Innovative Combination Strategies: Oncolytic and Systemic Therapy

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Overview

- What is oncolytic therapy?
- What is the data with single agent oncolytic agents?
- What is the data with combinations?
- Future directions and prospects

What is Oncolytic Therapy?

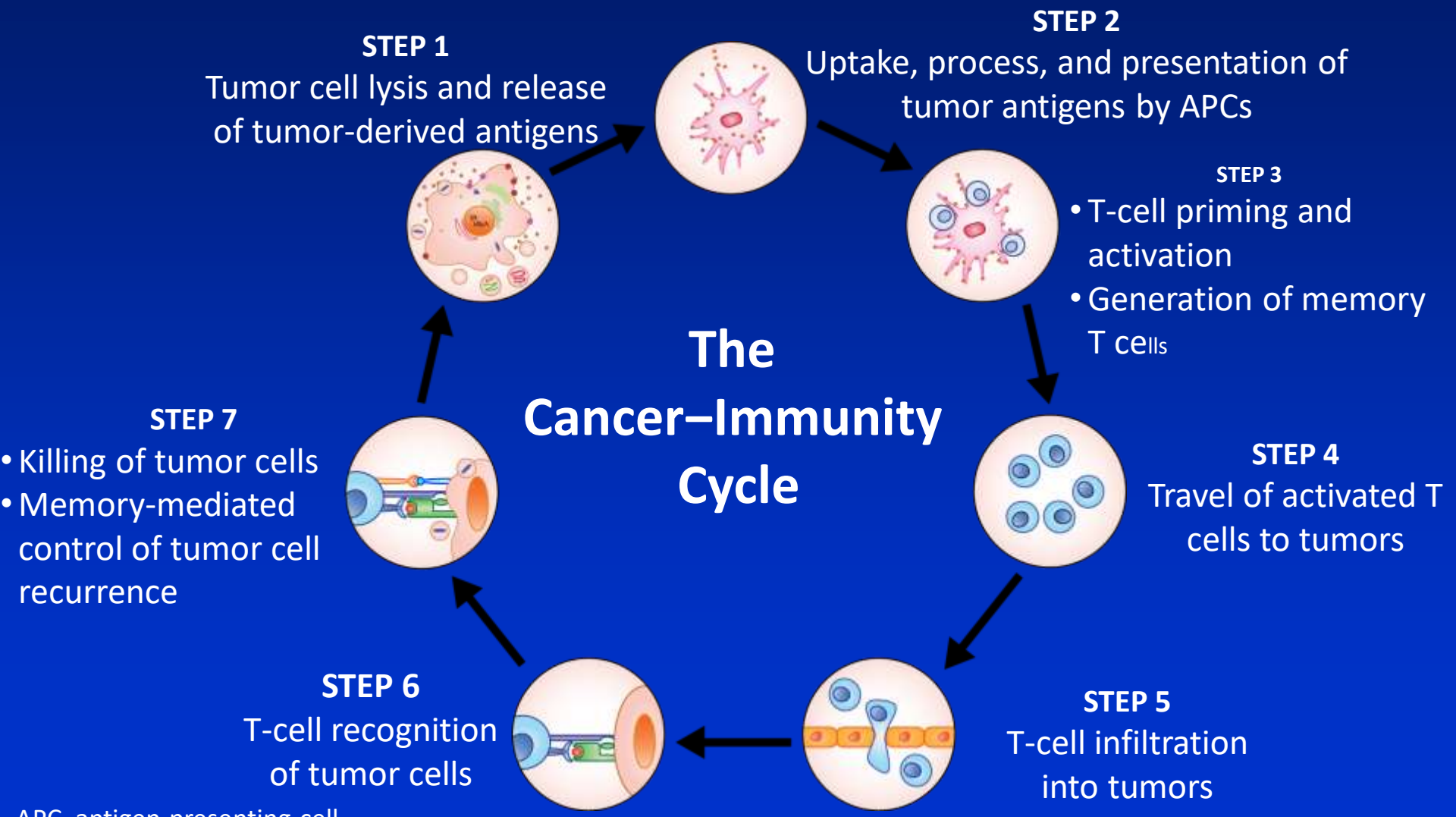
- Direct injection of tumors with agents that produce regression
- Produce a local and systemic effect that is immunologically mediated
- Viral based
  - TVEC, HF-10, CAVATAK
- Non-viral based
  - PV-10, IL-12

Oncolytic Immunotherapy: Mechanisms of Action

- Direct
  - Cell lysis (viral replication, chemical and mechanical ablation)
- Indirect “bystander response”
  - Induction of innate immune response
  - Induction of adaptive immune response

Mullen JT et al. *The Oncologist*. 2002;7:106-119.

Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects



APC, antigen-presenting cell

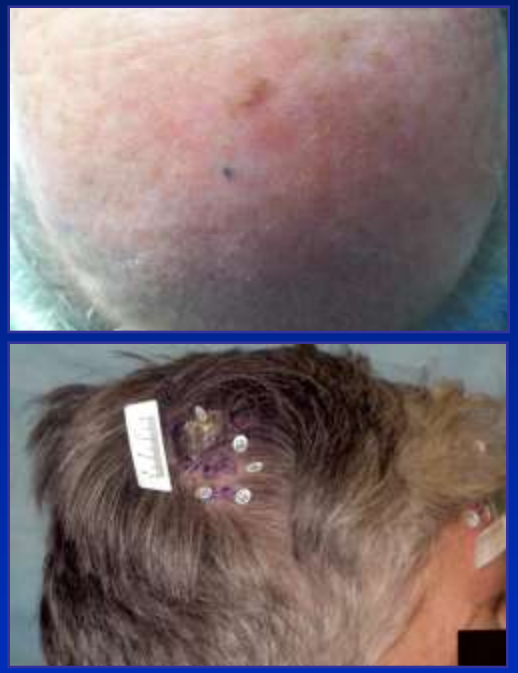
Chen DS et al. *Immunity*. 2013;39:1-10.

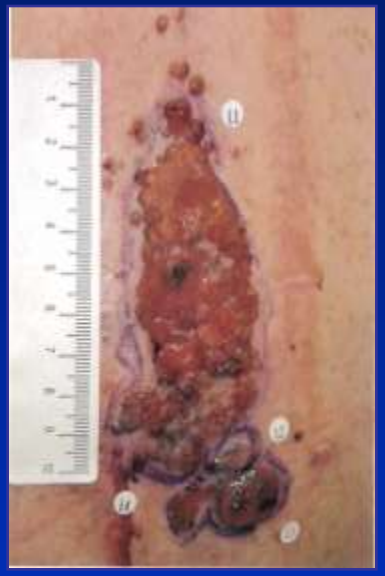
Soft Tissue/Skin Metastases
Role for Intralesional Oncolytic Therapy

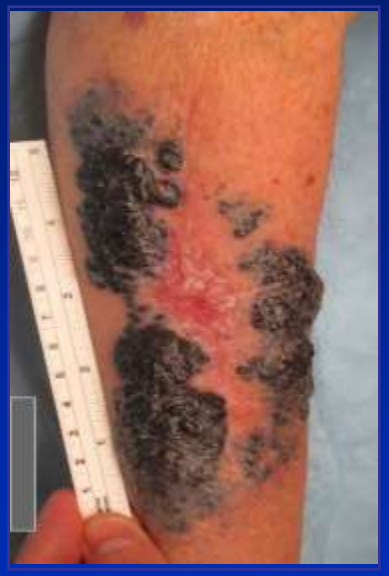
- Soft Tissue and Skin metastases occur frequently in melanoma
- Local-regional control is clinically important
- Systemic Therapy may not always be possible or appropriate
  - Newer IL agents produce systemic responses
  - Backbone for future combinations

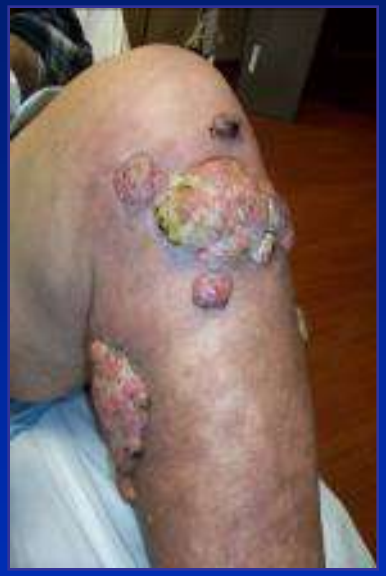
Melanoma intralymphatic metastasis

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

Courtesy of Robert Andtbacka, MD

Current Clinical Trials

- Single Agent (Monotherapy) Trials
  - PV-10 (phase III ongoing)
  - IL-12 electroporation
  - CAVATAK
- Combination Trials
  - TVEC
  - PV-10
  - HF-10

Rose Bengal Disodium 10% (PV-10)

- Small molecule fluorescein derivative
- Primary tumor lysis by entering lysososmes
- Tumor-infiltrating lymphocytes at local site and regression of distant tumors
- Necrotic tumor cells facilitate antigen presentation
- Secondary tumors are rejected in immuno-competent animals
- No immune response in immuno-compromised animals
- Response is tumor specific
- Adoptive transfer of spleen cells can convey immunity
  - T cell subsets have increased expression of Gamma IFN

Thompson JF, Agarwala SS. et al. *Melanoma Res*. 2008;18:405-411.
Toomey P et al. SSO, 2012

