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Long-term results of a randomized controlled trial of biosimilar CT-P16 and reference bevacizumab in patients with metastatic or recurrent non-small cell lung cancer

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ABSTRACT

Purpose: Data from the CT-P16 3.1 study demonstrated equivalent efficacy between CT-P16, a bevacizumab biosimilar, and European-approved reference bevacizumab (EU-bevacizumab) for the primary endpoint of objective response rate (ORR) during induction treatment in patients with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC). We now present long-term findings.

Methods: In this randomized, double-blind, multicenter phase 3 study, patients with metastatic or recurrent non-squamous NSCLC received CT-P16 or EU-bevacizumab (15 mg/kg every 3 weeks; ≤6 cycles) together with paclitaxel (200 mg/m^2) and carboplatin (area under the curve 6.0) for 4–6 cycles during the induction period. Patients with controlled disease entered the maintenance period, continuing with CT-P16 or EU-bevacizumab as monotherapy until disease progression/intolerable toxicity. They were then followed up every 9 weeks until death or end of study. Outcomes were evaluated ≤3 years after the last patient enrollment.

Results: Of 689 patients receiving CT-P16 ($N = 342$) or EU-bevacizumab ($N = 347$), 499 (72.4 %) completed the induction period (CT-P16, $n = 258$ [75.4 %]; EU-bevacizumab, $n = 241$ [69.5 %]), 466 (67.6 %) initiated the maintenance period (CT-P16, $n = 239$ [69.9 %]; EU-bevacizumab, $n = 227$ [65.4 %]), and 389 (56.5 %) entered follow-up (CT-P16, $n = 190$ [55.6 %]; EU-bevacizumab, $n = 199$ [57.3 %]). Whole study ORRs were similar for CT-P16 (45.61 % [95 % confidence interval 40.34–50.89]) and EU-bevacizumab (46.11 % [95 % confidence interval 40.86–51.35]). Response duration, time to progression, progression-free survival, and overall survival were similar. No new safety signals were detected.

Conclusions: Long-term results of the CT-P16 3.1 study confirm equivalent efficacy of CT-P16 and EU-bevacizumab in patients with metastatic or recurrent non-squamous NSCLC.

Trial registration number: NCT03676192.

Micro abstract: Equivalent efficacy between CT-P16, a bevacizumab biosimilar, and European-approved reference bevacizumab (EU-bevacizumab) was demonstrated in a phase 3 study of patients with metastatic or recurrent

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non-squamous NSCLC. Long-term findings in 689 patients confirmed equivalent efficacy of CT-P16 and EU-bevacizumab; objective response rates were 45.6 % and 46.1 %, respectively. Response duration, time to progression, progression-free survival, and overall survival were also similar.

1. Introduction

Vascular endothelial growth factor (VEGF), particularly the VEGF-A isoform, promotes tumor angiogenesis through its stimulatory action on endothelial cell survival and proliferation, and by increasing the permeability of blood vessels [1,2]. Overexpression of VEGF occurs in non-small cell lung cancer (NSCLC), playing a fundamental role in the recurrence, metastasis, and progression of NSCLC [3].

Bevacizumab is a VEGF-A–targeted monoclonal antibody [2]. By binding to VEGF-A and disrupting its interaction with the VEGF receptor, bevacizumab both inhibits further vessel growth and induces regression of newly formed vessels, with beneficial anti-cancer effects [2]. The availability of targeted therapies such as bevacizumab transformed outcomes for patients with advanced non-squamous NSCLC, extending median survival to beyond 1 year when added to paclitaxel plus carboplatin chemotherapy [4]. Data from subsequent clinical trials in this indication have shown first-line bevacizumab in combination with chemotherapy to improve progression-free survival (PFS) [5–9], while including bevacizumab in subsequent maintenance treatment can also benefit patients [8,9].

Initially approved for the treatment of NSCLC by the United States Food and Drug Administration in 2006, and by the European Medicines Agency in 2007, bevacizumab remains an important treatment option for non-squamous NSCLC [2]. However, adding bevacizumab to first-line paclitaxel plus carboplatin chemotherapy may not be cost-effective [10,11], use of bevacizumab combinations may be limited by health insurance policies [12], and value-driven healthcare strategies have encouraged the use of biosimilars as lower-cost alternatives to original reference products [13]. The approval of the bevacizumab biosimilar, CT-P16, in 2022, may increase patient access to treatment [14,15]. CT-P16 was approved based on the pharmacokinetic (PK) and efficacy equivalence observed in the CT-P16 1.1 and 3.1 trials, respectively [14–16].

After 1 year of follow-up, this pivotal CT-P16 3.1 study demonstrated equivalent efficacy between CT-P16 and EU-bevacizumab in terms of the primary endpoint—objective response rate (ORR) based on best overall response (BOR) during the 6-cycle induction period—in patients with metastatic or recurrent non-squamous NSCLC [16]. Secondary efficacy endpoints evaluable at the time of analysis—including PFS, overall survival (OS), safety, immunogenicity, and PK—were comparable between treatment groups [16]. Here, we present final efficacy, safety, immunogenicity, PK, and quality of life (QoL) findings up to 3 years after the last patient was enrolled in this now completed phase 3 study.

2. Materials and methods

2.1. Study design

The full study design has been published previously [16]. In summary, this was a randomized, active-controlled, double-blind, parallel-group phase 3 study (NCT03676192) involving 164 centers across 21 countries (as previously listed [16]). The study protocol and materials were approved by the institutional review board/independent ethics committee of each study center. The study was monitored by an independent data safety monitoring board. All participants gave written informed consent.

