Optimal Integration of Chemotherapy into the Management of Endocrine-Sensitive Prostate Cancer

Daniel W Lin, MD
Professor and Chief of Urologic Oncology
Pritt Family Endowed Chair in Prostate Cancer Research

University of Washington
Fred Hutchinson Cancer Research Center
Seattle, Washington

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Dislosures

Consulting Agreement	Astellas Pharma Global Development Inc
Contracted Research	GenomeDx, Genomic Health Inc, MDxHealth

Agenda and Objectives

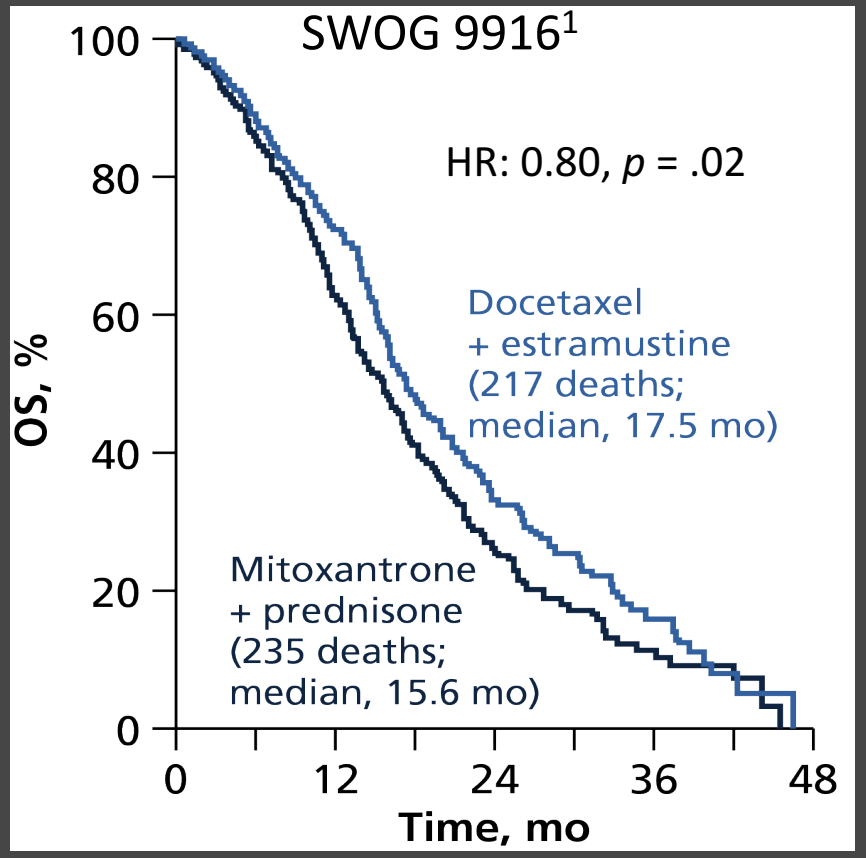
- Compare trial cohorts of docetaxel use in early hormone-sensitive metastatic disease
- Understand the relevant differences and similarities in trial results
- Describe the landscape of high risk localized disease and rationale for potential cytotoxic chemotherapy
- Present current standard of care in newly diagnosed M1 and high risk M0 disease

