Optimising the dose of capecitabine in metastatic breast cancer: confused, clarified or confirmed?

C. Zielinski1,2*, J. Gralow3 & M. Martin4

1Department of Medicine I and Clinical Division of Oncology, Medical University of Vienna, Vienna; 2Central European Cooperative Oncology Group (CECOG), Vienna, Austria; 3Department of Medicine, University of Washington, Seattle, WA, USA; 4Medical Oncology Department, Hospital Clínico San Carlos, Madrid, Spain

Received 2 September 2009; revised 25 November 2009 & 11 February 2010; accepted 12 February 2010

While ‘targeted’ drugs often take centre stage when considering developments in breast cancer, improved understanding, administration and use of chemotherapeutic agents also contribute to better outcomes for women with metastatic breast cancer. Moreover, these developments offer the potential for further improvements when chemotherapy and targeted agents are combined. In this article, we focus on capecitabine dosing in advanced breast cancer, review the available data and discuss the implications of this evidence on best treatment practice both for chemotherapy alone and for chemotherapy when combined with biological agents. It appears that a capecitabine starting dose of 1000 mg/m² twice daily enables treatment to be administered for longer periods, providing continuous exposure to cytotoxic therapy and thus prolonging the duration of disease control. Although no randomised data are available comparing different doses of capecitabine, the cumulative evidence supports this approach.

**Key words:** capecitabine, dose modification, dose reduction, metastatic breast cancer, therapeutic index

**introduction**

The range of treatment options for breast cancer continues to grow. The expanding number of agents leads to increasingly complex treatment decisions accompanied by better outcomes for our patients. Meanwhile, efforts to identify the most appropriate and effective way to use some of the ‘older’ drugs continue, not least because many of the targeted agents are combined with chemotherapy. These attempts include modification of scheduling, alternative delivery methods, improved management of toxicity and dose optimisation. For example, the administration schedule for taxanes has been investigated in depth in randomised, phase III trials, and it is now apparent that a weekly paclitaxel schedule offers benefits over 3-weekly dosing [1]. Numerous novel formulations of taxanes have been designed to improve tolerability and efficacy of this class by avoiding the need for toxic solvents (e.g. nanoparticle albumin-bound paclitaxel and tocopherol-based cremophor-free formulation) or using macromolecular conjugates (e.g. paclitaxel poliglumex). These adaptations have had varying success in clinical evaluation [2]. Similarly, pegylated and/or liposomal anthracyclines are now available and vinorelbine can be administered as either an i.v. or an oral formulation. Improved anti-emetic therapy and growth factor support enable more effective management or prevention of side-effects of chemotherapy. In addition, tailoring of dosing according to patient, tumour and genotypic characteristics can improve the balance of efficacy and toxicity. In this paper, we will focus on dose optimisation in relation to capecitabine monotherapy in breast cancer.

**why and how was the registered dose selected?**

The registered dose of capecitabine monotherapy [1250 mg/m² twice daily (b.i.d.), days 1–14 every 21 days] was determined in a classic phase I dose-escalation study in patients with a variety of solid tumours [3]. Dose-limiting toxicities included hand–foot syndrome (reported at grade 3 in one patient treated at the recommended dose level) and gastrointestinal effects, predominantly diarrhoea. This schedule was then compared with regimens identified in two additional phase I dose-finding studies in a randomised phase II trial in patients with colorectal cancer [4]. The intermittent regimen (administration on days 1–14 followed by a 7-day rest period) was selected in preference to either a continuous schedule or a regimen in combination with leucovorin because it was associated with the longest treatment duration and the highest dose intensity. The drug-free period appeared to enable recovery from treatment-related toxicity [4]. However, it is important to note that this study was carried out in a relatively small number of patients, all with colorectal rather than breast cancer. Furthermore, the phase I studies were conducted predominantly in Europe, and it has since become apparent that tolerability of fluoropyrimidines varies with geographic region, with patients from the United States showing poorer tolerability than European or Asian populations [5].
The clinical development programme of capecitabine in metastatic breast cancer (MBC) proceeded with this intermittent regimen, generating a wealth of data with capecitabine at a dose of 1250 mg/m² b.i.d. for 2 weeks followed by a 1-week drug-free period. The drug was initially approved by the Food and Drug Administration of the United States as monotherapy in anthracycline- and taxane-pretreated MBC on the basis of two single-arm phase II studies [6, 7]. Results of these two studies were confirmed first in additional single-arm studies in the same setting [8–10] and more recently in randomised phase III trials in which capecitabine was the reference treatment [11–14] (Table 1).