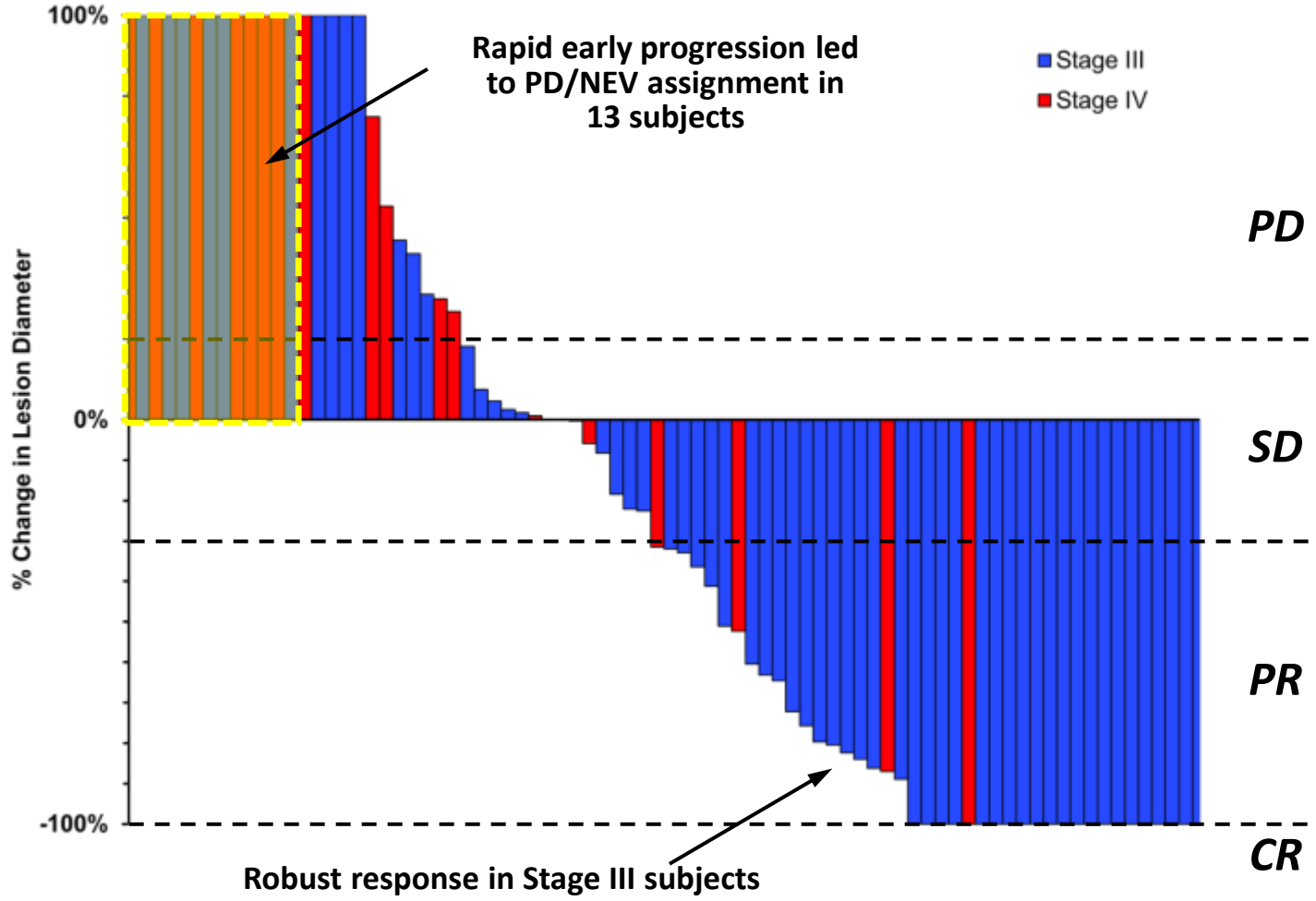
PV-10 Phase 2: *Efficacy*

Objective Response of Study Lesions (n = 80)

Best Response (RECIST, n = 80 through Wk 52)	**Target Lesions (n = 80)**	**Bystander Lesions (n = 38)**
CR	19 (24%)	9 (24%)
PR	20 (25%)	5 (13%)
SD	18 (22%)	7 (18%)
PD	23 (29%)	17 (45%)
ND	--	42
CR + PR	39 (49%)	14 (37%)
CR + PR + SD (locoregional disease control)	57 (71%)	21 (55%)

Thompson JF, Agarwala, SS et al. *Ann Surg Oncol*. 2015;22(7):2135-2142.

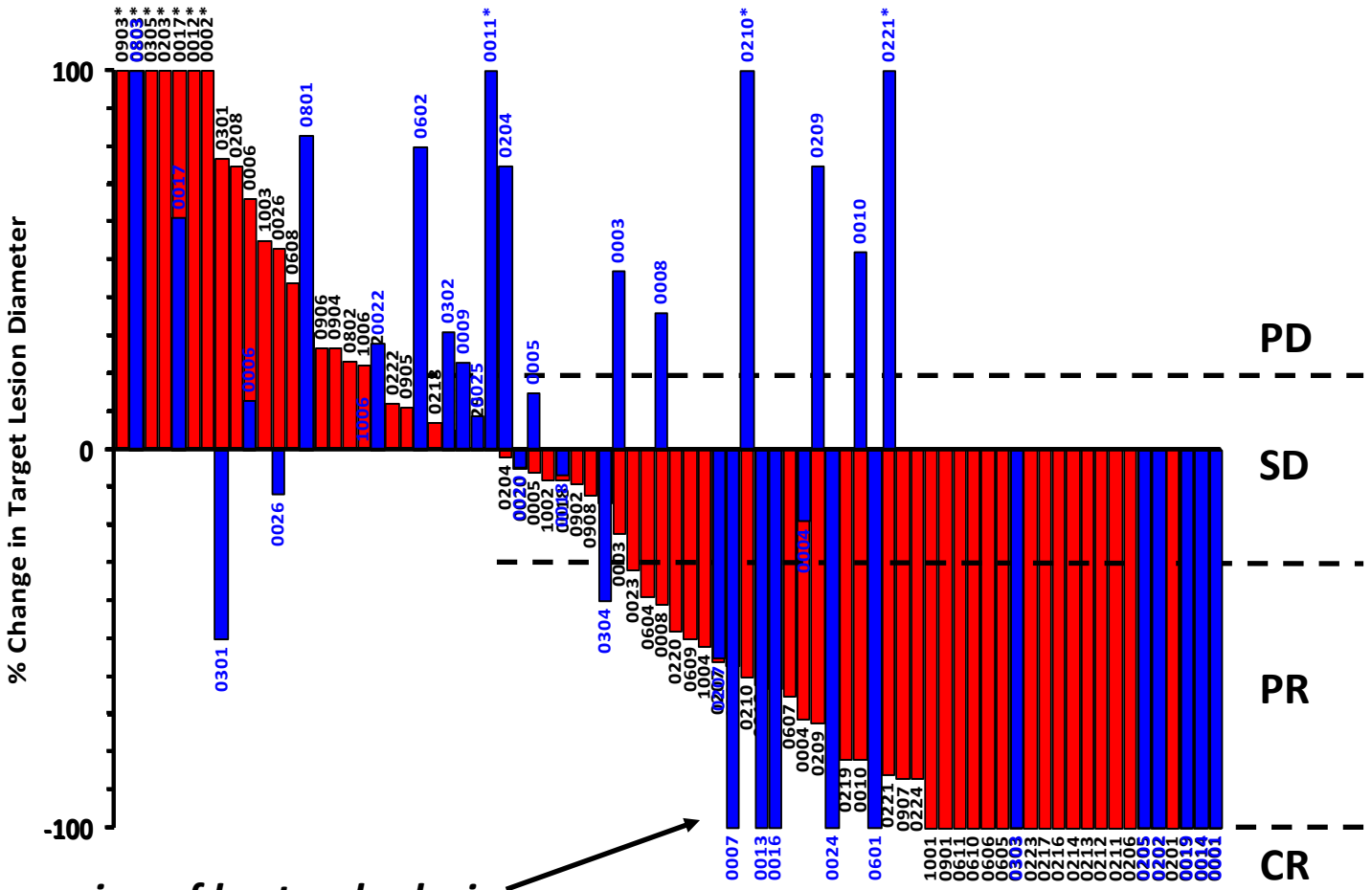
PV-10 Response in Target Lesions



NEV, not evaluable

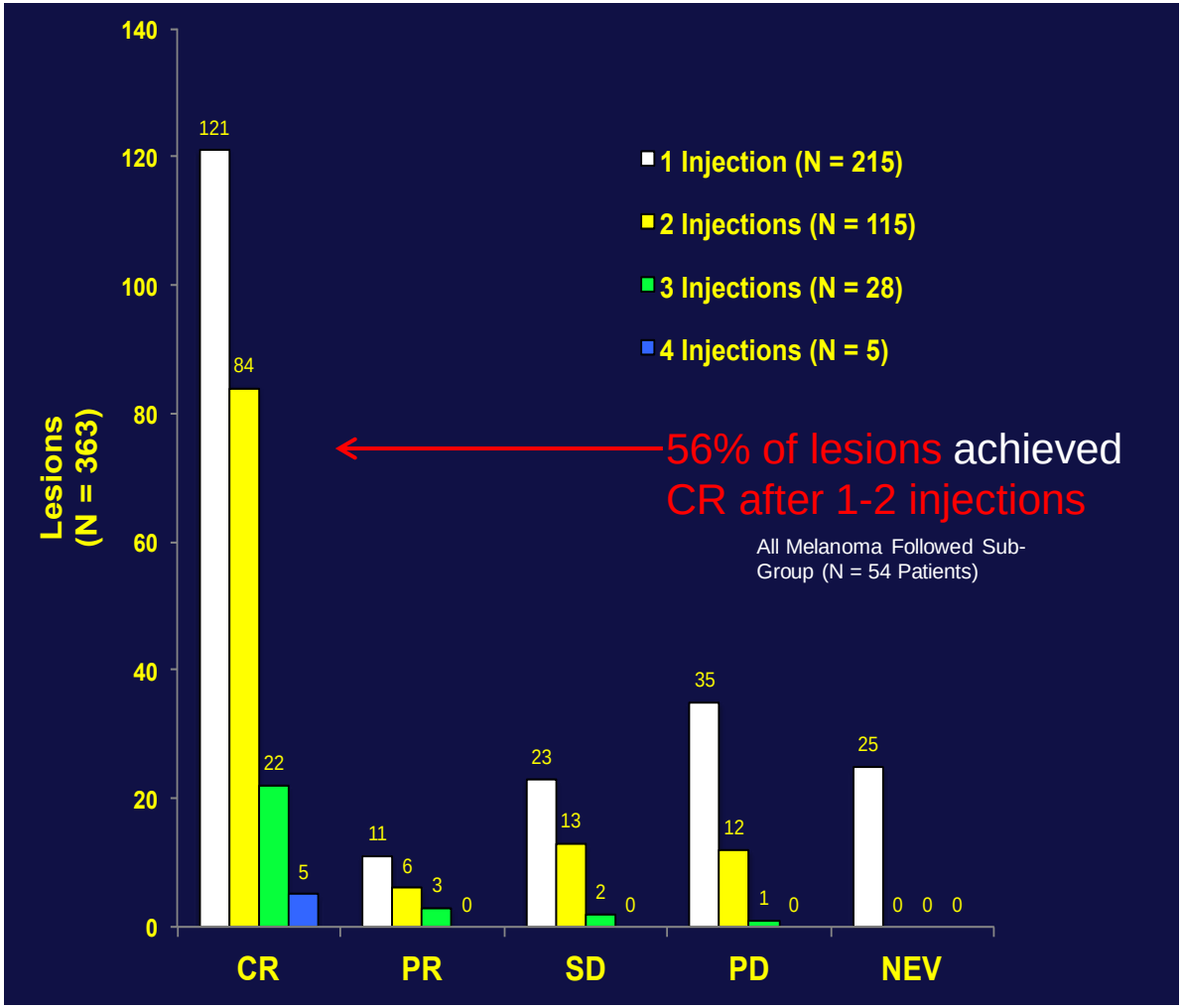
Agarwala SS et al. *J Clin Oncol*. 2014;32:5(suppl). Abstract 9027.

