

A Pilot, Phase II, Randomized, Open-Label Clinical Trial Comparing the Neurotoxicity of Three Dose Regimens of Nab-Paclitaxel to That of Solvent-Based Paclitaxel as the First-Line Treatment for Patients with Human Epidermal Growth Factor Receptor Type 2-Negative Metastatic Breast Cancer

EVA CIRUELOS,^{a,b} MARÍA APELLÁNIZ-RUIZ,^c BLANCA CANTOS,^{b,d} NOELIA MARTÍNEZ-JÁÑEZ,^{b,e} CORALIA BUENO-MUIÑO,^{b,f} MARIA-JOSE ECHARRI,^{b,g} SANTOS ENRECH,^{b,h} JUAN-ANTONIO GUERRA,^{b,i} LUIS MANO,^{a,b} TOMAS PASCUAL,^{a,b} CRISTINA DOMÍNGUEZ,^{a,b} JUAN-FRANCISCO GONZALO,^{a,b} JUAN-LUIS SANZ,^j CRISTINA RODRÍGUEZ-ANTONA,^{c,k} JUAN-MANUEL SEPÚLVEDA^{a,b}

^aMedical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; ^bOncosur Study Group, Madrid, Spain; ^cHereditary Endocrine Cancer Group, Human Cancer Genetics Programme, Spanish National Cancer Research Center (CNIO), Madrid, Spain; ^dMedical Oncology Department, Hospital Universitario Puerta de Hierro, Majadahonda, Spain; ^eMedical Oncology Department, Hospital Ramón y Cajal, Madrid, Spain; ^fMedical Oncology Department, Hospital Infanta Cristina, Parla, Spain; ^gMedical Oncology Department, Hospital Severo Ochoa, Leganes, Spain; ^hMedical Oncology Department, Hospital Universitario de Getafe, Getafe, Spain; ⁱMedical Oncology Department, Hospital de Fuenlabrada, Fuenlabrada, Spain; ^jClinical Research Department, Apoyo a la Investigación Clínica en España (APICES), Madrid, Spain; ^kNeurology Division, Neuromuscular Unit, ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Madrid, Spain

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic breast cancer • Paclitaxel • Nab-paclitaxel • Neurotoxicity • Polyneuropathy • Total neurotoxicity score

ABSTRACT

Background. This study aimed to characterize the neurotoxicity of three different regimens of nab-paclitaxel compared with a standard regimen of solvent-based (sb) paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer based on the Total Neurotoxicity Score (TNS), a tool specifically developed to assess chemotherapy-induced neurotoxicity.

Materials and Methods. This was a randomized, open-label study testing 4-week cycles of 80 mg/m² sb-paclitaxel (PACL80/w) on days 1, 8, and 15; 100 mg/m² nab-paclitaxel on days 1, 8, and 15 (NAB100/w); 150 mg/m² nab-paclitaxel on days 1, 8, and 15 (NAB150/w); and 150 mg/m² nab-paclitaxel on days 1 and 15 (NAB150/2w). In addition to the TNS, neuropathy was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). Tumor response and quality of life were also evaluated.

Results. Neurotoxicity, as evaluated by the TNS, did not significantly differ between the sb-paclitaxel group and any of the nab-paclitaxel groups. The frequency of (any grade) polyneuropathy, as measured by the NCI-CTCAE, was lower in the PACL80/w (*n* = 7, 50%) and NAB150/2w (*n* = 10, 62.5%) groups than in the NAB100/w (*n* = 13, 81.3%) or NAB150/w (*n* = 11, 78.6%) group. Although the differences were not statistically significant, compared with the other groups, in the

NAB150/w group, the time to occurrence of grade ≥2 polyneuropathy was shorter, and the median time to recovery from grade ≥2 polyneuropathy was longer. Dose delays and reductions due to neurotoxicity and impact of neurotoxicity on the patients' experience of symptoms and functional limitations was greater with NAB150/w. Among the seven polymorphisms selected for genotyping, the variant alleles of *EPHA5*-rs7349683, *EPHA6*-rs301927, and *EPHA8*-rs209709 were associated with an increased risk of paclitaxel-induced neuropathy.

Conclusion. The results of this exploratory study showed that, regardless of the dose, nab-paclitaxel did not differ from sb-paclitaxel in terms of neurotoxicity as evaluated with the TNS. However, results from NCI-CTCAE, dose delays and reductions, and functional tools consistently indicate that NAB150/w regimen is associated with a greater risk of chemotherapy-induced neuropathy. Thus, our results question the superiority of the TNS over NCI-CTCAE for evaluating chemotherapy-induced neuropathy and guiding treatment decisions in this context. The selection of the nab-paclitaxel regimen should be individualized based on the clinical context and potentially supported by pharmacogenetic analysis. Registry: EudraCT, 2012-002361-36; NCT01763710 *The Oncologist* 2019;24:e1024–e1033

Correspondence: Eva Ciruelos, M.D., Ph.D., Medical Oncology Department, Hospital Universitario 12 de Octubre, Avenida de Córdoba s/n, 28041 Madrid, Spain. Telephone: 34-659-228-621; e-mail address: eva.ciruelos@gmail.com Received December 19, 2017; accepted for publication March 28, 2019; published Online First on April 25, 2019. <http://dx.doi.org/10.1634/theoncologist.2017-0664>

Implications for Practice: The results of this study call into question the superiority of the Total Neurotoxicity Score over the National Cancer Institute Common Terminology Criteria for Adverse Events for evaluating chemotherapy-induced neuropathy and guiding treatment decisions in this context and suggest that a regimen of 150 mg/m² nab-paclitaxel administered on days 1, 8, and 15 is associated with a greater risk of chemotherapy-induced neuropathy and hematological toxicity compared with other lower-dose nab-paclitaxel regimens or a standard regimen of solvent-based paclitaxel. The selection of the nab-paclitaxel regimen should be individualized based on the clinical context and could benefit from pharmacogenetics analysis.