**Lowering the starting dose of capecitabine: rationale and phase III results**

With increasing experience of capecitabine after its introduction, many clinicians found that at the registered starting dose, a large proportion of patients required dose reduction to their individually tolerable dose. In the phase II studies, 27%–50% of patients required a 25% dose reduction [7–9, 19] and in the phase III trial by Miller et al. [11], 65% of patients had their dose reduced by at least 25%. The median time to dose reduction was typically <2 months [7, 9]. This relatively high rate of dose modification led to speculation that a lower starting dose might improve tolerability, enabling patients to continue treatment and thus maintain control of disease for longer. But can this approach be justified?

There is no randomised trial comparing the registered monotherapy dose with a lower dose, nor is there likely to be, as few oncologists would be willing to enrol patients into such a randomised trial. However, perhaps the most convincing evidence of the high efficacy of capecitabine at a lower starting dose comes from a randomised phase III trial in the first-line setting (Table 2), reported to date only in abstract form by investigators from the Australian New Zealand Breast Cancer Trials Group. Although the trial was terminated prematurely because of slow accrual, the investigators demonstrated a significant survival benefit with capecitabine monotherapy versus classical cyclophosphamide, methotrexate and 5-fluorouracil (CMF) combination therapy in patients unsuited to more intensive therapy [22]. The capecitabine starting dose was 1000 mg/m² b.i.d., given on days 1–14 every 21 days. A second capecitabine arm included patients treated with capecitabine 650 mg/m² b.i.d., days 1–21 (i.e. continuously, without a drug-free period). This dose gave an almost identical total capecitabine dose per cycle, but it was speculated that a more metronomic schedule may improve tolerability.

Efficacy data showed similar response rate (RR) and progression-free survival (PFS) in the three treatment arms. RR was within the range 18%–22% for each arm and the hazard ratio for PFS was 0.86 [95% confidence interval (CI): 0.67–1.10, \( P = 0.2 \); median 6 months with capecitabine versus 7 months

---

**Table 1.** Summary of efficacy according to starting dose: capecitabine monotherapy in anthracycline- and taxane-pretreated metastatic breast cancer

<table>
<thead>
<tr>
<th>Registered starting dose</th>
<th>Lower starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ranges reported in large single-arm, phase II studies [6–8, 10]</strong></td>
<td><strong>Ranges reported in randomised, phase III trials [11, 12, 14, 15]</strong></td>
</tr>
<tr>
<td>Confirmed overall response rate</td>
<td>15%–28%</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + SD)</td>
<td>57%–63%</td>
</tr>
<tr>
<td>Median time to progression (months)</td>
<td>3.1–4.6</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>10.1–15.9</td>
</tr>
</tbody>
</table>

**Table 2.** Summary of efficacy according to starting dose: first-line capecitabine monotherapy in metastatic breast cancer

<table>
<thead>
<tr>
<th>Registered starting dose</th>
<th>Lower starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised, phase II trial [20]</strong></td>
<td><strong>Randomised, phase III trials [22, 23]</strong></td>
</tr>
<tr>
<td>Confirmed overall response rate</td>
<td>30%</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + SD)</td>
<td>81%</td>
</tr>
<tr>
<td>Median time to progression (months)</td>
<td>4.1</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>19.6</td>
</tr>
</tbody>
</table>

| **Retrospective studies [25, 26]** | **Single-arm, phase II studies [21, 24]** |
| Confirmed overall response rate | 37% | 26%–35% |
| Clinical benefit rate (CR + PR + SD) | 70% | 64%–81% |
| Median time to progression (months) | 3.9 | 4.1–7.3 |
| Median overall survival (months) | 10 | 16–17.1 |

