Simulation Study of Two Dose Escalation Methods for Oncology Drug Combination Therapies (for Toxicity Outcome)

Jing Hu, KC Huang, and Ron Yu

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Ming Lin

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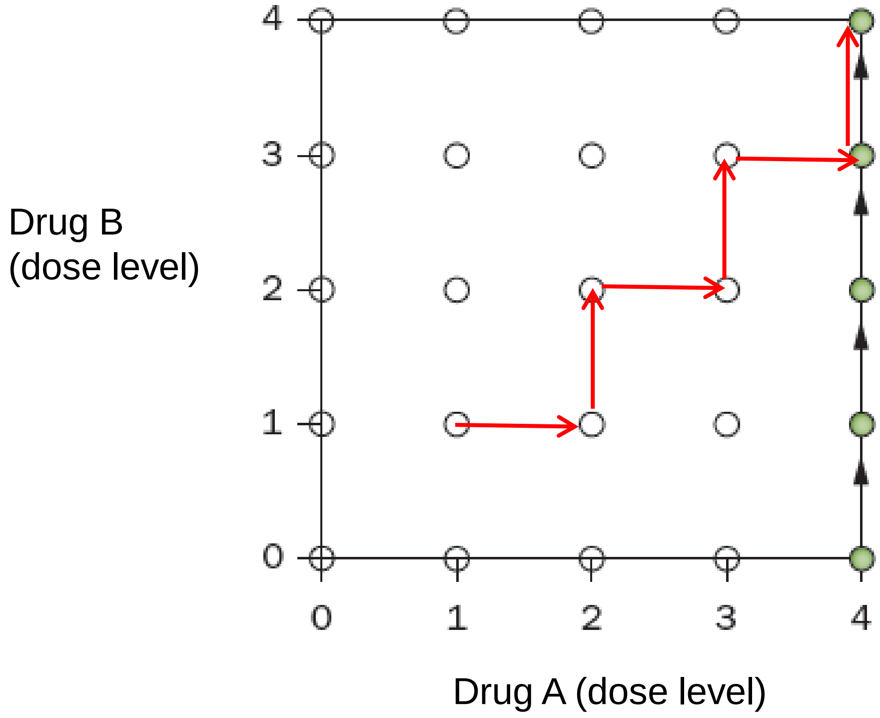
Ziqian Zhou

Some Current Practices



- Currently, many studies pre-specify a linear path in the two dimensional space and apply methods for single agent
- How to examine a much wider range of combinations, meanwhile efficiently, adaptively, and safely allocate patients

Two methods

- **B**ayesian **L**ogistic **R**egression **M**odel (BLRM) method
  - Model
  - Prior distribution and inference
  - Dose selection strategy
  - Stopping rules
  - MTD recommendation

- **P**roduct of **I**ndependent Beta **P**robabilities **E**scalation (PIPE) method

BLRM: Bayesian Logistic Regression Model

Two Single Agents:

$\text{logit}(\pi_1) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$, $\alpha_1, \beta_1 > 0$

$\text{logit}(\pi_2) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$, $\alpha_2, \beta_2 > 0$

Combination of Two Agents w/o Interaction:

$\text{odds}_{12}{}^0 = \text{odds}_1 + \text{odds}_2 + \text{odds}_1 \times \text{odds}_2$

Combination of Two Agents (any relationship):

$\text{odds}_{12} = \text{odds}_{12}{}^0 \times \exp(\eta \times d_1/d_1^* \times d_2/d_2^*)$

- $\eta = \log(\text{odds}_{12}/\ \text{odds}_{12}{}^0)$ at the reference doses
- $\eta \mathbf{>} 0$: $\text{odds}_{12} \mathbf{>} \text{odds}_{12}{}^0$ (Synergism)
- $\eta \mathbf{=} 0$: $\text{odds}_{12} \mathbf{=} \text{odds}_{12}{}^0$ (No Interaction)
- $\eta \mathbf{<} 0$: $\text{odds}_{12} \mathbf{<} \text{odds}_{12}{}^0$ (Antagonism)

