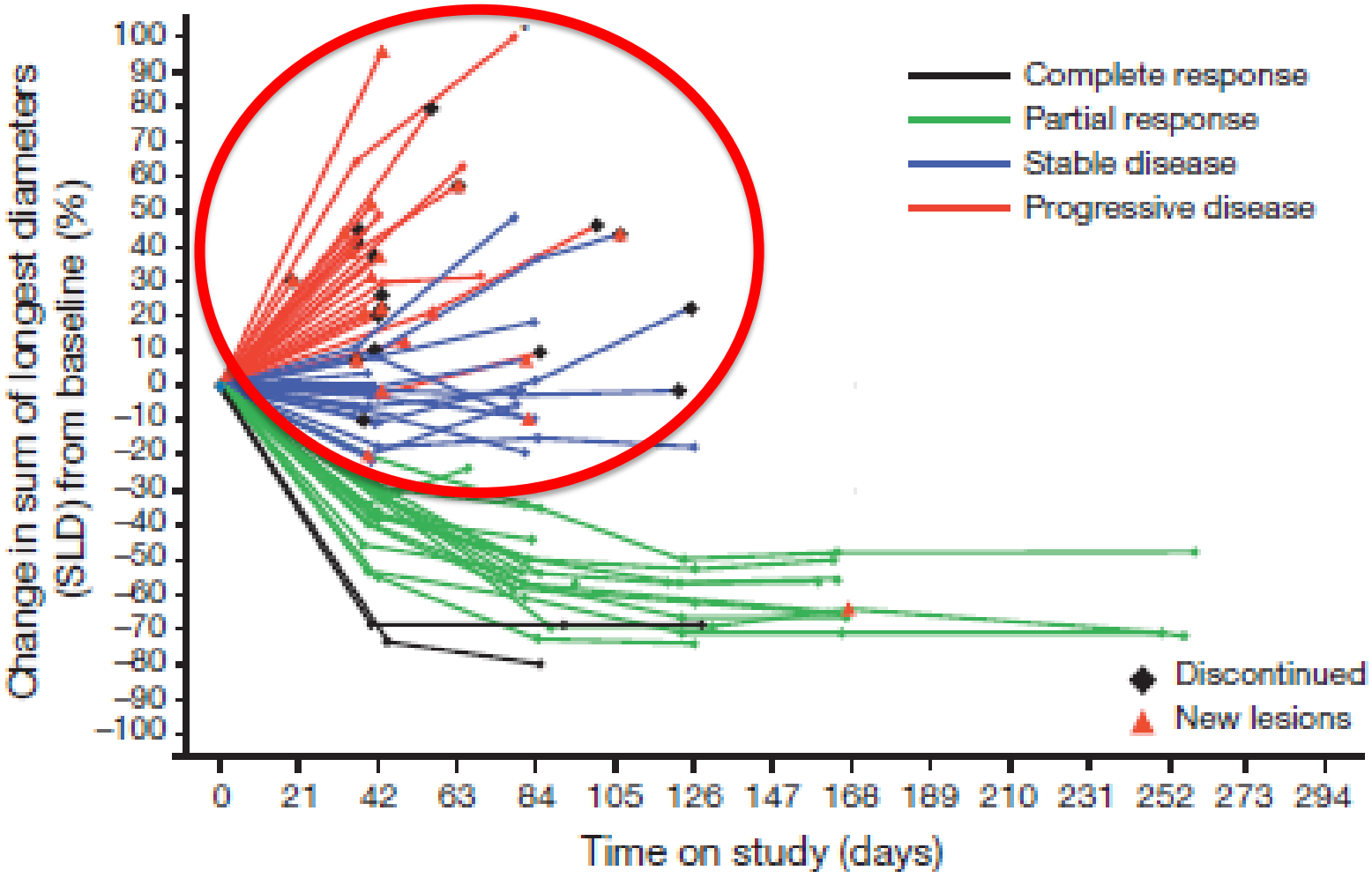
Combinations

MPDL3280A (anti-PD-L1) in metastatic bladder cancer



Powles T et al. *Nature* 515(7528), 558-562 (2014)

Targeted Therapy

- Any therapy that targets **cancer's specific** phenotype or genotype
  - Specific immune generating therapy/vaccines
  - T cell therapy
  - Molecular targeted therapy

Table 1. Final Rankings of Agents with High Potential for Use in Treating Cancer

Rank*	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
2	Anti-Programmed Death-1 (PD1)and/or anti–B7-H1 (PD1 Ligand)	**T-Cell Checkpoint Blockade Inhibitor
3	IL-12	Vaccine Adjuvant
4	Anti-CD40 and/or CD40L	Antigen Presenting Cell Stimulator
5	IL-7	T-Cell Growth Factor
6	CpG	Vaccine Adjuvant
7	1-Methyl Tryptophan	Enzyme Inhibitor
8	Anti-CD137 (anti–4-1BB)	T-Cell Stimulator
9	Anti–TGF-beta	Signaling Inhibitor
10	Anti–IL-10 Receptor and/or Anti-IL-10	Suppression Inhibitor
11	Flt3L	Dendritic Cell Growth Factor/ Vaccine Adjuvant
12	Anti-Glucocorticoid-Induced TNF Receptor (GITR)	T-cell Stimulator
13	CCL21 Adenovirus	T-Cell Attracting Chemokine
14	Monophosphoryl Lipid A (MPL)	Vaccine Adjuvant
15	Poly I:C and/or Poly ICLC	Vaccine Adjuvant
16	Anti-OX40	T-Cell Stimulator
17	Anti–B7-H4	T-Cell Checkpoint Blockade Inhibitor
18	Resiquimod and/or 852A	Vaccine Adjuvant
19	LIGHT and/or LIGHT vector	T-Cell Stimulator
20	Anti–Lymphocyte Activation Gene-3 (LAG-3)	T-Cell Checkpoint Blockade Inhibitor

? Combination

NCI Immunotherapy Agent Workshop Proceedings

Combinational Immunotherapy

- Vaccines
- Immune Modulators
  - Immune Agonists
    - Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
    - Co-stimulatory molecules (OX-40, GITR, 4-1BB)
  - Immune inhibitors
    - Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
    - Inhibitory cytokines/factors (IL-10, TGFb)
- Standard Therapy
  - Chemotherapy
  - Radiation Therapy
- Small Molecules
- T cell therapy/CARS

Challenges

- What pre clinical data would be needed to move with the combination ?
- Type of Combination/Schedule of combination

  Prediction of response
- What clinical trial design ?
  - Efficiency
  - Time
- How to enable combinations from different developers—pharm/bio
- Health Economics, “financial adverse” effect

Challenges

- What pre clinical data would be needed to move with the combination ?
- Type of Combination/Schedule of combination

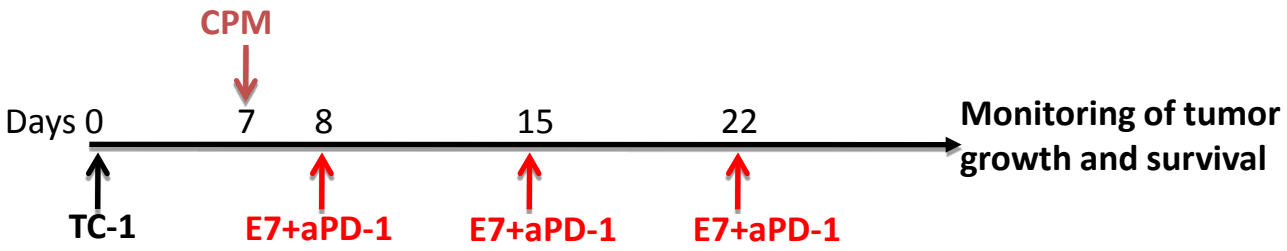
  Prediction of response

  – Biology

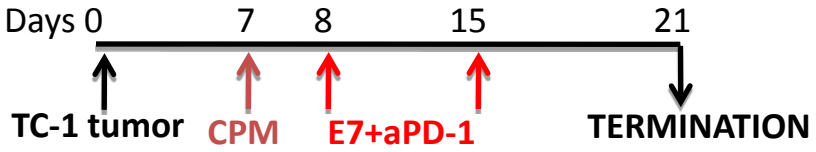
  – Activity in preclinical model **OPTIMUM RESPONSE**

