Novel Strategies to Overcome Cancer by Immunology-Based Attack: Oncolytic Viruses

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ICR

ORACLE cancer trust

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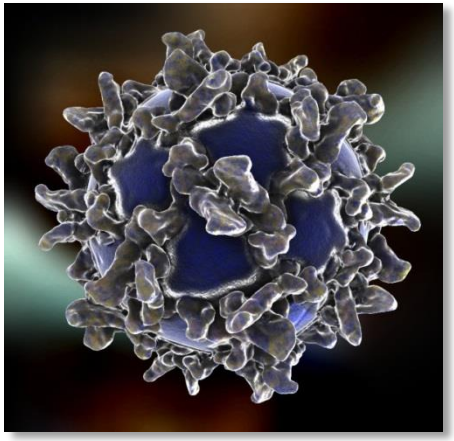
Conflicts of Interest

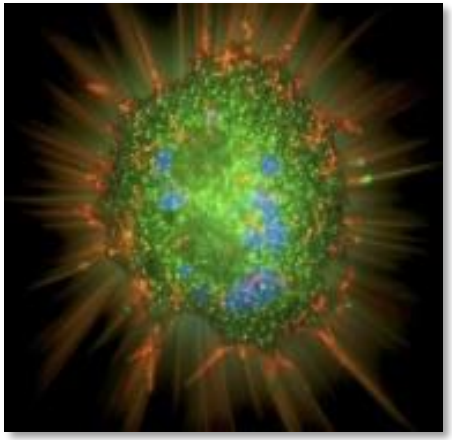
- Amgen – Travel Support, Advisory Board Membership
- Lytix Biopharma – Advisory Board Membership
- Oncolytics Biotech – Research grant funding, Advisory Board Membership
- Oncos Therapeutics - Advisory Board Membership
- Viralytics Inc. - Research grant funding, Advisory Board Membership

Viruses used for oncolytic therapy

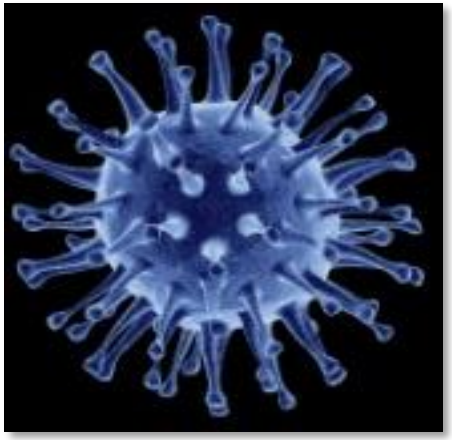
Reovirus

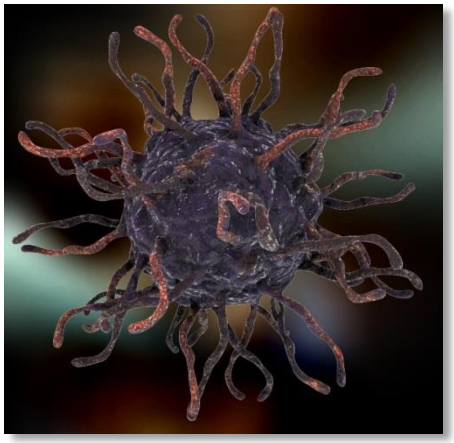


Vaccinia virus

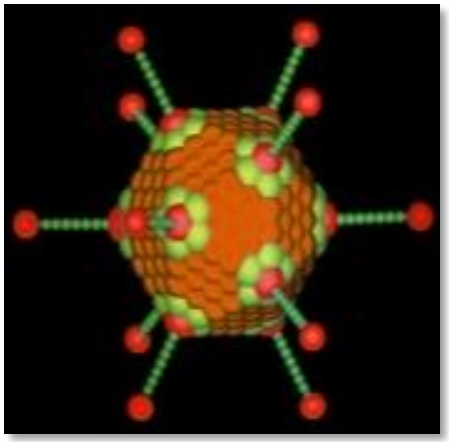


Measles virus

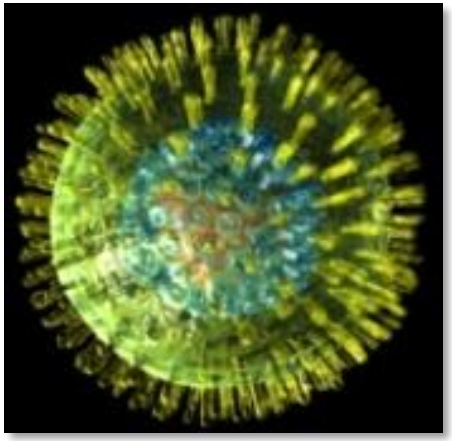




Coxsackievirus



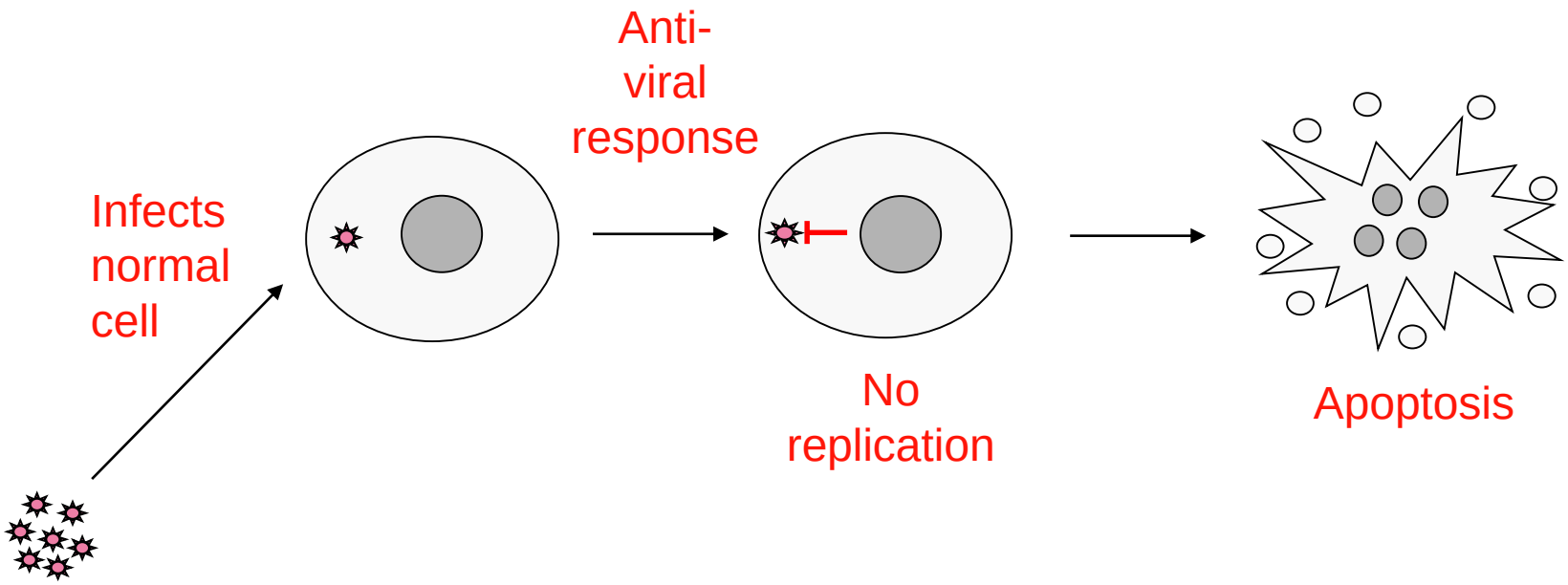
Adenovirus



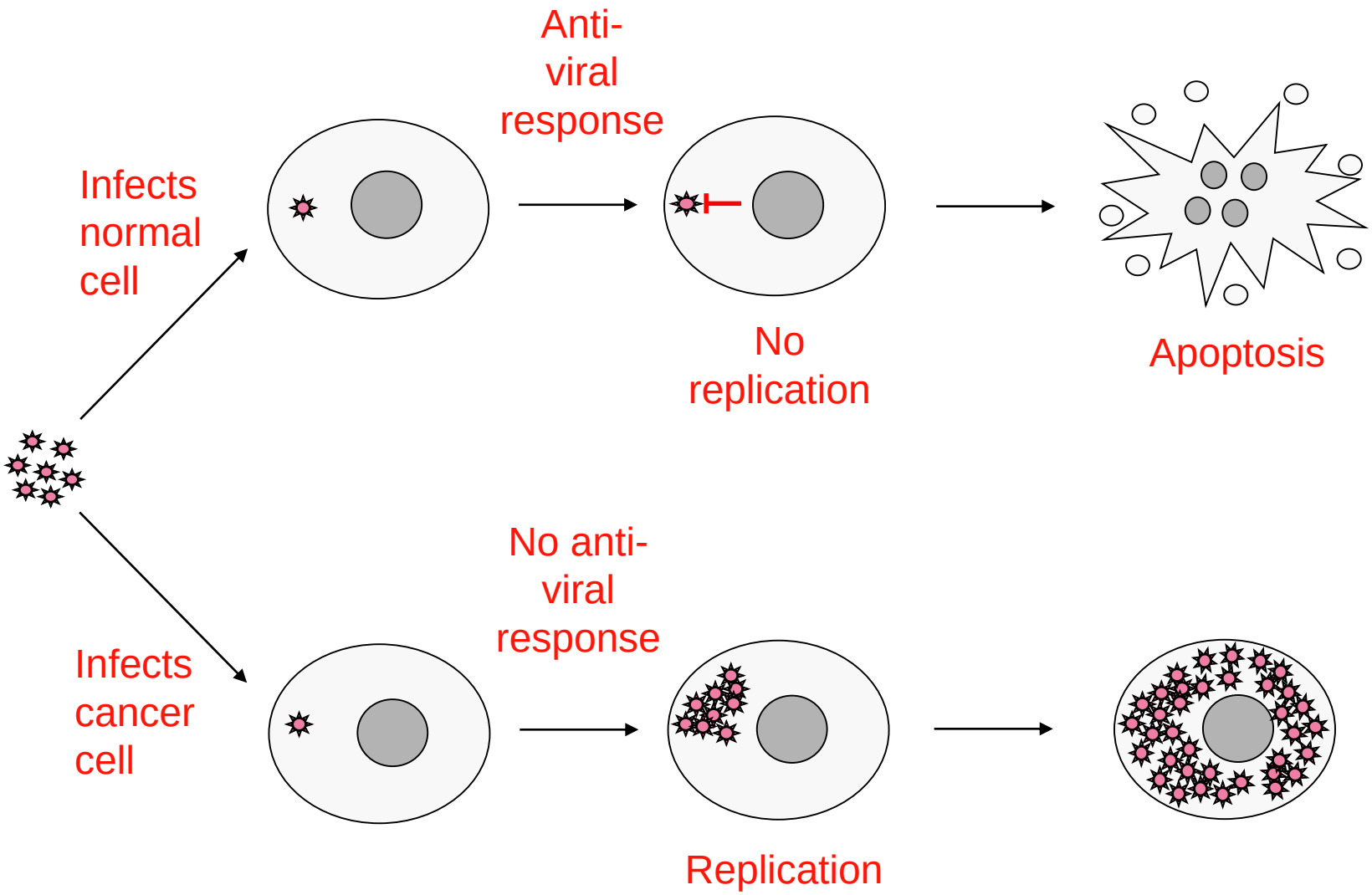
HSV

Everts B, van der Poel HG. Cancer Gene Ther 2005;12:141–61. Image credits: NEI/Science Source; Russell Kightley/Science Source; Dr. Dan Kalman/Katie Vicari/Science Source; Pasieka/Science Source; Laguna Design/Science Source; EM Data Bank (EMDB).