*Progression-free survival (time to progression not reported)
CR, complete response; PR, partial response; SD, stable disease.
with CMF]. However, capecitabine monotherapy demonstrated a significant overall survival (OS) benefit over CMF combination therapy (hazard ratio: 0.72; 95% CI: 0.55–0.94; log rank $P = 0.02$). Median OS was 22 months in the pooled capecitabine arms compared with 18 months in the CMF arm. The survival benefit could not be attributed to differences in post-study therapy and the most likely explanation appears to be the longer duration of capecitabine therapy. In the capecitabine arms, 40%–41% of patients continued therapy for >6 months compared with only 22% of those treated with CMF. Treatment was continued for >1 year in 17%–19% of those receiving capecitabine versus 5% of patients randomised to CMF. No differences in efficacy between the two capecitabine arms were observed, suggesting that the continuous regimen provides an acceptable alternative in patients who prefer to continue treatment without a drug-free interval. Some patients may find a continuous schedule simpler and more acceptable, while others prefer a ‘drug holiday’.

The demonstration of an OS benefit with a monotherapy versus a combination regimen is particularly unusual in the breast cancer literature and was achieved despite premature termination of the trial. The results provide convincing evidence of the efficacy of a lower starting dose and are very reassuring for clinicians adopting this approach. However, they do not directly answer the question of whether a lower starting dose offers similar efficacy to the registered starting dose. We sought to find supporting evidence from studies evaluating a lower starting dose. We searched PubMed and the major oncology and breast cancer meetings [American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium (SABCS), European Society for Medical Oncology (ESMO), European CanCer Organisation (ECCO) and European Breast Cancer Conference (EBCC)] from 2000 to 2009 for studies evaluating capecitabine at a starting dose lower than the registered regimen in any treatment line.

**impact of dose reduction on efficacy**

Indirect evidence that a lower dose might offer better tolerability without compromising efficacy comes from retrospective analyses of efficacy and tolerability in patients who continued capecitabine therapy without dose modification versus those whose dose was reduced to manage toxicity. In the pivotal trial of capecitabine monotherapy in paclitaxel-pretreated MBC, patients requiring dose modification for management of adverse events experienced no relevant increase in risk of disease progression compared with those not requiring dose modification (hazard ratio: 1.02, $P = 0.935$) [19]. Almost all adverse events (83%–100%) improved after dose modification. Similarly, results of a retrospective analysis of 321 patients treated in four phase II studies of capecitabine monotherapy, including the pivotal study described above, also suggested that dose reduction for the management of toxicity did not impair efficacy [27]. Safety analyses indicated that one capecitabine dose reduction (to 75% of the original starting dose) was usually sufficient to avoid a clinically significant recurrence of an adverse event. Efficacy analyses suggested a trend towards improved outcomes among the group of patients undergoing dose reduction. Interpretation of the results is not straightforward, since patients achieving a response are likely to continue treatment for longer, thus increasing the likelihood of dose reduction. Nevertheless, in the absence of a randomised trial comparing the registered versus a lower dose, this analysis provides some indication that dose reduction does not reduce efficacy.

**retrospective comparisons of different capecitabine doses**

Investigators from the United States conducted an analysis of patients receiving capecitabine monotherapy for MBC at the M.D. Anderson Cancer Center to determine whether a lower starting dose of capecitabine improved tolerability without compromising efficacy [18]. Patients receiving capecitabine outside a clinical trial were identified from pharmacy records and were divided into three subgroups according to the starting dose of capecitabine they received: 1250 mg/m² b.i.d. $\pm$ 5% ($n = 49$), 1125 mg/m² b.i.d. $\pm$ 5% ($n = 15$) or $<1000$ mg/m² b.i.d. $\pm$ 5% ($n = 41$). Patients in the lowest dose group were slightly younger and slightly more heavily pretreated than in the other two groups. Median time to progression (TTP) in the three subgroups was 2.8, 4.6 and 3.5 months, respectively. Grade $\geq$3 hand–foot syndrome and diarrhoea were most common at the highest starting dose. Although such a retrospective analysis has limitations and as with the study above, there is a risk of bias, a starting dose of 1000 mg/m² was recommended by the investigators on the basis of its superior therapeutic index.

