16:30-17:30h

UNA VISIÓN DISTINTA DE LA ESTADÍSTICA APLICADA A LA ONCOLOGÍA

Dr. José Ríos. Coordinador Plataforma de estadística médica IDIBAPS - Hospital Clínic, Barcelona
Profesor asociado de la Facultad de Medicina UAB, Barcelona

José Ríos, MSc, PhD
Cap de la Plataforma de Estadística Médica
Servei de Farmacologia Clínica Hosp Clínic Barcelona - IDIBAPS

Prof. Asociado de la Fac. Medicina (UAB)
jrios@clinic.cat
jose.rios@uab.cat

Clínic Barcelona IDIBAPS CERCAGINYS UAB Universitat Autònoma de Barcelona

[177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

Simron Singh, Daniel Halperin, Sten Myrehaug, Ken Herrmann, Marianne Pavel, Pamela L Kunz, Beth Chasen, Salvatore Tafuto, Secondo Lastoria, Jaume Capdevila, Amparo Garcia-Burillo, Do-Youn Oh, Changhoon Yoo, Thorvardur R Halfdanarson, Stephen Falk, Ilya Folitar, Yufen Zhang, Paola Aimone, Wouter W de Herder, Diego Ferone, on behalf of all the NETTER-2 Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

TRIAL DESIGN

In this open-label, phase 3 trial, we randomly assigned patients, in a 1:1 ratio, to receive ^{177}Lu-Dotatate plus best supportive care, consisting of octreotide LAR at a dose of 30 mg every 4 weeks for symptom control (^{177}Lu-Dotatate group) or to receive high-dose octreotide LAR, at a dose of 60 mg every 4 weeks (control group). Randomization was performed with the use of a centralized permuted block (block size of 4) randomization scheme, with stratification according to the highest tumor uptake score on somatostatin receptor scintigraphy (grade 2, 3, or 4 on a scale ranging from 0 [no uptake by tumor] to 4 [very intense uptake by tumor] with higher grades indicating a higher level of expression of somatostatin receptors)[12] and according to the length of time that a patient had been receiving a constant dose of octreotide (≤6 months or >6 months).

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to documented disease progression (as evaluated by independent central review by radiologists who were unaware of the treatment assignments) or death from any cause. Secondary end points included the objective response rate, overall survival (defined as the time from randomization to death from any cause), safety, and the side-effect profile. An objective tumor assessment on CT or MRI was performed every 12 weeks after the date of randomization in both treatment groups. The treatment was considered to have failed if a patient had progressive disease on imaging, according to central assessment with the use of RECIST criteria, and patients with treatment failure proceeded directly to the long-term follow-up phase. We calculated the response rate as the percentage of patients who had a response according to RECIST (sum of partial responses and complete responses). Definitions of all response categories are provided in the protocol.

¿Qué significa?

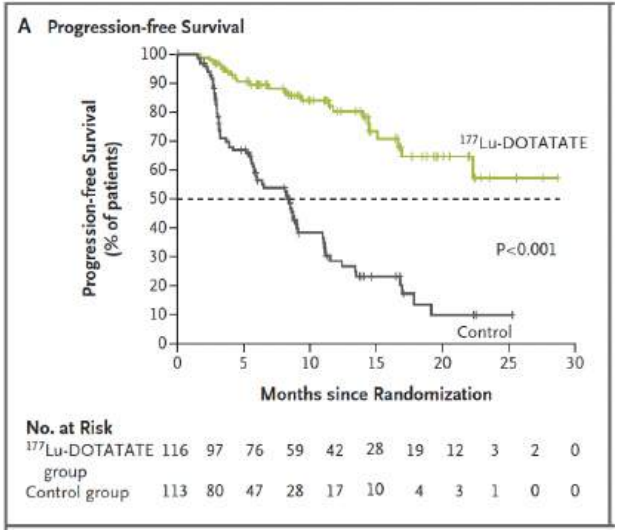
¿Qué implica?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators



¿Son resultado extrapolables como 'epidemiológicos?

The NEW ENGLAND JOURNAL of MEDICINE

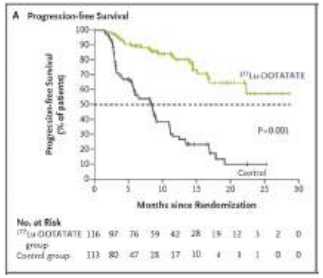
ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

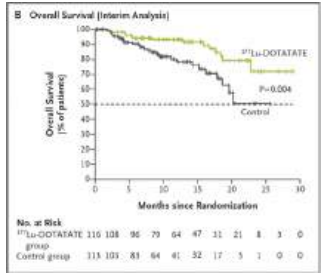
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

STATISTICAL ANALYSIS

We calculated the required number of patients for the trial assuming that the median progression-free survival would be 30 months in the ^{177}Lu-Dotatate group and 14 months in the control group, the study would have 90% nominal power at an alpha level of 5%, and the prespecified enrollment period and follow-up period for both groups would be 18 months. On the basis of those assumptions, we calculated that we needed a sample of 124 patients, and the analysis of the primary end point was planned to be conducted after at least 74 events of disease progression or death that were centrally confirmed and could be evaluated had occurred.



