First-line bevacizumab and eribulin combination therapy for HER2-negative metastatic breast cancer: Efficacy and safety in the GINECO phase II ESMERALDA study

Anne-Claire Hardy-Bessard a, *, Fabien Brocard b, Florian Clatot c, Alain Lortholary d, Benoît You e, f, Julien Grenier g, Jérôme Martin-Babau a, Brigitte Lucas h, Jérôme Meunier i, Jean-Marc Ferrero j, Aude-Marie Savoye k, Adina Marti i, Raymond Despax m, Isabelle Mouillet n, George Emile o

a Centre Armorican de Radiothérapie, D’Imagerie Médicale et D’Oncologie (CARIO)-Hôpital Privé des Côtes D’Armor (HPCA), Plévin, France
b Centre D’Oncologie de Gentilly, Nancy, France
c Centre Henri Becquerel, Rouen, France
d Hôpital Privé Du Confluent, Nantes, France
e Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CTIOHL, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Lyon, France
f Univ Lyon, Université Claude Bernard Lyon 1, Faculté de Médecine Lyon-Sud, Lyon, France
g Institut Du Cancer Avignon-Provence, Avignon, France
h Clinique Pasteur, Brest, France
i Centre Hospitalier Régional Orléans, Orléans, France
j Centre Antoine Lacassagne, Nice, France
k Institut Jean Godinot, Reims, France
l Centre Hospitalier Aix en Provence, Aix-en-Provence, France
m Clinique Pasteur-ONCOSUD, Toulouse, France
n Clinique de La Sauvegarde, Lyon, France
o Breast Cancer Unit, Centre François Baclesse (Institut Normand Du Sein), Caen, France

Article info
Article history:
Received 30 May 2020
Received in revised form 20 September 2020
Accepted 25 September 2020
Available online 30 September 2020

Keywords:
Bevacizumab
Eribulin
Metastatic breast cancer
Combination therapy
Neuropathy

Abstract
Purpose: Combining bevacizumab with paclitaxel significantly improves progression-free survival (PFS) versus paclitaxel alone in HER2-negative metastatic breast cancer (MBC). Eribulin is active and tolerable in pretreated MBC. To assess whether eribulin may offer a more tolerable yet effective combination partner for bevacizumab, we evaluated a bevacizumab/eribulin combination regimen as first-line therapy for MBC.

Methods: In this single-arm phase II study, patients with histologically confirmed HER2-negative MBC and no prior chemotherapy for MBC received eribulin 1.23 mg/m² on days 1 and 8 every 3 weeks for ≥6 cycles plus bevacizumab 15 mg/kg on day 1 every 3 weeks until disease progression. The primary endpoint was non-progression rate at 1 year. Secondary endpoints included objective response rate (ORR), PFS, and safety.

Results: The median age of the 61 treated female patients was 59 years, 16% had triple-negative MBC, 30% had ≥3 metastatic sites, and 71% had received prior (neo)adjuvant chemotherapy. Patients received a median of six eribulin and nine bevacizumab cycles. The non-progression rate at 1 year was 32% (95% confidence interval [CI]: 20–43%), ORR was 47% (95% CI: 34–60%), and median PFS was 8.3 months (95% CI: 7.0–9.6 months). The only grade ≥3 clinical adverse events in ≥5% of patients were hypertension (39%), neutropenia (26%), thrombosis (16%), and paresthesia/dysesthesia (7%).

Conclusion: First-line eribulin/bevacizumab combination therapy showed interesting activity in MBC with an acceptable safety profile, including a particularly low incidence of high-grade neuropathy.

© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

The treatment landscape for HER2-negative metastatic breast cancer (MBC) ineligible for hormonal therapy is founded upon chemotherapy, particularly the taxanes, but continues to evolve and expand with new chemotherapies and targeted agents. In the E2100, AVADO, RIBBON-1, and MERIDIAN randomized phase III trials, combining bevacizumab with first-line chemotherapy for HER2-negative MBC significantly improved progression-free survival (PFS) versus chemotherapy alone [1–4] but overall survival was not improved. Bevacizumab is approved in Europe as first-line therapy for HER2-negative MBC in combination with either paclitaxel or capetitabine, and is considered a standard of care option in some countries, particularly in patients with triple-negative MBC [5]. Although taxane-based regimens are among the most active in MBC, chemotherapy-induced peripheral neuropathy with microtubule inhibitors can be disabling [6]. Neuropathy is a well-known side effect of paclitaxel and has a major impact on patients’ well-being and daily activities. Recent research suggests that paclitaxel in particular is associated with delayed recovery from chemotherapy-induced peripheral neuropathy, resulting in severe, pervasive, and prolonged effects [7], which may continue long after treatment discontinuation [6,8,9].

