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Matching-adjusted indirect treatment comparison of [¹⁷⁷Lu]Lu-DOTA-TATE, everolimus and sunitinib in advanced, unresectable gastroenteropancreatic neuroendocrine tumours: Relative effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE in gastroenteropancreatic neuroendocrine tumours

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ARTICLE INFO

Article history:

Received 13 October 2020

Received in revised form

28 June 2021

Accepted 29 June 2021

Keywords:

Overall survival

Progression-free survival

Comparative effectiveness

Best supportive care

ABSTRACT

Head-to-head comparisons of the efficacy of treatments for gastroenteropancreatic neuroendocrine tumours (GEP-NETs) have not yet been reported. This study used a series of matching-adjusted indirect comparisons to indirectly compare the effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE to everolimus, sunitinib and best supportive care (BSC) for extending progression-free survival and overall survival in patients with advanced, unresectable gastrointestinal (GI)-NETs and P-NETs. The results of the main analysis suggest that after accounting for differences in key prognostic variables, the hazard of progression was 62% (hazard ratio [HR], 0.38; confidence interval [CI]₉₅ 0.25–0.58) and 65% (HR 0.35 CI₉₅ 0.21–0.59) lower in patients with GI-NETs treated with [¹⁷⁷Lu]Lu-DOTA-TATE than in those treated with everolimus and BSC, respectively. Similarly, the hazard of progression was 64% (HR 0.36 CI₉₅ 0.18–0.70), 54% (HR 0.46 CI₉₅ 0.30–0.71) and 79–87% (HR 0.21 CI₉₅ 0.13–0.32; HR 0.13 CI₉₅ 0.08–0.22) lower in patients with P-NET treated with [¹⁷⁷Lu]Lu-DOTA-TATE than in those treated with sunitinib, everolimus and BSC, respectively. The hazard of death was 58% (HR 0.42 CI₉₅ 0.25–0.72), 47% (HR 0.53 CI₉₅ 0.33–0.87) and 44–64% (HR 0.56 CI₉₅ 0.36–0.90; HR 0.34 CI₉₅ 0.20–0.57) lower in P-patients with NET treated with [¹⁷⁷Lu]Lu-DOTA-TATE than in those treated with sunitinib, everolimus and BSC, respectively. While our results must be interpreted with caution given the non-randomised nature of the comparisons and the potential for residual confounding, the magnitude of the effect sizes we observe and their consistency across comparators suggest that [¹⁷⁷Lu]Lu-DOTA-TATE may be a more effective treatment option than everolimus, sunitinib and BSC in advanced, unresectable GEP-NETs.

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<https://doi.org/10.1016/j.ejcsup.2021.06.002>

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1. Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are a heterogeneous group of tumours which can be classified based on the site of origin into tumours originating from neuroendocrine cells of the gastrointestinal system (GI-NETs) or pancreas (P-NETs) [1]. Currently, the only curative treatment for NETs is surgery, which is mostly reserved for fit patients with limited disease burden. In patients with advanced, unresectable GEP-NETs, therapeutic options have historically been limited. The approvals in 2011 of two biologically targeted therapies, everolimus (Afinitor®; Novartis International AG), an mTOR inhibitor, and sunitinib (Sutent®; Pfizer Inc.), an RTK inhibitor, therefore represented a significant advancement in the condition. Both everolimus and sunitinib were approved for the treatment of patients with advanced, progressive, well-differentiated P-NETs, whereas only everolimus received approval for the treatment of advanced, progressive, well-differentiated GI-NETs.

¹⁷⁷Lu]Lu-DOTA-TATE ([¹⁷⁷Lu-DOTA⁰,Tyr³]-octreotate, Lutathera®; Advanced Accelerator Applications), a peptide receptor radionuclide therapy (PRRT) that selectively targets the somatostatin receptor subtypes 2, 3 and 5 (SSTR 2, 3 and 5), received marketing authorisation for the treatment of GI-NETs and P-NETs in 2017 (European Union)/2018 (United States of America) on the basis of data from the NETTER-1 trial and ERASMUS study [2]. The NETTER-1 trial reported longer progression-free survival (PFS) and a significantly higher response rate for [¹⁷⁷Lu]Lu-DOTA-TATE relative to high-dose octreotide LAR in patients with advanced midgut neuroendocrine tumours and additionally reported preliminary data suggestive of improved overall survival (OS) [2]. The ERASMUS study reported single-centre real-world data on the outcomes of patients with GEP-NET, all of whom were treated with [¹⁷⁷Lu]Lu-DOTA-TATE between 2000 and 2015 (Brabander et al., 2017).