However, the sample size of the trial was adjusted to 230 patients to enable us to detect a statistically significant and clinically relevant difference between the two treatment groups in overall survival as a secondary end point. This calculation was based on the assumption that the median overall survival would be 50 months in the ^{177}Lu-Dotatate group and 32 months in the control group, with 80% nominal power at an alpha level of 5%, and a prespecified enrollment period of 18 months and a long-term follow-up period of 60 months. A prespecified interim analysis of overall survival was conducted at the time of the analysis of progression-free survival.



The final analysis of overall survival is planned to be performed either after 158 deaths have occurred or 5 years after the last patient underwent randomization, whichever occurs first.

STATISTICAL ANALYSIS

We calculated the required number of patients for the trial assuming that the median progression-free survival would be 30 months in the ^{177}Lu-Dotatate group and 14 months in the control group, the study would have 90% nominal power at an alpha level of 5%, and the prespecified enrollment period and follow-up period for both groups would be 18 months. On the basis of those assumptions, we calculated that we needed a sample of 124 patients, and the analysis of the primary end point was planned to be conducted after at least 74 events of disease progression or death that were centrally confirmed and could be evaluated had occurred.

Two group test of equal exponential survival (n large), no dropouts			
	1	2	3
Test significance level, α	0,050	0,050	0,050
1 or 2 sided test?	2	2	2
Length of accrual period	18,00	18,00	12,00
Maximum length of followup	18,00	20,00	20,00
Group 1 exponential parameter, λ_1	0,0231	0,0231	0,0231
Group 2 exponential parameter, λ_2	0,0495	0,0495	0,0495
Hazard ratio, $h=\lambda_1 / \lambda_2$	0,467	0,467	0,467
Power (%)	90	90	90
n per group	153	128	103

Conversion to alternate rates for exponential survival curves	
	1
Time t	30,0
Group 1 proportion π_1 at time t	0,500
median survival	30,000
exponential parameter, λ_1	0,0231
Group 2 proportion π_2 at time t	0,226
median survival	14,000
exponential parameter, λ_2	0,0495
Hazard ratio, $h=\ln(\pi_1)/\ln(\pi_2)=med_2/med_1=\lambda_1/\lambda_2$	0,467

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators

Cómo calculo el tamaño de la muestra en ensayos de oncología?

En estos diseños se ha de buscar el equilibrio en la planificación

- Tamaño de la muestra en ‘estudios de tiempo hasta evento’:
  - Magnitud del efecto mínimamente relevante: HR
  - Precisión necesaria: Amplitud del 95%CI

Número de eventos que necesito observar

Riesgo basal de presentar el evento

Tiempo de seguimiento

N ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

STATISTICAL ANALYSIS

We calculated the required number of patients for the trial assuming that the median progression-free survival would be 30 months in the ^{177}Lu-Dotatate group and 14 months in the control group, the study would have 90% nominal power at an alpha level of 5%, and the prespecified enrollment period and follow-up period for both groups would be 18 months. On the basis of those assumptions, we calculated that we needed a sample of 124 patients, and the analysis of the primary end point was planned to be conducted after at least 74 events of disease progression or death that were centrally confirmed and could be evaluated had occurred.

However, the sample size of the trial was adjusted to 230 patients to enable us to detect a statistically significant and clinically relevant difference between the two treatment groups in overall survival as a secondary end point. This calculation was based on the assumption that the median overall survival would be 50 months in the ^{177}Lu-Dotatate group and 32 months in the control group, with 80% nominal power at an alpha level of 5%, and a prespecified enrollment period of 18 months and a long-term follow-up period of 60 months. A prespecified interim analysis of overall survival was conducted at the time of the analysis of progression-free survival.

The final analysis of overall survival is planned to be performed either after 158 deaths have occurred or 5 years after the last patient underwent randomization, whichever occurs first.

STATISTICAL ANALYSIS

We calculated the required number of patients for the trial assuming that the median progression-free survival would be 30 months in the ^{177}Lu-Dotatate group and 14 months in the control group, the study would have 90% nominal power at an alpha level of 5%, and the prespecified enrollment period and follow-up period for both groups would be 18 months. On the basis of those assumptions, we calculated that we needed a sample of 124 patients, and the analysis of the primary end point was planned to be conducted after at least 74 events of disease progression or death that were centrally confirmed and could be evaluated had occurred.

