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A phase III randomized trial of adding topical nitroglycerin to first-line chemotherapy for advanced nonsmall-cell lung cancer: the Australasian lung cancer trials group NITRO trial

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Background: We sought to determine whether the substantial benefits of topical nitroglycerin with first-line, platinum-based, doublet chemotherapy in advanced nonsmall-cell lung cancer (NSCLC) seen in a phase II trial could be corroborated in a rigorous, multicenter, phase III trial.

Patients and methods: Patients starting one of five, prespecified, platinum-based doublets as first-line chemotherapy for advanced NSCLC were randomly allocated treatment with or without nitroglycerin 25 mg patches for 2 days before, the day of, and 2 days after, each chemotherapy infusion. Progression-free survival (PFS) was the primary end point.

Results: Accrual was stopped after the first interim analysis of 270 events. Chemotherapy was predominantly with carboplatin and gemcitabine (79%) or carboplatin and paclitaxel (18%). The final analysis included 345 events in 372 participants with a median follow-up of 33 months. Topical nitroglycerin had no demonstrable effect on PFS [median 5.0 versus 4.8 months, hazard ratio (HR) = 1.07, 95% confidence interval (CI) 0.86–1.32, $P = 0.55$], overall survival (median 11.0 versus 10.3 months, HR = 0.99, 95% CI 0.79–1.24, $P = 0.94$), or objective tumor response (31% versus 30%, relative risk = 1.03, 95% CI 0.82–1.29, $P = 0.81$). Headache, hypotension, syncope, diarrhea, dizziness, and anorexia were more frequent in those allocated nitroglycerin.

Conclusion: The addition of topical nitroglycerin to carboplatin-based, doublet chemotherapy in NSCLC had no demonstrable benefit and should not be used or pursued further.

Clinical Trials Number: Australian New Zealand Clinical Trials Registry Number ACTRN12608000588392.

Key words: lung cancer, nitroglycerin, chemotherapy, phase III clinical trial

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introduction

Platinum-based doublets are the standard of care as first-line chemotherapy in advanced nonsmall-cell lung cancer (NSCLC) [1]. Chemotherapy improves survival and symptoms in advanced NSCLC, but outcomes remain poor with a median time to progression of 5 months and median overall survival (OS) of 9 months in contemporary randomized trials [2].

Remarkable improvements were reported in a phase II trial testing the addition of topical nitroglycerin to first-line chemotherapy with cisplatin and vinorelbine in 120 patients with advanced NSCLC [3]. Application of a nitroglycerin 25 mg patch for 2 days before, the day of, and 2 days after chemotherapy infusions was associated with substantial improvements in objective tumor response (OTR) rate (72% versus 42%, $P < 0.001$), progression-free survival (PFS) (11 versus 6 months, $P = 0.006$) and OS (13 versus 9 months, $P < 0.001$). The only adverse effects attributed to nitroglycerin were mild headache (grade 1 or 2: 30% versus 2%, $P < 0.001$) and mild hypotension (grade 1: 5% versus 0%, $P = 0.2$).

Nitroglycerin is a nitric oxide donor. Possible mechanisms of action include reduced resistance to chemotherapy, reduced hypoxia inducible factor (HIF)-1 stabilization, direct effects of nitric oxide on cancer cells, increases in activated p53 protein, and increased drug delivery in tumor tissue [3, 4]. Nitric oxide donors may sensitize tumor cells to both chemotherapy and immunotherapy, and might also inhibit metastasis [5]. Studies in cell lines have reported that nitric oxide donors can reduce resistance to chemotherapy induced by hypoxia [6], perhaps by reducing levels of HIF-1a [7]. HIF-1a has been shown to activate transcription of many genes that code for proteins involved in angiogenesis, cell growth, metastasis, and chemotherapy resistance [6, 8, 9].

