Oncolytic Virus Therapy in Cancer Immunotherapy

Robert H. I. Andtbacka

M.D., C.M, FACS, FRCSC

Associate Professor of Surgery

Huntsman Cancer Institute

University of Utah

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Disclosures

- Travel support from:
  - Amgen
  - Viralytics
- Advisory Board:
  - Amgen: T-VEC
- Investigator:
  - Amgen: OPTiM and other T-VEC trials
  - Viralytics: CALM trial

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Objectives

- Discuss effect of viruses on cancer genesis and treatment
- Discuss how oncolytic viruses are used in metastatic melanoma
- Discuss future roles of oncolytic virus therapy in cancer immunotherapy

Viruses causing cancer

Major viral infectious agents that trigger cancer		
Mechanism	**Virus**	**Cancer**
Infect and transform lymphoid cells	Epstein–Barr virus (EBV)	Burkitt's lymphoma
	Human Herpesvirus 8 (HHV8)	Kaposis sarcoma
	Human T-lymphotropic virus 1 (HTLV-1)	T-cell leukemia
Transformation	Human papilloma virus (HPV)	Cervical cancer
		HPV+ ano-genital cancers
		HPV+ head-neck cancers
Inflammation / partial integration	Hepatitis B virus (HBV)	Hepatocellular carcinoma
Chronic inflammation / ongogenic proteins	Hepatitis C virus (HCV)	Hepatocellular carcinoma
Chronic stimulation of lymphocytes by pathogen antigens and/or autoantigens	Hepatitis C virus (HCV)	Spleen lymphoma
Immunosuppression	HIV	EBV+ CNS lymphomas
		HHV8+ sarcoma (Kaposi)
		HPV+ ano-genital cancers

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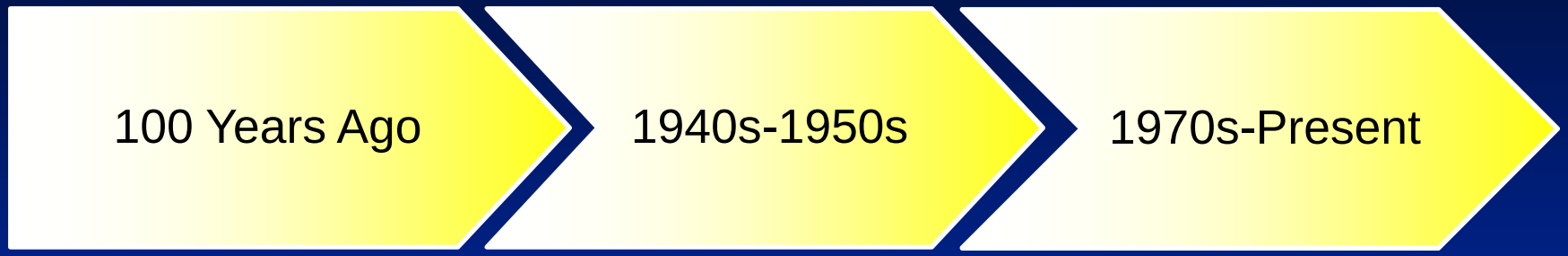
Rook et al. *Immunol Rev* 2011, 240: 141-159

Viruses can also elicit an antitumor response



- Women with cervical cancer experience short-term remission of cancer after administration of rabies vaccine[1]

- Patients with cancers experience clinical remission after viral infection[2,3]
- Inoculation of patients with cancer with crude viral preparations[3]

- Purified mumps virus induced tumor regression or decreased tumor size in patients with cancer[4]

1. Nuwer R. *New York Times*. March 19, 2012.
2. Bierman HR, et al. *Cancer*. 1953;6:591-605.
3. Kelly E, et al. *Mol Ther*. 2007;15:651-659
4. Asada T. *Cancer*. 1974;34:1907-1928

Lessons learned from viral infections in cancer

- Although the potential for use of wild-type viruses/vaccines was observed historically, limitations were recognized, including:
  - Lack of tumor selectivity[1]
  - Limited potency in tumor cells[1]
  - Weakened antitumor immune response[1]
  - Limited accessibility to the tumor[2-4]
  - May cause human disease[5]
- These limit the potential for wild-type viruses/vaccines to be viable treatment options for cancer

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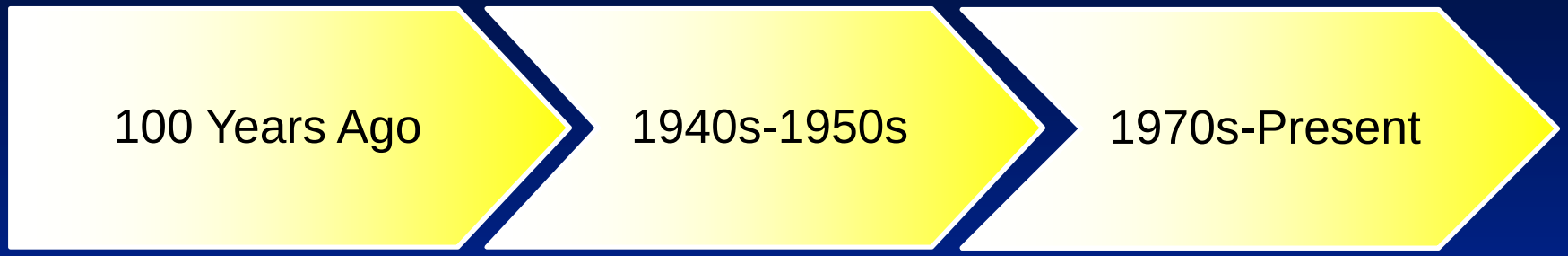
1. Everts B. *Cancer Gene Ther*. 2005;12:141-161.
2. Pol JG, et al. *Virus Adapt Treat*. 2012;4:1-21.
3. Kim J-H, et al. *J Natl Cancer Inst*. 2006;98:1482-1493
4. Guedan S, et al. *Mol Ther*. 2010;18:1275-1283.
5. Hoster HA, et al. *Cancer Res*. 1949;9:473-480.

Viruses can also elicit an antitumor response



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- **Recombinant DNA technology[5-7]**

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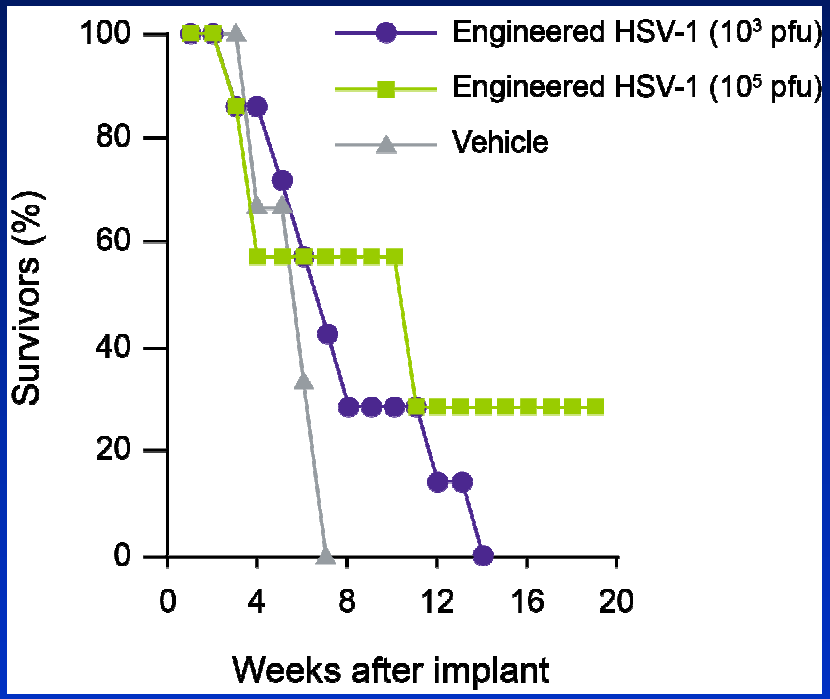
2. Bierman HR, et al. *Cancer*. 1953;6:591-605.
3. Kelly E, et al. *Mol Ther*. 2007;15:651-659
4. Asada T. *Cancer*. 1974;34:1907-1928

5. Pray L. *Nat Educ.* 2008;1.
6. Cohen SN, et al. *Proc Natl Acad Sci U S A*. 1972;69:2110-2114.
7. Martuza RL, et al. *Science.* 1991;252:854-856.

Recombinant DNA technology allows engineering of more effective viruses

- Genetically engineered mutant herpes simplex virus killed glioma cells in vitro and inhibited the growth of implanted gliomas in mice[1]

- Findings laid the groundwork for engineering of viruses to attempt to enhance **tumor selectivity** and the **systemic immune response**



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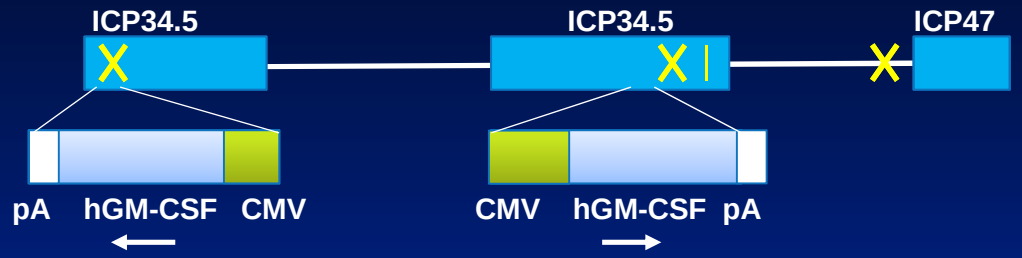
1. Martuza RL, et al. *Science*. 1991;252:854-856.

Talimogene laherparepvec (T-VEC) an HSV-1 derived oncolytic immunotherapy

T-VEC key genetic modifications:

JS1/ICP34.5-/ICP47-/hGM-CSF



Genetic modification	Result
Use of new HSV-1 strain (JS1)	Improved tumor cell killing ability compared with other strains
Deletion of ICP34.5	Prevents HSV infection of non-tumor cells, providing tumor-selective replication
Deletion of ICP47	Increased antigen presentation
Earlier insertion of US11	Increases replication and oncolysis of tumor cells
Insertion of human GM-CSF gene	Dendritic cell activation and enhancement of T-cell immunity

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Liu BL, et al. *Gene Ther.* 2003;10:292-303.

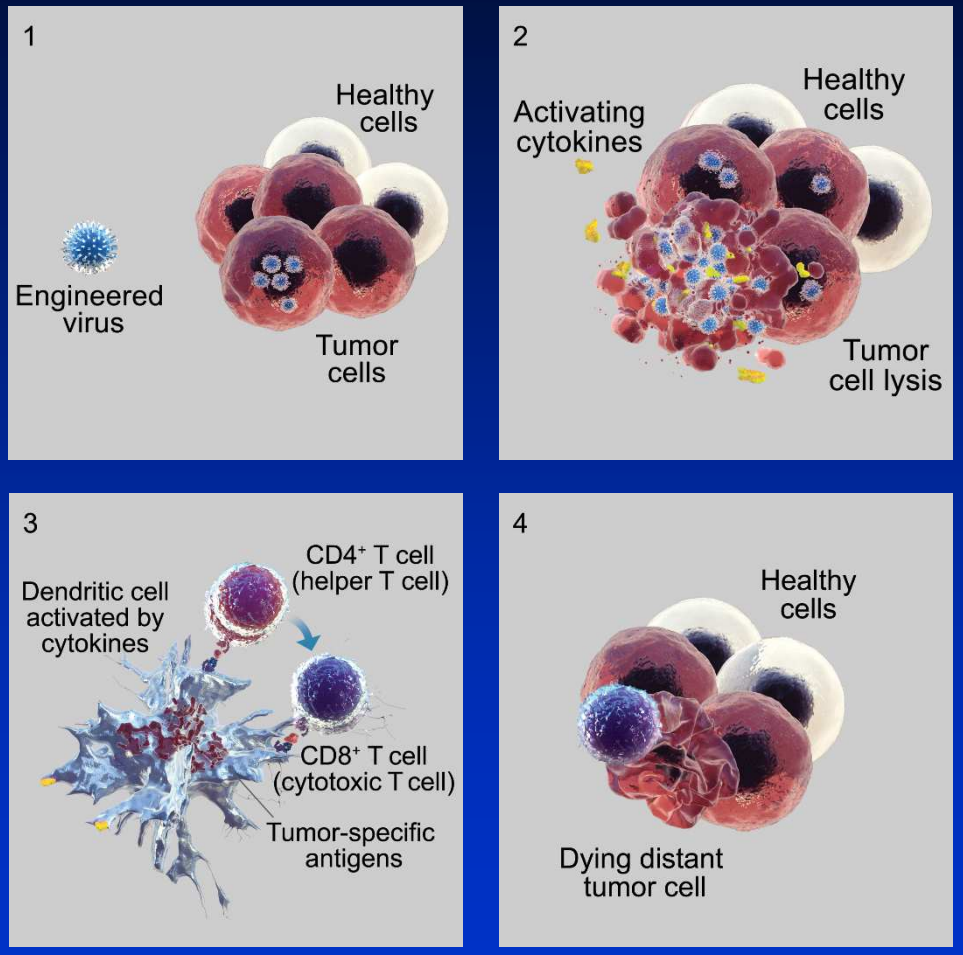
Oncolytic immunotherapy is being designed to induce local and systemic effects

- Combines the local effect of an oncolytic virus with the systemic effect of an antitumor immune response[1,2]
- Uses an engineered virus that selectively replicates in tumor cells for an antitumor effect[1]
  - **Oncolytic:** direct cytotoxic activity[3]
  - **Immunotherapy:** indirect induction of a systemic antitumor immune response[3]

1. Li H, et al. In: Yotnda P, ed. *Immunotherapy of Cancer: Methods in Molecular Biology*. 2010:279-290.
2. Liu BL, et al. *Gene Ther.* 2003;10:292-303.
3. Varghese S, et al. *Cancer Gene Ther*. 2002;9:967-978.

Oncolytic immunotherapy proposed mechanism of action

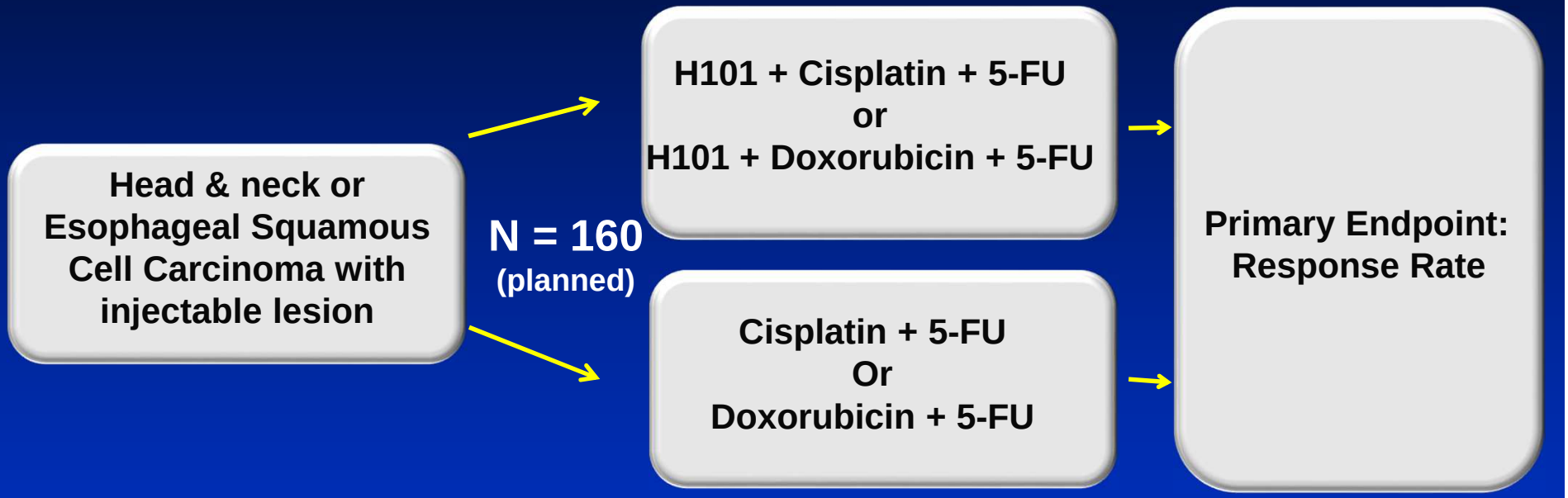
- Local effect
  1. Selective viral replication in target tumor cells[1,2]
  2. Tumor cells rupture for an oncolytic effect[1-3]
- Systemic effect
  3. Indirect systemic tumor-specific immune response[4,5]
  4. T-cell attack on distant tumor cells[6]
- Key players in oncolytic immunotherapy
  - Engineered virus
  - Tumor cells
  - Activating cytokines
  - Dendritic cells
  - Tumor-specific antigens
  - T cells



1. Hawkins LK, et al. *Lancet Oncol*. 2002;3:17-26.
2. Fukuhara H, et al. *Curr Cancer Drug Targets*. 2007;7:149-155.
3. Pol JG, et al. *Virus Adapt Treat*. 2012;4:1-21.
4. Melcher A, et al. *Mol Ther*. 2011;10:1008-1016.
5. Dranoff G. *Oncogene*. 2003;22:3188-3192.
6. Liu BL, et al. *Gene Ther*. 2003;10:292-303.

H101* Adenovirus Phase III trial

First international approval of oncoloytic virus in China



Treatment	Response rate	P-value
H101 + Cis + 5-FU	79% (41/52)	< 0.001
Cis + 5-FU	40% (21/53)	
H101 + Doxo + 5-FU	50% (7/14)	NS
Doxo + 5-FU	50% (2/4)	

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* Oncorine H101 is an E1B-55 kDa gene-deleted replication-selective adenovirus

Xia ZJ et al. *Ai Zheng* 2004;23:1666-70

Oncolytic viral treatment approaches are in development for multiple tumor types

Virus	Tumor(s)	Phase in development
Adenovirus	SCCHN	3
	Bladder	2/3
	CRC, hepatobiliary, pancreatic	2
	Glioma, prostate	1/2
	Ovarian	1
Coxsackie	Melanoma	1/2
	SCCHN	1
HSV	Melanoma	3
	Glioma, SCCHN	1/2
Measles	Glioma, mesothelioma, myeloma, ovarian, SCCHN	1
Retrovirus	Glioma	1/2
Vaccinia	HCC, CRC	2
	Melanoma	1/2
VSV	HCC	1

CRC, colorectal cancer; HCC, hepatocellular carcinoma; HSV, herpes simplex virus; SCCHN, squamous cell carcinoma of the head and neck; VSV, vesicular stomatitis virus.

