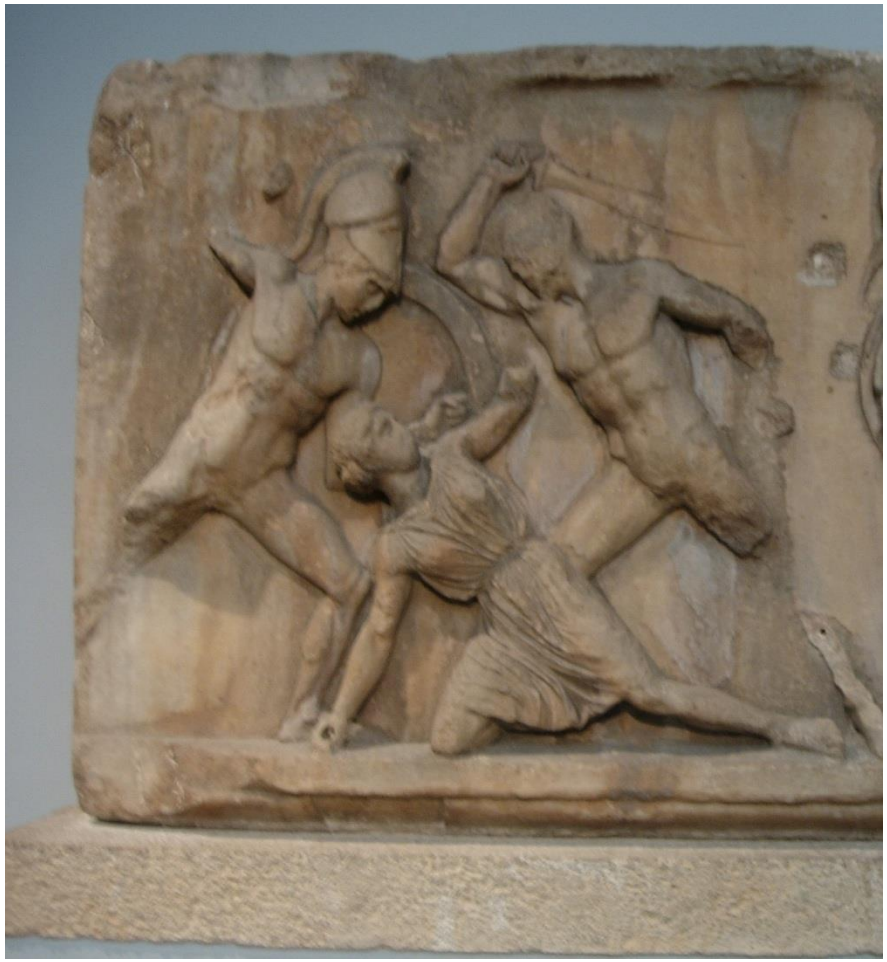
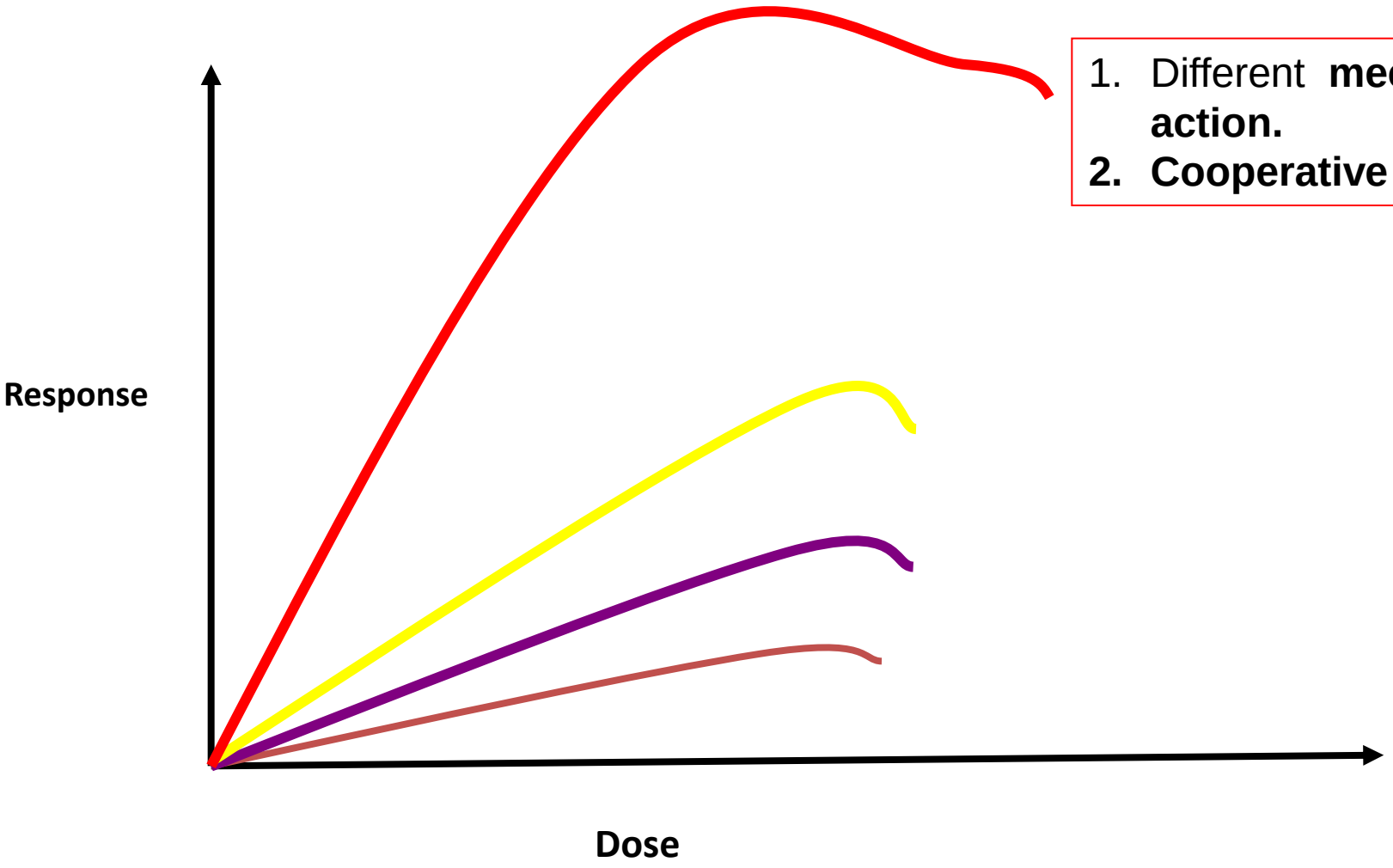
Combination opportunities in immunotherapy with **immunostimulatory mAb.**

SYNERGY

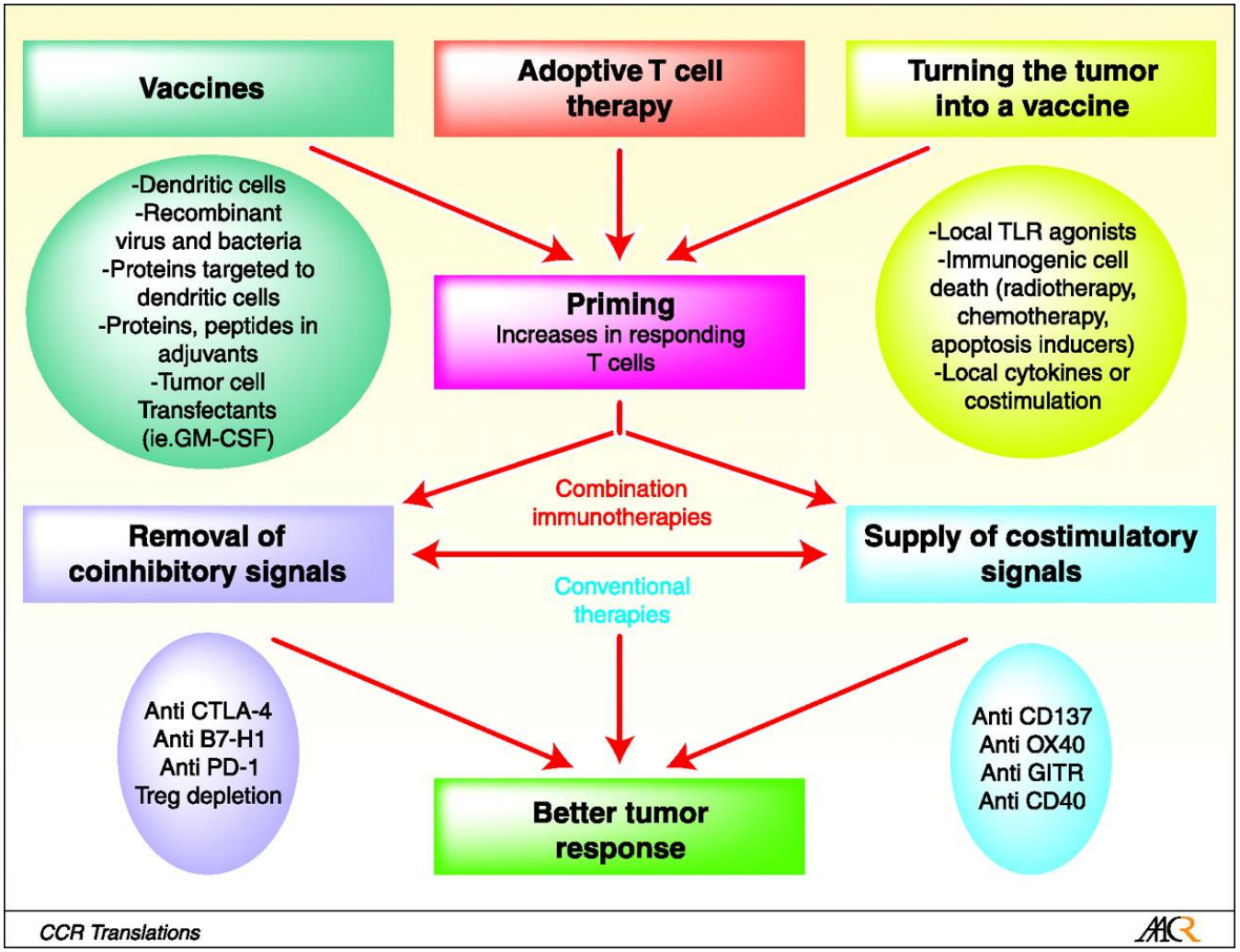
***syn-ergos*, *συνεργός*, meaning 'working together'.**





