Dose Selection Approaches for Combination Oncology/Immuno-Oncology Agents

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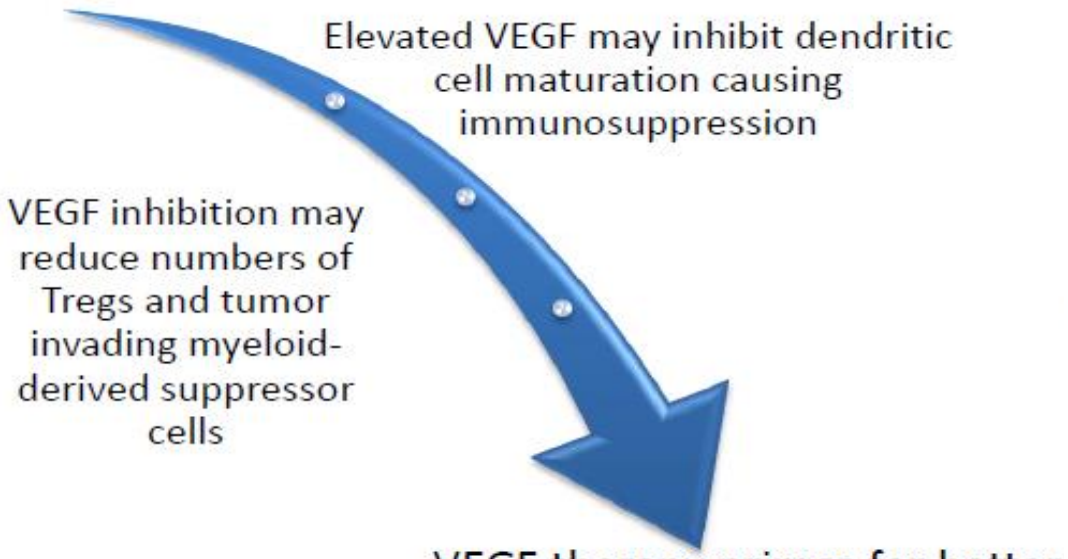
Proposed mechanisms of synergy VEGF + PD-1 inhibition