2.2. Treatments

Patients were randomized (1:1) to receive induction treatment with either CT-P16 15 mg/kg or EU-bevacizumab 15 mg/kg, given intravenously (IV) every 3 weeks (Q3W) for up to 6 cycles. All patients were also given IV paclitaxel 200 mg/m^2 and IV carboplatin (area under the curve 6.0) Q3W for 4–6 cycles (induction period). Patients achieving a complete response (CR), partial response (PR), or stable disease after induction treatment entered into a maintenance period, where they continued to receive their assigned treatment (CT-P16 or EU-bevacizumab) as monotherapy, given at the same dosing interval of Q3W until disease progression or intolerable toxicity. An end-of-treatment (EOT) visit was conducted 3 weeks after discontinuing study drug, after which patients entered the follow-up period and were followed-up every 9 weeks until death or end of study.

2.3. Participants

The full eligibility criteria for the study participants have been described previously [16]. Key inclusion criteria were: age ≥18 years; confirmed stage IV or recurrent non-squamous NSCLC; ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 or 1; adequate hematologic, hepatic, and renal function; and negative epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement results. Patients were excluded if they had: NSCLC with predominantly squamous histology or with small cell elements present; untreated or unstable central nervous system metastases (with bleeding risk, symptomatic, requiring steroid treatment); or invasion of major blood vessels. Patients were also excluded if they had previously been treated with cytotoxic chemotherapy, surgery, or radiotherapy for NSCLC, or had received previous treatment with biological therapy, immunotherapy, or targeted therapy for any cancer. Other exclusion criteria included: a history of malignancy other than NSCLC in the past 5 years, except adequately treated squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix; hemoptysis; any clinically significant allergic disease, including asthma, urticaria, and eczematous dermatitis; uncontrolled hypertension, diabetes, or cardiac disease; or a history of vascular disease such as cerebrovascular accident, transient ischemic attack, or thromboembolic event.

2.4. Outcomes

To evaluate efficacy, ORR during the whole study period was measured, based on BOR per RECIST version 1.1. Central review results (from a central independent reviewer) were used as the primary analysis. Sensitivity analyses were performed using local review results (from investigators). Other efficacy endpoints were response duration (defined as the time from initial response [partial or complete] to progressive disease [PD], recurrence, or death), time to progression (TTP), and assessment of PFS and OS survival at 6 (except for OS), 12, 24, and 36 months.

Safety evaluations considered the incidence and severity of treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs, and treatment-emergent adverse events of special interest (TEAESIs). TEAESIs comprised: hypersensitivity/infusion-related reactions, gastrointestinal perforations and fistulae, wound-healing complications, hypertension, posterior reversible encephalopathy syndrome, proteinuria, arterial or venous thromboembolism, hemorrhages, congestive heart failure, or ovarian failure/fertility. Other safety assessments involved electrocardiogram (ECG) monitoring, physical examination, determination of ECOG-PS, clinical laboratory analyses,

evaluation of prior and concomitant medications, hypersensitivity monitoring (through vital signs and ECG), and serological testing for hepatitis B, hepatitis C, and HIV.

Other outcomes evaluated were immunogenicity, assessed via the incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs), and PK, as determined by measuring trough serum concentrations of study drug (C_{trough}). In addition, QoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Core 30 (QLQ-C30) and lung cancer-specific module (QLQ-LC13) Quality of Life Questionnaires.

2.5. Assessments

For tumor evaluation with RECIST version 1.1, a range of assessments were performed. Computed tomography (CT) scans of the chest and abdomen were conducted at screening, at the end of Cycles 2, 4, and 6 of the induction period, at the end of every third cycle during the maintenance period, at EOT, and every 9 weeks during the follow-up period until PD, death, withdrawal, or start of new anti-cancer therapy if PD was not confirmed. Brain CT or magnetic resonance imaging, and bone scans were performed at screening and repeated at later timepoints if brain or bone metastases, respectively, were present at screening or new lesions were suspected. Brain metastases present during screening had to be treated and clinically stable before starting study treatment. Images for tumor response were assessed via both central review and local review.

TEAEs were monitored throughout and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Clinical laboratory tests were performed on Day 1 of each cycle and at EOT. Serological testing and ECG were done for the first cycle of the maintenance period and at EOT. A physical examination and ECOG-PS assessment were performed prior to study drug administration on Day 1 of each cycle, at EOT, and during the follow-up period. Hypersensitivity monitoring was performed on Day 1 of each cycle.

For immunogenicity assessment at a central laboratory, blood samples were collected on Day 1 of Cycle 1 and at the end of Cycles 2, 4, and 6 during the induction period, at the end of every third cycle during the maintenance period, at EOT, and at the first follow-up visit. The presence of ADAs and NAbs was detected using validated electrochemiluminescence assays. For PK analyses, blood samples were collected pre-dose on Day 1 of each cycle and at the end of Cycle 6 during the induction period, at the end of every third cycle during the maintenance period, and at EOT. Serum CT-P16 and EU-bevacizumab concentrations were measured at the central laboratory using a validated electrochemiluminescence assay with a lower limit of quantification of 50 ng/mL. QoL was assessed at the end of every third cycle and at EOT.

2.6. Statistical analysis

The populations used for analysis were defined as follows: The intent-to-treat (ITT) population consisted of all randomized patients. The per-protocol (PP) population comprised all randomized patients who had at least one response evaluation after receiving at least one full dose of study drug in the induction period and did not have any major protocol deviations. The PK population – maintenance period subset consisted of all randomly assigned patients who received at least one full dose of study drug and had at least one post-treatment PK result during the maintenance period. The safety population included all randomly assigned patients who received at least one partial or full dose of study drug.