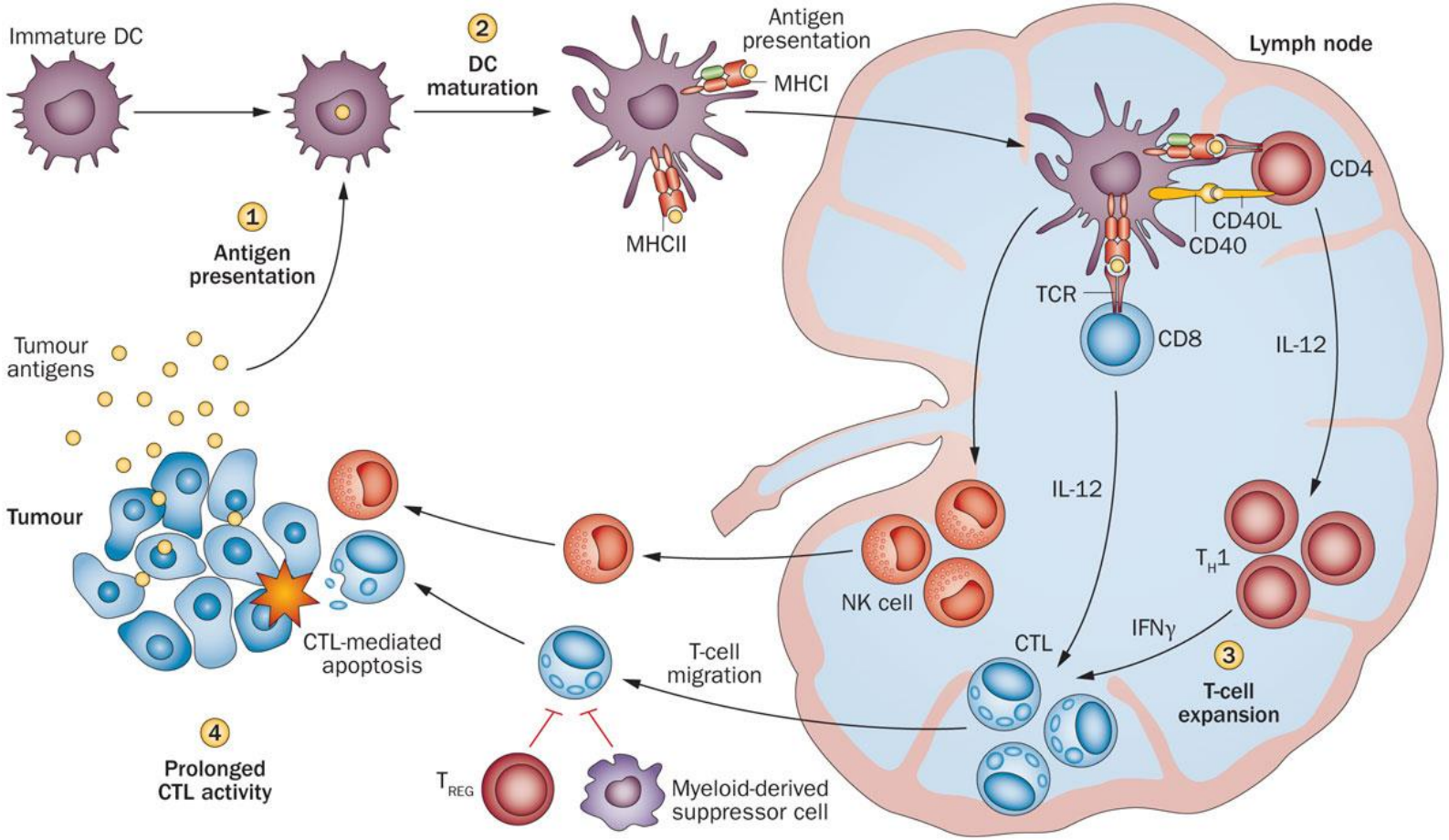
1. Different **mechanism of action.**
2. **Cooperative** effect

Strategies for immunotherapy combinations.

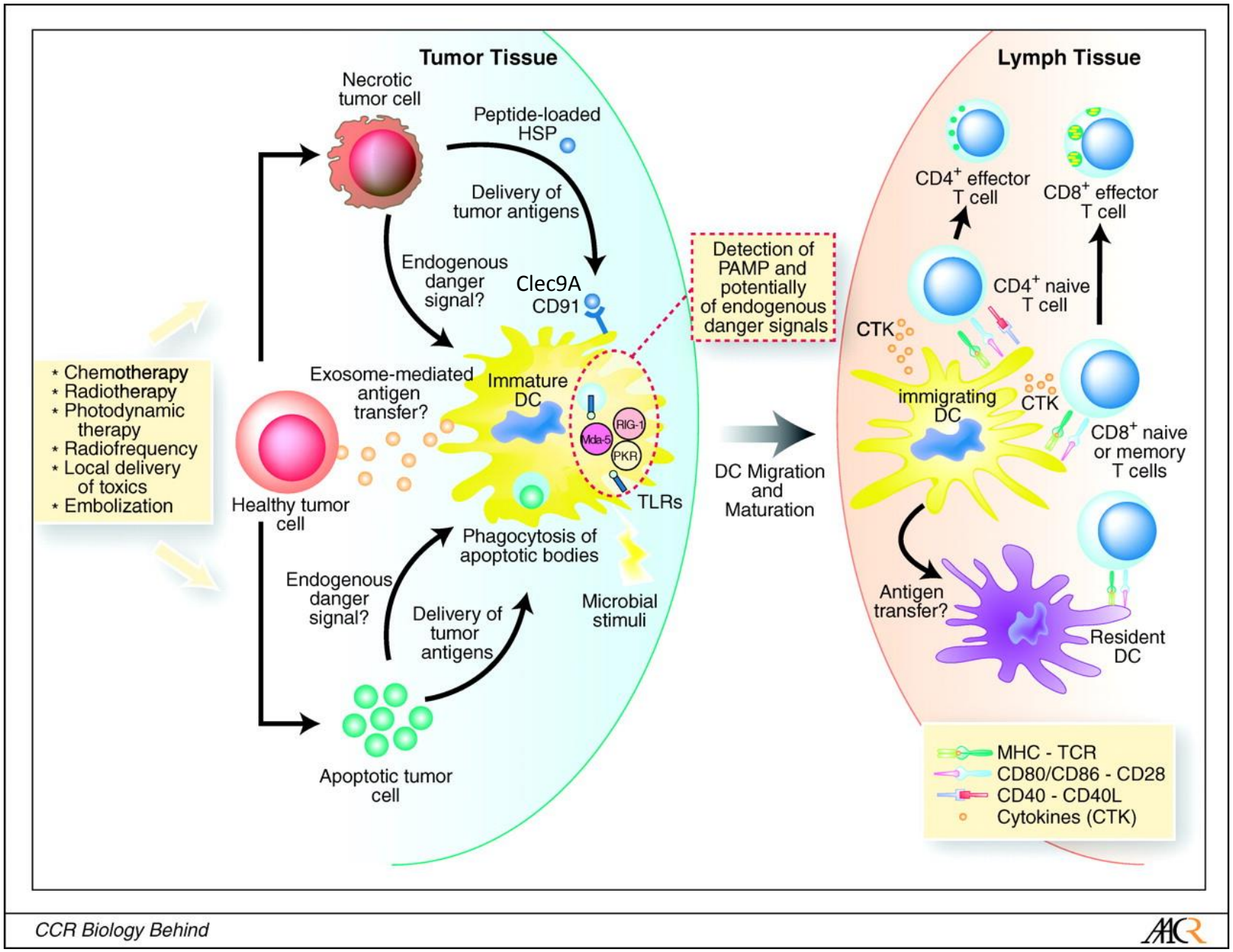


Melero I et al. Clin Cancer Res 2009;15:1507-1509

Steps in the development of a cellular immune response against tumour-associated antigen



Melero, I. *et al.* (2014) *Nat. Rev. Clin. Oncol.*



CCR Biology Behind

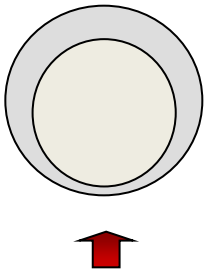
Melero I et al. Clin Cancer Res 2006;12:2385-2389

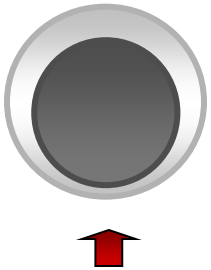
Clinical Cancer Research

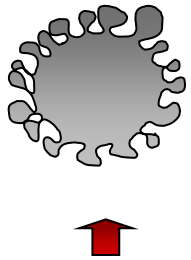
IGNORANT T CELL

ANERGIC T CELL

APOPTOTIC T CELL
(**DELETED**)







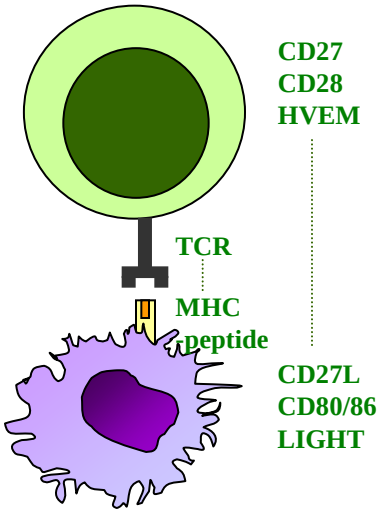
**Insufficient antigen/
lack of co-stimulatory signals**

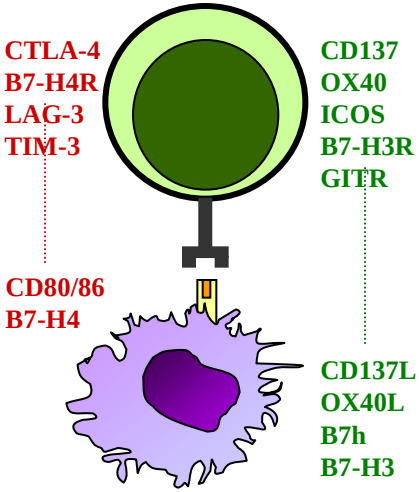
**Unsuccessful stimulation/
negative regulation**

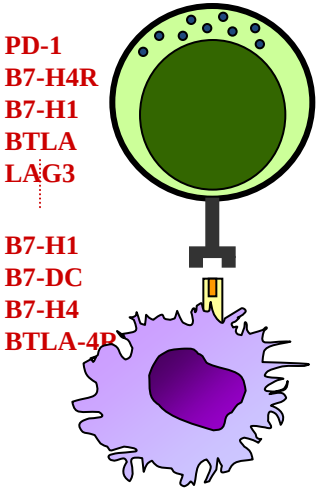
Programmed cell death

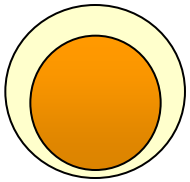
IL-12
IFN-α

NAIVE T CELL → **PRIMED** T CELL → **EFFECTOR** T CELL ⇢ **MEMORY** T CELL:
Central memory cell
Effector memory cell

