ESMO
IFEMA – Feria de Madrid
27.9.14

Rationale to Combine Immunotherapy with "Physical" Therapy

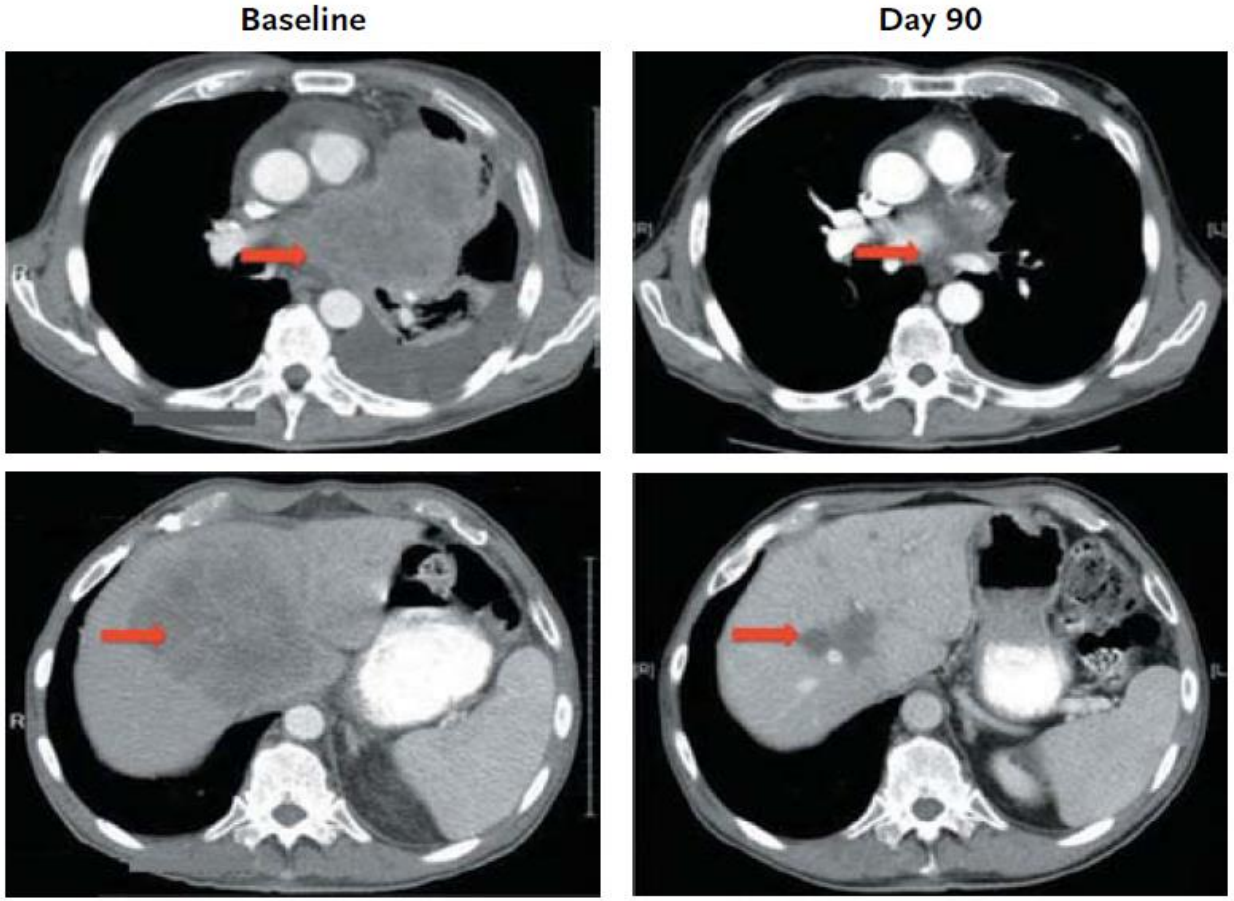
Kevin Harrington

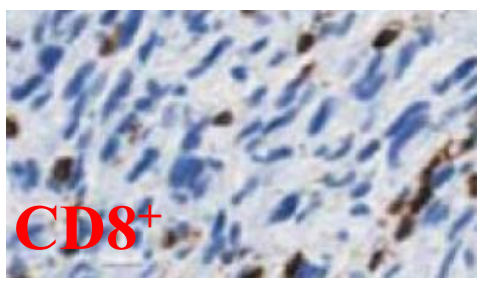
Conflicts of Interest

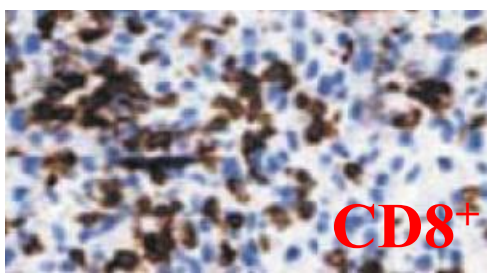
- Advisory Board member for Amgen, Merck, Viralytics
- Honoraria from Amgen, Merck
- Research funding from Viralytics

The Power of the New Immunotherapies

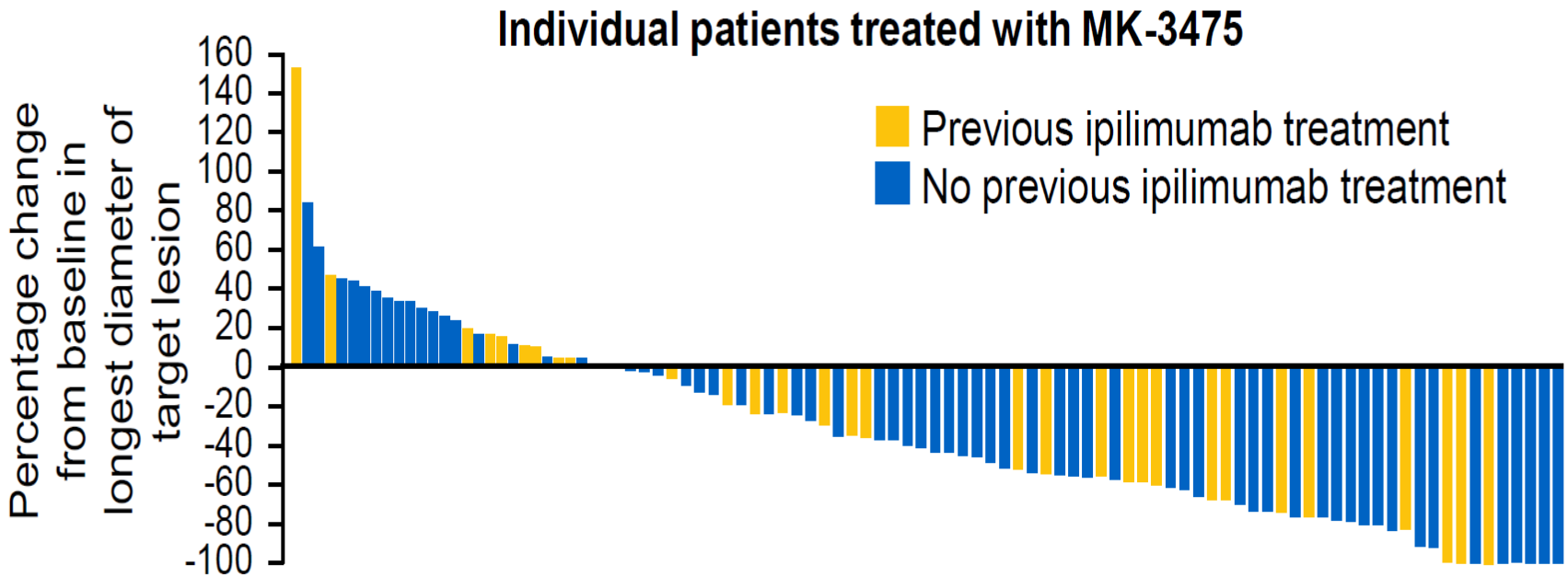
BRAF^{wt}
Biochemo
HD IL-2
Ipi







MK3475 (Pembrolizumab) in Melanoma

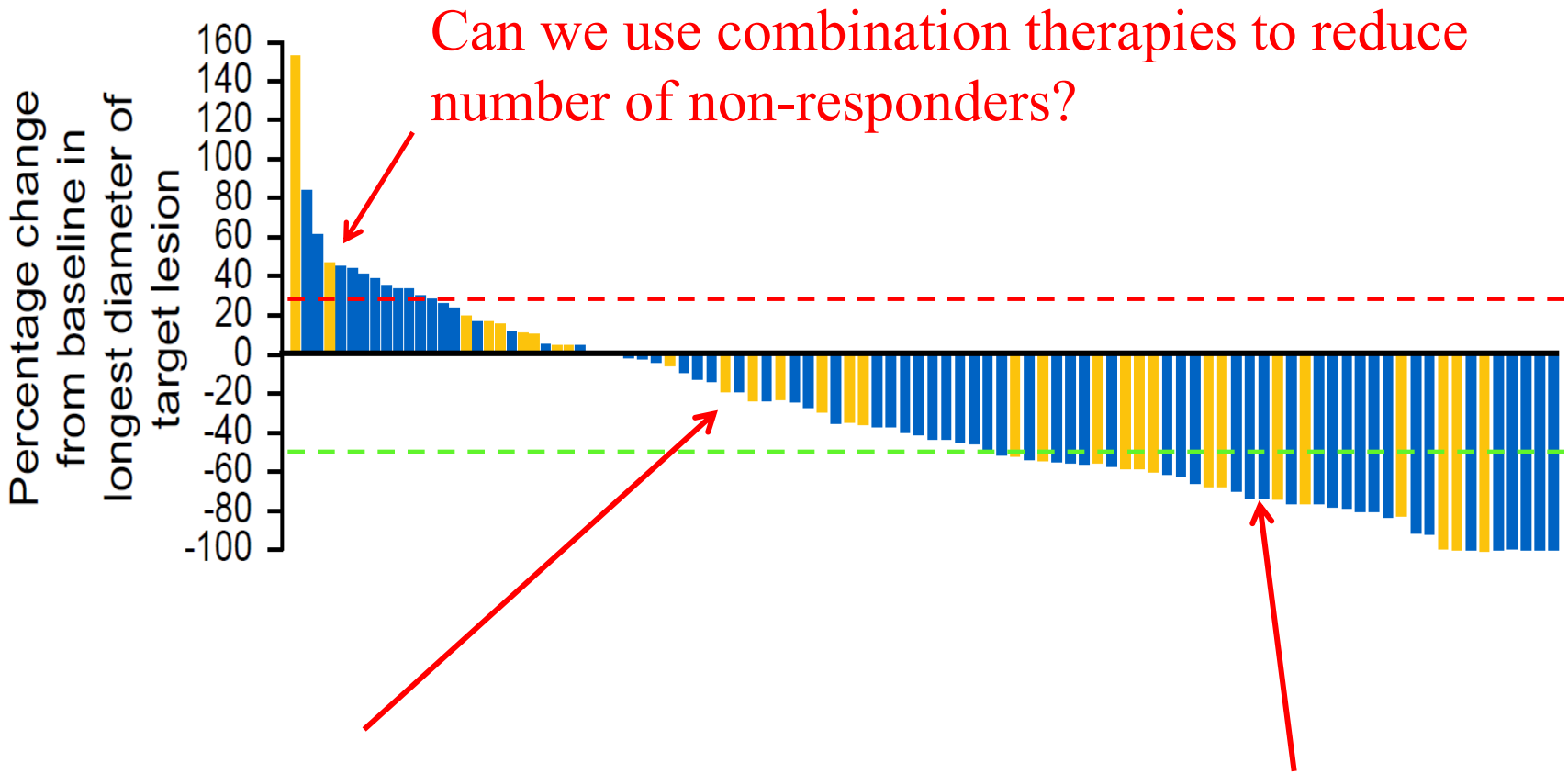


Cohort	ORR by RECIST, %	
	No previous ipilimumab	Previous ipilimumab
10 mg/kg Q2W (n = 52)	49	62
10 mg/kg Q3W (n = 45)	26	27
2 mg/kg Q3W (n = 20)	25	--

Hamid O, et al. N Engl J Med 2013;369:134–44; Ribas A, et al. ASCO 2013. Abstract 9009.