In another retrospective analysis ($n = 226$), this time in the first-line setting, Debled et al. found no difference in time to treatment failure (TTF) according to the capecitabine starting dose [25]. The starting dose was $>1000$ mg/m² in 32% of patients (median age 61.5 years); median TTF in this subgroup was 9.2 months. Among the 24% of patients who received a starting dose $<1000$ mg/m² b.i.d., median age was 75.8 years and median TTF was 8.6 months. In this retrospective analysis, the initial capecitabine dose was selected by the oncologist on the basis of age, comorbidities and experience. Consequently differences in patient and disease characteristics are possible. However, univariate analysis revealed no significant influence of prior adjuvant chemotherapy, prior endocrine therapy, visceral disease or initial capecitabine dose on the efficacy of treatment.

**prospective studies of a 1000 mg/m² b.i.d. starting dose**

Although the retrospective studies described above give an impression of the relative efficacy of different doses and provide information on the use of capecitabine in a population of patients typical of routine clinical practice, intrinsic physician bias complicates interpretation. For example, in both the analyses above, starting dose appeared to be influenced by age, although the trends were in opposite directions in the two studies. In addition, patients with more indolent, slowly evolving disease are likely to continue therapy for longer and have more opportunities for dose modification at some point during their treatment, introducing bias and weakening the
conclusions that can be drawn. Although prospective studies may also be affected by bias because of patient eligibility and willingness to enter a clinical trial, the effect may be slightly less pronounced. Three single-arm studies evaluated a capecitabine starting dose of 1000 mg/m² b.i.d. In the first, a phase II study evaluating capecitabine as first-line therapy in MBC patients ≥65 years old, the initial starting dose was 1250 mg/m² b.i.d. [21]. However, toxicity in the first 30 treated patients led to protocol modification, and the remaining 43 patients received a starting dose of 1000 mg/m² b.i.d., days 1–14 every 21 days. Only 5% of patients treated at the lower starting dose required dose modification compared with 30% treated at the higher starting dose. While the higher dose was associated with unacceptable toxicity, it should be mentioned that this study in older patients was initiated before the recommendation of a 25% lower starting dose in patients with moderately impaired renal function [28]. Thus, the lower starting dose may have been more advisable from the start of the study on the basis of some degree of renal function impairment in all enrolled patients and the median age of 73 years (range 65–89). The improved tolerability seen with the lower starting dose appeared to be achieved without compromising efficacy. The RR in the cohort treated at the lower capecitabine starting dose was 35%, median TTP was 4.1 months and median OS was 16 months. These efficacy results compare favourably with the median OS of 10 months in patients receiving capecitabine 1250 mg/m² b.i.d., although the non-randomised nature of the trial prevents meaningful comparison of the two dose cohorts.

Like Bajetta et al., another group of Italian investigators reported unacceptable toxicity in the first seven patients receiving capecitabine 1250 mg/m² b.i.d. in a small phase II study [29]. Consequently, a further 30 patients began treatment at a capecitabine starting dose of 1000 mg/m² b.i.d. The RR was 60% in the registered dose group (five evaluable patients) and 56% in the lower starting dose group (25 evaluable patients). Median TTP and OS in the overall population were 7 and 19 months, respectively.

In a third small, single-arm, phase II study, UK investigators evaluated capecitabine starting at 1000 mg/m² b.i.d., days 1–14 every 21 days. Results in 57 patients with pretreated MBC suggested that tolerability could be improved without impairing efficacy [30]. The RR was 28% and median PFS was 6 months. Among patients pretreated with anthracyclines and taxanes, the RR was 29% and median OS was 10 months, within the ranges reported in large phase II and III trials in this setting.

Very recently, first results from the German Breast Group MoniCa study (GBG39) evaluating capecitabine 1000 mg/m² b.i.d. as first-line monotherapy for MBC were reported [24]. In this single-arm phase II study in 161 patients, median TTP (the primary end point) was 7.3 months and median OS was 17.1 months. The median number of cycles delivered was 7 (range 1–39).