Prior Distribution

- Weakly informative BVN for ($\log(\alpha_1)$, $\log(\beta_1)$) and ($\log(\alpha_2)$, $\log(\beta_2)$):

$$\begin{pmatrix} \log(\alpha) \\ \log(\beta) \end{pmatrix} \sim \mathrm{N}\left(\begin{pmatrix} \mathrm{logit}(\pi^*) \\ \log(1) \end{pmatrix}, \begin{pmatrix} 2 & 0 \\ 0 & 2 \end{pmatrix} \right)$$

where π^* is the anticipated DLT rate at reference dose d^*

- Weakly informative normal distribution for η:

$$\eta \sim \mathrm{N}(0,2)$$

BLRM: Inference

- Categorize DLT rate into 3 intervals
  1. Underdosing (UD): $\pi_{12} < 0.20$
  2. Targeted toxicity (TT): $0.20 \le \pi_{12} < 0.35$
  3. Overdosing (OD): $\pi_{12} \ge 0.35$

- After each cohort, update the following 3 posterior interval probabilities for each dose combination
  1. Probability of OD
  2. Probability of TT
  3. Probability of UD

BLRM: Dose Selection Strategy

- Candidate dose combination must have probability of OD < 25%

  -- "Escalation with Overdose Control" (EWOC)

- Among the candidates, select the dose $\tilde{d}$ with the highest probability of TT

- If no dose meeting EWOC, STOP the trial (too toxic).

- Dose skipping options/constraints available in EAST.
  - Dose increase must not exceed a threshold
  - Do not allow diagonal escalation

BLRM: Stopping Rules

- Dose escalations continue until the recommended next dose $\tilde{d}$ meeting the following:
  - At least 6 patients have been treated at dose $\tilde{d}$.
  - This dose $\tilde{d}$ satisfies one of the following conditions:
    1. The probability of TT at $\tilde{d}$ exceeds 50%
    2. A minimum of 15 patients have already been treated in trial.

- If no MTD can be declared and the maximum sample size is met, STOP the trial.

PIPE

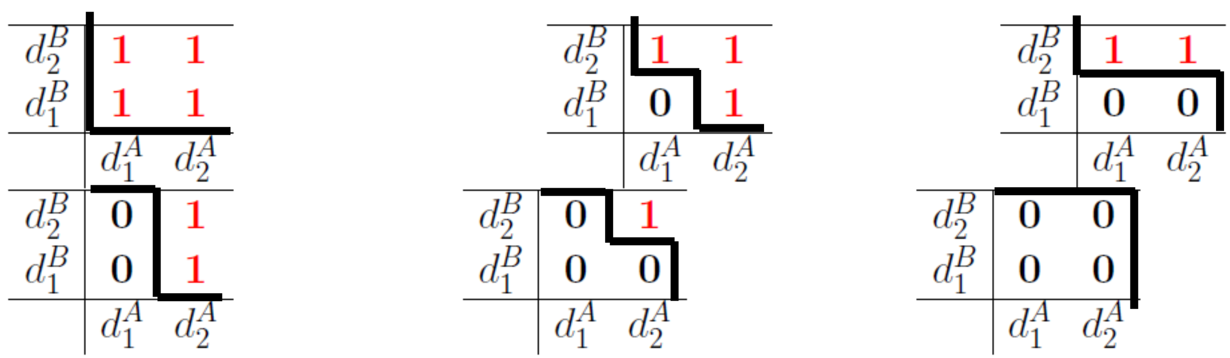
(Product of Independent beta Probabilities Escalation method)

- Core concept: maximum toxicity contour (MTC)
- Prior distribution and inference
- Dose selection strategy
- Stopping rules
- MTD recommendation

PIPE: Maximum Toxicity Contour (MTC)

- MTC is the contour that separates doses below a pre-specified target toxicity level (TTL) from those doses above the TTL (e.g. 30%)
- There are $\binom{I+J}{I}$ possible monotonic MTCs for two agents, with *I* and *J* different dose levels respectively

Examples of possible MTCs for two agents with two levels each, meeting monotonicity constraints.