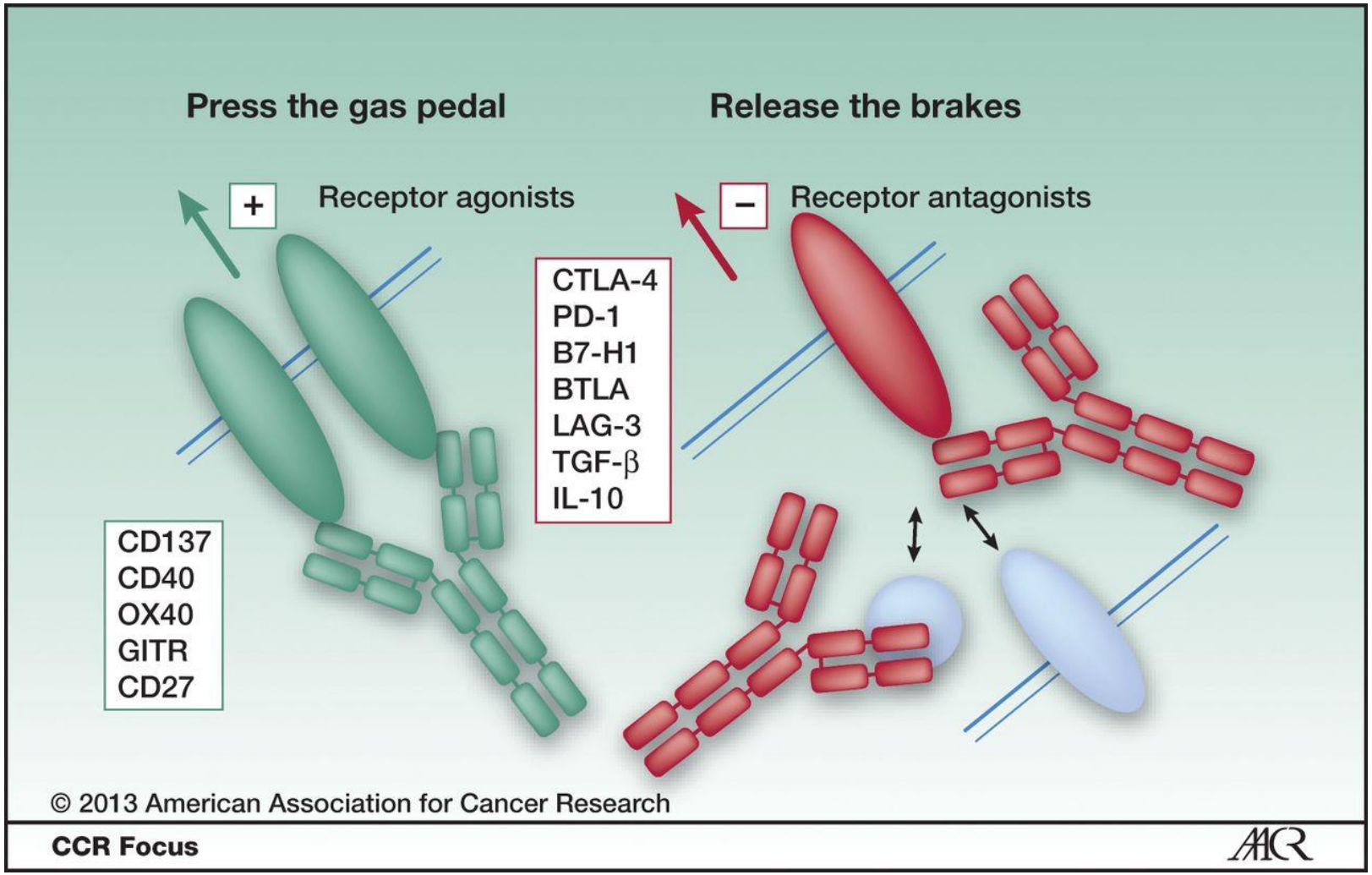






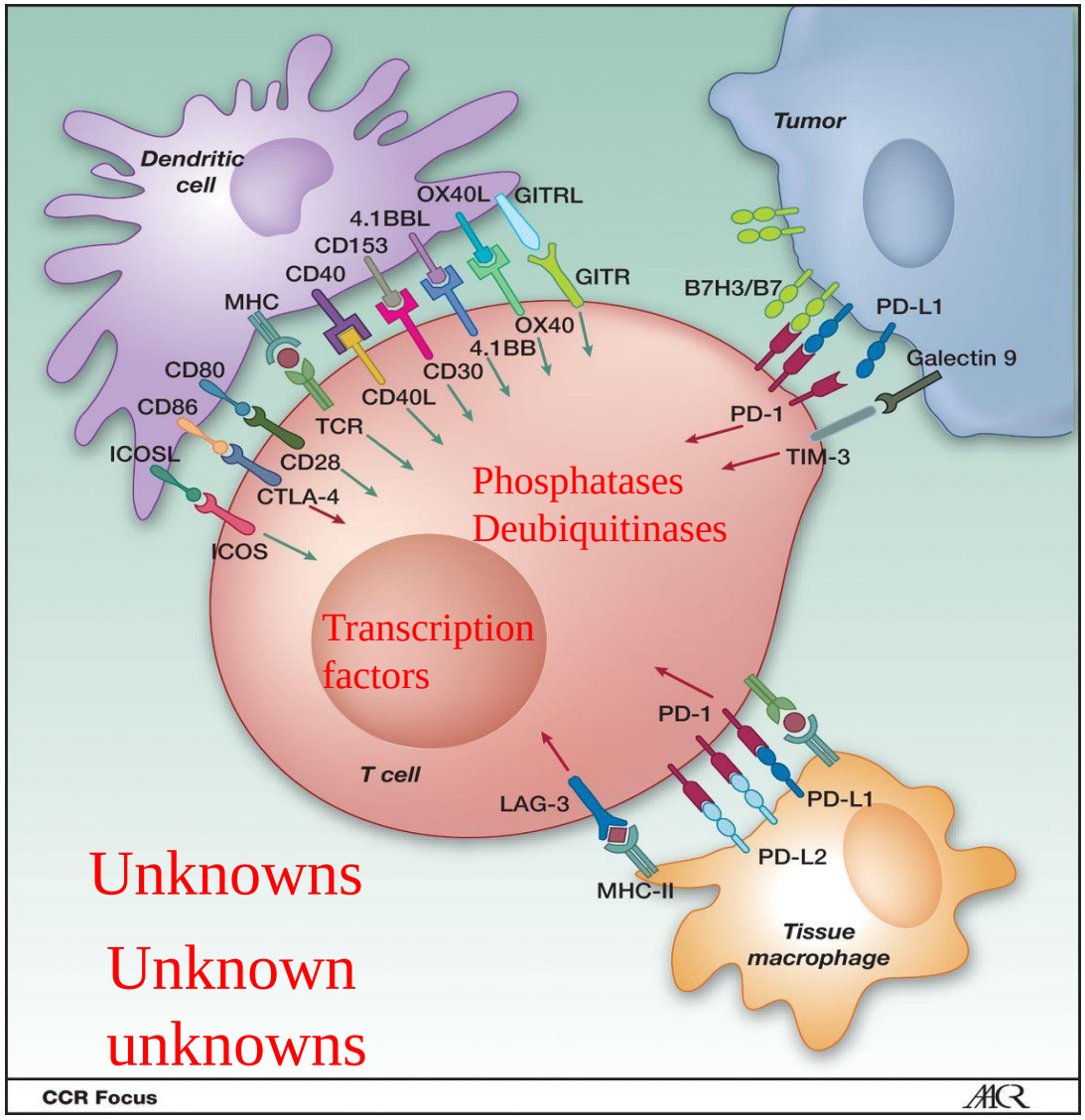


Schematic representation of the concept of immunostimulatory mAbs.



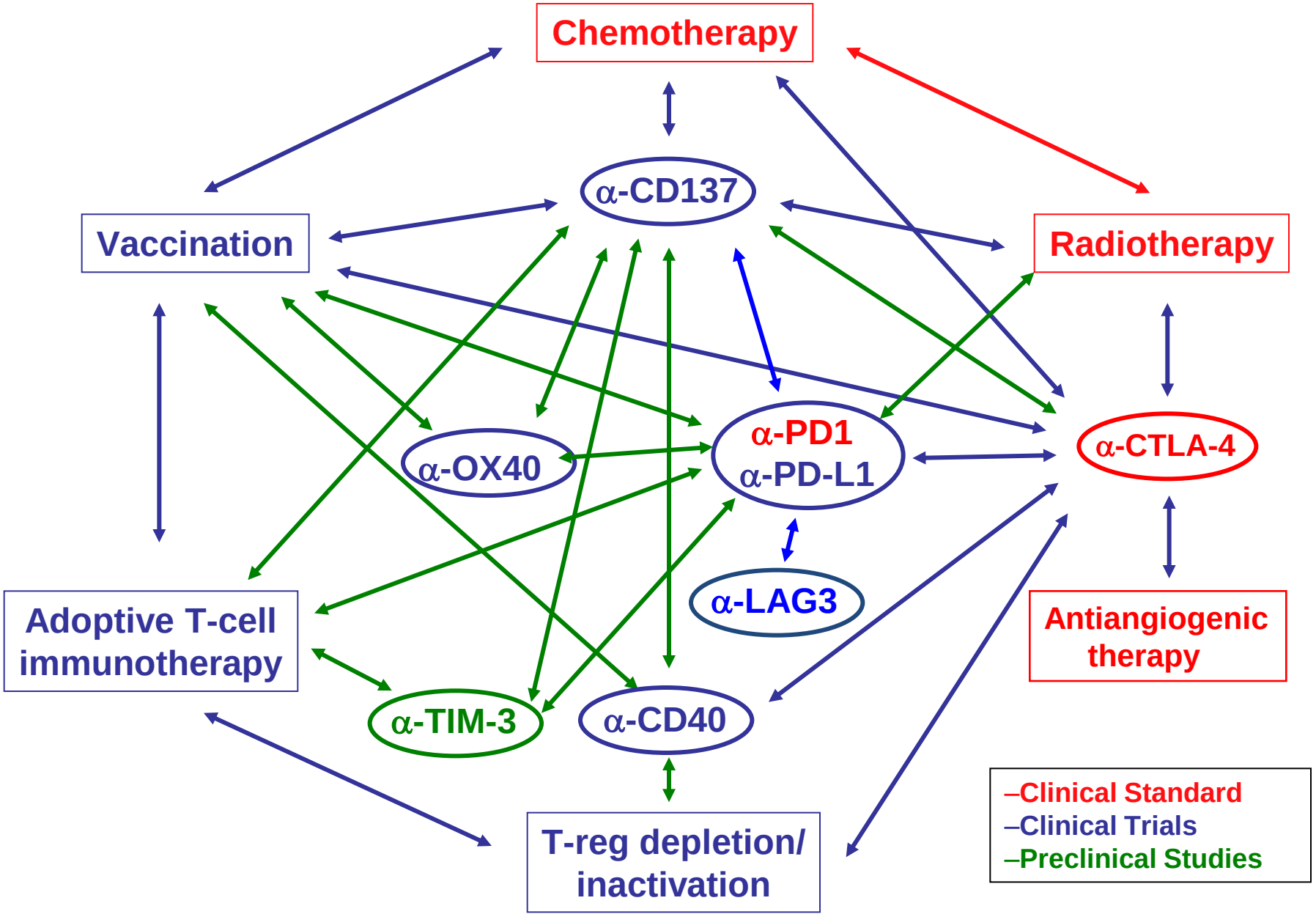
Melero I et al. Clin Cancer Res 2013;19:997-1008

