Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online October 8, 2013

DOI: 10.1634/theoncologist.2013-0061

Title: A Double-Blind, Randomized Phase II Study to Evaluate the Safety and Efficacy of Acetyl-L-Carnitine in the Prevention of Sagopilone-Induced Peripheral Neuropathy (REASON)

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ClinicalTrials.gov Identifier: NCT00751205

Sponsor(s): Bayer HealthCare Pharmaceuticals

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IRB Approved: Yes

Disclosures:
Natasja de Bont, Marjan van Dijk, Mario Campone, Dominique Berton-Rigaud, Jean-Francois Baurain, Frédéric Rolland, Michel Fabbro: None Reported
Florence Joly-Lobbedez: Consultant/Advisory Role: Sanofi, Novartis, Roche, Astellas, Janssen, Pfizer
Arnulf Stenzl: Consultant/Advisory Role: Novartis, Amgen, Alere; Research Funding/Contracted Research: Novartis
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Patricia Pautier: Consultant/Advisory Role: Roche

Author Summary: Abstract and Brief Discussion

Background
Peripheral neuropathy (PN) is a recognized side effect of microtubule-targeting agents and the most clinically relevant toxicity observed with the epothilone sagopilone (SAG). Studies suggest that acetyl-L-carnitine (ALC) may prevent chemotherapy-induced PN. We conducted a prospective, placebo (PBO)-controlled, double-blind, randomized trial to investigated the safety and efficacy of ALC for the prevention of SAG-induced PN.

Methods

Patients with ovarian cancer (OC) or castration-resistant prostate cancer (CRPC) and no evidence of neuropathy received SAG (16 mg/m^2 intravenously over 3 hours every 3 weeks) with ALC (1,000 mg every 3 days) or placebo (PBO). The primary endpoint was incidence of PN within six of fewer cycles in both treatment groups.

Results

Overall, 150 patients enrolled (98 OC patients, 52 CRPC patients), with 75 per treatment arm. No significant difference in overall PN incidence was observed between treatment arms. The incidence of grade ≥3 PN was significantly lower in the ALC arm in OC patients. Median duration of neuropathy was similar between treatment arms. The best overall response (according to the modified Response Evaluation Criteria in Solid Tumors), response according to tumor markers, time-to-event variables, and discontinuations because of adverse events (AEs) were comparable between treatment arms.

Conclusions

Administration of ALC with SAG did not result in a significant difference in overall PN incidence compared with a PBO. OC patients in the SAG/ALC arm had a significantly lower incidence of grade 3 or 4 PN compared with OC patients in the SAG/PBO arm.

Discussion

In this first randomized, prospective study of ALC for the prevention of chemotherapy-induced PN, no significant difference was observed in PN incidence between the two treatment arms. Consistent with previous clinical findings, however, ALC appeared to significantly reduce the incidence of high-grade neuropathy. Consequently, ALC given concurrently with SAG appears to significantly reduce the intensity of neurotoxicity but not the incidence. The reasons for the greater reduction in high-grade neuropathy in patients with recurrent OC, compared with those with CRPC, are not entirely clear. Almost all patients in this study had received prior taxane-based therapy, and it is possible that some patients developed taxane-induced PN diagnosed only after taxane cessation. A previously published SAG clinical study of patients with OC, however, suggested that SAG-induced PN does not appear to correlate with prior taxane treatment [1]. Our study supports previously reported safety findings that demonstrated SAG to be well tolerated by patients with CRPC or OC. PN was the most commonly reported grade ≥3 AE in our study, as also reported in earlier studies [1–6]. Incidence and types of AEs were broadly similar across treatment arms, with slightly more serious AEs and grade 3 or 4 AEs reported in the SAG/PBO arm. Few patients reported ALC-related AEs, and, consistent with previous studies, ALC appears to be very well tolerated [7, 8]. In our study, there was no notable difference in response, progression-free survival, or time to progression between the two treatment arms. This finding suggests that, consistent with previous clinical reports in patients treated with taxanes, ALC did not appear to compromise the antitumor activity of SAG [7, 8]. In conclusion, our study findings are encouraging regarding the therapeutic role of ALC in combination with SAG.

