Talimogene Laherparepvec

Cellular, Tissue and Gene Therapies & Oncologic Drug Advisory Committee Meeting

Sponsor Presentation Agenda

Topic	Presenter
Introduction	**Rhian Thomas, BSc** Amgen Inc. Executive Director, Global Regulatory Affairs
Metastatic Melanoma	**Howard Kaufman, MD, FACS** Chief Surgical Officer; Associate Director for Clinical Science; and Co-Leader, Clinical Investigations and Precision Therapeutics Program at the Rutgers Cancer Institute of New Jersey
Mechanism of Action and Clinical Efficacy Overview	**Jennifer Gansert, MD, PhD** Amgen Inc. Executive Director, Global Development Lead
Clinical Safety Overview and Risk Management Plan	**Deborah Arrindell, MD, MPH, JD** Amgen Inc. Executive Director, Global Patient Safety
Clinical Perspective	**Howard Kaufman, MD, FACS**
Conclusion	**Steven Galson, MD, MPH** Amgen Inc. Senior Vice President, Global Regulatory Affairs and Safety

External and Internal Experts

Name	Expertise and Affiliation
External Advisors*	
Frances Collichio, MD	Medical Oncology University of North Carolina Chapel Hill
Colin Love, PhD**	Manufacturing and Quality Consultant
Ian Mohr, PhD	Virology New York University School of Medicine
Merrick Ross, MD	Surgical Oncology University of Texas
Internal to Amgen, Inc.	
Elliott Levy, MD	Global Development
Caroline Lilley, PhD	Virology
Rafael Ponce, PhD	Preclinical Safety
Michael Wolf	Biostatistics

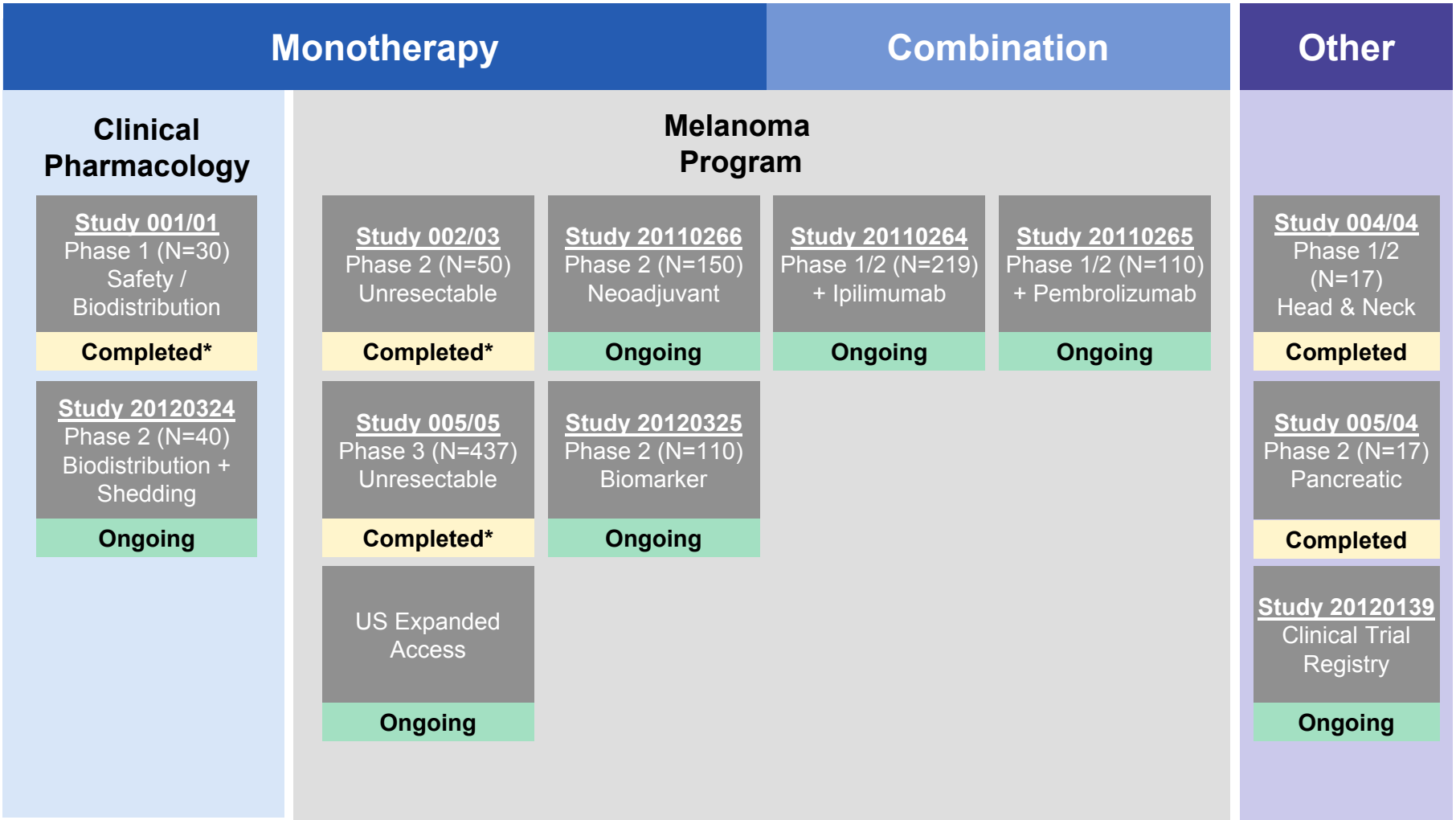
*Received consulting fees and had travel expenses covered by Amgen Inc.
**Owns stock in Amgen Inc. and has other financial interests based on Amgen acquisition of BioVex Group, Inc.

Talimogene Laherparepvec

- Innovative oncolytic immunotherapy based on herpes simplex type 1 virus (HSV-1)
- Virus modified to be attenuated
- Efficiently replicates in tumors but not normal tissues
- Retains sensitivity to anti-viral agents
- Results in tumor cell lysis for local control
- Results in release of tumor-derived antigens and GM-CSF to initiate a systemic anti-tumor immune response

GM-CSF: granulocyte macrophage colony stimulating factor

Clinical Development Program

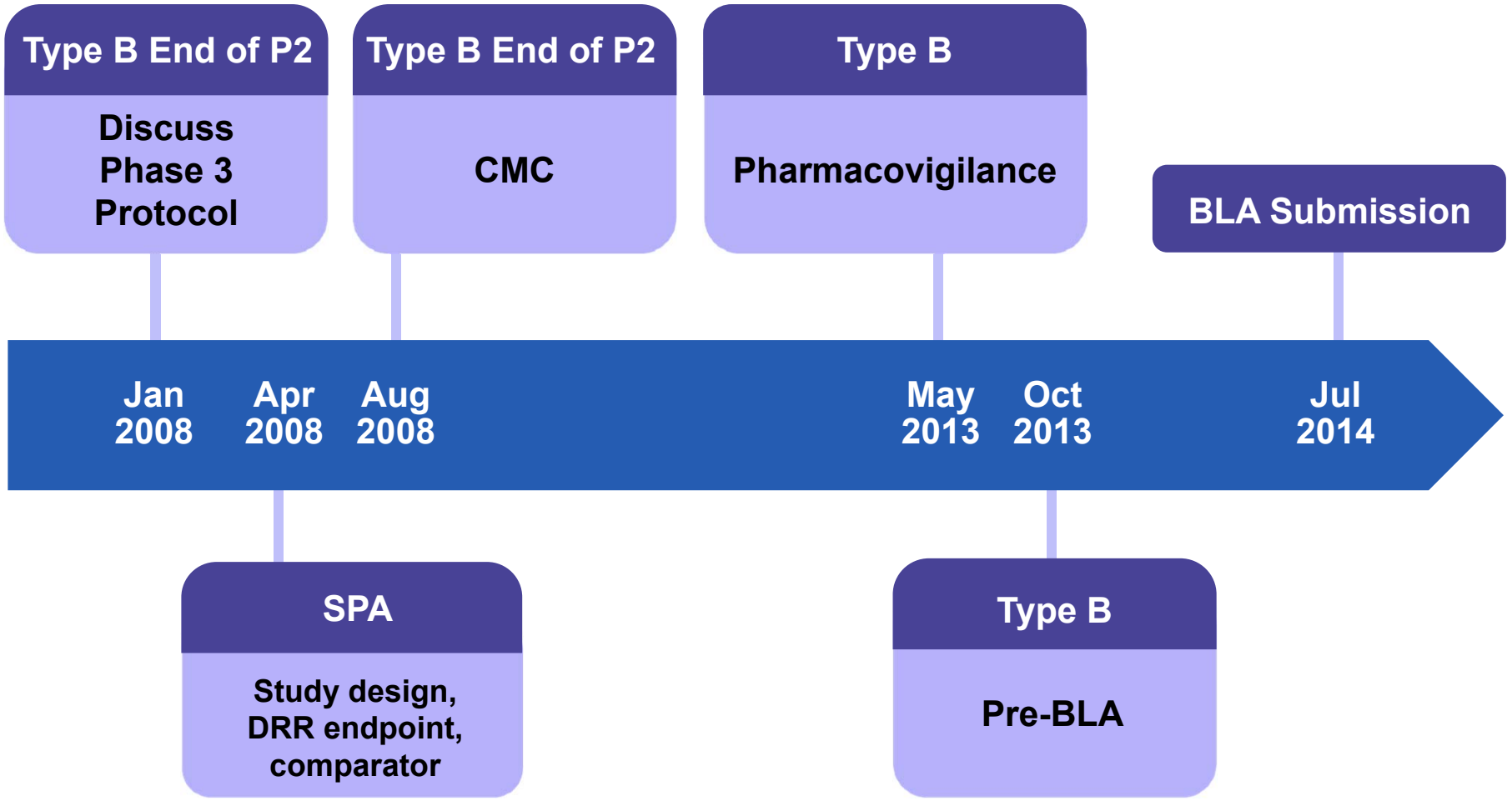


*Extension studies not included in this figure

Key Studies Contributing to the BLA

Phase	Study title	N =	Tumor	Status
1	**001/01:** First in Human Study of Safety, Biodistribution and Biological Activity	30	Refractory solid tumors	Complete
2	**002/03:** Phase 2 Study of Efficacy, Safety and Immunogenicity in Patients With Stage IIIC and Stage IV Melanoma	50	Melanoma	Complete
3	**005/05:** Randomized Phase 3 Trial Comparing Talimogene Laherparepvec to GM-CSF in Melanoma Patients with Unresectable Stage IIIB, IIIC and IV Disease (OPTiM)	436	Melanoma	Complete, positive primary endpoint

Key Regulatory Interactions for BLA



CMC: clinical, manufacturing, and control; SPA: special protocol assessment; BLA: Biologics License Application

Proposed Indication

Talimogene laherparepvec is an oncolytic immunotherapy indicated for the treatment of injectable regionally or distantly metastatic melanoma

Talimogene Laherparepvec Overview

- The need for innovative anti-cancer treatments for metastatic melanoma remains
- Pivotal study was well-controlled and demonstrated a highly statistically significant improvement in durable response rate
- Durable response was associated with clinical benefit
- Talimogene laherparepvec was very well tolerated
- A risk management plan is proposed
- Positive benefit:risk in the patient population studied

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Metastatic Melanoma

Howard Kaufman, MD, FACS

Chief Surgical Officer

Associate Director for Clinical Science

Co-Leader, Clinical Investigations and Precision Therapeutics Program

at the Rutgers Cancer Institute of New Jersey

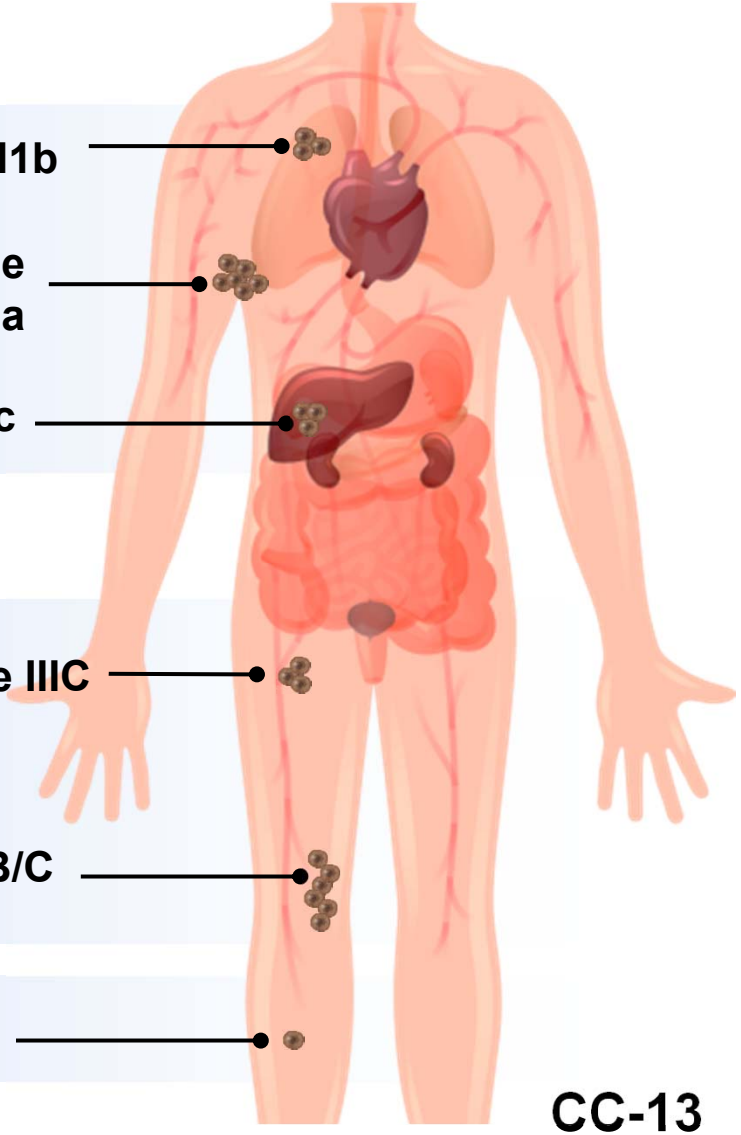
President, Society of Immunotherapy of Cancer

Melanoma Overview

- **The incidence of melanoma has been rising for at least 30 years: 74,000 new diagnoses expected in 2015**
- **Almost 10,000 people will die from this cancer in 2015**

Regionally and Distantly Metastatic Melanoma

5-Year Survival		
16%	Distant Metastases	Lung, Stage IVM1b Skin or Lymph node Stage IVM1a Liver, Stage IVM1c
20-70%	Regional Metastases	Lymph node, Stage IIIC In-transit, Stage IIIB/C
98%	Primary Tumor	



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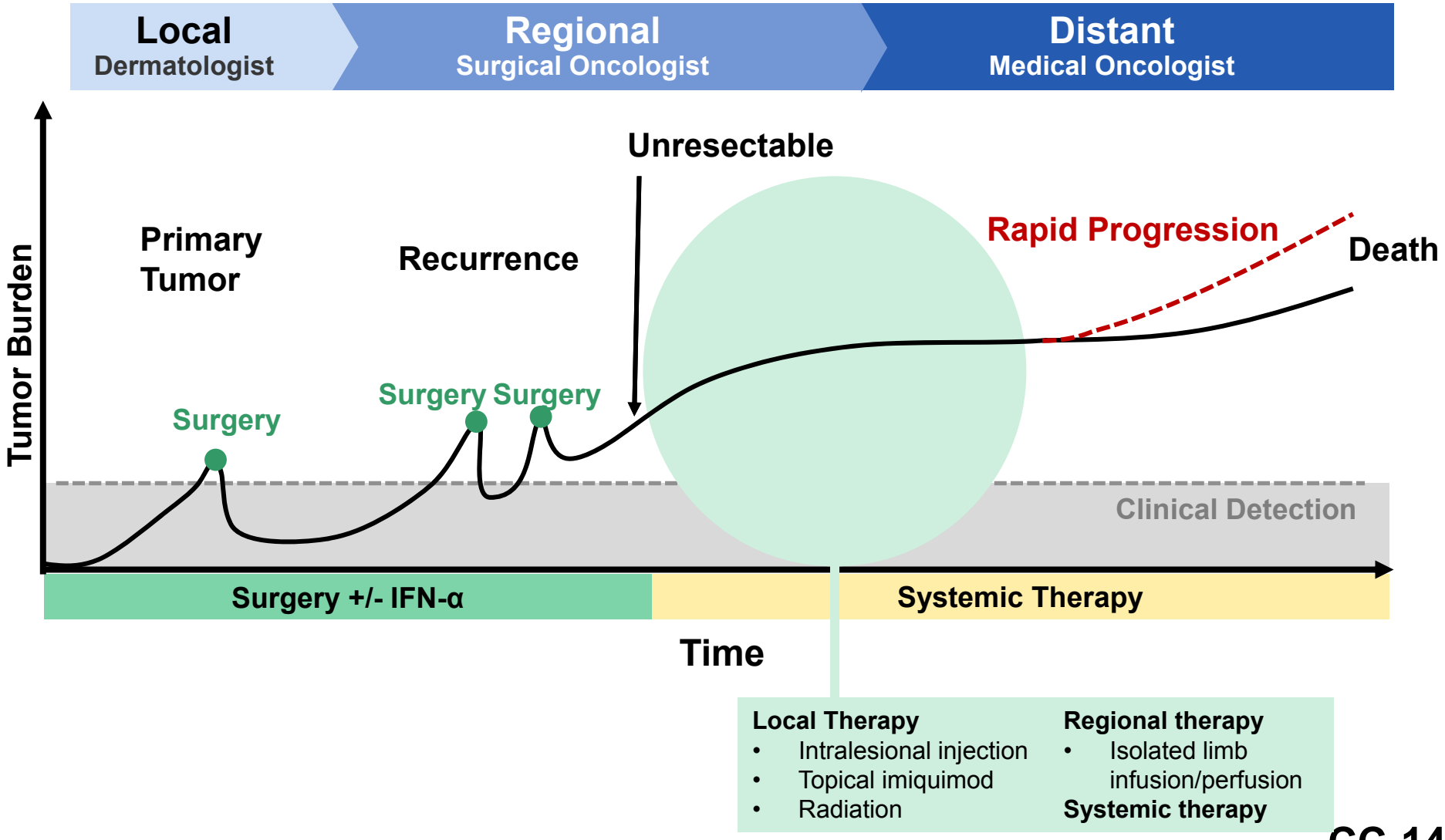
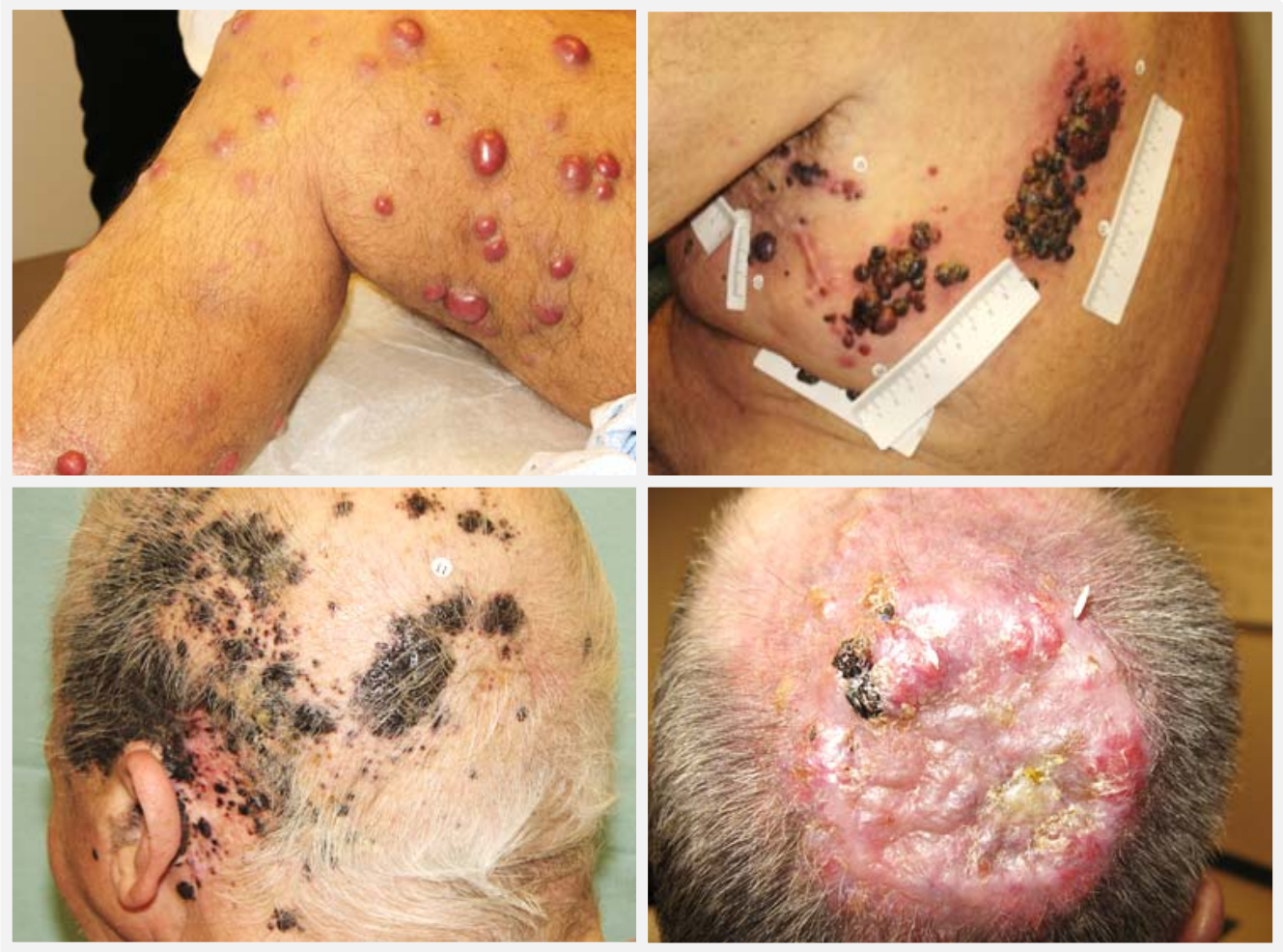
Melanoma Disease Continuum



