ICR The Institute of Cancer Research

Combinatorial Immune Therapies to Enhance Outcomes in Solid Cancers

Kevin Harrington

ORACLE cancer trust

Rosetrees Trust
Supporting the best in medical research

CANCER RESEARCH UK

MRC Medical Research Council

Get ahead Charitable Trust
A cancer charity fighting all head & neck diseases

The Mark Donegan Fellowship

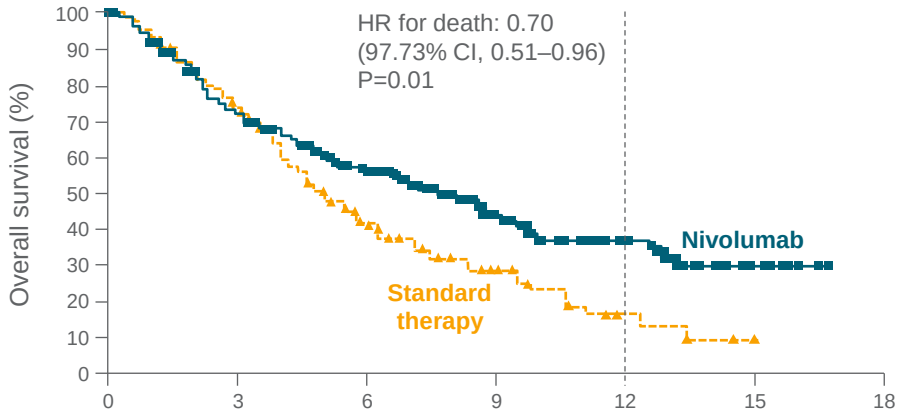
Disclosures

Honoraria/Travel: Amgen, AZ, BMS, Merck, MSD, Pfizer

Research Funding: Amgen, AZ, MSD, Oncolytics, Viralytics

IO Agents are Transforming Clinical Practice: SCCHN

	Number of patients	Number of deaths	1-year overall survival rate *% (95% CI)*	Median overall survival *months (95% CI)*
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



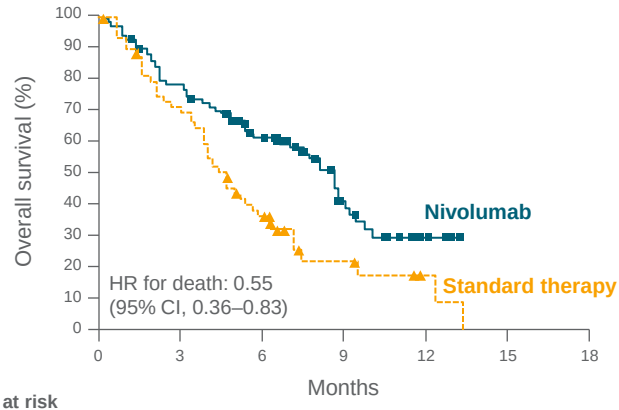
Number at risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

Ferris RL, *et al. N Engl J Med* 2016;375:1856–67.

IO Agents are Transforming Clinical Practice: SCCHN

Overall survival among patients with baseline PD-L1 ≥1%

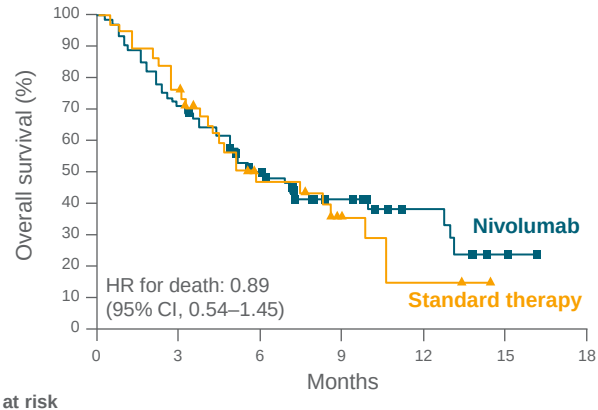
	Number of patients	Number of deaths	Median overall survival *months (95% CI)*
Nivolumab	88	49	8.7 (5.7–9.1)
Standard therapy	61	45	4.6 (3.8–5.8)



Number at risk							
Nivolumab	88	67	44	18	6	0	–
Standard therapy	61	42	20	6	2	0	–

Overall survival among patients with baseline PD-L1 <1%

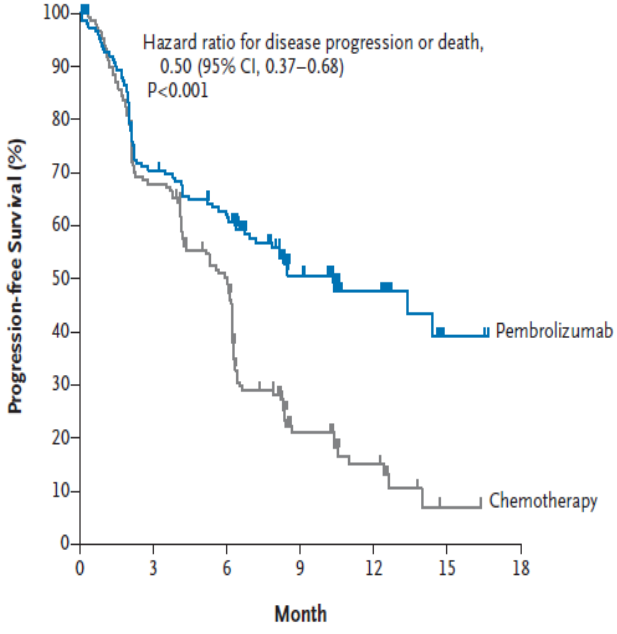
	Number of patients	Number of deaths	Median overall survival *months (95% CI)*
Nivolumab	73	45	5.7 (4.4–12.7)
Standard therapy	38	25	5.8 (4.0–9.8)



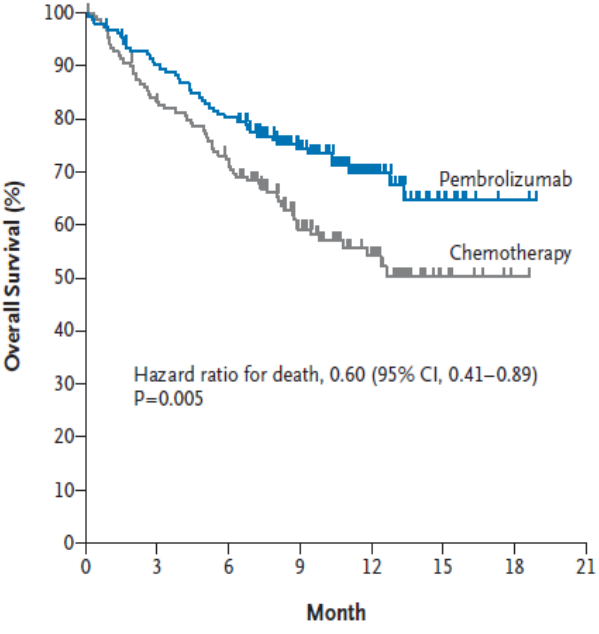
Number at risk							
Nivolumab	73	52	33	17	8	3	0
Standard therapy	38	29	14	6	2	0	0

Ferris RL, *et al. N Engl J Med* 2016;375:1856–67.

IO Agents are Transforming Clinical Practice: NSCLC



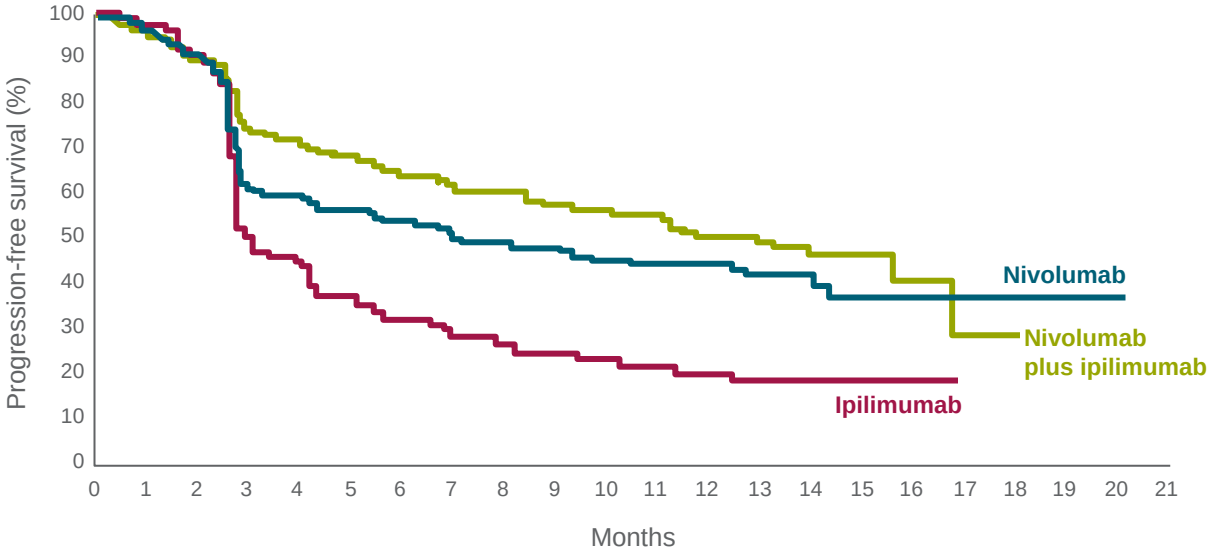
No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0



No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Reck M, *et al. N Engl J Med* 2016;375:1823–33.