We sought to determine the effects of adding topical nitroglycerin to first-line, platinum-doublet chemotherapy in patients with advanced NSCLC in a multicenter phase III trial. We hypothesized that adding nitroglycerin would improve PFS, OS, OTR, and health-related quality of life (HRQL); and that adverse events would be infrequent and mild.

methods

study design

We carried out a large-scale, multicenter, open-label, randomized phase III trial. Randomization was carried out centrally at the trial coordinating center using a computerized minimization algorithm to balance for gender, age >70 years, stage of disease (III or IV), histologic subtype (adenocarcinoma, squamous, or other), planned chemotherapy regimen (cisplatin and vinorelbine, carboplatin and gemcitabine, carboplatin and paclitaxel, and pemetrexed with either cisplatin or carboplatin), Eastern Cooperative Oncology Group performance status (ECOG PS 0–1 versus 2), and treating site.

The study protocol was approved by human-research ethics committees at all participating centers and was conducted in accordance with Good Clinical Practice guidelines. All patients provided signed, written, informed consent.

patients

The target population was adults with advanced NSCLC starting first-line chemotherapy. The main inclusion criteria were: pathologically confirmed

NSCLC, stage III or IV disease, unsuitable for surgery and/or chemoradiotherapy; adequate performance status (ECOG PS 0–2); and adequate bone-marrow, renal, and hepatic function. Target lesions were not required. The main exclusion criteria were: untreated brain or meningeal metastases; life expectancy <3 months; prior systemic therapy for advanced NSCLC [including cytotoxic, epidermal growth factor receptor (EGFR) inhibitors, or drugs targeting vascular endothelial growth factor]; current use of nitrates, dihydroergotamine, or phosphodiesterase inhibitors; and uncontrolled cardiovascular disease.

study treatments

Clinicians were permitted to choose any one of five, standard, first-line, platinum-based chemotherapy doublet regimens (Table 1). Patients were randomly assigned in a 1:1 ratio to chemotherapy with or without the application of a nitroglycerin 25 mg patch (Transiderm-NITRO 25 mg), applied for 12 h on each of the 2 days before, the day of, and the 2 days after each chemotherapy infusion. Chemotherapy was given every 3 weeks for a maximum of four to six cycles in the absence of progressive disease or prohibitive toxicity. Antiemetic prophylaxis and other supportive care were according to standard local practice. Maintenance chemotherapy was allowed if there was no evidence of disease progression during or after first-line

Table 1. Baseline characteristics

	Chemotherapy + nitroglycerin, N = 187 (%)	Chemotherapy alone, N = 185 (%)
Age (years)		
<50	11 (6)	8 (4)
50–59	49 (26)	43 (23)
60–69	77 (41)	80 (43)
70–79	48 (26)	51 (28)
≥ 80	2 (1)	3 (2)
Gender		
Female	73 (39)	74 (40)
Male	114 (61)	111 (60)
ECOG performance status		
0	60 (32)	65 (35)
1	114 (61)	106 (57)
2	13 (7)	14 (8)
Histology		
Adenocarcinoma	124 (66)	122 (66)
Squamous	41 (22)	39 (21)
Other	22 (12)	24 (13)
Stage at diagnosis (AJCC 2002)		
III	18 (10)	19 (10)
IV	169 (90)	166 (90)
Smoker		
Current	36 (20)	35 (19)
Within 15 years	90 (51)	92 (52)
>15 years or never smoker	51 (29)	50 (28)
Prior radiotherapy		
Yes	49 (26)	55 (30)
Planned chemotherapy		
Carboplatin and gemcitabine	148 (79)	146 (79)
Carboplatin and paclitaxel	35 (18)	34 (18)
Cisplatin and vinorelbine	3 (2)	3 (2)
(Cisplatin or carboplatin) and pemetrexed	1 (1)	2 (1)

chemotherapy. The choice of regimen for maintenance, second-line, and subsequent chemotherapy was left open to investigators.

study procedures

Study assessments were carried out at baseline before randomization, then every 3 weeks during chemotherapy, and every 4 weeks from completion of chemotherapy until disease progression. Computed tomographic (CT) scans of the chest and upper abdomen were done at baseline, then every 6 weeks during chemotherapy, and every 8 weeks after chemotherapy, until disease progression.

