VALIDATION OF METASTASIS-FREE SURVIVAL AS A SURROGATE ENDPOINT FOR OVERALL SURVIVAL IN LOCALIZED PROSTATE CANCER IN THE ERA OF DOCETAXEL FOR CASTRATION RESISTANT PROSTATE CANCER

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HIGHLIGHTS

- Metastasis-free survival (MFS) remains a valid surrogate for overall survival (OS) in localized prostate cancer
- This was amongst patients with greater access to docetaxel and other systemic therapies for advanced disease
- This has important implications for design and endpoints of (neo)adjuvant trials in localized prostate cancer

ABSTRACT

Background: Prior work from the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) consortium (ICECaP-1) demonstrated that metastasis-free survival (MFS) is a valid surrogate for overall survival (OS) in localized prostate cancer (PCa). This was based on data from patients treated predominantly before 2004, prior to docetaxel being available for the treatment of metastatic castrate-resistant prostate cancer (mCRPC). We sought to validate surrogacy in a more contemporary era (ICECaP-2) with greater availability of docetaxel and other systemic therapies for mCRPC.

Patients & Methods: Eligible trials for ICECaP-2 were those providing individual patient data (IPD) after publication of ICECaP-1 and evaluating adjuvant/salvage therapy for localized PCa, and which collected MFS and OS data. MFS was defined as distant metastases or death from any cause, and OS defined as death from any cause. Surrogacy was evaluated using a meta-analytic two-stage validation model, with an R^2 ≥0.7 defined *a priori* as clinically relevant.

Results: 15,164 IPD from 14 trials were included in ICECaP-2, with 70% of patients treated after 2004. Median follow-up was 8.3 years and median post-metastasis survival was 3.1 years in ICECaP-2, compared to 1.9 years in ICECaP-1. For surrogacy condition 1, Kendall's tau was 0.92 for MFS with OS at the patient-level, and R^2 from weighted linear regression (WLR) of 8-yr OS on 5-yr MFS was 0.73 (95% CI 0.53-0.82) at the trial level. For condition 2, R^2 was 0.83 (0.64-0.89) from WLR of log(HR)-OS on log(HR)-MFS. The surrogate threshold effect on OS was an HR(MFS) of 0.81.

Conclusion: MFS remained a valid surrogate for OS in a more contemporary era, where patients had greater access to docetaxel and other systemic therapies for mCRPC. This supports the use of MFS as the primary outcome measure for ongoing adjuvant trials in localized PCa.

INTRODUCTION

Globally, prostate cancer is one of the leading causes of cancer in men and accounted for more than 375,000 deaths in 2020.[1] The majority of prostate cancers in Western Europe and North America are localized at diagnosis and potentially curable with surgery (radical prostatectomy, RP) or radiotherapy (RT). For the cancers that relapse after local therapy, there still exists a potential for cure in a proportion of cancers, typically by means of salvage RT, often with concurrent androgen deprivation therapy (ADT).[2-4] However, the long natural history of localized prostate cancer – where median survival is typically measured in decades[5] – makes it difficult to conduct practice-changing trials in the localized setting that use the irrefutable “gold-standard” endpoint of OS.

The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) consortium was established in 2012 with the aim of pooling individual patient data (IPD) from randomized trials conducted in localized prostate cancer and attempting to develop and validate an intermediate clinical endpoint (ICE) with strong surrogacy for OS, thereby helping expedite trial conduct.[6] Prior work from ICECaP (“ICECaP-1”) showed that metastasis-free survival (MFS) is a valid surrogate for OS, satisfying both conditions of a widely-accepted surrogacy criterion, with surrogacy being independent of type of local therapy (RP or RT) and receipt or duration of adjuvant therapy[7]. This finding has since been validated in a trial-level meta-analysis.[8] As a result, MFS has been adopted as the primary endpoint for several ongoing trials evaluating systemic therapy with RP and RT in the localized setting, and served as the revised primary endpoint for the STAMPEDE trial evaluating the addition of abiraterone

+/- enzalutamide to ADT and radiotherapy for high-risk nonmetastatic prostate cancer.[9] Results from this trial confirmed that MFS was a viable ICE and a valid surrogate for OS, with the hazard ratio for MFS (0.54) producing almost exactly the hazard ratio for OS (0.63) that was predicted by the ICECaP-1 surrogate threshold effect.[10]

ICECaP-1[7] utilized IPD from more than 12,000 patients in 19 trials, the majority of whom were accrued between 1987-2004, an era during which mitoxatrone and corticosteroids formed the basis of management for metastatic castration resistant prostate cancer (mCRPC). In 2004, docetaxel was shown to significantly improve OS in mCRPC[11] and since then, several other therapies, including cabazitaxel, novel hormonal agents (abiraterone, apalutamide, enzalutamide, darolutamide), radiopharmaceuticals and PARP inhibitors have all demonstrated an OS benefit in CRPC.[12] In ICECaP-2, we sought to validate the surrogacy of MFS and time to metastasis (TTM) on OS and disease-specific survival (DSS) respectively by collecting IPD from more contemporaneous trials in localized prostate cancer, where patients would have had access to at least docetaxel, and potentially other life-prolonging therapies, for mCRPC.

PATIENTS & METHODS

Trial selection criteria

Between May 2020 and February 2023, the ICECaP-2 data repository collected IPD from 16,125 unique patients from 15 more recently completed randomized, controlled trials for localized prostate cancer. Eligible trials for this MFS surrogacy validation analysis were trials identified at the time of ICECaP-1 but from whom data was not available for use in that analysis.[7] All trials were evaluating adjuvant or early salvage therapies for localized or locally advanced prostate cancer, and which

collected the endpoints of interest (MFS and OS). The search strategy to enable identification of potentially eligible trials has been previously described and followed PRISMA guidelines.[7]

Definition of endpoints

MFS was measured from the date of randomization to date of first evidence of distant metastases (confirmed by conventional imaging – CT, MRI and/or bone scan – or histology) or death from any cause; or censored at the date of last follow-up. TTM was defined analogously to MFS but non-prostate cancer deaths without prior progression were censored or counted as competing risk. OS was measured from the date of randomization to death from any cause, censored at the date of last follow-up in patients who were alive. DSS was defined similarly as OS, but non-prostate deaths were censored or considered as competing risk in sensitivity analyses.

Surrogacy criteria

We evaluated the surrogacy of MFS with OS using a meta-analytic two-stage validation model as previously described.[7, 13] Two conditions must hold to claim MFS is a surrogate for OS. Condition 1 requires MFS and OS to be correlated. Condition 2 requires that the treatment effects on both endpoints are correlated. The validity of the surrogate is reflected by the strength of both correlations. To be consistent with our previous work, we again defined *a priori* that an $R^2 \geq 0.7$ was required to establish clinically relevant surrogacy in the contemporary era.