IO Agents are Transforming Clinical Practice: Melanoma

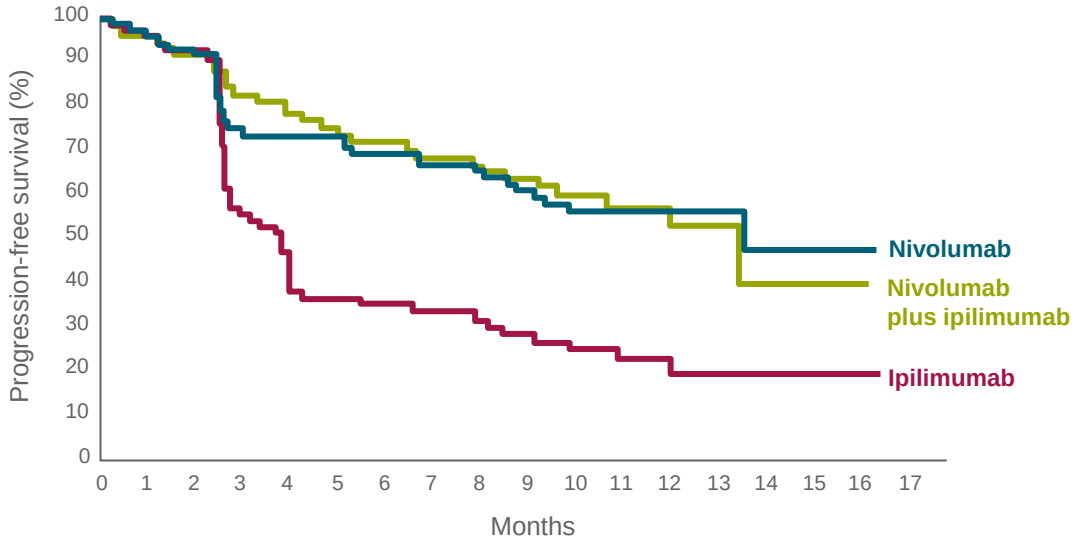


Number at risk																					
Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

Larkin J, *et al. N Engl J Med* 2015;373:23–34.

IO Agents are Transforming Clinical Practice: Melanoma

Patients with PD-L1-positive tumours



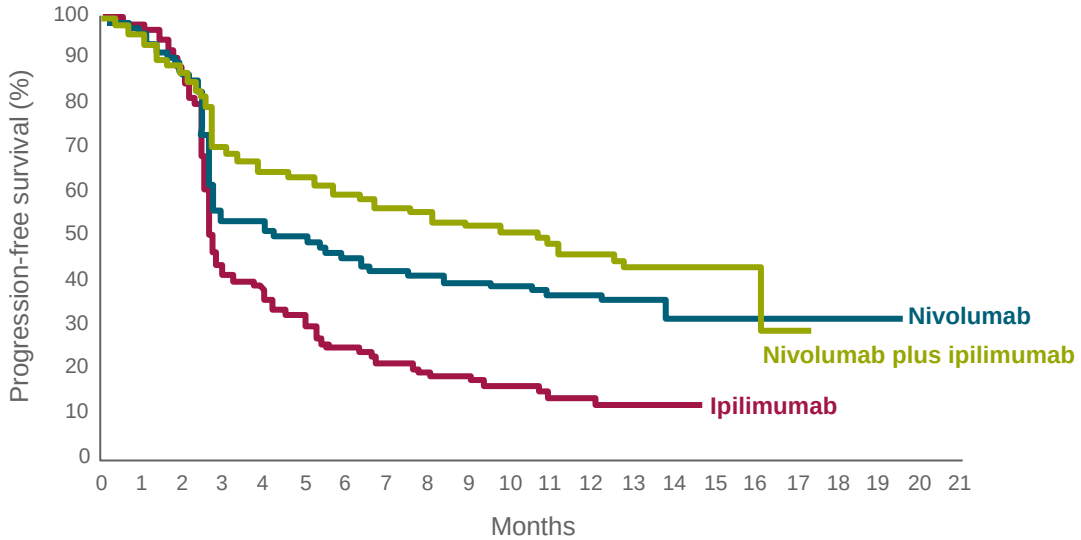
Number at risk

Nivolumab	80	76	71	57	56	54	51	49	49	43	38	32	16	13	5	4	2	0
Nivolumab plus ipilimumab	68	63	61	53	52	47	44	42	42	39	34	24	16	12	3	1	1	0
Ipilimumab	75	69	66	40	33	24	22	21	21	17	16	15	9	6	3	2	2	0

Larkin J, *et al. N Engl J Med* 2015;373:23–34.

IO Agents are Transforming Clinical Practice: Melanoma

Patients with PD-L1-negative tumours



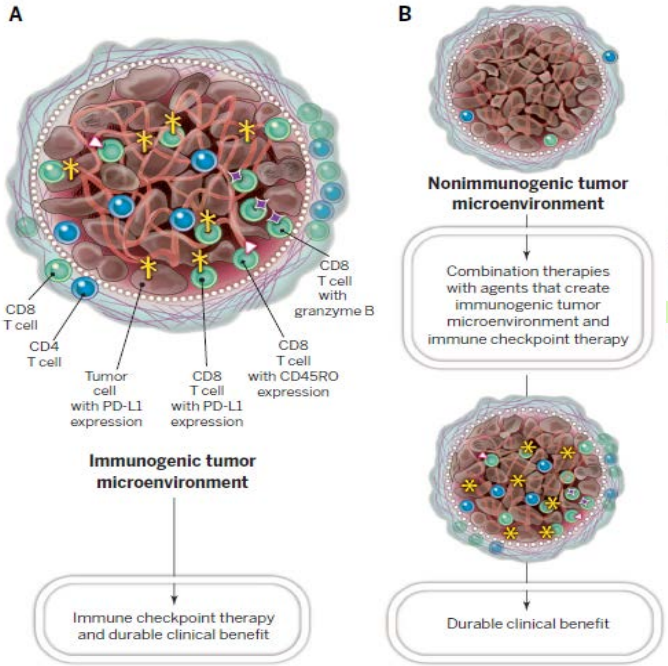
Number at risk

Nivolumab	208	192	178	108	105	98	88	80	76	74	63	50	31	24	9	5	4	2	1	1	1	0
Nivolumab plus ipilimumab	210	195	181	142	134	123	112	106	105	96	88	79	42	36	13	9	6	2	1	0	–	–
Ipilimumab	202	183	166	82	72	59	44	39	35	31	26	22	12	8	3	1	0	–	–	–	–	–

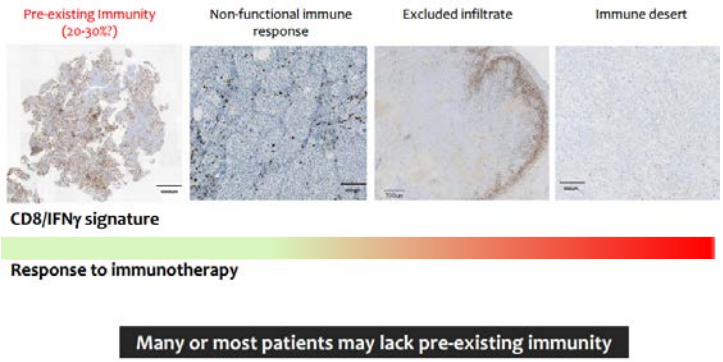
Larkin J, *et al. N Engl J Med* 2015;373:23–34.

Immunogenic and Non-Immunogenic Tumours – Rationale for Combination Therapy

Potential characteristic of immunogenic and non-immunogenic tumours[1]

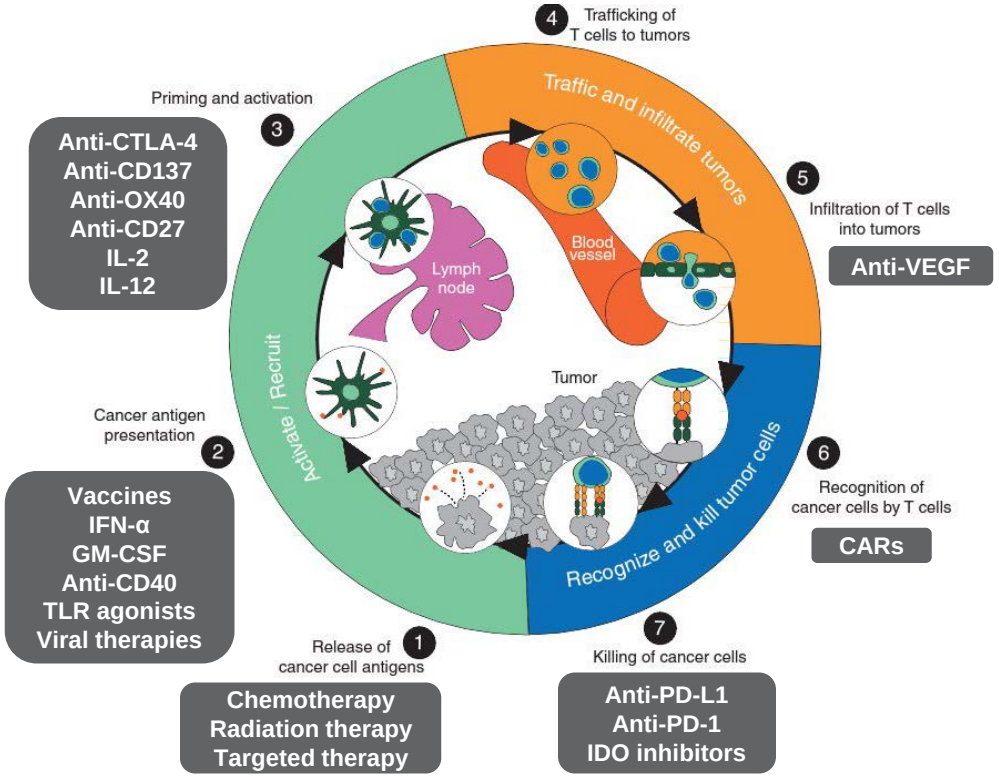


Pre-existing immunity and response to immunotherapy[2]



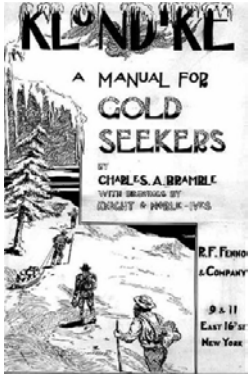
1. Sharma P, Allison JP. *Science* 2015;348:56–61;
2. Adapted from Hegde PS, *et al. Clin Cancer Res* 2016;22:1865–74.

The Cancer Immunity Cycle Includes Many Potential Therapeutic Targets



Adapted from Kim JM, Chen DS. *Ann Oncol* 2016;27:1492–504.