The primary outcome was PFS (the interval from randomization to progressive disease or death, which ever occurred first). We chose PFS as the primary end point because an improvement in PFS was considered sufficient to justify an intervention as safe, simple, and inexpensive as nitroglycerin. Secondary outcomes included OS (the interval from randomization to death from any cause), OTR (including complete and partial responses), adverse events, and HRQL. OTR was assessed at participating sites according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) [10]. Imaging for tumor assessments was reviewed at sites by a radiologist blinded to treatment group allocation. Radiographic reports, but not images, were reviewed centrally for pragmatic reasons.

Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [11]. HRQL was self-rated by participants with the EQ-5D-3L, an extensively validated, generic measure of HRQL which yields a single, preference-based, utility score from 0 (worst quality of life) to 1 (best quality of life) based on responses to five items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) rated on 3-point ordinal scales, and a visual analog scale rating current health [12, 13]. Clinicians rated patients' HRQL with Spitzer's Quality-of-Life Index (SQLI) which assesses activity, daily living,

health, support, and outlook on 3-point ordinal scales summed to give a score from 0 (worst quality of life) to 10 (best quality of life) [14].

statistical considerations

The planned sample size of 500 participants, accrued over 3 years and analyzed after 460 events for PFS, was designed to give 80% power to detect a hazard ratio (HR) of 0.75 at a two-sided significance level of 0.05. All analyses were carried out by intention to treat. The protocol specified interim analyses after 230 and 345 PFS events (~50% and 75% of the information expected). The results of interim analyses were reported to an independent safety and data-monitoring committee (ISDMC) that advised the trial management committee whether to continue, stop, or modify the trial.

The primary analyses of the effect of treatment allocation on PFS and OS used an unadjusted log-rank test. The effects of baseline factors on PFS and OS were assessed with multivariable Cox proportional hazards models derived with a stepwise model-building procedure. Differences between the two treatment groups in HRQL were analyzed with generalized estimating equation regression models accounting for treatment group, baseline HRQL scores, and repeated measurements at each study visit.

results

We recruited 372 participants from 29 sites in Australia and New Zealand between May 2009 and April 2014 (Figure 1). Recruitment was stopped on the advice of the ISDMC after the first interim analysis of 270 PFS events in 331 participants showed no demonstrable effect of nitroglycerin on PFS [HR 1.03, 95% confidence interval (CI) 0.81–1.31, $P = 0.79$], and that accrual of additional participants was unlikely to change the results or conclusions. The results reported below are based on