Condition 1 was tested at both patient and trial levels. At the patient level, the associations of OS with MFS were evaluated through a bivariate Clayton copula model over the entire follow-up of IPD. Kendall's tau (range 0-1) quantified the correlation between the endpoints. At the trial level, we

performed weighted linear regression (WLR) analyses of (1) trial- and arm-specific 8-year OS rates on 5-year MFS rates and (2) trial- and arm-specific restricted mean survival time (RMST) of OS at 8 years on RMST of MFS at 5 years. Regressions were weighted by the inverse variances of the 5-year estimates of the MFS. The R^2 was used to quantify the proportion of variance explained by the regressions.

Condition 2 was tested at the trial level. Cox proportional hazards regression models estimated the study-specific treatment effects—that is, the natural log (hazard ratio [HR]) of experimental versus control arm —on the MFS and OS. We then fit a WLR of log(HR)-OS on log(HR)-MFS across trials. Regressions were weighted by the inverse variance of the log(HR)-MFS, and R^2 was used to quantify the proportion of variance that was explained by the regressions.

On the basis of WLR between treatment effects, Surrogate Threshold Effect (STE) is defined based on the minimum treatment effect on the surrogate (HR-MFS) necessary to predict a significant OS benefit, corresponding to the upper 95% prediction limit for OS HR lower than 1.

The same approach was applied to the surrogacy analysis of TTM for DSS as a sensitivity analysis where endpoints of patients with non-prostate cancer deaths were censored. We also performed a sensitivity analysis to estimate trial-level correlation between cumulative incidence estimates of TTM and prostate cancer specific mortality (PCSM), and between the sub-distribution treatment effect HR (sHR) estimates for TTM and PCSM from competing risk models for which non-prostate cancer deaths were considered as the competing risk for each endpoint.

All analyses were performed using SAS Software version 9.4 (SAS Institute Inc, Carey, NC) and the R packages (www.r-project.org).

RESULTS

Trial and Patient Characteristics

For this analysis, 15,164 IPD from 14 trials with 21 treatment comparisons were included in ICECaP-2 (**Supplementary Figure S1**). Most patients were enrolled from 2005 to 2016 and the median follow-up was 8.3 years. Nine out of 14 trials were RT-based trials (for 16 treatment comparisons); five trials (for 6 treatment comparisons) investigated the benefit of docetaxel added to ADT and RT, while one trial investigated novel hormonal therapies added to ADT and RT (abiraterone with or without enzalutamide [**Supplementary Tables S1 and S2**]).

There were 3,953 events for the MFS endpoint: 44% metastasis, 4% prostate cancer deaths without recorded metastasis, and 52% non-prostate cancer deaths (**Supplementary Table S3**). From the Kaplan-Meier estimates, 5-year MFS was 86% (95% CI 86-87), and 8-year OS was 81% (95% CI 80-81, **Supplementary Table S4** and **Supplementary Figure S2**). For patients who were reported to have a metastasis (n=1,727 of 3,953 MFS events), median post-metastasis survival was 3.1 years (95% CI 2.8-3.3).

Surrogacy Condition 1: Correlation Between Endpoints

For surrogacy condition 1, the Kendall's tau correlation over the entire follow-up of IPD was 0.92 (95% CI 0.92-0.93) for MFS with OS. When non-prostate cancer deaths were censored, the correlation of TTM with DSS was 0.93 (95% CI 0.92-0.93). The Kendall's tau correlations between endpoints were also similar in subgroup analyses by type of primary therapies (RP or RT) or in patients who were allocated to docetaxel or novel hormonal therapies (**Table 1**).

The correlation between endpoints was also tested using trial-arm level estimates (**Table 2**). The R^2 was 0.73 (95% CI 0.53-0.82) from WLR of 8-year OS on 5-year MFS rates and was 0.79 (95% CI 0.62-0.86) of 8-year DSS on 5-year TTM rates across trials and treatment arms (**Figure 1**). Results were consistent for endpoint correlations when non-prostate cancer deaths were treated as a competing risk or in a WLR analysis of 8-year RMST of OS on 5-year RMST of MFS.

Surrogacy Condition 2: Correlation Between Treatment Effects on Endpoints

For condition 2, the R^2 from the WLR of log(HR)-OS on log(HR)-MFS was 0.83 (95% CI 0.64-0.89). When non-prostate cancer deaths were censored, the R^2 was 0.63 (95% CI 0.28-0.77) for the WLR of log(HR)-DSS on log(HR)-TTM. Similar R^2 were observed when the analysis was restricted to the 9 RT-based trials across 16 treatment comparisons (**Table 3**). Forest plots showing trial-specific treatment effects for each endpoint of interest are shown in **Supplementary Figure S3**.

Surrogate Threshold Effect

The STE was a HR(MFS) of 0.81 on OS (**Figure 2A**) and a HR(TTM) of 0.68 on DSS (**Figure 2B**), which indicates that a risk reduction of 19% and 32% would predict a significant treatment effect on OS and DSS, respectively.

Summary comparisons of the findings from ICECaP-1[7] and ICECaP-2 are shown in **Table 4**.

DISCUSSION

Delaying or preventing the emergence of metastases seen on conventional imaging was shown to be a valid surrogate for OS in men with localized, predominantly high-risk prostate cancer who mainly received treatment prior to 2005 in prior work from ICECaP-1.[7] This finding has informed the design and conduct of modern adjuvant trials in high-risk disease. In this analysis, we show that the surrogacy of MFS for OS remains valid in localized prostate cancer during a more contemporary era with ~70% of patients receiving treatment after 2005, the year after which docetaxel received regulatory approval for the treatment of mCRPC. This IPD analysis from ICECaP-2 provides corroborative evidence to support the use of MFS as a primary endpoint for ongoing adjuvant trials evaluating newer agents in localized prostate cancer.

Several findings from this study deserve further emphasis. ICECaP-2 collated IPD from 14 randomized trials and 15,164 patients across 21 treatment comparisons, which are very similar to the IPD analysis from ICECaP-1. Nearly 70% of patients in ICECaP-2 were randomized after 2005 (including ~30% after 2010), compared to <40% in ICECaP-1 (where no patient was randomized after 2011). The majority of patients in ICECaP-2 developing a metastatic event would therefore have had the opportunity to receive docetaxel[11] and potentially other proven life-prolonging therapies such as abiraterone,[14] enzalutamide,[15] cabazitaxel[16] and Ra-223,[17] all of which were approved between 2010-2013 for metastatic prostate cancer. This is borne out by the increase in median time from metastatic event to death from 1.9 years in ICECaP-1[7] to 3.1 years in the current ICECaP-2 analysis, reflective of the greater availability of docetaxel and other life prolonging therapies for mCRPC.