Q3W, every 3 weeks.

MK3475 (Pembrolizumab) in Melanoma



Can we use combination therapies to convert SD to responders?

Can we use combination therapies to increase number and durability of CR?

Points to Consider

- Not all patients present initially with disseminated metastatic disease
- “Local” therapies are frequently curative against locoregional disease
- Delayed systemic failure is a significant problem in many tumours that are apparently “cured” by locoregional therapies
- Not all solid tumours will respond to immunotherapy like melanoma
- The toxic effects of single- and combination-agent immunotherapies are significant
- The costs of long-term single- and combination-agent immunotherapies are significant
- The long-term effects of chronic checkpoint blockade remain to be elucidated

Local “Physical” Therapies Combined with Immunotherapy

- Radiation therapy
- Oncolytic immunotherapy
- High-intensity focused ultrasound
- Hyperthermia
- Cryotherapy
- Radiofrequency ablation
- Electrochemotherapy

Local “Physical” Therapies Combined with Immunotherapy

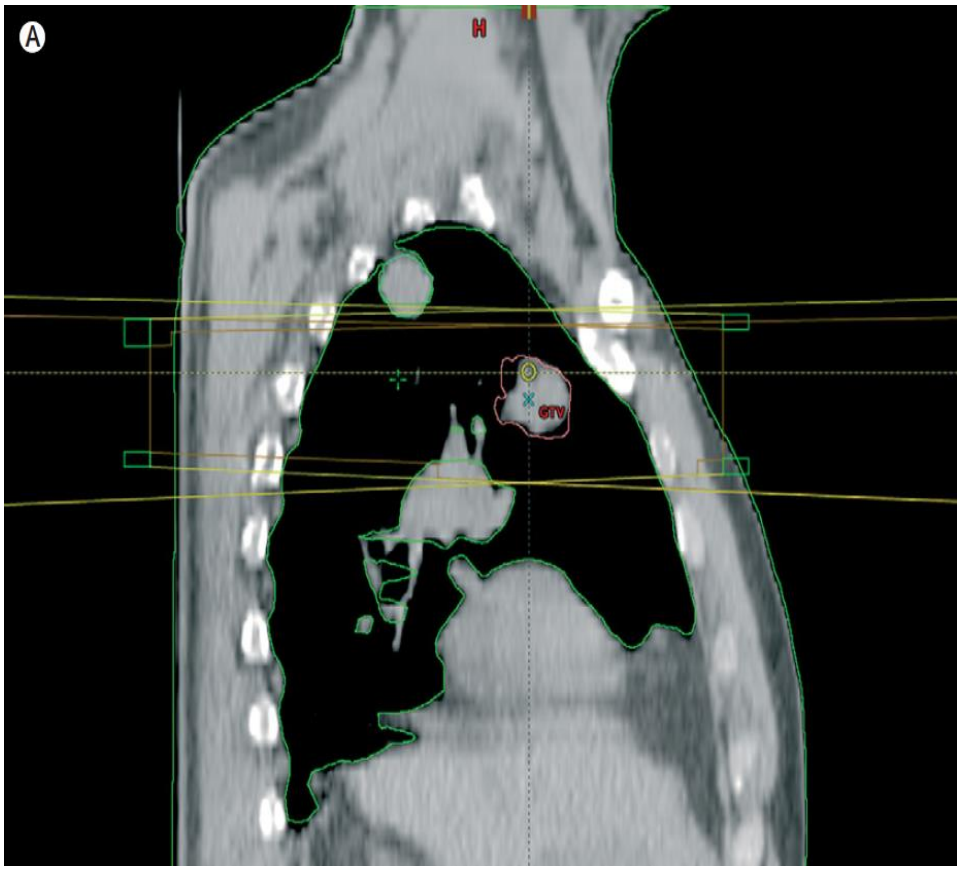
- Radiation therapy

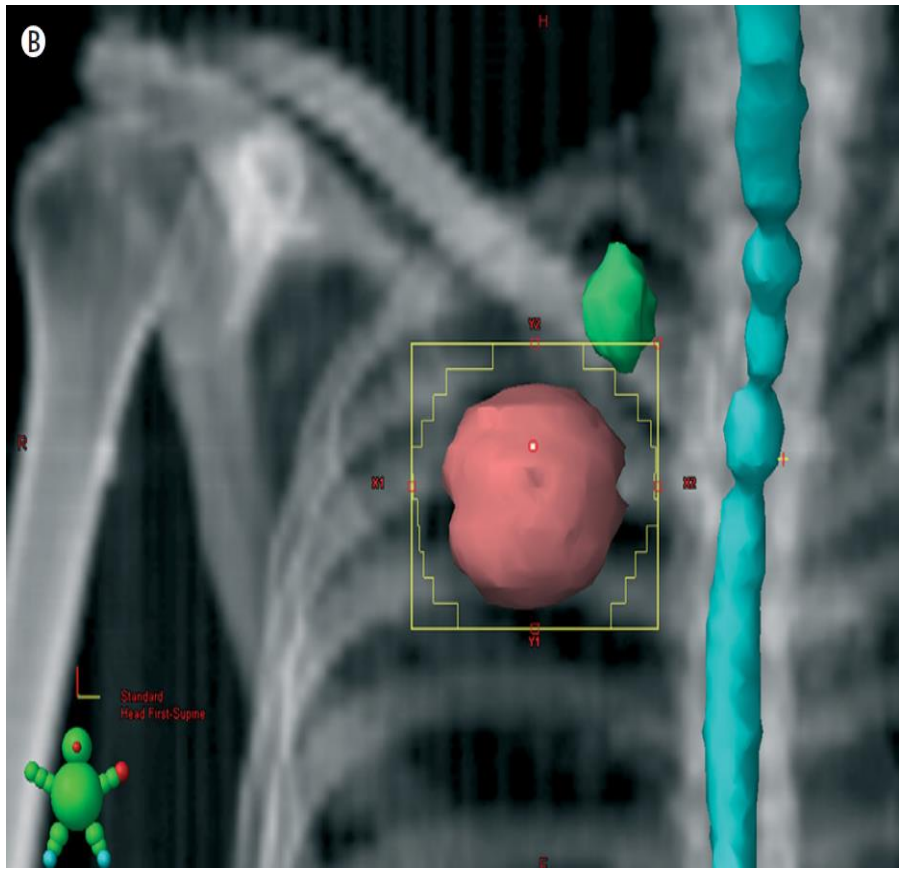
- Oncolytic immunotherapy

Systemic effects of local radiotherapy

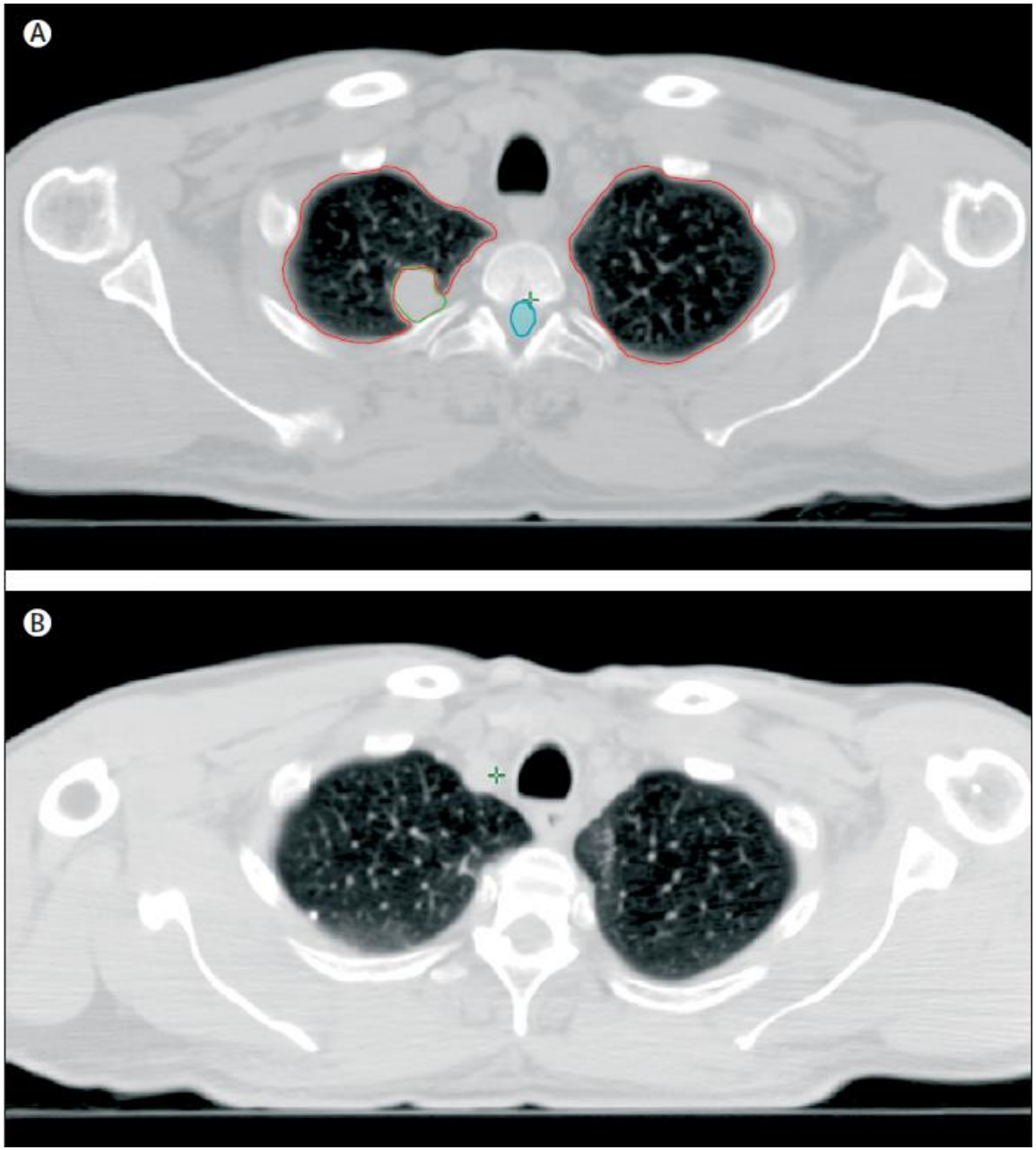
Silvia C Formenti, Sandra Demaria

- Patient with thymic carcinoma
- 2 Lung lesions, one irradiated, one not irradiated





