Supplementary Online Content

Terrisse S, Karamouza E, Parker CC, et al; MORPHEP Collaborative Group. Overall survival in men with bone metastases from castration-resistant prostate cancer treated with bone-targeting radioisotopes: a meta-analysis of individual patient data from randomized clinical trials. *JAMA Oncol*. Published online December 12, 2019. doi:10.1001/jamaoncol.2019.4097

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

eMethods 1. Trial search strategy from PubMed

The search strategy was performed for the period 1993-June 2013 using PubMed (see below), the Cochrane library, hand and internet searching of review articles, meeting proceedings (the American Society of Clinical Oncology (ASCO), the European CanCer Organisation (ECCO), the European Society for Medical Oncology (ESMO), the European SocieTy for Radiotherapy and Oncology (ESTRO), the American Society for Radiation Oncology (ASTRO), The European association of nuclear medicine (EANM), the European Association of Urology (EAU), the American Urological Association (AUA)), and one trials' register (clinicaltrials.gov with such terms: Type of Cancer: "Prostate cancer"; Type of Trial: "Treatment"; Drug: "Radiopharmaceutical", "radio-isotope", "strontium", "samarium", "radium"," rhenium").

Key search PubMed terms included: "prostate cancer", "castration-resistant prostate cancer", "hormone-refractory prostate cancer", "bone metastasis", "radiopharmaceuticals", "radioisotopes", "samarium", "strontium", "radium-223", "rhenium", "randomized" in Title and/or in Abstract.
Trialists have been asked to review. Differences between investigators were resolved through consensus.

eMethods 2. Statistical methods

Evaluation of the between-trial heterogeneity

The between trials heterogeneity of the treatment effect was tested by Q-Cochran[1], quantified by I^2 index[2] considered as small: <30%, moderate: 30-60% and substantial:>60%[3] and the between-study variance (tau^2) estimated by a random effect model (RE)[4]. In presence of significant heterogeneity ($p<0.10$), any trials with a 95% CI that did not overlap with that of the overall treatment effect were excluded in a sensitivity analysis. If heterogeneity was still significant, we used a RE model.

Subgroup analyses

To estimate the interaction between treatment effect and patients' subgroups (age, performance status, serum prostatic specific antigen, hemoglobin level, alkaline phosphatase level and number of bone metastases at baseline), we used the pooling of within trial covariate interaction (PWT)[5]. The PWT's approach consists firstly in estimating the interaction term between treatment effect and a patient subgroup within each trial, separately, by a Cox model. We also estimate the treatment effect for each category of the patient subgroup. Secondly, the treatment-covariate interaction effects are then pooled using the inverse-variance meta-analysis. The treatment effects of a category of a patient subgroup are also pooled. If between-trial heterogeneity of treatment-covariate interaction was observed ($p<0.10$) then the overall interaction was also estimated by a random approach (DerSimonian and Laird approach)[4]. If the treatment-covariate interaction remains significant by using a random approach ($p<0.10$) then the result of the subgroup analysis is reported through a forest plot. We then reported both the treatment effect in each category and the interaction term for each trial, and the overall treatment-covariate interaction. Some sensitivity analyses may be performed by excluding some trials in order to have homogeneous treatment effect in each category of the subgroup analysis.

Continuous covariates were categorized into 2 classes based on the median which was estimated from individual patient data of all trials (including the 2 trials for which individual patient data was not available for the different endpoints).

eMethods 3. Unplanned sensitivity analysis

Although all data comparing RI versus no RI arms (ratio 1:1) from the 2x2 randomized TRAPEZE trial were considered, i.e. including patients treated or not by zoledronic acid (ZA) because there is no known interaction between Sr-89 and ZA (p=0.40), we performed, as suggested by a reviewer, an unplanned sensitivity analysis including only no-ZA patients from TRAPEZE trial in the meta-analysis. Considering the high impact of this trial (one of the two largest trials) and the possible marginal effect of ZA it might be useful to examine whether this may affect the final conclusions. The only major change was the significant overall benefit of RI on SSE with an overall treatment effect of 0.74 95% CI [0.62-0.88] ($p_{heterogeneity}$=0.29, I^2=20%) (RE HR= 0.74, 95%CI [0.60-0.91]). This is explained by a larger effect size of TRAPEZE trial on SSE moving from 0.95 95% CI [0.78-1.16] to 0.90 [0.69-1.18] after excluding ZA-patients.

eMethods 4. Unplanned post hoc analysis

This analysis showed that RI was associated with a significant OS benefit compared with no RI (FE: HR=0.91, 95% CI [0.83,1.00]; p=0.05) but with a significant (p<0.001) and substantial (I^2=81%) heterogeneity between trials. A random effect (RE) model showed no significant treatment effect (HR=0.86 95% CI [0.67;1.10], p=0.24, (tau^2=0.08)). For the sensitivity analysis (excluding two trials[25,27]), fixed effect (FE) HR was 0.89 (95% CI [0.80;0.98], p=0.02) (I^2=73%) (RE HR=0.88, 95% CI [0.70;1.10], p=0.26 (tau^2=0.04)). In α-emitter subset, RI was associated with a significant OS benefit compared with no RI (FE: HR=0.85, 95% CI [0.74;0.98], p=0.026) but with a significant (p<0.001) and substantial (I^2=86%) heterogeneity. RE yields an HR=0.82 (95% CI [0.53;1.25], p=0.35).

eMethods 5. Unplanned sensitivity analysis

As suggested by a reviewer, we examined whether summary statistics extracted from published data of the three trials (See eReferences[12-14]) excluded due to the non-availability of individual patient data (no response to exchange or no possibility to access to the data) may have cause a availability bias and thus affect the conclusions (unplanned analysis). From these three trials all belong to β-emitter subset, only two HRs (HR=1.00, n=162 and 1.34, n=131) for OS could be estimated without precision from medians and assuming an exponential distribution. Regarding these point estimates higher or equal to the null value of 1, their combination in the current meta-analysis assuming a range of precision associated to these point estimates does not change the overall HR toward the null value and thus does not change the findings of non-significant difference between RI and no RI both for overall and in β-emitter subset.

eTable 1. Description of the 6 randomized clinical trials included for the meta-analysis

Trial	Nb. of patients	Inclusion period	Arm without RI	Arm with RI	Description of RI	Trial design	Cross over
Strontium-89 groups							
EORTC 30921[6]	203	1993-2000	Local ERT: usual radiotherapy regimen used at the study centre	Sr-89: 150 MBq (4mCi)	Single dose	Phase III	No
MDA 1996 [7]	72*	1996-1999	Doxorubicine 8020 mg/m2 once a week x 6 weeks	Sr-89:2.035 MBq/kg + doxorubicine	Single dose	Randomized phase II	No
Norway 1997 [8]	64	1997-2000	Local ERT: 3 Gy/fraction in 10 fractions or 8 Gy in one fraction. +Placebo	Sr-89:150 MBq at J1 of ERT + local ERT	Single dose	Phase III	No
TRAPEZE[9]	757	2005-2012	2 groups: A: Docetaxel 75mg/m²/3w+prednisolone 10mg od (ST**). B: ST+ zoledronic Acid 4 mg (Cycle 1-10)	2 groups C: ST+ Sr-89 150 MBq D: ST+ Zoledronic Acid 4 mg +Sr-89 150 MBq (Cycle 1-10)	Single dose day 28 cycle 6	Phase III	No
Radium-223 groups							
Bayer 15280[10]	64	2004-2005	SOC***	Ra-223: 50 kBq/kg/4weeks	4 IV administrations	Randomized phase II	No
ALSYMPCA [11 $]	921	2008-2011	Placebo	Ra-223:50 kBq/kg/4weeks	6 IV administrations	Phase III	Yes

ERT: external radiotherapy for bone metastases; Gy: Gray; MBq: Megabecquerel; od: once day; RI: radio-isotopes; Ra: radium, Sr: strontium, NA: Not available ; *: responders or stable after induction chemotherapy (maintenance treatment); ** ST: standard treatment, trial with a 2x2 design, the second randomization was zoledronic acid yes/no. $ Randomization 1:2 ***SOC: Standard Of Care

EORTC= European Organisation for Research and Treatment of Cancer, MDA= M D Anderson Cancer Center, TRAPEZE= Taxane RAdioisotoPE ZolEdronic acid, ALSYMPCA= ALpharadin in SYMptomatic Prostate CAncer patients

eTable 2. Distribution of the potential confounding factors in the eligible trials

