Original Article

# Efficacy of the Neurokinin-1 Receptor Antagonist Rolapitant in Preventing Nausea and Vomiting in Patients Receiving Carboplatin-Based Chemotherapy

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**BACKGROUND:** Rolapitant, a novel neurokinin-1 receptor antagonist, provided effective protection against chemotherapy-induced nausea and vomiting (CINV) in a randomized, double-blind phase 3 trial of patients receiving moderately emetogenic chemotherapy or an anthracycline and cyclophosphamide regimen. The current analysis explored the efficacy and safety of rolapitant in preventing CINV in a subgroup of patients receiving carboplatin. **METHODS:** Patients were randomized 1:1 to receive oral rolapitant (180 mg) or a placebo 1 to 2 hours before chemotherapy administration; all patients received oral granisetron (2 mg) on days 1 to 3 and oral dexamethasone (20 mg) on day 1. A post hoc analysis examined the subgroup of patients receiving carboplatin in cycle 1. The efficacy endpoints were as follows: complete response (CR), no emesis, no nausea, no significant nausea, complete protection, time to first emesis or use of rescue medication, and no impact on daily life. **RESULTS:** In the subgroup administered carboplatin-based chemotherapy (n = 401), a significantly higher proportion of patients in the rolapitant group versus the control group achieved a CR in the overall phase (0-120 hours; 80.2% vs 64.6%; $P < .001$) and in the delayed phase (>24-120 hours; 82.3% vs 65.6%; $P < .001$) after chemotherapy administration. Superior responses were also observed by the measures of no emesis, no nausea, and complete protection in the overall and delayed phases and by the time to first emesis or use of rescue medication. The incidence of treatment-emergent adverse events was similar for the rolapitant and control groups. **CONCLUSIONS:** Rolapitant provided superior CINV protection to patients receiving carboplatin-based chemotherapy in comparison with the control. These results support rolapitant use as part of the antiemetic regimen in carboplatin-treated patients. ***Cancer* 2016;122:2418-25**. 

**KEYWORDS:** carboplatin, chemotherapy-induced nausea and vomiting, moderately emetogenic chemotherapy, neurokinin-1 receptor antagonist, rolapitant.

## INTRODUCTION

Progress in our understanding of the pathophysiology of chemotherapy-induced nausea and vomiting (CINV) has led to therapeutic advances and improved antiemetic prophylaxis strategies.[1,2] For patients with cancer who receive highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC), 5-hydroxytryptamine type 3 (5-$HT_3$) receptor antagonists (RAs) have demonstrated efficacy in CINV control during the acute phase ($\leq$24 hours). However, the utility of 5-$HT_3$ RAs with or without dexamethasone for controlling CINV in the delayed phase (>24-120 hours) is limited.[1,3]

Antiemetic guidelines recommend the addition of a neurokinin-1 (NK-1) RA for patients receiving HEC on the strength of well-controlled trials demonstrating the benefit of these agents in CINV prevention.[4-6] Guidelines currently recommend that a 5-$HT_3$ RA and dexamethasone be used in all patients receiving MEC and that patients with additional CINV risk factors also receive an NK-1 RA.[4,5]

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The MEC category includes chemotherapeutic agents with an emetic potential ranging from 30% to 90%.[4,6] Carboplatin, a second-generation platinum analog, has an emetic potential greater than that of many agents classified as MEC.[4,7] According to a natural history study, without antiemetic prophylaxis, 89% of carboplatin-treated patients experienced some degree of nausea, and 82% of patients vomited.[7] Carboplatin is also associated with a risk of delayed emesis.[8,9] In an assessment of carboplatin-induced emesis patterns, a greater proportion of patients experienced vomiting in the delayed phase versus the acute phase after carboplatin administration despite ondansetron treatment (37% experienced delayed vomiting, whereas 22% experienced acute vomiting); delayed nausea was reported by 82% of patients.[8] Another study found that despite prophylaxis with a 5-$HT_3$ RA and dexamethasone, more than a third of patients with cancer treated with carboplatin experienced moderate-to-severe delayed CINV.[9] Because of the emetic risk associated with carboplatin, there is a need to improve CINV protection in patients administered carboplatin-based chemotherapy.