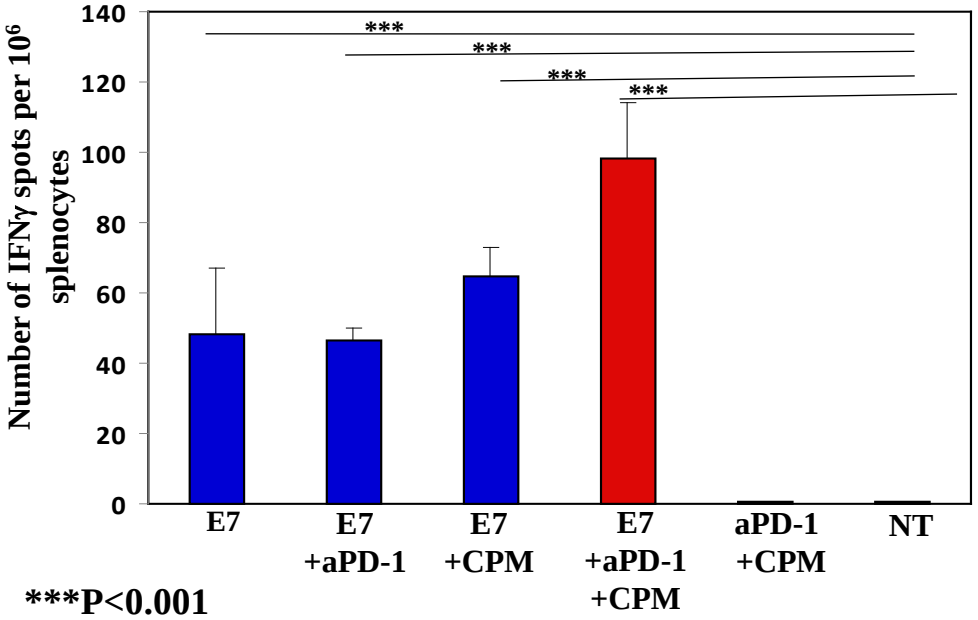
Treg cell inhibitor-cyclophosphamide (CPM)

Low Dose CPM selectively targets Treg cells, leaving other T cell populations intact ***(Lutsiak et al, Blood, 2005; Ikezawa et al, J Dermatol Sci, 2005).***



Vaccine/anti-PD-1/CPM combination induces potent antigen-specific immune responses in tumor bearing mice





***P<0.001

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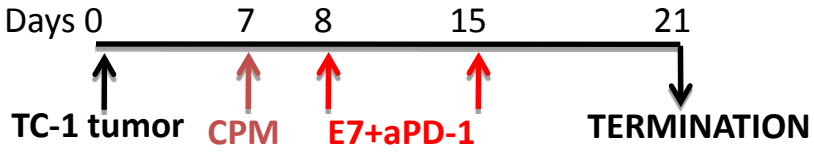