PIPE: Independent Beta Priors and Inference

- An independent beta prior is placed at each dose combination:

$$\pi_{ij}|a_{ij}, b_{ij} \sim Beta\left(a_{ij}, b_{ij}\right) \;\; \forall i, j$$

- The posterior distribution of π_{ij} after observing data from *m* cohorts is also a beta distribution:

$$\pi_{ij}|Y^{(m)}, a_{ij}, b_{ij} \sim Beta\left(a_{ij} + r_{ij}^{(m)}, b_{ij} + n_{ij}^{(m)} - r_{ij}^{(m)}\right)$$

- Consider the posterior probability of DLT rate ≤ θ (where θ denotes TTL) at each dose combination *(i, j)*:

$$p_{ij}\left(\theta \middle| Y^{(m)}\right) = P\left(\pi_{ij} \leq \theta \middle| Y^{(m)}\right),$$

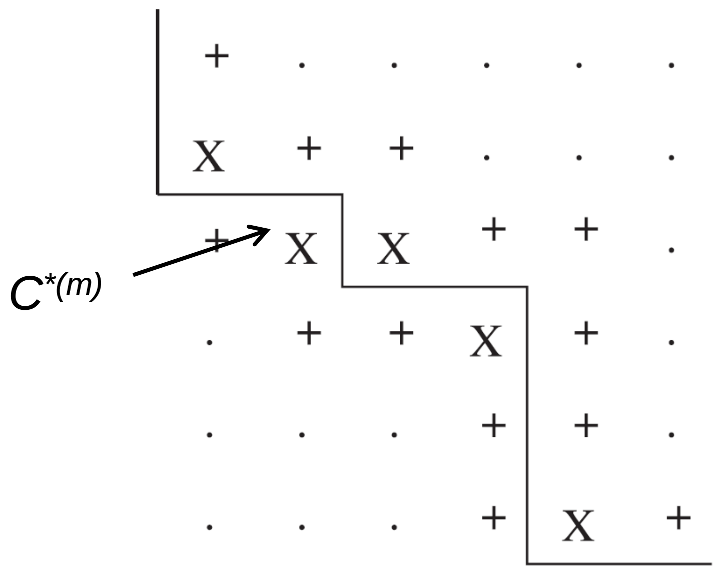
which is the CDF of posterior beta distribution evaluated at θ

- Dose escalation is based on finding the most likely MTC_θ
  - The contour with the largest posterior probability of being the true MTC_θ is selected.

$$P\left(MTC_\theta = C_s \middle| Y^{(m)}\right) \propto \prod_{i,j} \left\{1 - p_{ij}\left(\theta \middle| Y^{(m)}\right)\right\}^{C_s[i,j]} p_{ij}\left(\theta \middle| Y^{(m)}\right)^{1-C_s[i,j]}$$

PIPE: Dose Selection Strategy (1/3)

- Admissible doses are those close to the most likely contour in location
  - Adjacent: all dose combinations (X's and +'s) next to $C^{*(m)}$
  - Closest: X's only



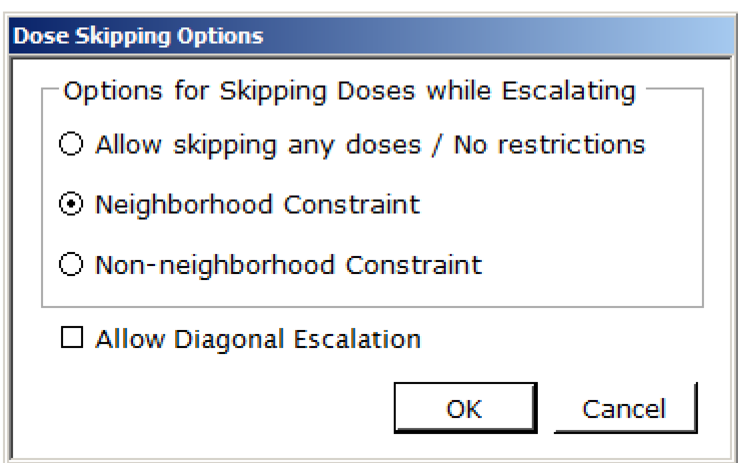
Adjacent: X's and +'s

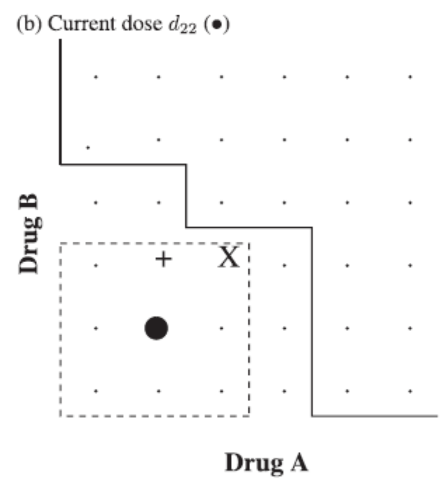
Closest: X's only

PIPE: Dose Selection Strategy (2/3)