The surrogacy effects in ICECaP-2 were on par with those observed in ICECaP-1. At the patient level, Kendall's tau was 0.92 compared to 0.91 in ICECaP-1 while the correlation (R^2) between 5-year MFS and 8-year OS at the trial level was 0.73 in ICECaP-2, which was above the prespecified 0.7

threshold we defined as clinically relevant. This is similar to the result seen in a trial-level meta-analysis[8] though lower than the R^2 of 0.83 between 5-year MFS and 8-year OS seen in ICECaP-1. Similarly, the surrogacy effects at trial level were slightly weaker in ICECaP-2 compared to ICECaP-1 (MFS:OS R^2 of 0.83 vs. 0.92; TTM:DSS R^2 of 0.63 vs.0.89; STE for OS: HR [MFS] of 0.81 vs. 0.88; STE for DSS: HR [TTM] of 0.68 vs.0.74). It is likely that this can be explained by the lower proportion of high-risk patients (51% vs. 66%), shorter follow-up (median 8.3 vs 9.9 years) and longer post-metastasis survival (3.1 vs. 1.9 years) in ICECaP-2 compared to ICECaP-1, which translated to a lower number of events for each endpoint. The trial level correlation of TTM with DSS could be more adversely impacted by the reduced number of events because the estimate of hazard ratio for DSS is sensitive when the risk (hazard) of CaP-death was extremely low (overall event rate of 6% for a median follow-up of 8.3 years). As such, the 95% confidence interval estimates are wide (particularly for the surrogacy of TTM on DSS) and include the pre-specified R^2 of 0.7; nevertheless, the observed R^2 of 0.83 and 0.63 (for MFS:OS and TTM:DSS respectively) correspond to a correlation (r) of 0.9 and 0.8 and are clinically meaningful.

It is important to appreciate the context in which MFS has been validated as a surrogate for OS. Both ICECaP-1 and ICECaP-2 collated IPD from trials evaluating different therapeutic strategies (i.e. different RT doses, receipt and duration of adjuvant therapy, type of adjuvant therapy) in localized prostate cancer or the salvage setting after definitive local therapy. As such, MFS can only be reliably used as a surrogate endpoint in these settings. MFS has been used as the primary endpoint in trials assessing novel hormonal agents in the non-metastatic (M0) CRPC setting[18-20] and positive MFS data from these studies were used in obtaining regulatory approval, while a significant improvement in MFS was noted with enzalutamide +/- ADT compared to ADT alone in patients with high-risk biochemical recurrence after prior local therapy.[21] While the three trials in M0 CRPC ultimately showed an OS benefit, formal surrogacy evaluation of MFS for OS in this disease setting is needed

since the MFS:OS surrogacy defined by ICECaP has been derived from the localized prostate cancer setting. This setting has a different biology and risk of death from prostate cancer and other non-cancer causes than high-risk biochemical recurrence and M0 CRPC, which are farther along the prostate cancer disease trajectory. This can be alluded to by the MFS hazard ratios in the three M0 CRPC studies ranging between 0.28-0.41, which ultimately only translated to OS hazard ratios of 0.69-0.78. Formal evaluation of the surrogacy of MFS for OS is required to define the STE in each unique clinical setting.

An additional point of consideration is that patients in trials contributing to ICECaP were staged and followed with conventional imaging, and therefore, metastatic disease was detected as such and not by more sensitive imaging modalities (such as whole-body MRI or PSMA-PET). PSMA-PET is now frequently used in many regions in staging high-risk disease as well as in detection of metastases after local therapy,[22] but whether detection of metastases on PSMA-PET that are not visualized on CT and bone scintigraphy equates to a true MFS event is unclear. It is possible that these PSMA-positive, conventional scan-negative lesions have more indolent disease biology and/or longer natural history than lesions that are detectable via conventional imaging in addition to PSMA-PET or it may simply be the case that the same metastases are “time-shifted” but with no effect on the surrogacy link.[23] The relationship between PET-MFS and conventional imaging-MFS on the one hand and PSA progression on the other needs to be explored as the latter previously been shown to not be a viable surrogate for OS in the localized disease setting.[24] Also, based on the median duration from emergence of metastasis to death of 3.1 years, it is likely that most of the MFS events we observed were patients developing metastases in the castrate-resistant setting (eg. after receiving ADT for rising PSA after local therapy, and then progressing to non-metastatic CRPC and finally mCRPC), which are very different to the low volume metastatic lesions often detected on PSMA-PET in the recurrent setting where PSA is rising with intact testosterone. Further work from ongoing adjuvant

trials, which allow PSMA-PET for disease assessment in addition to conventional imaging, is needed to confirm or refute this, and as such, MFS can only be considered a reliable surrogate for OS when metastatic events are observed using conventional scans at this time.

The strengths of these analyses are the availability of IPD from a large number of randomized trials with sufficient follow-up (median 8.3 years) to permit assessment of OS, accrual of the vast majority of patients in the docetaxel era for mCRPC, and the consistency of the results across RP and RT-based trials. Moreover, this dataset uniquely allowed us to characterize the advances in systemic therapy for mCRPC over the past 20 years, as highlighted by the increase in median post-metastasis survival between ICECaP-1 and ICECaP-2. As such, despite greater availability and impact of systemic therapies for mCRPC, MFS was a surrogate for OS in the localized disease setting. Given that this surrogacy is independent of class of drug use in the adjuvant setting, MFS is a clinically valid and meaningful endpoint for studies evaluating novel (neo)adjuvant strategies in localized prostate cancer.

Key limitations of this work include the lack of specific data on the proportion of patients receiving novel therapies for metastatic disease, relatively short follow-up for some of the included trials (notably CHHIP and some of the arms of STAMPEDE) and lack of access to data from trials that formed part of the initial search strategy but from which we ultimately did not receive IPD. Furthermore, less than half of the included trials evaluated adjuvant therapies other than ADT, with only two assessing the impact of novel hormonal agents: further validation of these findings with use of these agents in the adjuvant setting is needed. Finally, only five trials were RP-based (with four of these evaluating postoperative RT) and therefore, a formal analysis for surrogacy based on RP or RT as local therapy could not be performed.

In summary, the results presented here from an IPD of more than 15,000 patients treated in 14 trials in the ICECaP-2 database validate the surrogacy of MFS for OS in patients with localized prostate cancer treated in an era of greater access to docetaxel and other life-prolonging therapies for metastatic prostate cancer. These, together with the results from ICECaP-1, confirm the suitability of MFS as a primary endpoint for ongoing adjuvant studies in localized prostate cancer. Caution should be used when MFS is used outside of this disease state and when metastases detected on novel (PSMA-PET), but not conventional, imaging are counted as events.