Phase 2 – Efficacy



Regression of bystander lesions strongly correlated with response in target lesions

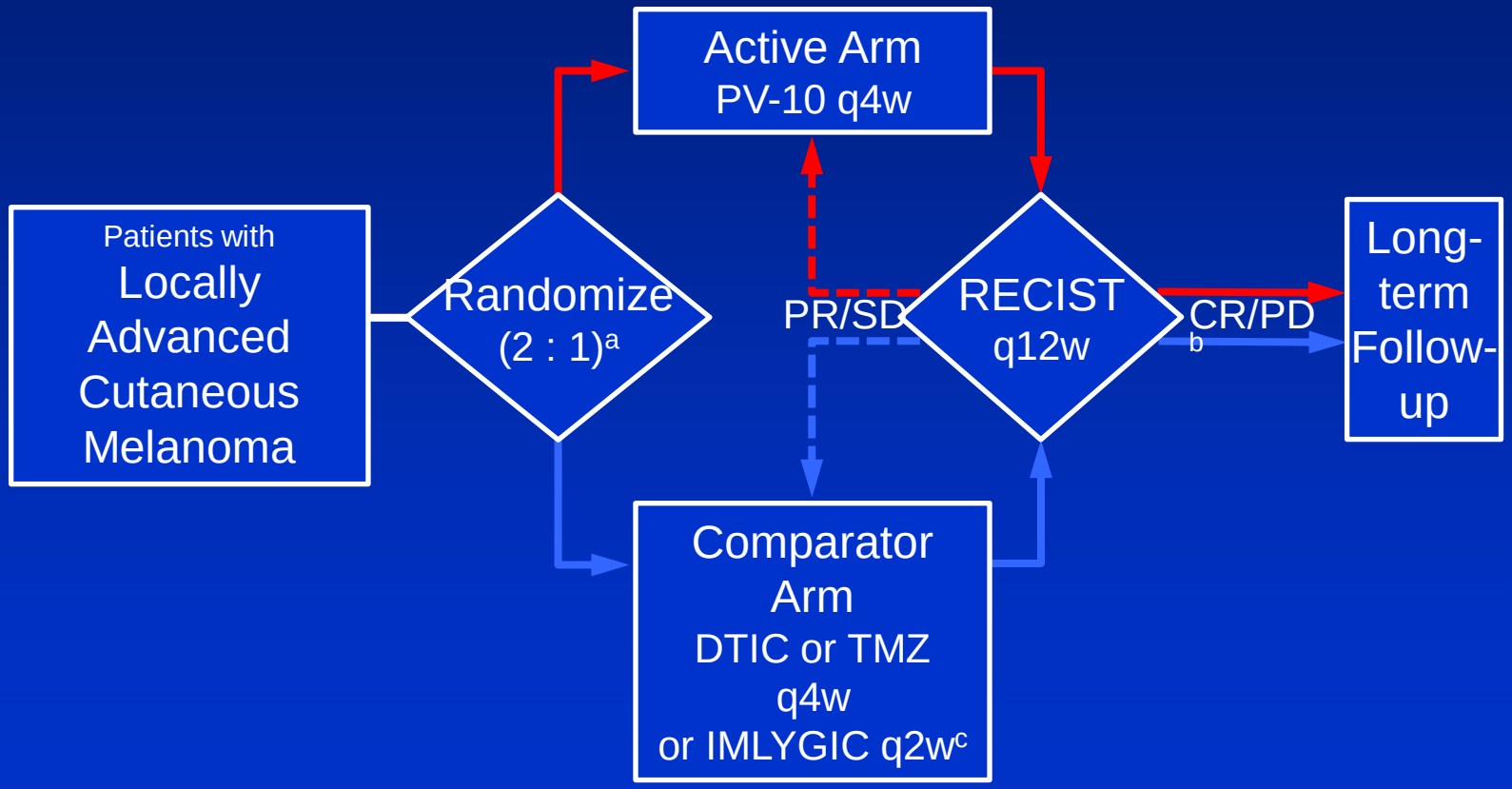
Responses with PV-10 Occur Early



Agarwala et al., ASCO 2014

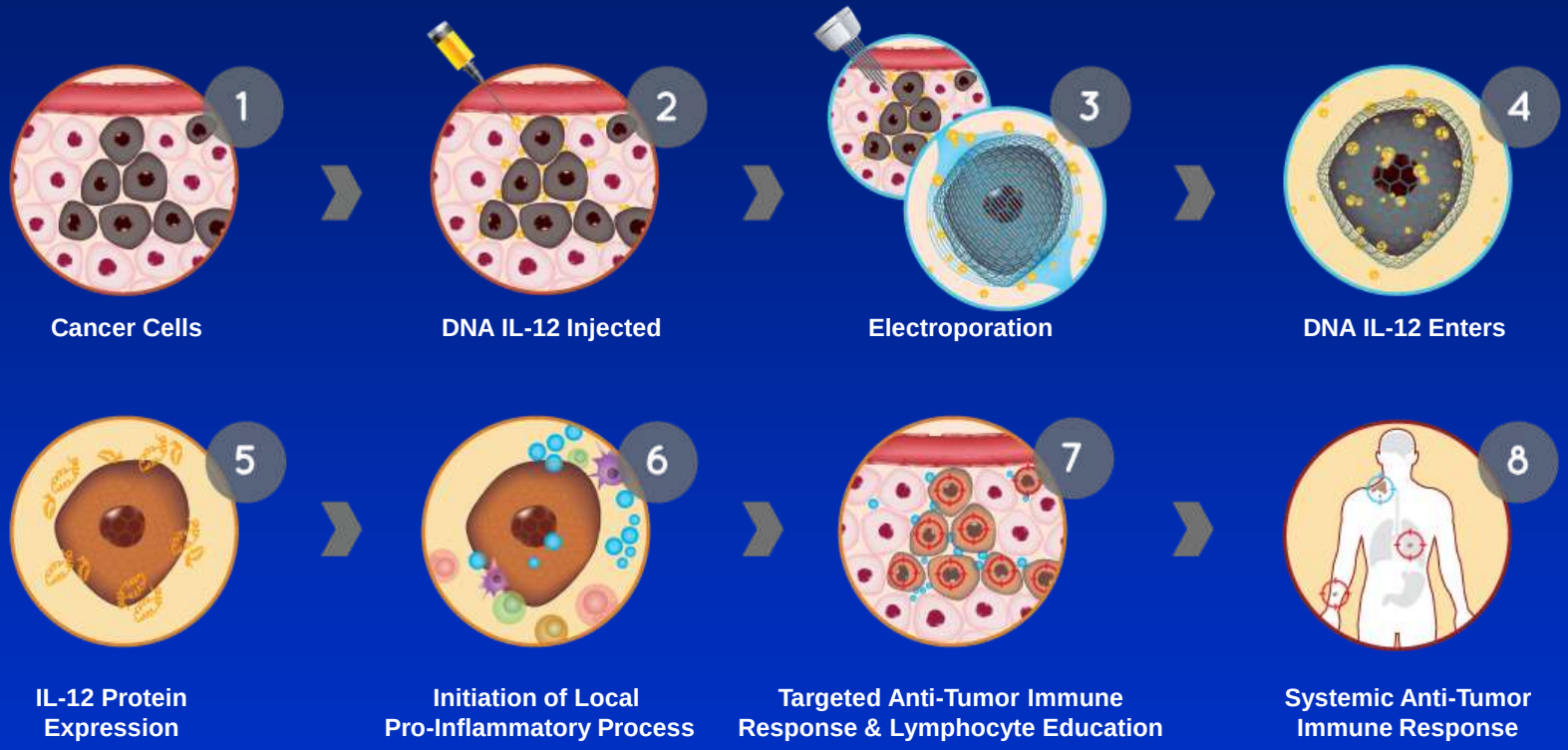
Phase III Design

Protocol PV-10-MM-31

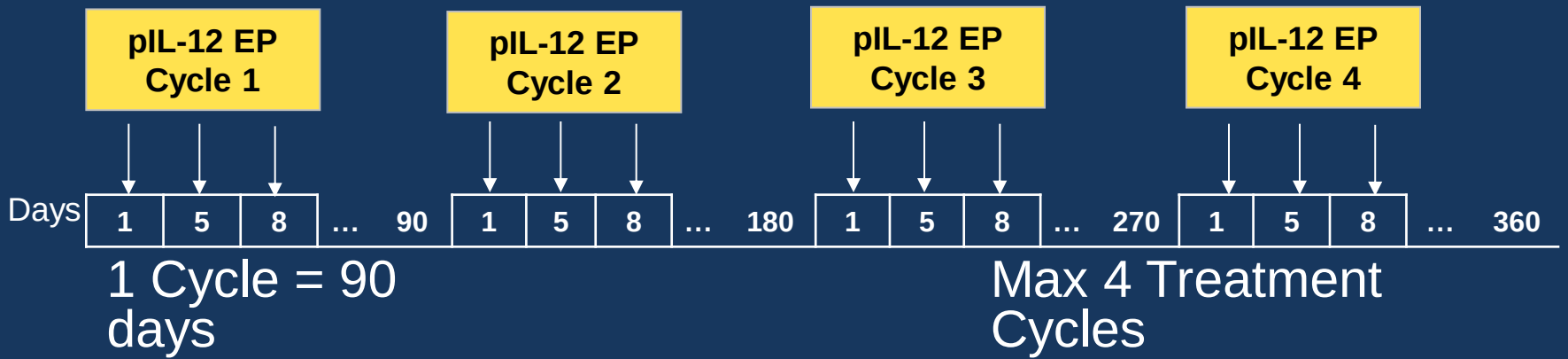


a. 225 patients randomized 2:1 (stratified for prior immune checkpoint inhibition)
b. Cross-over allowed upon documented PD in comparator arm
c. IMLYGIC repeated after 3 weeks then q2w

Intratumoral DNA-encoded IL-12 Electroporation (IT-pIL12-EP)