INTRODUCTION

Nab-paclitaxel is a solvent-free formulation of paclitaxel in albumin-bound nanoparticles that, in contrast to standard solvent-based (sb) paclitaxel, avoids the need for premedication to prevent hypersensitivity reactions and allows for the administration of higher doses with shorter infusion durations [1]. Nab-paclitaxel, administered in a 30-minute infusion of 260 mg/m² every 3 weeks (q3w), was superior to sb-paclitaxel administered at 175 mg/m² q3w in terms of the overall response rate, time to progression, and overall survival. However, the incidence of grade 3 sensory neuropathy was higher in the nab-paclitaxel group (10% vs. 2%; $p < 0.001$) [2] than in the standard paclitaxel group; this difference has been reported in other trials [3, 4] and shown to be dose dependent.

This randomized, open-label, multicenter, phase II study aimed to characterize the neurotoxicity of three different regimens of nab-paclitaxel compared with a standard regimen of sb-paclitaxel for the first-line treatment of metastatic breast cancer based on the Total Neurotoxicity Score (TNS).

MATERIALS AND METHODS

This randomized, open-label study was conducted at seven sites in Spain and approved by the ethics committee of each participating site. Written informed consent was obtained from every subject.

Study Population

We enrolled women aged ≥ 18 years with histologically or cytologically confirmed and measurable (RECIST criteria) stage IV breast cancer, an Eastern Cooperative Oncology Group performance status of 0–1, metastatic HER2-negative breast cancer with no prior chemotherapy for metastatic disease, and adequate organ function who were able and willing to provide two plasma samples for pharmacogenetic analysis.

Patients were excluded if they had clinical evidence of brain metastases, grade >1 preexisting peripheral neuropathy according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), any uncontrolled and serious medical or psychiatric concurrent disease, a grade ≥ 2 (NCI-CTCAE version 4.0) disease of the peripheral nervous or spinal cord at the time of inclusion, a history of other malignancies within the last 5 years with the exclusion of non-melanoma skin cancer or in situ cervical cancer, received treatment with investigational drugs within 2 weeks of inclusion, or a history of hypersensitivity to paclitaxel or Cremophor or were pregnant or lactating.

Randomization, Blinding, and Treatment

Randomization was performed centrally using a computer-generated list of random numbers and stratified by age (≥ 65 years and < 65 years) and the presence of diabetes mellitus. Patients were assigned in a 1:1:1:1 ratio to receive 4-week cycles of 80 mg/m² sb-paclitaxel (PACL80/w) on days 1, 8, and 15; 100 mg/m² nab-paclitaxel on days 1, 8, and 15 (NAB100/w); 150 mg/m² nab-paclitaxel on days 1, 8, and 15 (NAB150/w); or 150 mg/m² nab-paclitaxel on days 1 and 15 (NAB150/2w). Patients continued treatment until disease progression, unacceptable toxicity, or the patient's or physician's decision to terminate treatment. Dose reduction and treatment discontinuation rules are shown in supplemental online Table 1.

Assessments

Physical examination, performance status evaluation, and vital signs were performed at baseline, on days 1 and 15 of each cycle, and at the end of therapy. Hematological parameters were assessed at baseline, on days 1, 8, and 15 of each cycle, and at the end of therapy, whereas biochemical parameters were assessed at baseline, on day 1 of each cycle, and at the end of therapy. Blood for the polymorphism analysis was obtained at baseline. Chemotherapy-induced neurotoxicity was evaluated with the TNS [5]. The TNS and electromyography evaluations were conducted at baseline and after every three cycles of therapy or if grade 3–4 neurotoxicity occurred. In addition to the TNS, neuropathy was also assessed using the NCI-CTCAE, version 4.0.

Quality of life was evaluated with the European Organization for Research and Treatment of Cancer (EORTC) chemotherapy-induced peripheral neuropathy questionnaire (QLQ-CIPN20) [6] and the EORTC quality-of-life questionnaire (EORTC QLQ-C30) [7, 8]. The tumor response was evaluated according to RECIST version 1.1 at baseline and every 8–12 weeks thereafter, which is in accordance with the usual practice of each site. The overall toxicity was evaluated based on adverse events graded in accordance with the NCI-CTCAE, version 4.0.

Genotyping

Genomic DNA was isolated from blood samples using a FlexiGene DNA Kit (Qiagen, Germantown, MD), and the DNA concentration was measured by PicoGreen (Thermo Fisher Scientific, Waltham, MA). Two patients failed to provide a blood sample, and DNA extraction failed in one case; as a result, 57 patients were included in the pharmacogenetic

