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ORIGINAL ARTICLE

# Neu-horizons: neuroprotection and therapeutic use of riluzole for the prevention of oxaliplatin-induced neuropathy—a randomised controlled trial

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## Abstract

**Trial design** Peripheral neuropathy is a commonly reported adverse effect of oxaliplatin treatment, representing a significant limitation which may require discontinuation of effective therapy. The present study investigated the neuroprotective potential of riluzole in patients undergoing oxaliplatin treatment in a randomised-controlled trial comparing riluzole and placebo-control.

**Methods** Fifty-two patients (17 females, 58.1 ± 12.7 years) receiving oxaliplatin treatment were randomised into either a treatment (50 mg riluzole) or lactose placebo group. The primary outcome measure was the total neuropathy score-reduced (TNSr). Secondary outcome measures include nerve excitability measures, 9-hole pegboard and FACT-GOG NTX questionnaire. Patients were assessed at baseline, pre-cycle 10 or 12, 4-week and 12-week post-treatment.

**Results** Both the treatment and placebo groups developed objective and patient reported evidence of neurotoxicity over the course of oxaliplatin treatment, although there were no significant differences across any parameters between the two groups. However, across follow-up assessments, the treatment group experienced greater neuropathy, represented by a higher TNSr score at 4-week post-chemotherapy of 8.3 ± 2.7 compared with 4.6 ± 3.6 ($p = 0.032$) which was sustained at 12-week post-treatment ($p = 0.089$). Similarly, patients in the treatment group reported worse symptoms with a FACT-GOG NTX score of 37.4 ± 10.2 compared with 43.3 ± 7.4 ($p = 0.02$) in the placebo group at 4-week post-treatment.

**Conclusion** This study is the first to provide an objective clinical investigation of riluzole in oxaliplatin-induced peripheral neuropathy employing both functional and neurophysiological measures. Although the recruitment target was not reached, the results do not show any benefit of riluzole in minimising neuropathy and may suggest that riluzole worsens neuropathy associated with oxaliplatin treatment.

**Keywords** Neuropathy · Neurotoxicity · Neuroprotection · Riluzole · Oxaliplatin · Nerve excitability

## Introduction

Oxaliplatin is a first-line treatment for advanced colorectal cancer. Unlike other platinum derivatives, oxaliplatin does not cause renal impairment or ototoxicity [1, 2]. However, oxaliplatin produces prominent peripheral neurotoxicity, including a distinctive pattern of cold-associated acute neurotoxicity in 95% of patients immediately following an infusion that typically resolves over a period of a few days [3, 4]. Oxaliplatin treatment is also related to the development of chronic dose-limiting sensory peripheral neuropathy [5], present in up to 50% of patients at higher cumulative doses [6]. Paraesthesia and numbness are the most commonly reported symptoms [7] and remain a significant limitation

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to maintaining dose intensity. Neuropathic symptoms that impact on function require dose reductions, dose delays and possibly discontinuation of therapy [8]. This is particularly an issue in the setting of adjuvant therapy where the aim of treatment is cure and long-term neurotoxicity is an unacceptable outcome.

A number of studies have demonstrated that $Na^+$ channels have an important role in mediating axonal degeneration in models of toxic and inflammatory neuropathy [9–11]. In particular, the sodium channel isoform $Na_v1.6$ has been implicated in acute oxaliplatin-related neurotoxicity in rodent models, prolonging the repolarisation phase of the action potential and producing hyperexcitability [12, 13]. In the clinical setting, nerve excitability techniques have provided some insight into the pathophysiology of acute oxaliplatin-induced neuropathy [7, 14, 15], also revealing prominent alterations in $Na^+$ channel function.

There is some evidence that the development of acute and chronic oxaliplatin-induced neurotoxicity are linked—with the duration and intensity of acute oxaliplatin neurotoxicity predictive of the development of long-term chronic neuropathy [4, 16]. Furthermore, the degree of acute nerve excitability abnormalities appears to be linked to the subsequent development of chronic neuropathy [17]. Accordingly, there is rationale for the investigation of neuroprotective strategies based on modulation of $Na^+$ channel function for the prevention of chronic neurotoxicity.