Lancet Oncol 2009; 10: 718–26

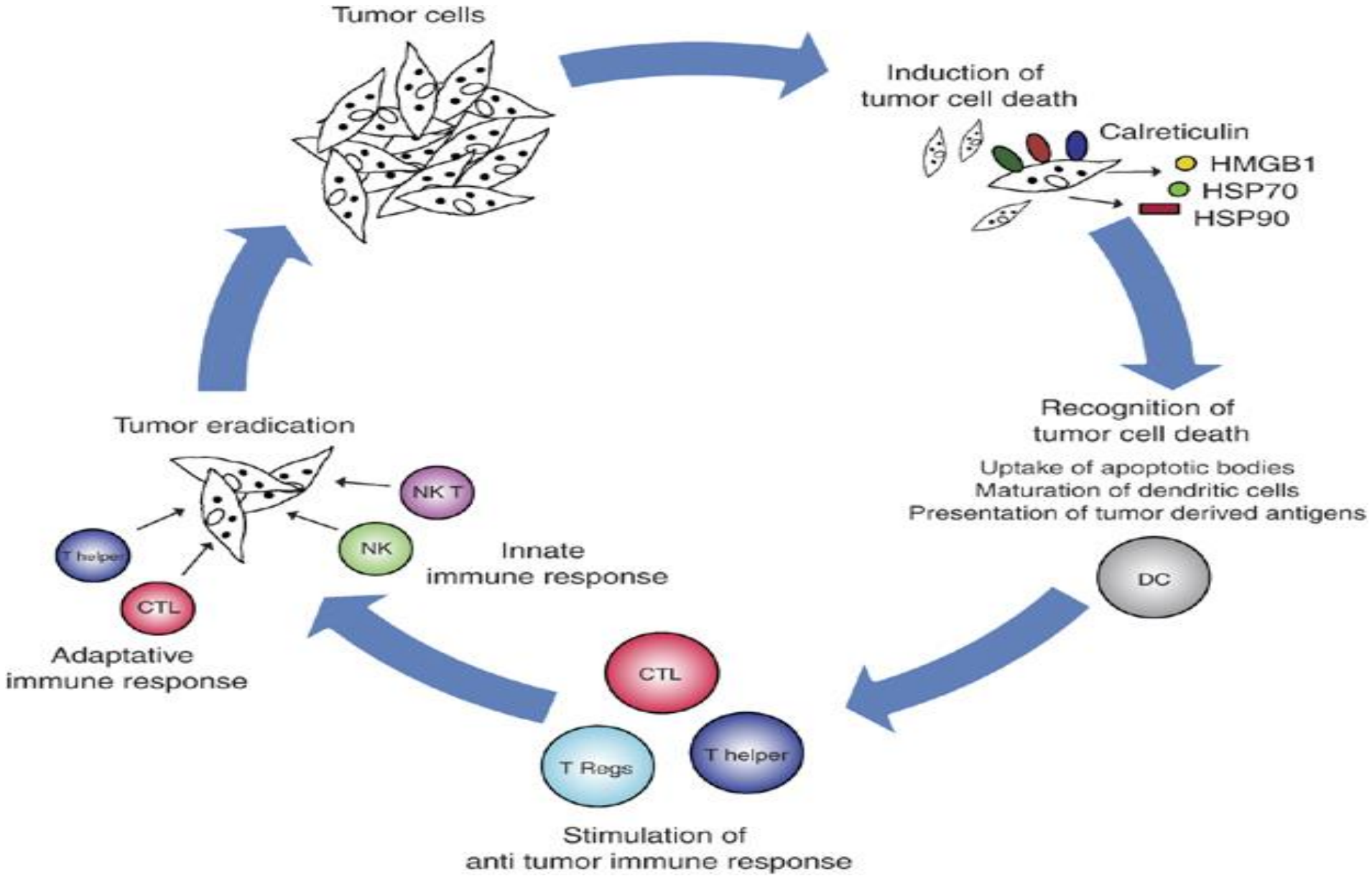


Abscopal response in unirradiated lesion

Ab = away from
Scopus = the target

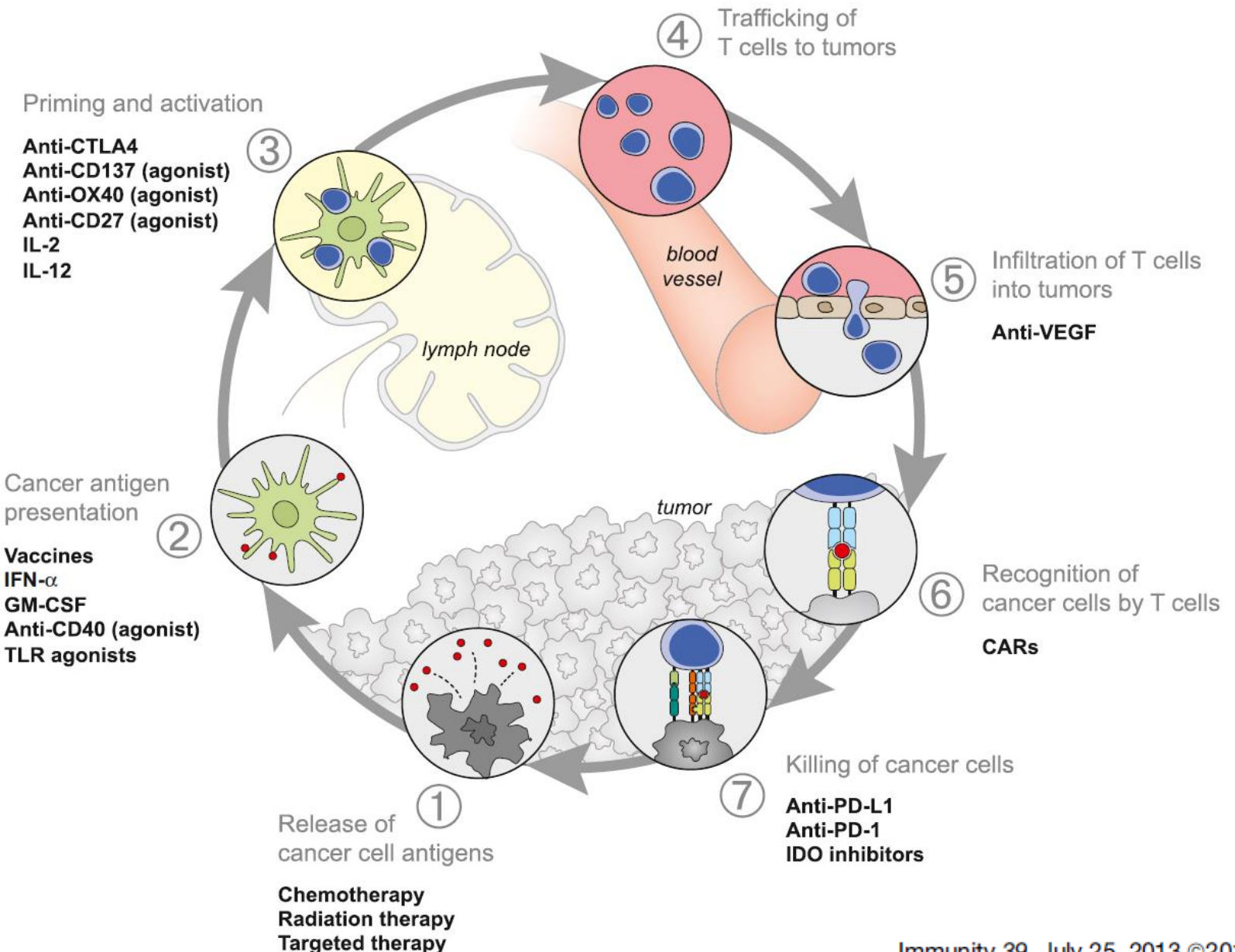
Lancet Oncol 2009; 10: 718–26

Steps in Generating Immune Responses

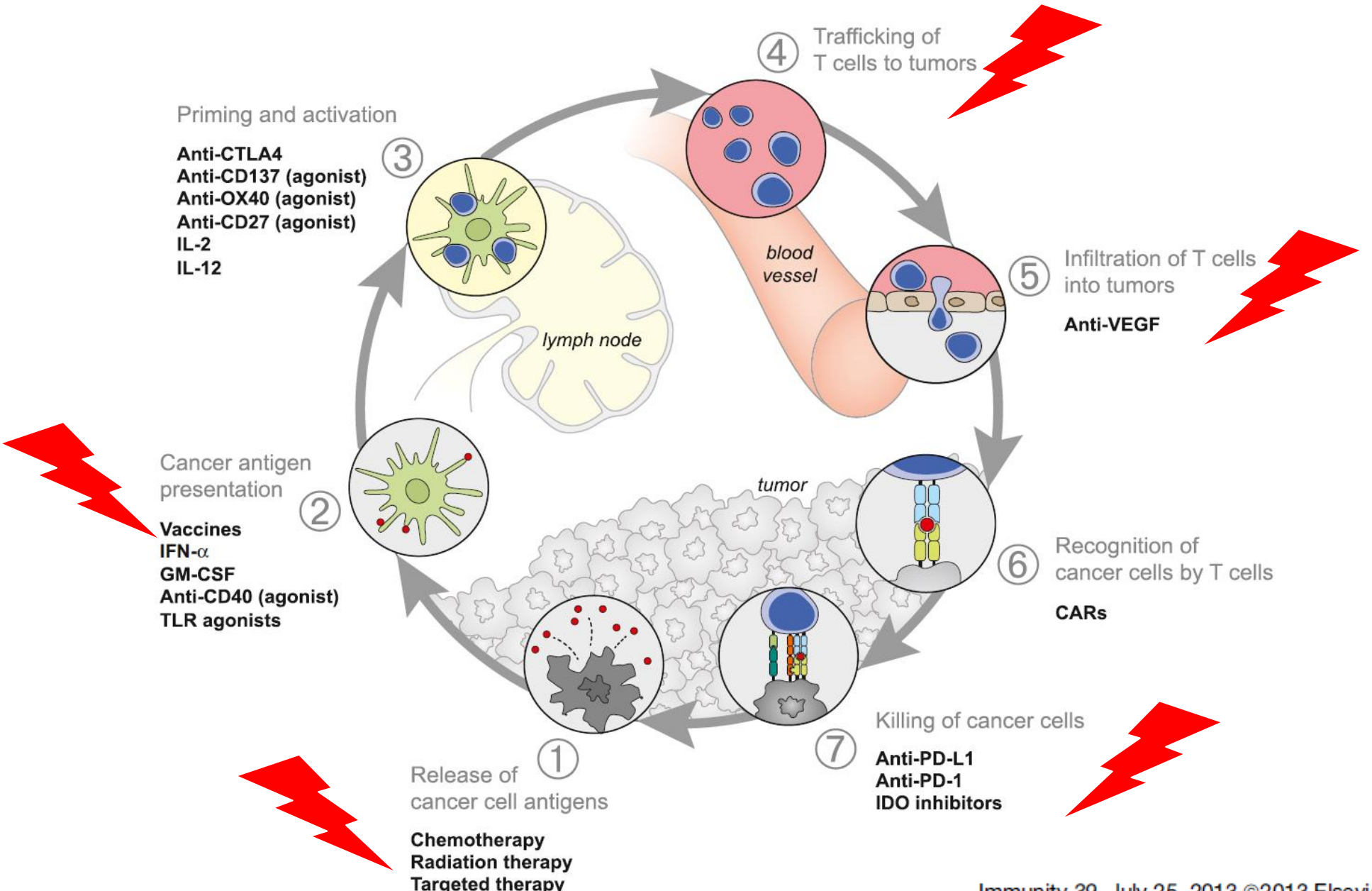


Tesniere et al. Cell Death & Differentiation 2008

Potential Therapeutic Modulation of Immune Responses