Trial Information

Disease:	Ovarian cancer
Disease:	Prostate Cancer
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	No designated number of regimens
Type of study - 1:	Phase II
Type of study - 2:	Randomized

Additional Details of Endpoints or Study Design:	This study was designed to evaluate the use of acetyl-L-carnitine (ALC) for the prevention of sagopilone-induced peripheral neuropathy (PN) in patients with OC or CRPC. The primary objective was to determine if the addition of ALC to sagopilone resulted in a lower overall incidence of PN compared with sagopilone plus placebo. Secondary objectives were to assess the safety and efficacy of sagopilone plus ALC. Eligible patients were randomized to receive a 3-hour infusion every 3 weeks of 16 mg/m^2 sagopilone plus either oral ALC (1000 mg three times a day) or an oral ALC-matching placebo (three times a day) for six treatment courses, and more than six based on investigator decision. ALC/placebo was continued for 30–33 days following the last sagopilone treatment. Patients with CRPC also received oral prednisone (5 mg every 2 days), as low-dose prednisone is known to improve quality of life in patients receiving chemotherapy.
Investigator's Analysis:	Correlative endpoints not met but clinical activity observed

Drug Information

Drug 1: **Generic/Working name:**	Sagopilone
Trade name:	
Company name:	
Drug type:	
Drug class:	Microtubule-targeting agent
Dose:	per
Route:	
Schedule of Administration:	
Drug 2: **Generic/Working name:**	Acetyl-L-carnitine (ALC)
Trade name:	
Company name:	
Drug type:	
Drug class:	Other
Dose:	per
Route:	
Schedule of Administration:	

Patient Characteristics

Number of patients, male:	52
Number of patients, female:	98
Stage:	Patients with prostate cancer: Median Gleason total score = 8 (range, 4–10). Patients with ovarian cancer: International Federation of Gynecology and Obstetrics staging system Stage I = 7 (7%), Stage II = 6 (6%), Stage III = 68 (69%) and Stage IV= 17 (18%)
Age:	Median (range): 62 (29–82) years

Number of prior systemic therapies:	Median (range): Not Collected
Performance Status:	ECOG ● 0 — ● 1 — ● 2 — ● 3 — ● unknown —
Other:	Not Collected
Cancer Types or Histologic Subtypes:	

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened:	188
Number of patients enrolled:	150
Number of patients evaluable for toxicity:	150
Number of patients evaluated for efficacy:	150
Evaluation method:	Other

Control Arm: Total Patient Population

Evaluation method:	Other

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades

*No Change from Baseline/No Adverse Event

Assessment, Analysis, and Discussion

Completion: Study completed

Pharmacokinetics / Pharmacodynamics: Not Collected

Investigator's Assessment: Correlative endpoints not met but clinical activity observed

Discussion

The REASON study is the first randomized, prospective clinical trial to examine the use of ALC for the prevention of sagopilone-induced PN. The primary endpoint was not met, as no statistically significant difference in PN incidence was observed between the two treatment arms. However, the incidence of higher-grade neuropathies was significantly reduced by ALC, with the most marked effect in patients with recurrent OC. The clinical features of CIPN depend on the chemotherapy agent used and range from predominantly motor or sensory to sensory-motor neuropathies, with or without autonomic impairment [9]. CIPN onset can result in chronic discomfort and severe impediment of quality of life. CIPN is an ongoing issue in the management of oncology patients. Survival rates for treated patients are improving, and the presence of debilitating or long-lasting iatrogenic adverse events (AEs) is a recognized challenge requiring new strategies. The reduction of CIPN incidence by ALC was initially demonstrated pre-clinically [10]. Subsequent clinical studies reported a reduction in CIPN severity with concurrent ALC treatment by at least one grade in patients with cisplatin- or paclitaxel-induced CIPN, without apparent effect on antitumor activity [7, 8]. However, in a randomized phase III study