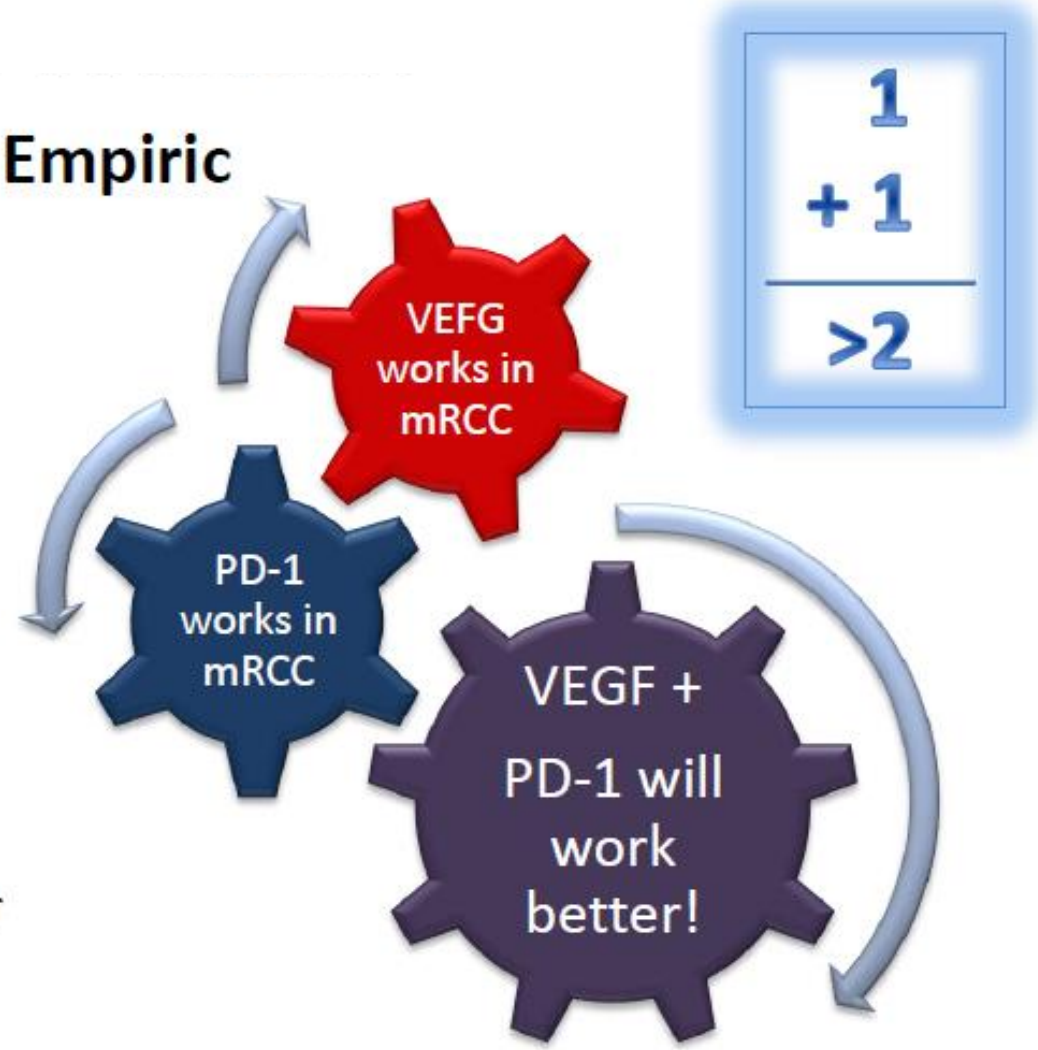
Immunologic



Gunturi A, McDermott DF: *Current treatment options in oncology* 2014

Combination dose and schedule may be based on PD modulation and MoA

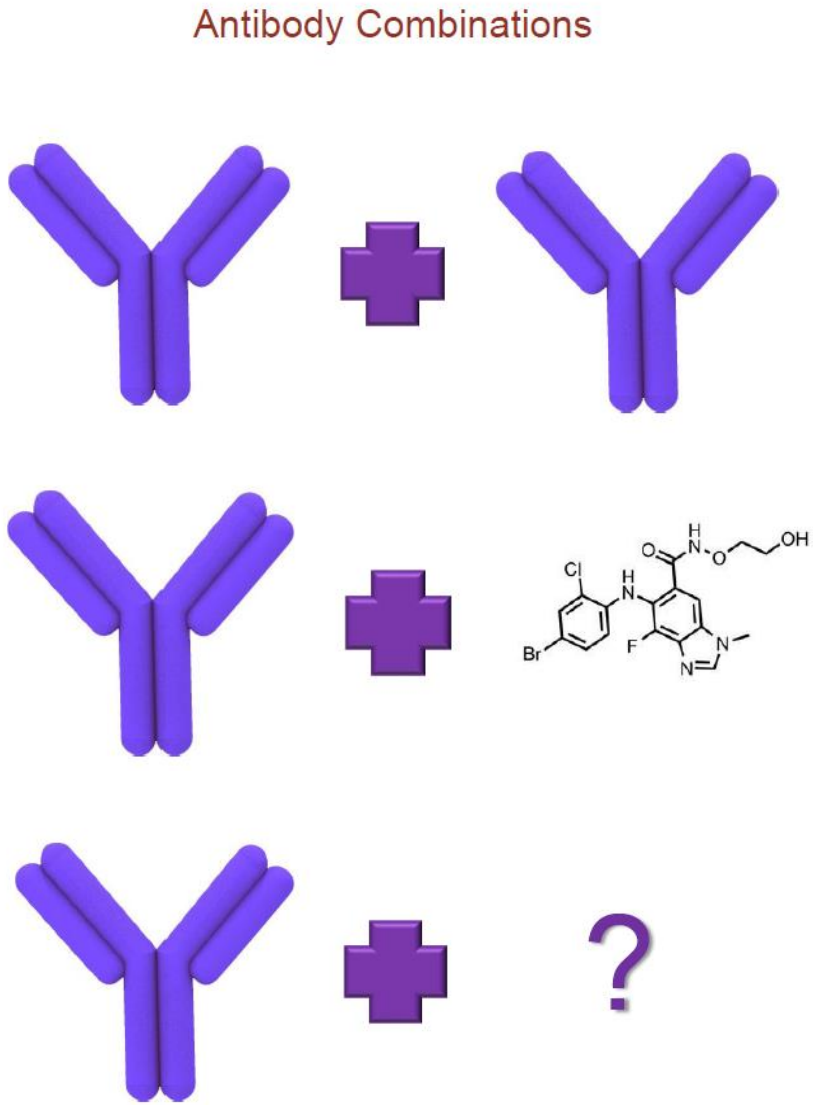
Empiric



Combination dose and schedule typically anchored on approved doses

Antibody combinations

- For most of biologic therapies in oncology, maximal tolerated doses become irrelevant as therapeutic effects are already achieved at lower doses
- PK interaction is highly unlikely when two monoclonal antibodies are combined
- Immunogenicity rates may be different for combination compared to monotherapy