Two group test of equal exponential survival (n large), no dropouts			
	1	2	3
Test significance level, α	0,050	0,050	0,050
1 or 2 sided test?	2	2	2
Length of accrual period	18,00	18,00	12,00
Maximum length of followup	18,00	20,00	20,00
Group 1 exponential parameter, λ_1	0,0231	0,0231	0,0231
Group 2 exponential parameter, λ_2	0,0495	0,0495	0,0495
Hazard ratio, $h=\lambda_1 / \lambda_2$	0,467	0,467	0,467
Power (%)	90	90	90
n per group	153	128	103
Total number of events required, E	72	72	72

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators

Two group test of equal exponential survival (n large), no dropouts			
	5	6	7
Test significance level, α	0,050		
1 or 2 sided test?	2		
Length of accrual period	18,00		
Maximum length of followup	60,00		
Group 1 exponential parameter, λ_1	0,0139		
Group 2 exponential parameter, λ_2	0,0217		
Hazard ratio, $h=\lambda_1 / \lambda_2$	0,641		
Power (%)	80		
n per group	138		
Total number of events required, E	158		

However, the sample size of the trial was adjusted to 230 patients to enable us to detect a statistically significant and clinically relevant difference between the two treatment groups in overall survival as a secondary end point. This calculation was based on the assumption that the median overall survival would be 50 months in the ^{177}Lu-Dotatate group and 32 months in the control group, with 80% nominal power at an alpha level of 5%, and a prespecified enrollment period of 18 months and a long-term follow-up period of 60 months. A prespecified interim analysis of overall survival was conducted at the time of the analysis of progression-free survival.

The final analysis of overall survival is planned to be performed either after 158 deaths have occurred or 5 years after the last patient underwent randomization, whichever occurs first.

All patients who underwent randomization were included in the analyses of efficacy, demographics, and baseline characteristics. The safety population, which comprised all patients who underwent randomization and received at least one dose of trial treatment, was used for all safety analyses. The median point estimate and 95% confidence interval for progression-free survival and overall survival were estimated by means of the Kaplan–Meier method. Objective response rates and corresponding 95% confidence intervals were calculated for each treatment group and were compared with the use of Fisher's exact test. Survival curves were compared with the use of an unstratified log-rank test and were tested against the null hypothesis. Hazard ratios were estimated with the use of an unstratified Cox proportional-hazards model.

No tendré en cuenta la estratificación de la aleatorización para el análisis

EFFICACY

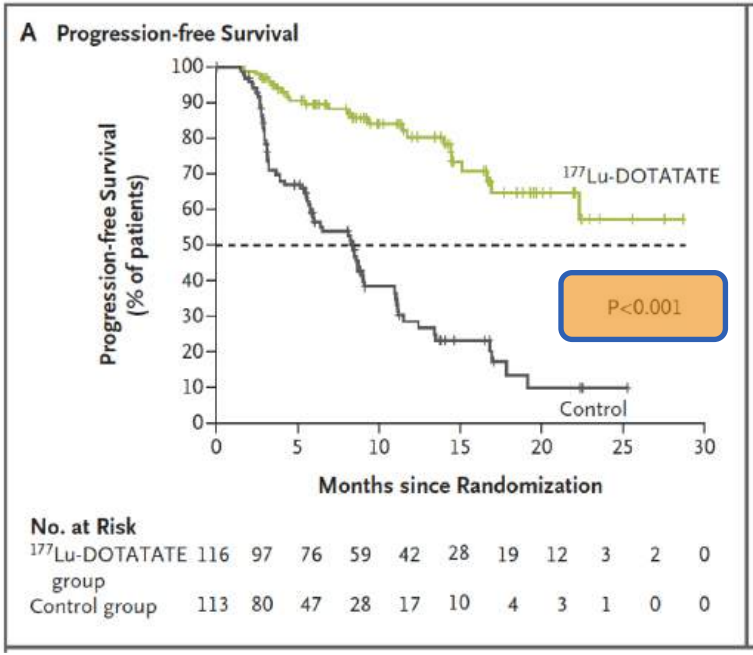
At the time of the data cutoff for the primary analysis (July 24, 2015), 23 events of disease progression or death had occurred in the ^{177}Lu-Dotatate group and 68 such events had occurred in the control group. The estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The median progression-free survival had not yet been reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with ^{177}Lu-Dotatate vs. control, 0.21; 95% CI, 0.13 to 0.33; P<0.001), which represented a 79% lower risk of disease progression or death in the ^{177}Lu-Dotatate group than in the control group (Fig. 1A). Consistent treatment benefits associated with ^{177}Lu-Dotatate were observed irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, sex, and tumor marker levels (Fig. 1C).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators



The NEW ENGLAND JOURNAL of MEDICINE

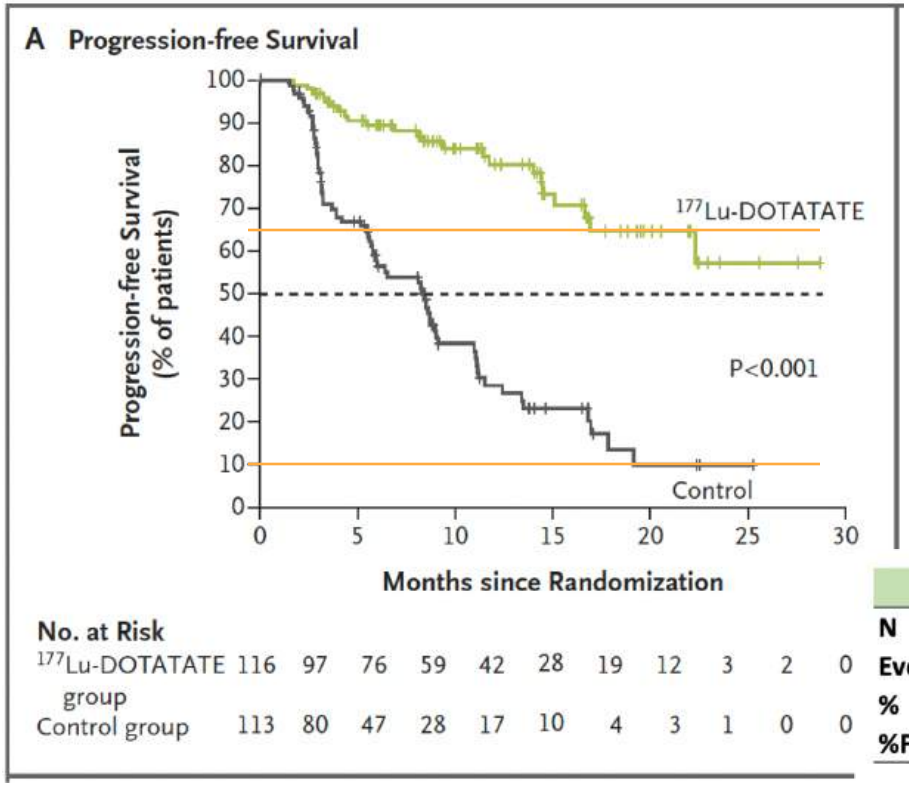
ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators

EFFICACY

At the time of the data cutoff for the primary analysis (July 24, 2015), 23 events of disease progression or death had occurred in the ^{177}Lu-Dotatate group and 68 such events had occurred in the control group. The estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The median progression-free survival had not yet been reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with ^{177}Lu-Dotatate vs. control, 0.21; 95% CI, 0.13 to 0.33; P<0.001), which represented a 79% lower risk of disease progression or death in the ^{177}Lu-Dotatate group than in the control group (Fig. 1A). Consistent treatment benefits associated with ^{177}Lu-Dotatate were observed irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, sex, and tumor marker levels (Fig. 1C).



	Lu-Do	Control
N	116	113
Events	23	68
%	19,8%	60,2%
%Free	80,2%	39,8%

¿A qué viene esa diferencia?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

EFFICACY

At the time of the data cutoff for the primary analysis (July 24, 2015), 23 events of disease progression or death had occurred in the ^{177}Lu-Dotatate group and 68 such events had occurred in the control group. The estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The median progression-free survival had not yet been reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with ^{177}Lu-Dotatate vs. control, 0.21; 95% CI, 0.13 to 0.33; P<0.001), which represented a 79% lower risk of disease progression or death in the ^{177}Lu-Dotatate group than in the control group (Fig. 1A). Consistent treatment benefits associated with ^{177}Lu-Dotatate were observed irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, sex, and tumor marker levels (Fig. 1C).

Two group test of equal exponential survival (n large), no dropouts			
	1	2	3
Test significance level, α	0,050	0,050	0,050
1 or 2 sided test?	2	2	2
Length of accrual period	18,00	18,00	12,00
Maximum length of followup	18,00	20,00	20,00
Group 1 exponential parameter, λ_1	0,0231	0,0231	0,0231
Group 2 exponential parameter, λ_2	0,0495	0,0495	0,0495
Hazard ratio, $h=\lambda_1 / \lambda_2$	0,467	0,467	0,467
Power (%)	90	90	90
n per group	153	128	103
Total number of events required, E	72	72	72

	Lu-Do	Control
N	116	113
Events	23	68
%	19,8%	60,2%
%Free	80,2%	39,8%

- No sólo por que lo dice ‘este’:

- También lo dice ‘este’:

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CHMP/27994/2008/Rev.1

Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man

Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials

Veamos…

Size of effect

The size of effect should be quantified by plotting the estimates of the survivor functions for PFS, estimating the hazard ratio, estimating median time-to-event and other percentiles (e.g. upper quartile, lower quartile), and estimating the percentage of patients event free at particular time-points (e.g. % patients event free at 1-year), based on semi-parametric procedures. Although from a clinical perspective the median PFS is considered the preferred summary measure of the location of the distribution of PFS survival times, over-reliance on differences in medians should be avoided because this will generally be less informative than considering the survival curve as a whole. In any case, the choice of the summary measure should be justified and pre-specified.

Veamos…

Size of effect

The size of effect should be quantified by plotting the estimates of the survivor functions for PFS, estimating the hazard ratio, estimating median time-to-event and other percentiles (e.g. upper quartile, lower quartile), and estimating the percentage of patients event free at particular time-points (e.g. % patients event free at 1-year), based on semi-parametric procedures. Although from a clinical perspective the median PFS is considered the preferred summary measure of the location of the distribution of PFS survival times, over-reliance on differences in medians should be avoided because this will generally be less informative than considering the survival curve as a whole. In any case, the choice of the summary measure should be justified and pre-specified.