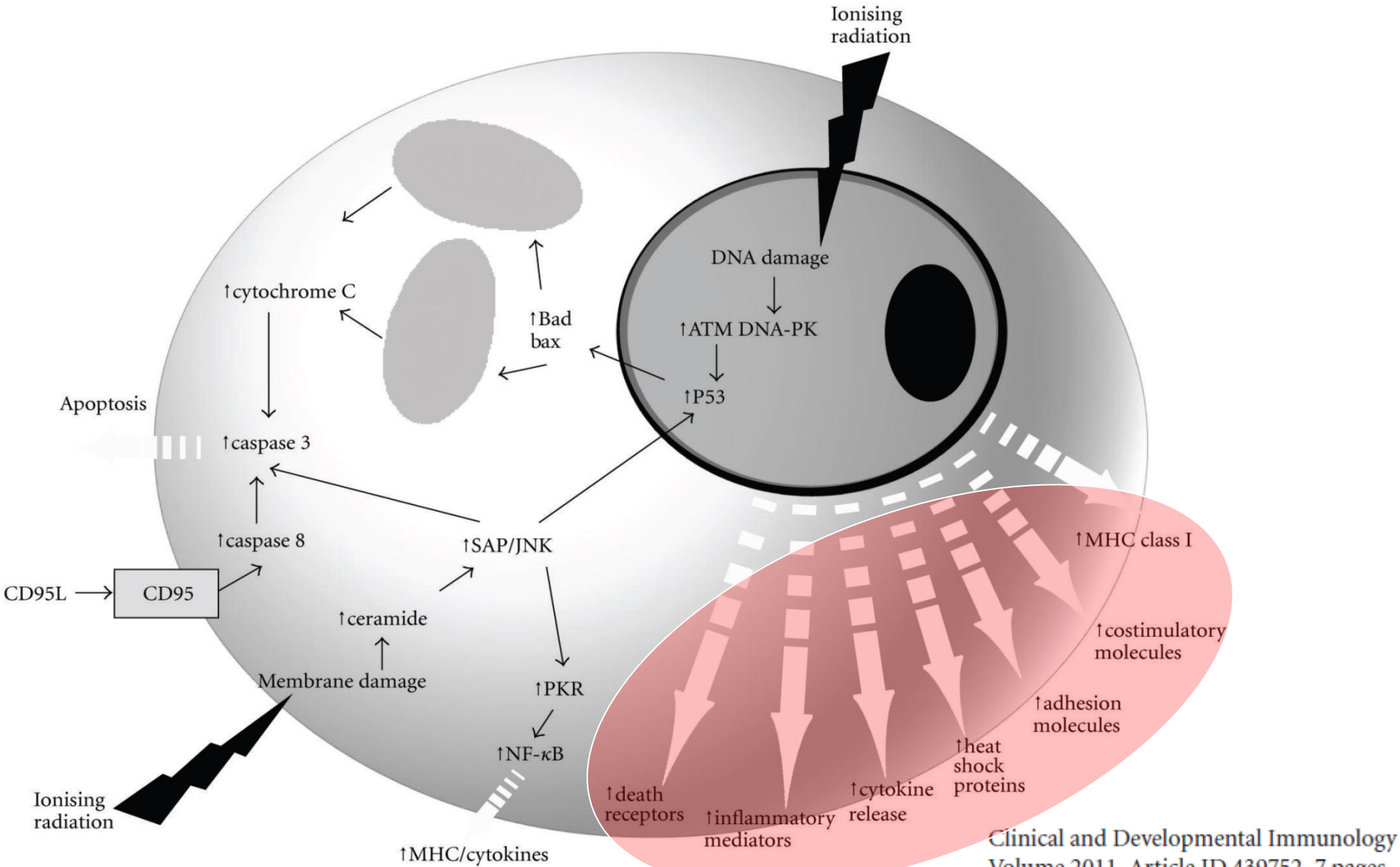


Potential Radiotherapeutic Modulation of Immune Responses



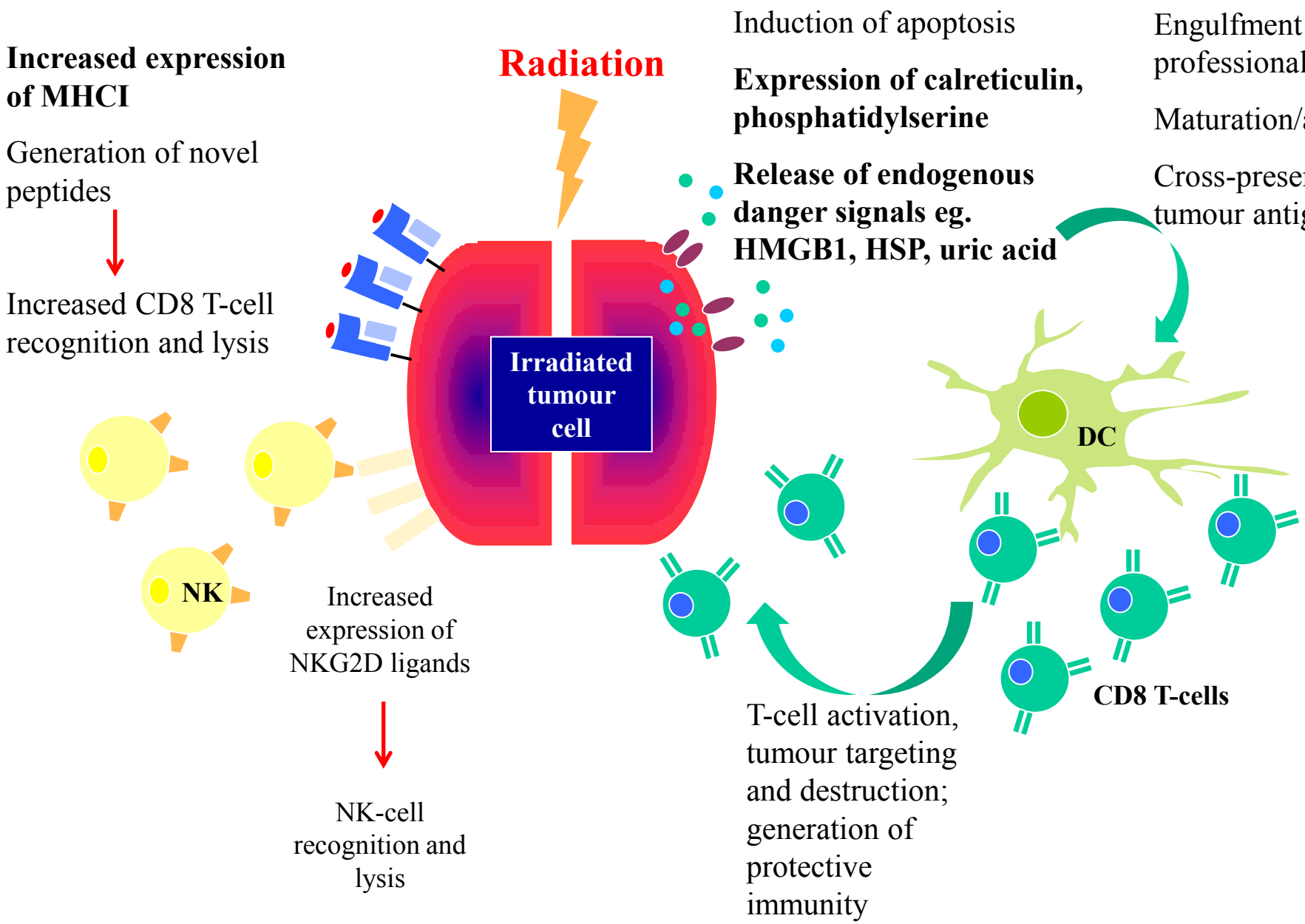
Immunity 39, July 25, 2013 ©2013 Elsevier Inc.

Immunological Effects of RT on Tumour Cells



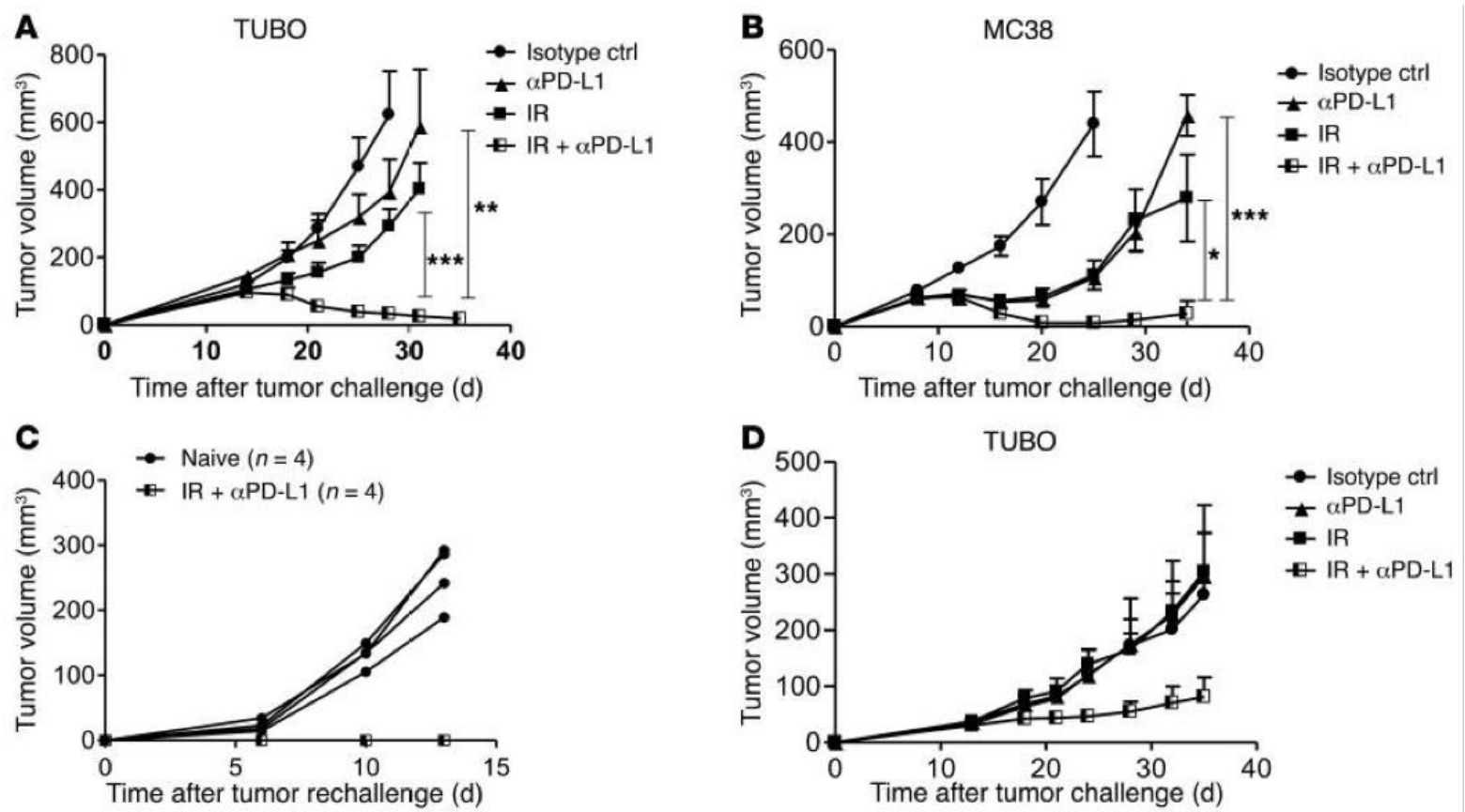
Clinical and Developmental Immunology
Volume 2011, Article ID 439752, 7 pages
doi:10.1155/2011/439752

