Talimogene Laherparepvec (T-VEC) at the SCCA: an update

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Outline

• What’s T-VEC & How does it work?
• What did the studies show?
• T-VEC experience at the SCCA
T-WHAT?

• Talimogene laherparepvec
T-WHAT?

• Talimogene laherparepVEC
• Brand name: Imlygic
T-VEC FDA-approved in October 2015

• First in class oncolytic virus therapy for the treatment of advanced melanoma
• First oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a Phase III trial
• 2016 NCCN guidelines: recommended as a Category 1 option for Stage III melanoma with nonresectable, recurrent, or intransit disease.
• Efficacy seen in Stage IIIIB, IIIC and IV M1a disease
• Efficacy more likely in treatment-naïve patients
• T-VEC has NOT been shown to affect OS or have a significant effect on visceral metastases
T-VEC is modified HSV-1

http://bryanmbrandenburg.com/herpes-simplex-virus-3d-

https://en.wikipedia.org/wiki/Herpes_simplex
T-VEC is modified HSV-1

- Deletion of the ICP34.5 gene
- Preferential killing of tumor cells (neurovirulence)

http://bryanmbrandenburg.com/herpes-simplex-virus-3d-animation/
T-VEC is modified HSV-1

- Insertion of gene cassette encoding human GM-CSF increasing influx and activation of APC’s
T-VEC is modified HSV-1

• Deletion of ICP47 gene permits antigen presentation for virus and tumor antigens & increase replication efficiency in tumors

http://bryanmbrandenburg.com/herpes-simplex-virus-3d-animation/
T-VEC is modified HSV-1

- Retention of viral thymidine kinase gene

http://bryanmbrandenburg.com/herpes-simplex-virus-3d-animation/
T-VEC proposed Mechanism of Action

T-VEC proposed Mechanism of Action

Tumor cells rupture for an oncolytic effect

GM-CSF

T-VEC proposed Mechanism of Action

T-VEC proposed Mechanism of Action

Death of distant cancer cells

Dying cancer cell

Oncolytic Virus Therapy: How to win the Game

Phase I Study showed biologic activity: tumor shrinkage, flattening and necrosis (Hu, 2006)

Single-Arm Phase II Study demonstrated 26% Overall Response Rate in Stage IIIC/IV melanoma. Responses seen in injected and non-injected lesions (including visceral lesions. (Senzer, 2009)

Tumor microenvironment analysis in the phase 2 study showed sig increase in MART-1-specific T-cells following CR with T-VEC, found in local and distant lesions (Kaufman, 2010)
OPTiM: Phase III Study

- Randomized, open-label, phase 3 study with histologically confirmed and surgically unresectable stage IIIB, IIIC, IV melanoma

- Randomized 2:1 to get T-VEC or SQ GM-CSF

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OPTiM Phase III Study

Durable response rate:
T-VEC: 16.3%
GM-CSF: 2.1%

Overall Response Rate:
T-VEC: 26.4%
GM-CSF: 5.7%

Median Overall Survival:
T-VEC: 23.3 months
GM-CSF: 18.9 months
OPTiM Phase III Study

- T-VEC is the 1st oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial.
- T-VEC is well-tolerated
- T-VEC efficacy most pronounced in Stage IIIB, IIIC, IVM1a Disease & in treatment-naïve disease
OPTiM Trial

- Median Time to Response: 4.1 months (95% CI 1.2-16.1 months)
- Median Time to Failure: 8.2 months (95% CI 6.5-9.9 months)
T-VEC at the SCCA

- To Date: 6 patients have been treated with T-VEC
- Ages 27-78 years
- Stage 1-Stage III Disease → recurrent melanoma
- All but 1 patients heavily pre-treated (dabrafenib, ipi, pembrolizumab, nivolumab, traditional chemotherapies)
- Some have h/o immune-related side effects to systemic immunotherapy
- 1 pCR, 2 PR, 1 6+ months into therapy with stable disease, 1 too soon to call, 1 off treatment following progression
First T-VEC Injection in Washington State: June 2016
63 yo male patient

- Stage T3aN2M0 2.3 mm MM of right lateral ankle in 2010
- s/p WLE and +SLN Bx → right inguinal lymphadenectomy
- Tolerated 6 months high-dose IFN
- Began developing intransit mets around WLE graft 2011, eventually unresectable
- Ipilimumab 11/11-2/12
- Vemurafenib 4/12-9/12, 11/12-3/14
- Dabrafenib/trametinib 3/14-9/15
- Pembrolizumab 10/14-4/15
- Clinical Trial intralesional IL-12 and electroporation, 3 cycles
- Pembrolizumab 3/16-8/16
- T-VEC initiated 8/2016
12/20/2016
Right Thigh, 2X
10/20/2016:
Right Calf
2X
Immune-related Adverse Events & T-VEC

• Scouting skin biopsies negative for residual melanoma
• Skin Bx inflammatory findings
• 3 days after last T-VEC injection developed diarrhea and abdominal pain
• Stool Cultures negative
• Sigmoidoscopy: biopsy c/w inflammatory colitis
• Sx resolved on prednisone
• T-VEC discontinued
T-VEC at the SCCA: Lessons Learned

• Generally well-tolerated, BUT the constitutional symptoms are impressive early in the course of treatment
• “progression prior to response”
• Treated and untreated lesions respond to therapy
• PR’s, 1 CR and 1 progression/failure, 2 TBD
• No infectious side effects (HSV-1 or cellulitis) to date
• Immune-related side effects are not unexpected, as with other immunotherapies (panniculitis & colitis)
T-VEC at the SCCA: What’s Next?

• Continue to build the program – we remain one of the only sites in Washington State offering this therapy
• -80 Freezer Space for T-VEC
• Adding ultrasound guidance for deeper subcutaneous nodules and/or involved lymph nodes
• Goal to train another provider to perform the injections
• Continue to build the T-VEC program
Thank You!
Big, Huge Thank You!

• Our nurses
• Our pharmacy team
• Our schedulers
• Martha Reed and the committees who developed the infectious precaution protocol to ensure maximum safety for all our patients at the SCCA
• Our T-VEC patients