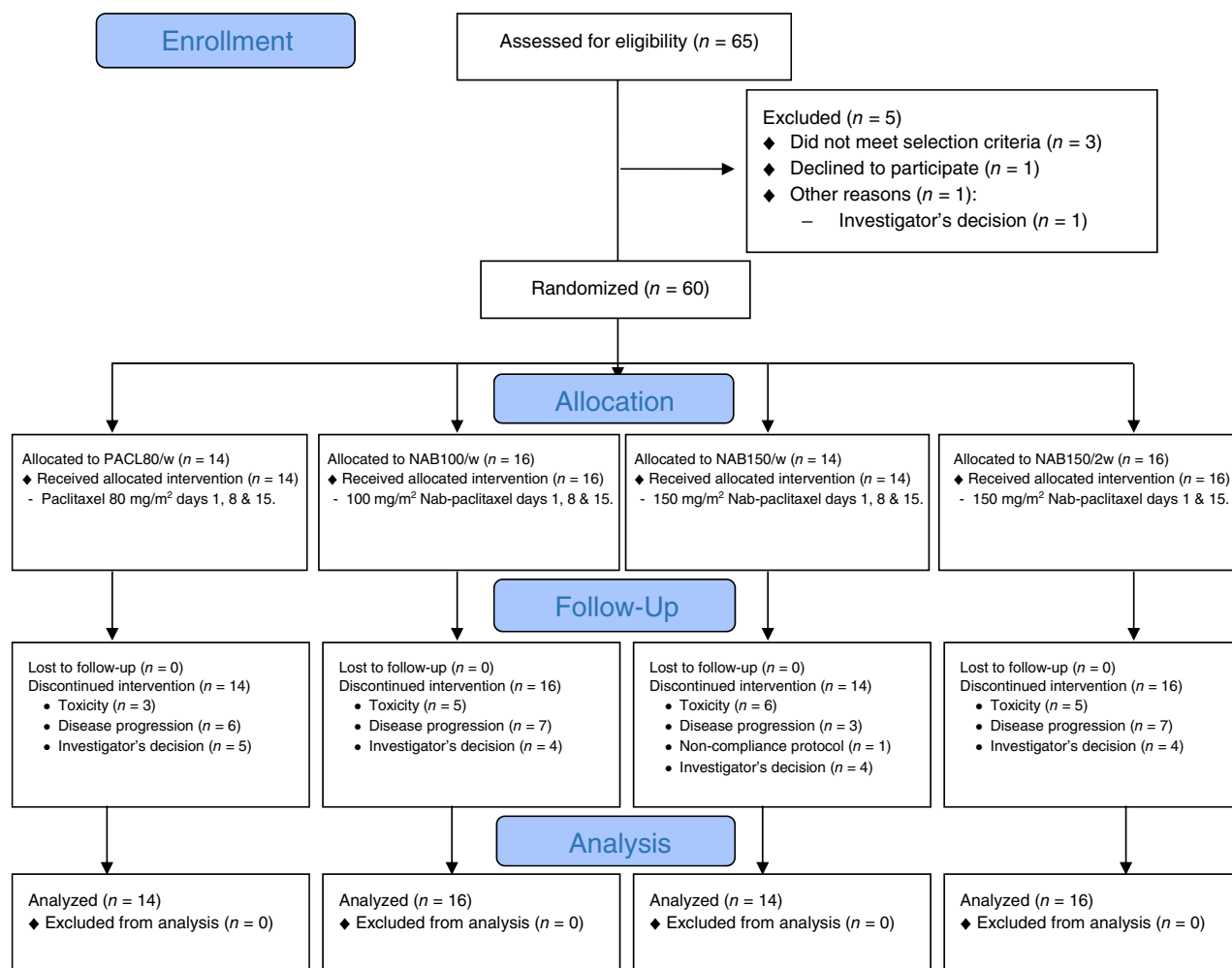


Figure 1. Patient disposition.

Abbreviations: NAB100/w, 100 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/w, 150 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/2w, 150 mg/m² nab-paclitaxel on days 1 and 15; PACL80/w, 80 mg/m² solvent-based paclitaxel on days 1, 8, and 15.

analysis. Seven single-nucleotide polymorphisms (SNPs) that were previously associated with paclitaxel-induced neuropathy were selected for genotyping, including four located in genes involved in paclitaxel pharmacokinetics (*CYP3A4*, *CYP2C8*, and *ABCB1*) and three in *EPHA* genes (*EPHA5*, *EPHA6*, and *EPHA8*; supplemental online Table 2) [9–15]. Genotyping was performed using KASPar Technology (Biosearch Technologies, London, U.K.) on a Sequence Detection System ABI PRISM 7900HT (Thermo Fisher Scientific). DNA samples with known genotypes and negative controls were included in the assays. Sanger sequencing was used in selected samples to confirm the accuracy of the genotyping. The allele frequencies of the SNPs were similar to those previously described, and all SNPs met Hardy-Weinberg equilibrium.

Statistical Analysis

Because of the exploratory nature of this pilot study, a sample size of 15 patients per treatment arm was estimated to be feasible and adequate to accomplish the primary objective.

The primary outcome was the mean change in the TNS from baseline to the end of treatment. Secondary outcomes included the frequency of grade ≥2 neuropathy, time to

resolution of grade 2–4 peripheral neuropathy, frequency of other toxicities according to the NCI-CTCAE, objective tumor response, clinical benefit, progression-free survival, mean change in the EORTC QLQ-CIPN20 and EORTC QLQ-C30 scores from baseline, and a pharmacogenetic evaluation. The primary efficacy analysis was performed in all randomized patients using an analysis of covariance with the TNS at baseline as a covariate; in this analysis, missing data were input with a last-observation-carried-forward approach. Other continuous outcomes were analyzed similarly to the TNS, but the quality of life was analyzed for the observed cases. The objective tumor response was compared among the treatment groups using Fisher's exact test. To analyze progression-free survival, we used the unadjusted Cox proportional hazards regression model and Kaplan-Meier curves.

The associations between the genotypes and paclitaxel neuropathy were tested with cumulative paclitaxel dose analysis [10, 15], which analyzes the cumulative dose of paclitaxel up to the development of ≥ grade 2 (NCI-CTCAE) neuropathy and censors patients with grade 0 or 1 at the total cumulative dose. Ordinal regression was used to evaluate the effect of the SNPs on the maximum neuropathy grade. For severe