Radiation as a Form of Active Immunotherapy



Preclinical Therapeutic Data

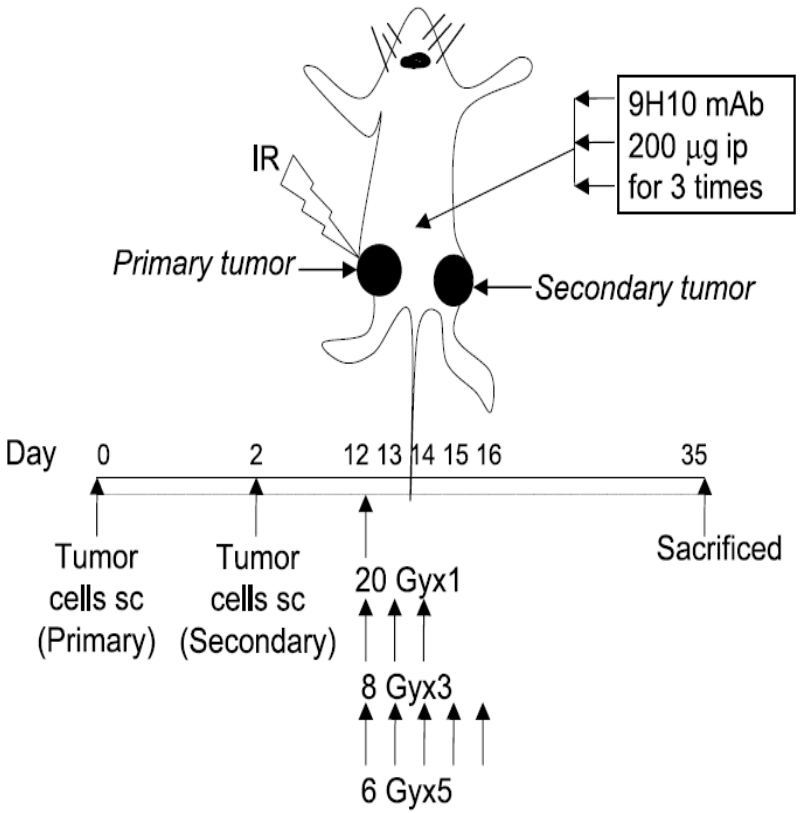
- Potential of combination immunotherapy and (chemo)radiation is great, but current data largely pre-clinical.

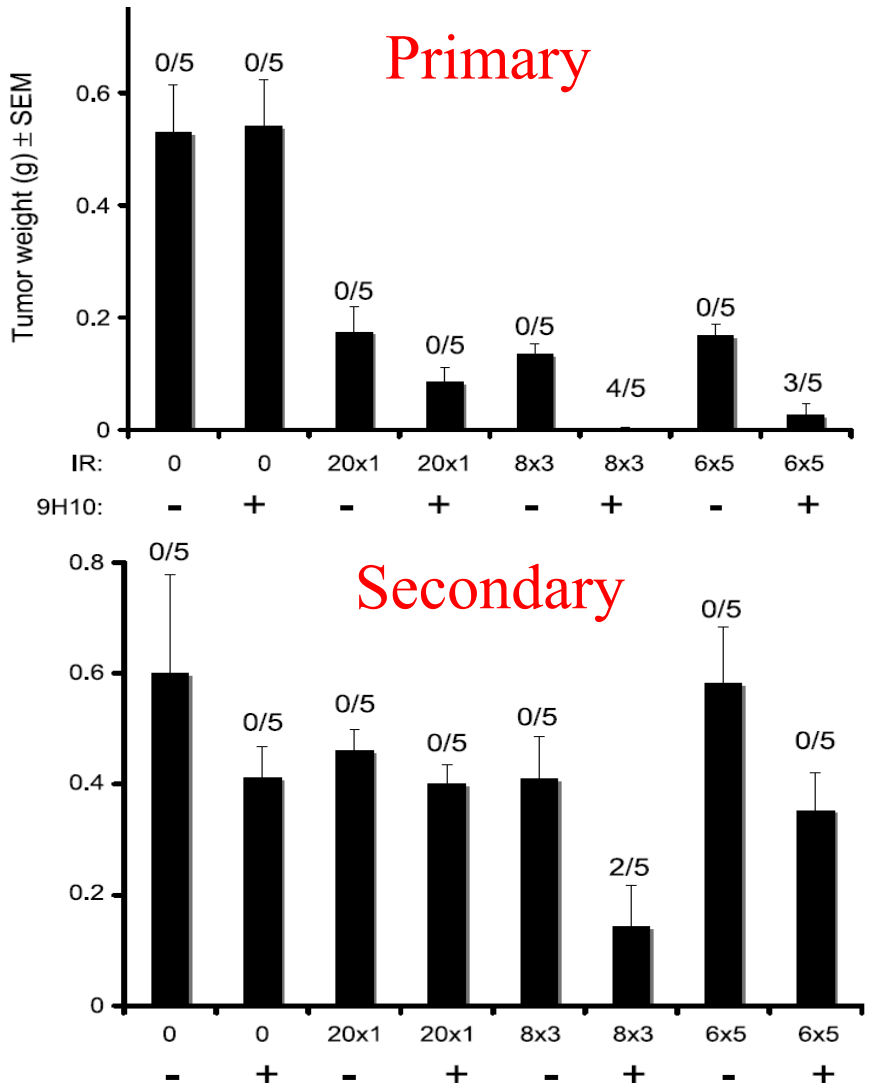


contralateral tumour

Fractionated but Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect when Combined with Anti–CTLA-4 Antibody

M. Zahidunnabi Dewan,[1] Ashley E. Galloway,[1] Noriko Kawashima,[1] J. Keith Dewyngaert,[3] James S. Babb,[2] Silvia C. Formenti,[3] and Sandra Demaria[1]

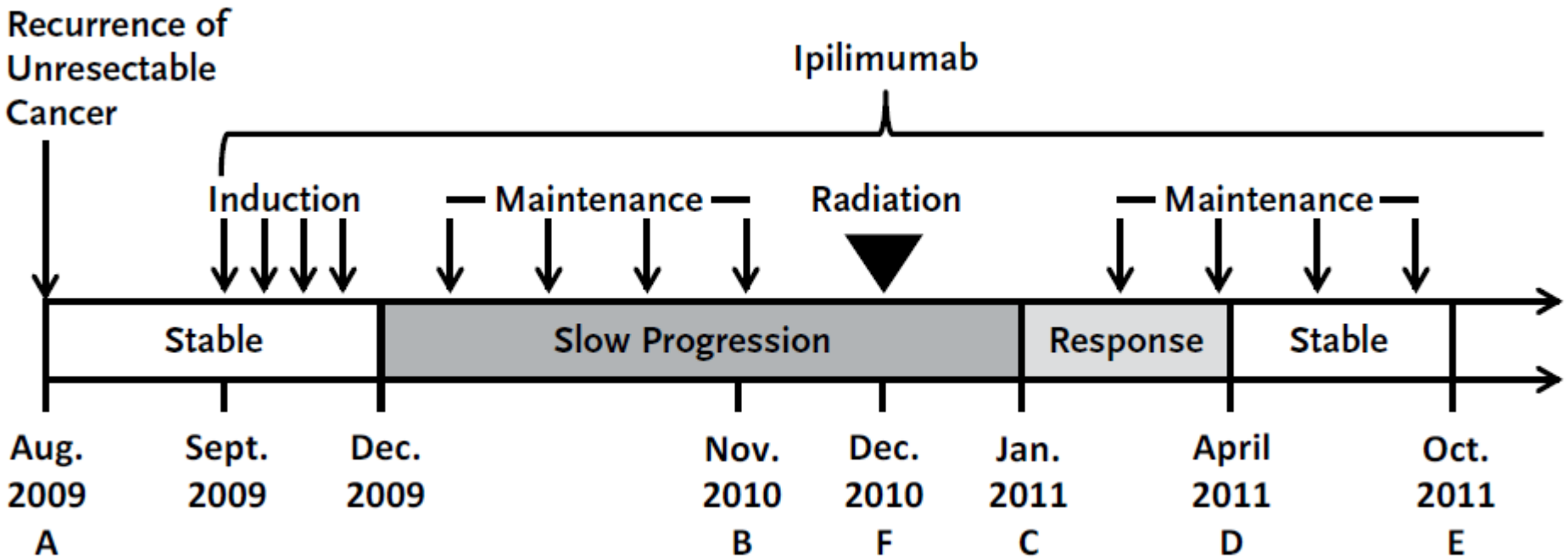




(Clin Cancer Res 2009;15(17):5379–88)