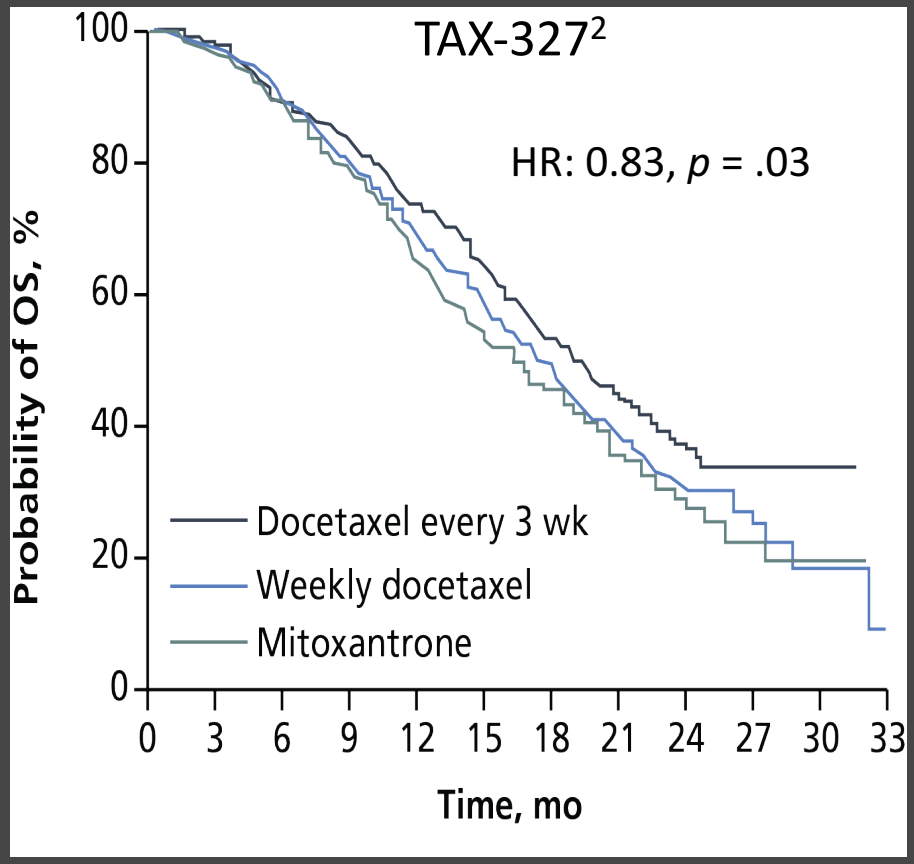
Background

- Androgen deprivation therapy is the cornerstone of treatment in metastatic, hormone-sensitive prostate cancer
- Various strategies to improve efficacy or reduce treatment burden
  - Intermittent ADT
  - Antiandrogen monotherapy
  - Combined blockade (antiandrogen + LHRH analogue)

Background

- Docetaxel was the first drug in mCRPC to improve disease-specific and overall survival





1. Petrylak DP et al. *N Engl J Med* 2004;351:1513-20. 2. Tannock IF et al. *N Engl J Med* 2004;351:1502-12.

Comparison of Study Cohorts in Hormone-Sensitive Disease

	GETUG-AFU 15	CHAARTED	STAMPEDE
N	385	790	1776
Accrual period	2004-2008	2006-2012	2005-2013
Treatment (Control = ADT)	Doc q 3 wk x nine cycles	Doc q 3 wk x six cycles	Doc q 3 wk x six cycles, plus prednisone
Metastatic status	M1	M1	M1* and M0
High/low volume (%)	52/48	66/34	NR
Gleason 8-10 (%)	55%	61%	70%
Treatment on progression (control arm only)	62% Docetaxel	51% Docetaxel	40% Docetaxel

*59% newly diagnosed M1

Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaelle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzeff, Remy Delva, Ivan Krakowski, Brigitte Laguerre, Fréderic Rolland, Christine Théodore, Gael Deplanque, Jean Marc Ferrero, Damien Pouessel, Loïc Mourey, Philippe Beuzeboc, Sylvie Zanetta, Muriel Habibian, Jean François Berdah, Jerome Dauba, Marjorie Baciuchka, Christian Platini, Claude Linassier, Jean Luc Labourey, Jean Pascal Machiels, Claude El Kouri, Alain Ravaud, Etienne Suc, Jean Christophe Eymard, Ali Hasbini, Guilhem Bousquet, Michel Soulie