Study	Type of RI	Type of radiation emitted from RI	Type of comparison	CT in both arms	RT in both arms	Cross-over
EORTC 30921[6]	Sr-89	β	RI vs ERT	No	No	No
MDA 1996 [10] ****	Sr-89	β	RI + CT vs CT	Yes	No	No
Norway 1997 [8]	Sr-89	β	RI + local ERT vs ERT	No	Yes	No
TRAPEZE [9]	Sr -89	β	RI + CT vs CT	Yes	No	No
Bayer 15280 [10]	Ra-223	α	RI vs SOC***	No	No	No
ALSYMPCA [11]	Ra-233	α	RI vs Placebo	No	No	Yes

Ra: radium, Sr: Strontium, RI: radio-isotope, ERT: external radiotherapy, CT: chemotherapy, ** responders or stable after induction chemotherapy, β: beta emitted radiation from RI, α: alpha emitted radiation from RI, *** SOC: Standard Of Care
see eTable 1 for other abbreviations

eTable 3. Patient characteristics, median follow-up, and number of events by trial and overall

Characteristics[†]	EORTC30921[6] (n=203) (6·8%)	MDA 1996[7] (n=72) (3·5%)	Norway 1997[8] (n=64) (3·1%)	Bayer 15280[10] (n=64) (3·1%)	TRAPEZE[9] (n=757) (36·4%)	ALSYMPCA[11] (n=921) (44·3%)	Overall (n=2081) (100%)
Age (years) Median [IQR]	70·0 [65·0-75·0]	67·0[60·2-70·9]	70·9[63·8-75·9]	72·5[68·0-78·0]	68·9 [63·9-73·4]	71·0 [64·0-76·0]	70·0[64·0-75·0]
<70	88 (43·4)	30 (46·9)	34 (53·1)	23 (35·9)	415 (54·8)	395 (42·9)	998 (48·0)
≥70	115 (56·6)	47 (65·3)	25 (34·7)	41 (64·1)	342 (45·2)	526 (57·1)	1083(52·0)
missing							
Performance status							
0,1	122 (60·4)	65 (90·3)	39 (60·9)	53 (82·8)	694 (91·7)	801 (87·2)	1774 (85·4)
≥2	80 (39·6)	7 (9·7)	25 (39·1)	11 (17·2)	63 (8·3)	118 (12·8)	304 (14·6)
missing	1					2	3
Serum PSA							
<143	110 (56·1)	48 (66·7)	36 (56·2)	29 (45·3)	362 (49·6)	433 (47·6)	1018 (50·0)
≥143	86 (43·9)	24 (33·3)	28 (43·8)	35 (54·7)	368 (50·4)	477 (52·4)	1018 (50·0)
missing	7				27	11	45
Hemoglobin							
<12·4	102 (52·8)	22 (30·6)	26 (40·6)	24 (37·5)	360 (48·1)	498 (54·1)	1032 (50·0)
≥12·4	91 (47·2)	50 (69·4)	38 (59·4)	40 (62·5)	388 (51·9)	423 (45·9)	1030 (50·0)
missing	10				9		19
Alkaline Phosphatases							
<248·5	83 (43·0)	44 (61·1)	11 (17·2)	31 (48·4)	341 (46·0)	518 (56·2)	1028 (50·0)
≥248·5	110 (57·0)	28 (38·9)	53 (82·8)	33 (51·6)	401 (54·0)	403 (43·8)	1028 (50·0)
missing	10				15		25
Number of bone metastases**	65 (32·8)	15 (20·8)	9 (14·1)	19 (29·7)	NA	138 (15·0)	246 (18·7)
≤6	133 (67·2)	57 (79·2)	55 (85·9)	45 (70·3)		779 (85·0)	1069 (81·3)
>6	5					4	9
missing							
Median follow-up (min-max) (months)	62·7 (1·8-62·7)	22·3 (1·0-32·3)	NE (2·6,188·1)	12·1 (0·5-25·6)	39·2 (0·4-75·1)	10·0 (0·4-36·6)	26·7 (0·4-188·1)
Number of deaths	194 (95·6)	41 (56·9)	64 (100)	50 (78·1)	618 (81·6)	528 (57·3)	1495 (71·8)
Number of symptomatic skeletal events	NA	NA	20 (31·3)	33 (51·6)	396 (52·3)	318 (34·5)	767 (42·5)
Spinal cord compression			4 (6·3)	5 (7·8)	58 (7·7)	23 (2·5)	90 (5·0)
			0	2 (3·1)	25 (3·3)	34 (3·7)	61 (3·4)

Pathologic bone fracture	0	0	1 (0·1)	2 (0·2)	3 (0·2)
Surgical intervention	16 (25·0)	26 (40·6)	312 (41·2)	259 (28·1)	613 (33·9)
External radiotherapy‡					

NA= not available, NE=Not estimable,† Continuous characteristics will be divided into 2 classes using the median
** For the Bayer152850 [10] and ALSYMPCA[11] trials, superscan was considered as higher than 6 bone metastases. For TRAPEZE trial[9], NA means that the number of bone metastases at baseline was not collected /available in this trial
‡ This category contains both external beam radiotherapy and use of radioisotope for TRAPEZE trial[9]
see eTable 1 for other abbreviations

eTable 4. Patient characteristics, median follow-up, and number of events by trial and by arm