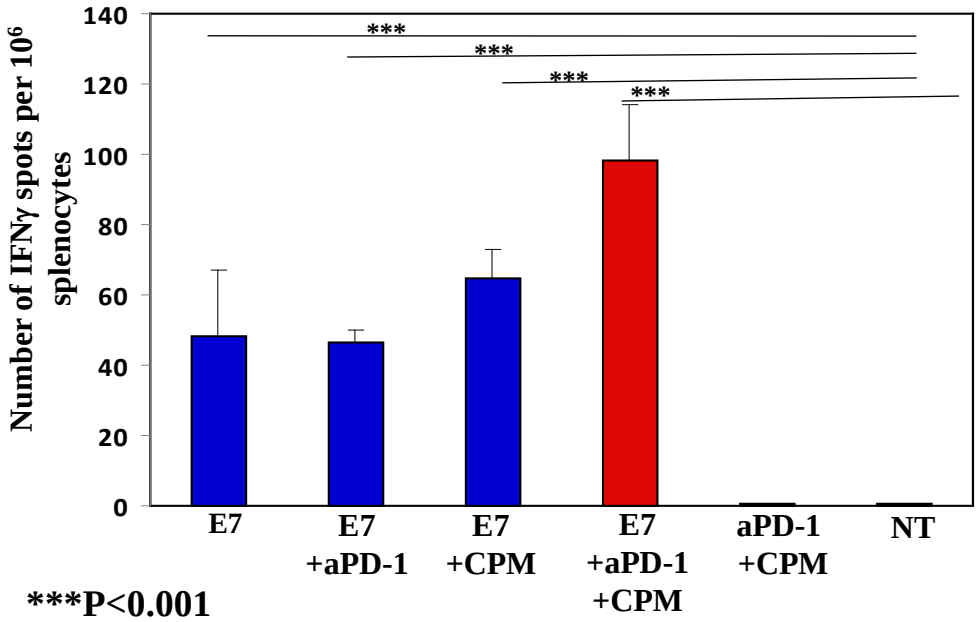

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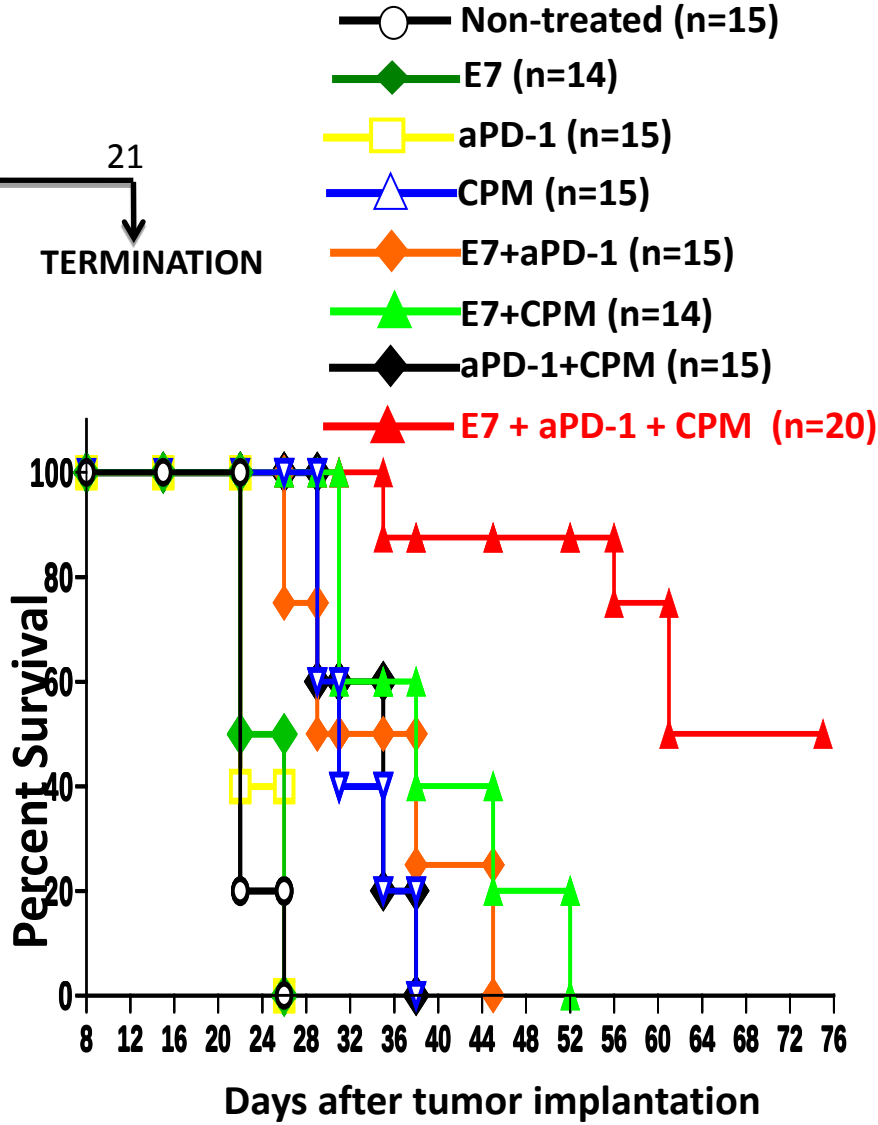
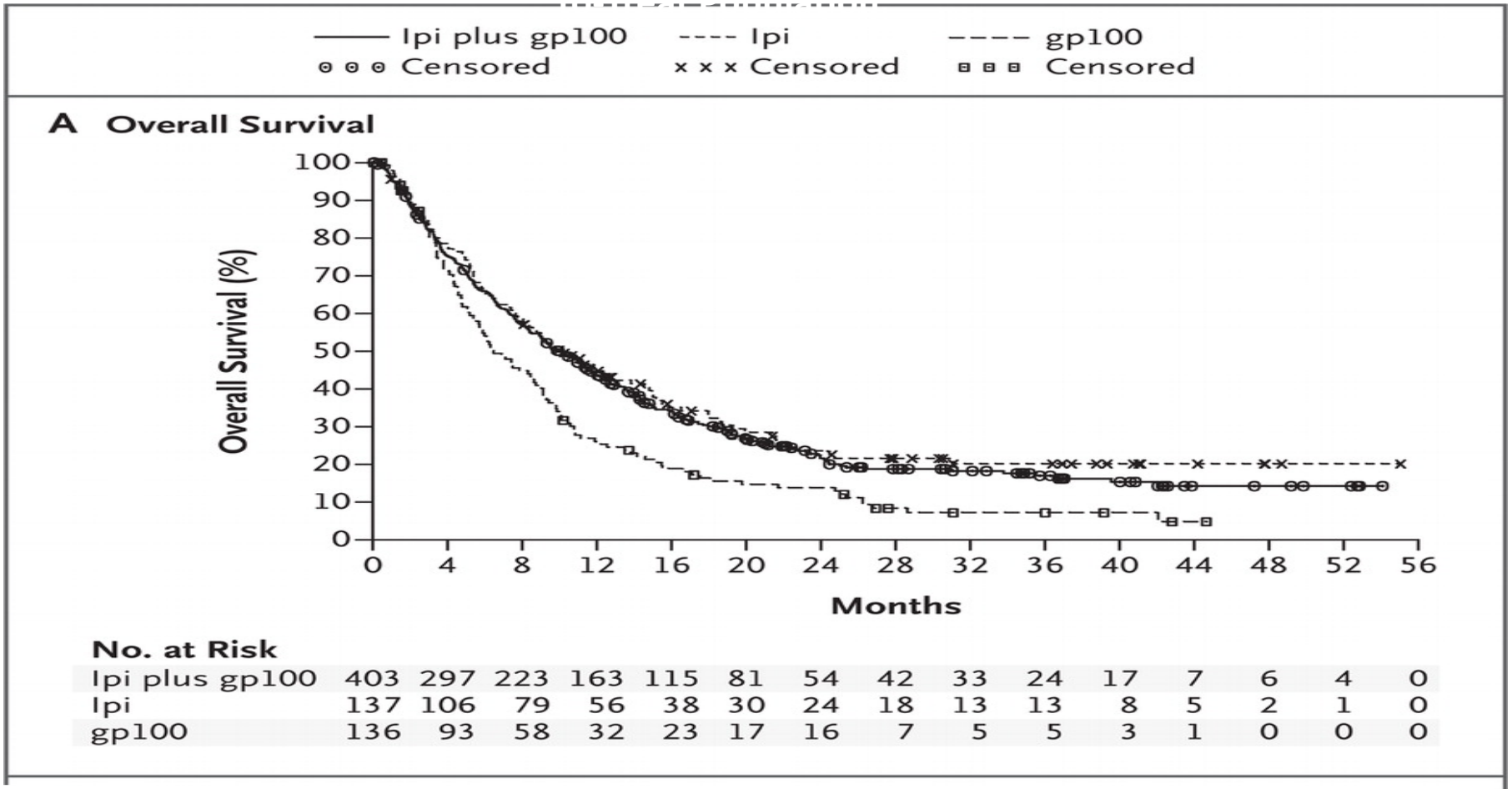


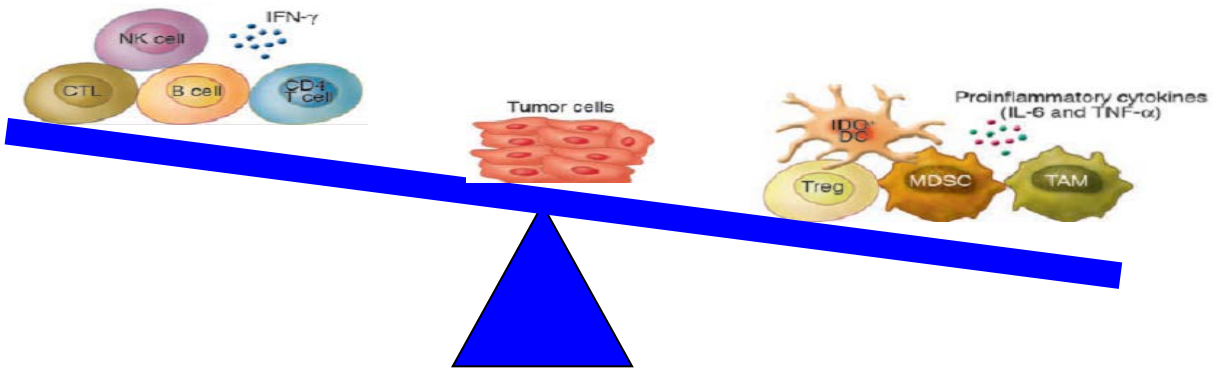


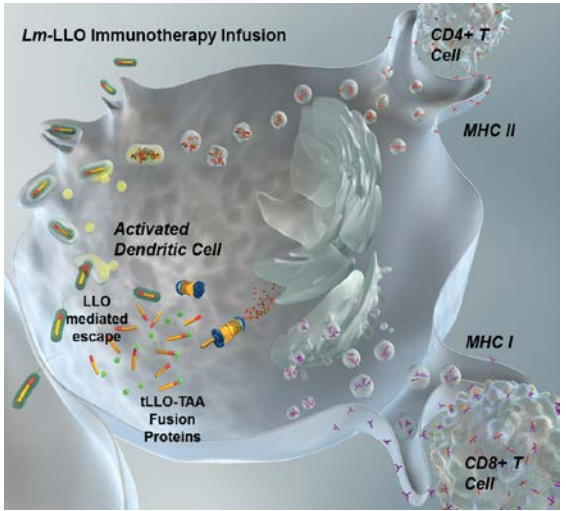
Hodi FS et al. N Engl J Med 2010;363:711-723.

Vaccines

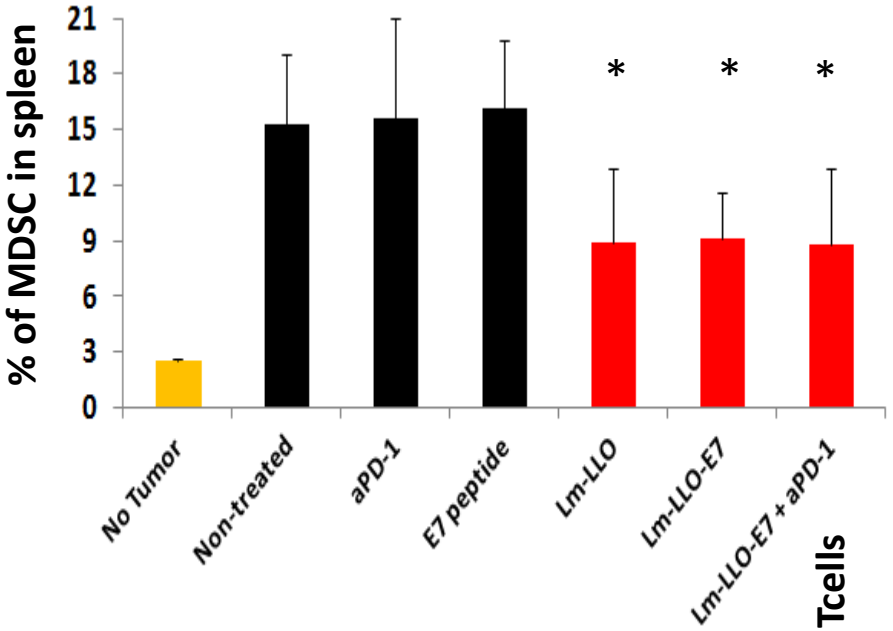
- Peptides, polypeptides
- DND/RNA
- Viral
- Bacterial