- The least experimented doses will be selected among admissible doses
  - Minimum sample size: Choose the admissible dose with the smallest sample size as the next dose combination, where sample size is defined as the prior and trial sample size combined

  - Weighted randomization method: Select one of the admissible doses at random, with selection probabilities weighted by the inverse of sample size
- Dose skipping constraints option is also available





PIPE: Dose Selection Strategy (3/3)

- Safety constraint to avoid overdosing
  - Consider the expected probability of dose combination *(i, j)* being above the MTC$_\theta$, averaged over the distribution of all possible monotonic curves

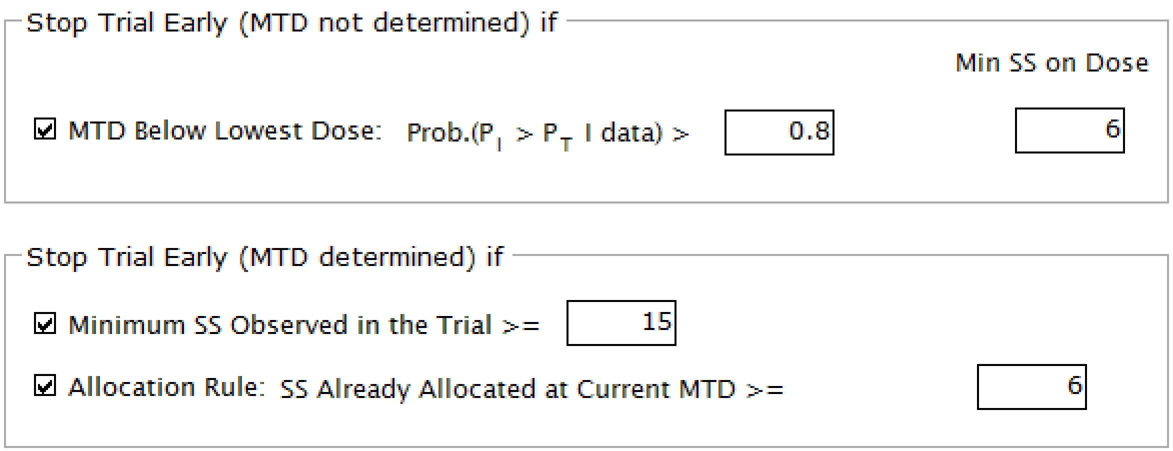
$$q_{ij}^{(m)} = \sum_{C_s} C_s[i,j]\, P_{C_s}(\theta | Y^{(m)})$$

  - Dose combination *(i, j)* is excluded from the admissible dose set if $q_{ij}^{(m)} >$ a pre-chosen threshold, e.g., 0.8.

PIPE: Stopping Rules

- The trial is terminated if
  - there are no available dose combinations that satisfy the safety constraint, or
  - a pre-specified maximum number of patients have been enrolled

- Additional stopping rules can be specified in EAST



PIPE: MTD Recommendation

- At the stop of escalation, dose combination(s) that meet the following three criteria
  1. Closest to MTC from below
  2. Have been experimented on
  3. Meet safety constraint

Simulation Studies

- Simulation scenarios
- Simulation set-up
- Simulation results and evaluation
  - Performance in MTD selection
  - Performance in patient safety

Simulation Scenarios

- A total of eight scenarios
  - Ranging from "All doses are unsafe" to "All doses are safe"

Scenario 1			
	All doses unsafe		
	Lo	Mid	Hi
Lo	0.45	0.55	0.75
Mid	0.5	0.7	0.8
Hi	0.6	0.75	0.85

Scenario 2			
	All doses safe		
	Lo	Mid	Hi
Lo	0.05	0.15	0.25
Mid	0.1	0.2	0.25
Hi	0.15	0.25	0.3

Scenario 3			
	Only lowest dose safe		
	Lo	Mid	Hi
Lo	0.3	0.45	0.55
Mid	0.45	0.6	0.7
Hi	0.55	0.7	0.8

Scenario 4			
	Hi/Lo Scenario		
	Lo	Mid	Hi
Lo	0.15	0.4	0.5
Mid	0.2	0.45	0.6
Hi	0.3	0.5	0.7

