Detailed analysis of a randomized phase III trial: can the tolerability of capecitabine plus docetaxel be improved without compromising its survival advantage?


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Background: In a phase III trial, 3-weekly capecitabine (1250 mg/m² twice daily days 1–14) plus docetaxel (75 mg/m² day 1) demonstrated significantly superior overall survival to 3-weekly docetaxel (100 mg/m² day 1). We report a retrospective analysis of the impact of capecitabine/docetaxel dose reduction on safety and efficacy.

Patients and methods: Safety and efficacy data were analyzed retrospectively according to the actual doses of capecitabine and docetaxel administered.

Results: More patients receiving capecitabine/docetaxel (65%) had dose reductions for adverse events than docetaxel alone (35%). In most patients requiring dose reduction with the combination (80%), capecitabine and docetaxel were simultaneously reduced to 950 mg/m² and 55 mg/m², respectively. Subsequently, there were fewer cycles (17%) with grade 3/4 adverse events than with the full doses (34%). Time to progression and overall survival appeared to be similar in patients starting the second cycle with reduced doses of capecitabine/docetaxel and those who continued to receive full doses of capecitabine/docetaxel for at least the first four cycles.

Conclusions: Capecitabine/docetaxel dosing flexibility allows management of side-effects without compromising efficacy. This retrospective analysis, as well as multiple phase II studies of taxanes with reduced-dose capecitabine, shows that reducing the starting dose of capecitabine with docetaxel is a reasonable strategy for the treatment of patients with metastatic breast cancer. In addition, reducing the dose of both agents may be appropriate.

Key words: capecitabine, docetaxel, metastatic breast cancer, safety, dose reduction

Introduction

For patients with metastatic breast cancer pretreated with anthracyclines, taxane-based therapy has been the most frequent treatment of choice. Docetaxel is the only single agent that has demonstrated a survival benefit in this setting, having significantly prolonged overall survival (from 8.7 months to 11.4 months at the median) in a randomized comparison with mitomycin C and vinblastine [1]. Until recently, docetaxel was considered optimal therapy for this group of women.

Capecitabine (Xeloda®, F. Hoffmann-La Roche, Basel, Switzerland) is a highly effective oral fluoropyrimidine that generates 5-fluorouracil (5-FU) preferentially in tumor tissue through a three-step enzymatic process. The final step in the generation of 5-FU from capecitabine is catalyzed by thymidine phosphorylase, an enzyme expressed at up to five times higher concentrations in tumor compared with healthy tissue [2, 3]. In patients with metastatic breast cancer who have received both anthracycline and taxane therapy, single-agent capecitabine is now considered standard therapy, having shown consistently high efficacy in trials including a total of 730 patients [4–9].

A phase I study in patients with advanced solid tumors [10] established a 3-weekly dosing regimen of capecitabine 1250 mg/m² twice daily, days 1–14, with docetaxel 75 mg/m² on day 1. This initial dose-finding study found these capecitabine and docetaxel doses to be tolerable. Indeed, there were no dose-limiting toxicities at this dose level among six patients who received 23 cycles of the combination.

The recommended regimen from the phase I study was evaluated versus standard 3-weekly docetaxel monotherapy (100 mg/m²) in a large, randomized, phase III trial in...
than in the single-agent docetaxel arm (100 mg/m²). Because the combination arm (26% versus 20% with docetaxel alone), but the incidence of treatment-related toxicities that were consistent with the known side-effects of the individual agents [11]. There was a higher incidence of gastrointestinal adverse events and hand–foot syndrome in the combination arm compared with the single-agent docetaxel arm, but a lower incidence of neutropenia. Of note, the higher incidence of grade 3 hand–foot syndrome (71% versus 49% with docetaxel alone, respectively). In the combination arm, the doses of both drugs were usually reduced (80% of the dose reductions) to 950 mg/m² and 35 mg/m².

