

## Supplemental Online Content

Klotz L, Chin J, Black PC, et al. Comparison of multiparametric magnetic resonance imaging–targeted biopsy with transrectal ultrasonography biopsy for biopsy-naïve men at risk for prostate cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online February 4, 2021. doi:10.1001/jamaoncol.2020.7589

**eTable 1.** Per protocol analysis

**eTable 2.** Quality of life data

**eTable 3.** Between site comparison

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Per-Protocol Analysis:

Results were similar between the ITT and the per protocol population, however, notably, the lower bound of the 95% one-sided confidence interval was slightly below the pre-determined 5% threshold at -6.2% i. There remains lack of consensus amongst statistical researchers as to the optimal population (ITT or PP) for non-inferiority analyses. It is generally agreed that analyses based on the PP population are more conservative in the event of large amounts of patient withdrawal/non-adherence, however, this could result in measurable or possibly unmeasurable population differences. While only 6.6% of patients were ineligible for the PP population in our study (our sample size assumption was <5%), the rate was much higher in the TRUS-Bx arm (10.6% vs 2.6%) indicating a potential differential bias in the PP populations. Additionally, as the MRI-TB arm had numerically lower rates of  $\geq$ GG2 cancers detected, the use of PP population may result in more similar detection rates (i.e. biasing towards no difference) which would bias the results towards inferiority.

**Outcomes based on all patients who started intervention (either underwent MRI or biopsy) as per protocol, ie excluding those who refused biopsy or withdrew from the study.**

		TRUS-Biopsy	MRI Arm
N		202	219
GG2 or higher cancer	N (%)	67 (33)	79 (36)
GG3 or higher cancer	N (%)	25 (12)	30 (14)
GG2 cancer	N (%)	42 (21)	49 (22)
GG1 cancer	N (%)	49 (24)	23 (10)
No Cancer Detected On Biopsy	N (%)	86 (43)	34 (15)
GG1 or no cancer	N (%)	135 (67)	57 (26)
Avoided Biopsy due to MRI	N (%)	-	83 (39)
95% CI			32%-45%
<b>Outcomes, of those Undergoing Biopsy</b>			
N		202	136
GG2 or higher cancer	N (%)	67 (33)	79 (58)
GG3 or higher cancer	N (%)	25 (12)	30 (22)
GG2 cancer	N (%)	42 (21)	49 (36)
GG1 or no cancer	N (%)	135 (67)	57 (42)
GG1 cancer	N (%)	49 (24)	23 (17)
No cancer Detected on Biopsy	N (%)	86 (43)	34 (25)
GG1 Cancer by PI-RADS Score	PI-RADS=3		7/24 (29%)
	4		13/82 (16%)
	5		3/30 (10%)
$\geq$ GG2 Cancer by PI-RADS Score	PI-RADS=3		4/24 (16)
	4		49/82 (60)
	5		26/30 (87)
$\geq$ GG3 Cancer by PI-RADS Score	PI-RADS=3		2/24 (8.3%)
	4		16/82 (19)
	5		12/30 (40)
GG2 Cancer by PI-RADS Score	PI-RADS=3		2/24 (8.3%)
	4		33/82 (40)
	5		14/30 (47)
<b>Analysis of Individual Targets</b>			

<b>Number of Tumor Sites Identified by MRI Per Patient</b>	0		83 (38)
	1		78 (35)
	2	-	50 (23)
	3		10 (4.5)
	Sum		208
<b>PI-RADS Score of Each Lesion (n=208)</b>	Missing*		1
	2		2 (1.0)
	3		54 (26)
	4		118 (57)
	5		33 (16)
<b>Number of Cores Taken Per Patient</b>	Mean (sd)	11.4 (1.3)	6.3 (2.6)
<b>Patients with <math>\geq 1</math> Positive Cores</b>	N (%)	120 (59.4)	107 (79)
<b>Number of Positive Cores Per Patient</b>	Mean (sd)	4.4 (3.0)	4.4 (2.4)
<b>Percent of Positive Cores Across All Patients</b>	n/N (%)	527/1433 (36.8)	466/844 (55.2)
<b>Adverse Events, Amongst those Undergoing Biopsy</b>			
<b>N</b>		202	136
<b>Number of Patients with <math>\geq 1</math> AE</b>	N (%)	143 (71)	80 (59)
<b>Most Frequent AE Experienced</b>	Erectile Dysfunction	8 (4)	10 (7)
	Hematochezia	36 (18)	22 (16)
	Hematospermia	95 (47)	51 (38)
	Hematuria	10 (53)	43 (32)
	Pain	72 (36)	34 (25)
	Prostatitis	9 (4)	0 (0)
	Urinary Incontinence	12 (6)	5 (4)
<b>Number of Patients with <math>\geq 1</math> Grade 3+ AE</b>	N (%)	9 (4.5)	4 (2.9)
<b>Chills</b>		1 (0.5)	0 (0.0)
<b>Erectile Dysfunction</b>		0 (0.0)	1 (0.7)
<b>Fever</b>		1 (0.5)	0 (0.0)
<b>Hematuria</b>		2 (1.0)	0 (0.0)
<b>Hematochezia</b>		0 (0.0)	1 (0.7)
<b>Left buccal mucosa-invasive cell carcin.</b>		0 (0.0)	1 (0.7)
<b>Malignant hyperglycemia</b>		0 (0.0)	1 (0.7)
<b>Metastatic SCC of buccal musosa to lung</b>		0 (0.0)	1 (0.7)
<b>Neoplasm</b>		0 (0.0)	1 (0.7)
<b>Pain</b>		1 (0.5)	0 (0.0)
<b>Prostatitis</b>		1 (0.5)	0 (0.0)
<b>Sepsis</b>		3 (1.5)	0 (0.0)
<b>Urinary retention</b>		1 (0.5)	0 (0.0)
<b>Urinary tract infection</b>		2 (1.0)	1 (0.7)