Case Report: Malignant Melanoma

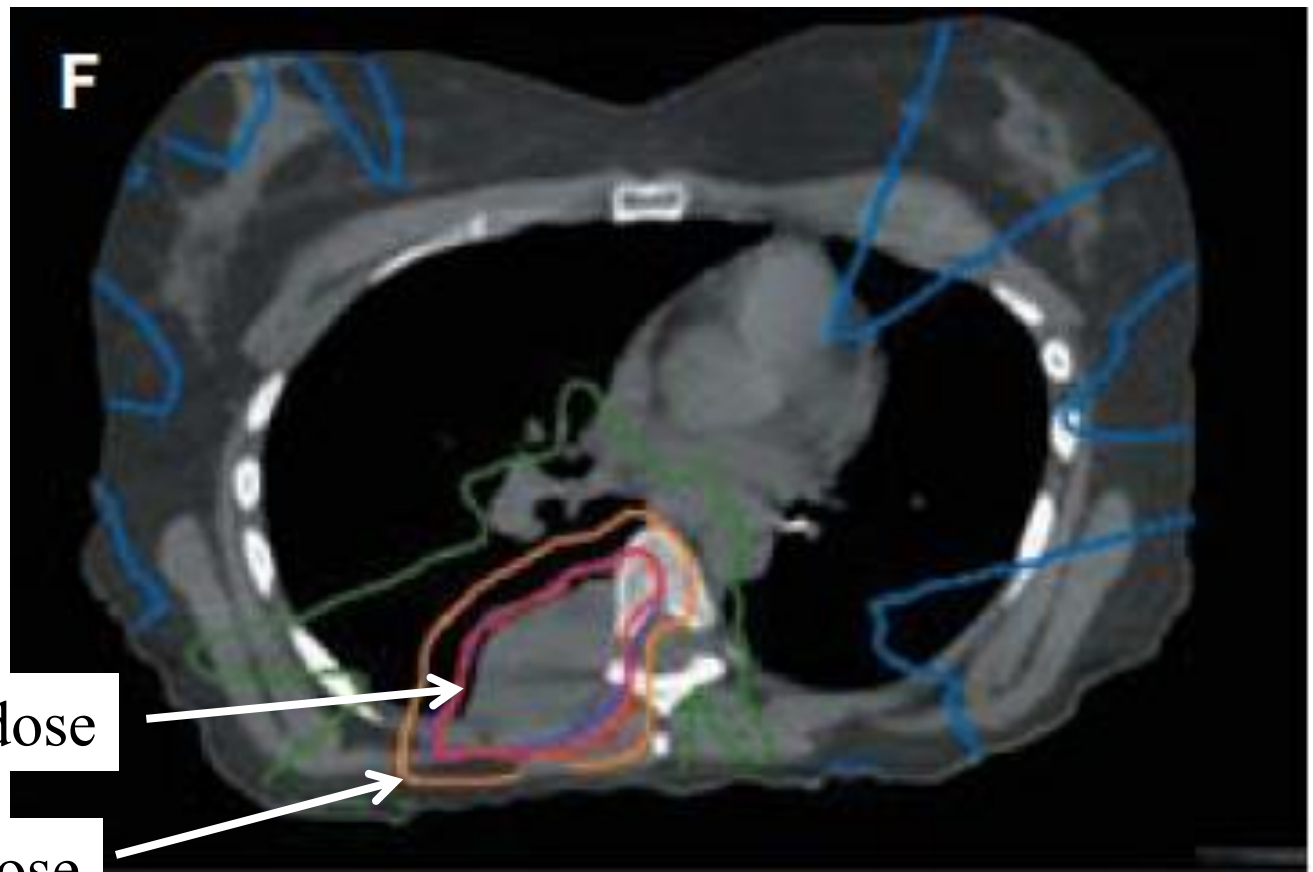
- 33 year old woman
- 2004 – 1.53 mm melanoma: Resected with clear margins, 0/5 LN
- 2008 – 2 cm lung metastasis: Chemotherapy and surgical removal (2009)
- August 2009 – Progressive pleural disease
- September 2009 – Commenced ipilimumab



N Engl J Med 2012;366:925-31.

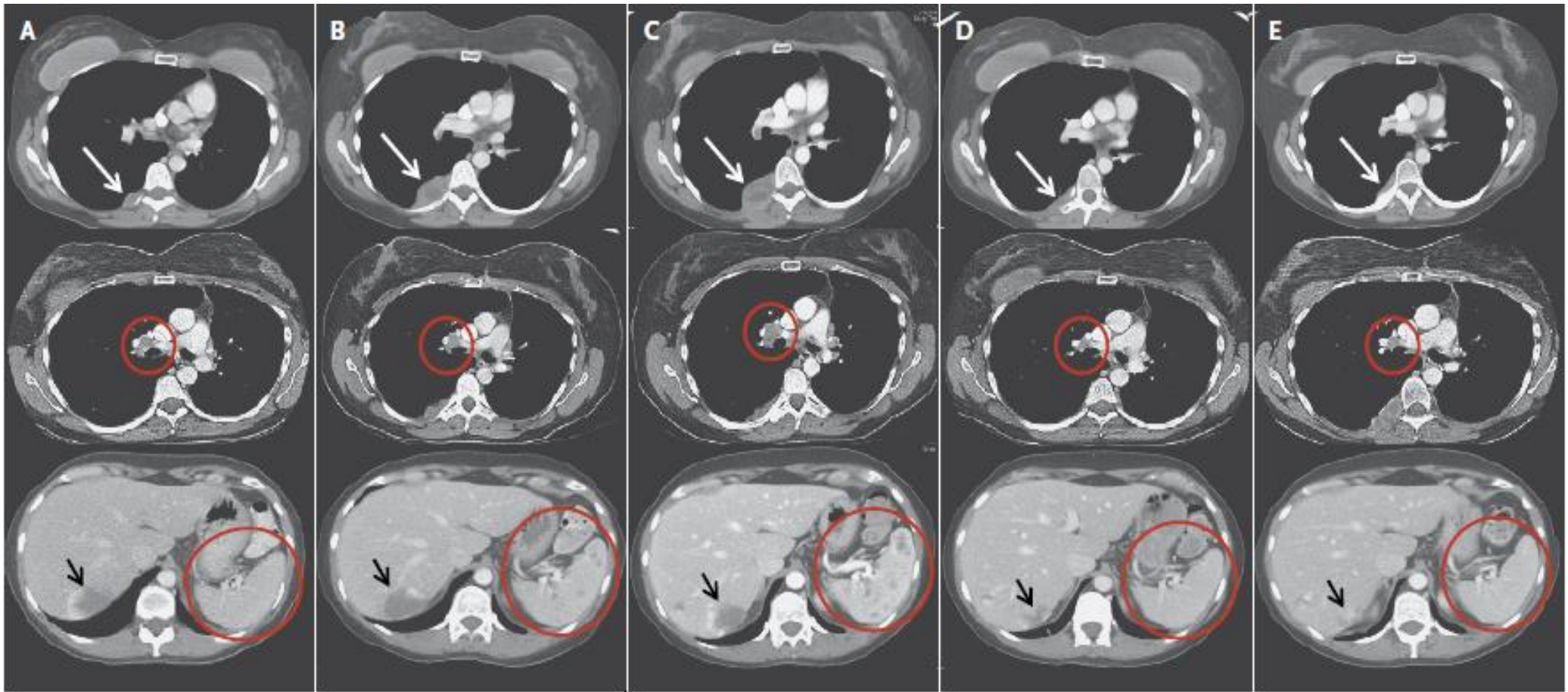
RT Delivery

- 6-field image-guided IMRT
- 28.5 Gy in 3 fractions over 7 days, 6 MV photons



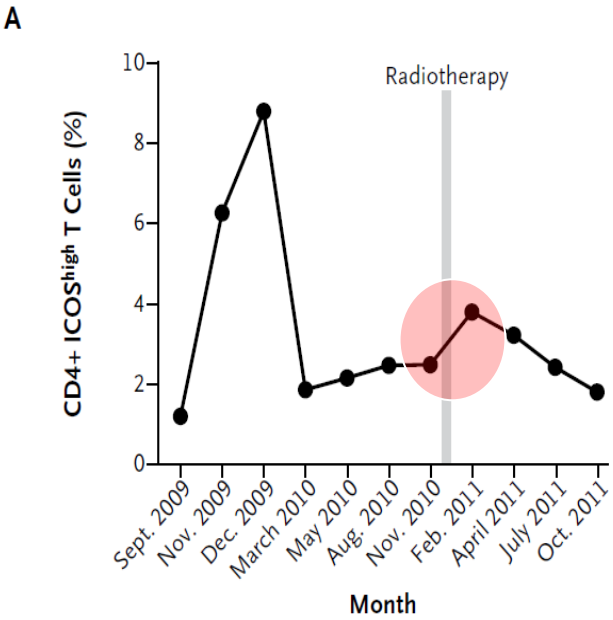
N Engl J Med 2012;366:925-31.

Clinical Course

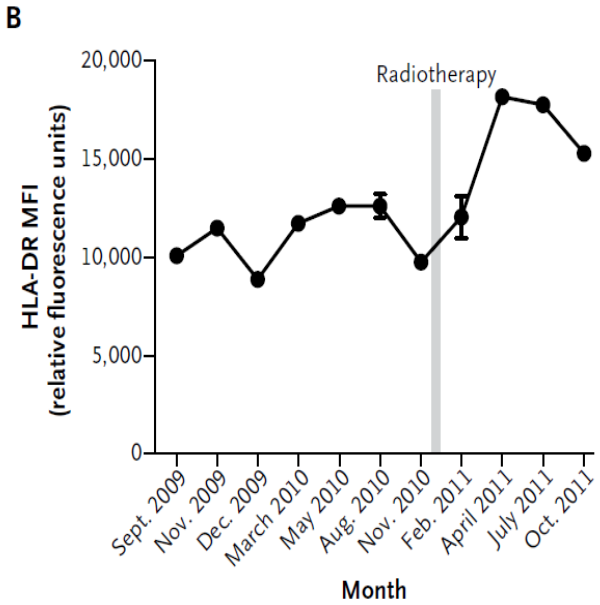


N Engl J Med 2012;366:925-31.

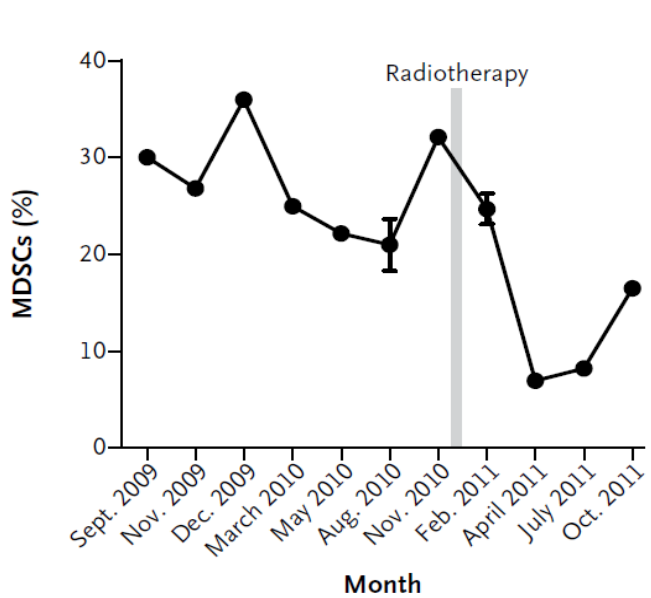
Immune Endpoints



Spike in CD4+ ICOS^{hi}



Spike in MHC Class II on monocytes



Fall in immune suppressive cells (CD14+ HLA-DR^{lo}

Future Challenges

- Modes of tumour cell death have different immunogenicity: apoptosis, necrosis, necroptosis, autophagy, mitotic catastrophe
- Can we be sure that radiation is inducing the ‘right’ sort of death?
- Radiation toxicity to immune effector cells
- Poorly understood in context of activatory vs suppressive immune cells against cancer
- Will anti-CTLA4/PD1/PDL1 etc inhibitors all behave the same way?
- How will concomitant/adjuvant chemotherapy affect activity?
- Dose fractionation and scheduling critical