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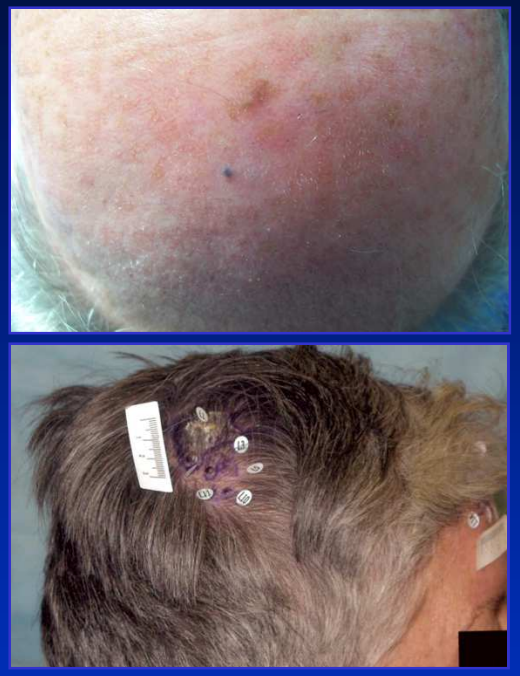
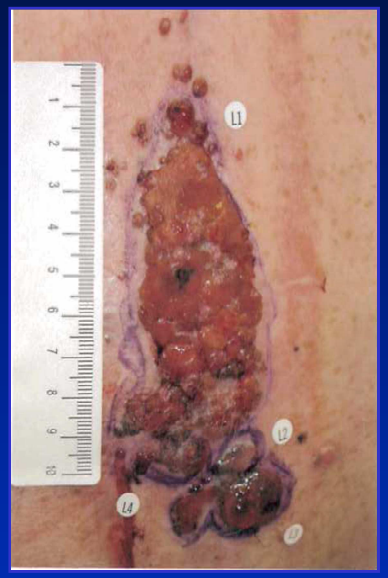
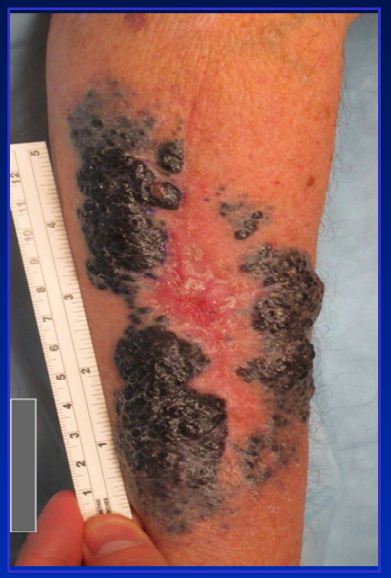
Russell SJ, et al. *Nat Biotechnol*. 2012;30:658-670.

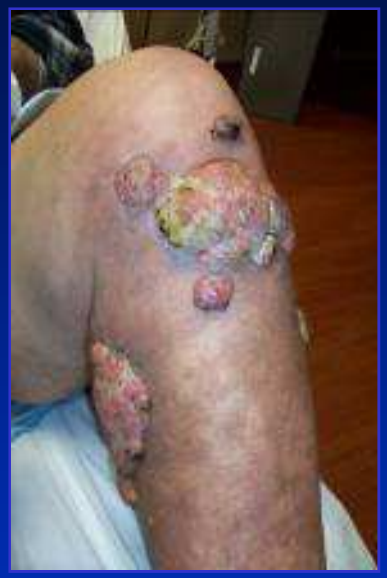
Melanoma intralymphatic metastasis

Spectrum of disease (AJCC IIIB/IIIC)









- 3 – 10% of primary melanoma develop local / in-transit recurrences
  - High risk groups: thick, ulcerated, positive SLN, lower extremity
- Source of significant morbidity
- Greater than 50% risk of distant disease and death

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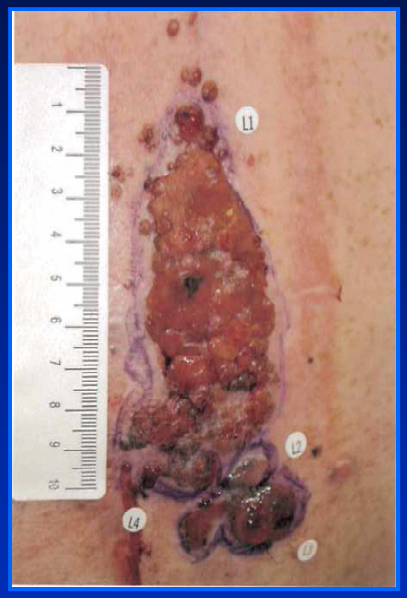
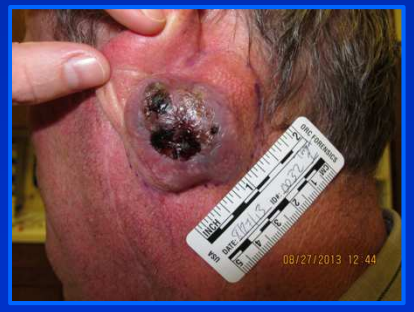
AJCC, American Joint Committee on Cancer; SLN, sentinel lymph node

Ross MI. *Int J Hyperthermia*. 2008;24(3):205-217. SEER Cancer Statistics Review, 1975-2009, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed 5/30/13.

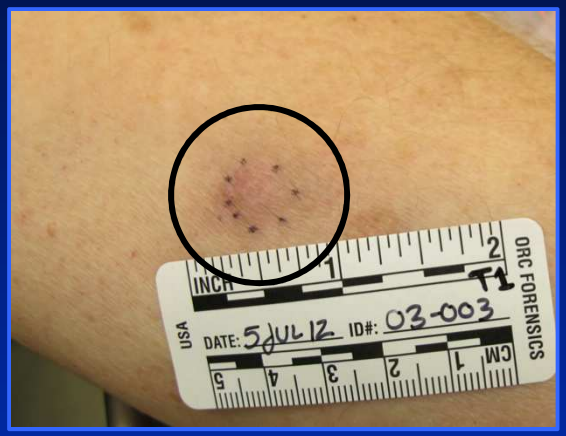
Lesions suitable for intratumoral injections

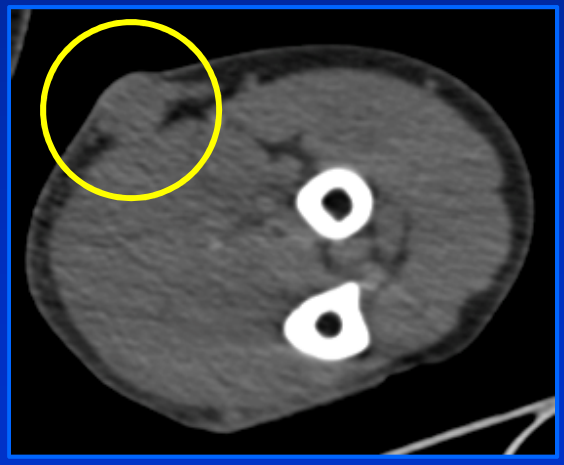
Dermal



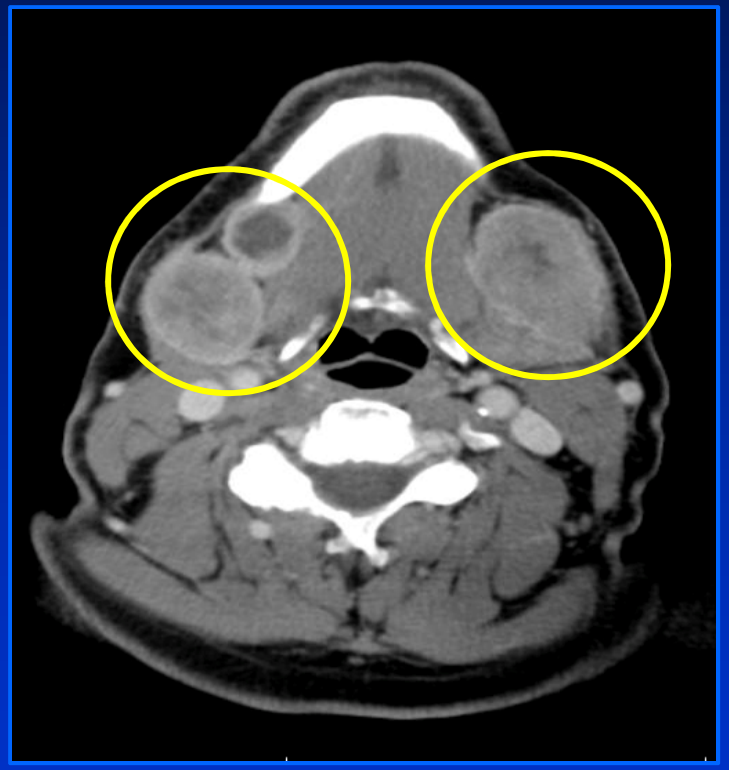


Subcutaneous





Superficial lymph nodes



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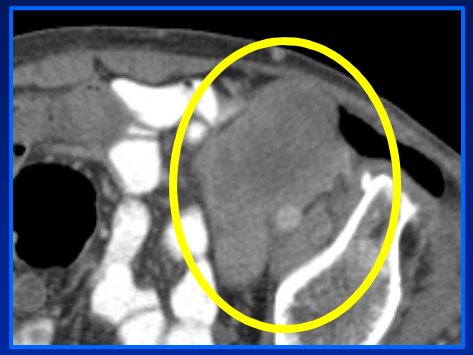
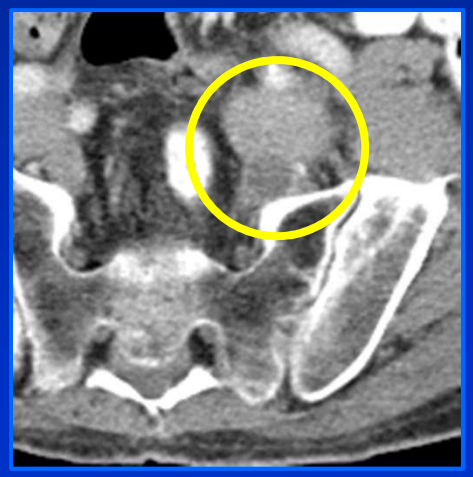
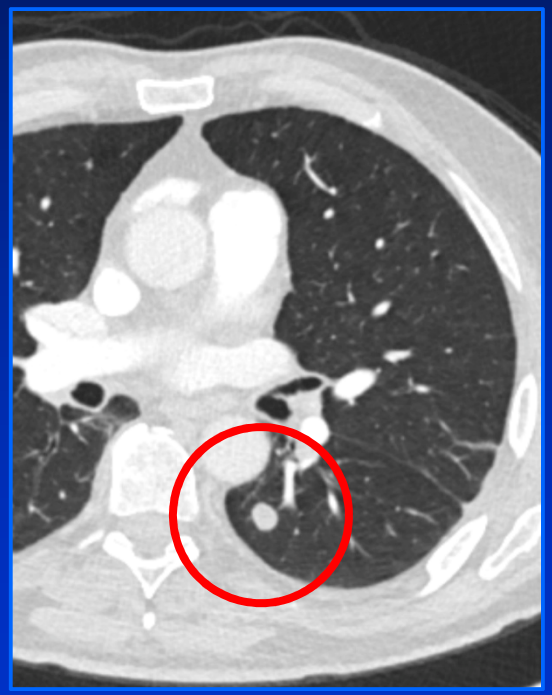
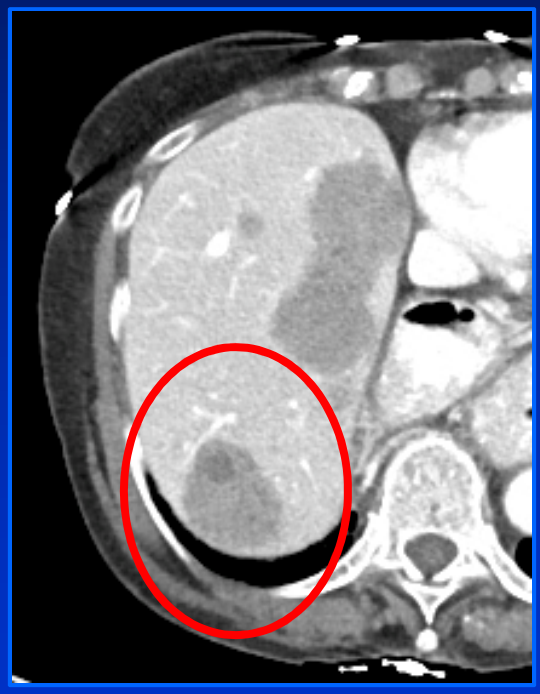
Lesions **less** suitable / available for intratumoral injections

Deep lymph nodes / visceral lesions?









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Injectable intralesional therapy

Goals

- Locally ablative therapy for local disease control
  - High local concentration
  - Palliation / local symptom control
- Induction of systemic host immune anti-tumor activity
  - Response in un-injected regional and distant metastases
  - Limited systemic toxicity
- Systemic neoadjuvant effect
  - Preventing stage IIIB / IIIC patients from developing stage IV melanoma
- Durable response

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Intralesional agents in development

- Antibodies
- Cytokines
- Glycolipids
- Microspheres
- Plasmids
- Small molecules
- Radiosensitizers
- Vaccines
- Viruses
- Xeno-antigen Cell Lines
- Combinations therapies

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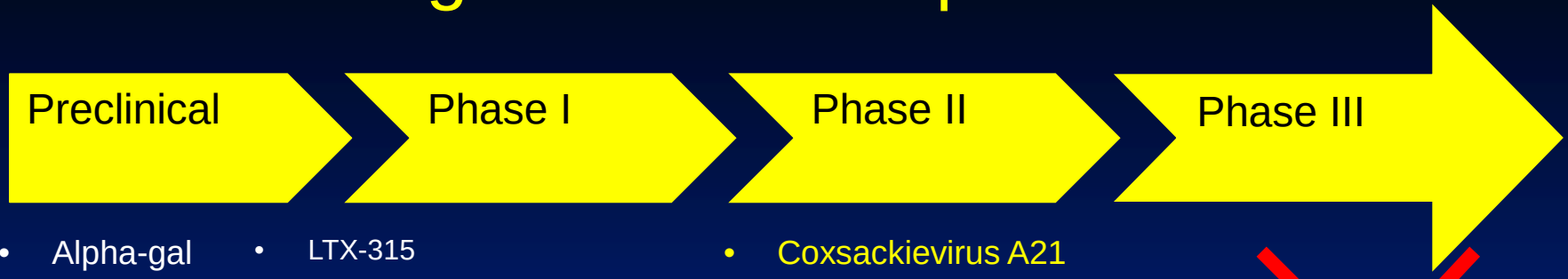
Intralesional agents in development in melanoma



Preclinical

- Alpha-gal glycolipids

Phase I

- LTX-315
- HF-10 (HSV-1)
- OrienX010 (hGM-CSF HSV-1)
- Retroviral IFN-γ
- Canarypox virus expressing B7.1 and IL-12
- Adenovirus expressing IFN-γ
- Recombinant vaccinia virus expressing B7.1
- Ganglioside D2 mAb
- Plasmid encoding IL-12
- Alpha-immunoconjugate of vector 9.2.27 with 213Bi radioactive Ab
- Polylactic acid microspheres with IL-12 +/- IL-18

Phase II

- Coxsackievirus A21
- Adenovirus expressing IL-2
- GM-CSF
- BCG
- IL-2
- Plasmid IL-12 Electroporation
- PV-10 *(Rose Bengal)*
- KORTUC II
- Monkey fibroblast Vero cells producing human IL-2
- Intralesional GM-CSF + subcutaneous IL-2
- Intralesional IL-2 and topical imiquimod
- IFN-alpha2b

Phase III

- ~~**Vetimogene aliplasmid**~~
- **Talimogene laherparepvec**

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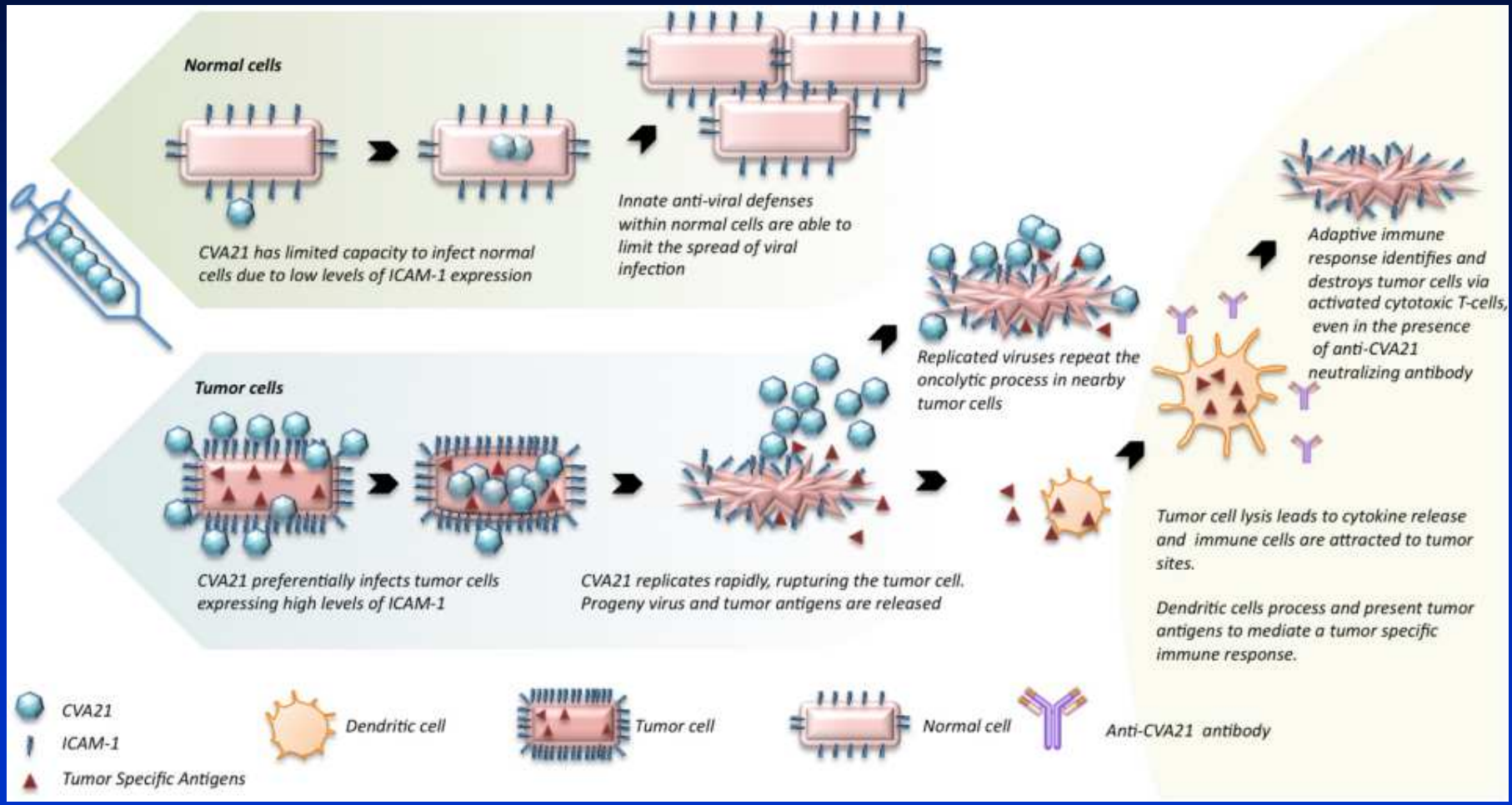
Coxsackievirus A21(CVA21)