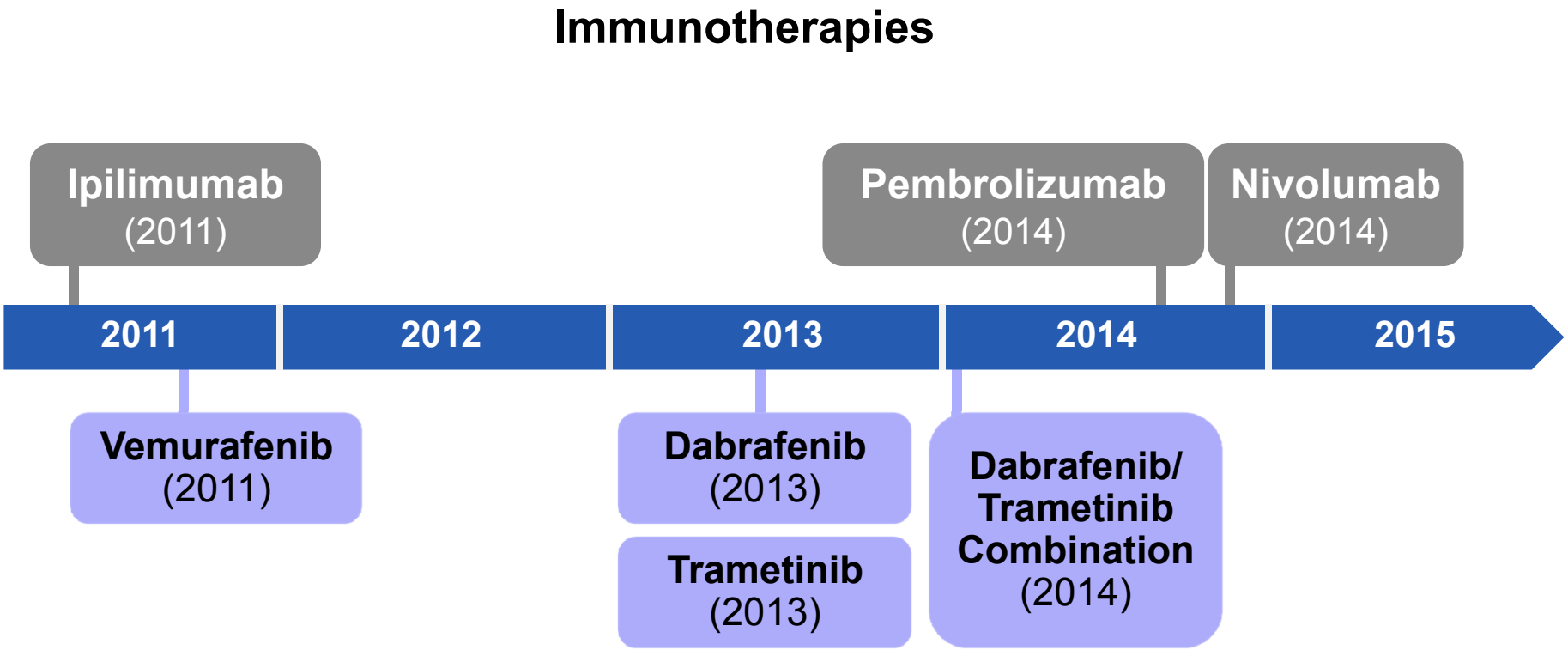
Patients with Loco-Regionally Advanced Melanoma in Study 005/05



Systemic Melanoma Treatment Prior to 2011

IL-2: interleukin-2

Six Drugs Approved for Melanoma in 4 Years



Efficacy of Targeted Therapy and Immunotherapy

	Targeted Therapy	Immunotherapy
Advantages	• High response rates • Rapid onset of effect	• Potential for durable response • Potential for long-term benefit even after the end of treatment
Disadvantages	• Only for ~50% of melanoma patients with BRAF mutant tumors • May elicit resistance within 6-8 months • Rare evidence of durable response off treatment • Survival curve separation not sustained	• Difficulty predicting patient responders • Low response rates • Delayed onset of effect

Adapted from McDermott et al Cancer Treatment Reviews 40 (2014) 1056-1064

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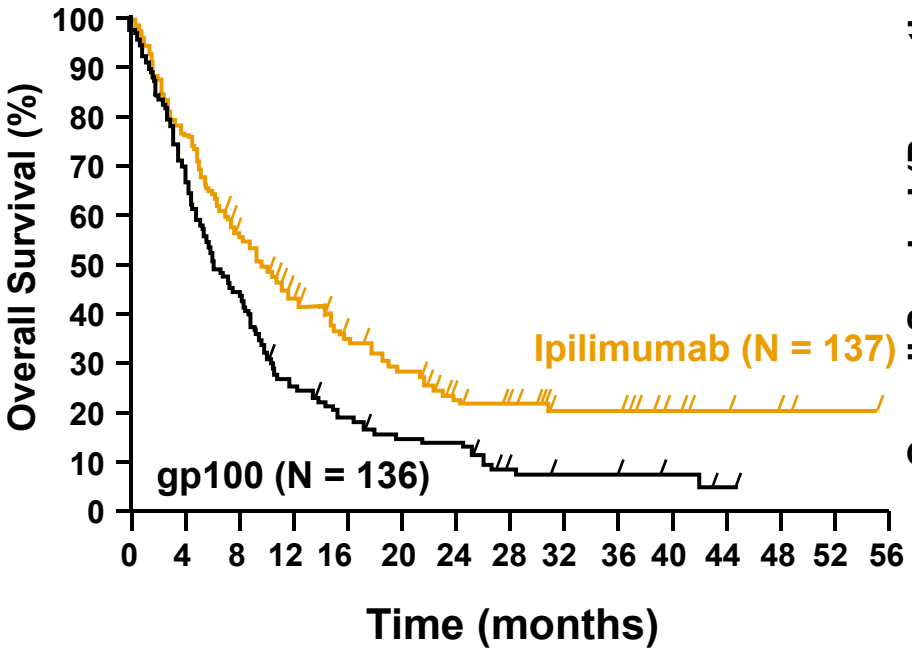
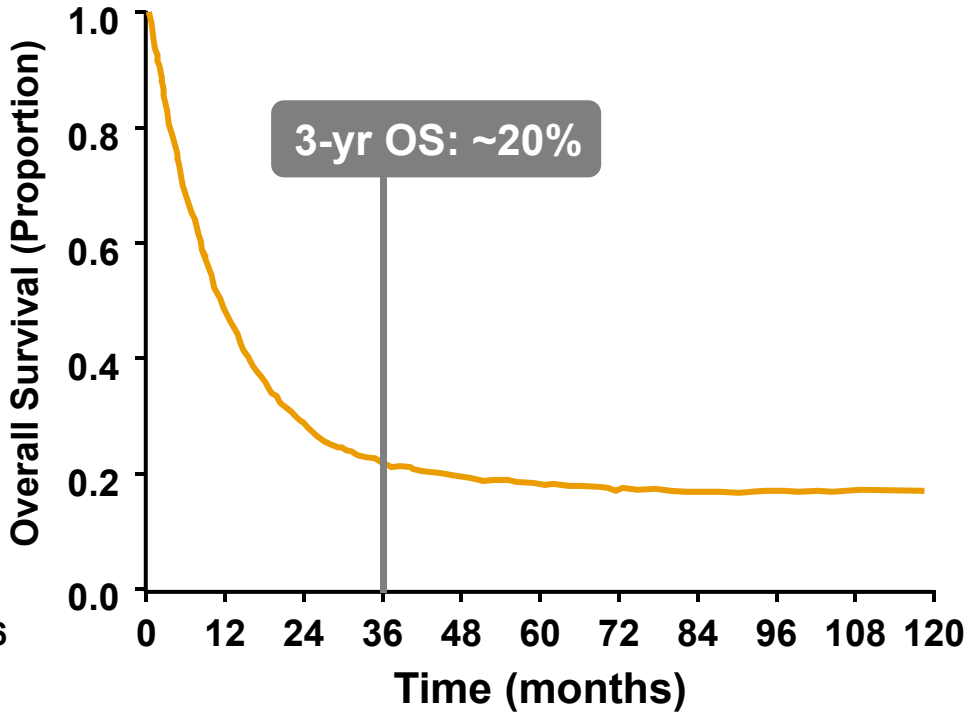
Survival Curves With Immunotherapies

Ipilimumab Trial in Previously Treated Patients[1]



Ipilimumab Pooled Overall Survival Data[2]



1. Hodi et al, NEJM, 2010: 363 (8)
2. Schadendorf et al, JCO, 2014.56.2736; published online on February 9, 2015

Toxicities Associated with Targeted Therapy and Immunotherapy

	Targeted Therapy	Immunotherapy
Toxicities	• Secondary skin malignancies • Severe photosensitivity • Serious febrile reactions	• Immune-related toxicities that must be carefully managed

Adapted from McDermott et al Cancer Treatment Reviews 40 (2014) 1056-1064

Existing Unmet Medical Need

- **The need for additional therapies still exists**
  - Melanoma is a complex cancer that requires the use of multiple treatment modalities over the course of the disease
  - Despite meaningful recent advancements, not all patients currently benefit
  - Some patients are not candidates for or cannot tolerate existing therapies
  - Durable response and survival rates for metastatic melanoma are still unacceptably low
- **Additional safe and effective treatment options like talimogene laherparepvec are required**

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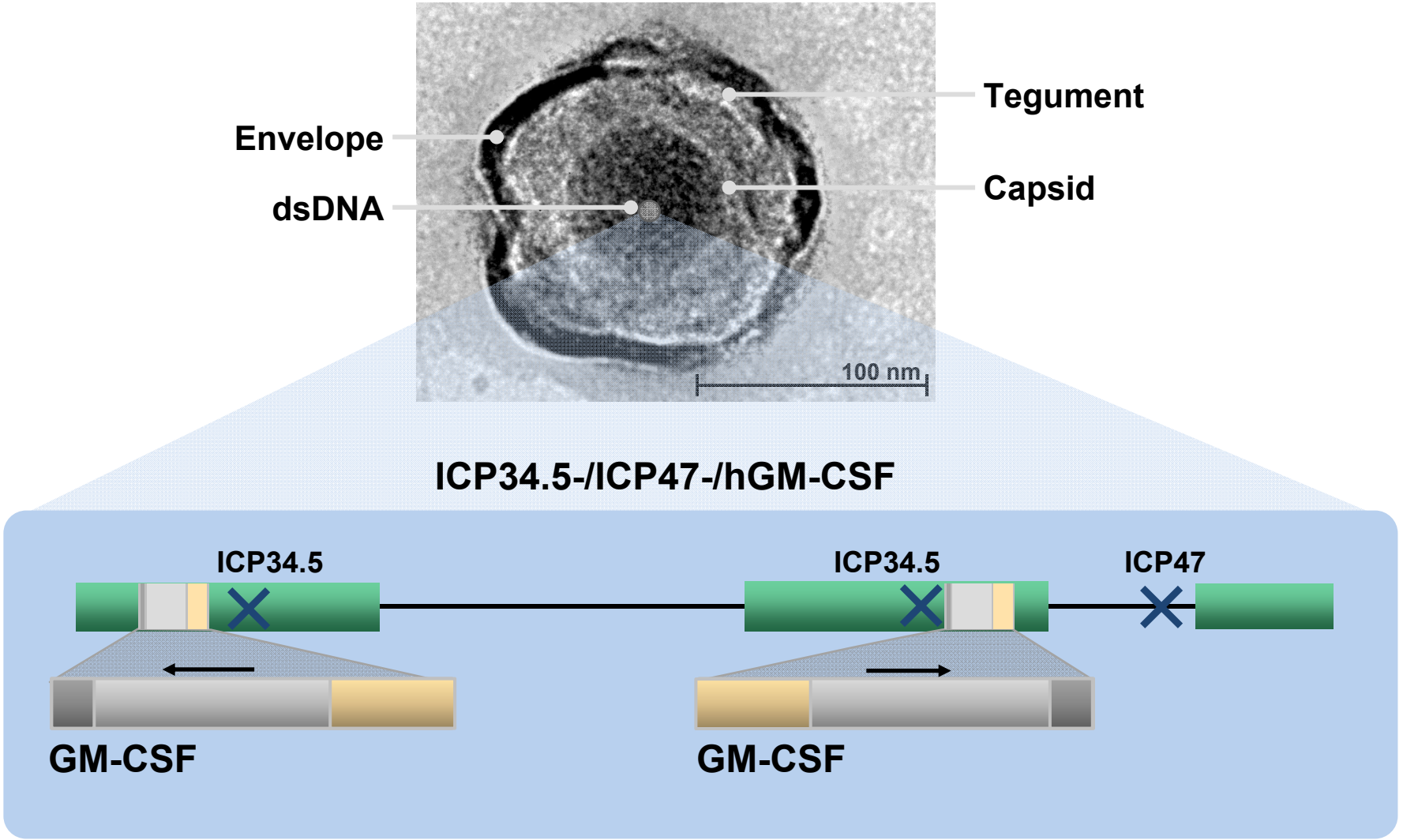
Design and Mechanism of Action

Jennifer Gansert, MD, PhD

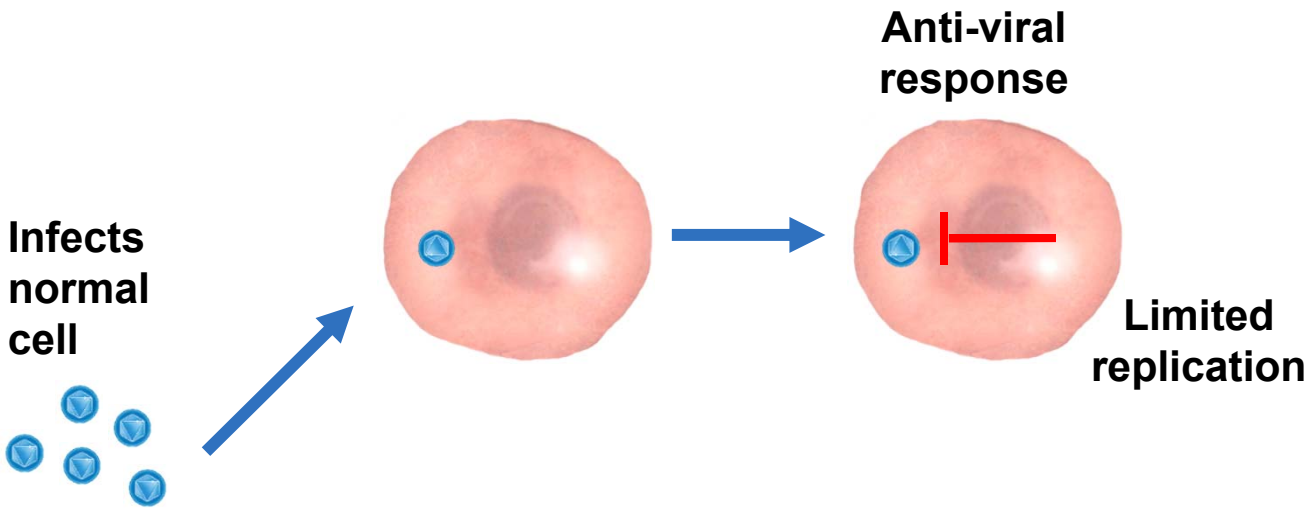
Amgen Inc.

Executive Director, Global Development Lead

Talimogene Laherparepvec
An HSV-1 Derived Oncolytic Immunotherapy



Tumor Selective Replication and Oncolysis



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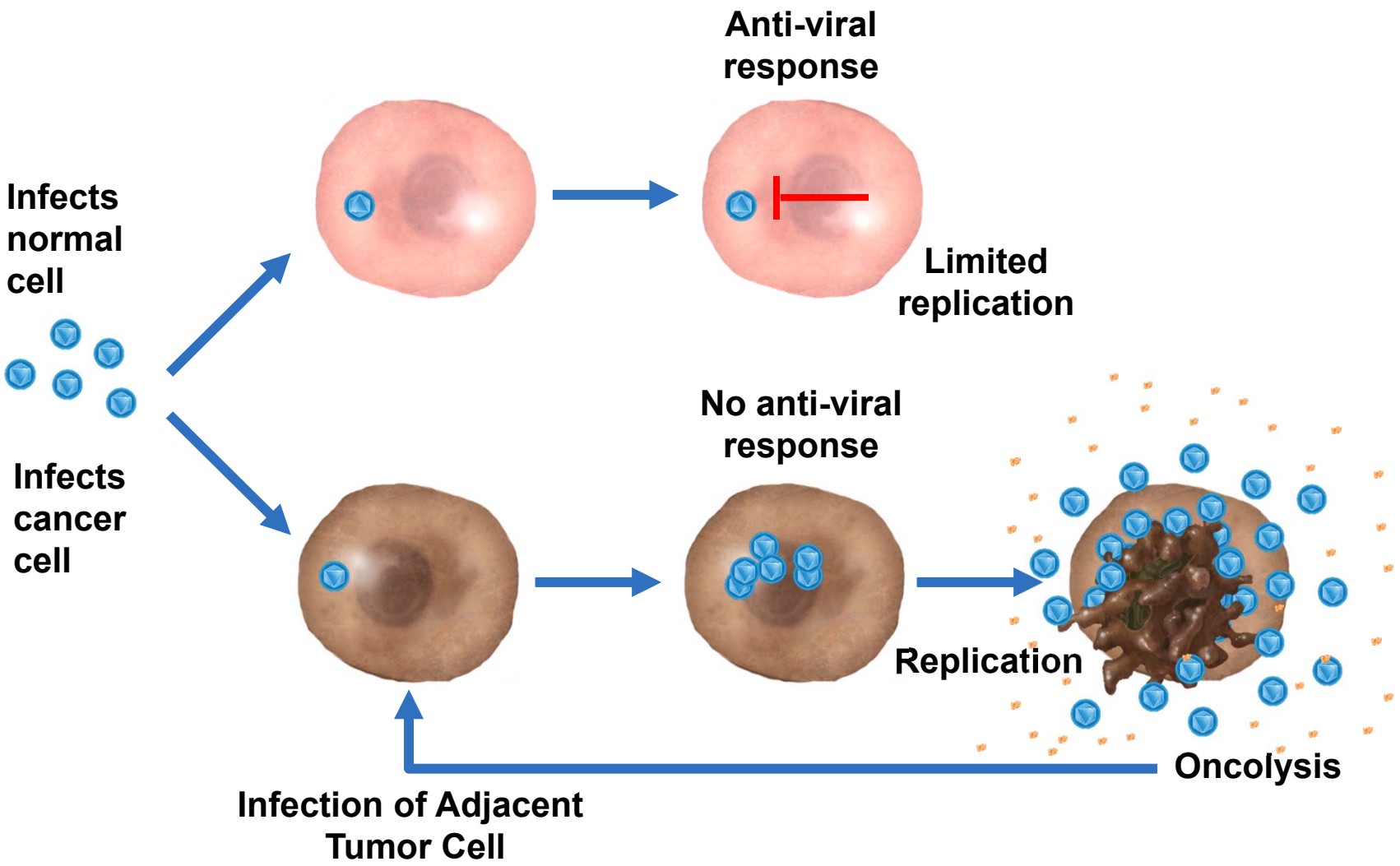
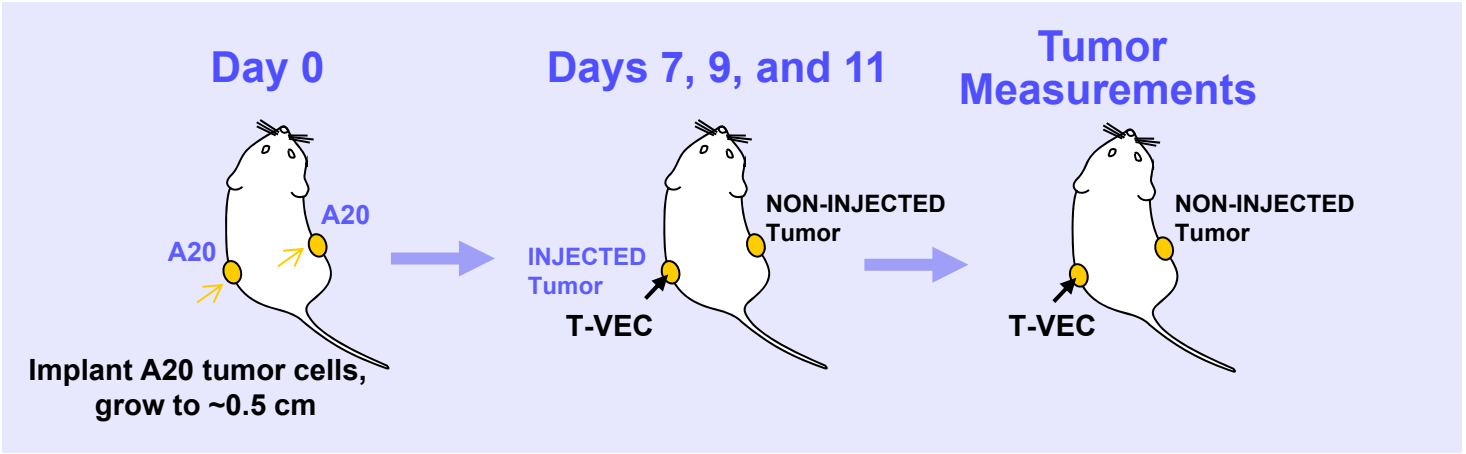
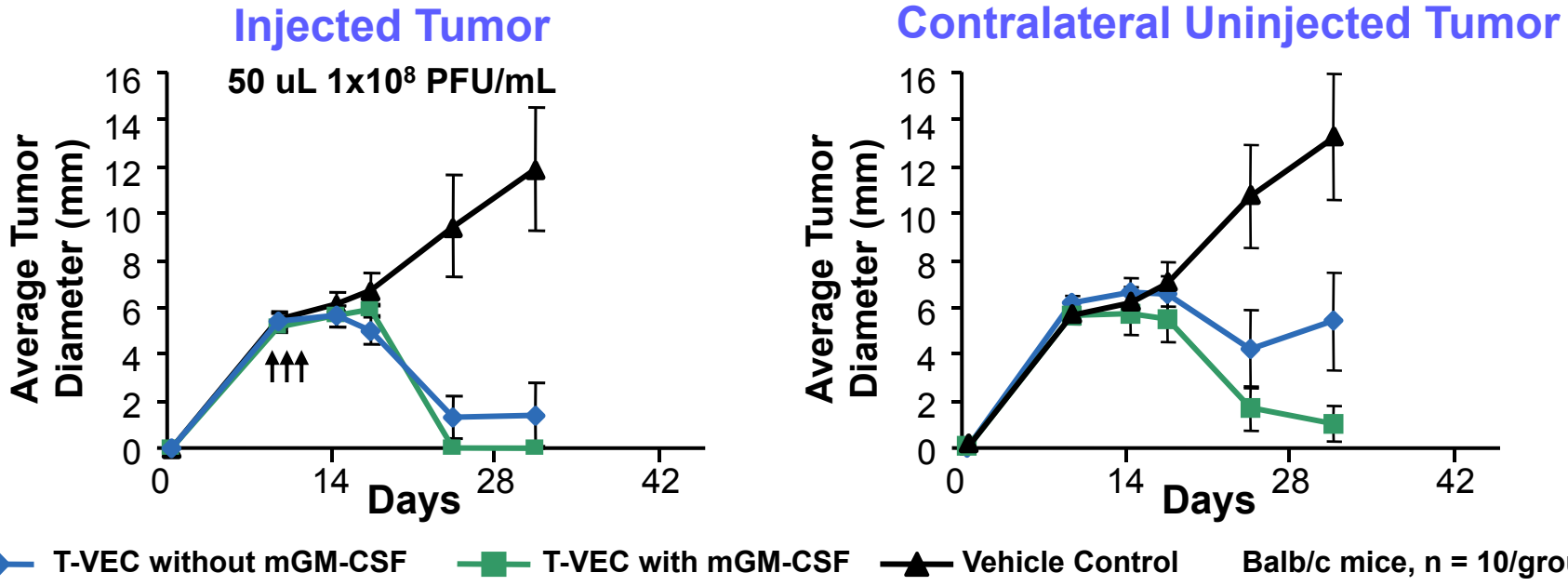