The apparently improved tolerability of a lower starting dose (less diarrhoea, vomiting and stomatitis) suggested by these non-randomised studies may be reflected in the ability to continue treatment for longer periods (Table 3; Figure 1). In the early trials of capecitabine 1250 mg/m² b.i.d., the median number of cycles was 4–6 [8, 9]. However, patients in Rossi et al.’s study with a lower starting dose received a median of nine cycles (range 1–35); among patients achieving a tumour response, the median duration of treatment was 13 cycles [29]. The authors suggested that the ability to deliver a greater number of cycles could have been a determining factor for the better RR in the low-dose group compared with historical data in the first-line setting. Table 3 shows that at the lower starting doses, continuation of treatment for at least 35 cycles is a common theme and is consistent with numerous anecdotal reports. At the higher starting dose, the median number of cycles is numerically lower, but there are nevertheless individual patients continuing treatment for up to 33 cycles. It would be interesting to know the dose at which the majority of these later cycles were administered.

**Table 3. Duration of therapy**

<table>
<thead>
<tr>
<th>Range</th>
<th>Median number of cycles (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1250 mg/m² b.i.d.</td>
<td></td>
</tr>
<tr>
<td>First-line</td>
<td></td>
</tr>
<tr>
<td>Bajetta et al. [21]</td>
<td>6 (1–8)</td>
</tr>
<tr>
<td>O’Shaughnessy et al. [20]</td>
<td>4</td>
</tr>
<tr>
<td>Pretreated</td>
<td></td>
</tr>
<tr>
<td>Thomas et al. [12]</td>
<td>4 (1–33)</td>
</tr>
<tr>
<td>Reichardt et al. [8]</td>
<td>4 (1–33)</td>
</tr>
<tr>
<td>Fumoleau et al. [9]</td>
<td>6 (1–15)</td>
</tr>
<tr>
<td>1000 mg/m² b.i.d.</td>
<td></td>
</tr>
<tr>
<td>First-line</td>
<td></td>
</tr>
<tr>
<td>Bajetta et al. [21]</td>
<td>6 (1–8)</td>
</tr>
<tr>
<td>Kaufmann et al. [24]</td>
<td>7 (1–39)</td>
</tr>
<tr>
<td>Rossi et al. [29]</td>
<td>9 (1–35)</td>
</tr>
<tr>
<td>Pretreated</td>
<td></td>
</tr>
<tr>
<td>Sezgin et al. [17]</td>
<td>7.6 (1–26)</td>
</tr>
<tr>
<td>Yap et al. [26]</td>
<td>5 (1–40)</td>
</tr>
</tbody>
</table>

**retrospective studies of a lower starting dose**

Observations from a retrospective study of 63 patients receiving capecitabine 1000 mg/m² b.i.d. (days 1–14) as first-line therapy for MBC [26] are similar to results of the prospective studies described above. The overall RR among 48 patients with measurable disease was 29%. Median TTP was 4.1 months (range 0.5–28 months); TTP was >1 year in 11%. Although the median number of cycles was five, treatment was continued for ≥10 cycles in 13% of patients (2.3 years in one patient). Only 3% stopped treatment prematurely because of toxicity. Similar small retrospective studies of patients treated at the same, modified starting dose of capecitabine have been reported, with median TTP of 3–6.5 months [17, 31] and median OS of 13.7 months in one study (range 2.5–56.6) [31]. Treatment was continued for up to 26 cycles (median 7.6) in one of these studies [17].
As mentioned above, a continuous regimen with capecitabine at a dose of 650 mg/m² b.i.d. showed similar efficacy to an intermittent regimen of capecitabine 1000 mg/m² b.i.d. A second randomised trial by the GEICAM group (Spanish Group for Breast Cancer Research), comparing an intermittent versus a continuous schedule of capecitabine, has recently completed enrollment. It differs from Stockler et al.’s trial [22] because both regimens are designed to deliver a total dose per cycle equivalent to the registered intermittent regimen of 1250 mg/m² b.i.d. Preliminary safety results suggest that continuous capecitabine 800 mg/m² b.i.d. is better tolerated than the registered intermittent regimen [32]. Efficacy data are not yet available.