Oncolytic immunotherapeutic modes of action



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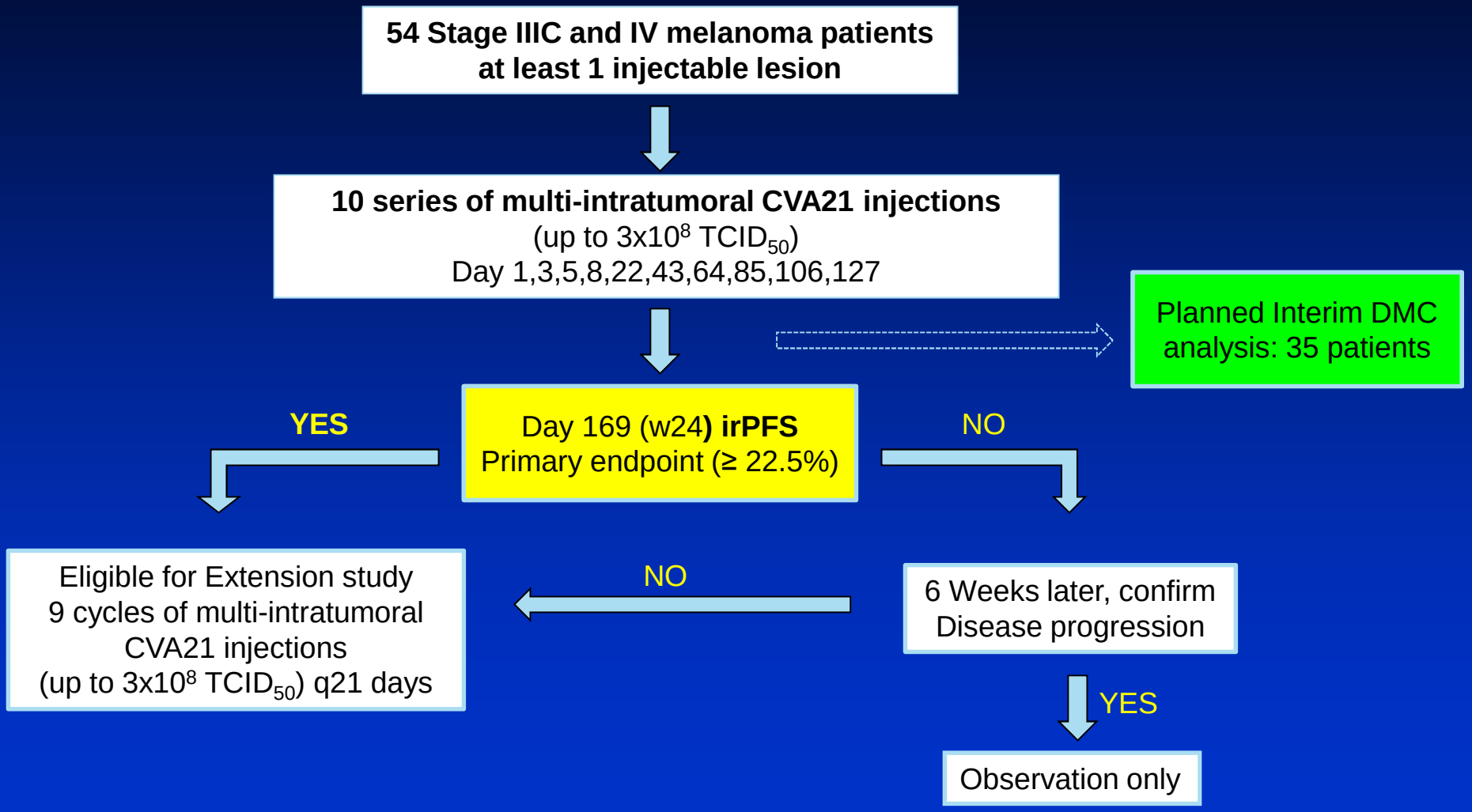
Andtbacka RHI, et al. World Melanoma Congress 2013

CALM Phase II study Design

CAVATAK in ***L***ate stage ***M***elanoma



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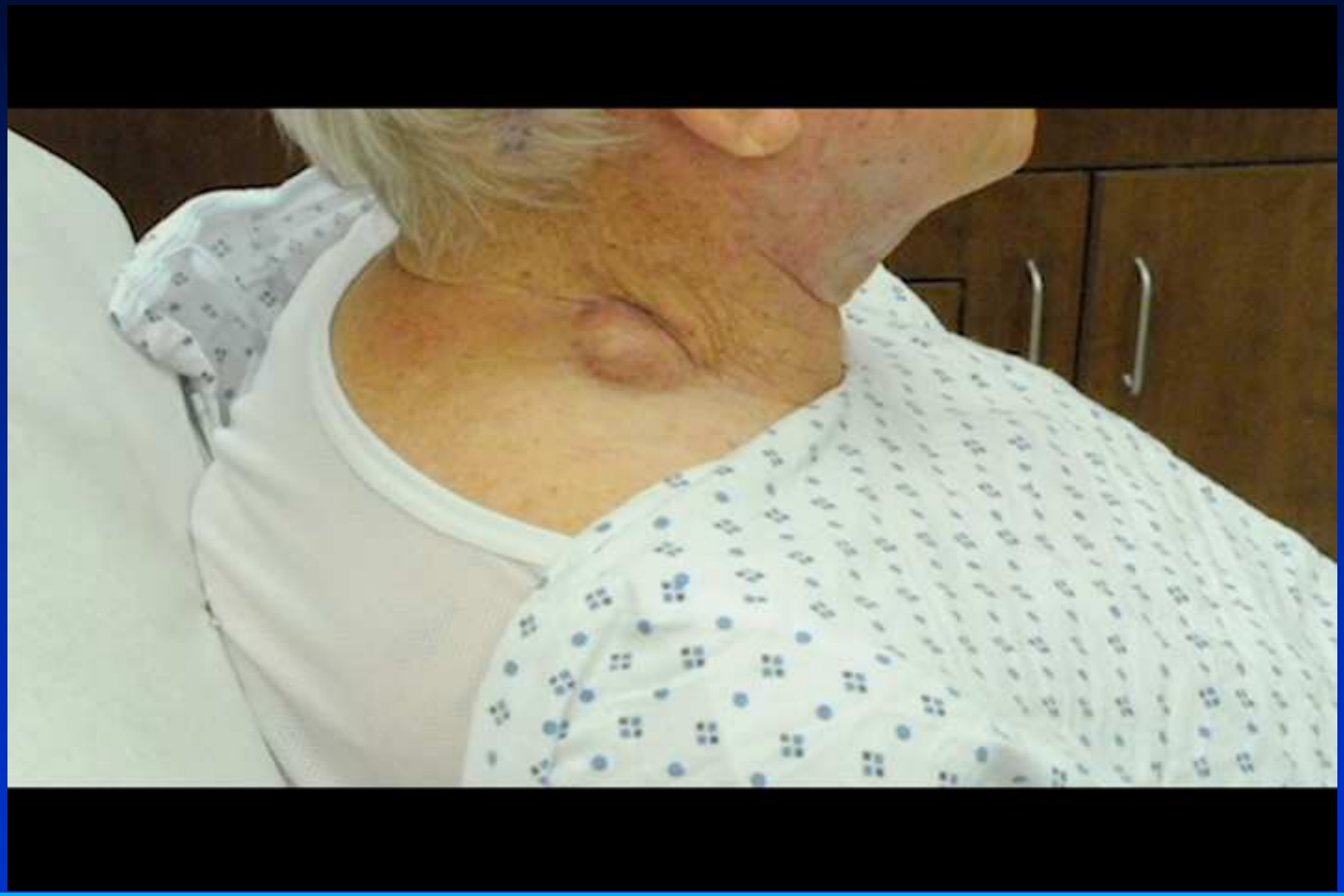
Injection of oncolytic immunotherapy virus



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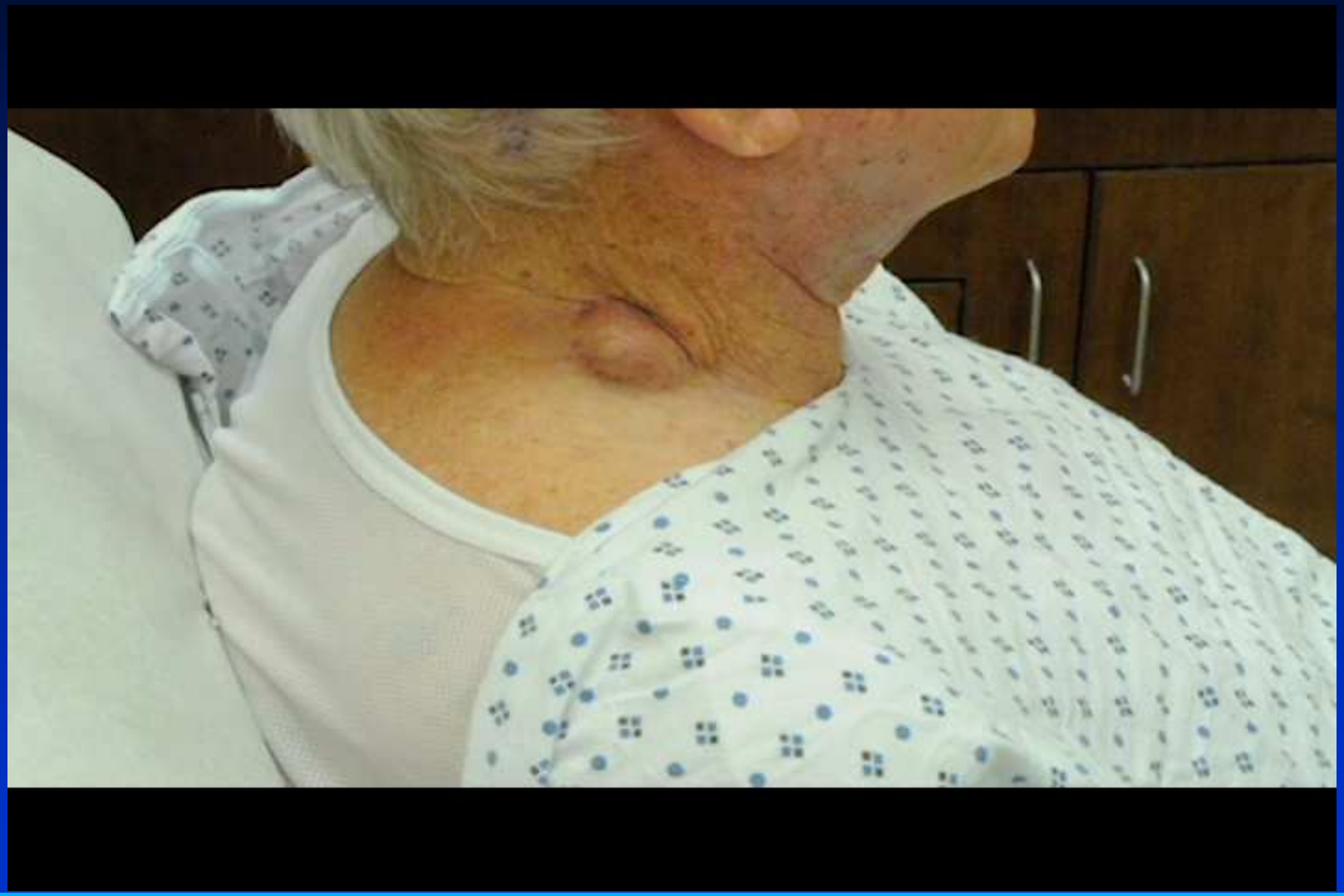

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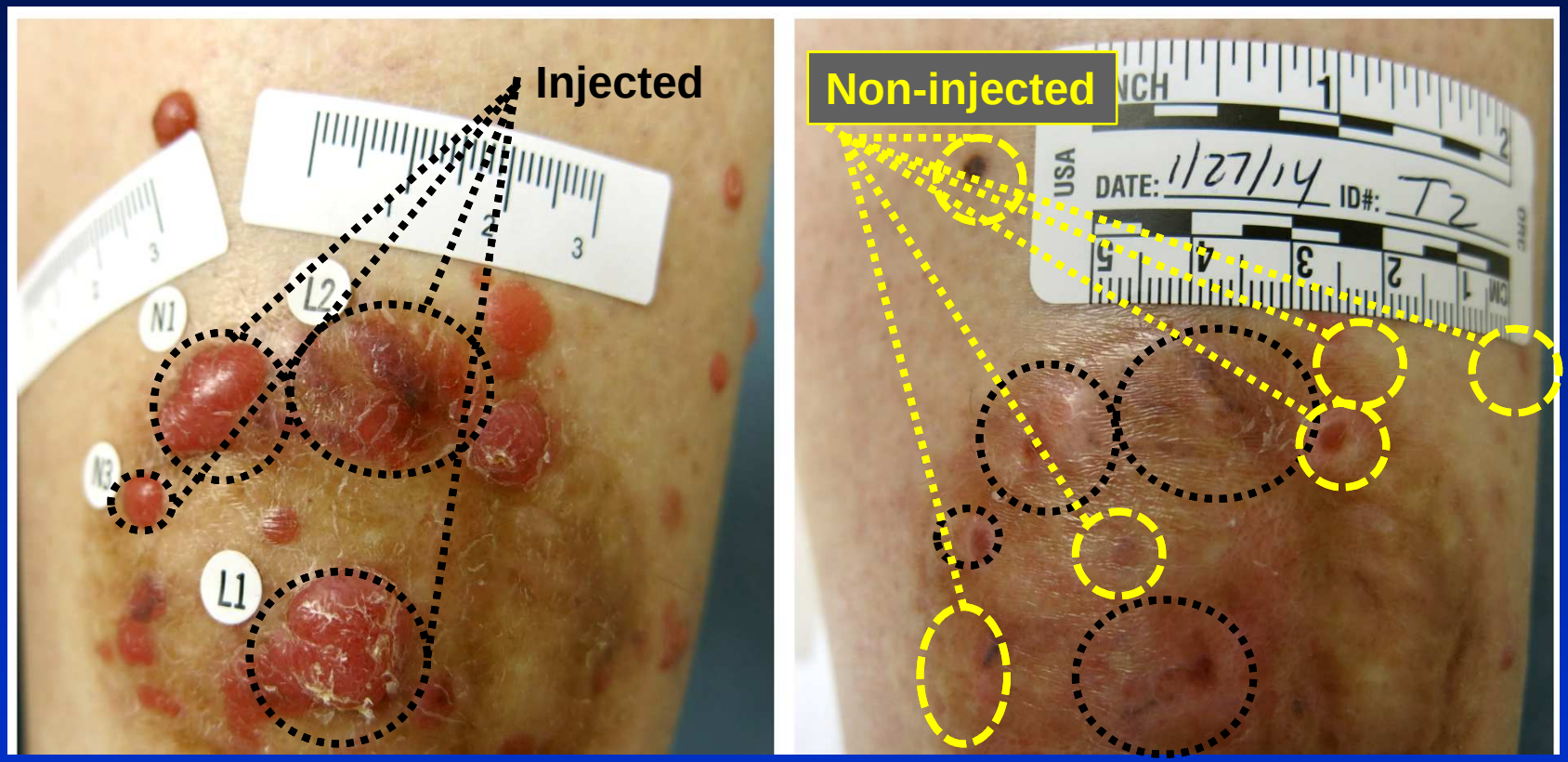
CALM Phase II trial

Local injected and non-injected lesion responses

Baseline

Day 85



Male with metastatic melanoma to the leg. Injection in leg lesions .

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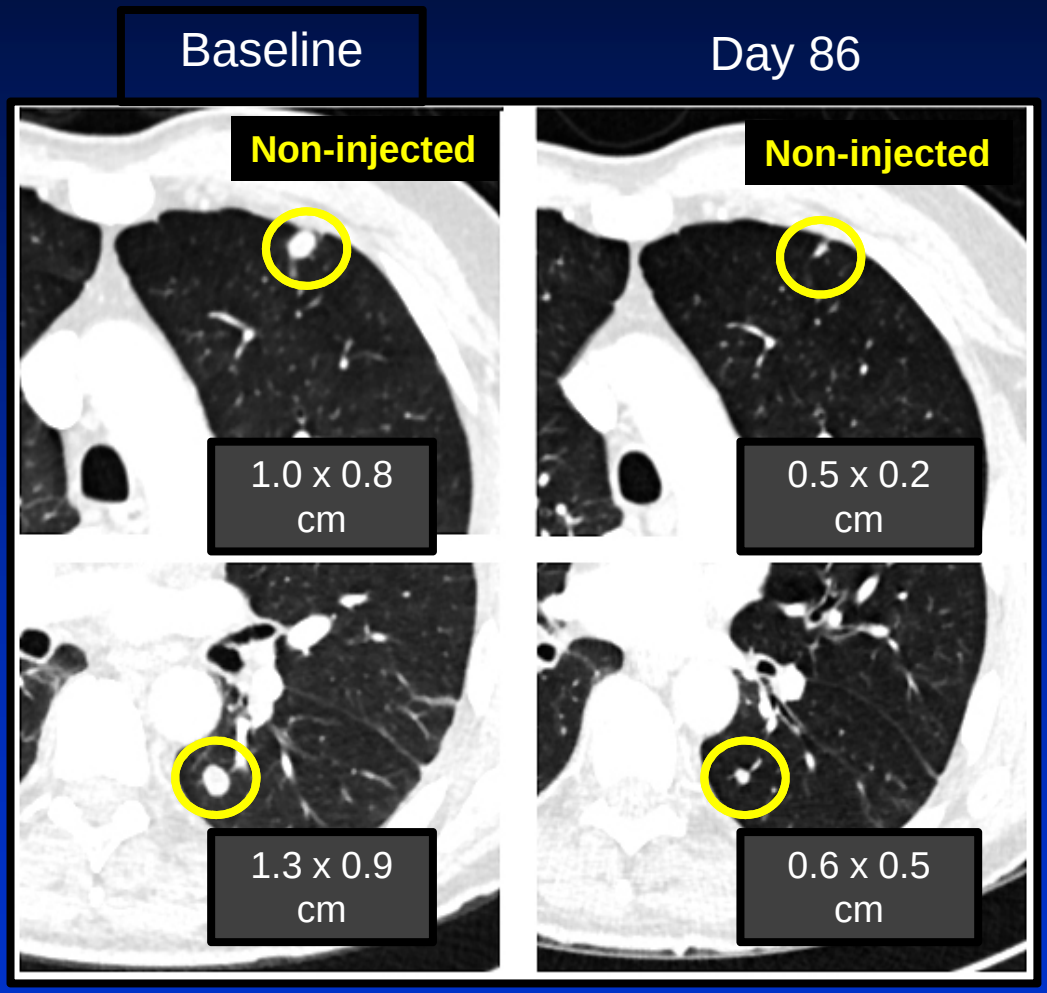
Andtbacka RHI, et al. AACR 2014

CALM Phase II trial

Non-injected distant visceral lesion response

Male with metastatic melanoma to left neck and lungs. Injection in left neck.