Local “Physical” Therapies Combined with Immunotherapy

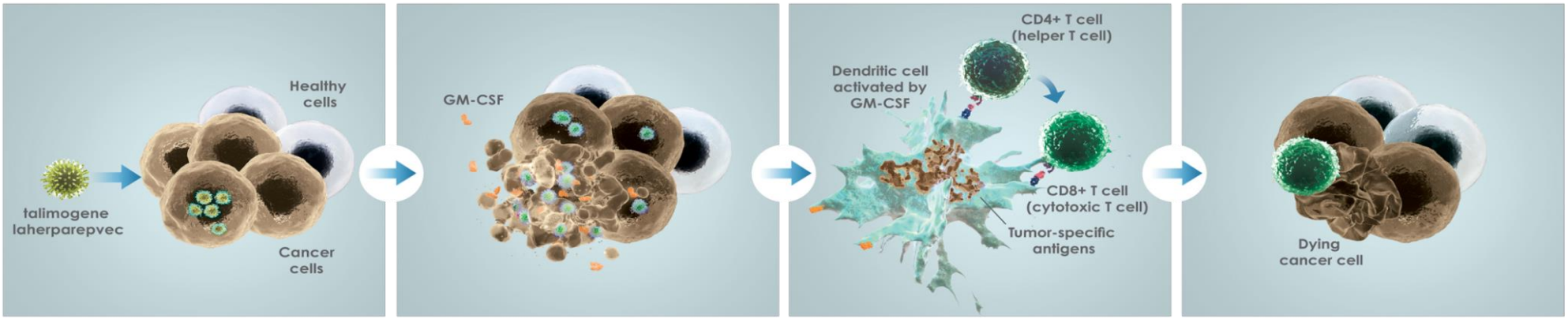
- Radiation therapy

- Oncolytic immunotherapy

T-VEC: HSV-1-derived oncolytic immunotherapy

Local effect:
tumour cell lysis

Systemic effect:
tumour-specific immune response

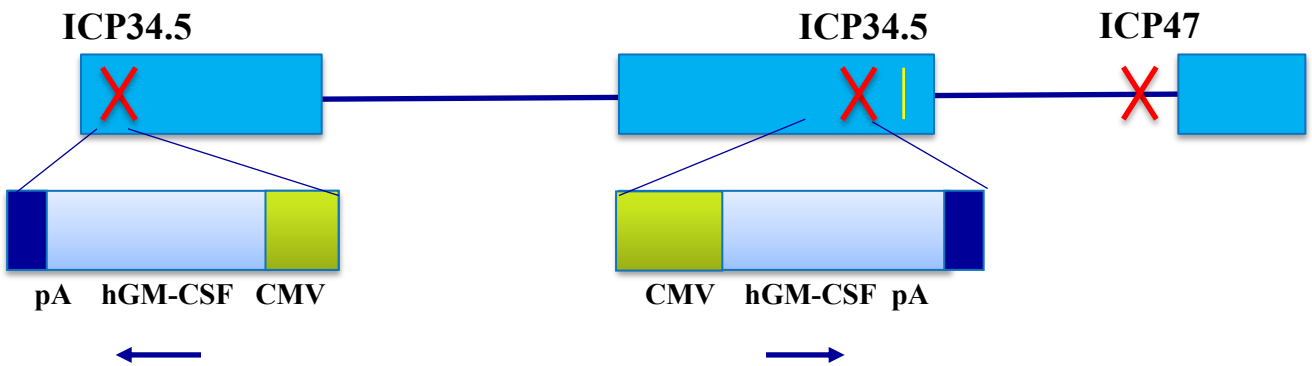


Selective viral replication in tumour tissue

Tumour cells rupture for an oncolytic effect

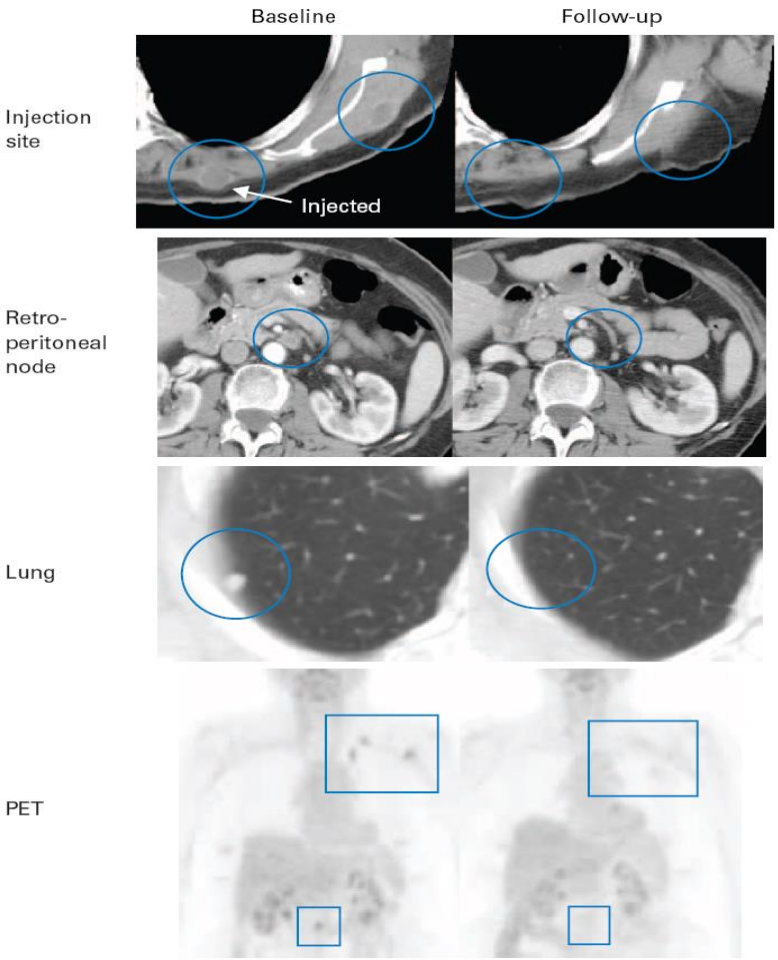
Systemic tumour-specific immune response

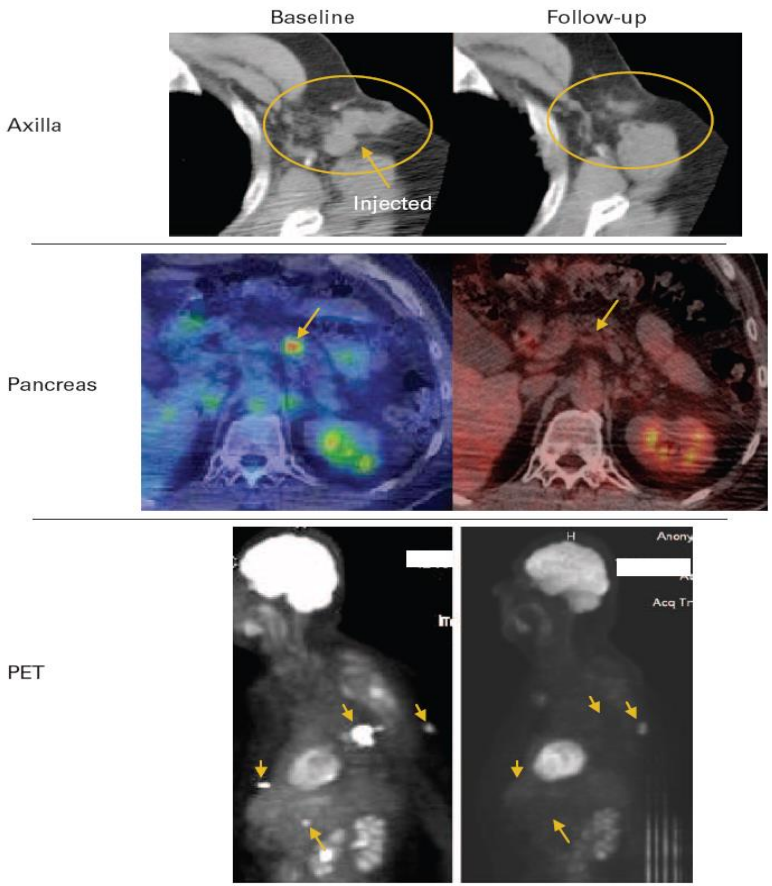
Death of distant cancer cells



Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor–Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma

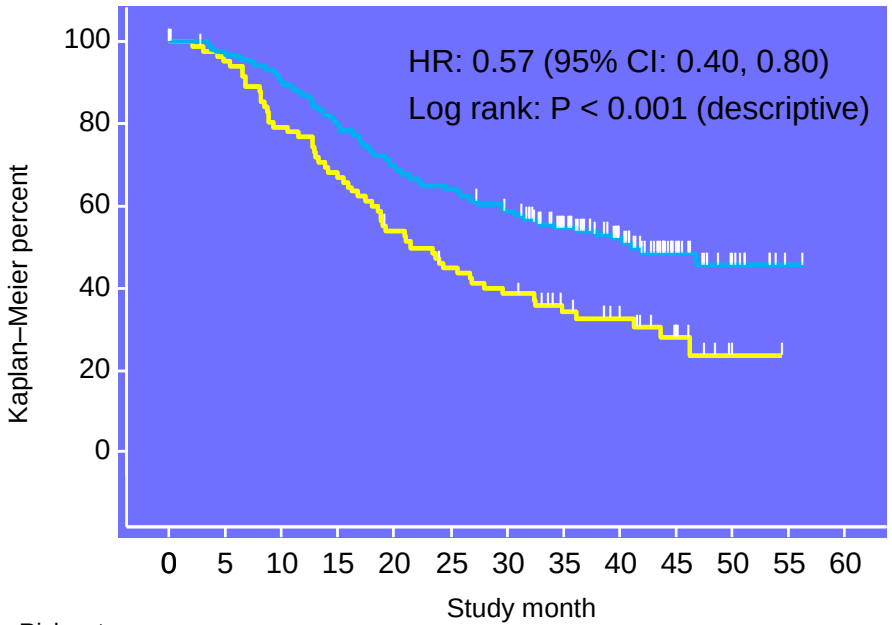
Neil N. Senzer, Howard L. Kaufman, Thomas Amatruda, Mike Nemunaitis, Tony Reid, Gregory Daniels, Rene Gonzalez, John Glaspy, Eric Whitman, Kevin Harrington, Howard Goldsweig, Tracey Marshall, Colin Love, Robert Coffin, and John J. Nemunaitis