The IO ‘Gold Rush’



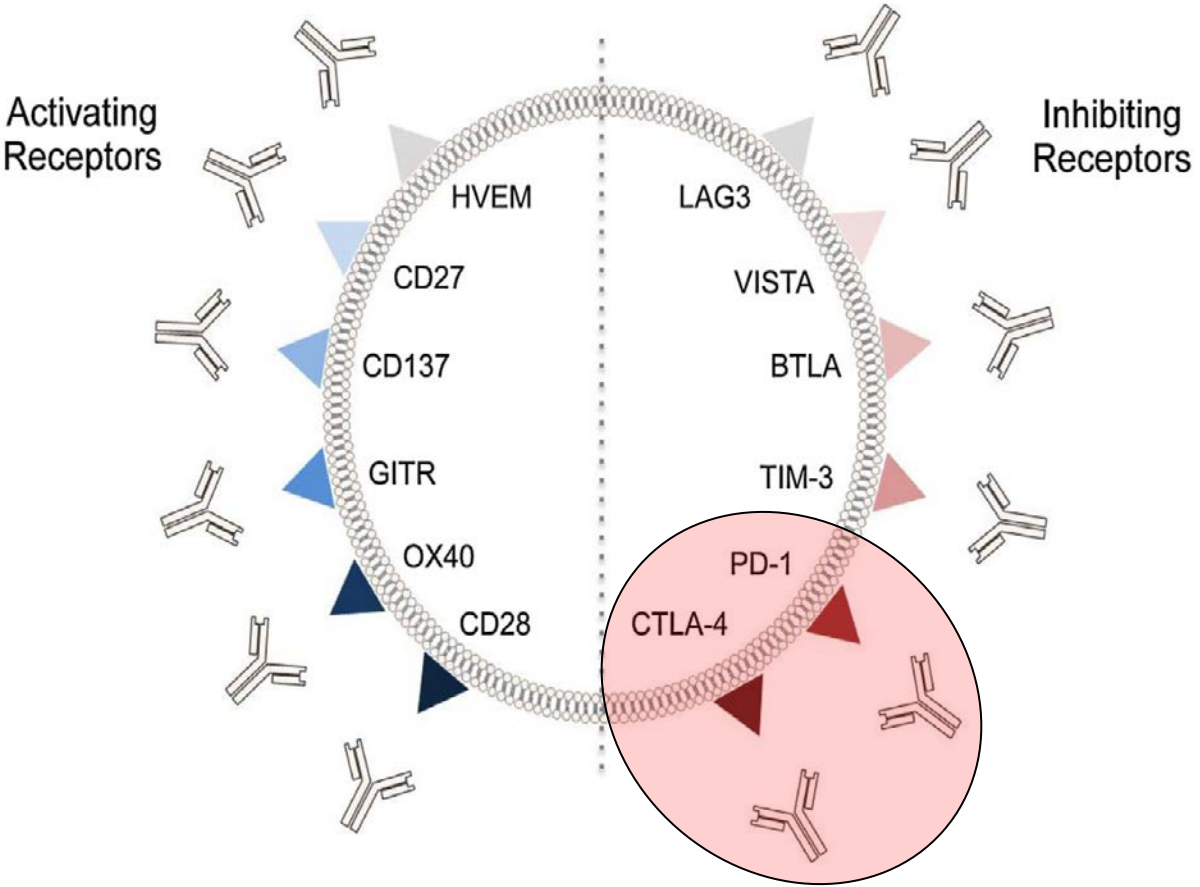
Where Will We Strike Gold Next?

Killing of cancer cells	Priming and activation	Cancer antigen presentation
• PD-L2 • LAG3 • TIM-3 • Adenosine A2aR • B7-H3 • VISTA • IDO inhibition • Inhibition of TGF-β signalling • Oncolytic virotherapy • DNA damage response inhibitors	• OX40 • CD137 • GITR • CD40 • CD27 • 4-1BB • ICOS • IL-2 • Vaccines • Oncolytic virotherapy	• KIR monoclonal antibodies • TLR • MUC1 • IFN-γ

…and they will provide further guidance on selection of therapeutic agents for combination, patient populations and treatment strategies.

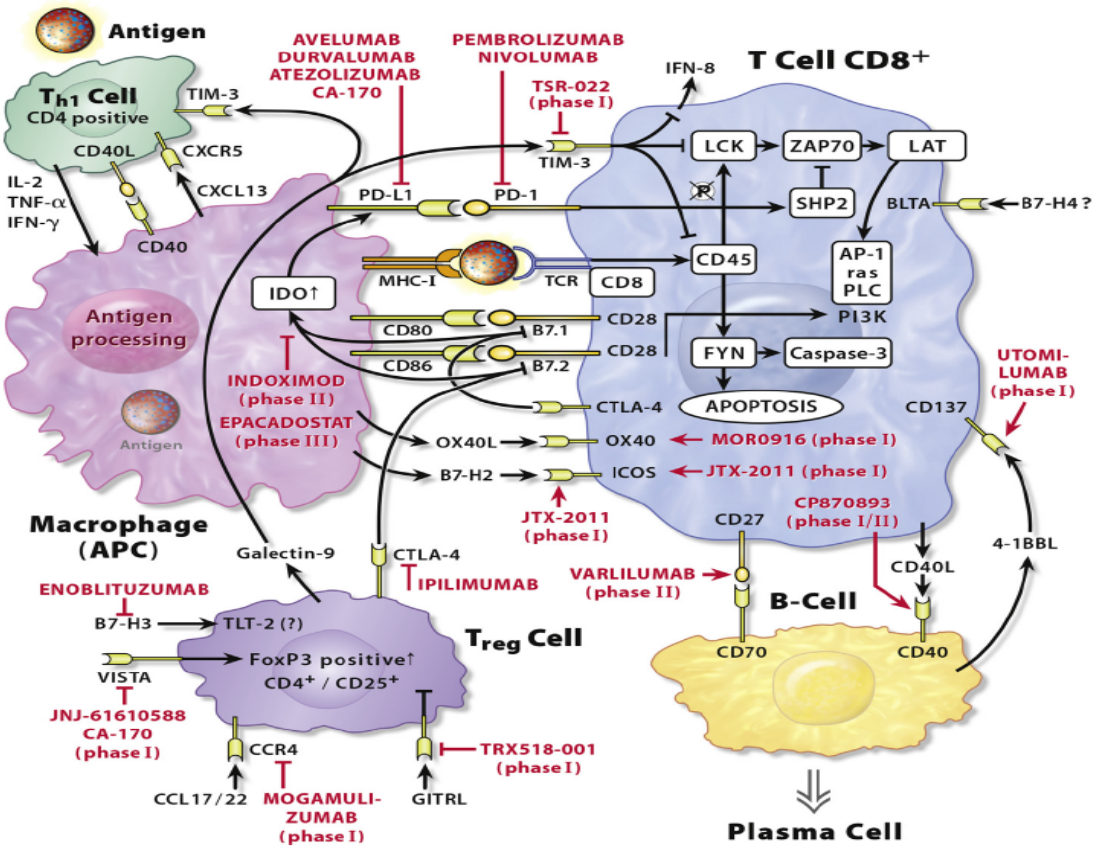
Chen DS, Mellman I. *Immunity* 2013;39:1–10; Dholaria B, *et al. J Hematol Oncol* 2016;9:138.

1. IO-IO Combinations



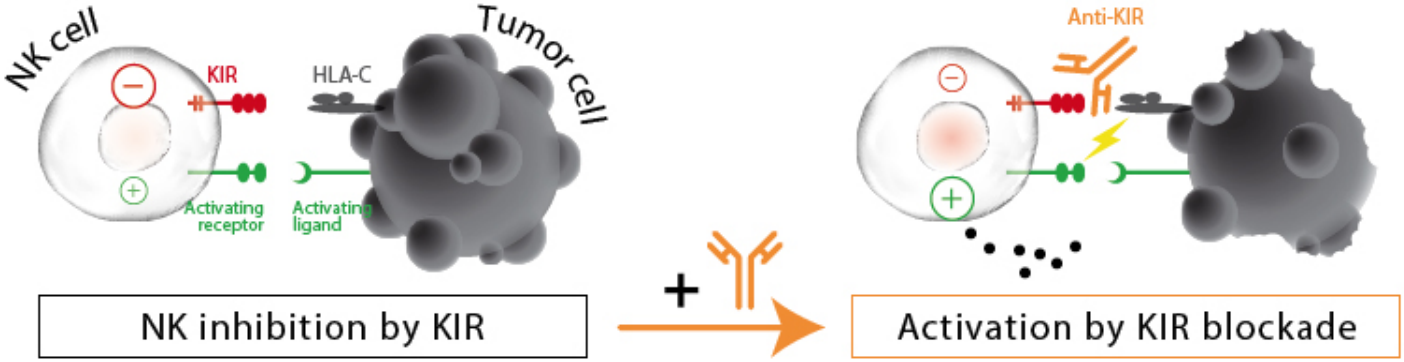
Critical Reviews in Oncology/Hematology 89 (2014) 140–165

Many Possible Targets and Opportunities



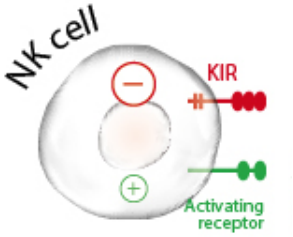
Dempke WCM, *et al. Eur J Cancer* 2017;74:55–72.

Anti-KIR Monoclonal Antibodies to Activate Innate Immune Response



Anti-KI Lirilumab/Nivolumab Combo Highly tivate Effective in Head and Neck Cancer

Silas Inman @silasinman
Published Online: Saturday, Nov 12, 2016

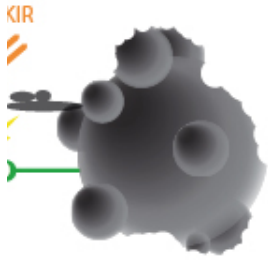


NK inhibi

Rom Leidner, MD

The combination of the killer-cell immunoglobulin-like receptors (KIRs) inhibitor lirilumab with the PD-1 inhibitor nivolumab (Opdivo) resulted in an objective response rate (ORR) of 24.1% in patients with squamous cell carcinoma of the head and neck (SCCHN), according to phase I/II findings presented at the Society for Immunotherapy of Cancer (SITC) 31st Annual Meeting & Associated Programs.