Phase 2 Study Design and Treatment Schedule



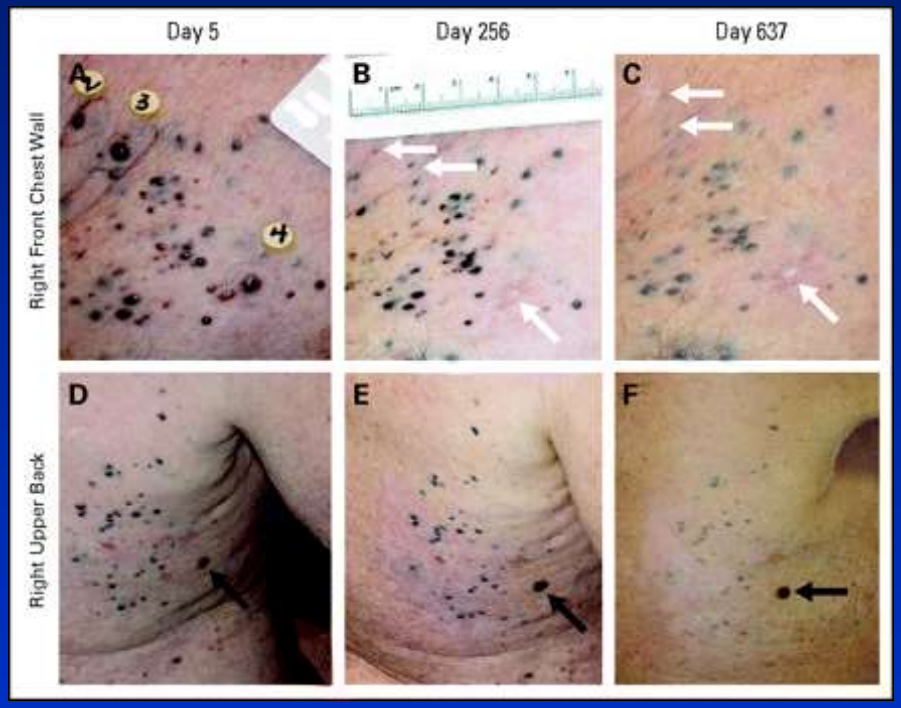
Primary Objective:

- Overall Response Rate by modified “skin” RECIST within 180 days (ORR = CR + PR)

Secondary Objectives

- Disease Control Rate (DCR = CR
- Distant Lesion Regression
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety

Plasmid Encoded DNA IL-12 Electroporation



Responses in electroporated and non-electroporated lesions

Phase II study (interim analysis; n=28)

- Primary endpoint ORR 24 wks
  - OR 32% (9/28)
  - CR 11% (3/28)
- Lesion responses (n=85)
  - SD 31% (26/85)
  - PR 8% (7/85)
  - CR 45% (38/85)
- Response untreated lesions
  - 59 % (13/22 patients)

Daud AI et al. ASCO 2014; Abstract 9025.

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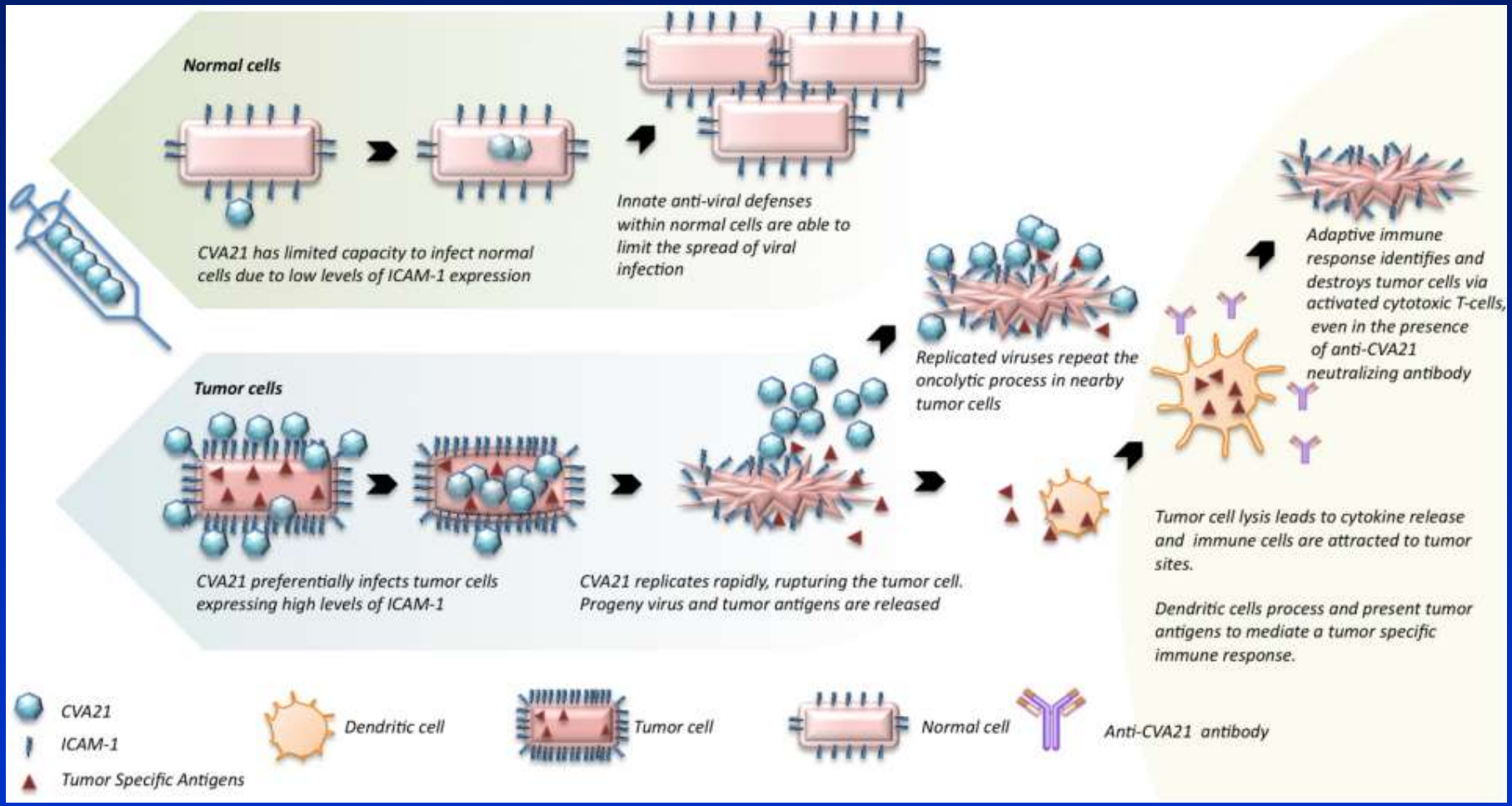
Coxsackievirus A21(CVA21)

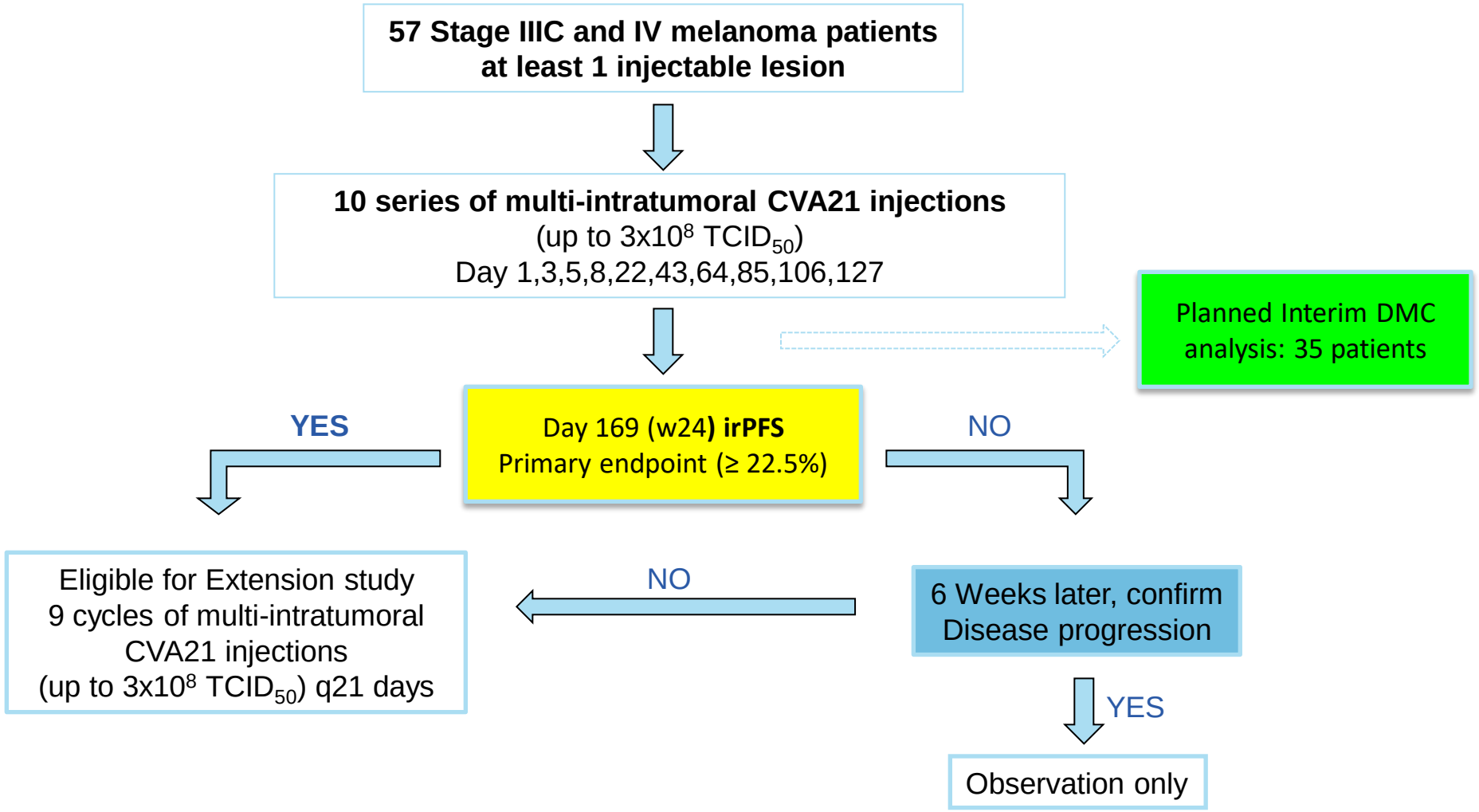
Oncolytic immunotherapeutic modes of action



