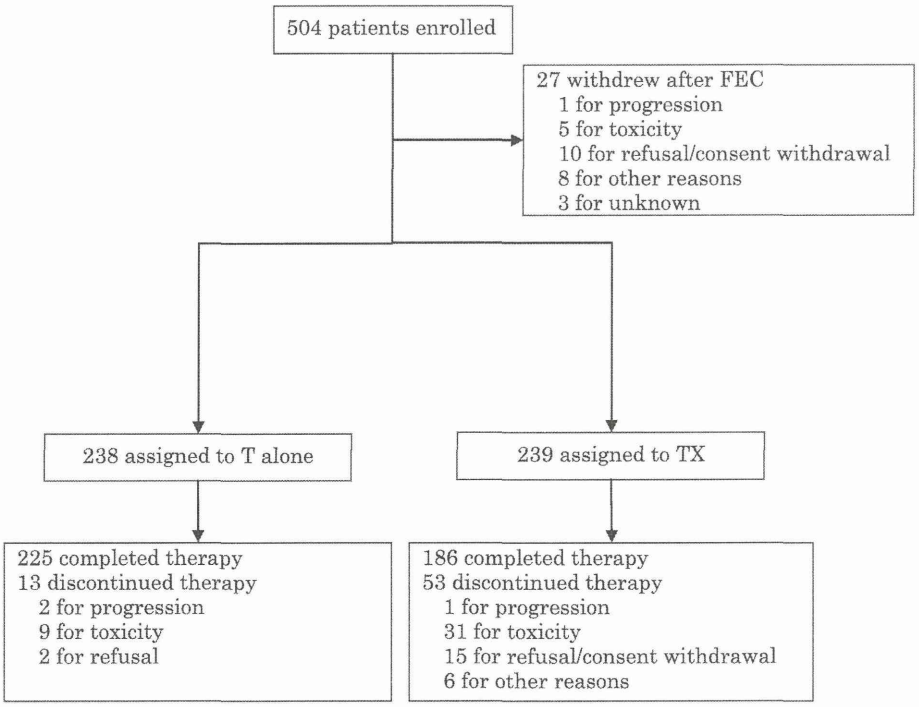


**Fig. 1** Study completion. FEC: fluorouracil/epirubicin/cyclophosphamide; T: docetaxel alone; TX: docetaxel plus capecitabine

**Table 2** Pathological response by (a) central assessment, (b) central assessment in patients who discontinued or received a reduced dose

| | FEC ($n$ = 27) % (95% CI) | TX ($n$ = 239) % (95% CI) | T ($n$ = 238) % (95% CI) | Difference (TX-T) (95 %CI) | $p$ value |
|---|---|---|---|---|---|
| (a) | | | | | |
| pCR | 7.4 | 23 (17.8–28.9) | 24.4 (19.1–30.3) | −1.4 (−9.0 to 6.3) | 0.7476 |
| pINV | 48.1 (28.7–68.1) | 72.4 (66.3–78.0) | 71.4 (65.2–77.1) | 1 | |
| Missing* | 44.4 (25.5–64.7) | 4.6 (2.3–8.1) | 4.2 (2.0–6.7) | 0.4 | |
| (b) | | | | | |
| pCR | 7.4 | 23 (17.8–28.9) | 24.4 (19.1–30.3) | −1.4 (−9.0 to 6.3) | 0.7476 |
| With discontinuation | | ($n$ = 12/53) | ($n$ = 1/13) | | |
| pCR | – | 22.6 (12.3–36.2) | 7.7 (0.2–36.0) | 14.9 (−3.4 to 33.3) | |
| With dose reduction | | ($n$ = 19/79) | ($n$ = 2/14) | | |
| pCR | – | 24.1 (15.1–35.0) | 14.3 (1.8–42.8) | 9.8 (−10.8 to 30.4) | |

*pCR* pathological complete response, *pINV* pathological presence of invasive tumor, * patients missing post-baseline mainly due to discontinuation as a result of toxicity, *CI* confidence interval, *FEC* 5-fluorouracil–epirubicin–cyclophosphamide, *TX* docetaxel plus capecitabine, *T* docetaxel alone

Table 2a). However, we observed an interesting trend in the subset of patients who had discontinued treatment or received a 25 % dose reduction. Despite treatment withdrawal, 12/53 in the docetaxel/capecitabine group and 1/13 in the docetaxel group achieved a pCR with rates of 22.6 and 7.7 %, respectively. A similar trend was observed in the 33.1 % (79/239) and 5.9 % (14/238) who received a 25 % dose reduction and achieved pCR rates of 24.1 % (19/79) and 14.3 % (2/14), respectively (Table 2b). Although not statistically significant, pCR rates were higher in the docetaxel/capecitabine group in comparison to the docetaxel group in this subpopulation.