The twice-daily administration of capecitabine provides numerous opportunities for management of adverse events through dose interruption and adjustment. Retrospective analyses have demonstrated that in patients receiving capecitabine monotherapy, dose modification is effective in managing adverse events [14], with no apparent loss of efficacy [6]. In the present report we provide a detailed review of the safety profile of the capecitabine/docetaxel combination arm of the study, analyzing the effect of dose reduction on tolerability and efficacy. The goal of these analyses was to optimize the dosing strategy and ensure that a broad patient population is able to safely benefit from the capecitabine/docetaxel combination.

patients and methods

patients and treatment

In this large phase III trial, previously reported by O’Shaughnessy et al. [11], patients with relapsed breast cancer previously treated with an anthracycline were randomized to 3-weekly cycles of either: oral capecitabine 1250 mg/m² twice daily, on days 1–14 followed by a 7-day rest period, plus docetaxel 75 mg/m² as a 1-h intravenous infusion on day 1 (combination arm); or docetaxel 100 mg/m² as a 1-h infusion on day 1 (single-agent docetaxel arm). The primary end point of the study was time to disease progression; secondary end points included overall response rate, overall survival and safety. Adverse events were recorded and graded according to National Cancer Institute of Canada common toxicity grading scale (revised 1991) throughout the study and for up to 28 days after the last administration of study drug. Hand–foot syndrome was graded 1 to 3, as defined in previous capecitabine clinical studies [4, 15].

dose modification

Treatment was continued without interruption or dose reduction if patients experienced grade 1 adverse events or other adverse events considered not to be drug related or unlikely to become serious or life-threatening (e.g. alopecia). For all other treatment-related adverse events of grade 2 or higher, the dose modification scheme described by O’Shaughnessy et al. [11] was implemented. The dose of capecitabine was reduced by 25% to 950 mg/m² twice daily and the dose of docetaxel was reduced to 35 mg/m².

assessment of impact of dose modification

All safety and efficacy data, and data on the incidence, timing and causes of dose modification (treatment interruption and/or dose reduction) were collected prospectively during the study. In addition, data on the doses of capecitabine and docetaxel administered at the start of each treatment cycle were collected. The overall incidence of grade 3/4 toxicities and the incidence of key grade 3/4 toxicities (diarrhea, stomatitis, hand–foot syndrome and neutropenic fever) were analyzed retrospectively in relation to the doses of capecitabine and docetaxel administered at the start of each cycle.

The impact of early dose reduction on efficacy was retrospectively assessed by comparing Kaplan–Meier curves of time to disease progression and overall survival in two groups of patients: (i) those receiving reduced doses beginning in cycle 2 and (ii) those receiving the full starting doses of capecitabine and docetaxel for at least the first four cycles of therapy. These two groups of patients were chosen because time-related efficacy end points can only be retrospectively analyzed if patients having early dose reductions are compared with patients who continued on the full doses for several cycles. Time to disease progression was defined as the time from randomization to the first recording of disease progression or the date of death in patients with no evidence of disease progression.

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results

patient population

In total, 511 women were randomized in the study, 255 to the combination arm and 256 to the single-agent docetaxel arm. The baseline characteristics and treatment histories of patients were well balanced between the two treatment groups and are described in detail by O’Shaughnessy et al. [11]. Median age was 52 years in the combination arm and 51 years in the single-agent arm. The baseline characteristics of patients in the two subgroups (patients requiring an early dose reduction and patients continuing with at least four cycles of full-dose therapy) were also well balanced. Median ages were 52 (range 37–71) and 49 (range 30–74); median Karnofsky performance status was 80 (range 70–100) and 90 (range 70–100); 51% and 30% of patients were ER/PR positive, respectively; 35% and 28% of patients were ER/PR negative, respectively. The number of metastatic sites (1/2/3 or more) were 19%/19%/62% and 17%/13%/70% and metastatic sites were: lymph nodes, 38% and 45%; liver, 62% and 42%; bone, 54% and 42%; lung, 35% and 36%; skin, 24% and 38%. As defined in the protocol, all patients had received previous anthracycline-based chemotherapy (doxorubicin in the majority of patients). The safety population (all patients who received at least one dose of study drug) included 251 patients in the combination arm and 255 patients in the single-agent docetaxel arm. Patients randomized who did not receive at least one dose of study medication and for whom no follow-up safety information was available were excluded from the analysis of safety. In this case, four patients in the capecitabine/docetaxel arm and one patient in the docetaxel arm did not receive study medication after randomization.