Given the introduction of [¹⁷⁷Lu]Lu-DOTA-TATE, there is an interest in considering how its effectiveness compares with that of established therapies in these two indications such as everolimus and sunitinib. In line with this, the clinical effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE for treating unresectable progressive well-differentiated P-NETs with disease progression relative to sunitinib is currently being assessed in the OCCLURANDOM trial (NCT02230176). However, because results from this trial are still pending, outcomes must currently be compared indirectly across trials.

As patient populations may differ across trials, the results of a naïve comparison of outcomes across trials may be biased. However, if a common treatment arm has been used across the trials to be compared (e.g. placebo), an anchored indirect treatment comparison (e.g. a network meta-analysis) [3] can be carried out. Anchored comparisons are advantageous as they preserve many of the advantages of randomisation. As one of the pivotal trials providing data for [¹⁷⁷Lu]Lu-DOTA-TATE in GI-NETs and P-NETs (the ERASMUS study) [4–6] was single arm in nature, it is not possible to have a common comparator arm, and anchored comparisons between this trial and everolimus and sunitinib trials are, therefore, not possible. Matching-adjusted indirect comparison (MAIC) [3] is an unanchored indirect comparison methodology, akin to propensity score

weighting, but suitable for use when individual patient data (IPD) are only available on one of the trials to be compared. The methodology addresses differences in the populations across trials by weighting the population for which IPD are available, such that it resembles the underlying distribution of patient characteristics in the treatment arms of the comparator trials; the population average outcome in this re-weighted population can be interpreted as that which would have been observed had the re-weighted trial been carried out in the same population as the comparator trial.

This study aimed to use a series of MAICs to indirectly compare PFS in patients with GI-NETs or P-NETs and OS in patients with P-NETs after treatment with [¹⁷⁷Lu]Lu-DOTA-TATE, everolimus, sunitinib or best supportive care (BSC) across separate randomised trials.

2. Material and methods

2.1. Data sources

Evidence for the efficacy of [¹⁷⁷Lu]Lu-DOTA-TATE in GEP-NETs was obtained from the ERASMUS study [4]. The ERASMUS study was a single-arm, uncontrolled, open, prospective study to test the efficacy and safety of [¹⁷⁷Lu]Lu-DOTA-TATE, for which IPD were fully available. Only Dutch patients were included as the non-Dutch patients had incomplete follow-up data.

To inform the comparison in GI-NETs, survival data from the everolimus arms of the GI-NET subgroup of the RADIANT-4 study [7] were obtained for PFS [7]. However, no data on OS were available for this trial subgroup.

For P-NETs, OS and PFS data on everolimus and sunitinib were obtained from the RADIANT-3 study [8,9] and the NCT00428597 study [10,11], respectively.

Data from the placebo arms of the everolimus and sunitinib trials were also obtained to enable comparisons to be made between [¹⁷⁷Lu]Lu-DOTA-TATE and BSC. Little information on the specific constituents of BSC administered across the trials was reported; however, a substantial proportion of patients were reported to have received somatostatin analogues (SSAs) as part of BSC (40% RADIANT-3; 28% NCT00428597; not reported for RADIANT-4).

Table 1 summarises the patient population, interventions and nature of the data available across the included studies.

2.2. Outcome measures

Across all trials, OS was defined as the time from randomisation to death from any cause and PFS was defined as the time from randomisation to disease progression or death from any cause. Tumour response in the ERASMUS trial was assessed on computerised tomography or magnetic resonance imaging as per the Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1). RADIANT-3 [8,9] and RADIANT-4 used investigator-assessed progression as per RECIST 1.0 criteria, as did NCT00428597 [10,11]. It was assumed that the criteria used across the studies were comparable.

For studies where Kaplan-Meier curves were available but IPD were not, the published Kaplan-Meier curves were

Table 1 – Eligible studies.

Trial	Patient population	Intervention(s) of interest	OS data	PFS data
ERASMUS	GI-NETs and P-NETs	[¹⁷⁷ Lu]Lu-DOTA-TATE	IPD	IPD
RADIANT-4	GI-NETs	Everolimus and BSC	Not available	Kaplan-Meier
RADIANT-3	P-NETs	Everolimus and BSC	Kaplan-Meier	Kaplan-Meier
NCT00428597	P-NETs	Sunitinib and BSC	Kaplan-Meier	Kaplan-Meier

OS, overall survival; PFS, progression-free survival; IPD, individual patient data; BSC, best supportive care; GI-NETs, gastrointestinal neuroendocrine tumours; P-NETs, pancreatic neuroendocrine tumours.

digitised and the Guyot method was used to reconstruct individual event times and censoring times from the digitised curves [12].