Riluzole is a neuroprotective agent currently used for the treatment of neurodegenerative diseases, particularly amyotrophic lateral sclerosis, where it prolongs survival [18, 19]. Riluzole acts to reduce axonal excitability and repetitive firing via suppression of persistent $Na^+$ currents, enhancement of calcium-dependent $K^+$ currents and reduction of neurotransmitter release [20]. The effects on $Na^+$ channels promote neuroprotection by blocking inward movement of $Na^+$ ions through persistent $Na^+$ channels to prevent the reverse activation of axonal $Na^+/Ca^{2+}$ exchanger and subsequent $Ca^{2+}$-mediated excitotoxicity [19]. Accordingly, riluzole has demonstrated neuroprotective properties in multiple neuronal cell populations, including enhancing neurite growth in dorsal root ganglion neurons [21]. Furthermore, in animal models, riluzole has shown efficacy in preventing the development of oxaliplatin-induced neurotoxicity symptoms including cold [22] and mechanical allodynia [23] with no evidence of tumour promotion [23, 24]. To examine the neuroprotective potential of riluzole in oxaliplatin neurotoxicity, we carried out a randomized controlled trial to assess whether treatment with riluzole results in a reduction in the development of chronic neuropathy. We hypothesised that riluzole treatment would be neuroprotective during oxaliplatin treatment and result in better neurophysiological and patient reported outcomes when compared with placebo-control.

## Methods

### Trial design

A randomised, double-blinded placebo-controlled trial was undertaken to determine the effect of riluzole on the development of neuropathy in patients receiving oxaliplatin chemotherapy. The trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry (12611000514909, 'neu-horizons'; 18/05/2011) and was conducted with ethical approval from the South Eastern Sydney and Illawarra Area Health Service—Human Research Ethics Committee, in accordance with the 1964 Helsinki Declaration. Patient recruitment and assessments were undertaken at the Prince of Wales Hospital, Sydney, Australia. Potential patients were given information to read regarding the benefits and risks of the study and provided written informed consent. Patients were recruited from July 2011 to December 2015, with the last follow-up assessment completed in September 2016. The study is reported in accordance with the Consolidated Standards for Reporting Trials Statement (CONSORT).

### Participants

The inclusion criteria were (i) 18–80 years of age; (ii) planned oxaliplatin treatment; (iii) able to provide written informed consent and (iv) histological or cytological confirmation of cancer. Exclusion criteria included (i) baseline clinical and nerve conduction evidence of pre-existing neuropathy; (ii) past history of neurotoxic chemotherapy, (iii) concurrent use of anticonvulsant medications that modulate nerve function, (iv) elevated hepatic transaminase levels, (v) administration of another investigational drug within 30 days prior to randomisation, (vi) a history of severe hypersensitivity reaction to riluzole or any of the tablet components, (vii) significant pre-existing neurological or psychiatric disorder and (viii) pregnancy or lactation.

### Intervention

Patients were randomly allocated to one of two groups: an intervention group that was prescribed riluzole 50 mg twice daily prior to the second oxaliplatin dose, continuing to the end of treatment, and for 2-week post-completion of treatment or matched daily lactose placebo. Randomisation was performed in a 1:1 ratio stratified by the frequency of oxaliplatin treatment (2 weekly vs 3 weekly). Each oxaliplatin cycle comprises of one oxaliplatin treatment dose. All patients had liver function tests performed at baseline and at monthly levels. Riluzole was discontinued if liver function testing demonstrated elevation in alanine aminotransferase levels to greater than five times the upper limit of normal.

## Outcomes

Neurophysiological and functional assessments were conducted at baseline, during treatment prior to cycle 10 and 12, and at 4- and 12-week post-treatment. The primary outcome measure was the severity of neuropathy assessed at 4-week post-treatment using a validated scoring system, the total neuropathy score-reduced (© Johns Hopkins University) [25, 26]. This scale is used to evaluate neuropathy across eight different clinical domains, graded from zero to four for each domain covering sensory neuropathic symptoms, examination findings such as pin-prick sensitivity, vibration sense, strength, tendon jerk reflexes and nerve conduction results of the sural and tibial nerves. The scores obtained in the different categories were added to give a total neuropathy score (TNSr; range 0–32). All assessments were conducted by a single technician qualified in neurophysiological assessment.