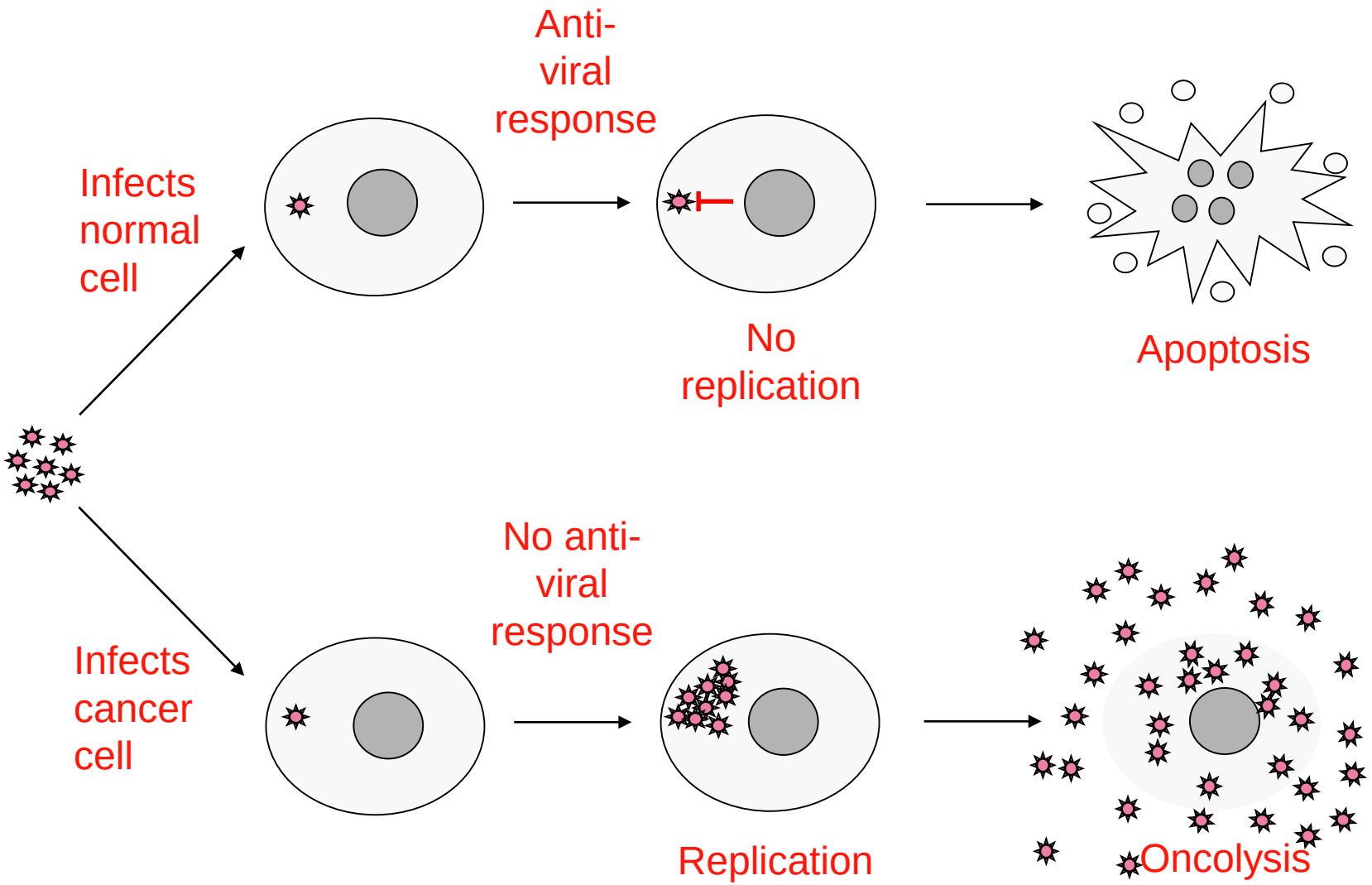
Oncolytic Virus Therapy



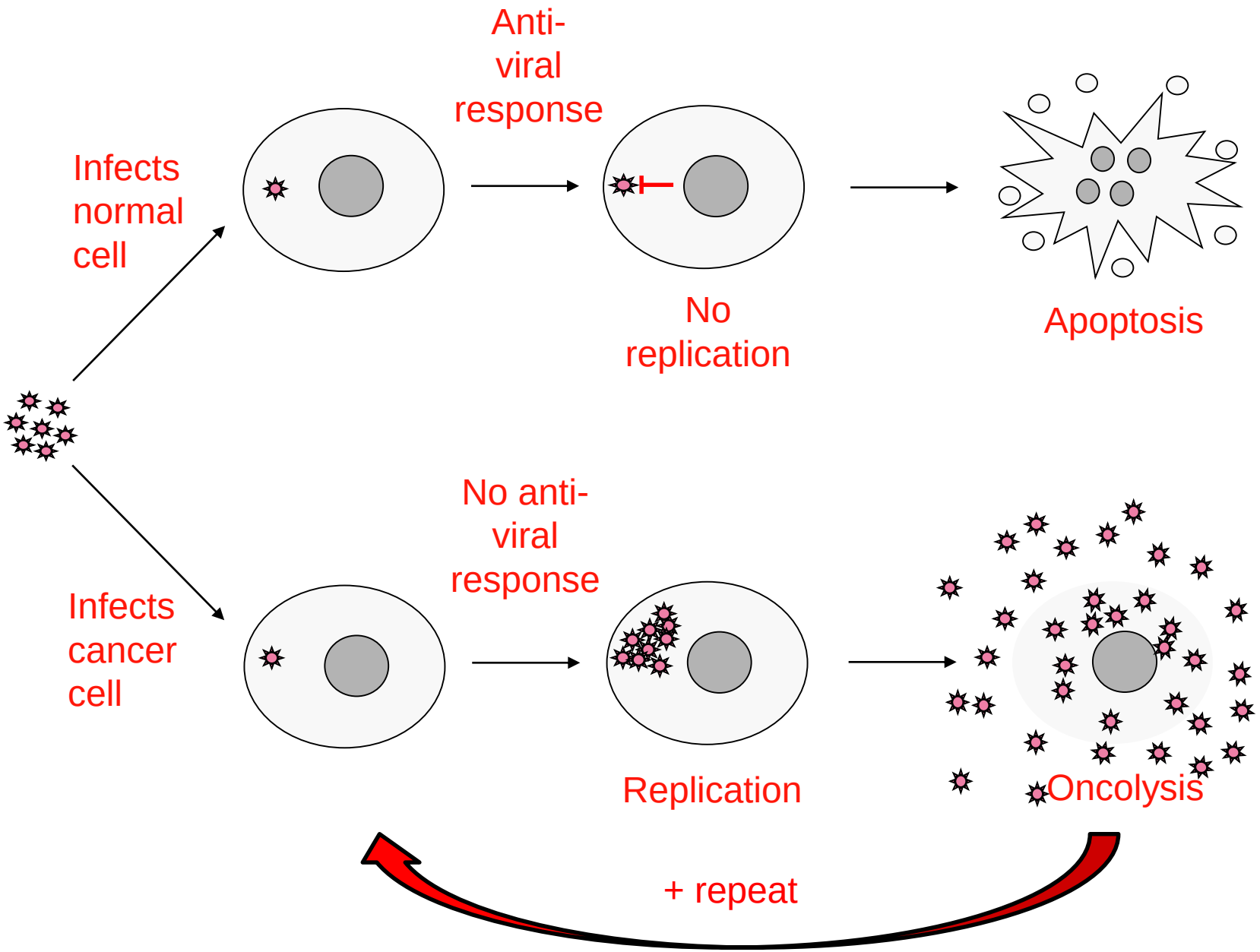
Oncolytic Virus Therapy



Oncolytic Virus Therapy

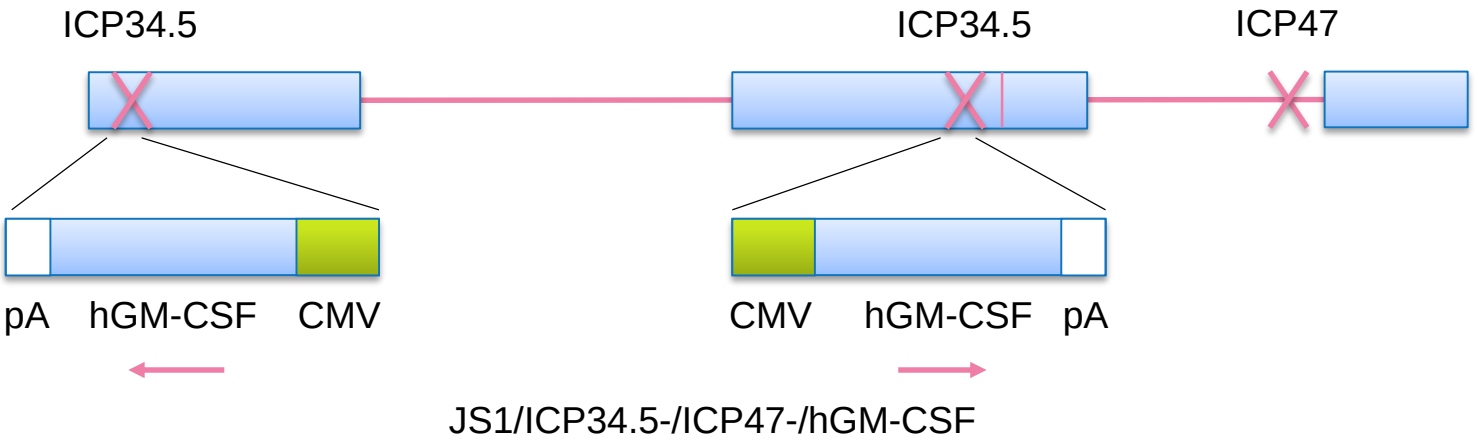


Oncolytic Virus Therapy



T-VEC: HSV-1 derived oncolytic immunotherapy

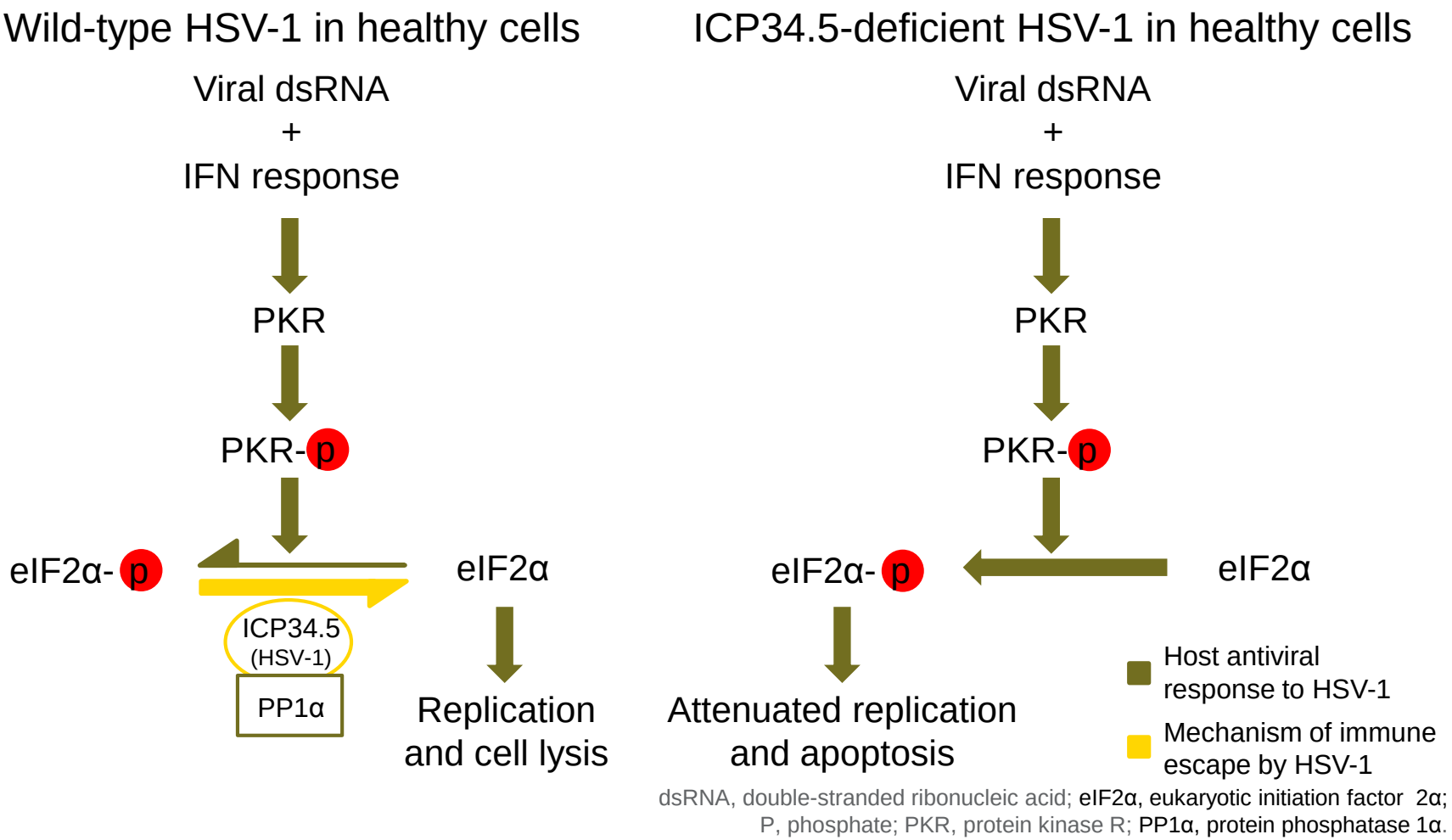
Modification	Rationale
Deletion of ICP34.5 (neurovirulence factor)	Provides tumour selective replication
Deletion of ICP47	Prevents ICP47 from blocking antigen presentation (enhances anti-tumour immune response)
Early/increased Us11	Increases replication of ICP34.5-deleted HSV
Insertion of human GM-CSF gene	Enhances anti-tumour response
New HSV-1 strain: JS1	Improves tumour cell lysis



T-VEC, talimogene laherparepvec; HSV-1, herpes simplex virus type 1; ICP, infected cell protein, Us11, unique short 11; CMV, cytomegalovirus promoter; pA, polyadenylation (from bovine growth hormone).

Liu BL et al. Gene Therapy 2003;10:292–303.

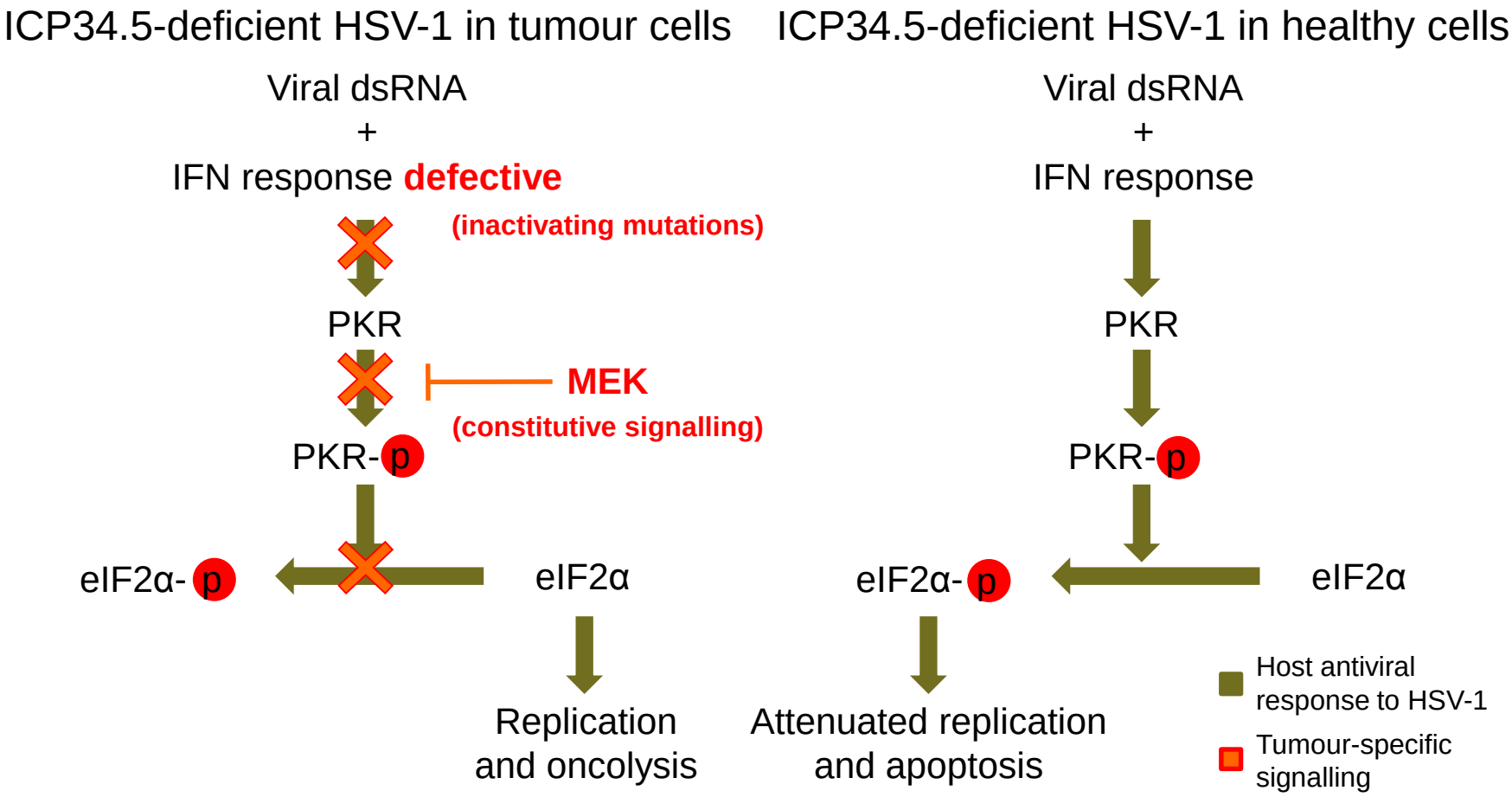
Deletion of ICP34.5 results in attenuated replication in healthy cells



dsRNA, double-stranded ribonucleic acid; eIF2α, eukaryotic initiation factor 2α; P, phosphate; PKR, protein kinase R; PP1α, protein phosphatase 1α.

Campadelli-Fiume G, et al. Rev Med Virol 2011;21:213–26;
Everts B, van der Poel HG. Cancer Gene Ther 2005;12:141–61;
Mullen JT, Tanabe KK. Oncologist 2002;7:106–19.

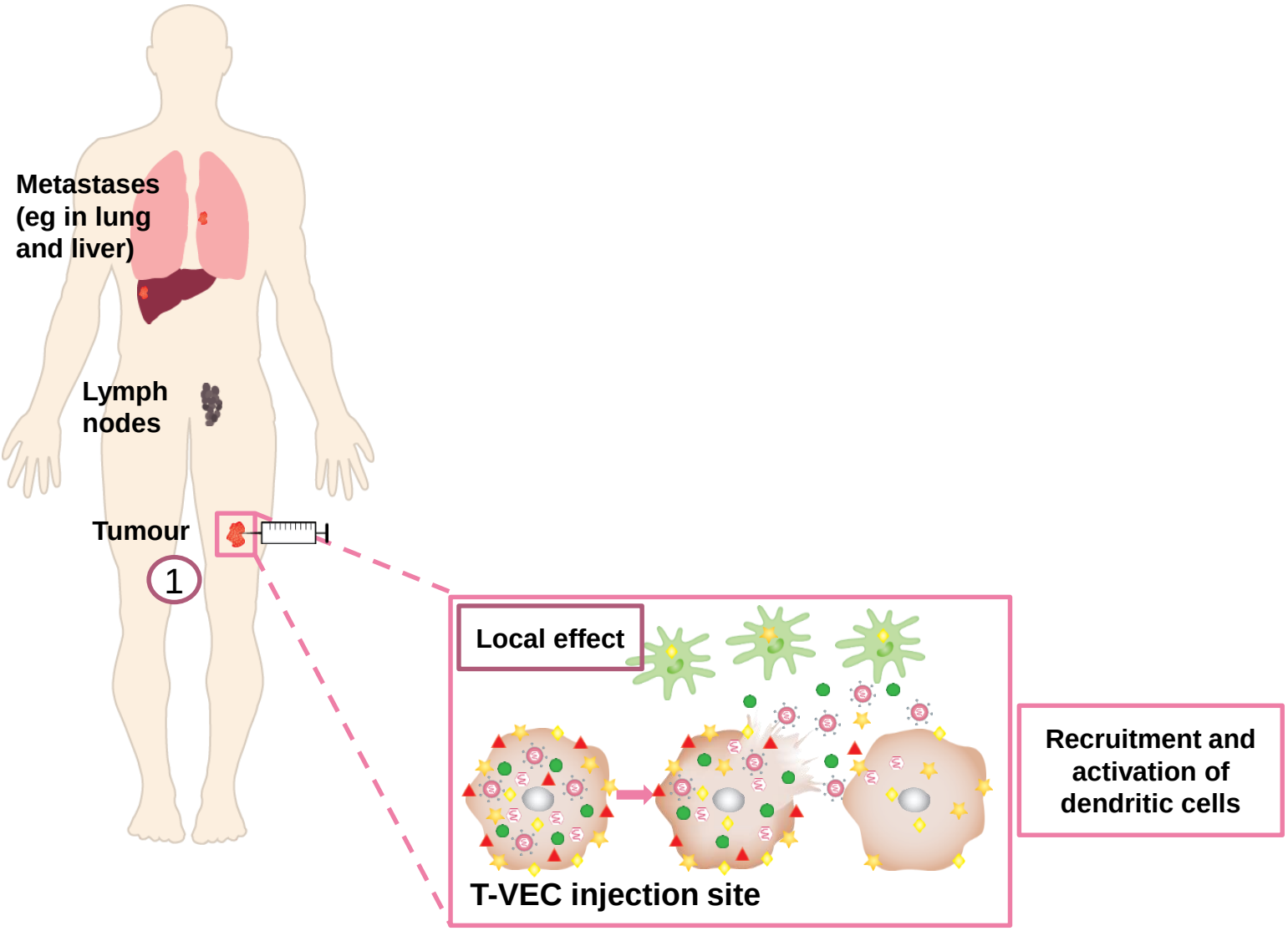
Deletion of ICP34.5 results in tumour-selective replication