Rolapitant (VARUBI®; TESARO, Inc, Waltham, Mass) is a highly selective, long-acting NK-1 RA that was recently approved by the US Food and Drug Administration for use in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC.[10] Rolapitant does not induce or inhibit the cytochrome P450 3A4 (CYP3A4) enzyme; therefore, dose adjustments of dexamethasone and certain other concomitantly administered medications metabolized by CYP34A are not required.[10,11]

Recently updated National Comprehensive Cancer Network antiemetic guidelines support the use of rolapitant (category 1 level of evidence and consensus) to protect against CINV in both patients with cancer receiving HEC and select patients receiving MEC.[4] The inclusion of rolapitant in the antiemetic guidelines was based on the results of 3 large, global, randomized, double-blind, controlled phase 3 studies demonstrating that oral rolapitant combined with a 5-$HT_3$ RA and dexamethasone was superior to a 5-$HT_3$ RA and dexamethasone alone in providing CINV protection in the delayed phase to patients receiving HEC or MEC.[12,13] The MEC trial was designed before antiemetic guidelines reclassified anthracycline and cyclophosphamide (AC)–based regimens as HEC; therefore, the MEC trial included AC-based chemotherapy in the analysis along with other MEC regimens as prespecified in the study protocol.[12] In all, 52.8% of the patients received AC-based chemotherapy in the MEC trial, and 30.1% received carboplatin-based chemotherapy; the remaining patients received a broad range of other MEC agents. The purpose of this analysis was to evaluate whether the addition of rolapitant provided protection against CINV in the large subgroup of patients who received carboplatin-based chemotherapy in the phase 3 MEC trial.

## MATERIALS AND METHODS

### *Study Design and Patients*

A global, multicenter, randomized, parallel-group, double-blind, controlled phase 3 study (NCT01500226) was conducted in 23 countries in North America, Central and South America, Europe, Asia, and Africa.[12] The protocol was approved by institutional review boards at each study site, all patients provided written informed consent, and all investigators and site personnel were required to follow ethical principles outlined in the Declaration of Helsinki and consistent with the International Conference on Harmonisation Good Clinical Practice guidelines and applicable local laws and regulations.

To be eligible for the phase 3 study, male and female patients were required to be 18 years old or older, naive to MEC or HEC, and scheduled to receive their first course of 1 or more of the following agents alone or in combination with other chemotherapeutics: intravenous cyclophosphamide ($<1500$ mg/m$^2$), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, and intravenous cytarabine ($>1$ g/m$^2$). The study protocol prespecified that at least 50% of the patients enrolled in the study would receive AC-based therapy.

Patients were required to have a Karnofsky performance score $\geq$ 60%, a predicted life expectancy $\geq$ 4 months, and adequate bone marrow, kidney, and liver function. Before the study treatment, patients were not permitted to use any of the following medications: 5-$HT_3$ RAs, phenothiazines, benzamides, domperidone, cannabinoids, NK-1 RAs, or benzodiazepines within 48 hours; palonosetron within 7 days; or systemic corticosteroids or sedative antihistamines (eg, dimenhydrinate or diphenhydramine) within 72 hours of day 1 with the exception of premedication for chemotherapy (eg, taxanes).

### *Treatment*

A central, interactive, Web-based system was used to randomly assign patients in a 1:1 ratio, stratified by sex, to the rolapitant or control treatment group, as shown in Figure 1. Blinding was maintained throughout the study

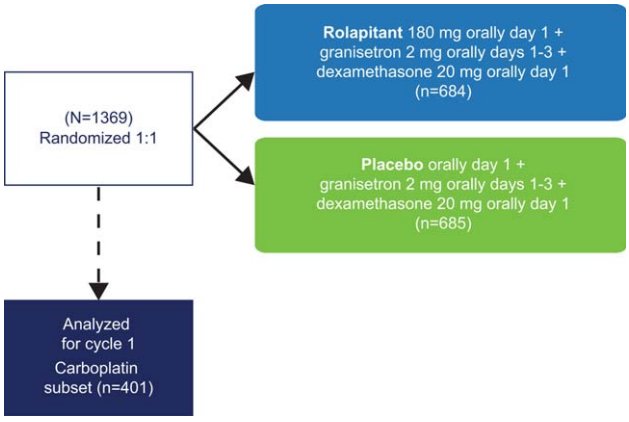


**Figure 1.** Treatment schema. Patients received a single oral dose of rolapitant (180 mg) or matching placebo capsules 1 to 2 hours before the administration of chemotherapy on day 1. All patients received granisetron plus dexamethasone before chemotherapy administration on day 1; granisetron was also administered once daily on days 2 and 3. Patients who were administered taxanes received dexamethasone according to the package insert.

