



Viernes, 25 de noviembre de 2016

MESA 3 - INVESTIGACIÓN CLÍNICA

# New tools in cancer therapy: Viruses

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# Disclosures

Advisory Boards for Amgen

The use of viruses as a cancer therapy is based on early observations in the mid-1950's, that some viruses could infect and kill leukemic peripheral blood cells in vitro.

# Viruses

- Are **nature's nanoparticles** – a vast untapped bioresource.
- More than 2400 viral species are known, **with extraordinarily diverse morphologies and biochemical compositions.**
- Their **diameters** range from **20 to 500 nm**, and their **genomes** from **3000 to 375 000 nucleotides.**

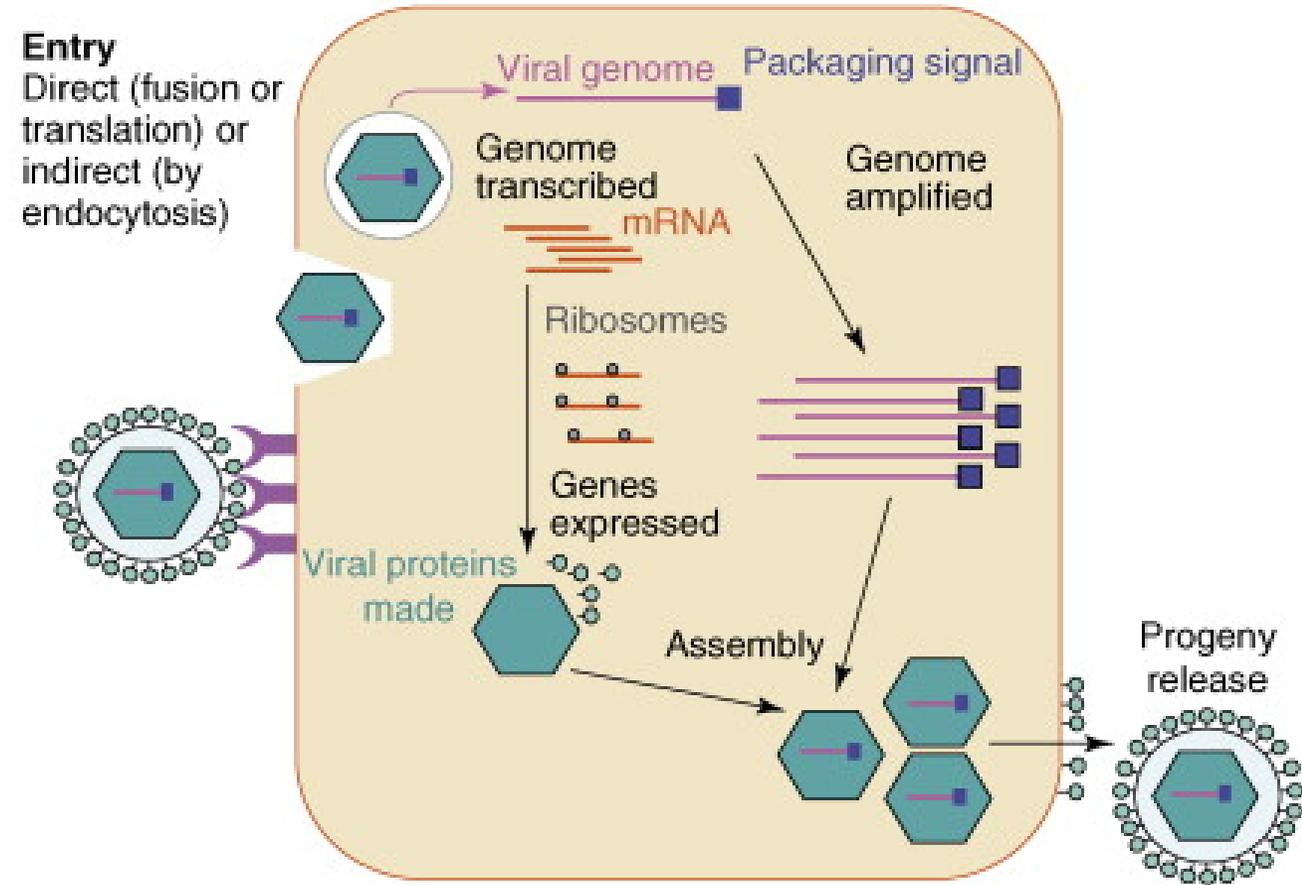
# Viruses

Have:

- **single- or double-stranded RNA or DNA genomes**
- **packaged into icosahedral or helical protein shells,**
- **which are sometimes wrapped in a lipid envelope.**

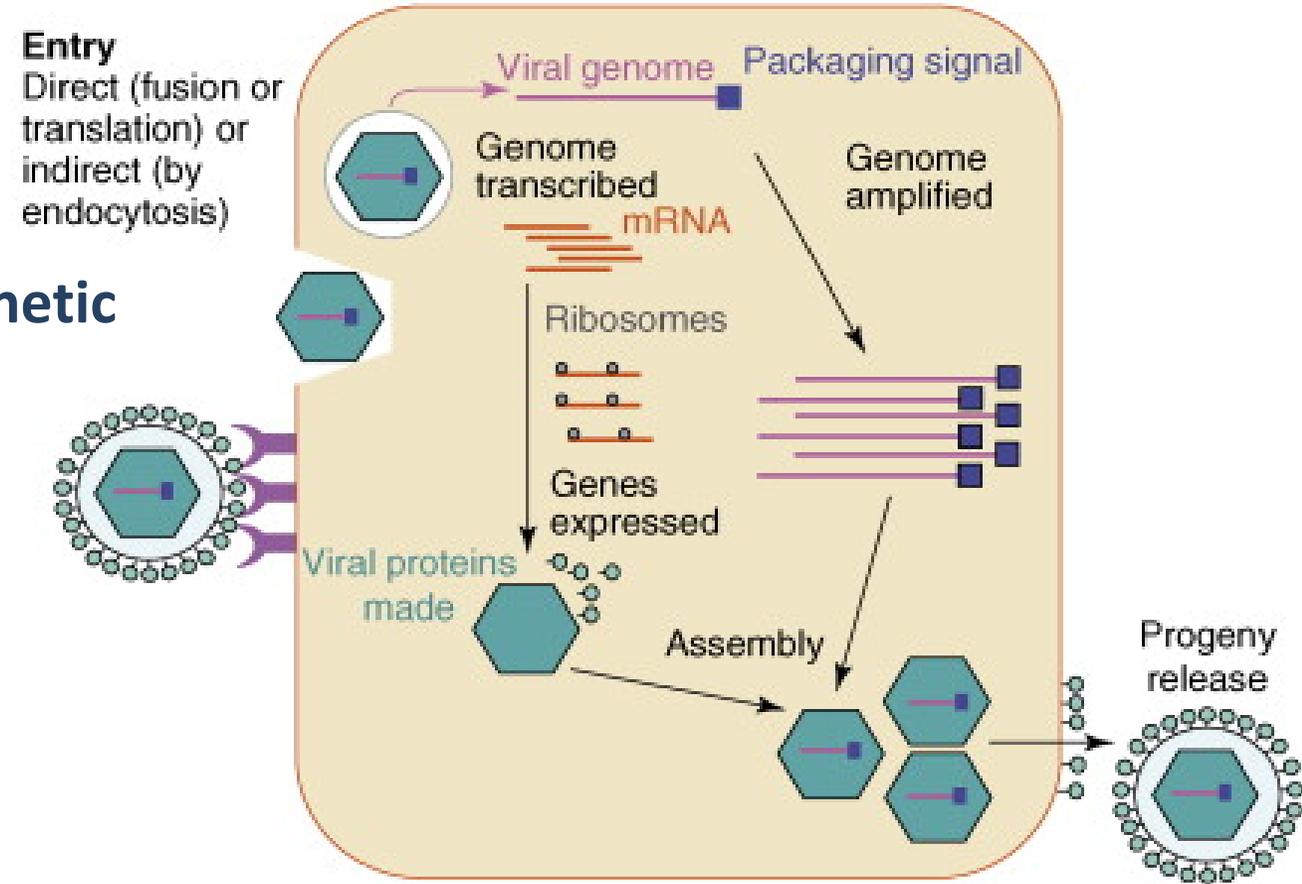
The particle protects the viral genome, carries it from cell to cell in the infected host organism and transmits it from infected to uninfected hosts.

# Viral invasion of the cell



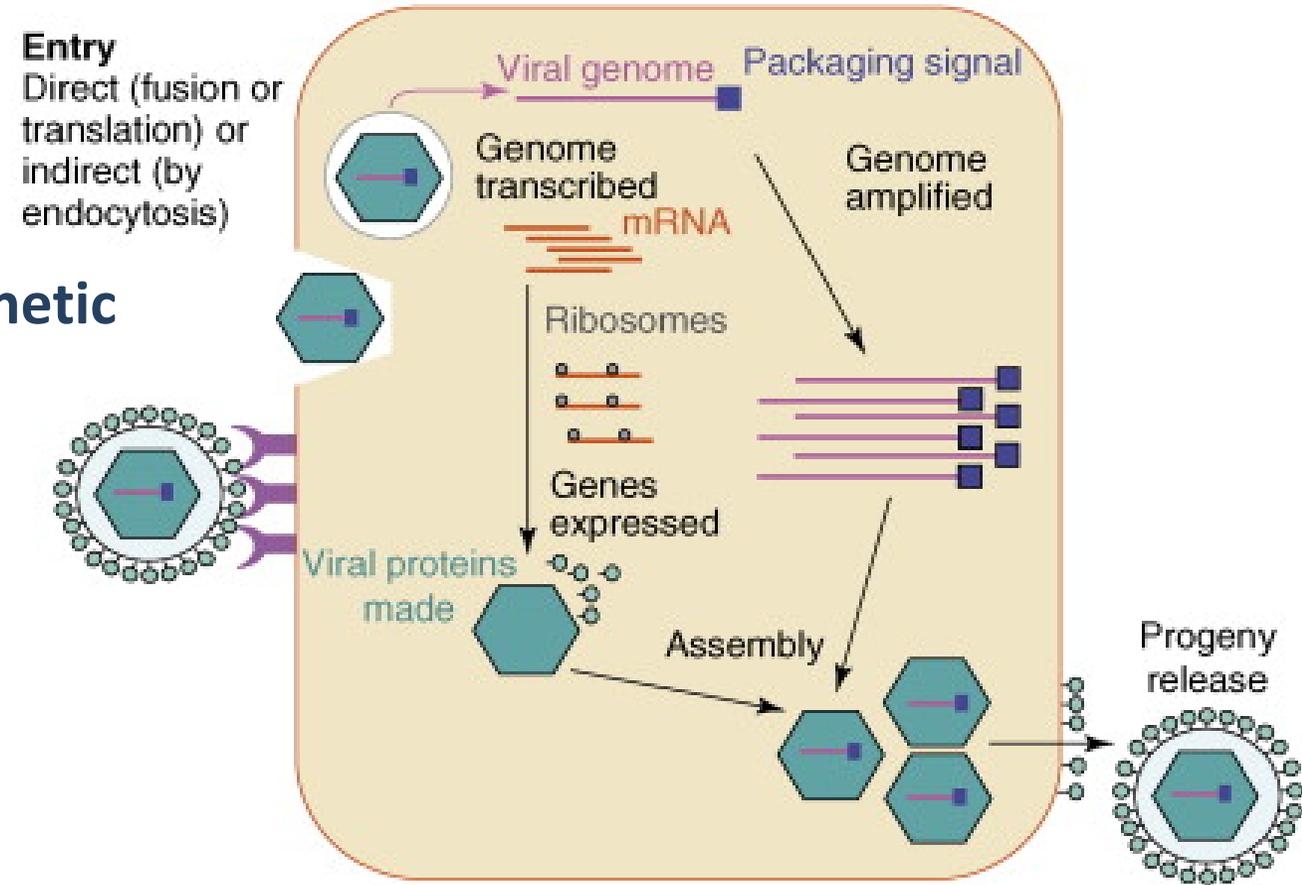
# Viral invasion of the cell

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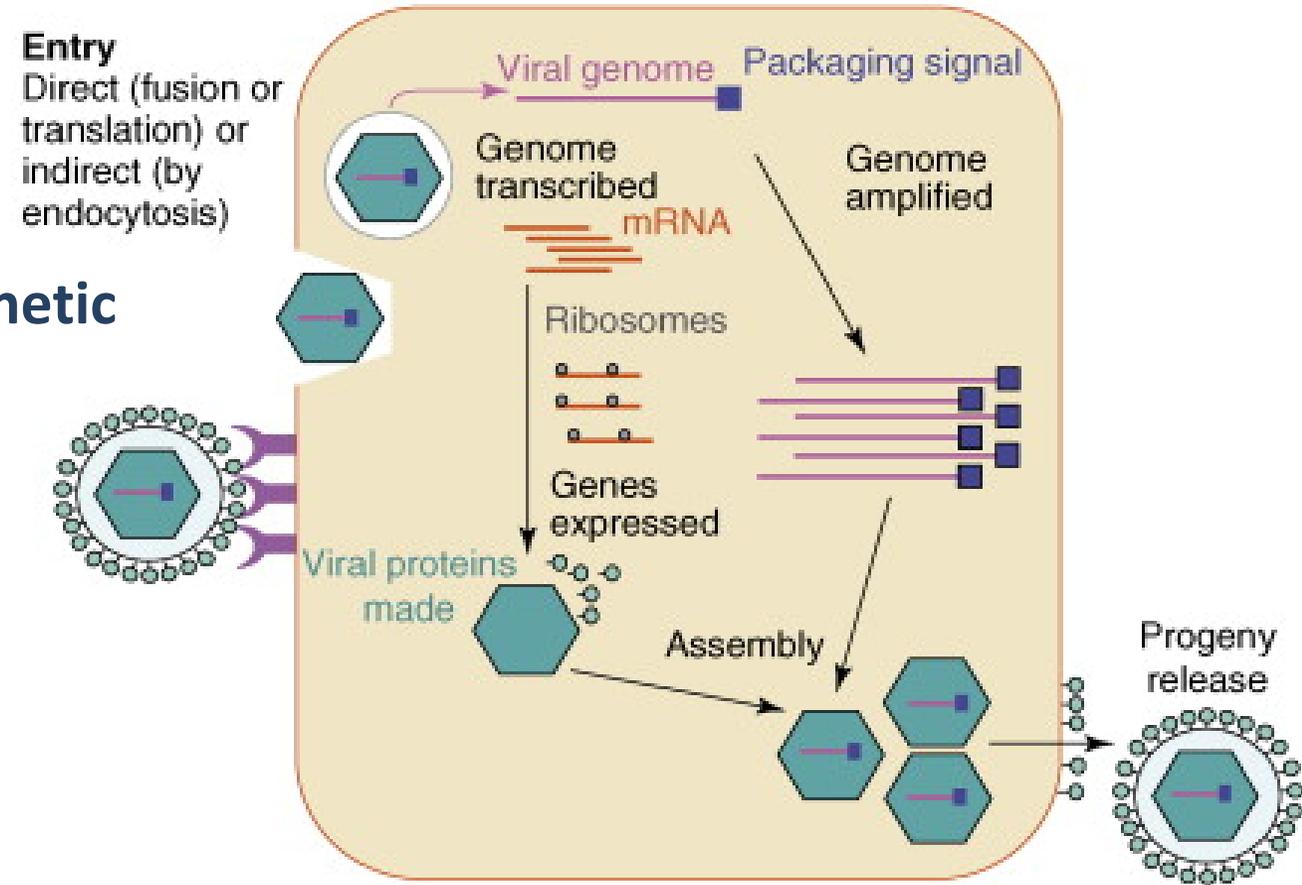
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- that **spread to adjacent cells,**
- leading to a characteristic pattern of **tissue destruction.**



# Viruses

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## Virus mediated tissue destruction

# Oncolytic viruses (OVs)

- Viruses that **selectively infect and kill cancer cells without damaging normal tissues.**