Secondary outcome measures included functional, neurophysiological and quality of life measures. The nine-hole pegboard test (Smith and Nephew Rehabilitation, Inc., USA) was included as a functional measure of upper limb dexterity. Neurophysiological studies included nerve conduction studies and nerve excitability techniques. Nerve conduction studies were administered using previously described methods [27, 28] with a Medelec Synergy system (Viasys Healthcare, USA) to obtain peak motor and sensory amplitude of the tibial and sural nerves, respectively. Nerve excitability techniques provide information regarding ion channel function in peripheral nerves [29]. Nerve excitability studies were conducted on the median nerve at the wrist recording sensory compound action potentials from digit 2 using QtracS threshold-tracking protocol (copyright Institute of Neurology, UCL) [30], with skin temperature maintained ≥ 32°. Excitability analysis was comprised of parameters of hyperpolarizing threshold electrotonus 90–100 ms, refractoriness at 2.5 ms and superexcitability at 7 ms [31]. The FACT-GOG-NTX [32] is a validated questionnaire to assess the severity of neurotoxicity and impact on quality of life. It contains 13-items with each question is graded on a 0–4 scale, a score of '0' representing 'not at all' and a score of 4 representing 'very much' inquiring neuropathic symptoms over a recent 7-day period. The total is tallied and reverse-scored so that the maximum score of 52 indicates no neuropathic symptoms.

## Randomisation and masking

Participants were randomised at the initial study visit, after they had provided informed consent and met the study inclusion criteria. Patients were randomised in a 1:1 ratio stratified according to the frequency of oxaliplatin treatment (2 weekly vs 3 weekly) and centrally randomised through the National Health and Medical Research Centre (NHMRC) Clinical Trials Centre. All participants and investigators were blinded to the treatment allocation.

## Statistical methods

Appropriate sample size was determined from the incidence of neuropathy in a previous open-label $Na^+$ channel blocker trial with a neuropathy incidence of 31% in the treatment arm compared with 75% in the control arm for patients treated with oxaliplatin [33]. In order to detect this extent of difference, it was determined that 90 patients were required to detect differences between placebo and riluzole treatment arms to achieve at least 80% power and a two-sided type I error rate of 10%. Due to a short-fall in accrual and funding restrictions, the data presented is for a total of 48 patients who were recruited.

All efficacy analyses were performed on the Full Analysis Set (FAS). All randomised subjects who received at least one treatment were eligible for inclusion in the FAS in accordance with the intention-to-treat analysis principle. Subjects with missing neuropathy assessment data were considered treatment failures and included in the primary analysis. Normally distributed data were presented as mean ± standard deviation; otherwise, data were presented as median and interquartile range. Change across time-points was analysed using *t* test, Wilcoxon-signed rank test or chi-squared tests. Due to an appreciable number of missing data due to withdrawal or death, a mixed model for repeated measures modelling has been used where applicable. Analyses were completed using SAS 9.3 (SAS Institute Inc., Cary, NC) and a conservative significance threshold of $p < 0.1$ was selected to determine whether the actions of riluzole would necessitate further investigation.

# Results

Fifty-two patients (32 males and 20 females) were recruited and consecutively randomised into the treatment group ($n = 27$) and control group ($n = 25$) (Fig. 1). Four patients (two in each group) withdrew participation before any study drug was administered and were therefore excluded from the final analysis. The final analysis included 48 patients. The mean age ±

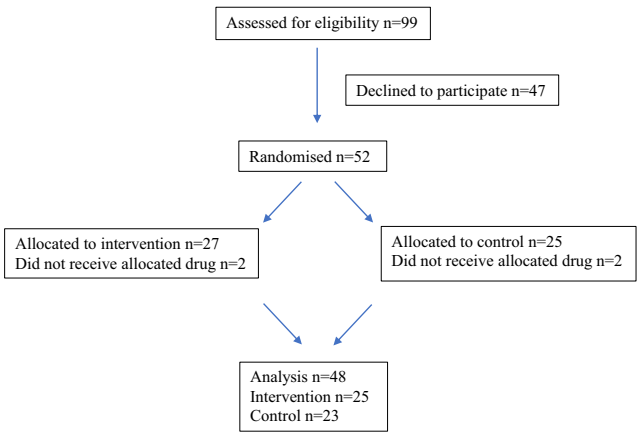


**Fig. 1** Diagram of patient allocation

SD for the cohort was 58 ± 12.6 years. The intervention and control groups did not differ in terms of age, sex or primary location of cancer tumour. Chemotherapy treatment duration was similar across both groups with 19.2 ± 6.6 weeks for the intervention group and 17.9 ± 6.1 weeks for the control group. Dose intensity did not differ between groups ($p = 0.42$, Table 1). There were no adverse events reported for the duration of the study. A majority of patients received riluzole/placebo before the first treatment of oxaliplatin. Ten patients received riluzole/placebo prior to the 2nd cycle of oxaliplatin, of whom 6 patients were from the riluzole group and 4 from the control group. Additional clinical characteristics of patients included in the final analyses are represented in Table 1.

