Gene Therapy for Prostate Cancer

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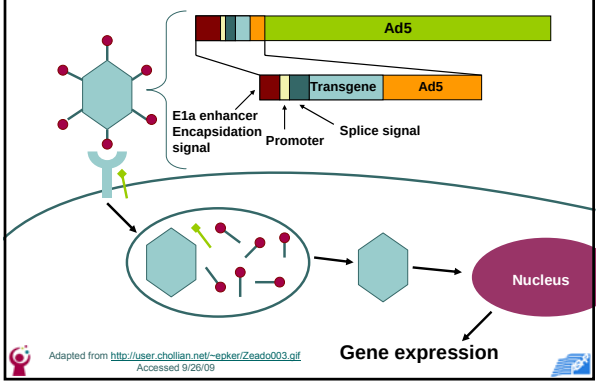
December 9, 2009

Learning Objectives

- Identify the advantages & disadvantages of combination gene therapy in low-risk and high-risk prostate cancer patients with localized disease
- Describe the role of immune modulators like granulocyte-monocyte colony stimulating factor (GM-CSF) in cancer cell vaccines
- Correlate available safety and efficacy data utilizing vaccines and antisense oligonucleotides as treatments for metastatic prostate cancer

Adenovirus Vector



Adapted from http://user.chollian.net/~epker/Zeado003.gif Accessed 9/26/09

Gene Therapy for Localized Disease

Combination Gene Therapy	Phase	Patients	Clinical Response
Double-suicide[1] Ad5-CD/TK*rep* + 5FC/GCV	I	16	PSA ↓ ≥ 25% in 7 PSA ↓ ≥ 50% in 3 At 5-yrs[2]: PSADT ↑ from 17 to 31 mo (p = 0.014)
Trimodal[3] Ad5-CD/TK*rep* + 5FC/GCV + EBRT	I	10	PSA ≤ 0.5 ng/mL in 5 4-yrs (n=9)[4]: intermediate-risk – no disease evidence

Adapted from [1] *Cancer Research* 2002;62:4968-4976; [2] *Molecular Therapy* 2007;15:636-642 [3] *Cancer Research* 2003;63:7497-7506; [4] *Molecular Therapy* 2007;15:1016-1023

Combination Gene Therapy ± ADT

Low-risk n = 29	Days 0, 14 Adv-TK intraprostatic (5 x 10^{11} vp) → Valacyclovir → IMRT
High-risk n = 26	Days 0, 56, 70 Adv-TK intraprostatic (5 x 10^{11} vp) → → → Valacyclovir → IMRT → Androgen deprivation therapy

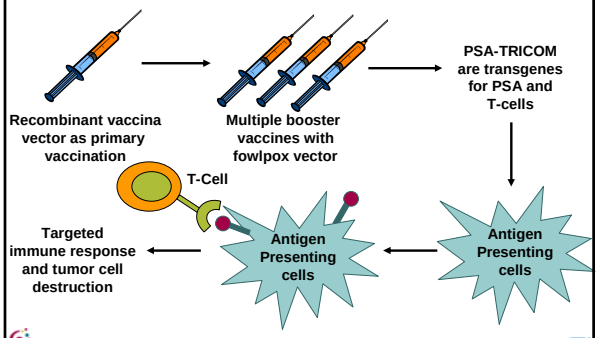
Low-risk and high-risk arm biopsy results showed no evidence of prostate carcinoma at 24 months

Adapted from *International Journal of Radiation Oncology Biology and Physics* 2004;58:1520-1529

True or False

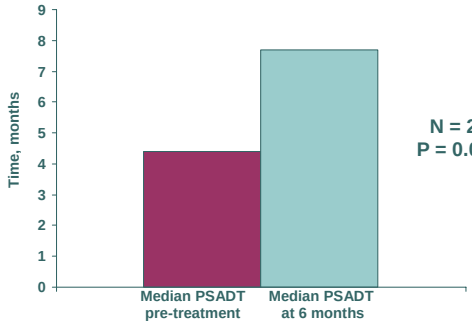
- Replication-competent adenovirus-mediated suicide gene therapy may lengthen prostate-specific antigen doubling time and delay the need for androgen suppression therapy in patients with low-risk prostate cancer.
- True

PROSTVAC-VF



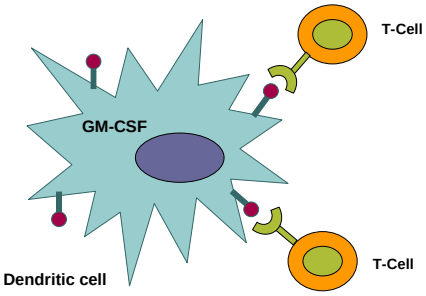
Adapted from *Expert Opinion on Investigational Drugs* 2009;18:1001-1011

ECOG 9802 PROSTVAC-VF + TRICOM



Adapted from DiPaola RS, Chen Y et al. A phase II study of PROSTVAC-V (vaccina)/TRICOM and PROSTVAC-F (fowlpox)/TRICOM with GM-CSF in patients with PSA progression after local therapy for prostate cancer: Results of ECOG 9802 [Abstract]. In ASCO 2009 Genitourinary Cancers Symposium; 2009 Feb 26-28; Orlando, FL, abstract 108.