(cycles 1-6). After cycle 1, patients were allowed to continue the same treatment regimen in a blinded fashion for up to 5 additional cycles.

### *Efficacy and Safety Assessments*

During the first 120 hours (5 days) after the administration of chemotherapy, patients recorded all events of vomiting and use of rescue medication in a daily diary. Patients also self-assessed nausea daily with a 100-mm horizontal visual analog scale (VAS; Supporting Fig. 1 [see online supporting information]).

The subgroup of patients who received carboplatin-based chemotherapy were evaluated for the following efficacy endpoints for cycle 1: complete response (CR; defined as no emesis and no use of rescue medication) in the overall phase (0-120 hours), CR in the acute phase ($\leq$24 hours), and CR in the delayed phase (>24-120 hours). Other efficacy endpoints examined in all phases were no emesis, no significant nausea (maximum VAS score $<$ 25 mm), no nausea (maximum VAS score $<$ 5 mm), and complete protection (no emesis, no rescue medication, and maximum VAS score $<$ 25 mm). The time to first emesis or use of rescue medication and no impact on daily life were also evaluated. The assessment of no impact on daily life was examined with the Functional Living Index–Emesis (FLIE) questionnaire, a validated measure of the impact of CINV symptoms on daily life.[14,15] Patients completed the FLIE questionnaire on day 6 during cycle 1. Responses for each of 9 questions on nausea and 9 questions on vomiting were marked on a 7-point VAS. We calculated the nausea score, vomiting score, and total score by summing the responses within each subdomain individually and in combination. No impact on daily life was defined as an average item score $>$ 6 on the 7-point scale (>108 for the total score).[15] Efficacy for the measure of CR in the overall phase was also evaluated by sex and age.

Safety variables included treatment-emergent adverse events (TEAEs), physical and neurological examinations, vital signs, electrocardiograms, and clinical laboratory results.

### *Statistical Analysis*

Patients in the modified intent-to-treat population (ie, patients who received at least 1 dose of the study drug of the phase 3 MEC trial and were enrolled at a Good Clinical Practice–compliant site) who received carboplatin-based chemotherapy were included in the post hoc analysis of efficacy. The results are presented for cycle 1 of chemotherapy.

Between-group comparisons of efficacy endpoints were conducted with the Cochran-Mantel-Haenszel $\chi^2$ test. The time to first emesis or use of rescue medication was summarized with Kaplan-Meier methodology, and the between-group treatment comparison was conducted with a log-rank test. Subgroup analyses were not prospectively powered and thus may have lacked the power to demonstrate statistical significance. $P$ values $<$ .05 were considered to be statistically significant and were not adjusted for multiplicity.

The safety population consisted of all randomized patients in the carboplatin subgroup who received at least 1 dose of the study drug.

## RESULTS

### *Patients*

Of the 1332 patients who composed the modified intent-to-treat population for the phase 3 MEC trial, 401 received their first course of chemotherapy with a carboplatin-based regimen and were included in the efficacy analysis for cycle 1. Baseline and disease characteristics were similar for patients in the rolapitant and control groups, as shown in Table 1. The median age of the patients was 62 years, and more patients were female (54.9%) than male (45.1%). The primary malignancy among patients treated with carboplatin-based chemotherapy was lung cancer (52.1%); other malignancies included ovarian, breast, and uterine cancer (13.7%, 13.7%, and 7.7%, respectively). The receipt of concomitant emetogenic chemotherapy with a Hesketh level $\geq$ 3 was low and occurred in 15.7% of the patients.

