Oncolytic Virus Immunotherapy for the Treatment of Cancer

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DISCLOSURES

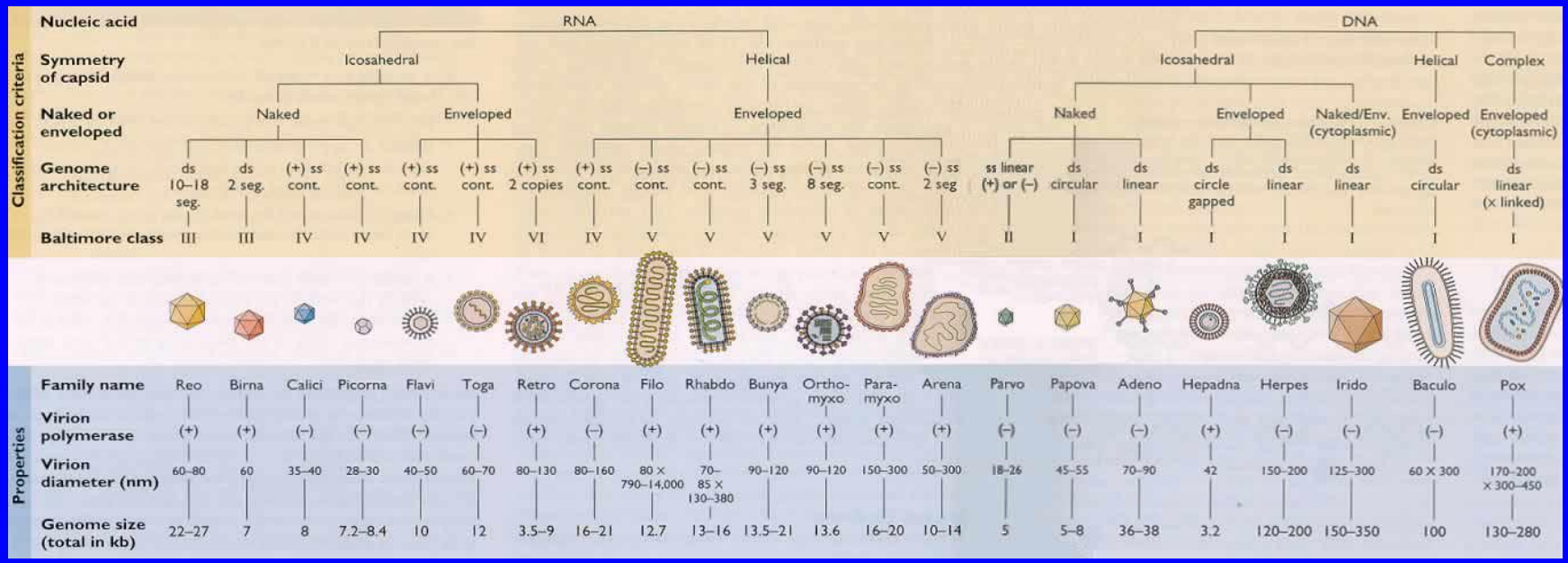
Relevant to This Session

Dr. Howard Kaufman is a consultant/advisor for BioVex and Amgen Inc. and receives research funding from Amgen Inc.

Malignant Melanoma in 2014

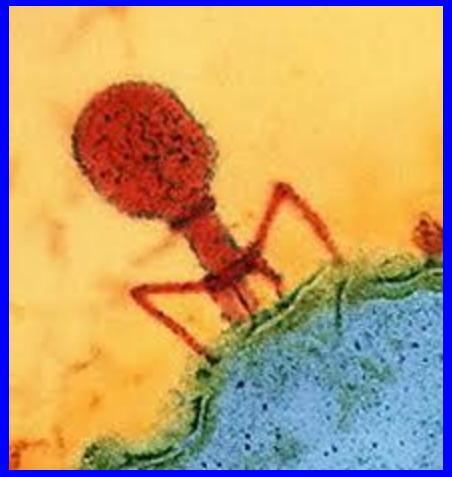
- 132,000 new cases worldwide
- 70,230 new invasive cases in the U.S.
- >800,000 Americans with a personal history of melanoma
- 9,710 deaths in the U.S. annually
  - >1 patient every hour
- Advances in treatment have been dramatic
  - Targeted therapy
  - Tumor immunotherapy

Classification of Animal Viruses



Oncolytic Virus Therapy: Advantages

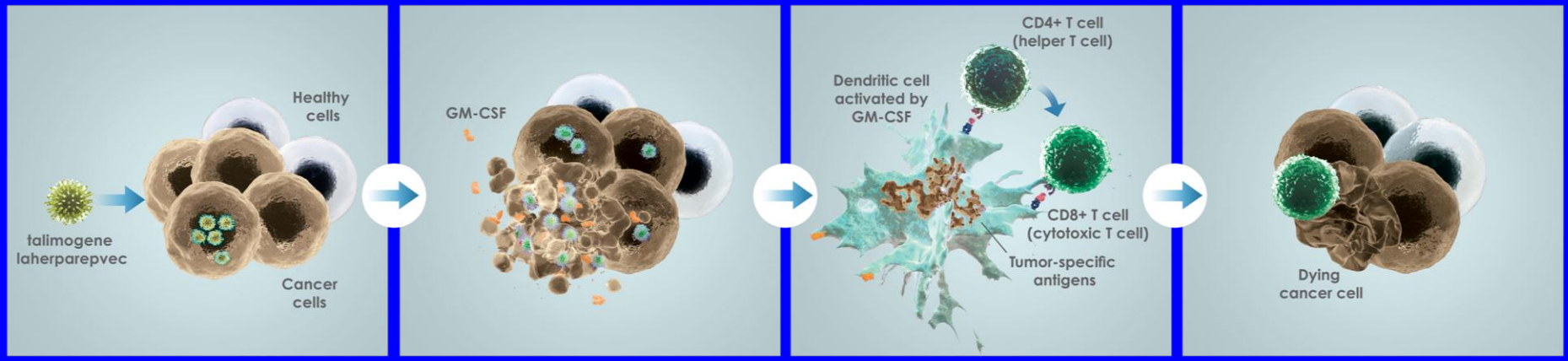
- Selective tumor targeting and replication
- Rapidly cleared
- Induction of host anti-tumor immunity
- Can be engineered with a variety of immune modulators
- Reasonable safety profile
- Off the shelf agent



T-VEC: HSV-1 Derived Oncolytic Immunotherapy

Local Effect:
Tumor Cell Lysis

Systemic Effect:
Tumor-Specific Immune Response



Selective viral replication in tumor tissue

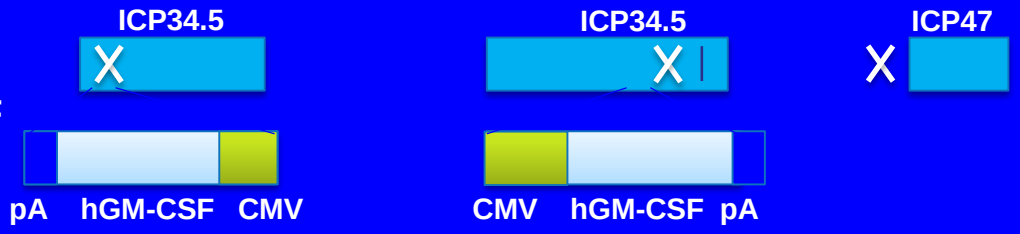
Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