2.3. Statistical methods

A total of ten separate MAIC analyses were carried out to provide indirect comparisons of [¹⁷⁷Lu]Lu-DOTA-TATE with everolimus, sunitinib and BSC (Table 2).

To select variables for inclusion in each of the MAICs, a list of all the covariates available in the ERASMUS trial and reported in at least one of the other trials was compiled. The relationship between each covariate in the list and OS and PFS was investigated in the GI-NET and P-NET subgroups of the ERASMUS population. For categorical covariates, the log-rank test was used, whereas for continuous covariates, Cox proportional hazards models were used. Kaplan–Meier plots and log-cumulative hazard plots were used to visualise the results. Variables found to be associated with OS or PFS at the 20% significance level were included in MAICs if the same variable was reported for the comparator study.

For each analysis, logistic regression was used to estimate a weight for each patient in the ERASMUS study describing their propensity to enrol in the ERASMUS study versus the relevant treatment arm of the comparator trial. When applied to the ERASMUS study population, these weights result in the mean covariate values for continuous covariates and proportions for categorical covariates, balancing the corresponding values in the relevant arms of the other trials. The balancing of covariates was checked after estimation of the set of weights for each analysis to confirm the reweighting has

been carried out correctly and the distribution of weights, including the number of individuals assigned zero weight, was summarised using appropriate summary statistics (medians, ranges) and graphical outputs (histograms). An effective sample size (ESS) of the weight-adjusted population was also calculated. This is determined by the extent of differences between the populations being matched, so the larger the differences between the populations, the smaller the ESS will be. Any models with markedly reduced ESS were not reported.

OS and PFS in the original ERASMUS population and the reweighted population were described using median time to the event and Kaplan-Meier curves and compared with the relevant statistics for the comparator treatment arms. Data from the weighted population and from each comparator treatment arm were also combined in Cox proportional hazards regression models to estimate hazard ratios.

To assess the sensitivity of the results to a number of key assumptions underlying the MAICs presented previously, we carried out three separate sensitivity analyses:

1. In our main analysis, we included only Dutch patients from the ERASMUS study as the non-Dutch patients had incomplete follow-up data. To assess whether inclusion of these patients would have impacted the results of the MAIC, we carried out a sensitivity analysis in which non-Dutch patients were also included in the analysis.
2. In the main analysis, we matched against only those variables observed to be significantly associated with the outcomes (OS/PFS) in the individual patient-level data available for the ERASMUS study. This approach was taken as it was considered to provide an appropriate balance between

Table 2 – Specification of analyses.

Analysis #	Indication	Outcome	Source of [¹⁷⁷ Lu]Lu-DOTA-TATE data	Nature of [¹⁷⁷ Lu]Lu-DOTA-TATE data	Treatment arm	Source of comparator data	Nature of comparator data
1	P-NETs	OS	ERASMUS (P-NETs subgroup)	IPD	Everolimus	RADIANT-3	KM
BSC							
Sunitinib							
NCT00428597							
2	GI-NETs	PFS	ERASMUS (GI-NETs subgroup)		BSC	RADIANT-3	
3					Everolimus		
4					BSC		
5					Sunitinib		
6					NCT00428597		
7					BSC		
8					Everolimus		
9					RADIANT-4		
10		BSC					

GI-NETs, gastrointestinal neuroendocrine tumours; P-NETs, pancreatic neuroendocrine tumours; OS, overall survival; PFS, progression-free survival; PLD, patient-level data; IPD, individual patient data; BSC, best supportive care; KM, Kaplan-Meier.

matching the strongest predictors of the outcome across trials and reducing the robustness of results by seeking to match for too many covariates. It is possible that this approach excluded some relevant covariates as the ERASMUS study may not have been powered to detect a significant association between the covariate and the outcome in question. We therefore carried out a sensitivity analysis in which we included all covariates available in both the ERASMUS study and the comparator trials regardless of the association observed in the ERASMUS data.

