

Critical Issues for Early Trial Design in Immunotherapy

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Disclosure

- Nothing to disclose

Is Phase 1 Clinical Trial Design a “Passé” For Cancer Vaccine Development?

FDA Regulation for Drug Development

- Safety
 - Federal Food, Drug, and Cosmetic Act in 1938
(Pub. L. No. 75-717, 52 Stat. 1040)
- Efficacy
 - The Kefauver-Harris Amendments in 1962

Clinical Trials in Drug Development

- Phase 1- Determine a safe dose
- Phase 2- Determine a preliminary efficacy
- Phase 3- Confirm efficacy

Phase 1

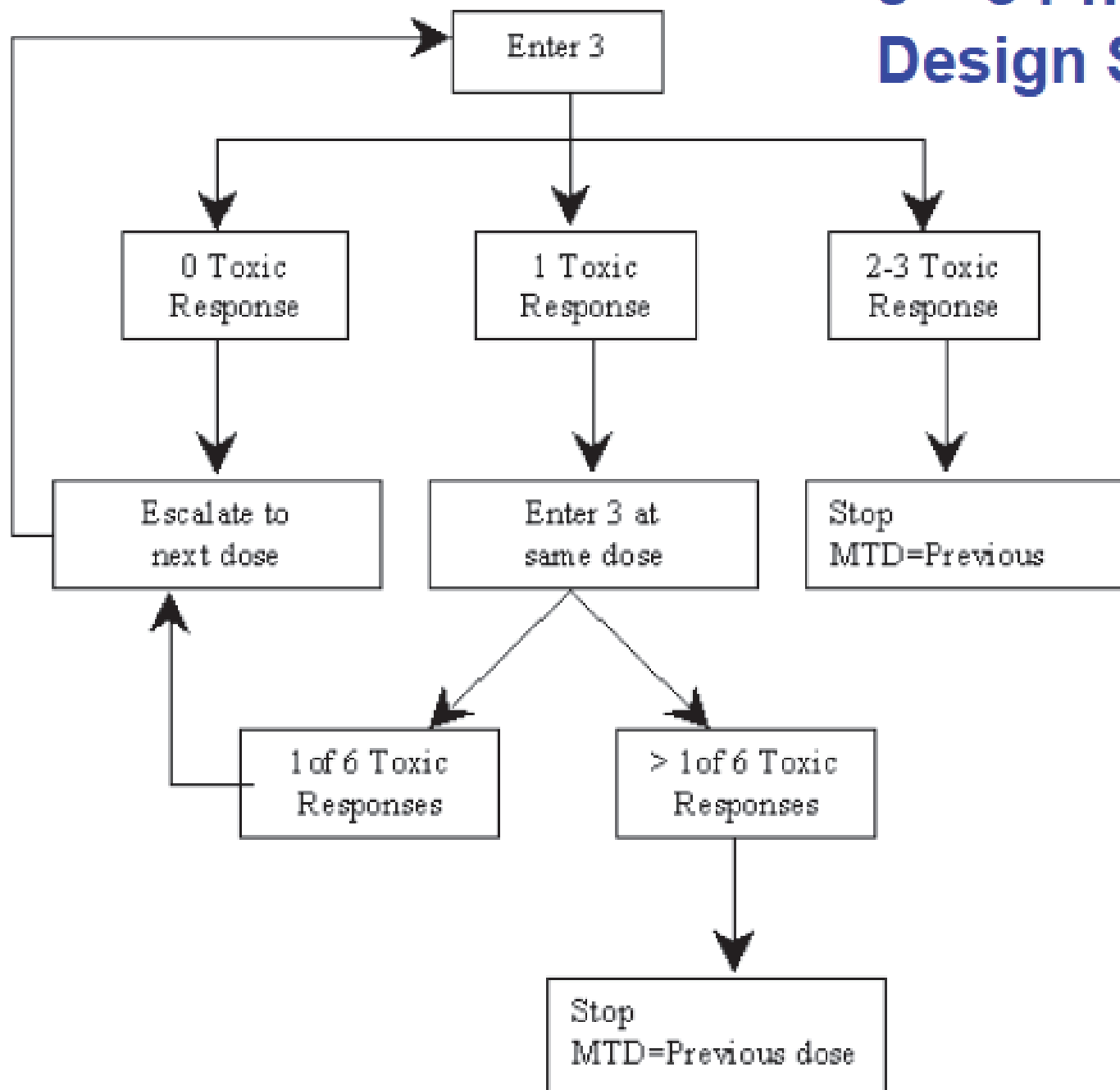
- Determine a Maximum Tolerated Dose (MTD)

The highest dose that will produce the desired effect without unacceptable toxicity

- Determine a Biological Active Dose (BAD)

The dose that will produce the desired effect on a specific molecule's function

3 + 3 Phase 1 Study Design Schematic



Questions in Early Cancer Vaccine Development

- Are cancer vaccines toxic?
- Does dose escalation determine MTD?
- Does dose escalation determine BAD?
- Is an alternative design needed?