Death of distant cancer cells

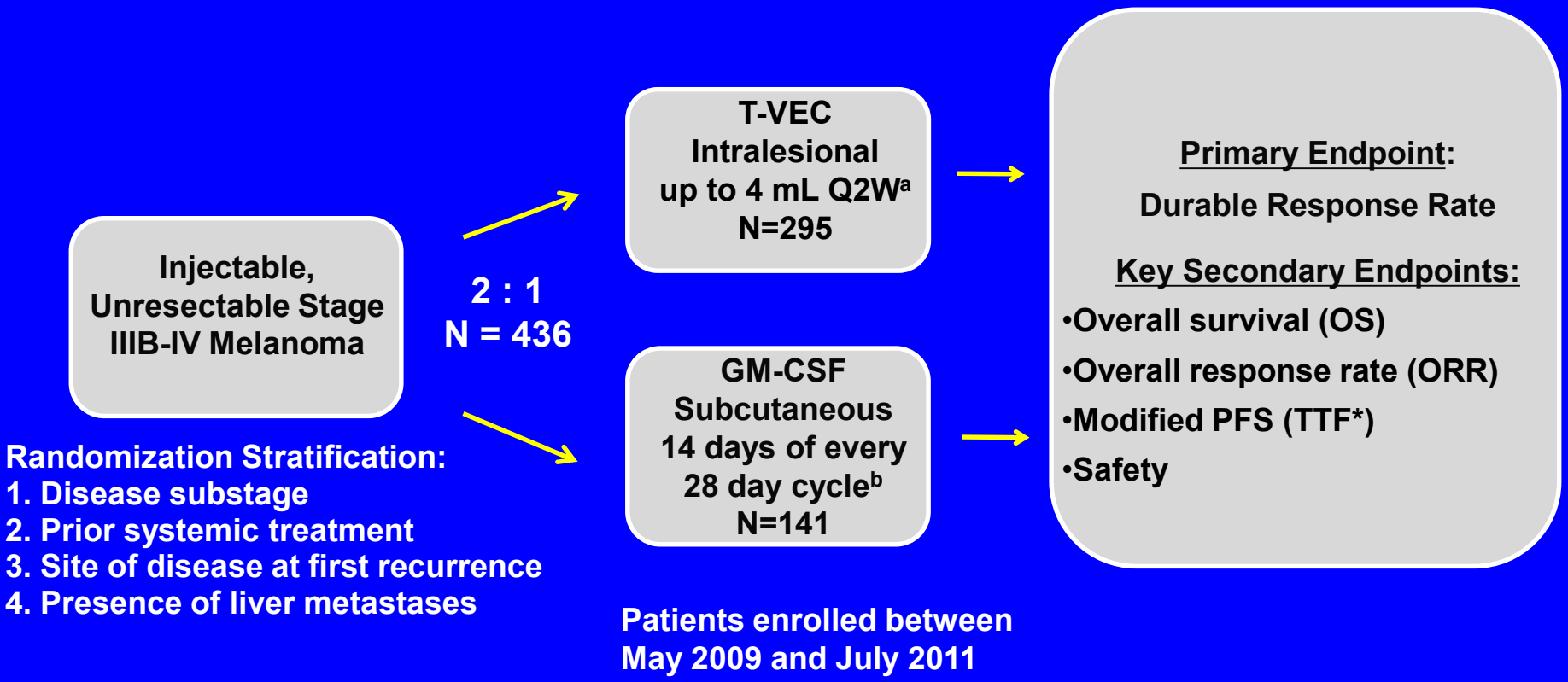
T-VEC key genetic modifications:

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



1. Varghese S, et al. *Cancer Gene Ther*. 2002;9:967-978. 2. Hawkins LK, et al. *Lancet Oncol*. 2002;3:17-26. 3. Fukuhara H, et al. *Curr Cancer Drug Targets*. 2007;7:149-155. 4. Sobol PT, et al. *Mol Ther*. 2011;19:335-344. 5. Liu BL, et al. *Gene Ther*. 2003;10:292-303. 6. Melcher A, et al. *Mol Ther*. 2011;19:1008-1016. 7. Fagoaga OR In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd ed. Philadelphia, PA: Elsevier; 2011:933-953. 8. Dranoff G. *Oncogene*. 2003;22:3188-3192.

OPTiM Phase III Study Design



Patients were to remain on treatment for at least 24 weeks despite progression (unless intolerability or investigator decision to start new therapy)

[a] **Dosing of T-VEC was ≤ 4 mL x10^6 pfu/mL once, then after 3 weeks, ≤ 4 mL x10^8 pfu/mL Q2W.**
[b] **Dosing of GM-CSF was 125 µg/m^2 subcutaneous daily x14 days of every 28 day cycle.**

*Andtbacka et al. ASCO 2013; LBA9008

Statistical Considerations

- For the durable response rate primary endpoint, overall responses (CR or PR) must have lasted continuously for at least 6 months and must have begun within 12 months of initiation of therapy
  - Responses were determined using modified WHO criteria by an independent, blinded endpoint assessment committee (EAC) based on evaluation of all lesions

- For the OS secondary endpoint, 290 events were required for the primary analysis
  - 90% power to detect a HR of 0.67 with two sided α=0.05

Key Eligibility Criteria

- Melanoma, not surgically resectable
  - Stage IIIB/C (with or without in-transit disease)
  - Stage IV with limited visceral burden
    - LDH ≤ 1.5x ULN
    - ≤ 3 visceral metastases (lung lesions excepted) and no lesion > 3 cm
    - Any liver lesion must have been stable for at least 1 month
    - Brain lesions must have been treated and stable for at least 2 months
- Injectable disease: at least one cutaneous, SC, or nodal lesion
- Measurable disease: lesion or aggregation of lesions ≥ 10 mm in greatest diameter
- ECOG Performance Status 0 or 1
- No open herpetic skin lesions or chronic anti-herpetic agents

Patient Demographics and Characteristics

	GM-CSF (N = 141)	T-VEC (N = 295)	Total (N = 436)
Disease substage, n (%)			
IIIB	9 %	8%	8%
IIIC	22%	22%	22%
IV M1a	30%	25%	27%
IV M1b	18%	22%	21%
IV M1c	21%	23%	22%
Line of therapy, n (%)			
1st line	46%	47%	47%
≥ 2nd line	54%	53%	53%
Sex – Men, n (%)	55%	59%	57%
ECOG PS* – 0, n (%)	69%	71%	70%
LDH* – ≤ ULN, n (%)	88%	90%	89%
HSV serostatus* – Positive, n (%)	55%	59%	58%
BRAF Status, n (%)			
Mutant	16%	16%	16%
Wild-type	16%	15%	16%
Unknown/missing	68%	69%	68%

Andtbacka et al. ASCO 2013; LBA9008

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%

Vitiligo was reported as an AE in 5% with T-VEC and 1% with GM-CSF

Of 10 total fatal AEs on the T-VEC arm, 8 were due to PD. The 2 fatal AEs on the T-VEC arm not associated with disease progression were sepsis (due to Salmonella infection) and myocardial infarction. No treatment-related fatal AEs were observed.

There were 2 fatal AEs on the GM-CSF arm, 1 due to dyspnea and 1 due to disease progression.

Median duration of treatment was 10 weeks for GM-CSF and 23 weeks for T-VEC

Kaufman et al. ASCO 2014

Overall Response Rate

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	**Treatment Difference (T-VEC – GM-CSF)**
Overall Response Rate (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)	20.8% (14.4, 27.1) *P* < 0.0001[a] descriptive
CR	0.7%	10.8%	
PR	5.0%	15.6%	

Durable Response Rate (Primary Endpoint)

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[a]

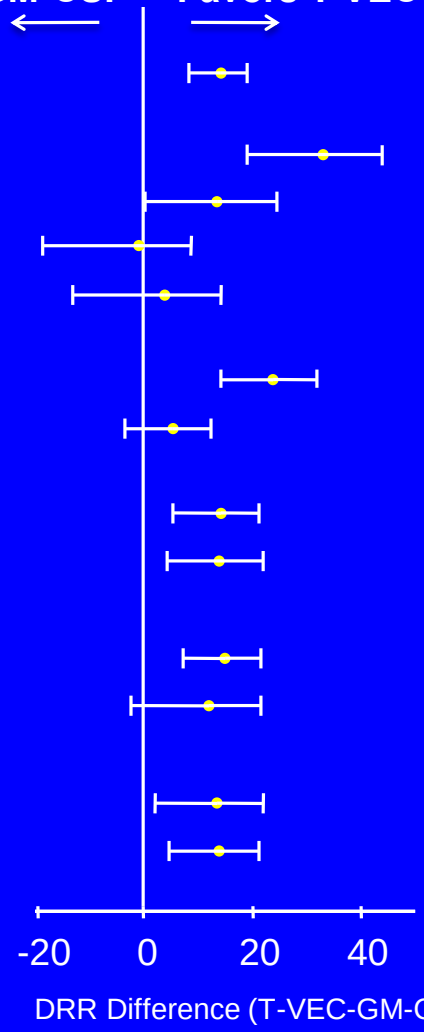
All responses presented are per independent EAC. Overall responses were not required to be confirmed.

[a]Unadjusted Fisher's exact test

Andtbacka et al. ASCO 2013; LBA9008

DRR By Key Covariates

(Exploratory Subgroup Analyses)

