Innovations in Immune Oncology Combination Clinical Trial Designs

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Disclosures

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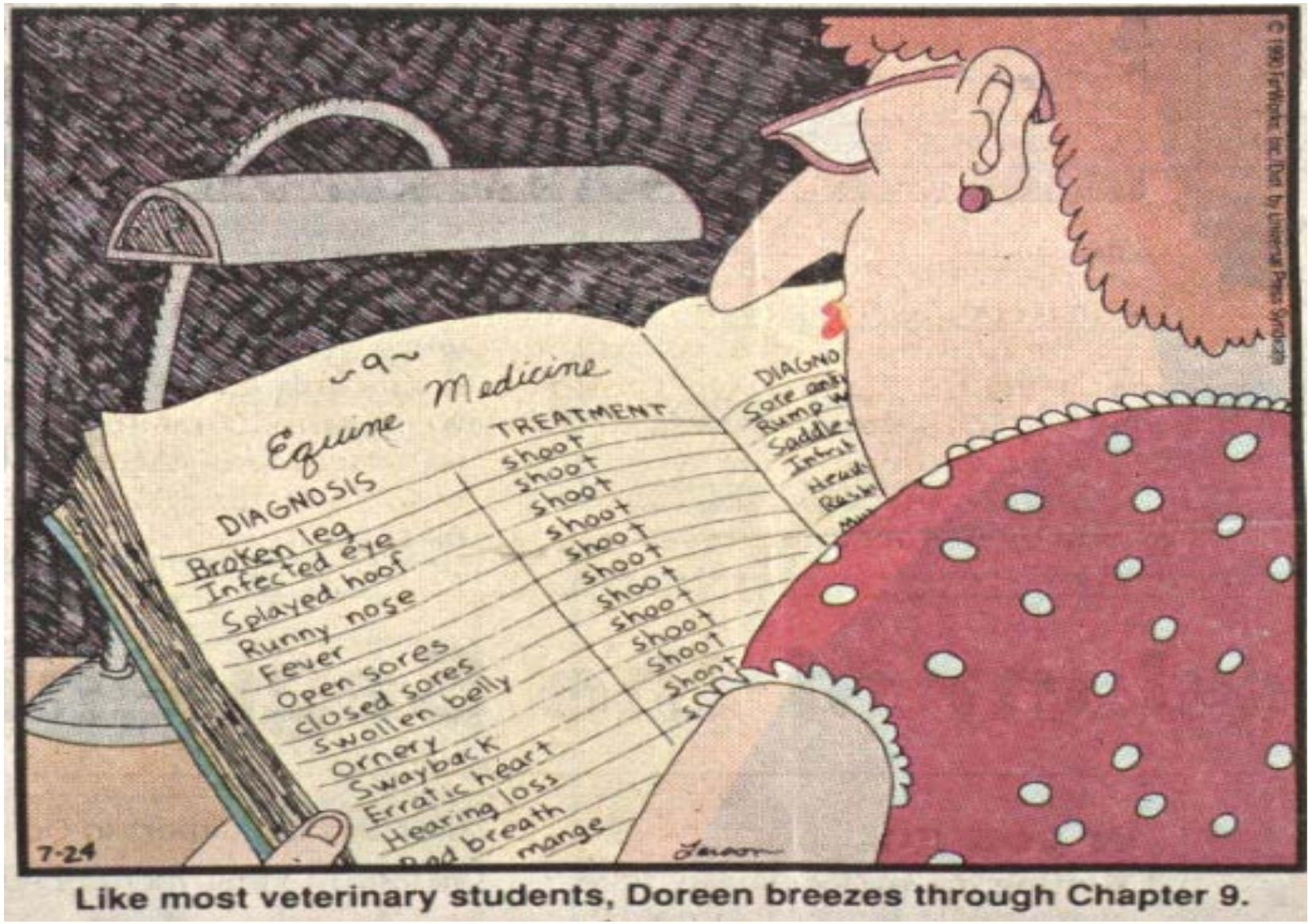
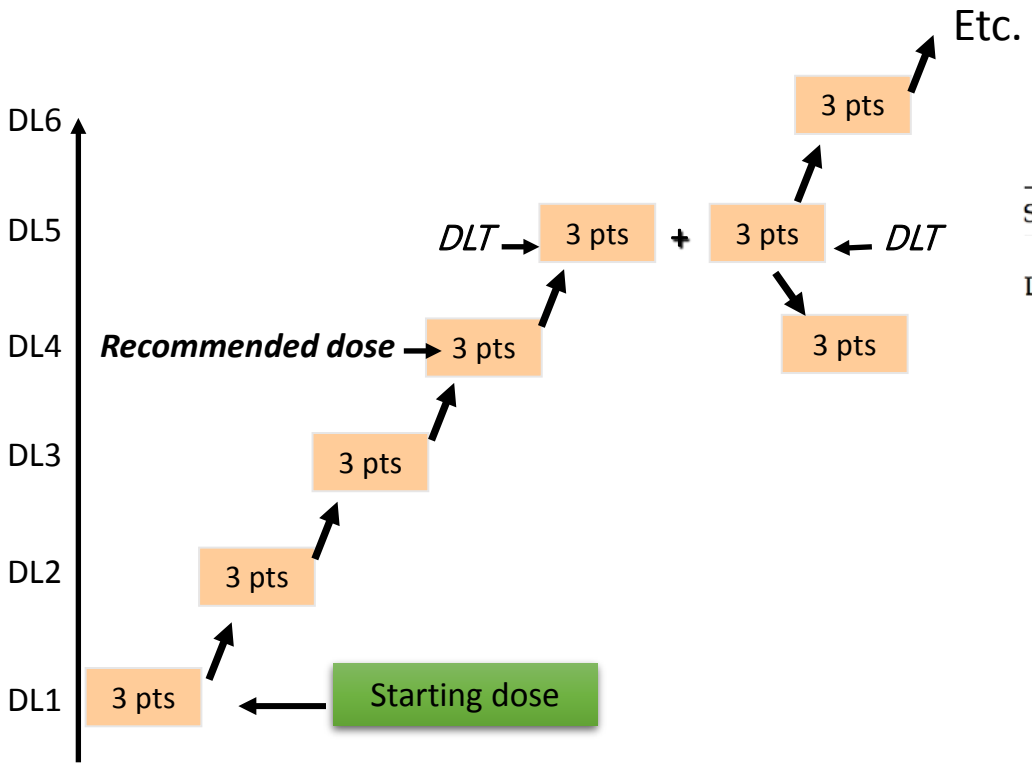
- Scientific Advisor/Steering Committee member to Roche/Genentech, Merck, Abbvie, Janssen, Genmab, Clovis, AstraZeneca, Gamamab, Immunogen, Tesaro

Clinical Studies – Traditional Options



Phase I: ”3+3” Mantra…



Eisenhauer et al.