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CALM Phase II trial

Current analysis: Response data (investigator assessed)

Primary endpoint (≥ 10 pts with irPFS 6 months from 54 evaluable pts)

irPFS 6 months[+] (CR+PR+SD)	8 / 23 pts (34.8%)
irPFS 3 months[++] (CR+PR+SD)	18 / 30 pts (60.0%)

Secondary endpoint

Overall response rate[*] (CR+PR, irRECIST 1.1)	26.7 % (8 / 30 pts; 2 CR and 6 PR)

Interim futility clause of ≥ 3 CR or PR in first 35 pts: (modified RECIST 1.1)	Achieved

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\+ analysis excludes patients satisfying protocol criteria but not on study long enough for 6 months evaluation

++ analysis excludes patients satisfying protocol criteria but not on study long enough for 3 months (~12 weeks) evaluation

* ongoing overall response continually assessed at ≥ 12 weeks up to 48 weeks.

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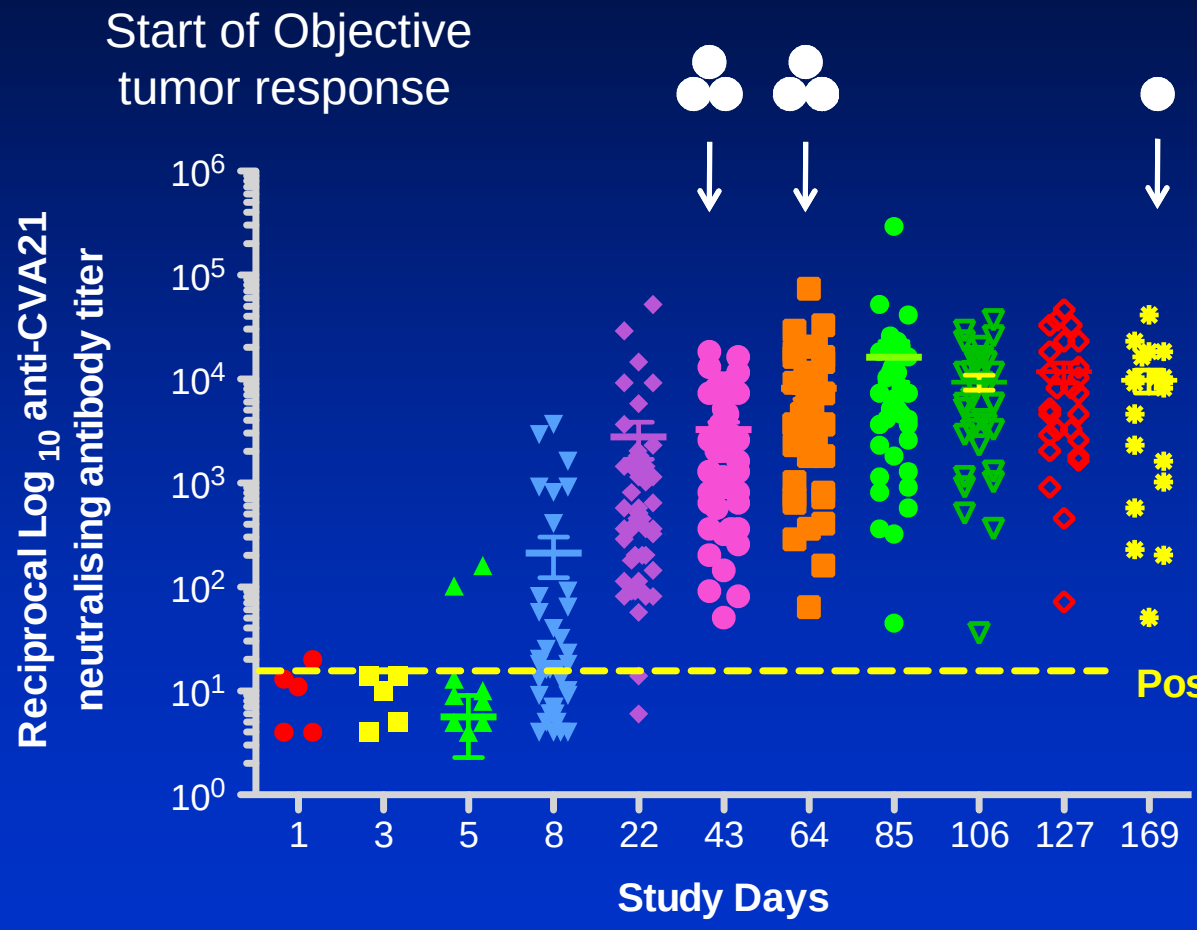
CALM Phase II trial

*Patient anti-viral immune response: Serum neutralizing antibody levels **



- All objective tumor responses started in the presence of high level of anti-CVA21 neutralizing antibody and absence of circulating infectious virus
- 96.5 % of patients developed significant anti-CVA21 antibody levels (>1:16) by study day 22

* Preliminary on-going analysis

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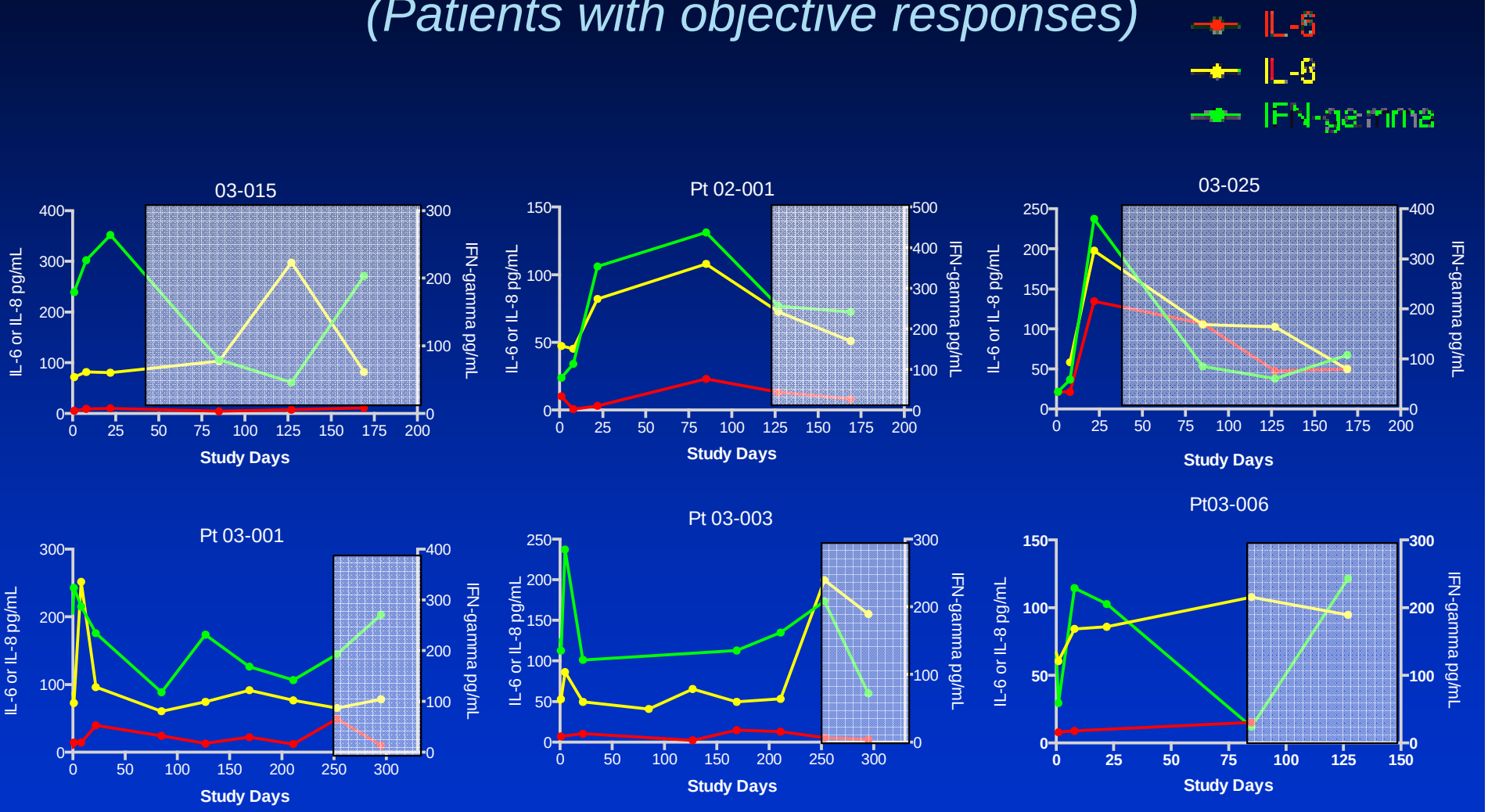
CALM Phase II trial

Preliminary analysis: Serum cytokine activity (Patients with objective responses)



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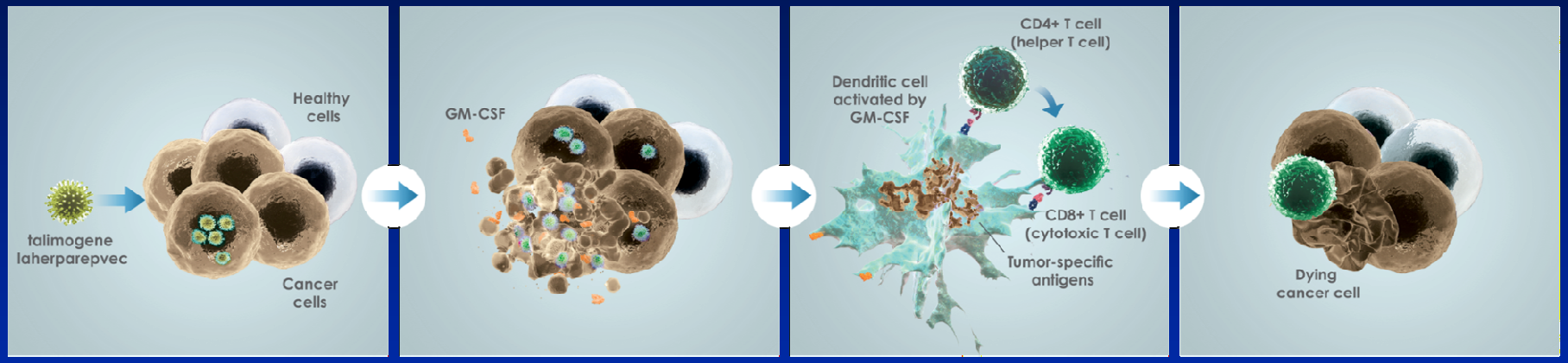
T-VEC: an HSV-1 derived oncolytic immunotherapy designed to produce both local and systemic effects

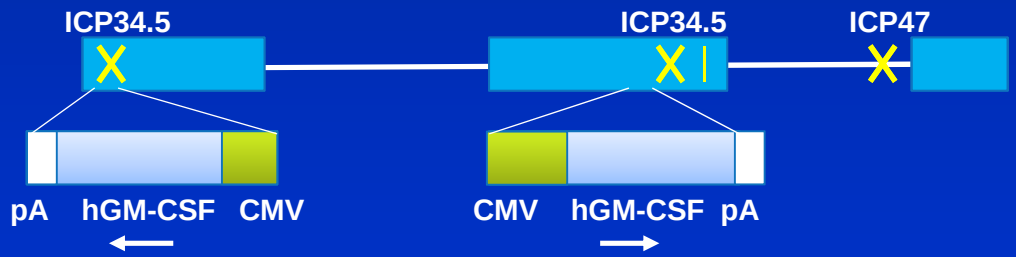
Local effect: tumor cell lysis → **Systemic effect: tumor-specific immune response**



Selective viral replication in tumor tissue → **Tumor cells rupture for an oncolytic effect** → **Systemic tumor-specific immune response** → **Death of distant cancer cells**

T-VEC key genetic modifications:

JS1/ICP34.5-/ICP47-/hGM-CSF



HSV, herpes simplex virus type 1; ICP, infected cell protein; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; CMV, cytomegalovirus; pA, polyadenylation (from bovine growth hormone).

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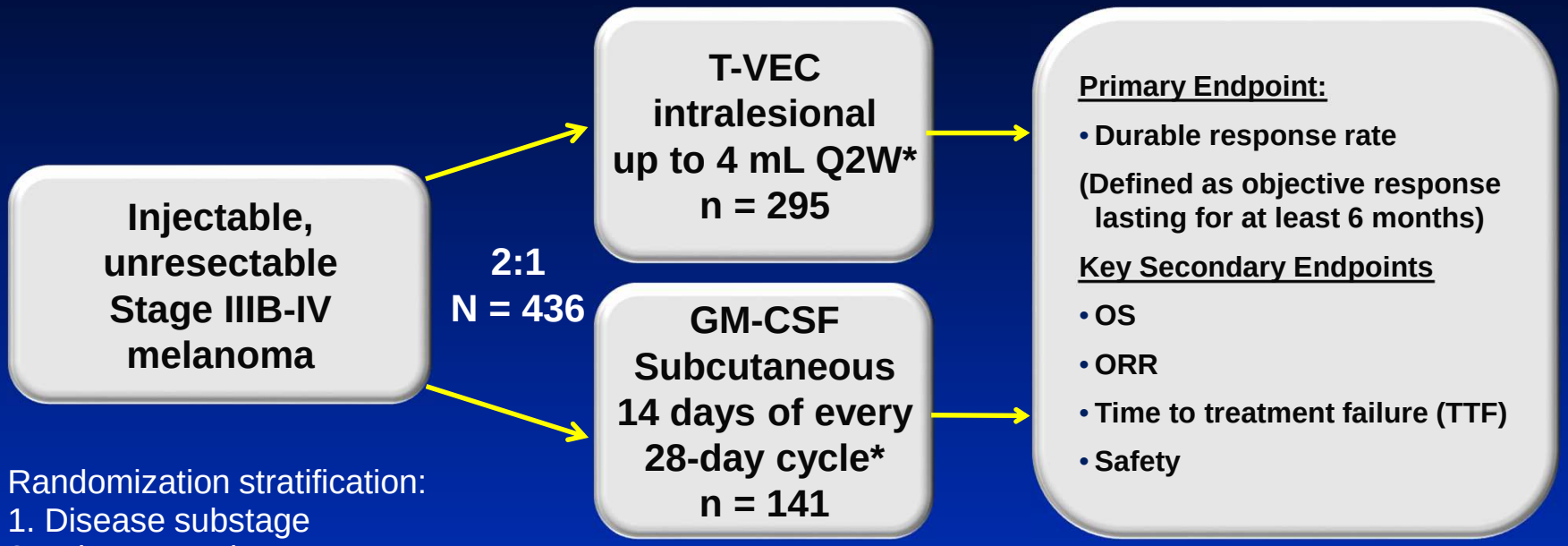
Varghese S and Rabkin SD. *Cancer Gene Ther*. 2002;9:967–978. Hawkins LK, et al. *Lancet Oncol*. 2002;3:17–26. Fukuhara H and Toda T. *Curr Cancer Drug Targets*. 2007;7:149–155. Sobol PT, et al. *Mol Ther*. 2011;19:335–344. Liu BL, et al. *Gene Ther*. 2003;10:292–303. Melcher A, et al. *Mol Ther*. 2011;19:1008–1016. Fagoaga OR. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods; 2011:933–953. Dranoff G. *Oncogene*. 2003;22:3188–3192.

OPTiM phase III study design



Randomization stratification:
1. Disease substage
2. Prior systemic treatment
3. Site of disease at first recurrence
4. Presence of liver metastases

- Patients enrolled between May 2009 and July 2011
- Patients enrolled at 64 sites in USA, UK, Canada, and South Africa

- Patients were to remain on treatment beyond progression unless clinically significant (ie, associated with reduced performance status) after 24 weeks

*Dosing of intralesional T-VEC was ≤ 4 mL x10^6 pfu/mL once, then after 3 weeks, ≤ 4 mL x10^8 pfu/mL every two weeks (Q2W). Dosing of GM-CSF was 125 µg/m^2 subcutaneous daily x 14 days of every 28 day cycle.

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Andtbacka RHI, et al. ASCO 2013 abstract LBA9008.
Kaufman H, et al. ASCO 2014 abstract 9008a.

OPTiM phase III study results

Primary endpoint: durable response rate per EAC*

Secondary endpoint: objective response per EAC

ITT set	GM-CSF (n = 141)	T-VEC (n = 295)	Treatment difference (T-VEC – GM-CSF)
Durable response rate	2.1%	16.3%	14.1% 95% CI (8.2, 19.2) P < 0.0001 (unadjusted odds ratio 8.9)

ITT Set	GM-CSF (n = 141)	T-VEC (n = 295)	Treatment difference (T-VEC – GM-CSF)
Objective overall response (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)	20.8% (14.4, 27.1) P < 0.0001 descriptive
CR	0.7%	10.8%	41% CR in T-VEC Responders
PR	5.0%	15.6%	

*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 (EAC).
ITT, intention to treat; CI, confidence interval.

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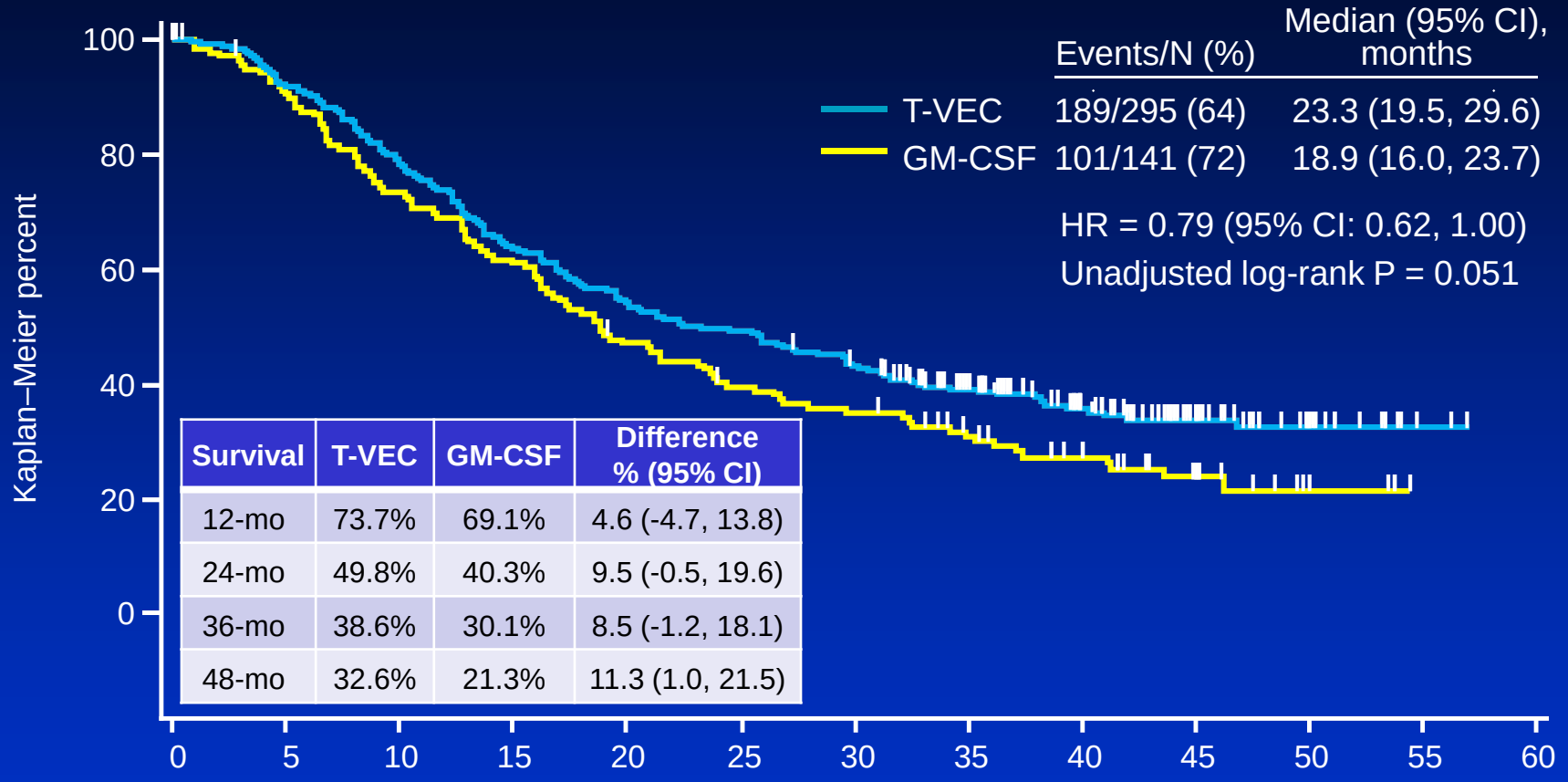
Andtbacka RHI, et al. ASCO 2013 abstract LBA9008.
Kaufman H, et al. ASCO 2014 abstract 9008a.