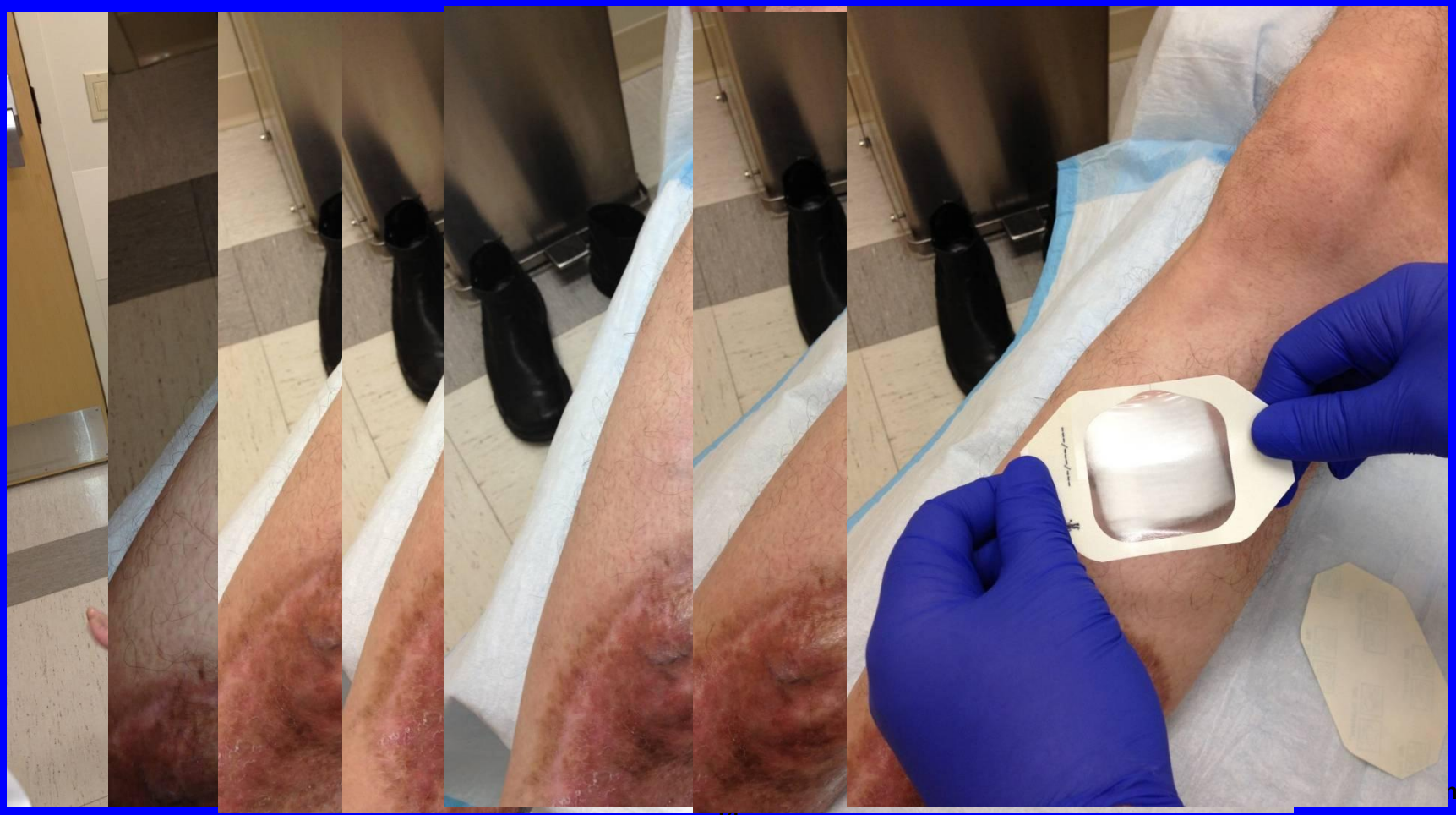


	N	GM-CSF (%)	T-VEC (%)	Diff. % (95% CI)
All randomly assigned	436	2.1	16.3	14.1 (8.2 – 19.2)
Disease stage – IIIB / IIIC	131	0.0	33.0	33.0 (19.1 – 43.9)
Disease stage - IVM1a	118	2.3	16.0	13.7 (0.2 – 24.6)
Disease stage - IVM1b	90	3.8	3.1	-0.7 (-18.6 – 8.7)
Disease stage - IVM1c	96	3.4	7.5	4.0 (-12.8 – 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)

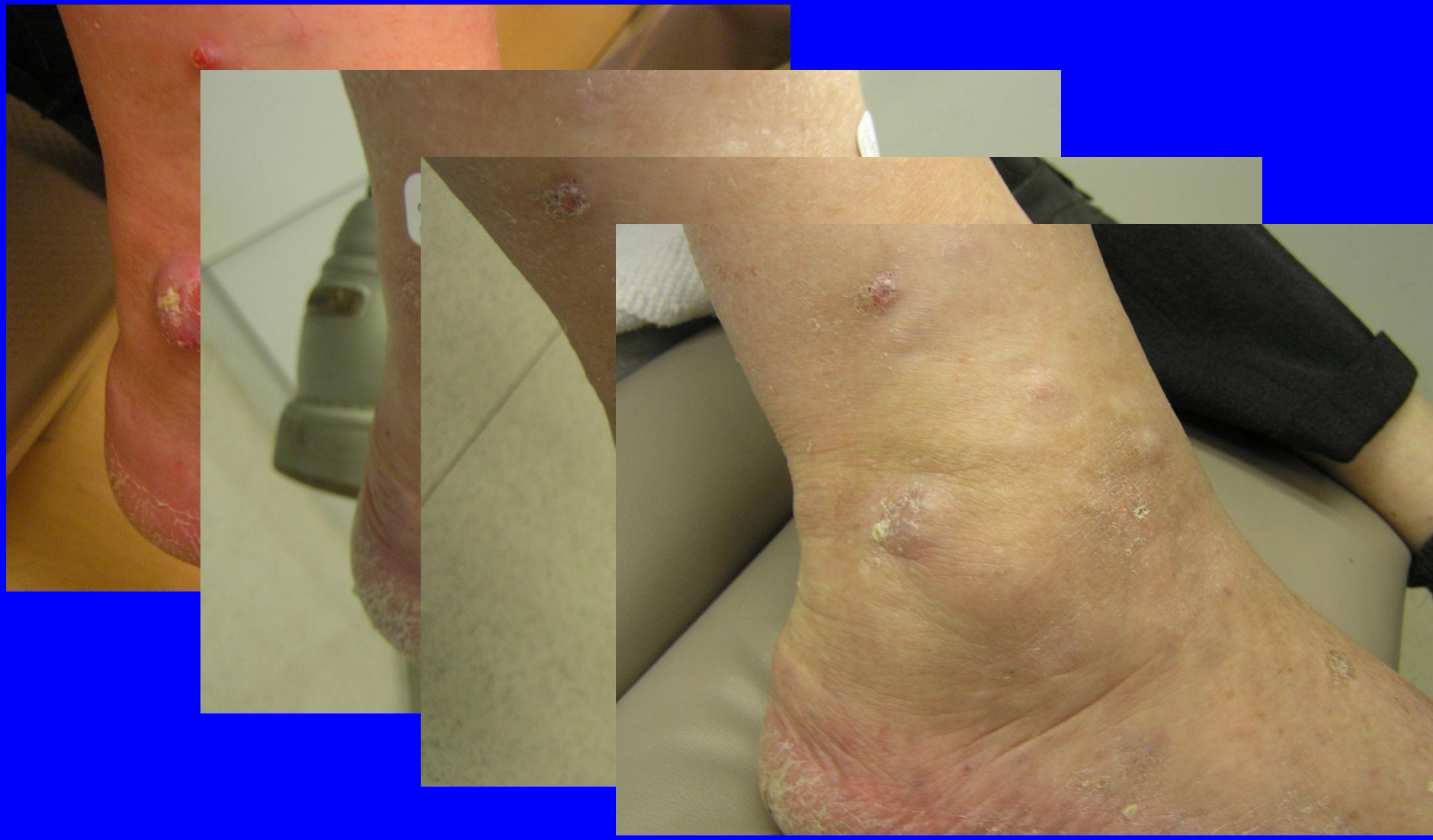
Andtbacka et al. ASCO 2013; LBA9008

T-VEC Adinistration

Drug Administration

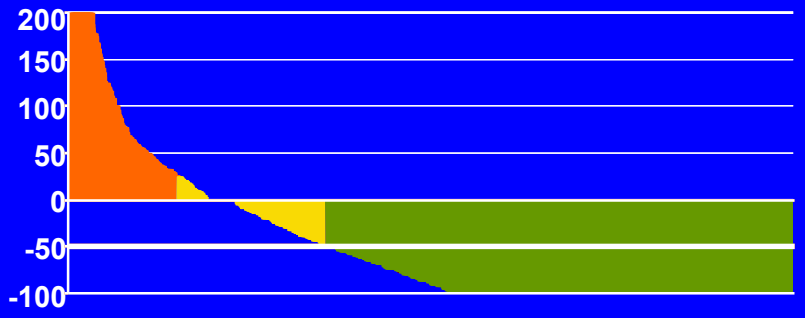


Complete regression of soft tissue melanoma after TVEC



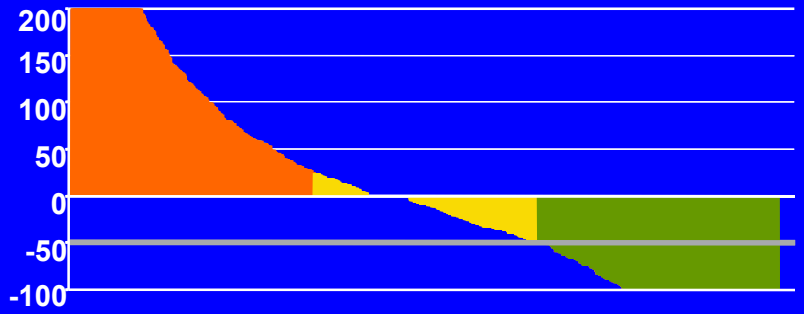
Lesion-Level and Patient-Level Responses to T-VEC