In the pivotal E2100 trial of paclitaxel and bevacizumab, 24% of patients experienced grade 3/4 peripheral neuropathy (compared with 18% in the single-agent paclitaxel arm; P < 0.05) [1]. Bevacizumab may exacerbate paclitaxel-associated peripheral neuropathy, as seen in post-marketing series [10] and meta-analyses [11]. However, in the subsequent placebo-controlled randomized phase III MERIDIAN trial, only 4% of patients experienced grade 3/4 peripheral neuropathy with bevacizumab/paclitaxel [4]. Analyses from a randomized phase II trial of paclitaxel and bevacizumab suggested that certain single nucleotide polymorphisms may identify patients at increased risk of peripheral neuropathy [12]. An alternative approach to reducing the risk of neuropathy is to use a different chemotherapy combination partner. The TURANDOT trial comparing bevacizumab/paclitaxel versus bevacizumab/capetitabine showed non-inferiority and a significantly lower incidence of peripheral neuropathy with the non-taxane regimen [13]. Conversely, the randomized phase III CALGB 40502/NCCCTG N063H (Alliance) trial comparing bevacizumab/paclitaxel with investigational bevacizumab-containing regimens showed an increased incidence of grade ≥3 sensory neuropathy with bevacizumab/nanoparticle albumin-bound (nab)-paclitaxel or bevacizumab/ixabepilone [14].

The microtubule inhibitor eribulin is an established therapy for MBC in later lines, based on results of the EMBRACE [15] and Study 301 [16] randomized phase III trials and, more recently, a randomized phase III trial versus vinorelbine in Chinese patients with anthracycline- and taxane-pretreated MBC [17]. Most data for eribulin have been generated in patients with heavily pretreated MBC. However, Study 206 evaluating first-line eribulin in HER2-negative MBC demonstrated a 29% objective response rate (ORR), a 52% clinical benefit rate, and median PFS of 6.8 months [18]. The subsequent MERIBEL study in taxane-pretreated patients with a poor prognosis demonstrated a 21% ORR and median time to progression of 4.1 months [19], whereas a small Japanese study (N = 35) in a broader first-line population demonstrated an overall response rate of 54%, median PFS of 5.8 months, and median overall survival (OS) of 35.9 months [20].

Eribulin has a similar mechanism of action to paclitaxel, but potentially offers a less neurotoxic treatment option [21]. The two agents appear to have differing effects on sciatic nerve axons, with more pronounced neurodegenerative effects from paclitaxel and greater microtubule stabilizing biochemical effects induced by eribulin [22]. The distinct mechanisms of microtubule-targeted action may contribute to variations in the development, persistence, and duration of chemotherapy-induced neuropathy. Preclinical studies of eribulin suggested less neuropathy than observed with paclitaxel or ixabepilone given at maximum tolerated doses in mice [21]. Furthermore, in mice with pre-existing paclitaxel-induced neuropathy, eribulin had limited additional neuropathic effect, in contrast to further paclitaxel, suggesting that in clinical settings, eribulin may have a reduced tendency to exacerbate pre-existing paclitaxel-induced neuropathy [23]. These preclinical data are supported by safety results in phase III trials in MBC, in which eribulin showed a relatively low incidence and severity of neuropathy (7–8% grade 3/4 incidence of neuropathy- and paresthesia-related adverse effects) [15,16]. These results were replicated in expanded access programs and observational studies [24–26]. In addition, a meta-analysis of 19 clinical trials including almost 5000 patients reported incidences of all-grade and high-grade peripheral neuropathy of 28% and 5%, respectively [27].

Based on phase III evidence showing significantly improved efficacy when combining bevacizumab with chemotherapy, we anticipated that the combination of bevacizumab and eribulin might provide an effective first-line treatment with a favorable safety profile, particularly with regard to neuropathy. Eribulin and bevacizumab demonstrated greater activity than either agent alone
in triple-negative breast and ovarian cancer xenograft models [28]. Therefore, our group initiated a study to assess the efficacy and safety of a bevacizumab/eribulin combination as first-line therapy for MBC.