Scenario 5			
	Hi/Mid Scenario		
	Lo	Mid	Hi
Lo	0.1	0.2	0.4
Mid	0.2	0.25	0.5
Hi	0.25	0.3	0.6

Scenario 6			
	Mid/Mid Scenario		
	Lo	Mid	Hi
Lo	0.1	0.2	0.4
Mid	0.25	0.3	0.6
Hi	0.37	0.55	0.75

Scenario 7			
	Multi-Region Scenario I		
	Lo	Mid	Hi
Lo	0.1	0.2	0.3
Mid	0.25	0.28	0.5
Hi	0.29	0.4	0.6

Scenario 8			
	Multi-Region Scenario II		
	Lo	Mid	Hi
Lo	0.1	0.2	0.3
Mid	0.15	0.37	0.55
Hi	0.28	0.45	0.65

Dose levels:
Drug A: Lo = 50, Mid = 100, Hi = 150
Drug B: Lo = 100, Mid = 200, Hi = 400

Simulation Set-Up

- Software: EAST ESCALATE module
- 10,000 simulated trials per method per scenario
- Average # of patients is closely matched for fair comparison
- Weakly or non-informative priors

BLRM	PIPE
Target toxicity interval 20-35%	Target toxicity level 0.3
EWOC threshold: 35%	Admissible doses: closest
Apply stopping rules	Dose skipping: Neighborhood constraint
Mid/mid dose as reference dos	Safety constraint threshold: 0.8
Weakly informative priors	Apply stopping rules
Max sample size 45	Prior: scenario 5, 1/9 pt. per dose
	Max sample size 45

Performance in MTD Selection

Proportion of Trials where MTD is

	Correctly Identified[a]		Over-Estimated[b]		Under-Estimated[c]	
Scenario	BLRM	PIPE	BLRM	PIPE	BLRM	PIPE
1	95.8%	77.7%	4.2%	22.3%	0%	0%
2	91.4%	62.5%	0%	0%	8.7%	37.5%
3	21.3%	29.5%	8.5%	26.7%	70.2%	43.8%
4	39.7%	61.3%	25.1%	14.9%	35.3%	23.8%
5	87.0%	90.6%	3.7%	4.5%	9.4%	4.9%
6	80.9%	59.6%	5.9%	31.6%	13.2%	8.9%
7	75.0%	78.6%	13.0%	14.7%	12.0%	6.7%
8	26.6%	48.5%	47.4%	20.3%	26.0%	31.3%

[a] True DLT rate in [20%, 35%). For Scenario 1, the percentage shown in this table was the proportion of trials which did not select an MTD because it was below the lowest dose

[b] True DLT rate ≥ 35%

[c] True DLT rate < 20%. For Scenario 3, the percentage shown in this table was the proportion of trials which did not select an MTD because it was below the lowest dose

Performance in MTD Selection – Evaluation

	BLRM			vs.	PIPE		
Scenario	**Much Better**	**Moderately Better**	**Slightly Better**	**Similar**	**Slightly Better**	**Moderately Better**	**Much Better**
1	X						
2	X						
3			X				
4							X
5				X			
6	X						
7				X			
8							X

Total score = (-3)*(# BLRM much better) + (-2)*(# BLRM moderately better) + (-1)*(# BLRM slightly better) + 0*(# Similar) + 1*(# PIPE slightly better) + 2*(# PIPE moderately better) + 3*(# PIPE much better)

= (-3)*3 + (-1)*1 + 3*2 = -4

Average score = -4/8 **(favoring BLRM)**

Performance in Patient Safety (1/2)

	Avg. # Patients per Trial		Avg. # DLTs per Trial		Avg. Prop. of DLTs per Trial	
Scenario	BLRM	PIPE	BLRM	PIPE	BLRM	PIPE
1	8.3	15.9	3.9	8.6	57.3%	59.0%
2	30.0	30.5	5.8	5.9	19.7%	19.0%
3	15.4	20.4	5.7	9.2	45.7%	47.5%
4	26.8	27.0	7.6	9.4	31.7%	35.6%
5	29.0	29.9	7.0	8.3	25.5%	27.9%
6	28.4	28.7	7.5	9.1	27.9%	32%
7	28.9	29.9	7.4	8.6	26.7%	29.0%
8	29.3	30.0	7.6	8.6	29.6%	29.0%