**TABLE 1.** Patient Baseline and Disease Characteristics

| Characteristic | Rolapitant 180 mg (n = 192) | Control (n = 209) |
|---|---|---|
| Age, median (range), y | 61 (31–83) | 64 (23–88) |
| Sex, No. (%) | | |
| Female | 104 (54.2) | 116 (55.5) |
| Male | 88 (45.8) | 93 (44.5) |
| Alcohol consumption, No. (%)[a] | | |
| 0 to ≤5 drinks/wk | 176 (92.1) | 184 (88.0) |
| >5 drinks/wk | 15 (7.9) | 25 (12.0) |
| Primary tumor site, No. (%) | | |
| Lung | 97 (50.5) | 112 (53.6) |
| Ovary | 33 (17.2) | 22 (10.5) |
| Breast | 21 (10.9) | 34 (16.3) |
| Uterus | 13 (6.8) | 18 (8.6) |
| Head and neck | 3 (1.6) | 4 (1.9) |
| Other | 25 (13.0) | 19 (9.1) |
| Receipt of concomitant emetogenic chemotherapy, No. (%)[b] | | |
| Yes | 26 (13.5) | 37 (17.7) |
| No | 166 (86.5) | 172 (82.3) |

[a] Based on self-reported data (191 patients in the rolapitant group).
[b] Hesketh level ≥ 3.

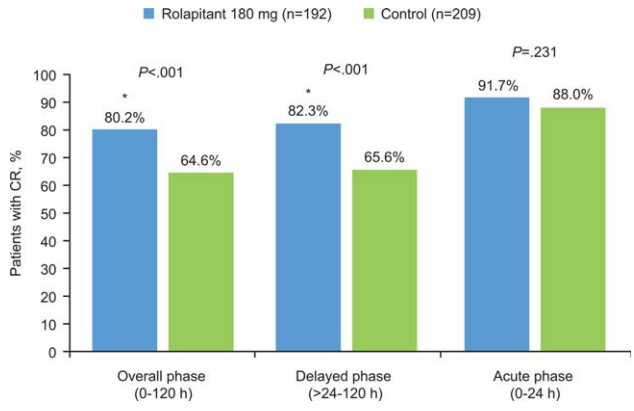


**Figure 2.** Complete response. The bar graph shows the percentages of patients who experienced a CR in the overall phase (0-120 hours), the delayed phase (>24-120 hours), and the acute phase (≤24 hours). An asterisk indicates a statistically significant difference versus the control. The presented *P* values are unadjusted. CR indicates complete response.

### *Efficacy*

Among patients who received carboplatin-based chemotherapy, a significantly higher proportion of patients in the rolapitant group versus the control group achieved a CR in the overall phase (80.2% vs 64.6%; $P < .001$) and in the delayed phase (82.3% vs 65.6%; $P < .001$; Fig. 2). In the acute phase, very few patients experienced CINV, regardless of treatment, and no significant difference in the CR rate was observed between the groups (91.7% vs 88.0%; $P = .231$; Fig. 2).

Significantly higher response rates were achieved in the rolapitant group versus the control group by the measures of no emesis, no nausea, and complete protection in the overall phase and in the delayed phase (Table 2). A higher proportion of patients in the rolapitant group versus the control group experienced no significant nausea in the overall and delayed phases, although the differences did not reach statistical significance (Table 2). The effect of rolapitant was numerically greater than the control for most other assessed endpoints; however, these differences did not reach statistical significance (Table 2).

Across the 120-hour study period, the time to first emesis or use of rescue medication was significantly improved in the rolapitant group versus the control group ($P < .001$). Kaplan-Meier curves showed that the separation of the curves was greatest in the delayed phase (Fig. 3), and this was consistent with the CR rates for the overall study population. The separation of the curves became pronounced after 48 hours and was sustained through 120 hours.

According to the FLIE patient-reported outcome tool, a higher proportion of patients in the rolapitant group versus the control group reported no impact on daily life (FLIE total score > 108), but the difference did not reach statistical significance (86.1% vs 80.4%; $P = .145$).

An evaluation of patient factors associated with CINV risk (sex and age[1,2]) was also examined for the measure of CR in the overall phase for the rolapitant and control groups. Consistent with the overall carboplatin subgroup analysis, responses favoring rolapitant over the control were maintained in the sex and age subgroups. Significantly higher percentages of male and female patients in the rolapitant group in comparison with sex-matched patients in the control group achieved a CR (Table 3). In addition, a greater proportion of patients in the rolapitant group versus the control group achieved a CR in each of the age subgroups examined (Table 3). The patient numbers in these subgroups were small; statistical significance was reached with rolapitant versus the control for patients aged 45 to <65 years, the age subgroup that contained the largest number of patients.