Lee L, Gupta M, Sahasranaman S. J Clin Pharmacol. 2016 Feb;56(2):157-69

Challenges in Dose Selection of Combination Oncology agents

- Dose-finding is primarily based on toxicity observed clinically
  - Pre-clinical toxicology studies are typically not conducted with combination agents

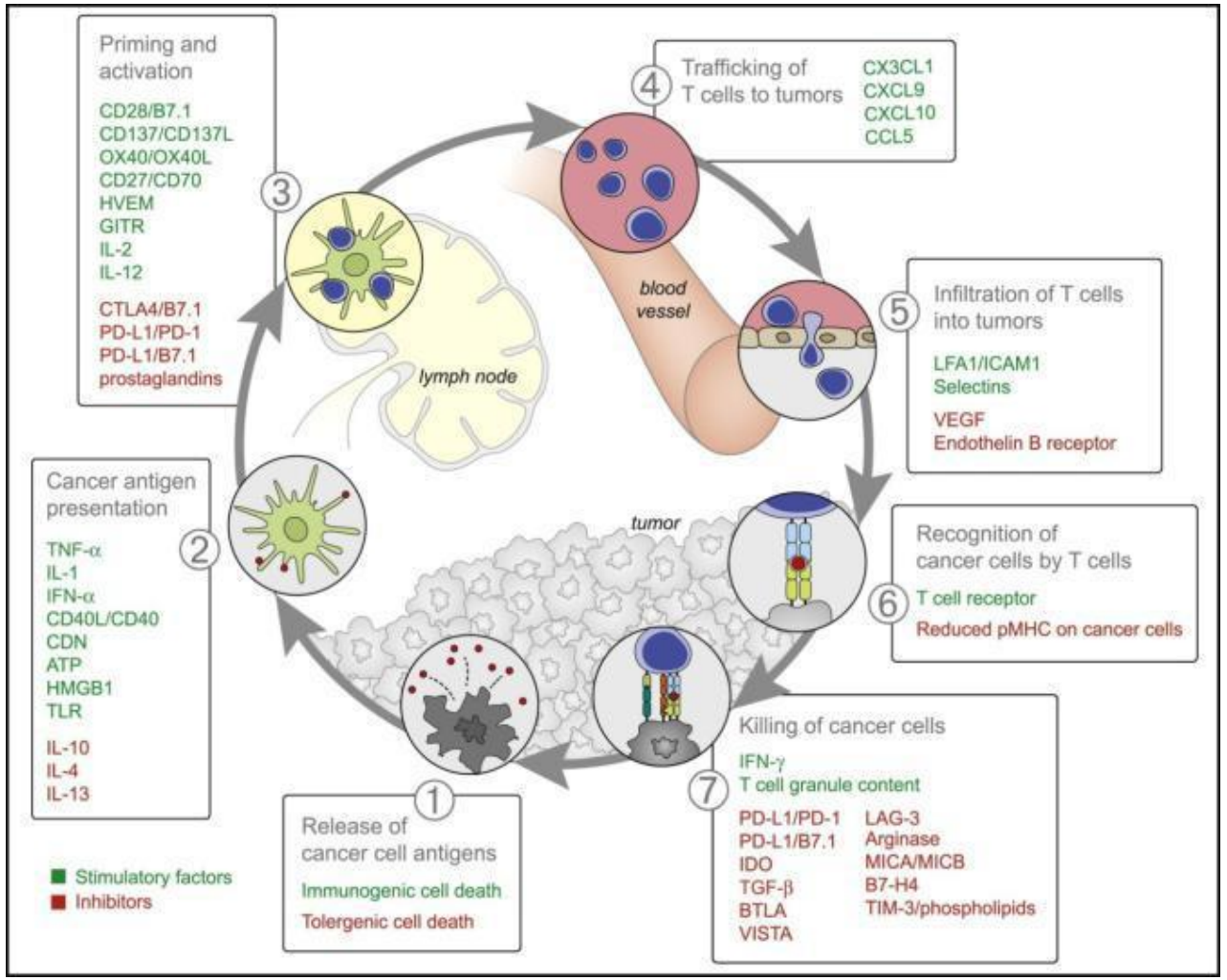
- Little may be known between the synergy of combination agents, as most of the information is primarily driven by Science and MoA
  - Prior information on each agent used alone in previous trials may be available
  - Activity in combination may need to benchmarked against historical data, as responses in combination may originate from combination partner