Performance in Patient Safety (2/2)

	Avg. # Patients per Trial		Avg. # Pts who are Over-Dosed per Trial		Avg. Prop. of Pts who are Over-Dosed per Trial	
Scenario	BLRM	PIPE	BLRM	PIPE	BLRM	PIPE
1	8.3	15.9	8.3	15.9	100%	100%
2	30.0	30.5	0	0	0%	0%
3	15.4	20.4	6.2	15.0	25.5%	68.1%
4	26.8	27.0	10.5	14.3	34.6%	51.2%
5	29.0	29.9	2.5	7.4	7.9%	24.0%
6	28.4	28.7	3.7	12.2	11.8%	41.2%
7	28.9	29.9	4.4	5.7	14.0%	17.5%
8	29.3	30.0	11.9	9.8	39.2%	31.4%

Patients who are treated at dose combinations with a true DLT rate ≥ 0.35 are said to be over-dosed.

Performance in Patient Safety – Evaluation

	BLRM			vs.	PIPE		
Scenario	**Much Better**	**Moderately Better**	**Slightly Better**	**Similar**	**Slightly Better**	**Moderately Better**	**Much Better**
1			X				
2				X			
3		X					
4			X				
5			X				
6		X					
7			X				
8					X		

Total score = (-3)*(# BLRM much better) + (-2)*(# BLRM moderately better) + (-1)*(# BLRM slightly better) + 0*(# Similar) + 1*(# PIPE slightly better) + 2*(# PIPE moderately better) + 3*(# PIPE much better)

= (-2)*2 + (-1)*4 + 1*1 = -7

Average score = -7/8 **(favoring BLRM)**

Summary of Simulation Results

- Overall, BLRM slightly out-performed PIPE in both MTD selection and patient safety;
- BLRM performed much better than PIPE in Scenarios 1, 2, and 6 for MTD selection;

Scenario 1			
	All doses unsafe		
	Lo	Mid	Hi
Lo	0.45	0.55	0.75
Mid	0.5	0.7	0.8
Hi	0.6	0.75	0.85

Scenario 2			
	All doses safe		
	Lo	Mid	Hi
Lo	0.05	0.15	0.25
Mid	0.1	0.2	0.25
Hi	0.15	0.25	0.3

Scenario 6			
	Mid/Mid Scenario		
	Lo	Mid	Hi
Lo	0.1	0.2	0.4
Mid	0.25	0.3	0.6
Hi	0.37	0.55	0.75

- PIPE performed much better than BLRM in Scenarios 4 and 8 for MTD selection;

Scenario 4			
	Hi/Lo Scenario		
	Lo	Mid	Hi
Lo	0.15	0.4	0.5
Mid	0.2	0.45	0.6
Hi	0.3	0.5	0.7

Scenario 8			
	Multi-Region Scenario II		
	Lo	Mid	Hi
Lo	0.1	0.2	0.3
Mid	0.15	0.37	0.55
Hi	0.28	0.45	0.65

Evaluation: BLRM vs. PIPE

	Pros	Cons
BLRM	• Better Operating characteristics (OC) • Enforces a monotonic dose-toxicity surface • Allow to specify a target interval (instead of a single target DLT rate)	• Not as fast as PIPE (~15 min to simulate 10,000 trials with an average sample size of 30 patients)
PIPE	• Nonparametric/curve-free • Very fast (10,000 simulations in ~15 sec) • Output of an MTC is visually intuitive	• Less appealing OC • Unable to specify early-stopping rules (except the safety constraint) using PIPE implementation in R (package ‘pipe.design’)

- Generally, we recommend BLRM for dual-agent dose escalation at Gilead.

References

- **BLRM**
  - B. Neuenschwander, A. Matano, Z. Tang, S. Roychoudhury, S. Wandel, S. Bailey. A Bayesian industry approach to phase I combination trials in oncology. *Statistical Methods in Drug Combination Studies.* 2015; Chapter 6 (2015): 95-135.
- **PIPE**
  - A.P. Mander, M.J. Sweeting. A product of independent beta probabilities dose escalation design for dual-agent phase I trials. *Statistics in Medicine*. 2015;34(8):1261-1276.

Thank You!