Characteristics[†]	EORTC30921[6] (n=203) (6·8%)		MDA 1996[7] (n=72) (3·5%)		Norway 1997[8] (n=64) (3·1%)		Bayer 15280[10] (n=64) (3·1%)		TRAPEZE[9] (n=757) (36·4%)		ALSYMPCA[9] (n=921) (44·3%)		Overall (n=2081) (100%)	
	RI (n=101)	no RI (n=102)	RI (n=36)	no RI (n=36)	RI (n=30)	no RI (n=34)	RI (n=33)	no RI (n=31)	RI (n=378)	no RI (n=379)	RI (n=614)	no RI (n=307)	RI (n=1192)	no RI (n=889)
Age (years) Median [IQR]	70 [66-77]	70 [65-75]	67·0 [59·0-71·6]	67·1 [61·9-70·7]	70·7 [65·5-73·6]	71·7 [62·5-76·3]	73·0 [68·0-79·0]	72·0 [67·0-78·0]	68·6 [63·2-73·1]	68·9 [64·3-73·8]	71·0 [64·0-76·0]	71·0 [65·0-77·0]	NE NE	NE NE
<70	43 (42·6)	45 (44·1)	24 (66·7)	23 (63·9)	14 (46·7)	16 (47·1)	11 (33·3)	12 (38·7)	209 (55·3)	206 (54·4)	263 (42·8)	132 (43·0)	564 (47·3)	434 (48·8)
≥70	58 (57·4)	57 (55·9)	12 (33·3)	13 (36·1)	16 (53·3)	18 (52·9)	22 (66·7)	19 (61·3)	169 (44·7)	173 (45·6)	351 (57·2)	175 (57·0)	628 (52·7)	455 (51·2)
Performance status														
0,1	67 (66·3)	55 (54·5)	35 (97·2)	30 (83·3)	20 (66·7)	19 (55·9)	27 (81·8)	26 (83·9)	346 (91·5)	348 (91·8)	536 (87·4)	265 (86·6)	1031 (86·6)	743 (83·8)
≥2	34 (33·7)	46 (45·5)	1 (2·8)	6 (16·7)	10 (33·3)	15 (44·1)	6 (18·2)	5 (16·1)	32 (8·5)	31 (8·2)	77 (12·6)	41 (13·4)	160 (13·4)	144 (16·2)
missing		1									1	1	1	2
Serum PSA														
<143	48 (49·0)	62 (63·3)	23 (63·9)	25 (69·4)	15 (50·0)	21 (61·8)	15 (45·5)	14 (45·2)	180 (49·5)	182 (49·7)	298 (49·3)	135 (44·3)	579 (49·7)	439 (50·5)
≥143	50 (51·0)	36 (36·7)	13 (36·1)	11 (30·6)	15 (50·0)	13 (38·2)	18 (54·5)	17 (54·8)	184 (50·5)	184 (50·3)	307 (50·7)	170 (55·7)	587 (50·3)	431 (49·5)
missing	3	4							14	13	9	2	26	19
Hemoglobin														
<12·4	46 (47·9)	56 (57·7)	8 (22·2)	14 (38·9)	15 (50·0)	11 (32·3)	12 (36·4)	12 (38·7)	174 (46·8)	186 (49·5)	329 (53·6)	169 (55·0)	584 (49·4)	448 (50·9)
≥12·4	50 (52·1)	41 (42·3)	28 (77·8)	22 (61·1)	15 (50·0)	23 (67·7)	21 (63·6)	19 (61·3)	198 (53·2)	190 (50·5)	285 (46·4)	138 (45·0)	597 (50·6)	433 (49·1)
missing	5	5							6	3			11	8
Alkaline Phosphatases														
<248·5	48 (49·0)	35 (36·8)	24 (66·7)	20 (55·6)	4 (13·3)	7 (20·6)	17 (51·5)	14 (45·2)	171 (46·5)	170 (45·5)	345 (56·2)	173 (56·4)	609 (51·7)	419 (47·8)
≥248·5	50 (51·0)	60 (63·2)	12 (33·3)	16 (44·4)	26 (86·7)	27 (79·4)	16 (48·5)	17 (54·8)	197 (53·5)	204 (54·5)	269 (43·8)	134 (43·6)	570 (48·3)	458 (52·2)
missing	3	7							10	5			13	12
Number of bone metastases**														
≤6	28 (28·6)	37 (37·0)	7 (19·4)	8 (22·2)	5 (16·7)	4 (11·8)	12 (36·4)	7 (22·6)	NA	NA	100 (16·4)	38 (12·4)	152 (18·8)	94 (18·5)
>6	70 (71·4)	63 (63·0)	29 (80·6)	28 (77·8)	25 (83·3)	30 (88·2)	21 (63·6)	24 (77·4)			511 (83·6)	268 (87·6)	656 (81·2)	413 (81·5)
missing	3	2									3	1	6	3
Median follow-up (min-max) (months)	62·7 (12·0-62·7)	50·3 (1·8-52·3)	22·0 (1·0-32·3)	22·3 (1·7-28·6)	NE (2·9-112·3)	NE (2·6-188·1)	15·0 (0·7-25·6)	9·8 (0·5-24·5)	38·4 (1·7-75·1)	39·1 (0·4-59·3)	10·8 (0·4-33·8)	9·1 (0·7-36·6)	NE (0·4-112·3)	NE (0·4- 188·1)
Number of deaths	97 (96·0)	97 (95·1)	14 (38·9)	27 (75·0)	30 (100)	34 (100)	23 (69·7)	27 (87·1)	308 (81·5)	310 (81·8)	333 (54 2)	195 (63·5)	805 (67·5)	690 (77·6)
Number of symptomatic skeletal events	NA	NA	NA	NA	8 (26·7)	12 (35·3)	16 (48·5)	17 (54·8)	199 (52·6)	197 (52·0)	202 (32·9)	116 (37·8)	425 (35·6)	342 (38·5)
Spinal cord compression														
Pathologic bone fracture					1(3·3)	3(8·8)	2 (6·1)	3 (9·7)	31 (8·2)	27 (7·1)	14 (2·3)	9 (2·9)	48 (4·0)	42 (4·7)
Surgical intervention					0	0	1 (3·0)	1 (3·2)	14 (3·7)	11 (2·9)	22 (3·6)	12 (3·9)	37 (3·1)	24 (2·7)
External radiotherapy[‡]					0	0	0	0	0	1 (0·3)	2 (0·3)	0	2 (0·2)	1 (0·1)
					7 (23·3)	9 (26·5)	13 (39·4)	13 (41·9)	154 (40·7)	158 (41·7)	164 (26·7)	95 (30·9)	338 (28·4)	275 (30·9)

NE= not estimable, NA= not available; IQR= Interquartile Range; RI= radio-isotopes, [†] Continuous characteristics will be divided into 2 classes using the median, ** For the Bayer152850 [10] and ALSYMPCA[11] trials, superscan was considered as higher than 6 bone metastases. [‡] This category contains both external beam radiotherapy and use of radioisotope for TRAPEZE trial[9], see eTable 1 for other abbreviations

eTable 5. Risk of bias summary: authors' judgments about each risk of bias item for each included study

Items	EORTC30921	MDA 1996	Norway 1997	Bayer 15280	TRAPEZE	ALSYMPCA
Random sequence generation (selection bias)	-	+	-	-	?	-
Allocation concealment (selection bias)	-	-	-	-	-	-
Follow-up quality (Kaplan-Meier inversed)	-	-	-	-	-	-
Blinding of participants and personnel (performance bias)	-	?	-	-	?	-
Blinding of outcome assessment (detection bias)	-	-	-	-	-	-
Incomplete outcome data (attrition bias)	-	-	-	-	-	-
Selective reporting (reporting bias)	-	-	-	-	-	-
Other bias	?	?	?	?	?	?

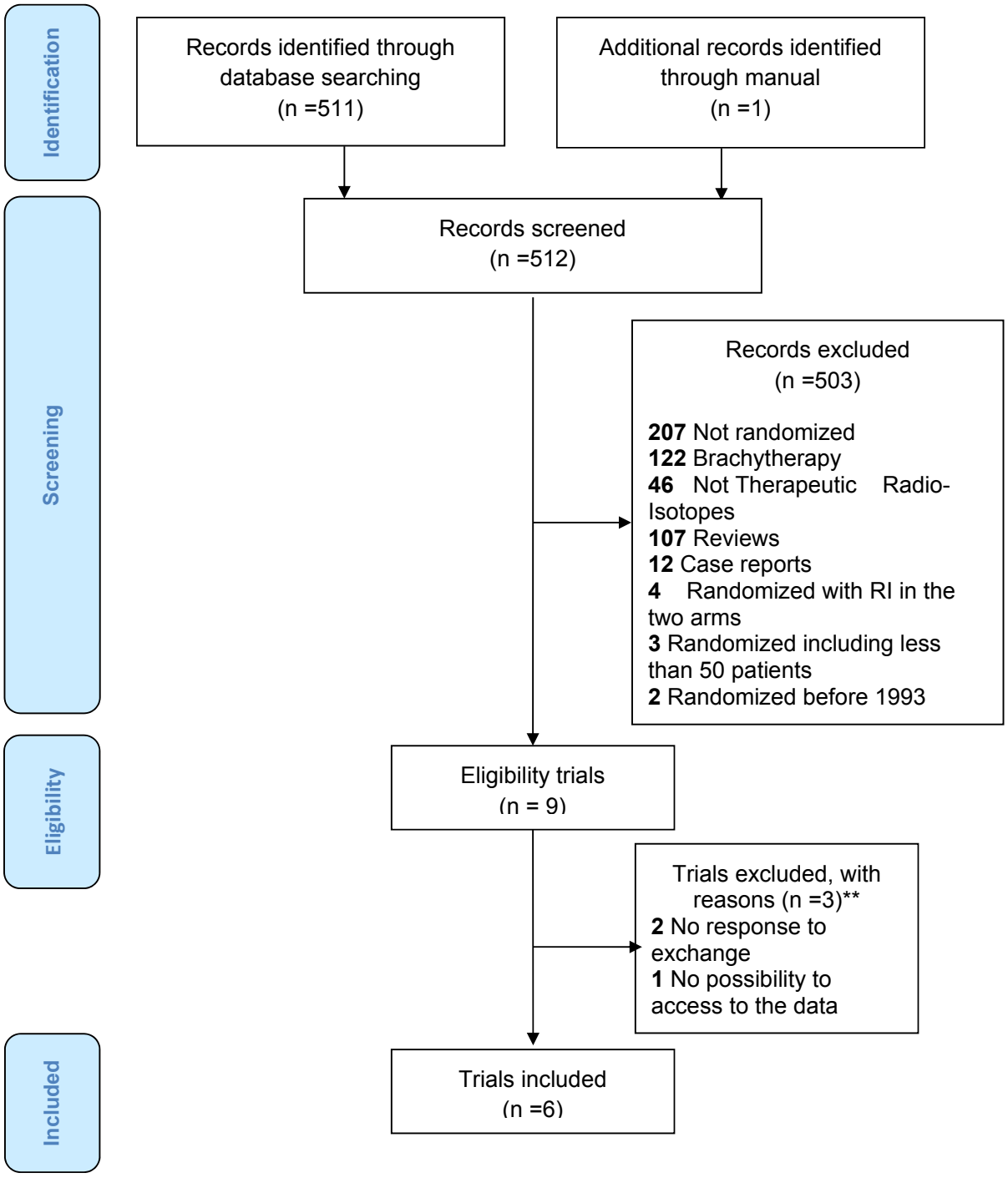
Each domain was judged as 'low risk of bias' (-), 'high risk of bias' (+), or 'unclear risk of bias' (?) in each study according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2011).