## Disease-free and overall survival

After a median 4.5-year follow-up, the 3-year DFS was estimated at 92.7 % in the docetaxel/capecitabine group and 90.7 % in the docetaxel group. Four patients were

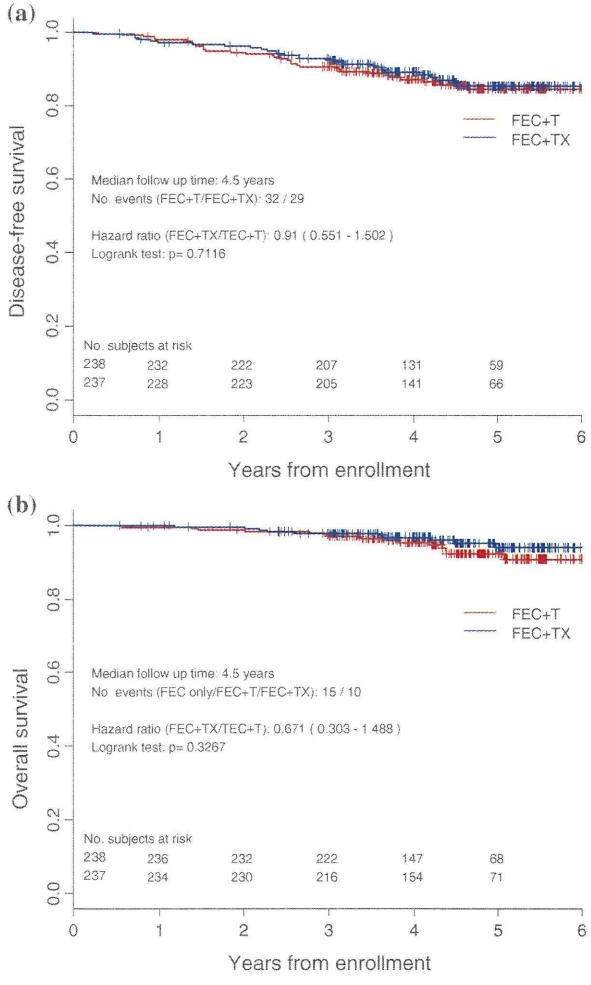


**Fig. 2** **a** Disease-free survival. **b** Overall survival. FEC: fluorouracil/epirubicin/cyclophosphamide; T: docetaxel alone; TX: docetaxel plus capecitabine

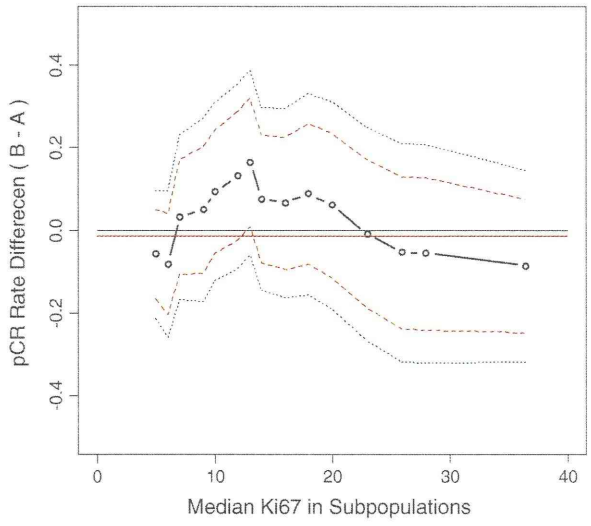


**Fig. 3** STEPP analysis of the treatment effect of docetaxel/capecitabine compared with single-agent docetaxel as measured by pCR. Values >0 suggested that the combination regimen was better; <0 indicated that single-agent docetaxel was better. Difference in pCR is shown (*dashed black lines*) with corresponding 95 % CI (*dashed red lines*) and corresponding 95 % confidence band (*dashed blue lines*). Overall difference in pCR (*solid horizontal red line*) is shown

excluded from the ITT population due to missing data. A total of 29 events occurred in the docetaxel/capecitabine group and 32 in the docetaxel group, with a HR of 0.910 (95 % CI 0.551–1.502; Fig. 2a). During follow-up, 10 deaths occurred in the docetaxel/capecitabine group and 15 in the docetaxel group, with a point of estimate HR of 0.671 (95 % CI 0.303–1.488; Fig. 2b).

## Predictive factor analyses for pathological response and survival status

Subpopulation analysis for pathological response showed no significant difference between treatment groups (data not shown). To identify predictive factors for pathological response using age and Ki67 as continuous variables, an overlapping subpopulation of 84 patients was constructed and analyzed using the STEPP method. Although no statistical significance was achieved, STEPP analysis indicated a trend in favor of improved pCR rate in patients with mid-range of Ki67LI (10–20 %) following docetaxel/capecitabine compared with docetaxel alone (Fig. 3). To further investigate the predictive value of Ki67 relative to pCR, univariate and multiple logistic regression models were fitted to calculate the odds ratio (OR) and 95 % CI for each risk factor.