In addition to evaluating ORR for all patients during the whole study period, analyses for various patient subgroups estimated risk differences using a logistic regression model and risk ratios using a log-binomial regression model. In both models, treatment groups (CT-P16 and EU-bevacizumab) were included as a fixed effect, while region (Europe, Middle East, and Africa vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrent vs. metastatic), and ECOG-PS score at baseline (0 vs. 1) were covariates. When one of the covariates was considered as a subgroup, the other three were adjusted for the model. Patients with missing values for ORR were considered non-responders. Time-to-event analyses were estimated using Kaplan–Meier methodology.

All statistical analyses were conducted using Statistical Analysis System (SAS®) software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

The study began on 1 February 2019 (first patient randomization) and was completed on 19 September 2023 (last patient last visit). Patient disposition is shown as a CONSORT diagram (Fig. 1). Of the 689 patients randomized to CT-P16 (N = 342) or EU-bevacizumab (N = 347), 499 (72.4 %) patients completed the induction period (CT-P16, n = 258 [75.4 %]; EU-bevacizumab, n = 241 [69.5 %]). Of these, 466 (67.6 %) patients initiated the maintenance period (CT-P16, n = 239 [69.9 %]; EU-bevacizumab, n = 227 [65.4 %]), and 389 (56.5 %) initiated the follow-up period (CT-P16, n = 190 [55.6 %]; EU-bevacizumab, n = 199 [57.3 %]). Nine (1.3 %) patients received study drug until the end of study (CT-P16, n = 6 [1.8 %]; EU-bevacizumab, n = 3 [0.9 %]).

The reasons for discontinuing study drug (Fig. 1) were similar in both treatment groups. PD was the most common reason for discontinuing study drug in both treatment groups during the induction and maintenance period, while patients in the follow-up period most commonly ended participation in the study due to death, which was most commonly owing to PD. Other reasons for ending participation during the follow-up period included withdrawal, loss to follow-up, and other reasons (Fig. 1).

Patient baseline characteristics are shown in Table 1 [16] and were generally well balanced between treatment groups. Most patients had metastatic disease. Stage IVA NSCLC was evident in 147 (43.0 %) patients in the CT-P16 group and 164 (47.3 %) patients in the EU-bevacizumab group, while the corresponding figures for stage IVB were 170 (49.7 %) and 149 (42.9 %), respectively. The representativeness of the study population to the real-world population is described in Supplementary Table S1.

3.2. Efficacy

The ORRs for the whole study period were similar between the CT-P16 and EU-bevacizumab groups in the ITT population (45.61 % [95 % confidence interval (CI) 40.34–50.89] and 46.11 % [95 % CI 40.86–51.35], respectively) (Table 2). Results for the PP population also showed the ORRs for the whole study period to be similar between the CT-P16 and EU-bevacizumab groups (48.74 % [95 % CI 43.25–54.24] and 51.82 % [95 % CI 46.19–57.44], respectively), while sensitivity analyses performed using local review results (ITT and PP populations) confirmed the primary analyses of the central review (Supplementary Table S2).

Additional analyses of the ITT population by patient subgroups of age (<65 or ≥65 years), race (American Indian or Alaska Native, Asian, Black or African American, White, or other), sex (female or male), smoking history (current smoker, former smoker, or never smoked), disease status (recurrent or metastatic), prior radiation therapy (yes or no), prior anti-cancer systemic therapy (yes or no), region (Europe, Middle East and Africa, America, or Asia), and baseline ECOG-PS score (0 or 1) did not indicate any differences between treatment groups in terms of the risk difference or risk ratio of ORR during the whole study period (Supplementary Figs. S1 and S2, respectively).