# Oncolytic viruses (OVs)

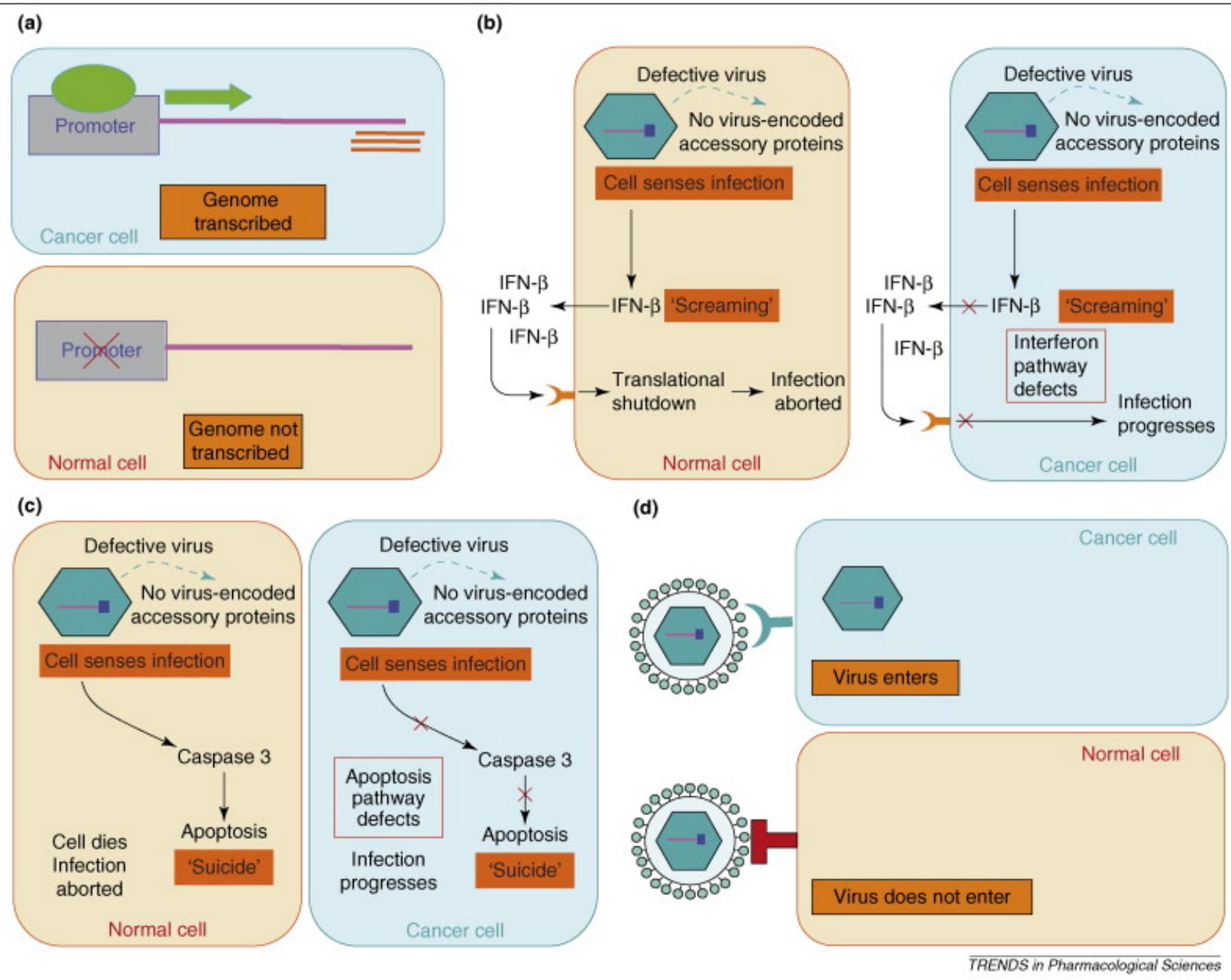
- Viruses that **selectively infect and kill cancer cells without damaging normal tissues.**

Represent a novel class of drugs in which **native or modified viral vectors are used for the treatment of cancer.**

# Mechanisms of tumor targeting by oncolytic viruses

## (a) Transcriptional targeting.

An essential viral gene is placed under the control of a tumor-specific promoter.



TRENDS in Pharmacological Sciences

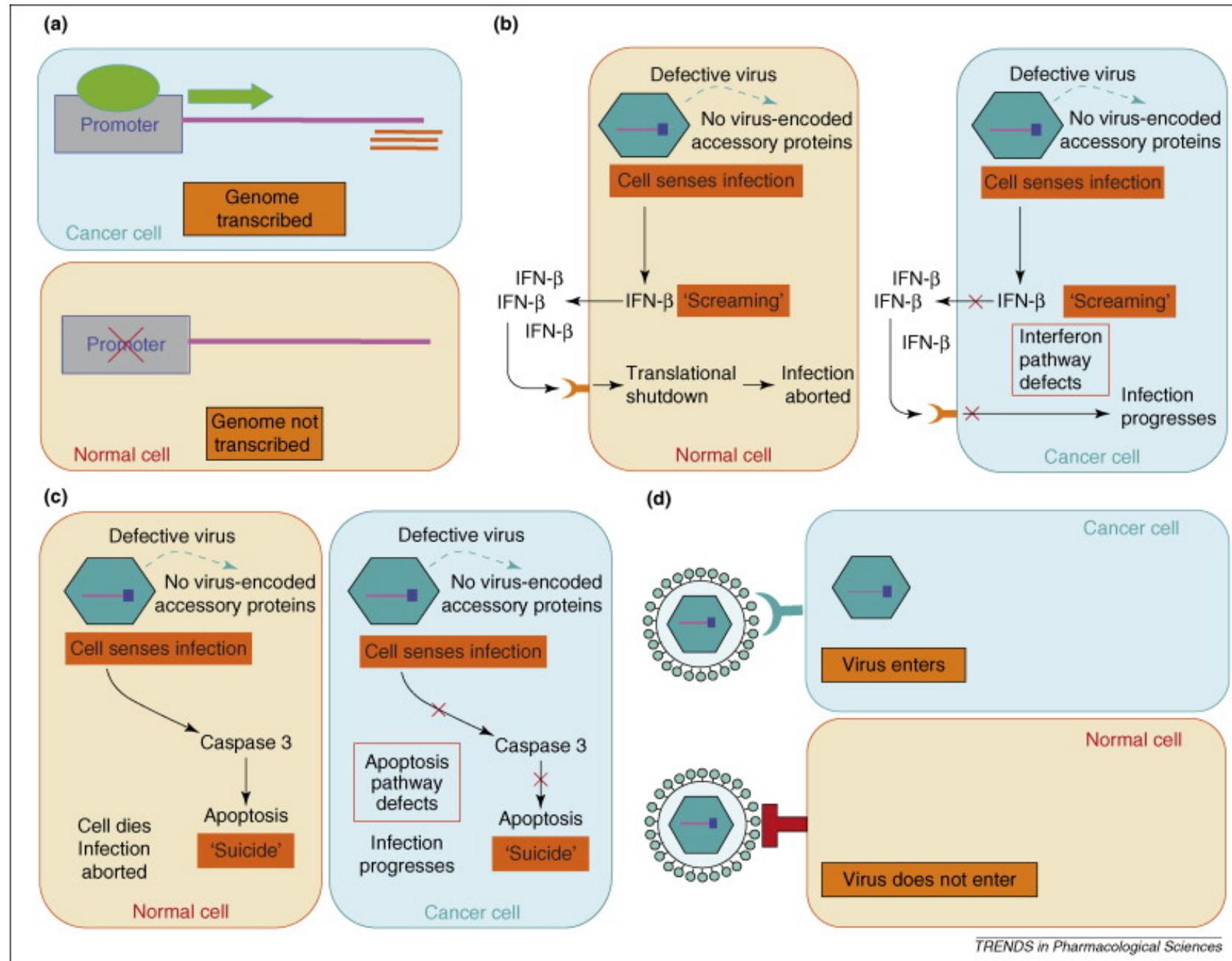
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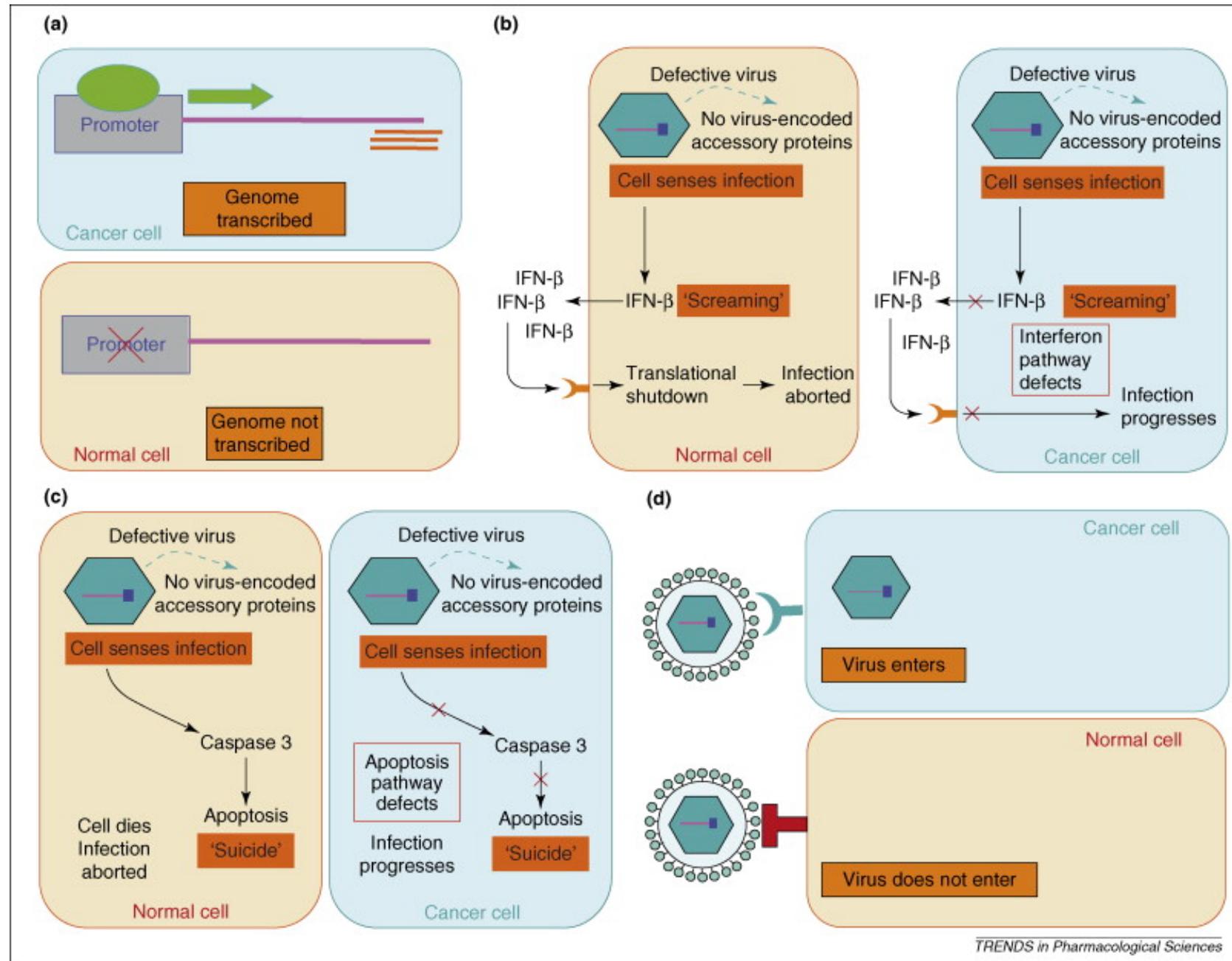
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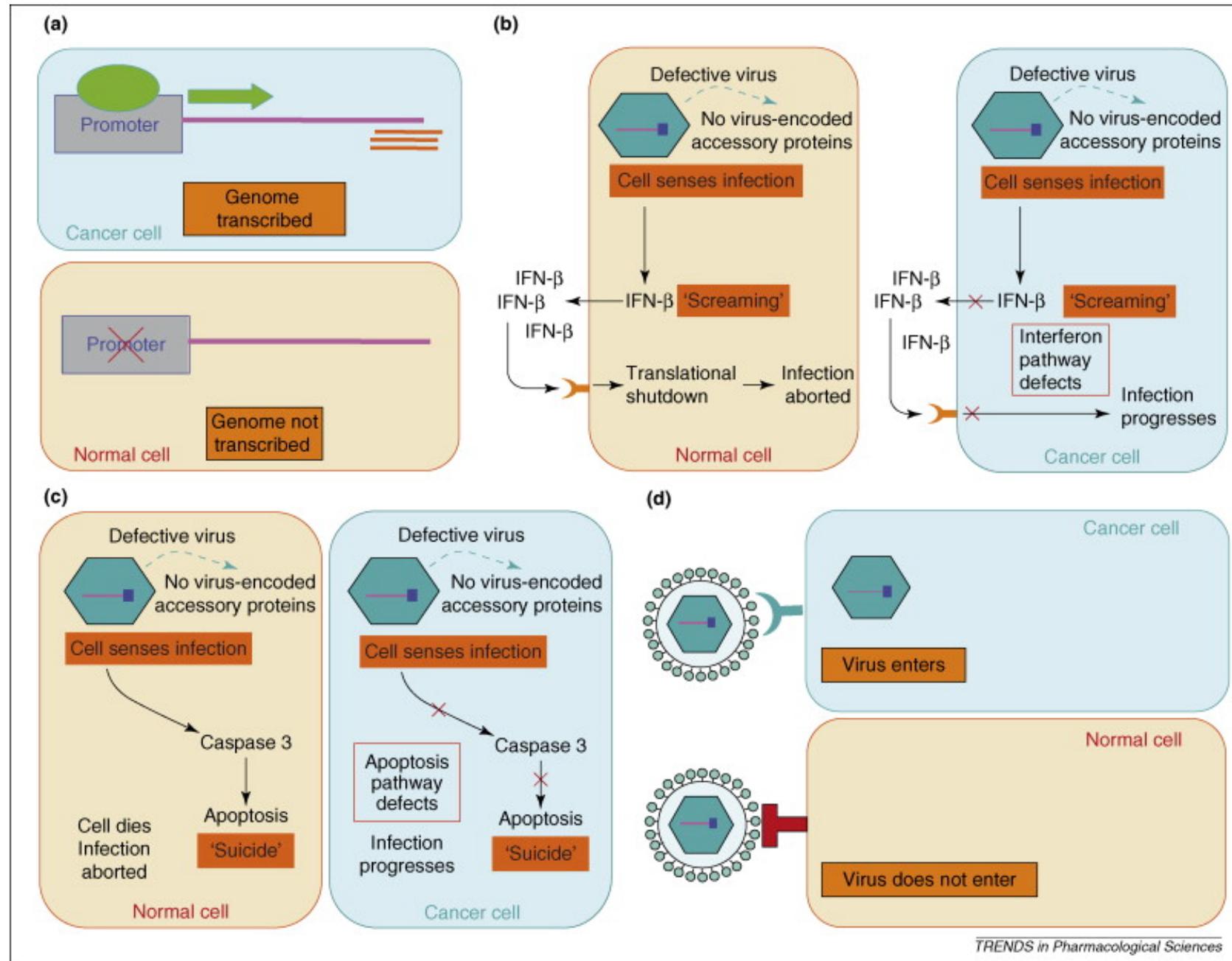
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### (d) Transductional targeting.

The virus gains entry to its target cells through a receptor expressed more abundantly on tumor cells than on normal cells.



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- **Gene therapy** aims to deliver and express therapeutic genes to cure or slow the progression of disease.
- A major obstacle in the application of gene therapy has been the development of the **vectors** used to deliver heterologous DNA to the cell or tissue of choice.
- At present, **no vector system possesses the full complement of properties that are generally believed necessary in an ideal gene delivery system.**
- Therefore, alongside attempts to improve current gene delivery vectors, the identification and **evaluation of new viral vectors is crucial** for the long-term success of gene therapy.

# Selected oncolytic viruses with different mechanisms of tumor selectivity

| <b>Family</b>     | <b>Genome (kb)</b> | <b>Structure</b> |
|-------------------|--------------------|------------------|
| •Adenoviridae     | dsDNA 36–38        | Non-enveloped    |
| •Herpesviridae    | dsDNA 120–200      | Enveloped        |
| •Parvoviridae     | ssDNA 5            | Non-enveloped    |
| •Poxviridae       | dsDNA 130–280      | Enveloped        |
| •Coronaviridae    | +ssRNA 16–21       | Enveloped        |
| •Orthomyxoviridae | –ssRNA 13.6        | Enveloped        |
| •Paramyxoviridae  | –ssRNA 16–20       | Enveloped        |
| •Piconarviridae   | +ssRNA 7.2–8.4     | Non-enveloped    |
| •Reoviridae       | dsRNA 22–27        | Non-enveloped    |
| •Retroviridae     | +ssRNA 8           | Enveloped        |
| •Rhabdoviridae    | –ssRNA 11–12       | Enveloped        |
| •Togaviridae      | +ssRNA 12          | Enveloped        |

# Oncolytic Adenoviruses

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# Oncolytic Adenoviruses

- Kill cancer cells, by seizing **control of their DNA replication machinery and utilizing it for the production of new virions**, ultimately resulting in the **rupture of the cell**.
- **Human safety data in cancer trials has been excellent** even when the dose of administered adenovirus has been high.
- Future approaches include **modifications of the adenoviral genome that prime them to attack cancer stem cells specifically**, utilizing lineage-specific cell surface markers, dysfunctional stem cell signaling pathways or up-regulated oncogenic genes.

# Oncolytic Herpesviruses

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# Oncolytic Herpesviruses

Large DNA viruses which possess a number of advantages as gene delivery vectors:

- Ability to **package large DNA insertions** and **establish lifelong latent infections** in which the genomic material exists as a stable episome.
- **Potential** of capable of infecting a range of human cell lines with **high efficiencies**, and
- **Persistency of the viral genome** as high copy number, circular, non-integrated episomes which segregate to progeny following cell division.

# Oncolytic Herpesviruses

## Gene Delivery Vectors in Cancer

Calderwood MA, White RE, Whitehouse A. Development of herpesvirus-based episomally maintained gene delivery vectors. *Expert Opin Biol Ther.* 2004 Apr;4(4):493-505.