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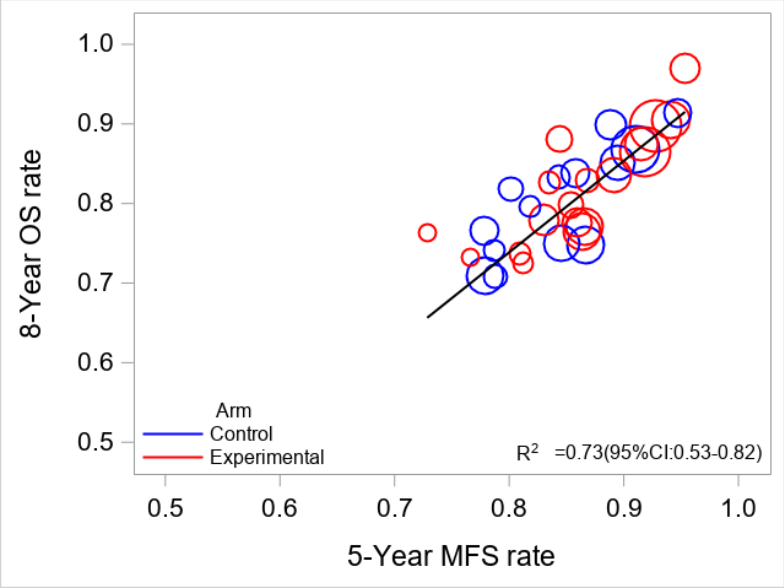
TABLES & FIGURES

Figure 1 – Bubble plots and regressions of (A) 8-year overall survival (OS) on 5-year metastasis-free survival (MFS), (B) 8-year disease specific survival (DSS) on 5-year time to metastasis (TTM). All rates were Kaplan-Meier estimates by trial and treatment arm. Circle size and regression were weighed by inverse variance of the 5-year rate estimate for the surrogates.

(A)



(B)

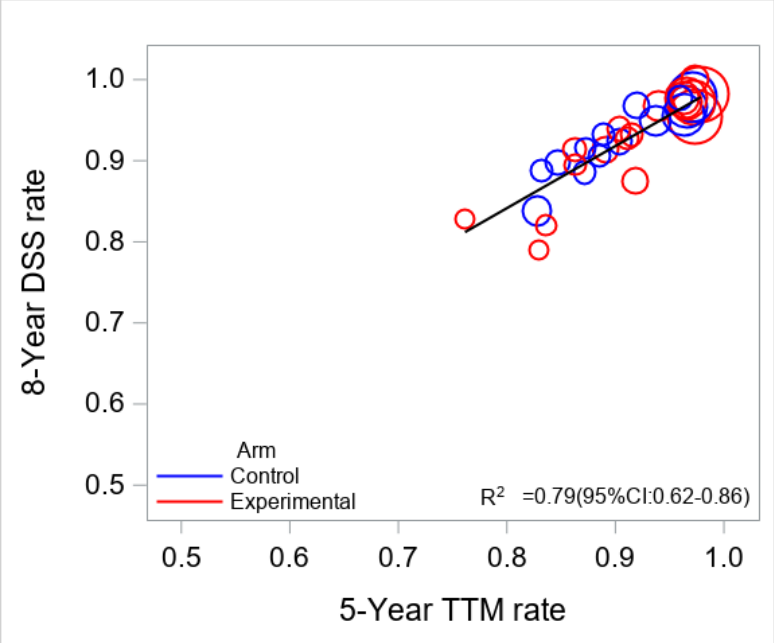


Figure 2 – Bubble plots and regressions of (A) hazard ratio for overall survival (OS-HR) on hazard ratio for metastasis-free survival (MFS-HR); (B) hazard ratio for disease-specific survival (DSS-HR) on hazard ratio for time to metastasis (TTM-HR). Cox proportional hazards regression estimated HR for each study, and values were natural logarithm transformed. Circle size and regression were weighted by inverse variance of log(HR) estimates for MFS or TTM.

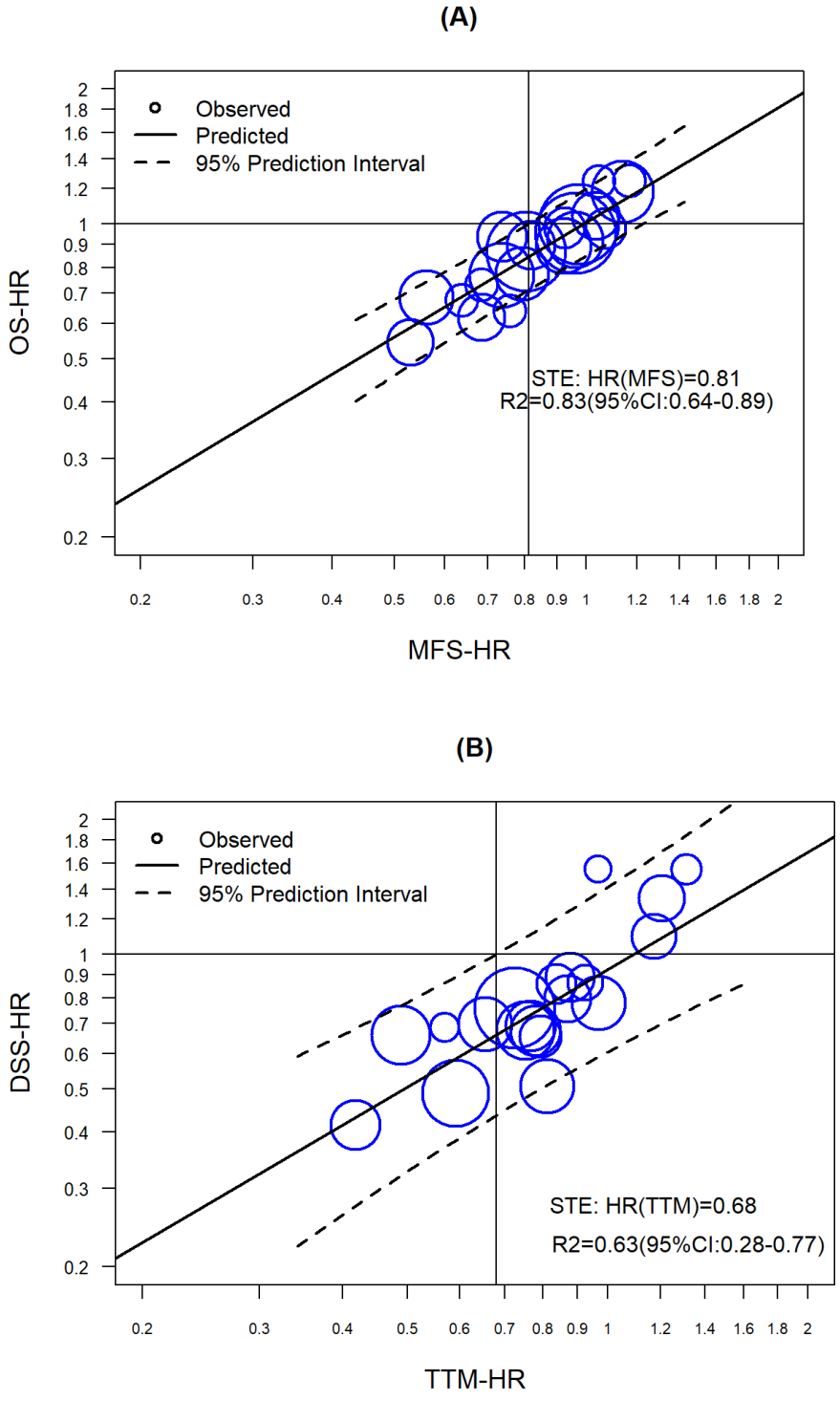


Table 1 – Surrogacy condition 1: Correlation between endpoints using patient-level data