Given the advanced stage of disease in the study population, a

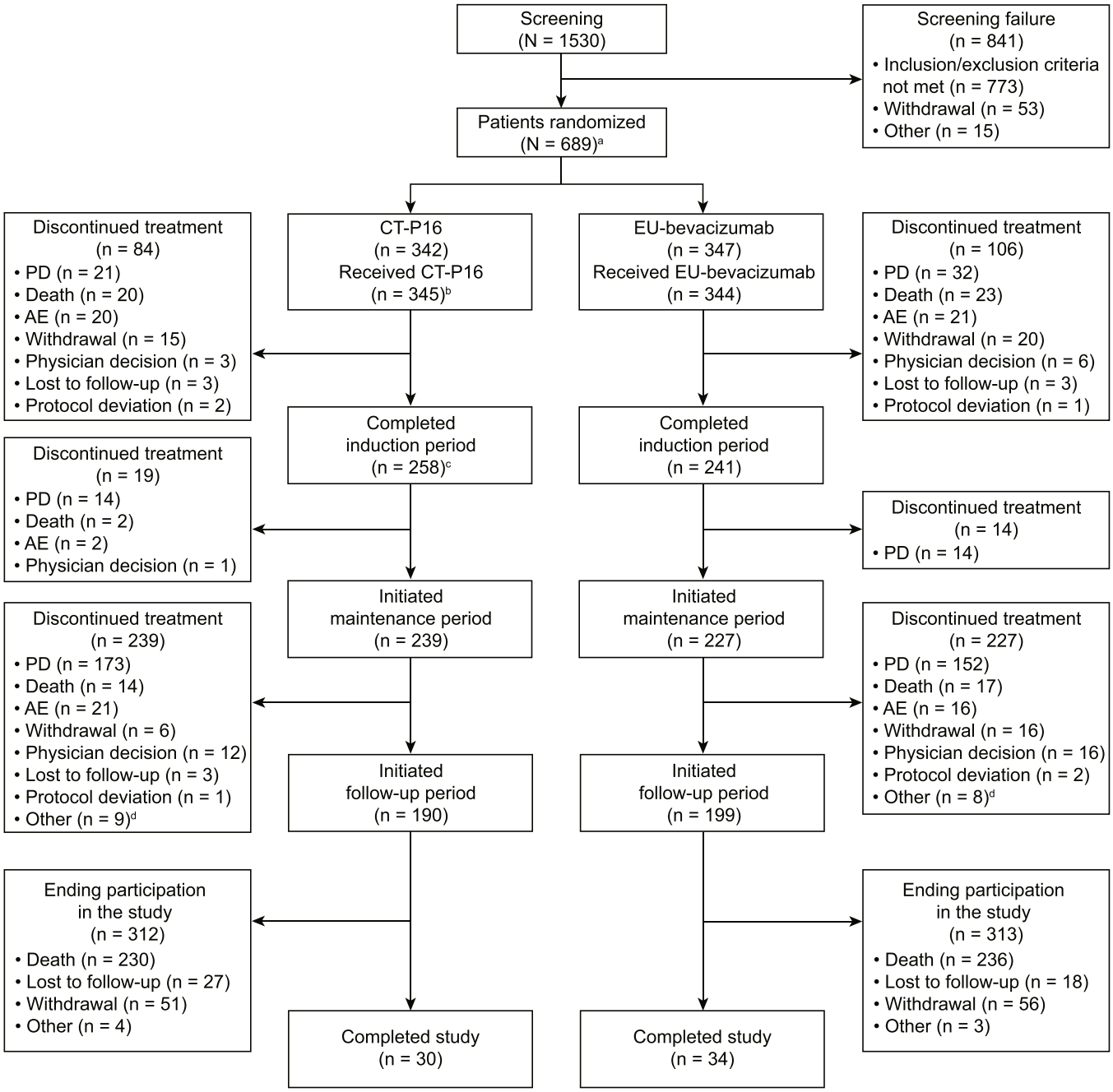

Fig. 1. CONSORT diagram (ITT population).

[a]Two patients randomized to the EU-bevacizumab group had EGFR exon 20 insertions associated with lack of responsiveness to EGFR TKI therapy, but were permitted to be enrolled by the investigator and sponsor since TKI therapy was not an option for their treatment.

[b]Three patients randomized to the EU-bevacizumab group were included in the CT-P16 safety population, as the patients incorrectly received at least one dose of CT-P16 at any time during the treatment period.

[c]One patient in the CT-P16 group accidentally missed receiving study drug in induction Cycle 4; the patient was considered as having completed the induction period due to entering the maintenance period according to the statistical analysis plan.

[d]Two patients in the CT-P16 group and three patients in the EU-bevacizumab group were discontinued since treatment could not be resumed within 6 weeks of the last dose. One patient in the CT-P16 group was discontinued due to a change in the patient's financial status. Six patients in the CT-P16 group and three patients in the EU-bevacizumab group were discontinued due to the end of study. Two patients in the EU-bevacizumab group were discontinued due to military aggression in their country of residence.

AE, adverse event; EGFR, epidermal growth factor receptor; EU-bevacizumab, European-approved reference bevacizumab; ITT, intent-to-treat; PD, progressive disease; TKI, tyrosine kinase inhibitor.

substantial number of participants died early during follow-up. Consequently, the median follow-up duration was 12.89 months, the mean was 16.34 months, and the maximum follow-up reached 53.65 months (Supplementary Fig. S3). In the 156 patients in the CT-P16 group and 160 patients in the EU-bevacizumab group who achieved either a CR or PR (ITT population), the median duration of response (7.2 months [95 % CI 6.3–8.2] and 6.5 months [95 % CI 5.9–7.6], respectively), and the estimated rate of response duration exceeding 6, 12, 24, and 36 months

Table 1
Patient baseline characteristics (ITT population).

Characteristic	CT-P16 (n = 342)	EU-bevacizumab (n = 347)
Age (years), median (min–max)	62.0 (32–82)	62.0 (26–82)
Sex, n (%)		
Female	119 (34.8)	125 (36.0)
Male	223 (65.2)	222 (64.0)
Race, n (%)		
American Indian or Alaska Native	9 (2.6)	9 (2.6)
Asian	59 (17.3)	55 (15.9)
Black or African American	2 (0.6)	1 (0.3)
White	264 (77.2)	264 (76.1)
Other	8 (2.3)	18 (5.2)
ECOG-PS score, n (%)		
0	105 (30.7)	110 (31.7)
1	237 (69.3)	237 (68.3)
Disease status, n (%)		
Recurrent	25 (7.3)	33 (9.5)
Metastatic	317 (92.7)	314 (90.5)
Final pathological diagnosis, n (%)		
Adenocarcinoma	336 (98.2)	340 (98.0)
Large cell carcinoma	3 (0.9)	2 (0.6)
NSCC NOS	1 (0.3)	1 (0.3)
Adenosquamous carcinoma	2 (0.6)	2 (0.6)
Other[a]	0	2 (0.6)
Clinical stage, n (%)		
IIIB[b]	0	1 (0.3)
IVA	147 (43.0)	164 (47.3)
IVB	170 (49.7)	149 (42.9)
Recurrent	25 (7.3)	33 (9.5)
Prior treatment, n (%)		
Surgery	27 (7.9)	37 (10.7)
Radiotherapy	41 (12.0)	42 (12.1)
Anti-cancer systemic therapy[c]	6 (1.8)	10 (2.9)

[a] Two patients in the EU-bevacizumab group had signet ring cell carcinoma.
[b] One patient in the EU-bevacizumab group was enrolled as stage IIIB adenocarcinoma and was excluded from the PP population due to violation of inclusion criterion.
[c] Cytotoxic chemotherapy was the only authorized prior anti-cancer systemic therapy, of which cisplatin was the most frequently reported (CT-P16, n = 4 [1.2 %]; EU-bevacizumab, n = 6 [1.7 %]).