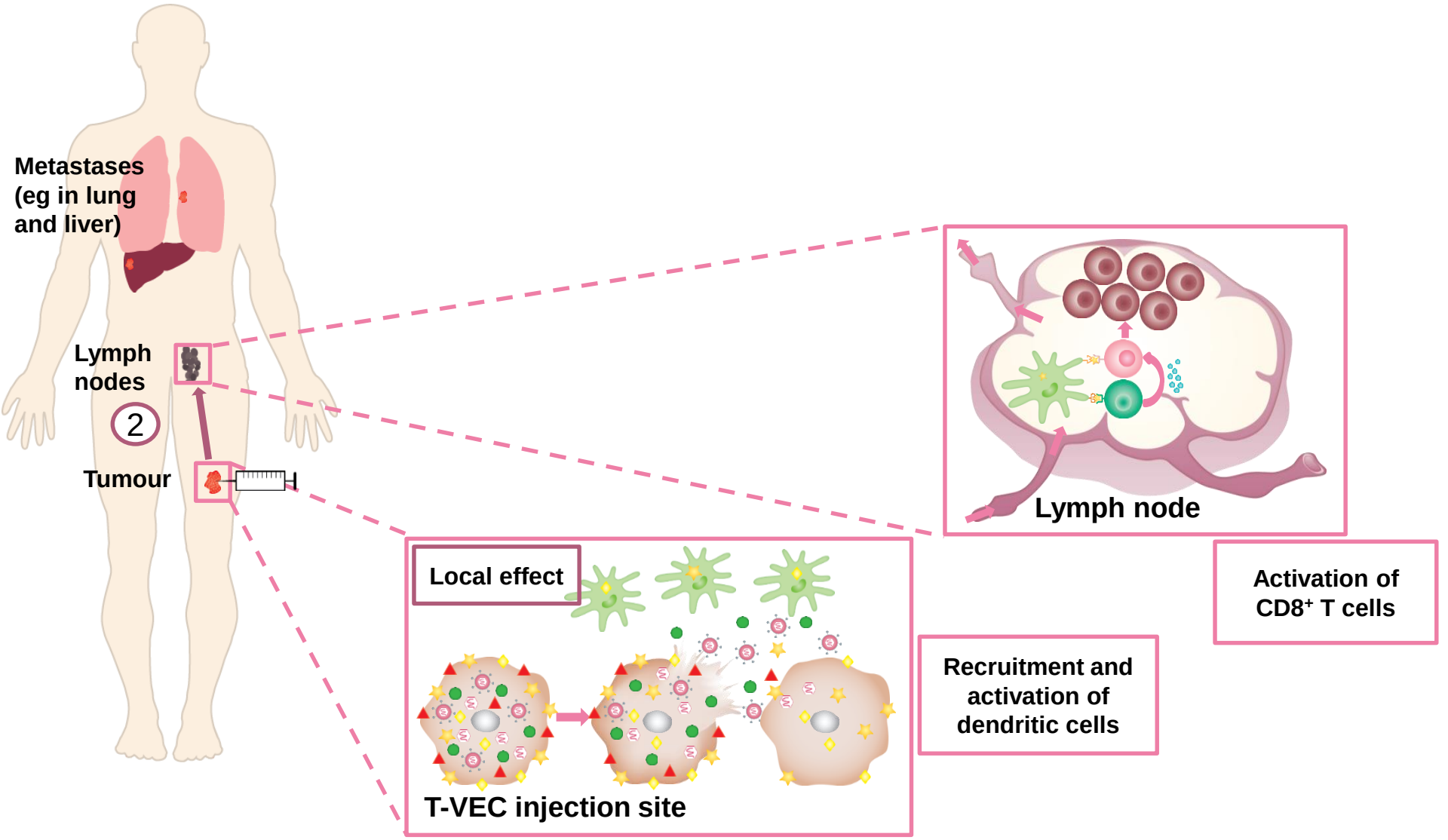


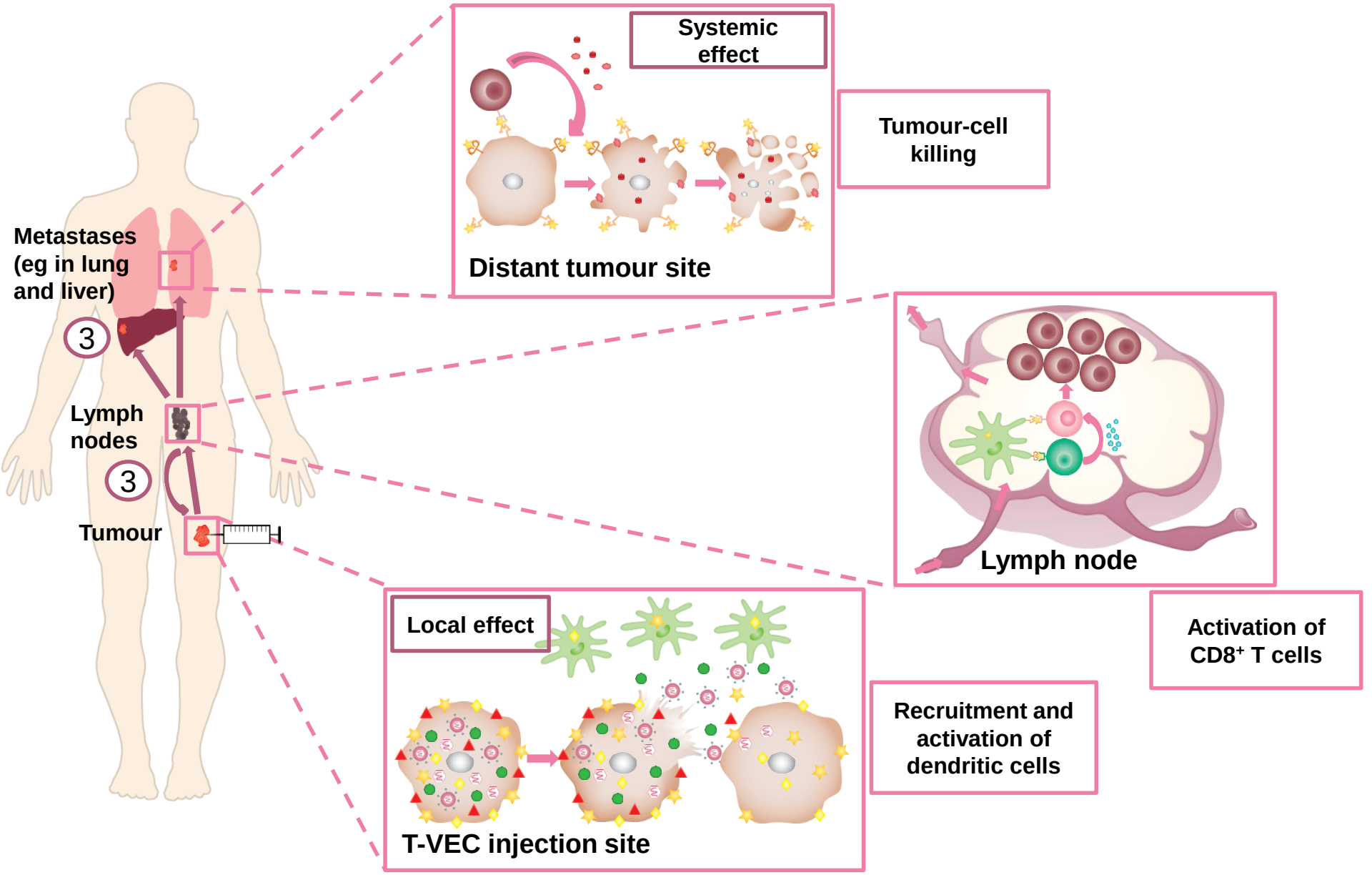
MEK, mitogen-activated protein kinase kinase.

Campadelli-Fiume G, et al. Rev Med Virol 2011;21:213–26;
Everts B, van der Poel HG. Cancer Gene Ther 2005;12:141–61;
Mullen JT, Tanabe KK. Oncologist 2002;7:106–19.

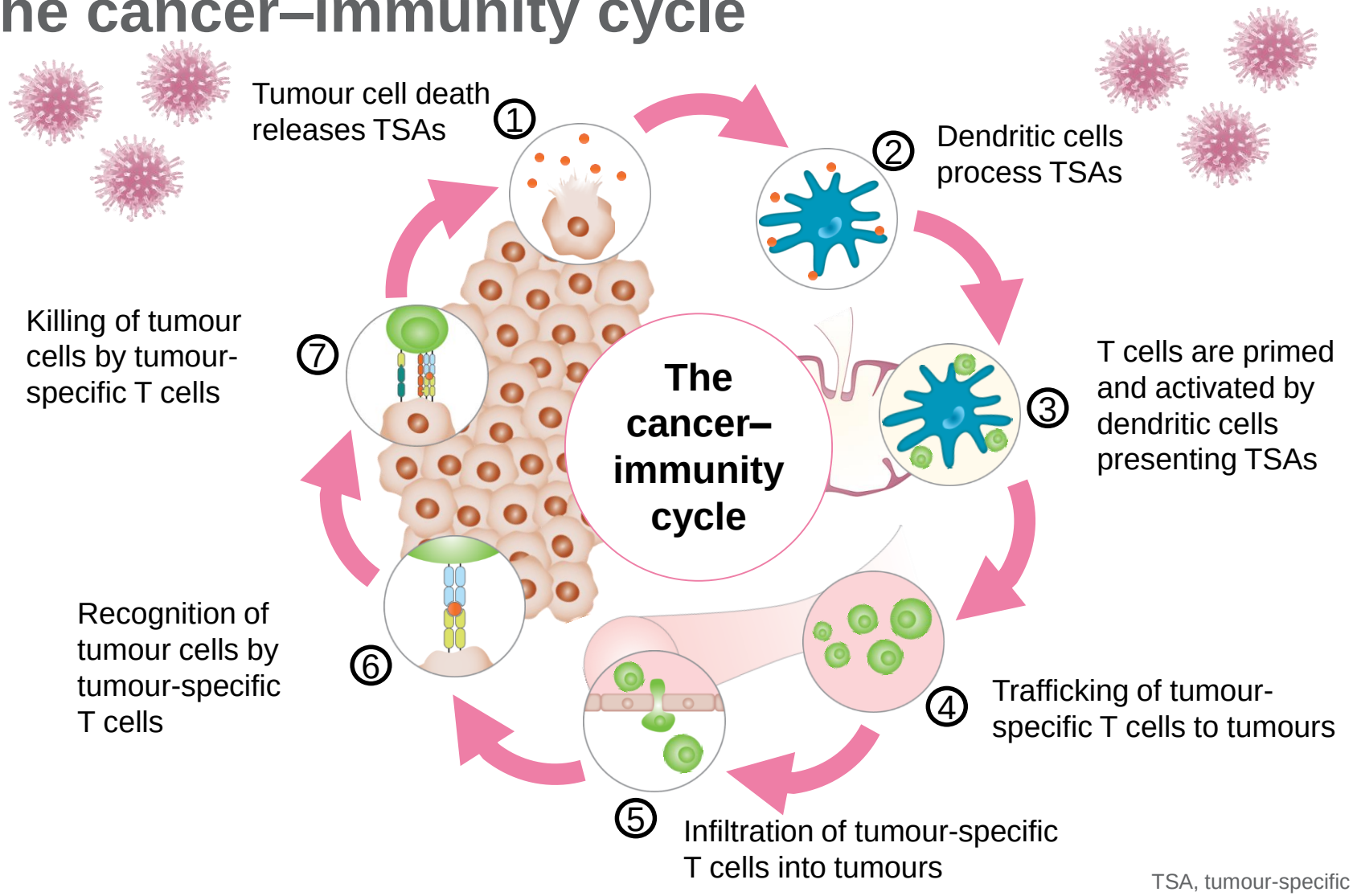
How does T-Vec work?




Metastases (eg in lung and liver)
Lymph nodes
2
Tumour
Lymph node
Activation of CD8+ T cells
Local effect
Recruitment and activation of dendritic cells
T-VEC injection site


Systemic effect
Tumour-cell killing
Distant tumour site
Metastases (eg in lung and liver)
3
Lymph nodes
3
Tumour
Lymph node
Activation of CD8+ T cells
Local effect
Recruitment and activation of dendritic cells
T-VEC injection site

Potential action points of T-VEC to enhance the cancer–immunity cycle



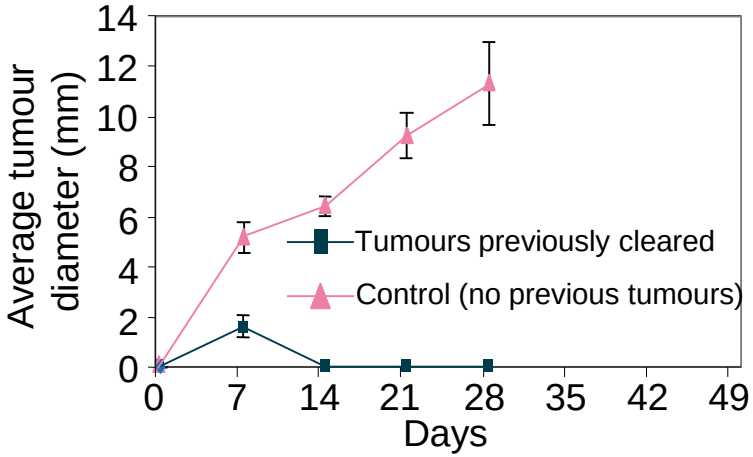
TSA, tumour-specific antigen.

Adapted from Chen DS, Mellman I. Immunity 2013;39:1–10;
Liu BL, et al. Gene Ther 2003;10:292–303.