eTable 6. Description of selected toxic effects of grade ≥3 per trial and per arm

Trials	Hematological toxicity[⊥]		Nausea and/or vomiting		Febrile neutropenia	
	# of toxicities / n in experimental arm Missing: n	# of toxicities / n in control arm Missing: n	# of toxicities / n in experimental arm Missing: n	# of toxicities / n in control arm Missing: n	# of toxicities / n in experimental arm Missing: n	# of toxicities / n in control arm Missing: n
EORTC 30921[6 *]	41/ 81 20	40/89 13	13/94 7	7/85 17	NA	NA
MDA 1996[7] ǂ	18/36 0	12/36 0	3/36 0	6/36 0	0/36 0	2/36 0
Norway 1997[8]	3/28 2	2/ 31 3	6/26 4	6/27 7	0/30 0	0/34 0
Bayer15280[10] †	2/33 0	2/31 0	1/9 24	0/10 21	0/33 0	0/31 0
TRAPEZE[9 ⊤]	54/ 378 0	47/ 379 0	11/378 0	7/379 0	28/ 378 0	26/ 379 0
ALSYMPCA[11] ††	122/ 606 8	35/ 301 6	16/ 259 355	10/120 187	1/ 614 0	1/307 0

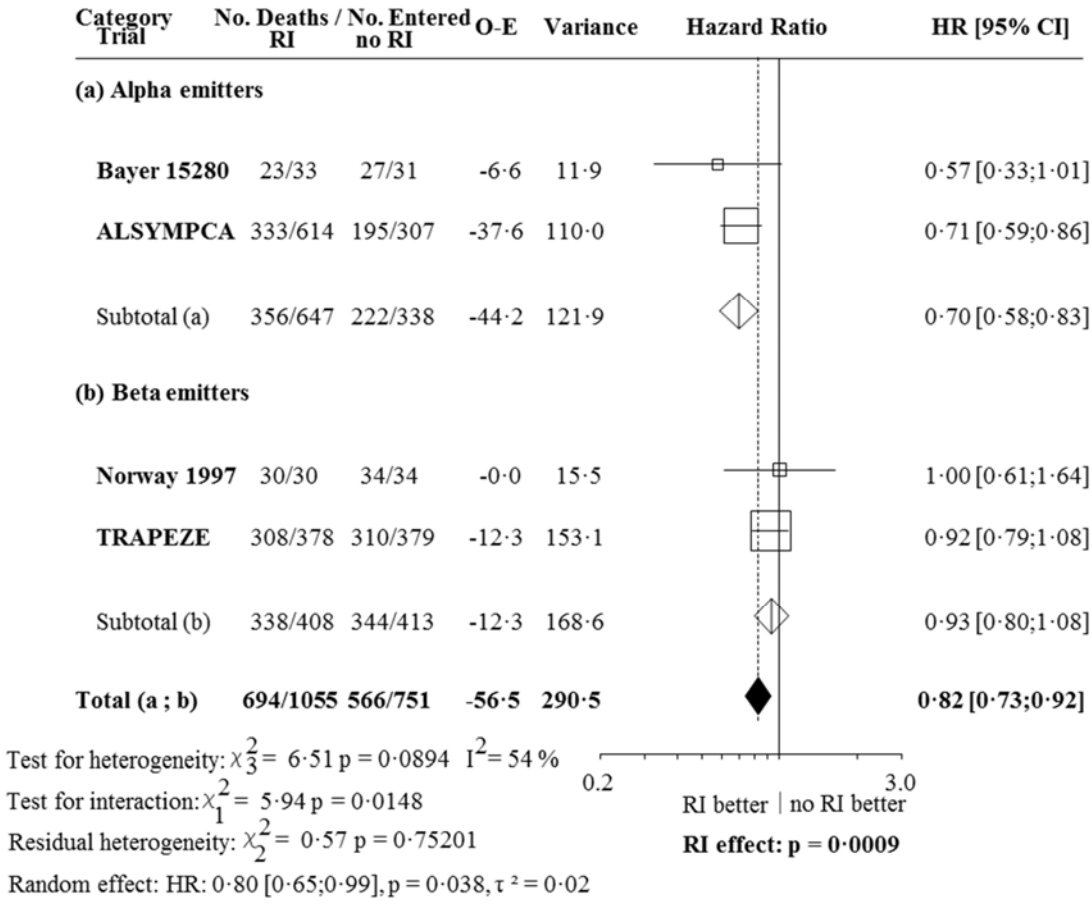
NA: not available, [⊥] hematological toxicity includes hemoglobin, white blood cells and platelets
[*] information related to the occurrence of febrile neutropenia was not available for EORTC 30921's trial [6] because not in the database
ǂ As MDA 1996[7]
is an old trial, individual data were available provided to go back in patient records and thus only some information was extracted from investigator for this meta-analysis. This excluded toxicities data. So, information from toxicity data was extracted from the publication doing some hypotheses. We considered (i) patients with a specific toxicity as different to patients with another toxicity and (ii) nausea and vomiting toxicity as toxicities of grade ≥3 although specified as grade ≥2 in the paper. A sensitivity analysis for nausea and/or vomiting was performed after excluding this trial
† for hematological toxicities, information was extracted from the publication
⊤ only events which were grade ≥3 were reported. So, missing data were considered as no toxicity or toxicity with grade <3
†† febrile neutropenia was extracted from the paper
see eTable 1 for other abbreviations

eFigure 1. Flow diagram of studies inclusion and exclusion



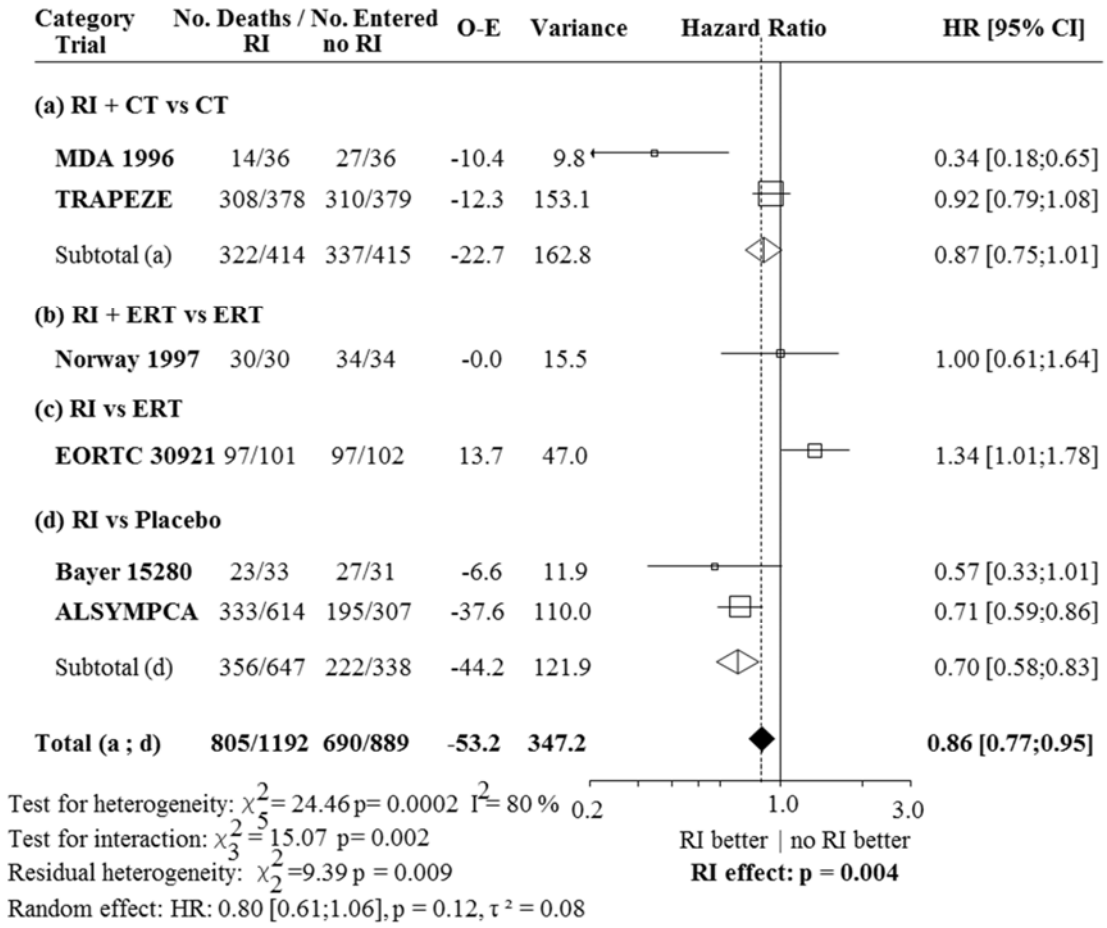
*Such as preclinical, biomarker, cost and epidemiological studies, **The sample size of these trials ranges from 80 to 152 patients. The only information we could extract from the published data is an estimation of overall survival hazard ratio without precision for 2 trials using the medians and assuming an exponential distribution (See eReferences[12-14]).