dose modification of capecitabine and docetaxel

In the docetaxel monotherapy arm, the median delivered dose was 100% of the planned dose. All patients in the capecitabine/docetaxel arm started the first treatment cycle receiving the full combination doses of capecitabine (1250 mg/m² twice daily, days 1–14) and docetaxel (75 mg/m², day 1) (Table 1). In the combination arm, the median delivered doses of capecitabine and docetaxel were 77% and 87%, respectively. During the whole study period, 65% of patients in the combination arm required dose reduction. Both agents were reduced in the majority of patients (51% overall; 80% of the 163 patients requiring dose reductions), while docetaxel only was reduced in 4%. Dose modification of capecitabine and docetaxel was the most frequent dose modification strategy. Of the 405 cycles administered with capecitabine at a dose of 950 mg/m² twice daily and docetaxel at 55 mg/m², 96 (23%) were subsequently associated with capecitabine dose interruption. In 31 cycles, capecitabine was administered at a reduced dose of 950 mg/m² twice daily but with a full dose of docetaxel (75 mg/m²), and 20 (64%) of these required subsequent dose interruption.

In the capecitabine/docetaxel arm 45 patients discontinued docetaxel treatment due to toxicity but continued on capecitabine treatment alone.

impact of capecitabine/docetaxel dose reduction on safety

Overall, a total of 1317 cycles of the combination were given. The vast majority of these (82%) were administered either with both treatments at full dose (670 cycles) or with capecitabine at a dose of 950 mg/m² twice daily and docetaxel at a dose of 55 mg/m² (405 cycles). The overall incidence of grade 3 and 4 adverse events occurring after both the capecitabine and docetaxel doses were reduced compares favorably with that occurring when full doses of both agents were used (Table 2). Grade 3/4 adverse events occurred in 34% of cycles with the full-dose combination, compared with 17% of cycles in which capecitabine 950 mg/m² twice daily and docetaxel 55 mg/m² were administered.

Specifically, when capecitabine and docetaxel were administered at the reduced doses indicated above, the proportion of cycles with grade 3/4 hand–foot syndrome, diarrhea, stomatitis or neutropenic fever were reduced compared with when the full doses of both agents were administered (Figure 1). In particular, the incidence of grade 3 hand–foot syndrome was substantially lower when the doses of both agents were reduced (occurring in 16 cycles compared with 45 cycles at the full doses). As shown in Table 2, no difference in the overall incidence of grade 2 toxicities was seen with reduced doses of both agents. However, with full-dose versus reduced-dose capecitabine plus docetaxel, grade 2 hand–foot syndrome was 13% versus 7%, respectively, grade 2 diarrhea was 13% versus 6%, respectively and grade 2 stomatitis was 12% versus 7%, respectively.

Table 1. Doses of capecitabine and docetaxel used at the start of each cycle of capecitabine/docetaxel combination therapy

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Patients receiving the combination: n (%)</th>
<th>Capecitabine 1250 mg/m² twice daily docetaxel 75 mg/m²</th>
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<tbody>
<tr>
<td>Cycle 1</td>
<td>(n = 251)</td>
<td>251 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>(n = 225)</td>
<td>164 (70.0)</td>
<td>33 (14.1)</td>
<td>20 (8.5)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>(n = 181)</td>
<td>89 (42.8)</td>
<td>57 (27.4)</td>
<td>25 (12.0)</td>
<td>10 (4.8)</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>(n = 148)</td>
<td>53 (29.3)</td>
<td>65 (35.9)</td>
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Dose interruption of capecitabine occurred in 243 of the 670 cycles (36%) administered at the full starting doses of capecitabine and docetaxel. As discussed above, simultaneous reduction of capecitabine and docetaxel was the most frequent dose modification strategy. Of the 405 cycles administered with capecitabine at a dose of 950 mg/m² twice daily and docetaxel at 55 mg/m², 96 (23%) were subsequently associated with capecitabine dose interruption. In 31 cycles, capecitabine was administered at a reduced dose of 950 mg/m² twice daily but with a full dose of docetaxel (75 mg/m²), and 20 (64%) of these required subsequent dose interruption.

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In the capecitabine/docetaxel arm 45 patients discontinued docetaxel treatment due to toxicity but continued on capecitabine treatment alone.
Few treatment cycles were administered with reduced capecitabine and full-dose docetaxel (31 cycles with capecitabine reduced to 950 mg/m² twice daily, and 14 with capecitabine reduced to 625 mg/m² twice daily). There was no apparent improvement in tolerability with these doses, but the small number of cycles administered precludes any meaningful comparison. Similarly, there were too few treatment cycles where reduced-dose docetaxel was administered with full-dose capecitabine for comparisons to be made.