Lesion Type: Injected



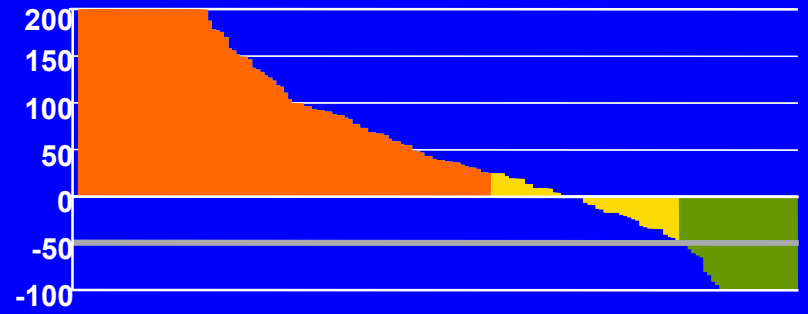
Lesion N=2116		Patient N=277	
≥ 50% decrease	64%	OR	33%
100% decrease	47%	CR	15%

Lesion Type: Uninjected Non-Visceral



Lesion N=981		Patient N=177	
≥ 50% decrease	34%	OR	18%
100% decrease	22%	CR	6%

Lesion Type: Uninjected Visceral



Lesion N=177		Patient N=79	
≥ 50% decrease	15%	OR	14%
100% decrease	9%	CR	3%

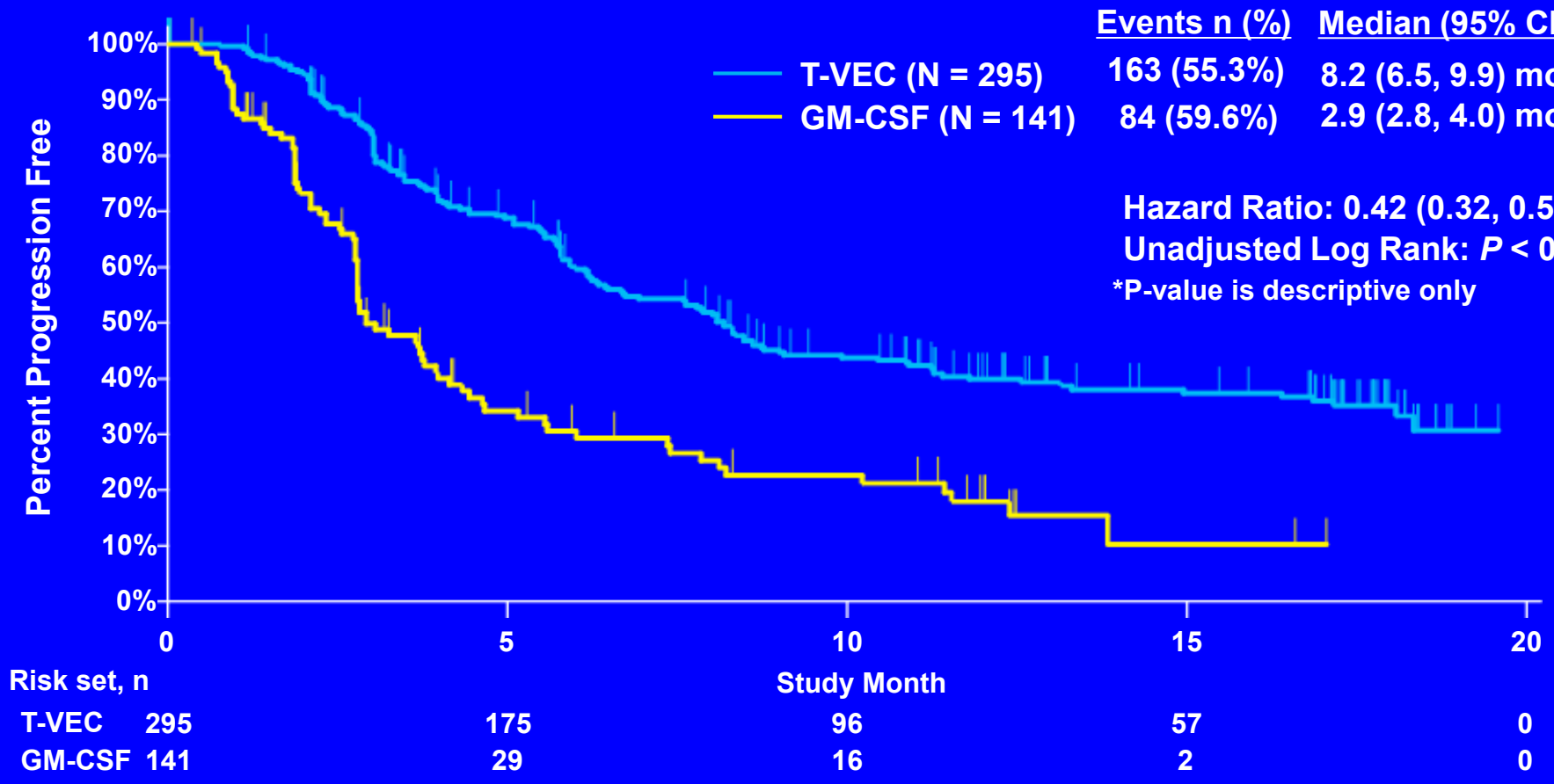
Percentage Change from Baseline

Tumor area change: ≥ 25% | > – 50% to < 25% | – 100% to ≤ – 50%

To be included in the lesion-level response analysis, lesions were required to have at least 2 measurements. For the patient-level response analysis, only patients with at least 1 lesion represented in the corresponding waterfall plot were included. Responses were per investigator

Andtbacka et al., SSO 2014, Abstract PCC-121.

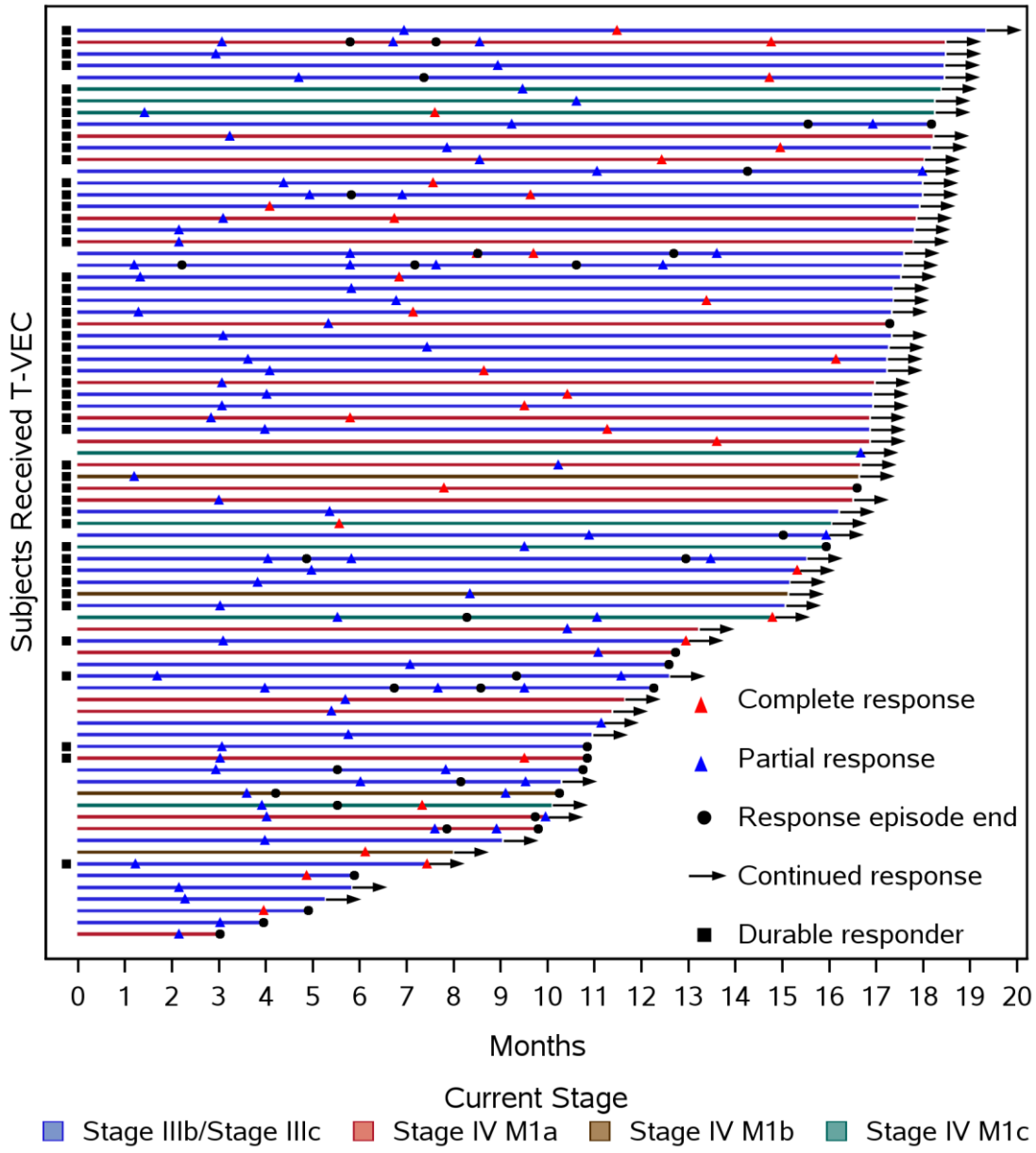
Modified Progression-Free Survival



- Modified PFS was defined as time from the first dose of study treatment until death or development of the first clinically significant progression for which no objective response was subsequently achieved