eFigure 2. Overall survival for trials comparing radioisotopes (RIs) with no RIs according to the type of radiation emitted from RIs after excluding the MDA 1996 and EORTC trials



ALSYMPCA= ALpharadin in SYMptomatic Prostate CAncer patients, TRAPEZE= Taxane RAdioisotoPE ZolEdronic acid, RI: radio-isotope, O-E: observed minus expected number of deaths in the experimental arm, HR: Hazard ratio, CI: confidence interval, τ^2 estimated by DerSimonian and Laird method, Test for heterogeneity: p=0·47, I^2=0% and p=0·75, I^2=0% for alpha emitters and beta emitters, respectively

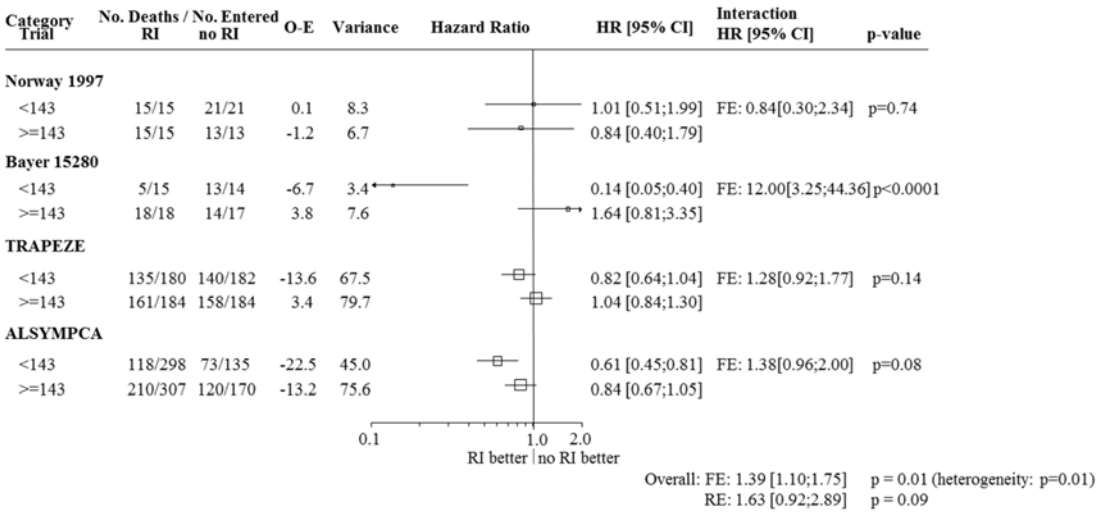
eFigure 3. Forest plot for subset analysis of overall survival according to the type of comparison



CT: Chemotherapy, ERT: External radiotherapy, RI: radio-isotope
ALSYMPCA= ALpharadin in SYMptomatic Prostate CAncer patients, EORTC= European Organisation for Research and Treatment of Cancer, MDA= M D Anderson Cancer Center, TRAPEZE= Taxane RAdioisotoPE ZolEdronic acid, O-E: observed minus expected number of deaths in the experimental arm, HR: Hazard ratio, CI: confidence interval, τ^2 estimated by DerSimonian and Laird method

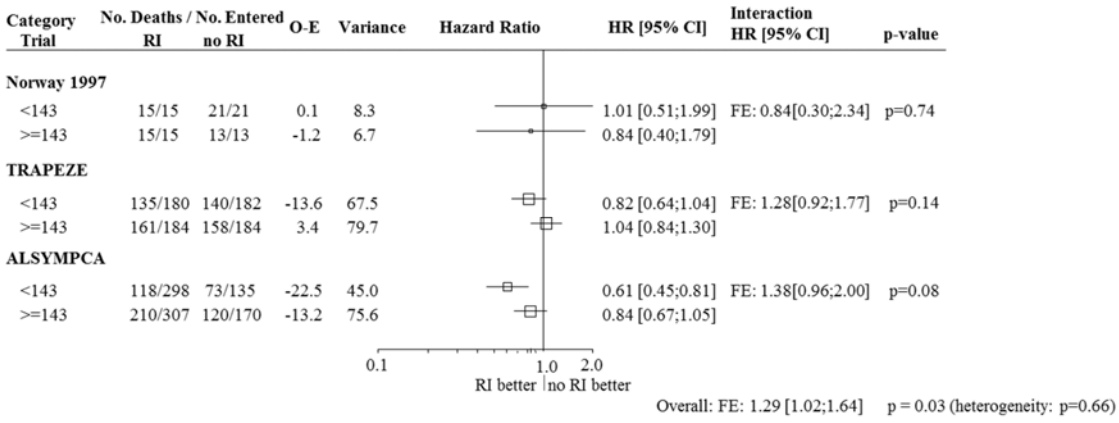
eFigure 4. Forest plots for serum prostate-specific antigen subgroup analysis for overall survival

A. PSA subgroup analysis after excluding MDA 1996 [7] and EORTC 30921[6]



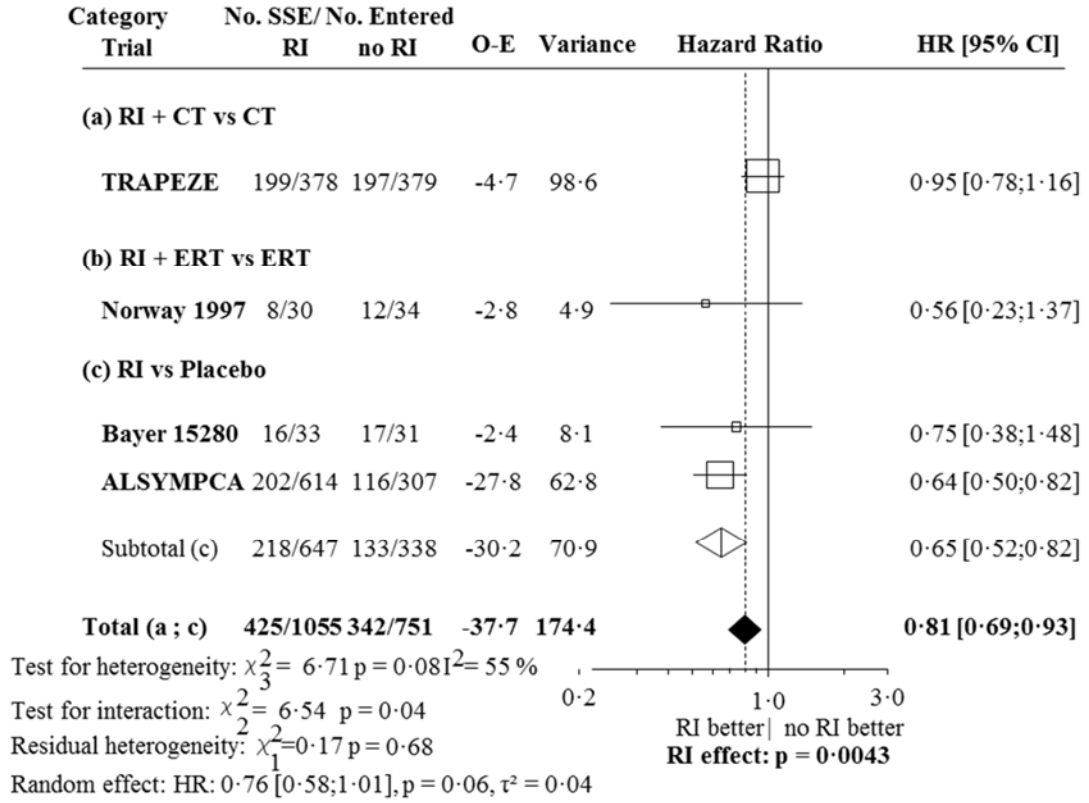
RI: radio-isotope, O-E: observed minus expected number of deaths in the experimental arm, HR: Hazard ratio, CI: confidence interval, FE: fixed effect model, RE: random effect model
see eFigure 3 for other abbreviations