Primary overall survival



	Events/N (%)	Median (95% CI), months
T-VEC	189/295 (64)	23.3 (19.5, 29.6)
GM-CSF	101/141 (72)	18.9 (16.0, 23.7)

HR = 0.79 (95% CI: 0.62, 1.00)
Unadjusted log-rank P = 0.051

Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-mo	73.7%	69.1%	4.6 (-4.7, 13.8)
24-mo	49.8%	40.3%	9.5 (-0.5, 19.6)
36-mo	38.6%	30.1%	8.5 (-1.2, 18.1)
48-mo	32.6%	21.3%	11.3 (1.0, 21.5)

Patients at risk:

T-VEC	295	269	230	187	159	145	125	95	66	36	16	2	0
GM-CSF	141	124	100	83	63	52	46	36	27	15	5	0	0

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HR, hazard ratio.

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

Injectable intralesional therapy

Goals

- Locally ablative therapy for local disease control
  - High local concentration
  - Palliation / local symptom control
- Induction of systemic host immune anti-tumor activity
  - Response in un-injected regional and distant metastases
  - Limited systemic toxicity
- Systemic neoadjuvant effect
  - Preventing stage IIIB / IIIC patients from developing stage IV melanoma
- Durable response

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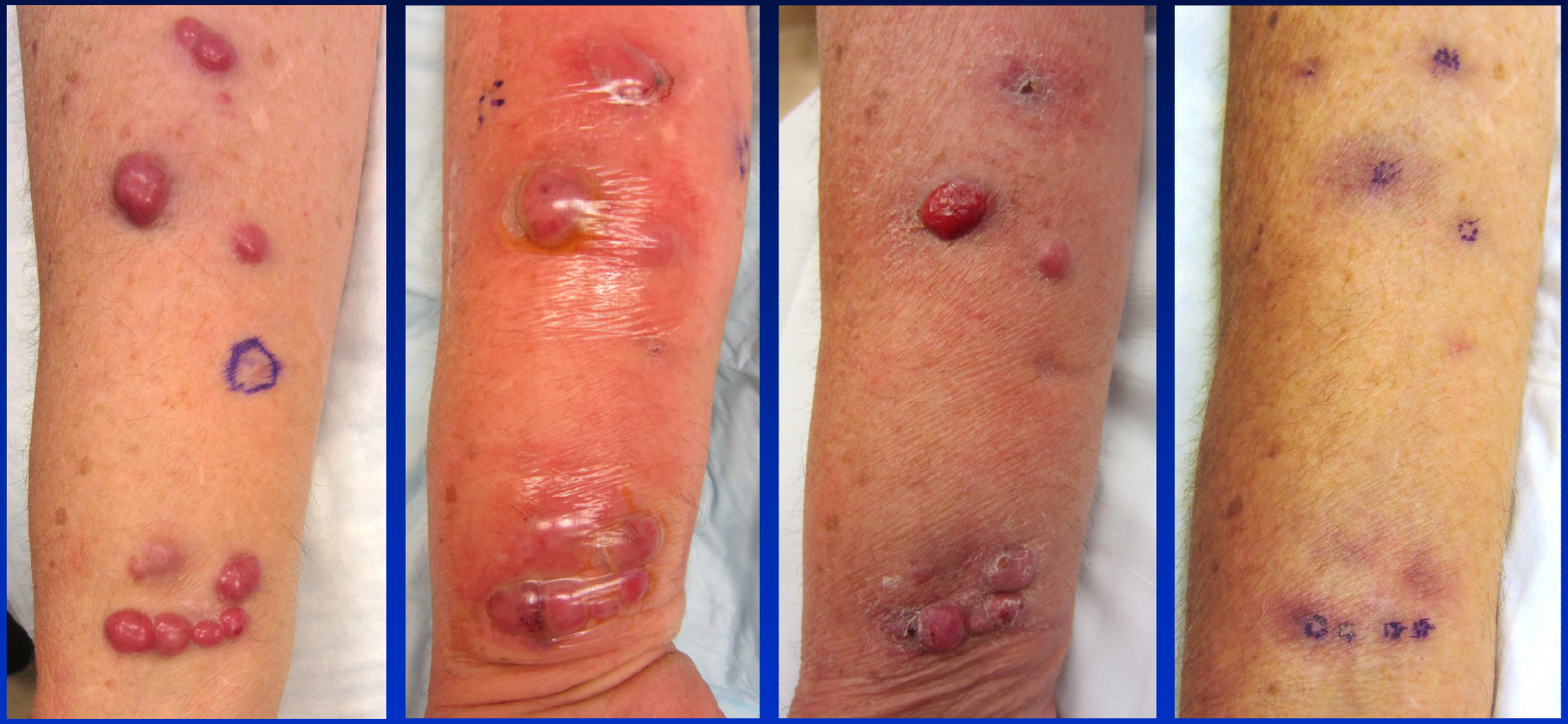
T-VEC responses in injected lesions

Screening (week 1)	1st injection (week 4)	2nd injection (week 6)	8th injection (week 16)



66 yo male with stage IIIC melanoma of the right arm. Intransit melanoma and axillary lymph node metastases. Prior adjuvant high dose IFN-α2b. Prior 4 cycles of 3mg/kg ipilimumab for unresectable stage IIIC melanoma.

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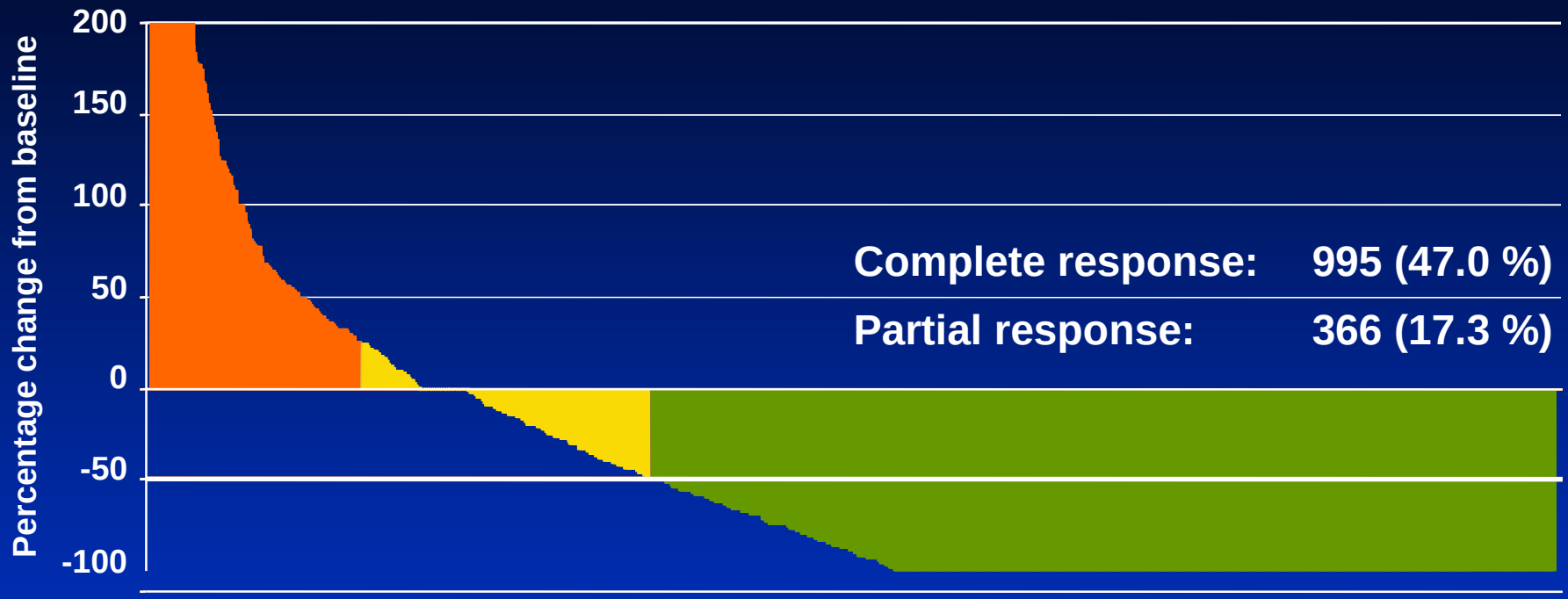
64% of injected lesions responded to T-VEC[1,2]



				Total n (%)
No. of lesions:	319 (15.1%)	436 (20.6%)	1361 (64.3%)	2116 (100%)
Tumor area change:	≥ 25%	> –50% to < 25%	–100% to ≤ –50%	

[1]Injected lesions were those lesions recorded as having been ever injected by investigators.

[2]To be considered in response, lesions must have the smallest recorded area measurement ≤ 50% of the first recorded area measurement (baseline).

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Andtbacka RHI, et al. SSO 2014 abstract PCC-121.

Injectable intralesional therapy
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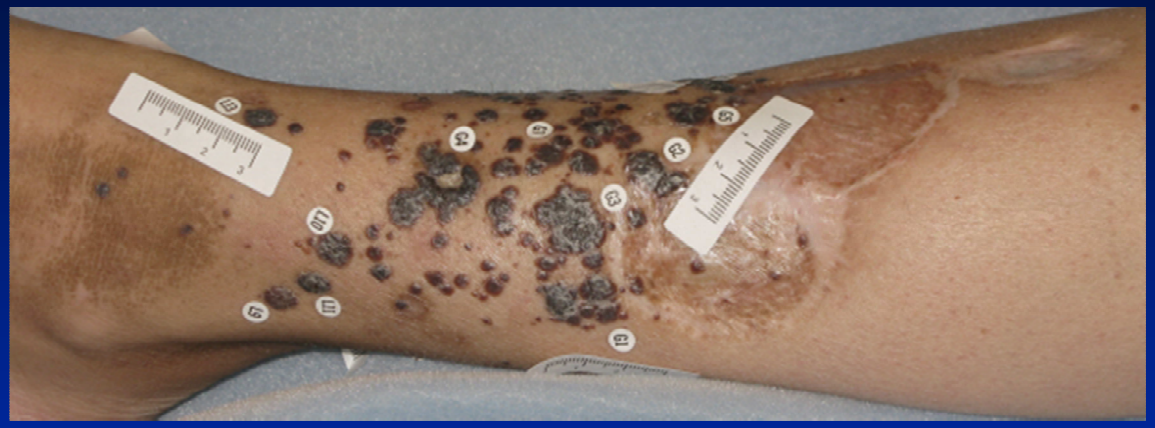
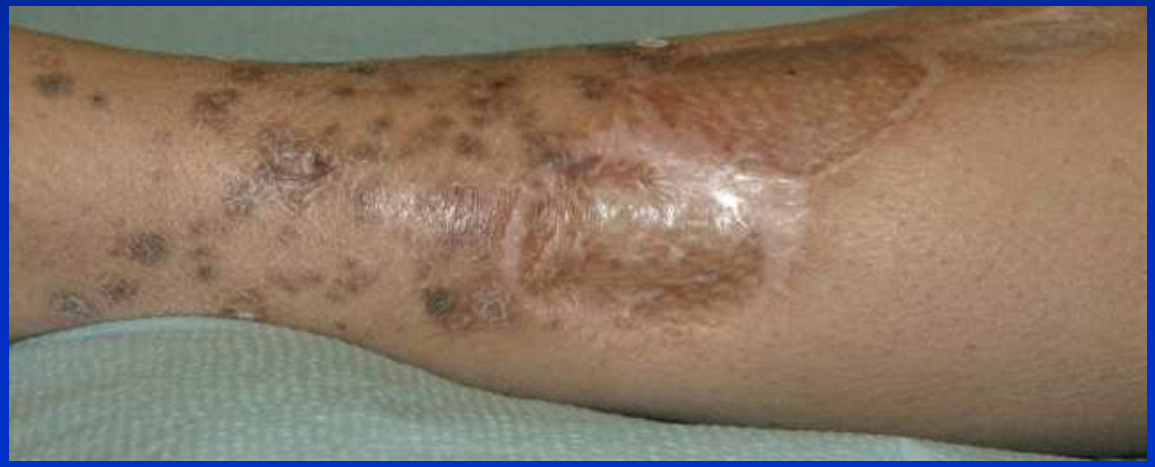
T-VEC responses in injected and uninjected lesions

Cycle 1



Cycle 13



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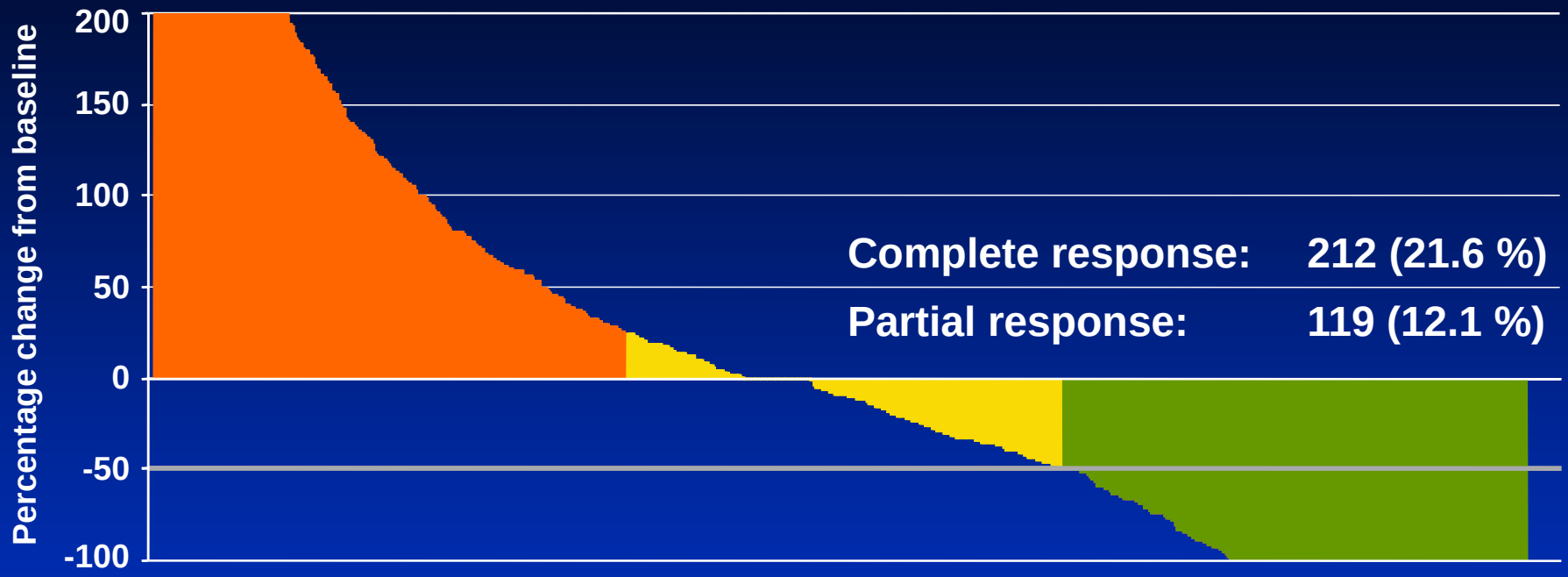
Andtbacka RHI, et al. ASCO 2013 abstract LBA9008.

34% of non-injected non-visceral lesions responded to T-VEC[1,2]



			Total n (%)
No. of lesions:	338 (34.5%)	312 (31.8%)	331 (33.7%)	981 (100%)
Tumor area change:	≥ 25%	> –50% to < 25%	–100% to ≤ –50%	

[1]Non-injected non-visceral lesions were those non-visceral lesions recorded as having been never injected by the investigator.

[2]To be considered in response, lesions must have the smallest recorded area measurement ≤ 50% of the first recorded area measurement (baseline).

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Andtbacka RHI, et al. SSO 2014 abstract PCC-121.

