Model-based design for the early development of cancer immunotherapy combinations

Nolan A. Wages, PhD

Division of Translational Research & Applied Statistics
Biostatistics Shared Resource
University of Virginia Cancer Center

August 2, 2017

University of Virginia Health System | Cancer Center

Vaccine-based Immunotherapy

Challenges

- Regimens often demonstrate minimal toxicity
- Higher regimens may not correlate with greater immune response
- **Goal**: locate optimal biological regimen
  - a safe regimen demonstrating the greatest immunogenicity, based on some pre-defined measure of immune response
- Protocol-specific immunologic endpoints indicate biologic activity and drive the design

Motivating Application (MEL63)

NCT02425306

- Early-phase evaluation of safety and immunogenicity of a vaccine comprised of a mixture of 6 synthetic melanoma helper peptides (6MHP) administered with one of three local adjuvant combinations, (IFA, IFA + polyICLC, AS-15); alone or with systematic low-dose cyclophosphamide (mCy)

Regimens ($\mathcal{X}$)	Zone	6MHP+
x_1	1	IFA
x_2	1	AS-15
x_3	1	IFA+PolyICLC
x_4	2	IFA+**mCy**
x_5	2	AS-15+**mCy**
x_6	2	IFA+PolyICLC+**mCy**

Design Considerations

Motivating Application

- Binary measures of DLT and immune response (IR)

$$Y_1 = \begin{cases} 0 & \text{if no DLT,} \\ 1 & \text{if DLT} \end{cases} \qquad Y_2 = \begin{cases} 0 & \text{if no IR,} \\ 1 & \text{if IR.} \end{cases}$$

- DLT: protocol-specific adverse events assessed using CTCAE v4.03.
- IR: $\geq$ 5-fold increase in IR measured by CD4+ T-cells during time period of vaccine administration
- Probability of observing outcome Y_i at regimen x_j by $\pi_i(x_j)$; $i = 1, 2; j = 1, \ldots, J$.

Trial Objective

- Based on the target toxicity upper bound ϕ_1, define the maximum tolerated regimen (MTR), $\nu \in \{1, \ldots, J\}$, as

$$\nu \equiv \arg\min_j |\pi_1(r_j) - \phi_1|.$$

- The primary objective of the study is to identify the regimen x_j that maximizes the activity of a regimen (MAR) according to the utility function

$$u(x_j) = \pi_2(x_j) \times \mathcal{I}\big(\pi_1(x_j) \leq \pi_1(x_\nu)\big),$$

where $\mathcal{I}(\cdot)$ is a function indicating whether the probability of DLT at x_j is less than that of the probability of DLT at the MTR.

Safety assumptions

Motivating Application

- Assumption: the addition of mCy does increase the probability of DLT.
  - e.g. $\pi_1(x_1) \leq \pi_1(x_4)$
  - Based on data from a series of previous melanoma studies at UVA
- Unknown whether regimens have higher or lower DLT probabilities than other regimens within the same zone.
  - $\pi_1(d_2) < \pi_1(d_3)$ or that $\pi_1(d_3) < \pi_1(d_2)$.
- **Overall strategy**: formulate a set of working models, indexed by k_1, that represent various possible relationships between the regimens and the DLT probabilities.