DRUG A dose and MTD set at 25%

Scenario		Dose	100	200	300	400	500	600	None
L2		True p_{TOX}	.01	.09	.26	.47	.64	.76	–
	BLR	% MTD	0	21	**72**	6	0	0	0
		#Pats	0.2	11.3	20.5	3.7	0.4	0	
	CRM	% MTD	0	16	**79**	5	0	0	0
		#Pats	0.9	10.0	21.7	3.2	0.2	0	
	3+3	% MTD	8	43	**41**	7	0	0	1
		#Pats	3.3	4.8	4.9	2.5	0.4	0	

Thall, Int J Gynecol Cancer

BLR: Bayesian logistic regression
CRM: Continuous reassessment model

Two Agents: More Complicated (Arbitrary?)

Dose Level	Olaparib Dose	AZD2014 Dose
1	100mg BID	25mg BID continuous
2	200mg BID	25mg BID continuous
3	200mg BID	50mg BID continuous
4	300mg BID	25mg BID continuous
5	300mgBID	50mg BID continuous

Dose Level	Olaparib Dose	AZD2014 Dose
-1	100 mg BID	75 mg BID 2 days on/5 days off
1	100 mg BID	125mg BID 2 days on/5 days off
1b	100 mg BID	100mg BID 2 days on/5 days off
1c	200 mg BID	100mg BID 2 days on/5 days off
1d	300 mg BID	100mg BID 2 days on/5 days off

"Octopus" Trial; PI: Shannon Westin

NRG-GY009: PLD With Atezolizumab and/or Bevacizumab in

Randomized Phase 2/3 Study (NCT02839707)

Enrollment Criteria

- Recurrent, platinum-resistant OC
- High-grade OC
- ≤2 prior regimens
- Measurable disease
- ECOG PS 0 or 1
- Mandatory submission of tumor tissue samples

RANDOMIZATION

1:1:1

Arm A
PLD + atezolizumab

Arm B
PLD + atezolizumab + bevacizumab

Arm C
PLD + bevacizumab

n = ~488

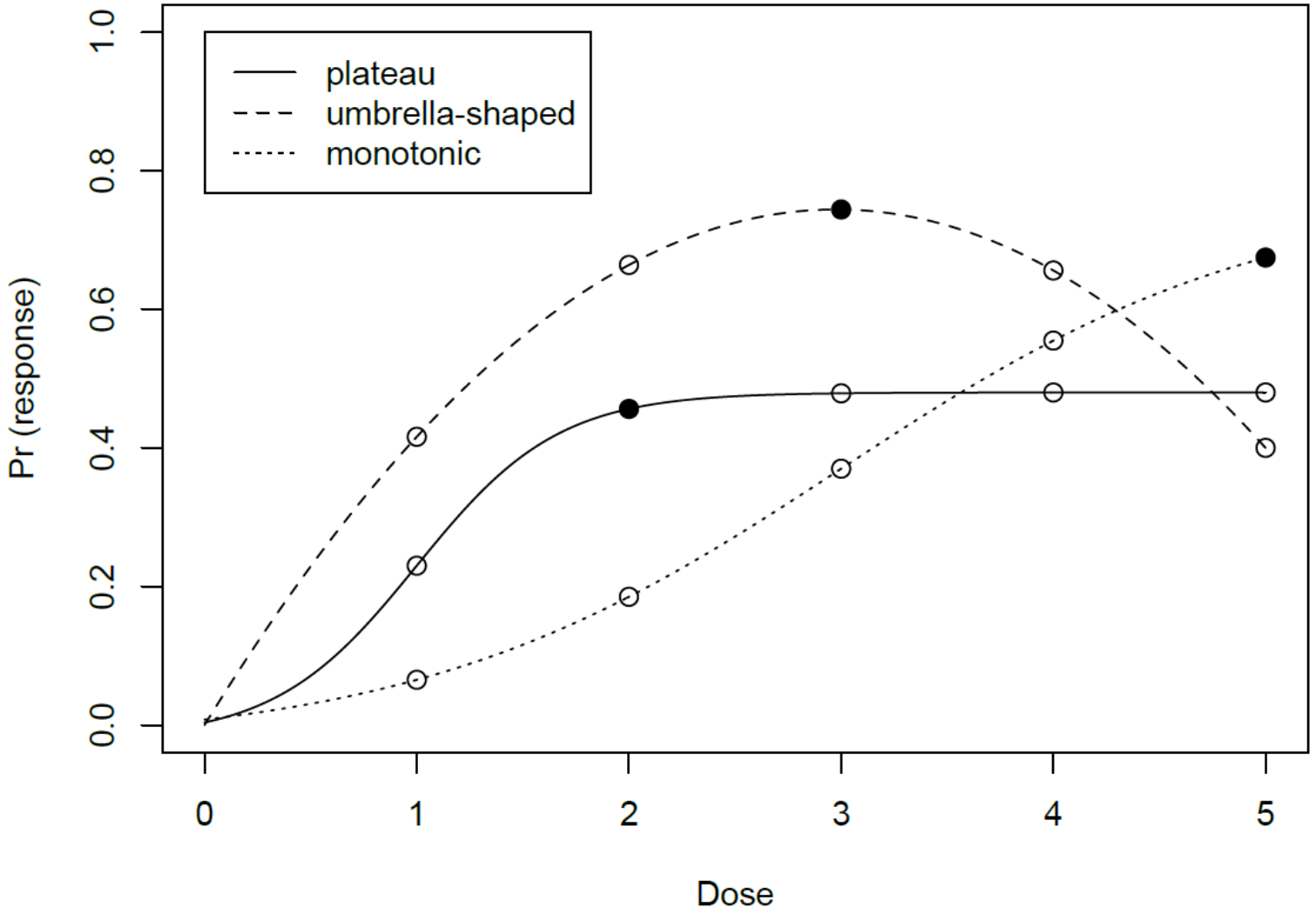
Primary Endpoint:	DLT, OS, PFS
Secondary Endpoints:	ORR, safety