3. In our main analysis, we matched the ERASMUS study population to each arm of the comparator trial individually because of concerns regarding the balance of patient characteristics across arms in some of the comparator trials. For example, there was some imbalance in the Eastern Cooperative Oncology Group (ECOG) variable across arms in the NCT00428597 [10,11]. Despite this, as MAICs are typically carried out by matching patient characteristics to those of the entire comparator trial population, we carried out a sensitivity analysis in which we have used this approach to illustrate the impact this would have on our results.

All analyses were conducted using R, version 3.3.2, and in line with the corresponding NICE Decision Support Unit guidelines [3,13].

3. Results

3.1. GI-NET

The RADIANT-4 trial included only individuals with an ECOG performance score of 0 or 1; therefore, 5 individuals with a performance score of 2 were excluded from the Erasmus data set used in the MAIC. An additional individual was excluded as they did not have an ECOG performance score recorded. The final Erasmus GI-NET population for the MAIC, therefore, contained 111 patients.

ECOG was the only covariate that was found to be significantly associated with outcomes in the ERASMUS data ($p < 0.20$) and was, therefore, the only variable adjusted for in the MAIC. Table 3 shows the baseline characteristics before and after matching. Covariates not adjusted for have been re-weighted for illustrative purposes. Matching was successful for the covariates included in the MAIC for the GI-only population; the ERASMUS effective sample size was 105 as a result of matching with the everolimus population, only a 5% reduction on the original sample size. For matching with BSC, this was a reduction of 14%. On re-weighting, sex and age were reasonably well balanced; however, previous surgery was not particularly well balanced with 56–57% of individuals in the reweighted ERASMUS population having previous surgery compared with 70% and 63% in the everolimus and BSC arms of RADIANT-4, respectively. Similarly, 7% of the ERASMUS population had had previous chemotherapy compared with 19% and 12% in the everolimus and BSC arms, respectively. On reweighting, 78% of the ERASMUS population had previously used SSA's, whereas this was 78% and 63% in the everolimus and BSC arms, respectively.

Hazard ratios with 95% confidence intervals for the main analysis are provided in Table 4, alongside hazard ratios from the three sensitivity analyses. Kaplan-Meier curves and median survival estimates are also presented in the data supplement. The results of the main analysis suggest that after accounting for differences in key prognostic variables, the hazard of progression is 62% and 65% lower in those treated with [¹⁷⁷Lu]Lu-DOTA-TATE than in those treated with everolimus and BSC, respectively (Table 4). Sensitivity analyses adjusting for all available covariates had the strongest impact on the results, suggesting that when additional covariates are accounted for the hazard is 39% and 61% lower, respectively (Table 4). However, ESS's of 57 (everolimus) and 80 (BSC) represent a reduction in available sample size of 49% and 28%, respectively, demonstrating a lack of population overlap and potentially unstable estimates.

3.2. P-NET

The inclusion and exclusion criteria of ERASMUS and the comparator trials for P-NETs were reviewed with respect to the ten key covariates. There were no differences between the ERASMUS trial, the RADIANT-3 trial and NCT00428597. Note that both the RADIANT-3 trial and NCT00428597 included only patients with a World Health Organisation performance status of two or less, which is also met by all the patients in the ERASMUS trial.

Age, ECOG, previous chemotherapy and previous radiotherapy were found to be significantly associated with outcomes in the ERASMUS data ($p < 0.20$) and were therefore adjusted for in the MAIC. Table 5 shows the baseline characteristics before and after matching for ERASMUS and NCT00428597. Covariates that were adjusted for in the MAIC are highlighted in the table; those not adjusted for have also been re-weighted for illustrative purposes. Matching was successful for the covariates included in the MAICs, but the ERASMUS effective sample size was considerably reduced as a result of matching. Covariates not adjusted for in the MAIC were not well balanced, with 53–58% men in the ERASMUS population but 47–49% men in the sunitinib and BSC arms of NCT00428597. Previous surgery was 40% in the ERASMUS population but 49–52% in the sunitinib and BSC arms of NCT00428597, and non-functionality was 40–44% in ERASMUS and 49–52% in the sunitinib and BSC arms of NCT00428597.

Table 6 shows the baseline characteristics before and after matching for ERASMUS and RADIANT-3. Results were similar to those observed for NCT00428597; however, the ERASMUS effective sample size was extremely low, indicating very little overlap in study populations; therefore, caution in interpretation of the results is recommended. As with NCT00428597, covariates not adjusted for in the MAIC were not well balanced.