Injectable intralesional therapy
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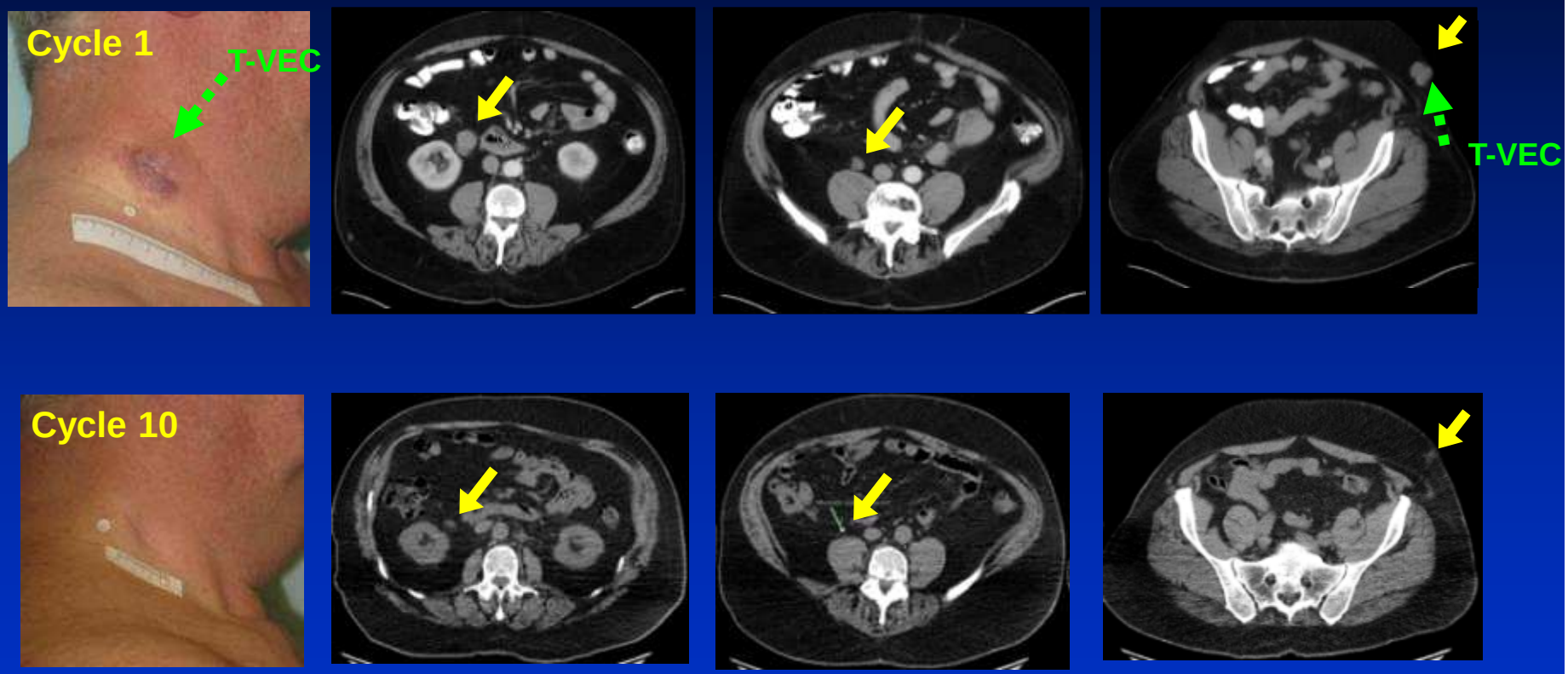
Injected and non-injected lesion response

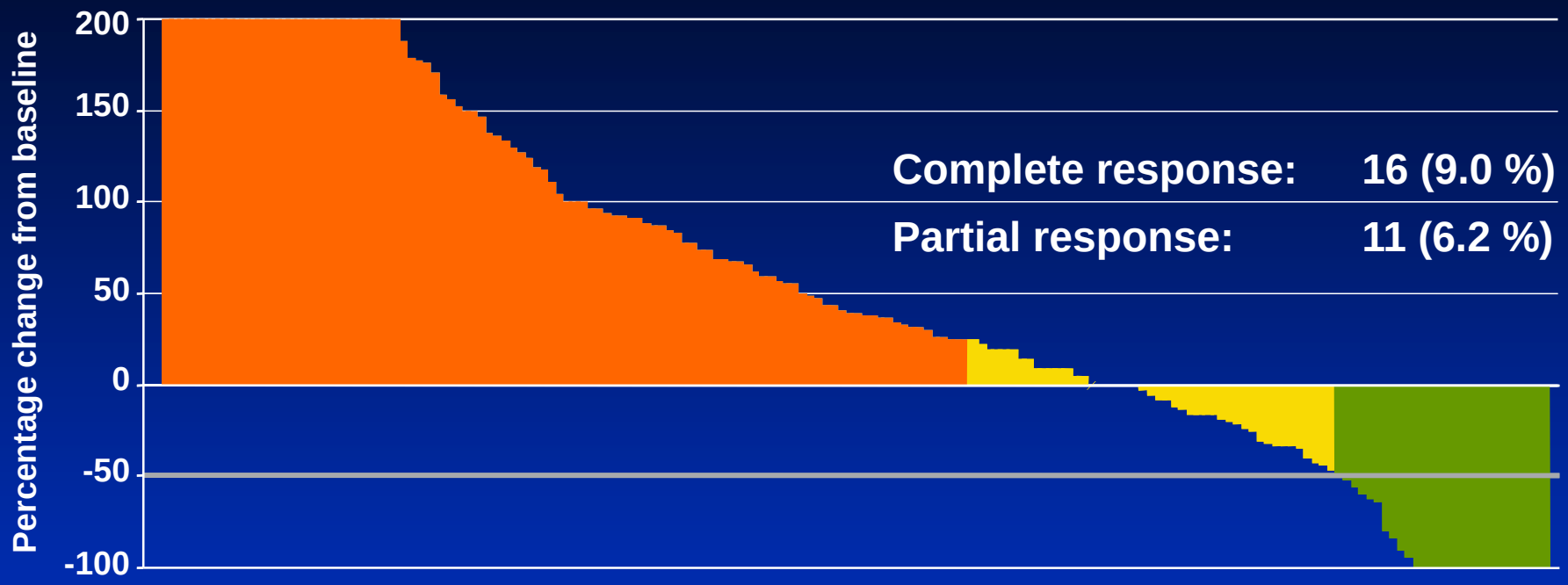


There were 6 measurable lesions at baseline including 1 cutaneous neck lesion, 2 subcutaneous abdominal wall lesions (1 of which is shown), 2 intra-abdominal lesions (which are shown), and 1 in musculature of right thigh (which completely resolved). Both injected lesions are indicated by a green arrow.

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

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

15% of visceral lesions responded to T-VEC[1,2]



	≥ 25%	> –50% to < 25%	–100% to ≤ –50%	Total n (%)
No. of lesions:	103 (58.2%)	47 (26.6%)	27 (15.3%)	177 (100%)
Tumor area change:				

[1]Visceral lesions were identified by medical review of investigator-described locations of baseline sites of the disease, and were not allowed to be injected.

[2]To be considered in response, lesions must have the smallest recorded area measurement ≤ 50% of the first recorded area measurement (baseline).

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Andtbacka RHI, et al. SSO 2014 abstract PCC-121.

Injectable intralesional therapy
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OPTiM safety: adverse events (AEs)

AEs of all grades occurring in ≥ 20% of T-VEC treated patients

Preferred term – % all grade AEs	GM-CSF (n = 127)	T-VEC (n = 292)
Fatigue	36.2%	50.3%
Chills	8.7%	48.6%
Pyrexia	8.7%	42.8%
Nausea	19.7%	35.6%
Influenza-like illness	15.0%	30.5%
Injection site pain	6.3%	27.7%
Vomiting	9.4%	21.2%

Grade 3/4 AEs occurring in ≥ 5 patients in either arm

Preferred term – % all grade AEs	GM-CSF (n = 127)	T-VEC (n = 292)
Cellulitis	<1%	2.1%
Fatigue	<1%	1.7%
Vomiting	0	1.7%
Dehydration	0	1.7%
Deep vein thrombosis	0	1.7%
Tumor pain	0	1.7%

Of 10 total fatal AEs on the T-VEC arm, 8 were due to progressive disease (PD). The only 2 fatal AEs on the T-VEC arm not associated with PD were sepsis (in the setting of cholangitis) and myocardial infarction. No treatment-related fatal AEs were observed.

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Andtbacka RHI, et al. ASCO 2013 abstract LBA9008.

Injectable intralesional therapy
Goals

- Locally ablative therapy for local disease control
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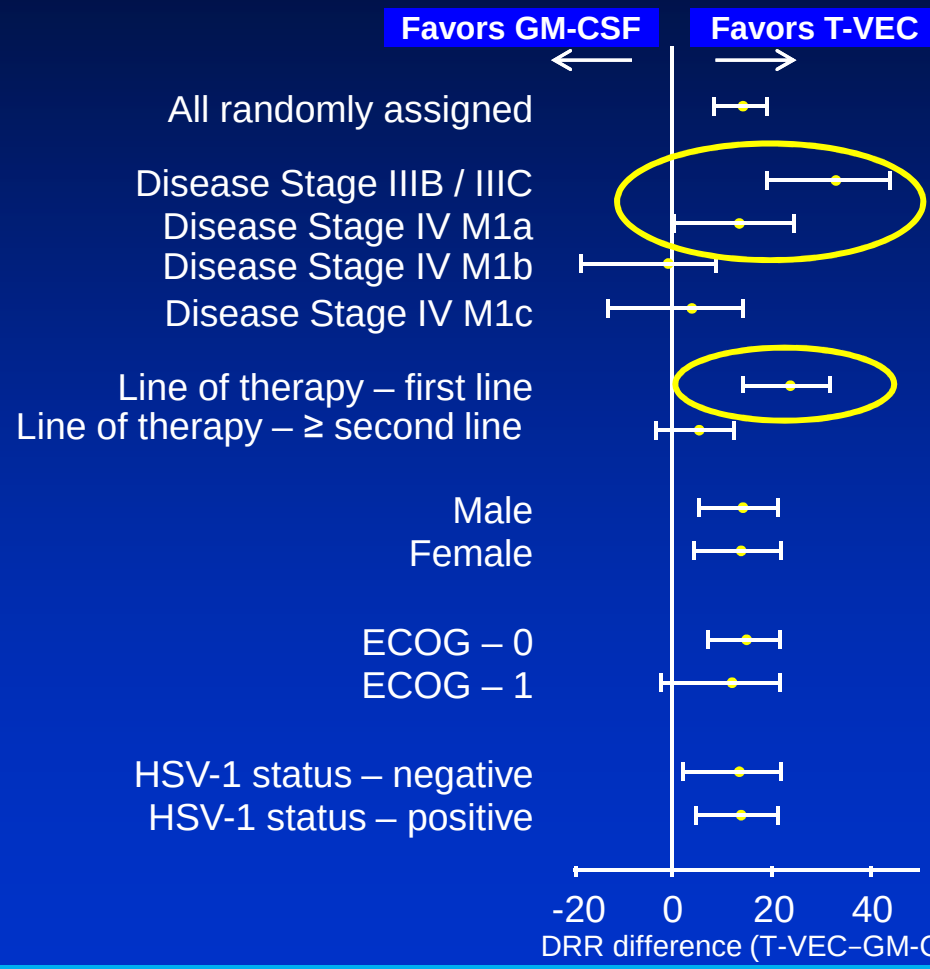
DRR by key covariates
(Exploratory Subgroup Analyses)



	n	GM-CSF (%)	T-VEC (%)	Diff. % (95% CI)
All randomly assigned	436	2.1	16.3	14.1 (8.2–19.2)
Disease Stage IIIB / IIIC	131	0.0	33.0	33.0 (19.1–43.9)
Disease Stage IV M1a	118	2.3	16.0	13.7 (0.2–24.6)
Disease Stage IV M1b	90	3.8	3.1	-0.7 (-18.6–8.7)
Disease Stage IV M1c	96	3.4	7.5	4.0 (-12.8–14.3)
Line of therapy – first line	203	0.0	23.9	23.9 (14.3–32.1)
Line of therapy – ≥ second line	233	3.9	9.6	5.6 (-3.2–12.3)
Male	250	2.6	16.8	14.2 (5.3–21.1)
Female	186	1.6	15.6	14.0 (4.2–22.1)
ECOG – 0	306	3.1	18.2	15.1 (7.1–21.6)
ECOG – 1	114	0.0	12.2	12.2 (-2.4–21.7)
HSV-1 status – negative	142	0.0	13.4	13.4 (2.0–22.2)
HSV-1 status – positive	253	3.8	17.7	13.9 (4.5–21.1)

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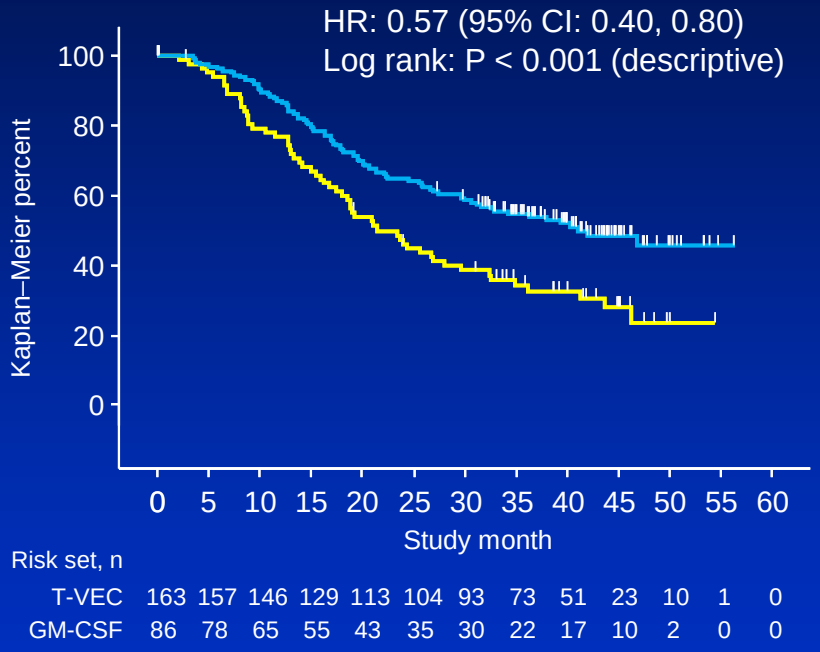
Andtbacka RHI, et al. ASCO 2013 abstract LBA9008.
Kaufman H, et al. ASCO 2014 abstract 9008a.

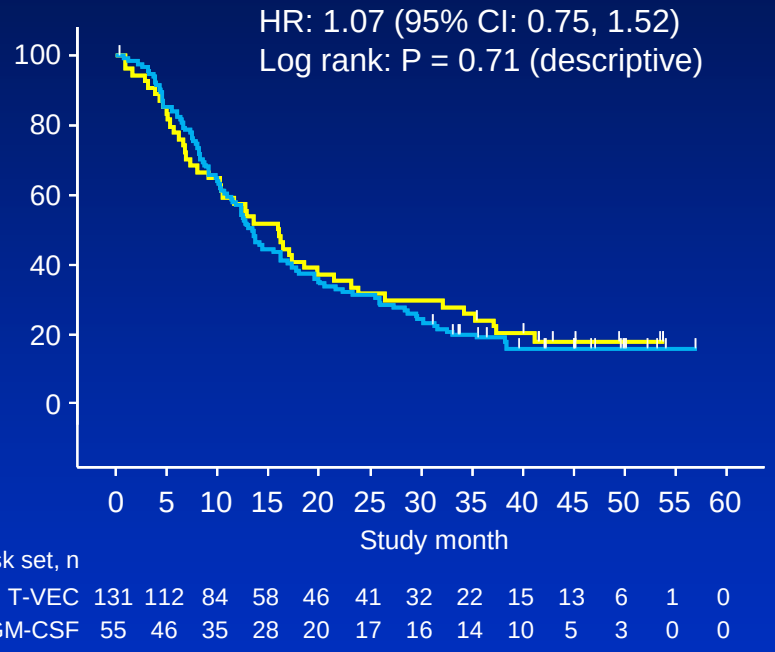
Exploratory OS subgroup analysis by disease stage

Stage IIIB/C, IV M1a



	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



	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)

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Mo, months.

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

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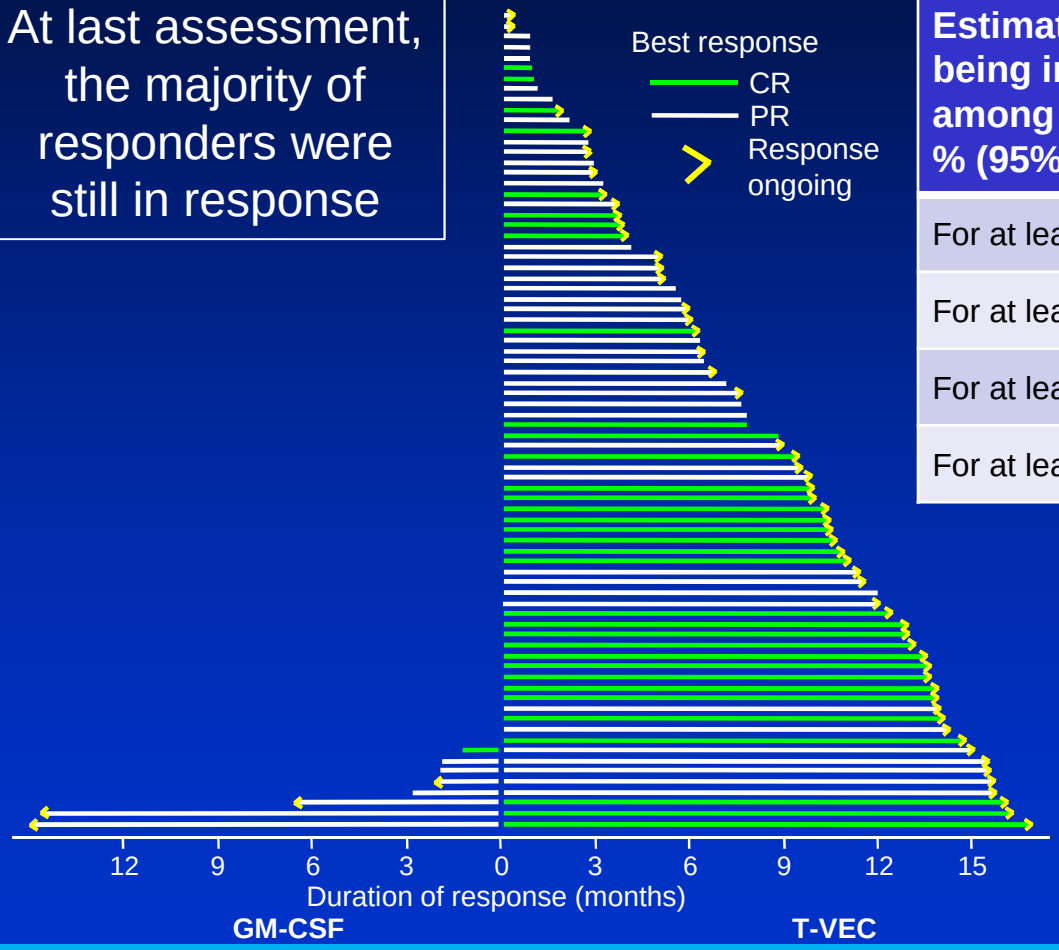
Duration of longest response among responders (per EAC)

At last assessment, the majority of responders were still in response



Estimated probability of being in response among all responders, % (95% CI)	GM-CSF (n = 8)	T-VEC (n = 78)
For at least 3 months	46.9 (12, 76)	86.7 (77, 93)
For at least 6 months	46.9 (12, 76)	80.6 (69, 88)
For at least 9 months	46.9 (12, 76)	68.0 (55, 78)
For at least 12 months	46.9 (12, 76)	65.0 (51, 76)

The estimated probability was obtained using the Kaplan–Meier method

The duration of response is censored (marked by an arrow **>**) if response continued at last tumor assessment within the main study, or at the initialization of sub-sequent anti-cancer therapy