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EU-bevacizumab, European-approved reference bevacizumab; ITT, intent-to-treat; NSCC NOS, non-small cell carcinoma not otherwise specified; PP, per-protocol.

Table 2
Objective response rates during the whole study period (central review, ITT population).

Central review	CT-P16 (n = 342)	EU-bevacizumab (n = 347)
Best overall response, n (%)		
Complete response	4 (1.2)	3 (0.9)
Partial response	152 (44.4)	157 (45.2)
Stable disease	145 (42.4)	126 (36.3)
Progressive disease	17 (5.0)	19 (5.5)
Non-evaluable	3 (0.9)	3 (0.9)
Missing	21 (6.1)	39 (11.2)
ORR, % (95 % CI)	45.61 (40.34–50.89)	46.11 (40.86–51.35)

CI, confidence interval; ITT, intent-to-treat; ORR, objective response rate.

were similar between treatment groups (Fig. 2).

Median TTP, PFS, and OS in the ITT population have been reported previously and were all similar between treatment groups [16]. Findings from this longer-term analysis were broadly similar: median TTP was 8.5 months (95 % CI 8.3–10.0) and 8.3 months (95 % CI 7.4–9.1) for the CT-P16 and EU-bevacizumab groups, respectively (Fig. 2). Median PFS was 7.9 months (95 % CI 6.9–8.3) and 7.3 months (95 % CI 6.7–8.3), respectively (hazard ratio [HR] 0.94, 95 % CI 0.79–1.13; p = 0.5094) (Fig. 2). A similar proportion of patients achieved 6-, 12-, 24-, and 36-month PFS (rates of 0.73, 0.23, 0.08, and 0.06, respectively, for CT-P16–treated patients vs. 0.71, 0.28, 0.09, and 0.04, respectively, for those receiving EU-bevacizumab). Median OS was 17.0 months (95 % CI 14.7–18.7) and 15.6 months (95 % CI 13.8–17.4), respectively (HR 0.98, 95 % CI 0.81–1.18; p = 0.8008) (Fig. 2). A similar proportion of patients achieved 12-, 24-, and 36-month OS (rates of 0.66, 0.35, and 0.19, respectively, for CT-P16–treated patients vs. 0.62, 0.34, and 0.21, respectively, for those receiving EU-bevacizumab) (Fig. 2).

Waterfall plots of the maximum percentage change of the sum of target lesions from baseline showed similar patterns for the CT-P16 and EU-bevacizumab groups (Supplementary Fig. S4).

3.3. Safety

The exposure to study treatment was comparable between treatment groups (Supplementary Table S3). Over the whole study period, a similar number of patients in the CT-P16 and EU-bevacizumab groups experienced at least one TEAE (CT-P16, n = 332 [96.2 %]; EU-bevacizumab, n = 320 [93.0 %]) (Table 3). Correspondingly, a similar proportion of patients experienced at least one TEAE during the maintenance period (CT-P16, n = 178 [51.6 %]; EU-bevacizumab, n = 160 [46.5 %]) (Supplementary Table S4).

TEAEs considered to be related to study drug by the investigator were reported in 183 (53.0 %) and 177 (51.5 %) patients over the whole study period and 90 (26.1 %) and 81 (23.5 %) patients during the maintenance period in the CT-P16 and EU-bevacizumab groups, respectively.

Overall, the most frequently reported TEAEs were alopecia (CT-P16, n = 220 [63.8 %]; EU-bevacizumab, n = 218 [63.4 %]) and anemia (CT-P16, n = 109 [31.6 %]; EU-bevacizumab, n = 93 [27.0 %]) (Table 4). The most frequently reported TEAE in both treatment groups during the maintenance period was proteinuria (CT-P16, n = 29 [8.4 %]; EU-bevacizumab, n = 30 [8.7 %]) (Supplementary Table S5), followed by dyspnea in the CT-P16 group (n = 18 [5.2 %]) and cough in the EU-bevacizumab group (n = 16 [4.7 %]). The majority of TEAEs were grade 1 or 2 in severity. A similar proportion of patients experienced at least one TEAE of severity grade 3 or higher in the two treatment groups over the whole study period (CT-P16, n = 155 [44.9 %]; EU-bevacizumab, n = 147 [42.7 %]) (Table 3) and during the maintenance period (CT-P16, n = 55 [15.9 %]; EU-bevacizumab, n = 40 [11.6 %]) (Supplementary Table S4).

The most frequently reported grade ≥3 TEAE over the whole study period was neutropenia in both the CT-P16 and EU-bevacizumab groups (n = 36 [10.4 %] and n = 25 [7.3 %], respectively). During the maintenance period, the most frequently reported grade ≥3 TEAE was dyspnea in the CT-P16 group (n = 6 [1.7 %]) and hypertension in the EU-bevacizumab group (n = 6 [1.7 %]).

A similar proportion of patients in the CT-P16 and EU-bevacizumab groups had a serious TEAE, TEAE leading to discontinuation, or TEAE leading to death over the whole study period (Table 3) and during the maintenance period (Supplementary Table S4). Eleven deaths (CT-P16, n = 4 [1.2 %]; EU-bevacizumab, n = 7 [2.0 %]) were considered to be due to a study drug-related TEAE. Details of 10 of these deaths were reported previously [16]. One additional death due to pulmonary hemorrhage in the CT-P16 group occurred during maintenance Cycle 24. During the maintenance period, only one patient (0.3 %) in each treatment group died due to a TEAE considered to be related to study drug (pulmonary hemorrhage and sudden death in the CT-P16 and EU-bevacizumab groups, respectively).

