

Supplementary Online Content

Kishan AU, Wang X, Seiferheld W, et al. Association of gleason grade with the effect of androgen deprivation therapy duration on survival outcomes: an individual patient-level meta-analysis of 6 randomized clinical trials [published online September 20, 2018]. *JAMA Oncol*. doi:10.1001/jamaoncol.2018.3732

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eTable 1. Summary of Trials Included in Network Meta-Analysis

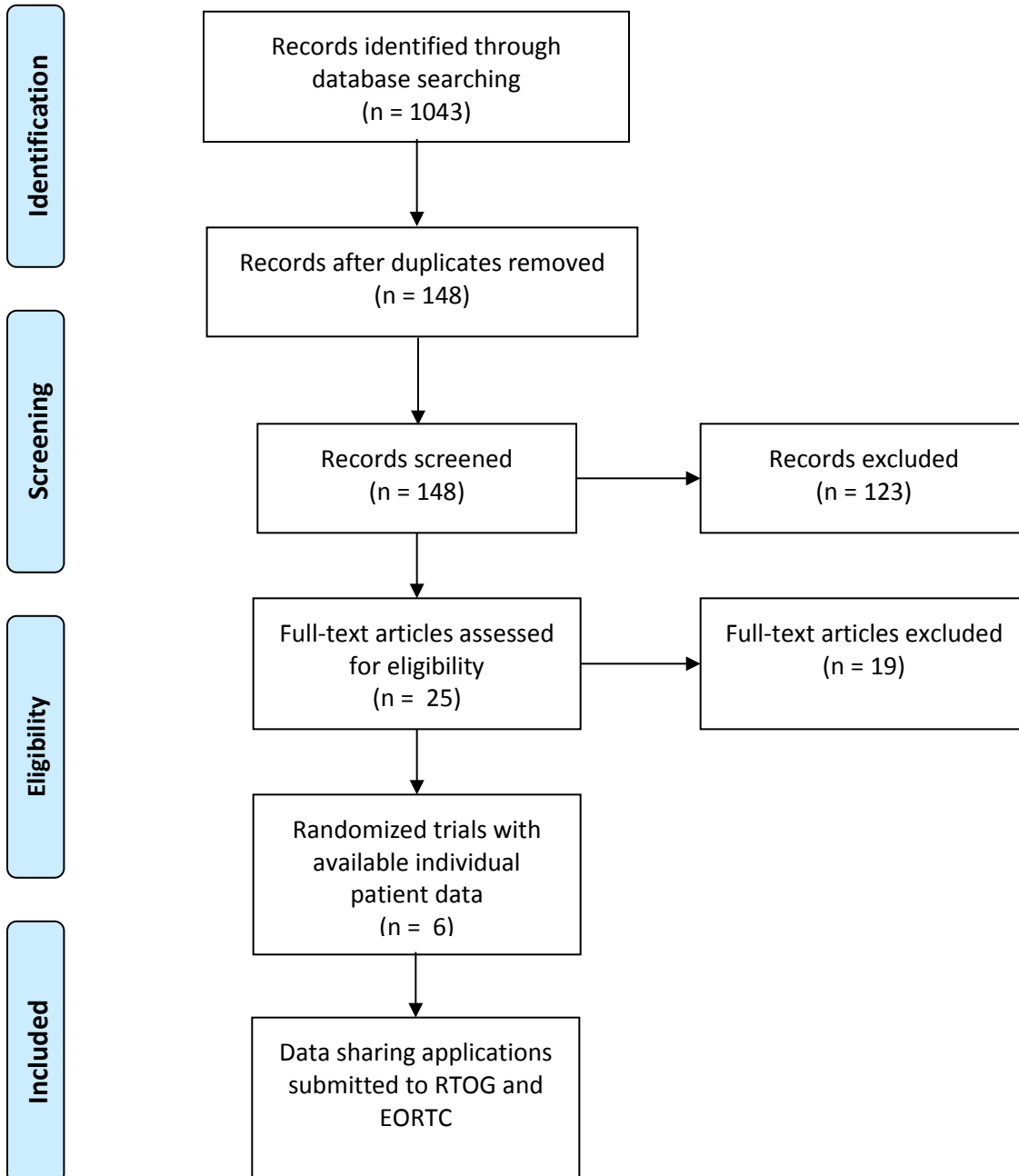
eTable 2. Patient Demographics

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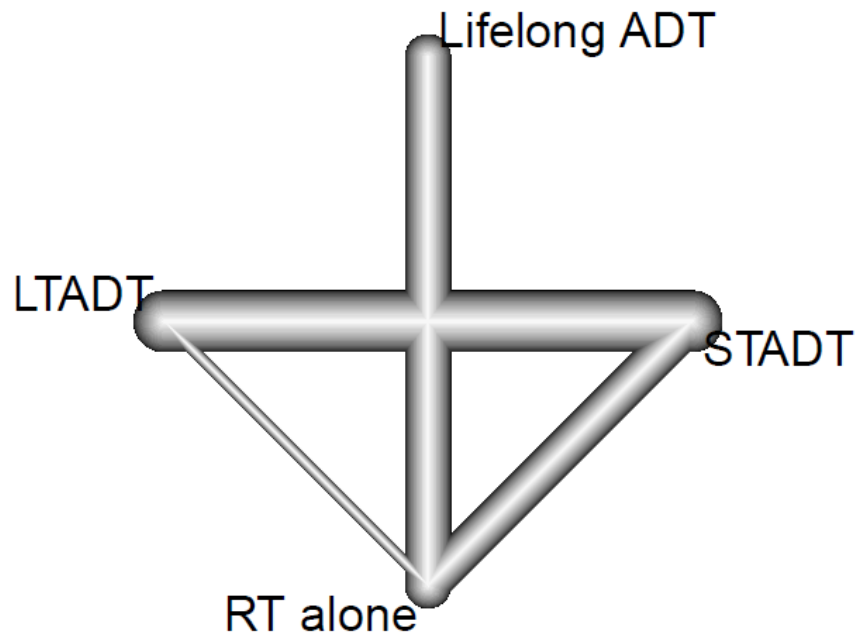
eTable 4. Network Meta-Analysis of Androgen Deprivation Therapy on Survival Outcomes

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

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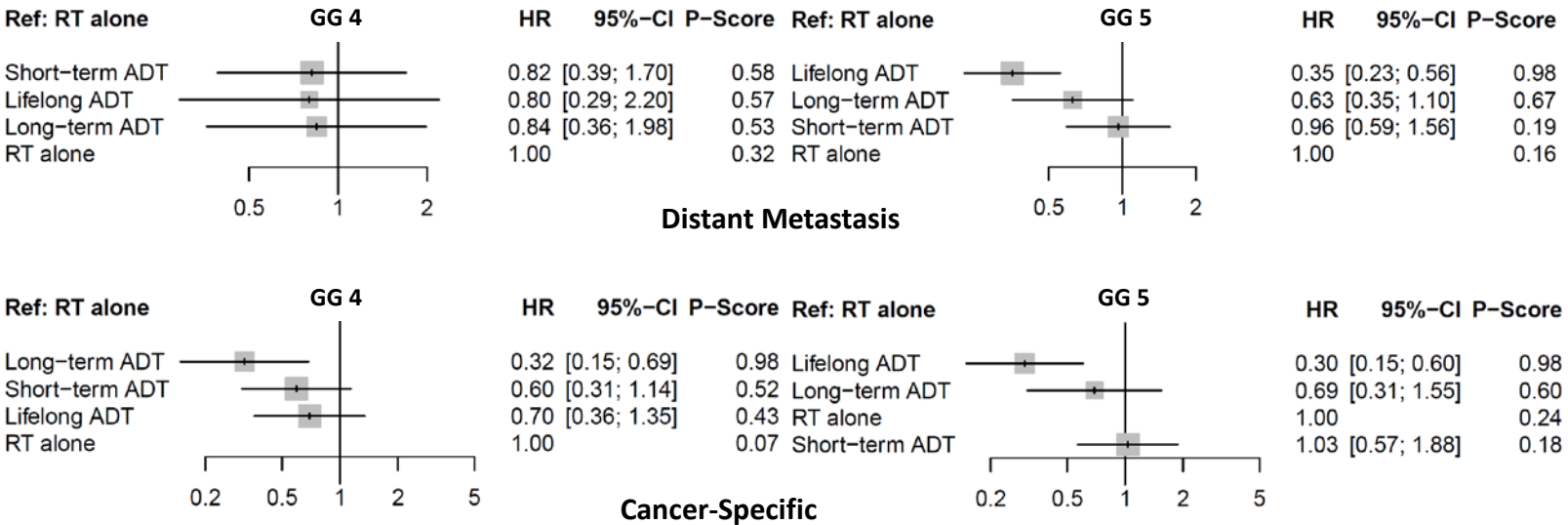