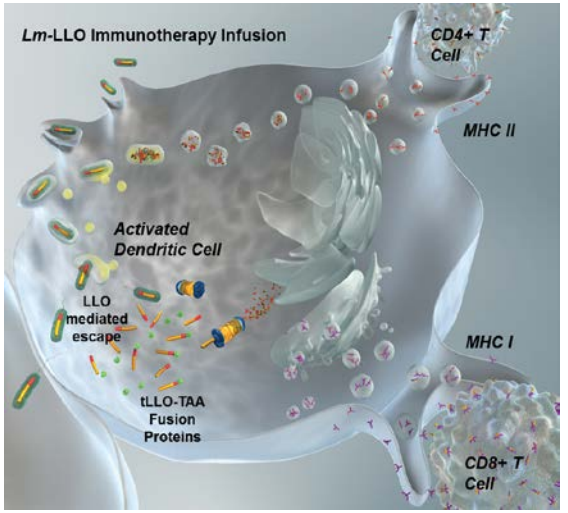
- Administered Directly or on DCs

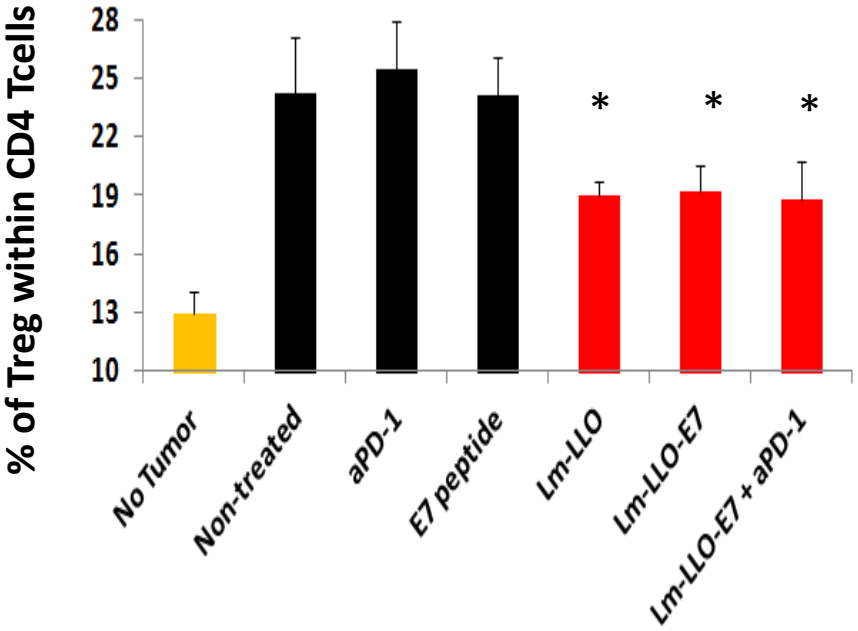




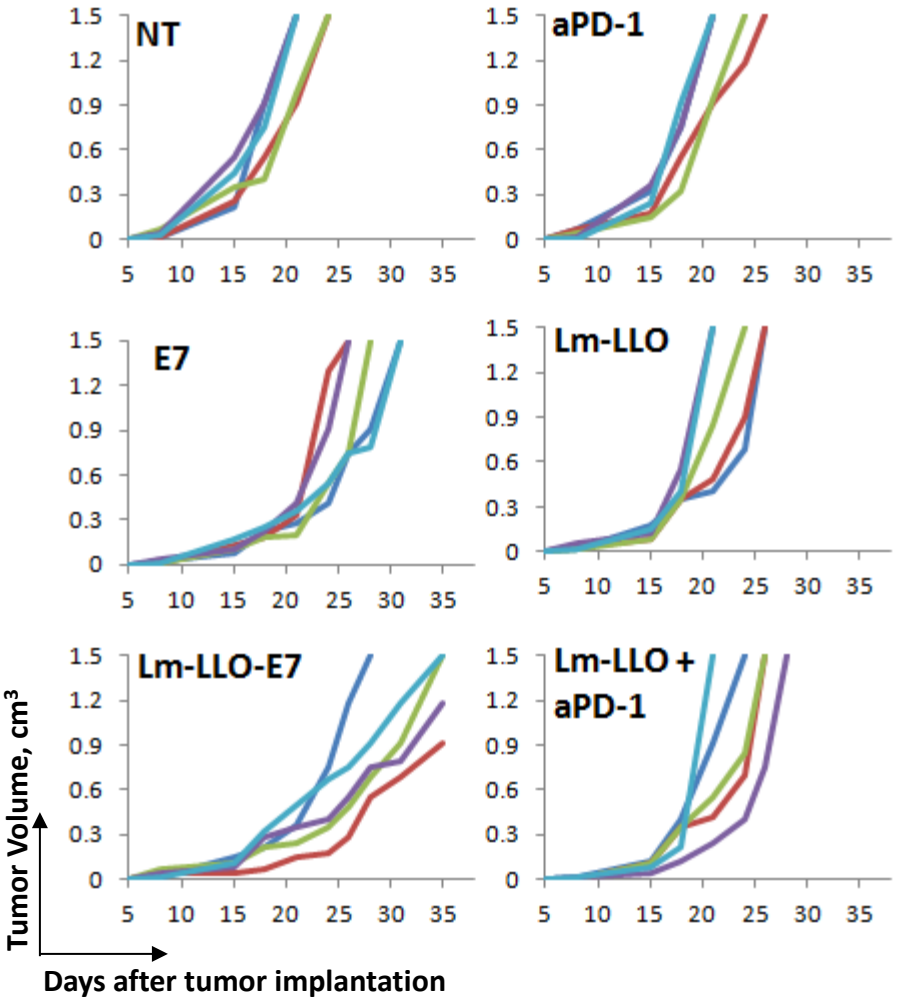
Vaccines

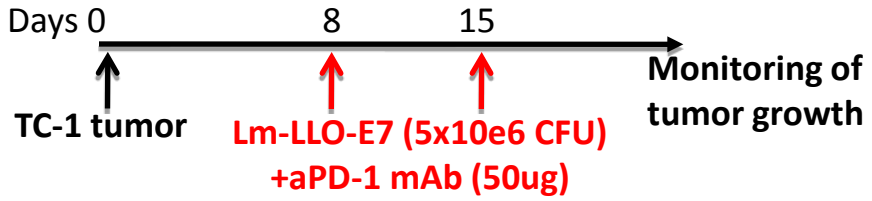

% of MDSC in spleen
21
18
15
12
9
6
3
0
*
*
*
No Tumor
Non-treated
aPD-1
E7 peptide
Lm-LLO
Lm-LLO-E7
Lm-LLO-E7 + aPD-1

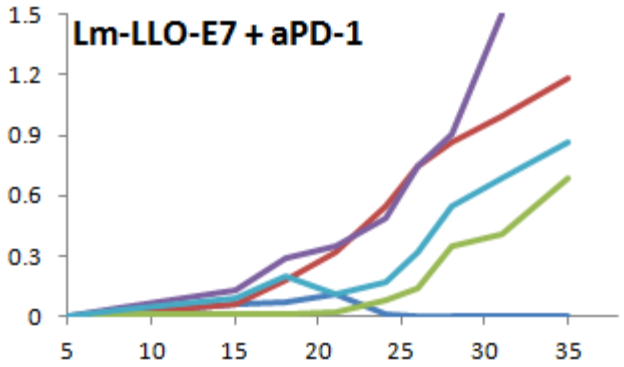

Lm-LLO Immunotherapy Infusion
CD4+ T Cell
MHC II
Activated Dendritic Cell
LLO mediated escape
MHC I
tLLO-TAA Fusion Proteins
CD8+ T Cell