Viral Safety Considerations

- **Deletion of ICP34.5 markedly reduces neurovirulence compared to wild-type HSV-1 in mouse models**
  - Administered intranasally, the lethal dose 50 (LD_{50}) was not reached at a dose of 10^6 viral particles, >100-fold reduction in virulence
  - Administered intracerebrally, the LD_{50} was 10^5, ~10,000-fold reduction in virulence
- **Functional viral thymidine kinase maintains susceptibility to acyclovir**

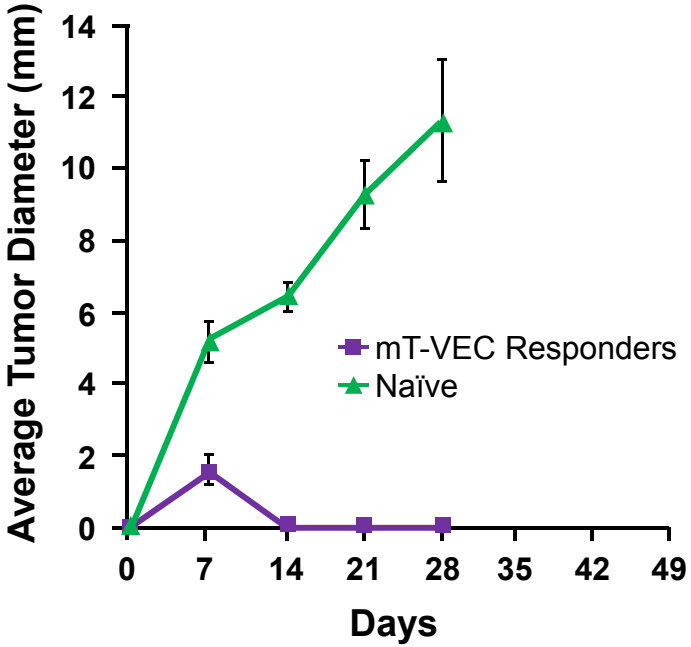
Enhanced Systemic Effect of Talimogene Laheprarepvec with GM-CSF





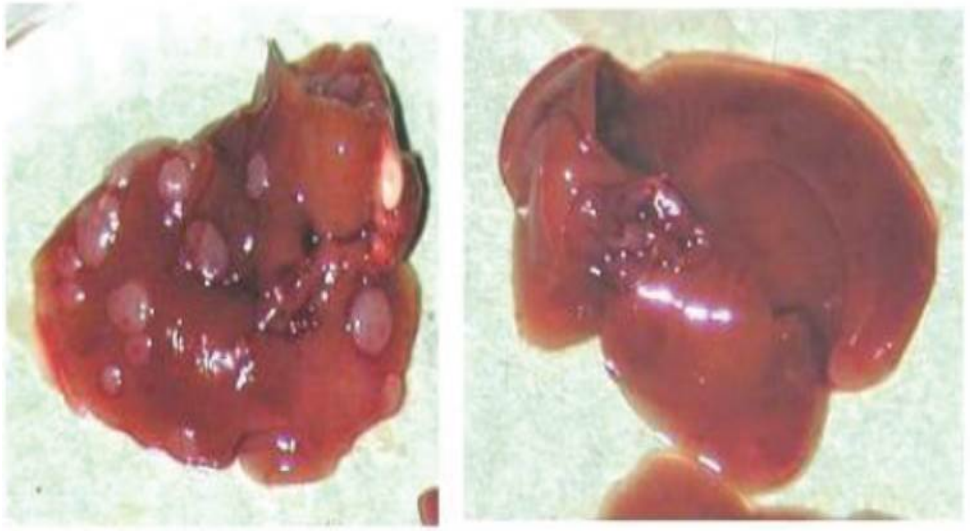
Tumor-protective Immune Response after T-VEC Treatment

Flank Injection



Experiment 1

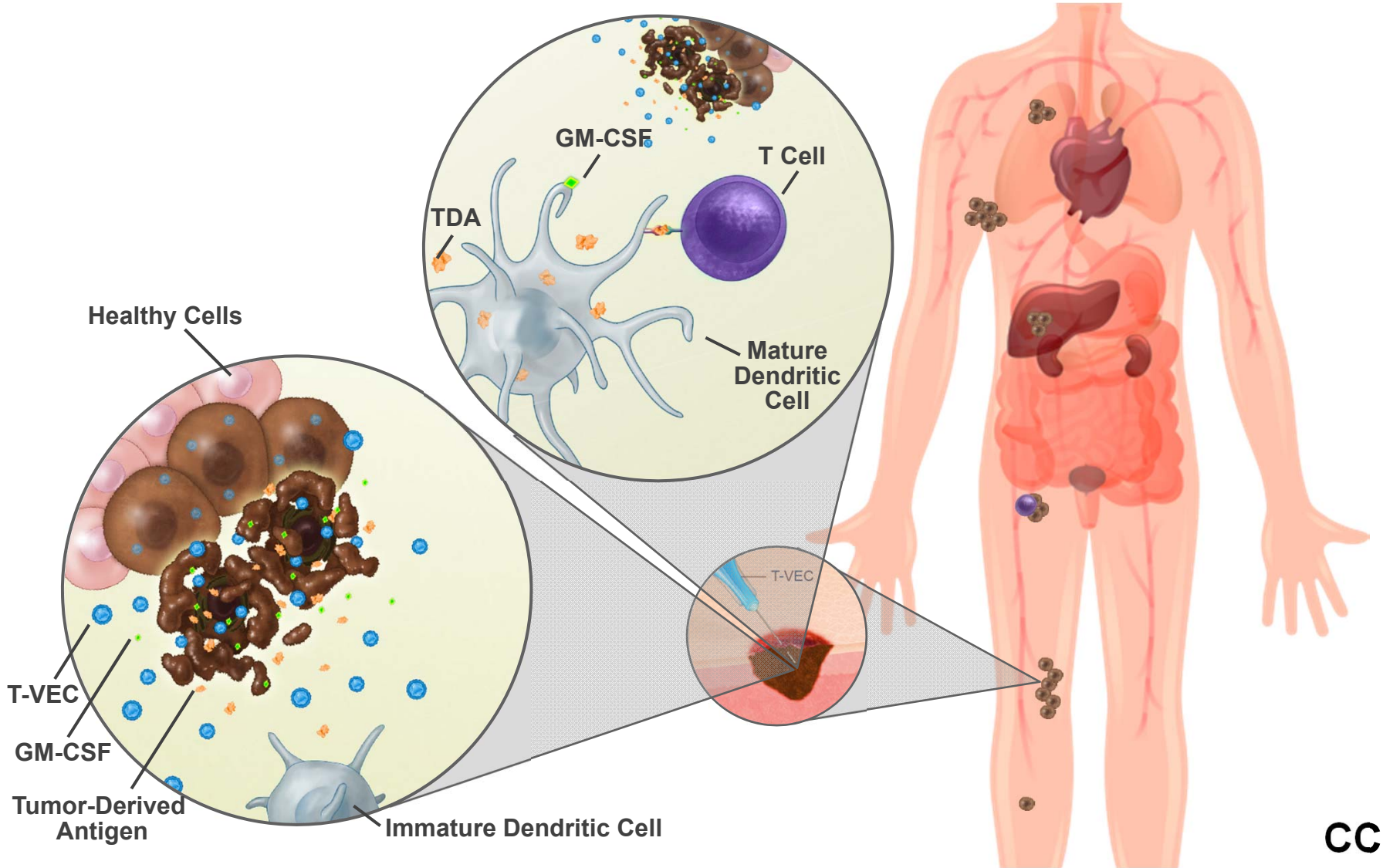
Tail Vein Injection



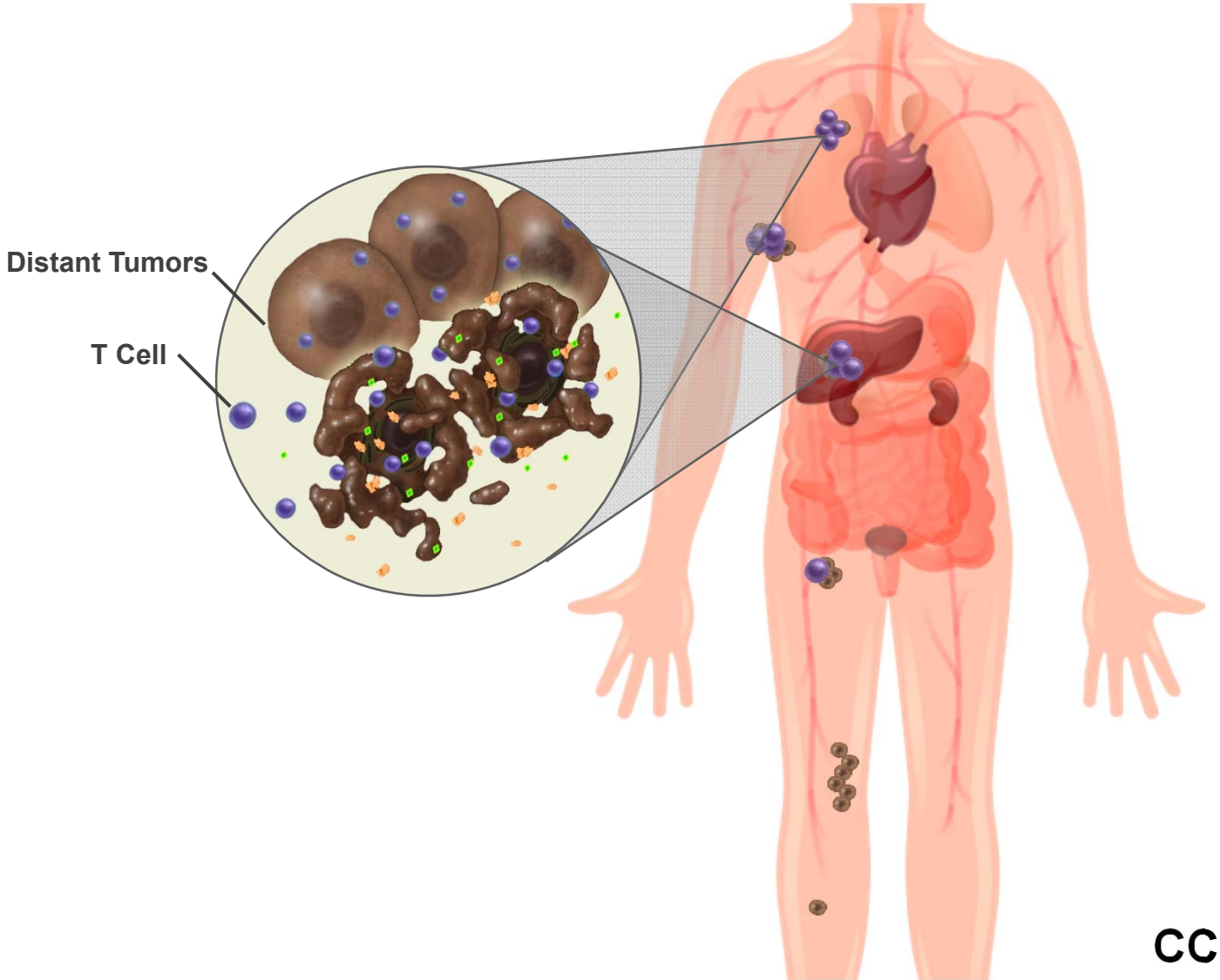
Naïve mT-VEC Responders

Experiment 2

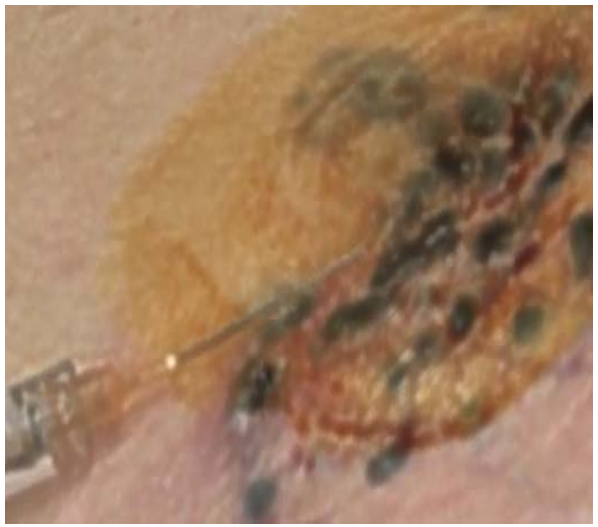
Dual Mechanism of Action

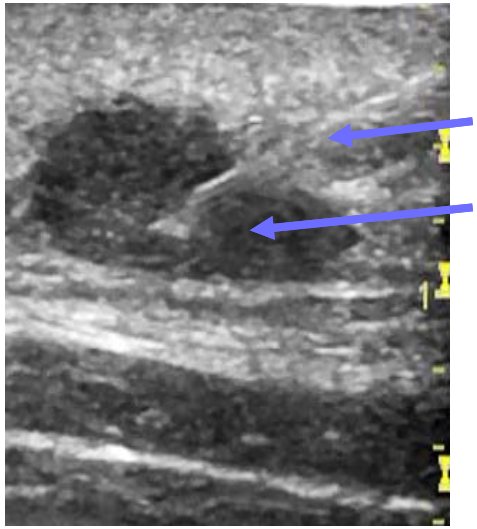


Dual Mechanism of Action



Dosing and Administration





Tumor Selection

Prioritized at each visit:

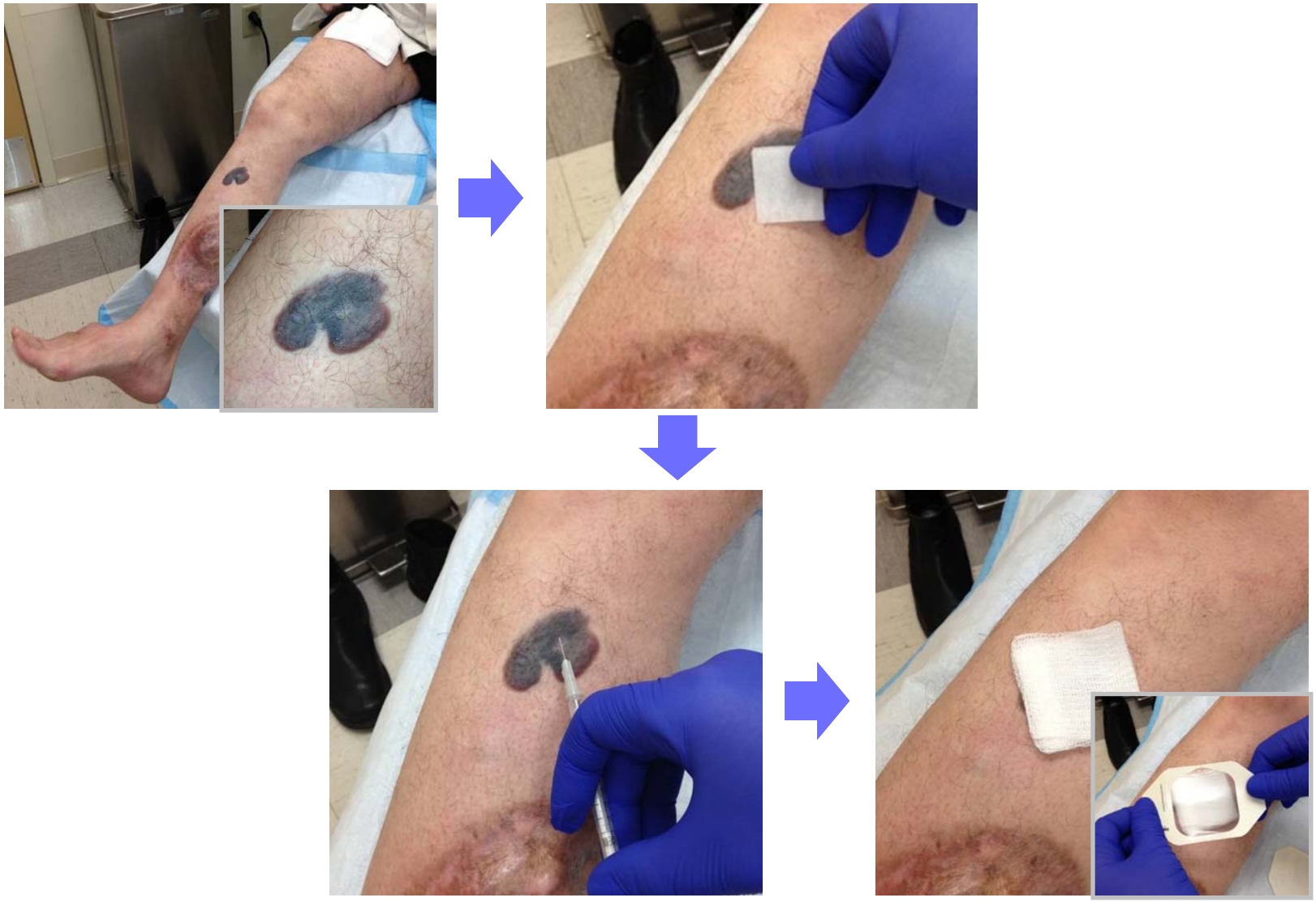
- New lesions
- Largest lesions
- The maximum dose was 4 mL at each treatment visit

Injection Volume

Determined by lesion size

Lesion Diameter	Injection Volume
> 5.0 cm	Up to 4.0 mL
> 2.5 cm to 5.0 cm	Up to 2.0 mL
> 1.5 cm to 2.5 cm	Up to 1.0 mL
> 0.5 cm to 1.5 cm	Up to 0.5 mL

Intralesional Injection



Clinical Efficacy Overview

Phase 2 Melanoma Study (002/03)

Study schema

Open-label

Talimogene Laherparepvec
N = 50
Dosing: Intralesional injection:
10^6 PFU/mL, after 3 weeks
10^8 PFU/mL, every 2 weeks

Baseline Characteristics

- Stage IIIC (20%), stage IVM1a/b (40%), stage IVM1c (40%)
- 74% previously treated
- All ECOG performance status: 0 or 1
- All had injection-accessible tumors

Results

Efficacy

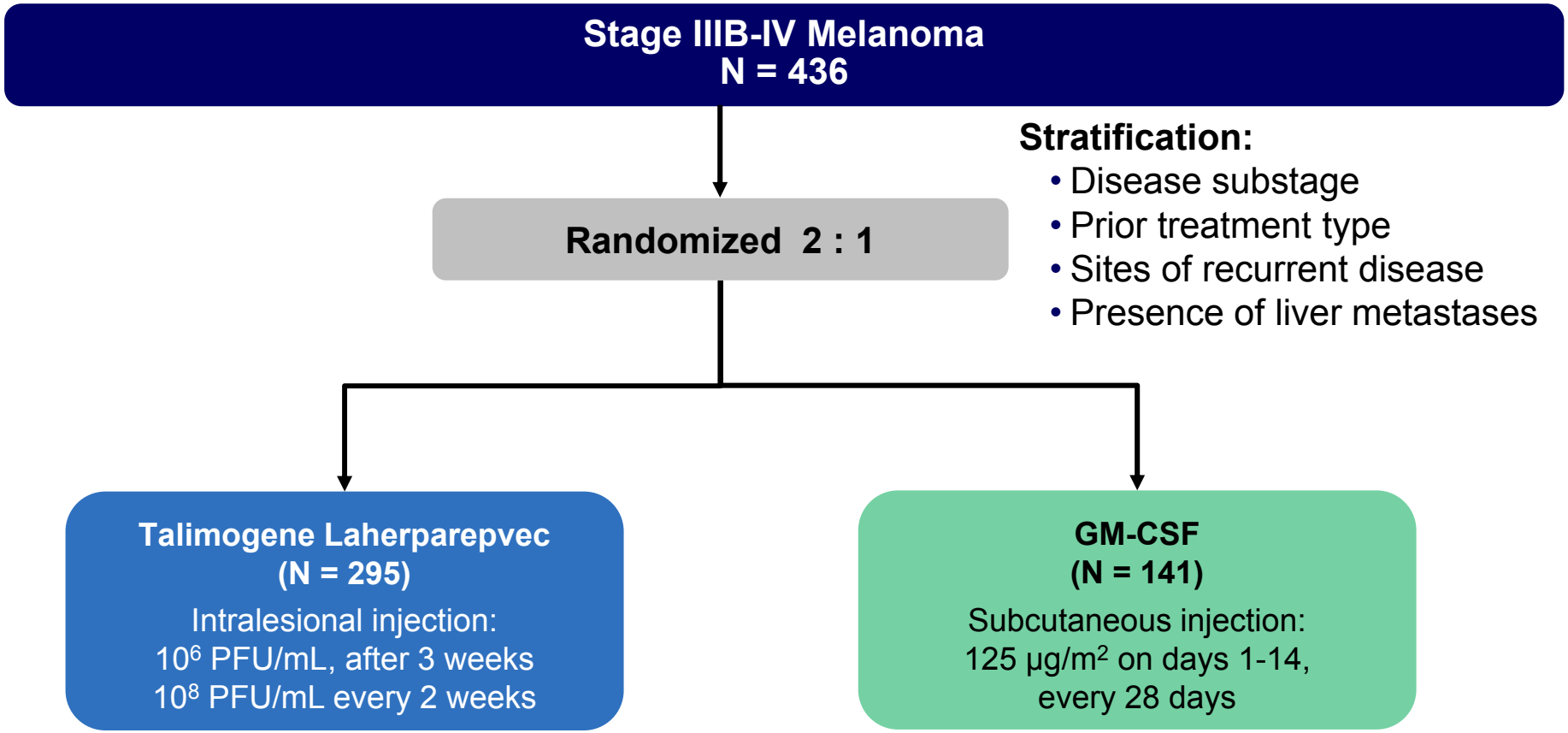
- ORR = 28% (8 CR, 6 PR)
- The majority of responses lasted for > 6 months
- Transient loco-regional or distant progression, including new lesions, sometimes preceded response.