# Oncolytic Herpesviruses

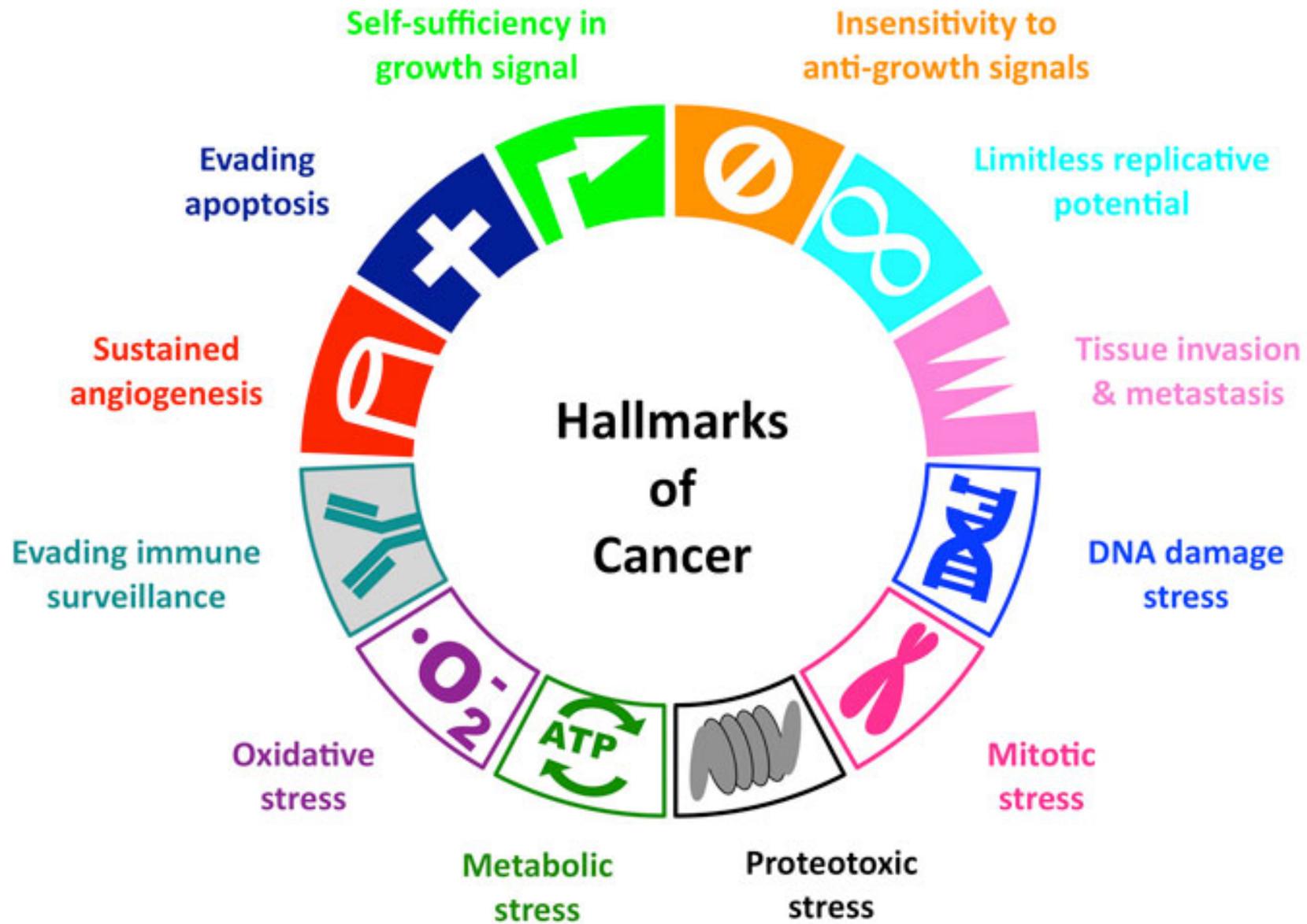
## Gene Delivery Vectors in Cancer

- **The insertion of an artificial chromosome cassette into the HSV genome simplifies the incorporation of large amounts of heterologous DNA for gene delivery.**

# Oncolytic Herpesviruses

## Gene Delivery Vectors in Cancer

- **The insertion of an artificial chromosome cassette into the HSV genome simplifies the incorporation of large amounts of heterologous DNA for gene delivery.**
- **These properties offer characteristics similar to an artificial chromosome combined with an efficient delivery system.**



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|------|--------|-------|

|   |            |   |
|---|------------|---|
| 1 | Recruiting | <a href="#">LOAd703 Oncolytic Virus Therapy for Pancreatic Cancer</a> |
|---|------------|---|

**Condition:** Pancreatic Cancer

**Interventions:** Biological: LOAd703; Drug: Gemcitabine; Drug: nab-paclitaxel

|   |           |   |
|---|-----------|---|
| 2 | Completed | <a href="#">Safety Study of GL-ONC1, an Oncolytic Virus, in Patients With Advanced Solid Tumors</a> |
|---|-----------|---|

**Condition:** Advanced Cancers (Solid Tumors)

**Intervention:** Biological: GL-ONC1

## Contemporary oncolytic virus therapy mediates tumor regression through two distinct mechanisms

- Many viruses possess an **innate tropism for cancer cells** where they can preferentially replicate **and kill established tumor cells.**

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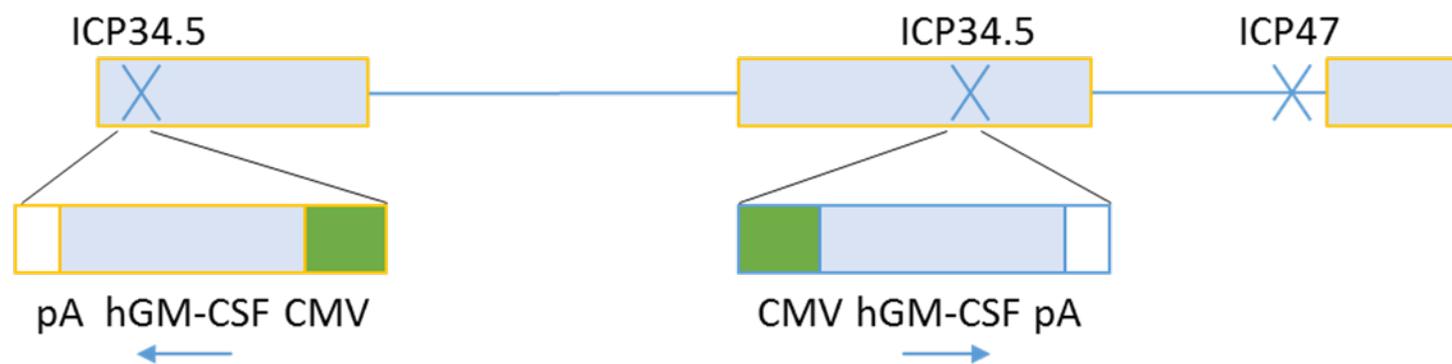
*Most oncolytic viruses are given by **direct injection** into established tumors, several viruses can be delivered by the **intravenous** route avoiding the need for tumor localization and/or complex interventional administration strategies.*

# JS1/34.5-/47-/Granulocyte-Macrophage CSF (OncoVEXGM-CSF, BioVex, Woburn, MA)

An *immune-enhanced, oncolytic herpes simplex virus type 1 (HSV-1)* strain engineered for:

- Replication in tumours and
- Generate antitumour immune responses

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

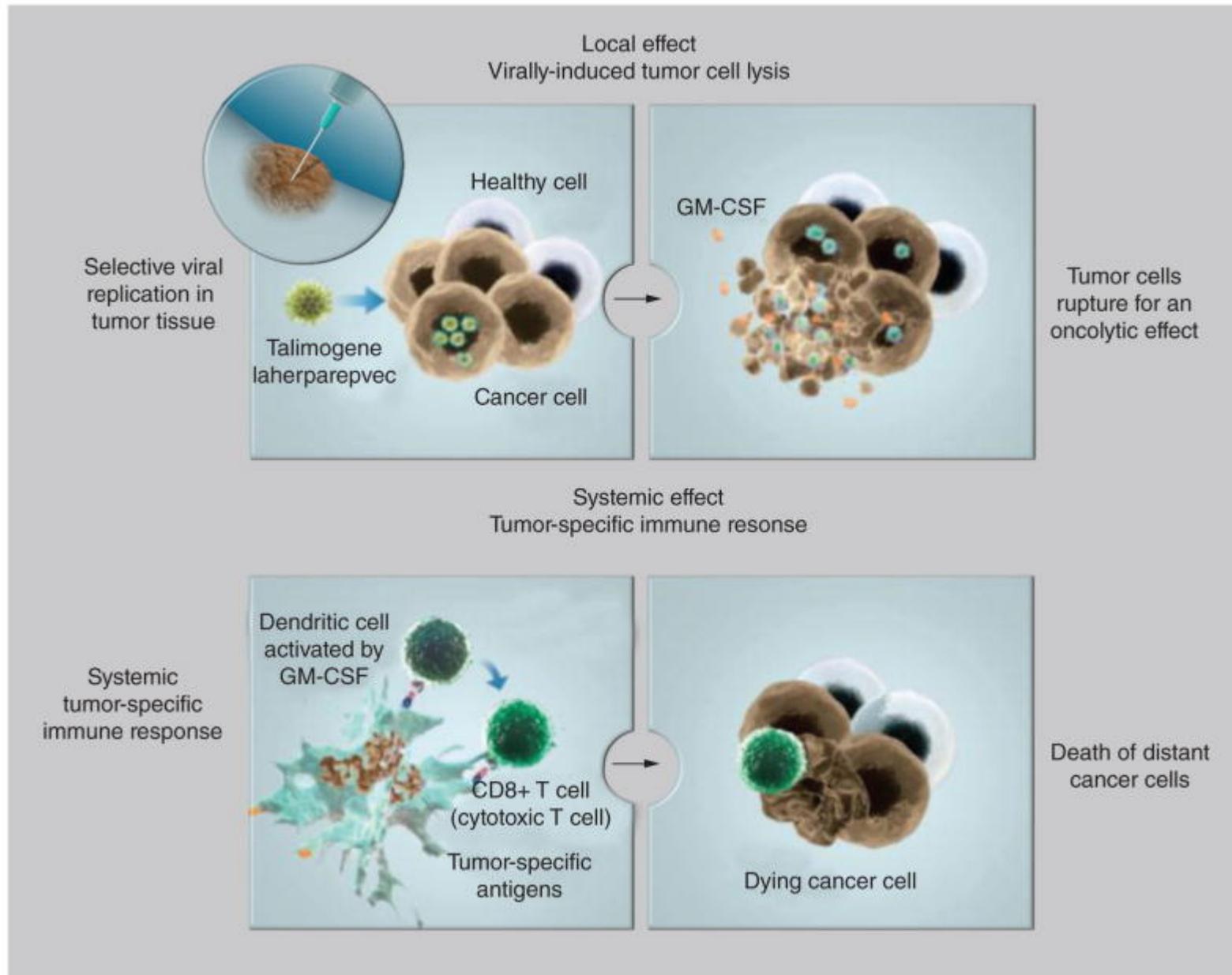


CMV, cytomegalovirus promoter; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; ICP, infected cell protein; pA, polyadenylation (from bovine growth hormone); US11, unique short 11.

# An oncolytic HSV-1 strain engineered for replication in tumours and generate antitumour immune responses

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

# Proposed mechanism of action for talimogene laherparepvec



# JS1/34.5-/47-/Granulocyte-Macrophage CSF Safety

- Safety and antitumor activity, including the clearance of injected and uninjected tumors, has been demonstrated with JS1/34.5-/47-/GM-CSF **in animal studies**.
- Phase I investigation established safety and clinical activity of JS1/34.5-/47-/GM-CSF **in patients** with various tumor types, including melanoma.

## Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor–Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma

*Neil N. Senzer, Howard L. Kaufman, Thomas Amatruda, Mike Nemunaitis, Tony Reid, Gregory Daniels, Rene Gonzalez, John Glaspy, Eric Whitman, Kevin Harrington, Howard Goldsweig, Tracey Marshall, Colin Love, Robert Coffin, and John J. Nemunaitis*

### **Primary objective:**

To assess clinical efficacy of JS1/34.5-/47-/GM-CSF in patients with unresectable stage IIIc and stage IV melanoma measured by **overall tumor response rate and survival.**

**Table 2.** Response Correlations

| Variable      | Overall No. of Patients (N = 50) | No. of Patients per Response Group |            |                  | % of Patients With CR + PR (n = 26) |
|---------------|----------------------------------|------------------------------------|------------|------------------|-------------------------------------|
|               |                                  | PR (n = 5)                         | CR (n = 8) | CR + PR (n = 13) |                                     |
| Stage         |                                  |                                    |            |                  |                                     |
| IIIc          | 10                               | 2                                  | 2          | 4                | 40                                  |
| IV M1a        | 16                               | 1                                  | 4          | 5                | 31                                  |
| IV M1b        | 4                                | 0                                  | 1          | 1                | 25                                  |
| IV M1c        | 20                               | 2                                  | 1          | 3                | 15                                  |
| LDH           |                                  |                                    |            |                  |                                     |
| < ULN         | 37                               | 4                                  | 8          | 12               | 32                                  |
| > ULN         | 13                               | 1                                  | 0          | 1                | 8                                   |
| ECOG PS       |                                  |                                    |            |                  |                                     |
| 0             | 31                               | 3                                  | 5          | 8                | 26                                  |
| 1             | 19                               | 2                                  | 3          | 5                | 26                                  |
| Prior therapy |                                  |                                    |            |                  |                                     |
| No*           | 13                               | 1                                  | 3          | 4                | 31                                  |
| Yes           | 37                               | 4                                  | 5          | 9                | 24                                  |

NOTE. Responses noted relate to those achieved with JS1/34.5-/47-/GM-CSF treatment alone (ie, without additional surgery) and also do not include responses that occurred after additional post-protocol extended treatment.

Abbreviations: PR, partial response; CR, complete response; LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG PS, Eastern Cooperative Oncology Group performance status.

\*Excludes surgery, radiation, and adjuvant therapy.

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| LDH      |                                  |                                    |            |                  |                                     |

*The 26% response rate, with durability in both injected and uninjected lesions including visceral sites, together with the survival rates, are evidence of systemic effectiveness*

|     |    |   |   |   |    |
|-----|----|---|---|---|----|
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|-----|----|---|---|---|----|

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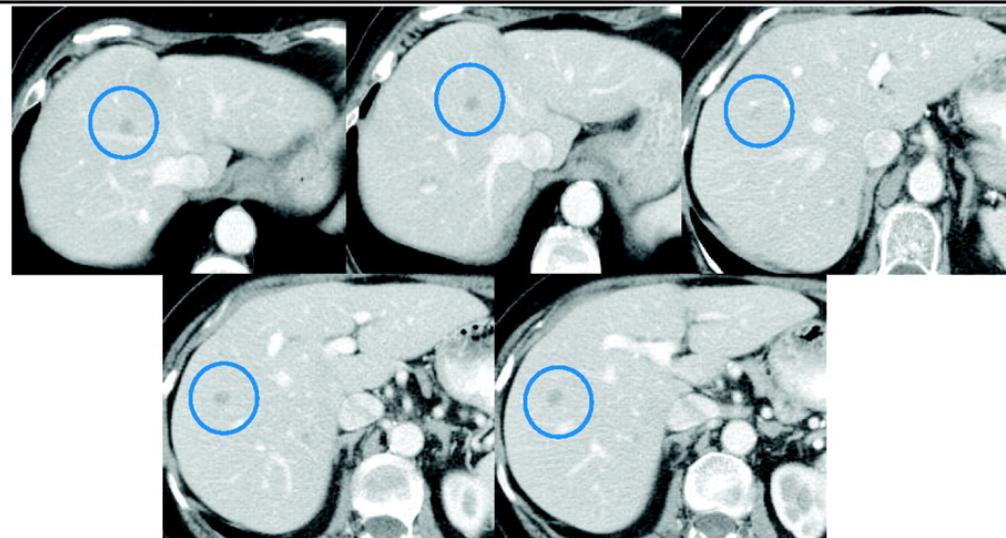
## Liver CT:

- at baseline (before)
- at 3 months (during therapy)
- at 6 months (during therapy)