investigating ALC for the prevention of neuropathy in patients receiving adjuvant taxane-based chemotherapy for stage I/II/IIIA breast cancer, there was no evidence that ALC improved CIPN [11]. In our study, no significant difference was observed in PN incidence between the two treatment arms. However, consistent with previous clinical findings, ALC did appear to significantly reduce the incidence of high-grade neuropathy. Therefore, ALC given concurrently with sagopilone appears to significantly reduce the intensity of neurotoxicities, but not the incidence. Reasons for the greater reduction in high-grade neuropathy in patients with recurrent OC, compared with those with CRPC, are not entirely clear. Almost all patients in this study had received prior taxane-based therapy, and it is possible that some patients developed taxane-induced PN diagnosed only after taxane cessation. However, a previously published sagopilone clinical study of patients with OC suggested that sagopilone-induced PN does not appear to correlate with prior taxane treatment [1]. Findings may be influenced by other factors, including agents known to be associated with CIPN, gender, or disease. Other previous sagopilone studies have reported a PN incidence of 74% in taxane-naïve CRPC patients and 76% in previously treated OC patients [2, 12]. Overall, our study supports previously reported safety findings that demonstrated sagopilone to be well tolerated in patients with CRPC or OC. PN was the most commonly reported grade $\geq$3 AE in our study, as also reported in earlier studies [1–6]. The incidence and type of AEs were broadly similar across treatment arms, with slightly more serious AEs and grade 3 or 4 AEs reported in the sagopilone/placebo arm. Few patients reported ALC-related AEs and, consistent with previous studies, ALC appears to be very well tolerated [7, 8]. In our study, there was no notable difference in response, progression-free survival, or time to progression between the two treatment arms, suggesting that, consistent with previous clinical reports in patients treated with taxanes, ALC did not appear to compromise the antitumor activity of sagopilone [7, 8]. In conclusion, our study findings are encouraging regarding the therapeutic role of ALC in combination with sagopilone. The addition of ALC to primary chemotherapy agents to minimize CIPN warrants further and wider investigation.

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Figures and Tables

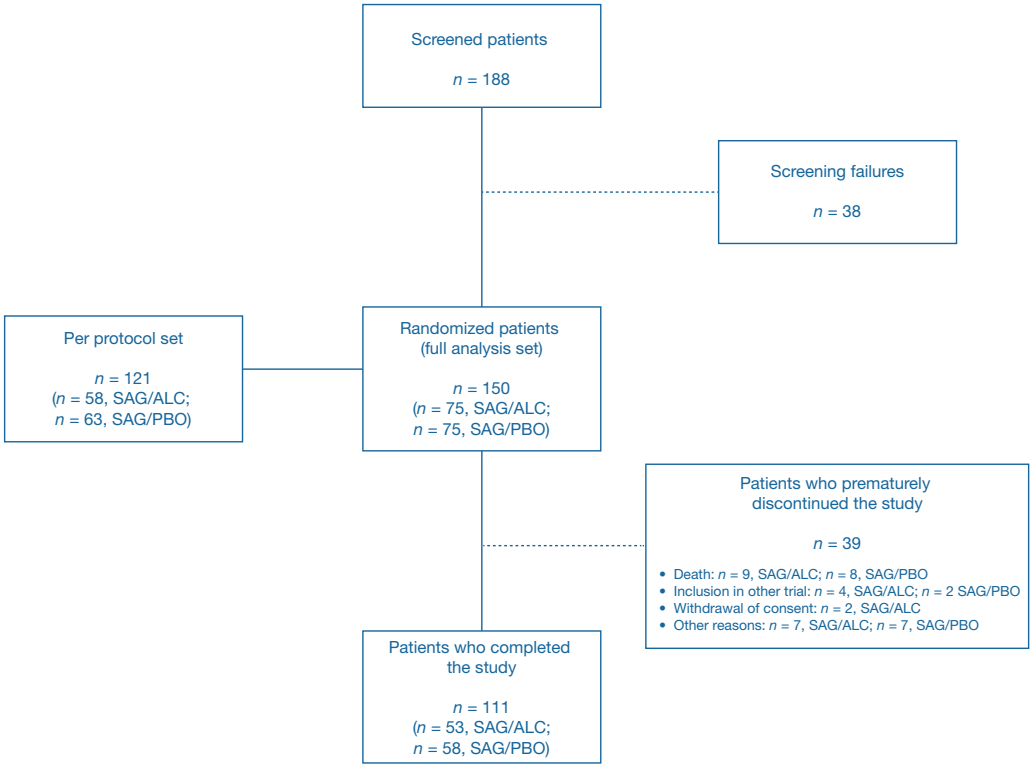

Figure 1. CONSORT diagram.
Abbreviations: ALC, acetyl-L-carnitine; PBO, placebo; SAG, sagopilone.