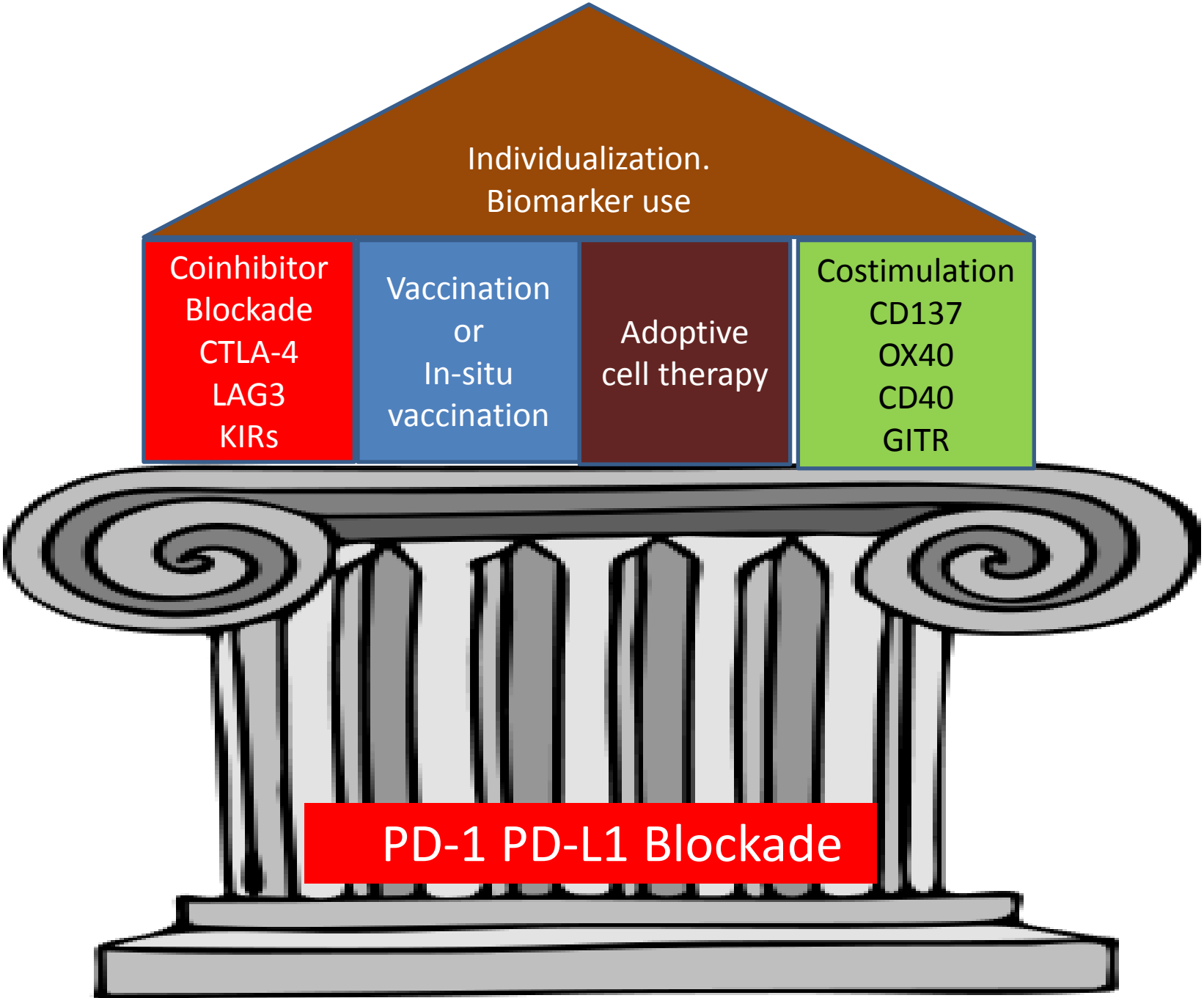
Costimulatory and coinhibitory ligand receptor pairs that are amenable to manipulation with immunostimulatory mAbs.



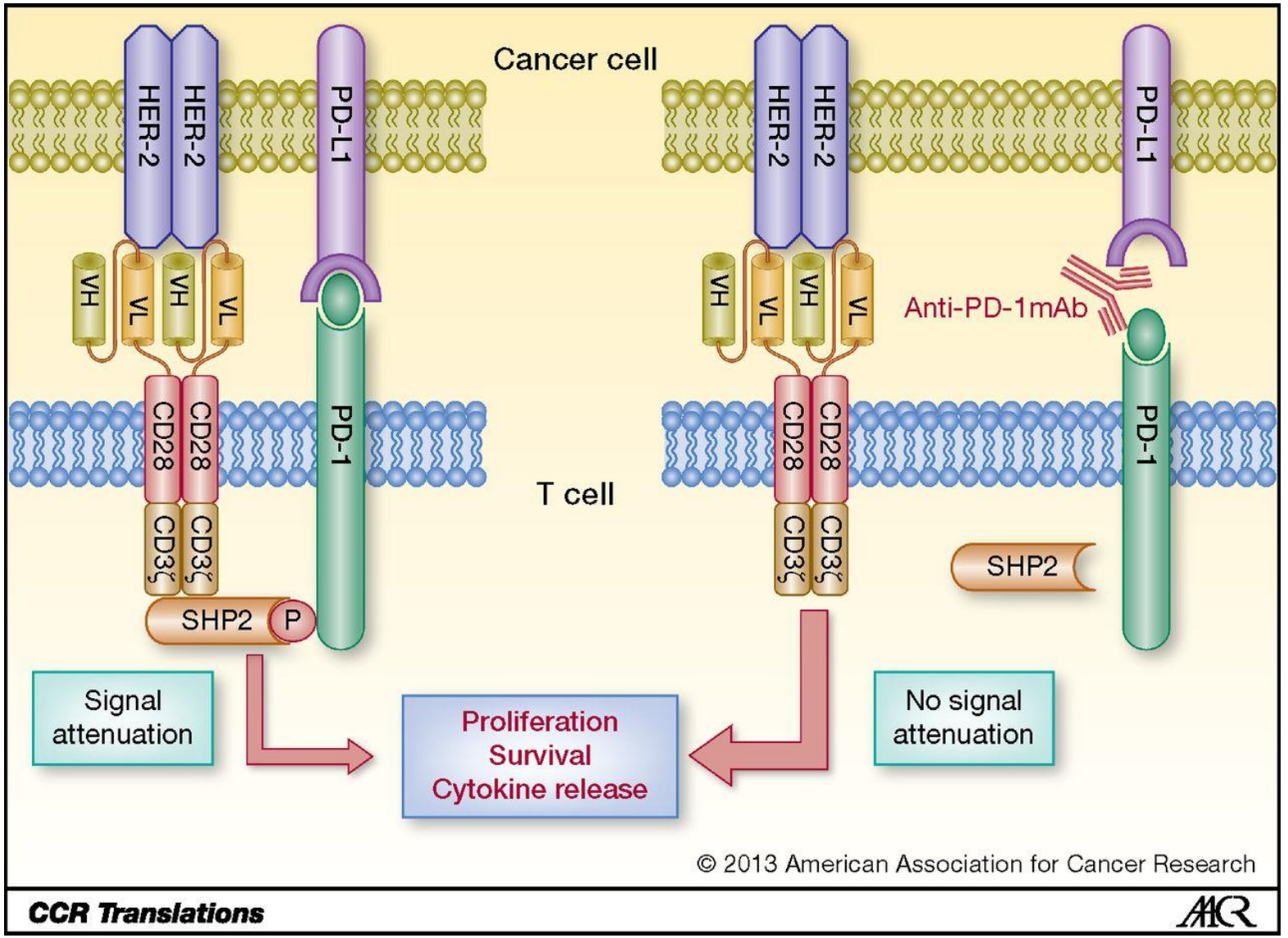
Melero I et al. Clin Cancer Res 2013;19:997-1008

Clinical Cancer Research


Chemotherapy
α-CD137
Vaccination
Radiotherapy
α-OX40
α-PD1
α-PD-L1
α-CTLA-4
α-LAG3
Adoptive T-cell immunotherapy
Antiangiogenic therapy
α-TIM-3
α-CD40
T-reg depletion/ inactivation
–Clinical Standard
–Clinical Trials
–Preclinical Studies


Individualization.
Biomarker use
Coinhibitor
Blockade
CTLA-4
LAG3
KIRs
Vaccination
or
In-situ
vaccination
Adoptive
cell therapy
Costimulation
CD137
OX40
CD40
GITR
PD-1 PD-L1 Blockade

CARs and PD-1 at tumor–T cell immune synapses.