Hazard ratios with 95% confidence intervals for PFS are provided in Table 7 and OS in Table 8 alongside hazard ratios from two of the three sensitivity analyses. Kaplan-Meier curves and median survival estimates are presented in the data supplement. The results of the main analysis suggest that after accounting for differences in key prognostic variables, the hazard of progression is 64%, 54% and 79–87% lower

Table 3 – Patient characteristics in [¹⁷⁷Lu]Lu-DOTA-TATE (ERASMUS) before and after matching to the RADIANT-4 GI subgroup.

Patient characteristic		ERASMUS (pre-match)	ERASMUS (post-match everolimus)	RADIANT-4 (GI only)	ERASMUS (post-match BSC)	RADIANT-4 (GI only)
		[¹⁷⁷ Lu]Lu-DOTA- TATE	[¹⁷⁷ Lu]Lu-DOTA- TATE	Everolimus	[¹⁷⁷ Lu]Lu-DOTA- TATE	BSC
N	N	111	111	118	111	57
	Effective sample size:		105		95	
Sex	Male	55%	53%	41%	52%	55%
	Female	45%	47%	59%	48%	45%
ECOG performance status	0	64%	75%	75%	84%	84%
	1	36%	25%	25%	16%	16%
Previous chemotherapy	Yes	6%	7%	19%	7%	12%
	No	94%	93%	81%	93%	88%
Age (years)	Mean (median)	61	61	NA (63)	61	NA (60)
	Previous surgery	Yes	54%	56%	70%	57%
Prior SSA use	No	46%	44%	30%	43%	37%
	Yes	78%	78%	59%	78%	63%
Weights ^a	No	22%	22%	41%	22%	37%
	Mean		1.00		1.00	
	Range		(0.69–1.17)		(0.44–1.31)	

BSC, best supportive care; GI, gastrointestinal; SSA, somatostatin analogue; ECOG, Eastern Cooperative Oncology Group; NA, not available. Tumour functionality and time from disease progression to randomisation are not available from either comparator trial so not included in the table.

^a A histogram describing the full distribution of weights is provided in the data supplement.

in those treated with [¹⁷⁷Lu]Lu-DOTA-TATE than in those treated with sunitinib, everolimus and BSC, respectively (Table 7). For OS, hazard ratios suggested the hazard of death was 58%, 47% and 44–64% lower in those treated with [¹⁷⁷Lu]Lu-DOTA-TATE than in those treated with sunitinib, everolimus and BSC, respectively (Table 8).

Sensitivity analysis 2 (adjusting for all covariates) is not reported in either Table 7 or Table 8, as the overlap in populations was too low to provide valid results. The sensitivity analysis including non-Dutch patients reduced the effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE relative to the comparators, with the hazard ratio describing the extension in OS observed with the [¹⁷⁷Lu]Lu-DOTA-TATE relative to comparators no longer remaining statistically significant.

4. Discussion

In the analyses presented, the single arm ERASMUS study has been used to infer the effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE in patients with GI-NETs relative to BSC and everolimus and its effectiveness in patients with P-NETs relative to BSC, sunitinib and everolimus using MAICs. Across these analyses, [¹⁷⁷Lu]Lu-DOTA-TATE demonstrated superior effectiveness in extending PFS and OS relative to everolimus, sunitinib and BSC.

To perform these analyses, a restricted set of prognostic covariates (age, sex, ECOG, previous radiotherapy and previous chemotherapy) were identified through expert clinical opinion and empirical investigation and used to fit propensity

Table 4 – Hazard ratios estimated from matching-adjusted indirect comparisons for PFS in GI-NETs.

	[¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. everolimus (RADIANT 4 GI-NET subgroup) Hazard ratio PFS (95% CI)	[¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. BSC (RADIANT 4 GI-NET subgroup) Hazard ratio PFS (95% CI)
Main analysis	0.38 [0.25, 0.58]	0.35 [0.21, 0.59]
Sensitivity analysis 1: Incl. non-Dutch ERASMUS patients	0.37 [0.24, 0.55]	0.33 [0.20, 0.55]
Sensitivity analysis 2: Adjusting for all available covariates	0.61 [0.42, 0.91]	0.39 [0.24, 0.65]
Sensitivity analysis 3: Matching to the full comparator population	0.41 [0.27, 0.62]	0.32 [0.20, 0.54]

PFS, progression-free survival; GI-NETs, gastrointestinal neuroendocrine tumours; CI, confidence interval.