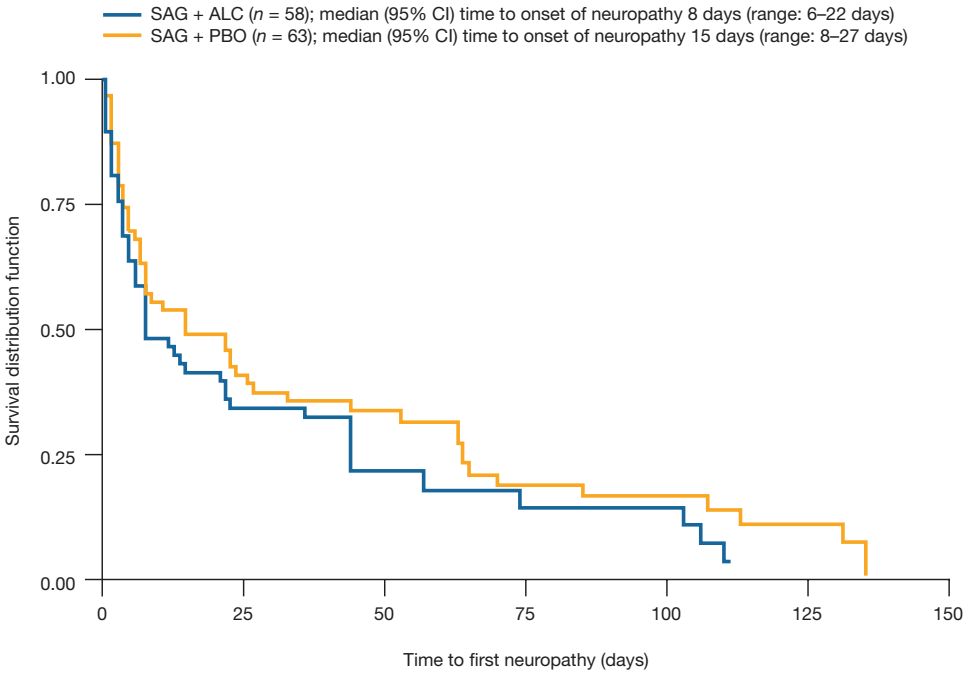

Figure 2. Time to recovery from neuropathy (per protocol set).
Abbreviations: ALC, acetyl-L-carnitine; CI, confidence interval; PBO, placebo; SAG, sagopilone.