Univariate analysis showed that nuclear grading, ER and/or PgR status, HER2 status, baseline Ki67 and TP-SI were all strongly associated with pCR (Table 3a). Multivariate analysis was performed using the predictive variables identified in the univariate analysis. To evaluate the effect of Ki67, a multivariate logistic regression analysis was undertaken in 410 patients with available baseline data for nuclear grading, ER and/or PgR, HER2, and Ki67. In the first model, all of these factors continued to be 15 % significant predictors for pCR. In the final model, pretreatment levels of Ki67 proved to be a predictive factor for pCR, with an OR of 1.031 (95 % CI 1.014–1.048; $p = 0.0004$). Using this model, the random cross-validated sensitivity and specificity were 83.3 and 63.4 %, respectively (Table 3b).

Predictive factors for DFS were analyzed using a multiple Cox model in a landmark analysis (Online Resource). When pCR and postKi67 were included in the final model, tumor stage (I, IIa/III: HR 0.144, 95 % CI 0.051–0.404; IIb/III: HR 0,264, 95 % CI 0.107–0.651; $p = 0.0006$), cancer cell TP status (continuous variables: HR 0.966,

**Table 3** Prediction of pCR using (a) simple logistic regression model, (b) multiple logistic regression model with Ki67

| Factor | # pat | # res | OR | 95 %CI | *p* value |
|---|---|---|---|---|---|
| (a) | | | | | |
| Age | | | | | |
| ≤49 | 248 | 56 | 0.880 | 0.577–1.343 | 0.5534 |
| ≥50 | 229 | 57 | 1 | | |
| Initial tumor size | | | | | |
| ≤2.0 | 29 | 7 | 1.047 | 0.409–2.682 | 0.9919 |
| 2.1–4.0 | 315 | 75 | 1.028 | 0.637–1.659 | |
| ≥4.1 | 133 | 31 | 1 | | |
| Axillary lymph node | | | | | |
| Positive | 268 | 62 | 0.932 | 0.610–1.426 | 0.7467 |
| Negative | 209 | 51 | 1 | | |
| Menopausal status | | | | | |
| Pre | 266 | 60 | 0.868 | 0.568–1.326 | 0.5135 |
| Post | 211 | 53 | | | |
| Stage | | | | | |
| I/IIa | 54 | 211 | 1.849 | 0.818–4.179 | 0.3355 |
| IIb | 51 | 215 | 1.671 | 0.738–3.786 | |
| III | 8 | 51 | 1 | | |
| Nuclear grading | | | | | |
| G1 | 78 | 9 | 0.240 | 0.112–0.517 | <.0001 |
| G2 | 229 | 46 | 0.463 | 0.293–0.731 | |
| G3 | 162 | 57 | 1 | | |
| ER and/or PgR | | | | | |
| Positive | 327 | 58 | 0.265 | 0.167–0.422 | <.0001 |
| Negative | 116 | 52 | 1 | | |
| HER2 | | | | | |
| Positive | 62 | 33 | 4.552 | 2.604–7.958 | <.0001 |
| Negative | 380 | 76 | 1 | | |
| Baseline of Ki67 (%) | | | | | |
| ≥10 | 299 | 95 | 4.572 | 2.348–8.903 | <.0001 |
| <10 | 119 | 11 | 1 | | |
| Continuous | 418 | | 1.043 | 1.027–1.059 | <.0001 |
| TP-CI | | | | | |
| 1 + , 2 + , 3+ | 282 | 73 | 1.715 | 0.851–3.456 | 0.1316 |
| 0 | 65 | 11 | 1 | | |
| 2 + , 3+ | 119 | 33 | 1.332 | 0.801–2.213 | 0.2690 |
| 0, 1+ | 228 | 51 | 1 | | |
| TP-SI | | | | | |
| 1 + , 2 + , 3+ | 324 | 84 | 4.025 | 0.929–17.438 | 0.0627 |
| 0 | 25 | 2 | 1 | | |
| 2 + , 3+ | 197 | 59 | 1.979 | 1.182–3.315 | 0.0095 |
| 0, 1+ | 152 | 27 | 1 | | |

| | OR | 95 %CI | *p* value | Sensitivity specificity | ROC (95 % CI) | Contrast with final model |
|---|---|---|---|---|---|---|
| (b) | | | | | | |
| Grading | | | | | | |
| 1 | 0.312 | 0.129–0.756 | 0.0027 | Random cv | Apparent | |
| 2 | 0.461 | 0.274–0.773 | | Sen: 0.8113 | 0.7510 | |