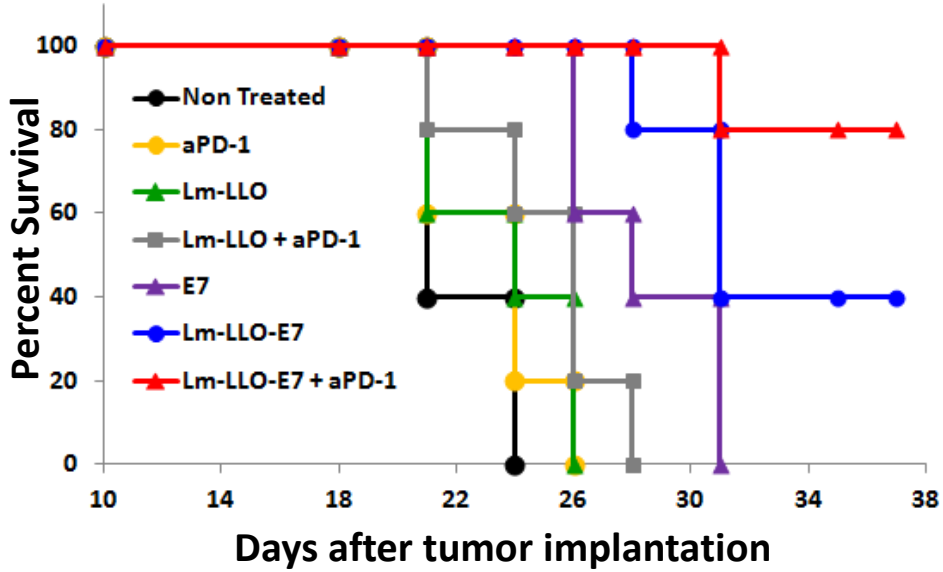

% of Treg within CD4 Tcells
28
25
22
19
16
13
10
*
*
*
No Tumor
Non-treated
aPD-1
E7 peptide
Lm-LLO
Lm-LLO-E7
Lm-LLO-E7 + aPD-1

Combination of Lm-LLO-E7 with anti-PD-1 mAb significantly improves therapeutic potency of immunotherapy









Mkrtichyan et al., JITC 2013

Combinational Immunotherapy

- Vaccines
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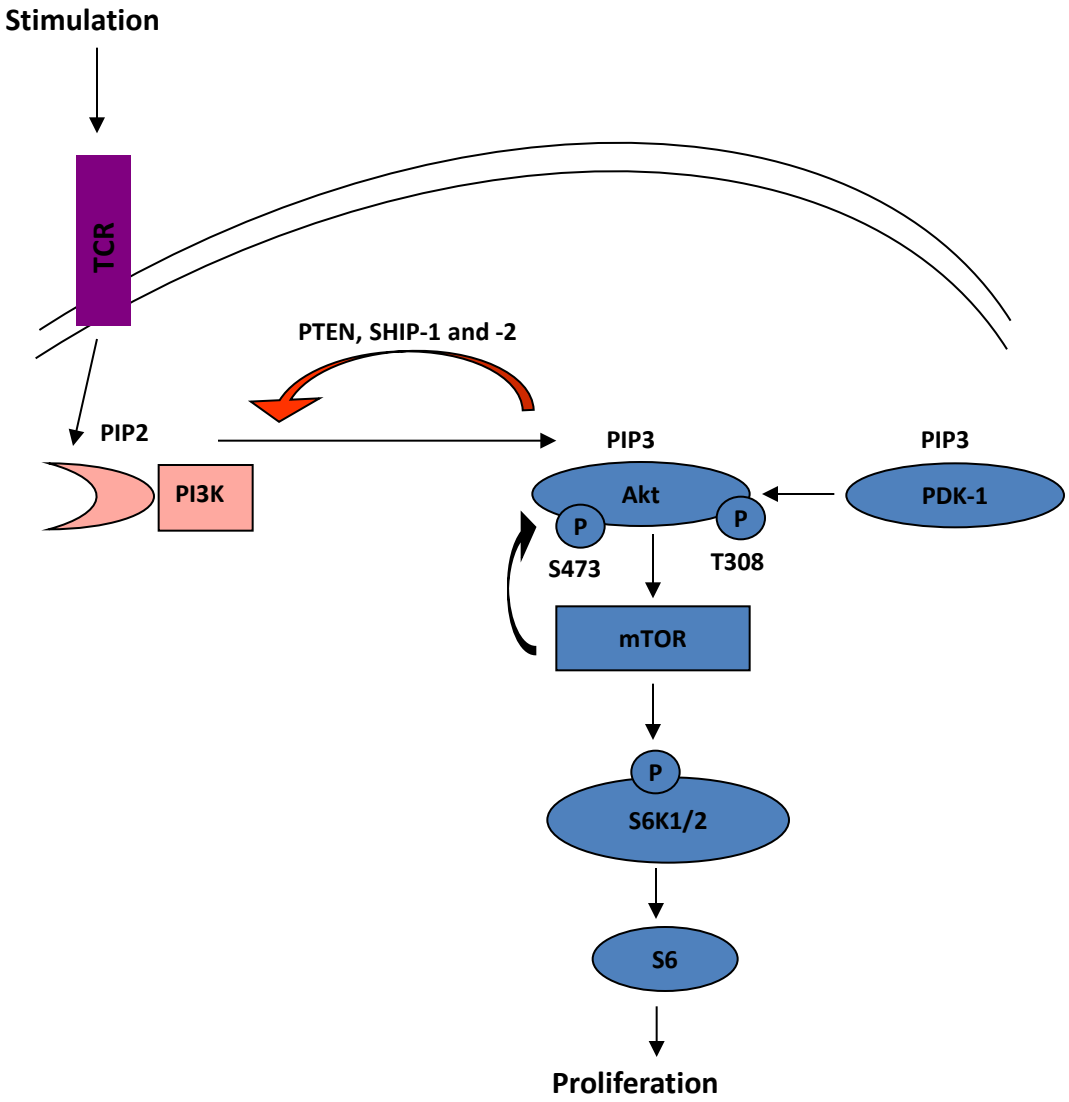
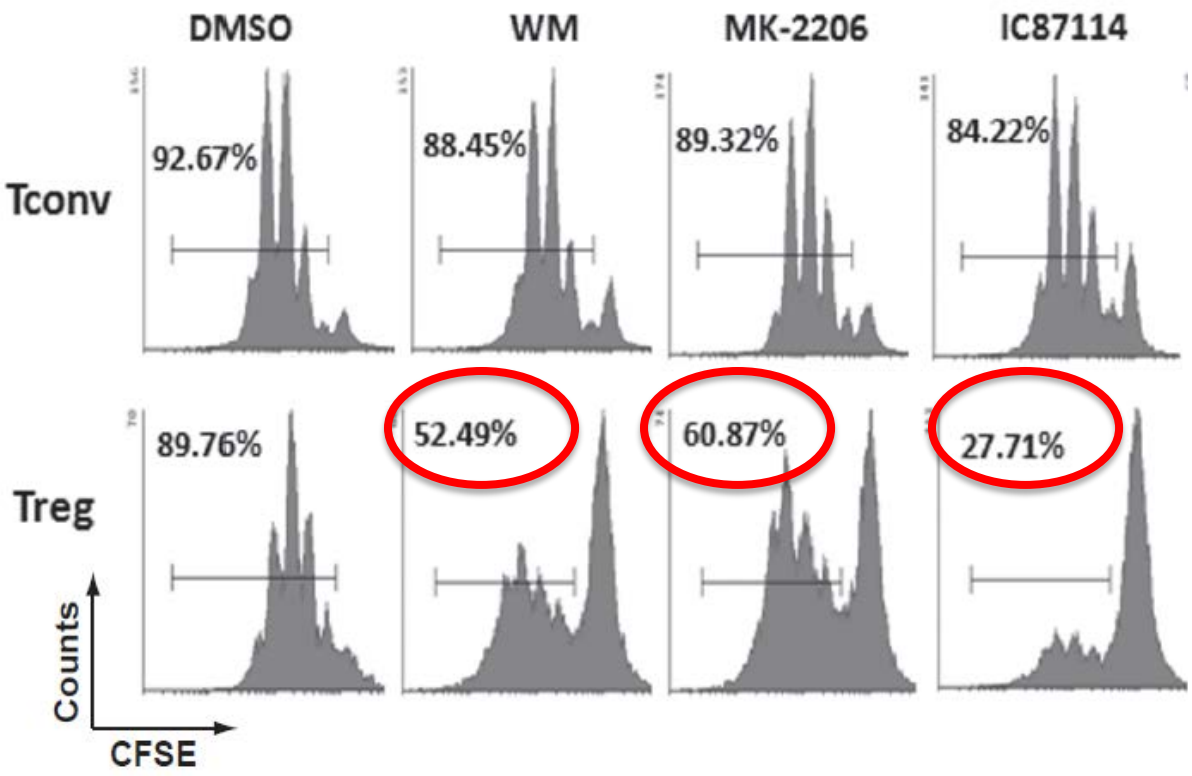
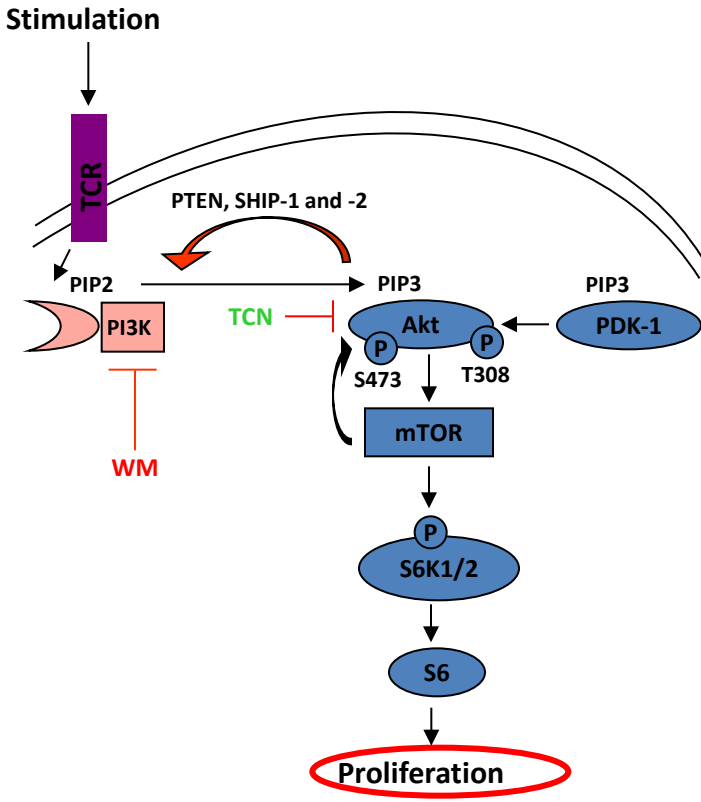
Effects of PI3K-Akt pathway inhibition in Tregs vs. Tconv cells