In addition to the analysis of progression-free survival, we performed a planned interim analysis of overall survival. A total of 14 deaths in the ^{177}Lu-Dotatate group and 26 deaths in the control group were observed, which represented an estimated risk of death that was 60% lower in the ^{177}Lu-Dotatate group than in the control group (hazard ratio for death with ^{177}Lu-Dotatate group vs. control, 0.40; P=0.004) (Fig. 1B). The O'Brien–Fleming threshold for significance at the first interim analysis was 0.000085. Data were not sufficiently mature to provide an estimate of the median overall survival in either treatment group. Within the population of patients who could be evaluated for tumor response (201 patients), the total number of complete and partial responses was 18 in the ^{177}Lu-Dotatate group and 3 in the control group, which corresponded to response rates of 18% and 3%, respectively (P<0.001) (Table 2).

The final analysis of overall survival is planned to be performed either after 158 deaths have occurred or 5 years after the last patient underwent randomization, whichever occurs first.

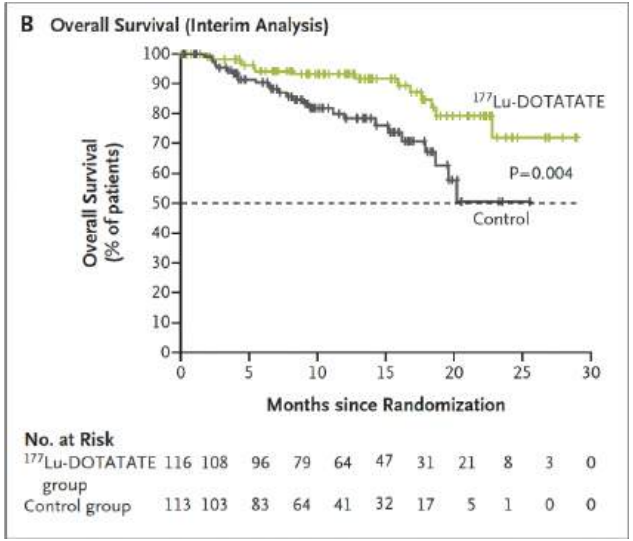
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators

No tiene nada que ver con la mediana!



RESULTS

At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the ^{177}Lu-Dotatate group and 26 in the control group (P=0.004). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the ^{177}Lu-Dotatate group as compared with no patients in the control group, with no evidence of renal toxic effects during the observed time frame.

CONCLUSIONS

Treatment with ^{177}Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the ^{177}Lu-Dotatate group. (Funded by Advanced Accelerator Applications; NETTER-1 ClinicalTrials.gov number, NCT01578239; EudraCT number 2011-005049-11.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srinivasaiah, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

13 December 2012
EMA/CHMP/27994/2008/Rev.1

Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man

Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials

Randomisation and masking

We used interactive response technologies (web and voice; Calyx, Nottingham, UK) to randomly assign patients (2:1) to the ^{177}Lu-Dotatate group or control group stratified by tumour grade (2 *vs* 3) and tumour origin (pancreas *vs* other). We chose a 2:1 randomisation design to increase patients' chances of receiving ^{177}Lu-Dotatate. To minimise a potentially high dropout rate in the control group, patients were offered to cross over to ^{177}Lu-Dotatate after centrally confirmed radiological progression. The randomisation list contained 240 pre-allocated records for each of the four strata in the study (960 records in total). The first patient in a specific stratum was assigned the first randomisation entry from the randomisation schedule pre-allocated to that stratum. Subsequent patients in the same stratum were assigned to the next available randomisation entry from the randomisation schedule pre-allocated to that stratum. We used a block size of six within each stratum. Forced randomisation was not allowed in this study. Tumour grade and origin are both important prognostic factors for gastroentero-pancreatic NETs and thus were used as stratification factors.[17,18] The trial was open label, so masking of treatments was not applicable.

[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

- Disponer de un control
- Maximizar conocimiento de grupo Experimental
- Placebo puede ser un problema con la viabilidad del ensayo

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

Realizado y publicado antes del 2020

Statistical analysis

The statistical analysis plan is available in appendix 3. We did the primary analysis at 101 progression-free survival events as the final progression-free survival analysis. We estimated that 99 progression-free survival events would be required to achieve 90% power using a one-sided log-rank test at the overall 2·5% level of significance, to detect a 50% reduction in hazard rate, corresponding to a doubling of median progression-free survival from an assumed 15 months for the control group to 30 months for the ^{177}Lu-Dotatate group. These assumptions were based on the results from NETTER-1 (progression-free survival was 28·4 months with ^{177}Lu-Dotatate).[19] We conservatively selected a hazard ratio (HR) of 0·5 and, therefore, a progression-free survival of 15 months for control was used for the sample size calculations. Assuming that enrolment would continue for approximately 22·2 months at a rate of ten patients per month and a 15% dropout rate by the time of primary progression-free survival analysis, we estimated that approximately 222 patients would need to be randomly assigned in a 2:1 ratio to the ^{177}Lu-Dotatate versus control groups.

To control for the overall type I error, we tested the primary and key secondary endpoints hierarchically at the time of the primary analysis. The order of the

nQuery | PASS Sample Size ?

¿Qué método?