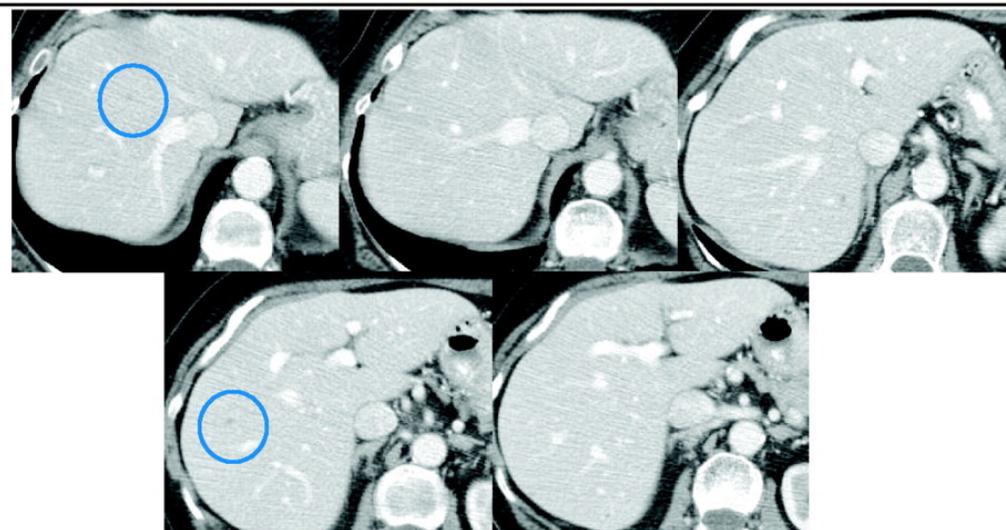
Baseline



3 months



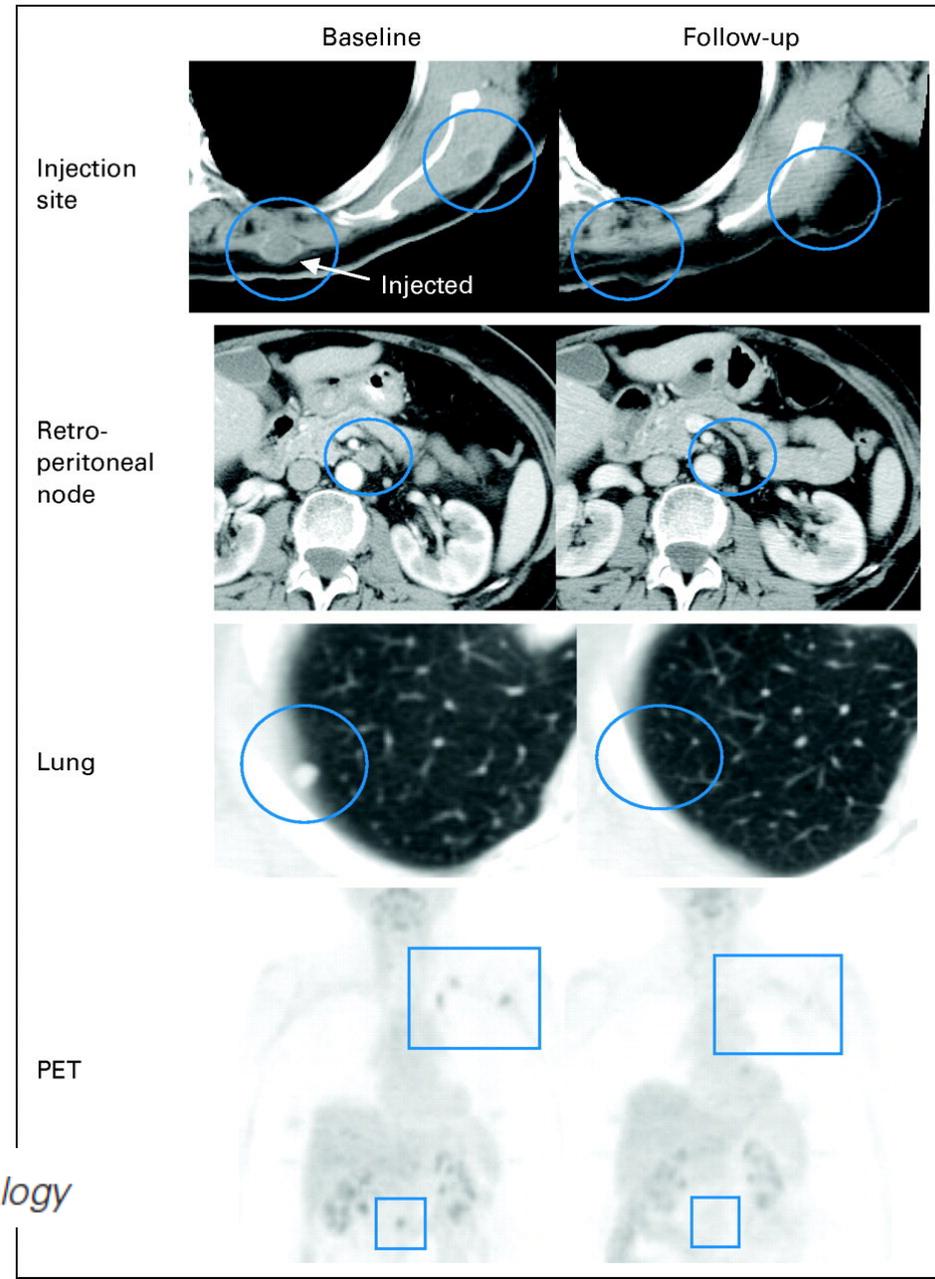
6 months



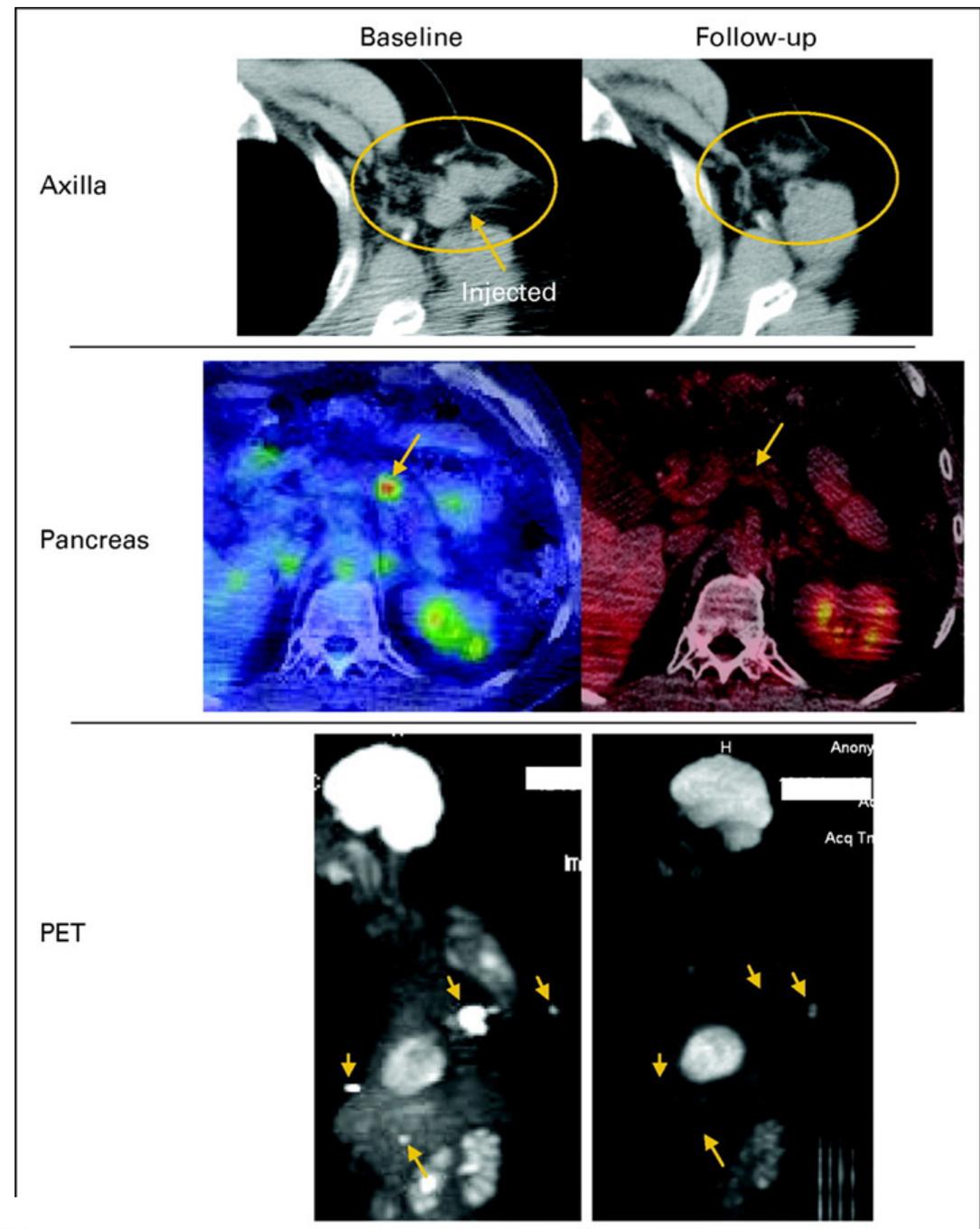
Baseline and at 3 months CT images of:

- The injection site in the left shoulder,
- retroperitoneal lymph node, and
- lungs.

PET images at baseline and at 8 months  
Matched sites of lesions before  
(baseline) and after (follow-up) therapy.



- CT images of the injection site in the axilla at baseline and at 16 months.
- PET/CT fusion images of the pancreas at baseline and at 12 months.
- PET images showing the lesions in the axilla, chest wall, pancreas, and left upper arm at baseline and at 12 months.

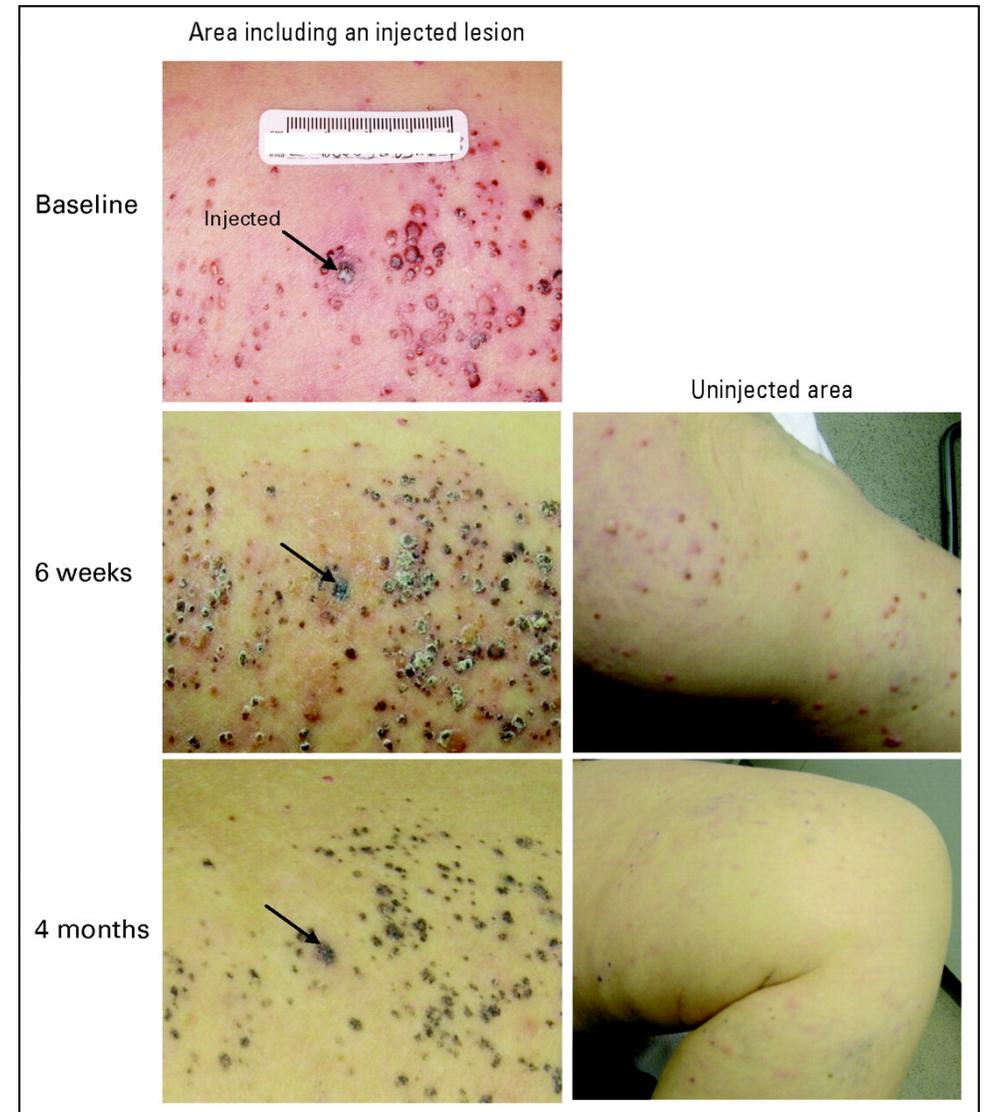


## Areas of cutaneous response:

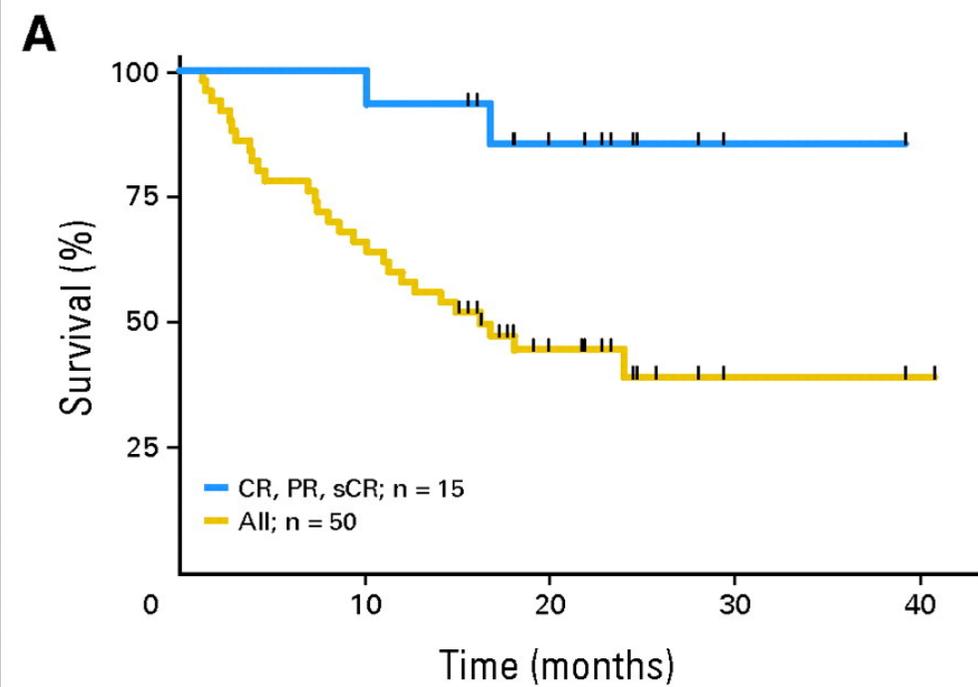
- At baseline,
- at 6 weeks, and
- at 4 months.

By 4 months, lesions either had completely resolved or only flat, pigmented areas remained.

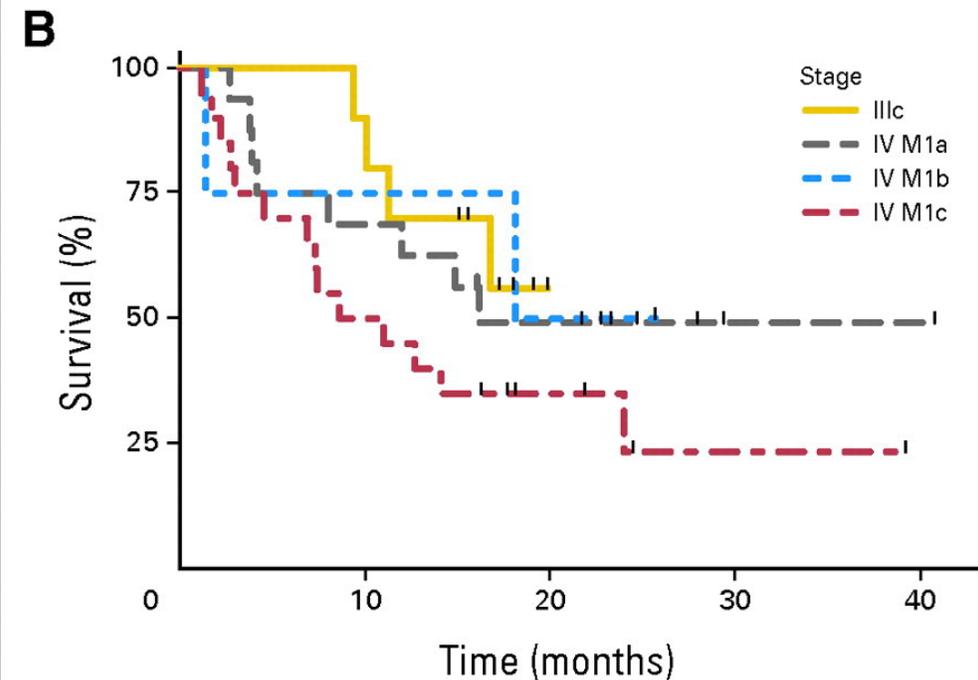
Representative biopsies taken at 8 months demonstrated no melanoma.



(A) Survival curves for **all patients enrolled** and for those who achieved **complete response (CR), partial response (PR), or surgical CR (sCR)**.



(B) Survival curves **by disease stage**.