2. Patients and methods

This prospective, open-label, single-arm, multicenter phase II study (NCT01941407) enrolled female patients with measurable or evaluable HER2-negative histologically confirmed MBC who had received no prior chemotherapy in the metastatic setting. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status ≤1, adequate hematologic, liver, and renal function, urine dipstick <1+ (or 24-h protein <1 g if urine dipstick ≥2+), and standard inclusion criteria for bevacizumab therapy. Exclusion criteria included prior bevacizumab and/or eribulin therapy, pre-existing grade ≥2 sensory or motor neuropathy, uncontrolled hypertension, ongoing grade ≥2 toxicity from adjuvant treatment, or brain metastases. Patients for whom the investigator considered other treatment options including taxane- or anthracycline-containing therapy to be appropriate were excluded, as were patients receiving or eligible for endocrine therapy. No limit to chemotherapy-free interval was specified in the eligibility criteria, allowing enrollment of patients with rapid progression after (neo)adjuvant therapy. Accordingly, data on disease-free interval at baseline were not collected, nor did we collect the reasons for an investigator considering other treatment options to be inappropriate. All patients provided written informed consent before undergoing any study-specific procedure.

Eligible patients received first-line eribulin administered at 1.23 mg/m² on days 1 and 8 every 3 weeks for at least six cycles (or until disease progression if continued treatment offered a favorable benefit/risk balance) in combination with bevacizumab 15 mg/kg on day 1 every 3 weeks, continued until disease progression or unacceptable toxicity. The primary endpoint was the proportion of patients with disease control (non-progression, comprising complete or partial response plus stable disease according to Response Evaluation Criteria in Solid Tumors [RECIST; version 1.1], as assessed by the investigator) 1 year after enrollment. This endpoint was chosen to provide a clear threshold rapidly and reliably in a single-arm study, whereas median time-related endpoints may not be reached and may be driven only by the patients with the worst prognosis experiencing an early event. Secondary endpoints were ORR according to RECIST (version 1.1), PFS, OS, safety, and health-related quality of life (assessed using a visual analog scale [VAS] of wellbeing from 0 [worst imaginable] to 10 [best]). The VAS was considered less laborious for patients and more appropriate to give a simple impression of neurotoxicity in a single-arm study than one of the available validated patient-reported outcome questionnaires. The sample size was calculated using the Simon’s two-stage design (MinMax) [29] to demonstrate a promising 1-year non-progression rate of 50% versus a not clinically relevant 1-year non-progression rate of 33%. With an alpha of 5% and 80% power, 54 eligible patients were required. The 50% progression-free rate was selected based on an estimate from the E2100 trial [1], in which the median PFS was 11.8 months with the combination of bevacizumab/paclitaxel. Analyses of efficacy and safety were based on the population of eligible patients who received at least one dose of study treatment. However, any patient withdrawing from the trial in the absence of disease progression was excluded from the primary endpoint analysis.

Tumor assessments were performed at baseline, every 9 weeks during bevacizumab/eribulin combination therapy, and every 3 months thereafter until disease progression (for up to 2 years). Adverse events were recorded at every cycle and at the treatment discontinuation visit, and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). If patients experienced grade 4 neutropenia for >7
3. Results

A total of 62 patients were enrolled between September 2013 and September 2014. One patient withdrew consent before receiving treatment, therefore the intention-to-treat population included 61 treated patients. Of these, one patient switched to another therapy before 12 months despite ongoing stable disease, thus the evaluable population for the primary endpoint included 60 patients.

The database was locked on July 10, 2017. Baseline characteristics are shown in Table 1.

Patient characteristics (N = 61).
The median age was 59 years, 16% had triple-negative MBC, 30% had ≥3 metastatic sites, and 71% had received prior (neo)adjuvant chemotherapy, including a taxane in approximately half of all patients. By the data cutoff date, patients had received a median of six cycles of eribulin (range 1–47 cycles) and nine cycles of bevacizumab (range 0–50 cycles) (Fig. 1).

All patients had discontinued treatment by the data cutoff date. Bevacizumab treatment was delayed in 29 patients (48%; 58 cycles [8%]), most commonly for organizational problems or neutropenia, and interrupted in 25 patients (41%; 57 cycles [8%]), most commonly for port-a-cath insertion, wound-healing complications, dental care, or hypertension. The eribulin dose was reduced in nine patients (15%) and 13 cycles (2%), most commonly for neuropathy (6 cycles; 1%) and neutropenia (3 cycles; 1%). Further details of treatment discontinuations and delays are provided in Table 2.