B. PSA subgroup analysis after excluding MDA 1996[7], EORTC 30921[6] and Bayer 15280 [10]: Sensitivity analysis



RI: radio-isotope, O-E: observed minus expected number of deaths in the experimental arm, HR: Hazard ratio, CI: confidence interval, FE: fixed effect model
see eFigure 3 for other abbreviations

eFigure 5. Forest plot for subset analysis according to the type of comparison for symptomatic skeletal event (SSE)–free survival[⊥]



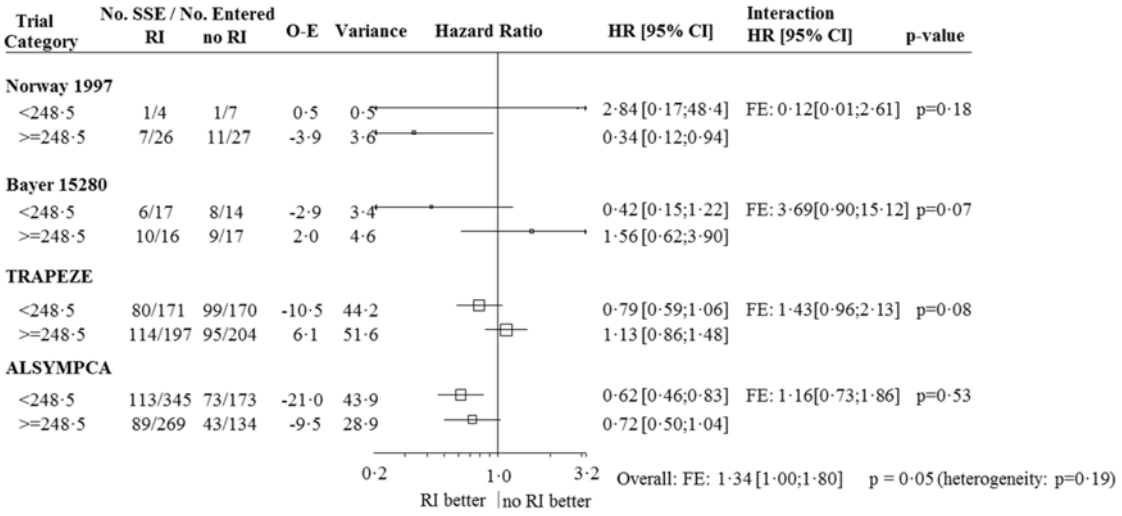
[⊥] MDA 1996 [7] and EORTC 30921's[6] trials were excluded for this analysis since no available information for the former and not reliability data from the latter

SEE: symptomatic skeletal event, CT: Chemotherapy, ERT: External radiotherapy, RI: radio-isotope, O-E: observed minus expected number of SSE in the experimental arm, HR: Hazard ratio, CI: confidence interval, τ^2 estimated by DerSimonian and Laird method

see eFigure 3 for other abbreviations

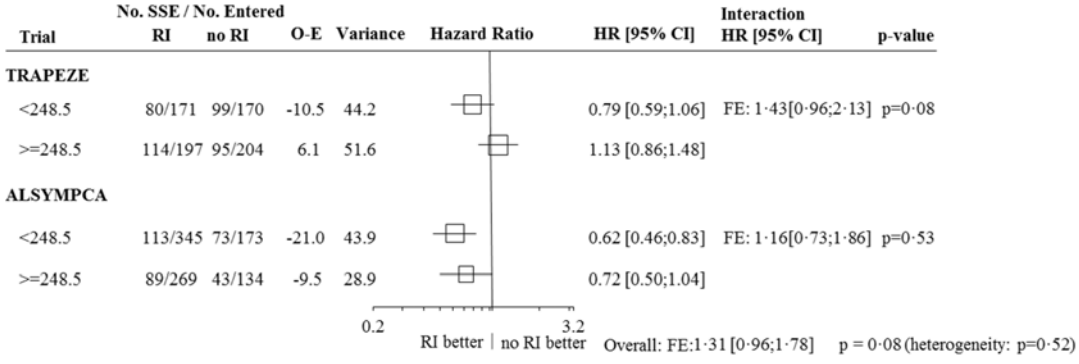
eFigure 6. Forest plots of alkaline phosphatase level subgroup analysis for symptomatic skeletal event (SSE)–free survival[⊥]

A. Alkaline Phosphatase Level (ALP) after excluding MDA 1996 [7] and EORTC 30921[6]



[⊥] MDA 1996 [7] and EORTC 30921'[6] trials were excluded for this analysis since no available information (MDA 1996[7]) and not reliability data (EORTC 30921 [6])
RI: radio-isotope, O-E: observed minus expected number of SSE in the experimental arm, HR: Hazard ratio, CI: confidence interval, FE: fixed effect model
see eFigure 3 for other abbreviations

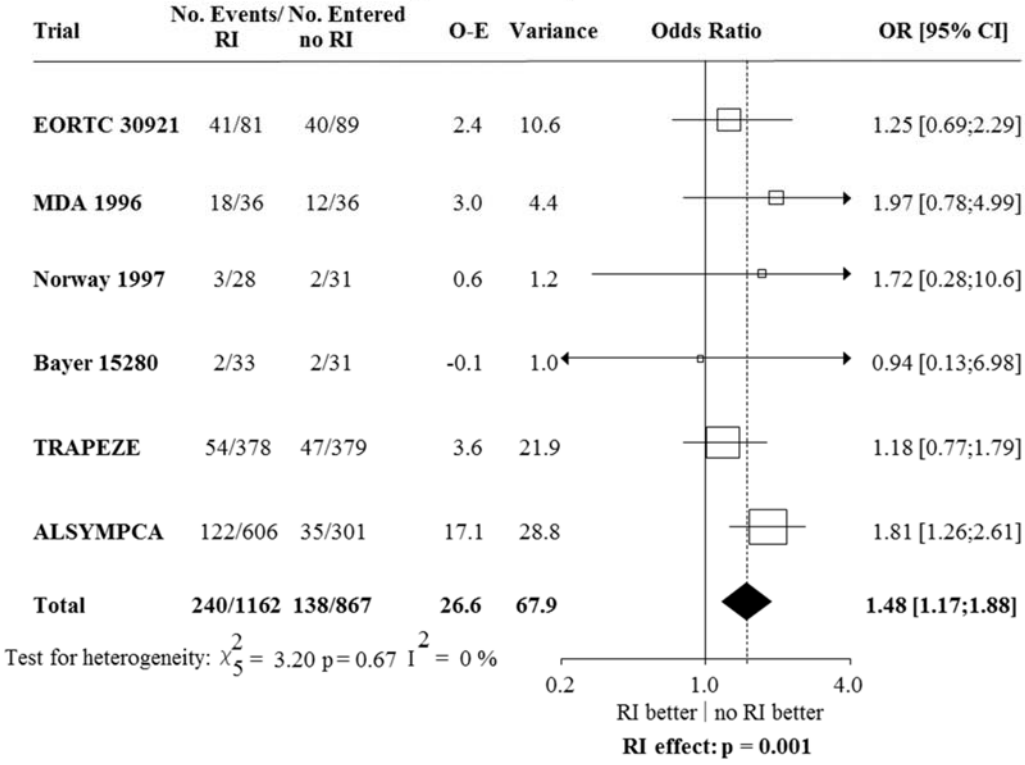
B. Alkaline Phosphatase Level (ALP) after excluding MDA 1996[7], EORTC 30921[6] Norway[8] and Bayer15280[10] : Sensitivity analysis