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

Comparison of Study Results

		GETUG	CHAARTED	STAMPEDE
N		385	790	1776*
Med F/U (mos)		83	29	43
OS (mos)				
	ADT	46.5	44.0	71
	Doc	60.9	57.6	81
	HR	0.9 (0.7-1.2)	0.60 (0.47-0.80)	0.78 (0.66-0.93)
Low volume				
	ADT	NYR	NYR	
	Doc	83.1	NYR	
	HR	1.0 (0.6-1.5)	0.63 (0.32-1.13)	NR
High volume				
	ADT	35.1	32.2	
	Doc	39.0	49.2	
	HR	0.8 (0.6-1.2)	0.60 (0.45-0.81)	NR

*59% newly diagnosed M1

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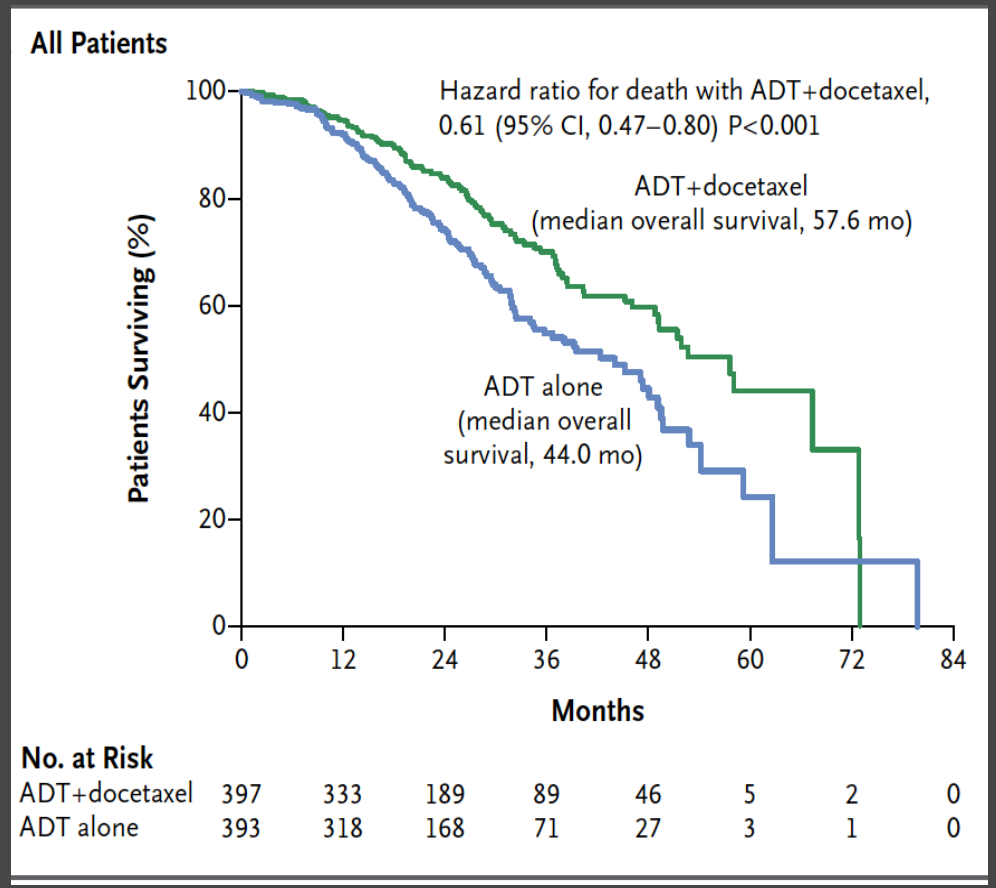
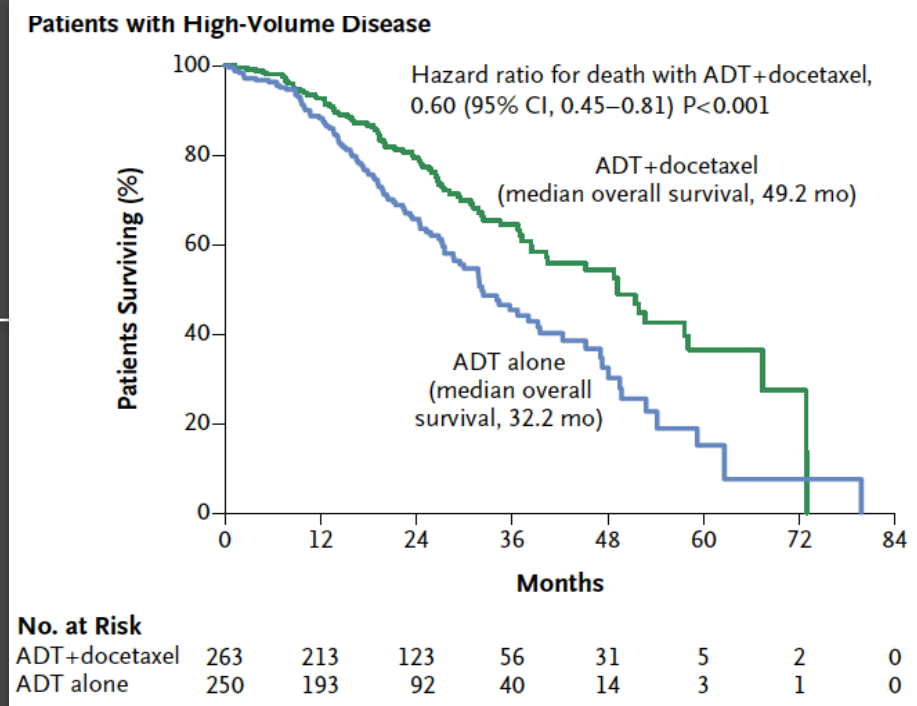
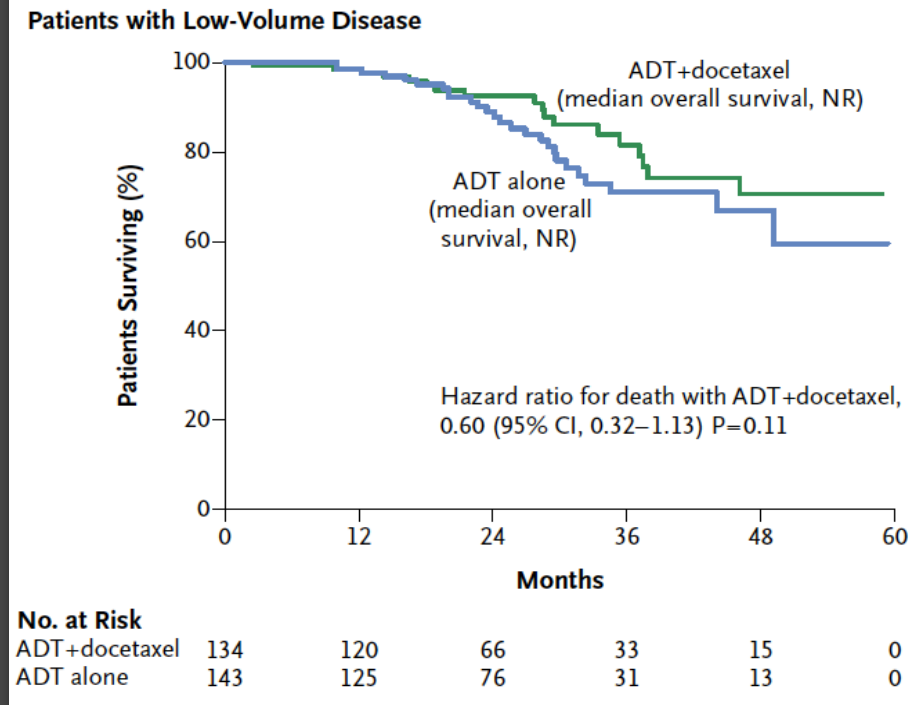
CHAARTED Results