## Primary outcome measure

The baseline TNSr was 0.7 ± 1.6 and 0.5 ± 1.2 for the intervention and control groups, respectively, indicating no neuropathy at baseline. The mixed model repeated measures analysis revealed a significant difference between the two groups following chemotherapy treatment at 4-week post-treatment and 12-week post-treatment. The TNSr at 4-week post-chemotherapy was 8.3 ± 2.7 for the intervention group and 4.6 ± 3.6 for the control group ($p = 0.032$), consistent with greater neuropathy severity in the intervention arm (Fig. 2a). The TNSr remained worse for the intervention group at 12-week post-chemotherapy with a score of 8.5 ± 2.5 in comparison with 6.5 ± 3.9 for the control group ($p = 0.09$).

**Table 1** Clinical characteristics

| Characteristic | Placebo | Riluzole |
|---|---|---|
| *N* | 23 | 25 |
| Age mean (SD) | 55.5 (13.7) | 60.5 (11.4) |
| Range | 31–76 | 37–80 |
| Sex | | |
| Female | 8 (34.8%) | 9 (36.0%) |
| Male | 15 (65.2%) | 16 (64.0%) |
| Cancer | | |
| Appendix | 1 (4.3%) | – |
| Caecum | 1 (4.3%) | 2 (8.0%) |
| Colon | 13 (56.5%) | 13 (52.0%) |
| Duodenum | 1 (4.3%) | |
| Pancreas | – | 1 (4.0%) |
| Rectum | 7 (30.4%) | 7 (28.0%) |
| Unknown primary | – | 2 (8.0%) |
| Oxaliplatin | | |
| Mean dose mg (SD) | 1346.4 (390.6) | 1377.2 (475.45) |
| Mean cycles completed (IQR) | 10 (7–11.5) | 10 (9–11) |
| Dose intensity (mg/m$^2$/week) (SD) | 40.6 (3.8) | 41.6 (3.2) |
| Patients with dose reduction | 9 (39.0%) | 15 (60.0%) |
| Chemotherapy frequency | | |
| 2 weekly (*n*) | 23 | 24 |
| 3 weekly (*n*) | 0 | 1 |
| Diabetes | 3 (13.0%) | 4 (16.0%) |

## Secondary outcome measures

There was a progressive reduction in the peak sural nerve sensory amplitude between both groups from a baseline mean ± SD of 11.9 ± 4.5 μV for the intervention group and 15.6 ± 6.6 μV for the control group to 3.5 ± 2.7 μV and 4.1 ± 4.0 μV at 12-week post-chemotherapy but no statistically significant was noted in the extent of peak decline between groups (Fig. 2b). Tibial nerve conduction responses were stable across the treatment and follow-up period. However, mixed model analyses revealed a statistically significant difference in tibial amplitude at 4-week post-chemotherapy with 11.7 ± 3.7 mV for the intervention group compared with 9.5 ± 4.0 mV ($p = 0.057$, Fig. 2c) for the control group, although mean values for both groups were within the normative range. Sensory nerve excitability studies were conducted on the median nerve to examine nerve membrane potential. Following repeated measures analysis, refractoriness at 2.5 ms was reduced for both groups indicating altered nerve excitability during treatment but at 4 week post-treatment, refractoriness remained lower for the intervention group at 7.1 ± 15.1% threshold while the control group recovered to 18.7 ± 19.7% ($p = 0.049$; Supplementary Fig. 1b). There were no other statistical differences at any time points for any measures of nerve excitability (Supplementary Table 1).

