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Regulatory Considerations for Intratumoral Drug Development

Maitreyee Hazarika, M.D.
Office of Oncologic Diseases, Office of New Drugs
Center for Drug Evaluation and Research, FDA

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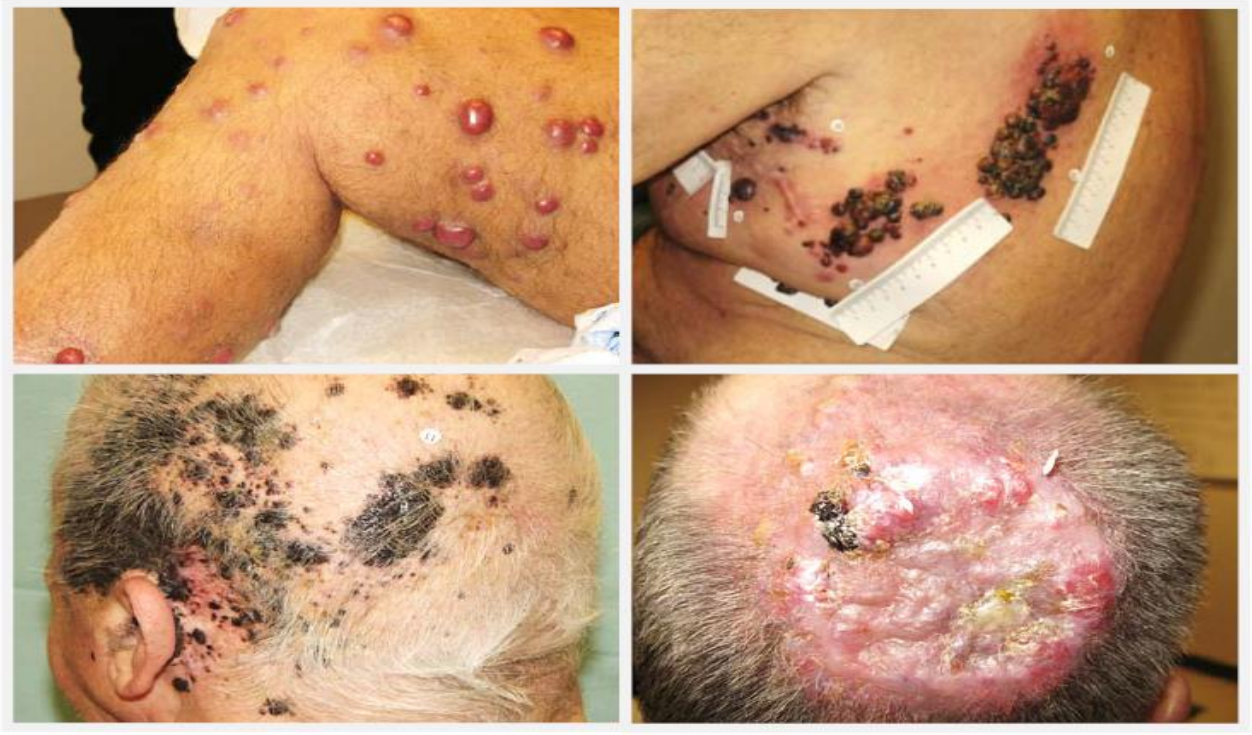
Disclosures

- No financial relationships to disclose
- Will not discuss off-label use of approved products

Talimogene laherparepvec (T-VEC) Approval in Melanoma

- Mechanism of action: Oncolytic viral therapy
- Efficacy: T-VEC vs. GM-CSF in unresectable Stage IIIB, IIIC, IV melanoma
  - Durable Response Rate (complete or partial response maintained for 6 months) by modified WHO Criteria: 16.3% vs. 2.1%
  - OS: No effect on overall survival
- FDA consulted with an Advisory Committee; voted 22-1 in favor of approval of T-VEC