eTable 2. Quality of Life

Baseline Characteristics		Baseline		Post-Treatment	
EQ5D					
		TRUS-Bx	MRI	TRUS-Bx	MRI
<b>N</b>		221	222	167	175
<b>Mobility</b>	I have no problems	187 (85)	197 (89)	145 (87)	151 (86)
	I have slight problems	22 (10)	18 (8.1)	12 (7.2)	16 (9.1)
	I have moderate problems	9 (4.1)	5 (2.3)	8 (4.8)	6 (3.4)
	I have severe problems	3 (1.4)	2 (0.9)	2 (1.2)	2 (1.1)
<b>Self Care</b>	I have no problems	213 (96)	218 (98)	162 (97)	172 (98)
	I have slight problems	6 (2.7)	4 (1.8)	5 (3.0)	3 (1.7)
	I have moderate problems	2 (0.9)	0	0	0
	I have severe problems	0	0	0	0
<b>Usual Activities</b>	I have no problems	197 (89)	205 (92.3)	146 (87)	160 (91)
	I have slight problems	21 (9.5)	14 (6.3)	11 (6.6)	9 (5.1)
	I have moderate problems	2 (0.9)	3 (1.4)	7 (4.2)	6 (3.4)
	I have severe problems	1 (0.5)	0	3 (1.8)	0
<b>Pain</b>	I have no pain	135 (61)	135 (61)	122 (73)	126 (72)
	I have slight pain	63 (28)	67 (30)	30 (18)	40 (23)
	I have moderate pain	20 (9.1)	17 (7.7)	12 (7.2)	8 (4.6)
	I have severe pain	3 (1.4)	3 (1.4)	2 (1.2)	1 (0.6)
	I have extreme pain	0	0	1 (0.6)	0
<b>Anxiety/Depression</b>	I have no anxiety/depressed	153 (69)	165 (75)	107 (64)	133 (76)
	I have slight anxiety/depressed	53 (24.0)	45 (20.4)	47 (28)	36 (21)
	I have moderate anxiety/depressed	13 (5.9)	10 (4.5)	10 (6.0)	6 (3.4)
	I have severe anxiety/depressed	2 (0.9)	1 (0.5)	2 (1.2)	0
	I have extreme anxiety/depressed	0	0	2 (0.6)	0
<b>State of Health</b>	Mean (sd)	84.5 (11.4)	85.1 (11.3)	84.7 (11.9)	85.8 (11.2)
QIMMB					
		TRUS-Bx	MRI	TRUS-Bx	MRI
<b>N</b>		183	124	172	121
<b>Fevers</b>	N (%) Yes	3 (1.6)	1 (0.8)	7 (4.1)	2 (1.7)
<b>Blood in Urine</b>	N (%) Yes	3 (1.6)	1 (0.8)	138 (80)	60 (50)
<b>Blood in Semen</b>	N (%) Yes	3 (1.6)	0 (0.0)	119 (70)	63 (52)
<b>Blood in Stool</b>	N (%) Yes	5 (2.7)	1 (0.8)	45 (26)	29 (24)
<b>Acute Urinary Retention</b>	N (%) Yes	1 (0.6)	2 (1.6)	3 (1.7)	1 (0.8)
<b>Erectile Dysfunction</b>	N (%) Yes	35 (19)	21 (17)	24 (14)	18 (15)
<b>Urinary Incontinence</b>	N (%) Yes	19 (10.4)	10 (8.1)	24 (14)	7 (5.8)
<b>Urinary Tract Infection</b>	N (%) Yes	1 (0.6)	2 (1.6)	6 (3.5)	1 (0.8)
<b>Pain</b>	N (%) Yes	6 (3.3)	1 (0.8)	59 (34)	36 (30)
<b>Discomfort Score</b>	Mean (sd)	3.8 (2.4)	3.0 (2.3)		
<b>Pain Score</b>	Mean (sd)	3.0 (2.2)	2.5 (2.3)		
<b>Unplanned Hospital Visit</b>	N (%) Yes			15 (8.7)	4 (3.3)
<b>Attended ER ≥1 Visit</b>	N (%) Yes			7 (4.1)	2 (1.7)
<b>Admitted as Inpatient ≥1 Night</b>	N (%) Yes			5 (2.9)	2 (1.7)
<b>Admitted Day Ward</b>	N (%) Yes			1 (0.6)	0 (0.0)