- ARM A: Patients receive PLD IV on day 1 and atezolizumab IV on days 1 and 8
- ARM B: Patients receive PLD IV on day 1, bevacizumab IV on days 1 and 8, and atezolizumab IV on days 1 and 8
- ARM C: Patients receive PLD IV on day 1 and bevacizumab IV on days 1 and 8
- In all arms, courses repeat every 28 days in the absence of disease progression or unacceptable toxicity

DLT, dose-limiting toxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

Clinicaltrials.gov. Accessed October 11, 2016.

Non-Monotonic Dose-Efficacy Relationship



Courtesy of Y. Yuan

Challenges of Clinical Trial Design: Immunotherapy

- Dose – Response relationship may break down
  - More = or ≠ better
- Efficacy endpoints may not be immediate or may be realized in subsequent lines of therapy
  - Can objective response be used?
- Combination IO trials have difficult attribution/mitigation strategies
  - “Who dunnit?”
  - Dose reductions?
- Unclear if duration of exposure is important for efficacy

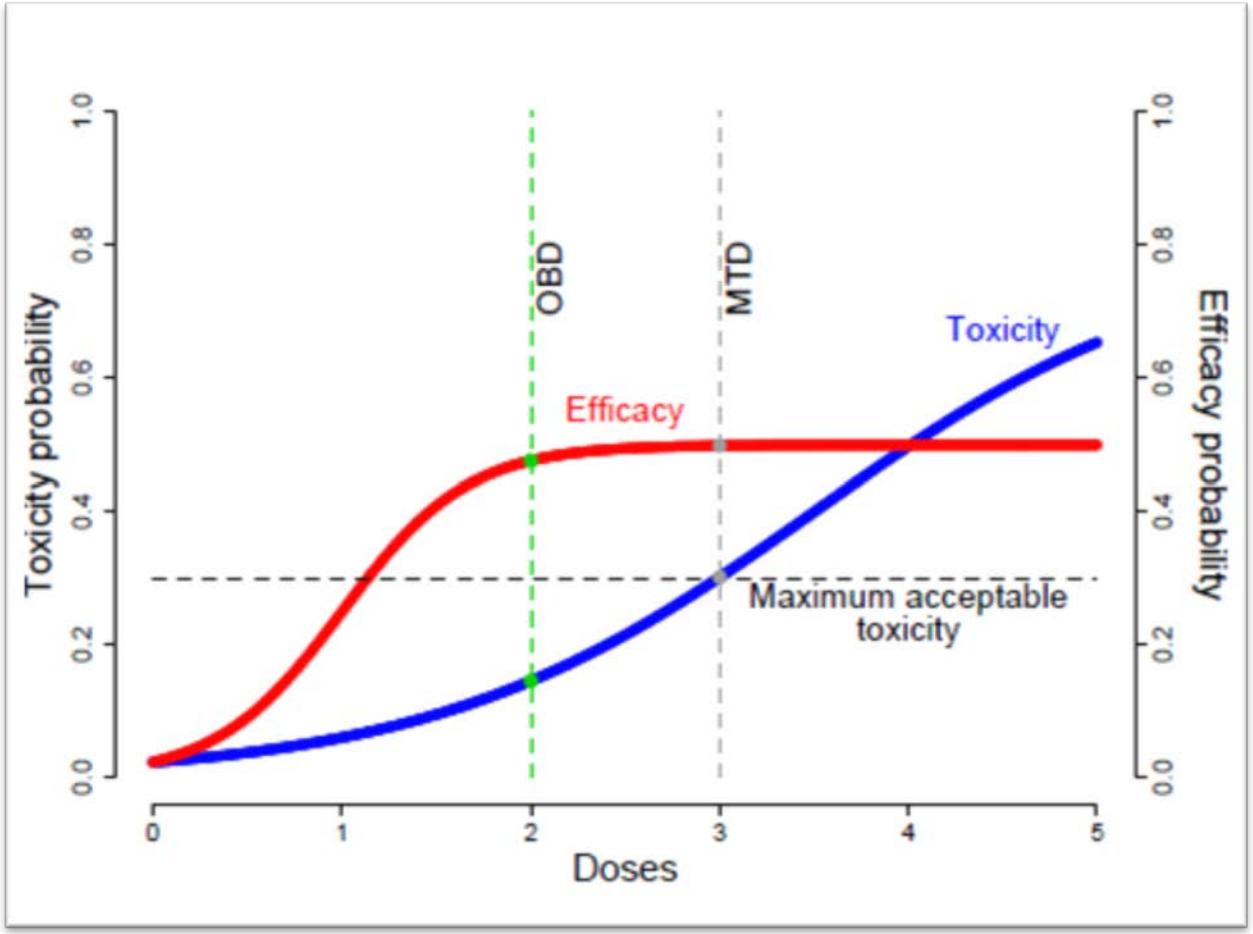
AE Management: Immunotherapy

Treatment-related Adverse Event	Grade of Event	Management/ Next Dose for *Nivolumab monotherapy (for patients who required discontinuation of ipilimumab)*	Management/Next Dose for *Combination Nivolumab plus Ipilimumab*
Neutropenia	≤ Grade 1	No change.	No change.
	Grade 2	Hold nivolumab until < Grade 2.	Hold both drugs until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2.	Hold both drugs until < Grade 2.
	Grade 4	Off protocol therapy.	If event continues >7 days, permanently discontinue ipilimumab