**Table 3** continued

| | OR | 95 %CI | *p* value | Sensitivity specificity | ROC (95 % CI) | Contrast with final model |
|---|---|---|---|---|---|---|
| 3 | 1 | | | (0.6034, 0.8958) | (0.6999, 0.8021) | |
| ER and/or PgR | | | | | | |
| Positive | 0.384 | 0.230–0.642 | 0.0003 | | | |
| Negative | 1 | | | Spe: 0.6097 | Random cv | |
| HER2 | | | | | | |
| Positive | 3.816 | 2.056–7.081 | <.0001 | (0.5517, 0.7391) | 0.7353 | |
| Negative | 1 | | | | (0.6664, 0.7901) | |
| Grading | | | | | | |
| 1 | 0.402 | 0.163–0.991 | 0.00281 | Random cv | Apparent | Apparent |
| 2 | 0.536 | 0.316–0.909 | | Sen: 0.8000 | 0.7657 | 0.0147 |
| 3 | 1 | | | (0.6599, 0.8889) | (0.7172, 0.8143) | (−0.0055, 0.0350) |
| ER and/or PgR | | | | | | |
| Positive | 00.413 | 0.247–0.692 | 0.0008 | | | |
| Negative | 1 | | | Spe: 0.6458 | | |
| HER2 | | | | | | |
| Positive | 3.522 | 1.890–6.563 | <.0001 | (0.5792, 0.7452) | Random cv | Random cv |
| Negative | | | | | 0.7489 | 0.0168 |
| Ki67 (%) | | | | | | |
| ≥10 | 2.718 | 1.331–5.549 | 0.0061 | | (0.6827, 0.7986) | (−0.0303, 0.041) |
| <10 | 1 | | | | | |
| Grading | | | | | | |
| 1 | 0.418 | 0.169–1.035 | 0.0298 | Random cv | Apparent | Apparent |
| 2 | 0.530 | 0.312–0.900 | | Sen: 0.8333 | 0.7774 | 0.0264 |
| 3 | 1 | | | (0.6735, 0.9400) | (0.7289, 0.8259) | (0.0015, 0.0513) |
| ER and/or PgR | | | | | | |
| Positive | 0.447 | 0.265–0.754 | 0.0026 | | | |
| Negative | 1 | | | Spe: 0.6344 | Random cv | Random cv |
| HER2 | | | | | | |
| Positive | 3.794 | 2.038–7.065 | <0.0001 | (0.5063, 0.7713) | 0.7607 | 0.0274 |
| Negative | 1 | | | | (0.6993, 0.8099) | (−0.0175, 0.0596) |
| Ki67 (continuous) | 1.031 | 1.014–1.048 | 0.0004 | | | |

*#pat* number of patients, *#res* number of responders, *CI* confidence interval, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *OR* odds ratio, *PgR* progesterone receptor, *TP-CI* thymidine phosphorylase, interstitial, *TP-SI* thymidine phosphorylase, stromal

*ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *PgR* progesterone receptor, *OR* odds ratio

95 % CI 0.941–0.993; $p = 0.0125$), pCR, and post-treatment Ki67LI (pCR/Ki67 <10/≥10: HR 0.269, 95 % CI 0.110–0.655; $p = 0.0038$) were all significantly associated with DFS (Table 4).

### Safety profile

The frequency of major adverse events (≥grade 3) of docetaxel/capecitabine and docetaxel group were as follows: leukopenia (36 and 34 %, respectively), neutropenia (38 and 34 %, respectively), febrile neutropenia (8 and 5 %, respectively), and hand-foot syndrome (15 and 2 %, respectively). Docetaxel/capecitabine was associated with more capecitabine-related toxicity, including hand-foot syndrome, nausea, mucositis, and increased alanine aminotransferase. Six serious adverse events were reported for 3 patients in the docetaxel/capecitabine group (pneumonitic cough, muscle pain, neutropenia fever) and 3 patients in the docetaxel group (suicide, loss of eyesight of left eye, hematological toxicity). The event of suicide in the docetaxel alone group occurred after completion of treatment and was considered as unrelated to study treatment.