### *Safety and Tolerability*

The safety data set for patients administered carboplatin-based chemotherapy comprised 404 patients: 194 received rolapitant, and 210 received the control. The overall incidence of TEAEs in cycle 1 was similar between the rolapitant and control groups (Table 4). The frequencies of individual TEAEs were generally comparable between the rolapitant and control groups. No patients

**TABLE 2.** Additional Efficacy Endpoints

| | Rolapitant 180 mg (n = 192), No. (%) | Control (n = 209), No. (%) | Absolute Benefit, %[a] | $P$[b] |
|---|---|---|---|---|
| No emesis | | | | |
| Overall phase (0–120 h) | 168 (87.5) | 154 (73.7) | 13.8 | <.001 |
| Delayed phase (>24–120 h) | 169 (88.0) | 156 (74.6) | 13.4 | <.001 |
| Acute phase (≤24 h) | 179 (93.2) | 193 (92.3) | 0.9 | .733 |
| No significant nausea | | | | |
| Overall phase (0–120 h) | 155 (80.7) | 152 (72.7) | 8.0 | .059 |
| Delayed phase (>24–120 h) | 158 (82.3) | 155 (74.2) | 8.1 | .050 |
| Acute phase (≤24 h) | 174 (90.6) | 191 (91.4) | −0.8 | .790 |
| No nausea | | | | |
| Overall phase (0–120 h) | 120 (62.5) | 107 (51.2) | 11.3 | .023 |
| Delayed phase (>24–120 h) | 123 (64.1) | 112 (53.6) | 10.5 | .034 |
| Acute phase (≤24 h) | 155 (80.7) | 161 (77.0) | 3.7 | .366 |
| Complete protection | | | | |
| Overall phase (0–120 h) | 142 (74.0) | 124 (59.3) | 14.6 | .002 |
| Delayed phase (>24–120 h) | 146 (76.0) | 127 (60.8) | 15.3 | .001 |
| Acute phase (≤24 h) | 170 (88.5) | 179 (85.6) | 2.9 | .389 |
| No impact on daily life: overall phase (0–120 h)[c] | 155 (86.1) | 152 (80.4) | 5.7 | .145 |

[a] Rolapitant versus the control.
[b] The presented $P$ values are unadjusted.
[c] Based on data from 180 patients in the rolapitant group and 189 patients in the control group with a valid Functional Living Index–Emesis questionnaire obtained on day 6.

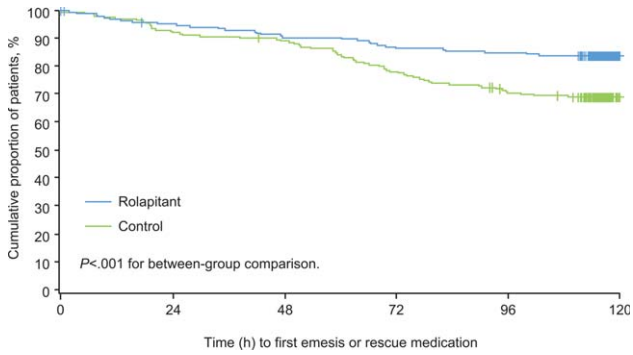


**Figure 3.** Time to first emesis or use of rescue medication. The Kaplan-Meier plot depicts the cumulative percentages of patients in the rolapitant and control groups who did not experience a first event of emesis or use rescue medication across the 120-hour study period. The presented $P$ values are unadjusted.

**TABLE 3.** Complete Response in the Overall Phase for Sex and Age Subgroups

| | Rolapitant 80 mg (n = 192), n/N (%) | Control (n = 209), n/N (%) | $P$[a] |
|---|---|---|---|
| Complete response by sex | | | |
| Female | 81/104 (77.9) | 72/116 (62.1) | .011 |
| Male | 73/88 (83.0) | 63/93 (67.7) | .018 |
| Complete response by age | | | |
| <45 y | 9/15 (60.0) | 8/15 (53.3) | .717 |
| 45 to <65 y | 94/109 (86.2) | 67/96 (69.8) | .004 |
| 65 to <75 y | 36/49 (73.5) | 40/66 (60.6) | .151 |
| ≥75 y | 15/19 (78.9) | 20/32 (62.5) | .226 |

[a] The presented $P$ values are unadjusted.

experienced a treatment-related serious adverse event, and no treatment-related deaths occurred during the study period.