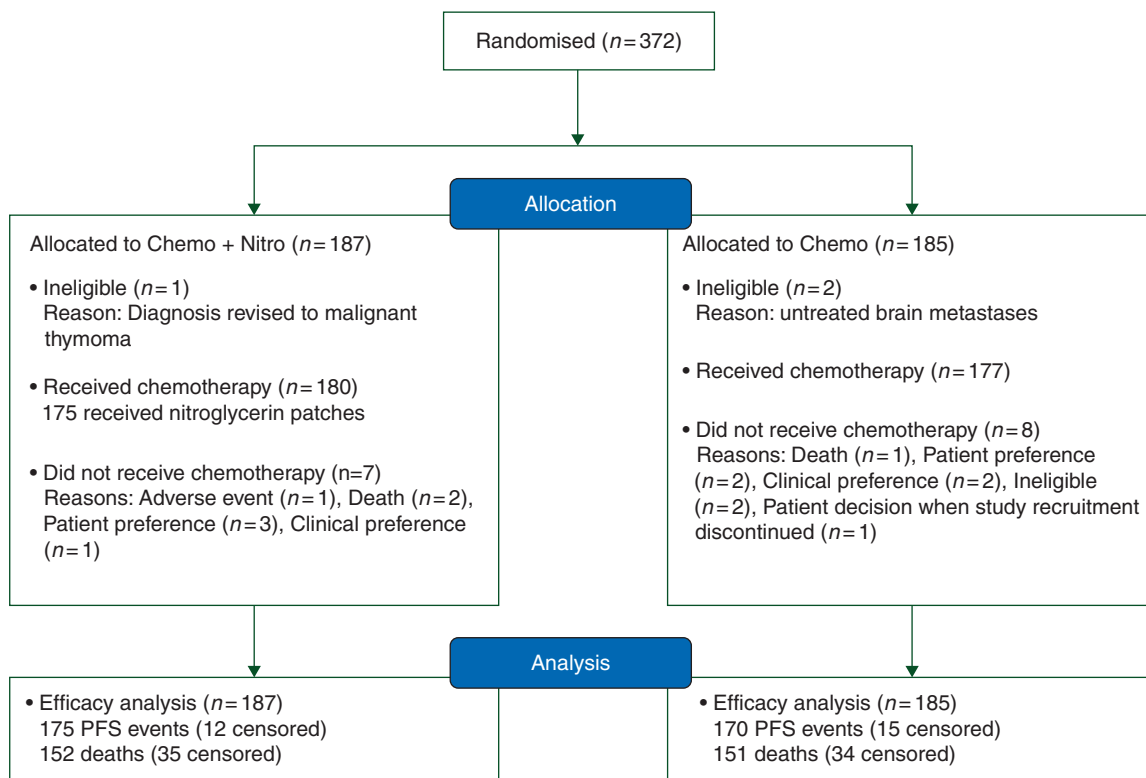


Figure 1. CONSORT diagram. Chemo, chemotherapy; Nitro, nitroglycerin; NSCLC, non small-cell lung cancer; PFS, progression-free survival.

all 372 participants followed for a median of 33 months (range 0–62 months).

Baseline characteristics were similar in the two treatment groups and typical of first-line chemotherapy trials in advanced NSCLC. The median age was 64 years, 28% were aged older than 70, and the majority had good performance status, presented with stage IV disease, and no prior radiation therapy (Table 1).

treatment

The chemotherapy regimens used most frequently were carboplatin and gemcitabine (79%), or carboplatin and paclitaxel (18%). The number of chemotherapy cycles (median 4), dose reductions, and delays was similar in the treatment groups. The most frequent reasons for stopping first-line chemotherapy were: completion of protocol treatment (36%), progressive disease (22%), adverse events (14%), clinician preference (14%), and patient preference (9%); these were equally frequent in the two treatment groups.

Compliance with the application of nitroglycerin patches reported in daily diaries was excellent. The proportion of participants reporting that they applied patches for at least 4 of the 5 days around day 1 of chemotherapy was 93% for cycle 1, and ranged from 79% to 90% in subsequent cycles. The proportion of participants reporting that they applied patches for at least 4 of the 5 days around day 8 of chemotherapy was 87% for cycle 1, and ranged from 79% to 88% in subsequent cycles.

There were no important differences between the two treatment groups in the use of anticancer treatments after first-line chemotherapy. Maintenance chemotherapy (started before disease progression) was used in 60 participants (16%). Radiation therapy was used before disease progression in 8 participants (2%). Second-line chemotherapy was used after disease progression in 168 participants (45%) and with similar frequency in the two treatment groups. No participants were treated with bevacizumab. Radiation therapy was used after disease progression in 67 participants (18%).

outcomes

The primary end point was observed in 345 of the 372 participants (93%): progression according to RECIST 1.1 in 259 (70%), clinical progression in 49 (13%), and death before documented progression in 37 (10%). PFS was identical in those assigned nitroglycerin plus chemotherapy versus those assigned chemotherapy alone (medians 5.0 versus 4.8 months, HR 1.07; 95% CI 0.86–1.32, log-rank $P = 0.55$, Figure 2A).

Baseline factors associated with shorter PFS in univariable analyses were squamous histology, liver metastases, ECOG PS 1 or 2 (v 0), anemia (hemoglobin <120 g/l), elevated white cell count (WCC $>11 \times 10^9$ /l), elevated absolute neutrophil count (ANC, $>4.5 \times 10^9$ /l), elevated neutrophil-to-lymphocyte ratio (NLR, >5), hypoalbuminemia (albumin <40 g/l), elevated alkaline phosphatase [ALP above the upper limit of normal (ULN)], and low SQLI (<9). Baseline factors independently associated with PFS in multivariable analysis were squamous histology, elevated ANC, elevated NLR, elevated ALP, and low SQLI. The addition of nitroglycerin to chemotherapy had no demonstrable effect on PFS after adjustment for these baseline factors.