Table 1. Patient and tumor characteristics at baseline

Characteristic	PACL80/w (n = 14)	NAB100/w (n = 16)	NAB150/w (n = 14)	NAB150/2w (n = 16)
Age, years				
Mean (SD)	58.2 (12.9)	59.5 (13.7)	57.3 (11.3)	60.9 (11.9)
≥65, n (%)	5 (35.7)	5 (31.3)	4 (28.6)	6 (37.5)
Prior diagnosis of diabetes, n (%)	1 (7.1)	4 (25.0)	1 (7.1)	4 (25.0)
Race (white), n (%)	14 (100.0)	14 (87.5)	12 (85.7)	15 (93.8)
Clinical stage at diagnosis, n (%)				
I	4 (28.6)	1 (6.3)	2 (14.3)	2 (12.5)
II	3 (21.4)	8 (50.0)	6 (42.9)	5 (31.3)
III	2 (14.3)	2 (12.5)	2 (14.3)	4 (25.0)
IV	4 (28.6)	5 (31.3)	4 (28.6)	3 (18.8)
Unknown	1 (7.1)	0 (0.0)	0 (0.0)	2 (12.59)
Time from diagnosis, mean (SD), months	78.2 (91.4)	69.3 (72.2)	109.8 (127.3)	84.3 (71.6)
Hormone receptor status, n (%)				
Estrogen receptor positive (yes)	13 (92.9)	14 (87.5)	11 (78.6)	11 (68.8)
Progesterone receptor positive (yes)	9 (64.3)	13 (81.3)	7 (50.0)	10 (62.5)
Previous radiotherapy (yes), n (%)	8 (57.1)	7 (43.8)	8 (57.1)	10 (62.5)
Previous surgery (yes), n (%)	11 (78.6)	12 (75.0)	10 (71.4)	13 (81.3)
Previous adjuvant CT (yes), n (%)	7 (50.0)	10 (62.5)	9 (64.3)	11 (68.8)
Taxane-based CT (yes), n (%)	5 (35.7)	5 (31.3)	6 (42.9)	4 (25.0)
Treatment duration, median, months	3.1	4.9	3.1	4.6
Time from study inclusion to last infusion, median, months	34.3	43.6	23.1	62.4
Anthracycline-based CT (yes), n (%)	6 (42.9)	9 (56.3)	7 (50.0)	9 (56.3)
Previous hormone therapy (yes), n (%)	11 (78.6)	10 (62.5)	11 (78.6)	10 (62.5)
One line	4 (36.4)	3 (30.0)	7 (63.6)	3 (30.0)
Two lines	5 (45.5)	7 (70.0)	2 (18.2)	6 (60.0)
At least two lines	2 (18.2)	0 (0.0)	2 (18.2)	1 (10.0)
Metastatic site, n (%)				
Lung	1 (7.1)	6 (37.5)	4 (28.6)	5 (31.3)
Liver	10 (71.4)	12 (75.0)	9 (64.3)	7 (43.8)
Bone	6 (42.9)	8 (50.0)	5 (35.7)	10 (62.5)
Pleura	3 (21.4)	3 (18.8)	3 (21.4)	3 (18.8)
Breast	2 (14.3)	3 (18.8)	3 (21.4)	5 (31.3)
Other	3 (21.4)	5 (31.3)	5 (35.7)	8 (50.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECOG, n (%)				
0	10 (71.4)	7 (43.8)	12 (85.7)	10 (62.5)
1	3 (21.4)	7 (43.8)	2 (14.3)	6 (37.5)
Unknown	1 (7.1)	2 (12.5)	0 (0.0)	0 (0.0)

Abbreviations: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NAB100/w, 100 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/w, 150 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/2w, 150 mg/m² nab-paclitaxel on days 1 and 15; PACL80/w, 80 mg/m² solvent-based paclitaxel on days 1, 8, and 15.

toxicities (grade ≥3) and treatment modifications caused by toxicities, binary logistic regression was used. In multivariate analyses, relevant clinical and demographic factors were included as covariates. An additive genetic model was used; however, based on the literature, alternative genetic models were also allowed. Values of $p < .05$ were considered statistically significant.

RESULTS

Patient Baseline Characteristics and Drug Exposure

From January 2013 to July 2014, we assessed 65 patients for eligibility, and 60 patients were randomized and included in the efficacy and safety analyses (Fig. 1). The demographic and clinical characteristics slightly differed among the study

Table 2. Least square mean changes from baseline to endpoint in the Total Neurotoxicity Score (LOCF-ANCOVA)

Treatment group	Baseline score	Change from baseline LS mean	Difference vs. solvent-based paclitaxel	
			Mean (SE) [95% CI]	<i>p</i> value
PACL80/w <i>n</i> = 14	2.4	3.8		
NAB100/w <i>n</i> = 16	2.8	3.7	−0.1 (1.1) [−2.4 to 2.2]	.924
NAB150/w <i>n</i> = 14	1.8	3.5	−0.4 (1.2) [−2.7 to 2.0]	.764
NAB150/2w <i>n</i> = 16	2.3	2.3	−1.5 (1.1) [−3.8 to 0.8]	.187

Missing data: PACL80/w (*n* = 1) and NAB150/w (*n* = 1); these patients required data imputation using a last-observation-carried-forward approach.

Abbreviations: CI, confidence interval; LOCF-ANCOVA, last-observation-carried-forward analysis of covariance; LS, least square; NAB100/w, 100 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/w, 150 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/2w, 150 mg/m² nab-paclitaxel on days 1 and 15; PACL80/w, 80 mg/m² solvent-based paclitaxel on days 1, 8, and 15.

groups, as shown in Table 1. Treatment delivery, dose reductions and treatment delays are presented in supplemental online Table 3. Dose delays and reductions due to neurotoxicity were more common among patients receiving NAB150/w (three and four patients, respectively). Patients were followed up for a median of 23 months.

Neurotoxicity

Neurotoxicity, as evaluated by the TNS, did not significantly differ between the sb-paclitaxel group and any of the nab-paclitaxel groups (Table 2). Increases in the TNS were low and did not differ between treatment arms.

The frequency of polyneuropathy, as measured by the CTCAE criteria, was lower with PACL80/w (*n* = 7, 50%) and NAB150/2w (*n* = 10, 62.5%) than with NAB100/w (*n* = 13, 81.3%) or NAB150/w (*n* = 11, 78.6%). Grade 4 polyneuropathy was not observed, and grade 3 polyneuropathy was more common with NAB150/w than with PACL80/w (five cases vs. one case). Grade 3 polyneuropathy did not occur in the NAB100/w and NAB150/2w groups. Although the differences were not significant, in patients treated with NAB150/w, the time to occurrence of grade ≥2 polyneuropathy was shorter (median, 4.2 months) than those in the other groups (the median with NAB100/w was 11.1 months, and it was not reached with NAB150/2w or PACL80/w). The median time to recover from grade ≥2 polyneuropathy was longer in the NAB150/w (14.6 months) and NAB150/2w (12.6 months) groups than in the other two groups (8.8 and 6.9 months for the PACL80/w and NAB100/w groups, respectively), but the differences were not statistically significant.

Patients in the NAB150/w group exhibited the greatest increases in each scale of the EORTC QLQ-CIPN20, and the difference with patients in the PACL80/w group was only significant for the sensory scale (estimated treatment difference [ETD], 19.0; 95% confidence interval [CI], 1.1–37.0; *p* = .039; Table 3).