Partial Order

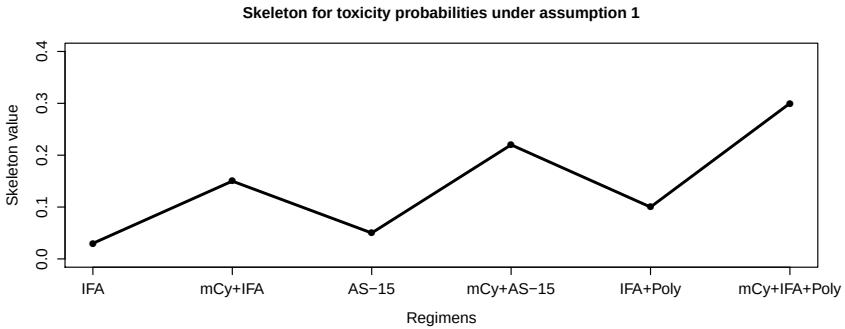
DLT Probabilities

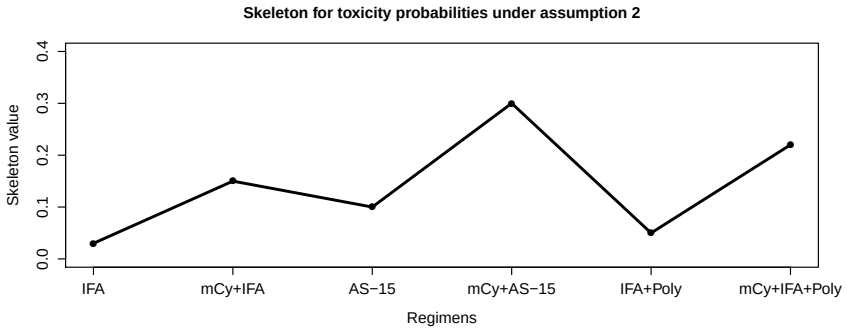
1. $k_1 = 1 : \pi_1(x_1) < \pi_1(x_2) < \pi_1(x_3) < \pi_1(x_4) < \pi_1(x_5) < \pi_1(x_6)$
2. $k_1 = 2 : \pi_1(x_1) < \pi_1(x_3) < \pi_1(x_2) < \pi_1(x_4) < \pi_1(x_6) < \pi_1(x_5)$
3. $k_1 = 3 : \pi_1(x_2) < \pi_1(x_1) < \pi_1(x_3) < \pi_1(x_5) < \pi_1(x_4) < \pi_1(x_6)$
4. $k_1 = 4 : \pi_1(x_2) < \pi_1(x_3) < \pi_1(x_1) < \pi_1(x_5) < \pi_1(x_6) < \pi_1(x_4)$
5. $k_1 = 5 : \pi_1(x_3) < \pi_1(x_1) < \pi_1(x_2) < \pi_1(x_6) < \pi_1(x_4) < \pi_1(x_5)$
6. $k_1 = 6 : \pi_1(x_3) < \pi_1(x_2) < \pi_1(x_1) < \pi_1(x_6) < \pi_1(x_5) < \pi_1(x_4)$

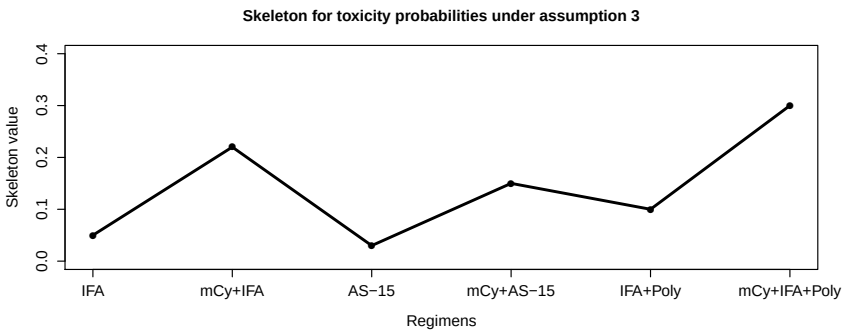
- Strategy: reflect order uncertainty through multiple "CRM-like" skeletons / one-parameter working models