Safety Profile

- Majority of adverse events were non-serious
- Most commonly reported adverse events were mild flu-like symptoms and injection-site reactions

Phase 3 Study Design, Methodology and Results

Phase 3 (005/05) Study Schema



For the first 24 weeks, treatment was to continue despite increases in tumor burden or appearance of new lesions, unless clinical deterioration or subsequent therapy was required

Key Entry Criteria

- **Stage IIIB – IV melanoma with measurable and injectable disease that was considered not to be surgically resectable**
  - Stage IVM1c capped at ≤ 40%
- **Limitations to disease burden included:**
  - ≤ 3 visceral metastases (except lung lesions)
  - No visceral lesion > 3 cm in diameter
  - LDH ≤ 1.5x ULN
  - 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
- **Prior treatment was allowed but not required**
- **ECOG PS: 0 or 1**
- **No open herpetic skin lesions or need for chronic anti-herpetic agents**

LDH: lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status

Primary Endpoint

Primary Endpoint: Durable response rate (DRR) as determined by a blinded central Endpoint Adjudication Committee (EAC)

- Durable response was defined as a response lasting continuously for a minimum of 6 months continuously with an onset within the first 12 months of treatment
- Responses were determined using bi-dimensional measurements (WHO criteria) of all baseline tumors and any new tumors
- DRR was expected to be associated with clinical benefit including improvement in quality of life, treatment free interval, and extension in survival

Secondary Endpoints

Key secondary endpoints included:

- Overall Response Rate
- Duration of Response
- Time to Response Onset
- Overall Survival (powered for HR = 0.67)
- Safety

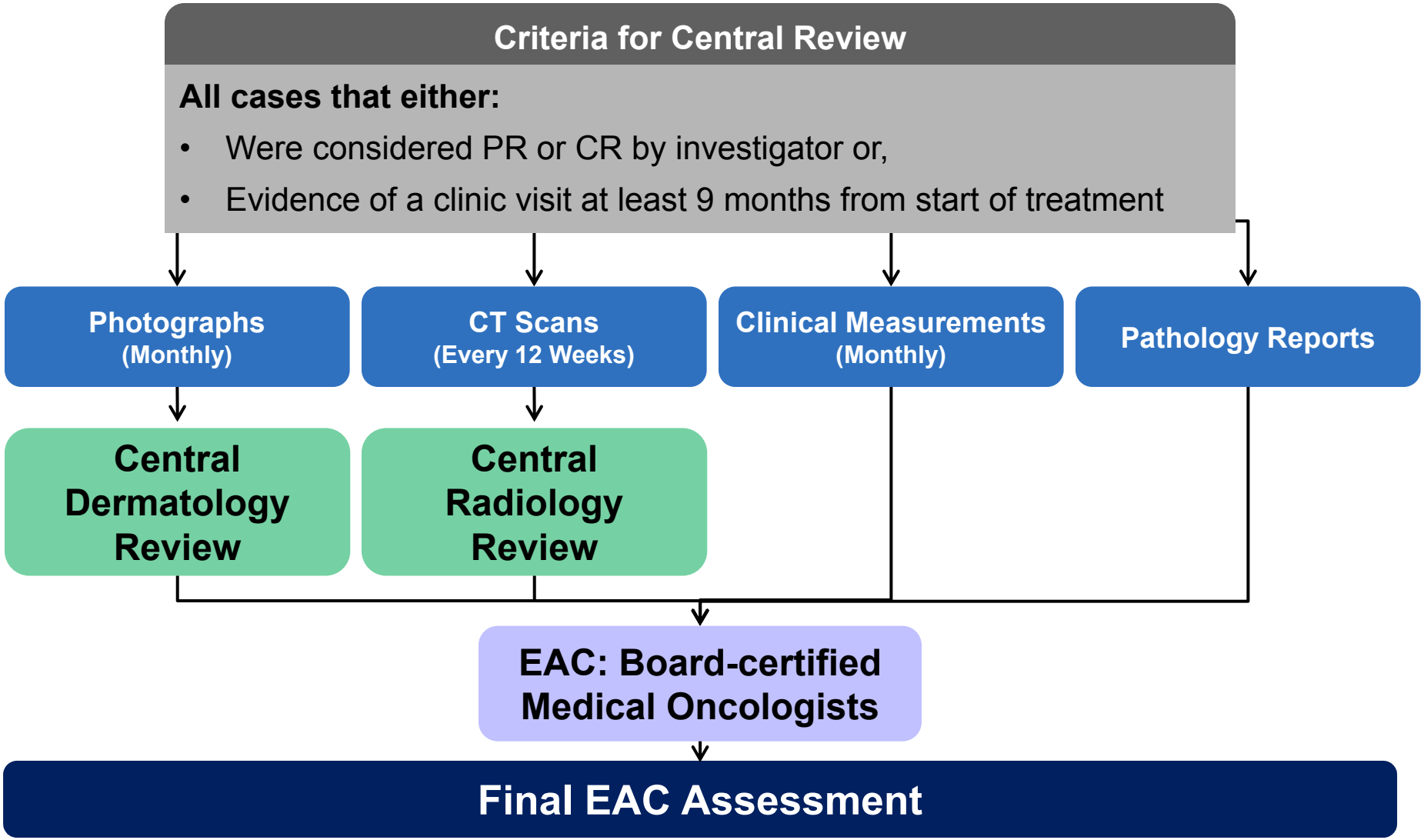
Rationale for GM-CSF Comparator

- No standard comparator for the patient population was accepted
- Systemic GM-CSF considered promising and tolerable cytokine-based agent for adjuvant therapy
- Talimogene laherparepvec and GM-CSF regarded as valid treatment options for this patient population

Statistical Analyses

- Primary analysis of DRR was planned when no further patients had the possibility of meeting the criteria for durable response
- DRR was tested at an overall 2-sided $\alpha = 0.05$
  - Conditional on a statistically significant difference in DRR, the primary analysis of OS was planned at 2-sided $\alpha = 0.05$; this analysis required 290 events
- Patients lost to follow-up or who withdrew consent were censored at the last contact date

Comprehensive Independent Review Process



Baseline Patient Characteristics

Characteristic		GM-CSF (N = 141) %	Talimogene Laherparepvec (N = 295) %
Disease substage	IIIB	9	8
	IIIC	22	22
	IV M1a	30	25
	IV M1b	18	22
	IV M1c	21	23
Line of therapy	1st line	46	47
	≥ 2nd line	54	53
Sex	Male	55	59
	Female	45	41
Age	≥ 65 years	49	48
	≥ 75 years	23	22
ECOG PS	0	69	71
	1	23	28
LDH	≤ ULN*	88	90
	> ULN	4	5
HSV serostatus	Positive	55	59
	Negative	32	33

May exclude some patients for whom baseline data were missing.
*ULN: upper limit of normal.

Patient Disposition in Study 005/05

Primary Reason for Treatment Discontinuation Intent to Treat Population, n (%)	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)
Patients who never received treatment	14 (10%)	4 (1%)
Patients continuing treatment	0 (0%)	0 (0%)
Discontinuation Reasons		
Progressive disease	95 (75%)	191 (66%)
PR or CR for at least 6 months*	0 (0%)	42 (14%)
Not in response*	9 (7%)	26 (9%)
Consent withdrawn	12 (9%)	10 (3%)
Physician decision	5 (4%)	6 (2%)
Adverse event	3 (2%)	11 (4%)
Deaths	3 (2%)	5 (2%)

* For patients who had received 12 months of treatment

Exposure in Study 005/05

	GM-CSF (n = 127)	Talimogene Laherparepvec (n = 292)
Median treatment duration (wks)	10	23
Range	(0.6-72)	(0.1-79)
Patients who completed 6 cycles, %	24%	54%
Patients who completed 12 cycles, %	13%	18%

Talimogene laherparepvec was administered twice per each 28 day cycle
GM-CSF was administered for the first 14 days of each 28 day cycle

The mean (SD) volume administered:

2.8 mL (1.2) [10^6 PFU/mL] at cycle 1 day 1
2.8 mL (1.2) [10^8 PFU/mL] for subsequent doses

Primary Endpoint Assessment

Durable Response Rate per EAC

ITT Set	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Unadjusted odds ratio
Durable response rate, N (%)	3 (2.1%)	48 (16.3%)	8.9 95% CI: (2.7, 29.2) *P* < 0.0001

Durable Response Rate per Investigator

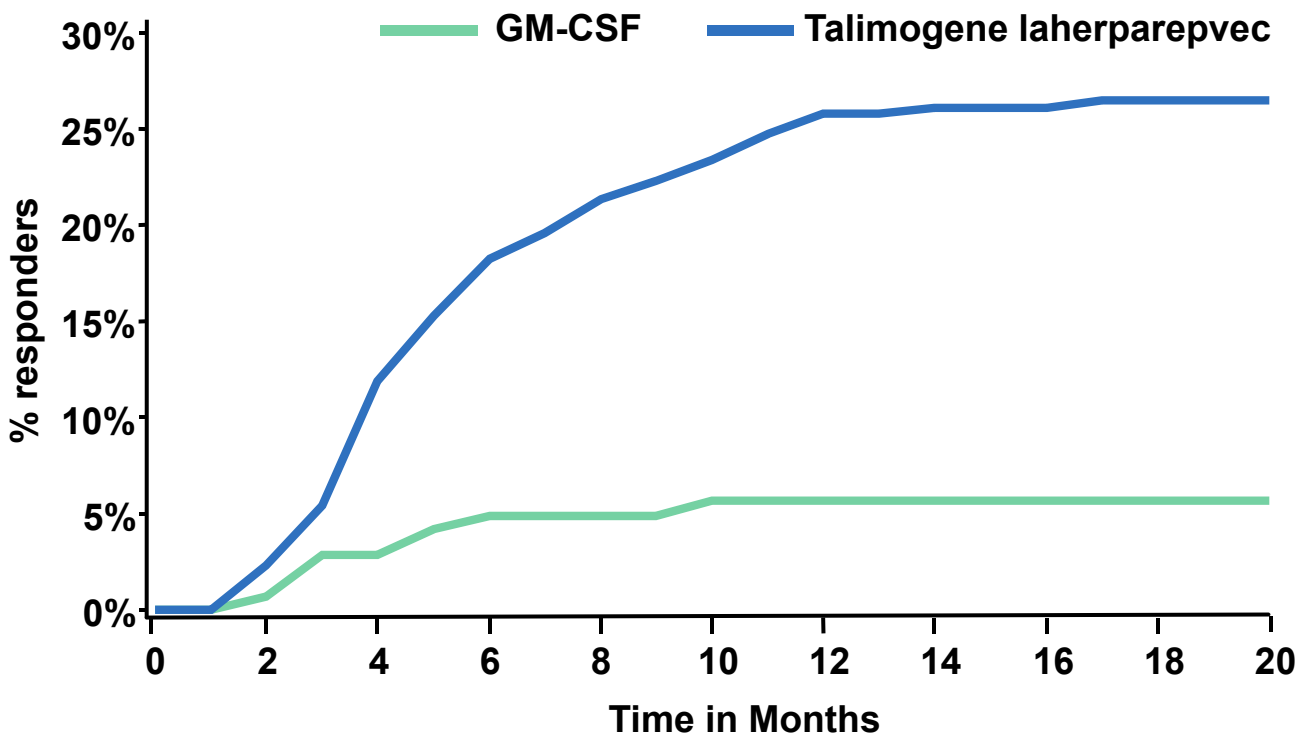
ITT Set	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Unadjusted odds ratio
Durable response rate, N (%)	2 (1.4%)	56 (19.0%)	16.3 95% CI (3.9, 67.8) *P* < 0.0001

Overall Response Rate per EAC

ITT set	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)
Overall response (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)
Complete Response	0.7%	10.8%
Partial Response	5.0%	15.6%
CR+PR+SD*	37.6%	67.5%

*Per investigator as SD, stable disease, was not assessed by EAC, duration of SD ≥ 39 days.

Time to Response Onset

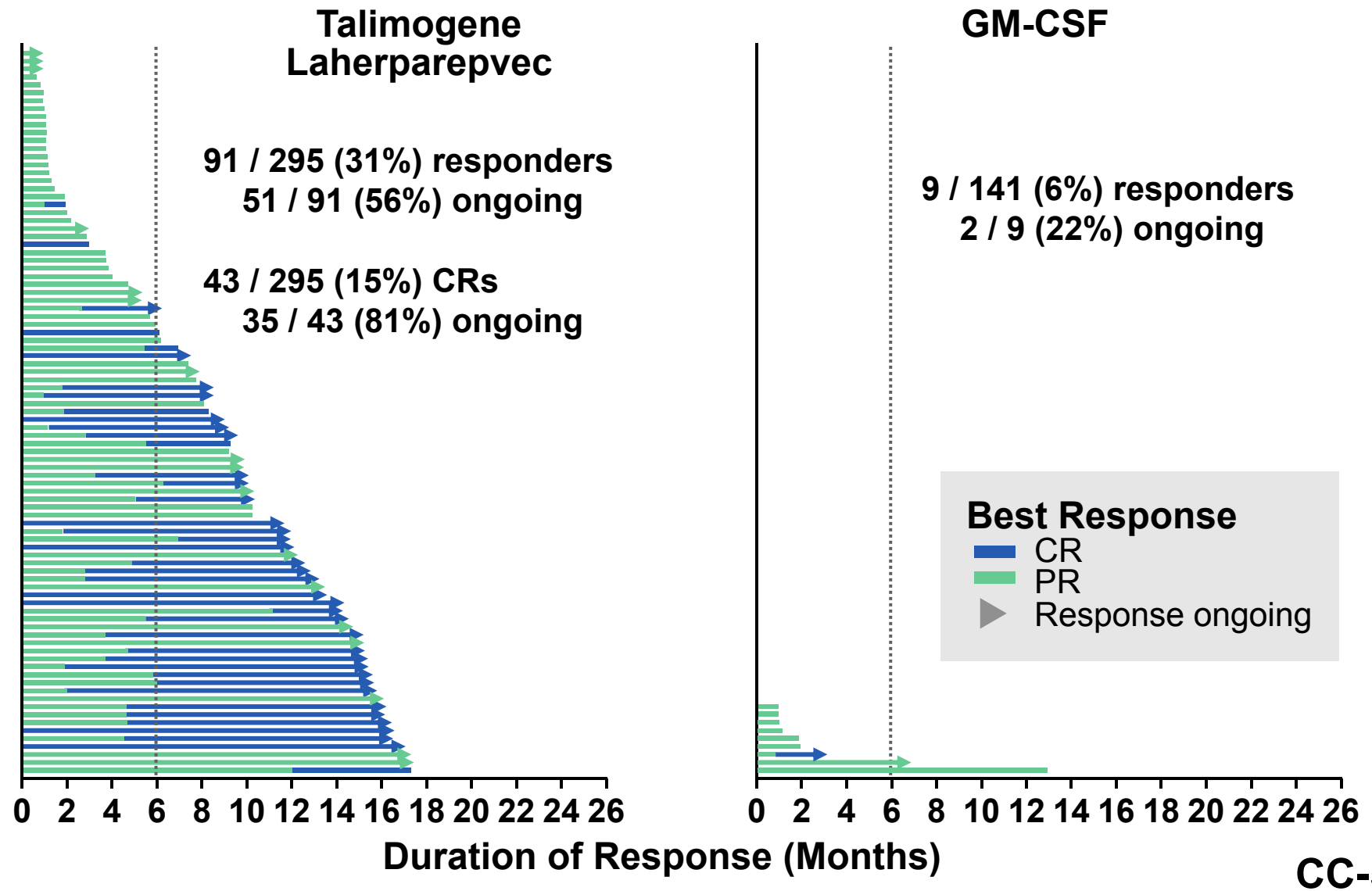


* The cumulative percent of response per EAC at time t = number of patients that have been in response at time t / number of patients randomized in the arm.

Response Onset Among Responders (from randomization)	Talimogene laherparepvec (n=78)	GM-CSF (n=8)
Median (min, max)	4.1 months (1.2, 16.7)	3.7 months (1.9, 9.1)

Duration of Response per Investigator

At Time of Durable Response Primary Analysis



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Kaplan-Meier Estimation of Duration of Response Among Responders

Estimated Probability of Being in Response Among All Responders

	Talimogene Laherparepvec (N = 78) % (95% CI)
For at least 6 months	81% (69, 88)
For at least 12 months	65% (51, 76)

Sensitivity Analysis of DRR for GM-CSF Subjects Discontinued Early

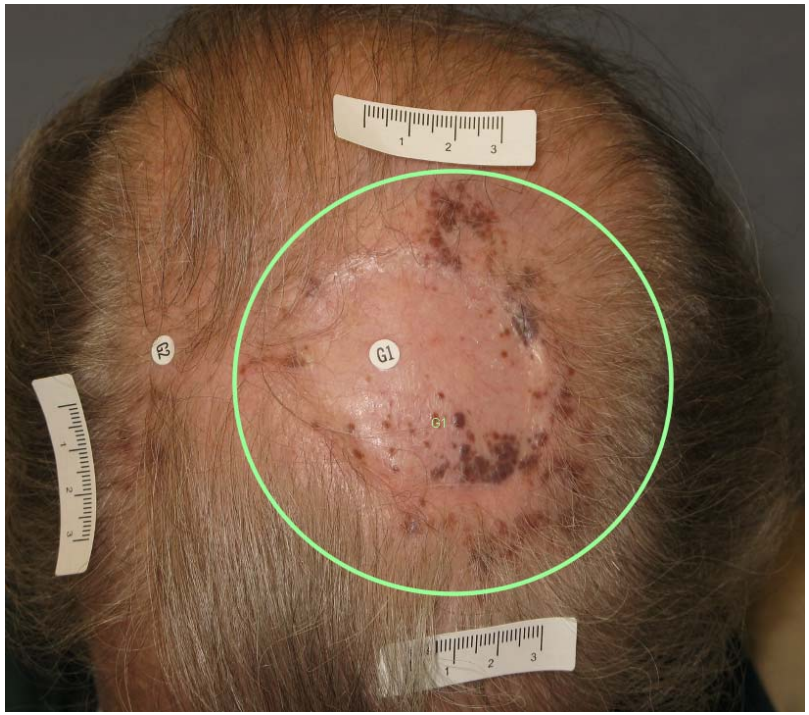
	GM-CSF (N=141)	T-VEC (N=295)	P-value *
ITT set primary analysis DRs	2% (3/141)	16% (48/295)	<0.0001
Discontinued early	41% (58/141)	25% (73/295)	
DRs	0% (0/58)	0% (0/73)	
Not discontinued early	59% (83/141)	75% (222/295)	
DRs	4% (3/83)	21% (48/222)	
ITT analysis imputing DRs for GM-CSF subjects discontinued early	4% (6/141)	16% (48/295)	0.0003

Discontinued early = ended treatment phase without evidence of clinically relevant disease progression

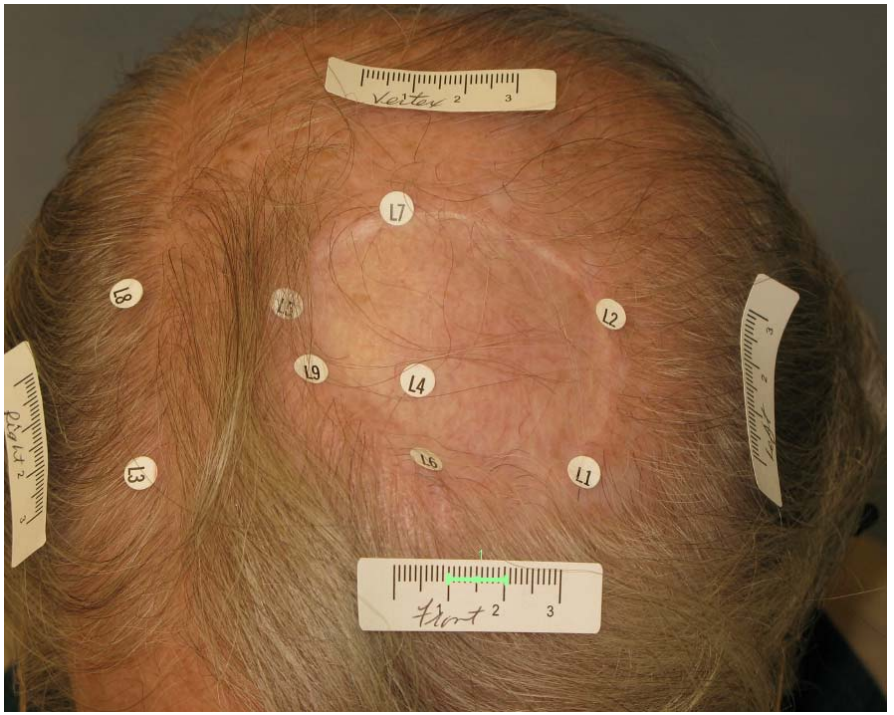
* Fisher's exact test (2-sided)
ITT: intent-to-treat; DR: Durable responders

Response in Injected Lesions (Stage IIIB)