In the phase I/II study, 29 patients with SCCHN were evaluable for response, of which 3 had a complete response (10.3%) and 4 had a partial response (13.8%), 2 of which were near complete responses with a ≥80% reduction in tumor size. The 6-month overall survival (OS) rate with lirilumab plus nivolumab was 90% and the 12-month OS rate was 60%.



KIR blockade

SITC 2016
NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

Preliminary efficacy from a phase 1/2 study of the natural killer cell–targeted antibody, lirilumab in combination with nivolumab in squamous cell carcinoma of the head and neck

Rom Leidner,[1] Hyunseok Kang,[2] Robert Haddad,[3] Neil H. Segal,[4] Lori J. Wirth,[5] Robert L. Ferris,[6] F. Stephen Hodi,[3] Rachel E. Sanborn,[1] Thomas F. Gajewski,[7] William Sharfman,[2] Dan McDonald,[8] Shivani Srivastava,[8] Xuemin Gu,[8] Penny Phillips,[8] Chaitali Passey,[8] Tanguy Y. Seiwert[7]

[1]Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, USA; [2]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Massachusetts General Hospital, Boston, MA, USA; [6]University of Pittsburgh, Pittsburgh, PA, USA; [7]University of Chicago Medical Center, Chicago, IL, USA; [8]Bristol-Myers Squibb, Princeton, NJ, USA

sitc
Society for Immunotherapy of Cancer

#SITC2016

Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy in SCCHN

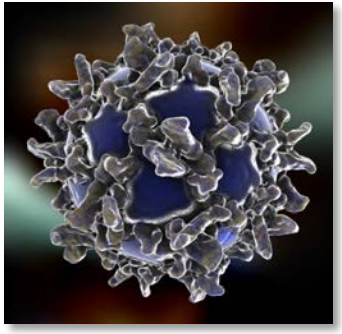
	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)*	**7/29 (24.1)**	**32/240 (13.3)**
Complete response*	3 (10.3)	6 (2.5)
Partial response*	4 (13.8)	26 (10.8)
DCR, n/N (%)	15/29 (51.7)	NR
ORR by PD-L1 expression, n/N (%)†		
<1%	0/9 (0)	9/73 (12.3)
≥1%	7/17 (41.2)	15/88 (17.0)
≥5%	6/11 (54.5)	12/54 (22.2)
≥50%	4/7 (57.1)	7/19 (36.8)
Overall survival in all patients, % (95% CI)		
At 6 months	90‡	55.6 (48.9, 61.8)
At 12 months	60§	36.0 (28.5, 43.4)

*Includes unconfirmed responses.
§Patients at risk, n = 10/41.

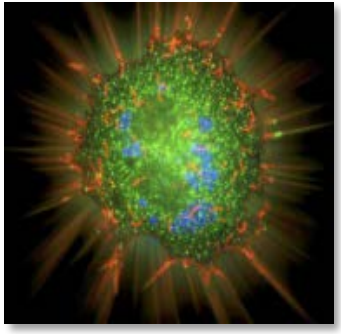
1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. Data on file.