## Discussion

We have presented results from a randomized study comparing preoperative capecitabine/docetaxel with docetaxel

**Table 4** Hazard ratio for disease-free survival using a multiple cox model in landmark analysis

| Factors | HR | (95 % CI) | *p* value |
|---|---|---|---|
| The final model | | | |
| Stage | | | |
| I/IIa | 0.160 | 0.059–0.436 | 0.0016 |
| IIb | 0.390 | 0.170–0.893 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.468 | 0.235–0.932 | 0.0308 |
| Negative | 0.974 | 0.953–0.996 | 0.0193 |
| TP-CP | | | |
| Continuous | 1 | | |
| Extended model 1 | | | |
| Stage | | | |
| I/IIa | 0.170 | 0.065–0.444 | 0.0011 |
| IIb | 0.360 | 0.165–0.787 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.327 | 0.160–0.670 | 0.0023 |
| Negative | 1 | | |
| TP-CP | | | |
| Continuous | 0.975 | 0.954–0.997 | 0.0253 |
| pCR | | | |
| Responder | 0.191 | 0.052–0.696 | 0.0121 |
| Nonresponder | | | |
| Extended model 2 | | | |
| Stage | | | |
| I/IIa | 0.133 | 0.051–0.349 | 0.0002 |
| IIb | 0.308 | 0.134–0.706 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.441 | 0.221–0.878 | 0.0198 |
| Negative | 1 | | |
| TP-CP | | | |
| Continuous | 0.974 | 0.953–0.996 | 0.0199 |
| Treatment | | | |
| Completion | 0.633 | 0.209–1.917 | 0.3560 |
| Reduction | 1.125 | 0.339–3.729 | |
| Discontinuation | 1 | | |
| Extended model 3 | | | |
| Stage | | | |
| I/IIa | 0.134 | 0.051–0.350 | 0.0002 |
| IIb | 0.309 | 0.135–0.706 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.439 | 0.220–0.878 | 0.0200 |
| Negative | 1 | | |
| TP-CP | | | |
| Continuous | 0.974 | 0.953–0.996 | 0.0183 |
| Treatment | | | |
| Completion | 0.584 | 0.278–1.226 | 0.1554 |
| Otherwise | 1 | | |
| Extended model 4 | | | |
| Stage | | | |
| I/IIa | 0.153 | 0.056–0.419 | 0.0006 |
| IIb | 0.279 | 0.116–0.673 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.577 | 0.229–1.454 | 0.2433 |
| Negative | 1 | | |
| TP-CP | | | |
| Continuous | 0.967 | 0.941–0.993 | 0.0144 |
| p CR & PostKi67 | | | |
| Responder | 0.137 | 0.034–0.549 | 0.0140 |
| PostKi67 < 10 | 0.388 | 0.143–1.052 | |
| PostKi67 ≧ 10 | 1 | | |
| Extended model 5 | | | |
| Stage | | | |
| I/IIa | 0.144 | 0.051–0.404 | 0.0006 |
| IIb | 0.264 | 0.107–0.651 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.756 | 0.334–1.712 | 0.5030 |
| Negative | 1 | | |
| TP-CP | | | |
| Continuous | 0.966 | 0.941–0.993 | 0.0125 |
| pCR & PostKi67 | | | |
| Responder | 0.269 | 0.110–0.655 | 0.0038 |
| PostKi67 < 10 | | | |
| PostKi67 ≧ 10 | 1 | | |
| Extended model 5 | | | |
| Stage | | | |
| I/IIa | 0.200 | 0.072–0.561 | 0.0031 |
| IIb | 0.264 | 0.103–0.676 | |
| III | 1 | | |
| ER and/or PgR | | | |
| Positive | 0.385 | 0.152–0.977 | 0.0445 |
| Negative | 1 | | |
| TP-CP | | | |
| Continuous | 0.970 | 0.943–0.997 | 0.0301 |

*ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *PgR* progesterone receptor, *OR* odds ratio, *TP-CP* thymidine phosphorylase, plasma

alone after FEC in early-stage breast cancer, and have identified Ki67 as a predictive biomarker that may be used to identify patients likely to respond to this neoadjuvant regimen.

In contrast to previous reports, we observed no difference in the pCR rate between the docetaxel/capecitabine and the docetaxel group. Our observation was similar to that from the GeparQuattro study, in which docetaxel/capecitabine did not improve pCR rate in comparison to docetaxel after epirubicin/cyclophosphamide treatment in the neoadjuvant setting [21]. Although a 16 % pCR rate was expected in the docetaxel group based on previous observations [5], the pCR rate in our study was higher (24 %). The variation in clinical outcome may be attributed to the currently limited means with which to select patient subpopulations most likely to respond to a given treatment regimen.

The docetaxel/capecitabine regimen was less well tolerated than docetaxel alone, with withdrawal rates of 22.2 and 5.5 % and dose reduction rates of 33.1 and 5.9 %, respectively. Despite treatment withdrawals and dose reductions, achievement of higher pCR rates in the docetaxel/capecitabine group in comparison to the docetaxel group in this subpopulation suggests that dose reduction does not negatively impact capecitabine efficacy. Our data confirms a similar observation in a MBC study, which reported no significant effect on efficacy when dose reduction occurred in 65 and 36 % of patients receiving the docetaxel/capecitabine regimen and docetaxel alone, respectively. However, an increased risk of disease progression was seen in patients with a dose reduction to 50 % of the starting dose in the docetaxel group (HR 1.91) [15]. As reported by other groups [22], our data demonstrate that the capecitabine dose can be reduced to minimize adverse effects without compromising efficacy. It was, however, interesting to observe that patients who discontinued or received a dose reduction in the docetaxel/capecitabine group achieved a higher pCR compared with the docetaxel alone group, while there was no difference in pCR between both groups in patients that completed the study at the original dose. Although the reason for this observation is unclear, the observation that the relative dose intensity for docetaxel was significantly lower in the combination arm compared with the single agent docetaxel arm may at least in part, account for the lack of difference in pCR. In addition, levels of toxicity may have had an impact on drug delivery and thus, pCR.