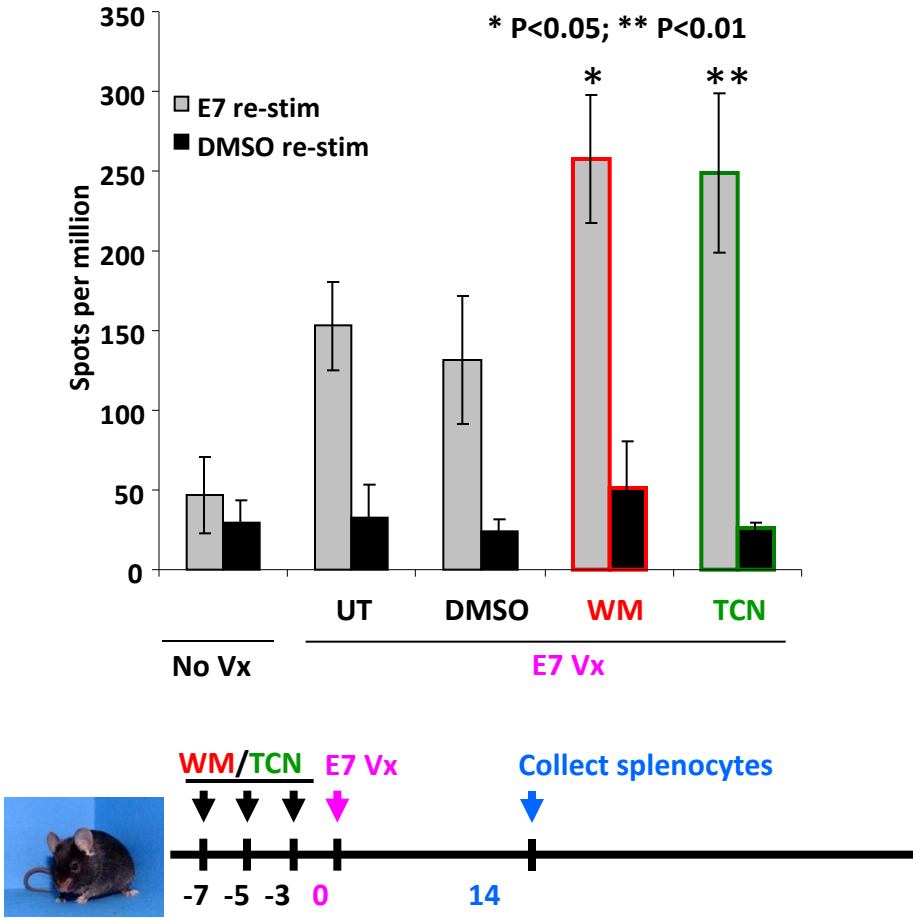
Effects of PI3K-Akt pathway inhibition on the TCR/IL2 Induced proliferation of Tregs vs. Tconv cells





Abu Eid R.et al, CIR, 2014

PI3K-Akt inhibition enhances vaccine efficacy



Abu Eid R.et al, CIR, 2014

Challenges

- What pre clinical data would be needed to move with the combination ?
- Type of Combination/Schedule of combination

  Prediction of response

  – Biology

  – Activity in preclinical model **OPTIMUM RESPONSE**

Challenges

- What pre clinical data would be needed to move with the combination ?
- Type of Combination/Schedule of combination

  Prediction of response
- What clinical trial design ?
  - Efficiency
  - Time

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

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**

Rahma et al, Clin Cancer Research, 2014

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Rahma et al, Clin Cancer Res, 2014

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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**

Rahma et al, Clin Cancer Res, 2014

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Rahma et al, Clin Cancer Res, 2014

Does dose escalation determine MTD?

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**

Rahma et al, Clin Cancer Res, 2014

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Rahma et al, Clin Cancer Res, 2014

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/m2 GM-CSF
Maciag et al. 2009	*L. monocytogenes* secreting HPV-16 E7 fused to *Lm* listeriolysin O (IV)	Hypotension	3 patients at highest dose level
Guthmann et al. 2004	GM3 ganglioside with *N. meningitidis* outer membrane (IM)	Hypotension	1 patient at highest dose level

Rahma et al, Clin Cancer Res, 2014

Conclusion

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

Does dose escalation determine BAD?

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

Rahma et al, Clin Cancer Res, 2014

Alternative Clinical Trial Design For Combination Immune Therapy

Step 1. Determining a starting dose of a vaccine

Vaccine class and toxic
(e.g., bacterial vector)

Rahma et al, Clin Cancer Res, 2014

Alternative Clinical Trial Design For Combination Immune Therapy

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Proceed to traditional phase 1 trial

Rahma et al, Clin Cancer Res, 2014

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Vaccine class non-toxic
(e.g., peptide)

Rahma et al, Clin Cancer Res, 2014

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Vaccine class and toxic (e.g., bacterial vector) → Proceed to traditional phase 1 trial

Vaccine class non-toxic (e.g., peptide) → Use Immune Active Dose (IAD) from previous clinical trials

Rahma et al, Clin Cancer Res, 2014

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Step 1. Determining a starting dose of a vaccine

Vaccine class and toxic (e.g., bacterial vector) → Proceed to traditional phase 1 trial