Table 3. Least square mean changes from baseline to endpoint in the EORTC QLQ-CPIN20 dimension scores

Treatment group	Baseline score	Change from baseline LS mean	Difference vs. solvent-based paclitaxel	
			Mean (SE) [95% CI]	<i>p</i> value
Sensory scale				
PACL80/w <i>n</i> = 14	11.2	14.4		
NAB100/w <i>n</i> = 16	8.4	28.4	14.0 (9.3) [−4.8 to 32.9]	.140
NAB150/w <i>n</i> = 14	11.4	33.4	19.0 (8.8) [1.1 to 37.0]	.039
NAB150/2w <i>n</i> = 16	9.6	14.0	−0.4 (8.6) [−17.8 to 17.1]	.967
Motor scale				
PACL80/w <i>n</i> = 14	12.8	9.9		
NAB100/w <i>n</i> = 16	15.4	7.6	−2.3 (9.4) [−21.4 to 16.7]	.806
NAB150/w <i>n</i> = 14	18.8	20.6	10.7 (8.9) [−7.4 to 28.7]	.239
NAB150/2w <i>n</i> = 16	12.9	11.3	1.4 (8.7) [−16.3 to 19.2]	.871
Autonomic scale				
PACL80/w <i>n</i> = 14	6.9	3.3		
NAB100/w <i>n</i> = 16	20.6	8.3	5.0 (13.3) [−22.2 to 32.2]	.710
NAB150/w <i>n</i> = 14	19.0	10.0	6.7 (11.8) [−17.4 to 30.8]	.575
NAB150/2w <i>n</i> = 16	6.7	−1.3	−4.6 (11.5) [−28.1 to 18.9]	.693

Abbreviations: CI, confidence interval; EORTC QLQ-CPIN20, European Organization for Research and Treatment of Cancer chemotherapy-induced peripheral neuropathy questionnaire; LS, least square; NAB100/w, 100 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/w, 150 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/2w, 150 mg/m² nab-paclitaxel on days 1 and 15; PACL80/w, 80 mg/m² solvent-based paclitaxel on days 1, 8, and 15.

Clinical Efficacy

The objective response rate was higher in the NAB150/w group (*n* = 6, 42.9%; 95% CI, 16.9–68.8) than in the PACL80/w group (*n* = 3, 21.4%; 95% CI, 0.0–42.9), but this difference was not significant (*p* = .420). Objective response was achieved for six patients (37.5%; 95% CI, 13.8–61.2) in the NAB100/w group and two patients (12.5%; 95% CI, 0.0–28.7) in the NAB150/2w group, but these rates did not significantly differ from those in the PACL80/w group (*p* = .440 and *p* = .642, respectively).

Differences in progression-free survival were seen, albeit not significantly (log-rank test *p* = .128), with a median time to progression of 11.6 months for NAB100/w, 15.7 months for NAB150/w, 7.4 months for NAB150/2w, and 6.0 months for PACL80/w.

Safety

Overall, the frequency of adverse events (AEs) and number of grade 3–4 AEs were highest with NAB150/w (Table 4). The most frequent hematological toxicities were leucopenia and

Table 4. Adverse events reported in more than 10% of the patients and/or of grade 3–4 in any group (NCI-CTCAE 4.0)

Adverse event	PACL80/w (<i>n</i> = 14), <i>n</i> (%)		NAB100/w (<i>n</i> = 16), <i>n</i> (%)		NAB150/w (<i>n</i> = 14), <i>n</i> (%)		NAB150/2w (<i>n</i> = 16), <i>n</i> (%)	
	G 1–2	G 3–4	G 1–2	G 3–4	G 1–2	G 3–4	G 1–2	G 3–4
Hematological								
Anemia	3 (21.4)	—	7 (43.8)	1 (6.3)	8 (57.2)	1 (7.1)	8 (50.0)	1 (6.3)
Leukopenia	8 (57.1)	—	7 (43.8)	1 (6.3)	3 (21.4)	4 (28.6)	3 (18.8)	1 (6.3)
Lymphopenia	1 (7.1)	—	2 (12.6)	—	1 (7.1)	—	2 (12.6)	—
Monocytopenia	1 (7.1)	—	—	—	1 (7.1)	—	—	—
Neutropenia	2 (14.2)	—	6 (37.5)	—	2 (14.2)	7 (50.0)	3 (18.8)	—
Febrile neutropenia	—	—	—	—	—	1 (7.1)	—	—
Thrombocytopenia	1 (7.1)	—	1 (6.3)	—	1 (7.1)	—	1 (6.3)	—
Nervous system disorders								
Aphonia	—	—	—	1 (6.3)	—	—	—	—
Polyneuropathy	6 (42.8)	1 (7.1)	13 (81.3)	—	6 (42.9)	5 (35.7)	10 (62.6)	—
Other nonhematological toxicities								
Alopecia	6 (42.8)	—	6 (37.5)	—	5 (35.7)	—	2 (12.5)	—
Onycholysis	4 (28.6)	—	3 (18.8)	2 (12.5)	2 (14.3)	—	2 (12.6)	—
Nail dystrophy	—	—	1 (6.3)	—	1 (7.1)	1 (7.1)	1 (6.3)	—
Decreased appetite	2 (14.3)	—	—	—	1 (7.1)	—	2 (12.6)	1 (6.3)
Asthenia	8 (57.2)	—	6 (37.6)	1 (6.3)	7 (50.0)	2 (14.3)	14 (87.6)	—
Blood alkaline phosphatase increased	—	—	—	—	2 (14.3)	—	—	—
Alanine aminotransferase increased	—	—	3 (18.8)	—	1 (7.1)	—	—	—
Aspartate aminotransferase increased	—	—	2 (12.5)	—	1 (7.1)	—	—	—
Gamma-glutamyltransferase increased	—	—	1 (6.3)	—	—	1 (7.1)	—	—
Hyperglycemia	—	—	2 (12.5)	—	—	—	1 (6.3)	1 (6.3)
Hypocalcemia	—	—	1 (6.3)	—	—	—	1 (6.3)	1 (6.3)
Diarrhea	2 (14.2)	—	1 (6.3)	1 (6.3)	2 (14.3)	1 (7.1)	2 (12.5)	—
Vomiting	1 (7.1)	—	2 (12.5)	—	1 (7.1)	—	2 (12.6)	—
Nausea	—	—	1 (6.3)	—	3 (21.3)	—	5 (31.3)	—
Cold	—	—	2 (12.5)	—	—	—	—	—
Cellulitis	—	—	—	—	1 (7.1)	1 (7.1)	—	—
Mucosal inflammation	—	—	—	—	2 (14.3)	—	2 (12.5)	—
Pain in an extremity	1 (7.1)	—	—	—	2 (14.3)	—	—	—
Abdominal pain	—	—	—	—	1 (7.1)	—	—	1 (6.3)
Arthralgia	—	—	—	—	—	—	2 (12.5)	—
Muscle spasms	1 (7.1)	—	—	—	2 (14.3)	—	1 (6.3)	—
Chest discomfort	1 (7.1)	—	—	—	—	—	2 (12.5)	—
Cough	—	—	1 (6.3)	—	—	—	2 (12.5)	—