A similar proportion of patients in both treatment groups experienced at least one TEAESI over the whole study period and during the maintenance period (Table 3 and Supplementary Table S4). Overall, the most frequently reported TEAESIs were proteinuria (45 [13.0 %] and 45 [13.1 %] patients in the CT-P16 and EU-bevacizumab groups, respectively), hypertension (46 [13.3 %] and 40 [11.6 %] patients in the CT-P16 and EU-bevacizumab groups, respectively), and hemorrhage (42 [12.2 %] and 38 [11.0 %] patients in the CT-P16 and EU-bevacizumab

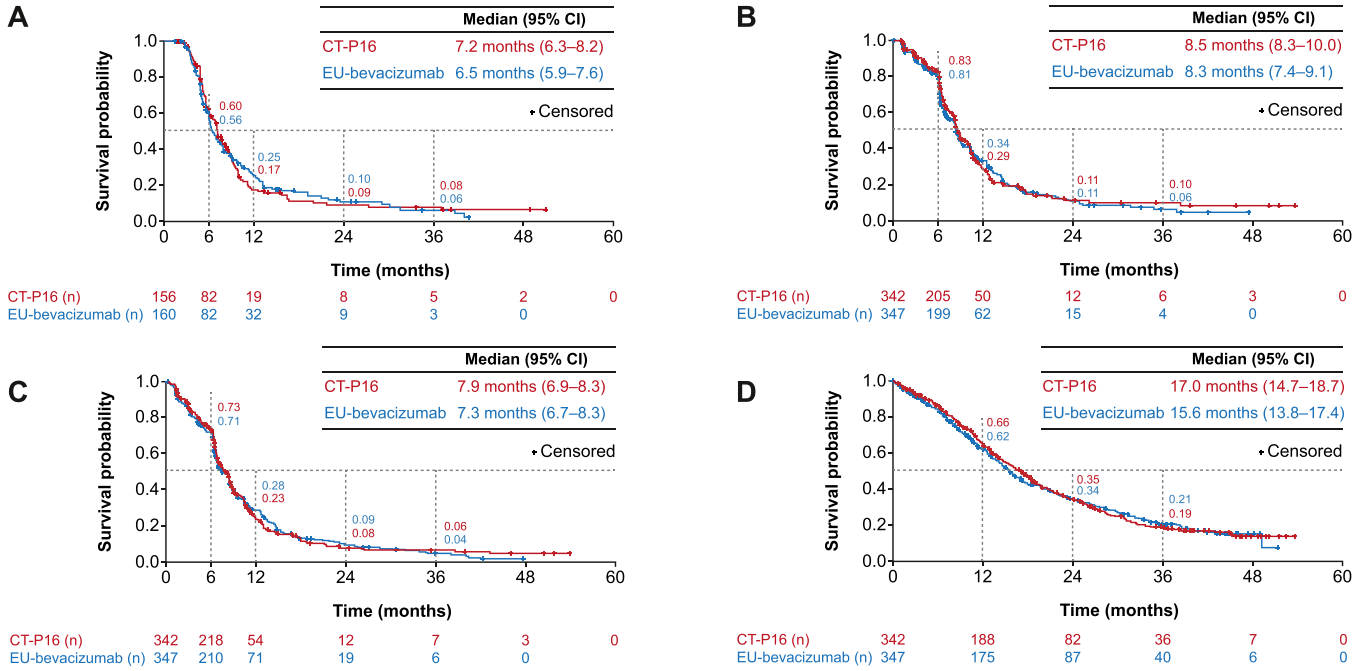

Fig. 2. Kaplan–Meier plots (ITT population) of (A) response duration, (B) time to progression, (C) progression-free survival (all central review), and (D) overall survival.
Estimates and corresponding 95 % CIs are based on the Kaplan–Meier method.
CI, confidence interval; EU-bevacizumab, European-approved reference bevacizumab; ITT, intent-to-treat.

Table 3
Summary of TEAEs during the whole study period (safety population).

	CT-P16 ($n = 345$[a])	EU-bevacizumab ($n = 344$)
Patients with ≥1 TEAE of any cause, n (%)		
Any	332 (96.2)	320 (93.0)
Grade ≥3	155 (44.9)	147 (42.7)
Serious	71 (20.6)	75 (21.8)
Leading to discontinuation	62 (18.0)	60 (17.4)
Leading to death	24 (7.0)	25 (7.3)
Patients with ≥1 TEAESI, n (%)		
Hypersensitivity/IRR	11 (3.2)	16 (4.7)
Gastrointestinal perforation/fistulae	3 (0.9)	5 (1.5)
Wound-healing complications	1 (0.3)	0
Hypertension	46 (13.3)	40 (11.6)
PRES	1 (0.3)	0
Proteinuria	45 (13.0)	45 (13.1)
Arterial thromboembolism	2 (0.6)	4 (1.2)
Venous thromboembolism	10 (2.9)	5 (1.5)
Hemorrhage	42 (12.2)	38 (11.0)
Congestive heart failure	4 (1.2)	2 (0.6)
Ovarian failure/fertility	0	0

[a] Three patients randomized to the EU-bevacizumab treatment group were included in the CT-P16 safety population, as the patients incorrectly received at least one dose of CT-P16 at any time during the treatment period.