In addition to comparing the efficacy of neoadjuvant docetaxel/capecitabine with docetaxel alone, our study also sought to identify biomarkers that can identify patients likely to respond to treatment with docetaxel/capecitabine in early-stage breast cancer. Previously identified biomarkers, such as nuclear grading, ER and/or PgR status, HER2 status and Ki67, correlated with pCR in our study, as in other published studies [23]. Of particular interest was pre-treatment Ki67LI, which had a strong correlation with pCR and added to the predictive value of the multivariate logistic regression model. Indeed, data from several other studies suggest that high Ki67 levels in breast cancer are a predictive factor for pCR rate [5, 24–27]. This effect was present in our study, as patients with $\geq$10 % pre-treatment Ki67LI achieved a higher pCR rate in both the docetaxel/capecitabine (32.6 %) and docetaxel alone (31 %) groups, in comparison to patients with <10 % pre-treatment Ki67LI (pCR rates 6.5, 12.3 %, respectively). These findings support the suggestion that detection of pre-treatment Ki67LI could identify patients most likely to benefit from neoadjuvant chemotherapy. The prognostic value of Ki67 was also confirmed in our study, as post-treatment Ki67LI and pCR were significantly associated with DFS using a multiple Cox model in a landmark analysis. Thus, prognostic and predictive value was detected for Ki67, showing it to be a feasible marker for development of individualized treatment options for early-stage breast cancer patients.

To our knowledge, this is the first multicenter randomized study showing that assessment of pre- and post-treatment Ki67 may be a useful tool in predicting pCR and DFS with neoadjuvant docetaxel treatment with or without capecitabine in patients with early-stage breast cancer. Although further studies are required, our data suggests that the routine detection of the Ki67 proliferation marker in early-stage breast cancer could be a useful prognostic tool for the identification of patients most likely respond to preoperative docetaxel with or without capecitabine. As such, in addition to the current leading parameters (ER, PgR, and HER2 status), we propose that Ki67 should be included in the list of required routine biological markers that are used to define treatment recommendations in patients with early-stage breast cancer. Indeed, detection of predictive biomarkers prior to chemotherapy is likely to prove to be of the greatest advantage for neoadjuvant chemotherapy.

**Acknowledgments** This study was made possible by the generous support and supply of knowledge by Product Research Department, Kamakura Research Laboratories, Chugai Pharmaceutical Co., Ltd. and Sanofi K.K., Japan. This work was supported by an unconditional grant from Sanofi K.K., Japan.

**Conflict of interest** The authors have declared no conflicts of interest.



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III がん薬物治療薬の作用機序

がん免疫療法・細胞療法

# 革新的がんワクチン，helper/killer-hybrid epitope long peptide(H/K-HELP)の開発とその作用

Development of an innovative cancer vaccine, helper/killer-hybrid epitope long peptide(H/K-HELP)



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Key words：がんワクチン治療，H/K-HELPがんワクチン，ヘルパーT細胞，Th1細胞，CTL

## はじめに

1991年のテリー・ブーン博士らによるがん抗原の発見[1]以来，アミノ酸8-9個からなるクラスI結合性がん抗原キラーペプチド(ショートペプチド)を用いたがんワクチン治療が盛んに行われてきている．しかし，最近，ショートペプチドとIFAのワクチンではCTLが投与部位で死滅し，CTLメモリーが形成されず，十分な抗腫瘍免疫が誘導できない機構が明確にされた[2]．また，このショートペプチドによるトレランスはヘルパーペプチドの添加あるいはロングペプチドへの改変によって克服されることも示された．したがって，ここで紹介する，ヘルパーペプチドとキラーペプチドのハイブリッドロングペプチド，H/K-HELPは期せずしてこれらの条件を兼ね備えており，今後，更に革新的がんワクチンペプチドとして注目を集める可能性が高い．H/K-HELPはMelief ら[3]によって開発された単にクラスIペプチドを伸張したsynthetic long peptide(SLP)より強い抗腫瘍活性を有しており，ロングペプチドゆえに，投与部位の所属リンパ節においてのみ，プロフェッショナルDCによりヘルパー/キラーエピトープがプロセッシング，提示され，強力に抗原特異的なTh1，Tc1を活性化してがんの拒絶をも誘導することができる理想的ながんペプチドワクチンと考えられる．