- Extremely difficult to find the right dose combination in small subset of patients from Phase I
  - Short-term endpoints (objective response rate, dose-limiting toxicities, etc.) used in Phase I may not be reflective of long-term outcome (OS)
  - DLT criteria for dose selection based on early data (1-2 cycles) and may not account for delayed toxicity

- Challenges in Dose selection of combination oncology agents
  - Sample Sizes typically are very small in early trials
  - Patient Heterogeneity may be substantial
  - Overlapping toxicities for combination agents may not be apparent in short DLT period
  - Limited pharmacodynamics data to assess biological activity

Barrett JS, Gupta M, Mondick J. Expert Opinion on Drug Discovery 2;2 (2007) 185-209.

Stimulatory and Inhibitory Molecules During Immune Tumor Surveillance



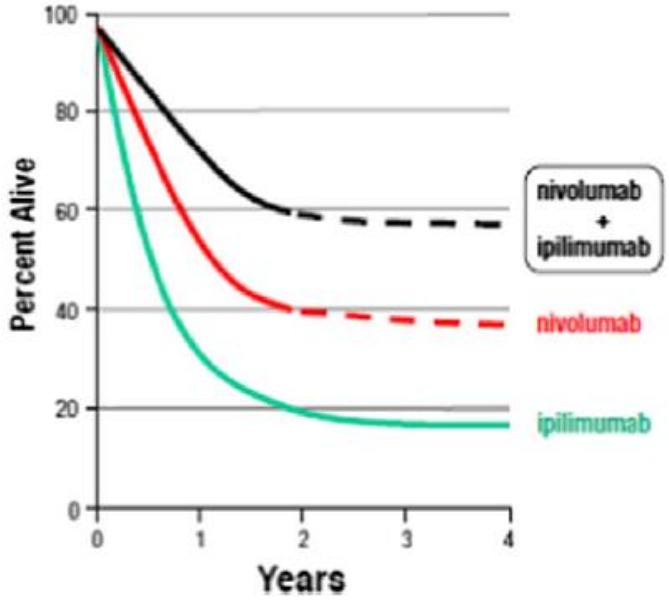
Chen, et al. Immunity. 2013

Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

- PD-1 and CTLA-4 are non-redundant immune checkpoints in T-cell differentiation and function
- Anti-tumor synergy demonstrated in several synergy models
- Both agents are active in metastatic melanoma

Agent	Dose, mg/kg	ORR, %	CR, n	Median OS, months	2- / 3-yr OS rate, %	Grade 3/4 treatment-related AE, %
Ipilimumab[1,2]	3	11	2	10.1	24 / 20	23%
Nivolumab[3,4]	0.1-10	31	1	16.8	43 / —	14%
Nivolumab + ipilimumab[5]	Nivo 0.3 + Ipi 1 Nivo 1 + Ipi 3 Nivo 3 + IPI 1 Nivo 3 + IPI 3	40	5	Not reached	82 (1 year)	53%

[1]Hodi et al. *N Engl J Med.* 2010;363:711-23.; [2]Wolchok et al. *Ann Oncol* 2013;24:2174-80.; [3]Sznol et al. ASCO 2013, oral presentation, abs CRA9006.; [4]Topalian S, et al. *N Engl J Med* 2012;366:2443-54; [5]Wolchok et al. *N Engl J Med.* 2013;369:122-33



D. Berman et al. Pharmacology & Therapeutics 148 (2015) 132–153

Presented By Mario Sznol at 2014 ASCO Annual Meeting

Exposure-Response analysis with Ipilimumab and Nivolumab in metastatic melanoma

- **Higher doses of ipilimumab monotherapy produce greater Cminss that may be associated with increased tumor responses, longer survival, and higher rates of irAEs**
  - Model-based estimates indicate that the probabilities of a CR or PR at median Cminss for the 0.3, 3, and 10 mg/kg groups were 0.6%, 4.9%, and 11.6%, respectively.
  - Overall survival at the median Cminss for ipilimumab at 0.3 mg/kg was estimated to be 0.85- and 0.58-fold lower relative to that at the median Cminss for 3 and 10 mg/kg, respectively.
  - Model-based estimates indicate that the probabilities of a grade 3 or more irAE at the median Cminss for the 0.3, 3, and 10 mg/kg doses were 3%, 13%, and 24%, respectively.
- **Exposure-response of Nivolumab is relatively flat for melanoma at doses ≥1 mg/kg**