Andtbacka RHI, et al. World Melanoma Congress, 2013

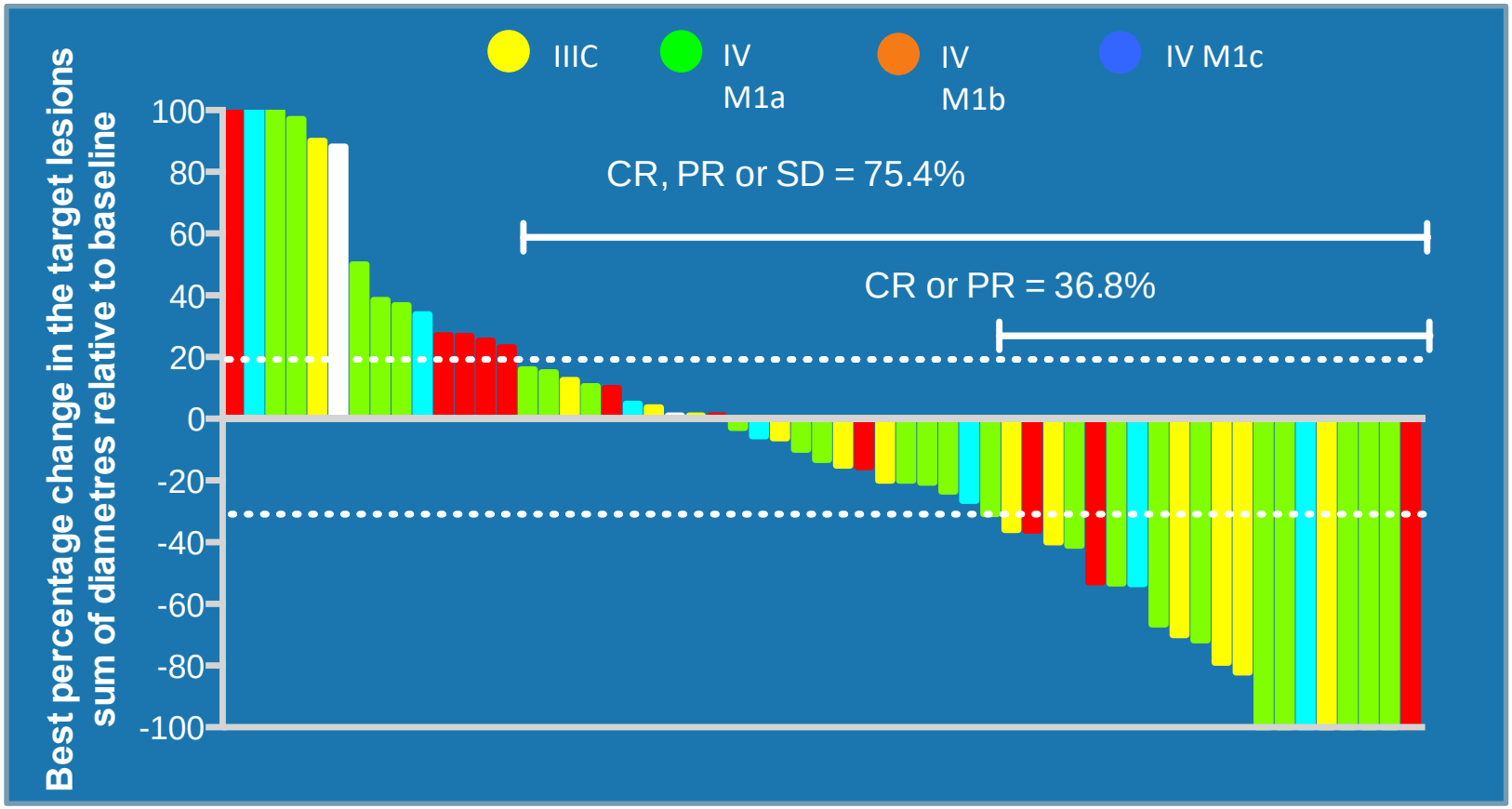
CALM Phase II study Design

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



CALM Phase II

Best Percentage Change in Target Lesions*



Analysis excludes patients satisfying protocol criteria but not on study long enough for 6 week tumor response assessment.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Andtbacka RHI et al. SSO Annual Cancer Symposium 2015.

*Investigator assessed

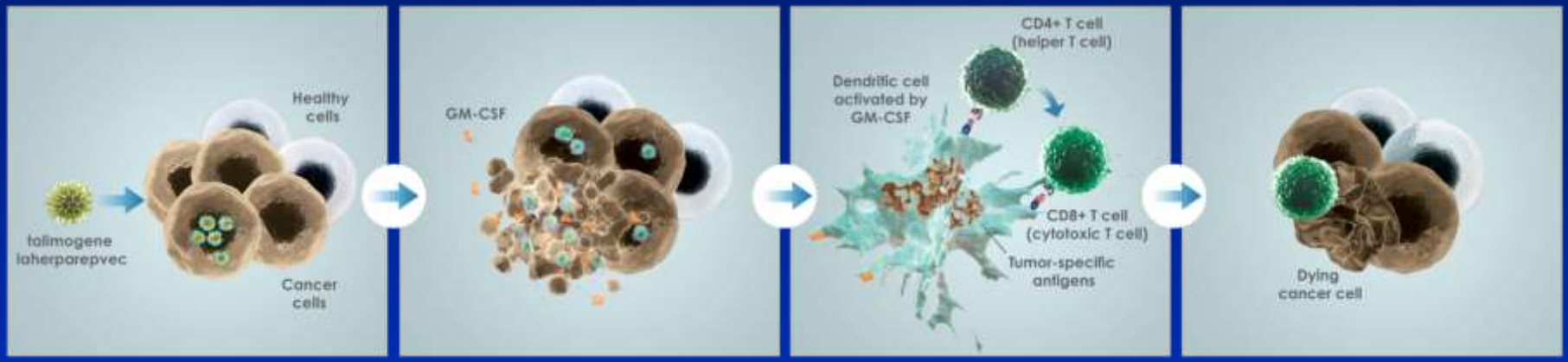
Current Clinical Trials

- Single Agent (Monotherapy) Trials
  - PV-10 (phase III ongoing)
  - IL-12 electroporation
  - CAVATAK
  - HF10
- Combination Trials
  - TVEC
  - PV-10
  - HF-10

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

Local effect: tumour cell lysis

Systemic effect: tumour-specific immune response



Selective viral replication in tumour tissue

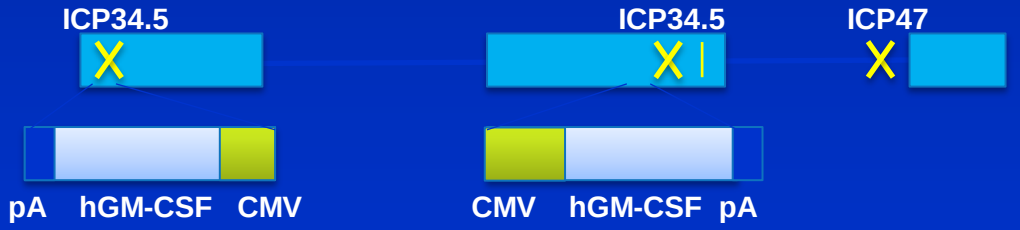
Tumour cells rupture for an oncolytic effect

Systemic tumour-specific immune response

Death of distant cancer cells

T-VEC key genetic modifications:

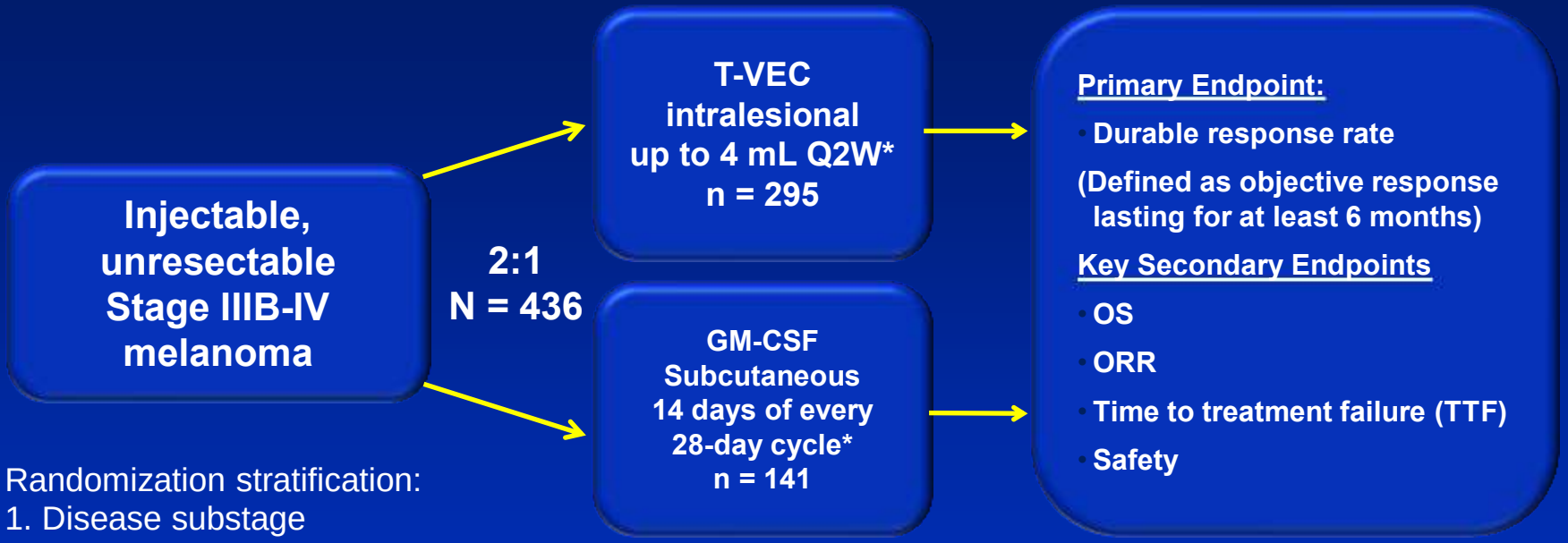
JS1/ICP34.5-/ICP47-/hGM-CSF



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

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

*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.

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%	
PR	5.0%	15.6%	

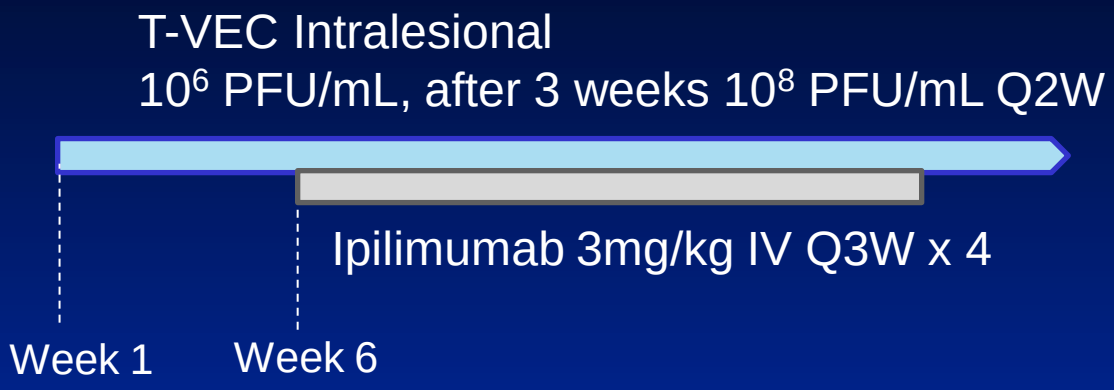
*Rate of CR or PR that began at any point within 12 months of initiation of therapy and lasted continuously for 6 months or longer.
Determined using modified WHO criteria by an independent, blinded endpoint assessment committee (EAC).
ITT, intention to treat; CI, confidence interval.

