Disease free survival (DFS) is a surrogate for Overall Survival (OS) in Localized Prostate Cancer (CaP).

INTERMEDIATE CLINICAL ENDPOINTS IN CANCER OF THE PROSTATE (ICECaP) Working Group

Background

- The most promising approach for decreasing the death rate from prostate cancer is by preventing relapse after localized therapy when the disease is of very low burden and most vulnerable to therapy (e.g. build upon the benefits of ADT plus radiation over radiation alone)
- The conduct of adjuvant CaP clinical trials is hampered by taking longer than a decade to reach the meaningful endpoint of OS.
- An intermediate clinical endpoint (ICE) that is a robust surrogate for OS could accelerate conduct of adjuvant trials
- There are potential challenges in identifying an ICE for CaP
  - heterogeneous disease with a variable natural history after disease relapse
  - heterogeneous treatments in the localized disease setting
  - impact of comorbidities and non-prostate cancer deaths in older population
- ICECaP is an international collaboration to determine whether an ICE for OS can be identified when assessing the efficacy of localized CaP therapy.

Objectives

- Determine whether disease free survival (DFS) is a surrogate for OS for localized prostate cancer
- Determine whether time to disease recurrence (TDR) is a surrogate for disease specific survival (DSS) for localized prostate cancer

Primary Objective (DFS as a surrogate for OS)

Secondary Objective (TDR as a surrogate for DSS)

Surrogate Endpoint

Disease Free Survival (DFS)
Events
local/regional progression
distant metastases
death from any cause

Time to Disease Recurrence (TDR)
Events
local/regional progression
distant metastases
death from CaP*

True Endpoint

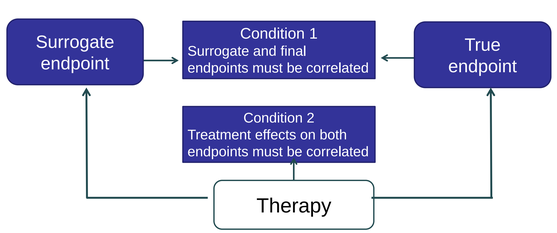
Overall Survival (OS)
Events
death from any cause

Disease Specific Survival (DSS)
Events
death from CaP*

*Non-CaP death is censored or considered as a competing risk

Study Design

- Meta analysis of pooled data from early stage CaP randomized trials.
- Systematic reviews of studies are performed following the PRISMA statement (http://www.prisma-statement.org).
- Trial Eligibility:
  Randomized, controlled trials for localized CaP
  Conducted in Canada, UK, Europe, Australia/New Zealand, US
  Studies with accrual completed /terminated
  Exclude trials that have a primary endpoint such as safety, toxicity, QOL, feasibility, dosimetry, patient decision making without systematic long-term follow-up
- Buyse's two-stage validation model (Buyse et al, 2000, 2011)



102 trials Identified* (completed or ongoing)
*as of June 2013

→ Letters sent 99 trials

- Not Suitable (36 trials)
- Still in Discussion (8 trials)
- Future participate*(12 trials)

*Pending publication/data maturity

→ Agreed to participate (43 trials: 28,905 pts)

→ 28 trials with IPD on 22,825 in repository

→ **24 trials with 21,140 pt data suitable for DFS analysis**

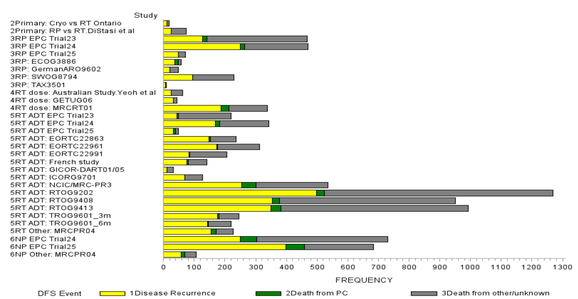
*No. of units for analyses = 31 as 5 trials were split to multiple units by type of primary therapy or if there were multiple experimental arms.

