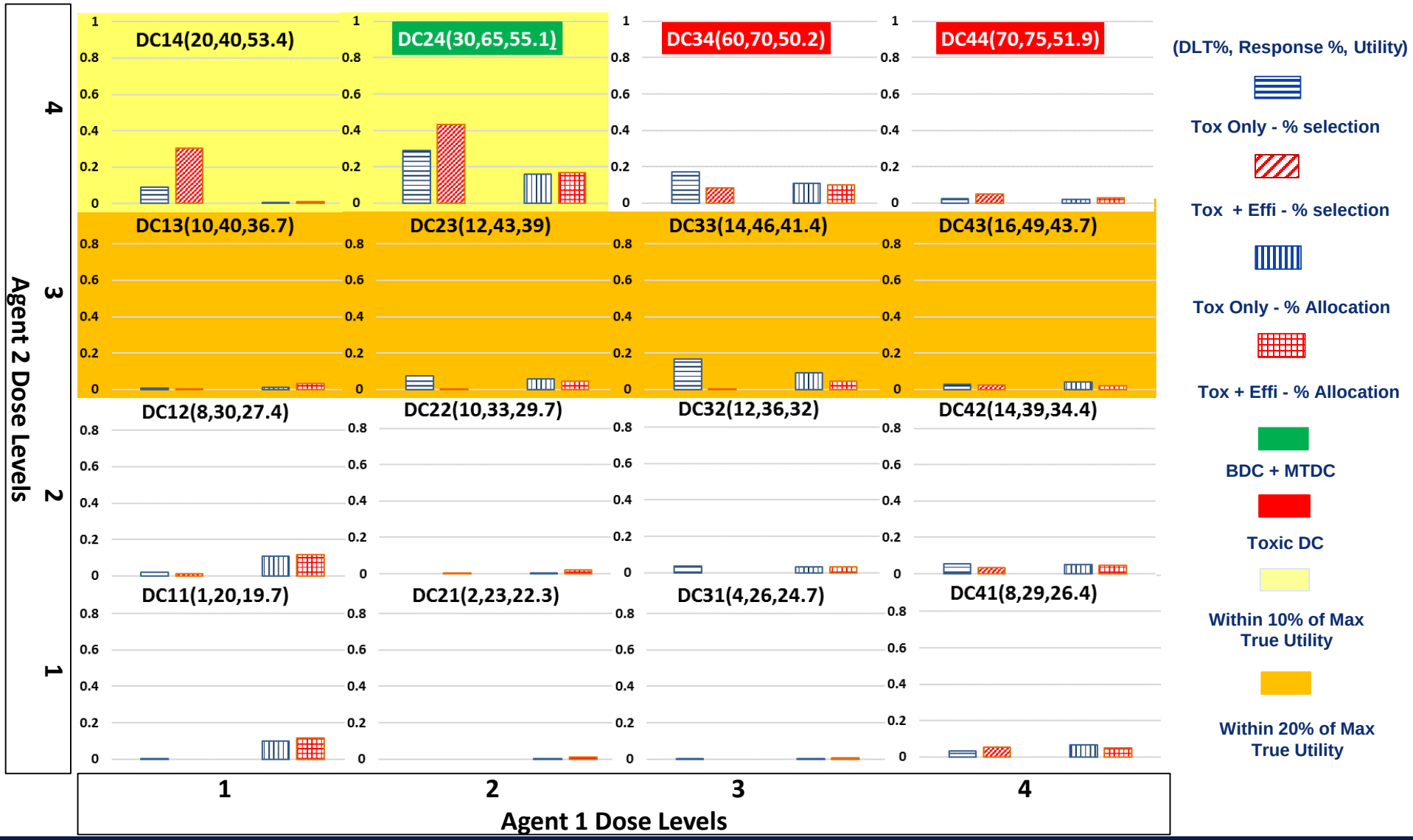
Scenario 3: All available DCs are safe and no change in efficacy after DC41 as agent 2 dose increases



Scenario 4: up to DC13 are safe and good efficacy as agent 1 dose increases with same agent 2 dose



Scenario 5: up to DC24 are safe and good efficacy as agent 2 dose increases with same agent 1 dose



Discussion

- Quantitative method using well established model to accommodate dual-agent dual-outcomes (binary) setting
- Utility function helps to establish some trade-off between independently modelled outcomes
- Based on simulated data, the proposed algorithm is reasonably able to capture BDCs rather than MTDC
- May capture umbrella shape in dose-binary efficacy outcome relationship based on interaction parameter setting
- Need some early anti-tumor activity measure

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