Baseline

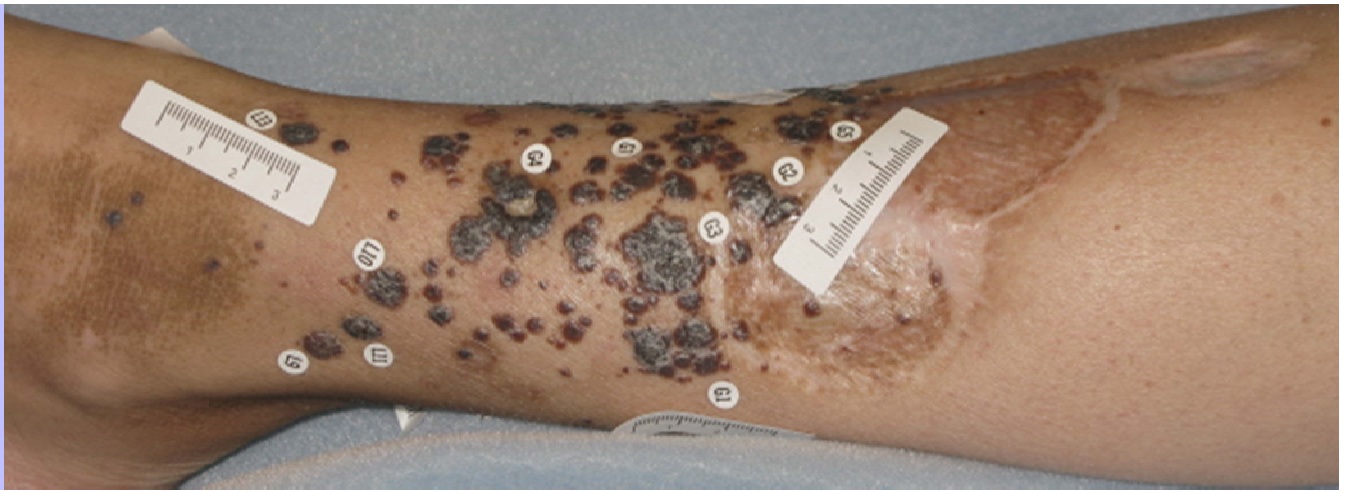
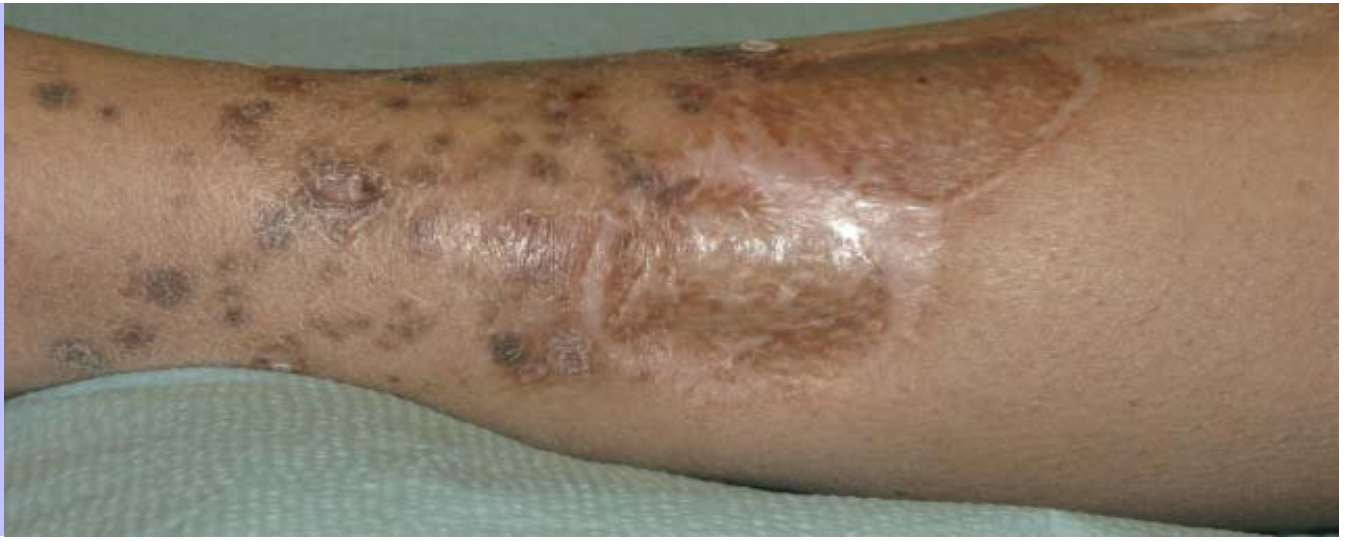


Cycle 14



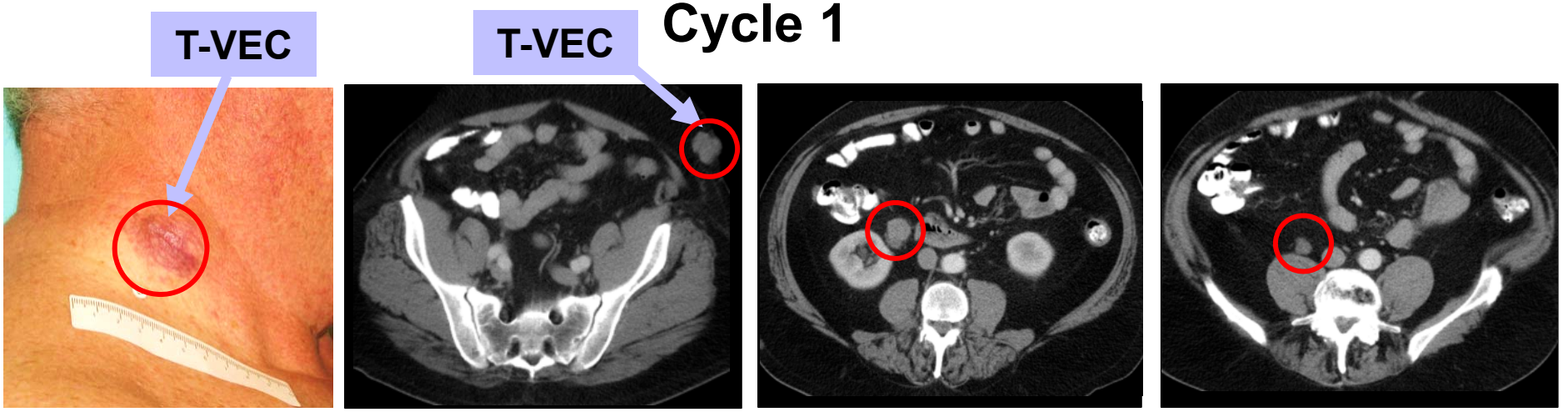
PR by cycle 5 and CR by cycle 11 per EAC
CR ongoing at last EAC assessment at cycle 19

Responses in Injected And Uninjected Skin Metastases

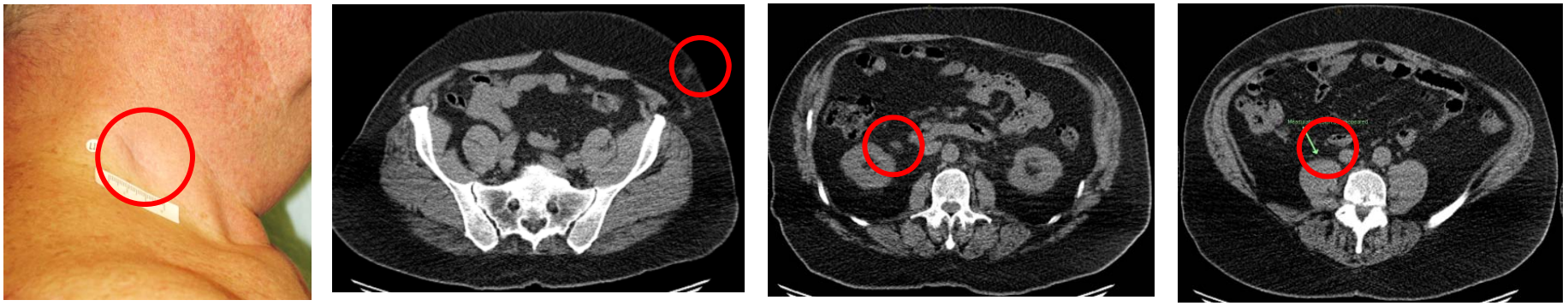
Cycle 1	
Cycle 13	

Responses in Deep Non-injected, Non-visceral Lesions

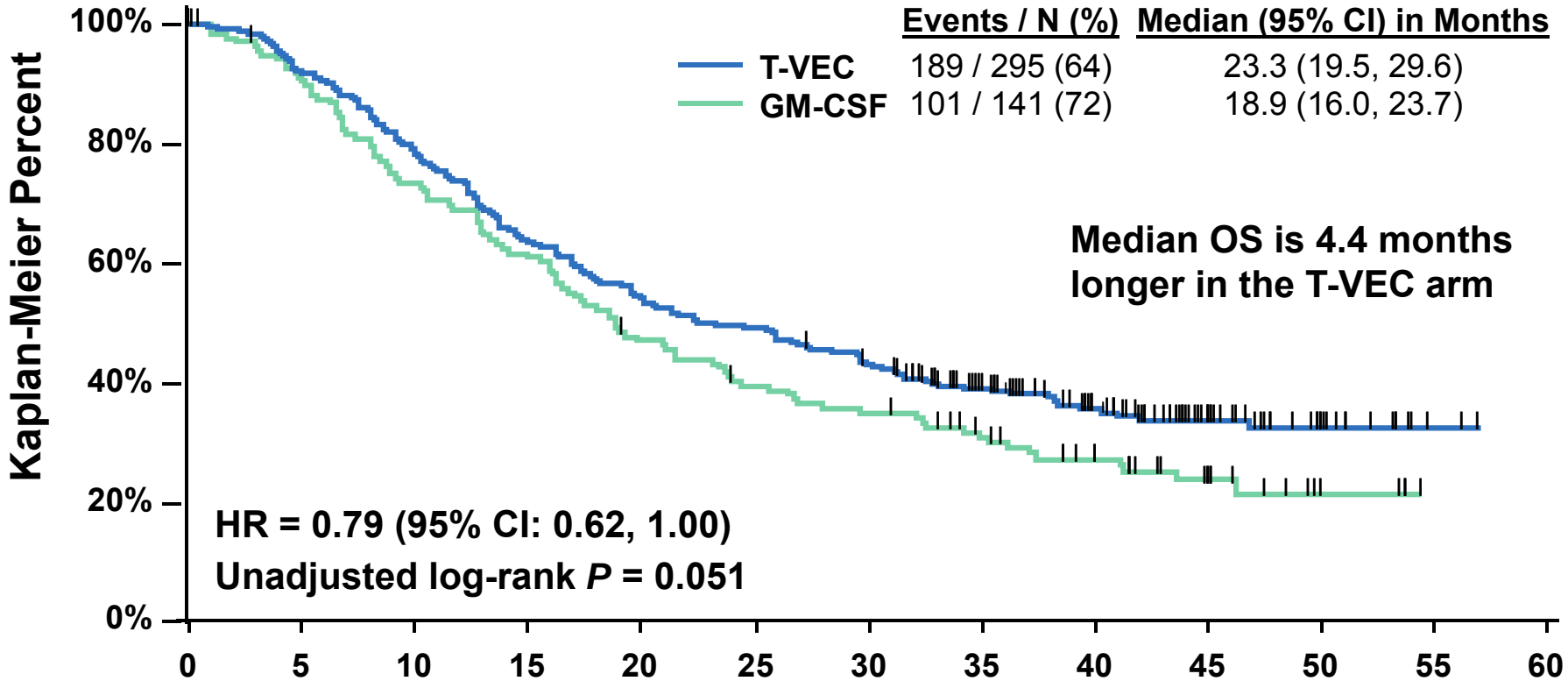
Cycle 1



Cycle 10



Overall Survival

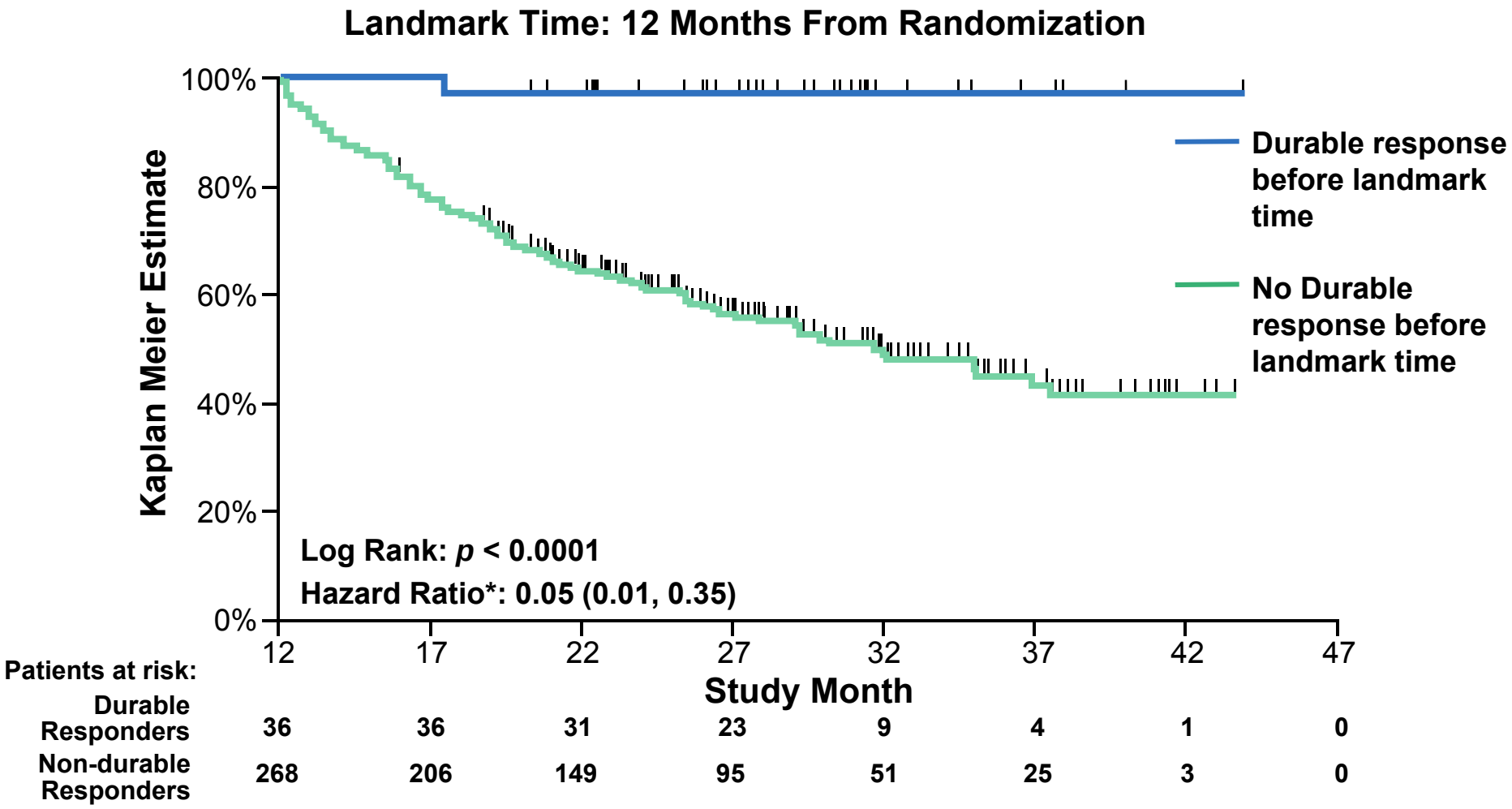


Patients at risk:

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

CI, confidence interval; HR, hazard ratio;

Correlation of DRR with OS

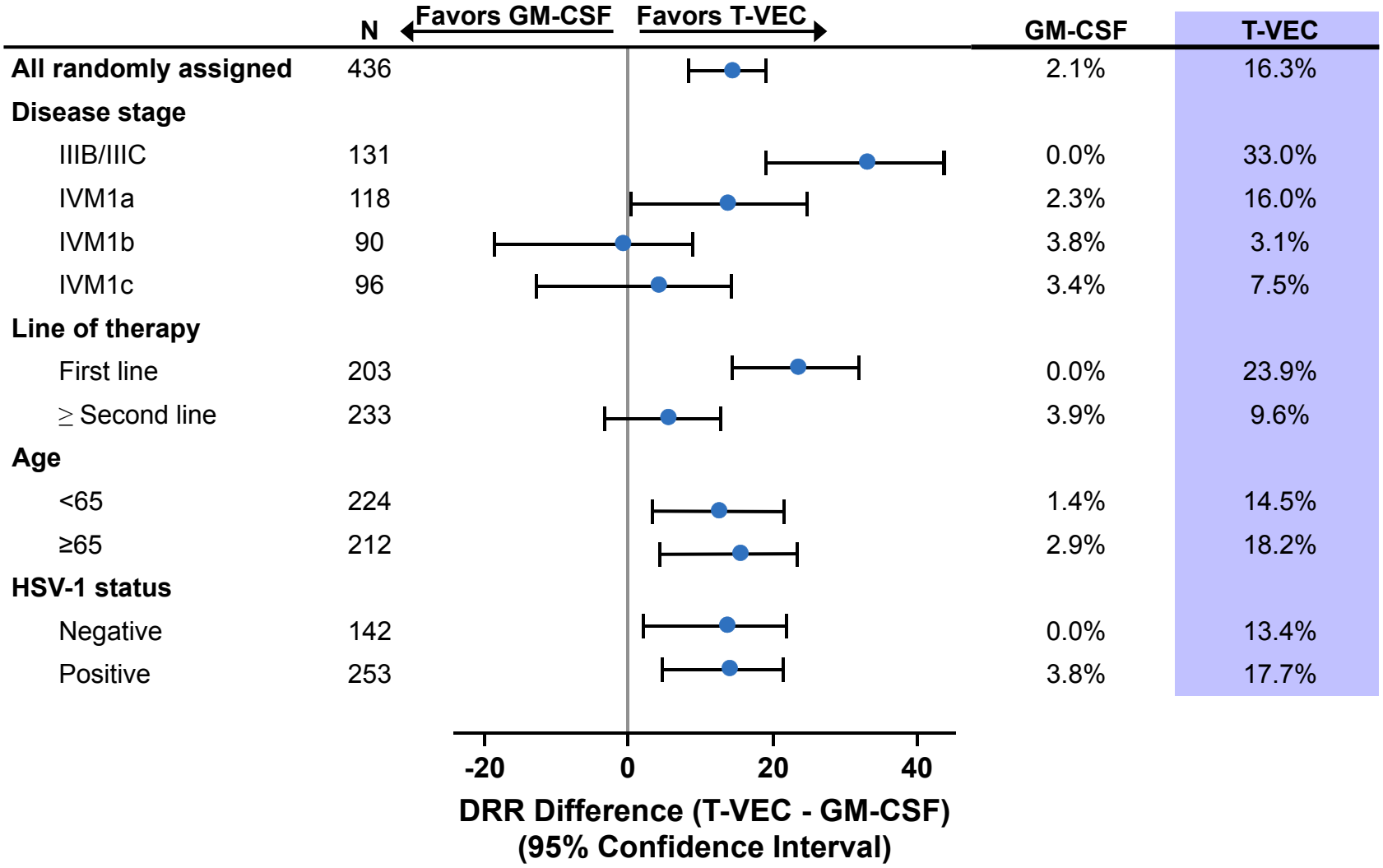


*Hazard Ratio adjusted for disease stage and line of therapy

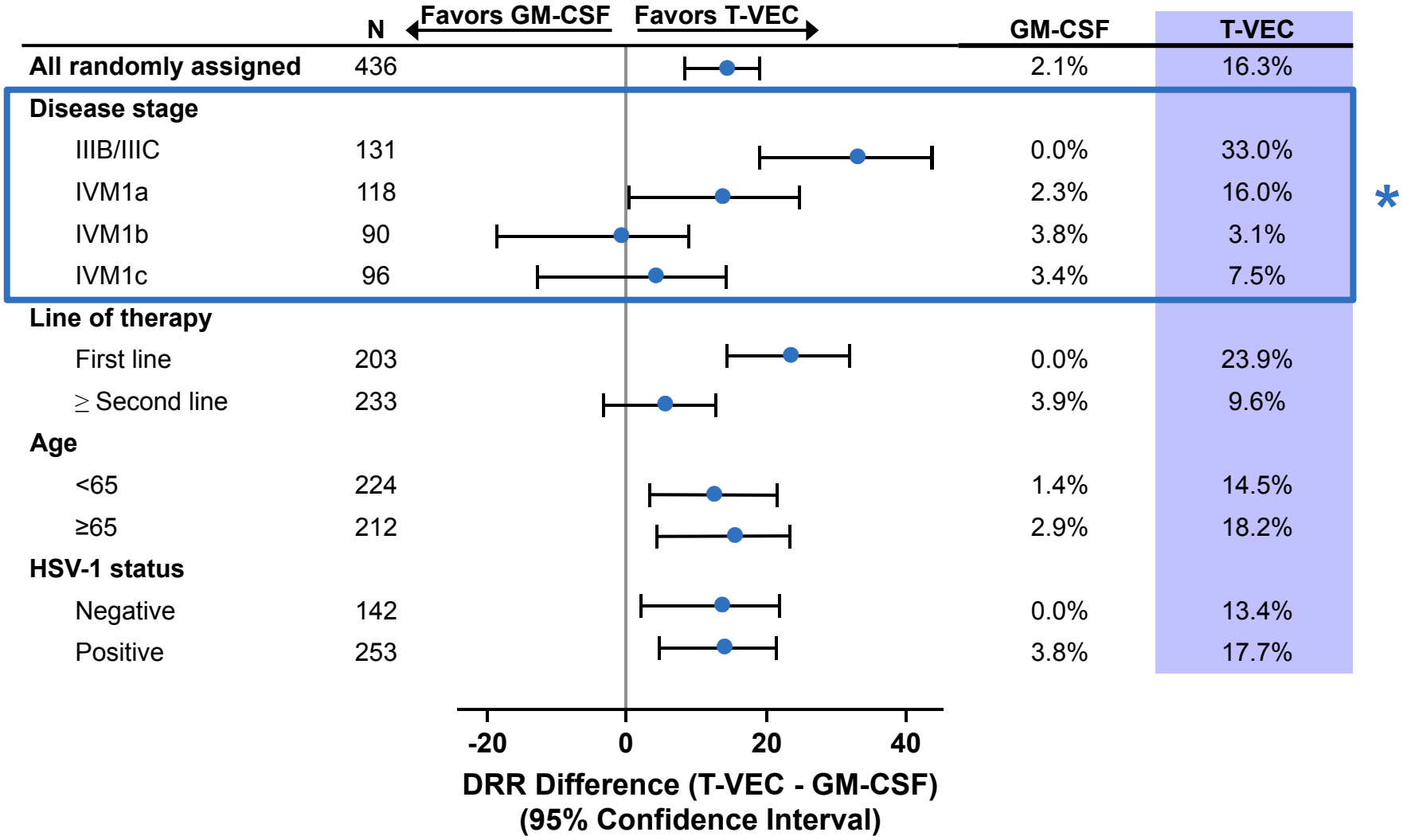
Additional Analyses

1) Do specific subsets of patients benefit more from talimogene laherparepvec?
2) Are systemic effects demonstrated in the Phase 3 study?
3) Is there evidence of a persistent survival effect?