Sweeney C et al. N Engl J Med, 2015

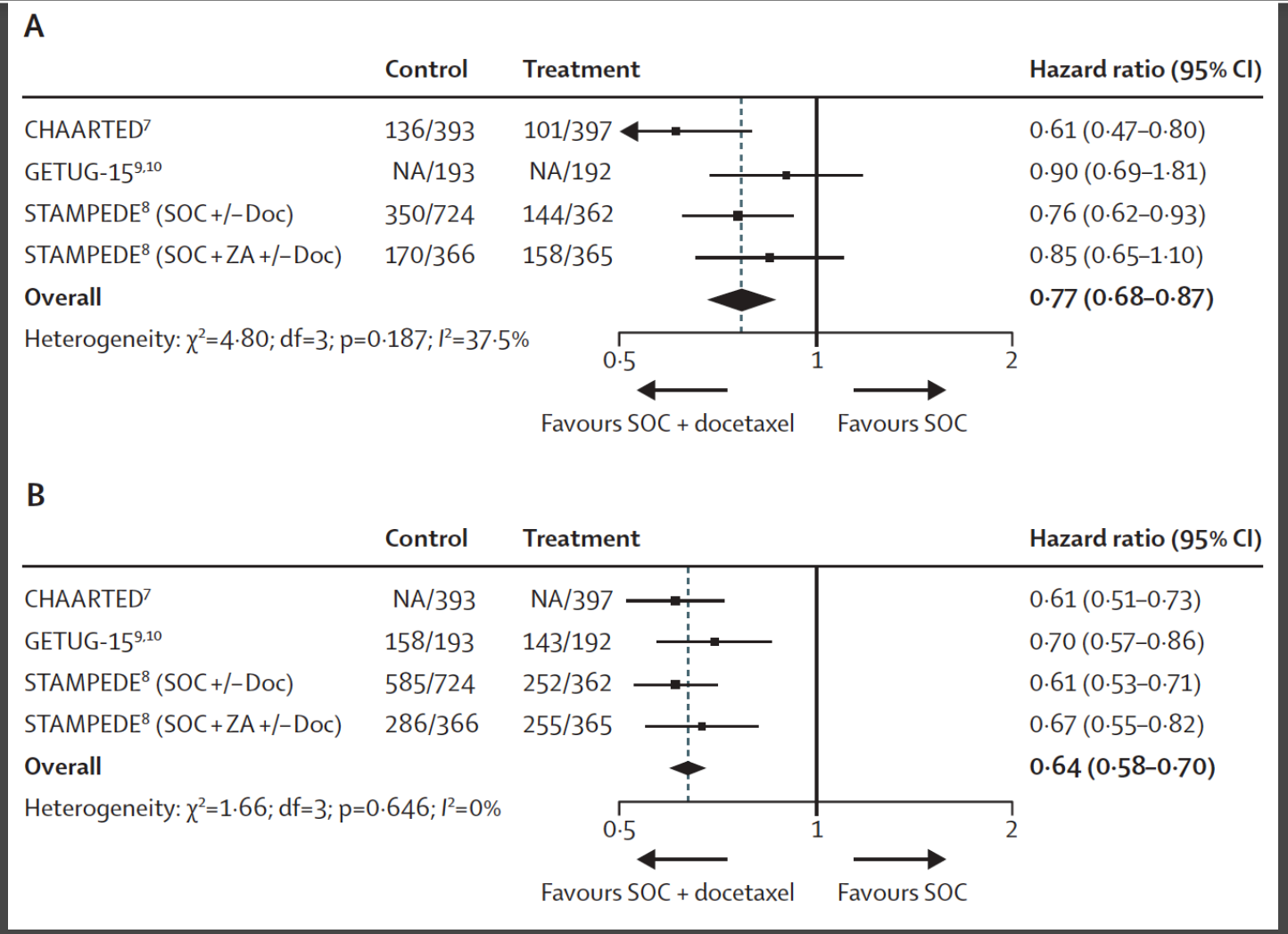




Meta-analysis in M1 Disease

Overall Survival

Progression-free Survival



Vale et al, Lancet Oncology, 2016

Caveats to Broad Treatment Recommendations

- Metastatic, hormone-sensitive disease is heterogeneous
  - Consistency in reporting low vs high volume variable between studies
- Most patients (~70%) presented with *de novo* metastatic disease
  - Different biology than previously treated and followed
- Few events in low volume cohorts
  - Wide confidence intervals and non-significant in CHAARTED
- Toxicity of docetaxel use