[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

Power	N1	N2	N	Haz Ratio HR	Ctrl Med Surv Time M1	Trt Med Surv Time M2	Acc-rual Pat'n	Acc-rual Time/ Total Time
0,90151	59	118	177	0,5	15	30	Equal	22 / 36

Power	Ctrl Evts E1	Trt Evts E2	Total Evts E	Haz Ratio HR	Ctrl Med Surv Time T1	Trt Med Surv Time T2	Acc-rual Pat'n	Acc-rual Time/ Total Time
0,90151	39,6	51,1	90,7	0,5	15	30	Equal	22 / 36

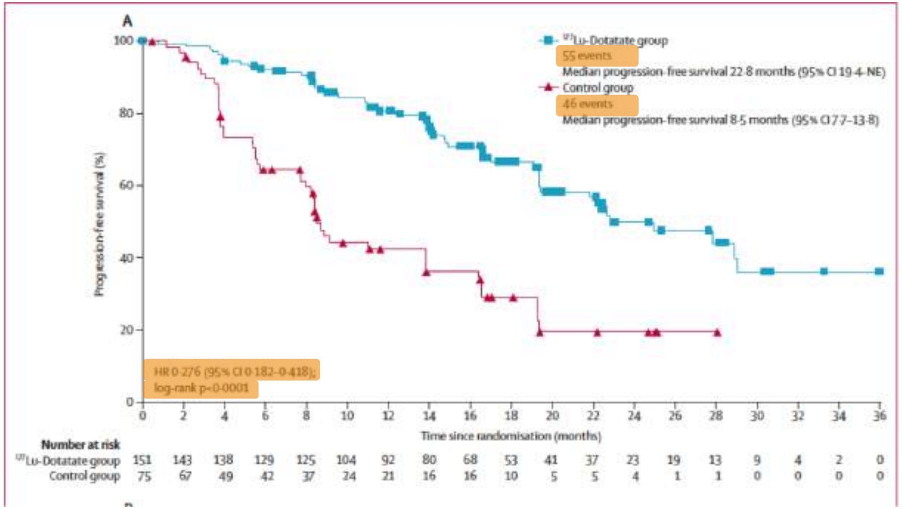
Numeric Results

Solve For: Sample Size
Hypotheses: H0: HR = 1 vs. Ha: HR ≠ 1

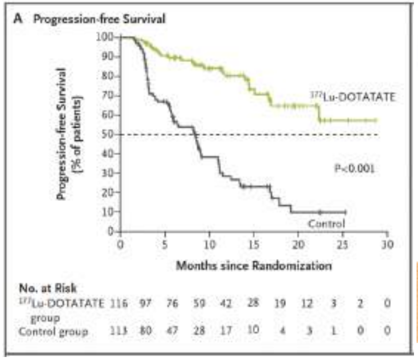
Power	Total Sample Size N	Control Sample Size N1	Trtmnt Sample Size N2	Percent Control %N1	Actual Hazard Ratio HR1	Control Prob Event Pev1	Trtmnt Prob Event Pev2	Control Events E1	Trtmnt Events E2	Alpha
0,90168	297	99	198	33,33333	0,5	0,6	0,2	59,4	39,6	0,05

PFS → ORR →QLQ-C30 → diarrea→ fatiga→ dolor …. Mortalidad no entra?

We used the full analysis set for efficacy analyses and summary for demographic and baseline characteristics, which comprised all randomly assigned patients, and patients were analysed according to the randomised treatment. All safety analyses were based on the safety set, which included all patients who received at least one administration of study treatment. We compared progression-free survival using a log-rank test stratified by randomisation stratification factors (tumour grade and origin). We calculated the rank statistic and its variance separately for each stratum, then calculated the final statistic as the sum of rank statistics from all four strata divided by the square root of the sum of variances from all four strata, and compared the result with the normal distribution to obtain the p value. We estimated the survival distribution of progression-free survival using the Kaplan–Meier method. We estimated HRs with 95% CIs using a stratified Cox model. We compared objective response rate between treatment groups, and the corresponding odds ratio along with 95% CIs was calculated using the stratified Cochran–Mantel–Haenszel method. We analysed time to deterioration in QoL using the same method as progression-free survival. Unless specified otherwise, we summarised categorical data as n (%) and continuous data as median (IQR).



[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

ratio for disease progression or death with ^{177}Lu-Dotatate vs. control, 0.21; 95% CI, 0.13 to 0.33; P<0.001), which represented a 79% lower risk of

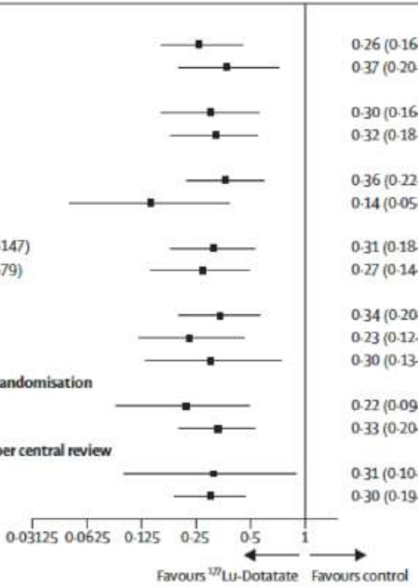
Aquí el análisis tiene en cuenta que la aleatorización es estratificada

¿Importa?