GVAX Allogenic Whole Cell Vaccine



Adapted from *Cancer Letters* 2008;266:116-134

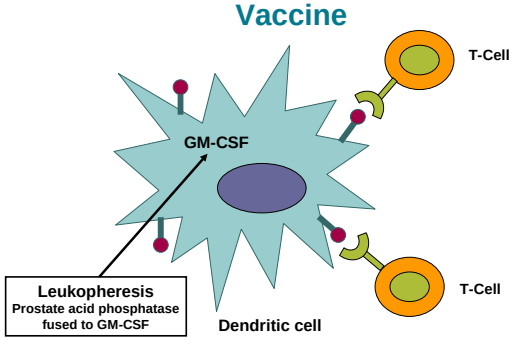
VITAL-2 Phase III Clinical Trial of GVAX for Prostate Cancer

N = 408	GVAX + Docetaxel 75 mg/m^2 q 3 wk + Prednisone 10 mg/day	Docetaxel 75 mg/m^2 q 3 wk + Prednisone 10 mg/day	P-value
Docetaxel cycles completed (no.)	5	7	0.01
Overall survival (mo.)	12.2	14.1	0.0076 HR 1.7 95% CI (1.15-2.53)
Deaths	67	47	

Study stopped prematurely due to an imbalance in deaths in GVAX arm

Adapted from Small E, Demkow T et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC) [Abstract]. In ASCO 2009 Genitourinary Cancers Symposium; 2009 Feb 26-28; Orlando, FL, abstract 7.

Sipuleucel-T Autologous / Dendritic Cell Vaccine



Adapted from *Cancer Letters* 2008;266:116-134

Results of D9901 & D9902A with Sipuleucel-T in Advanced Prostate Cancer

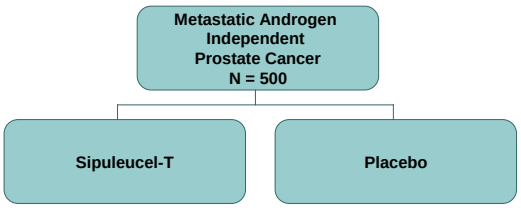
	Sipuleucel-T N = 147	Placebo N = 78	Hazard ratio
Median survival, mo	23.2	18.9	1.5 (1.1-2.05) P = 0.011
Median time to progression, wk	11.1	9.7	1.26 (0.95-1.68) P = 0.111

Note: Hazard ratio is expressed as risk in placebo treated patients divided by the risk for patients treated with sipuleucel-T

Adapted from *Cancer* 2009;115:3670-3679

D9902B

A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Immunotherapy With Autologous Antigen Presenting Cells Loading with PA2024 (Sipuleucel-T, APC8015) in Men with Metastatic Androgen Independent Prostatic Adenocarcinoma



Primary Objective: Overall survival
Secondary Objectives: Time to disease progression

Adapted from www.clinicaltrials.gov Accessed 9/17/09

True or False

- Granulocyte-monocyte colony stimulating factor (GM-CSF)-secreting cancer cell vaccines induce anti-tumor immune responses by recruiting antigen presenting cells and activating CD4+ and CD8+ T-cells.
- True

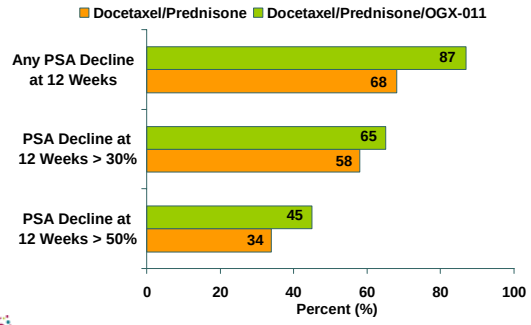
Antisense Oligonucleotides

- Chemically modified DNA-like molecules 17-22 nucleotides in length

Resulting inhibition of gene expression

Current Opinion in Urology 2007;17:182-187

Docetaxel/Prednisone ± OGX-011 in Metastatic Prostate Cancer



Adapted from *Journal of Clinical Oncology* 2009;27:15s(suppl;abstr 5012)

Docetaxel + Oblimersen Sodium (Bcl-2 Antisense Oligonucleotide)

	Docetaxel N = 57	Docetaxel + Oblimersen N = 54
Confirmed PSA response (%)	46	37
Partial response (RECIST) (%)	18	24
Major toxic events (%)	22.8	40.7

Primary end points of study were not met with docetaxel-oblimersen

Adapted from *Annals of Oncology* 2009;20:1264-1269

True or False

- Oblimersen should be combined with docetaxel in all patients with castrate-resistant prostate cancer.
- False

Conclusions

- Limiting factors of current trials:
  - Efficiency
  - Selectivity
  - Immunogenicity
  - Lack of specific outcome improvement
- Continue research in transcriptional targeting
- Future gene therapy trials are needed combining hormonal, chemotherapy and radiation

Questions?

Thank you for your attention.

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