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

T-VEC + ipilimumab Phase Ib trial

Unresectable Stage IIIB-IV Melanoma

- Injectable
- Treatment naïve
- ECOG PS 0 or 1
- No evidence of CNS mets



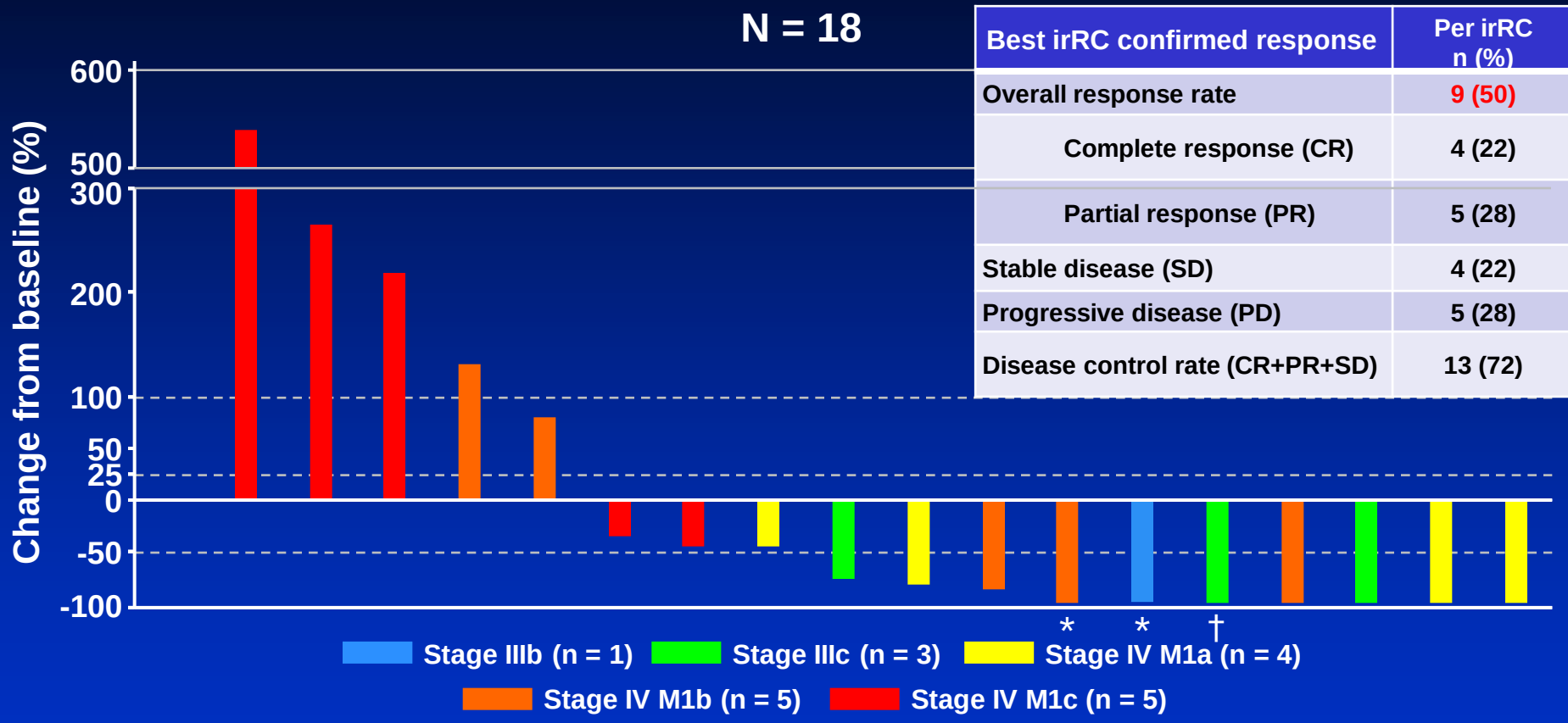
N = 19

- T-VEC dosing until CR, all injectable tumors disappear, PD per irRC, or intolerance, whichever is first
- Safety follow-up occurs 30 (+7) days after last dose of T-VEC or 60 (+7) days after last dose of ipilimumab, whichever is later

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

Puzanov et al J Clin Oncol 2016; JCO671529.

Best overall response



Best irRC confirmed response	Per irRC n (%)
Overall response rate	9 (50)
Complete response (CR)	4 (22)
Partial response (PR)	5 (28)
Stable disease (SD)	4 (22)
Progressive disease (PD)	5 (28)
Disease control rate (CR+PR+SD)	13 (72)

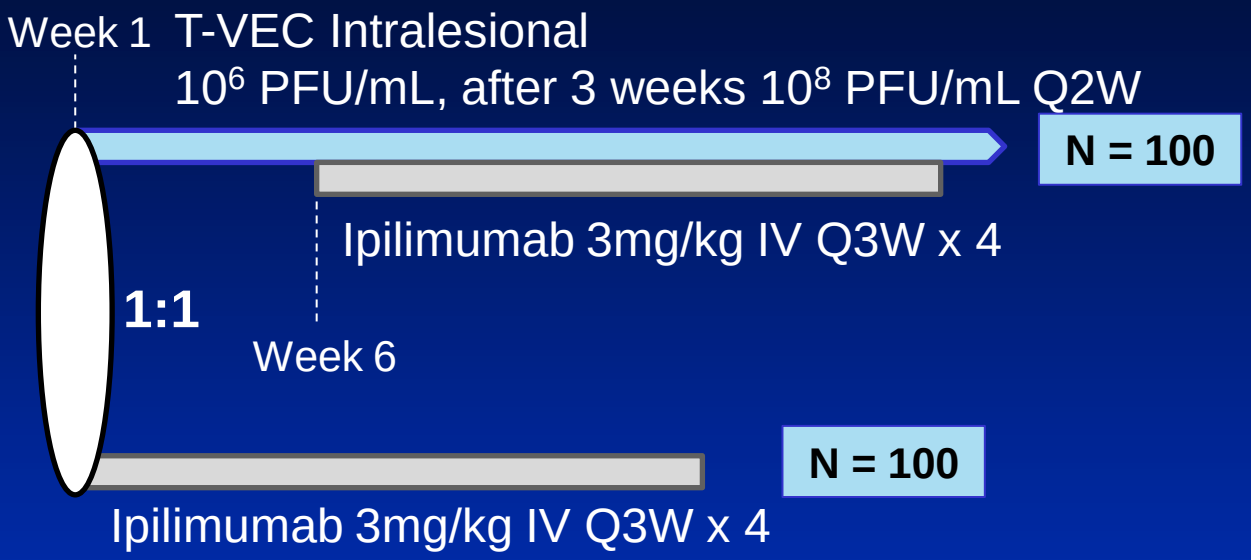
The waterfall plot shows best reductions in tumor burden at a single time point.
For the irRC response table, CR, PR, and PD needed to be confirmed by consecutive assessments no less than 4 weeks apart to be considered confirmed with the following exception: if PD was the last tumor assessment, it was considered as confirmed.
*≤ -98%, but > -100% , †Unconfirmed CR

Puzanov I et al Clin Oncol 2016; JCO671529

T-VEC + ipilimumab Phase II trial (20110264)

Unresectable Stage IIIB-IV Melanoma

- Injectable
- ≤ 1 line of systemic therapy for BRAF wt, or ≤ 2 lines of systemic therapy including BRAFi regimen for BRAF mutated
- ECOG PS 0 or 1
- No evidence of active CNS mets



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- Safety follow-up occurs 30 (+7) days after last dose of T-VEC or 60 (+7) days after last dose of ipilimumab, whichever is later

Primary Endpoint	**ORR^{irRC}**
Secondary Endpoints	**PFS, OS, DRR, BOR, DCR, DoR, TTR, resection rate**

T-VEC + ipilimumab Phase II trial (20110264)

Initial results

	Confirmed[a] n (%)		Unconfirmed[b] n (%)	
	T-VEC+ IPI (N=42)	IPI (N=40)	TVEC+IPI (N=42)	IPI (N=40)
ORR – n (%)	15 **(35.7)**	7 **(17.5)**	21 **(50.0)**	11 **(27.5)**
(95% CI)	(21.6, 52.0)	(7.3, 32.8)	(34.2, 65.8)	(14.6, 43.9)
CR	4 (9.5)	4 (10.0)	6 (14.3)	7 (17.5)
PR	11 (26.2)	3 (7.5)	15 (35.7)	4 (10.0)
SD	13 (31.0)	11 (27.5)	7 (16.7)	7 (17.5)
PD	6 (14.3)	5 (12.5)	11 (26.2)	17 (42.5)
UE*	5 (11.9)	13 (32.5)	0 (0.0)	1 (2.5)
Odds ratio (95% CI) for ORR	2.6 (0.9, 7.3)		2.6 (1.0, 6.6)	
DCR (%) – n (%)	28 (66.7)	18 (45.0)	28 (66.7)	18 (45.0)
(95% CI)	(50.5, 80.4)	(29.3, 61.5)	(50.5, 80.4)	(29.3, 61.5)
Odds ratio (95% CI) for DCR	2.4 (1.0, 6.0)		2.4 (1.0, 6.0)	

[a]Confirmation of initial CR/PR/PD by subsequent assessment by ≥ 4 w apart. A CR/PR without confirmation is classified as SD and *an unconfirmed PD is classified as UE. Further follow up is ongoing.

[b]Unconfirmed is response or PD without confirmation requirement. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = unable to evaluate; DCR = disease control rate (SD or better).

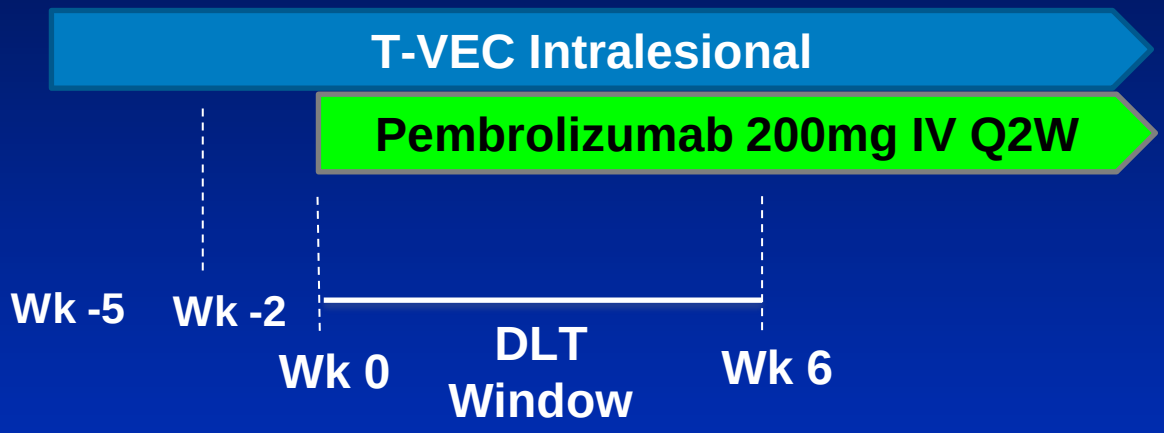
Chesney J., et al. ESMO 2016

T-VEC + Pembrolizumab Phase 1b Trial (Masterkey – 265)