Treatment exposure.
At the data cutoff, disease progression or death had been recorded in 58 (95%) of the 61 treated patients. The 1-year non-progression rate was 32% (95% confidence interval [CI]: 20–43%). The ORR in 59 evaluable patients was 47% (95% CI: 34–60%), including complete response in six patients (10%). Median PFS was 8.3 months (95% CI: 7.0–9.6 months) (Fig. 2).

A baseline VAS score was available in 60 of the 62 patients enrolled. The mean score was 6.55 (standard deviation [SD] 2.20). At cycle 4, 38 patients reported a VAS score. The mean score at cycle 4 was 6.66 (SD 2.16), showing no deterioration of quality of life with treatment.

Safety results are shown in Table 3.
Summary of safety (N = 61): any grade 3/4 adverse event and any adverse event in >10% of patients (CTCAE version 4.03).

The most common all-grade adverse events were hypertension, pain, fatigue, hematologic effects, and alopecia. The most common grade 3/4 adverse events were hypertension, hematologic toxicities, gamma glutamyltransferase increase, and thrombosis. During the study period, 17 patients (28%) were hospitalized (23 of 706 cycles [3%]). The most common causes of hospitalization were chemotherapy observation (four patients; 7%) and pulmonary embolism (three patients; 5%). The only other causes reported in more than one patient were infection, general condition deterioration, and medullary compression, each reported in two patients (3%). The median duration of hospitalization was 7 days (range 1–26 days). Supportive treatments were frequently administered, particularly antibiotics (25 patients [41%]; 41 of 706 cycles [6%]) and granulocyte colony-stimulating factor (nine patients [15%; 32 of 706 cycles [5%]). Seven patients (11%) received antihypertensive therapy (58 of 706 cycles [8%]).

4. Discussion

In this study, the bevacizumab/eribulin combination demonstrated interesting activity as first-line chemotherapy for HER2-negative MBC. The 1-year non-progression rate was 32% and median PFS was 8.3 months. Grade 3/4 neurotoxicity was infrequent,
with only 7% of patients experiencing paresthesia/dysesthesia and 2% neuropathy. Our aim with this combination was to reduce the incidence of neuropathy by administering bevacizumab with an alternative chemotherapy backbone. Since designing our trial, results have been published from a randomized phase II trial with a similar aim but in the context of gemcitabine-containing doublets. The Korean Cancer Study Group compared eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for HER2-negative MBC [30,31]. The two regimens showed similar clinical outcomes and almost identical 6-month PFS rates (eribulin plus gemcitabine 72% vs paclitaxel plus gemcitabine 73%). However, the eribulin-containing regimen was less neurotoxic, a finding that was supported by analyses of neuropathy-specific quality of life. Patients receiving paclitaxel had significantly earlier and more severe neuropathic symptoms than those receiving eribulin, and the authors concluded that eribulin would be a reasonable substitute for paclitaxel.

Limitations of our trial include the single-arm design with no standard comparator, the lack of detailed information on the evolution and resolution of neuropathy over time, the heterogeneity of the patient population, and arguably the relevance of this regimen in the context of emerging options, such as immunotherapeutic strategies and polyADP ribose polymerase (PARP) inhibitors, which are increasingly used in triple-negative and BRCA-mutated MBC, respectively. Cross-trial comparisons have well-known limitations and there are several caveats when comparing our results with the well-documented efficacy of bevacizumab plus paclitaxel. Median PFS in our study is shorter than the median PFS of 11 months consistently reported with the approved bevacizumab/paclitaxel regimen in phase III trials [1,4,13,14]. However, there are clear differences in the patient populations — for example, eligibility for taxane therapy was an exclusion criterion in the present study, and more than half of the patients had already received taxane and
The Breast 54 (2020) 256–263

A.-C. Hardy-Bessard, F. Brocard, F. Clatot et al.