	Correlation of OS and MFS (Non-CaP deaths counted as events)			Correlation of DSS and TTM (non-CaP deaths censored)		
	No. of trials	**No. of unique subjects**	**Kendall's *tau* (95% CI)**	**No. of trials**	**No. of unique subjects**	**Kendall's *tau* (95% CI)**
All patients	14	15,164	0.92(0.92-0.93)	13*	14,831	0.93(0.92-0.93)
RP-based trials	5	3,628	0.89(0.88-0.90)	4*	3,295	0.89(0.88-0.91)
RT based trials	9	11,536	0.92(0.92-0.93)	9	11,536	0.94(0.93-0.94)
Patients allocated to docetaxel	6	1,364	0.88(0.86-0.89)	6	1,364	0.91(0.89,0.93)
Patients allocated to novel hormonal therapy**	2	876	0.93(0.93-0.93)	2	876	0.93(0.93,0.93)
in ICECaP high risk population	13	7,670	0.89(0.88-0.89)	12*	7,604	0.91(0.90-0.92)

*Exclude 1 trial that reported <3 CaP deaths

** Abiraterone with or without Enzalutamide

CaP: Cancer of prostate, OS: Overall survival, DSS: Disease specific survival, MFS: Metastasis-free survival, TTM: Time to metastasis, RP: Radical prostatectomy, RT: Radiation therapy

Table 2 – Surrogacy condition 1: Correlation between endpoints using trial-arm level estimates

	All trials (32 Arms*/14 trials)	RT-based trials (22 Arms*/9 trials)
	R^2 (95% CI)	R^2 (95% CI)
Non-CaP deaths counted as events		
WLR of 8-year OS on 5-year MFS	0.73 (0.53-0.82)	0.77 (0.53,0.86)
WLR of 8-year RMST(OS) on 5-year RMST(MFS)	0.69 (0.46-0.79)	0.81 (0.61,0.88)
Non-CaP deaths censored		
WLR of 8-year DSS on 5-year TTM	0.79 (0.62-0.86)	0.84(0.65,0.90)
WLR of 8-year RMST(DSS) on 5-year RMST(TTM)	0.83 (0.68-0.88)	0.91 (0.80,0.94)
Non-CaP deaths as competing risk		
WLR of 8-year PCSM on 5-year TTM	0.80 (0.64-0.86)	0.84 (0.66,0.90)
WLR of 8-year RMTL(PCSM) on 5-year RMTL(TTM)	0.83 (0.70-0.89)	0.91 (0.81,0.94)

*The analysis units were treatment arms. Overall, there were 35 unique arms from 14 trials: 3 arms from CHIPP, 8 arms from STAMPEDE (1 control+7 experimental arms), and 24 arms from the remaining 12 trials. For RT-based trials, there were 25 unique arms from 9 RT-based trials (Supplemental Table S1). The analysis excluded 3 experimental arms from the STAMPEDE trial (RT-based) with median follow-up less than 5 years (Arm B - "RT + AADT ≥2year + Zoledronate" and Arm E – "RT + AADT ≥2y + Zoledronate/Docetaxel") or maximum follow up <7 years (Arm J - RT + AADT ≥2y + Abiraterone/Enzalutamide).

CaP: Cancer of prostate, OS: Overall survival, DSS: Disease specific survival, PCSM: prostate cancer specific mortality, MFS: Metastasis-free survival, TTM: Time to metastasis, RMST: Restrict mean survival time, RMTL: Restrict mean time loss, WLR: Weighted linear regression

Table 3 – Surrogacy condition 2: treatment effects on endpoints are correlated

	All trials		RT-based trials	
	No. of comparisons /No. of trials	**R^2(95% CI)**	**No. of comparisons /No. of trials**	**R^2(95% CI)**
Non-CaP deaths counted as events				
WLR of $Log(HR)_{OS}$ on $Log(HR)_{MFS}$	21/14	0.83(0.64-0.89)	16/9	0.87(0.65-0.92)
Non-CaP deaths censored				
WLR of $Log(HR)_{DSS}$ on $Log(HR)_{TTM}$	20/13*	0.63(0.28,0.77)	16/9	0.62(0.22,0.77)
Non-CaP deaths as competing risk				
WLR of $Log(sHR)_{PCSM}$ on $Log(sHR)_{TTM}$	20/13*	0.61(0.27,0.76)	16/9	0.61(0.20,0.77)

*Exclude 1 trial (1 comparison) with <3 CaP deaths

OS: Overall survival, DSS: Disease specific survival, PCSM: Prostate cancer specific mortality, MFS: Metastasis free survival, TTM: Time to metastasis, HR: Hazard Ratio, sHR: sub-distribution hazard ratio (from competing risk regression), RT: Radiation therapy, WLR: Weighted linear regression

Table 4 – Comparison of ICECaP-1 and ICECaP-2

	ICECAP-1 (19 trials, 12,712 patients)	ICECAP-2 (14 trials, 15,164 patients)
Years of enrollment, N (%)		
1987-2004	11539 (91)	4716 (31)
2005-2009	1111 (9)	6059 (40)
2010-2016	62 (1)	4389 (29)
Age at randomization, median (IQR)	69 (65-73)	67 (62-72)
% of patients with high risk disease*	66	51
Median follow-up, years	9.9	8.3
5-year MFS, % (95% CI)	79 (79-80)	86 (86-87)
8-year OS, % (95% CI)	70 (69-70)	81 (80-81)
Median time from metastasis to death (years)	1.9	3.1
No. of OS events (%)	5350 (42)	3168 (21)
Event type: CaP death vs Non-CaP death	27% vs 73%	29% vs 71%
No. of MFS events (%)	5733 (45)	3953 (26)
Event type: metastasis vs Non-CaP death	38% vs 62%	48% vs 52%
Surrogacy Condition 1		
Kendall's tau	0.91	0.92
R^2 WLR 8-year-OS on 5-year MFS	0.83 (0.71–0.88)	0.73 (0.53 - 0.82)
Surrogacy Condition 2		
R^2 WLR log(HR)-OS on log(HR)-MFS	0.92 (0.81-0.95)	0.83 (0.64 - 0.89)
Surrogate threshold effect	0.88	0.81

CaP: Cancer of prostate, IQR: Interquartile range, MFS: Metastasis free survival, OS: Overall survival, WLR: Weighted linear regression

*****defined as high risk if patient had one of these features: high risk by NCCN or D'Amico criteria, clinical N1 staging, high risk by pathological criteria (pathological Gleason>7, or seminal vesicles involvement, or ≥pT3b stage) or Pathology N1 staging

Validation of Metastasis Free Survival as a Surrogacy Endpoint for Overall Survival in Patients with Localized Prostate Cancer Treated with Adjuvant Hormone or Chemotherapy [Intermediate Clinical Endpoints of Cancer of the Prostate (ICECaP)]

Supplemental Material

Contents

Tables

Figures

Table S1 Trials included for ICECaP-2 MFS surrogacy validation analysis (14 trials for 15,164 unique subjects and 21 treatment comparisons).