Morales-Kastresana A et al. Clin Cancer Res 2013;19:5546-5548

PD-1 + CTLA-4 Blockade

A case Study for combined immunotherapy

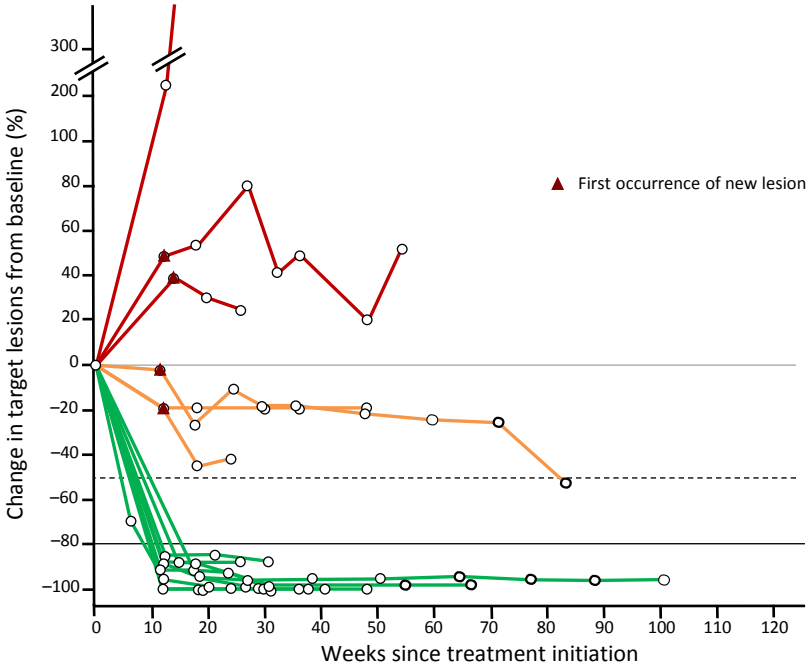
The NEW ENGLAND JOURNAL of MEDICINE

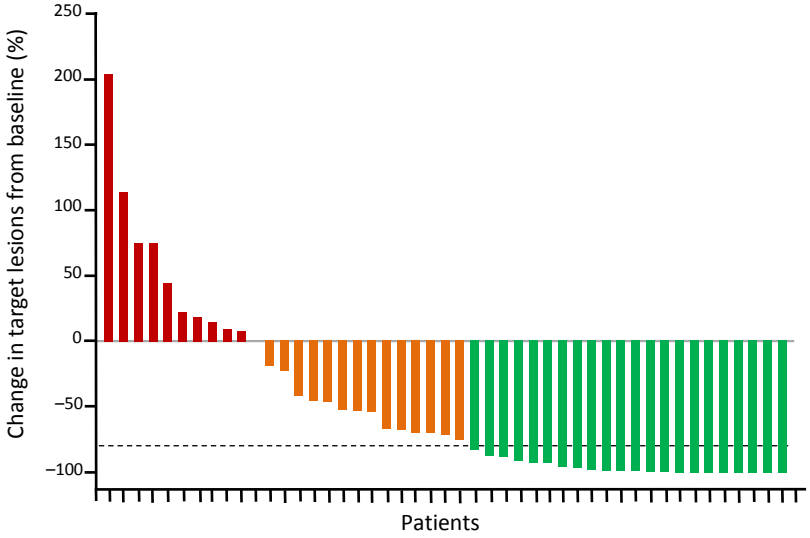
ORIGINAL ARTICLE

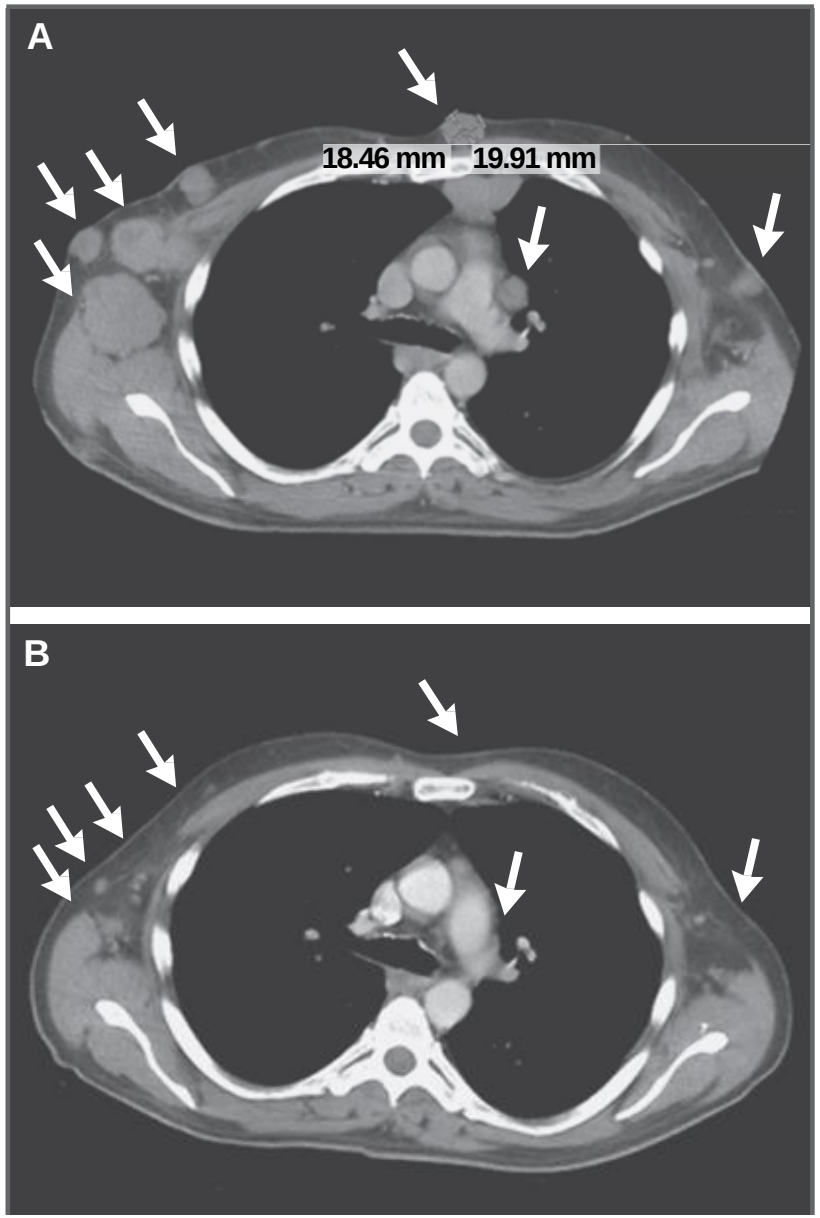
Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

Wolchok et al. N Engl J Med 2013;369:122–33







Adapted from Wolchok et al. N Engl J Med 2013;369:122–33

CA209-004 Phase I Study: Dose Cohorts

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

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

Activity Summary: Concurrent and Sequenced Cohorts from 004

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:

PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Safety Overview

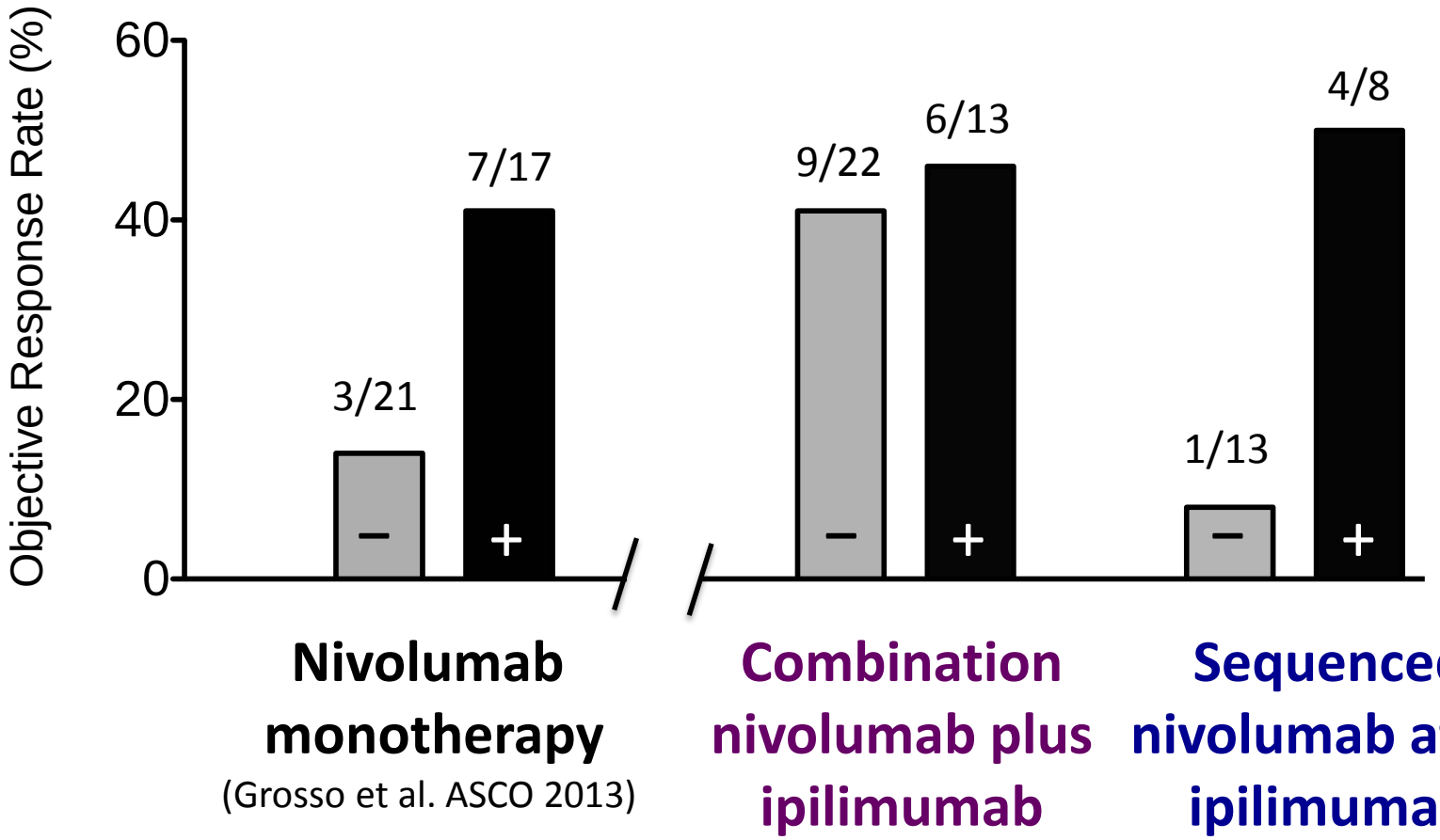
AE, %	Concurrent Cohorts 1-3 n=53		Cohort 8 n = 41		All Concurrent n=94	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
All Related AEs	96	62	95	61	96	62
Select AEs						
Gastrointestinal	43	9	34	20	39	14
Hepatic	30	15	12	12	22	14
Skin	79	4	73	15	77	9
Endocrine	17	4	22	2	19	3
Renal	6	6	0	0	3	3
Other				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

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Evaluating PD-L1 status as a candidate biomarker



Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)

Overview of efficacy and safety for anti-PDL1/PD1 therapies in NSCLC

Therapy	Number of patients	Key efficacy data	Key safety data
MPDL3280A[1]	175 (85 with NSCLC: 53 evaluable, 85% PDL1+	ORR 23%	• 66% related AEs, 11% Grade 3–4 AEs (fatigue) • No grade 3–5 pneumonitis
MEDI4736[2]	367 (155 with NSCLC, 58 evaluable)	ORR 16%	• 29% related AEs, 3% Grade 3–4 AEs • Pneumonitis: 1%, no Grade 3–4 pneumonitis • No colitis
Nivolumab[3]	129 with NSCLC	ORR 17.1% (21.7%*)[4] • 50% responded in 8 weeks • median OS 9.9 months	• 53% related AEs, 5% Grade 3–4AEs • Pneumonitis – 6%, Grade 3–4: 3 patients (2%) – 2 deaths
Pembrolizumab	38 with NSCLC[4]	ORR 21% (24%*)[4]	
	221 with NSCLC (80% PDL1+)[5]	ORR 15% (21%‡)[5]	• 48% related AEs (fatigue), 6% Grade 3–4 AEs[5] • Pneumonitis – Grade 3–4: 3 patients (1%)[5]

