Supplemental Material

Manuscript

Comparison of toxicity and effectiveness between fixed-dosed and body-surface area (BSA)-dosed capecitabine

Authors:
Femke M. de Man, Geerten D.M. Veerman, Esther Oomen-de Hoop, Maarten J. Deenen, Didier Meulendijks, Caroline M.P.W. Mandigers, Marcel Soesan, Jan H.M. Schellens, Esther van Meerten, Teun van Gelder, and Ron H.J. Mathijsen

Contents

Supplementary Methods: page 2
Supplementary Results: page 3-4
## Supplementary Methods

**Table 1. Detailed description administered treatment regimens**

| Treatment | Schedule | Fixed dose (mg/day)* | BSA-dosed dose (mg/ m²/day)† |
|-----------|----------|----------------------|-----------------------------|
| CAPE + RT Capecitabine | Continuous** | 3,000 | 1,650 |
| CAPOX Capecitabine Oxaliplatin | D1-14 (Q3W) D1 (Q3W) | 3,500 | 2,000 130 |
| MONO Capecitabine | D1-14 (Q3W) | 3,500 (BC) 4,000 (CRC) | 2,000 |
| TRIPLET ECC Capecitabine | D1-14 (Q3W) | 3,500 | 2,000 50 |
| | Epirubicin | D1 (Q3W) | 50 |
| | Cisplatin | D1 (Q3W) | 60 |
| EOX Capecitabine | D1-21 (Q3W) D1 (Q3W) D1 (Q3W) | 3,500 | 2,000 50 130 |
| EOX Epirubicin | D1 (Q3W) | 50 |
| Oxaliplatin | D1 (Q3W) | 130 |
| DOC Capecitabine | D1-14 (Q3W) | *** | 1,700 50 |
| Docetaxel | D1 (Q3W) | 100 |
| Oxaliplatin | D1 (Q3W) | |

* Capecitabine total daily dose was divided over two daily doses according to standard of care
** For the fixed-dosed cohort was capecitabine administered continuously the whole period of radiotherapy (also on non-radiotherapy days), for the BSA-dosed cohort was capecitabine administered continuous only on days of radiotherapy
*** The DOC-regimen was not administered in the fixed-dosed cohort

Abbreviations: BC = breast cancer; BSA = body surface area; CAPE = capecitabine; CAPOX = capecitabine combined with oxaliplatin; CRC = colorectal cancer; D = day; HFS = hand-foot syndrome; mono = monotherapy; RT = radiotherapy; Q3W = 3-weekly schedule
## Supplementary Results

### Table 2. Fixed daily dose compared to calculated BSA-dosed daily dose

| Treatment       | Mean fixed dose (mg/day) | Mean BSA-dosed dose (mg/day) | Difference (%) | Difference 95% CI (%) | P-value |
|-----------------|--------------------------|-----------------------------|----------------|------------------------|---------|
| CAPE + RT*      | 3.000mg                  | 3.202mg                     | 6.3            | 3.7-7.1                | <0.001  |
| CAPOX*          | 3.500mg                  | 3.796mg                     | 7.8            | 6.3-9.4                | <0.001  |
| CAPE MONO*      | 3.701mg                  | 4.128mg                     | 10.3           | 7.5-13.1               | <0.001  |
| CAPE TRIPLET*   | 3.500mg                  | 3.839mg                     | 8.8            | 6.3-11.4               | <0.001  |
| Total           | 3.175mg                  | 3.421mg                     | 7.2            | 6.5-7.9                | <0.001  |

* The administered treatment regimens are described in more detail in supplemental table 1.

Abbreviations: BSA = body surface area; CAPE = capecitabine; CAPOX = capecitabine combined with oxaliplatin; HFS = hand-foot syndrome; mono = monotherapy; RT = radiotherapy.
### Table 3. Toxicity compared between lowest BSA-quartile of the fixed-dosed cohort and BSA-dosed cohort per treatment regimen

| TREATMENT          | TOXICITY                                                                 |
|--------------------|--------------------------------------------------------------------------|
|                    | Diarrhea ≥ 3 (%) | HFS ≥ 2 (%) | Neutropenia ≥ 2 (%) | Cape-specific toxicity (%)<sup>a</sup> | Dose reduction (%) | Stop (%) | Hospital admission (%) | Clinically relevant events (%)<sup>b</sup> |
| CAPE+RT* FIXED N=204 | 26 (12.7)         | 6 (2.9)     | 8 (3.9)              | 33 (16.2)                               | 2 (1.0)           | 37 (18.1) | 33 (16.2)              | 45 (22.1)                                   |
| CAPE+RT* BSA N=117  | 13 (11.1)         | 7 (6.0)     | 1 (0.9)              | 20 (17.1)                               | 4 (3.4)           | 17 (14.5) | 11 (9.4)               | 21 (17.9)                                   |
| P-value            | 0.666             | 0.183       | 0.163                | 0.831                                   | 0.196             | 0.406      | 0.089                  | 0.381                                       |
| CAPOX* FIXED N=48  | 7 (14.6)          | 4 (8.3)     | 8 (16.7)             | 18 (37.5)                               | 15 (31.3)         | 12 (25.0) | 9 (18.8)               | 25 (52.1)                                   |
| CAPOX* BSA N=84    | 11 (13.1)         | 9 (10.7)    | 23 (27.4)            | 33 (39.3)                               | 18 (21.4)         | 20 (23.8) | 12 (14.3)              | 32 (38.1)                                   |
| P-value            | 0.811             | 0.768       | 0.162                | 0.839                                   | 0.210             | 0.878      | 0.500                  | 0.119                                       |
| CAPE MONO* FIXED N=25 | 0               | 7 (28.0)    | 4 (16.0)             | 9 (36.0)                                | 7 (28.0)          | 6 (24.0)   | 2 (8.0)                | 11 (44.0)                                   |
| CAPE MONO* BSA N=97 | 9 (9.3)           | 34 (35.1)   | 5 (5.2)              | 41 (42.3)                               | 26 (26.8)         | 20 (20.6)  | 9 (9.3)                | 38 (39.2)                                   |
| P-value            | 0.201             | 0.506       | 0.084                | 0.570                                   | 0.904             | 0.713      | 1.000                  | 0.661                                       |
| CAPE TRIPLET* FIXED N=17 | 1 (5.9)       | 2 (11.8)    | 13 (76.5)            | 13 (76.5)                               | 3 (17.6)          | 9 (52.9)   | 6 (32.3)               | 11 (64.7)                                   |
| CAPE TRIPLET* BSA N=12 | 1 (8.3)        | 0           | 10 (83.3)            | 11 (91.7)                               | 3 (25.0)          | 3 (25.0)   | 3 (25.0)               | 6 (50.0)                                   |
| P-value            | 1.000             | 0.498       | 0.653                | 0.286                                   | 0.669             | 0.251      | 1.000                  | 0.428                                       |

<sup>a</sup> Capcitabine-specific toxicity was defined as at least one of the following toxicity scores: diarrhea ≥ 3, HFS ≥ 2, neutropenia ≥ 2

<sup>b</sup> Clinically relevant events was defined as at least one of the following events due to toxicity: dose reduction, stop with capecitabine, hospital admission

* The administered treatment regimens are described in more detail in Appendix table 1

Abbreviations: BSA = body surface area; CAPE = capecitabine; CAPOX = capecitabine combined with oxaliplatin; HFS = hand-foot syndrome; mono = monotherapy; RT = radiotherapy