## DISCUSSION

This large subgroup analysis demonstrates that rolapitant, combined with a 5-$HT_3$ RA and dexamethasone, provided patients who received carboplatin-based chemotherapy with superior CINV protection in comparison with a standard 2-drug regimen using a 5-$HT_3$ RA and dexamethasone. The CR rate was significantly higher with the rolapitant treatment than the control in the overall and delayed phases. Furthermore, a significantly higher proportion of patients receiving carboplatin-based chemotherapy achieved complete protection and experienced no emesis and no nausea with rolapitant versus the control in the delayed and overall phases.

Routine prophylaxis with an NK-1 RA is not included in antiemetic guidelines for patients administered carboplatin-based chemotherapy.[4-6] According to criteria set forth by the Multinational Association of Supportive Care in Cancer and the European Society for Medical Oncology, a >10% absolute benefit is sufficiently clinically meaningful to warrant a change in guidelines.[6] The absolute benefit observed with rolapitant in the carboplatin subgroup of 401 patients was 16.7% for the measure of CR in the delayed phase. Furthermore, a

**TABLE 4.** Overview of TEAEs

| | Rolapitant 180 mg (n = 194), No. (%) | Control (n = 210), No. (%) |
|---|---|---|
| ≥1 TEAE | 120 (61.9) | 133 (63.3) |
| TEAEs occurring in ≥5% of rolapitant-treated patients and exceeding the rate in control-treated patients by >1% | | |
| Anemia | 15 (7.7) | 3 (1.4) |
| Dizziness | 10 (5.2) | 8 (3.8) |
| ≥1 treatment-related TEAE[a] | 22 (11.3) | 14 (6.7) |
| ≥1 TESAE | 16 (8.2) | 25 (11.9) |
| ≥1 treatment-related TESAE[b] | 0 | 0 |
| TEAE leading to study-drug discontinuation | 7 (3.6) | 11 (5.2) |
| TEAE with outcome of death | 6 (3.1) | 3 (1.4) |
| Treatment-related TEAE with outcome of death | 0 | 0 |

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
TEAEs for cycle 1 (the safety population) are shown. The safety population included all patients who received at least 1 dose of the study drug, including 2 patients in the rolapitant group and 1 patient in the control group who were enrolled at a site not compliant with Good Clinical Practice.
[a] Any adverse event considered possibly, probably, or definitely related to the study drug.
[b] Any TESAE considered possibly, probably, or definitely related to the study drug.

consistent clinically meaningful benefit of approximately 10% to 14% with the addition of an NK-1 RA for patients receiving carboplatin-based chemotherapy has begun to emerge in the literature.[2,16,17] In a recent double-blind, randomized phase 3 study of patients receiving non–AC-based MEC, 53% of whom received carboplatin-based chemotherapy, the addition of fosaprepitant to a 5-$HT_3$ RA and dexamethasone regimen provided absolute benefits of 10.4% and 10.2% for a CR in the delayed phase and the overall phase, respectively.[18] The addition of aprepitant to standard antiemetic regimens yielded absolute benefits of 14% for the measure of no emesis in the overall phase[16,19] and for the CR rate in the overall phase[20] in carboplatin-treated patients. Smaller studies have produced inconsistent results for the benefit of aprepitant in patients administered carboplatin therapy.[21-23] Data on netupitant also suggest a similar benefit based on measures of no emesis and CR in the overall phase with historical controls used for comparison.[17,24] Given the consistency of recently available evidence, including the clinically meaningful benefit observed with rolapitant in this large carboplatin-treated subgroup from a recently completed phase 3 study, guideline committees may consider recommending an NK-1 RA as part of a triple regimen with a 5-$HT_3$ RA and dexamethasone for patients with cancer receiving carboplatin-based chemotherapy.

The impact of the established patient risk factors of sex and age[1,2,17] was also examined in this carboplatin subgroup. Regardless of sex or age subgroup, rolapitant provided better CINV protection than the control. More patients attained a CR with rolapitant than the control in all subgroups examined, although statistical significance was not reached in all of the age subgroups. Patient numbers were too small to be conclusive; however, results were generally consistent with those of the overall carboplatin subgroup analysis.