## 1 Helper/killer-hybrid epitope long peptide(H/K-HELP)ワクチンの開発と臨床研究への応用

MHCクラスI結合性がん抗原ペプチド(8-10アミノ酸：ショートペプチド)を用いたがんワクチン治療の臨床研究が一般的に行われている[4]．しかし，CTLを軸としたがん免疫治療は当初期待されたほどの有効な治療効果は報告されていない．①担がん生体における強い免疫抑制と②CTLの活性化のみに照準を合わせ，Thの活性化を無視していることが大きな要因と思われる．それに加え，最近，ショートペプチドとIFAを用いたがんワクチン方法は最良の方法ではなく，CTLの死滅を誘導し，CTLメモリーは誘導されないことが示された[2]．この負のワクチン効果はThエピトープの添加やロングペプチドへの変換によって克服されることが証明された．すなわち，ヘルパーペプチドの存在とロ

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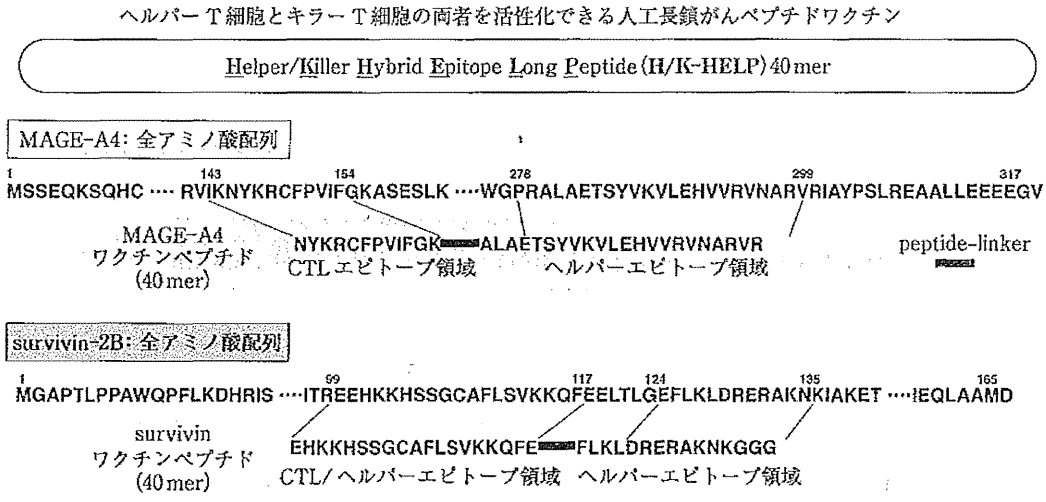



| がん抗原 | 非小細胞がん | 食道がん | 大腸がん | 胆道がん | 黒色腫 | 卵巣がん | 頭頸部がん | 乳がん |
|---|---|---|---|---|---|---|---|---|
| MAGE-A4 | 28.4% | 58.8% | 30.0% | 16.7% | 20.0% | 25.0% | 42.9% | 13.0% |
| survivin | 83.5% | 70.6% | 63.5% | − | 98.4% | − | 80.0% | 93.6% |

| | HLA抗原 | 発現頻度 日本人 | 発現頻度 白人 | | HLA抗原 | 発現頻度 日本人 | 発現頻度 白人 |
|---|---|---|---|---|---|---|---|
| MAGE-A4 | DPB1*0501 | 64% | little | survivin | DRB1*0101 | 10% | 15% |
| | DRB1*1403 | 10% | 0% | | DR53 | 50%> | 50%> |
| | DRB1*1501 | 20% | 33% | | DQB1*0601 | 30% | 3% |
| | DRB1*1502 | 19% | 0.7% | | DPB1*050 | 64% | little |
| | DRB1*0101 | 10% | 15% | | | | |