N=21

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

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



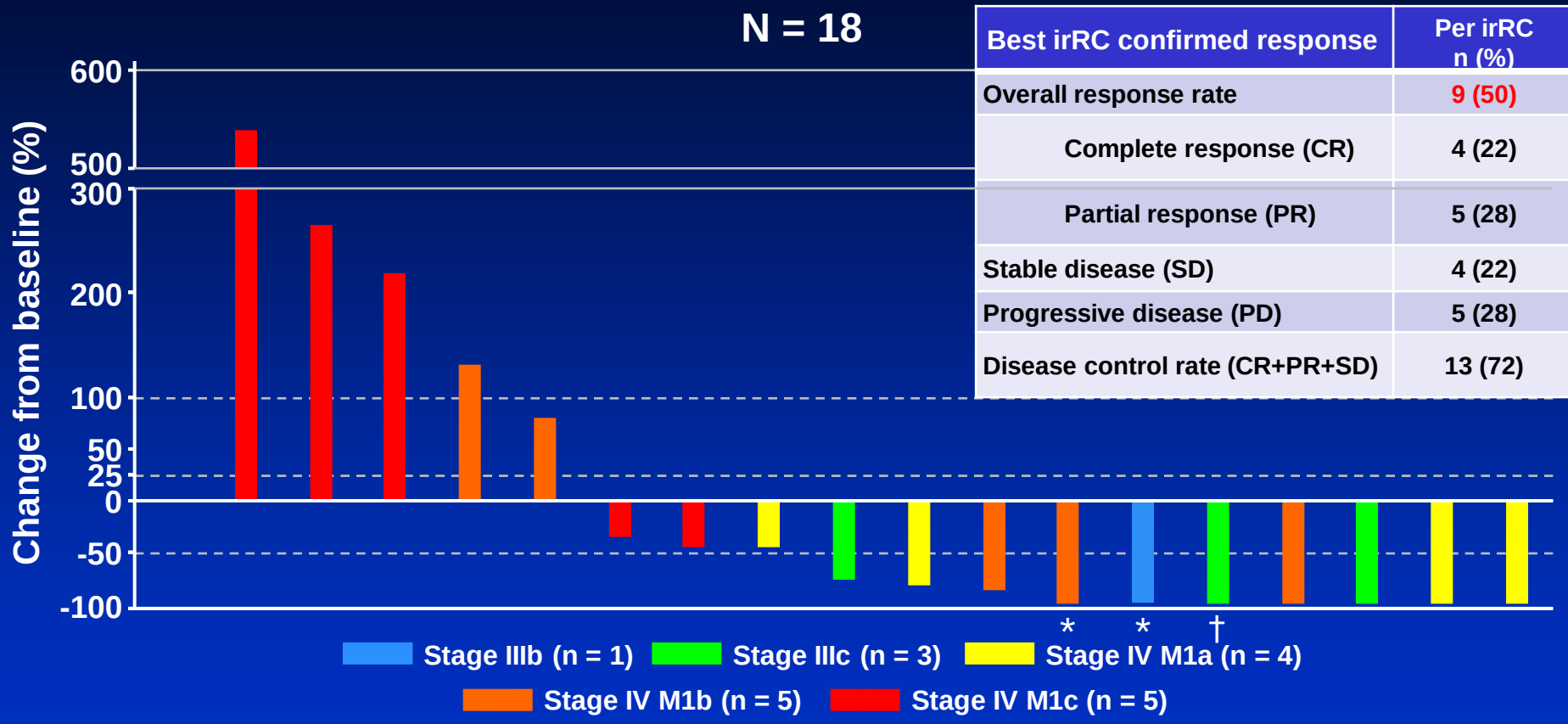
Treatment until whichever occurs first:
- Progressive disease (PD) per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

T-VEC: talimogene laherparepvec

Long, et al. ECC 2015
Long, et al. SMR 2015

Amgen study 20110265.
Available at: https://clinicaltrials.gov/ct2/show/NCT02263508. Accessed January 2016

Best overall response



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*≤ -98%, but > -100% , †Unconfirmed CR

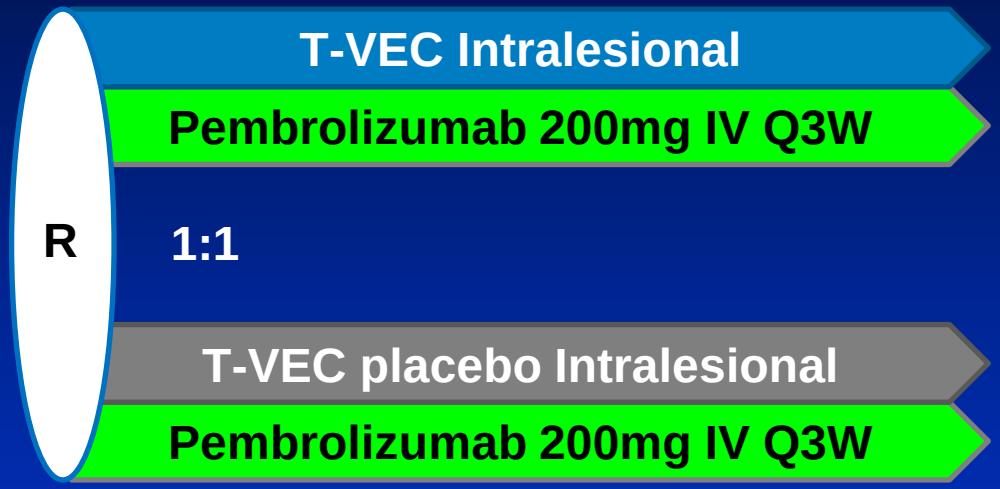
Puzanov I,....Andtbacka, RHA J Clin Oncol 2016; JCO671529. [Epub ahead of print]

MASTERKEY-265 Phase 3 Study Design

N = 660

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

T-VEC intralesional
- Up to 4 mL per treatment
- 1st dose 10^6 PFU/mL
- Then 10^8 PFU/mL Q2W x 4, then Q3W



N = 330

N = 330

Treatment until whichever occurs first:
- Complete Response (CR)
- Progressive disease (PD) per irRC-RECIST
- Intolerance
- All injectable tumors disappeared (T-VEC/placebo only)
- 2 Years

SAFETY FOLLOW-UP

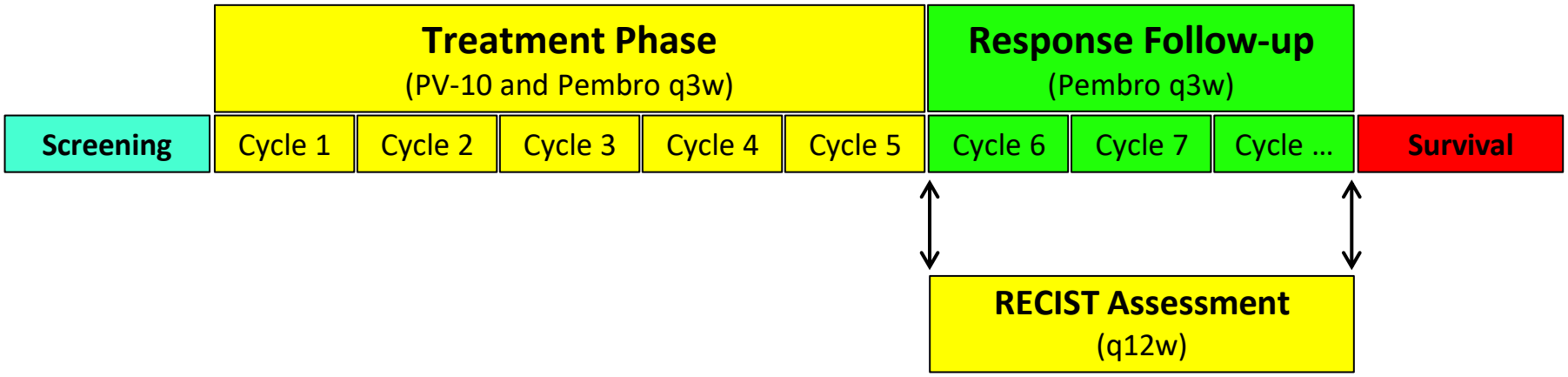
30 (+7) days after end of treatment

T-VEC: talimogene laherparepvec

Amgen study 20110265. Available at: https://clinicaltrials.gov/ct2/show/NCT02263508. Accessed January 2016

PV-10 + Pembrolizumab

- **Phase 1b**



- Patients receive up to 5 cycles of PV-10 and Pembro (q3w)
- Patients continue to receive treatment until PD (q3w)
- Patients remain on active portion of study for up to 24 months

HF10 – Oncolytic HSV-1

- Spontaneous mutant strain of HSV-1 with no external gene.

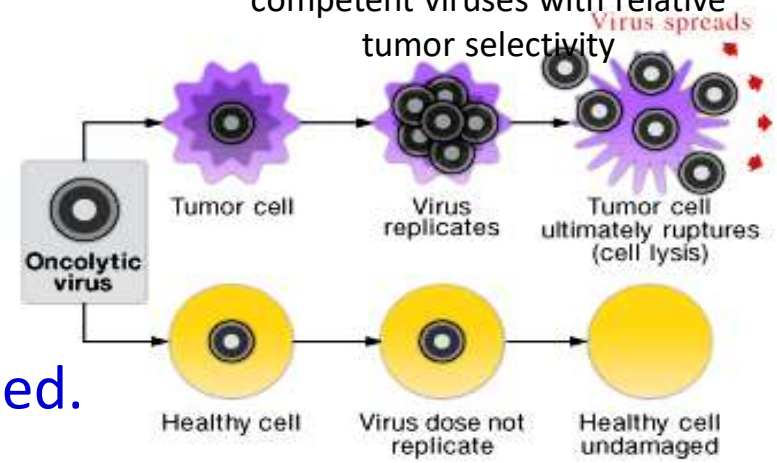
→ Greater replication ability = effective dose is lower

→ No toxicity to be caused by exogenous gene (ex. GM-CSF) inserted.