DART trial

Phase I-II Design Paradigm: Immunotherapy

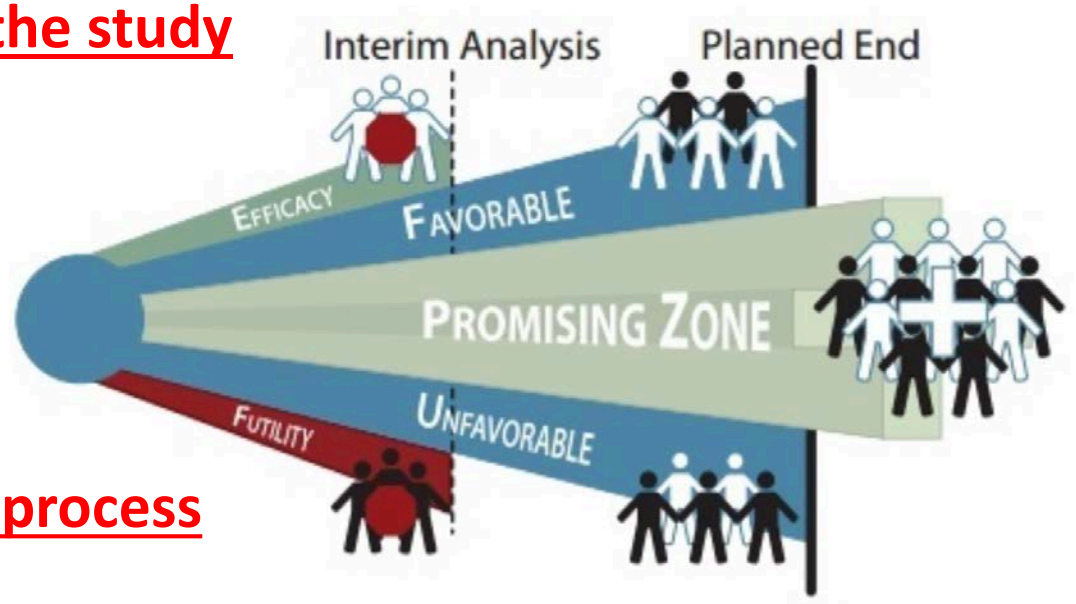
- It is imperative to consider efficacy and toxicity simultaneously, aka “phase I-II trial”.
- The primary objective of the phase I-II trial for immunotherapy is to find the optimal biological dose (OBD), rather than the maximum tolerated dose (MTD)