Note: the only grade 4 adverse events were three cases of leukopenia, two cases of neutropenia, and one case of febrile neutropenia in the NAB150/w arm. Abbreviations: —, no cases; CI, confidence interval; G, grade; NAB100/w, 100 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/w, 150 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/2w, 150 mg/m² nab-paclitaxel on days 1 and 15; PACL80/w, 80 mg/m² solvent-based paclitaxel on days 1, 8, and 15.

neutropenia, although most cases were grades 1–2. Grades 3–4 leukopenia and neutropenia were more frequent in the NAB150/w arm (*n* = 4 [28.4%] and *n* = 7 [50.0%], respectively). Grades 3–4 hematological or nonhematological toxicities were not observed in the sb-paclitaxel group. In addition to polyneuropathy, the most frequent nonhematological toxicities were asthenia, alopecia, onycholysis, and nausea (Table 4).

Twelve patients (85.7%) in the NAB150/w group interrupted treatment because of AEs, whereas only three (21.4%) patients in the PACL80/w group and three (18.8%) and four (25.0%) patients in the NAB100/w and NAB150/2w groups,

respectively, terminated their treatment because of AEs. Moreover, 12 serious AEs were reported for NAB150/w patients, ten for NAB100/w, and four cases each for NAB100/w and NAB150/2w. All serious AEs had resolved by the end of the follow-up, except two cases each for NAB150/w (a case of neutropenia and a case of pyrexia) and NAB100/w (a case of acute cholecystitis and a case of polyneuropathy).

Eight patients (57.1%) died in the PACL80/w group (six deaths due to disease progression, one due to respiratory failure considered unrelated to the study medication, and one of an unknown cause), one patient (6.3%) died in the NAB100/w

Table 5. Least square mean changes from baseline to endpoint in the EORTC QLQ-C30 dimension scores and general health status score (observed cases – ANCOVA)

Treatment group	Baseline score	Change from baseline LS mean	Difference vs. solvent-based paclitaxel	
			Mean (SE) [95% CI]	p value
Physical functioning				
PACL80/w n = 14	78.3	−12.7		
NAB100/w n = 16	66.7	−6.6	6.1 (13.7) [−21.7 to 33.9]	.657
NAB150/w n = 14	75.5	−24.7	−12.0 (12.8) [−38.1 to 14.1]	.355
NAB150/2w n = 16	70.4	−8.9	3.7 (12.5) [−21.6 to 29.1]	.765
Role functioning				
PACL80/w n = 14	74.4	−19.2		
NAB100/w n = 16	53.6	−5.0	14.1 (15.0) [−16.4 to 44.7]	.354
NAB150/w n = 14	63.9	−27.3	−8.1 (14.2) [−37.0 to 20.7]	.570
NAB150/2w n = 16	70.0	−12.5	6.7 (13.6) [−21.0 to 34.4]	.626
Emotional functioning				
PACL80/w n = 14	66.9	−0.2		
NAB100/w n = 16	65.9	1.2	1.4 (9.5) [−18.0 to 20.8]	.885
NAB150/w n = 14	75.0	−9.8	−9.6 (8.9) [−27.7 to 8.5]	.289
NAB150/2w n = 16	68.5	6.0	6.2 (9.0) [−12.2 to 24.5]	.498
Cognitive functioning				
PACL80/w n = 14	89.7	−12.7		
NAB100/w n = 16	86.9	−8.2	4.5 (11.9) [−19.8 to 28.8]	.708
NAB150/w n = 14	73.1	−2.5	10.2 (11.4) [−13.1 to 33.4]	.380
NAB150/2w n = 16	84.4	−7.5	5.2 (10.9) [−16.9 to 27.4]	.636
Social functioning				
PACL80/w n = 14	79.5	−4.3		
NAB100/w n = 16	65.4	17.6	21.9 (16.7) [−12.7 to 56.5]	.203
NAB150/w n = 14	83.3	−18.0	−13.7 (17.9) [−50.7 to 23.3]	.452
NAB150/2w n = 16	77.4	−5.2	−0.9 (14.5) [−30.8 to 29.0]	.950
General health status				
PACL80/w n = 14	52.4	−7.4		

(continued)

Table 5. (continued)

Treatment group	Baseline score	Change from baseline LS mean	Difference vs. solvent-based paclitaxel	
			Mean (SE) [95% CI]	p value
NAB100/w n = 16	46.4	–18.0	–10.6 (12.1) [–34.9 to 13.8]	.387
NAB150/w n = 14	57.7	–14.6	–7.2 (12.6) [–32.5 to 18.2]	.571
NAB150/2w n = 16	48.4	–5.7	1.7 (12.3) [–23.0 to 26.5]	.888

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least square; NAB100/w, 100 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/w, 150 mg/m² nab-paclitaxel on days 1, 8, and 15; NAB150/2w, 150 mg/m² nab-paclitaxel on days 1 and 15; PACL80/w, 80 mg/m² solvent-based paclitaxel on days 1, 8, and 15.

group, three patients (21.4%) died in the NAB150/w group, and five patients (21.4%) died in the NAB150/2w group due to disease progression, except for one death in the NAB150/2w group that was caused by bronchoaspiration (considered unrelated to the study medication).

Quality of Life

Except for cognitive function, which showed greater deterioration in the PACL80/w group, patients in the NAB150/w group showed a greater deterioration in all functional scales and general health status for the EORTC QLQ-C30 than patients in the PACL80/w group, but none of these changes was significant compared with the PACL80/w group (Table 5).