Table 5 – Patient characteristics in [¹⁷⁷Lu]Lu-DOTA-TATE (ERASMUS) before and after matching to NCT00428597.^a

Patient characteristic		ERASMUS (pre-match)	ERASMUS (post-match Sunitinib)	NCT00428597	ERASMUS (post-match BSC)	NCT00428597
		[¹⁷⁷ Lu]Lu-DOTA-TATE	[¹⁷⁷ Lu]Lu-DOTA-TATE	Sunitinib	[¹⁷⁷ Lu]Lu-DOTA-TATE	BSC
N	N	62	62	86	62	85
	Effective sample size:		48		35	
Age	Mean (median)	58	56	NA (56)	57	NA (57)
ECOG performance status	0	23%	62%	62%	48%	48%
	1	77%	38%	38%	52%	52%
Previous radiotherapy	Yes	3%	9%	10%	14%	14%
	No	97%	91%	90%	86%	86%
Previous chemotherapy	Yes	13%	9%	8%	16%	16%
	No	87%	91%	92%	84%	84%
Sex	Male	45%	58%	49%	53%	47%
	Female	55%	42%	51%	47%	53%
Previous surgery	Yes	45%	40%	88%	40%	91%
	No	55%	60%	12%	60%	9%
Non-functional	Yes	48%	40%	49%	44%	52%
	No	52%	60%	51%	56%	48%
Median time from initial diagnosis	Years	1.24	1.24	2.4	1.24	2.4
Weights	Mean		1.00		1.00	
	Range		(0.00–5.32)		(0.13–6.95)	

^a A histogram describing the full distribution of weights is provided in the data supplement. BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; NA, not available.

weighting models to produce measures of relative effectiveness adjusted for imbalance in baseline prognosis across trials. As such, the results are only adjusted for differences in these covariates. Given that differences in the distribution of other patient characteristics were observed across trials (e.g.

in prior SSA use), these may confound the relative effectiveness results reported. In an effort to explore this, we carried out sensitivity analyses in which all covariates available across trials were included in the MAIC procedure. In GI-NETs, the relative effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE was

Table 6 – Patient characteristics in [¹⁷⁷Lu]Lu-DOTA-TATE (ERASMUS) before and after matching to RADIANT-3.^a

Patient characteristic		ERASMUS (pre-match)	ERASMUS (post-match everolimus)	RADIANT-3	ERASMUS (post-match BSC)	RADIANT-3
		[¹⁷⁷ Lu]Lu-DOTA-TATE	[¹⁷⁷ Lu]Lu-DOTA-TATE	Everolimus	[¹⁷⁷ Lu]Lu-DOTA-TATE	BSC
N	N	62	62	207	62	203
	Effective sample size:		22		18	
Age	Mean (median)	58	58	NA (58)	57	NA (57)
ECOG performance status	0	77%	67%	67%	66%	66%
	1	23%	33%	33%	34%	34%
Previous radiotherapy	Yes	3%	23%	23%	20%	20%
	No	97%	77%	77%	80%	80%
Previous chemotherapy	Yes	13%	50%	50%	50%	50%
	No	87%	50%	50%	50%	50%
Sex	Male	45%	58%	49%	52%	58%
	Female	55%	42%	51%	48%	42%
Previous surgery	Yes	45%	40%	88%	34%	88%
	No	55%	60%	12%	66%	12%
Time from initial diagnosis ≤18 m	Yes	58%	58%	43%	58%	37%
	No	42%	42%	57%	42%	63%
Weights	Mean		1.00		1.00	
	Range		(0.39–12.23)		(0.31–11.22)	

^a A histogram describing the full distribution of weights is provided in the data supplement.

Table 7 – Hazard ratios estimated from matching-adjusted indirect comparisons for PFS in P-NETs.

	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. NCT00428597 (sunitinib) Hazard ratio PFS (95% CI)	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. NCT00428597 (BSC) Hazard ratio PFS (95% CI)	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. RADIANT-3 (everolimus) Hazard ratio PFS (95% CI)	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. RADIANT-3 (BSC) Hazard ratio PFS (95% CI)
Main analysis	0.36 [0.18, 0.70]	0.13 [0.08, 0.22]	0.46 [0.30, 0.71]	0.21 [0.13, 0.32]
Sensitivity analysis 1: Incl. non-Dutch ERASMUS patients	0.47 [0.26, 0.83]	0.27 [0.18, 0.40]	0.47 [0.31, 0.70]	0.48 [0.33, 0.69]
Sensitivity analysis 2: Adjusting for all available covariates	NR	NR	NR	NR
Sensitivity analysis 3: Matching to the full comparator population	0.38 [0.191, 0.73]	0.12 [0.07, 0.21]	0.46 [0.30, 0.71]	0.18 [0.11, 0.28]