*including immune responders, irRECIST, ‡unconfirmed response

1. Soria. European Cancer Congress 2013 (abstract 3408); 2. Brahmer et al. ASCO 2014 (Abstract 8021); 3. Brahmer et al. IASLC WCLC, 2013; 4. Garon et al. IASLC WCLC, 2013; 5. Garon et al. ASCO 2014 (abstract 8020)

Table 3. Tumor response in NSCLC patients treated with nivolumab plus ipilimumab

	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	
	Squamous (n = 9)	Non-squamous (n = 15)	Squamous (n = 9)	Non-squamous (n = 16)
ORR, n (%) [95% CI]	1 (11) [0.3, 48]	2 (13) [2, 41]	3 (33) [8, 70]	2 (13) [2, 38]
Ongoing responders, n (%)	1 (100%)	2 (100%)	1 (33%)	2 (100%)
Best overall response, n (%)				
Complete response[a]	0	0	0	0
Partial response[a]	1 (11)	2 (13)	3 (33)	2 (13)
SD	2 (22)	5 (33)	5 (56)	4 (25)
Progressive disease	4 (44)	4 (27)	0	6 (38)
Unable to determine	2 (22)	3 (20)	1 (11)	2 (13)
Estimated median DOR,[b] weeks (95% CI)	NR	NR	21 (12, 21)	NR
Response duration by patient, weeks	27+	6+, 45+	12, 14+, 21	32+, 49+
Patients with ongoing SD, n (%)	0	1 (20)	1 (20)	1 (25)
SD duration, weeks	16, 45	16, 33, 34, 35+, 47	14, 14, 15, 24+, 27	13, 16, 22, 36+

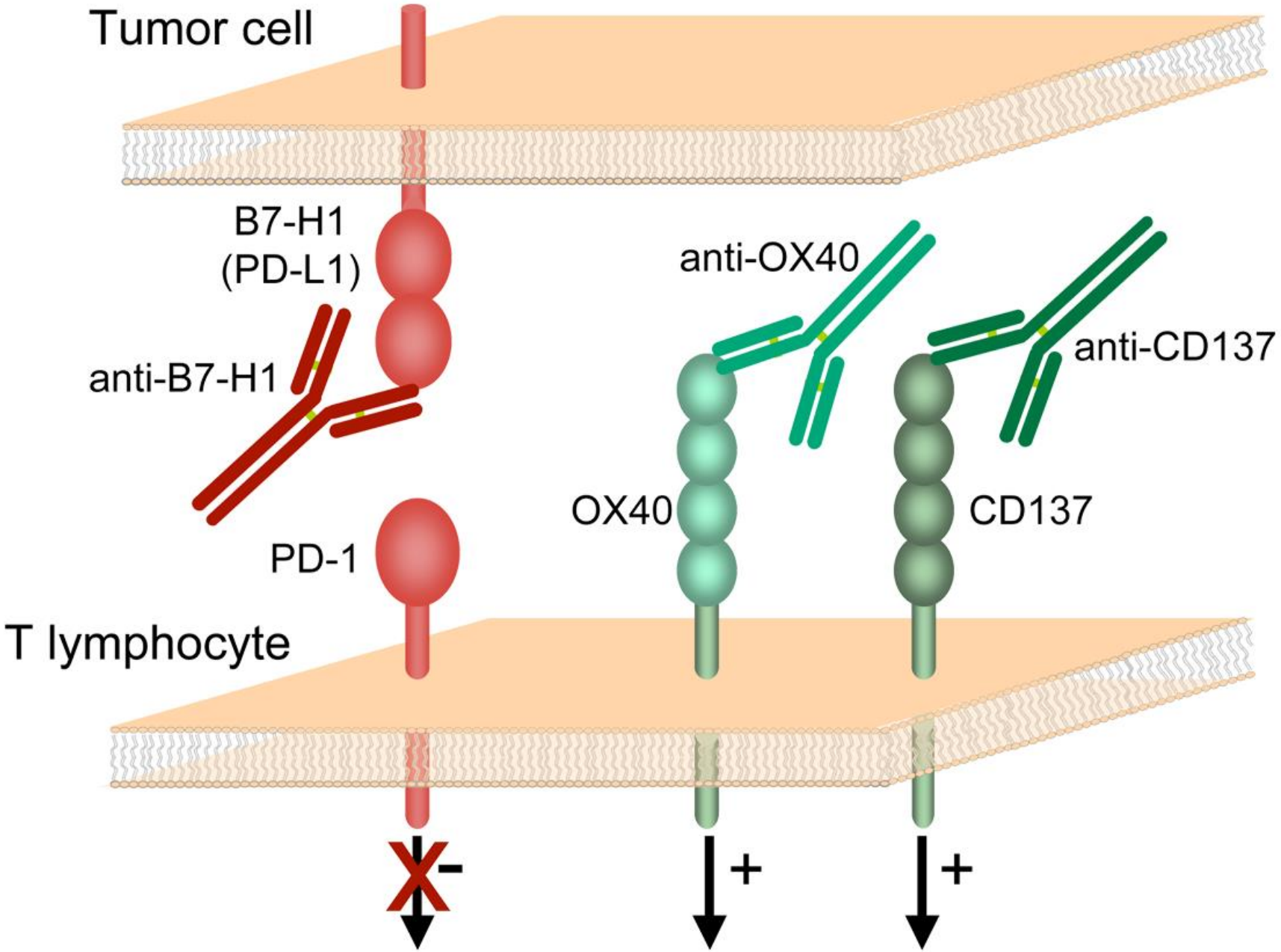
[a]All complete and partial responses were confirmed by a subsequent tumor assessment per RECIST 1.1. Patients with an unconfirmed response are not shown

[b]Time from first response to documented progression, death within 100 days of last nivolumab dose, or last tumor assessment (for censored + data). Estimated median DORs were determined from Kaplan-Meier curves

+ = response ongoing; CI = confidence interval; NR = not reached

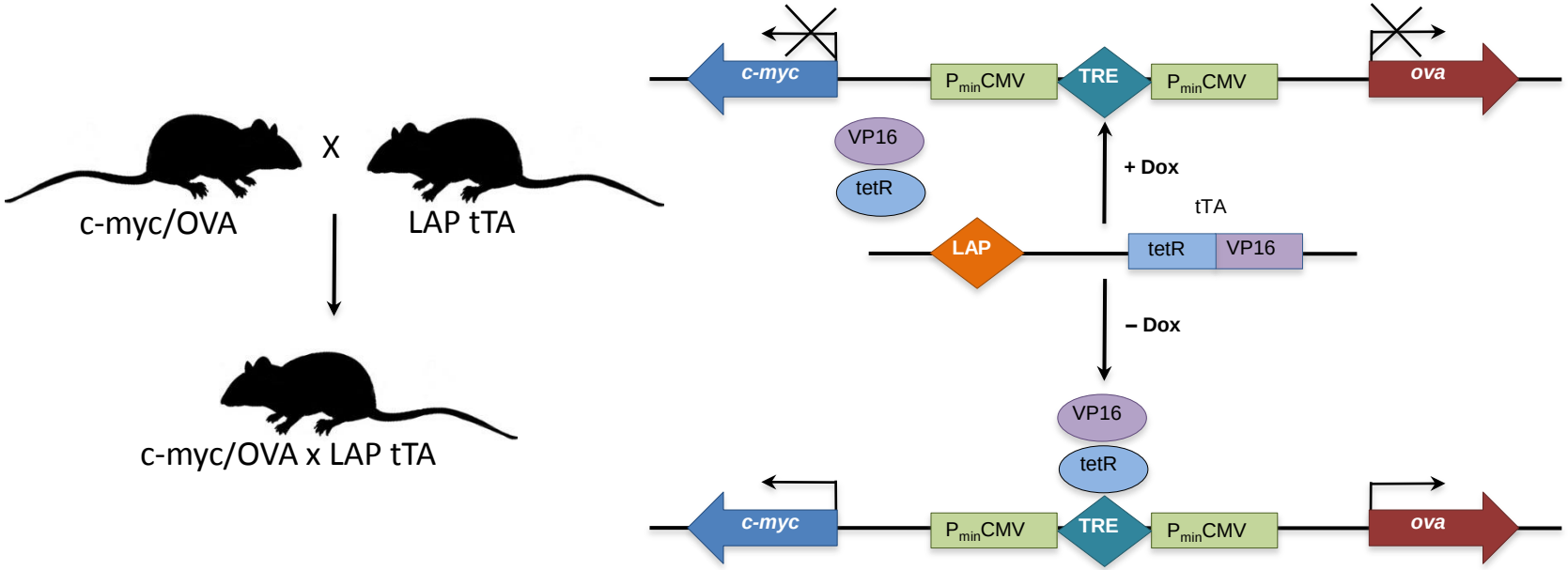
Combinations

Ready for triplets?