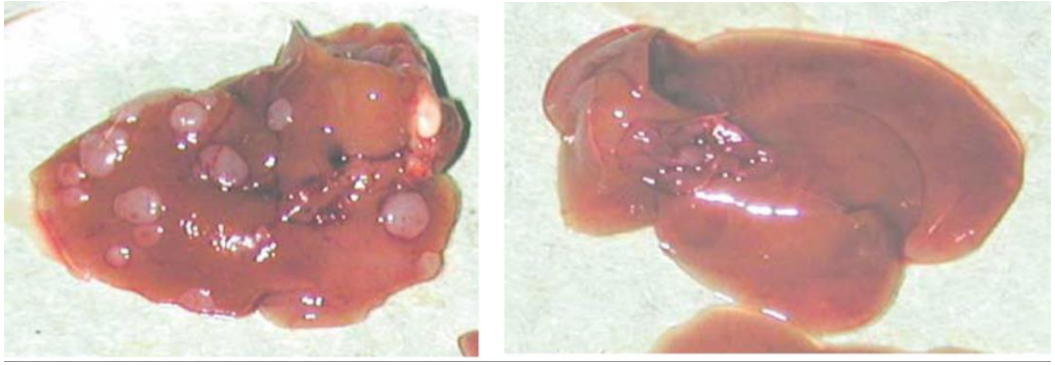
Protection against tumour cell challenge after initial T-VEC-induced anti-tumour immune response

Tumour challenge model

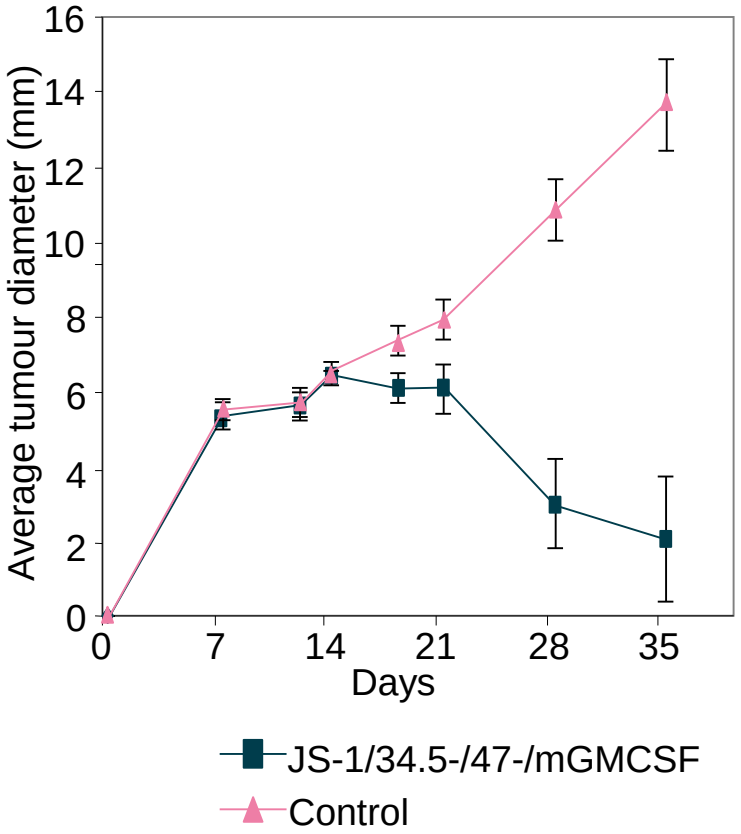
Injection of tumour cells into flank



Injection of tumour cells through tail vein

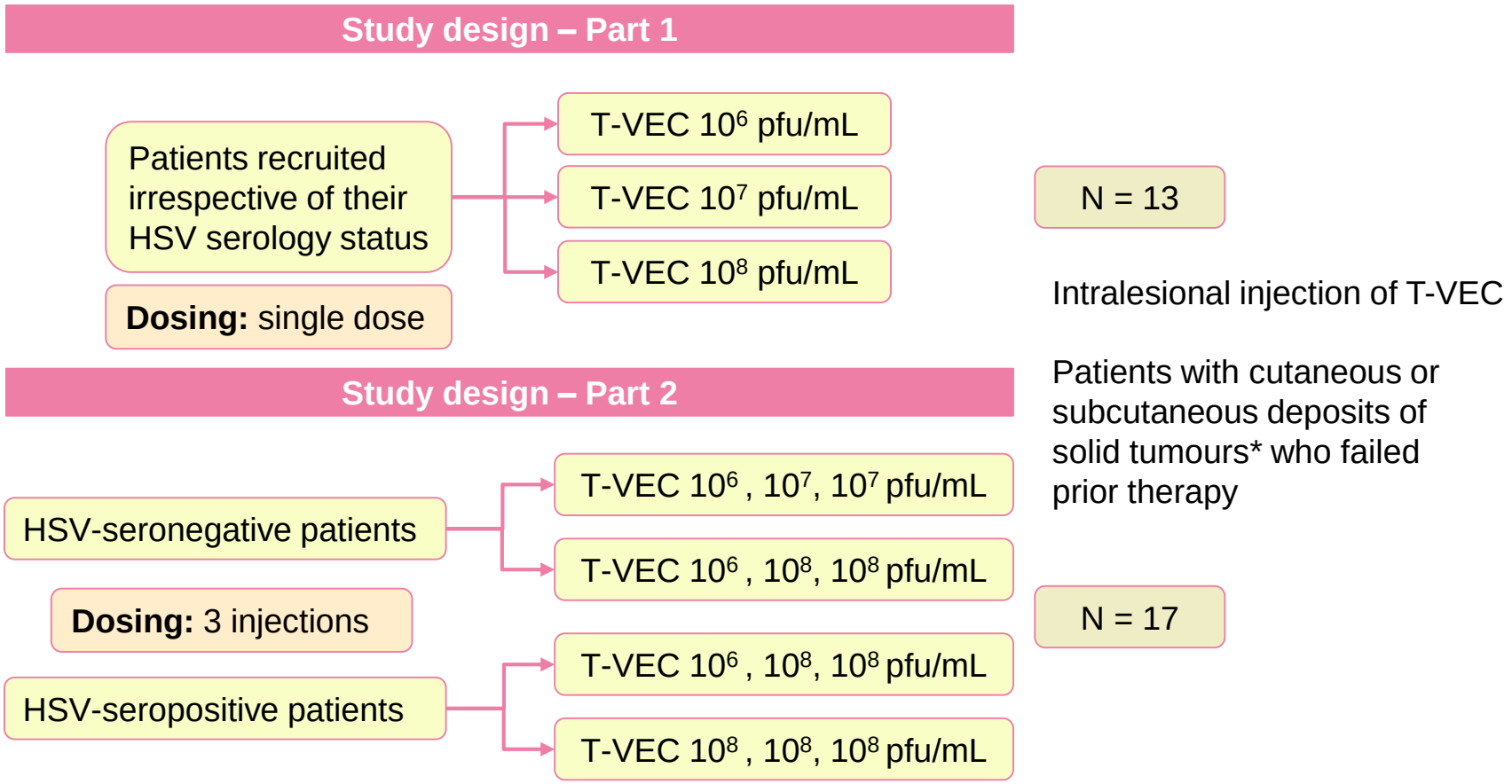


Therapy in pre-immune setting (pre-existing anti-HSV immunity)



Liu BL et al. Gene Therapy 2003;10:292–303.

First in-human T-VEC study in patients with refractory solid tumours

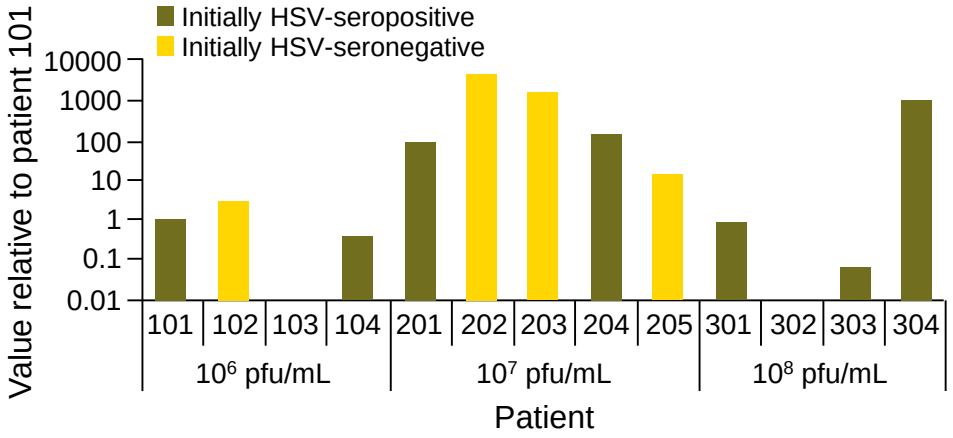


*9 out of 30 patients had a melanoma.

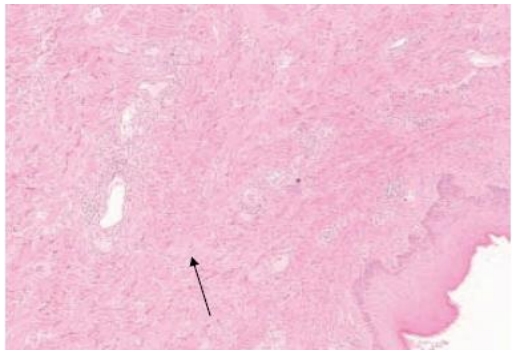
Hu JCC, et al. Clin Cancer Res 2006;12:6737–47.

First in-human T-VEC study – biological activity

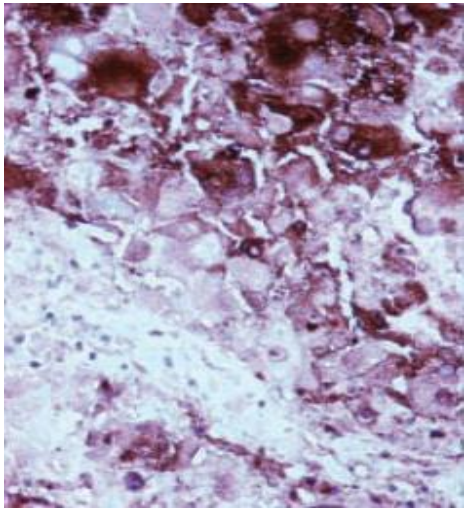
GM-CSF RNA level

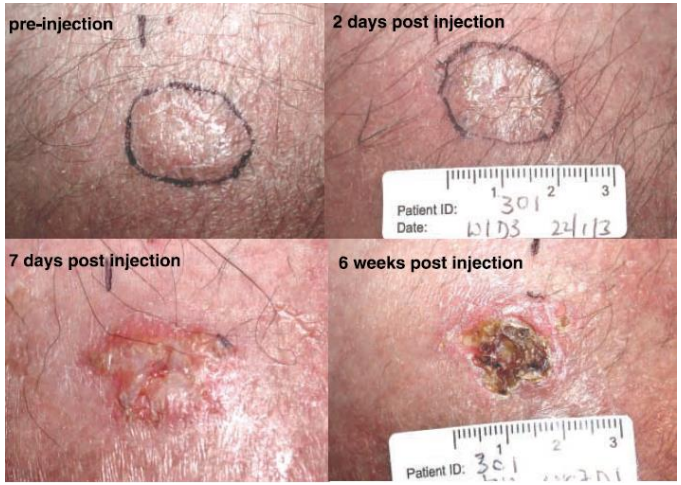


Tumour necrosis



HSV IHC





Hu JCC, et al. Clin Cancer Res 2006;12:6737–47.

T-VEC single-arm Phase 2 study design

- Stage IIIC (n = 10) or Stage IV (n = 40) melanoma
- ECOG PS: 0 or 1
- 74% previously treated
- Injection-accessible tumours

→ Intralesional T-VEC up to 4 mL 10^6 pfu/mL Week 1 Day 1 followed by 10^8 pfu/mL Week 4 Day 1 then Q2W × 8 cycles* →

Primary endpoint
- ORR

Secondary endpoints
- Median survival
- 1-year and 2-year survival rates
- AEs

N = 50

Multiple sites (US and UK)
NCT00289016

Endpoint	T-VEC, % (n = 50)
Response rate	
Overall	26
Complete	16
Survival rate	
1-year	58
2-year	52

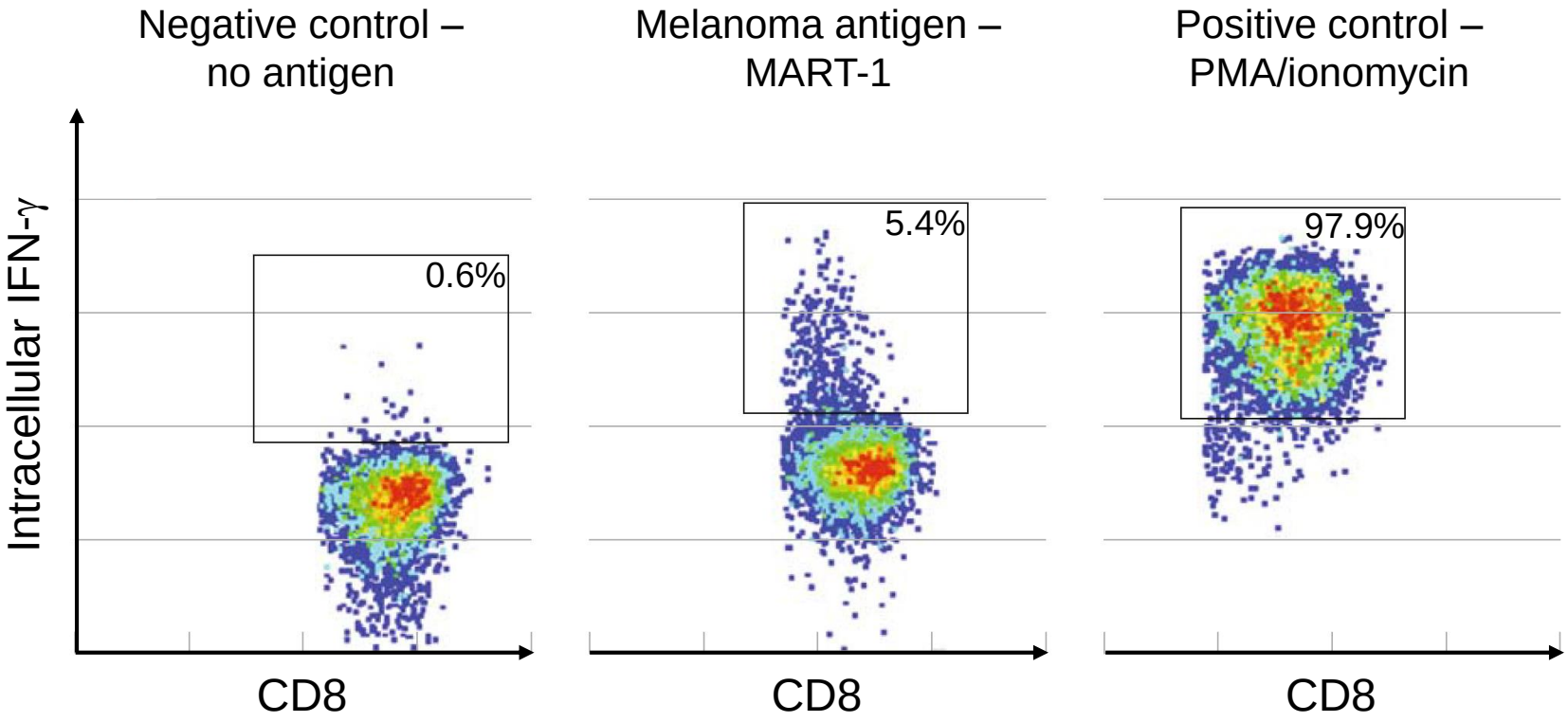
*Extended by a further 16 cycles if inflammatory reaction, partial response or stable disease seen.

ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PS, performance status; Q2W, every 2 weeks.

Senzer NN, et al. J Clin Oncol 2009;27:5763–71.

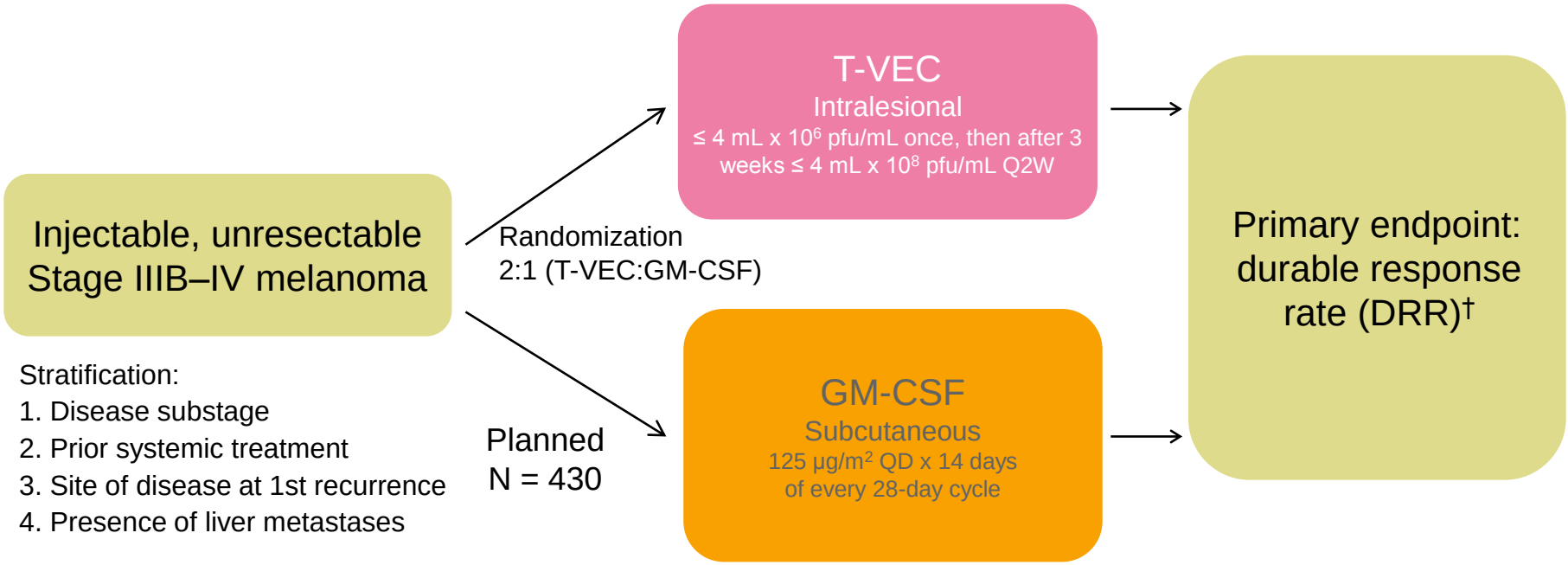
T-VEC single-arm Phase 2 – melanoma-specific effector T cells in tumour biopsies of patients receiving T-VEC

IFN-γ production by tumour-infiltrating CD8+ T cells in response to MART-1



PMA, phorbol 12-myristate 13-acetate.