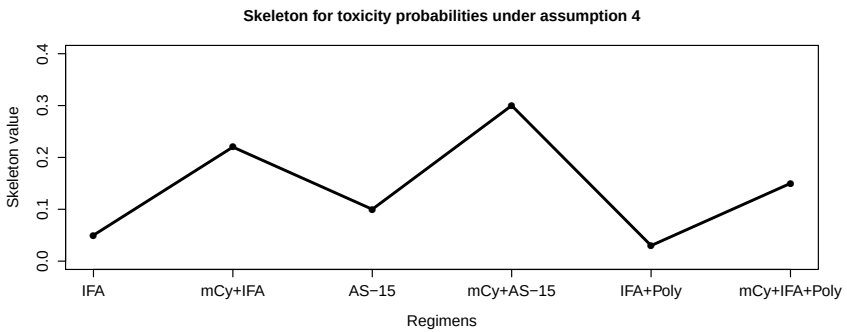
Class of Working Models

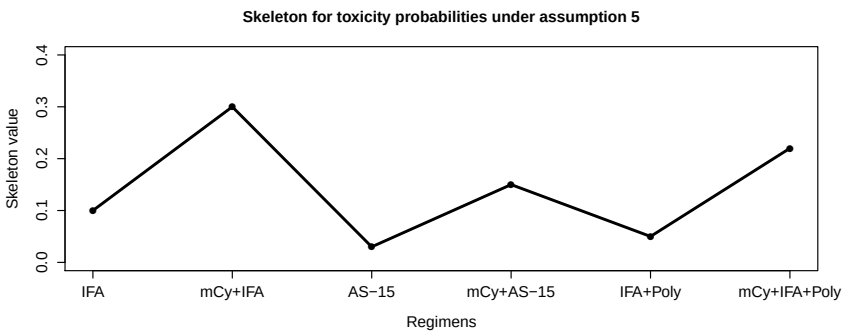
Skeletons for DLT Probabilities

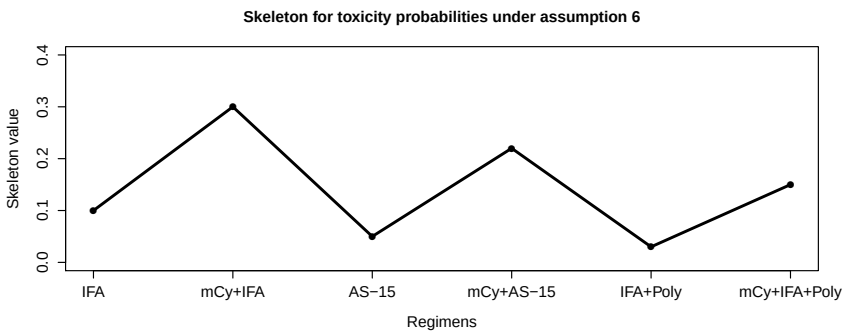










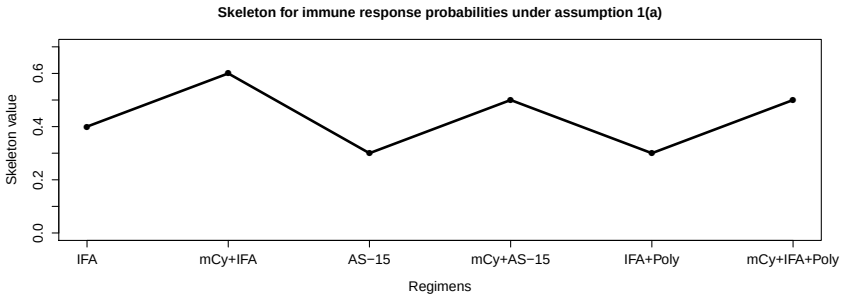


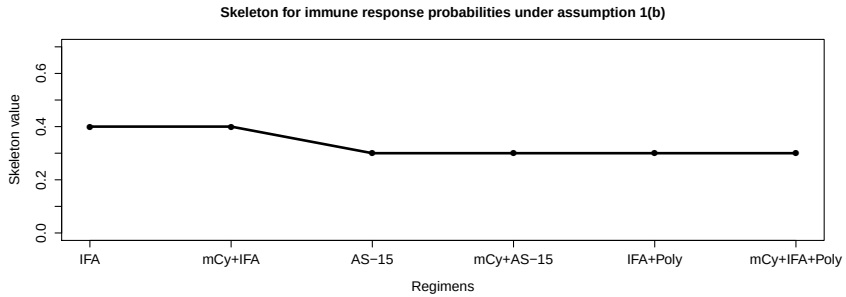
Activity assumptions

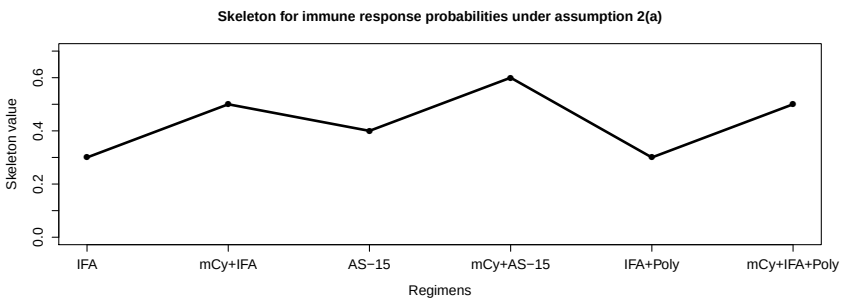
1. IFA generates the highest immunogenecity
2. AS-15 generates the highest immunogenecity
3. IFA+Poly-ICLC generates the highest immunogenecity
4. *Within* each of these assumptions:
   (a) The addition of cyclophosphimide (mCy) increases immunogenecity