PFS, progression-free survival; P-NETs, pancreatic neuroendocrine tumours; CI, confidence interval; BSC, best supportive care. NR: not reported as lack of overlap in populations across all covariates resulted in unreliable results.

reduced in these sensitivity analyses. However, the marked reduction in ESS, especially when ERASMUS data are reweighted to match the everolimus arm, calls into question the reliability of the estimates from this sensitivity analysis. For P-NETs, this sensitivity analysis was not feasible given the low sample size and poor overlap in characteristics across trials. These sensitivity analyses cannot explore the impact of characteristics not reported in one or both trials; therefore, residual confounding by unmeasured characteristics such as underlying tumour burden may exist.

This approach adjusted the ¹⁷⁷Lu]Lu-DOTA-TATE population to match the distribution of characteristics in the specific treatment arms of the comparator trials, BSC, sunitinib or everolimus. As such, results should be interpreted as pairwise comparisons with each of these arms, rather than providing a single set of adjusted ¹⁷⁷Lu]Lu-DOTA-TATE results which can be compared with both comparators. We used this approach in our main analysis as there was evidence of imbalance in patient characteristics across the comparator trials arms. A sensitivity analysis exploring the impact of matching to the

Table 8 – Hazard ratios estimated from matching-adjusted indirect comparisons for OS in P-NETs.

	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. NCT00428597 (sunitinib) Hazard ratio OS (95% CI)	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. NCT00428597 (BSC) Hazard ratio OS (95% CI)	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. RADIANT-3 (everolimus) Hazard ratio OS (95% CI)	¹⁷⁷ Lu]Lu-DOTA-TATE (reweighted ERASMUS) vs. RADIANT-3 (BSC) Hazard ratio OS (95% CI)
Main analysis	0.42 [0.25, 0.72]	0.34 [0.20, 0.57]	0.53 [0.33, 0.87]	0.56 [0.36, 0.90]
Sensitivity analysis 1: Incl. non-Dutch ERASMUS patients	0.72 [0.44, 1.16]	0.45 [0.28, 0.72]	0.95 [0.13, 1.48]	0.85 [0.55, 1.32]
Sensitivity analysis 2: Adjusting for all available covariates	NR	NR	NR	NR
Sensitivity analysis 3: Matching to the full comparator population	0.44 [0.27, 0.75]	0.33 [0.20, 0.56]	0.53 [0.33, 0.86]	0.49 [0.30, 0.80]

OS, overall survival; CI, confidence interval; BSC, best supportive care; P-NETs, pancreatic neuroendocrine tumours. NR: not reported as lack of overlap in populations across all covariates resulted in unreliable results.

full trial population had minimal impact on the results, suggesting this is not a major limitation of the study.

The inclusion of non-Dutch patients from ERASMUS had little impact on the results in GI-NETs but reduced the effectiveness of [¹⁷⁷Lu]Lu-DOTA-TATE in P-NETs, suggesting that outcomes in the non-Dutch patients with P-NETs in the ERASMUS were worse than those in the Dutch patients. Although this should be considered in the interpretation of our findings, we believe that because of issues in the follow-up of these patients, their exclusion in our main analysis is appropriate.

As outlined, head-to-head comparisons with everolimus and sunitinib have not yet been carried out. However, our findings for BSC are consistent with those of the NETTER-1 trial which compared [¹⁷⁷Lu]Lu-DOTA-TATE with high-dose octreotide LAR for patients with advanced midgut neuroendocrine tumours. NETTER-1 reported longer PFS and a significantly higher response rate for [¹⁷⁷Lu]Lu-DOTA-TATE relative to high-dose octreotide LAR and additionally reported preliminary data suggestive of improved OS [2]. NETTER-1 has also illustrated that [¹⁷⁷Lu]Lu-DOTA-TATE provides significant improvements in quality of life relative to high-dose octreotide LAR in the same population [14]. Taken together with our results, the accumulating evidence suggests [¹⁷⁷Lu]Lu-DOTA-TATE to be the most effective treatment available in both patients with GI-NETs and P-NETs with advanced unresectable disease. Although this suggests its use as first-line therapy may be warranted, further work is needed to establish the relative benefits of utilising differing sequences of treatments in each of these indications and the extent to which personalised treatment approaches may improve outcomes.