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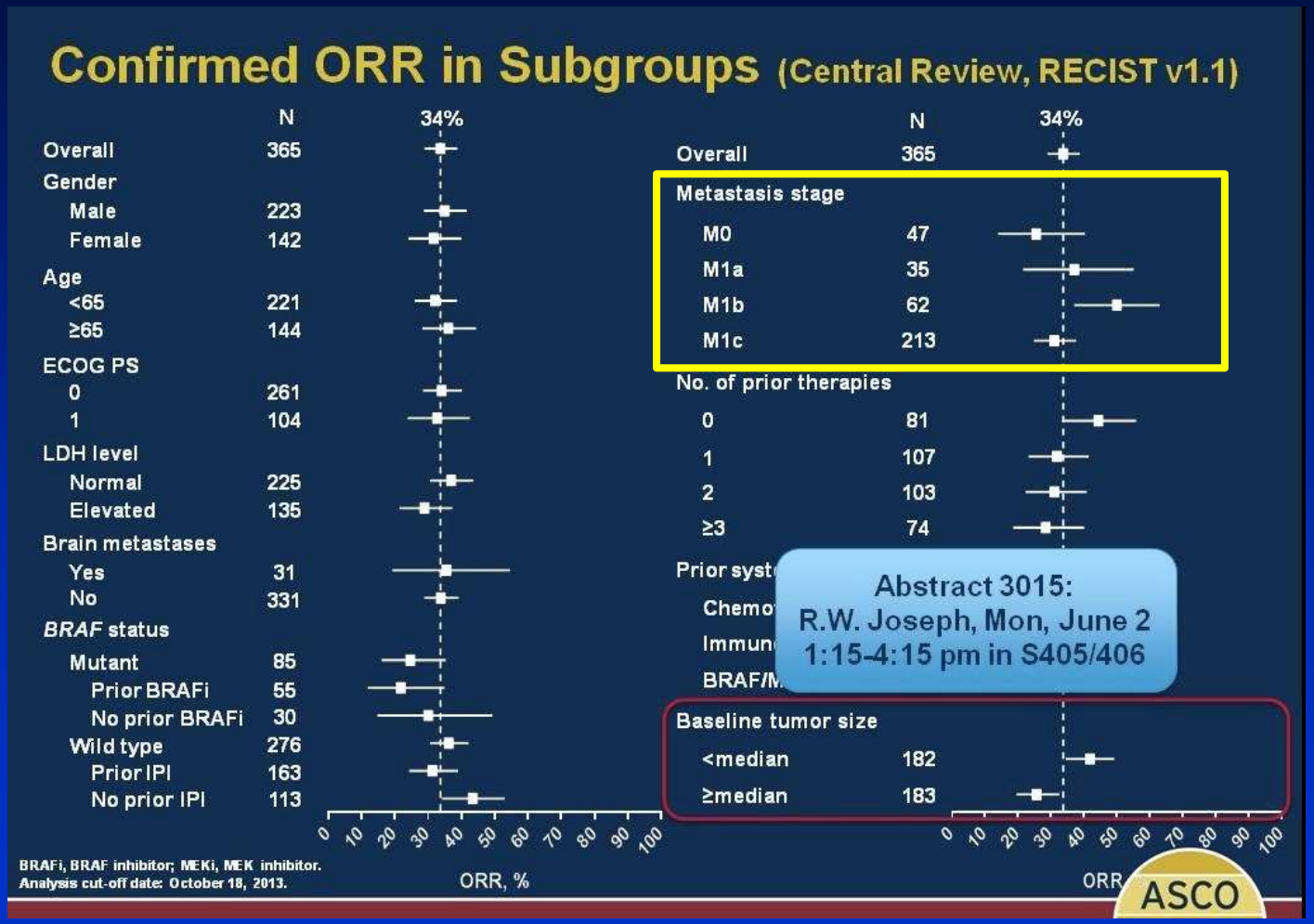
Andtbacka RHI, et al. COSA 2013.
Ross MI, et al. ASCO 2014 abstract 9026.

Future role for oncolytic immunotherapy (OT)

- Is there a role for Oncolytic Immunotherapy monotherapy?
  - Yes, especially unresectable stage IIIB/C (IV M1a) disease

Pembrolizumab ORR in unresectable metastatic melanoma



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Presented By Antoni Ribas at 2014 ASCO abstract LBA9000

Immunotherapy responses in patients with unresectable stage IIIB/C melanoma

Therapy	Objective Response Rate*
T-VEC[1]	52%
Ipilimumab	< 30% (stage IV 11-20%)
Pembrolizumab[2]	27%

* These treatments have not been compared in a trial and the ORR represents data in the presented / published literature.

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1. Andtbacka RHI, et al. unpublished data
2. Ribas A, et al. ASCO 2014 abstract LBA9000

Future role for oncolytic immunotherapy (OT)

- Is there a role for Oncolytic Immunotherapy monotherapy?
  - Yes, especially unresectable stage IIIB/C (IV M1a) disease
  - Yes, patients not eligible for other therapies due to comorbidities
  - Yes, neoadjuvant prior to surgery in resectable stage IIIB/C
    - Planned Phase II trial surgery +/- T-VEC (NCT02211131)
- Is there a role for Oncolytic Immunotherapy combo-therapy?
  - Yes, ongoing Phase Ib/II ipilimumab +/- T-VEC

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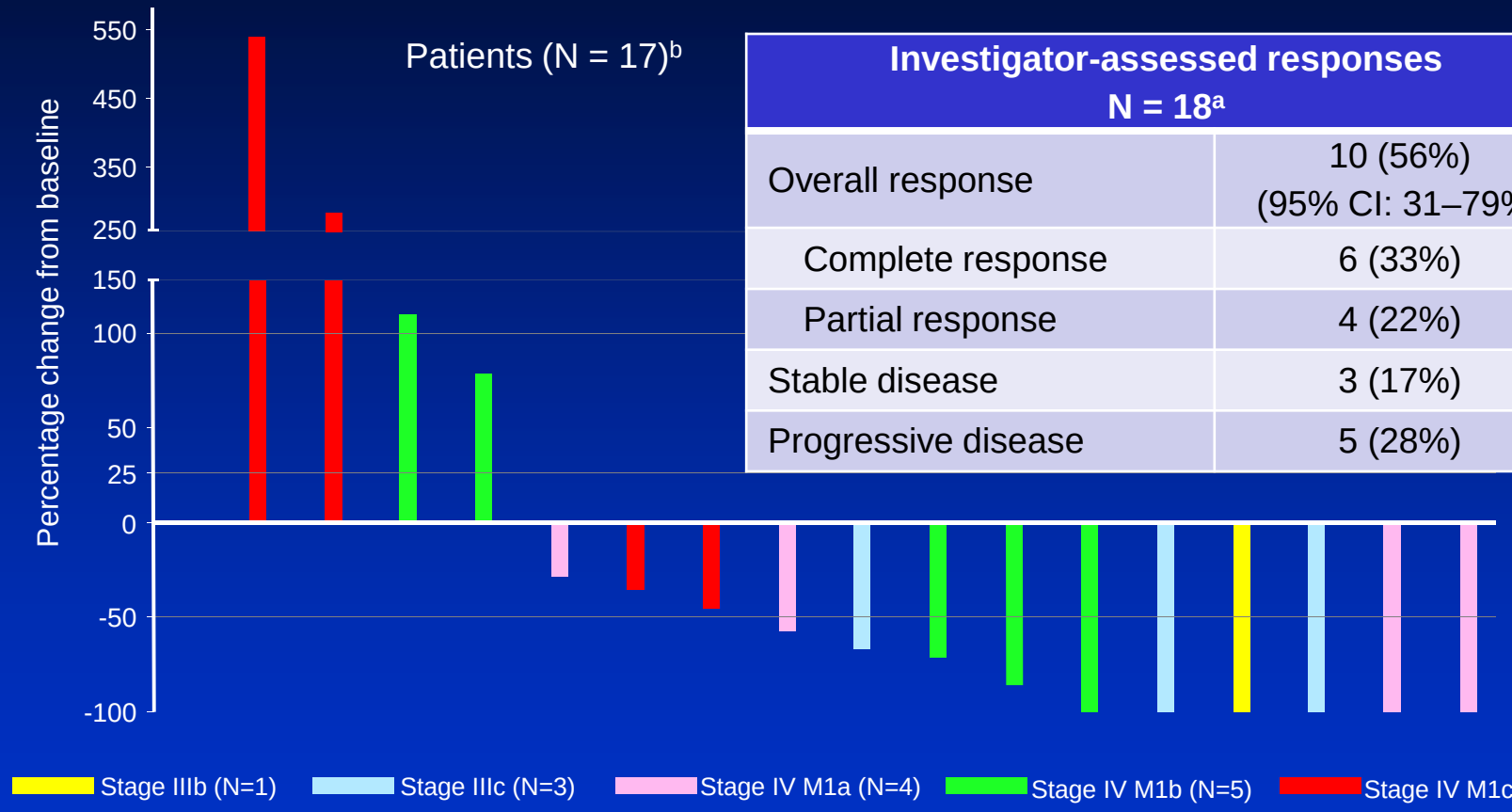
Maximal change in tumor burden



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 tumor burden could not be accurately calculated based on missing post-baseline data.

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Puzanov I, et al. ASCO 2014 abstract 9029.

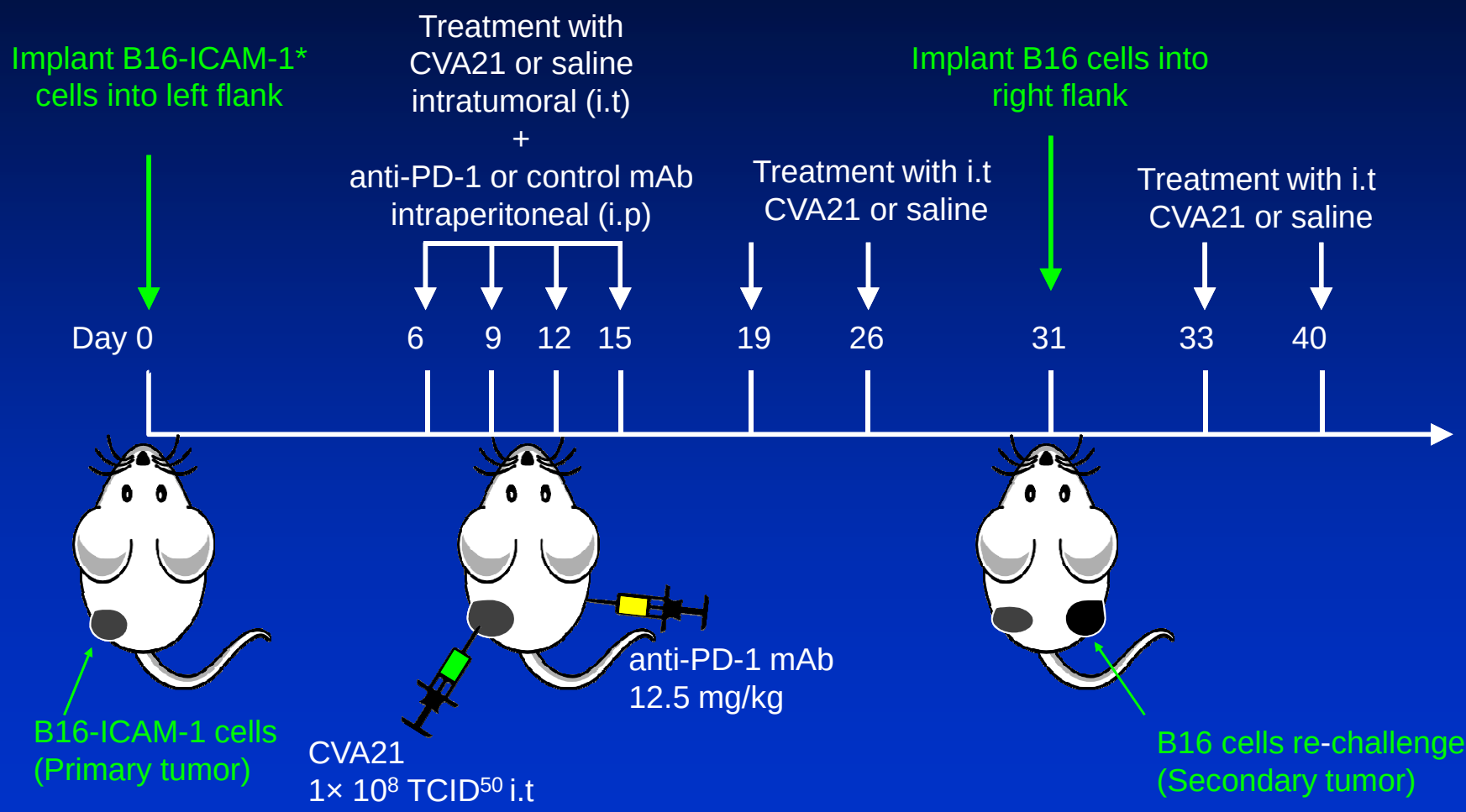
Future role for oncolytic immunotherapy (OT)

- Is there a role for Oncolytic Immunotherapy monotherapy?
  - Yes, especially unresectable stage IIIB/C (IV M1a) disease
  - Yes, patients not eligible for other therapies due to comorbidities
  - Yes, neoadjuvant prior to surgery in resectable stage IIIB/C
    - Planned Phase II trial surgery +/- T-VEC (NCT02211131)
- Is there a role for Oncolytic Immunotherapy combo-therapy?
  - Yes, ongoing Phase Ib/II ipilimumab +/- T-VEC
  - Yes, planned:
    - Phase Ib/II pembrolizumab +/- T-VEC
    - Phase Ib/II ipilimumab + HF-10
    - Phase II anti-PD-1 +/- CVA21
  - Yes, other agents: B-raf inh., MEK inh., PD-L1, chemo, radiation

Future role for oncolytic immunotherapy (OT)

- Need to understand
  - Mechanism of action mono- and combination therapy

Assessment of combination of intralesional CVA21 and immune checkpoint antibody blockade (anti-PD-1) in an immune-competent C57BL mouse melanoma model



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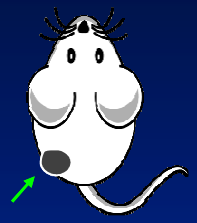
* B16-ICAM-1 cells are murine melanoma B16 cells stably transfected to express human ICAM-1 to allow CVA21 binding and cell infection

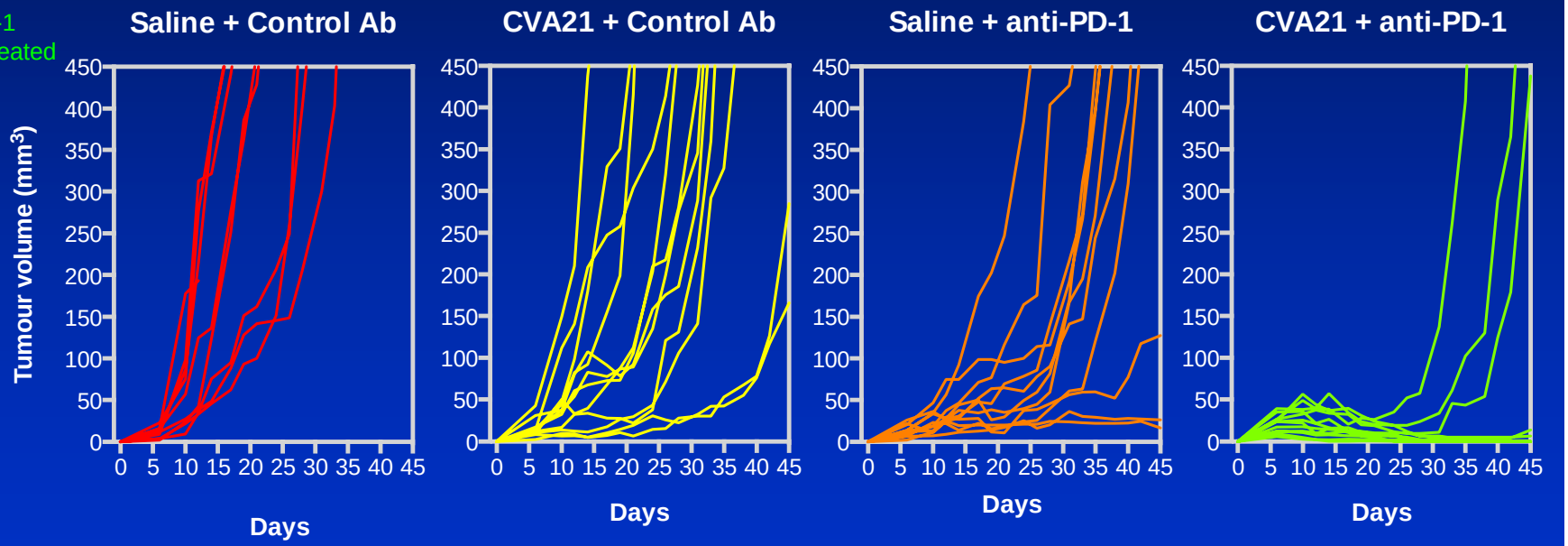
Andtbacka RHI, et al. AACR 2014

Combination of intralesional CVA21 and immune checkpoint antibody blockade (anti-PD-1)

*Spider plot of Individual primary B16-ICAM-1 tumor growth**



B16-ICAM-1 (Primary treated tumor)



Study Day 45	0% Tumor-free	0% Tumor-free	0% Tumor-free	75 % Tumor-free

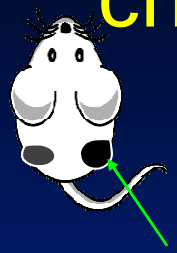
HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

* Preliminary on-going analysis

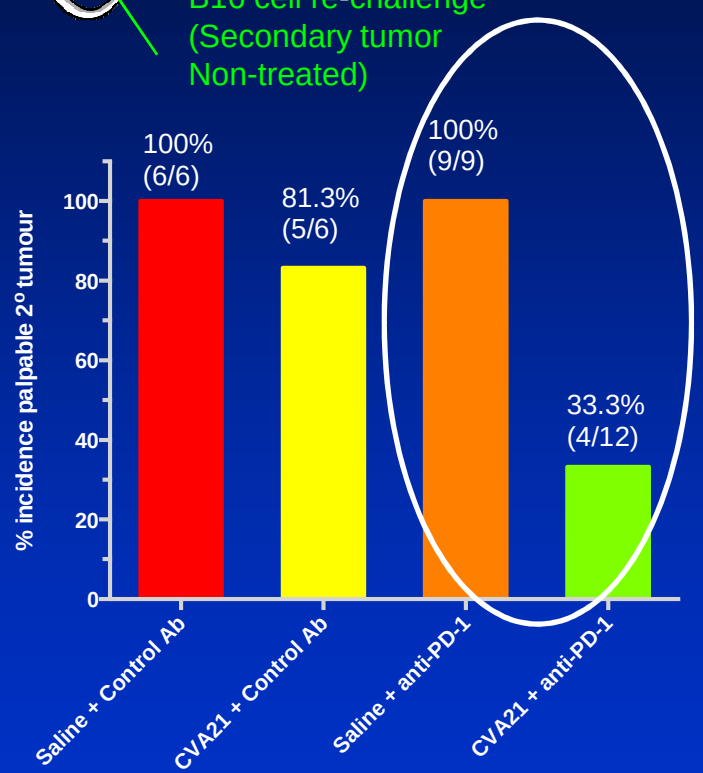
Andtbacka RHI, et al. AACR 2014

Combination of intralesional CVA21 and immune checkpoint antibody blockade (anti-PD-1)