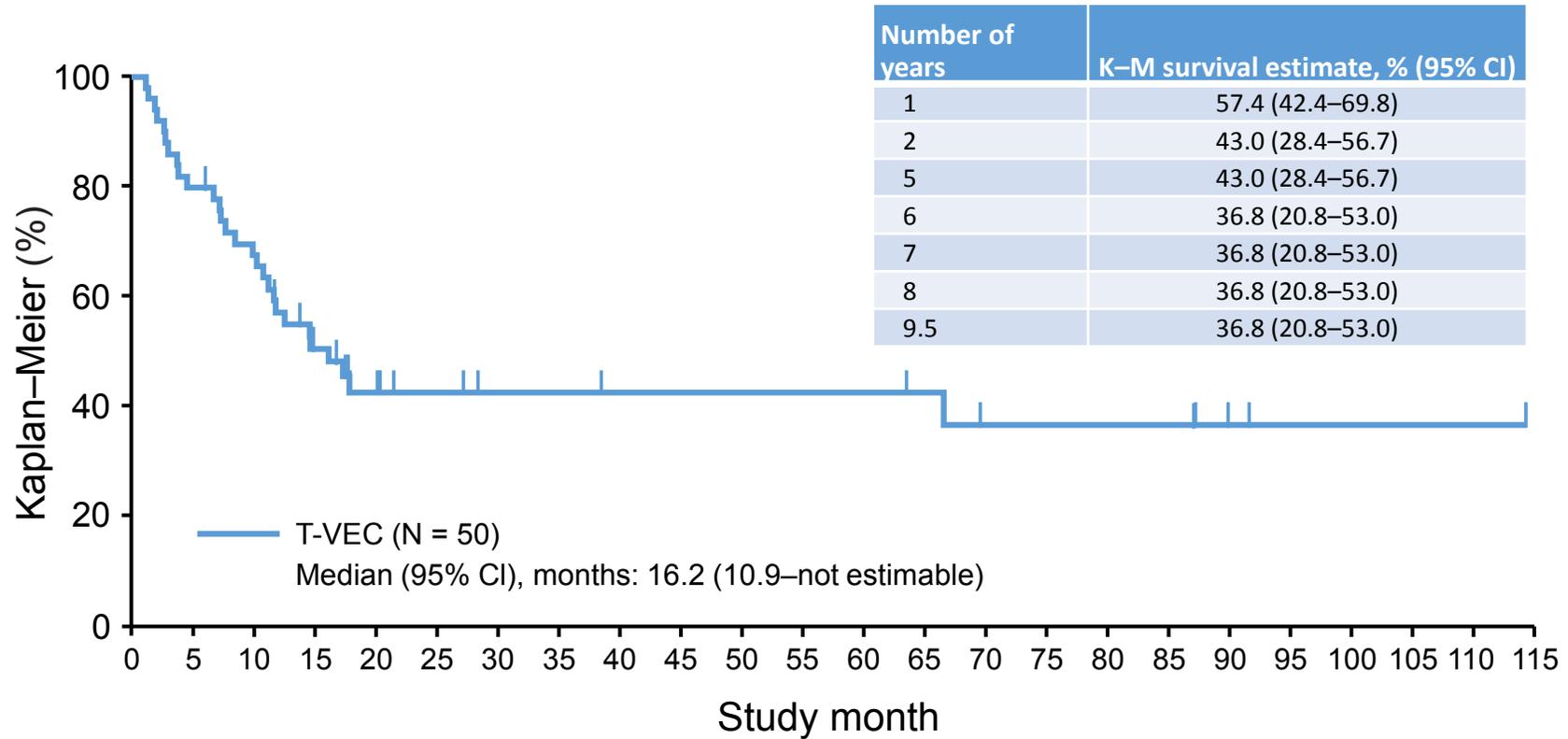
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### Conclusion:

... on the basis of the **high frequency and durability of overall objective responses**, the promising **1-year and overall survival rates** of the patients enrolled, and the **low toxicity** and straightforward **outpatient administration** of the agent, the results of this phase II trial clearly justify that a randomized, controlled, phase III study is performed.

# Long-term follow-up of T-VEC single-arm Phase 2 study – Overall Survival



Number of patients at risk: 50 40 33 21 14 11 9 9 8 8 8 8 8 7 5 5 5 5 3 1 1 1 1 0

# Long-term follow-up of T-VEC single-arm Phase 2 study – patients in the registry study

8/23 alive patients were enrolled in the registry study

| Baseline age, years | Sex | Disease stage | Prior therapy  | Treatment duration, months | Best overall response on study | Last status of response at end of study | OS, months |
|---------------------|-----|---------------|--|----------------------------|--------------------------------|---|------------|
| 86                  | M   | IV M1a        | Surgery  | 6.77                       | PR                             | PR                                      | 69.6       |
| 62                  | M   | IIIc          | Dacarbazine, vincristine, cisplatin; interferon; lymph node dissection; temodar; surgery x 2 | 0.03                       | PD                             | PD                                      | 63.6       |
| 74                  | F   | IV M1c        | Temodar; surgery x 2   | 7.16                       | CR                             | CR                                      | 114.4      |
| 82                  | M   | IV M1a        | Interferon; surgeries (multiple); radiotherapy x 2; temodar                                  | 5.82                       | CR                             | CR                                      | 66.6       |
| 68                  | M   | IV M1a        | Temodar; surgery   | 2.56                       | CR                             | CR                                      | 91.7       |
| 58                  | M   | IV M1c        | Surgery, radiation, interferon, GM-CSF, NY-ESO-1 vaccine                                     | 19.65                      | PR                             | PD                                      | 90.0       |
| 63                  | F   | IV M1c        | Lymph node dissection  | 10.84                      | PR                             | PR                                      | 87.1       |
| 79                  | F   | IV M1a        | Imiquimod cream; GM-CSF; lymph node dissection; surgery                                      | 20.30                      | SD                             | SD                                      | 87.3       |

- No subsequent anticancer therapy was reported in the registry study for the 8 enrolled patients
- No long-term T-VEC treatment-related AEs were reported in the registry study for the 8 patients

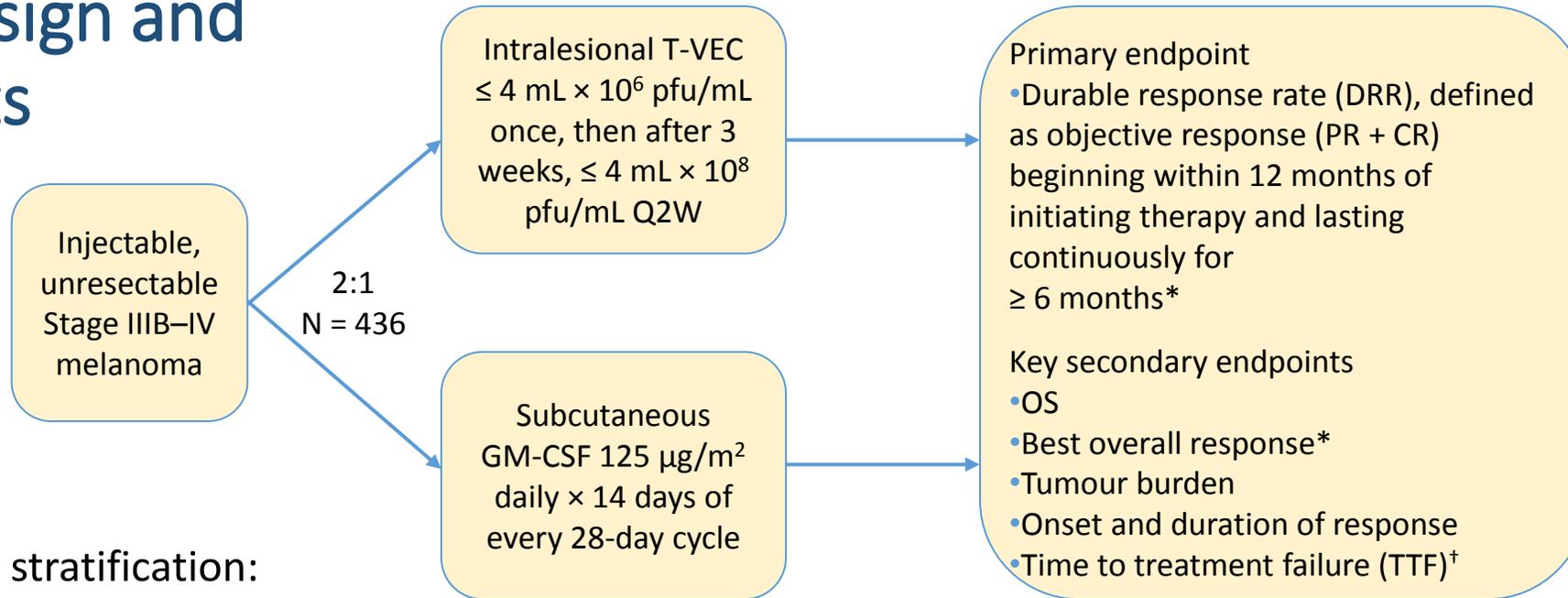
PD, progressive disease; SD, stable disease.

## Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

*Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin*

# Phase 3 OPTiM, OncoVEXGM-CSF Pivotal Trial

## Study design and endpoints



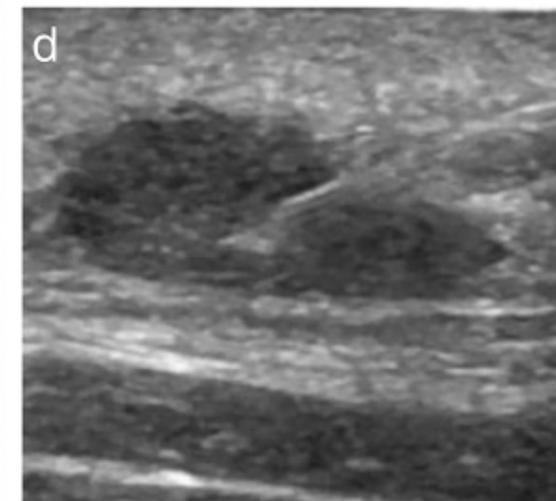
### Randomisation stratification:

1. Disease stage
2. Prior non-adjuvant systemic treatment
3. Site of disease at first recurrence
4. Presence of liver metastases

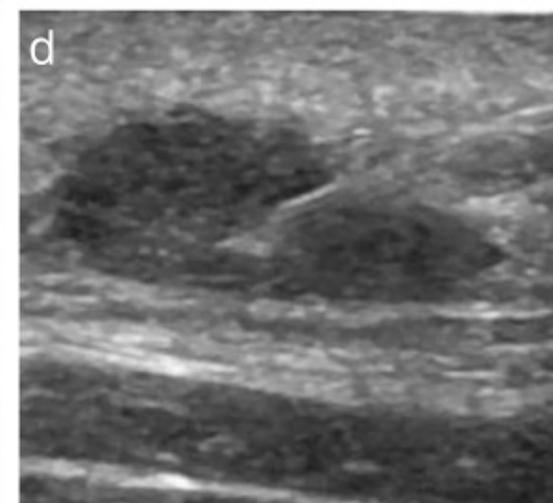
Patients enrolled between May 2009 and July 2011.

Discontinuation of treatment because of progressive disease was not required before 24 weeks unless alternate therapy was clinically indicated.

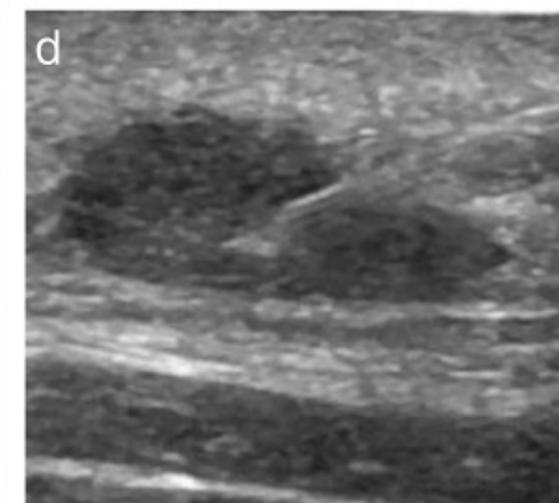
\*Responses were determined using modified WHO criteria by a blinded EAC;  
†TTF was defined as time from baseline to first clinically relevant disease progression for which no objective response was subsequently achieved or until death.  
EAC, endpoint assessment committee;



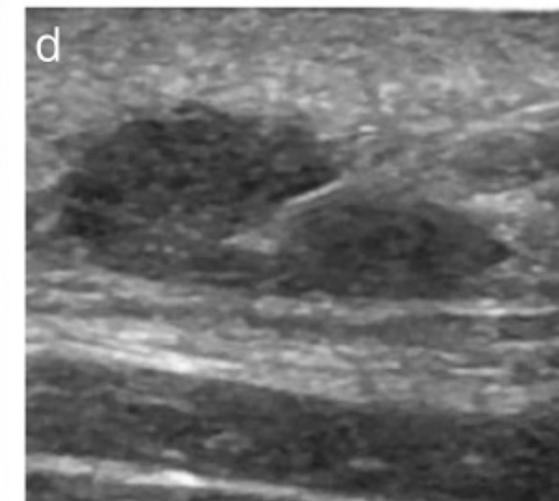
- T-VEC administered into cutaneous, SC or nodal lesions ( $\pm$  ultrasound guidance)



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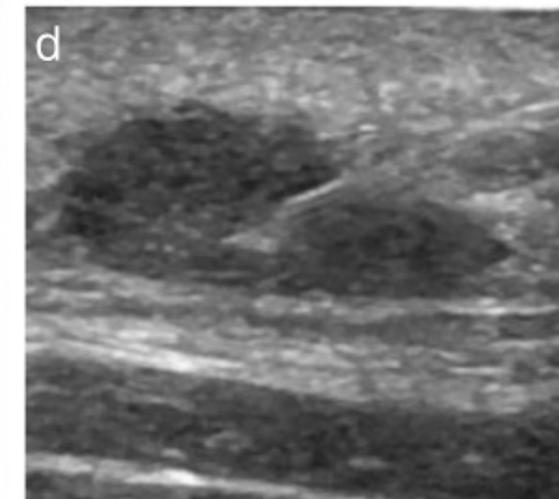
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| Lesion size (diameter) | T-VEC injection volume |
|------------------------|------------------------|
| > 5.0 cm               | $\leq$ 4.0 mL          |
| 2.5–5.0 cm             | $\leq$ 2.0 mL          |
| 1.5–2.5 cm             | $\leq$ 1.0 mL          |
| 0.5–1.5 cm             | $\leq$ 0.5 mL          |
| $\leq$ 0.5 cm          | $\leq$ 0.1 mL          |

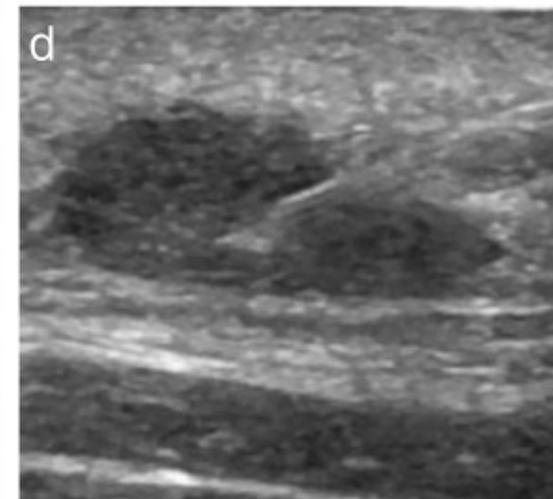
The total dose administered in any one treatment session should not exceed 4.0 mL

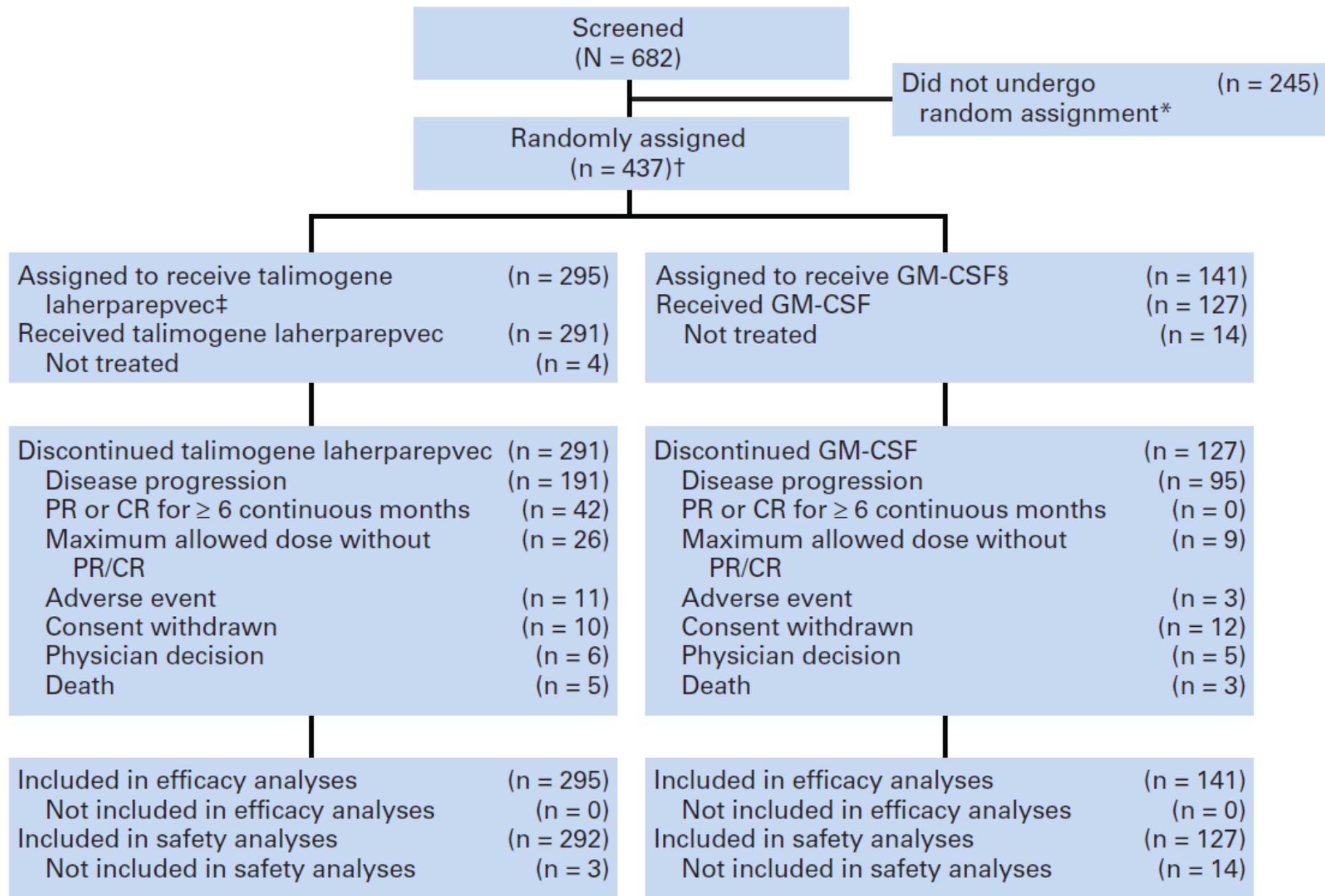


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- Limits on amount to be injected per lesion by size (see table)
- No specific limits on numbers of lesions injected per visit
- Precedence given to new lesions, then larger lesions