**impact of capecitabine/docetaxel dose reduction on efficacy**

The impact of dose-reduction on time to disease progression was compared retrospectively in the subgroups of patients requiring early dose reductions of both agents (from cycle 2 onwards; \( n = 33 \)) versus those who received at least four cycles of full-dose therapy (i.e. those still receiving full doses of capecitabine and docetaxel at the beginning of cycle 4, \( n = 53 \)). The Kaplan–Meier curves for time to disease progression in both groups of patients were similar (Figure 2).

The impact of dose-reduction on overall survival was also compared retrospectively in the subgroups of patients requiring early dose reductions of both agents versus those continuing to receive full doses for at least four cycles. The Kaplan–Meier curves for overall survival were also similar in both groups of patients (Figure 3).

In a similar analysis, there was no difference in time to disease progression (median 6.2 versus 6.8 months) or death (median 14.6 versus 15.0 months) in patients receiving full-dose capecitabine/docetaxel at cycle 2 (\( n = 164 \)) versus those

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**Table 2. Adverse events (unrelated and related) during treatment cycles administered at different dose combinations of capecitabine and docetaxel**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Capecitabine 1250 mg/m² twice daily docetaxel 75 mg/m²</th>
<th>Capecitabine 950 mg/m² twice daily docetaxel 55 mg/m²</th>
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<th>Capecitabine 625 mg/m² twice daily docetaxel 75 mg/m²</th>
</tr>
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<tbody>
<tr>
<td>Total number of treatment cycles</td>
<td>670</td>
<td>405</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>All AEs: ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 (none)</td>
<td>87 (13)</td>
<td>110 (27)</td>
<td>5 (16)</td>
<td>8 (57)</td>
</tr>
<tr>
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<td>94 (14)</td>
<td>92 (23)</td>
<td>4 (13)</td>
<td>1 (7)</td>
</tr>
<tr>
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<td>260 (39)</td>
<td>136 (34)</td>
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**Figure 1.** Impact of capecitabine and docetaxel dose reduction on the incidence of key grade 3/4 treatment-related adverse events.

**Figure 2.** Time to disease progression in the subgroups of patients requiring dose reduction of capecitabine and docetaxel from cycle 2 onwards versus those who received the full starting doses for at least four cycles.

**Figure 3.** Overall survival in the subgroups of patients requiring dose reduction of capecitabine and docetaxel from cycle 2 onwards versus those who received the full starting doses for at least four cycles.
receiving reduced doses of both agents from cycle 2 onwards ($n = 33$).

While time to disease progression and overall survival seem to be similar in the two subgroups, the small number of patients in each group does not allow definitive conclusions to be made.

**discussion**

The results of the large phase III randomized trial showed that the combination of capecitabine plus docetaxel is a highly effective treatment for patients with anthracycline-pretreated metastatic breast cancer [11]. The combination was significantly superior to docetaxel monotherapy in all major efficacy endpoints and is the only cytotoxic combination regimen shown to significantly extend survival compared with single-agent docetaxel. In the phase III trial [11], the safety profile of capecitabine plus docetaxel was manageable, although the combination arm had a higher incidence of grade 3 adverse events (primarily hand–foot syndrome), dose reductions and treatment-related withdrawals compared with single-agent docetaxel. The current retrospective analyses of data from the phase III trial were conducted to investigate the optimal dosing strategy that would enable a broad population of patients with metastatic breast cancer to benefit from the high efficacy of the capecitabine/docetaxel combination.

A phase I study in patients with advanced solid tumors [10] established a 3-weekly dosing regimen of capecitabine 1250 mg/m$^2$ twice daily, days 1–14, with docetaxel 75 mg/m$^2$ on day 1 in six patients who received 23 cycles of the combination. It might, however, have been prudent to treat a larger cohort of patients at a recommended dose to define tolerability across a broader group of patients. This is perhaps especially relevant when, as with the combination of capecitabine and docetaxel, formal phase II evaluation was not undertaken because of clear antitumor activity demonstrated in a phase I trial.