There were 303 deaths among the 372 participants (81%). Those assigned nitroglycerin plus chemotherapy had similar OS to those assigned chemotherapy alone (medians 11 versus 10.3 months, HR 0.99; 95% CI 0.79–1.24; log-rank $P = 0.94$, Figure 2B).

Baseline factors associated with OS in univariable analyses included ECOG PS 1 or 2 (v 0), anemia, elevated WCC, elevated ANC, elevated NLR, hypoalbuminemia, elevated ALP, elevated lactate dehydrogenase (above ULN), and low SQLI (<9). Baseline factors independently associated with OS in multivariable analysis included performance status, anemia, and elevated NLR. The addition of nitroglycerin to chemotherapy had no demonstrable effect on OS after adjustment for these baseline factors.

Target lesions were documented at baseline in 359 of the 372 participants (97%). OTRs were equally frequent in the two treatment groups (supplementary Table S1, available at *Annals of Oncology* online). Complete responses were observed in three participants, all assigned chemotherapy alone (2%). Partial responses were observed in 108 participants, 57 (31%) were assigned to nitroglycerin plus chemotherapy, and 51 (29%) to chemotherapy alone.

Compliance with HRQL questionnaires was excellent and similar in the two treatment groups. Self-ratings of HRQL with EQ-5D were available for 97% of participants at baseline, and over 91% of expected forms were completed after each chemotherapy cycle. Clinicians' ratings of HRQL with SQLI were available for 96% of participants at baseline, and over 81% of expected forms were completed after each chemotherapy cycle. Assignment to nitroglycerin had no demonstrable effect on HRQL rated either by participants with EQ-5D (difference 0.00 on a scale from 0 to 1; 95% CI -0.03 to 0.04 ; $P = 0.97$) or by clinicians with SQLI (difference 0.21 on a scale from 0 to 10; 95% CI -0.07 to 0.49 ; $P = 0.14$).

The frequency and severity of most types of adverse event was similar in the two treatment groups and typical of first-line chemotherapy in NSCLC (supplementary Table S2, available at *Annals of Oncology* online). Adverse events of any grade more frequently observed in the nitroglycerin group included headache (52% versus 25%, $P < 0.001$), hypotension (21% versus 14%, $P = 0.03$), syncope (6% versus 2%, $P = 0.04$), diarrhea (23% versus 14%, $P = 0.03$), dizziness (33% versus 20%, $P = 0.007$), and anorexia (50% versus 35%, $P = 0.005$). Serious adverse events were reported in 224 participants (61%) and equally frequent in the two treatment groups. Hospitalizations were reported in 218 participants (59%) and equally frequent in the two treatment groups. There were four deaths within 30 days of study treatment: three assigned chemotherapy with nitroglycerin and one assigned chemotherapy alone ($P = 0.30$).

discussion

The addition of topical nitroglycerin to standard first-line chemotherapy did not affect disease progression, OS, OTR, or HRQL in this large-scale, randomized, phase III trial. We allowed the use of five different chemotherapy regimens, but the predominantly used regimens were carboplatin and gemcitabine (79%), or carboplatin and paclitaxel (18%). Topical nitroglycerin was associated with a higher frequency of expected mild-to-moderate adverse effects including not only headache, hypotension, syncope, and