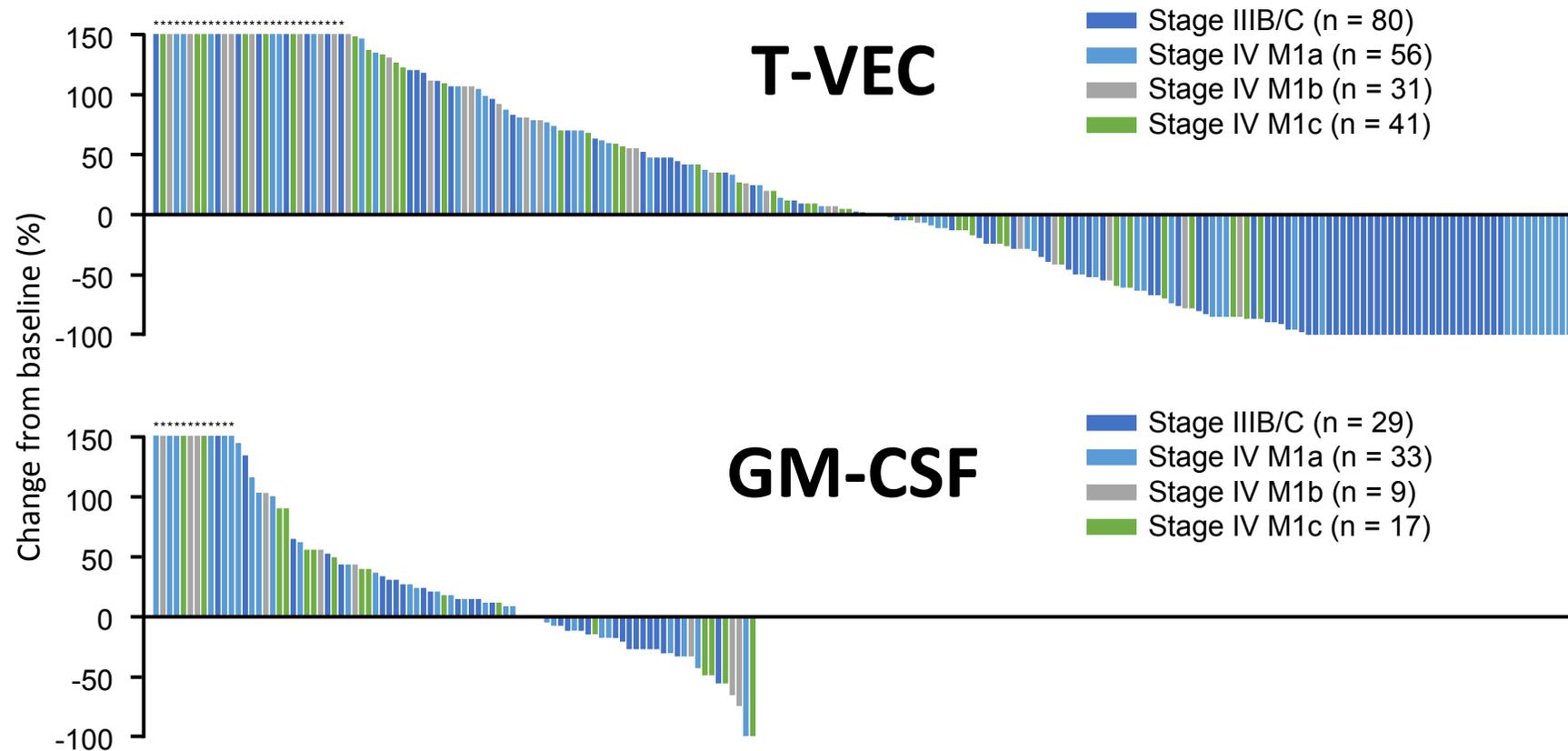
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# Antitumour activity seen with T-VEC



\*Patients with > 150% increase in tumour dimensions.

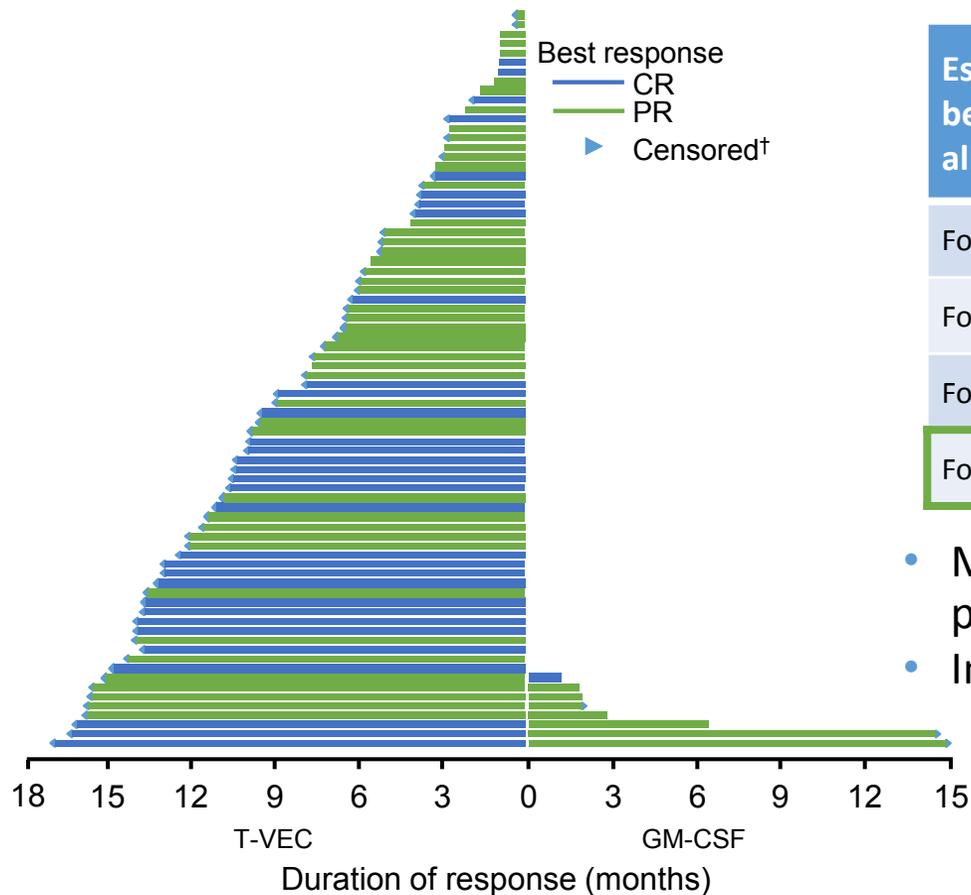
Waterfall plot of best response for all patients per investigator assessment.

Response assessments per EAC were not available for all patients.

EAC only reviewed the subset of patients with overall response per investigator or who received treatment for 9 months.

# Durable response seen with T-VEC

Duration of longest response among responders (per EAC)

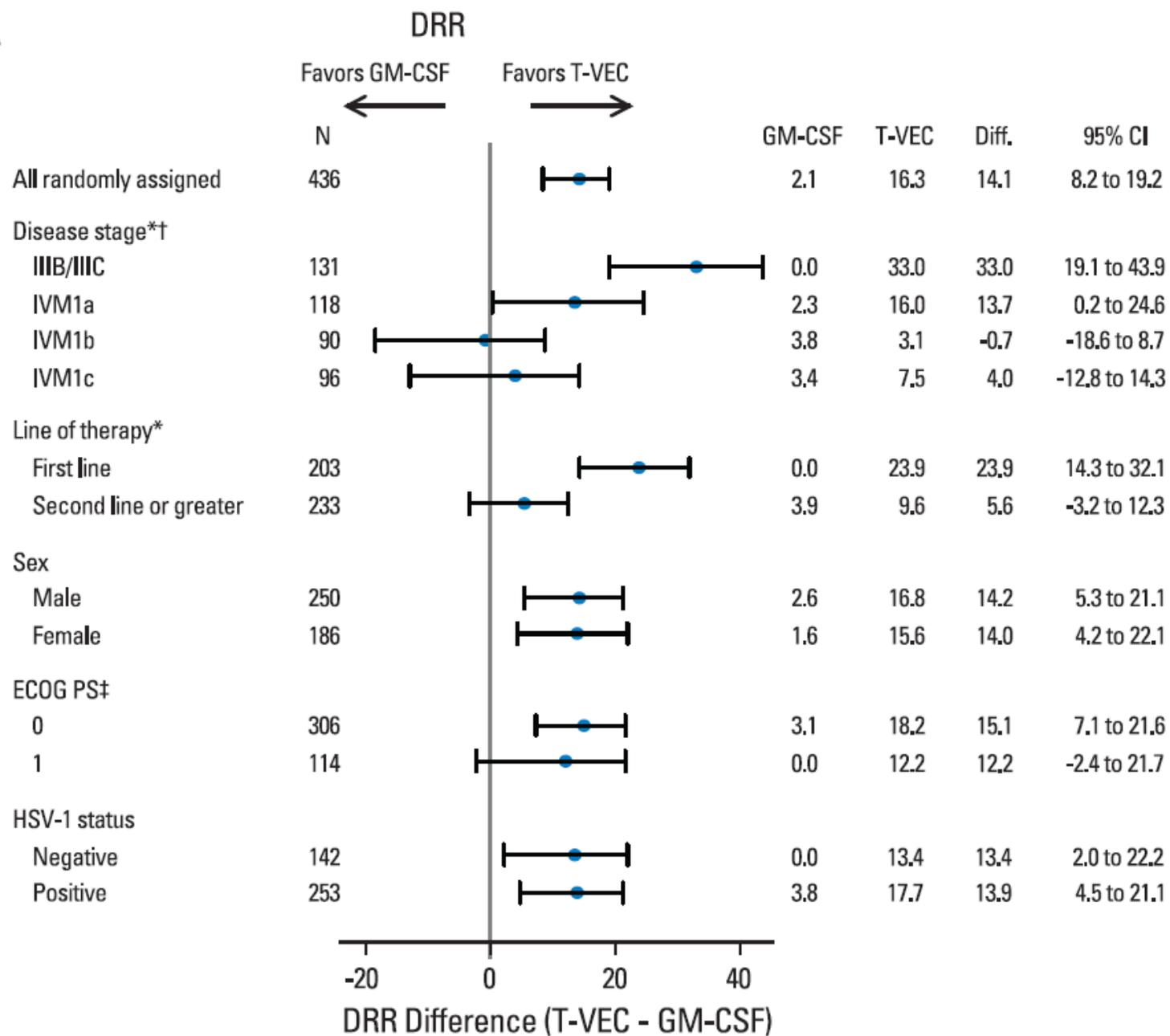


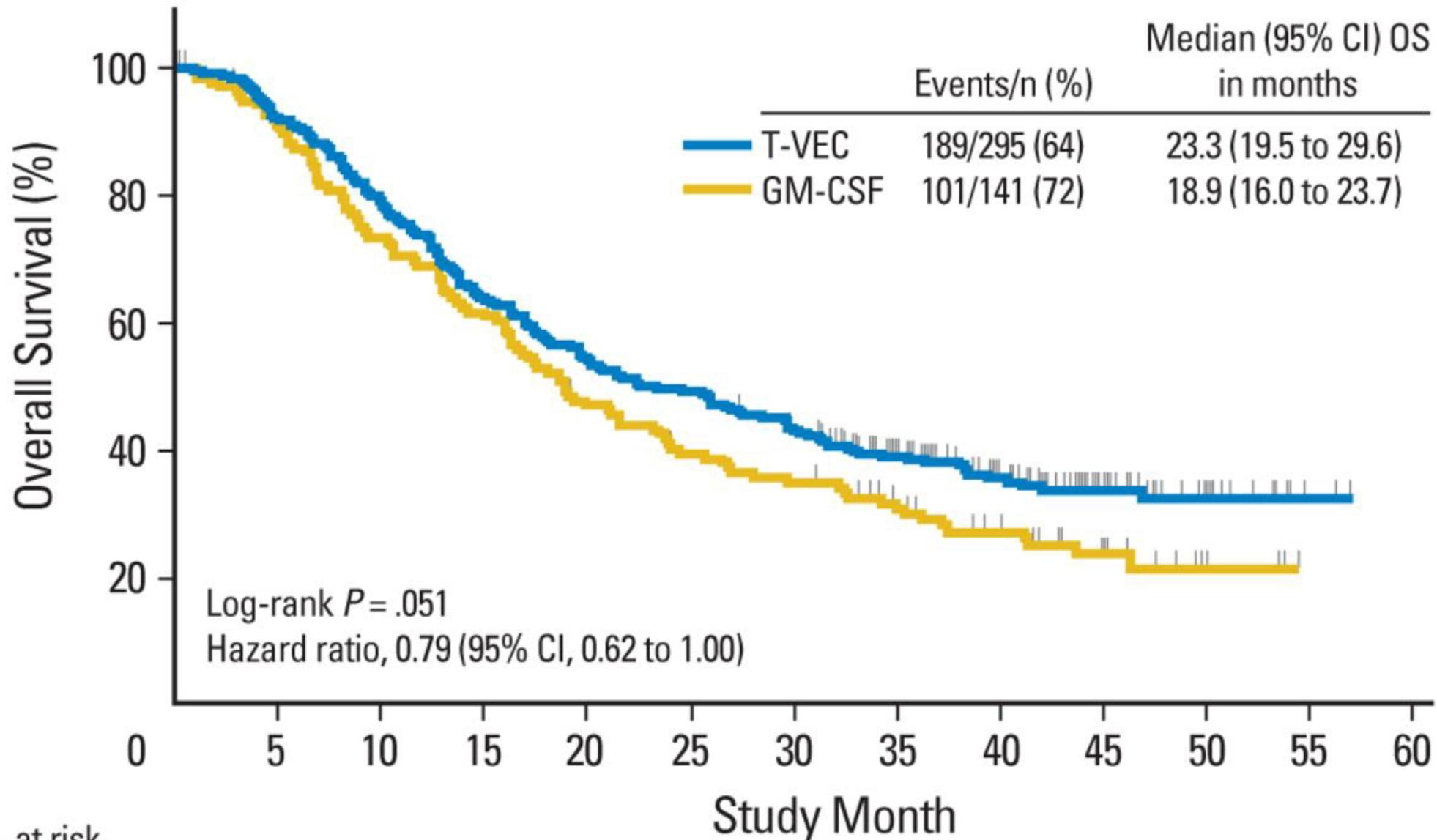
| Estimated probability* of being in response among all responders, % (95% CI) | GM-CSF (n = 8) | T-VEC (n = 78) |
|--|----------------|----------------|
| For at least 3 months  | 46.9 (12–76)   | 86.7 (77–93)   |
| For at least 6 months  | 46.9 (12–76)   | 80.6 (69–88)   |
| For at least 9 months 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

- Majority of responders still in response at end of evaluation period
- In ITT population, median (range) time to follow-up was:
  - 20.6 months (0.0–44.3) in the T-VEC arm
  - 18.5 months (0.0–43.0) in the GM-CSF arm

\*The estimated probability was obtained using the Kaplan–Meier method;

†Arrows indicate patients for whom duration of response was censored at last tumour assessment because there was no evidence (per EAC assessment) that their response had ended.

**A**



No. at risk

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

## Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

*Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin*

### Conclusion

This randomized phase III study demonstrated that treatment with **T-VEC**, an oncolytic virus immunotherapy, **improved DRR compared with GM-CSF in patients with unresected stage IIIB, IIIC, or IV melanoma**. T-VEC treatment **resulted in long-lasting CRs**, suggesting T-VEC could delay or prevent relapses or preclude progression to later stages of disease. T-VEC represents a novel potential **new treatment option** for patients with injectable metastatic melanoma and limited visceral disease.