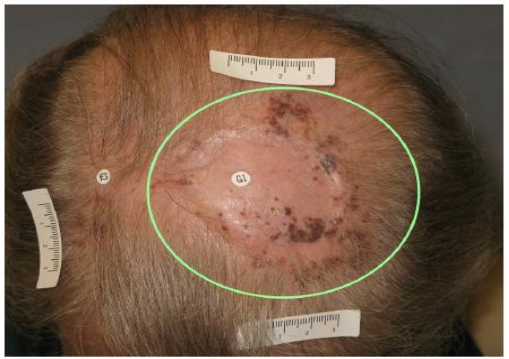
Skin Lesions



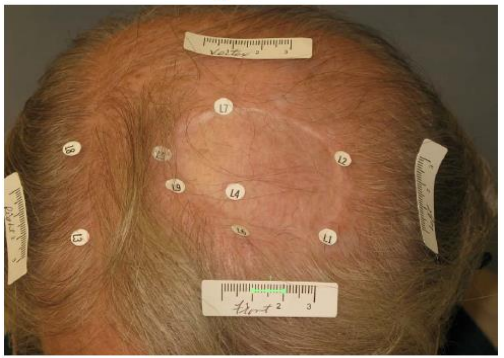
Advisory Committee Meeting, 2015

Responses

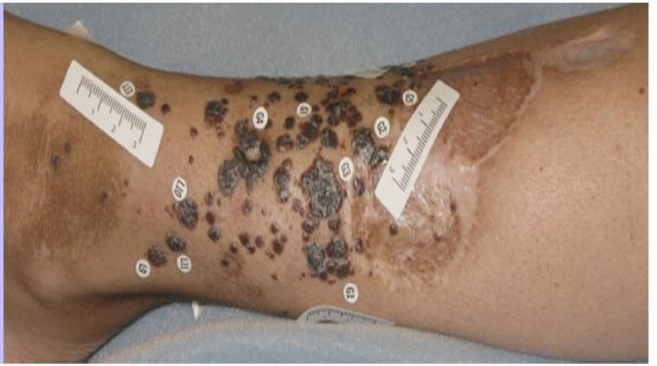
Baseline



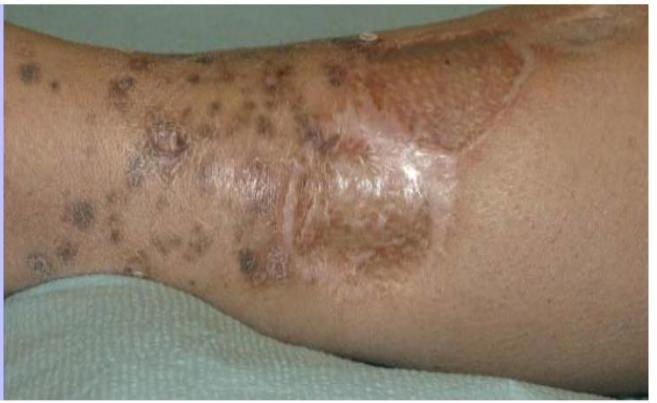
Cycle 14



Cycle 1



Cycle 13



FDA Approval

- Indications and Usage
  - Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
- Limitations of use
  - not been shown to improve overall survival or have an effect on visceral metastases

Lessons from T-VEC

Dosing Regimen Variable

- Investigator decision on volume, frequency, and lesions to inject
- Variation in drug product concentration for initial vs. subsequent doses, dose volume, and dosing schedules

Dosing variability could lead to uncertainty in determining a safe and effective dose and schedule

Control Arm

- Open-label
- Different routes of administration
  - T-VEC injected intratumorally in cutaneous, subcutaneous, and nodal lesions
  - GM-CSF subcutaneous injection
- Early drop-outs on control arm
  - 2/3rd in GM-CSF arm dropped out by the 3rd month
  - Imbalance in the duration of the treatment and primary endpoint assessments, potential bias for T-VEC
  - Due to subsequent therapy, no potential advantage for T-VEC

Assessment of Response

- Modified WHO criteria
  - Continued treatment in the presence of new lesions and progression of existing lesions
  - Bi-dimensional measurements
- Impact of sizes of baseline lesions
  - Predominance of small lesions
  - Concerns with inaccuracies in assessment of response
  - Impact of shearing force from repeated injections on very small lesions
- New lesions injected at each visit
  - Difficult to determine response in injected vs. noninjected lesions when injected lesions change over time

Clinical meaningfulness of response challenging in the context of a localized therapy for patients with a systemic disease

Systemic Effect

- Effect on noninjected lesions
- Difficulty in determining which lesions were never injected
- Noninjected lesions not identified/followed
- No OS benefit

Systemic effect on distant metastatic lesions were difficult to quantitate

Intratumoral Study Design Considerations

Optimal Dose and Delivery

- Optimal dose and delivery to ensure safe and effective use
  - Choice of lesions
  - Number of lesions
  - Dose administered to each lesion
  - Dosing volume per treatment
  - Frequency of injections
  - Mode of delivery and techniques

Controls

- Bias in assessment in open-label study design
- Contribution of effect
- Double-blind study for a combination regimen
- Concurrent intratumoral control to address a concern regarding potential physical effect of the injection procedure on tumor regression, especially on small lesions

Contribution of Effect

- Depends on activity of the intratumoral drug product and disease

Examples:

- Investigational Drug Product X + Unapproved Drug Product Y
  - Four-arm factorial design
  - XY vs. X vs. Y vs. placebo or SOC
- Investigational Drug Product X + Approved Drug Product Y
  - Add-on design