Functional testing using the 9-hole peg test at baseline was 23.3 ± 5.3 s duration for the intervention group and 23.1 ± 5.9 s for the control group (Supplementary Fig. 1d). There were no significant differences across any time points and following repeated measures. Patient reported outcomes for neuropathy were assessed using the FACT-GOG-NTX. The baseline mean score for two groups was similar with patients in the intervention group scoring 49.4 ± 2.6 points and control group scoring 50.6 ± 1.8 points. There was a consistent worsening of FACT-GOG scores for both groups during treatment, with a statistically significant difference between the two groups only at 4-week post-chemotherapy. The intervention group reported worse perceived neuropathic symptoms with a reduced score of 37.4 ± 10.2 points in comparison with the control group with 43.3 ± 7.4 points ($p = 0.02$, Fig. 2d). This difference did not persist at 12-week post-chemotherapy.

# Discussion

The present study was the first to investigate the neuroprotective potential of riluzole in patients receiving oxaliplatin treatment. Although there was convincing evidence to suggest the

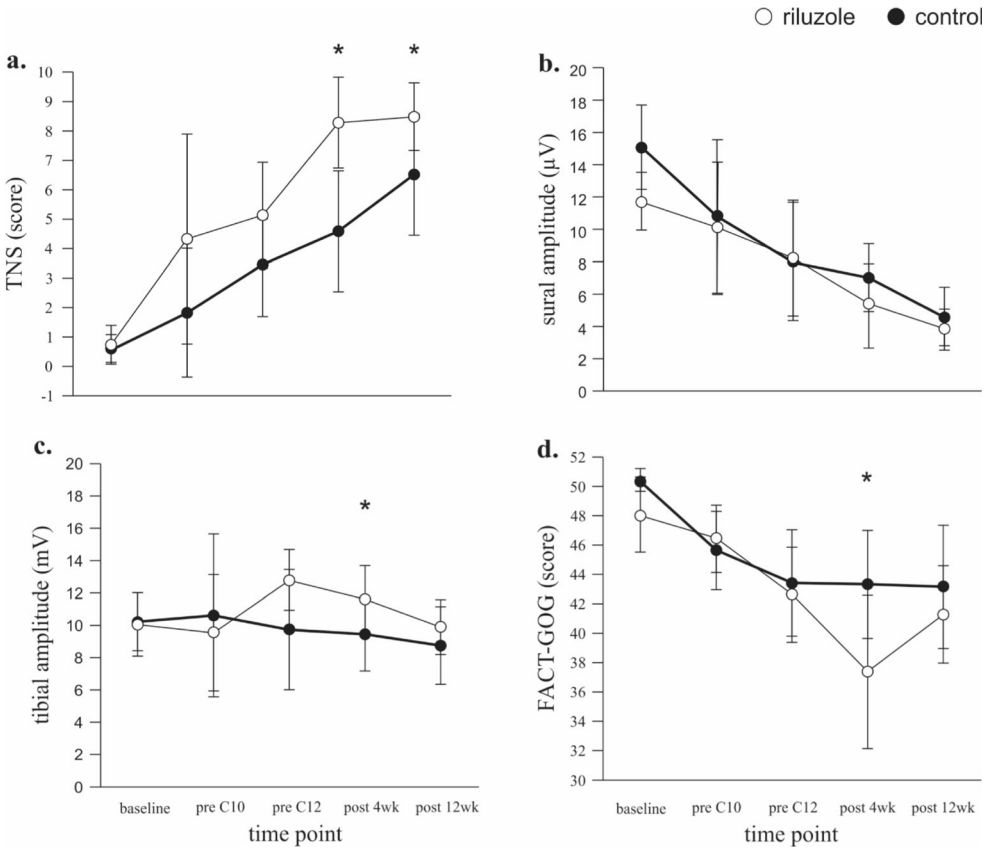


**Fig. 2** Total Neuropathy Score and patient reported neuropathy symptoms. **a** Total neuropathy score continued to increase beyond the chemotherapy treatment period for both groups and was significantly higher for the riluzole group in the follow-up period. **b** Sural amplitude decreased following chemotherapy with no differences between the riluzole and control groups. **c** Tibial motor activity remained relatively stable across the assessment period. **d** Functional Assessment of Cancer Therapy-Gynaecologic Oncology Group-Neurotoxicity (FACT-GOG) questionnaire was reported as having worsening symptoms for the riluzole group in comparison to the control group at 4-week post-chemotherapy which resolved at 12-week post-chemotherapy

actions of riluzole may be beneficial in oxaliplatin chemotherapy treatment, we were unable to demonstrate neuroprotection that was superior to placebo. The primary end point of 4-week post-chemotherapy suggested that there were worsening objective and subjective outcomes in the riluzole group as represented by a greater TNSr and lower FACT-GOG score, respectively.