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**SUBMIT** ▶

- Name
- Active substance or common name
- Therapeutic indication
- ATC Code

- Authorised medicine
- Withdrawn post-approval
- Suspended
- Refused

| Name        | Active substance            | Therapeutic area  | Date of authorisation / refusal |   | O | C | E |  | Status     |
|-------------|-----------------------------|---|---------------------------------|---|---|---|---|--|------------|
| Imlygic     | talimogene laherparepvec    | Melanoma  | 16/12/2015                      | ▼ |   |   |   |  | Authorised |
| Cotellic    | cobimetinib hemifumarate    | Melanoma  | 20/11/2015                      | ▼ |   |   |   |  | Authorised |
| Keytruda    | pembrolizumab               | Melanoma  | 17/07/2015                      | ▼ |   |   |   |  | Authorised |
| Opdivo      | nivolumab                   | Melanoma  | 19/06/2015                      | ▼ |   |   |   |  | Authorised |
| Lymphoseek  | tilmanocept                 | Radionuclide Imaging  | 19/11/2014                      | ▼ |   |   |   |  | Authorised |
| Mekinist    | trametinib                  | Melanoma  | 30/06/2014                      | ▼ |   |   |   |  | Authorised |
| Tafinlar    | dabrafenib                  | Melanoma  | 26/08/2013                      | ▼ |   |   |   |  | Authorised |
| Zelboraf    | vemurafenib                 | Melanoma  | 17/02/2012                      |   |   |   |   |  | Authorised |
| Yervoy      | ipilimumab                  | Melanoma  | 13/07/2011                      |   |   |   |   |  | Authorised |
| Genasense   | oblimersen                  | Melanoma  | 15/10/2007                      |   |   |   |   |  | Refused    |
| IntronA     | interferon alfa-2b          | Carcinoid Tumor<br>Hepatitis B, Chronic<br>Hepatitis C, Chronic<br>Leukemia, Hairy Cell<br>Leukemia, Myelogenous, Chronic, BCR-ABL Positive<br>Lymphoma, Follicular<br>Melanoma<br>Multiple Myeloma | 09/03/2000                      |   |   |   |   |  | Authorised |
| Tecnemab K1 | anti-melanoma mab fragments | Radioimmunodetection  | 05/09/1996                      |   |   |   |   |  | Withdrawn  |

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- Has both **local oncolytic and systemic immune effects**, and could act to enhance the cancer–immunity cycle
- Is **the first oncolytic immunotherapy** to demonstrate a therapeutic benefit against melanoma in a well-controlled, randomised Phase 3 trial
- Has now been **approved** for the treatment of adults with unresectable **melanoma** or distant metastatic (**Stage IIIB, IIIC and IV M1a**).

# Treatment of Melanoma

There have been significant advances in the treatment of melanoma over the last five years:

- Immunotherapy
- Targeted therapy and
- Oncolytic virus therapy

# T-VEC COMBINATION STUDIES

- **20110264:** Phase 1b T-VEC + ipilimumab<sup>2</sup>

irRC = immune-related response criteria; T-VEC = talimogene laherparepvec

Puzanov I et al. ASCO 2015

Long G V et al, SMR congress 2015, San Francisco, USA

# T-VEC COMBINATION STUDIES

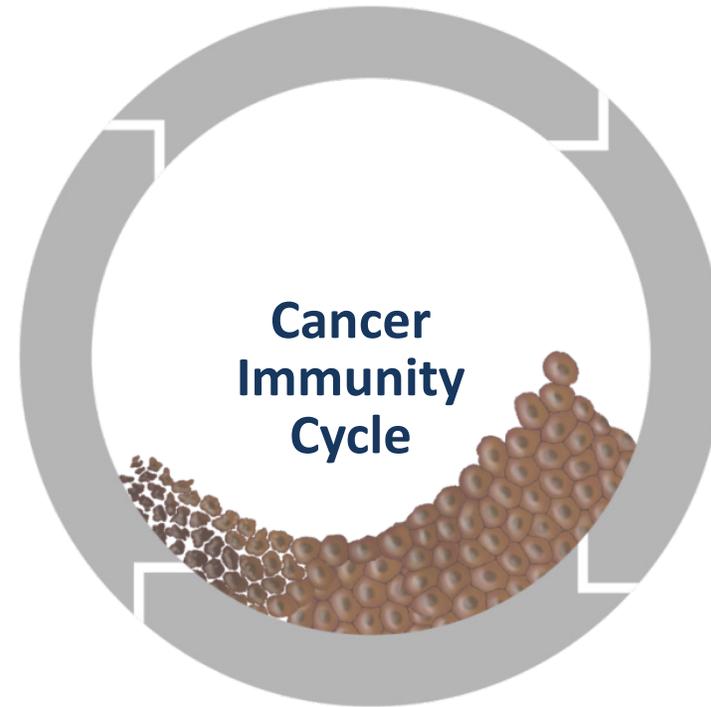
- **20110264: Phase 1b T-VEC + ipilimumab<sup>2</sup>**
  - ORR<sup>irRC</sup> 50%
  - Durable Response Rate of 44%
  - Tolerable safety profile

irRC = immune-related response criteria; T-VEC = talimogene laherparepvec

Puzanov I et al. ASCO 2015

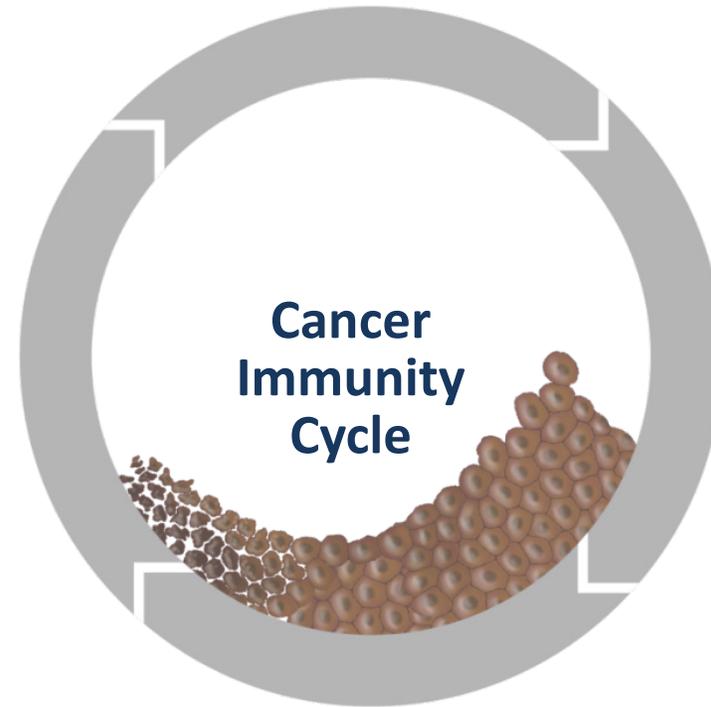
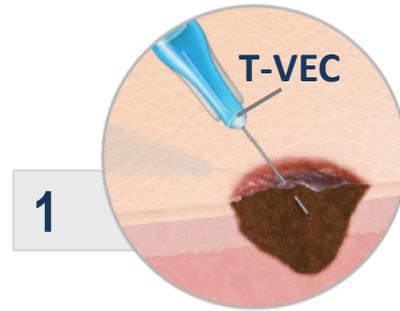
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# Proposed Mechanism of Action of T-VEC With PD-1 Inhibitor



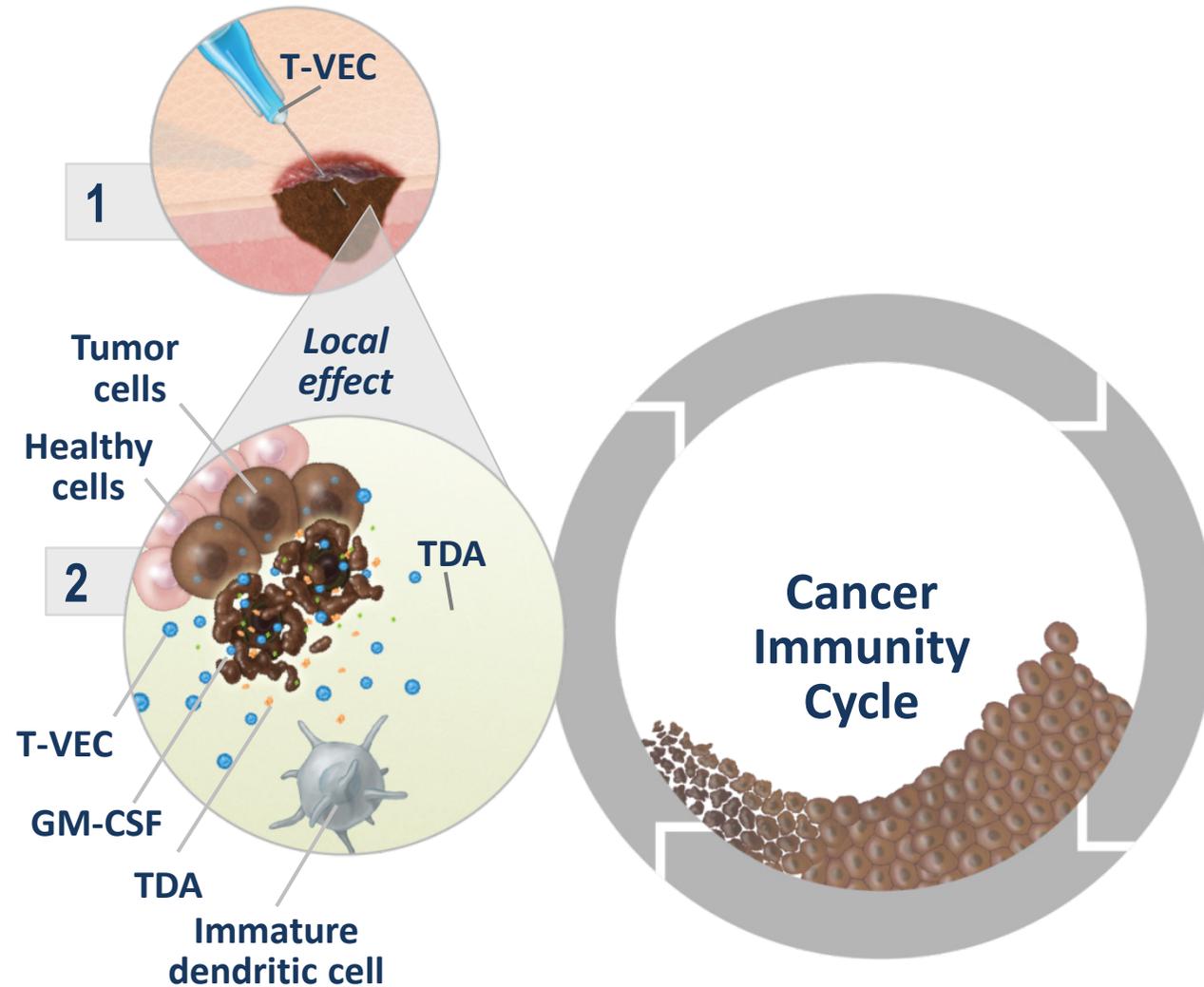
TDA: tumour-derived antigen  
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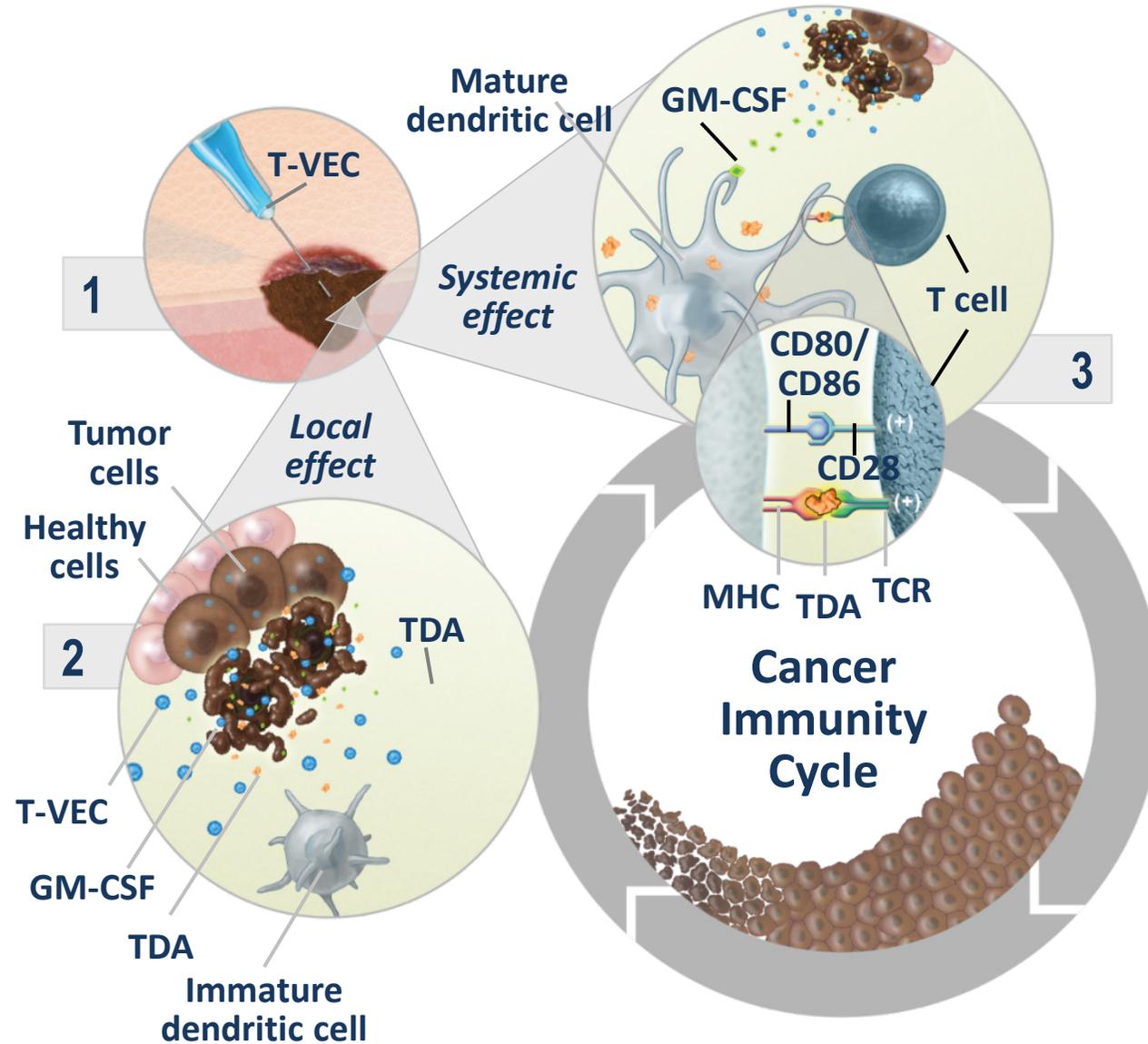
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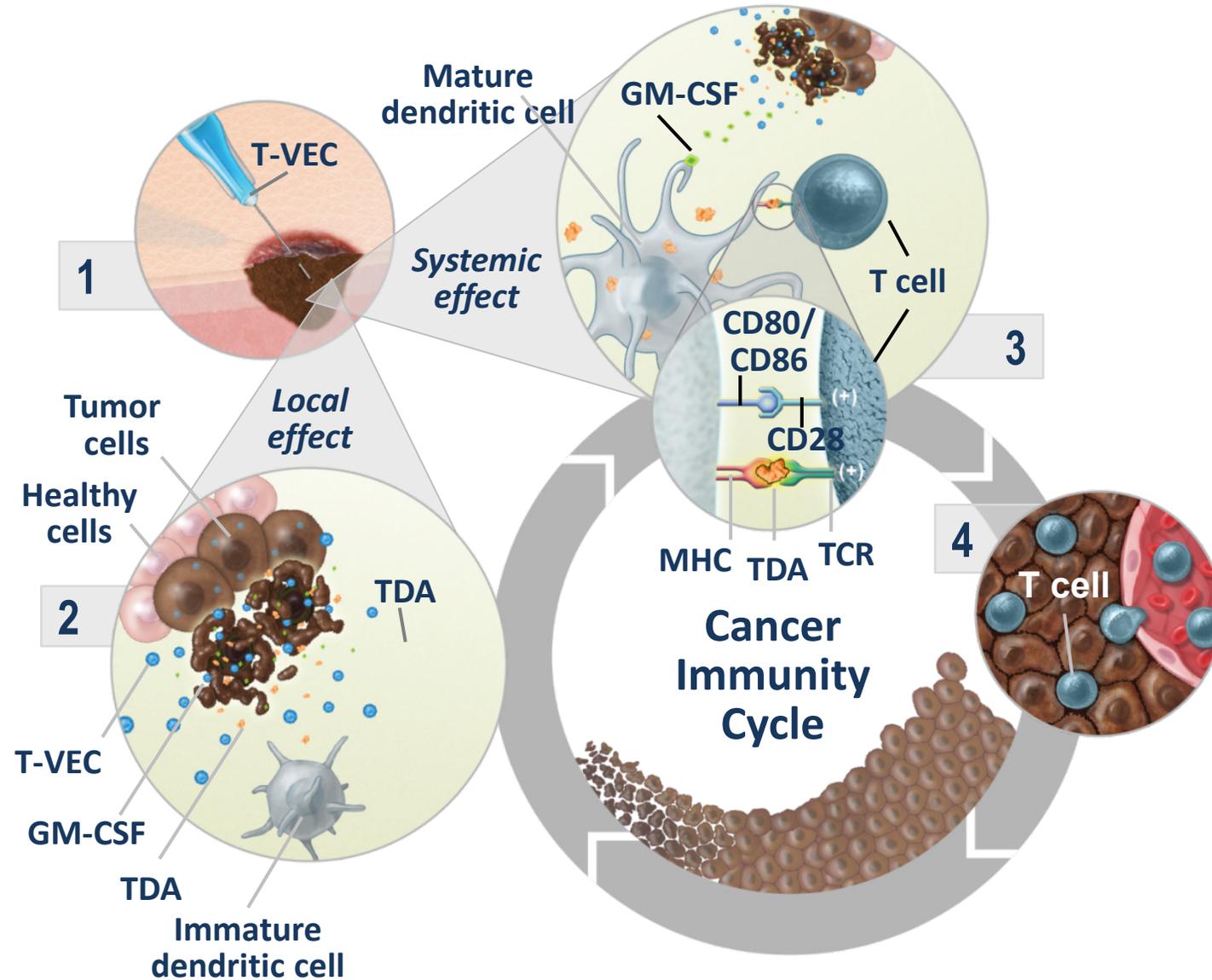
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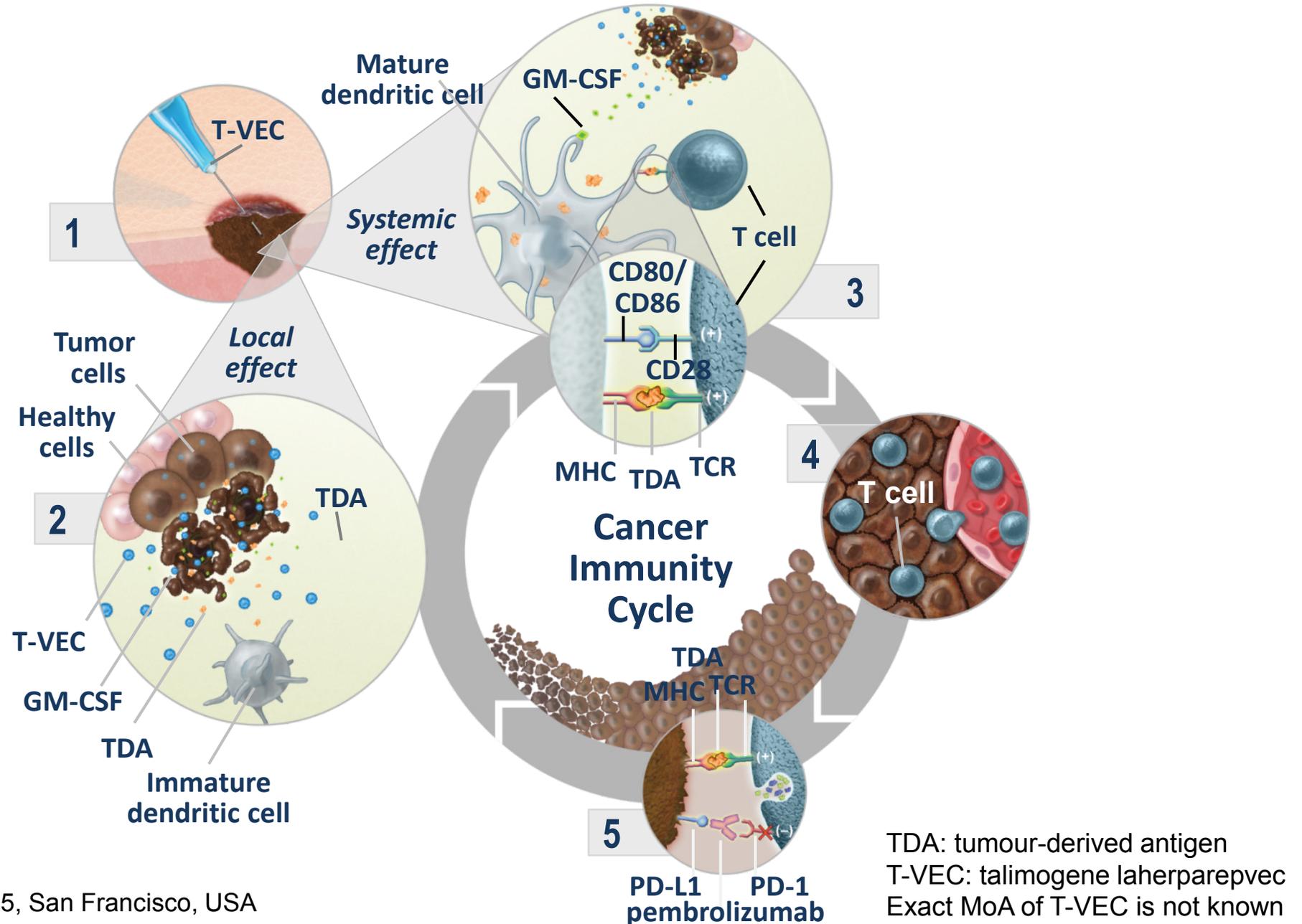
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# MASTERKEY-265 Phase 1b Study Schema