2. Oncolytic Immunotherapy

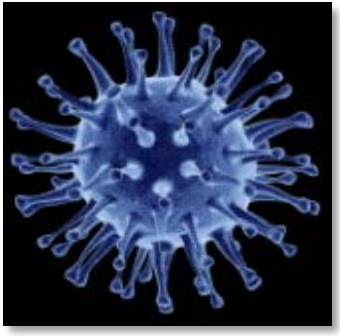
Reovirus

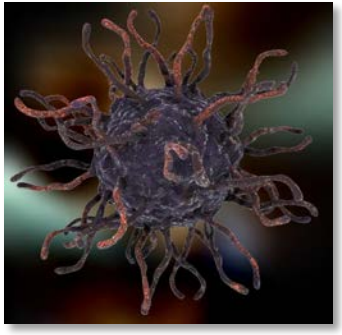


Vaccinia virus

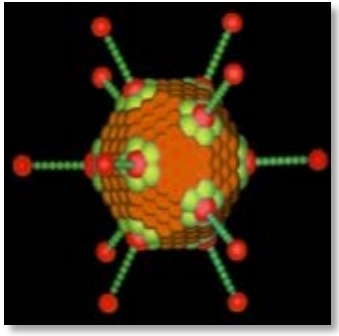


Measles virus

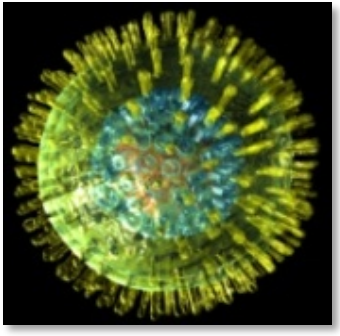




Coxsackievirus

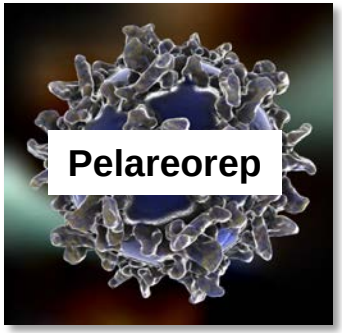


Adenovirus



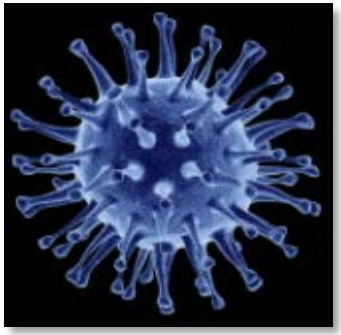
HSV

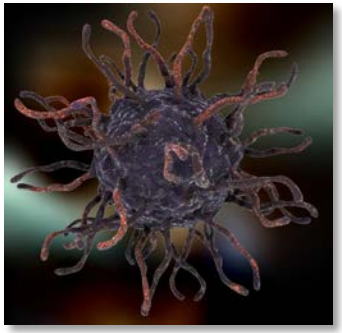
Reovirus

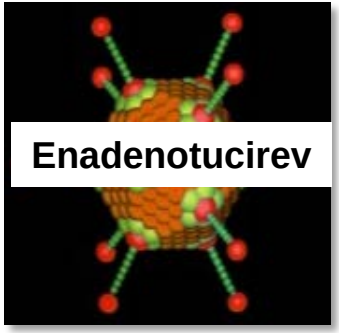


Vaccinia virus

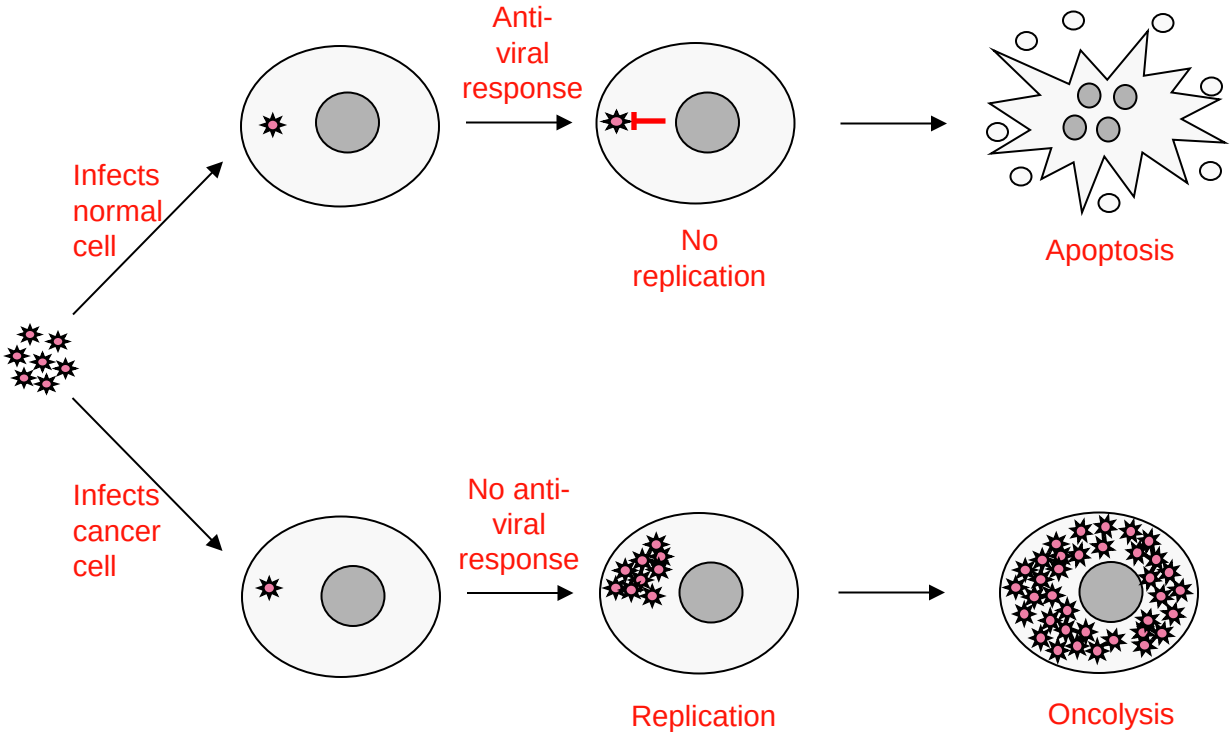
Measles virus

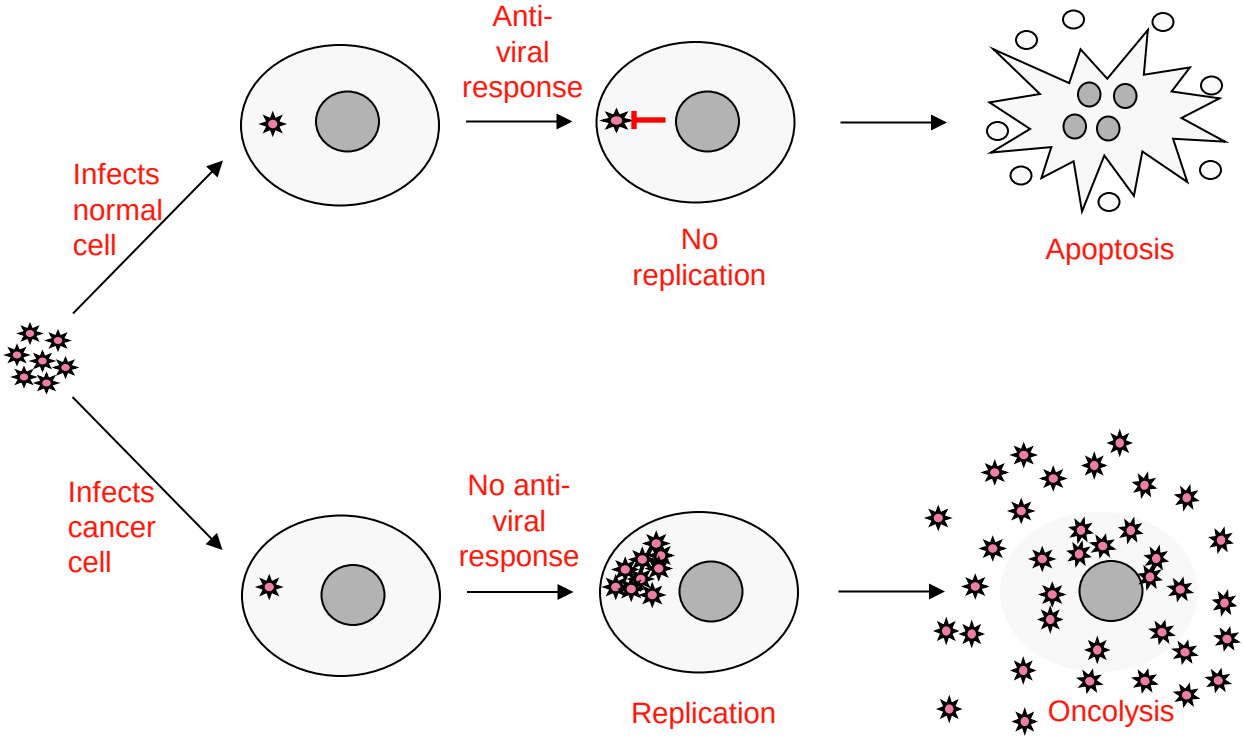


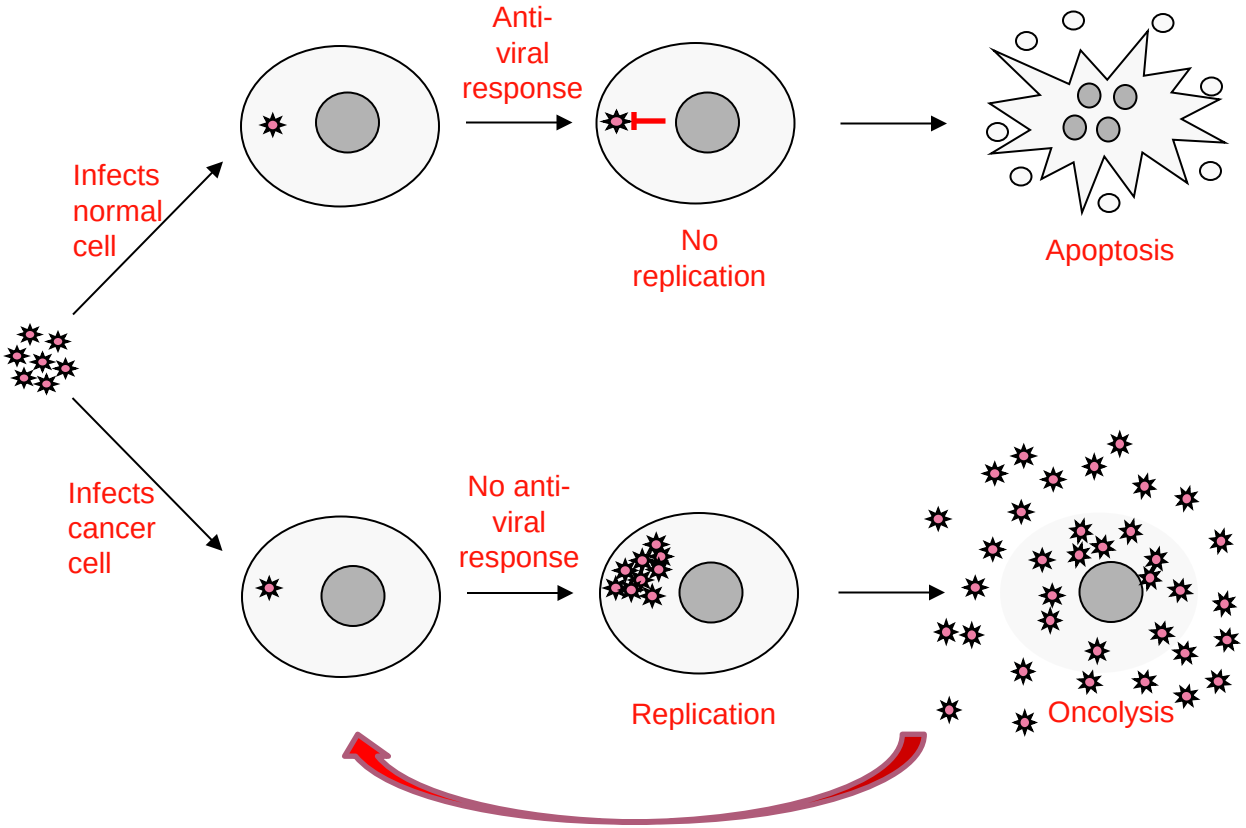




Oncolytic Viruses: Mechanism of Action



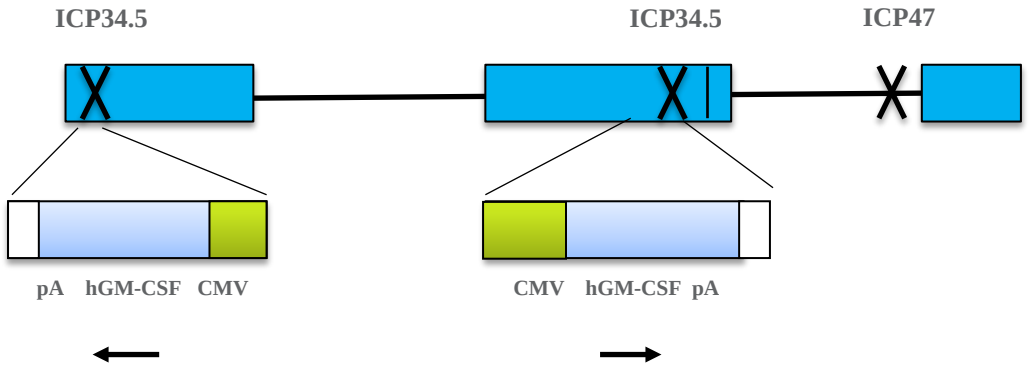

Anti-
viral
response
Infects
normal
cell
No
replication
Apoptosis
Infects
cancer
cell
No anti-
viral
response
Replication
Oncolysis


Anti-
viral
response
Infects
normal
cell
No
replication
Apoptosis
Infects
cancer
cell
No anti-
viral
response
Replication
Oncolysis