OPTiM Phase III Trial (005/05)



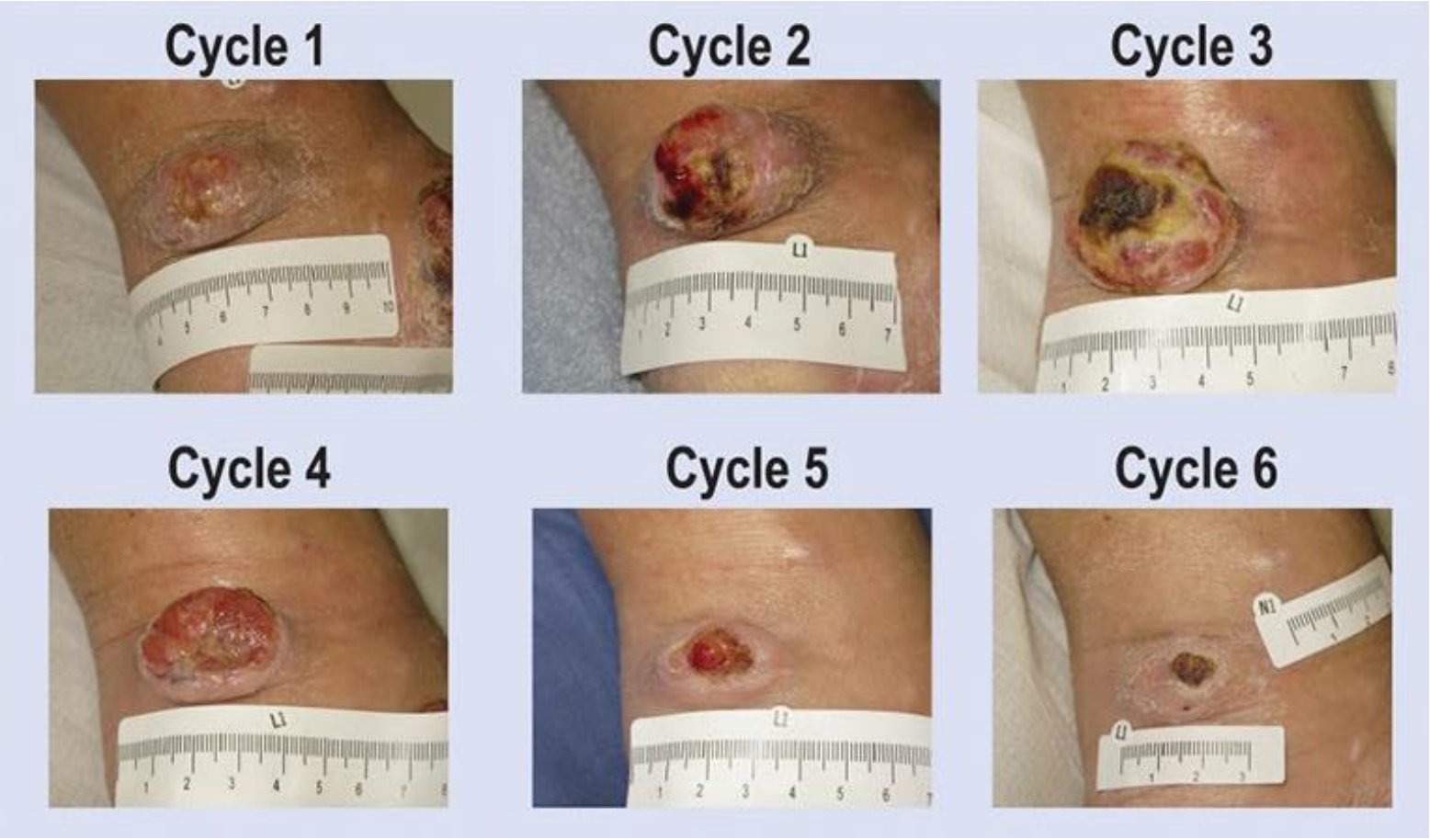
Primary endpoint: DRR: rate of CR or PR that began at any point within 12 months of initiation of therapy and lasted continuously for 6 months or longer*

Secondary endpoints: OS, objective overall response (CR and PR) rate, safety

*Determined using modified WHO criteria by an independent, blinded endpoint assessment committee. †Patients were to remain on treatment for at least 24 weeks despite progression (unless intolerable AEs or investigator decision to start new therapy). QD, once daily.

Andtbacka RH, et al. SSO 2014.

Example of Interval Progression Prior to Response with T-VEC



54% of T-VEC objective responders and 48% of T-VEC durable responders exhibited interval progression before ultimately achieving response

Kaufmann H et al. European Journal of Cancer 49; suppl 3

OPTiM Endpoints

Primary endpoint: DRR*†

Intention-to-treat (ITT) set	GM-CSF, % (n = 141)	T-VEC, % (n = 295)	Unadjusted odds ratio
DRR	2.1	16.3	8.9 (95% CI: 2.7, 29.2); P < 0.0001

Secondary endpoint: objective overall response†

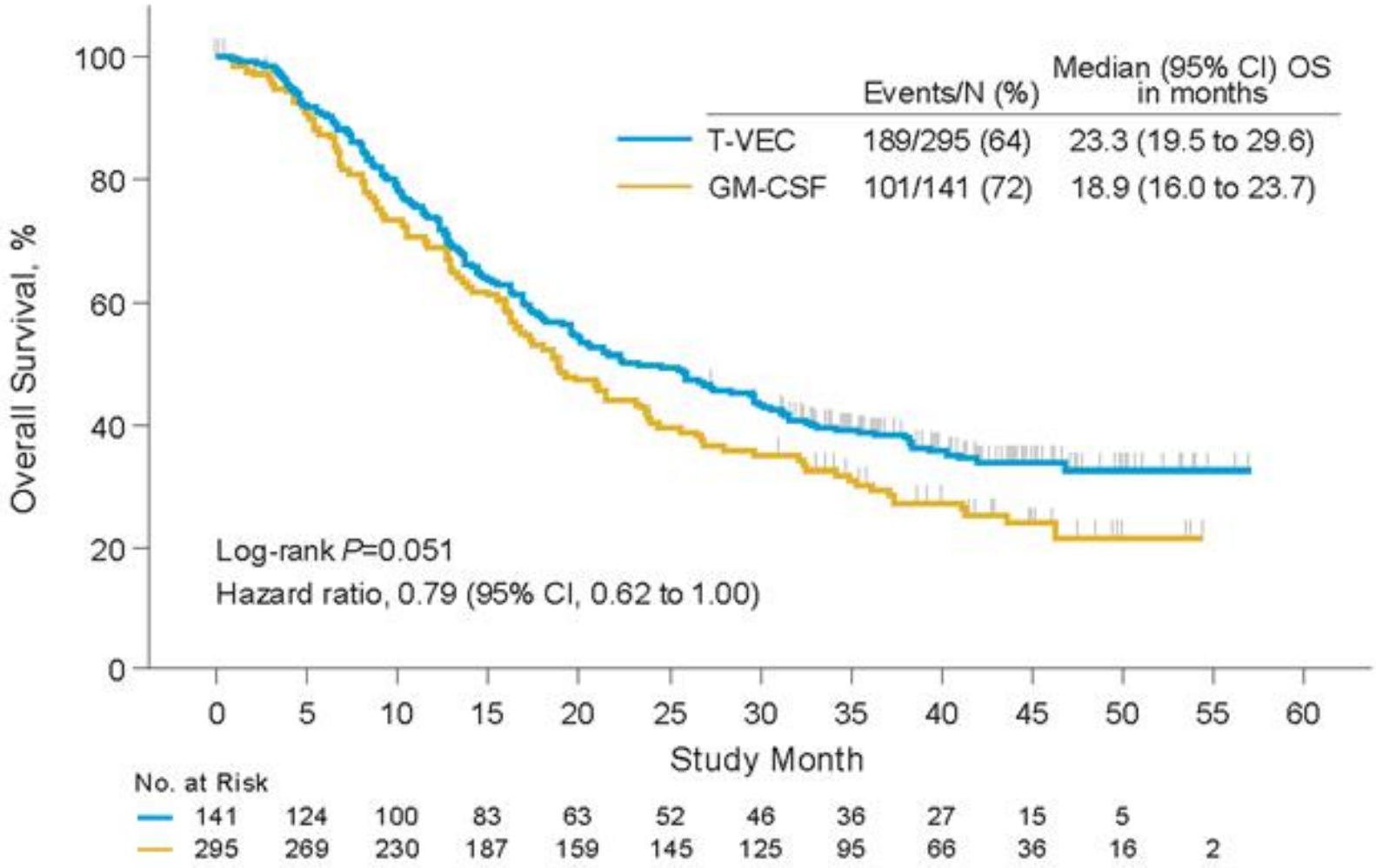
ITT set	GM-CSF, % (n = 141)	T-VEC, % (n = 295)
Objective overall response (95% CI)	5.7 (1.9, 9.5)	26.4 (21.4, 31.5)
CR	0.7	10.8
PR	5.0	15.6

- 41% of responses in T-VEC patients were CRs

*Rate of CR or PR that began at any point within 12 months of initiation of therapy and lasted continuously for 6 months or longer.
†Determined using modified WHO criteria by an independent, blinded endpoint assessment committee. CI, confidence interval.

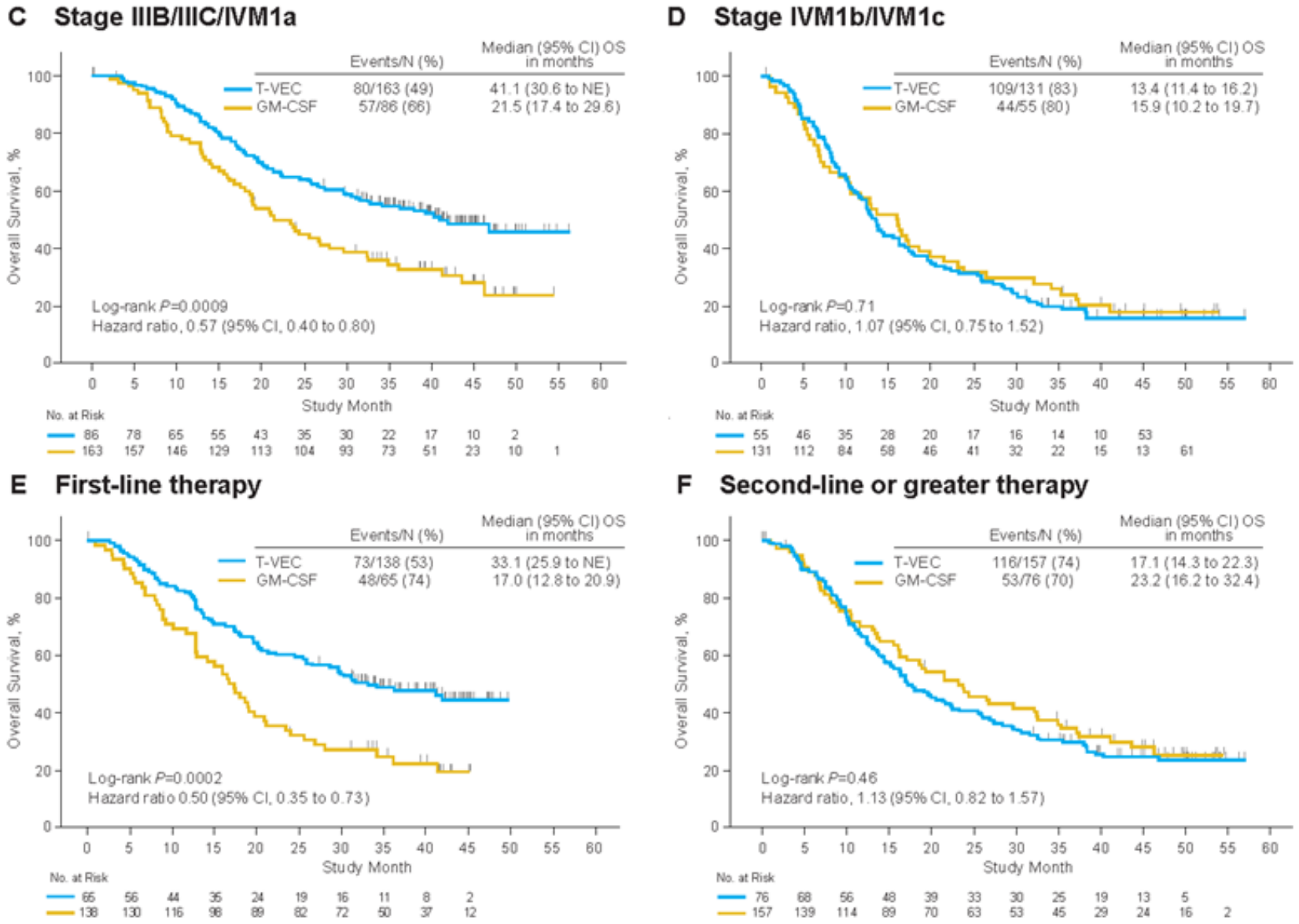
Andtbacka RH, et al. SSO 2014;
Andtbacka RH, et al. ASCO 2013. Abstract LBA9008.

Secondary Endpoint: OS



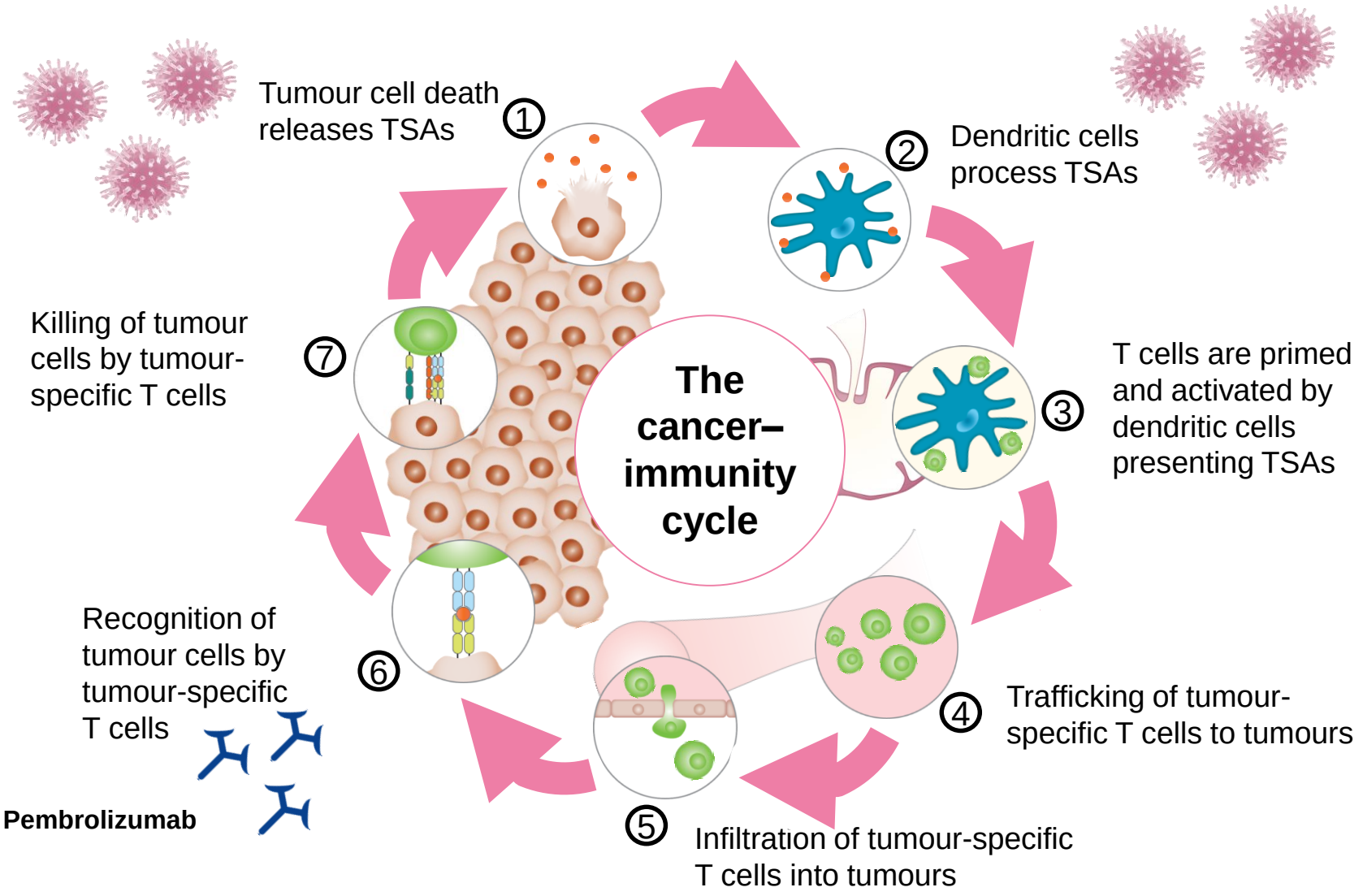
1. Andtbacka RH, et al. ASCO 2013. Abstract LBA9008;
2. Kaufman HL, et al ASCO 2014. Abstract LBA9008a.