[⊥] MDA 1996 [7] and EORTC 30921'[6] trials were excluded for this analysis since no available information (MDA 1996[7]) and not reliability data (EORTC 30921 [6])
RI: radio-isotope, O-E: observed minus expected number of SSE in the experimental arm, HR: Hazard ratio, CI: confidence interval, FE: fixed effect model
see eFigure 3 for other abbreviations

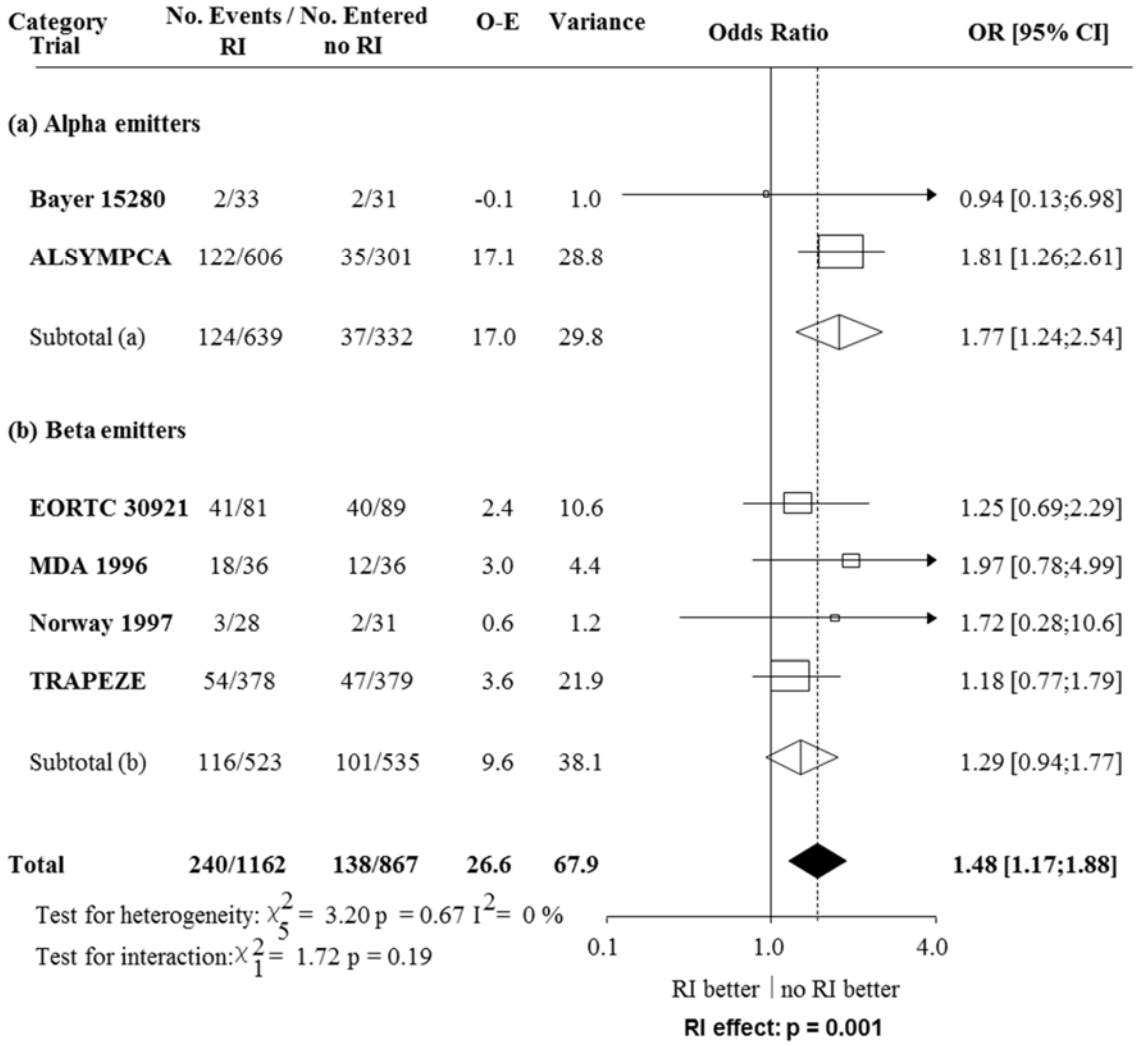
eFigure 7. Hematological toxic effects analysis

A. Forest plot of hematological toxicity



RI: radio-isotope, O-E: observed minus expected number of hematological toxicity events in the experimental arm, OR: Odds ratio, CI: confidence interval
see eFigure 3 for other abbreviations

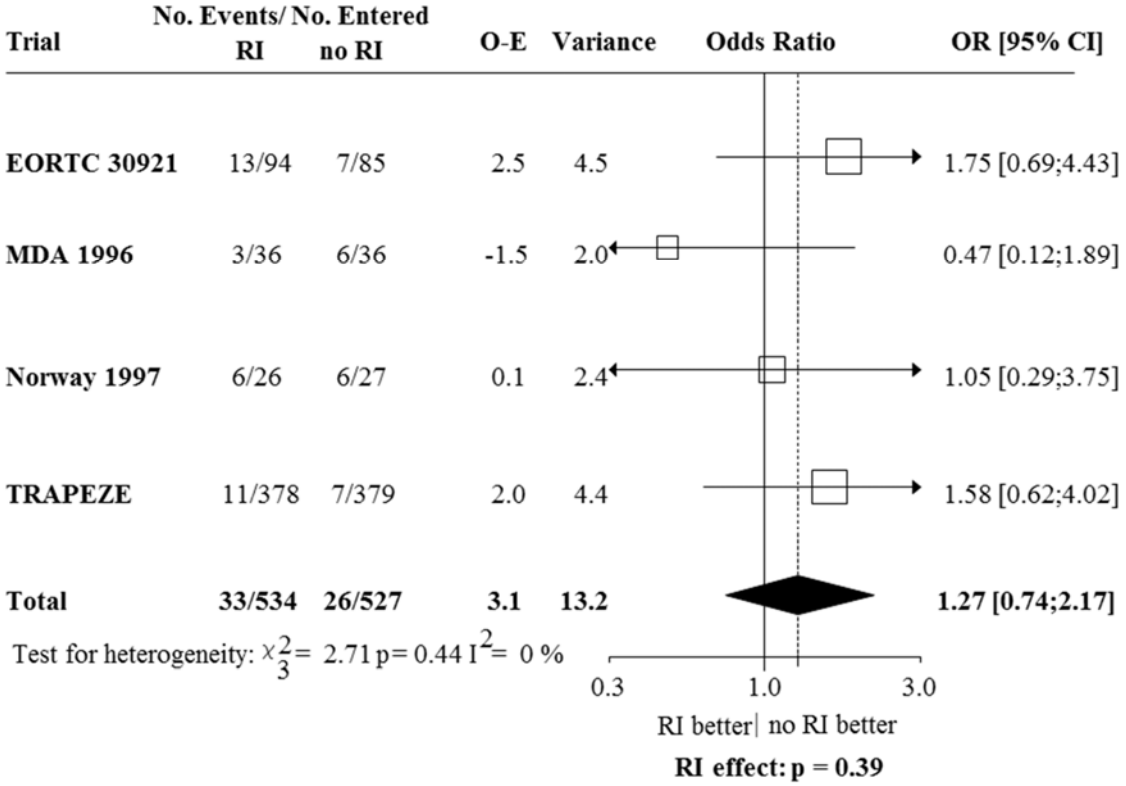
B. Forest plot of hematological toxicity according to the type of radiation emitted from radio-isotopes (RI) (unplanned analysis)



RI: radio-isotope, O-E: observed minus expected number of hematological toxicity events in the experimental arm, OR: Odds ratio, CI: confidence interval
see eFigure 3 for other abbreviations