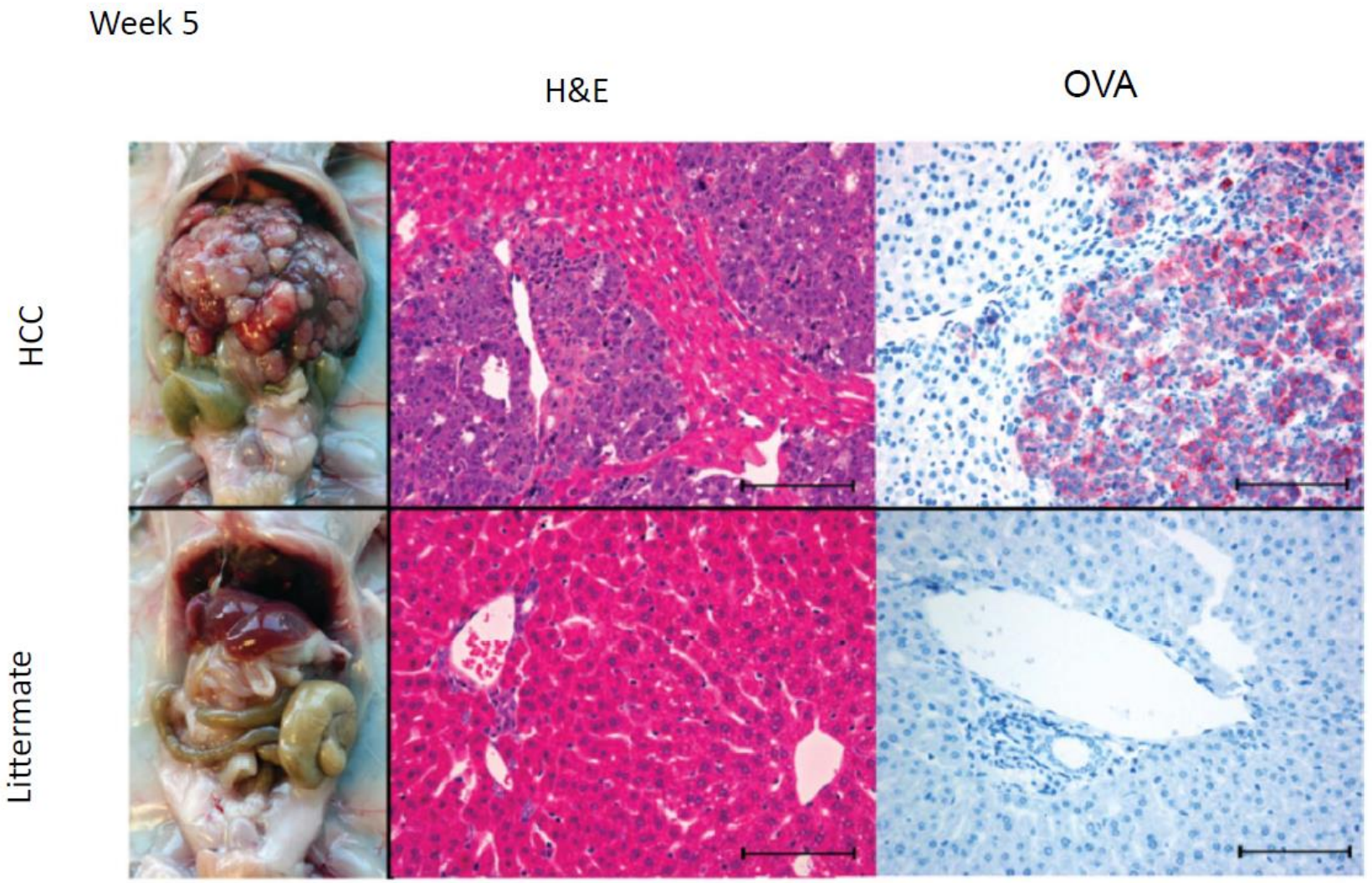

Tumor cell
B7-H1
(PD-L1)
anti-B7-H1
PD-1
anti-OX40
anti-CD137
OX40
CD137
T lymphocyte
-
+
+

Anti-CD137 + anti-PD-L1 + anti-OX40

Spontaneous HCC (c-mycOVA75/tTALAP)

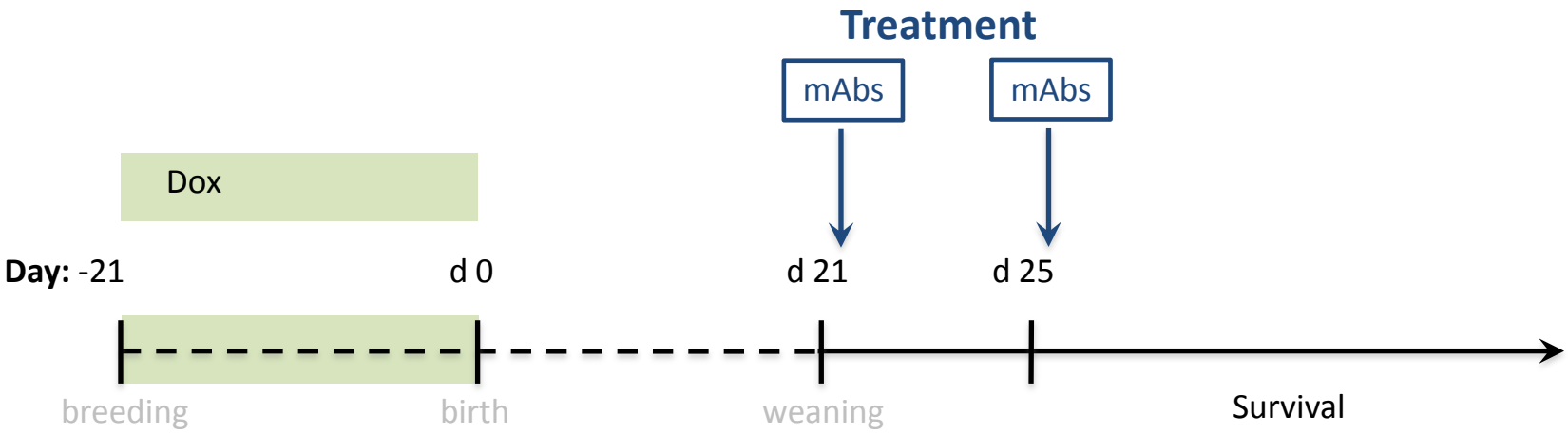


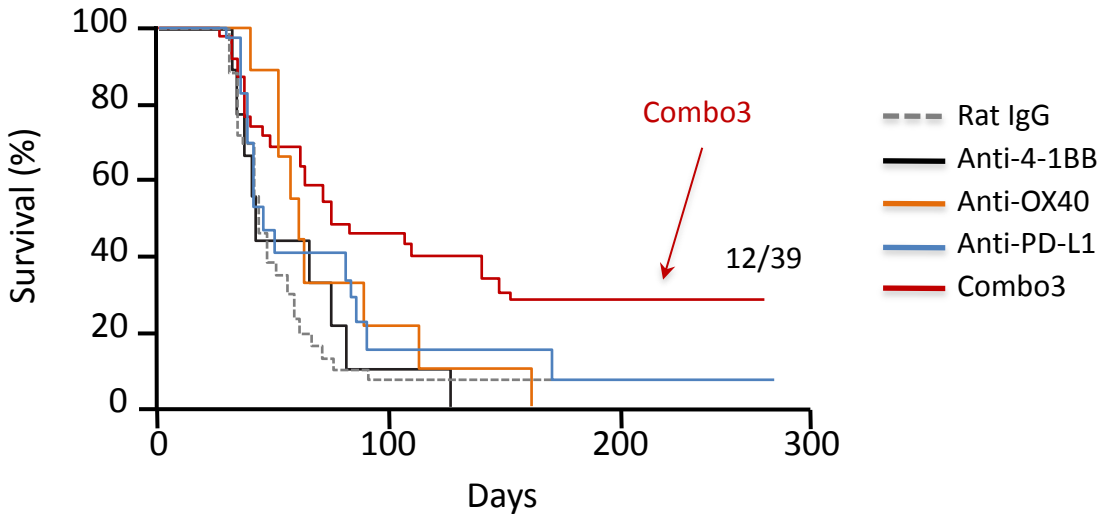
Adapted from Ney et al. Hepatol 2009;49:471–81



Reproduced from Ney et al. Hepatol 2009;49:471–81

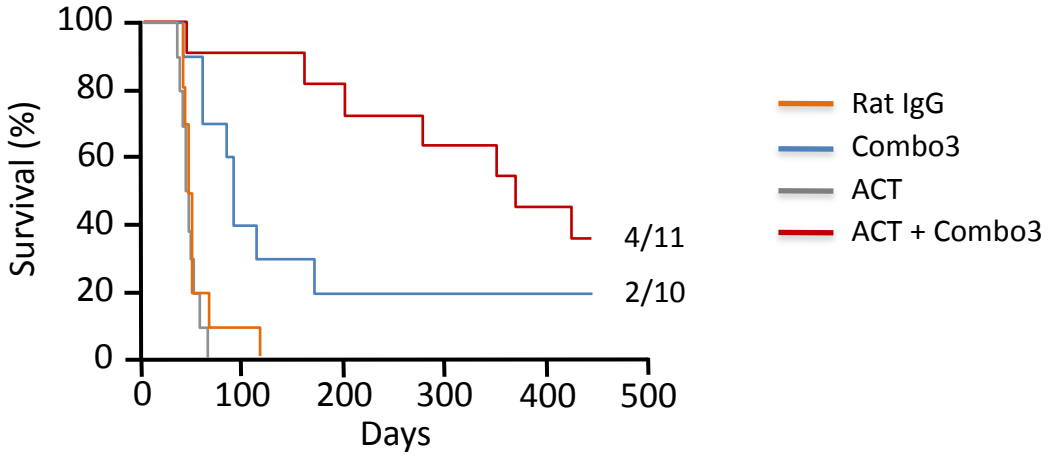
Efficacy of combination therapies: Preclinical data