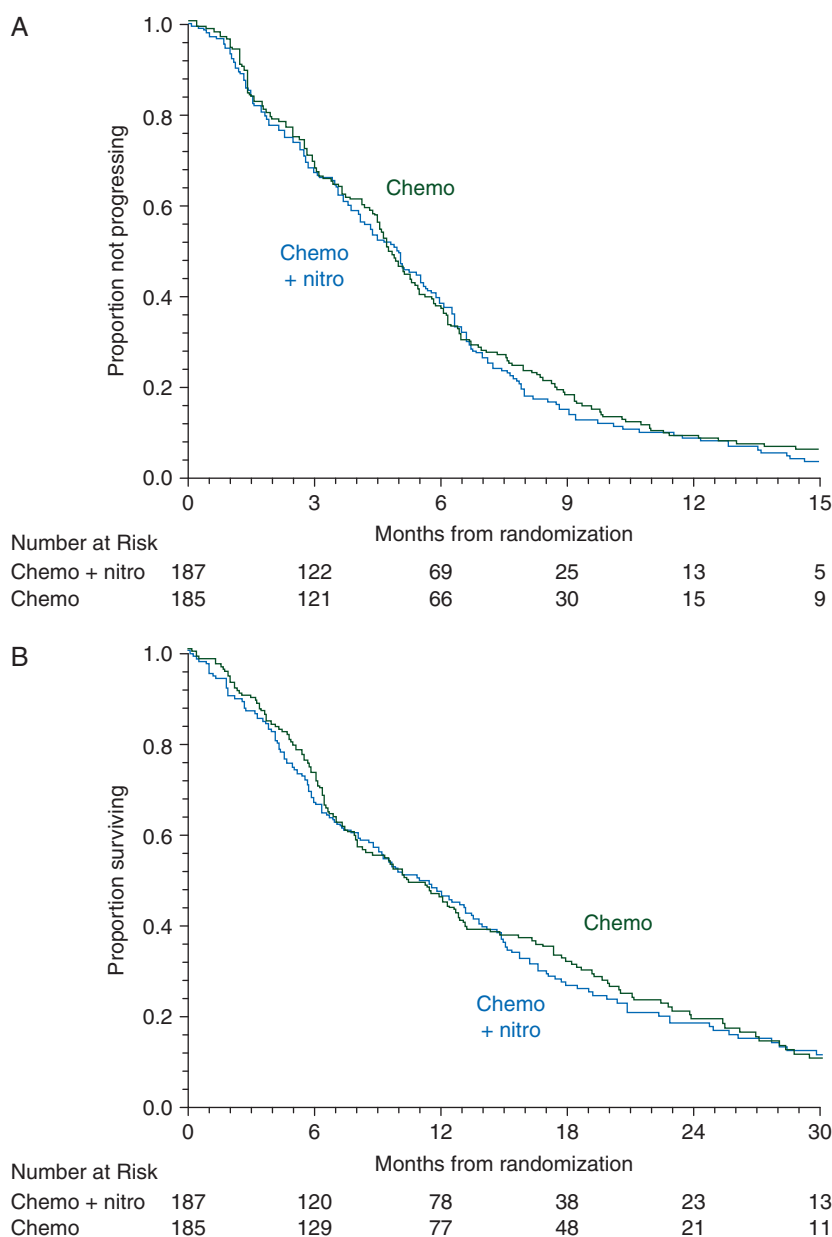


Figure 2. Kaplan–Meier curves according to randomly allocated treatment: (A) progression-free survival, and (B) overall survival. Chemo, chemotherapy; Nitro, nitroglycerin.

dizziness, but also diarrhea and anorexia. The frequency and severity of other adverse events was typical of first-line chemotherapy in advanced NSCLC. This trial provides strong evidence that topical nitroglycerin is not beneficial when added to carboplatin with either gemcitabine or paclitaxel as first-line chemotherapy in NSCLC.

The rationale for our trial was the substantial improvements in OTR, PFS, and OS reported in a randomized phase II trial testing the addition of topical nitroglycerin to cisplatin and vinorelbine in 120 participants with stage IIIB or IV NSCLC [3]. Compared with our trial, the Japanese trial included higher proportions of smokers (78% versus 64%), squamous cell carcinomas (48% versus 20%), and stage IIIB disease (40% versus 9%). Cisplatin and vinorelbine were only used by six participants in our trial. These differences in baseline characteristics and

chemotherapy regimens are judged unlikely to explain the differences between the results of the two trials.

Our results are consistent with two recently reported trials that also showed no effect of adding topical nitroglycerin to chemotherapy. The Dutch NVALT-12 trial, also reported in this issue of *Annals of Oncology*, tested the addition of nitroglycerin to carboplatin, paclitaxel, and bevacizumab in a randomized trial of 223 participants with stage IV NSCLC [15]. They reported no significant differences in tumor response, PFS, or OS. Reinmuth et al. [16] tested the addition of topical nitroglycerin to cisplatin with oral vinorelbine in 66 participants with stage IIIB or IV NSCLC and reported no demonstrable effects on tumor response, PFS, or OS.