   (b) Immunogenecity plateaus with the addition of cyclophosphimide (mCy)

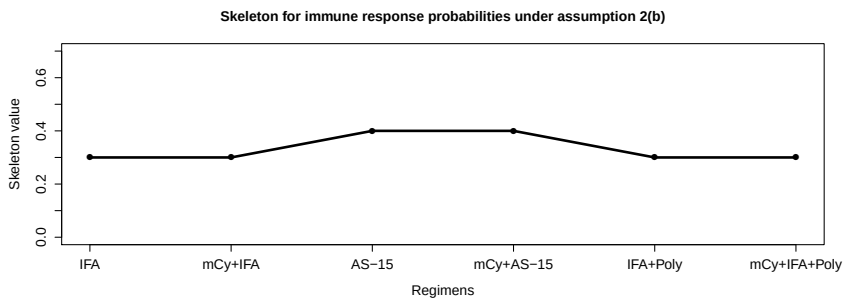
Class of Working Models

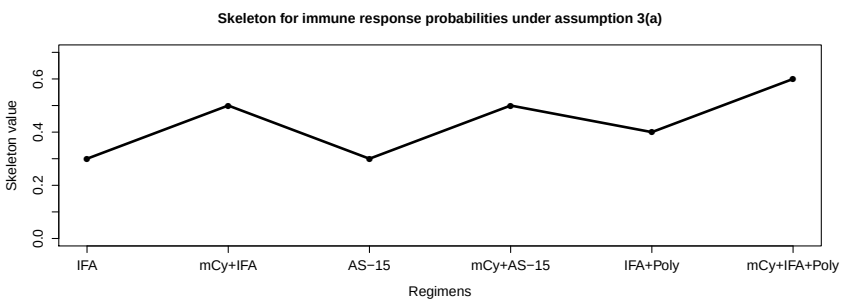
Skeletons for activity probabilities

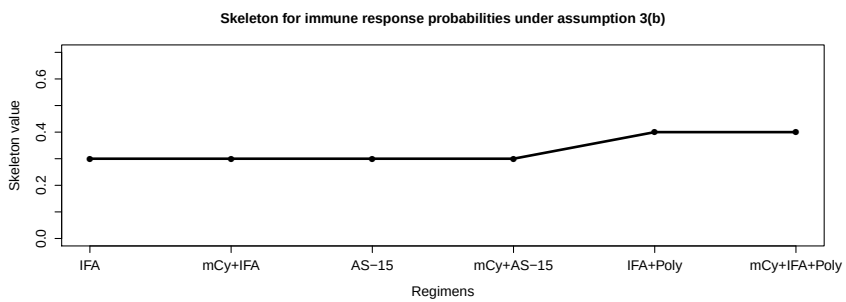












Class of Regimen-Outcome Models

For each outcome i

- K_1 possible working models (skeletons) for DLT indexed by $k_1 \in \{1, \ldots, K_1\}$
- K_2 possible working models (skeletons) for activity indexed by $k_2 \in \{1, \ldots, K_2\}$
- Probability of observing Y_i at regimen x_j is given by