Feng Y, Roy A, et al. Clin Cancer Res. 2013 Jul 15;19(14):3977-86.
Opdivo® Case Study-Refractory Melanoma at the AADAV workshop, May 6-8, 2015

CA209004 Phase I Study: Dose Cohorts Nivolumab + Ipilimumab in Metastatic Melanoma

		Dose (mg/kg),		Treatment Schedule	
Regimen Cohort No.	N	Nivolumab	Ipilimumab	Induction	Maintenance
Concurrent					
1	14	0.3	3	Nivo Q3W x 8 + IPI Q3W x 4	Nivo + IPI Q12W x 8
2	17	1	3		
2a	16	3	1		
3	6	3	3		
8*	41	1	3	Nivo Q3W x 8 + IPI Q3W x 4	Nivo 3 mg/kg Q2W (Max. 48 doses)
Sequenced					
6	17	1	Prior	Nivo Q2W (Max of 48 doses)	
7	16	3	Prior		

*Insufficient follow-up at this data collection to report survival endpoints

Presented By Mario Sznol at 2014 ASCO Annual Meeting

CA209004 Phase I Study: Activity Summary Nivolumab + Ipilimumab in Metastatic Melanoma

Nivolumab (mg/kg) + IPI (mg/kg)	N	ORR[a], %	CR, %	Aggregate Clinical Activity Rate	≥80% tumor burden reduction at 36 wks[b], %
Concurrent Cohorts 1-3	53	42	17	70	42
0.3 + 3	14	21	14	57	36
1 + 3	17	53	18	65	53
3 + 1	16	44	25	81	31
3 + 3	6	50	0	83	50
1 + 3 [Cohort 8][c]	40	43	10[d]	53	28
Sequenced	33	31	3	44	31

[a]per RECIST, [CR+PR]/N x 100; [b] Best overall response; [c]Cohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. [d]2 confirmed and 2 unconfirmed responses

n: no. response-evaluable pts.

Presented By Mario Sznol at 2014 ASCO Annual Meeting

CA209004 Phase I Study: Safety Overview Nivolumab + Ipilimumab in Metastatic Melanoma

AE, %	Concurrent Cohorts 1-3 n=53		Cohort 8 n = 41		All Concurrent n=94	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
All Related AEs	**96**	**62**	**95**	**61**	**96**	**62**
Select AEs						
Gastrointestinal	43	9	34	20	39	14
Hepatic	30	15	12	12	22	14
Skin	79	4	73	15	77	9
Endocrine	17	4	22	2	19	3
Renal	6	6	0	0	3	3
Other						
Uveitis	6	4	2	2	4	3
Pneumonitis	6	2	2	2	4	2
Lipase increased	26	19	15	10	21	15
Amylase increased	21	6	12	7	17	6

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8

Presented By Mario Sznol at 2014 ASCO Annual Meeting

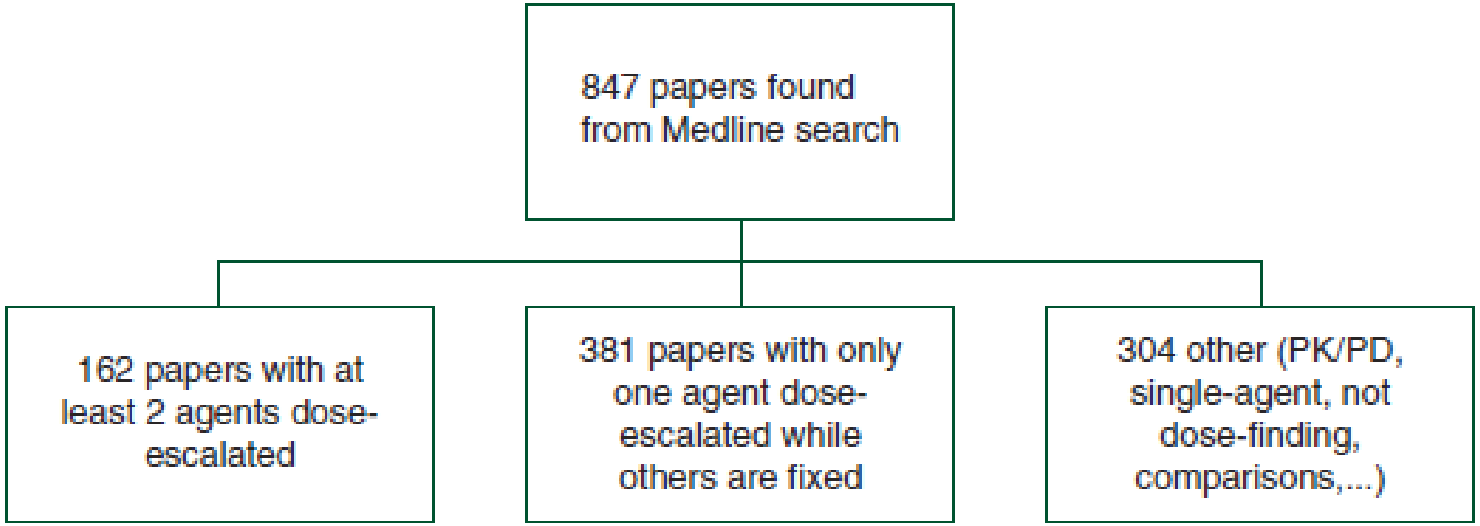
Summary: Dose Selection of Nivolumab + Ipilimumab in Metastatic Melanoma