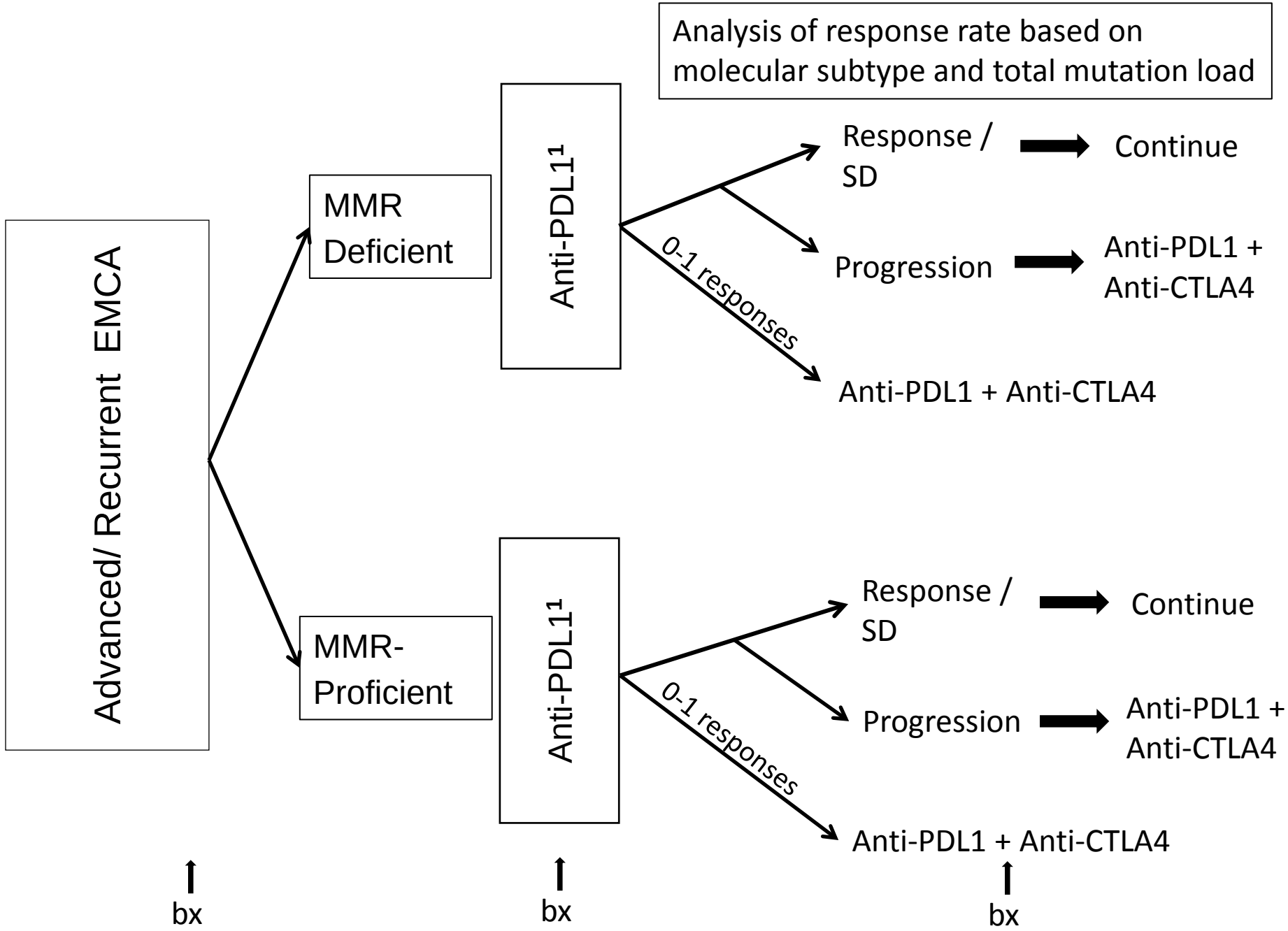


Efficacy-Driven Trial Design: Immunotherapy

Adaptation – How To Measure

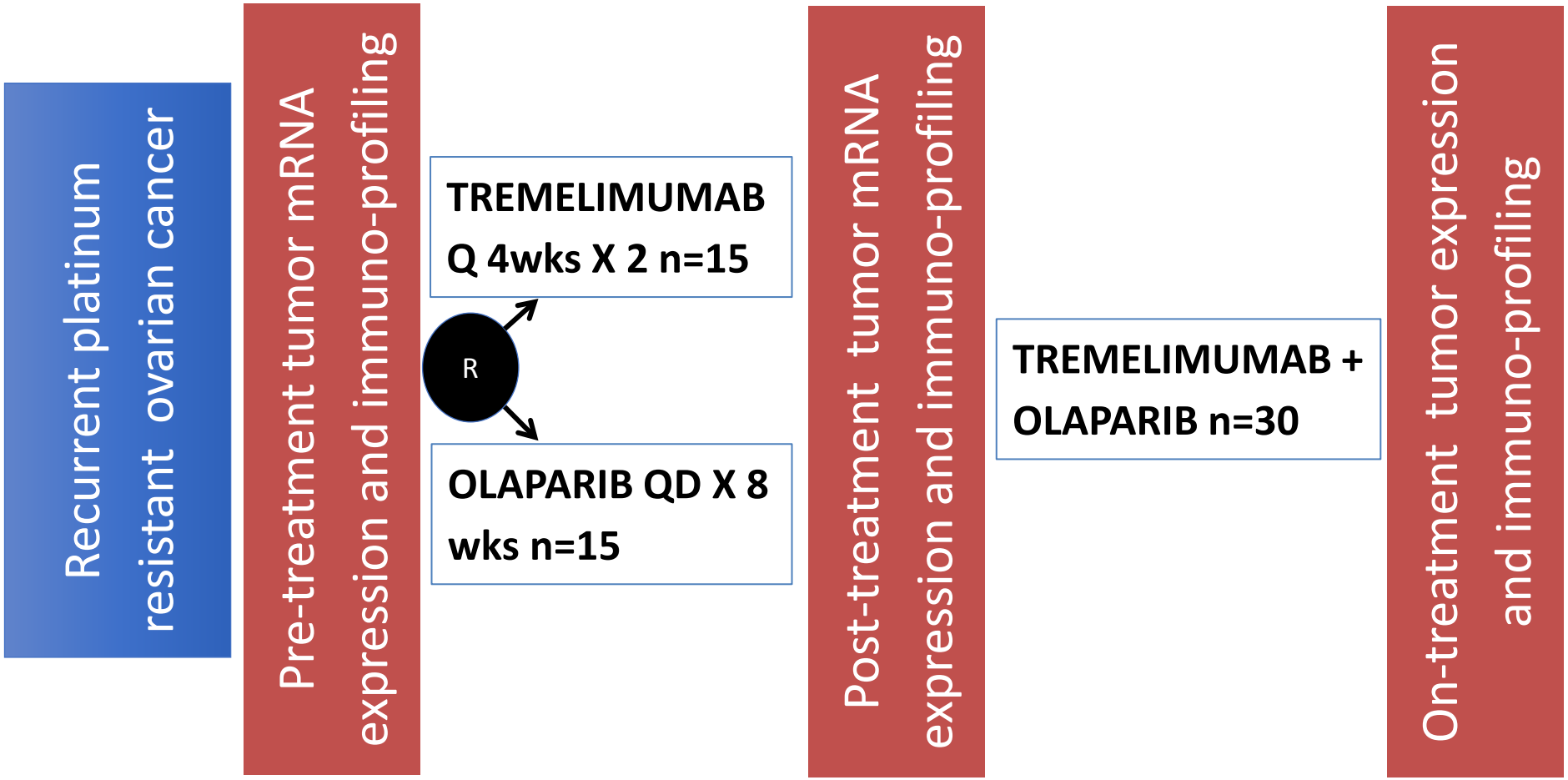
- Allows assessment of response to treatment **while the study is running**
- Can incorporate new findings from outside the trial
  - Redefine populations for study inclusion or exclusion
  - Incorporate new biomarker information
- Investigators can alter aspects of the study **while in process**
  - Add additional cohorts
  - Modify treatment schedule or dose
  - Redefine treatment for specific population needs
- This allows the trial to stay current with the latest updates