**N = 21**

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

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## T-VEC intralesional

- Up to 4 mL per treatment
- 1<sup>st</sup> dose  $10^6$  PFU/mL
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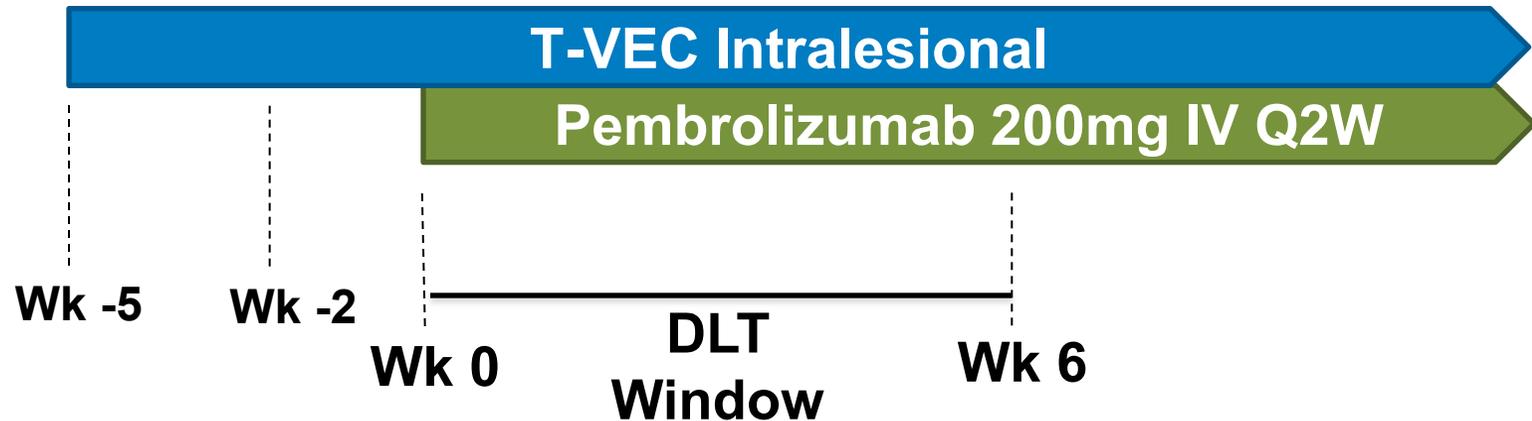
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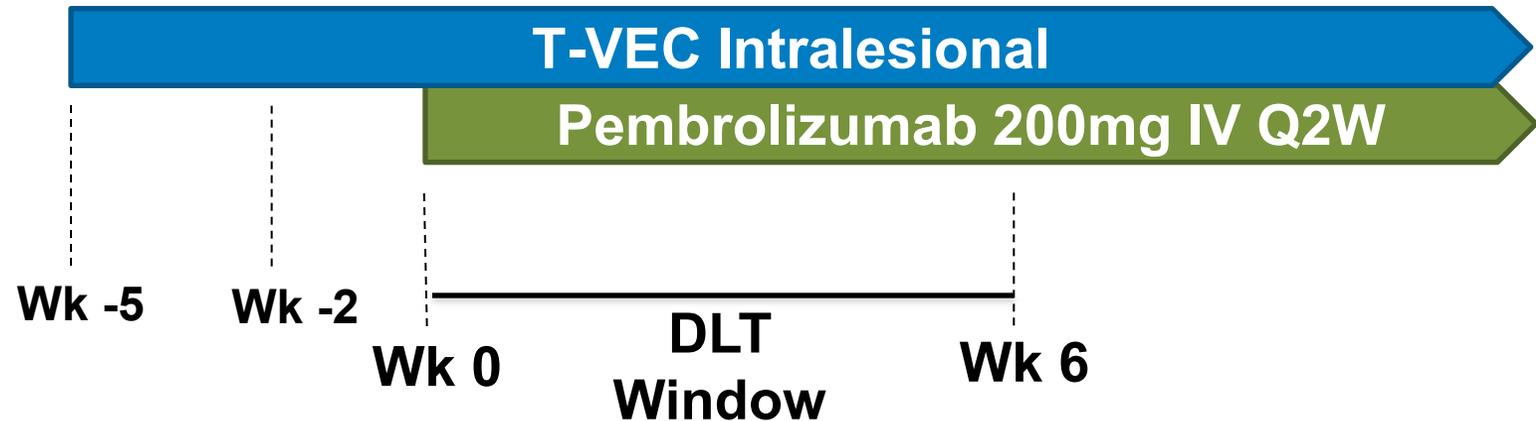
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Treatment until whichever occurs first:

- Progressive disease per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

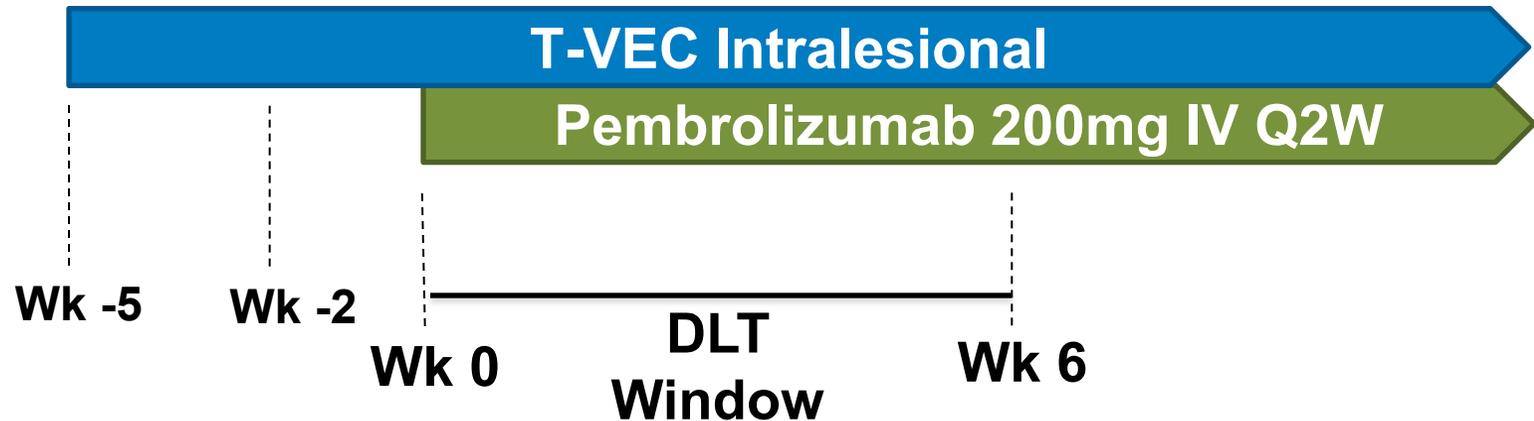
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SA  
FE  
TY  
  
FO  
LL  
OW-  
UP

30 (+7) days  
after end of  
treatment

# Preliminary Efficacy – Best Overall Response (Unconfirmed)

- 16 patients had evaluable responses prior to data cutoff<sup>a</sup>

| <b>T-VEC + pembrolizumab</b> |                   |
|------------------------------|-------------------|
| <b>N=16</b>                  |                   |
| <b>Response Rate</b>         | <b>9 (56.3%)</b>  |
| (95% CI)                     | (19.8%, 70.1%)    |
| <b>Best response</b>         |                   |
| Complete Response            | 2 (12.5%)         |
| Partial Response             | 7 (43.8%)         |
| Stable Disease <sup>b</sup>  | 2 (12.5%)         |
| Progressive Disease          | 5 (31.3%)         |
| <b>Disease control rate</b>  | <b>11 (68.8%)</b> |
| (95% CI)                     | (11.0%, 58.7%)    |

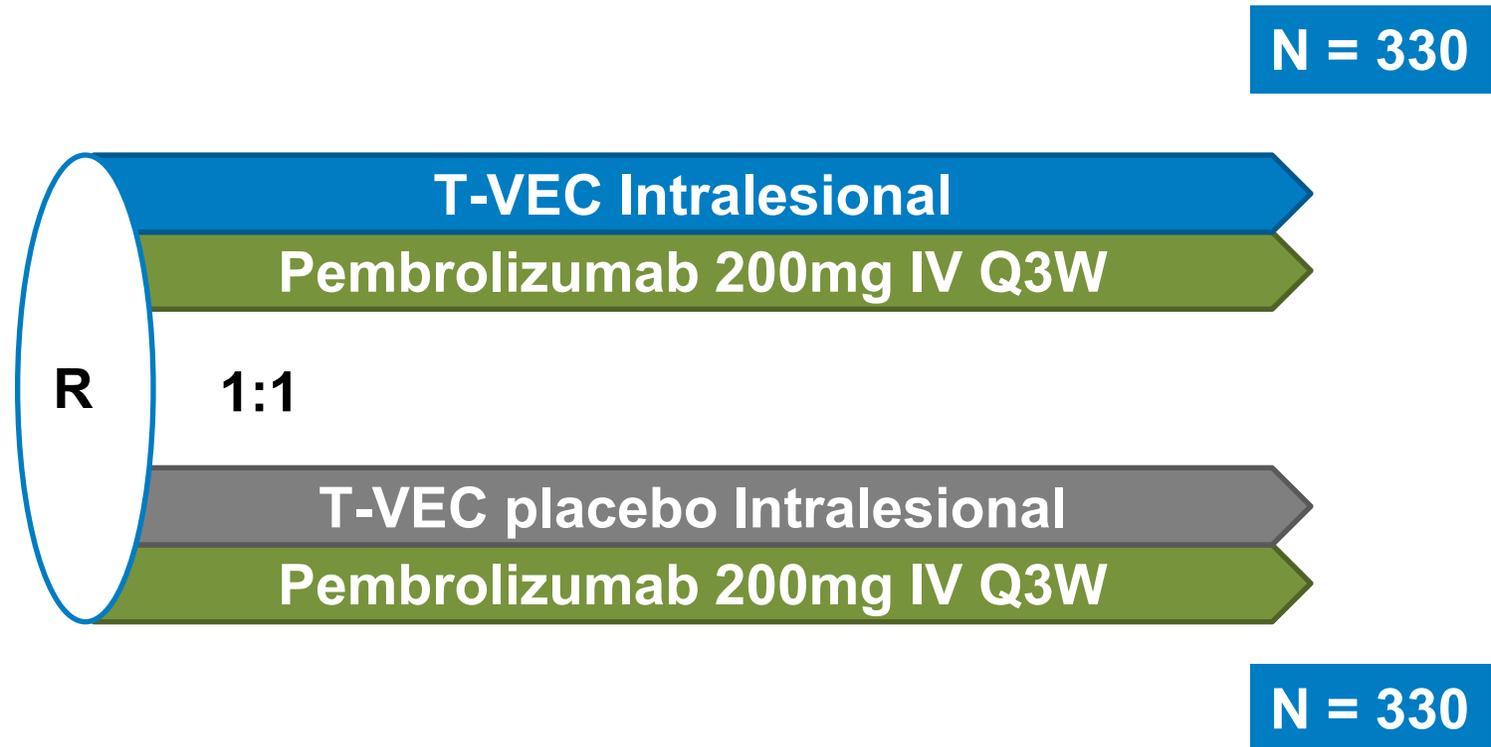
<sup>a</sup>All 16 patients were followed at least 12 weeks from the first dose of pembrolizumab and must have had an evaluable response assessment

<sup>b</sup>Stable disease must be > 77 days to be considered evaluable

# MASTERKEY-265 Phase 3 Study Design

**N = 660**

- **Unresectable stage III or IV melanoma**
- **Treatment naive**
  - **Prior BRAFi allowed**
- **Injectable lesions**



**Primary Endpoints: PFS and OS**

# CONCLUSIONS

- The development of oncolytic viruses has led to an **emerging new class of cancer therapeutics**.
- **Specificity for neoplastic tissue** is the key to safety, and this goal can be achieved through a variety of ingenious virus-engineering strategies.
- When used as drugs, they must meet **stringent criteria for safety and efficacy** and be amenable to pharmacological study in human subjects.

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- T-VEC can be considered in patients with **accessible lesions** for injection by clinical palpation or ultrasound guided injection and are not surgical candidates.
- The integration of T-VEC into the clinic need healthcare provider **education, universal precautions, special storage and handling procedures.**
- Further studies of **T-VEC combinations**, most notably with T cell checkpoint inhibitors, will be especially interesting.