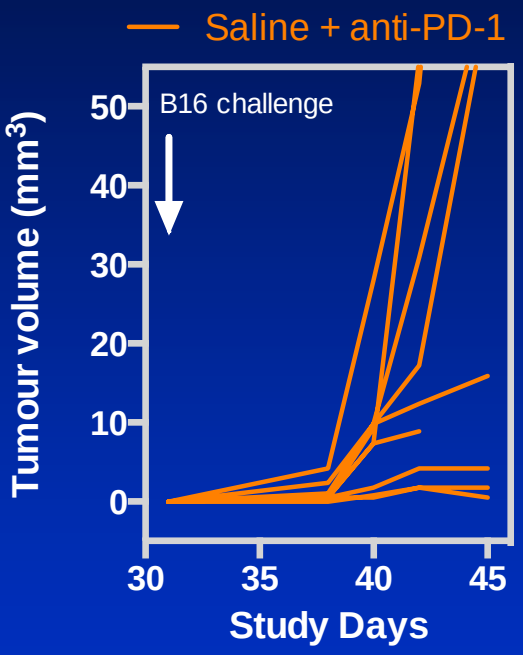
*Incidence of palpable secondary B16 tumor **

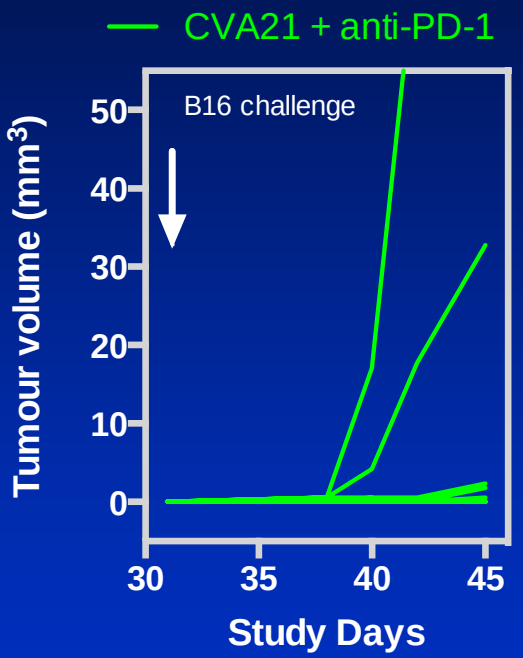


B16 cell re-challenge
(Secondary tumor
Non-treated)



Study Day 42





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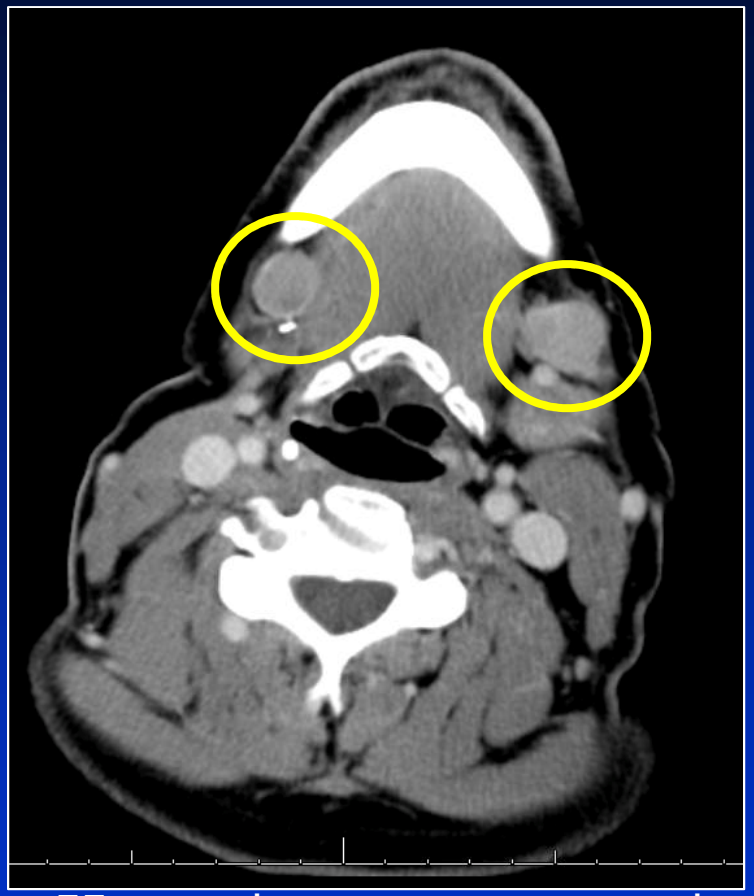
* Preliminary on-going analysis

Andtbacka RHI, et al. AACR 2014

Future role for oncolytic immunotherapy (OT)

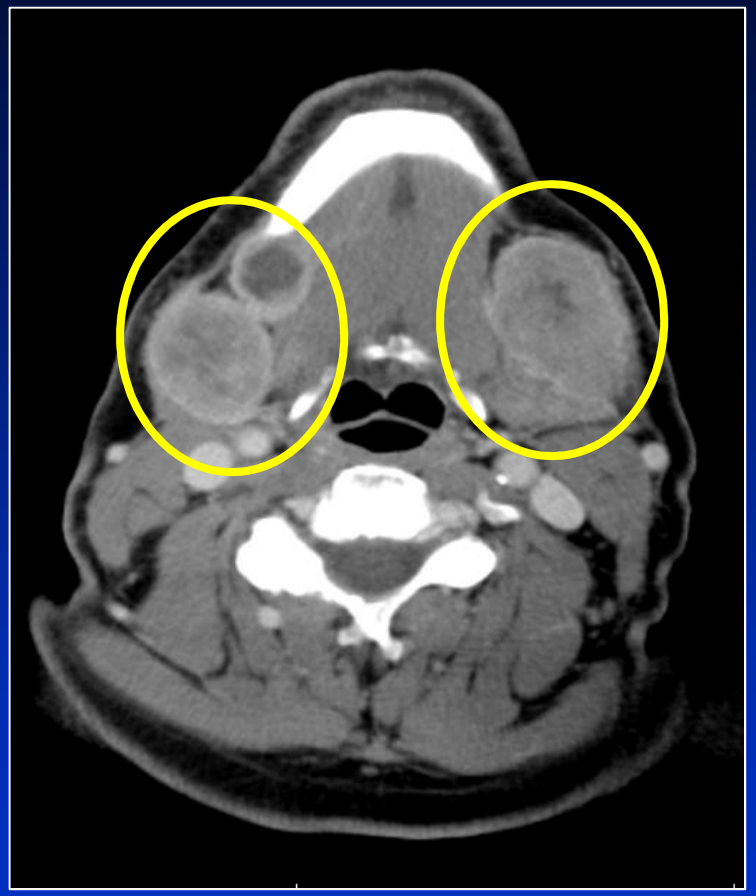
- Need to understand
  - Mechanism of action mono- and combination therapy
  - Prognostic and predictive biomarkers
  - Sequencing

Injectable Oncolytic immunotherapy



55 yo male recurrent metastatic melanoma in neck

5 mo



Progression of disease

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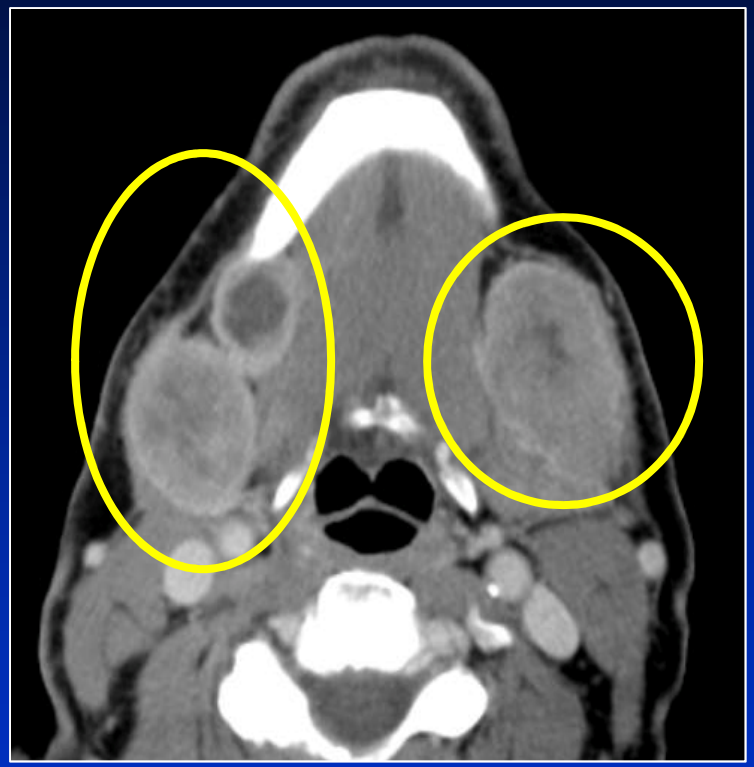
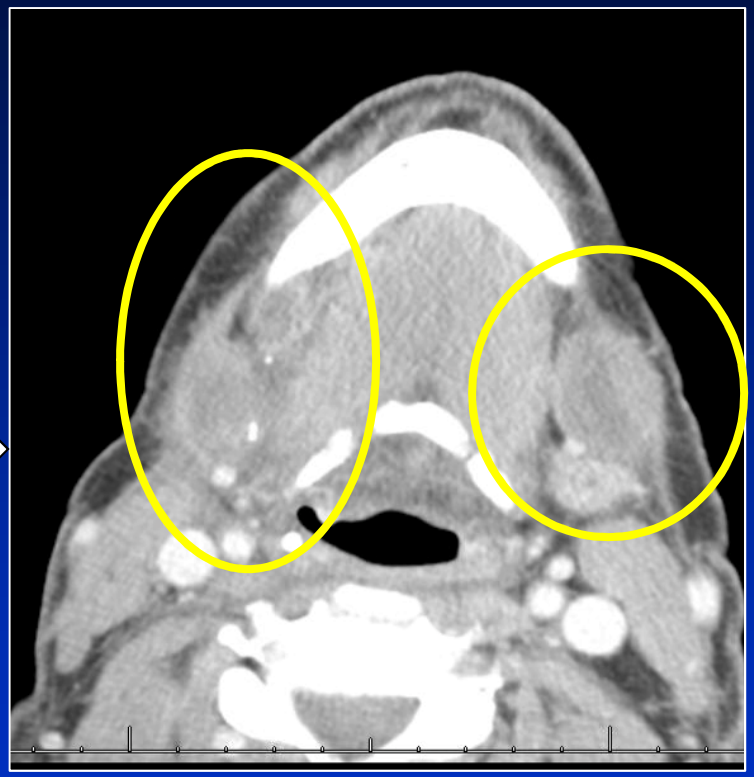
Ipilimumab and concomitant XRT to neck



5 mo



Stable disease,
but no regression

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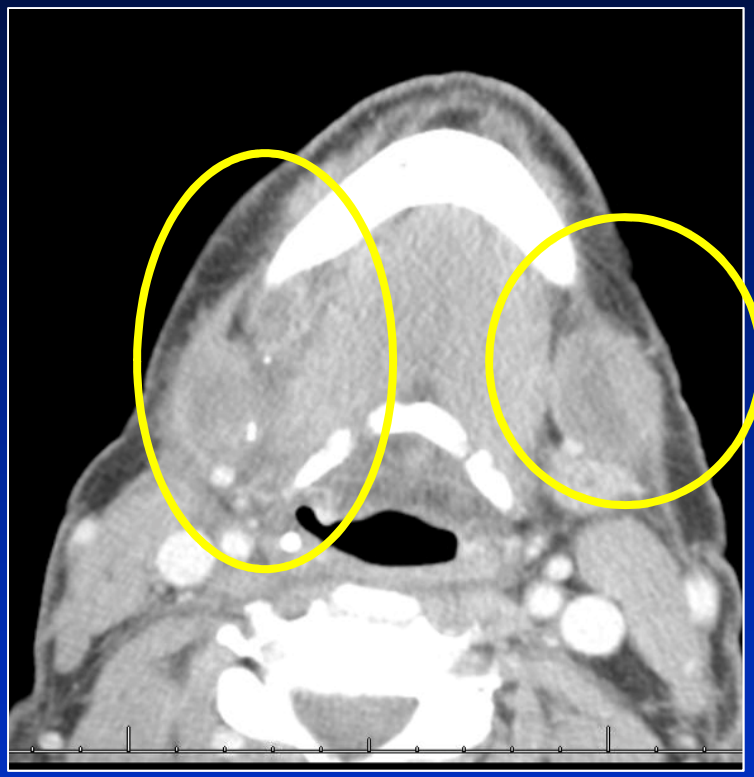
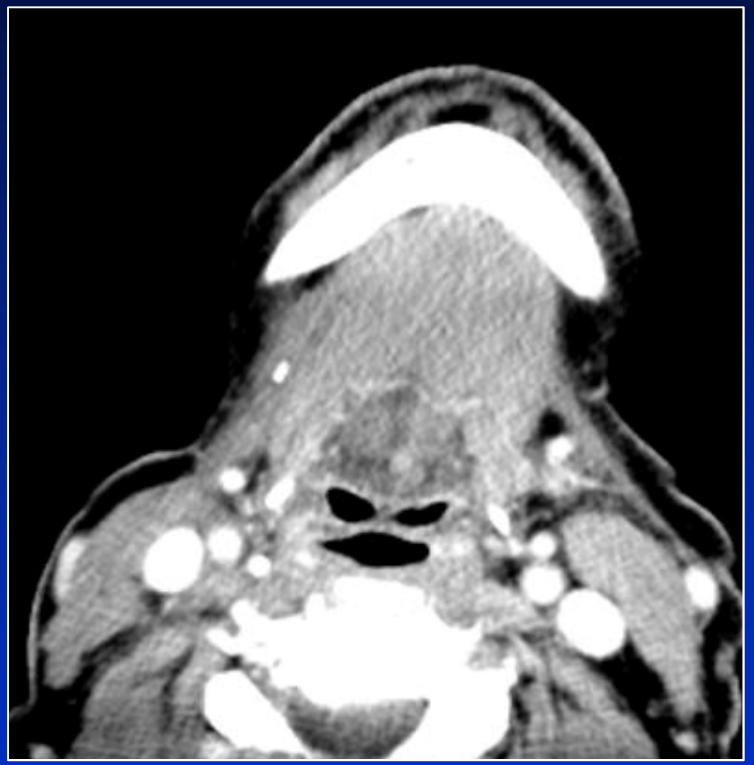
Second injectable oncolytic immunotherapy



4 mo



Complete response

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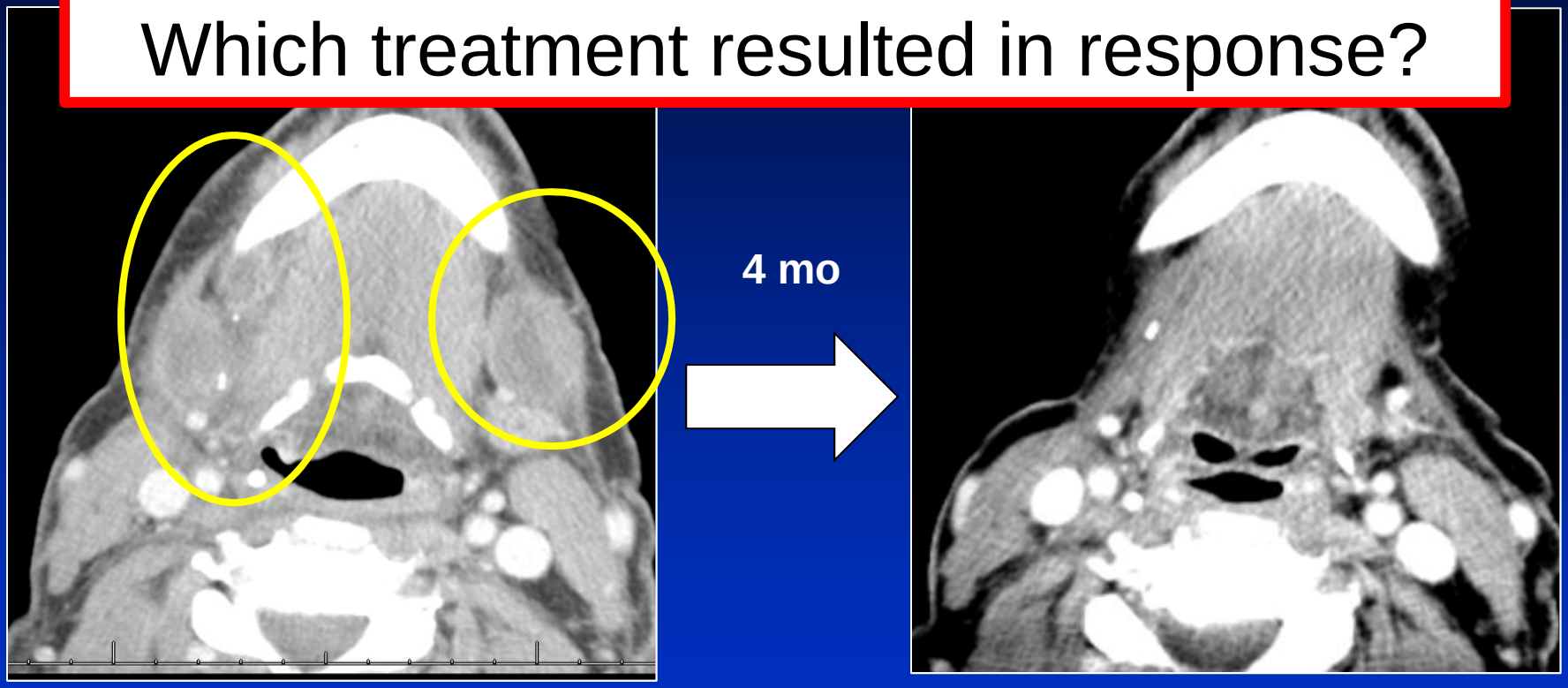
Second injectable oncolytic immunotherapy

Which treatment resulted in response?



Complete response

Thank you

Questions

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Oncolytic virus therapy has been associated with the following in the treatment of metastatic melanoma

A. No response

B. Response in injected metastatic lesions only

C. Response in injected lesions and close by non-injected metastatic lesions only

D. Response in injected lesions, close by non-injected metastatic lesions, and distant (visceral) non-injected metastatic lesions

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Talimogene laherparepvec (T-VEC) oncolytic virus therapy has been associated with the following in the treatment of metastatic melanoma

A. Good response rates, but limited durability of the response

B. Low rate of Grade 3 / 4 adverse events

C. Increased adverse events when combined with ipilimumab, compared to ipilimumab monotherapy

D. No improvement in response rate when combined with ipilimumab

E. C and D

In the OPTiM metastatic melanoma study, treatment with talimogene laherparepvec (T-VEC) compared to GM-CSF resulted in:

A. A worse response rate

B. Improvement in durable response rate and objective response rate

C. Improvement in overall survival

D. B+C

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