eFigure 2. Network Plot of Randomized Trials with Available Direct Comparisons



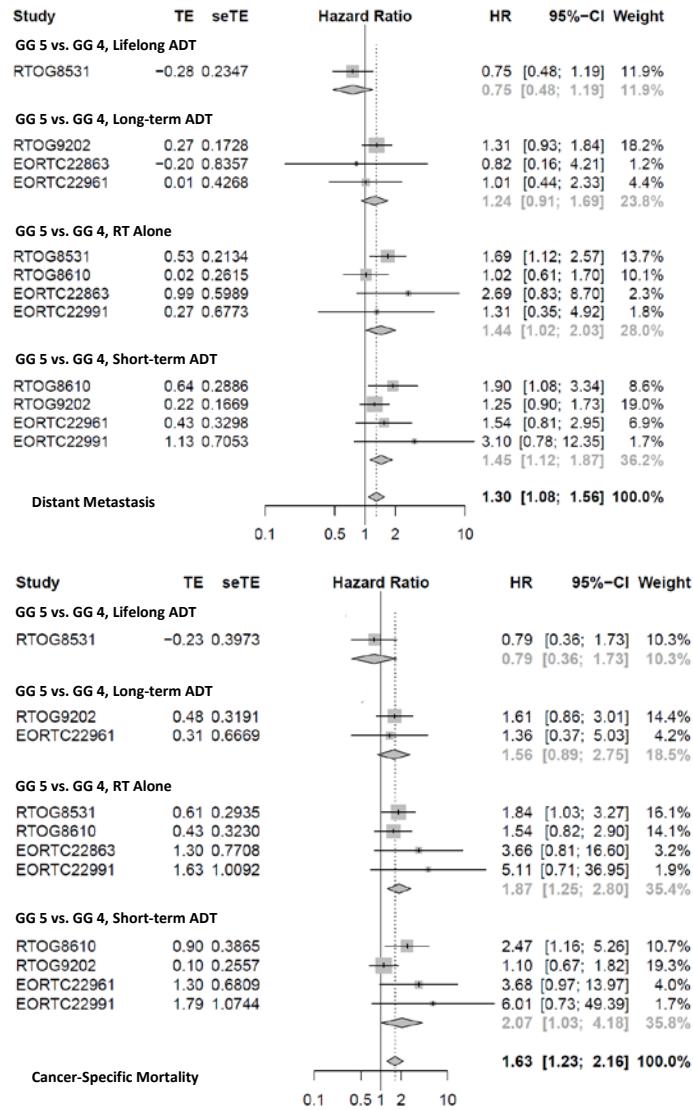
eFigure 2: Network Plot to Illustrate Randomized Trials with Available Direct Comparisons. Lines represent the presence of direct comparison trial(s). The width of the line is proportional to the number of trials with direct comparisons.

eFigure 3. Forest Plots Derived from Network Meta-Analysis of Androgen Deprivation Therapy Effect on Survival Outcomes, Stratified by Gleason Grade Group 4 vs. 5



eFIGURE 3. Forest Plots Derived from Network Meta-Analysis of Androgen Deprivation Therapy Effect on Survival Outcomes, Stratified by Gleason Grade Group 4 vs. 5. Note that the reference value (HR 1.00) for each forest plot is radiation therapy (RT) alone. The hazard ratios (HRs) and 95% confidence intervals (95% CI) are presented in ascending order, with their associated P-score (a frequentist analogue to the surface under the cumulative ranking curve). GG, Gleason grade group.