Pharmacogenetic Study

Only polymorphisms in *EPHA* genes showed significant associations with paclitaxel-induced neuropathy. The variant alleles of *EPHA5*-rs7349683, *EPHA6*-rs301927, and *EPHA8*-rs209709 were associated with an increased risk of paclitaxel-induced neuropathy (Fig. 2). In multivariate analysis, these three SNPs gave a hazard ratio (HR) >2.5 with significant *p* values (Table 6). Regarding the maximum neuropathy grade for the patients, *EPHA5*-rs7349683 showed a trend toward greater neurotoxicity grades (*p* = .096; data not shown).

The *EPHA6*-rs301927 variant allele was significantly associated with an increased risk of any toxicity with grade ≥3, both in univariate analysis (HR, 5.36; 95% CI, 1.04–27.57; *p* = .045) and when adjusting for age and diabetes (HR, 6.59; 95% CI, 1.06–40.8; *p* = .043). No SNP was significantly associated with treatment modifications due to neuropathy or other toxicities.

DISCUSSION

This pilot trial showed that nab-paclitaxel administered as 4-week cycles of 100 mg/m² or 150 mg/m² on days 1, 8, and 15 or as 150 mg/m² on days 1 and 15 did not differ from 4-week cycles of 80 mg of sb-paclitaxel on days 1, 8, and 15 in terms of neurotoxicity, as evaluated with the TNS scale. The increase in the TNS with NAB100/w and NAB150/w overlapped that of PACL80/w. However, the neurotoxicity reported using the NCI-CTCAE showed somewhat different

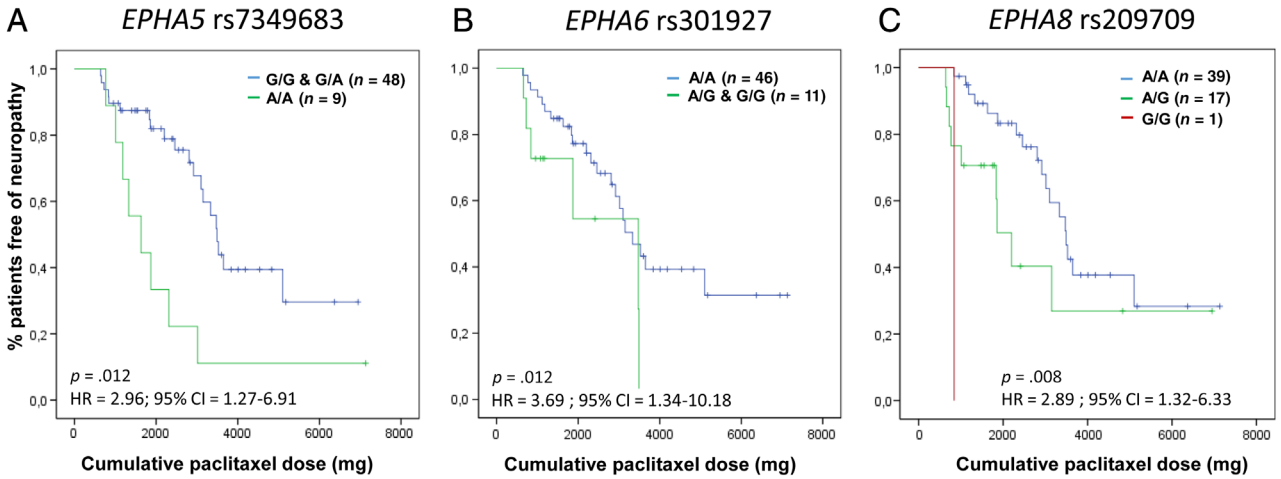


Figure 2. Kaplan-Meier curves for paclitaxel-induced neuropathy grouped by *EPHA* polymorphism. Paclitaxel-treated patients were grouped according to *EPHA5*-rs7349683 (**A**), *EPHA6*-rs301927 (**B**), and *EPHA8*-rs209709 (**C**), and the cumulative dose of paclitaxel up to the development of grade 2 neuropathy was analyzed. Genetic models correspond to recessive, dominant, and additive, respectively. The *p* values correspond to multivariate Cox regression analysis adjusted by age and previous neuropathy. Abbreviations: A/A, adenine/adenine genotype; A/G, adenine/guanine genotype; CI, confidence interval; G/A, guanine/adenine genotype; G/G, guanine/guanine genotype; HR, hazard ratio.

Table 6. Pharmacogenetic study of paclitaxel-induced neuropathy

Gene	SNP ^a	MAF	Univariate analysis		Multivariate analysis ^b	
			HR (95% CI)	<i>p</i> value ^c	HR (95% CI)	<i>p</i> value ^c
<i>CYP2C8</i>	rs11572080	0.15	0.93 (0.43–2.04)	.865	0.91 (0.41–2.03)	.814
<i>CYP3A4</i>	rs67666821	0.02	2.26 (0.52–9.76)	.276	1.80 (0.40–8.02)	.442
<i>CYP3A4</i>	rs35599367	0.04	1.43 (0.43–4.79)	.562	2.12 (0.60–7.49)	.241
<i>ABCB1</i>	rs1045642	0.44	0.89 (0.53–1.51)	.675	0.85 (0.48–1.51)	.577
<i>EPHA5</i>	rs7349683 (r)	0.38	3.08 (1.34–7.08)	.008	2.96 (1.27–6.91)	.012
<i>EPHA6</i>	rs301927 (d)	0.11	2.25 (0.89–5.67)	.087	3.69 (1.34–10.18)	.012
<i>EPHA8</i>	rs209709	0.17	2.43 (1.17–5.05)	.017	2.89 (1.32–6.33)	.008