Andtbacka et al. ASCO 2013; LBA9008

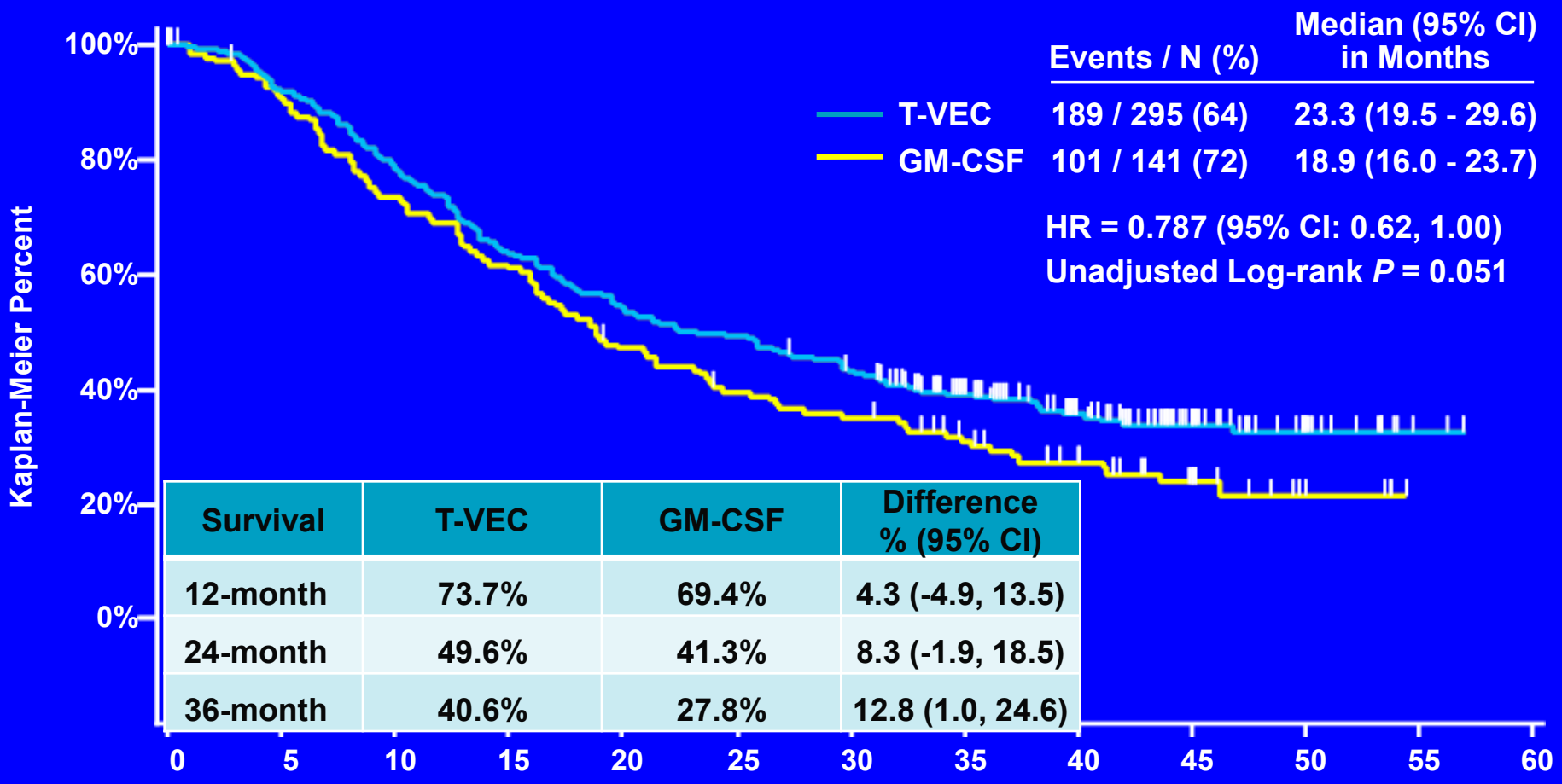
Time to Response And Duration of Response



- To be a durable responder, patient had to have response of at least 6 continuous months
- Patients were to continue treatment beyond progression, allowing for reinitiation of response after progression
- PD displayed when it represents the end of an objective response. PD also occurred prior to objective responses in many cases (not shown).

- Both PRs and CRs were seen across all stages
- 72% of patients with an ORR were still in response at the time of the last available tumor assessment
- 54% ORR and 48% DRR exhibited interval progression before achieving response
-

Primary Overall Survival



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

HR = 0.787 (95% CI: 0.62, 1.00)
Unadjusted Log-rank *P* = 0.051

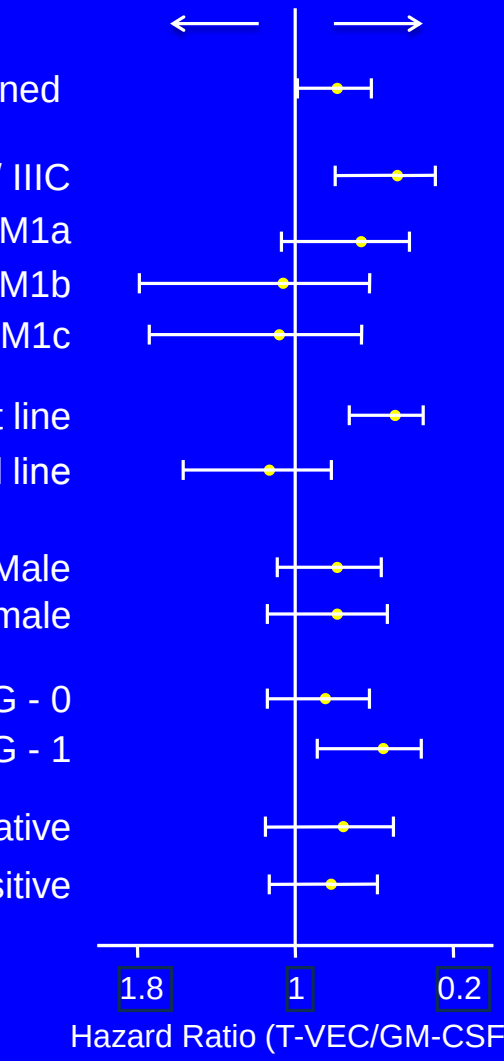
Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-month	73.7%	69.4%	4.3 (-4.9, 13.5)
24-month	49.6%	41.3%	8.3 (-1.9, 18.5)
36-month	40.6%	27.8%	12.8 (1.0, 24.6)

Patients at risk:

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

OS by Key Covariates

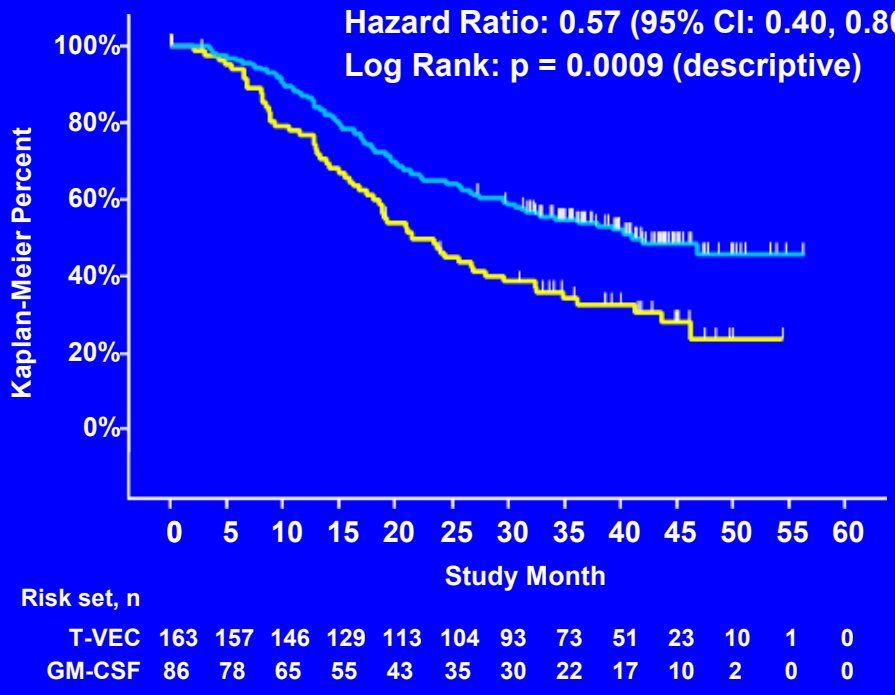
(Exploratory Subgroup Analyses)



	GM-CSF n	T-VEC n	HR (95% CI)
All randomly assigned	141	295	0.79 (0.62 – 1.00)
Disease stage - IIIB / IIIC	43	88	0.48 (0.29 – 0.80)
Disease stage - IVM1a	43	75	0.67 (0.42 – 1.07)
Disease stage - IVM1b	26	64	1.06 (0.63 – 1.79)
Disease stage - IVM1c	29	67	1.08 (0.67 – 1.74)
Line of therapy - First line	65	138	0.50 (0.35 – 0.73)
Line of therapy - ≥ Second line	76	157	1.13 (0.82 – 1.57)
Male	77	173	0.79 (0.57 – 1.09)
Female	64	122	0.79 (0.54 – 1.14)
ECOG - 0	97	209	0.85 (0.63 – 1.14)
ECOG - 1	32	82	0.56 (0.36 – 0.89)
HSV-1 Status - Negative	45	97	0.76 (0.51 – 1.15)
HSV- 1 Status - Positive	78	175	0.82 (0.59 – 1.13)