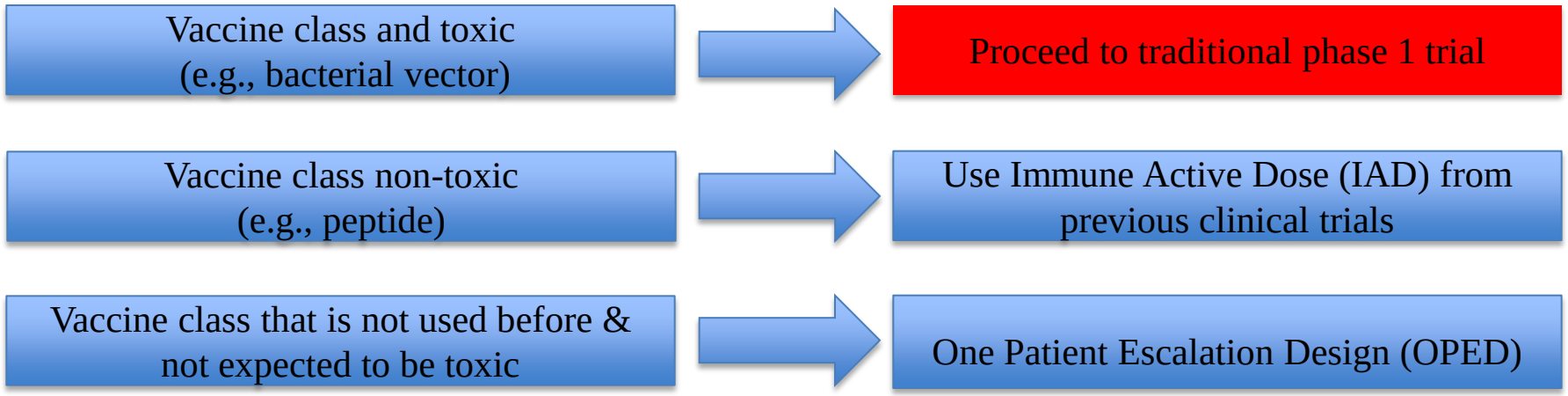
Vaccine class non-toxic (e.g., peptide) → Use Immune Active Dose (IAD) from previous clinical trials

Vaccine class that is not used before & not expected to be toxic

Rahma et al, Clin Cancer Res, 2014

Alternative Clinical Trial Design For Combination Immune Therapy

Step 1. Determining a starting dose of a vaccine



Rahma et al, Clin Cancer Res, 2014

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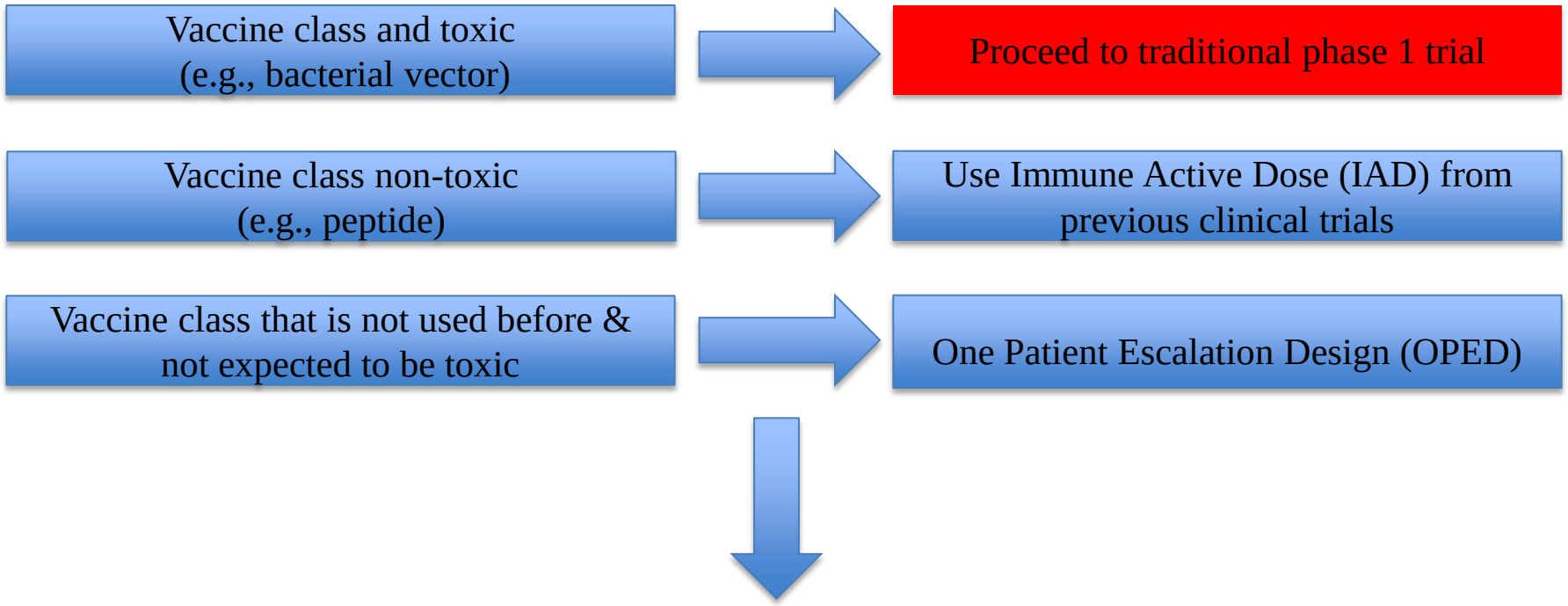

Step 2. Combination Design "Vaccine + X"
(X is an immune modulator, chemotherapy or targeted agent)

Rahma et al, Clin Cancer Res, 2014

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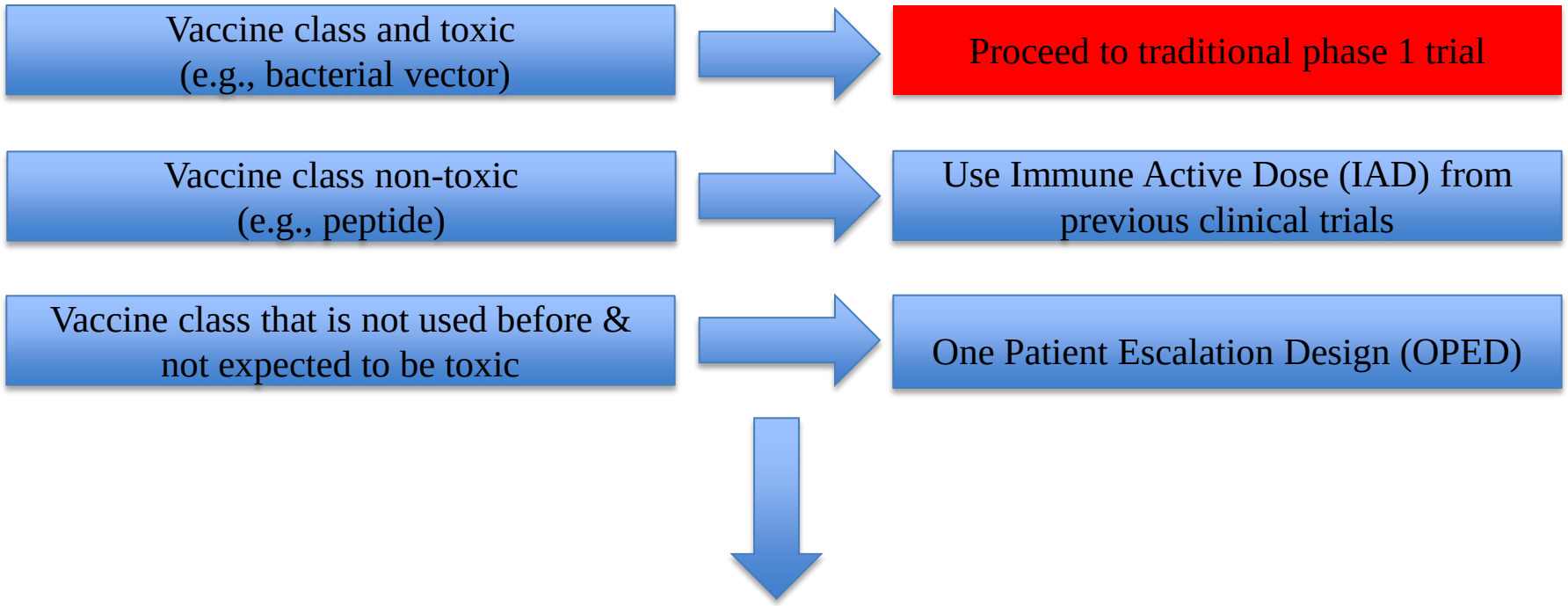