The results reported here highlight that dosing flexibility allows management of side-effects with the capecitabine/docetaxel combination. All patients in the trial started treatment on the full starting doses of capecitabine 1250 mg/m$^2$ twice daily days 1–14 plus docetaxel 75 mg/m$^2$ on day 1, repeated every 3 weeks. During the study period, 65% of patients in the combination arm required dose reduction, with both agents simultaneously reduced in the majority of these patients (51%). Capecitabine alone was reduced in only 4% of patients and docetaxel alone was reduced in 10%. Cycles with reduced doses of capecitabine and docetaxel were associated with a lower incidence of grade 3/4 treatment-related adverse events compared with those using the full starting doses. This in turn led to a lower incidence of capecitabine treatment interruptions and dose reductions.

Although the numbers of patients were small, meaning that definitive conclusions cannot be made, early capecitabine/docetaxel dose reduction (from cycle 2 onwards) did not appear to compromise efficacy. Time to disease progression and overall survival were similar in the subgroup of patients requiring dose reductions from cycle 2 onwards compared with those who continued to receive the full starting doses for at least four cycles of therapy. Although it may appear from the Kaplan–Meier curves in Figures 2 and 3 that reduced-dose capecitabine/docetaxel has an efficacy advantage over full-dose capecitabine/docetaxel, it should not be interpreted this way because a retrospective analysis cannot show superiority. However, the position of the curves does increase confidence that reduced-dose capecitabine/docetaxel is not less efficacious than the full doses.

The benefits of dosing flexibility with the combination can only be derived with implementation of effective patient management strategies to ensure appropriate use of treatment interruption and dose reduction. Patients should be educated to recognize the key side-effects of the combination, interrupt capecitabine upon development of grade 2 or more severe side-effects, and contact a member of their healthcare team for advice. Prescribing information for both capecitabine and docetaxel provides detailed guidelines for the implementation of treatment interruption and dose modification with the combination.

In patients older than 60 years, treatment-related withdrawals during the first two cycles were particularly frequent and were typically due to adverse events rather than disease progression [11]. This led to a recommendation that a 25% reduction in the starting dose of capecitabine (to 950 mg/m$^2$ twice daily) should be considered for older patients [11]. In addition, further refinement of the regimen with a 25% reduction of both the starting doses of capecitabine (to 950 mg/m$^2$ twice daily) and docetaxel (to 55–60 mg/m$^2$) may allow a broader population of patients to safely benefit from this combination, given that overall survival is not compromised by using a reduced dose of docetaxel in this regimen. A phase III study that evaluated a range of 3-weekly docetaxel doses in patients with metastatic breast cancer provides further evidence to support this strategy [16]. Data from this trial showed that 3-weekly docetaxel 60 versus 75 mg/m$^2$ had similar efficacy (response rate, time to disease progression and overall survival). A dose of 75 mg/m$^2$ docetaxel did not provide a significant benefit in terms of time to disease progression or overall survival compared with 60 mg/m$^2$. This study also demonstrated that lower doses of docetaxel (60 or 75 mg/m$^2$) were associated with reduced leucopenia, anemia, febrile neutropenia, infection, asthenia and stomatitis compared with 100 mg/m$^2$ [16].

The early separation between the combination and single-agent docetaxel arms of the Kaplan–Meier curves for time to disease progression and overall survival, however, indicates that in the overall patient population there was benefit early in treatment with the combination [11]. The impact of using reduced doses of capecitabine and docetaxel during the first cycle of treatment in patients with metastatic breast cancer is currently not known. Several ongoing clinical trials evaluating docetaxel 60–75 mg/m$^2$ i.v. on day 1 plus capecitabine 825–1000 mg/m$^2$ twice daily on days 1–14 should provide further guidance.