$$\pi_{ij} = \Pr(Y_i = 1 | x_j) = F_{k_i}\left(x_j, \beta_{ik_i}\right) \approx \left(p_{ij}(k_i)\right)^{\exp(\beta_{ik_i})}$$

under working model M_{ik_i}.

Likelihood and Prior

For each outcome i

- Data is $\mathcal{D}_i = \{(y_{ij}, n_{ij}) : i = 1, 2; j = 1, \ldots, J\}$
- Likelihood under working model M_{ik_i}

$$\mathcal{L}(\mathcal{D}_i | \, \beta_{ik_i}, M_{ik_i}) \propto \prod_{j=1}^{J} \left(F_{k_i}(x_j, \beta_{ik_i})\right)^{y_{ij}} \left(1 - F_{k_i}(x_j, \beta_{ik_i})\right)^{n_{ij} - y_{ij}}$$

- Prior probabilities on M_{ik_i} are $P(M_{ik_i})$
- Prior distribution on β_{ik_i} is $g(\beta_{ik_i} | M_{ik_i})$

Sequential Bayesian Model Choice

For each outcome i

- Posterior probability for model M_{ik_i} is

$$P(M_{ik_i} | D_i) = \frac{\mathcal{L}(\mathcal{D}_i | M_{ik_i}) P(M_{ik_i})}{\sum_{k_i=1}^{K_i} \mathcal{L}(\mathcal{D}_i | M_{ik_i}) P(M_{ik_i})}$$

- *For each outcome* Y_i, choose a single model $h_i \in \{1, \ldots, K_i\}$ such that

$$M_{ih_i} = \arg\max_{M_{ik_i}} P(M_{ik_i} | D_i)$$

Probability Estimates

For each outcome i

- Posterior mean for the probability of outcome i at regimen x_j

$$\widehat{\pi}_{ij} = \int F_{h_i}(x_j, \beta_{ih_i}) \frac{\mathcal{L}(\mathcal{D}_i|\, \beta_{ih_i}, M_{ih_i})\, g(\beta_{ih_i}|M_{ih_i})}{\int \mathcal{L}(\mathcal{D}_i|\, \beta_{ih_i}, M_{ih_i})\, g(\beta_{ih_i}|M_{ih_i})\, d\beta_{ih_i}} d\beta_{ih_i}$$

Trail conduct

Stage 1: MTR-based allocation

- Treat the first cohort of patients at the physician-specified combination.
- After each cohort, estimate the MTD $\widetilde{\nu}$ as the combination with estimated DLT probability closest to the target toxicity upper bound ϕ_1 such that

$$\widetilde{\nu} = \arg\min_j |\widetilde{\pi}_1(x_j) - \phi_1|.$$

- Allocate the next cohort of patients to $\widetilde{\nu}$
- Otherwise, once the number of patients accrued to the study exceeds the stage 1 sample size n_1, go to Stage 2.

Trail conduct

Stage 2: MAR-based allocation

- After each cohort inclusion, estimate the utility function using the probability estimates $\widetilde{\pi}_{ij}$

$$\widetilde{u}(x_j) = \widetilde{\pi}_{2j} \times I(\widetilde{\pi}_{1j} \leq \widetilde{\pi}_{1\widetilde{\nu}})$$

- Allocate the next cohort of patients to x_m that maximizes $\widetilde{u}_j$

$$x_m = \arg\max_j \widetilde{u}_j$$

- Once the maximum sample size, N, is reached, the optimal biological combination (OBC) is defined as the combination x_m that would have been administered to the next cohort, had one been included.