eFigure 4. Forest Plots of the Effect of Gleason Grade Group 4 vs. 5 on Survival Outcomes, Stratified by Androgen Deprivation Therapy (ADT) Duration



eFIGURE 4. Forest Plots of the Effect of Gleason Grade Group 4 vs. 5 on Survival Outcomes, Stratified by Androgen Deprivation Therapy (ADT) Duration. An overall hazard ratio (HR) and 95% confidence interval (95% CI) bestowed by having Gleason score 9-10 vs. Gleason score 8 disease is presented in boldface at the bottom right. HRs and 95% CI for each ADT duration stratum are presented, along with corresponding treatment effect (TE; log[HR]) and the standard error of the TE (seTE).

eTable 1. Summary of Trials Included in Network Meta-Analysis

Trial	Arms	Inclusion*	Staging Workup	Primary Endpoint	ADT Regimen	RT Dose
ROTG 8531	RT vs RT+Lifelong ADT	cT1-T2N+ or cT3-4 <25 cm ^{2**}	Bone scan, chest x-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling	Survival and disease progression	q1month LHRH agonist	65-70 Gy to prostate 44-46 Gy to pelvis
ROTG 8610	RT vs RT+ STADT	cT2-T4 ≥25 cm ²	Bone scan, chest x-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling	Locoregional control	q1month LHRH agonist + 4 months AA	65-70 Gy to prostate 44-46 Gy to pelvis
ROTG 9202	RT+STADT vs RT+LTADT	cT2-4N0-X, PSA<150	Bone scan, chest x-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling	Disease free survival	Q1month LHRH agonist + 4 months AA	65-70 Gy to prostate 44-46 Gy to pelvis
EORTC 22863	RT vs RT + LTADT	cT1-2N0 WHO grade 3 cT3-4N0	Bone scan, chest X-ray, liver ultrasound or CT; allowed lymph node assessment by CT, bipedal lymphangiography, lymphadenectomy	Disease free survival	q1month LHRH agonist + 1 month AA	70 Gy to prostate 50 Gy to pelvis
EORTC 22961	RT+STADT vs RT+LTADT	cT1c-2bN+ cT3-4N0 PSA<40xULN	Bone scan, chest X-ray, CT or MRI of abdomen and pelvis; lymphadenectomy allowed	Overall survival	q1-3 month LHRH agonist + 6 mos AA	70 Gy to prostate 50 Gy to pelvis
EORTC 22991	RT vs RT+ STADT	cT1b-c, with PSA≥ 10 ng/mL or Gleason ≥ 7 cT2a with PSA≤50	Bone scan for PSA>10 ng/mL, chest x-ray, CT or MRI of abdomen and pelvis	Biochemical disease free survival	q3month LHRH agonist + 1 month AA	70-78 Gy to prostate 46 Gy to pelvis

AA, anti-androgen; ADT, androgen deprivation therapy; CT, computed tomography; LHRH, luteinizing hormone releasing hormone; LTADT, long term ADT; MRI, magnetic resonance imaging; RT, radiation therapy; STADT, short-term ADT

*Patients with cN+ or pN+ disease were included on several protocols, but were not included in our analysis.

**ROTG 8531 also included patients with high-risk features after radical prostatectomy, who were not included in our analysis.

eTable 2. Patient Demographics

	Overall	GG 4	GG 5
Age, mean, median (range, min-maximum) (years)	69.8, 70 (43-88)	69.5, 70 (49-88)	70.2, 71 (43-88)
Initial PSA, mean, median (range, min-maximum) (ng/dL)*	30.3, 18.8 (0.12-200)	28.76, 18.62 (1.2-172.7)	32.5, 18.9 (0.12-200)
Clinical Tumor Stage			
1	48 (5%)	35 (6%)	13 (3%)
2	270 (27%)	175 (29%)	95 (24%)
3	636 (64%)	368 (62%)	268 (67%)
4	38 (4%)	15 (3%)	23 (6%)