The main strengths of our trial are its rigorous and pragmatic, randomized, phase III, multicenter design incorporating widely

used chemotherapy regimens. Our trial is the largest to examine this question and its results rule out any clinically important benefits of adding topical nitroglycerin to standard first-line chemotherapy including carboplatin and either gemcitabine or paclitaxel in advanced NSCLC. Despite stopping early, the boundaries of our 95% CIs exclude any clinically important benefits in tumor response, PFS, and OS.

The main limitation of our study is that most participants were treated with carboplatin and either gemcitabine or paclitaxel. It therefore leaves unanswered the question of whether topical nitroglycerin might have different effects when added to chemotherapy with cisplatin and vinorelbine, or other first-line regimens. Pemetrexed was not widely accessible for first-line chemotherapy during much of the accrual to our study. A biological rationale for nitroglycerin's effects to differ according to chemotherapy regimen is not apparent. The heterogeneity of metastatic NSCLC is increasingly being recognized, as is the importance of molecular drivers such as EGFR-activating mutations and the EML4-ALK translocation [17]. Our trial did not account for specific molecular subtypes of lung cancer. Imbalances in unmeasured characteristics, known or unknown, were unlikely to have had important effects on our results or conclusions.

Japanese and US populations with advanced NSCLC differ in pharmacogenomic parameters and the outcomes of chemotherapy [18]. We think it unlikely that such differences are responsible for the divergent findings of the original Japanese trial and the subsequent three trials testing the effects of adding nitroglycerin to chemotherapy for NSCLC. We judge that the differences in results between these four trials are more likely due to the play of chance than the differences in the participants or regimens. Reviews of randomized trials have demonstrated that the probability of a positive phase II trial resulting in a subsequent positive phase III trial within 5 years was as low as 0.038 [19, 20].

Nitroglycerin did not improve the outcomes of first-line chemotherapy with carboplatin-based doublets for advanced NSCLC, but it did increase the frequency and severity of adverse events. Based on these findings, we conclude that there is no role for the addition of nitroglycerin to standard first-line chemotherapy in advanced NSCLC and we do not recommend further research on this treatment combination.

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disclosure

The authors have declared no conflicts of interest.

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A randomized phase II study comparing paclitaxel–carboplatin–bevacizumab with or without nitroglycerin patches in patients with stage IV nonsquamous nonsmall-cell lung cancer: NVALT12 (NCT01171170)[†]

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Background: Nitroglycerin (NTG) increases tumor blood flow and oxygenation by inhibiting hypoxia-inducible-factor (HIF)-1. A randomized phase II study has shown improved outcome when NTG patches were added to vinorelbine/cisplatin in patients with advanced nonsmall-cell lung cancer (NSCLC). In addition, there is evidence that the combination of bevacizumab and HIF-1 inhibitors increases antitumor activity.

Patients and methods: In this randomized phase II trial, chemo-naïve patients with stage IV nonsquamous NSCLC were randomized to four cycles of carboplatin (area under the curve 6)–paclitaxel (200 mg/m²)–bevacizumab 15 mg/kg on day 1 every 3 weeks with or without NTG patches 15 mg (day –2 to +2) followed by bevacizumab with or without NTG until progression. Response was assessed every two cycles. Primary end point was progression-free survival (PFS). The study was powered (80%) to detect a decrease in the hazard of tumor progression of 33% at $\alpha = 0.05$ with a two-sided log-rank test when 222 patients were enrolled and followed until 195 events were observed.

Results: Between 1 January 2011 and 1 January 2013, a total of 223 patients were randomized; 112 control arm and 111 experimental arm; response rate was 54% in control arm and 38% in experimental arm. Median [95% confidence interval (CI)] PFS in control arm was 6.8 months (5.6–7.3) and 5.1 months (4.2–5.8) in experimental arm, hazard ratio (HR) 1.27 (95% CI 0.96–1.67). Overall survival (OS) was 11.6 months (8.8–13.6) in control arm and 9.4 months (7.8–11.3) in experimental arm, HR 1.02 (95% CI 0.71–1.46). In the experimental arm, no additional toxicity was observed except headache (6% versus 52% in patients treated with NTG).

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