Phase III Study: OS by Stage

Stage IIIB/C, IV M1a

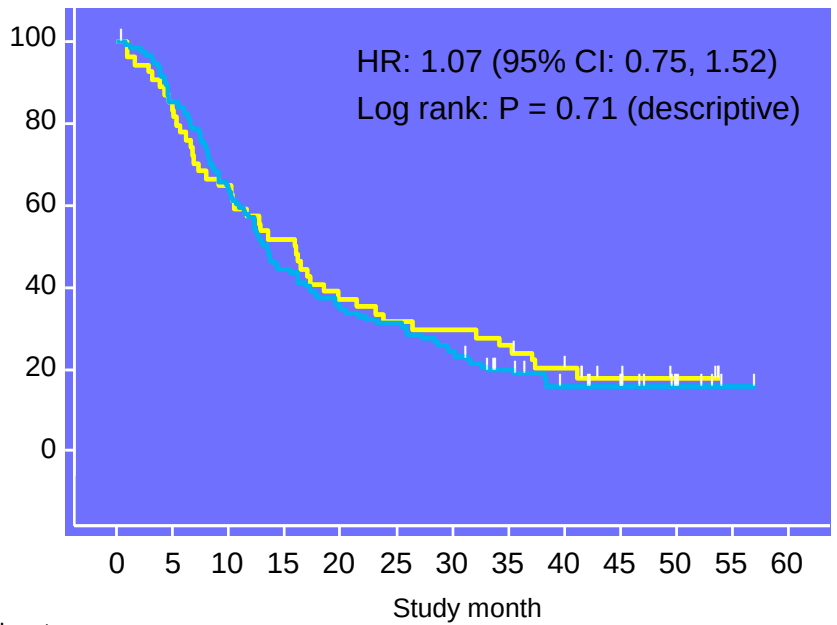


Risk set, n

T-VEC	163	157	146	129	113	104	93	73	51	23	10	1	0
GM-CSF	86	78	65	55	43	35	30	22	17	10	2	0	0

	Events/n (%)	median (95% CI), mo
T-VEC	80/163 (49)	41.1 (30.6, NE)
GM-CSF	57/86 (66)	21.5 (17.4, 29.6)

Stage IV M1b/c



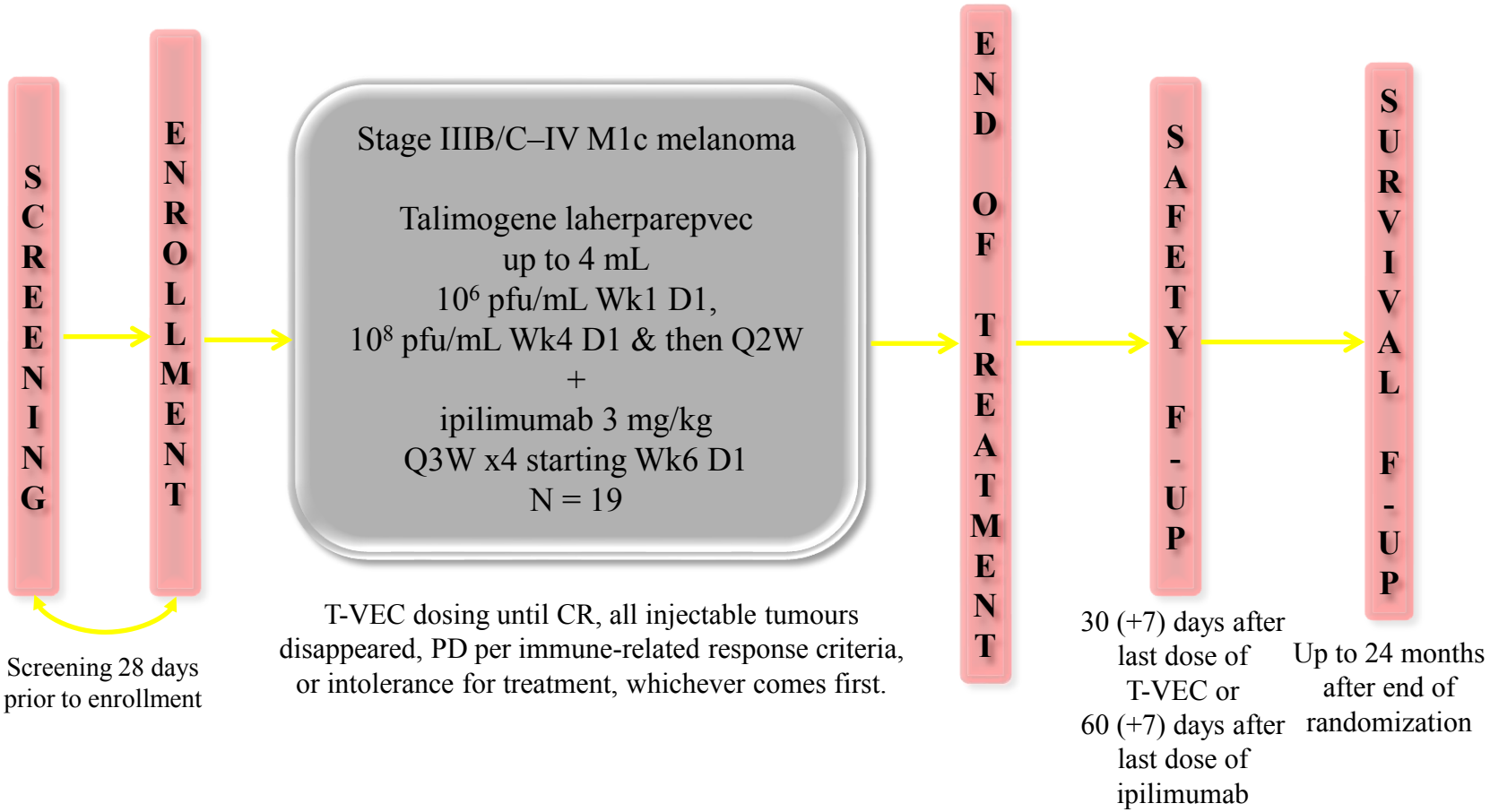
Risk set, n

T-VEC	131	112	84	58	46	41	32	22	15	13	6	1	0
GM-CSF	55	46	35	28	20	17	16	14	10	5	3	0	0

	Events/n (%)	median (95% CI), mo
T-VEC	109/131 (83)	13.4 (11.4, 16.2)
GM-CSF	44 /55 (80)	15.9 (10.2,19.7)

Kaufman H, et al. ASCO 2014 abstract 9008a.

T-VEC + Ipilimumab Phase Ib



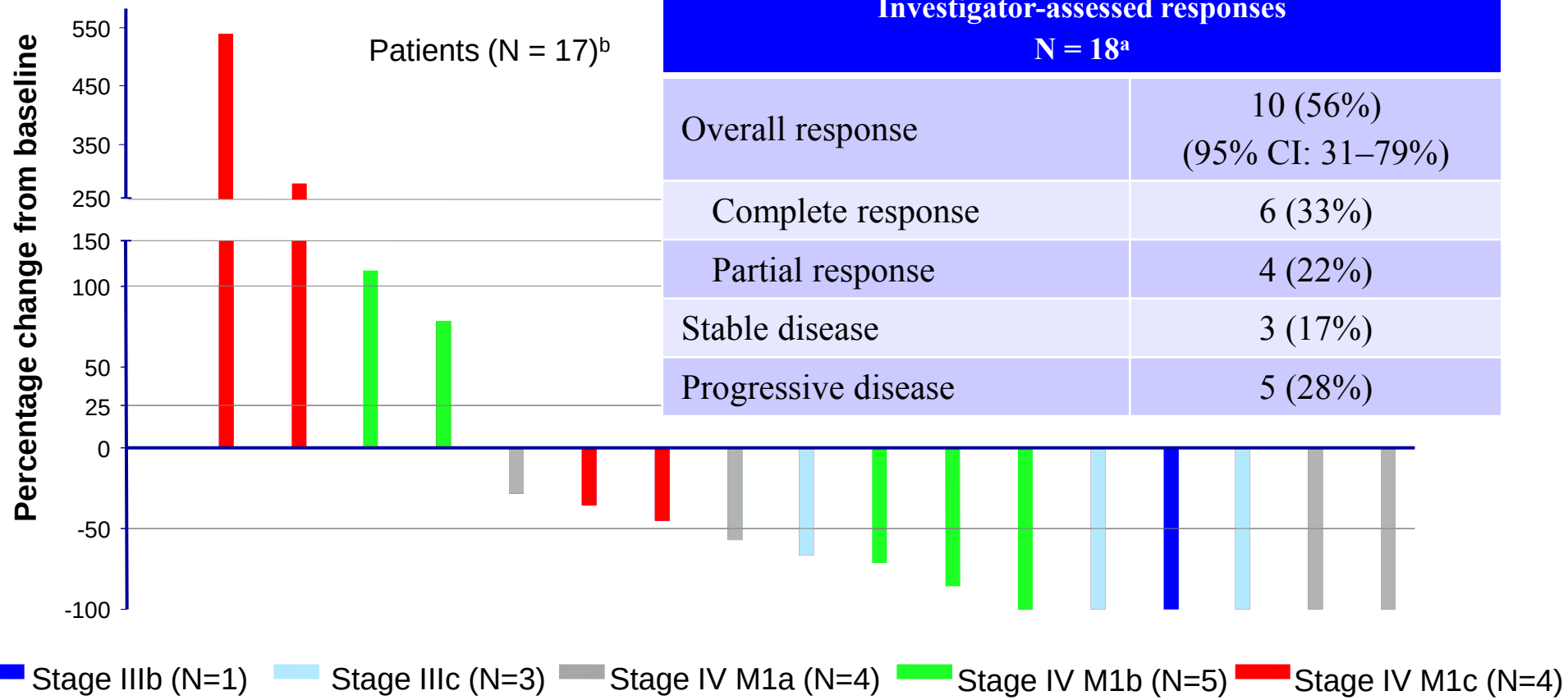
- **Primary endpoint:** DLT
- **Secondary endpoints:** ORR, safety: all AEs, Grade ≥ 3 AEs, serious AEs, events requiring discontinuation of study drug, events with local effects on tumours (pain, inflammation, ulceration)

Puzanov I, et al. ASCO 2014 abstract 9029.
NCT01740297. Available at: ClinicalTrials.gov. Accessed September 2014.

Results – Baseline Characteristics

	Total (N = 19)
Sex, n (%)	
Men	8 (42)
Women	11 (58)
Age, median (min, max) – years	61 (29, 84)
ECOG PS, n (%)	
0	14 (74)
1	5 (26)
Disease stage, n (%)	
IIIB	1 (5)
IIIC	3 (16)
IV M1a	4 (21)
IV M1b	5 (26)
IV M1c	6 (32)
BRAF mutation status	
Mutant	11 (58)
Wild-type	6 (32)
Unknown	2 (11)

Maximal Change in Tumour Burden



Investigator-assessed responses N = 18[a]	
Overall response	10 (56%) (95% CI: 31–79%)
Complete response	6 (33%)
Partial response	4 (22%)
Stable disease	3 (17%)
Progressive disease	5 (28%)

[a]Efficacy analysis set includes only the patients who received both T-VEC and ipilimumab.
[b]One patient assessed to have PD by the investigator was not shown in the plot because tumour burden could not be accurately calculated based on missing post-baseline data.

Puzanov I, et al. ASCO 2014 abstract 9029.

Conclusions

- Immunotherapies have changed the treatment paradigm for a limited number of tumours (so far)
- Local/Loco-regional therapies will remain important in a large number of solid tumours
- There are sound reasons to combine immunotherapy with radiation therapy
- Oncolytic viral immunotherapy represents an exciting approach to inducing local immune activation with systemic effects
- Combining oncolytic immunotherapy with immune checkpoint blockade deserves active evaluation