DRR Subgroup Treatment Effects

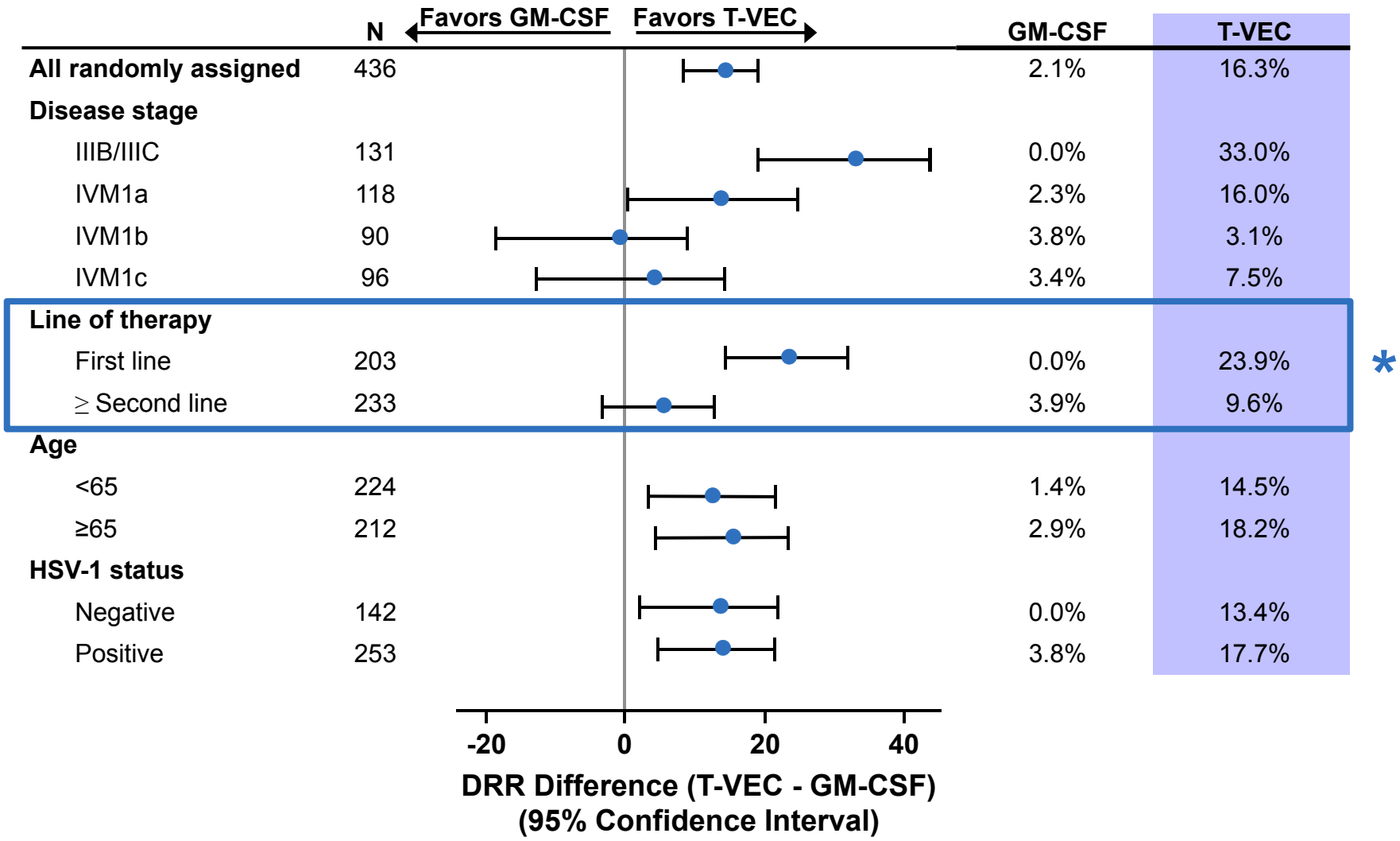


Larger Effect in Earlier Stage



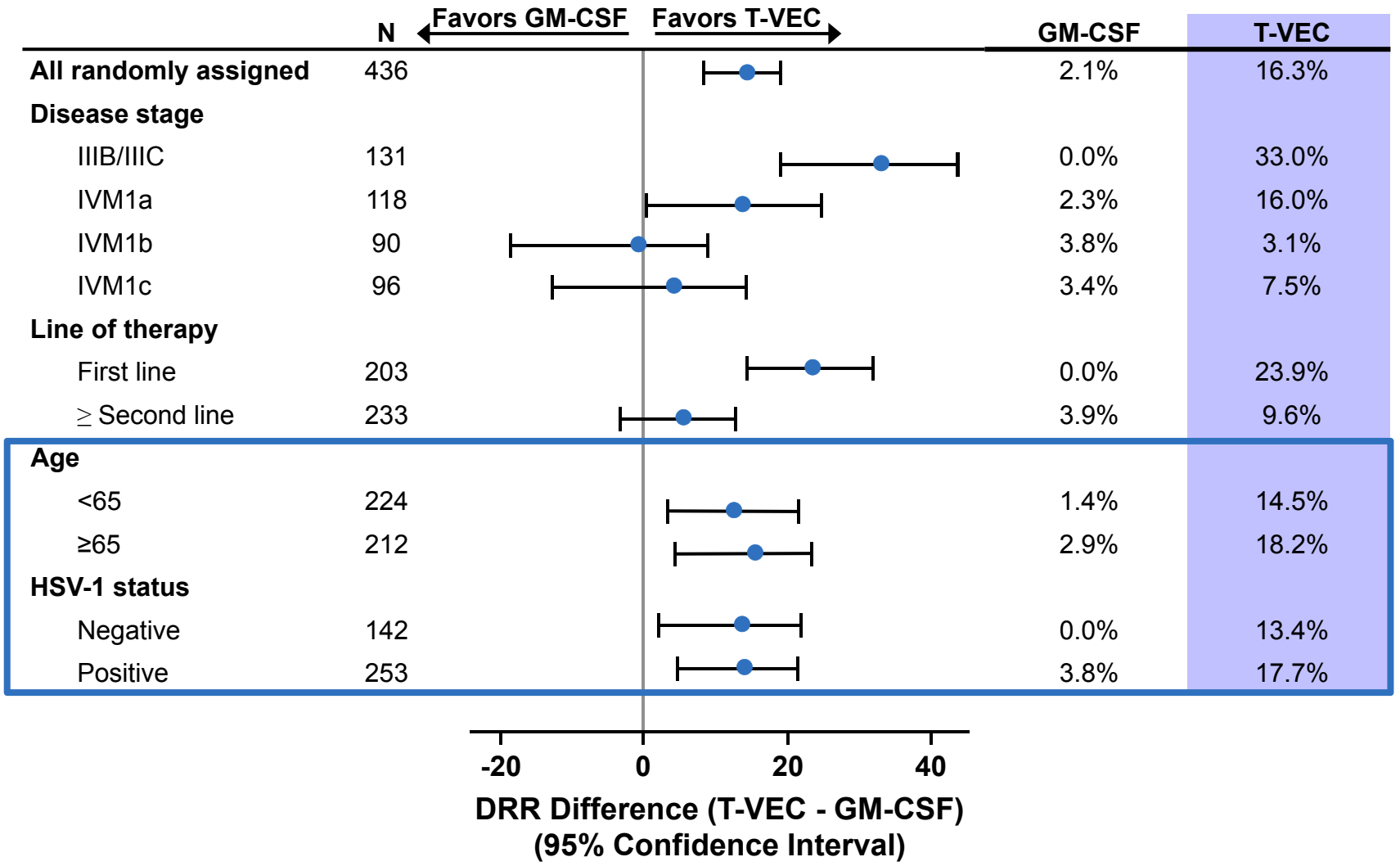
*Gail-Simon Interaction Test (p <0.0001)

Larger Effect in First Line

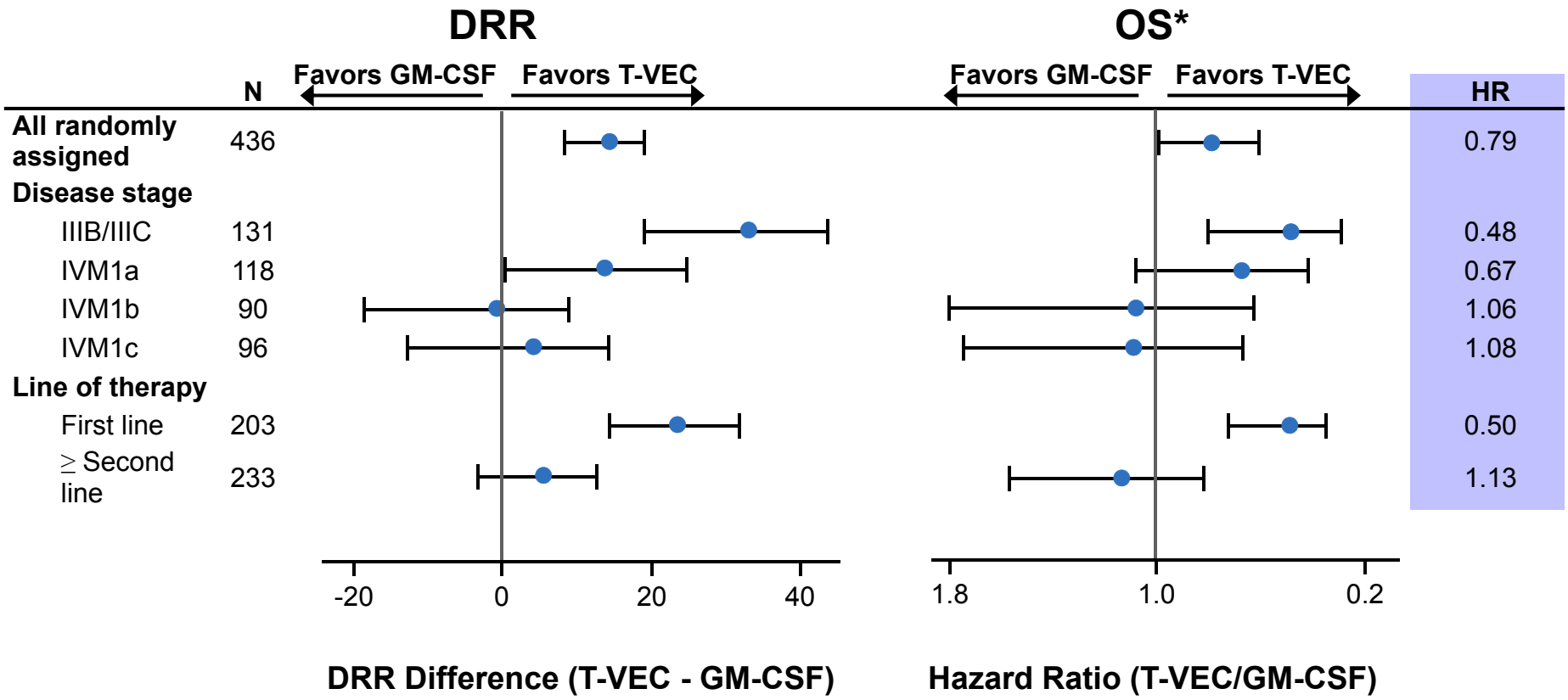


*Gail-Simon Interaction Test (p = 0.0002)

Consistent Effect by Age and HSV-1 Serostatus

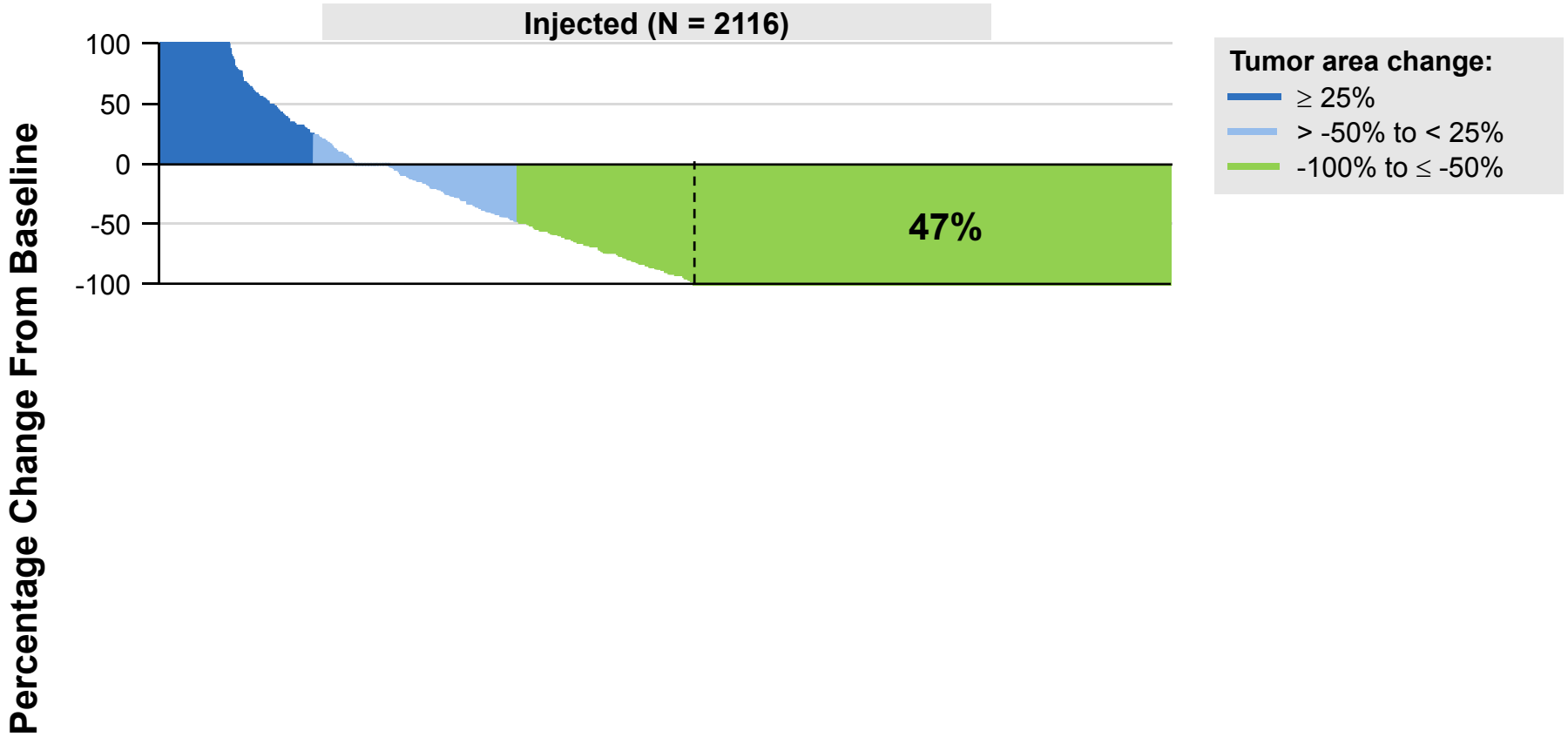


DRR and OS by Key Covariates

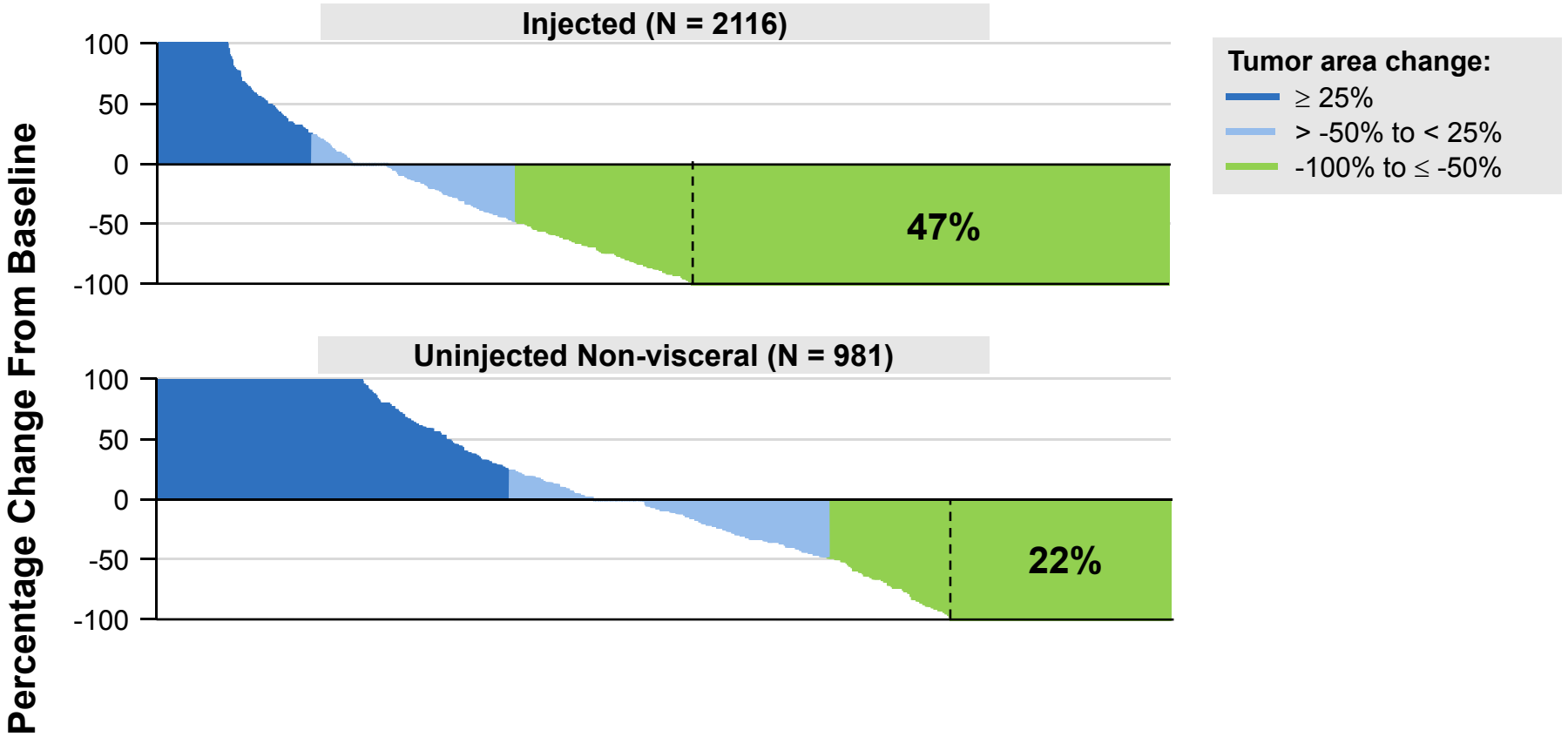


*Gail-Simon Interaction Test (p = 0.0729) by disease stage
*Gail-Simon Interaction Test (p = 0.0012) by line of therapy

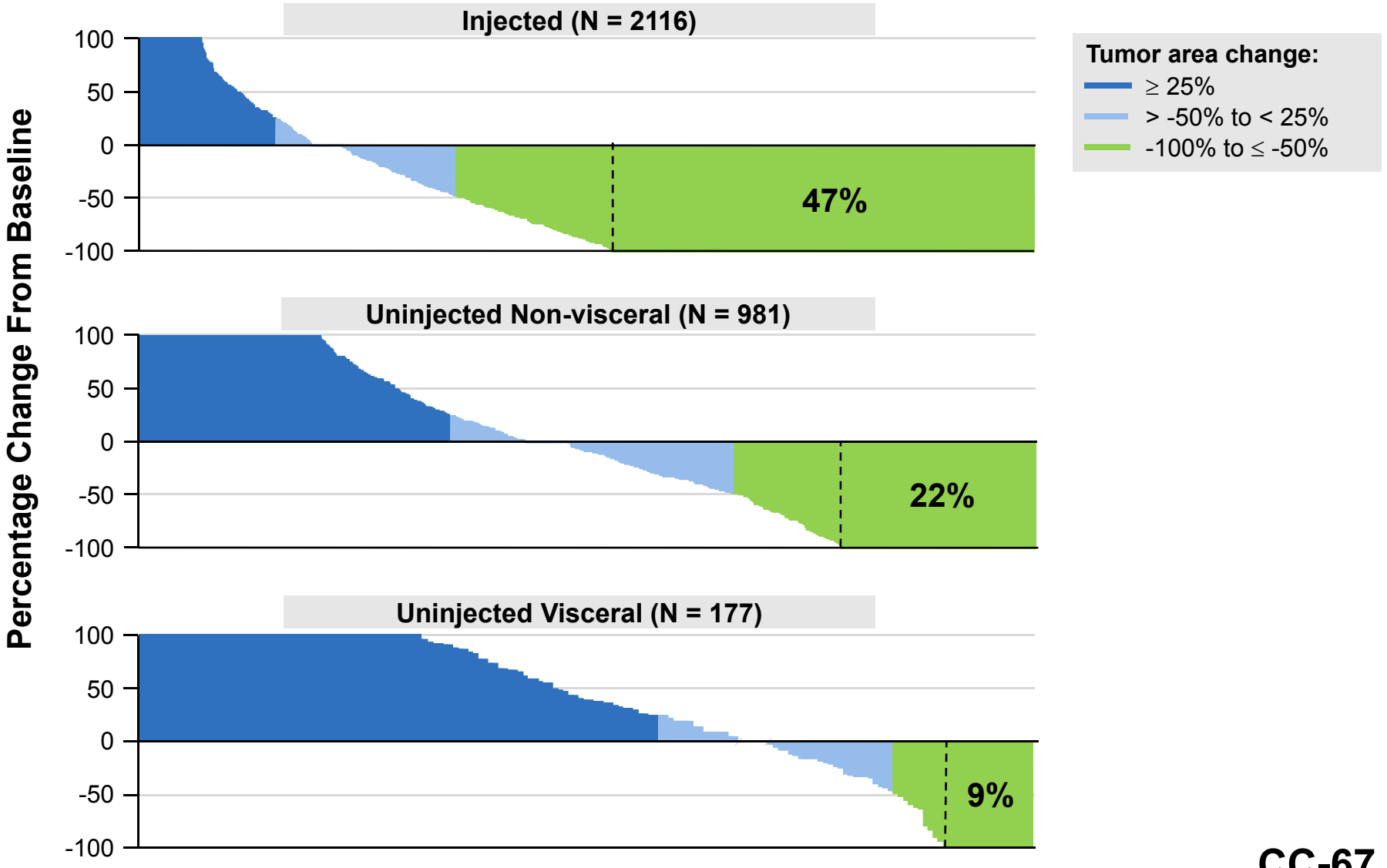
Lesion-Level, Lesion-Type Response Analysis