OS by Stage and Line of Therapy



1. Andtbacka RH, et al. ASCO 2013. Abstract LBA9008;
2. Kaufman HL, et al ASCO 2014. Abstract LBA9008a.

Pembrolizumab could enhance the action of T-VEC to boost the cancer–immunity cycle

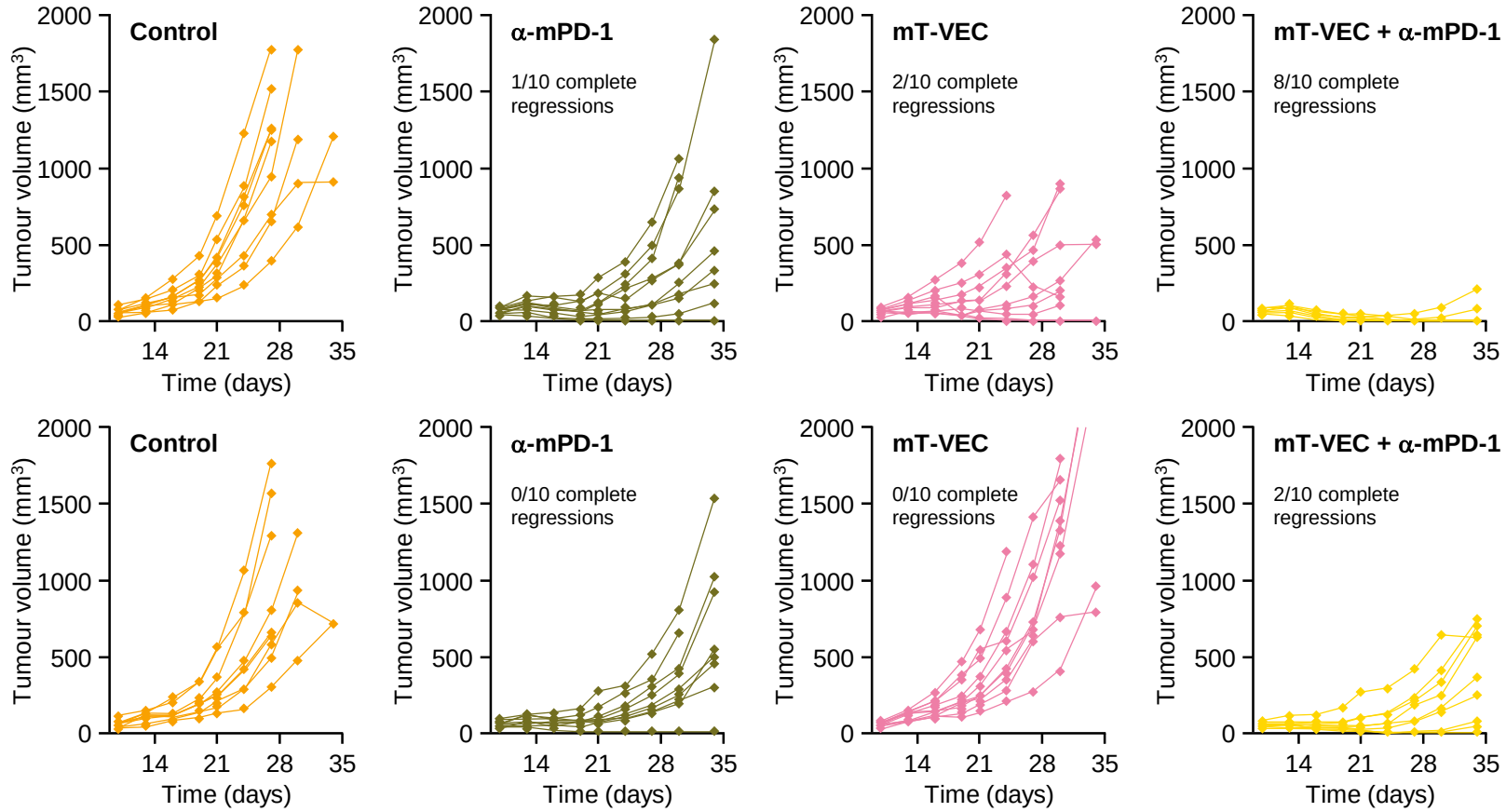


Adapted from Chen DS, Mellman I. Immunity 2013;39:1–10; Liu BL, et al. Gene Ther 2003;10:292–303.

Preclinical research – combination therapy increased tumour regression in mice vs single agents

Right side (injected)

Left side (uninjected)



- mT-VEC plus α-mPD-1 generates increased antitumour activity over either agent alone

α-mPD-1, mouse anti-mPD-1 monoclonal antibody.

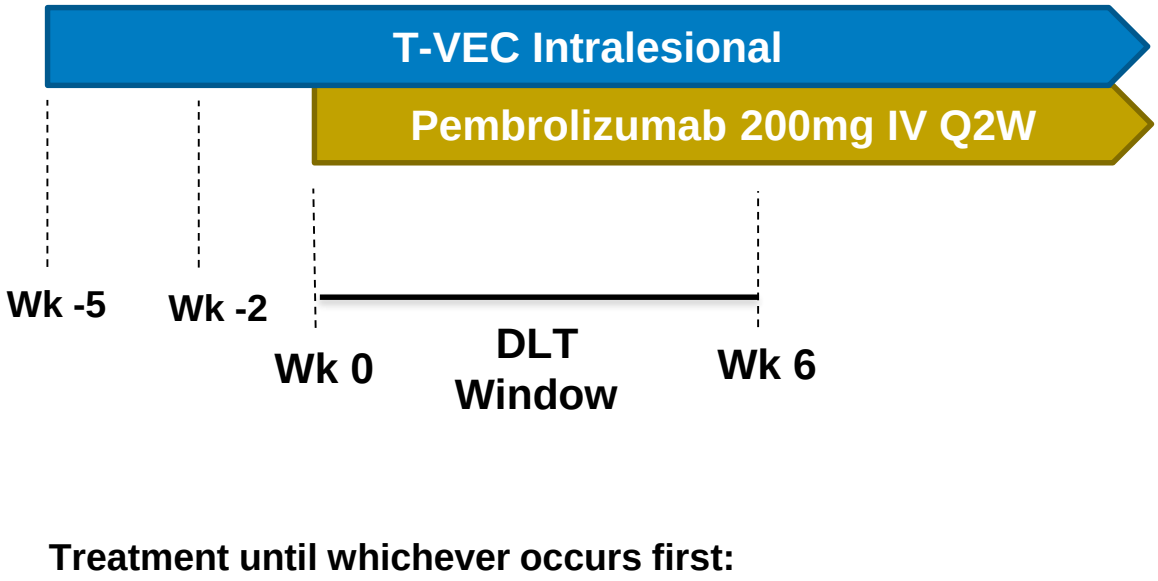
Piasecki J, et al. AACR 2015: Abstract 258 (and poster).

MASTERKEY-265 Phase 1b Study Schema

N = 21

- Unresectable stage III or IV melanoma
- Treatment naive
- Injectable lesions
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

T-VEC intralesional
- Up to 4 mL per treatment
- 1st dose 10^6 PFU/mL
- Then 10^8 PFU/mL Q2W



Treatment until whichever occurs first:
- Progressive disease per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

30 (+7) days after end of treatment

Long G V et SMR 2015

T-VEC = talimogene laherparepvec

Preliminary Efficacy – Best Overall Response (Unconfirmed)

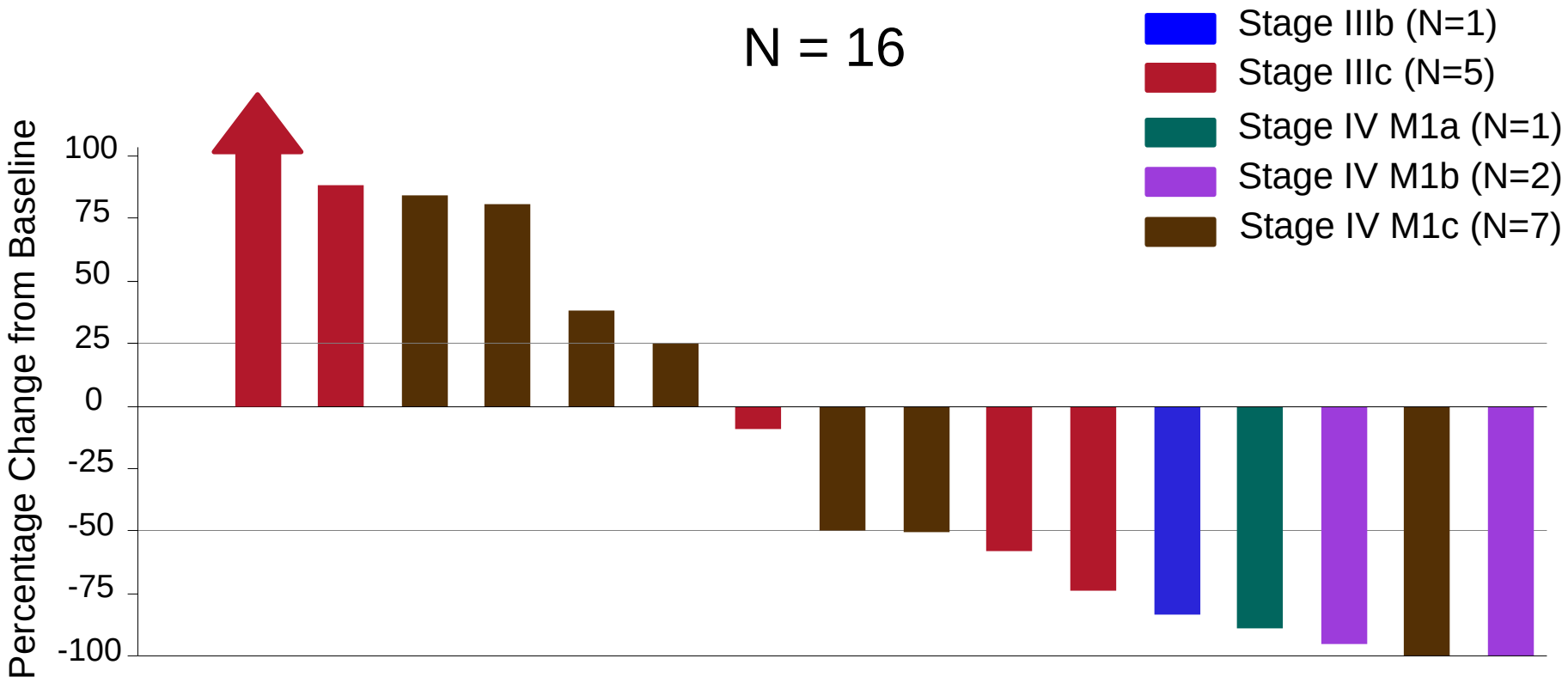
- 16 patients had evaluable responses prior to data cutoff[a]

	T-VEC + pembrolizumab N=16
Response Rate (95% CI)	**9 (56.3%)** (19.8%, 70.1%)
Best response	
Complete Response	2 (12.5%)
Partial Response	7 (43.8%)
Stable Disease[b]	2 (12.5%)
Progressive Disease	5 (31.3%)
Disease control rate (95% CI)	**11 (68.8%)** (11.0%, 58.7%)

[a]All 16 patients were followed at least 12 weeks from the first dose of pembrolizumab and must have had an evaluable response assessment
[b]Stable disease must be > 77 days to be considered evaluable

Long G V et SMR 2015

Best Change in Tumor Burden



All 16 patients were followed at least 12 weeks from the first dose of pembrolizumab and must have had an evaluable response. Stable disease must be > 77 days to be considered evaluable.

Long G V et SMR 2015

T-VEC Phase 1/2 study in SCCHN patients – tumour response

N = 17

100% compliance

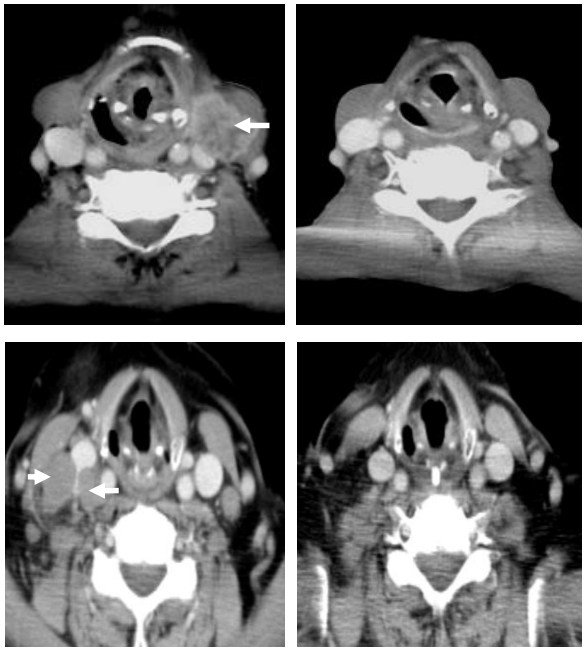
No drug-related DLTs

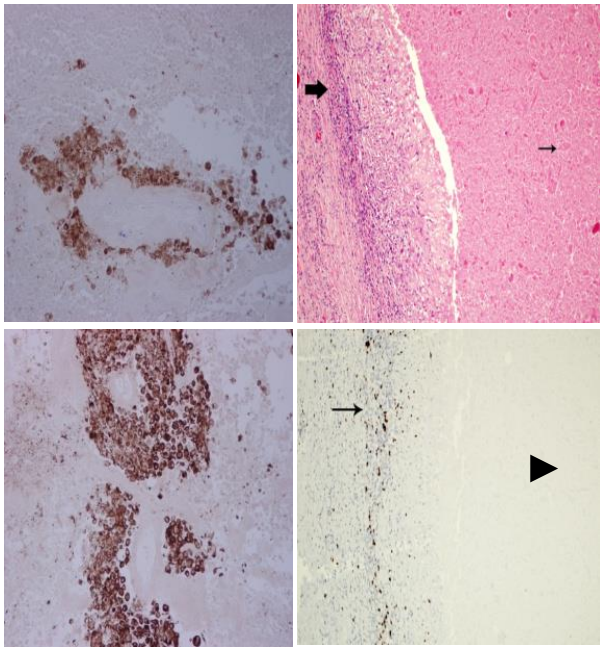
HSV detected in tumours

93% pathological complete remission

Local control = 100%

Overall survival = 70.5%

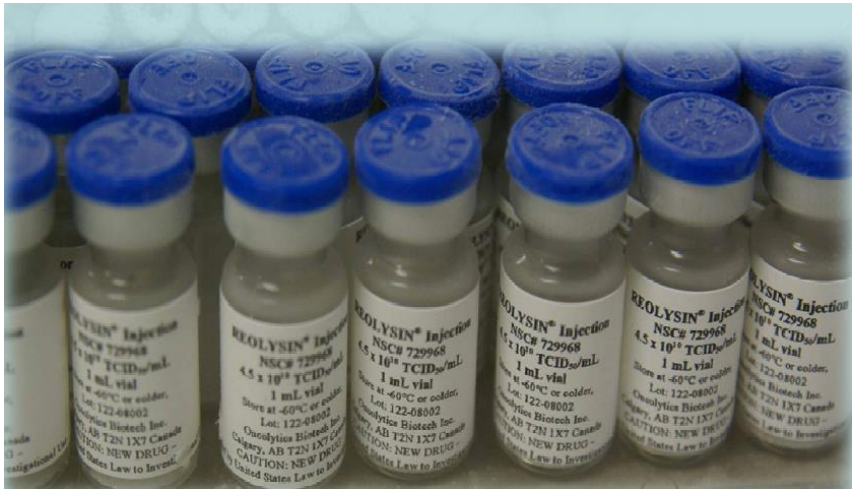


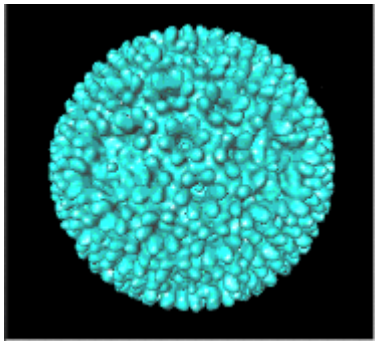


DLT, dose-limiting toxicities.