Tannock and Sternberg, Annals Oncology, 2015

Supporting Considerations

- Effect size for high vs low volume disease similar
  - HR 0.60 (0.45-0.81) for high volume
  - HR 0.60 (0.32-1.13) for low volume
- CHAARTED and STAMPEDE positive trials
  - In negative trials: positive subgroup analyses are generally deemphasized
  - In positive trials: should we emphasize negative subgroup analyses?
- Provocative data in M0 and in high risk locally advanced

Studies of Docetaxel in M0, High Risk Prostate Cancer

	GETUG-12	RTOG 0521	VA CSP553	SPCG12
n	413	612	297	790
Accrual period	2002-2006	2005-2009	2006-2011	2005-2009
Treatment	ADT + Doc/estramustine vs ADT	Doc + ADT vs ADT (RT in both)	Doc q 3 wk x six cycles plus prednisone vs observation	Doc q 3 wk x six cycles vs observation
Med f/u (yrs)	8.8	6	5.2	4.7
PFS HR (95% CI)	0.71 (0.54-0.94)	0.76 (0.58-0.99)	0.82 (0.59-1.14)	1.30 (0.98-1.72)
OS HR (95% CI)	NR	0.70 (0.51-0.98)	NR	NR

Scandanavian Prostate Cancer Group Trial 12
Docetaxel Compared with Observation After Prostatectomy

RRP→
- pT3b or pT4
- pT3a, GI ≥ 4+3
- pT2R1, GI ≥ 4+3
- PLND if PSA ≥ 10 ng/mL

Post-RP: PSA ≤ 0.5 ng/mL

RANDOMIZE

Observation
(Standard of Care)

Docetaxel 75 mg/m^2 q 21 days
(Duration of treatment = 6 cycles)

n=396

PI: G. Ahlgren

•Primary Endpoint: Time to PSA Progression

VA Cooperative Studies 553: Adjuvant Chemotherapy in High Risk Disease

cT1-T2b
↓
RRP→
- pT3b or pT4
- pT3a and G7-10
- pT2R1, G8-10
- Preop PSA > 20 ng/mL
- Must be Node (-)

Post-RP:
PSA ≤ 0.1

RANDOMIZE

n=297

1:1

Observation
(Standard of Care)