	N	%
Type of treatment		
Comparing primary therapies	201	1
RP+/-Adj RT or ADT	5518	26
RT dose	1366	6
RT+/-ADT	11619	55
No primary therapy +/- ADT/other	2436	12
Age at randomization		
NA	14	0
64 or younger	6043	29
65-74	11857	56
75 or older	3226	15
D'Amico risk group		
NA	1618	8
Low	2096	10
INTM	4453	21
High	12973	61

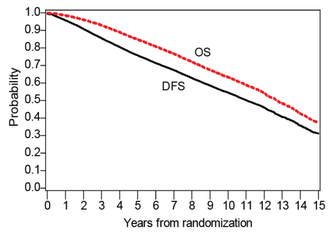
		Type of First Failure Event					
		Disease recurrence				PC death	Non-PC death /unknown
	No. (%) of Events	Local/ Regional	Distant Metastasis**	Unknown sites***	Total		
OS	7996(37.8)					2269(28)	5727(72)*
DSS	2269(10.7)					2269(100)	
DFS	9509(45.0)	1560	1511	1233	4304(45)	381(4)	4824(51)
TDR	4685(22.2)	1560	1511	1233	4304(92)	381(8)	

*other causes: n=5082 (64%); unknown cause: n=645 (8%); **if metastasis occurs prior to local/regional recurrence or within 3 months of a local/recurrence event; ***Recurrence site cannot be determined for 4 studies (EPC24, EPC25, ECOG3886, Australian Study Yeoh et al).

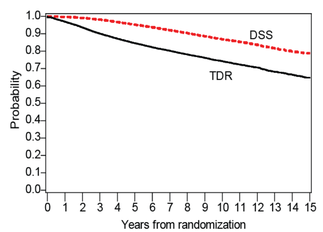
Type of first failure event for DFS by Study



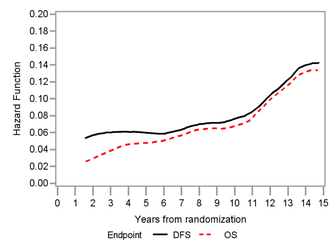
Kaplan Meier estimates of OS and DFS (all patients)



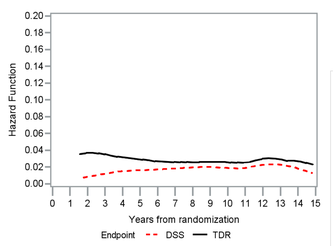
Kaplan Meier estimates of DSS and TDR (all patients)



Death and DFS failure hazard over time (all patients)



DSS and TDR failure hazard over time (all patients)



Condition 1: Surrogate and final endpoints must be correlated

Correlation at the patient level estimated from Plackett's copula

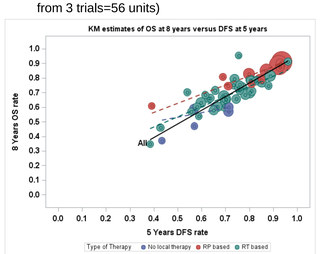
	Between DFS and OS		Between TDR and DSS	
	No. of units (patients)	Kendall's Tau (95%CI)	No. of units (patients)	Kendall's Tau (95%CI)
All patients	31(21,140)	**0.85(0.85,0.86)**	28(20,496)*	**0.68(0.67,0.69)**
RT based	21(13,186)	**0.84(0.83,0.84)**	19(12,770)	**0.66(0.65,0.67)**

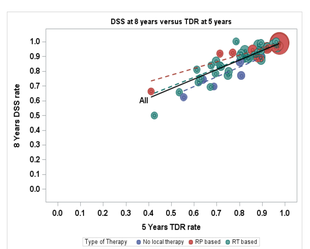
*excluding 3 studies with number of PC- death <3

R-square from weighted linear regression of Kaplan Meier estimates of endpoints

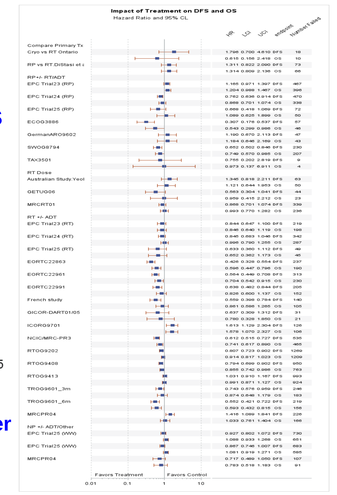
	OS at 8 yrs versus DFS at 5 yrs		DSS at 8 yrs versus TDR at 5 yrs	
	No. of unit	R-square (95% CI)	No. of unit	R-square (95% CI)
All	56*	**0.86 (0.78,0.90)**	56*	**0.80 (0.70,0.85)**
RT-based	37	**0.68 (0.48,0.78)**	37	**0.71 (0.52,0.80)**