These trials include the Mexican Oncology Study Group phase II trial comparing the efficacy of sequential capecitabine (1250 mg/m$^2$ twice daily) followed by a taxane (docetaxel 100 mg/m$^2$ or paclitaxel 175 mg/m$^2$) with the capecitabine/docetaxel combination (825/75) or capecitabine in combination with paclitaxel (825/175) in patients with anthracycline-pretreated metastatic breast cancer [17]. In an interim analysis, patients receiving the reduced-dose capecitabine/docetaxel combination...
between docetaxel 60 mg/m² and 75 mg/m² as second-line treatment of patients with metastatic breast cancer. In addition, that reducing the dose of both agents may be appropriate. Therapy for metastatic breast cancer. Therefore, it is also possible that reducing the dose of capecitabine/docetaxel in the adjuvant setting are using a lower starting dose of capecitabine. A US oncology study is investigating four cycles of doxorubicin/cyclophosphamide followed by docetaxel (100) versus capecitabine/docetaxel (825/75) and a Finnish study (FinXX) is investigating adjuvant docetaxel (80) followed by 5-FU/epirubicin (75)/cyclophosphamide compared with capecitabine/docetaxel (900/60) followed by cyclophosphamide/epirubicin (75)/capecitabine (900). Interim results from the FinXX study have shown a manageable safety profile for capecitabine/docetaxel, including a lower incidence of neutropenic fever than with docetaxel alone [20].

In summary, this retrospective analysis of the phase III study demonstrates that dosing flexibility with the capecitabine/docetaxel combination allows effective management of side-effects. Early capecitabine and docetaxel dose reduction is associated with improved tolerability and fewer treatment interruptions, with no evidence of loss of the efficacy advantage over single-agent docetaxel. Final results from ongoing studies will provide definitive data on using reduced doses of capecitabine and doxetaxel in combination beginning with cycle one. Based on the analysis herein of reduced-dose capecitabine/docetaxel and multiple phase II studies of paclitaxel or docetaxel in combination with reduced-dose capecitabine, reducing the starting dose of capecitabine to 950 mg/m² twice daily in combination with doxetaxel is a reasonable strategy for the treatment of patients with metastatic breast cancer. In addition, a phase III single-agent study [16] suggested that there is no difference in objective response rates and overall survival between docetaxel 60 mg/m² and 75 mg/m² as second-line therapy for metastatic breast cancer. Therefore, it is also possible that reducing the dose of both agents may be appropriate.

**appendix**

In addition to the authors, the following investigators participated in this trial: S. P. Ackland, Newcastle, Australia; D. R. Bell, St. Leonards, Australia; M. J. Boyer, Camperdown, Australia; J. J. McKendrick, Melbourne, Australia; G. C. Toner, Melbourne, Australia; G. Van Hazel, Perth, Australia; M. J. Inbar, Tel Aviv, Israel; S. Rizel, Tel Hashomer, Israel; R. Catane, Jerusalem, Israel; D. B. Geffen, Beer Sheva, Israel; B. Uzieli, Jerusalem, Israel; G. Fried, Haifa, Israel; I. Ben-Shahar, Nahariya, Israel; E. Gonzalez, Monterrey, Mexico; J. A. Silva, Mexico City, Mexico; G. Cervantes, Mexico City, Mexico; Chan Navarro, Guadalajara, Mexico; B. Eriksen, Oslo, Norway; E. A. Wist, Oslo, Norway; M. P. N. Findlay, Wellington, New Zealand; V. J. Harvey, Auckland, New Zealand; R. D. Chacon, Buenos Aires, Argentina; E. Michlewicz, Buenos Aires, Argentina; T.-Y. Chao, Taipei, Taiwan; A. L. Cheng, Taipei, Taiwan; W.-Y. Liu, Taipei, Taiwan; M. Lichinitser, Moscow, Russia; V. Gorbunova, Moscow, Russia; A. A. Borisov, Moscow, Russia; V. Moiseyenko, St Petersburg, Russia; D. C. Talbot, Oxford, UK; J. Mansi, London, UK; D. Miles, London, UK; S. O’Reilly, Merseyside, UK; K. J. O’Byrne, Leicester, UK; A. Makris, Northwood, UK; C. Twelve, Glasgow, UK; R. Leonard, Swansea, UK; J. A. O’Shaughnessy, Dallas and Houston, USA; S. Vukelja, Dallas and Houston, USA; S. Jones, Dallas and Houston, USA; P. R. Kaywin, Miami, USA; M. R. Modiano, Tucson, USA; W. G. Harker, Salt Lake City, USA; E. Tai, Sunnyvale, USA; J. F. Kroener, La Jolla, USA; K.-Y. Yeung, Clinton, USA; M. R. Moore, Decatur, USA; and W. D. Henner, Portland, USA.

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