Exploratory OS Subgroup Analysis By Disease Stage

Stage IIIB/C, IVM1a

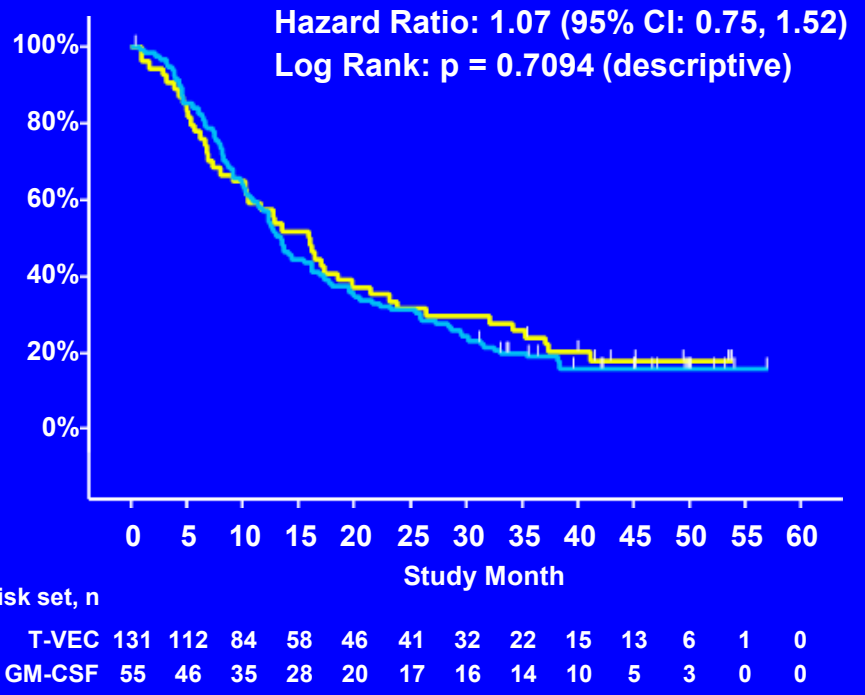


Risk set, n

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), mos
T-VEC	60 / 183 (49)	41.1 (30.6, NE)
GM-CSF	57 / 86 (66)	21.5 (17.4, 29.6)

Stage IVM1b/c



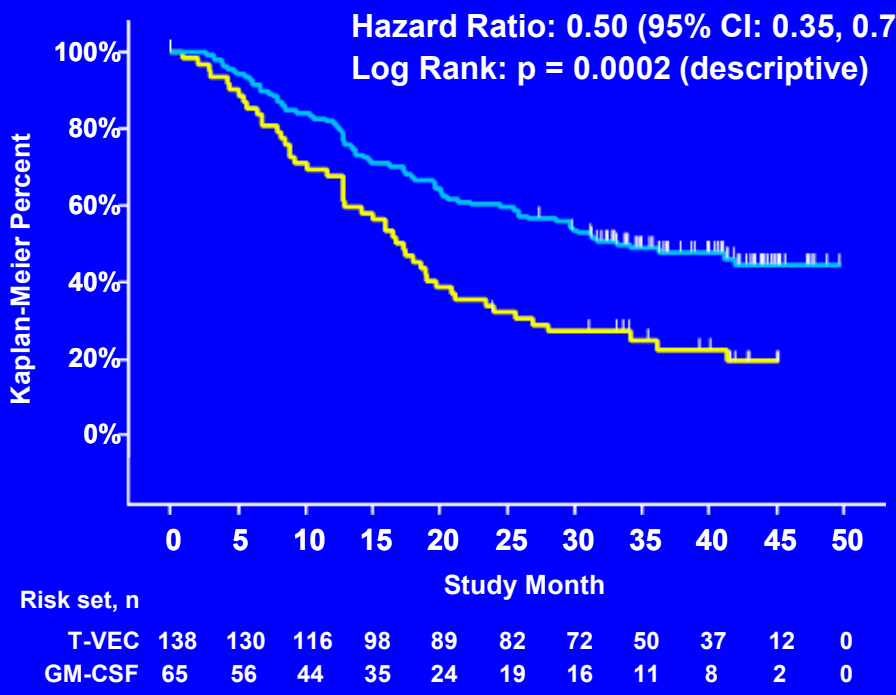
Risk set, n

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), mos
T-VEC	109 / 131 (83)	13.4 (11.4-16.2)
GM-CSF	44 / 55 (80)	15.9 (10.2-19.7)

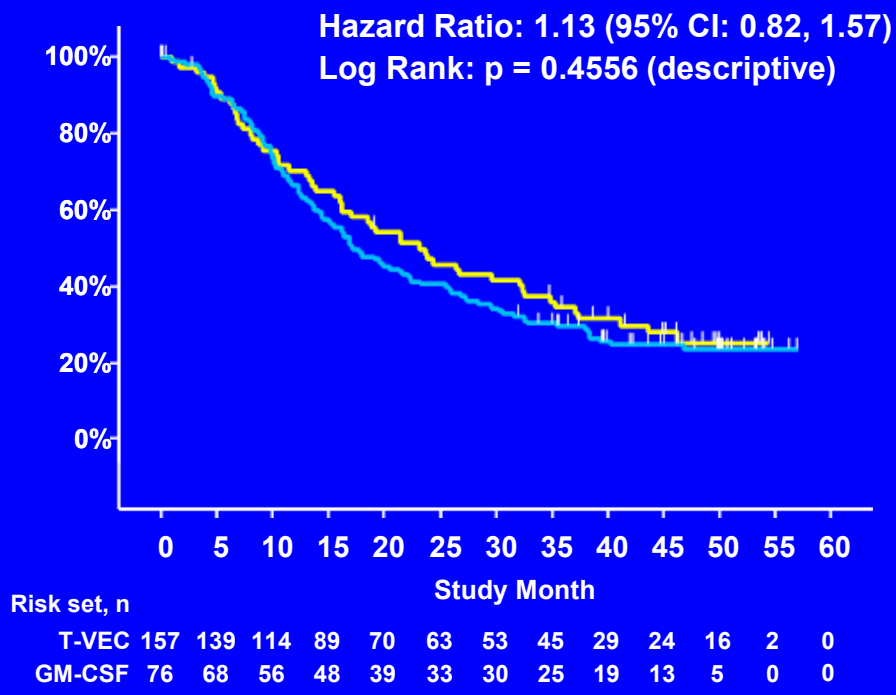
Exploratory OS Subgroup Analysis By Treatment Line

First-Line Therapy



	Events / N (%)	Median (95% CI), mos
T-VEC	73 / 138 (53)	33.1 (25.9, NE)
GM-CSF	48 / 65 (74)	17.0 (12.8, 20.9)

≥ Second-Line Therapy

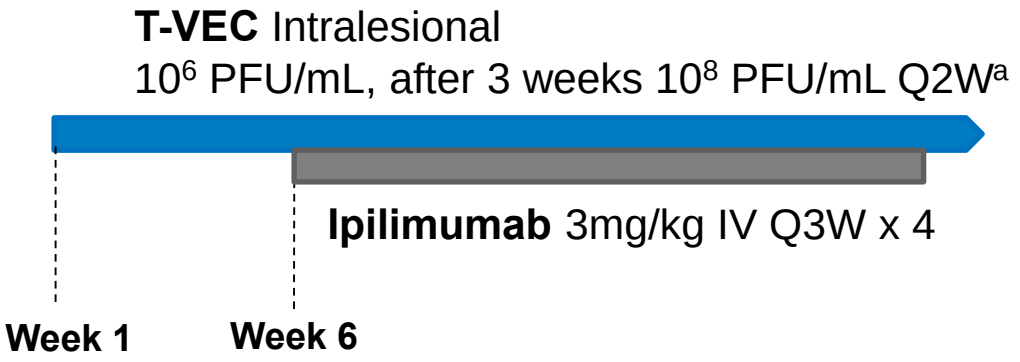


	Events / N (%)	Median (95% CI), mos
T-VEC	116 / 157 (74)	17.1 (14.3, 22.3)
GM-CSF	53 / 76 (70)	23.2 (16.2, 32.4)

Study Schema – Phase 1b Trial of T-VEC and Ipilimumab

N = 19

Unresectable Stage IIIB-IV Melanoma
- **Injectable**
- **Treatment naive**
- **ECOG PS 0 or 1**
- **No evidence of CNS mets**



T-VEC dosing until CR, all injectable tumors disappeared, PD per irRC, or intolerance whichever comes first.

Primary Endpoint:	Incidence of dose-limiting toxicities (DLTs)
Key Secondary Endpoints:	ORR^{irRC}, Safety

[a] Dosing of T-VEC was δ 4 mL × 10^6 PFU/mL once, then after 3 weeks, δ 4 mL × 10^8 PFU/mL Q2W.