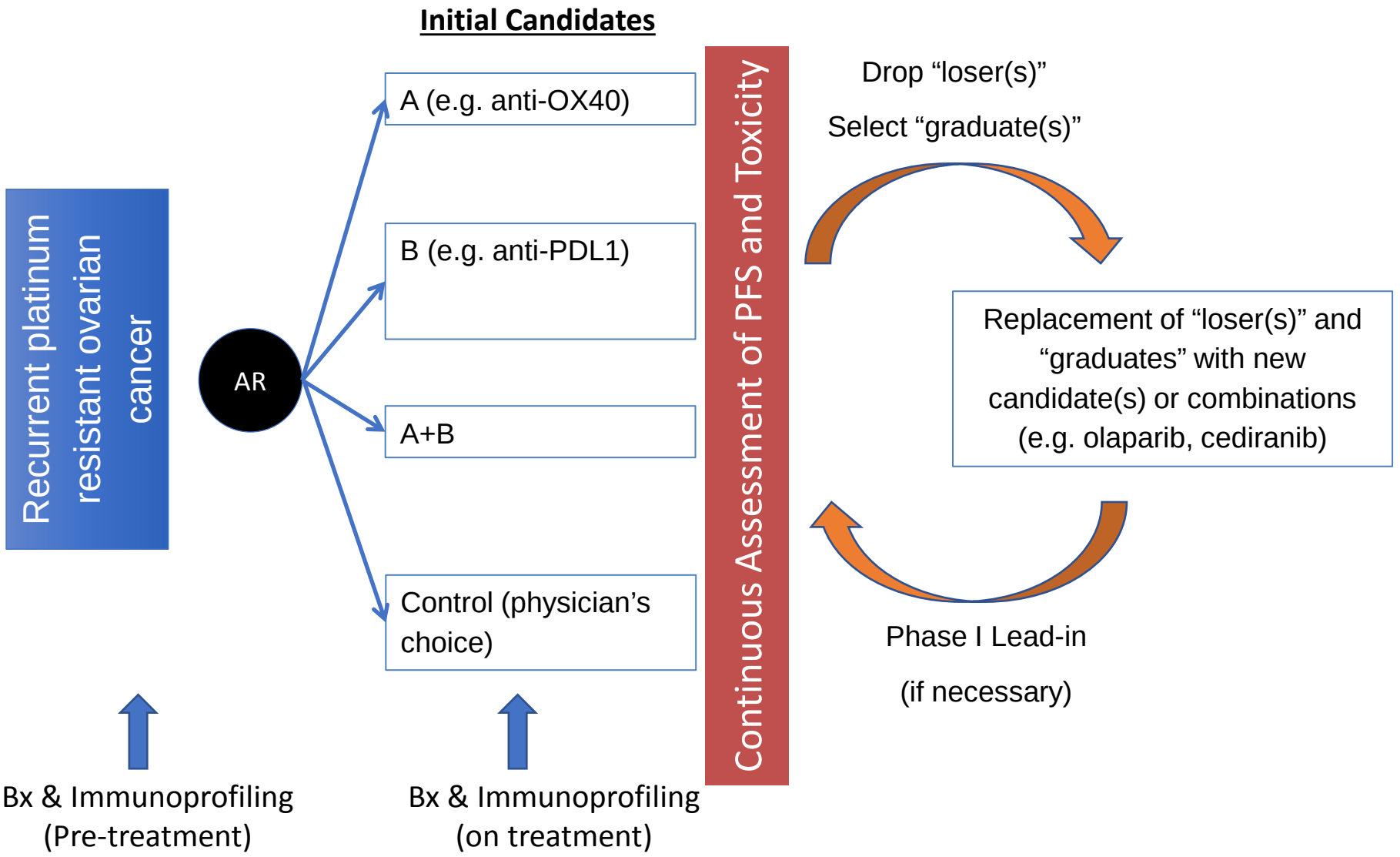


1 If zero or one responses in the first 9-10 patients, subsequent subjects will be treated with combination

Combination Biomarker + Phase II



Multi-candidate Iterative Design with Adaptive Selection (MIDAS)



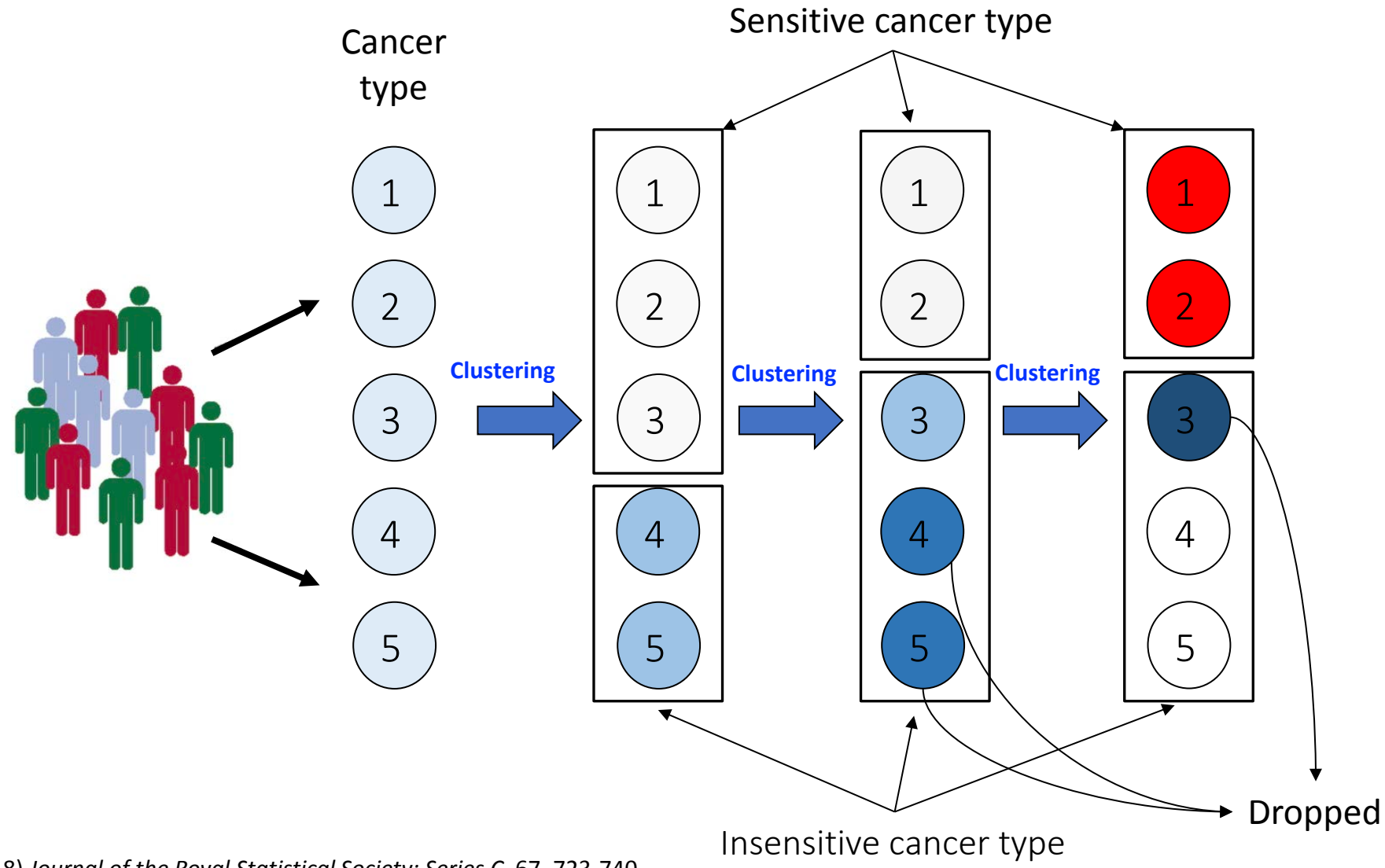
Yuan, Y., Guo, B, Munsell, M., Lu, K. and Jazaeri, A. (2016) *Stats Med*, 35, 3892-3906.