- Based on cumulative evidence of safety/ activity, Nivolumab 1 mg/kg and Ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by Nivolumab 3 mg/kg every 2 week, was picked as a regimen for pivotal trials in metastatic melanoma
- Does the same Ipilimumab/ Nivolumab combination dose/ regimen work in other tumor types?

Challenges in Dose Selection of Combination Oncology agents

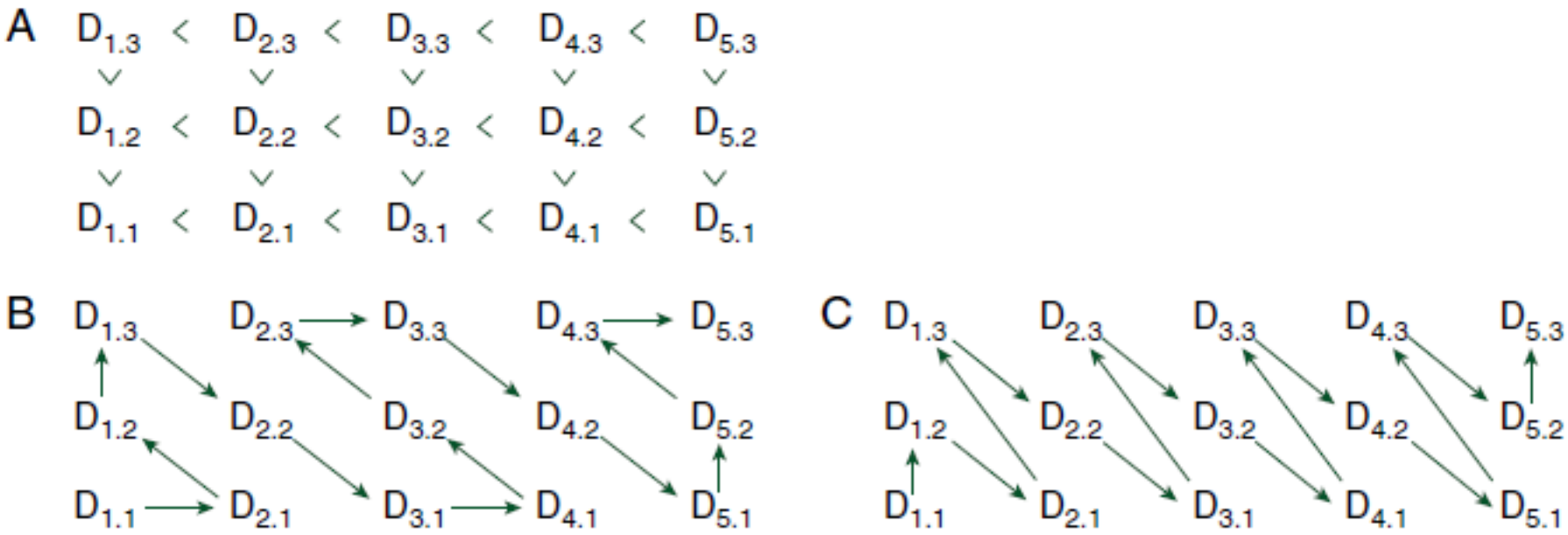
- **The set of possible dose pairs is much larger than the usual interval of doses in the single-agent case**
- **Dose pairs are typically chosen to maximize Cancer-Killing Potential and/or Information**
  - Dose of the approved drug is typically anchored, and dose of experimental drug titrated
  - Selection of the dosing schedule (weekly vs. every 3 week) also driven by schedule of the combination drug (for example, patient visits, approved cytotoxic regimen, etc.)
  - Limited precedence to select more than one combination dose pair for pivotal trials
- **Several dose related questions of interest in therapeutic development of combination oncology agents**
  - Dose-efficacy association
  - Dose-safety association
  - Schedule-efficacy association
  - Interactions between therapies (i.e. combinations of treatments)
- **Safety/ Efficacy is typically tumor-specific and may be different for different dose combinations**