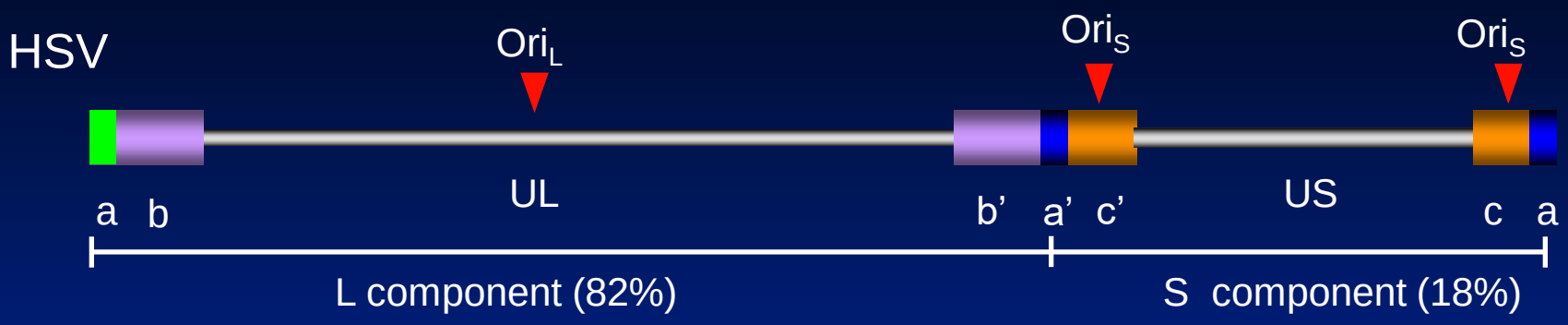
- Attenuation of neurovirulence to be attributable to the lack of the UL56 gene.
- In addition to local oncolytic tumor destruction, systemic anti-tumor immune response observed.

Oncolytic Cancer Therapy

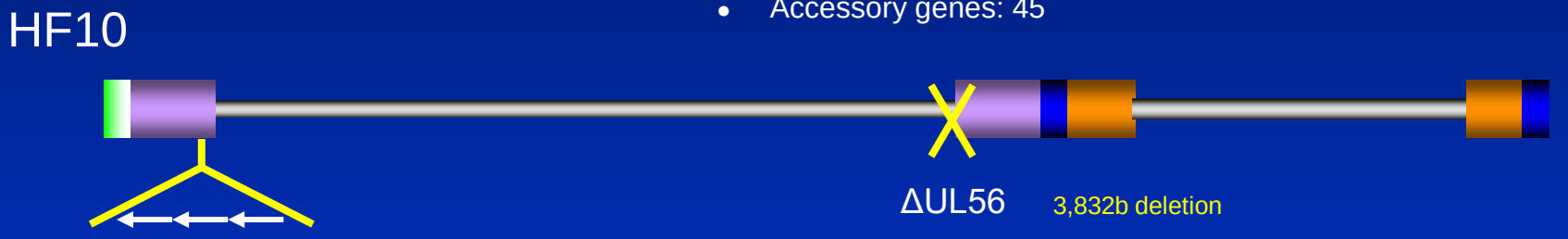
Treatment for cancer, using replication-competent viruses with relative tumor selectivity



HSV Genome Structure & HF10



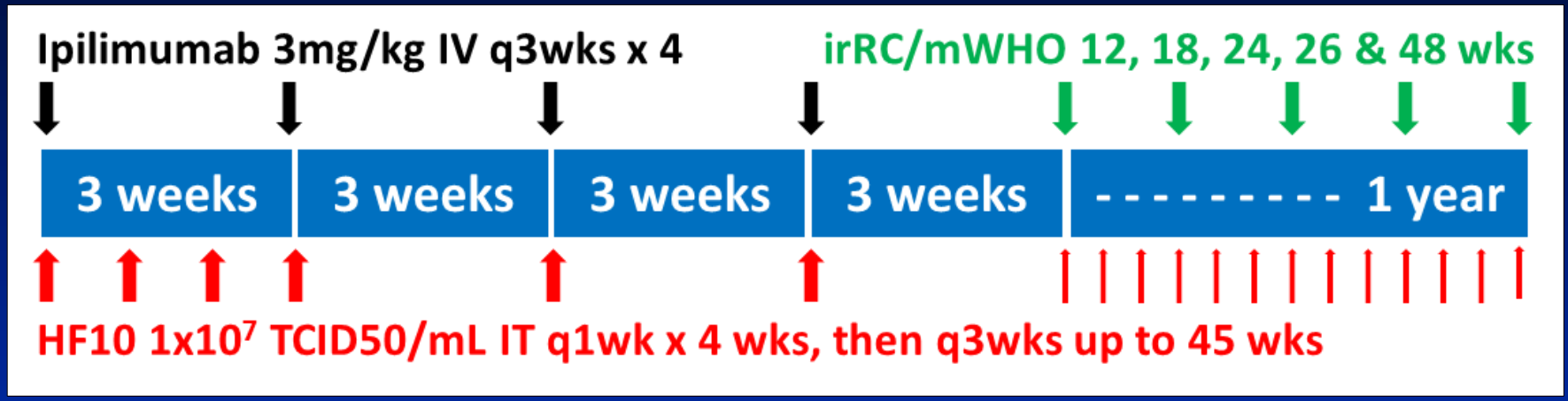
- Since 1988, DNA all base sequence
- UL: 65, US: 14, Inverted repetitive sequence: 10 (Total 89)
- Accessory genes: 45



- UL56 deletion
- Partial deletion and insertion of inverted repetitive sequence at the left end in L component
- Stability of genome in transfer of cultured cells

Lack of UL56 gene decreases HSV-1 pathogenicity without affecting viral replication ability

HF10 + Ipilimumab Phase II trial in unresectable stage IIIB – IV melanoma



- Multicenter trial
- **Primary objective:** Best Overall Response Rate (BORR) at week 24
- **Secondary objective:** safety, tolerability, ORR, PFS, DRR, 1-year OS, correlative studies

Andtbacka, RHA et al. ASCO 2016 Abstract 9543 (and poster presentation)

HF10 + Ipilimumab Phase II trial in unresectable stage IIIB – IV melanoma

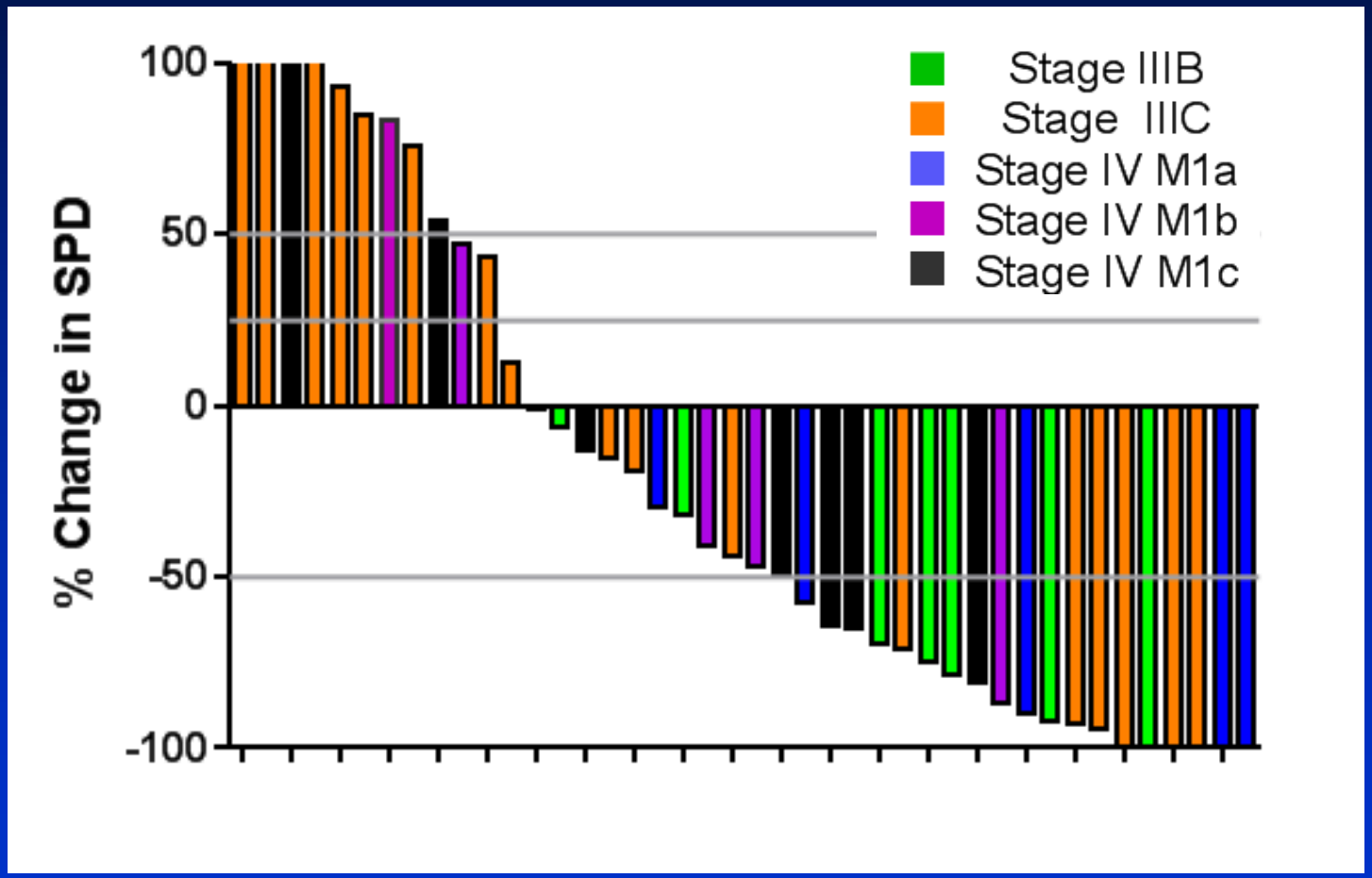
Patient demographics N=46

Characteristics	N (%)	Characteristics	N (%)
Age (Years)		Sex	
Median	67	Male	27 (59%)
Range	29-92	Female	19 (41%)
ECOG Status		Disease Stage	
0	34 (74%)	IIIB	9 (20%)
1	12 (26%)	IIIC	20 (43%)
2	0 (0%)	IV	17 (37%)
HSV-1 antibody		≥ 1 Prior Cancer Therapy	
(+)	30 (65%)	Yes	20 (43%)
(-)	16 (35%)	No	26 (57%)

Andtbacka, RHA et al. ASCO 2016 Abstract 9543 (and poster presentation)

HF10 + Ipilimumab Phase II trial in unresectable stage IIIB – IV melanoma

Maximum change in index lesions



Andtbacka, RHI et al. Int. Meeting on Replicating Oncolytic Virus Therapeutics, 2016 (abstract and oral presentation

Current Melanoma Landscape: Is there a role for IL monotherapy?

Yes	No
Not all patients candidates for systemic therapy (co-morbidities, toxicity)	Systemic therapies in 2015 are safe and effective
After progression on other therapies	Melanoma is a systemic disease
Alternative to surgery?	Surgery is an instant CR
Neoadjuvant potential	Not yet proven

Summary & Conclusions

- Soft tissue and cutaneous metastases are a major clinical problem in melanoma
- Oncolytic intralesional approaches may have value
  - Local direct effect
  - Systemic immune effect
  - Low toxicity
- Several agents in development appear promising
  - TVEC approved by US and EU regulators
- Combination therapies are likely to be the future and may be the best way to integrate them into clinical practice