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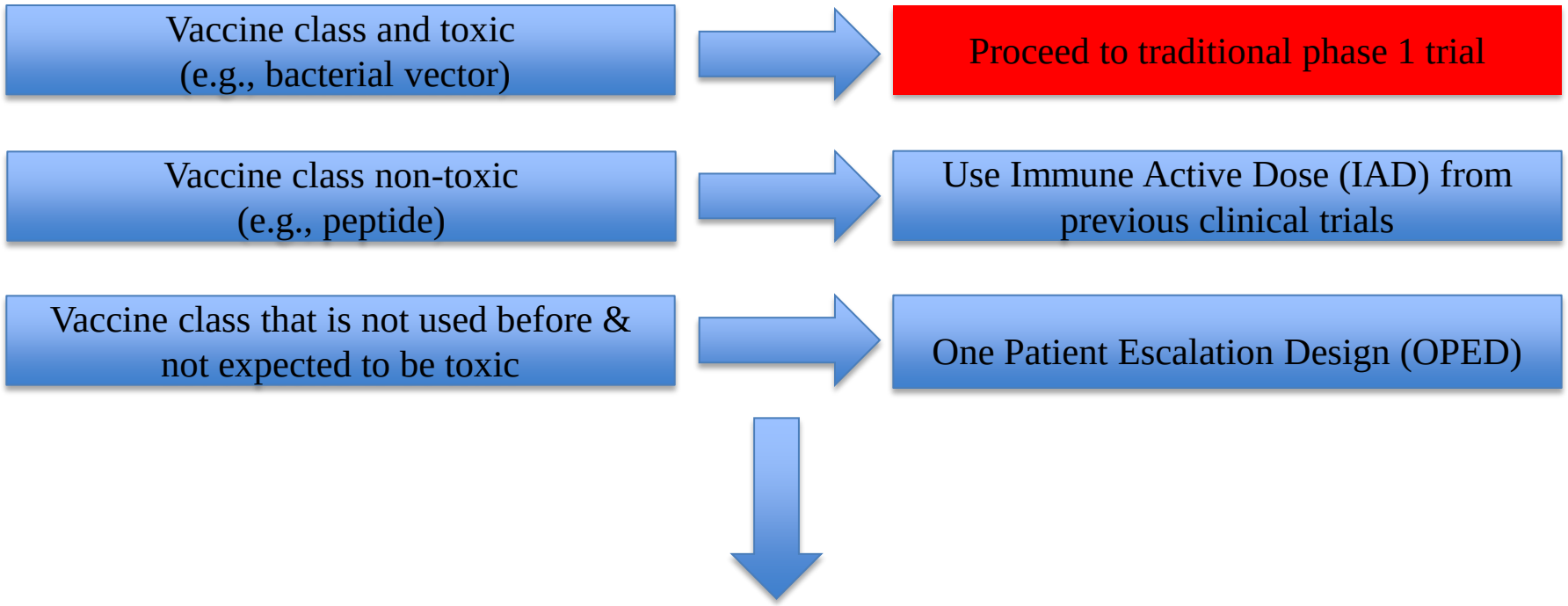
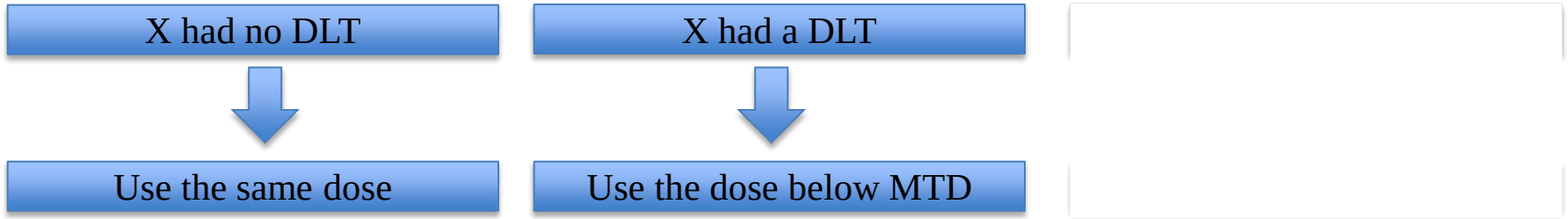


Step 2. Combination Design "Vaccine + X"
(X is an immune modulator, chemotherapy or targeted agent)



Rahma et al, Clin Cancer Res, 2014

Alternative Clinical Trial Design For Combination Immune Therapy

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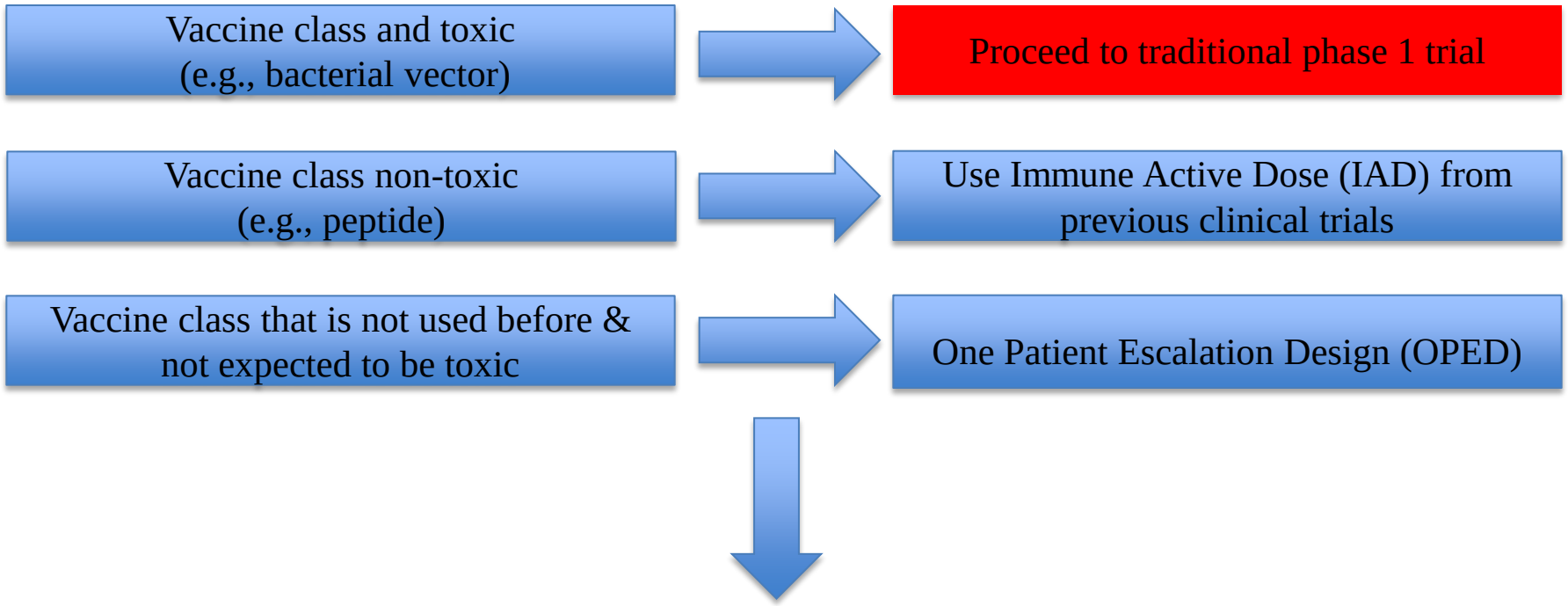

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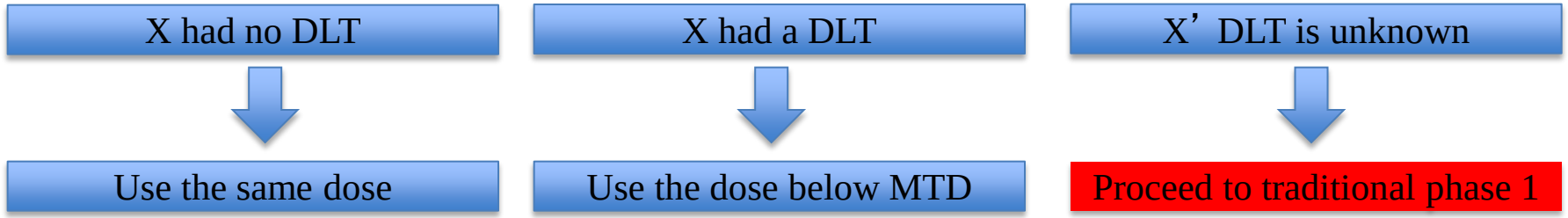

Rahma et al, Clin Cancer Res, 2014

Challenges

- What pre clinical data would be needed to move with the combination ?
- Type of Combination/Schedule of combination

  Prediction of response
- What clinical trial design ?
  - Efficiency
  - Time
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- Health Economics, “financial adverse” effect