Lesion-Level, Lesion-Type Response Analysis



Lesion-Level, Lesion-Type Response Analysis



Overall Survival
Pre-Specified Final Analysis (ITT)

Survival	Talimogene Laherparepvec	GM-CSF	Difference (95% CI)
1-year	73.7%	69.1%	4.6% (-4.7, 13.8)
2-year	49.8%	40.3%	9.5% (-0.5, 19.6)
3-year	38.9%	30.4%	8.4% (-1.2, 18.0)
4-year	34.5%	23.9%	10.6% (1.2, 20.0)
5-year	33.4%	NE	NE

HR = 0.79 (95% CI: 0.62, 1.00) p=0.049 (descriptive)

NE= not estimable

Evidence of Systemic Effect

- **Non-clinical data directly demonstrate a systemic anti-tumor effect**
- **Clinical evidence of systemic effect include:**
  - Regression in uninjected lesions
    - 20% complete regression (n = 212 uninjected non-visceral and visceral lesions)
    - Emergence of a “plateau” in the survival curve is characteristic of an immunotherapy
  - Appearance of vitiligo

Study 005/05: Efficacy Summary

- **The 005/05 study met the primary endpoint, demonstrating a highly statistically significant improvement in DRR**
  - Well-conducted study prospectively designed to minimize bias associated with open label design
  - Sensitivity analyses confirmed robust DRR result with no change to conclusion of study
- **Systemic effect was demonstrated**
  - Complete responses in uninjected lesions including visceral lesions
  - Plateau in survival curve
- **Clinical Benefit has been demonstrated**
  - DRR associated with overall survival,
  - DRR also associated with improvement in quality of life and treatment free interval

Sponsor Presentation Agenda

Topic	Presenter
Introduction	**Rhian Thomas, BSc** Amgen Inc. Executive Director, Global Regulatory Affairs
Metastatic Melanoma	**Howard Kaufman, MD, FACS** Chief Surgical Officer; Associate Director for Clinical Science; and Co-Leader, Clinical Investigations and Precision Therapeutics Program at the Rutgers Cancer Institute of New Jersey
Mechanism of Action and Clinical Efficacy Overview	**Jennifer Gansert, MD, PhD** Amgen Inc. Executive Director, Global Development Lead
Clinical Safety Overview and Risk Management Plan	**Deborah Arrindell, MD, MPH, JD** Amgen Inc. Executive Director, Global Patient Safety
Clinical Perspective	**Howard Kaufman, MD, FACS**
Conclusion	**Steven Galson, MD, MPH** Amgen Inc. Senior Vice President, Global Regulatory Affairs and Safety

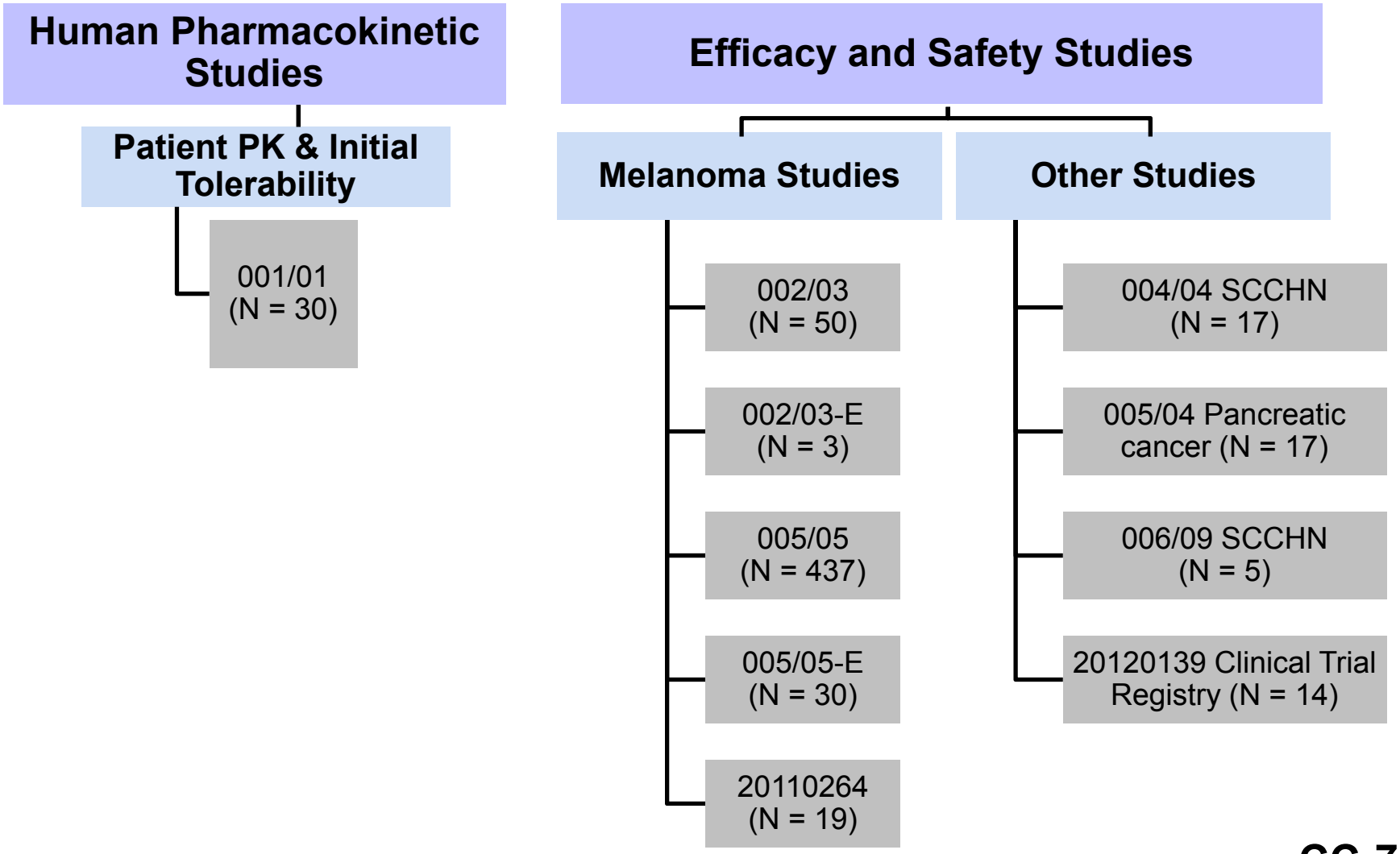
Clinical Safety Overview

Deborah Arrindell, MD, MPH, JD

Amgen Inc.

Executive Director, Global Patient Safety

Overall Safety Evaluation



Duration of Cumulative Exposure

	≥ 1 dose	0 to < 6 months	6 to < 12 months	12 to <18 months	18 months and longer
Melanoma Studies (Supportive Melanoma Set)*	342	206	94	22	20
Non-melanoma Studies**	66	63	2	1	0
Overall Total Exposure (Program-wide Analysis Set)	408	269	96	23	20

*Includes exposure data from patients in Studies 002/03, 002/03-E, 005/05 and 005/05-E
**Includes exposure data from patients in Studies 001/01, 004/04, 005/04, and 006/09

The Program-wide Analysis set includes all patients who were enrolled in Studies 001/01, 002/03, 002/03-E, 004/04, 005/04, 005/05 and 005/05-E and 006/09 and received ≥ 1 dose of study treatment. Data from patients in the extensions of Studies 005/05 and 002/03 were combined with data from the parent study on the patient level prior to being summarized

Primary Melanoma Safety Set (Study 005/05)

Summary of Adverse Events (Study 005/05)

	GM-CSF (n = 127)	Talimogene Laherparepvec (n = 292)
All Adverse Events	95%	99%
Grade ≥ 3 Adverse Events	21%	36%
Serious Adverse Events	13%	26%
On-Treatment Deaths	2%	3%
Treatment-related Deaths	**0%**	**0%**

Most Common Adverse Events (Study 005/05)

AEs of All Grades Occurring in > 20% of Talimogene Laherparepvec Treated Patients

Preferred Term	GM-CSF (n = 127)	Talimogene Laherparepvec (n = 292)
Fatigue	36%	50%
Chills	9%	49%
Pyrexia	9%	43%
Nausea	20%	36%
Influenza-like illness	15%	31%
Injection site pain	6%	28%
Vomiting	9%	21%

Serious Adverse Events (Study 005/05) ≥ 1% in the Talimogene Laherparepvec Arm

Preferred Term, n (%)	GM-CSF (n = 127)	Talimogene Laherparepvec (n = 292)
Disease Progression	2 (<2%)	9 (3%)
Cellulitis	1 (<1%)	7 (2%)
Pyrexia	0 (0%)	5 (2%)
Tumor pain	0 (0%)	4 (1%)
Cerebral hemorrhage	0 (0%)	3 (1%)
Deep vein thrombosis	0 (0%)	3 (1%)
Gastrointestinal hemorrhage	0 (0%)	3 (1%)
Infected neoplasm	0 (0%)	3 (1%)
Metastases to central nervous system	1 (<1%)	3 (1%)
Metastatic malignant melanoma	0 (0%)	3 (1%)
Pleural effusion	0 (0%)	3 (1%)

Summary of Supportive Melanoma Set

	Melanoma with Unresectable Disease Phase 3 (005/05 + 005/05E) Talimogene Laherparepvec (N = 292)	Malignant Melanoma Phase 2 (002/03 + 002/03E) Talimogene Laherparepvec (N = 50)
All Treatment Emergent AEs – n (%)	**290 (99.3)**	**48 (96.0)**
Treatment emergent SAEs – n (%)	**80 (27.4)**	**17 (34.0)**
Treatment Related AEs – n (%)	**271 (92.8)**	**40 (80.0)**
Treatment Related SAEs – n (%)	**20 (6.8)**	**2 (4.0)**
All AEs Leading to Permanent Discontinuation of Study Treatment – n (%)	**32 (11.0)**	**2 (4.0)**
Serious	24 (8.2)	2 (4.0)
Non-serious	8 (2.7)	0 (0.0)
Fatal AEs on Study – n (%)	**12 (4.1)**	**5 (10.0)**
Treatment-related Fatal AEs on Study – n (%)	**0 (0)**	**0 (0)**

Selected Adverse Events of Interest

- Immune-mediated adverse events
- Herpetic events

Adverse Events with Possible Immune-Mediated Etiology (005/05, 005/05-E)

Preferred Term, n (%)	GM-CSF (n = 127)	Talimogene Laherparepvec (n = 292)
Glomerulonephritis (Grade 4)	0	1 (<1%)
Pneumonitis (Grade 3)	0	1 (<1%)
Vasculitis (1 Grade 3 and 1 Grade 2)	0	2 (<1%)
Psoriasis exacerbation (Grade 1)	0	1 (<1%)
Hypothyroidism	0	1 (<1%)
Vitiligo	1	18 (6.2%)

Herpetic Infections (005/05)

Preferred Term, n (%)	GM-CSF (n = 127)	Talimogene Laherparepvec (n = 292)
Herpes Simplex Virus infections	2 (2%)	16 (6%)
Oral Herpes*	2 (2%)	14 (5%)
Herpes Keratitis	0	1
Herpes Simplex	0	1

*The most common investigator-reported (verbatim) term was “cold sore”

Accidental Exposure and Risk of Transmission to Untreated Individuals

- Accidental exposure
- Shedding and transmission to untreated individuals

Accidental Exposure

- **4 reports of accidental exposures in 3 healthcare providers (HCP) out of 4,100 treatment visits**
  - Needle sticks (n=3)
    - 1 HCP, herpetic whitlow; treated with an antiviral and then experienced 2nd needle stick with no symptoms
    - 1 additional HCP, asymptomatic treated empirically with an antiviral
  - Splash back to the eye (n=1)
    - HCP; asymptomatic
- **2 additional needle sticks in the pre-clinical setting**
- **The risk of developing a symptomatic herpetic infection is low due to the deletion of both copies of the ICP34.5 gene in talimogene laherparepvec**
- **Suspected herpetic infections can be treated empirically with acyclovir**

Biodistribution and Shedding: Potential for Transmission

- **In animal studies, viral DNA was primarily restricted to tumor, blood, and tissues associated with immune-mediated viral clearance**
- **Clinical shedding studies have been performed in over 100 patients**
  - Transient and low levels of talimogene laherparepvec in blood, urine and swabs of injected lesions have been detected
  - Virus was generally cleared prior to the next injection
  - Live virus was never detected on outside of occlusive dressing
- **Together this indicates that the potential risk of talimogene laherparepvec transmission from patients is low**

Ongoing Study 20120324 to Evaluate the Potential Risk of Shedding & Transmission

Sample type	Subjects*, n/N (%)	Samples*, n/N (%)
Blood	17/20 (85%)	111/309 (36%)
Urine	4/20 (20%)	6/306 (2%)
Swabs of Injected Lesions	18/20 (90%)	156/302 (52%)
Viral Infectivity	--	3/156 (2%)
Exterior of Occlusive Dressing	14/20 (70%)	45/266 (17%)
Viral Infectivity	--	0
Oral Mucosa	1/20 (5%)	1/140 (<1%)
Viral Infectivity	--	0
Suspicious Herpetic Lesions	0/7	0/15

*As of February 6, 2015

- 25 subjects enrolled
- 1538 samples available from 20 subjects

Safety Summary

Talimogene laherparepvec has a favorable safety profile in the proposed indication

- **With more than 400 patients exposed:**
  - Most adverse events associated with talimogene laherparepvec were mild to moderate in nature
  - The most common AEs were flu-like symptoms
  - Deaths were generally reported in setting of disease progression
  - Adverse events infrequently led to discontinuation of treatment
  - Safety data from non-melanoma studies consistent with data from melanoma studies
- **Accidental exposures have been reported infrequently**
- **Low risk of transmission from patient to untreated individuals due to shedding from injected lesions**
- **Suspected herpetic adverse events can be treated with acyclovir**

Risk Management Plan

Risk Management Plan (RMP)

Risks

- Herpetic Lesions
- Accidental Exposure (HCPs)
- Secondary transmission
- Pregnancy

Labeling

- Product labelling
- Contraindications
- Warnings & Precautions
- Adverse Drug Reactions
- Medication Guide

RMP

Pharmacovigilance

- Routine PV
- Post-market observational study
- Shedding study
- Herpetic infection
  - PCR testing
  - Questionnaire

REMS Elements: Communication Plan

- Dear Health Care Provider Letter
- REMS information available at oncology meetings
- Patient Safety Brochure
- Dedicated REMS website

Product Support:

- Scientific Affairs/Medical Information
- Call Center

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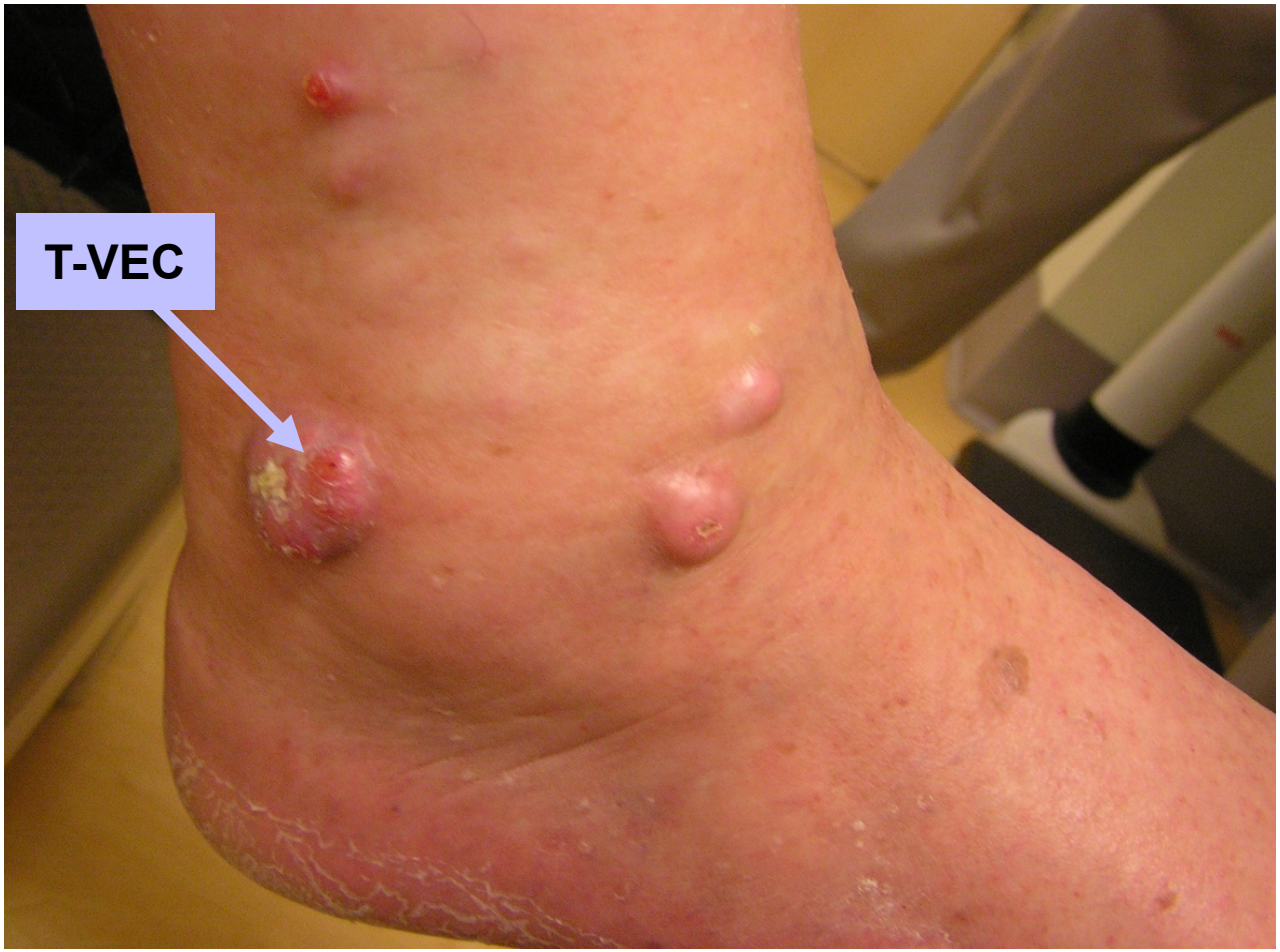
Clinical Perspective

Howard Kaufman, MD, FACS
Chief Surgical Officer
Associate Director for Clinical Science
Co-Leader, Clinical Investigations and Precision Therapeutics Program
at the Rutgers Cancer Institute of New Jersey
President, Society of Immunotherapy of Cancer

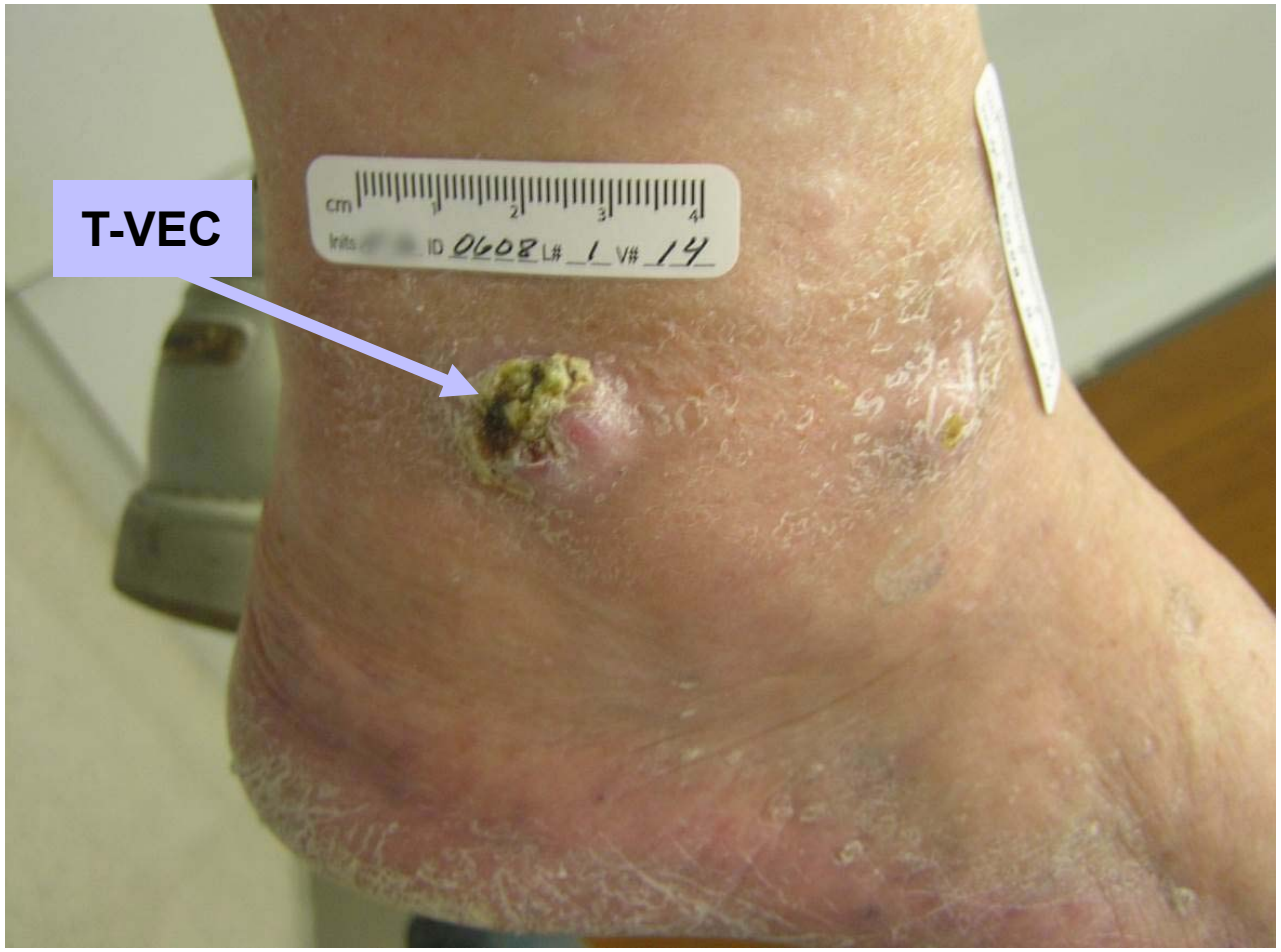
Example of Durable Complete Response (>9 Years) from Phase 2 Study 002/03