- Search for cancer vaccine trials on PubMed
- Phase 1, phase1/2, and pilot studies in therapeutic cancer vaccines
- Reported from 1990 through 2011

Questions in Early Cancer Vaccine Development

- Are cancer vaccines toxic?
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- Does dose escalation determine BAD?
- Is an alternative design needed?

What is the rate of vaccine-related toxicity in relation to the number of vaccinated patients?

Vaccine trials			All Grade 3/4 Toxicities		Systemic Vaccine Related Grade 3/4 Toxicities	
Vaccine Category	No. Trials	No. Patients	No. Events	%	No. Events	%
Autologous	88	1692	37	2.19	23	1.36
DC	58	922	9	0.98	3	0.33
Tumor	30	770	28	3.64	20	2.60
Allogeneic	17	407	22	5.41	5	1.23
Synthetic	136	2853	108	3.79	35	1.23
Peptide	68	1333	40	3.00	11	0.83
DNA	17	311	1	0.32	1	0.32
RNA	2	36	0	0	0	0
Virus	31	662	23	3.47	13	1.96
Bacteria	6	126	27	21.43	7	3.97
Anti-idiotypic	10	362	15	4.14	0	0
Liposomal	2	23	2	8.70	2	8.70
TOTAL	241	4952	167	3.37	62	1.25

What is the rate of vaccine-related toxicity in relation to the number administered vaccines?

Vaccine Trials				All Grade 3/4 Toxicities		Systemic Vaccine Related Grade 3/4 Toxicities	
Vaccine Category	No. Trials	No. Patients	No. Vaccines	No. Events	%	No. Events	%
Autologous	73	1301	5722	20	0.35	8	0.14
DC	51	796	3424	9	0.26	3	0.09
Tumor	22	505	2298	11	0.48	5	0.22
Allogeneic	16	347	1874	22	1.17	5	0.26
Synthetic	117	2376	14239	78	0.55	30	0.21
Peptide	61	1183	7637	37	0.48	9	0.12
DNA	15	259	1388	1	0.07	1	0.07
RNA	2	36	335	0	0	0	0
Virus	27	535	2365	22	0.93	13	0.55
Bacteria	4	80	530	9	1.70	5	0.94
Anti-idiotypic	7	266	1938	7	0.36	0	0
Liposomal	1	17	46	2	4.35	2	4.35
TOTAL	206	4024	21835	120	0.55	43	0.20

Questions in Early Cancer Vaccine Development

- Are cancer vaccines toxic?
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- Is an alternative design needed?

Vaccine Category	No. Trials	No. Patients	Grade 3/4			Trials with DLT
			No. Trials	No. AE	No. *Related AE	
Autologous	40	847	2	11	8	0
DC	27	466	0	0	0	0
Tumor	13	381	2	11	8	0
Allogeneic	5	130	3	20	5	1
Synthetic	83	2008	17	67	27	2
Peptide	36	852	7	10	7	0
DNA	12	208	1	1	1	0
Virus	26	592	7	47	17	0
Bacteria	4	81	4	27	7	2
Anti-idiotypic	8	339	1	7	0	0
Liposomal	1	17	1	2	2	0
TOTAL	127	2985	22	98	40	3

Trials with DLT

Trial	Vaccine	Toxicity	DLT
Dols et al. 2003	Allogeneic HER2/neu(+) breast cancer cells (SC) with GM-CSF or BCG	Nausea/Vomiting	1 patient at 250 µg/m ² GM-CSF
Maciag et al. 2009	<i>L. monocytogenes</i> secreting HPV-16 E7 fused to <i>Lm</i> listeriolysin O (IV)	Hypotension	3 patients at highest dose level
Guthmann et al. 2004	GM3 ganglioside with <i>N. meningitidis</i> outer membrane (IM)	Hypotension	1 patient at highest dose level

Conclusion

- Dose escalation design has no role in defining
 - The maximum tolerated dose (MTD)
 - Except for bacterial vector vaccines

Questions in Early Cancer Vaccine Development

- Are cancer vaccines toxic?
- Does dose escalation determine MTD?
- Does dose escalation determine BAD?
- Is an alternative design needed?

Trials with Dose Related Cellular Immune Response

Vaccine Category	No. Trials	Dose Related Cellular Immune Response
Autologous	32	0
Allogeneic	4	0
Synthetic	80	0
Total	116	0

Conclusion

- Dose escalation design has not been shown to define
 - The biologically active dose (BAD)

Questions in early cancer vaccine development

- Are cancer vaccines toxic?
- Does dose escalation determine MTD?
- Does dose escalation determine BAD?
- Is an alternative design needed?

Vaccine dose cannot be determined by traditional dose escalation design since it does not determine:

- Safety (except for bacterial vector vaccines)
- Or biological activity

- A new design paradigm is needed
- The new paradigm will be the subject of discussion in the April workshop

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