Study Title	Year Enrolled	Control Arm	Experimental Arm	Total N	Median Follow-up,Y
RP based (5 trials for 3,628 unique subjects and 5 treatment comparisons)					
CALGB90203[1]	2007-2015	RP	RP + NADT 6m + Docetaxel	788	6.4
EORTC22911[2]	1992-2001	Wait and see	Irradiation	1005	10.6
GETUG16[3]	2006-2010	Salvage RT	salvage RT + ADT 6m	742	9.4
RTOG9601[4]	1998-2003	Salvage RT+Placebo	salvage RT + Bicalutimide	760	13.1
TROG0803[5]	2009-2015	Adjuvant RT	Salvage RT	333	6.5
RT based (9 trials for 11,536 unique subjects and 16 treatment comparisons)					
CHHIP_57g[6]	2002-2011	RT 74 Gy+ADT 4-6m*	RT 57 Gy + ADT 4-6m	2142	5.2
CHHIP_60g[6]	2002-2011	RT 74 Gy+ADT 4-6m*	RT 60 Gy + ADT 4-6m	2139	5.2
DFCI05043[7]	2005-2015	RT+ADT 6m	RT + ADT 6m + Docetaxel	350	10.2
GETUG12[8]	2002-2006	RT+AADT 3y	RT + AADT 3y + Docetaxel/Estramustine	413	12.1
RTOG0126[9]	2002-2008	RT 70.2 Gy	RT 79.2 Gy	1499	9.2
RTOG0521[10]	2005-2009	RT+AADT 2y	RT + AADT 2y + Docetaxel	563	10.6
RTOG9902[11]	2000-2004	RT+AADT 2y	RT + AADT 2y + Paclitaxel/Estramustine/Eoposide	397	10.2
RTOG9910[12]	2000-2004	NADT 2m+RT+ AADT 2m	NADT 7m + RT + AADT 2m	1490	9.5
STAMPEDE_AB[13]	2006-2013	RT + AADT ≥2y*	RT + AADT ≥2y + Zoledronate	471	3.5
STAMPEDE_AC[14]	2006-2013	RT + AADT ≥2y*	RT + AADT ≥2y + Docetaxel	483	6.1
STAMPEDE_AD[15]	2006-2011	RT + AADT ≥2y*	RT + AADT ≥2y + Celecoxib	214	5.6
STAMPEDE_AE[13]	2006-2013	RT + AADT ≥2y*	RT + AADT ≥2y + Zoledronate/Docetaxel	476	3.5
STAMPEDE_AF[15]	2006-2011	RT + AADT ≥2y*	RT + AADT ≥2y + Zoledronate/Celecoxib	208	5.8
STAMPEDE_AG[16]	2011-2014	RT + AADT ≥2y*	RT + AADT ≥2y + Abiraterone	775	7.0
STAMPEDE_AJ[16]	2014-2016	RT + AADT ≥2y	RT + AADT ≥2y + Abiraterone/Enzalutamide	972	5.0
TROG0304[17]	2003-2007	NADT 6m + RT	NADT 6m + RT+ AADT12mo	1071	11.3

*****CHIPP: same control subjects have been used for 2 treatment comparisons. STAMPEDE: same control subjects have been used for comparisons of one or more experimental drugs for arms B,C,D,E,F and G (i.e.,1,658 controls from 596 unique subjects).

ADT: Androgen deprivation therapy, AADT: Adjuvant ADT, NADT: Neoadjuvant ADT, RP: Radical prostatectomy, RT: Radiation therapy. M: Month, Y: year

References of included trials

RP-based trials

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RT-based trials

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Table S2 Trial and patient characteristics for 14 randomized control trials (15,164 unique subjects)

	N	%
Year randomization		
1987-1994	179	1.2
1995-1999	767	5.1
2000-2004	3770	25
2005-2009	6059	40
2010-2016	4389	29
Type of treatment		
RP+ADT/CT/Other	788	5.2
RP+Salvage RT/HT	2840	19
RT dose	4715	31
RT+ADT/CT/Other	6821	45
Age at randomization		
Median, IQR	67	62-72
64 or younger	5407	36
65-74	7728	51
75 or older	2026	13
Unknown	3	0.02
NCCN risk group		
Low	419	2.8
INTM	5948	39
High	6960	46
Unknown	1837	12
ICECaP high risk*		
No	7479	49
Yes	7670	51
Unknown	15	0.1

***defined as high risk if patient had one of these features: high risk by NCCN or D'Amico criteria, clinical N1 staging, high risk by pathological criteria (pathological Gleason>7, or seminal vesicles involvement, or ≥pT3b stage) or Pathology N1 staging

ADT: Androgen deprivation therapy, CT: Chemotherapy, HT: Hormone therapy, RP: Radical prostatectomy**,** RT: Radiation therapy, NCCN: National Comprehensive Cancer Network

Table S3 Number of events for each endpoint (14 trials with 15,164 unique subjects)

	MFS		TTM		OS		DSS	
	No. of events	**%**	**No. of events**	**%**	**No. of events**	**%**	**No. of events**	**%**
Metastasis	1727	44	1727	91	N	%		
CaP death	168	4.3	168	8.9	932	29	932	100
Non-CaP deaths/Unknown causes	2058	52			2236	71		
Total No. of events	3953		1895		3168		932	

CaP: Cancer of prostate, OS: Overall survival, DSS: Disease specific survival, MFS: Metastasis-free survival, TTM: Time to metastasis

Table S4 Kaplan Meier estimates of endpoints at 5-, 8, and 10-years from randomization (14 trials with 15,164 unique subjects)

		Event free rate, % (95%)	
Endpoint	**year**	**All**	**High risk***
OS	5	91(90-91)	89(89-90)
OS	8	81(80-81)	78(77-79)
OS	10	73(72-74)	70(69-72)
DSS	5	97(97-98)	96(95-96)
DSS	8	94(93-94)	90(90-91)
DSS	10	91(91-92)	87(86-88)
MFS	5	86(86-87)	83(82-84)
MFS	8	75(74-76)	70(69-71)
MFS	10	67(66-68)	62(60-63)
TTM	5	92(92-93)	88(87-89)
TTM	8	87(86-87)	80(79-81)
TTM	10	83(82-84)	76(75-77)

***defined as high risk if patient had one of these features: high risk by NCCN or D'Amico criteria, high risk by pathological criteria (pathological Gleason>7, or seminal vesicles involvement, or ≥pT3b stage) or Pathology N1

OS: Overall survival, DSS: Disease specific survival, MFS: Metastasis-free survival, TTM: Time to metastasis