^aAn additive genetic model was used unless otherwise indicated: recessive model (r) or dominant model (d).
^bMultivariate analyses included age and previous neuropathy events as covariates.
^cSignificant *p* values are shown in bold.
Abbreviations: CI, confidence interval; HR, hazard ratio; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

results. Therefore, 35.7% patients treated with NAB150/w compared with 7.1% patients treated with PACL80/w showed grade 3 polyneuropathy. These latter findings are consistent with the dose delays and reductions due to neurotoxicity observed among patients treated with NAB150/w as well as with the greater impact of neurotoxicity in the patients' experience of symptoms and functional limitations, as evaluated with the QLQ-CIPN20 in the NAB150/w group. The differences among these neurotoxicity evaluation scales could be due to the involvement of different outcome assessors (the physician in the TNS and patient in the NCI-CTCAE). The different schedules for the evaluations, every three cycles for the TNS and every cycle for the NCI-CTCAE, might also play a role in these differences. However, it has been previously reported that the TNS has a significant correlation with the NCI-CTCAE in scoring the severity of chemotherapy-induced neuropathy; also, the TNS has a higher sensitivity to change [5]. Our results do not support that correlation; instead, evaluating neurotoxicity with NCI-CTCAE could better guide the clinical management of these patients. Overall, we think there is no consensus on the best method to assess

chemotherapy-induced peripheral neuropathy. In fact, there are numerous methods available, but some, such as TNS, are complex and time-consuming, whereas the NCI-CTCAE grading scale is widely used among clinical oncologists in every patient visit. NCI-CTCAE is a subjective method that is also quick and easy to perform in the clinical setting because the scale is commonly recognized by oncologists. In the other hand, TNS requires a complex training and invasive neurophysiological assessments [16]. A study by Cavaletti et al. [5] showed that the TNS grading system provided more accurate classification of chemotherapy-induced peripheral neuropathy. However, our study found that, in a homogeneous group of breast cancer patients treated with taxanes, CTCAE was a valuable method to manage chemotherapy-induced peripheral neuropathy in these patients, whereas TNS did not guide physicians' decisions.

Regarding the pharmacogenetic study, our results show that *EPHA5*-rs7349683, *EPHA6*-rs301927, and *EPHA8*-rs209709 play a relevant role in the susceptibility to paclitaxel-induced peripheral neuropathy. This is in agreement with previous results using sb-paclitaxel [10, 14, 17] and demonstrates that

these markers are relevant, independent of the type of paclitaxel administration.

Although the differences did not reach significance, the efficacy was numerically higher with NAB150/w with an objective response rate in this arm that overlaps that reported by Gradishar et al. in a phase III study of the subgroup of patients who received first-line therapy [2]. However, NAB150/w was also associated with more frequent grade 3–4 hematological toxicities and treatment interruptions due to adverse events than PAcl80/w. The best results for toxicity were observed with NAB150/2w, but this regimen had the worst results for efficacy. Overall, our results suggest that the best nab-paclitaxel regimen remains to be elucidated. The SNAP trial, a randomized phase II clinical trial evaluating three maintenance regimens of nab-paclitaxel after induction therapy with 4-week cycles 150 mg/m² on days 1, 8, and 15 [18] has been conducted to clarify this issue.

CONCLUSION

The main limitations of this study are the small sample size, lack of correction for multiplicity, and lack of blinding. The results of this exploratory study showed that, regardless of the dose, nab-paclitaxel did not differ from sb-paclitaxel in terms of neurotoxicity as evaluated with the TNS. However, results from NCI-CTCAE, dose delays and reductions, and functional tools consistently indicate that NAB150/w regimen is associated with a greater risk of chemotherapy-induced neuropathy. Thus, our results question the superiority of the TNS over CTCAE criteria for evaluating chemotherapy-induced neuropathy and guiding treatment decisions in this context. Therefore, the selection of the nab-paclitaxel regimen should be individualized based on the clinical context and could benefit from pharmacogenetics analysis.

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AUTHOR CONTRIBUTIONS

Conception/design: Eva Ciruelos, María Apellániz-Ruiz, Cristina Rodríguez-Antona, Juan-Manuel Sepúlveda

Provision of study material or patients: María Apellániz-Ruiz, Blanca Cantos, Noelia Martínez-Jáñez, Coralía Bueno-Muñoz, María-José Echarri, Santos Enrech, Juan-Antonio Guerra, Luis Manso, Tomas Pascual, Cristina Domínguez, Juan-Francisco Gonzalo

Collection and/or assembly of data: María Apellániz-Ruiz, Blanca Cantos, Noelia Martínez-Jáñez, Coralía Bueno-Muñoz, Santos Enrech, Juan-Antonio Guerra, Luis Manso, Tomas Pascual, Cristina Domínguez, Juan-Francisco Gonzalo

Data analysis and interpretation: Eva Ciruelos, María Apellániz-Ruiz, Juan-Francisco Gonzalo, Juan-Luis Sanz, Cristina Rodríguez-Antona, Juan-Manuel Sepúlveda

Manuscript writing: Eva Ciruelos, María Apellániz-Ruiz, Juan-Luis Sanz, Cristina Rodríguez-Antona, Juan-Manuel Sepúlveda

Final approval of manuscript: Eva Ciruelos, María Apellániz-Ruiz, Blanca Cantos, Noelia Martínez-Jáñez, Coralía Bueno-Muñoz, María-José Echarri, Santos Enrech, Juan-Antonio Guerra, Luis Manso, Tomas Pascual, Cristina Domínguez, Juan-Francisco Gonzalo, Juan-Luis Sanz, Cristina Rodríguez-Antona, Juan-Manuel Sepúlveda

DISCLOSURES

Eva Ciruelos: Novartis, Celgene, Pfizer, Roche, Eli Lilly & Co. (SAB, H); **Blanca Cantos:** Celgene (SAB); **Noelia Martínez-Jáñez:** AstraZeneca, Roche, Novartis, Celgene, Eisai, Pfizer (SAB, H); **Coralía Bueno-Muñoz:** Roche, AstraZeneca, Pierre Fabre, PharmaMar, Merck Sharp & Dohme (H), Roche (C/A), Roche, Pfizer (other—travel grants); **Luis Manso:** Celgene, Novartis, AstraZeneca, Roche, Tesaro SL, Pfizer, Clovis, Eisai (SAB), Roche, Celgene, Eisai, Novartis (H), Tesaro SL (RF), Riche, Celgene, Novartis, Tesaro SL (other—travel grants); **Juan-Manuel Sepúlveda:** Abbvie, Celgene, Bayer, GW Pharma (SAB), Astellas (H), Pfizer, Catalysis (RF), Abbvie, Ipsen, Celgene (other—travel grants). The other authors indicated no financial relationships.

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