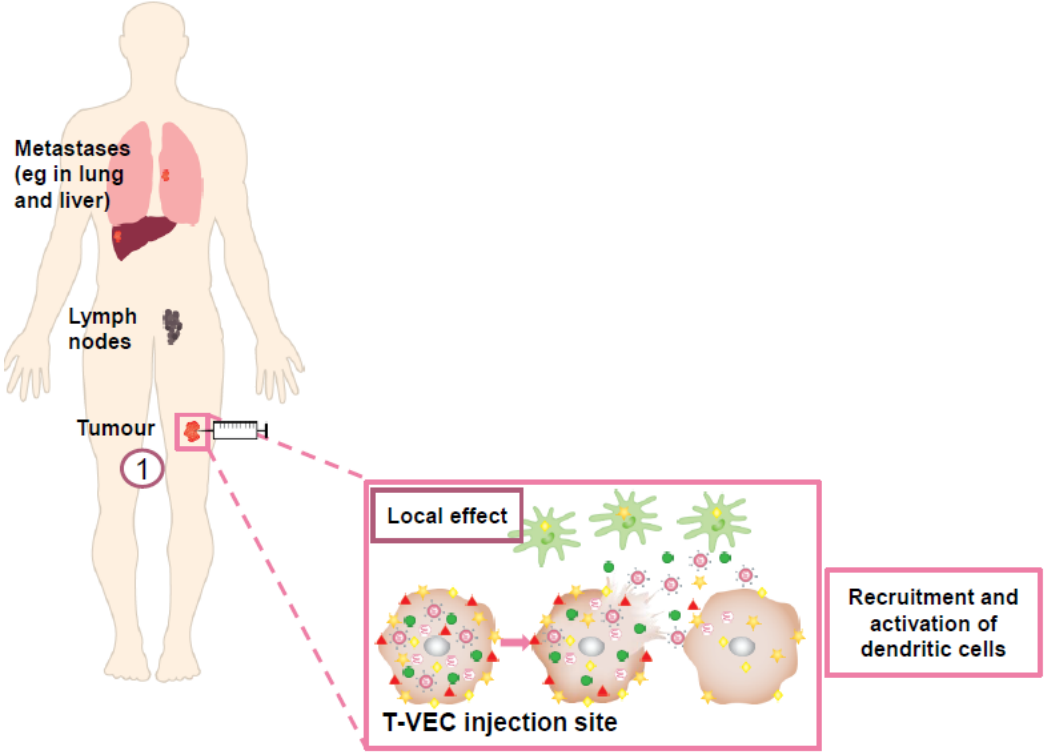
……. and repeat

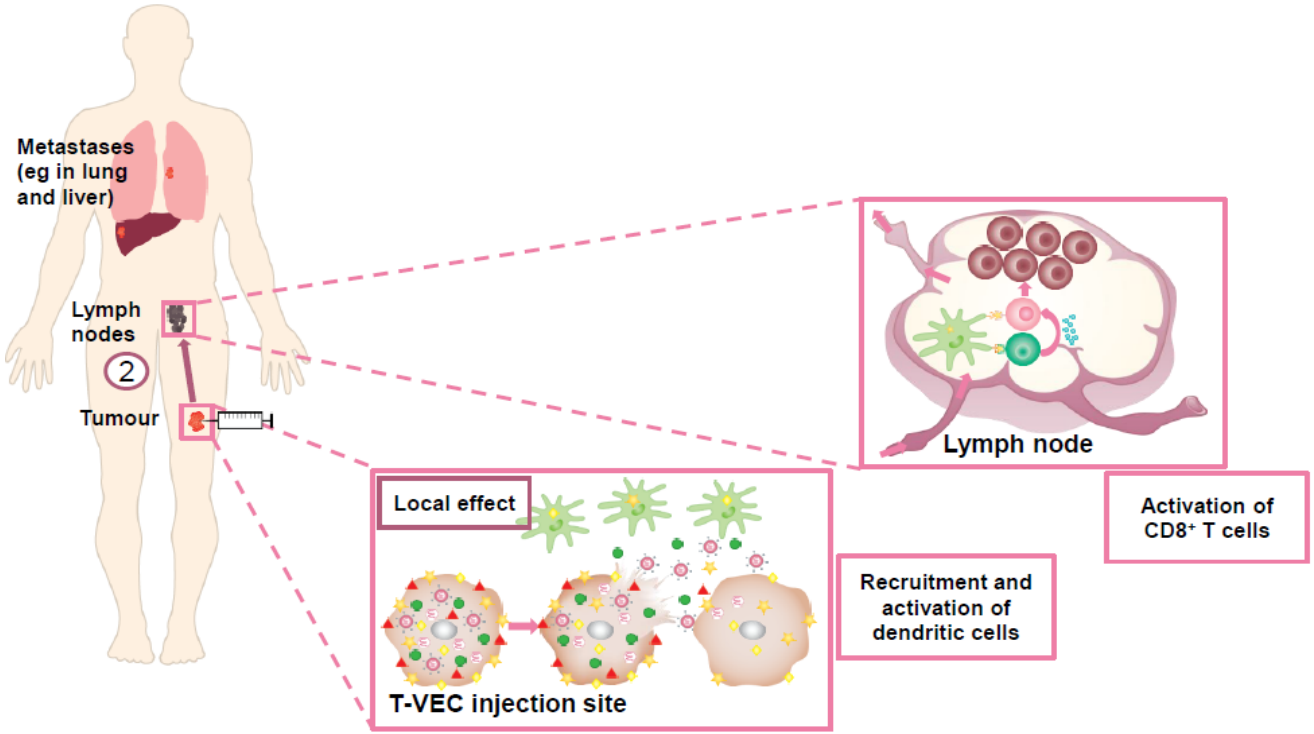
T-VEC: HSV-1-derived oncolytic immunotherapy

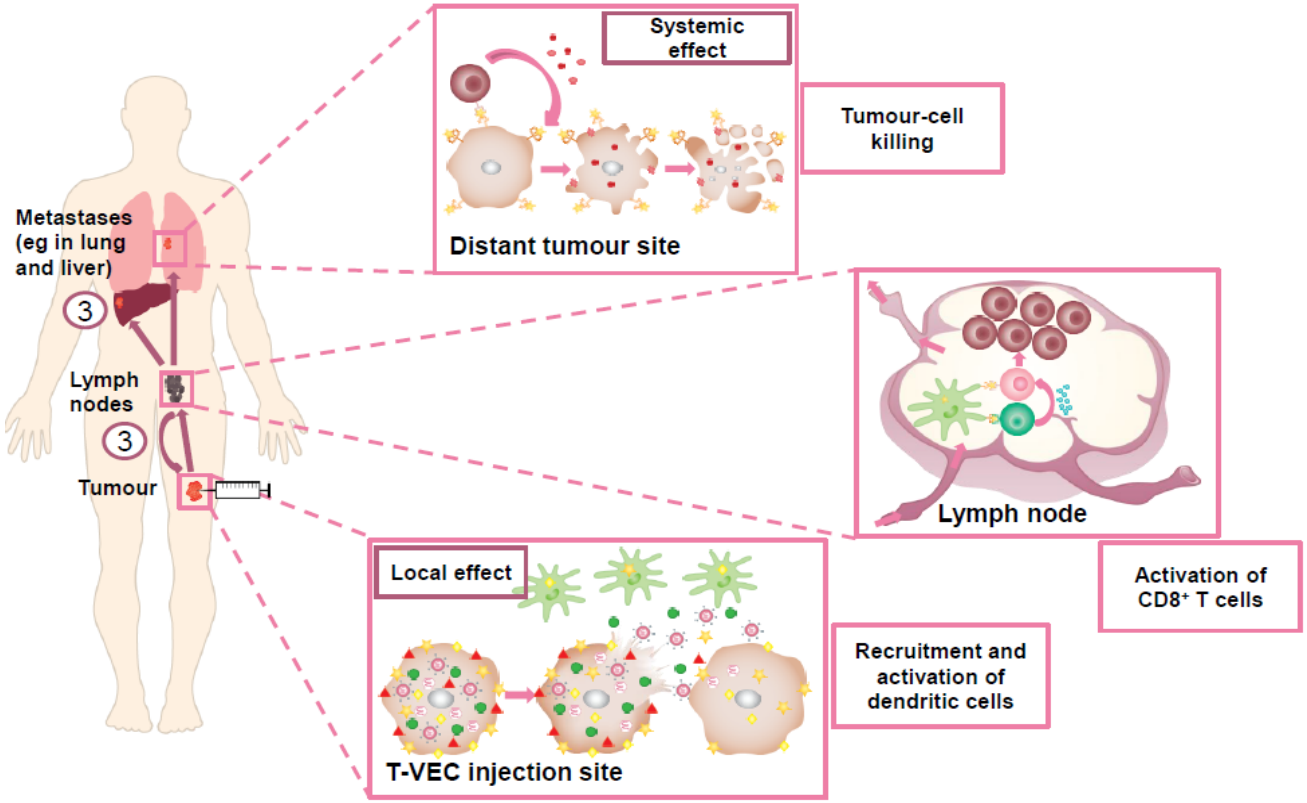
Modification	Rationale
HSV-1 strain, JS1	Improves tumour-cell lysis compared with other strains
Deletion of ICP34.5	Provides tumour-selective replication
Deletion of ICP47	Prevents ICP47 from blocking antigen presentation (restores antitumour immune response)
Early/increased US11 (as a result of ICP47 deletion)	Increases replication of ICP34.5-deleted HSV-1 in tumour cells
Insertion of human GM-CSF (2 copies replacing ICP34.5)	Enhances antitumour immune response



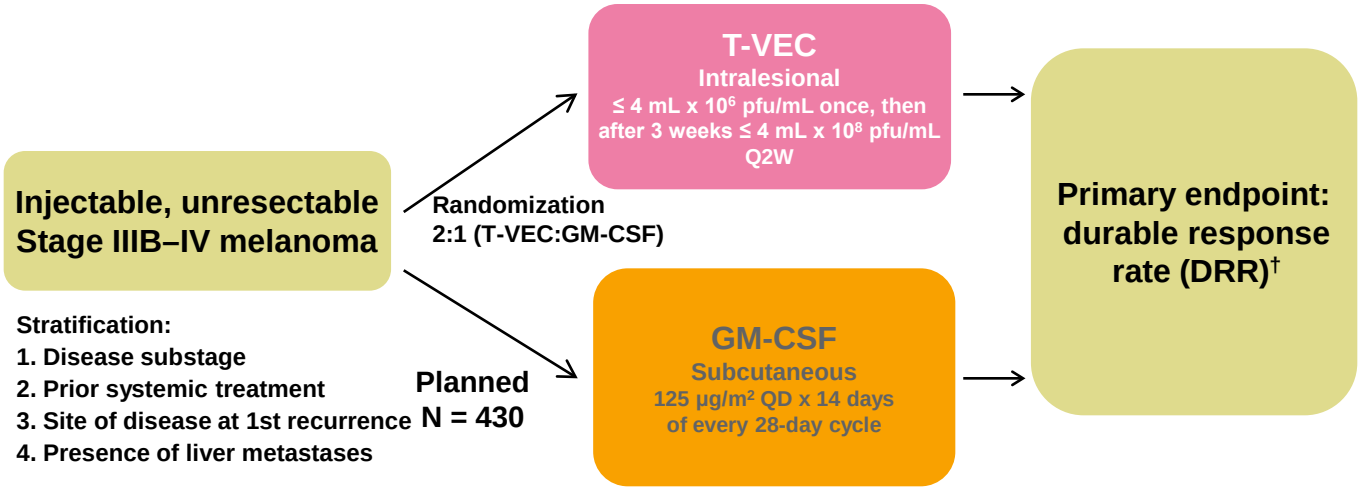
How does T-Vec work?