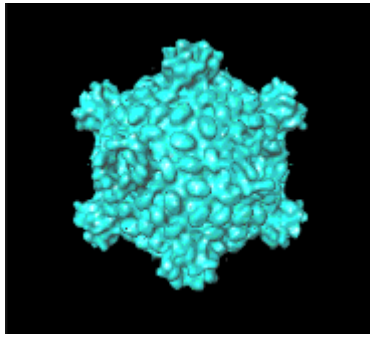
Harrington KJ, et al. Clin Cancer Res 2010;16:4005–15 and supplementary figures.

Reovirus (Pelareorep)

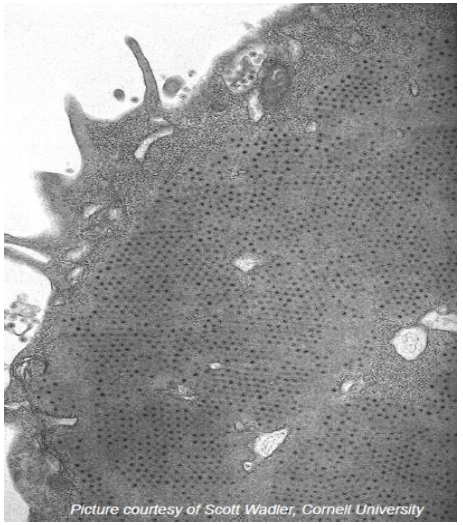




Virion

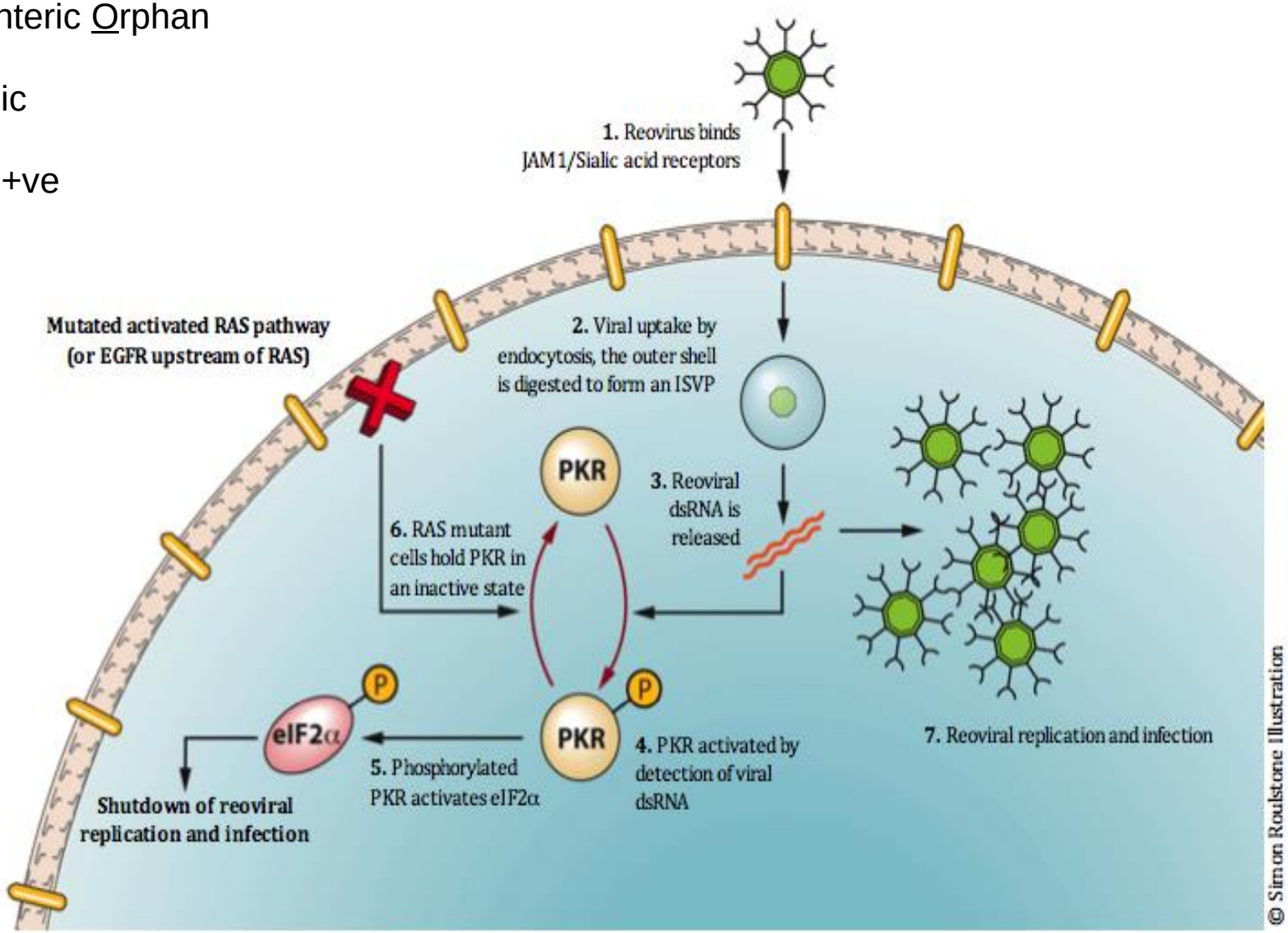


Core



Biological Basis of Tumour Selectivity of Reovirus

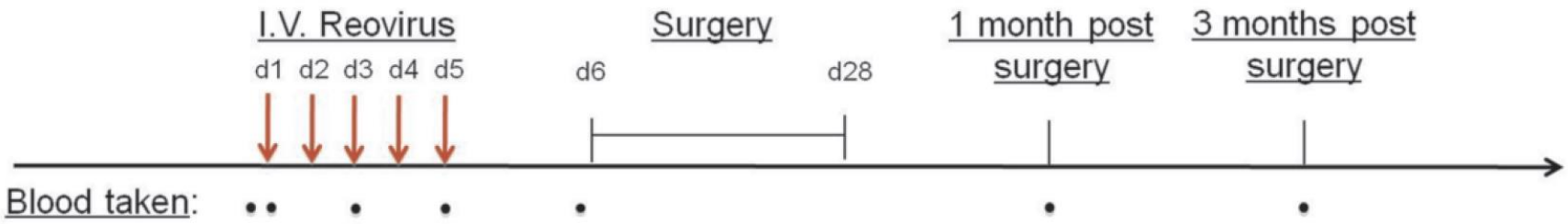
- Respiratory Enteric Orphan
- Non-pathogenic
- 90% antibody +ve
- Linear dsRNA

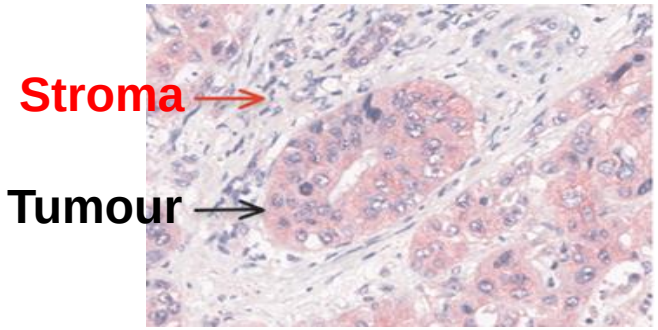


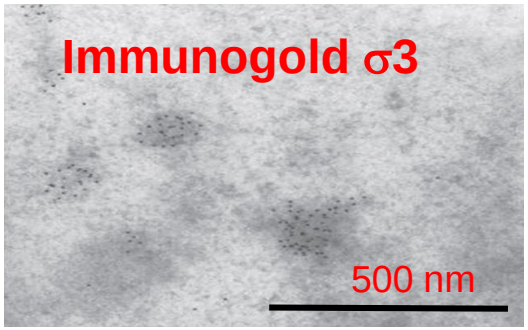
Harrington et al. Cytokine Growth Factor Rev 2010; 21: 91-98
Kyula et al. Expert Opin. Biol. Ther. 2012; 12: 1669-78

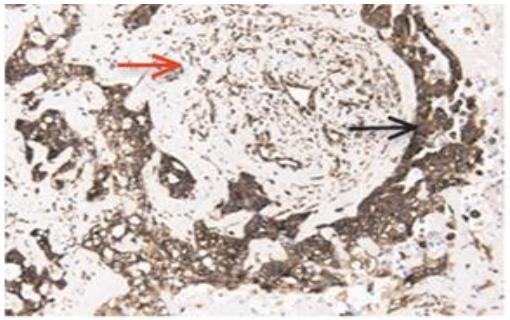
Cell Carriage, Delivery, and Selective Replication of an Oncolytic Virus in Tumor in Patients

Robert A. Adair,[1]* Victoria Roulstone,[2]* Karen J. Scott,[1] Ruth Morgan,[1] Gerard J. Nuovo,[3] Martin Fuller,[4] Deborah Beirne,[1] Emma J. West,[1] Victoria A. Jennings,[1] Ailsa Rose,[1] Joan Kyula,[2] Sheila Fraser,[1] Rajiv Dave,[1] David A. Anthoney,[1] Alison Merrick,[1] Robin Prestwich,[1] Amer Aldouri,[1] Oliver Donnelly,[1] Hardev Pandha,[5] Matt Coffey,[6] Peter Selby,[1] Richard Vile,[7] Giles Toogood,[1] Kevin Harrington,[2]* Alan A. Melcher[1]*†



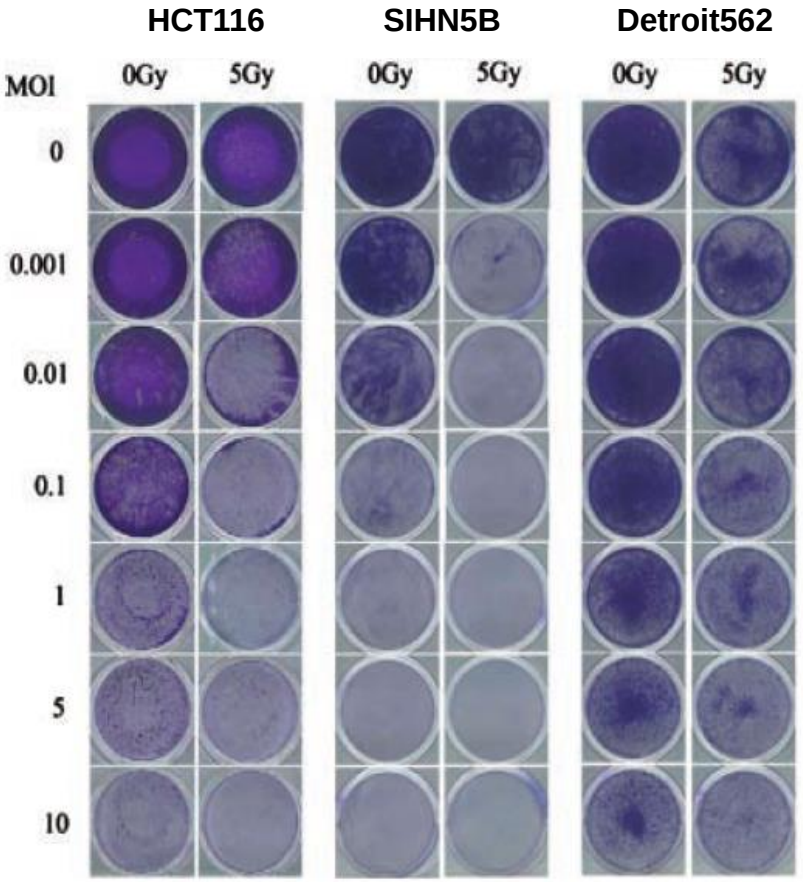


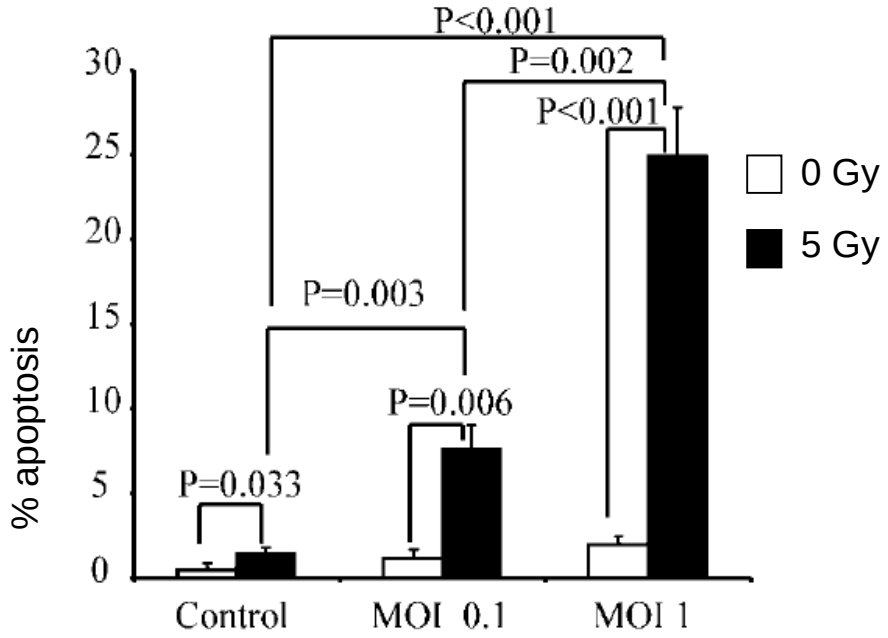




Enhanced *In vitro* and *In vivo* Cytotoxicity of Combined Reovirus and Radiotherapy

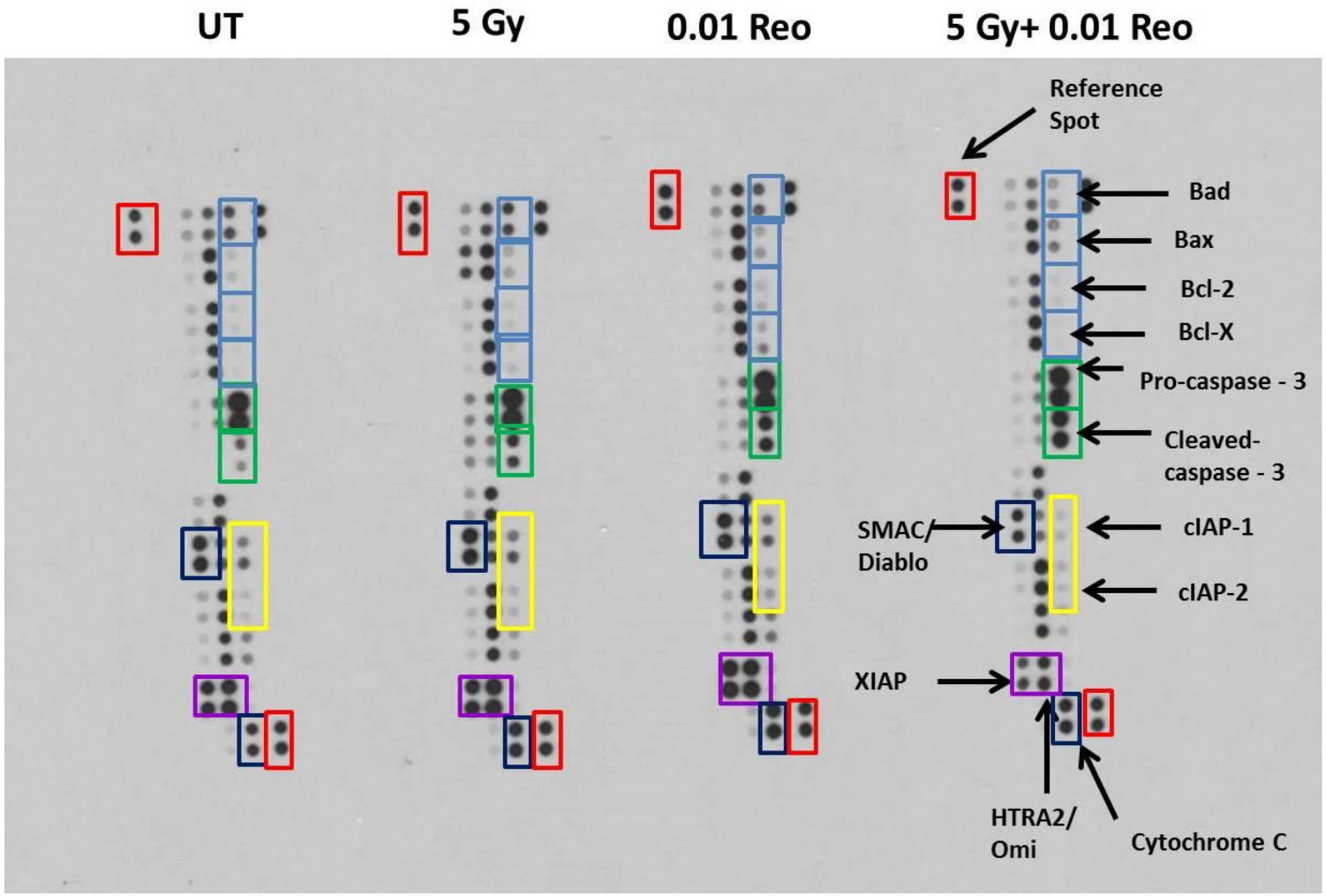
Katie Twigger,[1] Laura Vidal,[1] Christine L. White,[1] Johann S. De Bono,[2] Shreerang Bhide,[1] Matt Coffey,[3] Brad Thompson,[3] Richard G. Vile,[4] Lucy Heinemann,[5] Hardev S. Pandha,[5] Fiona Errington,[6] Alan A. Melcher,[6] and Kevin J. Harrington[1]