Collichio et al. SMR 2014, Zurich

Phase 1b: Treatment-Emergent Adverse Events*

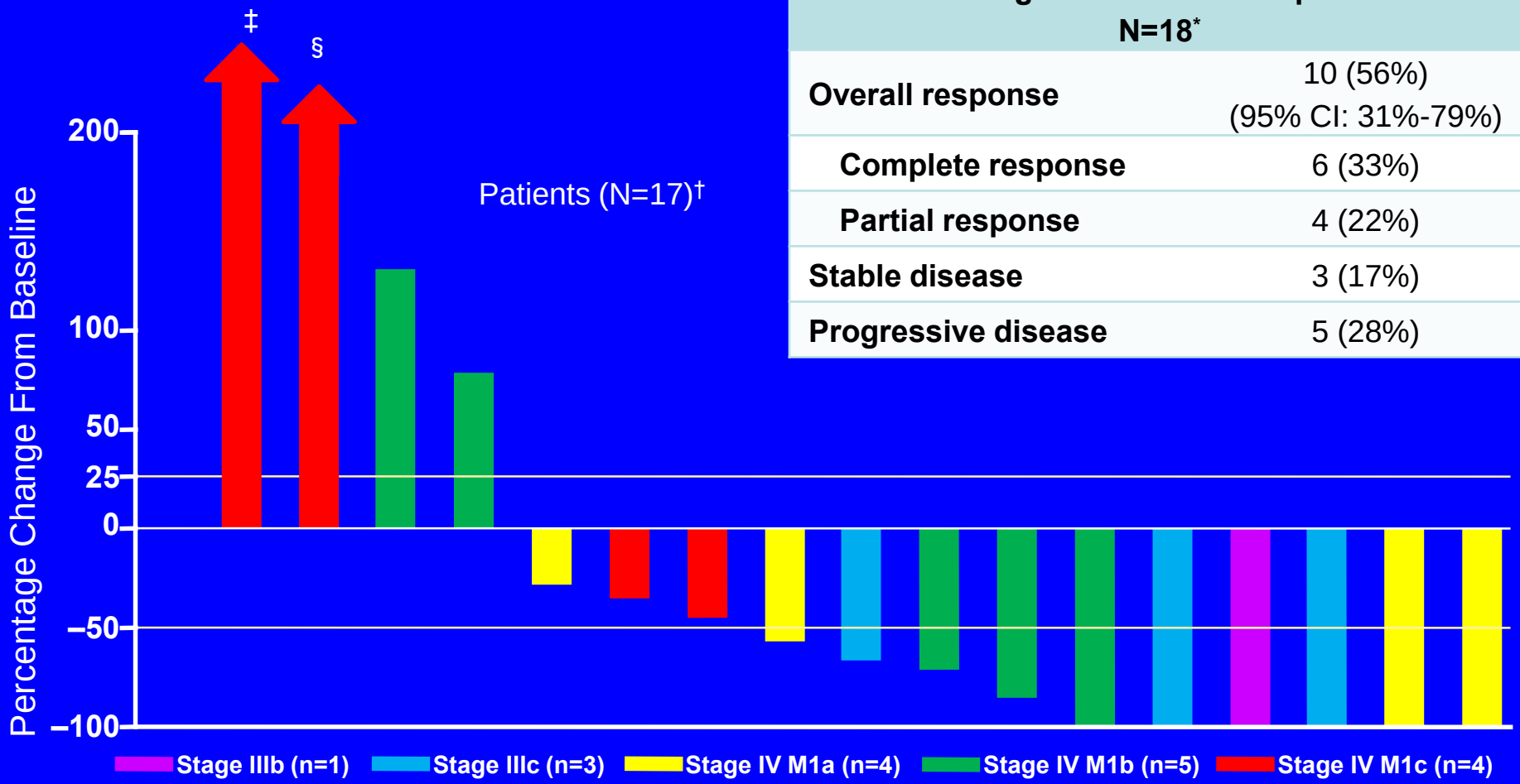
Preferred Term	Total N (%)	Grade 3 N (%)
Any event	19 (100)	5 (26)
Any attributed to T-VEC	17 (90)	3 (16)†
Any attributed to ipilimumab	15 (80)	3 (16)†
Chills	11 (58)	-
Fatigue	11 (58)	1 (5)
Pyrexia	11 (58)	1 (5)
Nausea	9 (47)	2 (11)
Rash	9 (47)	-
Diarrhea	8 (42)	1 (5)
Headache	8 (42)	-
Pruritis	7 (37)	-
Decreased appetite	4 (21)	-
Hyperglycemia	4 (21)	-
Vomiting	4 (21)	1 (5)
ALT increased	3 (16)	-
Back pain	3 (16)	1 (5)
Influenza-like illness	3 (16)	1 (5)
Pain	3 (16)	-
Vision blurred	3 (16)	-

- The only grade 3 event occurring in > 1 patient was nausea
- The only two grade 4 events were in a patient with elevated amylase and lipase (attributed to ipilimumab)
- There was one grade 5 event of metastases to central nervous system (preferred term)

*All events of any grade occurring in > 15% of patients during treatment or up to 30 days after last T-VEC or 60 days after last ipilimumab, whichever is later; †Grade 3 events in these patients: pyrexia attributed to T-VEC; hypophysitis and abdominal distention attributed to ipilimumab; and nausea, diarrhea, fatigue, influenza-like illness, vomiting, adrenal insufficiency, and dehydration attributed to both; ALT: alanine aminotransferase

Phase 1b – Maximal Change in Tumor Burden

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



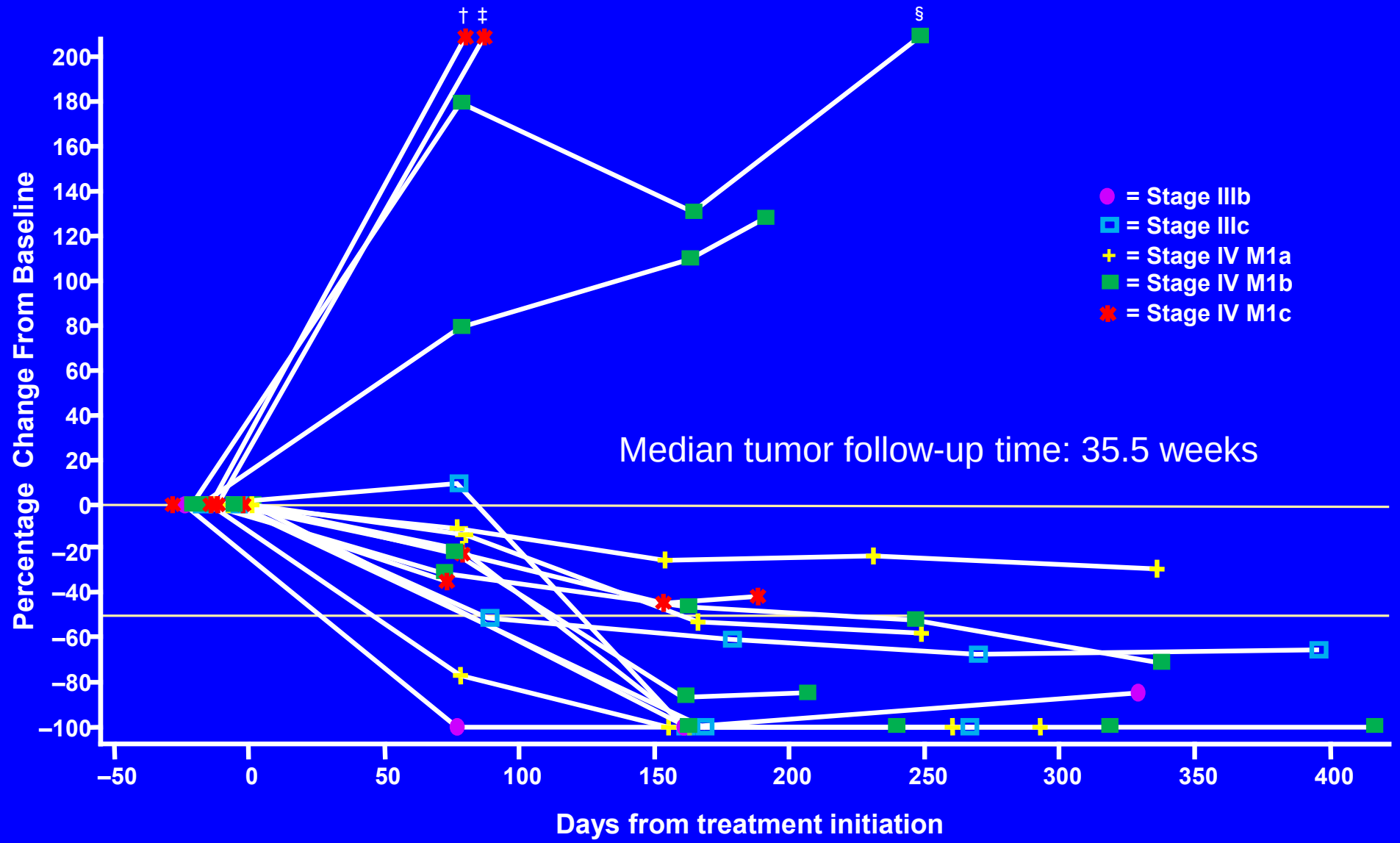
* Efficacy analysis set includes only the patients who received both T-VEC and ipilimumab. Both responses and progressions are included; nine of the 10 responses are confirmed, and one is unconfirmed