Figure S1 – Flowchart of selection of randomized clinical trials for MFS surrogacy analysis in ICECaP

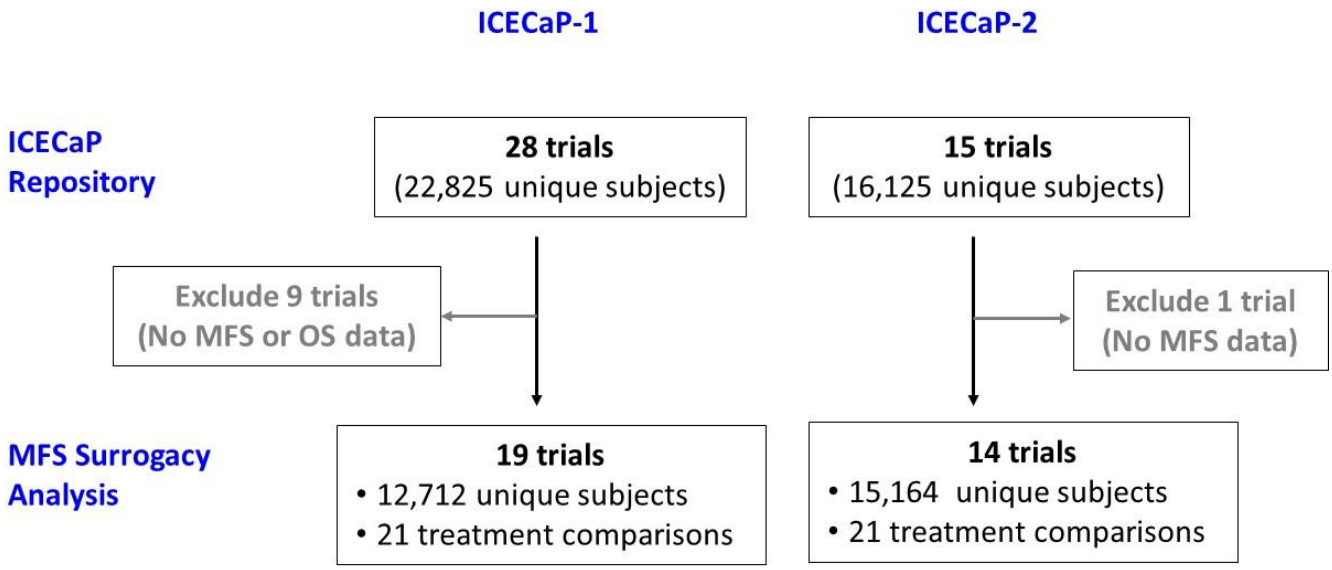
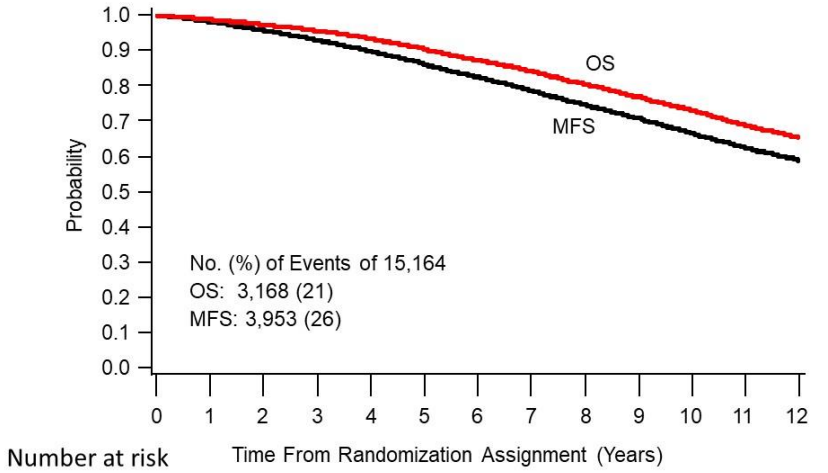


Figure S2 – (A) Kaplan-Meier estimates of overall survival (OS) and metastasis-free survival (MFS) where non-prostate cancer deaths were counted as events; (B) Kaplan-Meier estimates of disease-specific survival (DSS) and time to metastasis (TTM) where non-prostate cancer deaths were censored.

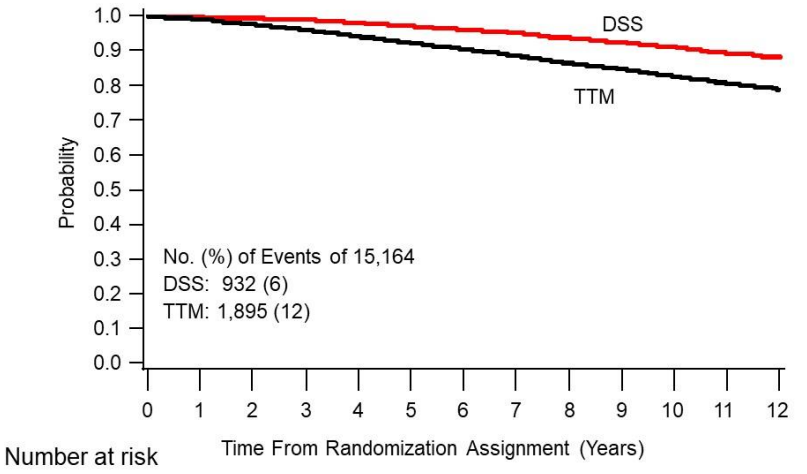
(A)



Number at risk

MFS	15164	13497	8639	4550	1093
OS	15164	13929	9252	4987	1212

(B)