Analysis of secondary outcomes measures demonstrated no significant change in the nine-hole peg test, a measure of upper limb functional dexterity. Nerve excitability measures demonstrated a difference only in refractoriness, a marker of recovery from inactivation of nodal transient $Na^+$ channels. However, previous work has failed to demonstrate an effect of riluzole alone on refractoriness or the relative refractory period [34]. Accordingly, changes in refractoriness independent of any change in threshold electrotonus or superexcitability may be due to inter-individual patient factors such as ion channel properties or skin temperature fluctuations [31], reflected by a single time-point difference at 4-week post-chemotherapy which did not persist at 12-week post-chemotherapy. Similarly, tibial nerve amplitude did not vary greatly across the testing period and this was expected as oxaliplatin produces a sensory neuropathy [7]. The significant difference observed at 4-week post-chemotherapy may be a reflection of the sample size as there were no sustained differences at 12-week post-chemotherapy and mean values for both groups remained within the normal range. Although we did not observe any significant changes in patients treated with riluzole during the test period, neuropathic symptoms did not appear to improve by the 12-week period and future studies may benefit from observing the rate of recovery across the two test groups in a longer follow-up period.

It is difficult to pinpoint the exact mechanisms underlying the greater neuropathy severity in the riluzole arm. Riluzole is known to target a number of pathways, including $Ca^{2+}$ channels, glutamatergic pathways and both persistent and transient $Na^+$ channels [19, 34–36]. In addition to $Na^+$ channels, riluzole causes reversible $Ca^{2+}$ channel blockade and specifically targets the alpha-2 subunit [37] as well as having effects on $K^+$ channels including TREK channels [24]. Several previous trials have examined the effects of other $Na^+$ channel blockers on oxaliplatin neurotoxicity. A previous study of the $Na^+$ channel blocker, oxcarbazepine, demonstrated maintenance of nerve conduction peak amplitude in sural and peroneal nerves [38], although long-term follow-up assessments were not available to assess the long-term effects of neuropathy outcomes. Oxcarbazepine has a different effect to riluzole on $Na^+$ channels and acts on processes relating to high frequency firing [39, 40]. However, its analogue carbamazepine did not exhibit beneficial effects on oxaliplatin treated patients, with no evidence of preservation of nerve conduction amplitudes [41]. In previous animal studies, riluzole has

shown efficacy in preventing the development of oxaliplatin-induced neurotoxicity [22–24]. However, this is the first study to investigate riluzole in combination with oxaliplatin treatment in a clinical cohort, and previous investigations have been on rodent models which are often not predictive of outcomes in neuroprotective trials. While it remains possible that there may be a synergistic effect of riluzole and oxaliplatin on sodium channel kinetics which may exacerbate axonal degeneration, previous trials of sodium channel blockers in oxaliplatin-treated patients have not demonstrated worsening of neuropathy outcomes. However, there are many individual factors which govern the development and severity of CIPN, including multiple genetic contributors which are not fully characterized. Given the limited sample size, it is possible that intrinsic variation in neuropathy outcomes developed between the cohorts led to more severe neuropathy in the riluzole arm.

The present study design incorporated multiple methods of neuropathy assessment, including patient reported outcomes and objective assessment tools, in line with recommended trial protocols [42]. However, our study did not identify any benefits of riluzole treatment—with treated patients developing worse patient reported and clinical outcomes at 4-week post-oxaliplatin treatment. While it is acknowledged that sample size considerations may impact the study power, it is important to note that several prior neuroprotection trials have identified unexpected worsening of neuropathy compared with placebo in chemotherapy-treated patients [43, 44]. This is an important consideration for future trials, as the possibility of detrimental effects may necessitate the addition of interim analyses. Of note, there is currently an ongoing study of riluzole treatment in oxaliplatin-treated patients [45] which may benefit from such analyses.

In conclusion, although there was a good rationale to suggest that riluzole could prevent oxaliplatin-induced peripheral neuropathy, this was not supported by the findings of this randomised trial. Using both functional and neurophysiological testing methods, we identified no benefit of riluzole on the severity of neuropathy during chemotherapy treatment and up to 12 week post-treatment.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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