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

OPTiM Phase III Trial (005/05)



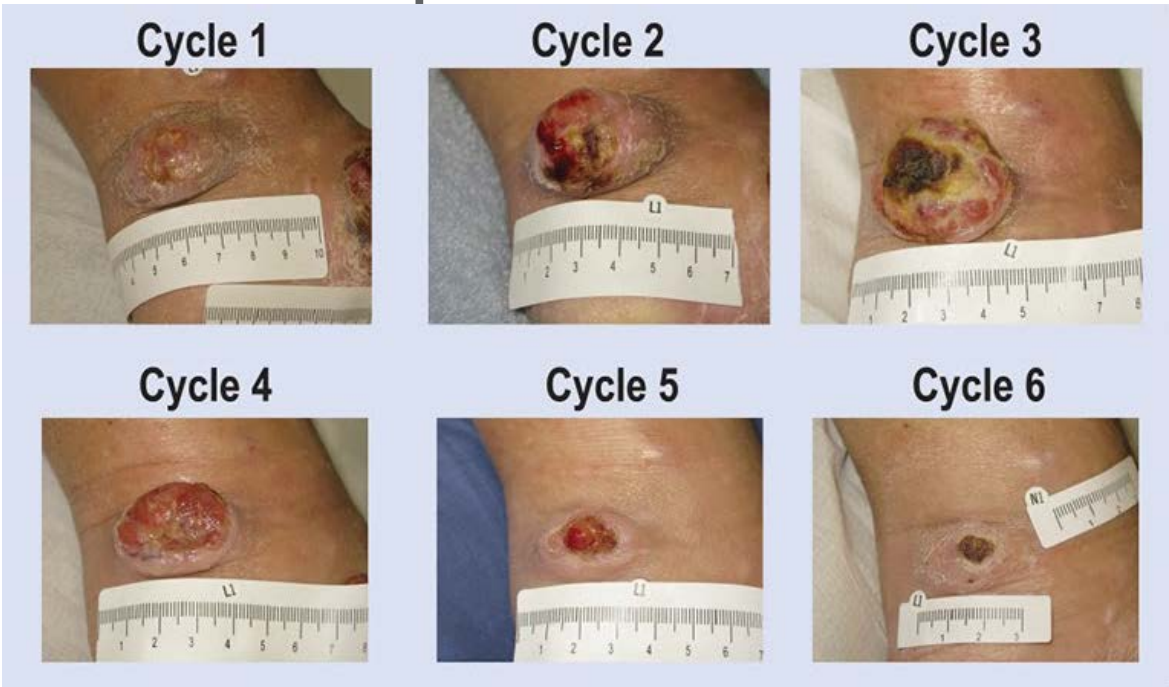
Primary endpoint: DRR: rate of CR or PR that began at any point within 12 months of initiation of therapy and lasted continuously for 6 months or longer*

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. JCO 2015

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

Endpoints

Primary: DRR

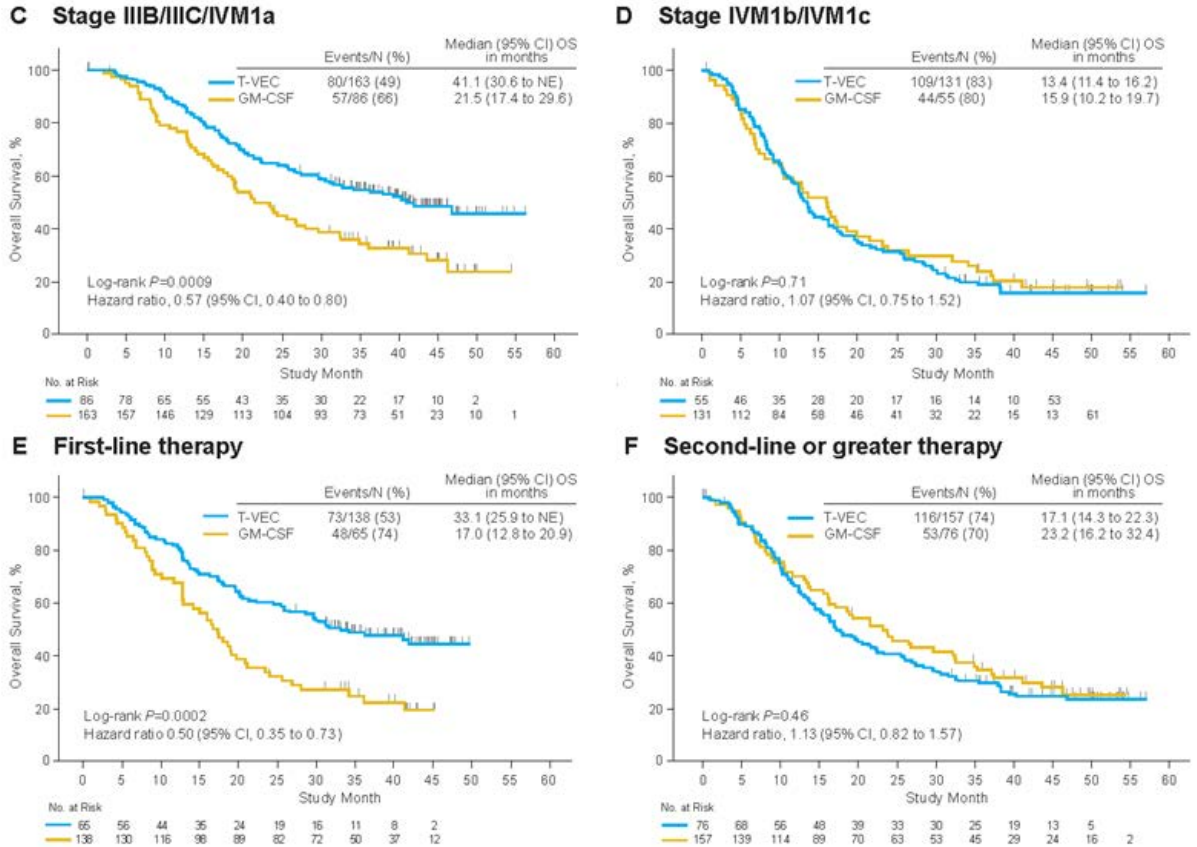
Intention-to-treat (ITT) set	GM-CSF, % (n = 141)	T-VEC, % (n = 295)	Unadjusted odds ratio
DRR	2.1	16.3	8.9 (95% CI: 2.7, 29.2); P < 0.0001

Secondary: ORR

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

Andtbacka et al. JCO 2015

OS by Stage and Line of Therapy



Harrington et al. OncoTarget Ther 2016

FDA News Release

FDA approves first-of-its-kind product for the treatment of melanoma

For Immediate Release October 27, 2015

Release The U.S. Food and Drug Administration today approved Imlygic (talimogene laherparepvec), the first FDA-approved oncolytic virus therapy, for the treatment of melanoma lesions in the skin and lymph nodes.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Talimogene Laherparepvec in Combination With Ipilimumab in Previously Untreated, Unresectable Stage IIIB-IV Melanoma

Igor Puzanov, Mohammed M. Milhem, David Minor, Omid Hamid, Ai Li, Lisa Chen, Michael Chastain, Kevin S. Gorski, Abraham Anderson, Jeffrey Chou, Howard L. Kaufman, and Robert H.I. Andtbacka

- 79% stage IV disease
- 21% stage IVM1a
- No DLT
- Grade 3/4 adverse events in 26.3%
- 18-month PFS = 50%
- 18-month OS = 67%

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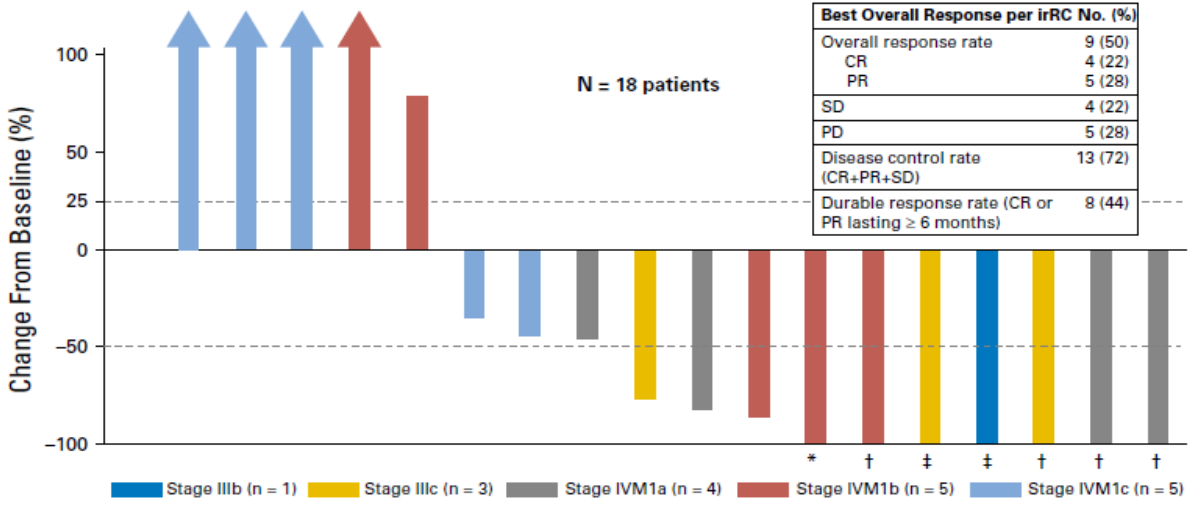

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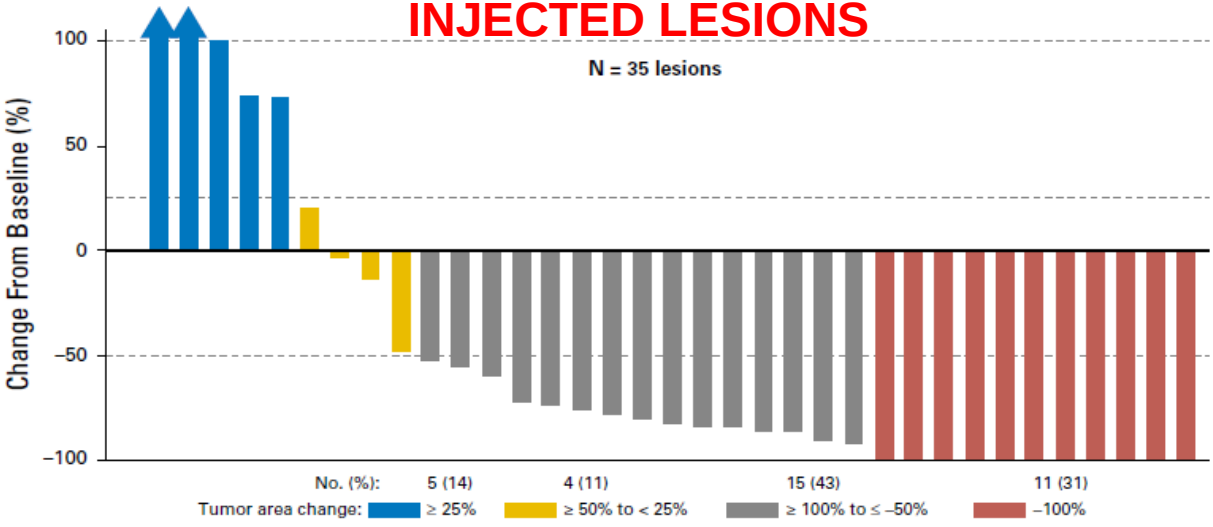
INJECTED LESIONS