Adaptive trial designs when appropriate

Measurement of Lesions

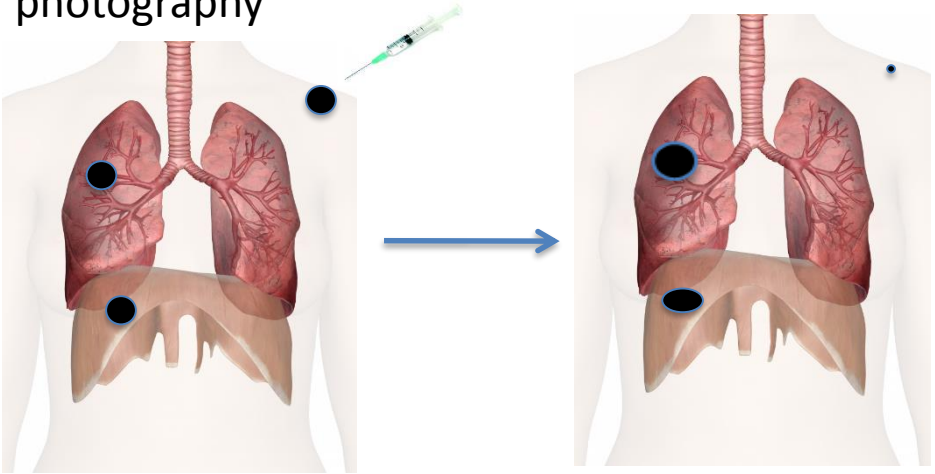
- Measurement of lesions at baseline and during assessments
  - Minimum target lesion size
  - Reliability of assessment
  - Method of measurement: ruler, calipers, CT scan/MRI
  - Record target and non-target lesion size and location

Response Criteria

- RECIST v1.1 for systemic disease
- Modifications to RECIST v1.1
  - Since lesions injected intratumorally, important to capture overall response rate
  - Response in visceral lesions
  - Increasing the number of target lesions may bias the response towards response in the injected lesions
  - Adequate representation from noninjected target lesions to capture a systemic response

Progression of Tumors Not Injected

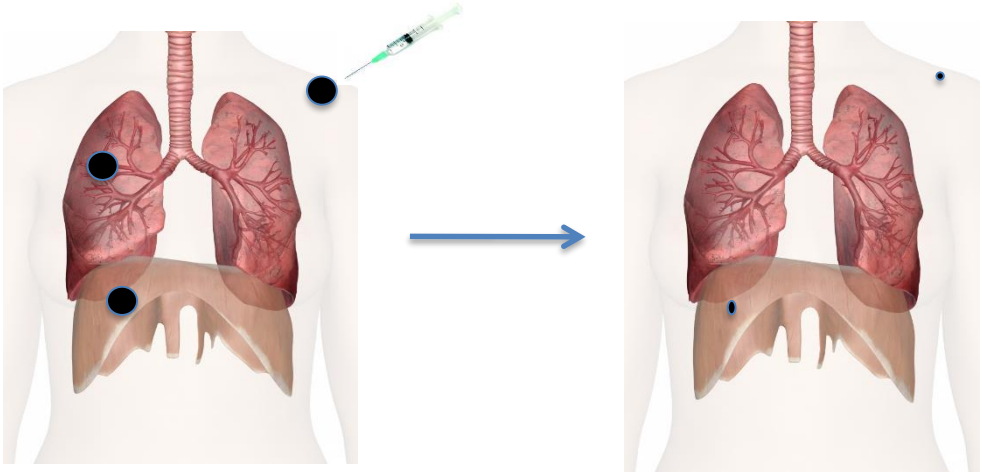
- Evidence of progression of tumors not injected
  - Visceral (e.g., lung or liver) lesions
  - Cutaneous / nodal lesions: documentation, including photography



  - Lack of response or progression observed in noninjected lesions cannot be a responder on basis of local response

Efficacy of Intratumoral Drug product as a Single Agent

- Demonstration of efficacy of a local therapy as a single-agent in the setting of metastatic disease
  - Crucial to obtain evidence of systemic treatment effect
  - Regression of noninjected tumors



Efficacy of Intratumoral Drug Product with Systemic Therapy

- Understanding of how intratumoral drug product is acting systemically
- Contribution of effect
- Demonstration of direct clinical benefit, i.e., OS

Intratumoral and Systemic Therapy used in Combination Approach

- Biological rationale and early activity
- Optimize the doses of the combination
- Demonstrate the contribution of each component of the combination
- Evidence of the effectiveness of the combination
- Evidence of the safety of the combination, adequate data
- Companion diagnostic
- Cross-labeling

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