Table 3

| Adverse event                        | Grade | 1/2 | 3     | 4     |
|--------------------------------------|-------|-----|-------|-------|
| Leukocytopenia                        |       | 37  | (61)  | 7     | 11  |
| Neutropenia                           |       | 27  | (44)  | 11    | 18  | 5   | 8   |
| Lymphocytopenia                       |       | 22  | (36)  | 6     | 10  | 1   | 0   |
| Anemia                                |       | 26  | (43)  | 0     |     |     |     |
| Febrile neutropenia                   |       | 0   | 3     | 5     | 3   | 0   |
| Non-hematologic toxicity              |       |     |       |       |     |     |     |
| Hypertension                          |       | 26  | (43)  | 24    | 39  | 0   |
| Pain                                  |       | 44  | (72)  | 3     | 5   | 0   |
| Fatigue                               |       | 42  | (69)  | 3     | 5   | 0   |
| Alopecia                              |       | 34  | (56)  | 3     |     | 5   |
| Paresthesia/dysesthesia               |       | 22  | (36)  | 3     | 5   | 1   | 2   |
| Nausea                                |       | 23  | (38)  | 0     |     |     |     |
| Constipation                          |       | 23  | (38)  | 0     |     |     |     |
| Hemorrhage                            |       | 22  | (36)  | 0     |     |     |     |
| Diarrhea                              |       | 20  | (33)  | 1     | 2   | 0   |
| GGT increased                         |       | 9   | (15)  | 8     | 13  | 2   | 3   |
| Headache                              |       | 18  | (30)  | 0     |     |     |     |
| Mucositis                             |       | 15  | (25)  | 1     | 2   | 0   |
| Transaminase increased                |       | 14  | (23)  | 1     | 2   | 0   |
| Peripheral motor neuropathy           |       | 14  | (23)  | 1     | 2   | 0   |
| Edema                                 |       | 13  | (21)  | 0     |     |     |     |
| Dyspnea                               |       | 9   | (15)  | 3     | 5   | 0   |
| Anthralgia                            |       | 12  | (20)  | 0     |     |     |     |
| Vomiting                              |       | 11  | (18)  | 1     | 2   | 0   |
| Thrombosis                            |       | 3   | (5)   | 5     | 8   | 1   | 2   |
| Proteinuria                           |       | 6   | (10)  | 3     | 5   | 0   |
| Myalgia                               |       | 8   | (13)  | 1     | 2   | 0   |
| Fever                                 |       | 9   | (15)  | 0     |     |     |     |
| Rhinitis                              |       | 9   | (15)  | 0     |     |     |     |
| Anorexia                              |       | 7   | (11)  | 1     | 2   | 0   |
| Urinary infection                     |       | 8   | (13)  | 0     |     |     |     |
| Weight loss                           |       | 8   | (13)  | 0     |     |     |     |
| Dysphonia                             |       | 8   | (13)  | 0     |     |     |     |
| Cramp                                 |       | 6   | (10)  | 1     | 2   | 0   |
| Cough                                 |       | 7   | (11)  | 0     |     |     |     |
| Dysgeusia                             |       | 7   | (11)  | 0     |     |     |     |
| Rhinopharyngitis                      |       | 7   | (11)  | 0     |     |     |     |
| Depression                            |       | 3   | (5)   | 0     |     | 1   | 2   |
| Aspiration                            |       | 2   | (3)   | 1     | 2   | 0   |
| Arterial ischemia                     |       | 1   | (2)   | 1     | 2   | 0   |
| Tachycardia                           |       | 1   | (2)   | 1     | 2   | 0   |
| Septicemia                            |       | 0   | 0     |     | 1   | 2   |
| Myocardial infarction                 |       | 0   | 0     |     | 1   | 2   |
| Osteonecrosis                         |       | 0   | 1     | 2   | 0   |
| Appendicitis                          |       | 0   | 1     | 2   | 0   |
| Colitis                               |       | 0   | 1     | 2   | 0   |
| LVEF decreased                        |       | 0   | 1     | 2   | 0   |

Abbreviations: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; GGT = gamma glutamyltransferase; LVEF = left ventricular ejection fraction.

anthracycline pretreatment (compared with 17% prior taxane and 39% prior anthracycline in E2100). Together, these factors point to a population in our study with a poorer prognosis compared with the unselected real-world population of patients. A small randomized trial of eribulin combined with the anti-angiogenic vascular endothelial growth factor receptor-2 inhibitor ramucirumab showed no unexpected toxicities with the combination, nor any significant improvement in efficacy compared with eribulin alone [34]. However, unlike bevacizumab, ramucirumab has failed to show clinical benefit in MBC [35] and therefore the lack of efficacy of the combination versus eribulin alone is unsurprising.