In Japan, an alternative, 4-week schedule (828 mg/m² b.i.d., days 1–21 every 28 days) is widely used with proven efficacy. As with the schedules described above, a lower mean capecitabine dose per week of capecitabine is delivered, but efficacy is maintained [33–35]. A single-arm study in docetaxel-pretreated patients [34] demonstrated efficacy almost identical to that seen in the initial phase II study of the standard intermittent regimen [6]. Hand–foot syndrome was the most common grade ≥3 adverse event, but diarrhoea was not problematic. In two additional single-arm studies of the 4-weekly regimen, RR and TTP were slightly more favourable than in the original monotherapy studies, reflecting the less heavy pretreatment of the study populations. Although the only prospective data on the Japanese regimen come from these three, small, single-arm studies, data from a larger patient population (n = 102) treated with the Japanese regimen as monotherapy for MBC in routine clinical practice were recently published [16]. The majority (79%) of the patients had previously received both an anthracycline and a taxane. The investigators reported an overall RR of 17% (95% CI: 9–24), within the range reported in phase II studies in anthracycline- and taxane-pretreated patients receiving the standard, 21-day intermittent regimen. However, median OS with the Japanese regimen in this retrospective study was notably longer at 24.3 months after a median follow-up of 16.4 months. Only 2% of patients experienced grade 3 diarrhoea; grade 4 diarrhoea was absent. Taken together, these findings suggest that a 4-weekly intermittent regimen produces similar efficacy to the more commonly used, 3-weekly intermittent regimen. Thus, the exact dosing schedule of capecitabine can be adapted to fit individual preference and to simplify scheduling when using capecitabine in combination with agents typically administered using a 2-weekly or 4-weekly schedule.

Various other schedules of capecitabine have been investigated, most notably the ‘7/7’ regimen in the United States.

**Figure 1.** Summary of grade 3/4 non-haematological adverse events: (A) starting dose 1250 mg/m² b.i.d.; (B) starting dose 1000 mg/m² b.i.d.
(capecitabine on days 1–7 followed by a 7-day rest period) [36, 37] and a weekday schedule (capecitabine on days 1–5 followed by a 2-day rest period) in France [38]. Limited efficacy data are available from these studies and evaluation is ongoing.

discussion

The survival benefit in Stockler et al.’s trial gives an indication that a lower starting dose of capecitabine is the most appropriate way to give this drug [22]. In the studies of capecitabine at a lower starting dose, patients consistently stayed on therapy for longer than in studies evaluating the registered dose. Although the considerably longer duration of therapy in the first-line, phase III trial reported by Stockler et al. may be due in part to the earlier stage of disease (the pivotal studies of capecitabine at the registered dose were conducted typically in the third-line setting), data reported by Sezgin et al. in heavily pretreated patients support the hypothesis that a lower, more tolerable starting dose enables treatment to be continued for longer periods [17].

It is possible that a dose less than 1000 mg/m² might offer further improvements in tolerability without compromising efficacy. Even at a starting dose of 1000 mg/m², some patients require dose reduction [18, 26]. On the other hand, some patients may benefit from a higher dose and consequently it has been proposed that dose escalation may be implemented if patients tolerate a starting dose of 1000 mg/m² well [18, 22]. This strategy merits further prospective evaluation.