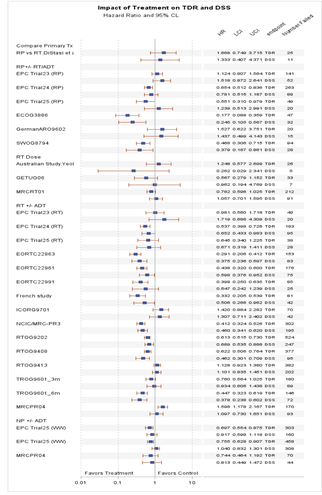
*The analysis unit comprised of 24 trials with 31 units and when arm specific units are used excluding 3 studies with median follow-up < 6 years, we have 56 units (31units x 2 arms - 6arms from 3 trials=56 units)



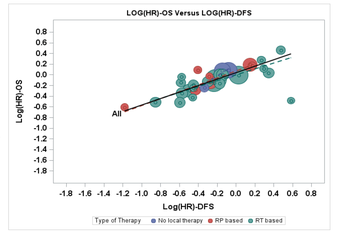


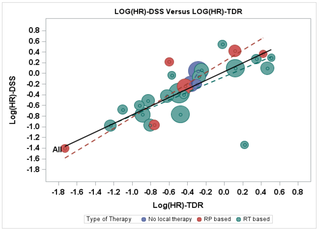
Condition 2: Treatment effects on both endpoints must be correlated*





*Hazard ratios were estimated from Cox proportional hazards models





R-square from weighted linear regression of treatment effects (log-HR) on endpoints

	Log(HR)-OS versus Log(HR)-DFS		Log(HR)-DSS versus Log(HR)-TDR	
	No. of units	R-square (95% CI)**	No. of units	R-square (95% CI)**
All	31	**0.73 (0.53,0.82)**	28*	**0.63 (0.36,0.75)**
RT-based	21	**0.75 (0.48,0.84)**	19	**0.63 (0.27,0.77)**

*excluding 3 studies with number of PC- death <3

Conclusions and Future Work

- DFS can be used as a surrogate of OS and TDR as a surrogate of DSS in both RT and RP based studies.
- The trend is consistent when RT based trials are analyzed separately.
- Future work:
  - Determine surrogacy threshold effect
  - Assess surrogacy of Metastasis Free Survival
  - Pharmaco-economic analyses of using surrogate and preventing relapses

Acknowledgments

Funding: Prostate Cancer Foundation (PCF) Challenge Award; Grants from Industry (awarded to PCF or DFCI: Millennium-Takeda, Sotio, Janssen, Astellas/Medivation, Sanofi. *Industry funders: no role in the writing.*
Executive Committee: Christopher Sweeney (DFCI)-Chair; Philip Kantoff (PCF); Howard Soule (PCF)
Writing Committee:
Co-ordinating Center at Dana Farber Cancer Institute (DFCI): Christopher Sweeney (Chair DFCI)), Brandon Bernard (DFCI), Mari Nakabayashi (DFCI), Meredith Regan (DFCI), Wanling Xie (DFCI),
Members Independent of Coordinating Center overseeing Statistical Analysis Plan: Marc Buyse (International Drug Development Institute), Susan Halabi (Duke University), Philip Kantoff (PCF), A. Oliver Sartor (Tulane University), Howard Soule (PCF).
ICECaP Working Group Members (in alphabetical order) Ove Andren, John Armstrong, Donald Berry, Michel Bolla, Marc Buyse, Simon Chowdhury, Noel Clarke, Laurence Collette, Matthew Cooperberg, Jim Denham, Mario Eisenberger, James Dignam, Karim Fizazi, Boris Freidlin, Martin Gleave, Muriel Habibian, Susan Halabi, Julia Hayes, Nick James, Jonathan Jarow, Nancy Keating, Philip Kantoff, Gary Kelloff, Laurence Klotz, Suhui Li, Himu Lukka, Brandon Mahal, Malcolm Mason, Andrea Miyahira, Mari Nakabayashi, Wendy Parulekar, Tomas Philipson, Meredith Regan, Howard Sandler, Oliver Sartor, Peter Scardino, Howard Scher, Richard Simon, Jonathan Simons, Eric Small, Howard Soule, Christopher Sweeney, Matthew Sydes, Catherine Tangen, Ian Thompson, Bertrand Tombal, Anders Widmark, Thomas Wiegel, Scott Williams and Wanling Xie