We acknowledge that the 39% incidence of grade 3 hypertension is higher than in other trials of bevacizumab-containing therapy and is at odds with the proportion of patients receiving antihypertensive therapy. There are anecdotal reports that during clinic visits, patients frequently presented with grade 3 hypertension, which subsequently disappeared and did not require treatment (white coat hypertension). In at least some of the participating centres, blood pressure is typically monitored before the clinic visit, either at home or by a nurse. A potential explanation for the apparent discrepancy between the present trial and others is the acceptance or not of such measurements within the trial protocol.

In conclusion, the combination of bevacizumab and eribulin demonstrated interesting activity in this phase II trial. The regimen may be an alternative for patients at high risk and for whom taxane therapy is not an option.

Role of the funding source
This trial was funded by Eisai and Roche. No role of the funder in study design, collection, analysis and interpretation of data, writing manuscript and decision to submit.

Data sharing statement
Currently no mechanism is in place to allow sharing of individual deidentified participant data. Requests sent to ARCGAY–GINECO (bvan@arcagy.org) will be considered on a case-by-case basis.

Declaration of competing interest
FC reports grants, personal fees, and non-financial support from AstraZeneca, grants from Roche Diagnostics, and personal fees and non-financial support from Roche and Lilly, outside the submitted work. BY reports consulting/advisory roles for AstraZeneca and advisory boards for Roche, GSK/Tesaro, Clovis, Novartis, MSD, BMS, Amgen, and ECS Progastrin, all outside the submitted work. GE reports personal fees and research support from Roche and Novartis, personal fees from Pfizer and Amgen, and research support from MSD, Odonate, Dompé Farmaceutici, AstraZeneca, and MacroGenics, outside the submitted work. A–CH—B, FB, AL, JG, JMF, A-MS, AMA, RD, and IM have nothing to disclose.

Acknowledgments
We thank the patients who participated in the trial and their
families. We acknowledge Bénédicte Votan, Sébastien Armanet, Alexandra Rohel, Nicolas Gane from the Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) study office. We also thank the following investigators who participated in the trial: Sylvie Kirscher (Institut du Cancer Avignon-Provence, Avignon); Brigitte Lucis (Clinique Pasteur Saint-Éprit, Brest); Corinne Delcambre, Carine Segura-Djezzar, Nédjla Allouache, and Jean-Michel Ollivier (Centre François Baclesse, Caen); Erika Viel (Hôpital Privé Saint-Marie, Chalon-sur-Saône); Elisabeth Angellier (Clinique Notre-Dame de Bon Secours, Chartres); Emmanuel Guardiola (Centre Hospitalier la Dracenie, Draguignan); Philippe Ardissin (Clinique de la Sauvegarde, Lyon); Jérôme Dauba (Centre Hospitalier Mont-de-Marsan, Mont-de-Marsan); Célia Roemer-Becue and Dominique Spaeath (ORACLE – Centre d’Oncologie de Gentilly, Nancy); Philippe Follana (Centre Antoine Lacassagne, Nice); Nabil Baba-Hamed (Groupe Hospitalier Saint-Joseph, Paris); Gilles Freyer and Amandine Bruyas (Hospices Civils de Lyon – Centre Hospitalier Lyon Sud, Pierre-Benite); Stéphanie Catala and Nicolas Barbier (Centre Catalan d’Oncologie, Perpignan); Marianne Leheurteur, Corinne Veyret, Isabelle Tennevet, and Christina-Ramona Alexandru (Centre Henri Becquerel, Rouen); Khoutrih Mahour-Bacha (Centre Hospitalier Thonon-les-Bains, Thonon-les-Bains), Emmanuel Blot (Centre Hospitalier Bretagne-Atlantique, Vannes), all members of the study team, all the pharmacists from all the sites, as well as Roche and Eisai for their financial support. Medical writing assistance was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashbourne, UK), funded by ARCAGY-GINECO.