EU-bevacizumab, European-approved reference bevacizumab; IRR, infusion-related reaction; PRES, posterior reversible encephalopathy syndrome; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest.

groups, respectively) (Table 3).

3.4. Immunogenicity

The proportion of patients with a positive ADA result at any time during the study was similar between treatment groups (CT-P16, $n = 85$ [24.6 %]; EU-bevacizumab, n = 93 [27.0 %]). Of these, a low and similar number between treatment groups tested positive for NAbs (CT-P16, $n =$ 13 [3.8 %]; EU-bevacizumab, $n = 11$ [3.2 %]). There was no apparent impact of ADAs or NAbs on efficacy, safety (in terms of infusion-related reactions and/or anaphylaxis), or PK.

3.5. Pharmacokinetics

The mean (standard deviation) C_{trough} at each cycle in the maintenance period was generally similar for the CT-P16 and EU-bevacizumab treatment groups in the PK population – maintenance period subset (data not reported).

3.6. Quality of life

There was no notable difference between the CT-P16 and EU-bevacizumab treatment groups in mean scores for EORTC QLQ-C30 global health status (Supplementary Fig. S5) and QLQ-C30 functioning items across the whole study period (Supplementary Fig. S6).

There was a significant aggravation of mean scale score in EORTC QLQ-LC13 symptoms of alopecia and peripheral neuropathy (≥10 points) for both treatment groups compared with baseline during the induction period, with significant peripheral neuropathy persisting into the maintenance period (Supplementary Fig. S7). Coughing was significantly reduced during the induction period and at various timepoints throughout the maintenance period in both treatment groups. All other symptom scores were generally stable in both treatment groups throughout the whole study period.

4. Discussion

The final study results of this phase 3 clinical trial in patients with recurrent or metastatic non-squamous NSCLC confirm the equivalent efficacy of CT-P16 and EU-bevacizumab demonstrated in the previously published interim analysis [16].

The whole study period ORRs were similar with CT-P16 and EU-bevacizumab (45.61 % and 46.11 %, respectively) and remained stable compared with those reported during the induction period (42.40 %

Table 4
TEAEs by preferred term reported in ≥5 % of patients during the whole study period (safety population).

	CT-P16 ($n = 345$[a])	EU-bevacizumab ($n = 344$)
TEAE by System Organ Class and Preferred Term, n (%)		
Blood and lymphatic system disorders		
Anemia	109 (31.6)	93 (27.0)
Leukopenia	30 (8.7)	23 (6.7)
Neutropenia	75 (21.7)	55 (16.0)
Thrombocytopenia	63 (18.3)	48 (14.0)
Gastrointestinal disorders		
Constipation	38 (11.0)	33 (9.6)
Diarrhea	44 (12.8)	47 (13.7)
Nausea	74 (21.4)	65 (18.9)
Vomiting	30 (8.7)	30 (8.7)
General disorders and administration site conditions		
Asthenia	63 (18.3)	54 (15.7)
Fatigue	45 (13.0)	40 (11.6)
Pyrexia	22 (6.4)	17 (4.9)
Infections and infestations		
Pneumonia	17 (4.9)	18 (5.2)
Urinary tract infection	20 (5.8)	9 (2.6)
Investigations		
Alanine aminotransferase increased	24 (7.0)	19 (5.5)
Aspartate aminotransferase increased	23 (6.7)	17 (4.9)
Gamma-glutamyltransferase increased	22 (6.4)	19 (5.5)
Neutrophil count decreased	16 (4.6)	19 (5.5)
Platelet count decreased	29 (8.4)	23 (6.7)
Weight decreased	34 (9.9)	31 (9.0)
Metabolism and nutrition disorders		
Decreased appetite	43 (12.5)	43 (12.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	36 (10.4)	30 (8.7)
Myalgia	16 (4.6)	18 (5.2)
Pain In extremity	18 (5.2)	20 (5.8)
Nervous system disorders		
Headache	25 (7.2)	21 (6.1)
Peripheral neuropathy	53 (15.4)	50 (14.5)
Paresthesia	35 (10.1)	29 (8.4)
Peripheral sensory neuropathy	35 (10.1)	35 (10.2)
Renal and urinary disorders		
Proteinuria	44 (12.8)	44 (12.8)
Respiratory, thoracic, and mediastinal disorders		
Cough	17 (4.9)	24 (7.0)
Dyspnea	24 (7.0)	21 (6.1)
Epistaxis	14 (4.1)	19 (5.5)
Skin and subcutaneous tissue disorders		
Alopecia	220 (63.8)	218 (63.4)
Vascular disorders		
Hypertension	36 (10.4)	34 (9.9)

[a] Three patients randomized to the EU-bevacizumab group were included in the CT-P16 safety population, as the patients incorrectly received at least one dose of CT-P16 at any time during the treatment period.

EU-bevacizumab, European-approved reference bevacizumab; TEAE, treatment-emergent adverse event.

and 42.07 %, respectively, based on BOR) [16]. The median duration of response at the end of the study was similar between treatment groups (CT-P16: 7.2 months; EU-bevacizumab: 6.5 months), representing no change from the earlier study findings for CT-P16 and a slight increase (from 6.3 months) with EU-bevacizumab [16]. Similar proportions of patients in each treatment group remained progression free at 6, 12, 24, and 36 months and survived to 12, 24, and 36 months.