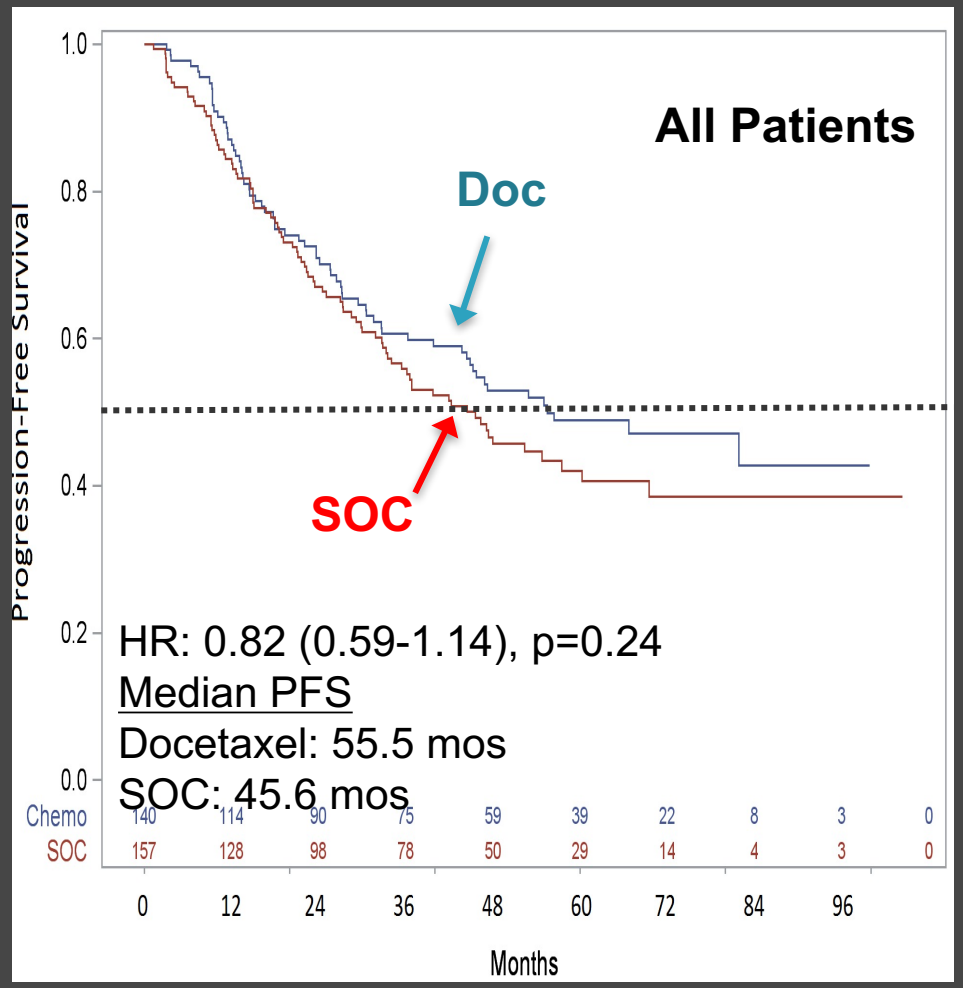
Docetaxel 75 mg/m^2 q 21 days + Prednisone

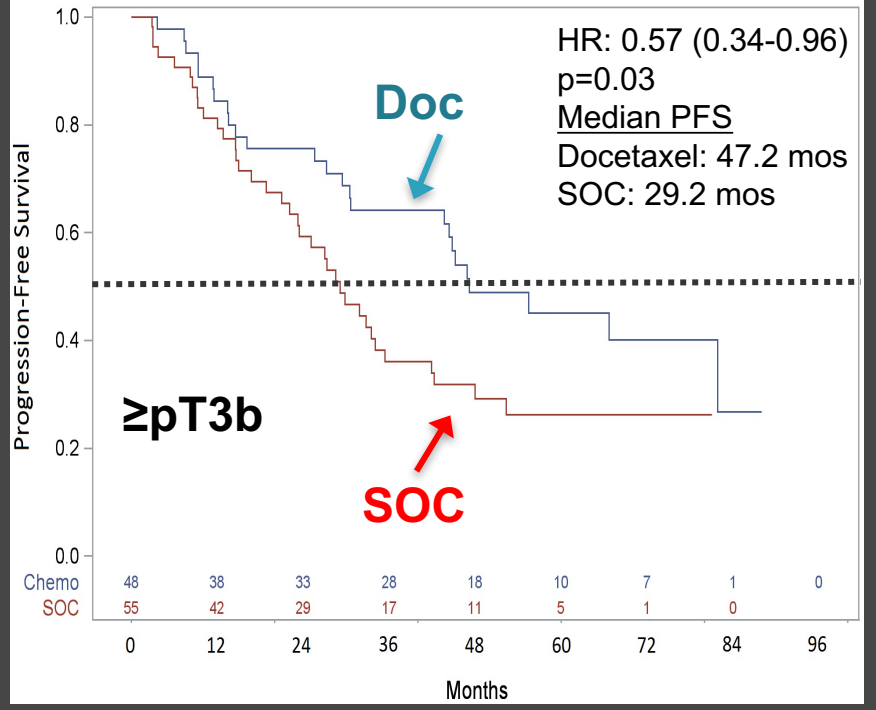
(Duration of treatment = 6 cycles)