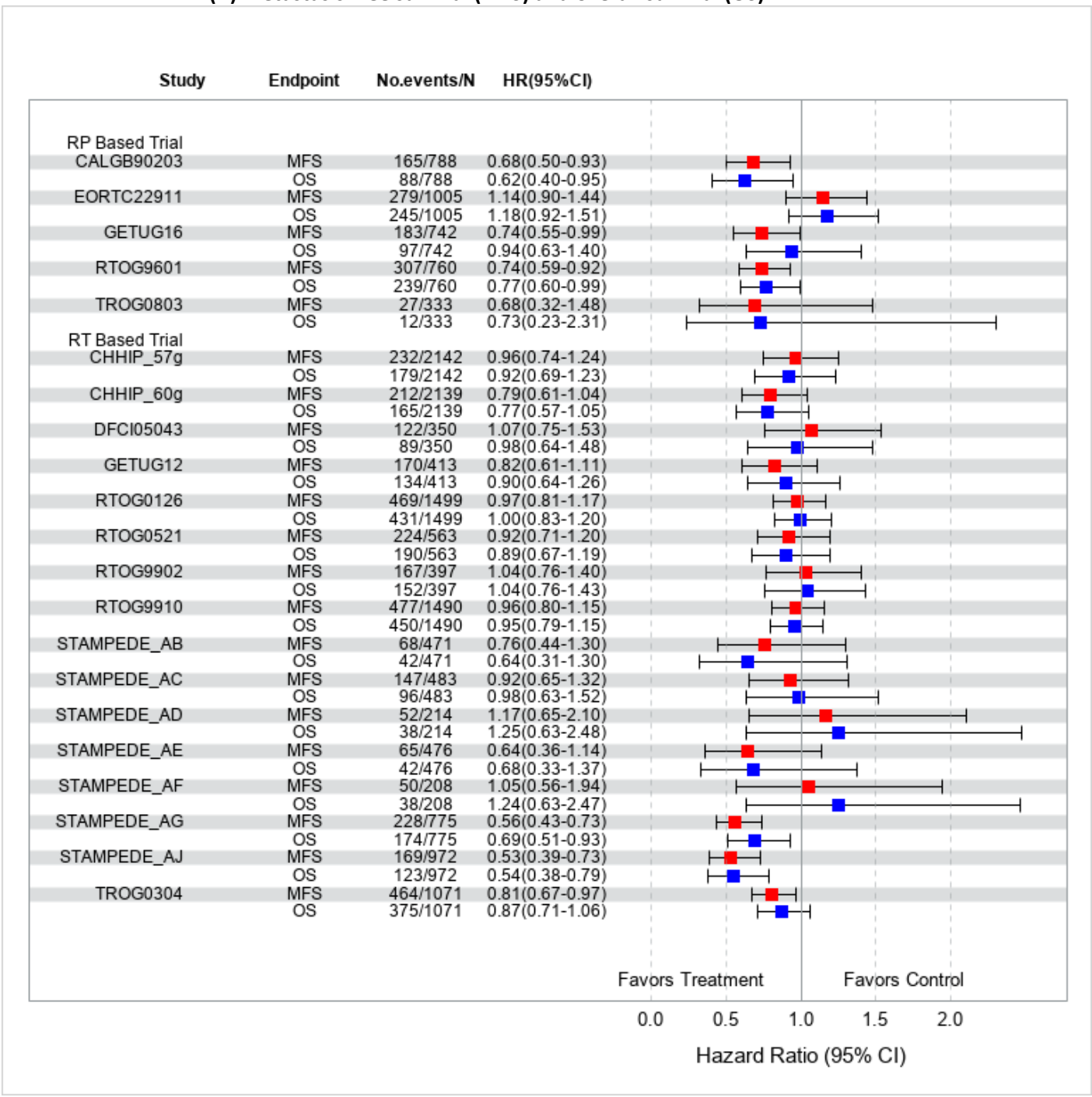


Number at risk

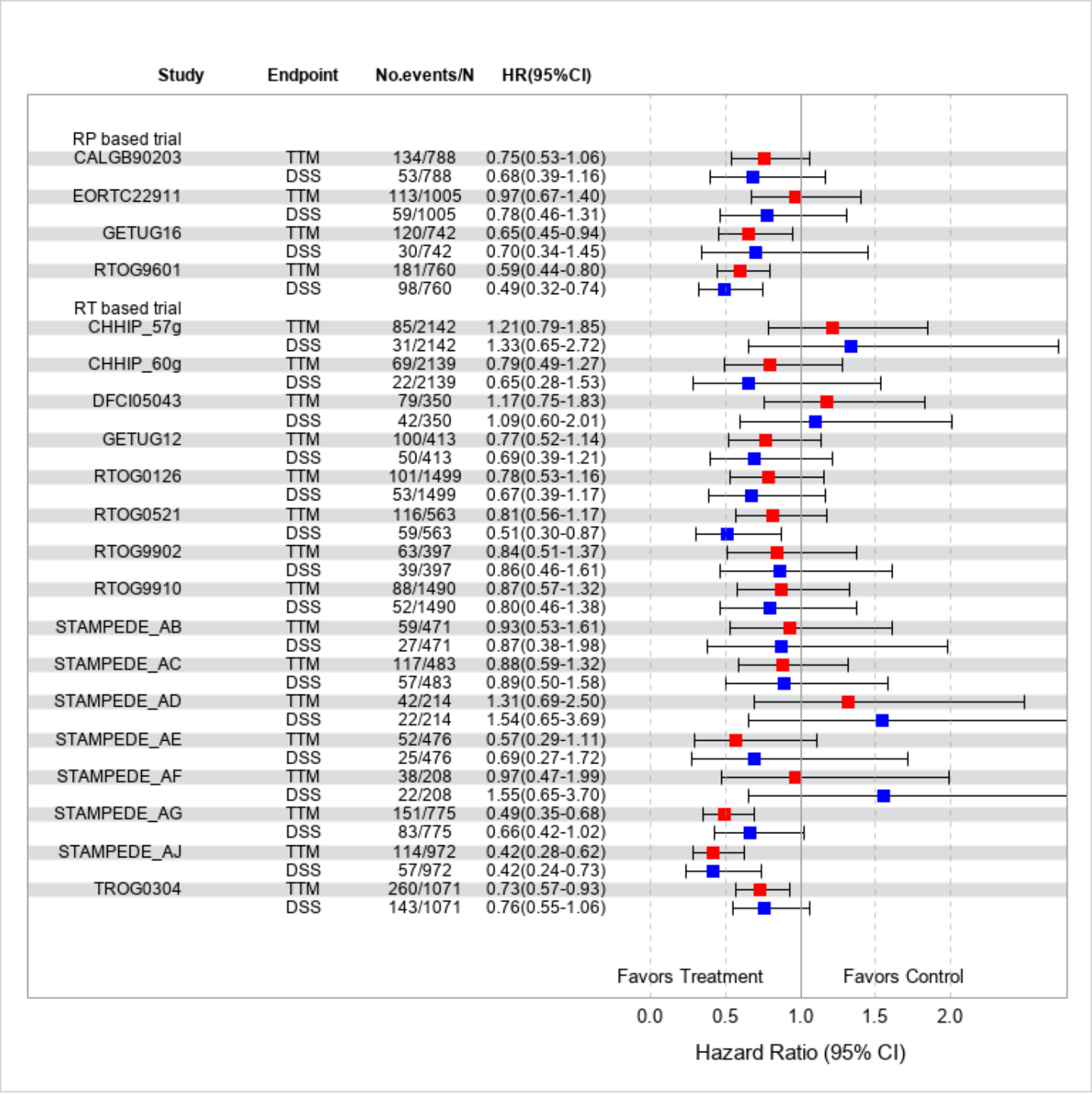
DSS	15164	13929	9252	4987	1212
TTM	15164	13497	8639	4550	1093

Figure S3 Forest plots of study-specific treatment effects (hazard ratios) on endpoints, estimated from Cox proportional hazards regression models for each trial and endpoint

(A) Metastasis-free survival (MFS) and overall survival (OS)



(B) Time to metastasis (TTM) and disease-specific survival (DSS)*



HR: hazard ratio, CI: confidence interval

*Excluding 1 study with number of prostate cancer death < 3 for DSS endpoint