Bayesian Platform Design: MIDAS

Agent	Hazard Ratio	True toxicity rate	Entry Time (Months)	Percentage of			Number of patients
				Dropped due to toxicity	Dropped due to futility	Graduation	
				Scenario 1			
Control	1.00	0.15	0.0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	44.5 (81.0)
1	0.83	0.03	0.0	0.0 (0.0)	69.4 (68.8)	30.6 (31.2)	19.1 (13.2)
2	0.56	0.04	0.0	0.0 (0.4)	33.8 (41.8)	66.2 (57.8)	24.3 (15.0)
3	0.42	0.03	0.0	0.0 (0.2)	13.6 (24.2)	86.4 (75.6)	25.2 (16.3)
4	1.25	0.05	9.3	0.4 (0.2)	90.9 (90.2)	8.7 (9.6)	14.3 (10.5)
5	1.67	0.04	12.7	0.1 (0.4)	97.1 (96.8)	2.8 (2.8)	12.0 (9.2)
6	2.50	0.04	16.3	0.0 (0.2)	100.0 (99.6)	0.0 (0.2)	10.7 (8.5)
7	2.50	0.03	19.5	0.2 (0.0)	99.3 (99.8)	0.5 (0.2)	11.0 (8.5)

Yuan, Y., Guo, B, Munsell, M., Lu, K. and Jazaeri, A. (2016) *Statistics in Medicine*, 35, 3892-3906.

Adaptive Basket Trial Design: BLAST

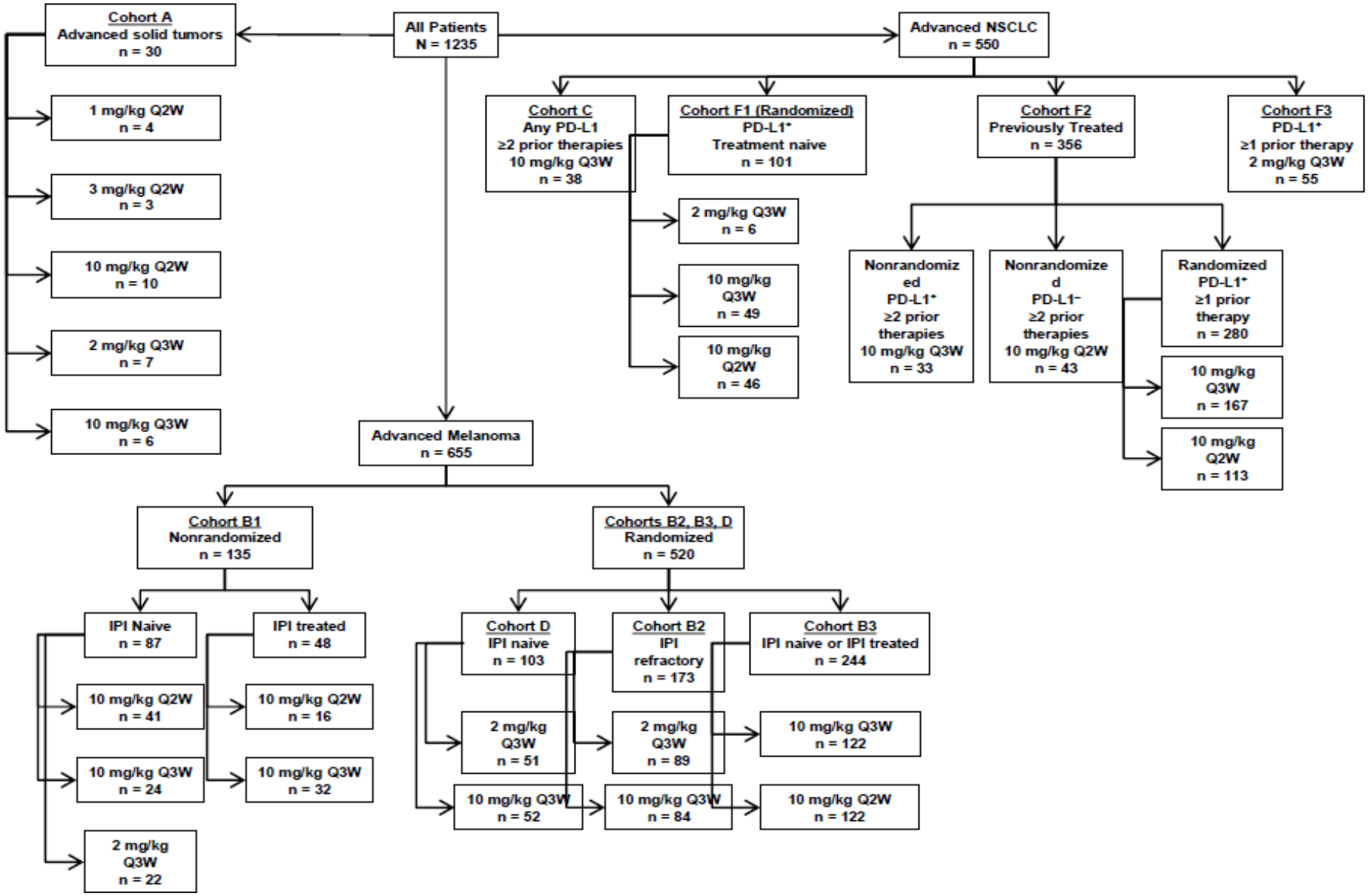


Chu, Y and Yuan, Y. (2018) *Journal of the Royal Statistical Society: Series C*, 67, 723-740.