Lo que importa es que esté preespecificado

B

	HR (95% CI)	^{177}Lu-Dotatate plus octreotide 30 mg LAR (n=151)	High-dose octreotide 60 mg LAR (control group; n=75)
Age, years			
<65 (n=134)	0·26 (0·16–0·45)	30/86 (35%)	30/48 (63%)
≥65 (n=92)	0·37 (0·20–0·71)	25/65 (38%)	16/27 (59%)
Sex			
Female (n=105)	0·30 (0·16–0·55)	26/70 (37%)	19/35 (54%)
Male (n=121)	0·32 (0·18–0·54)	29/81 (36%)	27/40 (68%)
Race			
White (n=165)	0·36 (0·22–0·59)	43/115 (37%)	27/50 (54%)
Asian (n=34)	0·14 (0·05–0·38)	10/23 (43%)	10/11 (91%)
Tumour grade			
Grade 2 Ki67 ≥10% and ≤20% (n=147)	0·31 (0·18–0·53)	29/99 (29%)	25/48 (52%)
Grade 3 Ki67 >20% and ≤55% (n=79)	0·27 (0·14–0·49)	26/52 (50%)	21/27 (78%)
Tumour origin			
Pancreas (n=123)	0·34 (0·20–0·56)	39/82 (48%)	27/41 (66%)
All non-pancreas (n=103)	0·23 (0·12–0·46)	16/69 (23%)	19/34 (56%)
Small intestine (n=66)	0·30 (0·13–0·74)	11/45 (24%)	10/21 (48%)
Serum chromogranin A before randomisation			
≤2×ULN (n=67)	0·22 (0·09–0·49)	11/43 (26%)	14/24 (58%)
>2×ULN (n=144)	0·33 (0·20–0·53)	39/100 (39%)	28/44 (64%)
Somatostatin receptor uptake per central review			
Score 3 (n=34)	0·31 (0·10–0·89)	9/24 (38%)	6/10 (60%)
Score 4 (n=185)	0·30 (0·19–0·47)	46/123 (37%)	38/62 (61%)



[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

¿Qué uso le dais?

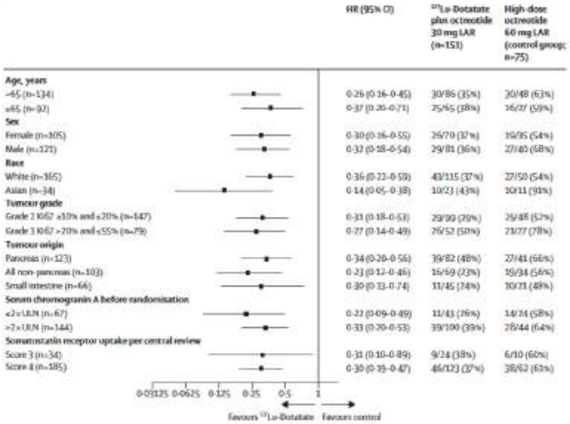
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the investigation of subgroups in confirmatory clinical trials

[[177]Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

B



4.3. *Key concepts in the assessment of subgroups*

A number of concepts and the respective definitions required in the following discussion about the role of subgroups for decision making about efficacy and benefit of a new drug are introduced here:

a. **Heterogeneity** relates to the extent of differences within the target patient population, or a clinical trial population, in factors that are prognostic for outcome or predictive of treatment effects. The more heterogeneous the population, the more important the investigation of treatment effects in well-defined subgroups.

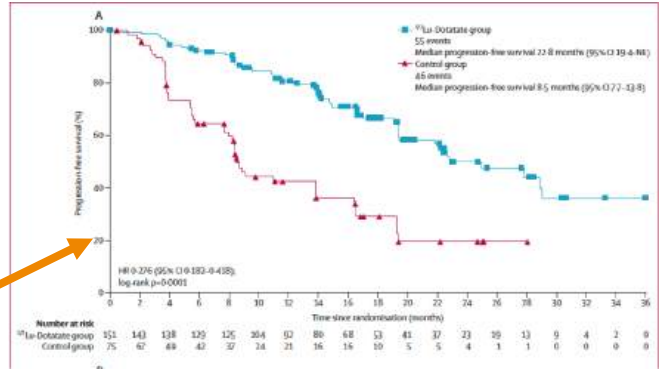
b. **Consistency** describes the extent to which estimated treatment effects in relevant subgroups assures that the overall treatment effect applies to the breadth of the trial population. In each specific indication, it is required to judge the extent of differences in effect size between subgroups that are of potential clinical importance, and hence that would indicate inconsistency. Inconsistency in estimated treatment effects is one indicator for further assessment in particular subgroups.