† 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

‡ Percentage change from baseline for this patient was 538

§ Percentage change from baseline for this patient was 265

Phase 1b – Changes in Tumor Burden by Disease Stage*



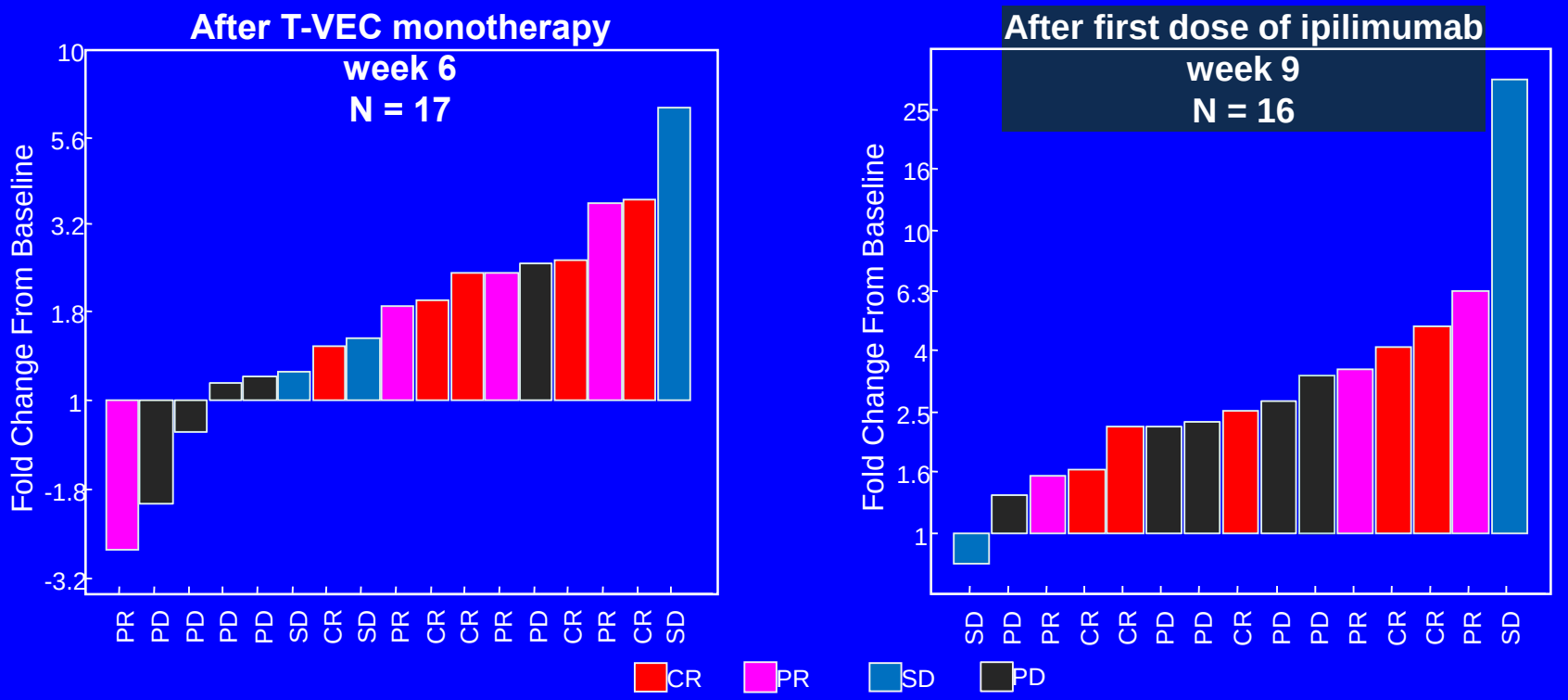
* One patient with PD is not represented in the plot because post-baseline overall tumor burden was not provided

† Percentage change from baseline for this patient was 538 at study day 87

‡ Percentage change from baseline for this patient was 265 at study day 80

§ Percentage change from baseline for this patient was 770 at study day 248

Changes in activated CD8+ T cells* after T-VEC and Ipilimumab according to best response



- At week 6 after receiving 2 doses of T-VEC, 10 of 12 patients with disease control (SD+PR+CR) had > 1.4x increase in activated CD8 T cell count
- 4 of 5 patients with PD did not
- This pattern was no longer evident after ipilimumab was given

*Activated CD8 T cells defined as HLA-DR+CD3+CD4- cells;

Comparison of melanoma monotherapy agents

Drug	ORR (%)	DCR (%)	DRR (%)	Median OS (months)	1-yr OS (%)	3-yr OS (%)	Grade 3-4 AEs (%)	Mortality (%)*	References
Vemurafenib	48	N/A	N/A	13.6	58	26	38	0	Chapman et al. NEJM 2011; McArthur et al. Lancet Oncol 2014
Ipilimumab	10.9	28.5	N/A	10	45.6	22	10-15	2.1	Hodi et al. NEJM 2011
Pembrolizumab	24	51	N/A	N/R	58	N/A	12	0	Robert et al. Lancet 2014
Interleukin-2 (IL-2)	16-28	41	N/A	11.4	59	31	80-90	0-2	Atkins et al. JCO 1999l; Payne et al. JITC 2014; Hughes et al. CII 2015
Talimogene laherparepvec (T-VEC)	26.4	76	16.3	23.3	73.6	40.6	29	0	Kaufman et al. ASCO 2014 and In press, 2015

*Drug-related

CONCLUSIONS

- T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a well-controlled, randomized phase III trial
  - Improvement in DRR and ORR compared to control
  - Improved OS
  - Evidence for induction of activated antigen-specific CD8+ T cells
- T-VEC monotherapy provides a novel potential therapeutic approach for metastatic melanoma
  - Exploratory analyses suggest a particular benefit in patients with limited visceral disease and when administered as first-line therapy
  - T-VEC compares favorably with other monotherapy agents available for the treatment of melanoma
- Combinatory treatment approaches with T-VEC are rational and showing further promise for treating more advanced disease
  - T-VEC and Ipilimumab Phase II in progress
  - T-VEC and pembrolizumab planned
- Are we ready for prime time?

ACKNOWLEDGEMENTS: Patients & Families

- **UNITED STATES**
  - Thomas Amatruda, MN
  - Amy Abernethy, NC
  - Robert Andtbacka, UT
  - Sanjiv Agarwala, PA
  - Ernest Borden, OH
  - Peter Brett, CA
  - Jason Chesney, KY
  - Frances Collichio, NC
  - Lee Cranmer, AZ
  - Brendan Curti, OR
  - Gregory Daniels, CA
  - Keith Delman, GA
  - Troy Guthrie, Jr., FL
  - Howard Kaufman, IL
  - Laura Hutchins, AR
  - Eddy Hseuh, MO
  - Karl Lewis, CO
  - Gerald Linette, MO
  - Theodore Logan, IN
  - Jose Lutsky, FL
  - David Minor, CA
  - Dirk Noyes, UT
  - Kendra Feeney, PA
  - Neil Senzer, TX
  - Leslie Oleksowicz OH
  - Gregory Pennock, FL
  - Madhavi Venigalla, FL
  - Merrick Ross, TX
  - Neal Rothschild, FL
  - Saenger Yvonne, NY
  - Lynn Spitler, CA
  - Mark Cohen, KS
  - Eric Whitman, NJ
  - Jonathan Richards,, IL
  - Paul Richards, VA
  - Stephen Schultz, IN
  - Joseph Stephanson, SC
  - Igor Puzanov, TN
  - Nikhil Khushalani, NY
  - David Watkins, TX
  - Anton Melnyk, Jr., TX
  - Mohammed Milhem, IA
  - Jonathan Zager, FL
  - Keisuke Shirai, SC
  - Clair Verschraegen, NM
  - Bret Taback, NY
  - Nash Gabrail, OH
- **UNITED KINGDOM**
  - Pippa Corrie, Cambridge
  - Kevin Harrington, London
  - Mark Middleton, Oxford
  - Alan Melcher, Leeds
  - Neil Steven, Birmingham
  - Stephen Nicholson, Leicester
  - Christian Ottensmeier, Southampton
- **SOUTH AFRICA**
  - Samuel Fourie, Pretoria
  - Graham Cohen, Pretoria
  - Lee-Ann Jones, Port Elizabeth
  - Conrad Jacobs, Cape Town
  - Lydia Dreosti, Pretoria
  - Susan Fourie, Free State
  - Georgina Mc Adam, Cape Town
  - Shane Cullis, Kwa-Zulu Natal
- **CANADA**
  - Wilson Miller, Montreal
  - David Hogg, Toronto

Jennifer Gansert
- Michael Wolf
- Jeffrey Chou
- Yining Ye
- Rob Coffin