GG, Gleason grade group

*Initial PSA not available for RTOG 8531 and EORTC 22961, and only available for some patients on RTOG 8610, EORTC 22863, and EORTC 22991

eTable 3. Individual Study Cox Proportional Hazard Models

Study	DMFS		CSS		OS	
	GG 4	GG 5	GG 4	GG 5	GG 4	GG 5
RTOG 8531: Lifelong ADT vs RT alone	0.80 (0.52- 1.22)	0.36 (0.23- 0.56)	0.70 (0.36- 1.34)	0.3 (0.15- 0.60)	0.84 (0.54- 1.30)	0.48 (0.31- 0.76)
RTOG 8610: STADT vs RT alone	0.63 (0.37- 1.08)	1.17 (0.69- 1.99)	0.68 (0.32- 1.44)	1.09 (0.58- 2.05)	0.79 (0.46- 1.37)	1.43 (0.83- 2.44)
RTOG 9202: LTADT vs STADT	0.69 (0.5- 0.95)	0.72 (0.51- 1.03)	0.45 (0.26- 0.79)	0.67 (0.37- 1.19)	0.72 (0.52- 0.99)	0.79 (0.55- 1.13)
EORTC 22863: LTADT vs RT alone	0.30 (0.12- 0.81)	0.09(0.02- 0.49)*	0.19 (0.04- 0.97)	0.03 (0.00- 0.57)*	0.26 (0.09- 0.79)	0.09 (0.01- 0.56)
EORTC 22961: LTADT vs STADT	0.88 (0.49- 1.57)	0.57 (0.24- 1.39)	1.89 (0.51- 6.97)	0.70 (0.19- 2.63)	0.91 (0.48- 1.73)	0.60 (0.23- 1.56)
EORTC 22991: STADT vs RT alone	0.42 (0.15- 1.13)	0.99 (0.20- 4.88)	0.53 (0.07- 3.78)	0.62 (0.09- 4.34)	0.33 (0.12- 0.95)	0.66 (0.12- 3.78)

ADT, androgen deprivation therapy; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; GG, Gleason grade group; LTADT, long term ADT; OS, overall survival; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses.

*The DMFS and CSS estimates from EORTC 22863 are unstable

eTable 4. Network Meta-Analysis of Androgen Deprivation Therapy on Survival Outcomes

	DMFS		CSS		OS	
	GG 4	GG 5	GG 4	GG 5	GG 4	GG 5
RT Alone As Reference (n=140 GG 4, 91 GG 5)*						
STADT	0.82 (0.39, 1.70)	0.96 (0.59, 1.56)	0.60 (0.31, 1.14)	1.03 (0.57, 1.88)	0.59 (0.38, 0.93)**	1.13 (0.69, 1.87)
LTADT	0.84 (0.36, 1.98)	0.63 (0.35, 1.10)	0.32 (0.15, 0.69)**	0.69 (0.31, 1.55)	0.43 (0.26, 0.72)**	0.80 (0.45, 1.44)
Lifelong ADT***	0.80 (0.29, 2.20)	0.35 (0.23, 0.56)**	0.70 (0.35, 1.35)	0.30 (0.15, 0.60)**	0.84 (0.54, 1.30)	0.48 (0.31, 0.76) **
STADT as Reference (n=214 GG 4, 151 GG 5)						
LTADT	1.04 (0.54, 2.00)	0.65 (0.47, 0.90)**	0.54 (0.33, 0.87)**	0.67 (0.39, 1.14)	0.73 (0.55, 0.96)**	0.71 (0.51, 0.99) **
Lifelong ADT	0.98(0.28, 3.42)	0.37 (0.19, 0.72)**	1.17 (0.46, 2.96)	0.29 (0.12, 0.73)**	1.42 (0.76, 2.66)	0.43 (0.22, 0.83)**
LTADT as Reference (n=59 GG 4, 49 GG 5)						
Lifelong ADT	0.94 (0.25, 3.55)	0.57 (0.27, 1.17)	2.18 (0.79, 6.00)	0.43 (0.15, 1.26)	1.94 (1.00, 3.87)	0.60 (0.29, 1.26)

ADT, androgen deprivation therapy; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; GG, Gleason grade group; LTADT, long term ADT; OS, overall survival; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses.

*Due to instability in estimates (due to the small sample size and event size), GG 6 patients enrolled on EORTC 22863 were excluded from analysis for CSS, hence the slightly different numbers than in Table 1**Indicates p<0.05