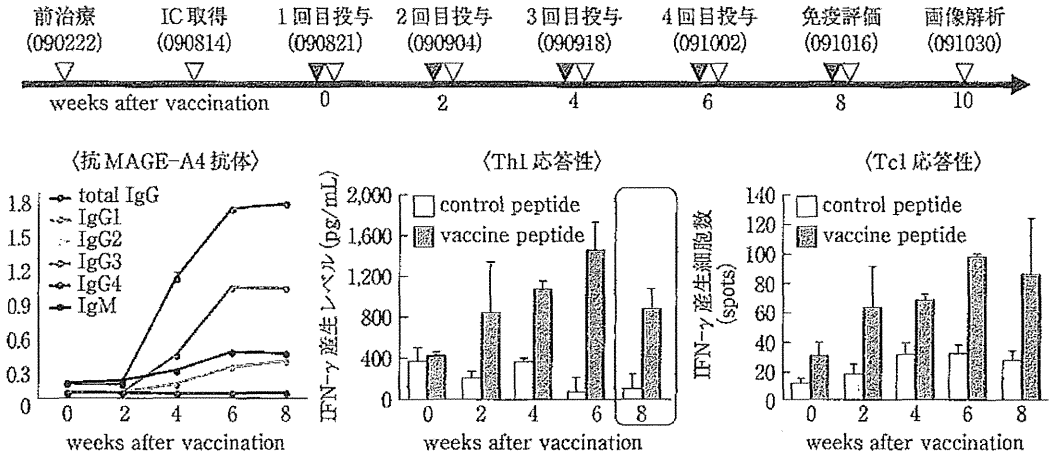
**図1　Th1細胞とCTLの両者を活性化するH/K-HELPの開発**

がん抗原であるMAGE-A4およびsurvivinについて，キラーエピトープとヘルパーエピトープをpeptide-linkerを用いて結合した40個のアミノ酸からなるロングペプチド(helper/killer-hybrid epitope long peptide (H/K-HELP)を作出した．MAGE-A4，survivinは多くのがん種で高頻度に発現が認められ，がん免疫治療の標的として非常に有用である．また，H/K-HELP作成に用いたキラーエピトープ，ヘルパーエピトープは様々なHLAアレルへの拘束性を確認しており，ほぼ100%の日本人に適応可能である有効ながんワクチンペプチドである．

ングペプチドのデザインが優れたがんワクチン開発には重要であることが示された．

著者らは，MAGE-A4やsurvivinがん抗原からMHCクラスIIがん抗原ヘルパーペプチドを単離し[5]，ヘルパーエピトープとキラーエピトープを人工的に結合させた40アミノ酸からなるH/K-HELPを開発し(図1)[6]，その第一相試験を北海道大学病院を中心として終了している．OK-432とMontanideをアジュバントとして用いて，MAGE-A4-H/K-HELPおよびSurvivin-H/K-HELPがんワクチン治療の臨床研究を施行したところ，驚くべきことに，従来のキラーT細胞のみをターゲットとしたショートペプチドに比べ，ワクチン投与後，早期にがん特異Th1細胞，Tc1細胞の活性化誘導が確認された．更に，がんペプチド特異的な抗体価も早期に上昇，特筆すべきは，Th1依存的に誘導されるIFN-γ依存的にクラススイッチを起こす補体結合性のIgG1，IgG3サブクラスのがん特異的抗体の上昇が確認された[6]．これまで評価可能患者11例中9例でH/K-HELP特異的な免疫反応が確認されている．この中には，トリプルネガティブの乳がん患者の制がん剤耐性，放射線耐性，頸部転移がんがCT画像上消失するCR 1

a. MAGE-A4-H/K-HELPがんワクチン投与による大腸がん患者におけるがん特異的免疫応答の誘導




b. survivin-H/K-HELPがんワクチン投与による制がん剤耐性・放射線耐性の転移性乳がん患者のCR例


**図2 MAGE-A4-H/K-HELPおよびSurvivin-H/K-HELPがんワクチンを用いた臨床研究**

MAGE-A4-H/K-HELPの投与によって，がん患者生体内でペプチド特異的な抗体産生が誘導された．また，その抗体の種類は，Th1(IFN-γ)依存的にクラススイッチを起こす補体結合性IgG1およびIgG3サブタイプであることが確認された．更に，ペプチド特異的なTh1，Tc1免疫応答も増強していたことから，H/K-HELPはがん患者生体内で効果的にTh1依存的免疫応答を惹起できることが確認された(a)[北海道大学第一外科，高橋先生，藤堂教授との共同研究]．

また，survivin-H/K-HELPがんワクチン投与によって，制がん剤耐性・放射線耐性のトリプルネガティブ乳がん患者のリンパ節転移がん細胞がCT画像上消失したことが確認された(b)[近畿大学外科，奥野教授との共同研究]．

例，およびがんの増殖が抑えられたSD 1例も観察された(図2)．この結果を受けて，著者らは，厚生労働省の創薬基盤研究推進事業でSurvivin-H/K-HELPの大腸がん，乳がんに対する効果に関する第二相臨床研究を北海道大学と近畿大学で開始している．

## 2 ロングペプチド(H/K-HELP)がんワクチンはなぜ従来のショートペプチドより有効なのか？

従来のショートペプチドを上回るH/K-HELPのワクチン効果のメカニズム解明のため，著者らは再び，bedsideからbenchへと戻りマウス基盤研究を開始した．その結果，H/K-HELPとショートペプチドの間で，驚くべき免疫賦活機構の差異が示された(図3)．マウス足蹠に