Although our deliberations on capecitabine dosing are important for patients receiving capecitabine as monotherapy, they also have implications for treatment in the so-called ‘era of targeted therapy’. Increasingly, patients with MBC receive chemotherapy in combination with a targeted or biological therapy, such as trastuzumab, bevacizumab or lapatinib. As mentioned at the beginning of this article, both bevacizumab and lapatinib were initially tested in combination with capecitabine in randomised, phase III trials in patients with heavily pretreated MBC [11, 13]. Trastuzumab has also been evaluated with capecitabine in a recently published phase III trial, GBG26 [39]. While lapatinib was combined with capecitabine 1000 mg/m² b.i.d., both bevacizumab and trastuzumab were combined with the registered dose. On the basis of the available data, capecitabine 1000 mg/m² b.i.d. may be a better starting dose, maximising the good tolerability achieved by combining agents such as bevacizumab with single-agent chemotherapy. At the 2009 ASCO annual meeting, results of the RIBBON-1 trial evaluating bevacizumab in combination with taxane, anthracycline-based therapy or capecitabine 1000 mg/m² b.i.d. in the first-line setting were reported [23]. The trial demonstrated significantly improved PFS (the primary end point) and RR when bevacizumab was combined with capecitabine (or with taxane or anthracycline-based therapy). The hazard ratio for PFS was 0.69 (95% CI: 0.56–0.84; \( P = 0.0002 \)) and median PFS was 8.6 months with first-line capecitabine combined with bevacizumab versus 5.7 months with capecitabine alone. Data on the duration of therapy in RIBBON-1 have not yet been reported, but may shed light on the feasibility of prolonged treatment with such a regimen. A second randomised trial, conducted by the Central European Cooperative Oncology Group, is comparing capecitabine 1000 mg/m² b.i.d. in combination with bevacizumab versus a combination of bevacizumab and weekly paclitaxel. In both these trials, capecitabine and bevacizumab combination therapy is continued until disease progression, unacceptable toxicity or patient refusal.

Another avenue being explored to refine and optimise capecitabine therapy is the identification of markers that may predict tolerability. If a reliable and practical marker can be found, those patients particularly at risk of toxicities can receive a dose tailored to their individual profile (or receive an alternative treatment if the risk of capecitabine-associated toxicity is too high, for example, in patients with dihydropyrimidine dehydrogenase deficiency). Currently, there are only very limited data available on potential markers for tolerability of capecitabine. Preliminary data from a pilot study by Largillier et al. [40] suggested an increased risk of capecitabine-related grade 3/4 adverse events in patients homozygous for the TS 3RG allele compared with patients heterozygous for the 3RG allele or patients not carrying the 3RG allele (50% versus 19% versus 13% respectively, \( P = 0.064 \)). The authors state that these preliminary data require further confirmation in a larger number of patients. Similarly, Ribelles et al. reported a trend towards increased incidence of grade 3 hand–foot syndrome (\( P = 0.07 \)) and grades 3–4 diarrhoea (\( P = 0.09 \)) in patients with polymorphisms in CDD 943insC and CES 2 Exon3 6046 G/A [41]. In the move towards individualised therapy, such observations provide interesting opportunities for tailoring treatment to each patient.

conclusion

Despite the lack of a randomised trial comparing the registered capecitabine monotherapy dose with a lower starting dose, there are several datasets showing that a lower starting dose is well tolerated and highly active. Therefore, we suggest a starting dose of 1000 mg/m² b.i.d., thus providing patients with an active therapy that can be continued for prolonged periods to achieve long-term disease control. The cumulative evidence for this lower starting dose perhaps overcomes the infeasibility of a randomised trial of the registered versus a lower dose. As well as improving treatment in patients receiving capecitabine monotherapy, these conclusions have implications for patients receiving capecitabine and targeted therapy, with which the possibility of long-term disease control is becoming a reality, as seen in the RIBBON-1 trial.

funding

F. Hoffmann-La Roche Ltd, Basel, Switzerland.

acknowledgements

Literature searching and medical writing support were provided by Jennifer Kelly, supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland. The authors critically reviewed and revised the paper at all stages of development, take full
responsibility for the content of this article and retain control of the decision to submit the manuscript for publication.

disclosure
CZ has received speaker honoraria from Roche, Eli Lilly and Bristol-Myers Squibb. MM has received speaker honoraria from Roche. JG has received research funding from Roche.

references
14. Hortobagyi GN, Perez E, Vrdoljak E et al. Analysis of overall survival (OS) among patients (pts) with metastatic breast cancer (MBC) receiving either ixabepilone (I) plus capecitabine (C) or C alone: results from two randomized phase III trials ASCO 2008 Breast Cancer Symposium (Abstr 149).