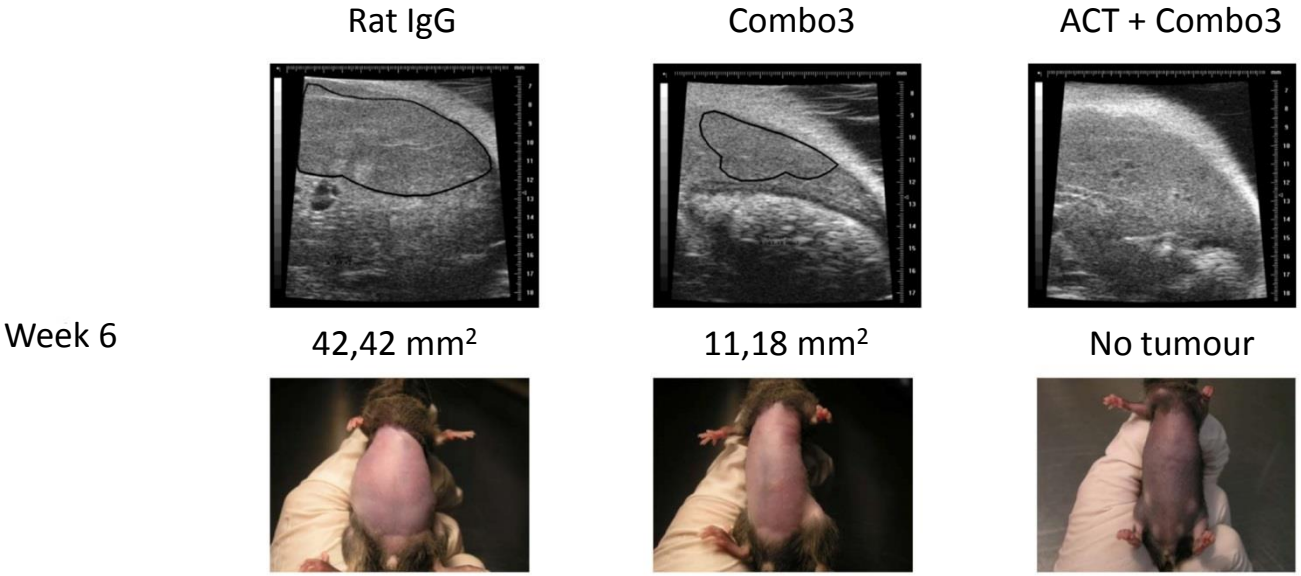




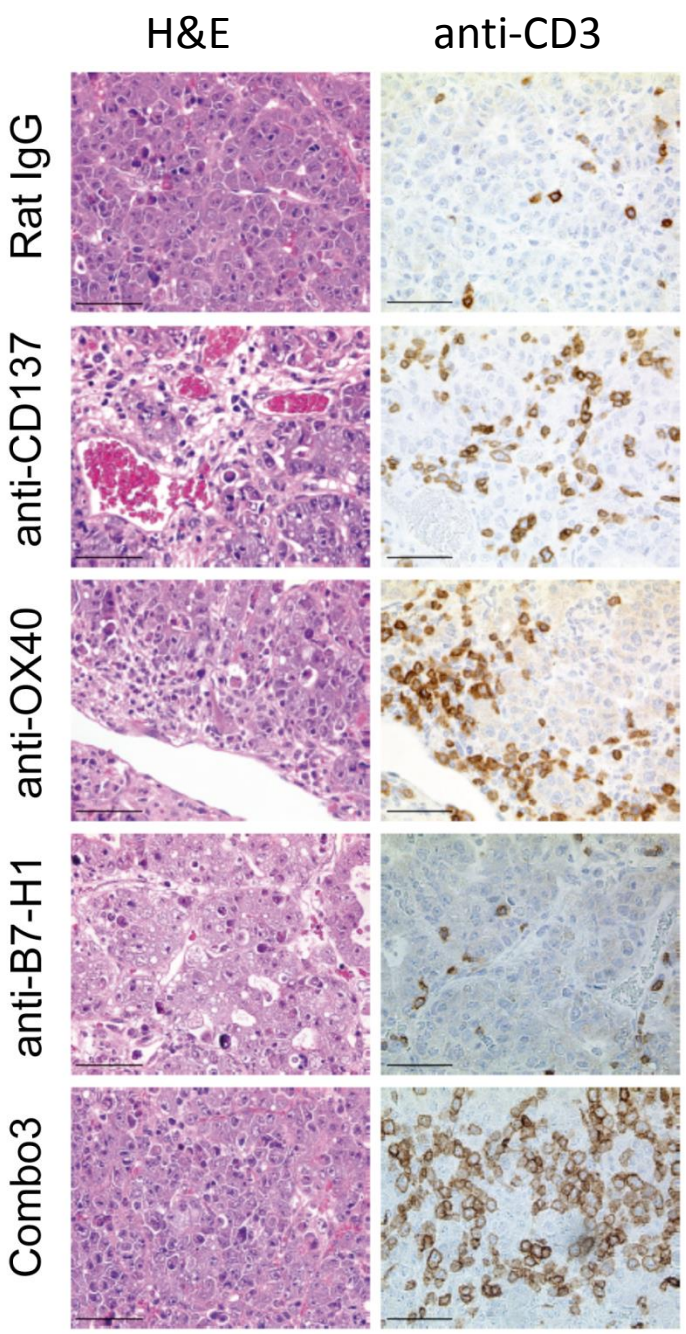
Morales-Kastresana et al. Clin Cancer Res 2013;19:6151–62

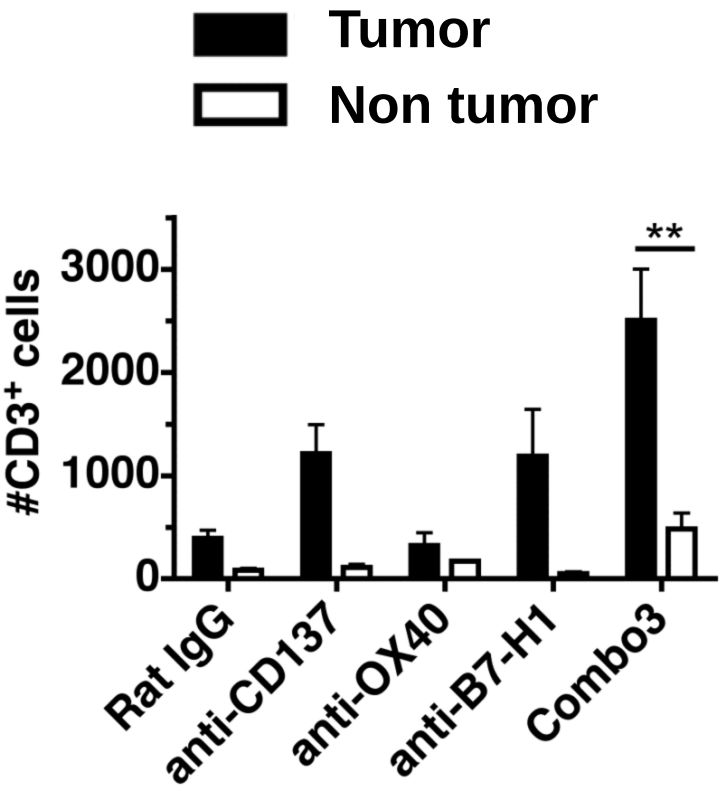
Efficacy of combination therapies: Survival





Morales-Kastresana et al. Clin Cancer Res 2013;19:6151–62


H&E
anti-CD3
Rat IgG
anti-CD137
anti-OX40
anti-B7-H1
Combo3


Tumor
Non tumor
#CD3+ cells
3000
2000
1000
0
**
Rat IgG
anti-CD137
anti-OX40
anti-B7-H1
Combo3

NEW PARADIGMS

from Greek paradeigma "pattern"

Set of assumptions, concepts, values, and practices

"I'm afraid you've had a paradigm shift."

So what is it going to look like?

Arch Immunol Ther Exp (Warsz). 2002;50(1):13-8.

Effective tumor immunotherapy: start the engine, release the brakes, step on the gas pedal,...and get ready to face autoimmunity.

Tirapu I, Mazzolini G, Rodriguez-Calvillo M, Arina A, Palencia B, Gabari I, Melero I.

Abstract

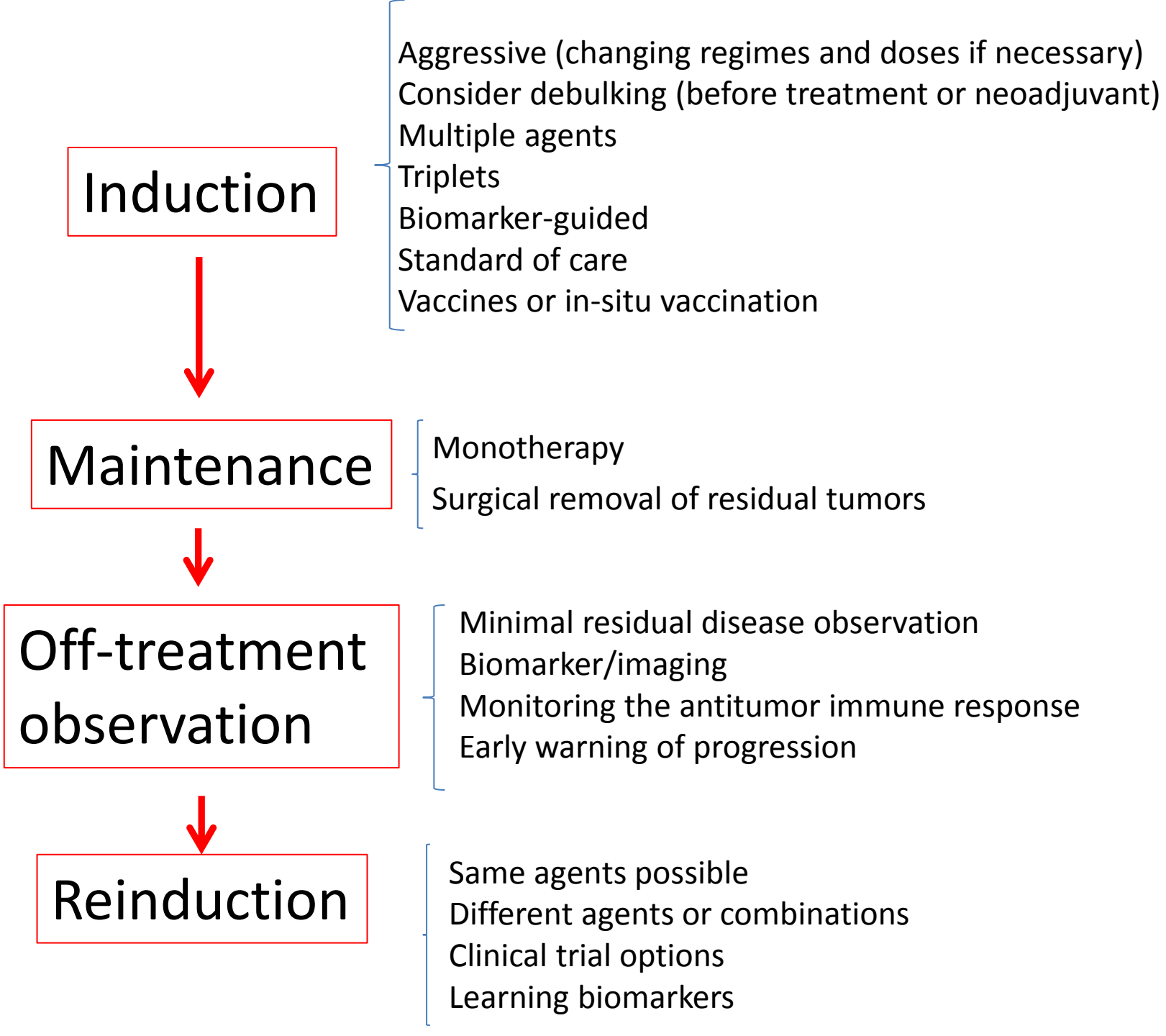
Cellular immune responses can destroy cancer cells, achieving the cure of experimental malignancies. An expanding wealth of knowledge on the molecular basis of how to prime and amplify a T cell response has fueled a number of strategies successful at treating established tumors (rather than merely preventing tumor grafting). The most efficacious approaches operate at different stages, including: 1) priming the immune response using tumor antigen-expressing dendritic cells or tumor cells transfected with genes that render them immunogenic, 2) sustaining and amplifying immunity using agonistic monoclonal antibodies against costimulatory molecules or immune-potentiating cytokines, and 3) eliminating mechanisms that self-regulate the strength of the immune response, such as inhibitory receptors or regulatory T cells. A rational combination of such approaches holds great hope for cumulative and synergistic effects, but there is also evidence that they can open the flood-gates for unwanted inflammatory reactions. The next decade can be envisioned as the time when the first reproducibly **efficacious combination regimes** for cancer immunotherapy will become available and widely used in the clinic, as clinicians learn the best strategies and try to harness their potentially damaging effects.

1. Sequenced therapy schemes in time (induction, maintenance, reinduction)

2. Debulking (before treatment or in a neoadjuvant setting)

3. Surgical removal of residual tumors in sustained PR or long-lasting SD.

4. Stop treatment if CR or PR and watchful expectation (closely observing the tumor and the anti-tumor immunity)


Induction
Aggressive (changing regimes and doses if necessary)
Consider debulking (before treatment or neoadjuvant)
Multiple agents
Triplets
Biomarker-guided
Standard of care
Vaccines or in-situ vaccination
Maintenance
Monotherapy
Surgical removal of residual tumors
Off-treatment observation
Minimal residual disease observation
Biomarker/imaging
Monitoring the antitumor immune response
Early warning of progression
Reinduction
Same agents possible
Different agents or combinations
Clinical trial options
Learning biomarkers

Isn't it damned simple my lord?
It looks like witchcraft to me
…and yet fascinating

Sancho, my friend: COMBINING
THESE IMMUNOTHERAPIES
will keep us on
the road for sometime…