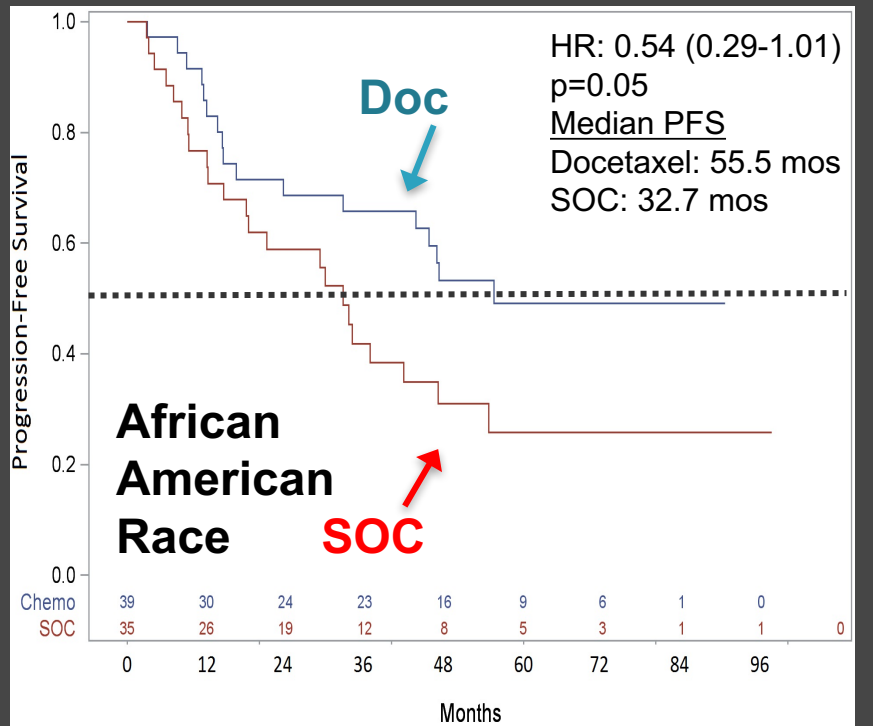
CSP 553

Primary Endpoint: Progression Free Survival

VA CSP553 Results







ESMO Guidelines

- ESMO Guidelines 2015
  - "ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy"
  - "Options for patients with high-risk or locally advanced prostate cancer include external beam RT plus hormone treatment [I, B] or RP plus pelvic lymphadenectomy"

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

RISK GROUP	INITIAL THERAPY
Very high: • T3b-T4 or • Primary Gleason pattern 5/ Gleason grade group 5 or • >4 cores with Gleason score 8–10/ Gleason grade group 4 or 5	EBRT[i] + ADT[m] (2–3 y; category 1)[q] or EBRT[i] + brachytherapy ± ADT[m] (2–3 y) or RP[j] + PLND (in select patients)[r] → Adverse feature(s) and no lymph node metastases:[k] EBRT[i] or Observation[l]; No adverse features or lymph node metastases; Lymph node metastasis: ADT[m] (category 1) ± EBRT[i] (category 2B) or Observation[l] or ADT[m] or observation for patients who are not candidates for definitive therapy
Regional: Any T, N1, M0	EBRT[i] + ADT[m] (2–3 y; category 1) or ADT[m]
Metastatic: Any T, Any N, M1	ADT[m]

Take Home Points

- Multiple Phase III trials of systemic chemotherapy in metastatic, hormone-sensitive prostate cancer
  - Differences in cohort demographics
    - Inclusion of non-metastatic patients, high vs low volume metastases
  - Study results conflicting
- Ideal patient for docetaxel and ADT in metastatic, hormone-sensitive setting
  - Newly diagnosed metastatic disease
  - High volume metastatic disease
  - Healthy with good PFS
- Promising PFS results in M0/high risk disease