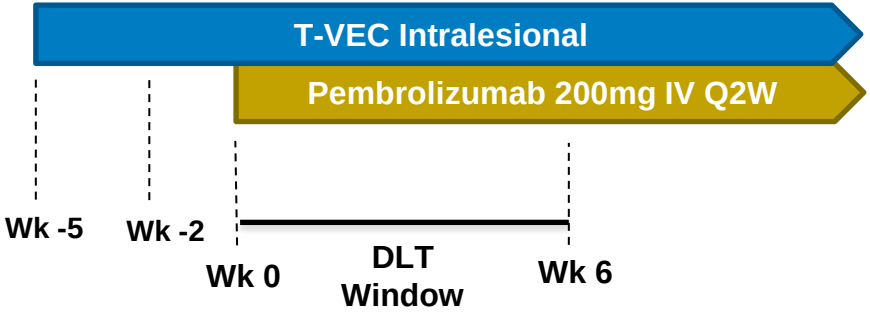


MASTERKEY-265 Phase 1b Study Schema

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

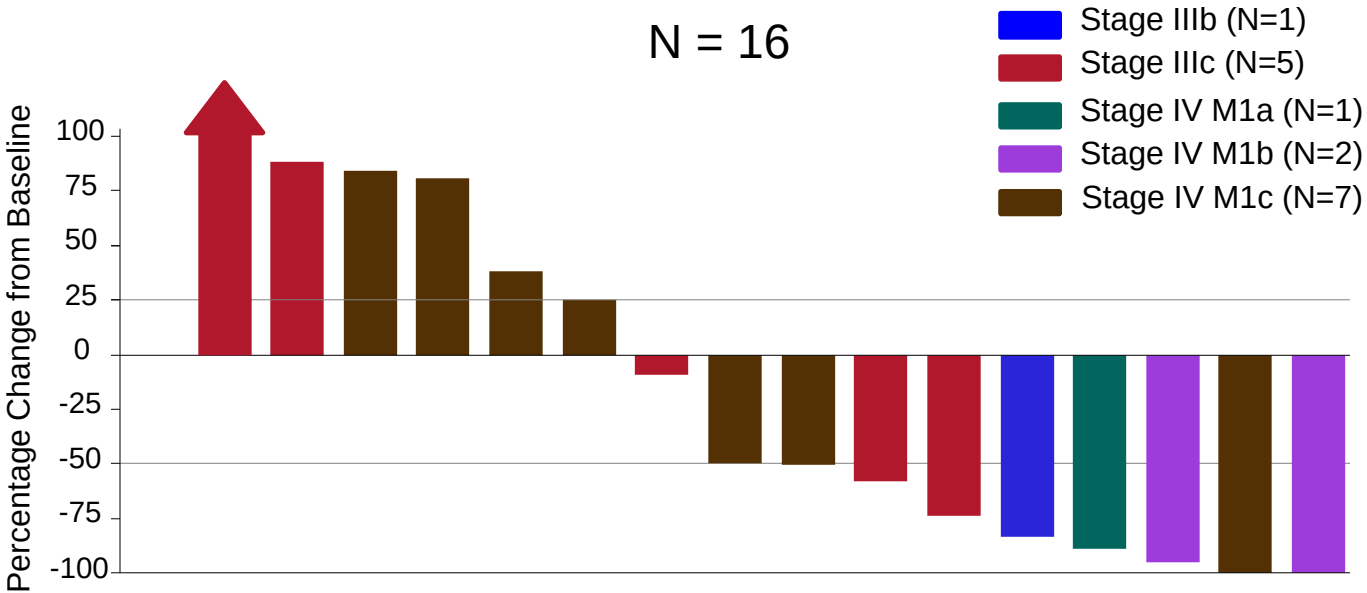


SAFETY FOLLOW-UP

30 (+7) days after end of treatment

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

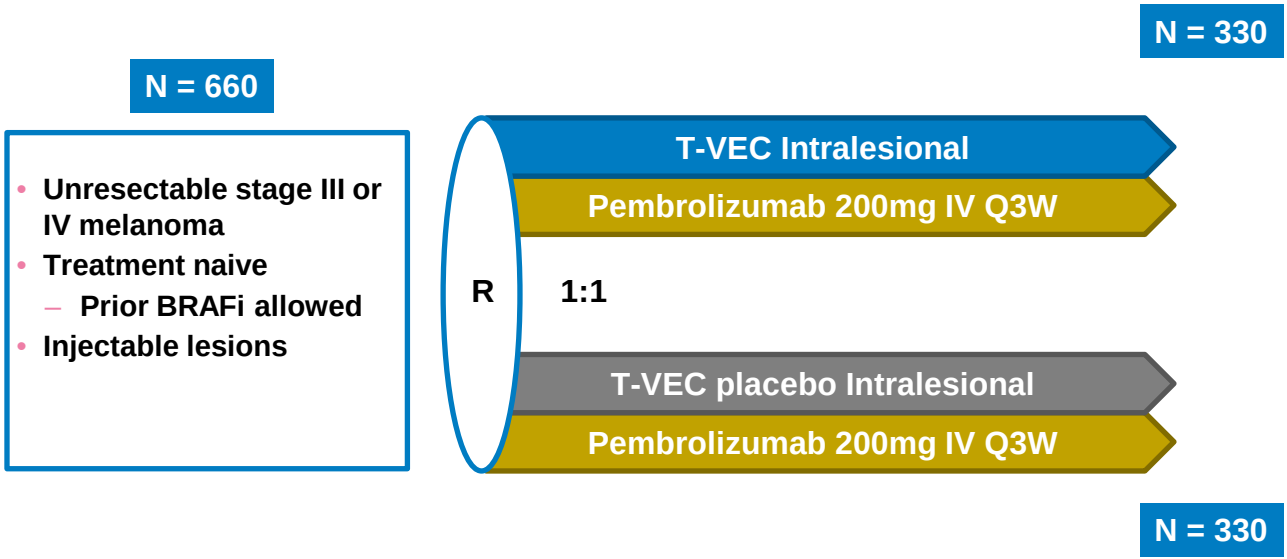
Best Change in Tumor Burden



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 et SMR 2015

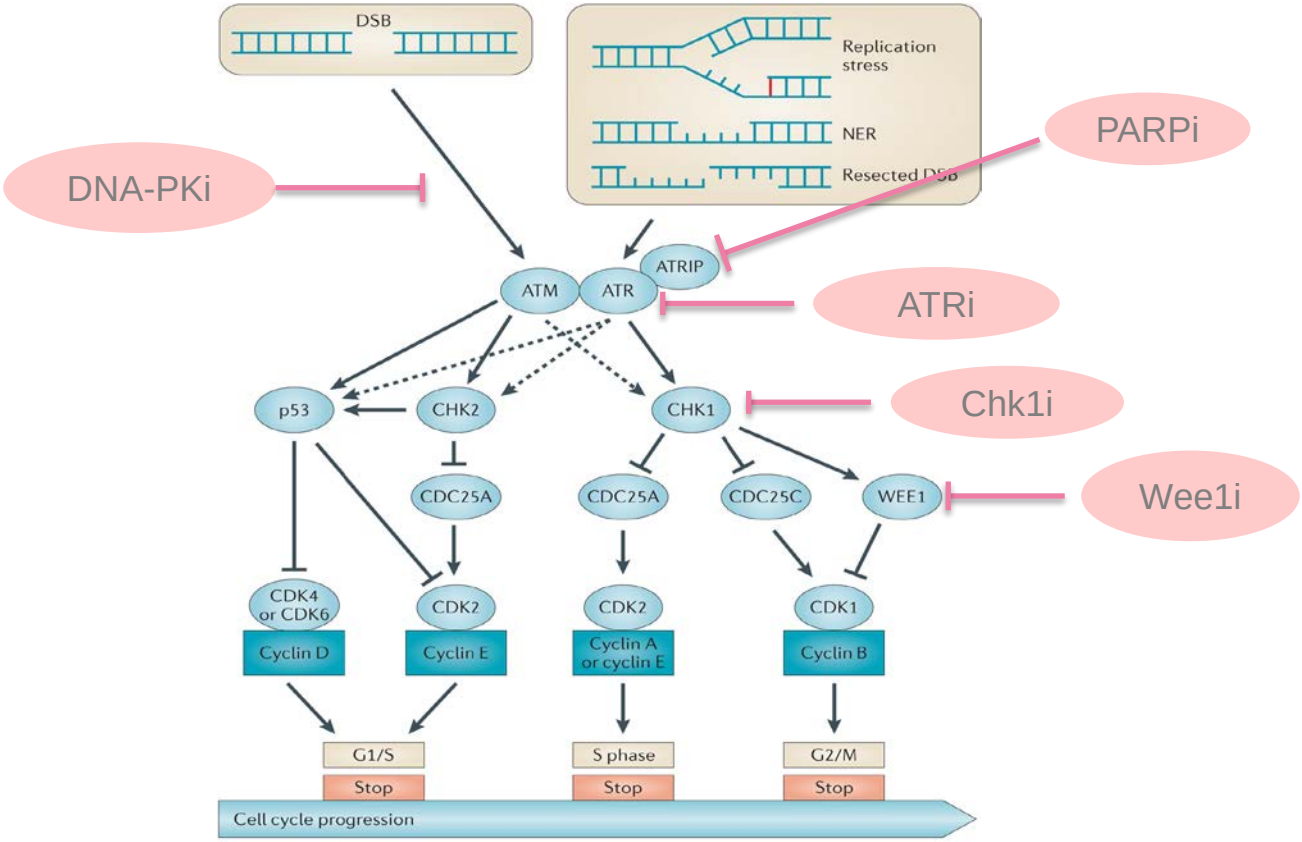
MASTERKEY-265 Phase 3 Study Design



Primary Endpoints: PFS and OS

IDENTICAL CLINICAL DESIGN IN RELAPSED/METASTATIC HEAD AND NECK CANCER (MASTERKEY 232)

3. DNA Damage Response Inhibition



Curtin NJ, *et al. Nat Rev Cancer* 2012;12:801–17.

Conclusions

- IO drugs are transforming clinical practice
- Single agent activities are relatively modest in many tumour histologies
- Combination therapies, with acceptable toxicity profiles, need to be developed
- Potential combinatorial gains may be accrued with IO-IO combination, oncolytic immunotherapy and DDRi
- There are still many trials to be designed, conducted and completed

THANK YOU