Flowchart of the publications found from the Medline Pubmed search on Combination doses



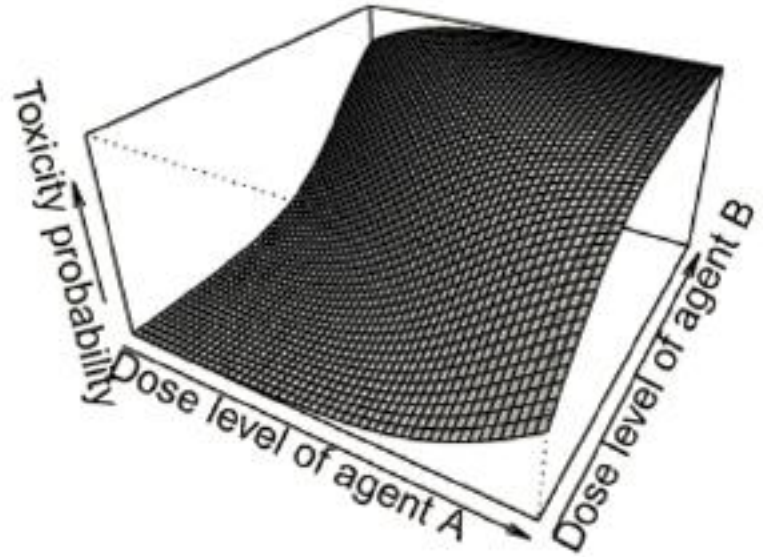
Riviere et al. Annals of Oncology. 2015

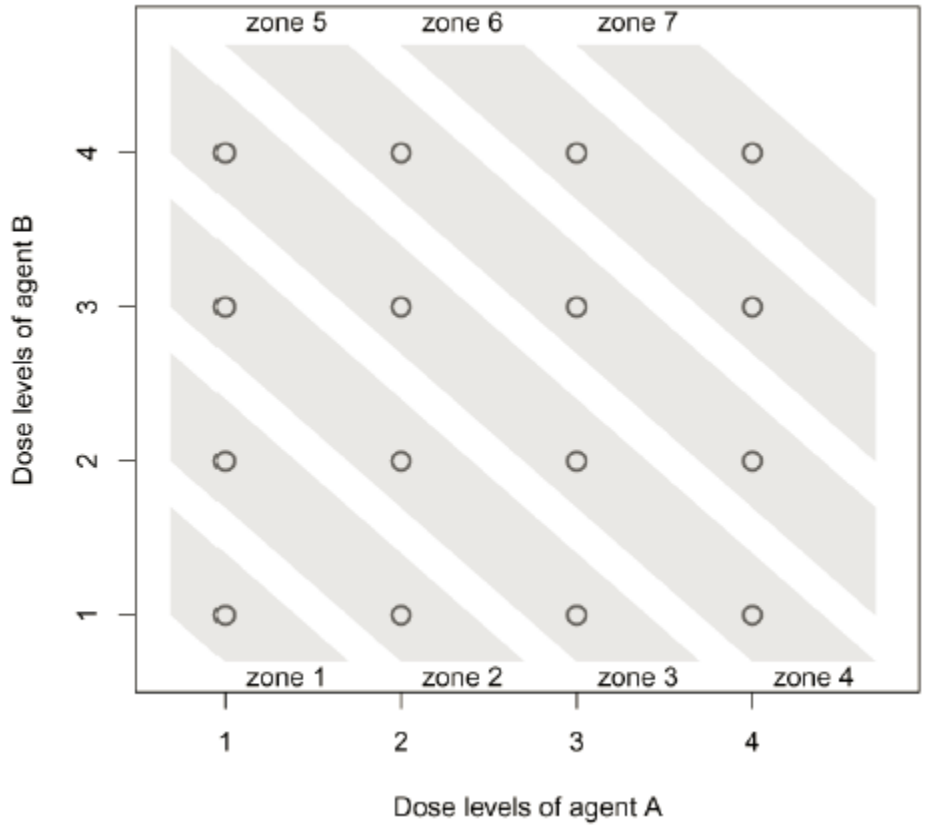
Orderings between Combinations



Riviere et al. Annals of Oncology. 2015

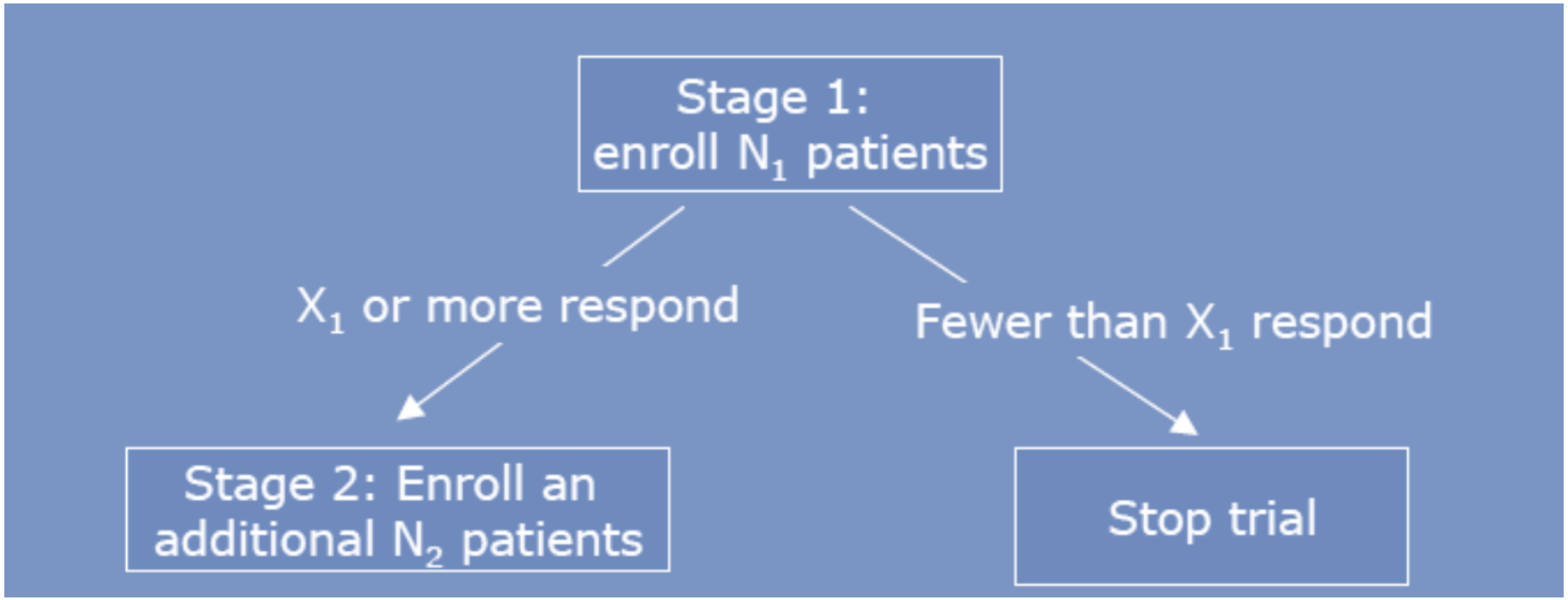
Dose-Toxicity relationship for Combinational agents





Implementation of Futility Designs in Early clinical development of Oncology Combination agents

- For example, Fleming/ Simon-2 Stage can be used in early clinical development of Oncology combination agents, and efficacy data can be benchmarked against historical data



Trial Designs for Optimal Dose Selection of Combination Oncology agents

- Starting doses of the drugs, as well as the dose levels and the dose-escalation steps, need to be appropriately justified with aim to
  - Ensure patient safety
  - Treat as few patients as possible at presumably infra-therapeutic doses
  - Identify the optimal drug combination for further evaluation
- Innovative Phase I trial designs are needed; dose-finding needs to be sequential and adaptive for ethical reasons
  - Balance of speed and rigor for optimal dose-finding for combinations
  - Dose-finding using alternative approaches (e.g. model-based approaches)
- CRM methods introduced with the potential to improve the precision of such studies to determine a dose with a certain toxicity threshold
- More flexible two-parameter Bayesian logistic models developed to better characterize the dose-toxicity relationship
- Futility designs can be used for Go/No Go decisions in early clinical development of combination oncology agents