<b>Admitted to ICU</b>	N (%) Yes			0 (0.0)	0 (0.0)
<b>Community Health Care Visit</b>	N (%) Yes			12 (7.0)	2 (1.7)
<b>Felt Unwell</b>	N (%) Yes ≥6 days			15 (8.9) 11 (6.4)	4 (3.3) 2 (1.7)
<b>How Much of a Problem to Undergo Another Biopsy</b>	Not a Problem Minor Problem Moderate Problem Major Problem			79 (46) 56 (33) 23 (13) 12 (7.1)	75 (62) 31 (26) 11 (9.2) 3 (2.5)

**eTable 3. Between Site Comparison**

	London	Sunnybrook	Jewish General	UHN	Vancouver
<b>MRI Arm</b>					
<b>N</b>	52	50	30	51	44
<b>Median Baseline PSA</b>	6.70	6.81	7.86	6.40	6.40
<b>N with MRI</b>	52	49	29	50	41
<b>N (%) MRI Result Positive</b>	22 (42)	30 (61)	24 (83)	34 (68)	28 (68)
<b>N (%) PI-RADS Score</b>					
<b>3</b>	4 (17)	4 (8.2)	7 (24)	9 (18)	2 (4.9)
<b>4</b>	11 (21)	19 (39)	12 (41)	22 (44)	18 (44)
<b>5</b>	7 (13)	7 (14)	5 (17)	3 (6.0)	8 (19)
<b>N (%) No Biopsy Recommended</b>	30 (58)	29 (39)	5 (17)	16 (32)	13 (32)
<b>GG2 or Higher Cancer (those undergoing biopsy)</b>	13/21 (62)	22/29 (76)	10/24 (42)	19/34 (56)	15/28 (54)
<b>GG3 Cancer or Higher (those undergoing biopsy)</b>	5/21 (24)	9/29 (31)	4/24 (17)	4/34 (12)	8/28 (29)
<b>GG2 or Higher Cancer (all patients)</b>	13/52 (25)	22/50 (44)	10/30 (33)	19/51 (37)	15/44 (34)
<b>GG3 Cancer or Higher (all patients)</b>	5/52 (9.6)	9/50 (18)	4/30 (13)	4/51 (7.8)	8/44 (18)
<b>GG2 or Higher Cancer, By PI-RADS Score</b>					
<b>3</b>	1/3 (33)	1/3 (33)	1/7 (14)	1/9 (11)	0/2 (0.0)
<b>4</b>	7/11 (64)	15/19 (79)	4/12 (33)	15/22 (68)	8/18 (44)
<b>5</b>	5/7 (71)	6/7 (86)	5/5 (100)	3/3 (100)	7/8 (87)
<b>TRUS Bx Arm</b>					
<b>N</b>	52	49	30	53	42
<b>Median Baseline PSA</b>	5.87	5.82	6.79	5.50	7.05
<b>N Undergoing Biopsy</b>	50	44	25	44	39
<b>GG2 or Higher Cancer (those undergoing biopsy)</b>	22 (44)	8 (18)	14 (56)	11 (25)	12 (31)
<b>GG3 Cancer or Higher (those undergoing biopsy)</b>	8 (16)	4 (9.1)	5 (20)	4 (9.1)	4 (10)
<b>GG2 or Higher Cancer (all patients)</b>	22 (42)	8 (16)	14 (47)	11 (21)	4 (29)
<b>GG3 Cancer or Higher (all patients)</b>	8 (15)	4 (8.2)	5 (17)	4 (7.5)	4 (9.5)