References

[1] Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone in metastatic breast cancer. N Engl Med 2007;357:2666–76. https://doi.org/10.1056/NEJMoa072113.
[2] Miles DW, Chan A, Dirix LY, Cortés J, Pivot X, Tomczak P, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28:3239–47. https://doi.org/10.1200.JCO.2008.21.6457.
[3] Robert NJ, Deiras V, Glasp Y, Brujšky AM, Bondarenko I, Lipatov ON, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011;29:1252–60. https://doi.org/10.1200/JCO.2010.32.0836.
[4] Miles D, Cameron D, Bondarenko I, Manzyuk Y, Alcedo JC, Lopez RI, et al. Bevacizumab plus paclitaxel versus placebo plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer (MERI2dAN): a double-blind placebo-controlled randomized phase III trial with prospective biomarker evaluation. Eur J Canc 2017;70:146–55. https://doi.org/10.1016/j.ejca.2016.09.024.
[5] Schilling J, Busch S, Heinrich G, Heing K, Martin Kurbacher C, Käpe P, et al. Treatment patterns, health care resource use and outcomes in metastatic triple-negative breast cancer in Germany: retrospective chart review study (OBTAIN). Curr Med Res Opin 2019;35:1405–14. https://doi.org/10.1185/03007995.2019.165551.
[6] Seretny M, Currie GL, Senas ES, Ramaraine S, Grant R, Macleod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain 2014;155:2461–70. https://doi.org/10.1016/j.pain.2014.09.005.
[7] Wozniak KM, Forony B, Wu Y, Liu Y, Carozza V, Rodrigues-Mendez V, et al. Peripheral neuropathy induced by microtubule-targeted chemotherapies: insights into acute injury and long-term recovery. Canc Res 2018;78:817–29. https://doi.org/10.1158/0008-5472.CAN-17-1407.
[8] Hershman DL, Weimer LH, Wang A, Ziegler D, Stenzl A, et al. Incidence and relative risk of peripheral neuropathy in cancer patients treated with eribulin: interim data from a post-marketing observational study. Breast Canc Res Treat 2019;263:235–43. https://doi.org/10.1007/s10549-019-05905-7.
[9] Peng L, Hong Y, Ye X, Shao J, Zhang W, et al. Incidence and relative risk of peripheral neuropathy in cancer patients treated with eribulin: a meta-analysis. Oncotarget 2017;8:112076–84. https://doi.org/10.18632/oncotarget.21057.
[10] Asano M, Matsui J, Towe MJ, Wu J, McGonigle S, De Boisferon MH, et al. Broad-spectrum preclinical antitumor activity of eribulin (Halaven®): combination with anticancer agents of differing mechanisms. Canc Res 2018;78:3735–85. https://doi.org/10.1158/0008-5472.CAN-18-0204.
[11] Simon R. Optimal two-stage designs for phase II clinical trials control. Clin...
Trials 1989;10:1–10. https://doi.org/10.1016/0197-2456(89)90015-9.

[30] Park YH, Im SA, Kim SB, Sohn JH, Lee KS, Chae YS, et al. Korean Cancer Study Group (KCSG). Phase II, multicentre, randomised trial of eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line chemotherapy in patients with HER2-negative metastatic breast cancer. Eur J Canc 2017;86:385–93. https://doi.org/10.1016/j.ejca.2017.10.002.

[31] Kim JY, Park S, Im SA, Kim SB, Sohn J, Lee KS, et al., Korean Cancer Study Group. Quality of life outcomes including neuropathy-associated scale from a phase II, multicenter, randomized trial of eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line chemotherapy for HER2-negative metastatic breast cancer: Korean Cancer Study Group Trial (KCSG BR13-11). Canc Commun 2019;39:29. https://doi.org/10.1186/s40880-019-0375-7.

[32] Gligorov J, Doval D, Bines J, Alba E, Cortes P, Pierga JY, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1351–60. https://doi.org/10.1016/S1470-2045(14)70444-9.

[33] Inoue K, Ninomiya J, Saito T, Kimizuka K, Kurosumi M. Induction therapy with paclitaxel and bevacizumab followed by switch maintenance therapy with eribulin in Japanese patients with HER2-negative metastatic breast cancer: a multicenter, collaborative, open-label, phase II clinical study for the SBCCSG 35 investigators. BMC Canc 2018;18:671. https://doi.org/10.1186/s12885-018-4556-6.

[34] Yardley DA, Reeves J, Dees EC, Osborne C, Paul D, Ademuyiwa F, et al. Ramucirumab with eribulin versus eribulin in locally recurrent or metastatic breast cancer previously treated with anthracycline and taxane therapy: a multicenter, randomized, phase II study. Clin Breast Canc 2016;16:471–479.e1. https://doi.org/10.1016/j.clbc.2016.07.005.

[35] Mackey JR, Ramos-Vazquez M, Lipatov O, McCarthy N, Krasnozhon D, Semiglazov V, et al. Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. J Clin Oncol 2015;33:141–8. https://doi.org/10.1200/JCO.2014.57.1513.