Trail conduct

Stopping rules

- If, *at any point*, the "lowest" combination is deemed too toxic, as evaluated by

$$\Pr(\pi_{1\ell} > \phi_1 | \mathcal{D}_1) > 0.95,$$

  then **stop the trial for safety**, and no combination is recommended.
- Based on a lower limit of desirable activity ϕ_2, if, *in stage 2* the MAR x_m is deemed to have to little activity, as evaluated by

$$\Pr(\pi_{2m} < \phi_2 | \mathcal{D}_2) > 0.95,$$

  then **stop the trial for futility**, and no combination is recommended. In a small study, it may undesirable to stop the trial for futility.

Simulation Setting

- 1000 simulated trials
- Maximum sample size $N = 70$
  - Cohort size is 2
  - Accrual will end if recommendation is to assign next patient to regimen that already has treated 30 patients.
- Uniform prior on working models
- $\beta_{ik_i} \sim \mathcal{N}(0, 2)$
- $\phi_1 = 0.20;\ \phi_2 = 0.30;$

Operating Characteristics

True π_{1j}	0.05	0.01	0.07	0.08	0.17	0.18
True π_{2j}	0.19	0.15	0.30	0.50	0.40	0.70
Selection %	2.5	0.5	6.9	17.4	7.1	65.4
# of pts	3.4	2.8	5.1	8.2	6.3	21.3

True π_{1j}	0.05	0.01	0.07	0.08	0.17	0.18
True π_{2j}	0.35	0.40	0.60	0.35	0.40	0.60
Selection %	4.4	7.0	49.3	2.8	5.8	30.7
# of pts	4.5	5.3	16.9	4.6	6.4	12.9

True π_{1j}	0.05	0.01	0.07	0.08	0.17	0.18
True π_{2j}	0.40	0.15	0.30	0.60	0.35	0.40
Selection %	20.0	0.4	6.1	53.7	6.2	13.6
# of pts	9.2	2.9	4.7	18.2	6.5	8.9

Design Flexibility

NCT02126579

- Early phase trial of a Long Peptide Vaccine (LPV7) plus TLR Agonists (MEL60)

Zone	Regimen	LPV7+
1	x_1	IFA
1	x_2	PolyICLC
1	x_3	Resiquimod
2	x_4	IFA+PolyICLC
2	x_5	IFA+Resiquimod
2	x_6	Resiquimod+PolyICLC
3	x_7	IFA+PolyICLC+Resiquimod

An Ongoing Study

- Early-phase study of evaluating safety and immunogenicity of 3 schedules of Pembro, with and without IL-2 and GMCSF. Schedules are designated by time of Pembro administration.

		Pembro Schedule		
		Sch 1	Sch 2	Sch 3
IL-2/ GM-CSF	Yes	x_3	x_5	x_6
	No	x_1	x_2	x_4

An Ongoing Study

NCT02419560

- Early-phase study of ibrutinib with ABT-199 in relapsed/refractory mantle cell lymphoma. (open to accrual)
- Efficacy: response (CR+PR) at 2 months from start of treatment

		Ibrutinib (mg/day)		
		280	420	560
ABT-199 (mg/day)	400	x_3	x_5	x_6
	200	x_1	x_2	x_4

Conclusions

- Number of working models increases as dimension/complexity of problem grows
- Use available data at time decision needs to be made
  - even if amount of DLT data differs from amount of IR data
- Design performs well in terms of
  - selecting true optimal regimens in a high percentage of trials
  - allocating a high percentage of patients to regimens at and around optimal regimens
- Can be applied to a broad class of partial order problems using multiple endpoints

Acknowledgements

- Funding:
  - NCI: K25181638
  - Mel 63: U01CAA178846
- Collaborators:
  - Craig Slingluff, MD
  - Gina Petroni, PhD
  - Lawrence Lum, MD
  - Patrick Dillon, MD
  - Craig A. Portell, MD
- Thank You!