The overall safety profile was similar between CT-P16 and EU-bevacizumab, and no new safety signals were detected. The most common TEAEs during the maintenance period were consistent with a patient population with advanced lung cancer. CT-P16 and EU-bevacizumab showed the same level of immunogenicity, with only a small increase in both treatment groups compared with the earlier study findings [16] (final results found positive ADAs [NAbs] in 24.6 % [3.8 %] of the CT-P16 group vs. 22.6 % [2.3 %] in the interim analysis, with corresponding values of 27.0 % [3.2 %] and 24.1 % [2.3 %], respectively, for the EU-bevacizumab group). These antibodies were not found to have any clinical significance in terms of efficacy, safety, or PK.

In general, QoL was similar with both treatments. Significant changes (≥10 points in EORTC QLQ-LC13 mean scale score) in alopecia and peripheral neuropathy in both the CT-P16 and EU-bevacizumab treatment groups were deemed to be caused by the co-administration of paclitaxel and carboplatin during the induction period. These adverse effects are known to be common with those two drugs [17].

CT-P16 and EU-bevacizumab had similar PK profiles, consistent with the findings from a phase 1 study in which CT-P16 demonstrated PK equivalence to EU-bevacizumab and United States-licensed reference bevacizumab (NCT03247673) [18].

The strengths of this study include its multicenter, multinational nature. This contributed to the evaluation of patients with greater ethnic diversity than have been included in other bevacizumab biosimilar clinical trials [19,20], in which White patients comprised >90 % of the study population (compared with <80 % in the current study). Furthermore, the 3-year length of follow-up allowed full capture of longer-term efficacy, safety, immunogenicity, and QoL outcomes.

A limitation is that as the study inclusion criteria specified enrollment of patients with metastatic or recurrent disease, the findings may not apply to patients with locally advanced/stage III disease who may also be eligible for bevacizumab treatment in real-world settings. Treatment safety is a particular concern in the elderly (i.e., those aged 75 years and older), who represent a substantial proportion of lung cancer diagnoses and may be more vulnerable to adverse events due to frailty. However, only 42 patients aged 75 years or older were included in this study (18 and 24 patients in the CT-P16 and EU-bevacizumab groups, respectively). The treatment duration was relatively short, as the study targeted patients with advanced or recurrent cancer. The efficacy and safety of combination treatment with multiple immunotherapies is an important question; however, it was beyond the scope of the current study.

Oncology is an area of medicine with particularly high costs [21], and biosimilars offer opportunities to reduce costs and increase patient accessibility to treatments [22]. For this potential to be fully realized, non-economic factors should be addressed alongside economic considerations [21]. Biosimilar markets are in early development, and stakeholder collaboration will help to enable biosimilar adoption [21–23]. The results of the current study demonstrate the equivalent efficacy of CT-P16 and EU-bevacizumab when treating patients with non-squamous NSCLC, with no new safety concerns, adding to the body of evidence that stakeholders can draw upon when considering options. In line with reference bevacizumab, CT-P16 has been approved for treating multiple types of cancer [24–27]; as well as non-squamous NSCLC, these include metastatic breast cancer, metastatic colorectal cancer, recurrent glioblastoma, metastatic renal cell carcinoma, persistent recurrent or metastatic cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer. The availability of bevacizumab biosimilars with demonstrable therapeutic equivalence to reference bevacizumab for the treatment of non-squamous NSCLC would be expected to be cost-saving for healthcare systems [28–30]. In Spain, the introduction of bevacizumab biosimilars for unresectable or relapsed NSCLC was estimated to result in a 1-year cost-saving of 9740€ per patient [31]. In the US, the introduction of bevacizumab-bvzr with a 20 % biosimilar discount was associated with a 1-year cost saving of $6827 per patient across various indications, including NSCLC, colorectal cancer, renal cell carcinoma, glioblastoma, and cervical cancer [32].

As more evidence becomes available, this may help to realize the potential of biosimilar treatment in oncology.

5. Conclusion

In conclusion, the long-term results of this phase 3 study confirm that CT-P16 demonstrates clinical equivalence to EU-bevacizumab in terms of efficacy, safety, immunogenicity, and pharmacokinetic (PK) characteristics in patients with recurrent or metastatic non-squamous NSCLC. These findings support the availability of additional treatment options for patients with non-squamous NSCLC and may facilitate the appropriate adoption of biosimilars in oncology. Future research should focus on evaluating the performance of CT-P16 in special populations and in combination treatment regimens.Clinical practice points

- Long-term results confirm equivalent efficacy of CT-P16 and bevacizumab for NSCLC.
- ORRs, response duration, TTP, PFS and OS were similar for both treatments.
- No new safety concerns were detected.
- Immunogenicity, PK and quality of life were similar for both treatments.
- These results help inform decision-making with biosimilar treatments in oncology.

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Data availability

The data that support the findings of this study are available to request from Celltrion, Inc.

CRediT authorship contribution statement

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Declaration of competing interest

Zoran Andric, Tamta Makharadze, Alona Oleksiienko, and Claire Verschraegen have nothing to declare. Fedor Moiseenko has received consulting fees from AstraZeneca, BMS, Eli Lilly, and Roche; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Biocad, Eli Lilly, MSD, Novartis, Pfizer, and Roche; payment for expert testimony from Novartis and Pfizer; support for attending meetings and/or travel from AstraZeneca, Biocad, MSD, Novartis, Pfizer, and Roche; and has participated on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, BMS, Eli Lilly, and Roche. Eduardo Yañez Ruiz declares financial support from Celltrion, Inc. for conducting the current study. SungHyun Kim, KeumYoung Ahn, TaeHong Park, Hana Ju, Soonbum Kwon, IlSung Chang, SinHye Kim, HyunAh Kim, and EunKyung Lee are employees of, and hold stocks in, Celltrion, Inc. Eric Hyungseok Baek is an employee of Celltrion, Inc.

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Supplementary materials

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