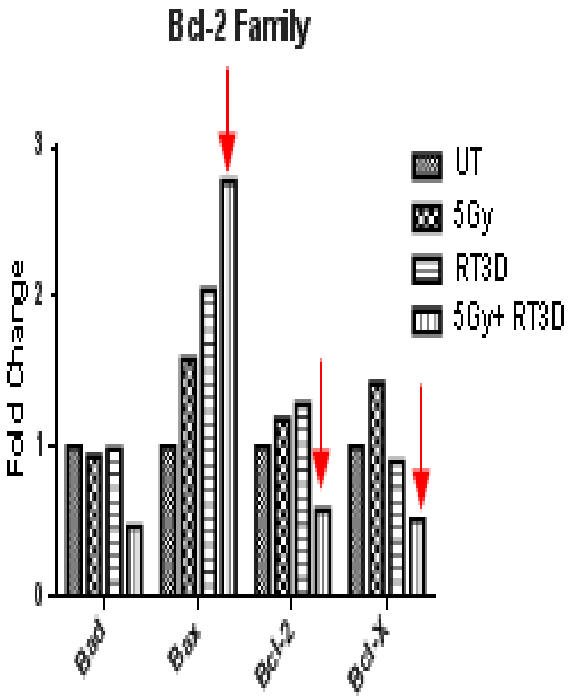
Twigger et al. Clin Cancer Res 2008; 14: 912-23

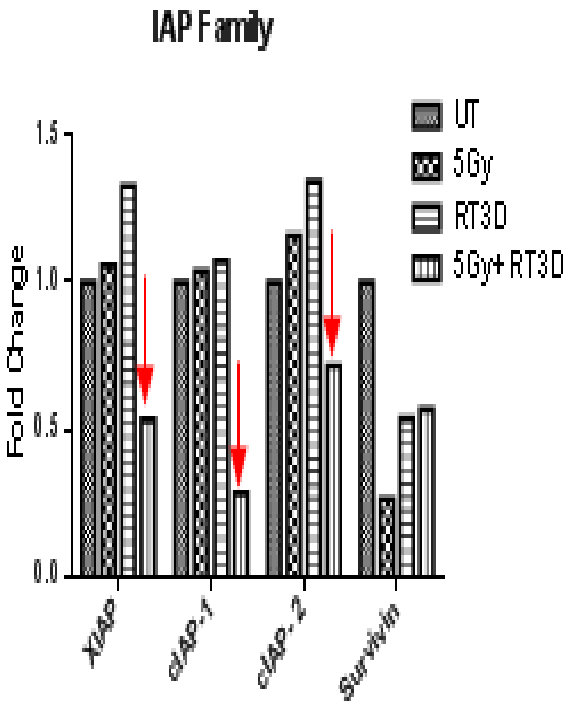
Pro-apoptotic Effects of Reovirus + RT

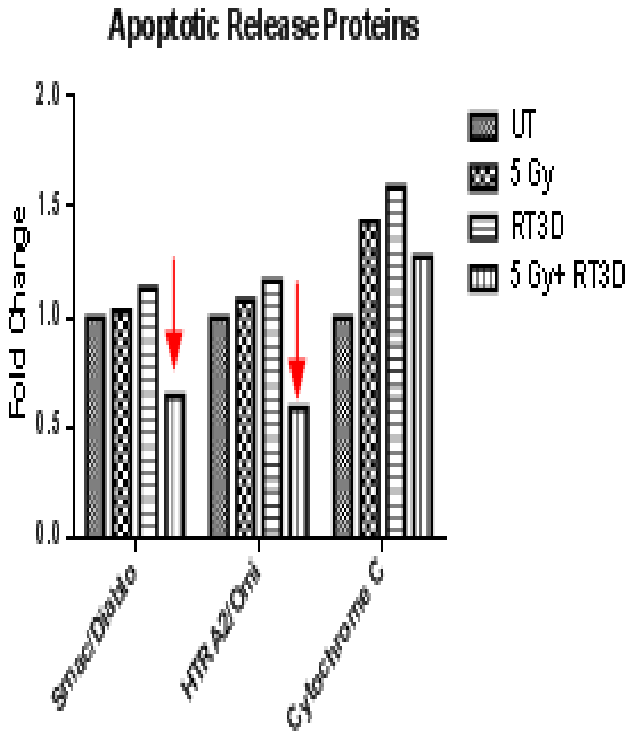


McEntee (unpublished)

Pro-apoptotic Effects of Reovirus + RT

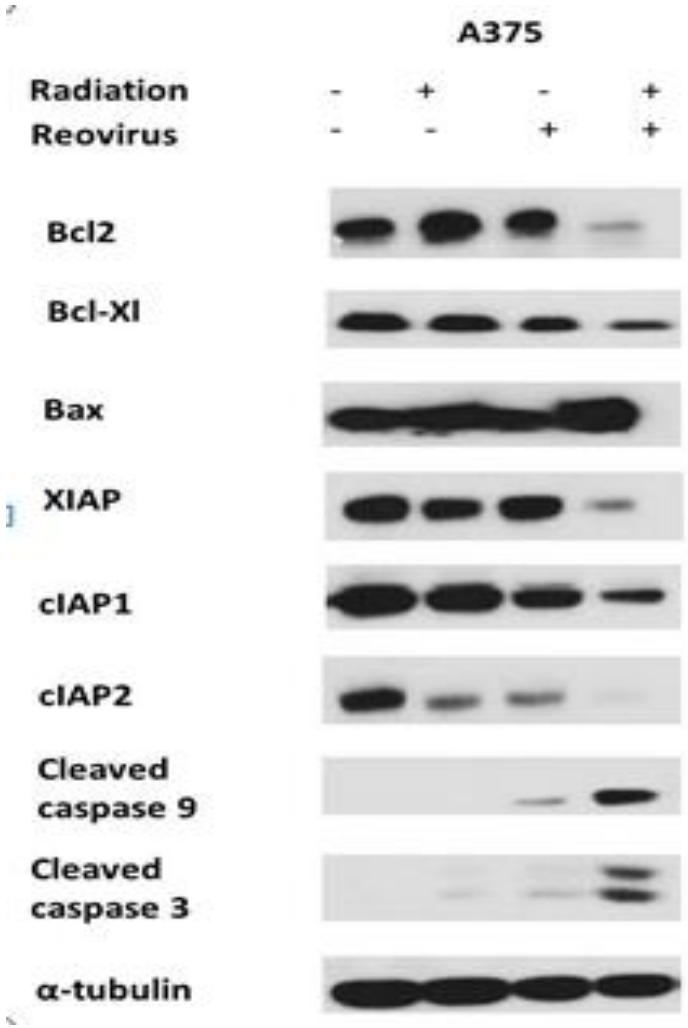


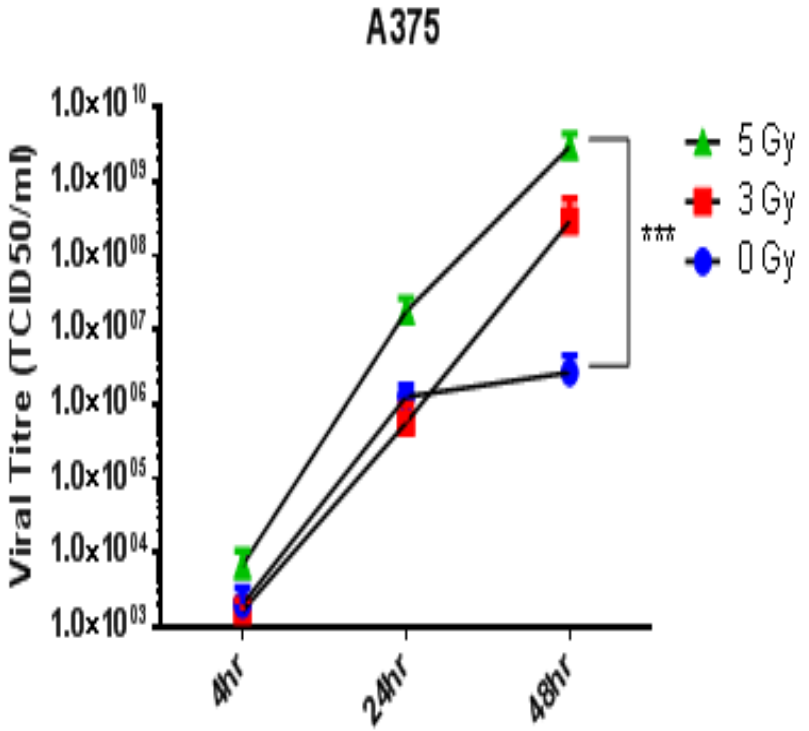




McEntee (unpublished)

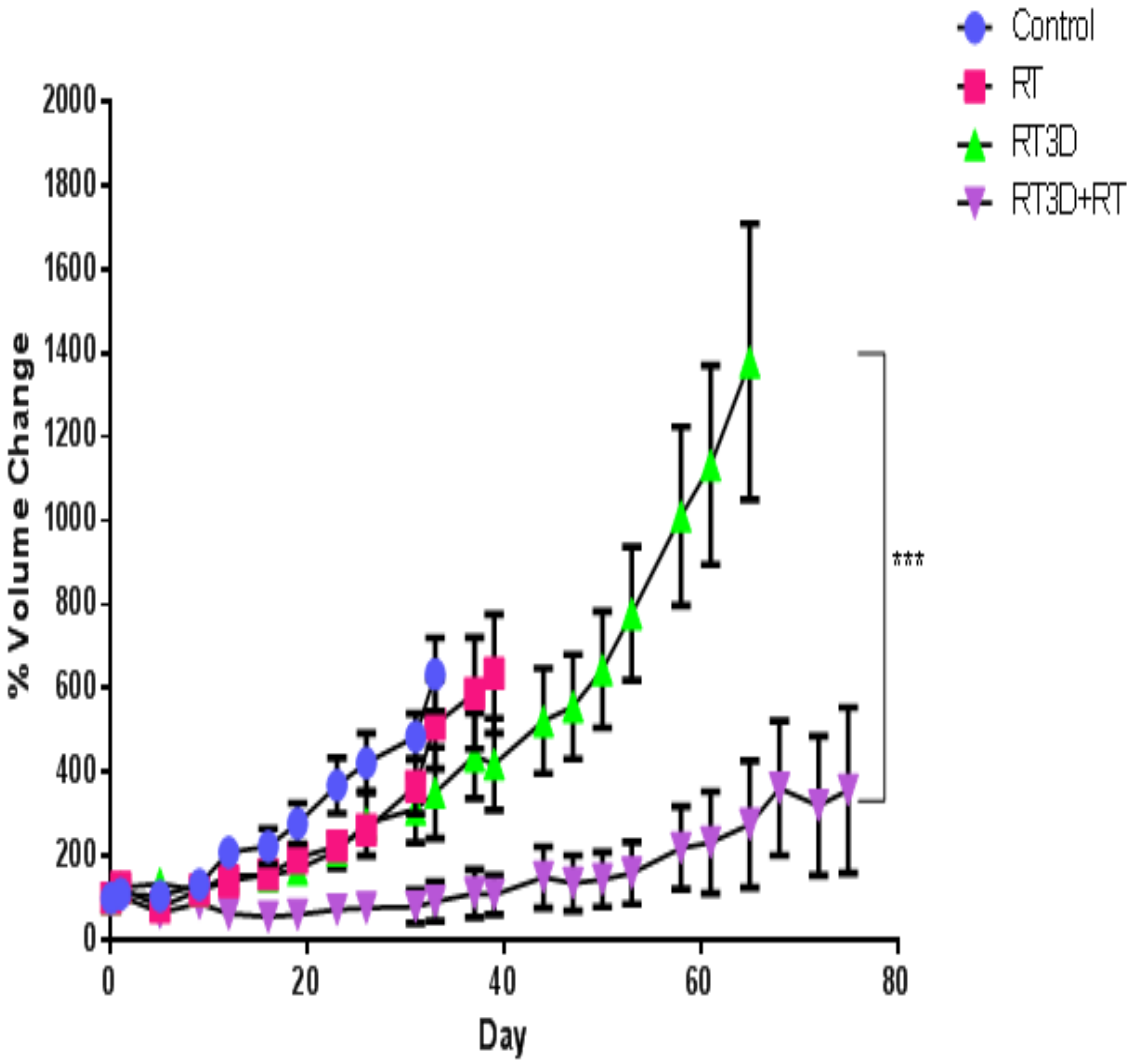
Downregulation of Anti-apoptotic Signalling and Increased Viral Replication

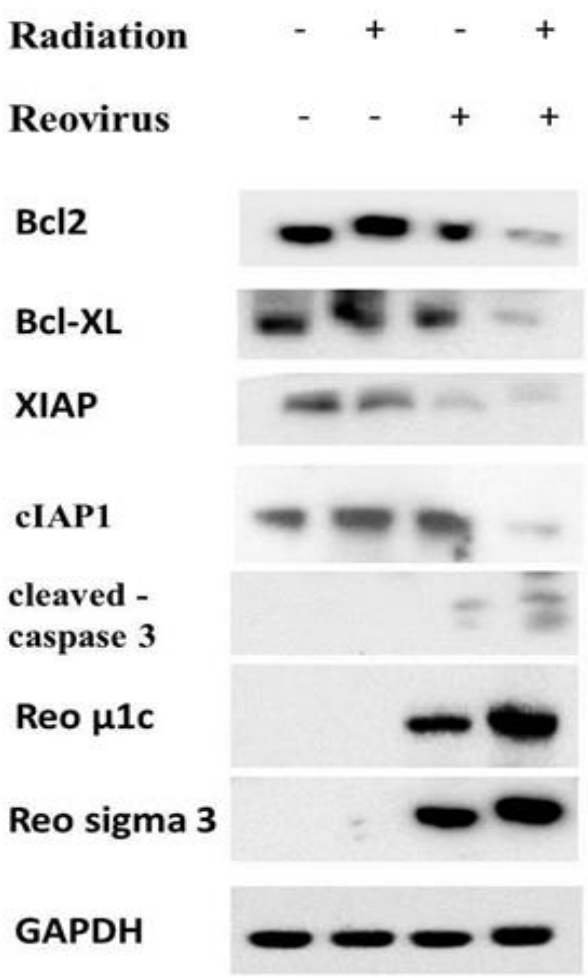




McEntee (unpublished)

In vivo efficacy





McEntee (unpublished)

Conclusions

- Oncolytic viruses represent a new class of cancer therapy
- Studies in immune competent mice confirm direct oncolytic and indirect immunotherapeutic actions
- T-VEC/Imlygic is an FDA-approved First-in-Class oncolytic immunotherapy
- Future development will include combinations with immune checkpoint blockade
- Synergistic interactions with RT (+/- targeted drugs)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