KEYNOTE (KN-001): Pembrolizumab Trial

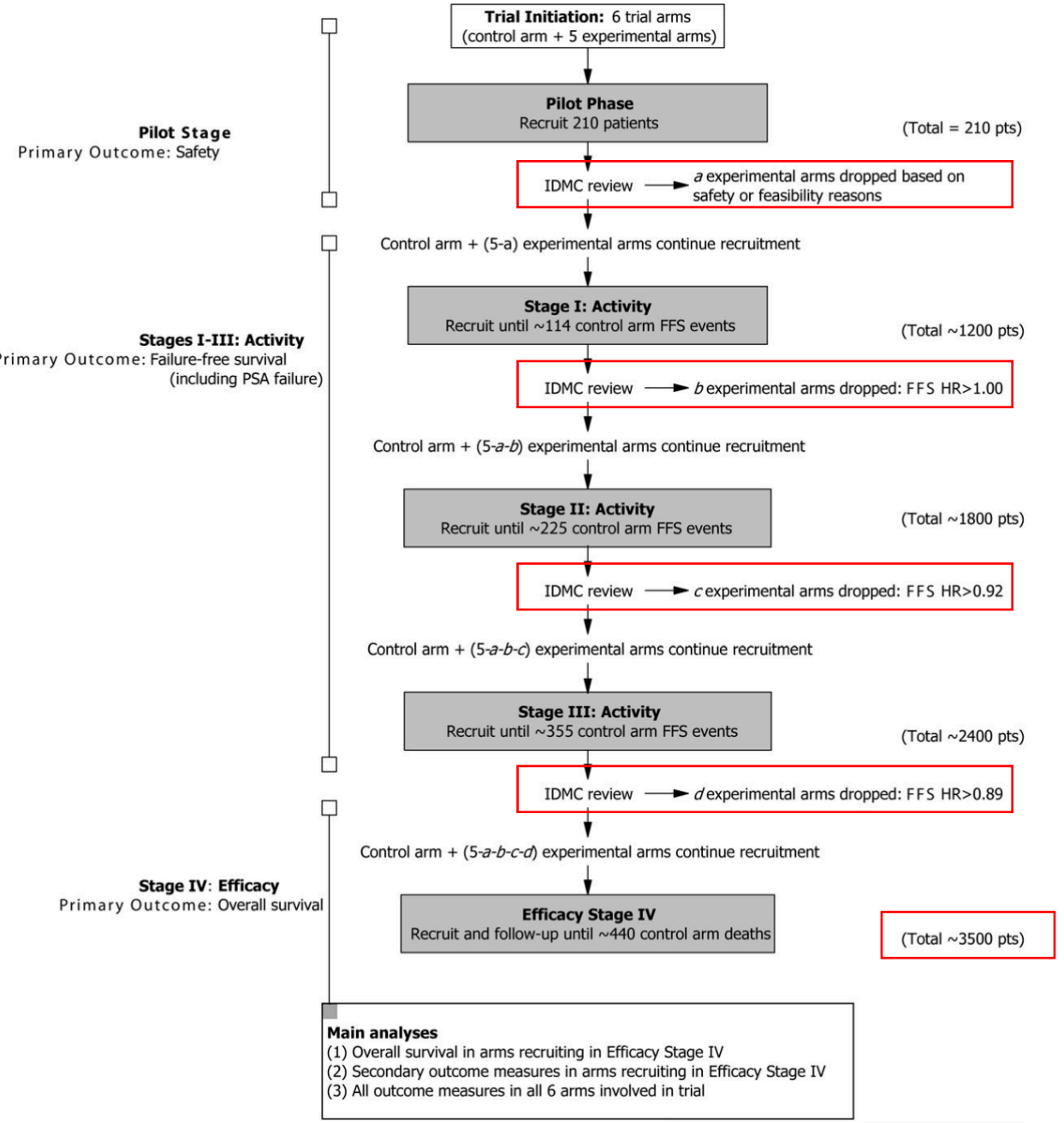
- Phase I in “advanced solid tumors” (n=40)
  - Showed high efficacy in melanoma
- Added expansion cohorts:
  - Non–small cell lung cancer
  - Testing lower doses in NSCLC and melanoma
  - To provide training and validation sets for the PD-L1 biomarker expression test
  - More disease cohorts were added as more information was collected
- Incorporated aspects of:
  - Basket trial design: different diseases
  - Umbrella trial design: biomarker variability, variable prior therapies within disease cohorts
  - Adaptive trial design: additional cohorts, different dosing
- Ultimately enrolled 1260 patients
- FDA approval (melanoma) 3.5 years after study initiation without a randomized, controlled trial
  - Other data from the study has led to approval in NSCLC, head and neck cancer, Hodgkin lymphoma, urothelial carcinoma, MSI-high cancer, and gastric cancer

KN-001: Pembrolizumab Seamless Design Study



STAMPEDE Trial: Advanced Prostate

- Outcomes:
  - Pilot: toxicity
  - Stage I: PFS (HR ≤ 0.75)
  - Stage II: PFS (HR ≤ 0.75)
  - Stage III: PFS (HR ≤ 0.75)
  - Stage IV: OS (HR ≤ 0.75)
- Overall analysis: pairwise with multiple comparisons correction ($p < 0.017$)



Take Home Messages

- Clinical trial designs based on dose to response relationships provide poor guidance for immunotherapy
- Multiagent biological trials are tricky to conduct and best leverage existing and emerging information to optimize OBD identification
- Adaptive designs are most efficient for constructing the dose-toxicity trade-offs
- Seamless designs can develop information for regulatory intent