Rolapitant was well tolerated in the carboplatin subgroup, and this was consistent with the safety profile reported in phase 3 studies.[12,13] The incidence of adverse events with rolapitant was comparable to the incidence with the control, and these adverse events were generally considered to be related to chemotherapy or the underlying disease.

In addition, rolapitant, a long-acting NK-1 RA, may help to simplify the medical management of patients with cancer undergoing emetogenic chemotherapy. Rolapitant, which does not inhibit or induce CYP3A4,[10] reduces the potential for CYP3A4-mediated drug-drug interactions and eliminates the need for dose modifications of certain drugs metabolized by CYP3A4 such as dexamethasone.

The results of this large carboplatin subgroup post hoc analysis demonstrate that oral rolapitant (180 mg), combined with a 5-$HT_3$ RA and dexamethasone, resulted in superior CINV prevention in comparison with a 5-$HT_3$ RA and dexamethasone alone, despite some limitations (ie, no adjustment for multiplicity, not prospectively powered, and numerical but not significant differences in FLIE scores > 108). These data support the use of rolapitant as part of the antiemetic prophylaxis regimen for patients with cancer undergoing carboplatin-based chemotherapy.

## FUNDING SUPPORT

This phase 3 study was designed through a collaboration of academic researchers and the study sponsor, TESARO, Inc. Study data

were collected by the clinical investigators, and the conduct of the trial was monitored by TESARO, Inc. Statistical analyses were managed by TESARO, Inc, according to a predefined statistical plan; the data presented here include post hoc analyses. This article was developed with full author participation and assistance from a medical writer in accordance with Good Publication Practice 3 guidelines and International Committee of Medical Journal Editors guidelines. All authors had access to the full data and analyses presented in this article.

## CONFLICT OF INTEREST DISCLOSURES

Paul J. Hesketh has served as a uncompensated consultant for Helsinn and TESARO, Inc. Ian D. Schnadig has served on an advisory board for TESARO, Inc, and is a consultant for Heron Therapeutics. Lee S. Schwartzberg has served as a consultant for TESARO, Inc, Helsinn, and Eisai. Manuel R. Modiano has declared no conflicts of interest. Karin Jordan is a consultant for MSD, Merck, and Helsinn. Sujata Arora received contracting fees from TESARO, Inc, during this study and outside the submitted work. Dan Powers is an employee of TESARO, Inc. Matti Aapro reports personal fees (honoraria, speakers' bureau, and expert testimony) from Amgen, personal fees (advisory role and speakers' bureau) and research funding from Helsinn Healthcare, personal fees (advisory role and speakers' bureau) and research funding from Hospira, personal fees (advisory role and speakers' bureau) from Teva, personal fees (advisory role) from Merck KGaA, personal fees (advisory role) from Merck, personal fees (advisory role and speakers bureau) and research funding from Sandoz, personal fees (advisory role and speakers' bureau) and research funding from Pierre Fabre Medicament, personal fees (advisory role and speakers' bureau) from Vifor Pharma, personal fees (advisory role and speakers' bureau) from TESARO, personal fees (speakers' bureau) and research funding from Novartis, personal fees (speakers' bureau) from Roche, and personal fees (speakers' bureau) from Johnson & Johnson.

## AUTHOR CONTRIBUTIONS

**Paul J. Hesketh:** Acquisition and interpretation of the data; critical review, commentary, revision, and approval of the manuscript; and responsibility for the overall content of the manuscript as the guarantor. **Ian D. Schnadig:** Acquisition and interpretation of the data and critical review, commentary, revision, and approval of the manuscript. **Lee S. Schwartzberg:** Acquisition and interpretation of the data and critical review, commentary, revision, and approval of the manuscript. **Manuel R. Modiano:** Acquisition and interpretation of the data and critical review, commentary, revision, and approval of the manuscript. **Karin Jordan:** Acquisition and interpretation of the data and critical review, commentary, revision, and approval of the manuscript. **Sujata Arora:** Formal analysis of the data and critical review, commentary, revision, and approval of the manuscript. **Dan Powers:** Interpretation of the data and critical review, commentary, revision, and approval of the manuscript. **Matti Aapro:** Acquisition and interpretation of the data and critical review, commentary, revision, and approval of the manuscript.

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