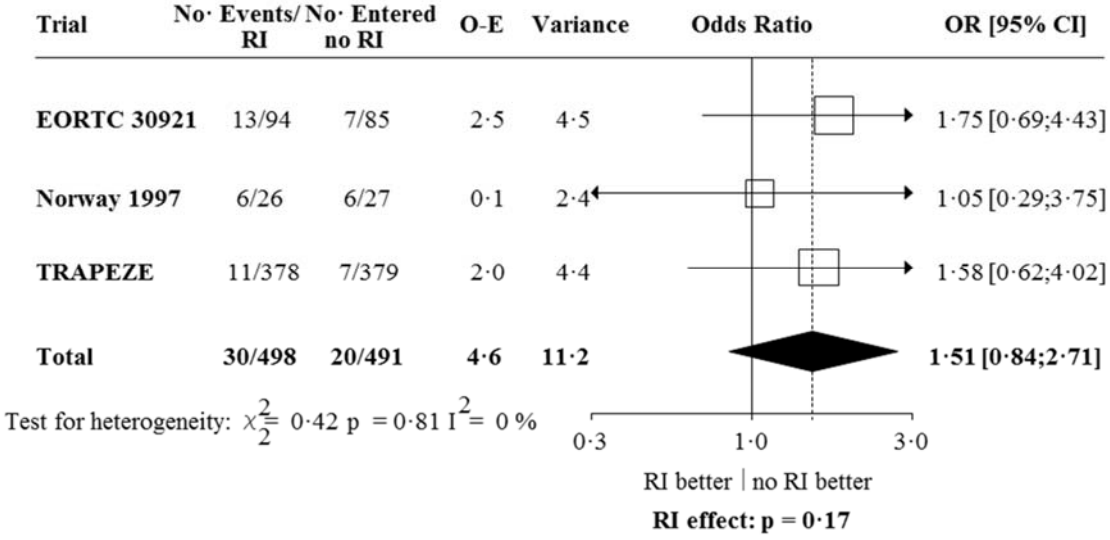
eFigure 8. Nausea and/or vomiting analysis

A. Forest plot of nausea and/or vomiting



RI: radio-isotope, O-E: observed minus expected number of nausea and/or vomiting events in the experimental arm, OR: Odds ratio, CI: confidence interval
see eFigure 3 for other abbreviations

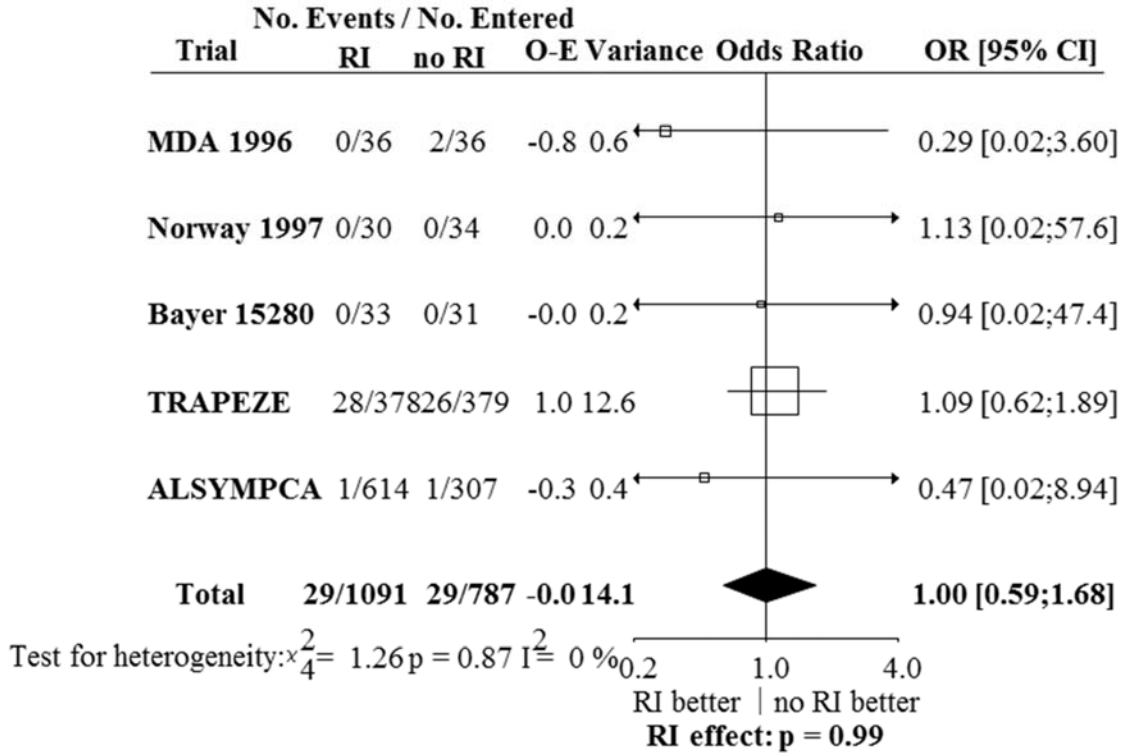
B. Forest plot of nausea and/or vomiting after excluding MDA 1996's trial [7] (sensitivity analysis)



RI: radio-isotope, O-E: observed minus expected number of nausea and/or vomiting events in the experimental arm, OR: Odds ratio, CI: confidence interval
see eFigure 3 for other abbreviations

eFigure 9. Febrile neutropenia toxic effects analysis*

A. Forest plot of febrile neutropenia

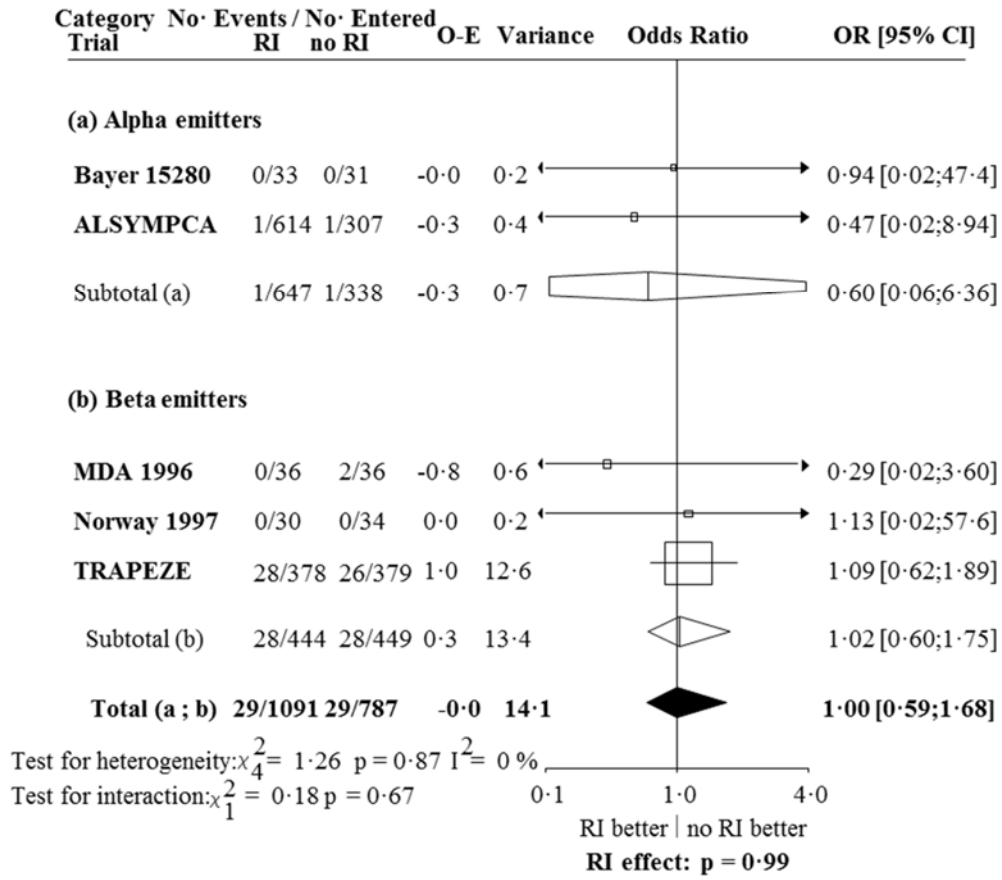


RI: radio-isotope, O-E: observed minus expected number of febrile neutropenia events in the experimental arm, OR: Odds ratio, CI: confidence interval

* we imputed the value of 0.5 for trials with no event for the computation of the odds ratio and its confidence interval, febrile neutropenia is not available for EORTC 309216

see eFigure 3 for other abbreviations

B. Forest plot of febrile neutropenia according to the type of radiation emitted from radio-isotopes (RI)* (unplanned analysis)



RI: radio-isotope, O-E: observed minus expected number of febrile neutropenia events in the experimental arm, OR: Odds ratio, CI: confidence interval

* we imputed the value of 0.5 for trials with no event for the computation of the odds ratio and its confidence interval, febrile neutropenia is not available for EORTC 309216

see eFigure 3 for other abbreviations

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