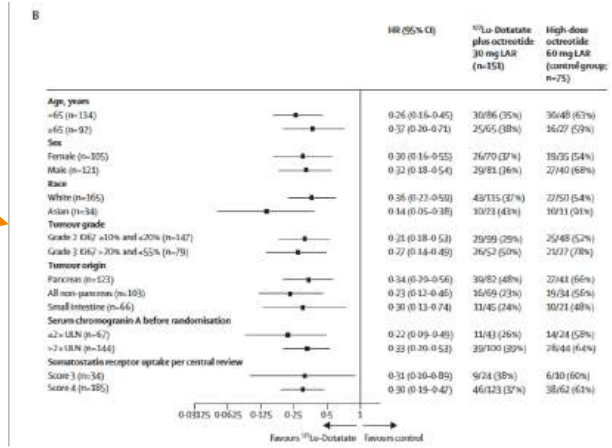
c. **Credibility** describes the extent to which subgroup findings can be concluded as being well substantiated and hence relied on for decision making. Credibility depends on the degree of well-founded, a priori definition, the **biological plausibility** for a particular finding and **replication** (see below).

d. **Biological plausibility** is a concept describing the extent to which a particular effect (in this case differential effects of treatment between subgroups) might be predicted, or might have been expected, based on clinical, pharmacological, and mechanistic considerations, and considerations of other relevant external data sources. Plausibility is primarily a clinical and pharmacological judgement and, unless already considered at the planning stage, is usually not a directly quantifiable or measurable concept.

e. **Replication** refers to whether an effect of a particular covariate, or differential effects between particular subgroups, is seen in multiple data sources: specifically, whether an inconsistency in one confirmatory clinical trial are also seen in independent clinical trial data (another phase III trial, phase II exploratory trial, or a trial from outside the development programme, but with similar experimental conditions).

The study met its primary objective of progression-free survival. At data cutoff, progression-free survival events had occurred in 55 (36%) patients in the ^{177}Lu-Dotatate group and 46 (61%) in the control group. The median progression-free survival, as per blinded central assessment according to RECIST 1·1, was 22·8 months (95% CI 19·4–not estimated [NE]) in the ^{177}Lu-Dotatate group versus 8·5 months (7·7–13·8) in the control group. We found a reduction in the risk of disease progression or death by around 72% in the ^{177}Lu-Dotatate group compared with the control group (HR for progression-free survival with ^{177}Lu-Dotatate *vs* control 0·276 [0·182–0·418]; p<0·0001; figure 2A). The progression-free survival benefit observed in the ^{177}Lu-Dotatate group was consistent across all prespecified subgroups (figure 2B). Progression-free survival results based on local tumour response assessment by investigators were in agreement with the centrally reviewed data (median progression-free survival 22·6 months [17·7–NE] in the ^{177}Lu-Dotatate group and 8·2 months [5·6–11·1] in the control group).





[^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

[177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study

Table S1: **Time to deterioration in health-related quality of life**

EORTC QLQ-C30 subscale	Median time to deterioration* in months (95% CI) 177Lu-DOTATATE vs control	Hazard ratio (95% CI)	p value
GHS	13·2 (8·8–17·2) vs 8·6 (5·8–14·0)	0·856 (0·570–1·283)	0·22
Diarrhoea	17·4 (14·4–28·2) vs 17·3 (8·1, NE)	0·877 (0·555–1·386)	Not tested
Fatigue	6·0 (3·4–6·8) vs 6·0 (3·9–11·0)	0·998 (0·695–1·432)	Not tested
Pain	10·3 (6·0–13·4) vs 8·6 (3·9–13·7)	0·918 (0·623–1·351)	Not tested

CI=confidence interval. EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire. GHS=Global Health Status. NE=not estimated. *Time to deterioration is the time from randomisation to the first deterioration of at least 10 points in the domain score compared with the baseline score, or death while on treatment on each scale.

The objective response rate was significantly higher in the 177Lu-Dotatate group (43·0% [95% CI 35·0–51·3]) than in the control group (9·3% [3·8–18·3])—ie, an improvement of 33·7% (23·4–44·0) and a stratified odds ratio of 7·81 (3·32–18·40; p<0·0001; table 3). Eight (5%) patients in the 177Lu-Dotatate group had a complete response versus none in the control group (table 3). The median duration of response was

We found no significant difference between treatment groups for the key secondary endpoint of time to deterioration in QoL, as per EORTC QLQ-C30 scores (appendix 1 p 4).

Overall survival data were immature at the time of primary progression-free survival analysis. Median overall survival was not reached for either treatment group, and we found no difference in overall survival between treatment groups at the time of follow-up. By the cutoff date, 36 (48%) patients in the control group had progressed and crossed over to 177Lu-Dotatate treatment (n=29 during the crossover phase) or received 177Lu-Dotatate or 177Lu-Dotatoc (n=7 during the follow-up phase), which might have confounded the overall survival results in addition to the data immaturity. Overall survival monitoring is ongoing in the long-term follow-up and will be analysed at the final analysis.

PFS → ORR →QLQ-C30 → ~~diarrea → fatiga → dolor~~

…. Mortalidad no entra?

Gracias!

José Ríos Guillermo

jrios@clinic.cat
Jose.ríos@uab.cat