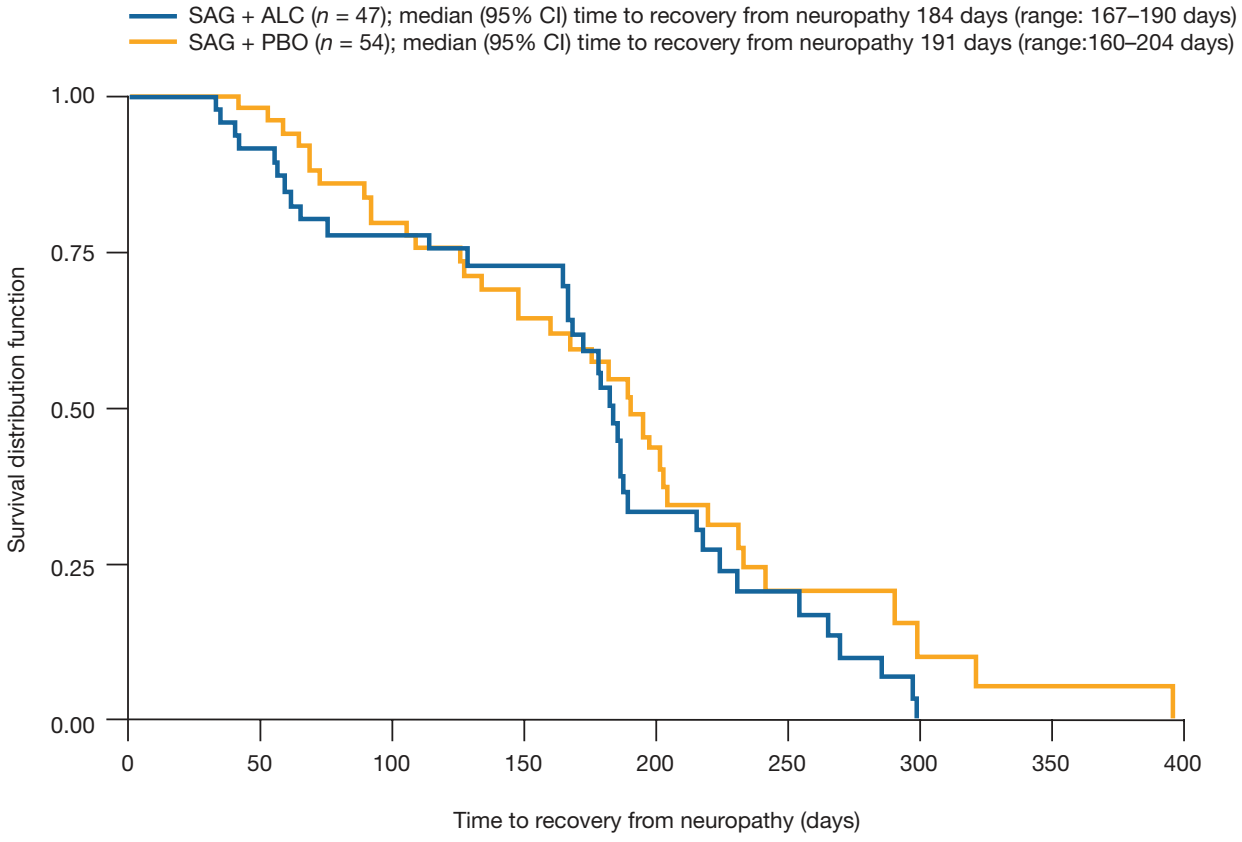

Figure 3. Time to onset of neuropathy (per protocol set).
Abbreviations: ALC, acetyl-L-carnitine; CI, confidence interval; PBO, placebo; SAG, sagopilone.

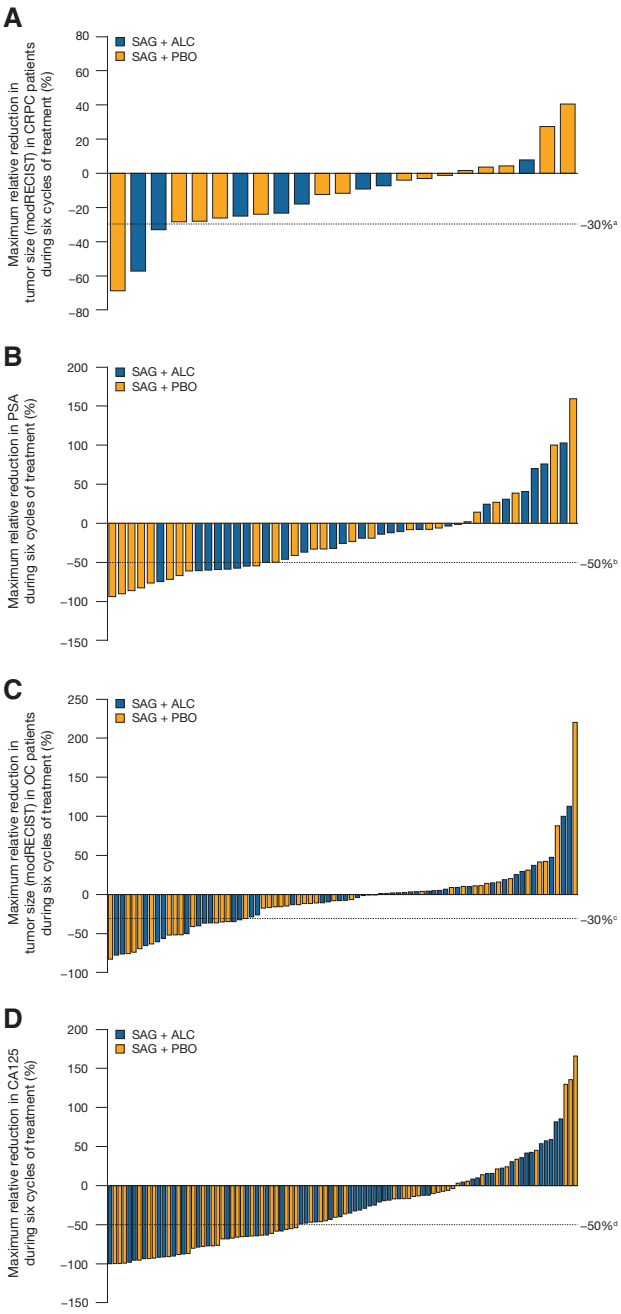

Figure 4. Maximum relative reduction in: A) tumor size by modRECIST in CRPC patients; B) PSA levels; C) tumor size by modRECIST in OC patients; and D) CA125 levels, during six cycles of treatment (full analysis set). [a]Indicates a reduction of over 30% in tumor size compared with baseline; [b]Response was defined as a 50% reduction in PSA within 3 months compared with baseline; [c]Indicates a reduction of over 30% in tumor size compared with baseline; [d]Response was defined as a 50% reduction in CA125 within 3 months compared with baseline.

Abbreviations: ALC, acetyl-L-carnitine; CRPC, castration-resistant prostate cancer; modRECIST, modified Response Evaluation Criteria in Solid Tumors; OC, ovarian cancer; PBO, placebo; PSA, prostate-specific antigen; SAG, sagopilone.

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