Other lesions not injected

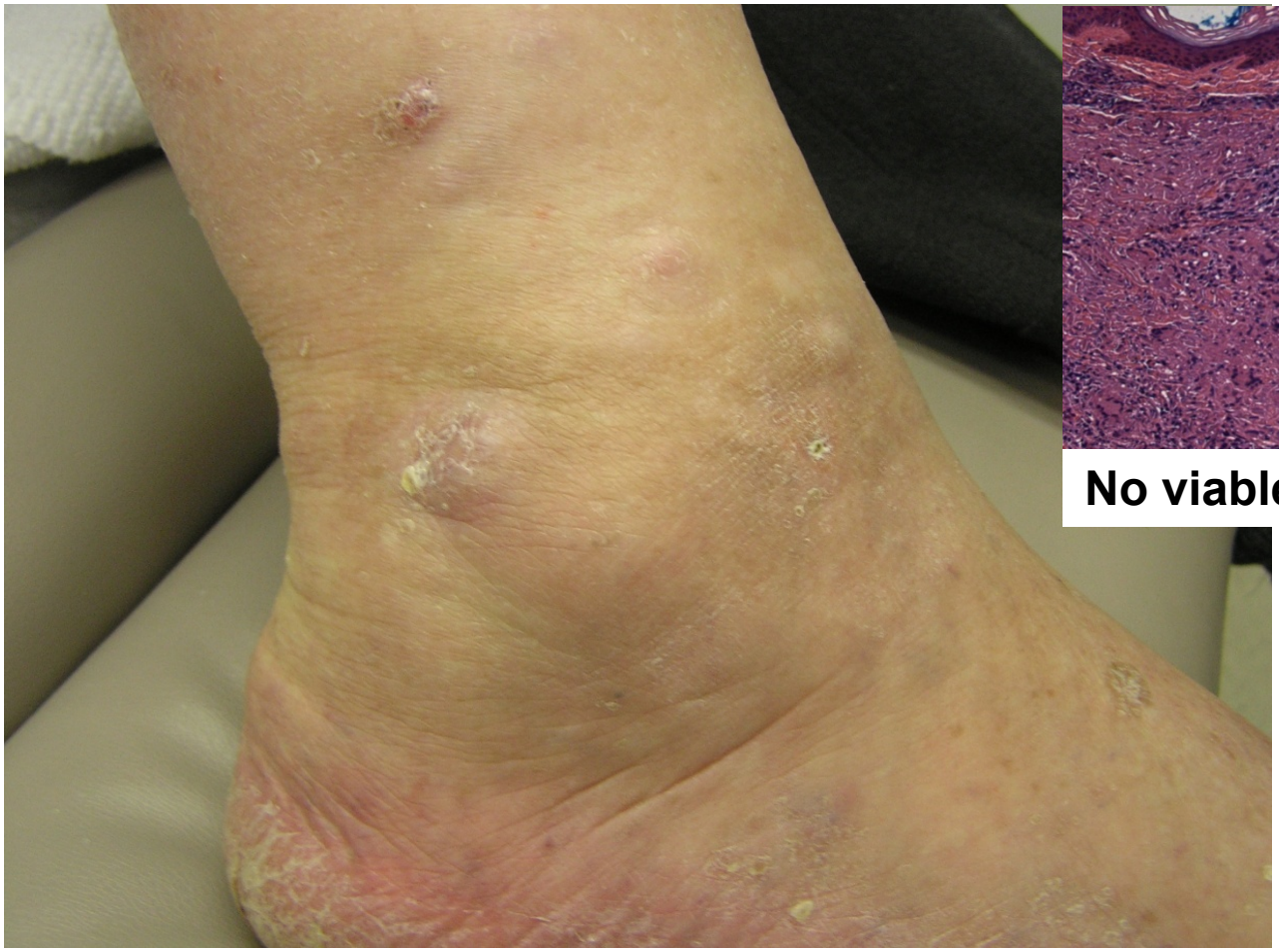
Example of Durable Complete Response (>9 Years) from Phase 2 Study 002/03

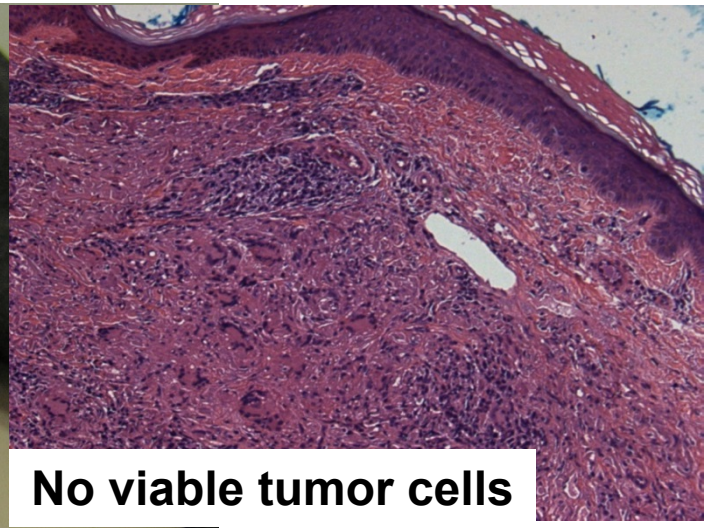
6 injections



Example of Durable Complete Response (>9 Years) from Phase 2 Study 002/03

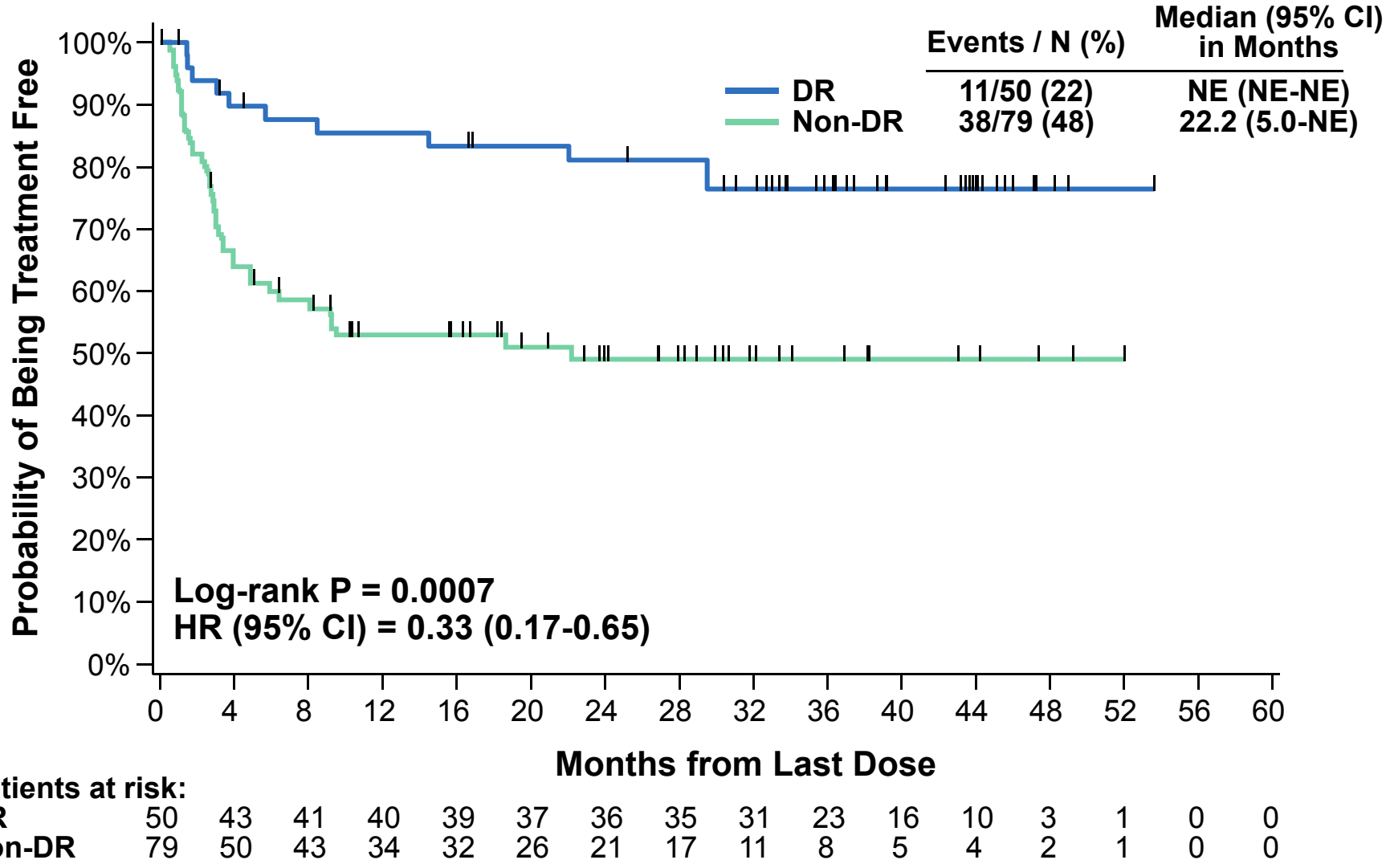
6 months after first injection





No viable tumor cells

Durable Response is Associated with a Prolonged Treatment Free Interval



*All subjects followed for at least 9 months

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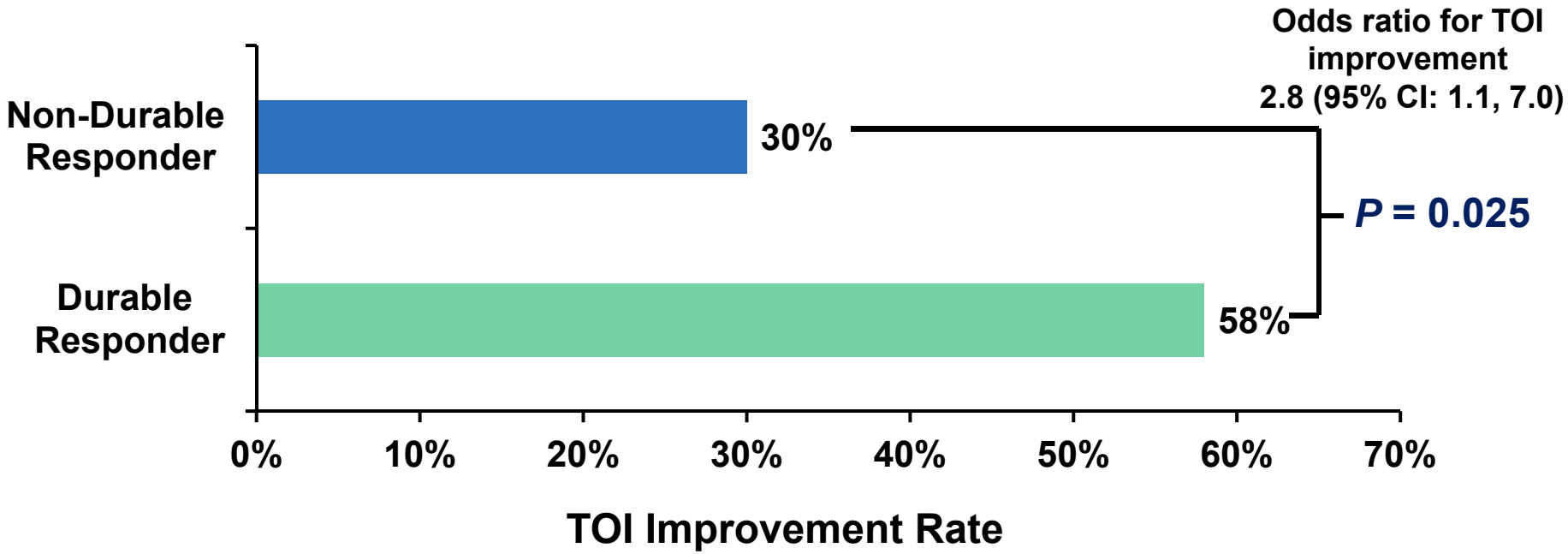
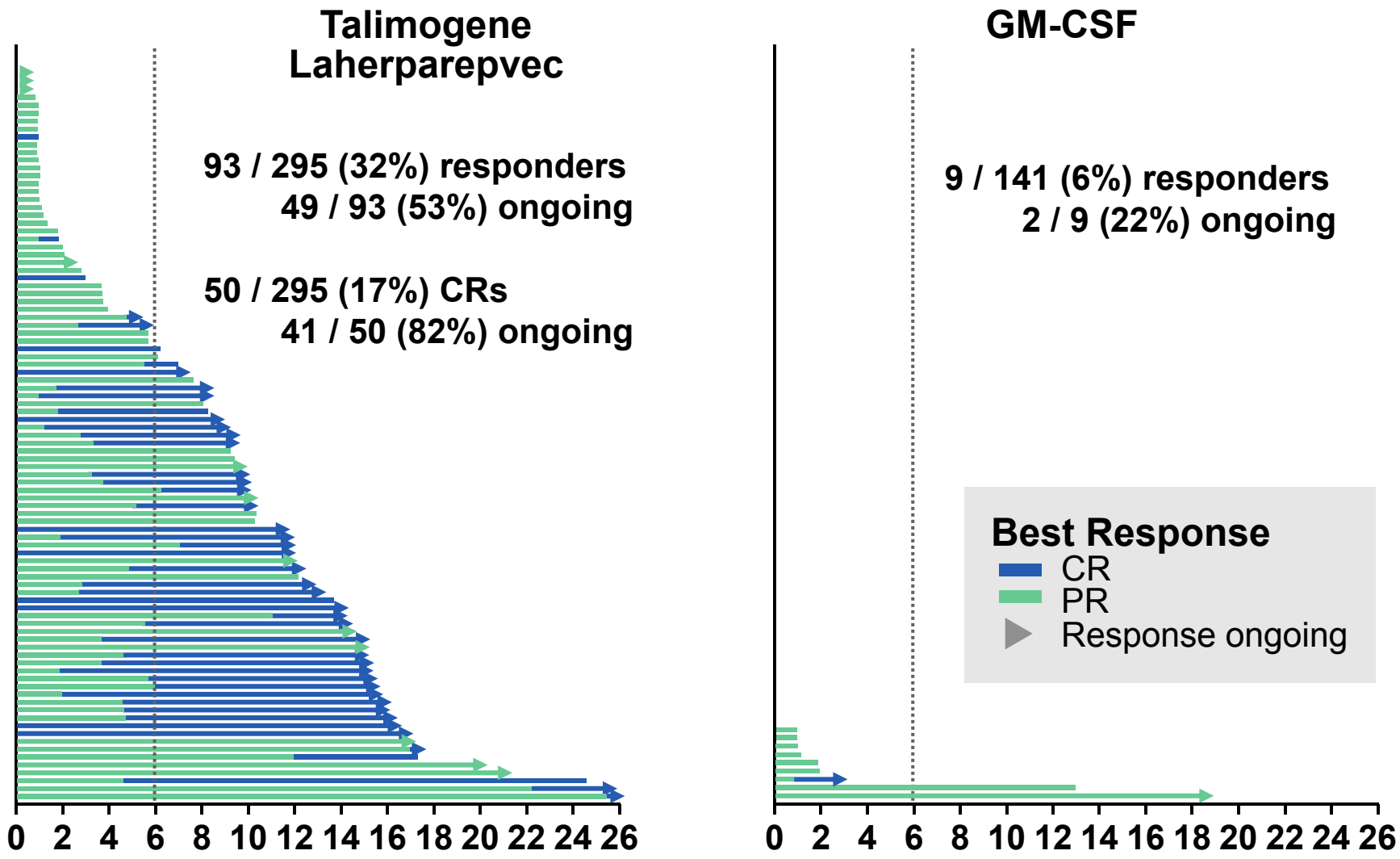
Durable Responses Associated with Improvement in Quality of Life



- The TOI is a 27-item measure that is the sum of the domains for physical and functional well-being and the BRM subscale scores of the FACT-BRM, a validated quality of life instrument
- Improvement in TOI is defined as at least a 5 point increase from baseline for at least 4 weeks
- A stratified 9-month landmark analysis was used to evaluate an association between achieving a DR and the TOI improvement rate to control for lead-time and responder bias

Duration of Response per Investigator

At Time of Overall Survival Final Analysis



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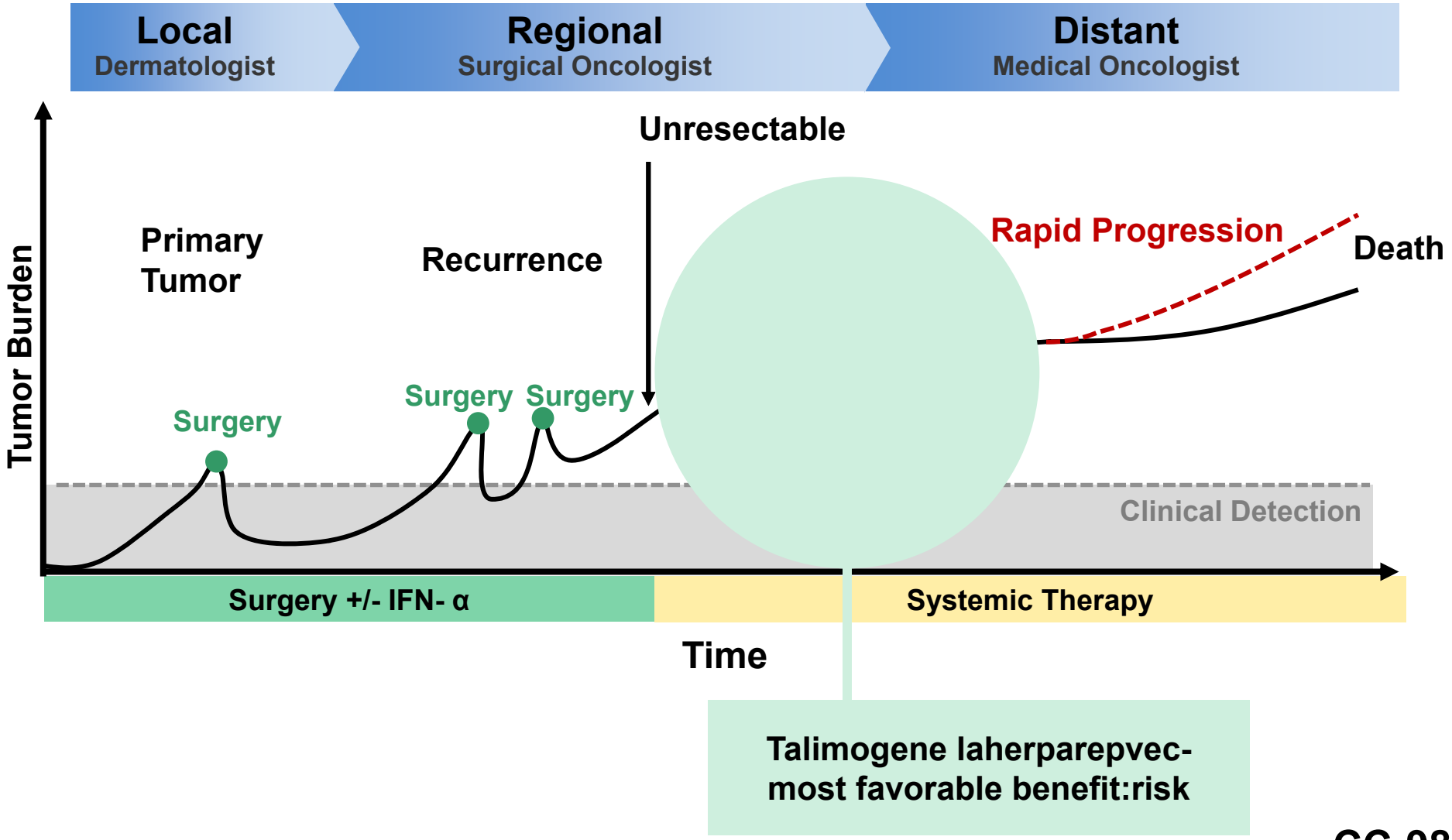
Talimogene Laherparepvec Addresses A Persistent Unmet Need



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Conclusion	**Steven Galson, MD, MPH** Amgen Inc. Senior Vice President, Global Regulatory Affairs and Safety

Conclusion

Steven Galson, MD, MPH
Amgen Inc.
Senior Vice President, Global Regulatory Affairs and Safety

Talimogene Laherparepvec Summary

- Potential to be first virus-based cancer therapy
- Study concurred with FDA during rapid evolution of the treatment landscape
- Favorable benefit:risk in patients with metastatic melanoma where an unmet medical need remains

Conclusion

- **Experts in the care of melanoma believe additional treatments are necessary**
- **Amgen is dedicated to the continued development of talimogene laherparepvec**
- **Amgen is committed to:**
  - Conducting post-marketing pharmacovigilance activities
  - Providing right type and level of product support to patients, household contacts, and physicians
  - Appropriate use of talimogene laherparepvec in patients who will receive greatest benefit