Our analysis focused on efficacy end-points; however, any treatment decision must consider the comparative risk–benefit profile of a therapeutic strategy. As such, it should be noted that a safety analysis of the ERASMUS study data (n = 443) revealed that four patients developed acute leukaemia (0.7%) and 9 patients developed myelodysplastic syndrome (1.5%) after [¹⁷⁷Lu]Lu-DOTA-TATE treatment. In the NETTER-1 trial [2], one patient (0.9%) in the [¹⁷⁷Lu]Lu-DOTA-TATE arm had cytopenia, which on further investigation was consistent with myelodysplastic syndrome, and was considered to be possibly related to treatment. In a large study looking at long-term tolerability of PRRT in three treatment groups, [¹⁷⁷Lu]Lu-DOTA-TATE and ⁹⁰Y-octreotide and a combination of the two were analysed retrospectively in patients with NETs (including bronchial) [15]. It found that myelodysplastic syndrome occurred in 2.35% of patients and acute leukaemia in 1.1% of patients. Finally, we consider a study which investigated the incidence, severity and reversibility of long-term haematotoxicity in a large cohort of patients being treated with [¹⁷⁷Lu]Lu-DOTA-TATE for metastatic NETs [16]. Myelodysplastic syndrome was documented in 3 patients (1.4%). One patient with myelodysplastic syndrome developed acute myeloid leukaemia. These findings suggest that although the risk of myelodysplastic syndrome and acute leukaemia after [¹⁷⁷Lu]Lu-DOTA-TATE treatment should be considered in any treatment decision, the consistently low rates of these events across studies support a positive risk–benefit profile for the product. While our study did not

assess relative safety, future work assessing the relative safety of treatments for GEP-NETs may be warranted.

5. Conclusion

Although our results must be interpreted with caution given the non-randomised nature of the comparisons and the potential for residual confounding, the magnitude of the effect sizes we observe and their consistency across comparators suggest that [¹⁷⁷Lu]Lu-DOTA-TATE appears to be a more effective treatment option than everolimus, sunitinib and BSC in GI-NETs and P-NETs.

Conflict of interest statement

This article is part of a supplement supported by Advanced Accelerator Applications (AAA), a Novartis company. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.S.K. has received speaker fees from AAA, Ipsen and Novartis and consultancy fees from Ipsen and Novartis. E.S., C.S., T.B., W.W.d.H. and M.E.P. have no known competing financial interests or personal relationships to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejcsup.2021.06.002>.

REFERENCES

- [1] Hofland J, Kaltsas G, de Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocr Rev* 2019;41(2):371–403.
- [2] Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of ¹⁷⁷Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med* 2017;376(2):125–35.
- [3] Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. *Med Decis Making* : an international journal of the Society for Medical Decision Making 2018;38(2):200–11.
- [4] Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-term efficacy, survival, and safety of [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Canc Res* 2017;23(16):4617–24.
- [5] Kwekkeboom DJ, Mueller-Brand J, Paganelli G, Anthony LB, Pauwels S, Kvols LK, et al. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. *J Nucl Med* 2005;46(Suppl 1). 62s-6s.
- [6] Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008;26(13):2124–30.
- [7] Singh S, Carnaghi C, Buzzoni R, Pommier RF, Raderer M, Tomasek J, et al. Efficacy and safety of everolimus in

- advanced, progressive, nonfunctional neuroendocrine tumors (NET) of the gastrointestinal (GI) tract and unknown primary: a subgroup analysis of the phase III RADIANT-4 trial. *J Clin Oncol* 2016;34(4_suppl):315.
- [8] Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study. *J Clin Oncol* 2016;34(32):3906–13.
- [9] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364(6):514–23.
- [10] Faivre S, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Ann Oncol : official journal of the European Society for Medical Oncology* 2017;28(2):339–43.
- [11] Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364(6):501–13.
- [12] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.
- [13] Faria R, Hernandez-Alava M, Manca A, Wailoo AJ. NICE DSU Technical Support Document 17: the use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: methods for comparative individual patient data. 2015.
- [14] Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with ¹⁷⁷Lu-dotatate in the phase III NETTER-1 trial. *J Clin Oncol* 2018;36(25):2578–84.
- [15] Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imag* 2015;42(1):5–19.
- [16] Sabet A, Ezziddin K, Pape UF, Ahmadzadehfar H, Mayer K, Pöppel T, et al. Long-term hematotoxicity after peptide receptor radionuclide therapy with ¹⁷⁷Lu-octreotate. *J Nucl Med* 2013;54(11):1857–61.