

THE EFFECT OF TRIFLURIDINE/TIPIRACIL IN PATIENTS TREATED IN RECOURSE BY PROGNOSTIC FACTORS AT BASELINE: AN EXPLORATORY ANALYSIS

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Supplementary material

Table S1 Treatment duration and dose delays/reductions

| | GPC subgroup | | PPC subgroup | |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| | FTD/TPI (n=261) | Placebo (n=125) | FTD/TPI (n=272) | Placebo (n=140) |
| No. of cycles | | | | |
| Mean (SD) | 4.1 (2.9) | 2.5 (1.8) | 2.8 (2.0) | 2.1 (1.1) |
| Median (range) | 3 (1–18) | 2 (1–16) | 2 (1–11) | 2 (1–8) |
| Treatment duration, weeks | | | | |
| Mean (SD) | 18.3 (13.9) | 10.2 (7.5) | 12.2 (8.7) | 8.5 (4.3) |
| Median (range) | 13 (4–80) | 8.1 (4–66) | 8.4 (4–49) | 8.1 (4–32) |
| Delays or dose reductions, n (%) | | | | |
| Delay in ≥1 cycle ^a | 140 (53.6) | 7 (5.6) | 105 (38.6) | 7 (5.0) |
| ≥1 dose reduction | 47 (18.0) | 0 | 26 (9.6) | 3 (2.1) |

FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; PPC, poor prognostic characteristics; SD, standard deviation.

GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

^aA delay of ≥4 days in initiation of ≥1 cycle.

Table S2 The effect of various prognostic factors on OS at 6 and 12 months

| | 6 month OS FTD/TPI /Placebo | 12 month OS FTD/TPI /Placebo | 6 month OS FTD/TPI /Placebo | 12 month OS FTD/TPI /Placebo |
|--------------|--------------------------------|---------------------------------|--------------------------------|---------------------------------|
| | ITT RECOURSE | | | |
| Overall | 57.8% / 43.5% | 26.6% / 17.6% | | |
| GPC subgroup | 71.7% / 53.9% | 37.5% / 25.2% | | |
| PPC subgroup | 44.4% / 34.1% | 15.3% / 10.7% | | |
| | No liver metastases | | Liver metastases | |
| GPC subgroup | 83.4% / 71.0% | 65.1% / 34.8% | 64.8% / 40.1% | 22.1% / 17.3% |
| PPC subgroup | 62.7% / 52.4% | 36.1% / 22.2% | 41.7% / 31.0% | 12.4% / 8.7% |
| | No lung metastases | | Lung metastases | |
| GPC subgroup | 73.8% / 60.0% | 30.8% / 19.5% | 70.6% / 52.3% | 41.2% / 27.0% |
| PPC subgroup | 38.5% / 37.5% | 11.9% / 16.7% | 46.0% / 33.5% | 16.2% / 9.8% |
| | No lymph metastases | | Lymph metastases | |
| GPC subgroup | 71.3% / 53.3% | 36.4% / 27.8% | 73.6% / 55.8% | 41.5% / 19.1% |
| PPC subgroup | 40.8% / 32.0% | 16.8% / 7.7% | 47.2% / 35.3% | 14.7% / 12.3% |
| | No peritoneal metastases | | Peritoneal metastases | |
| GPC subgroup | 70.3% / 54.1% | 35.6% / 26.1% | 89.5% / 50.0% | 59.8% / 0.0% |
| PPC subgroup | 44.1% / 35.0% | 16.0% / 10.5% | 45.4% / 31.7% | 13.6% / 11.3% |
| | ECOG PS = 0 | | ECOG PS = 1 | |
| GPC subgroup | 76.4% / 59.4% | 41.3% / 30.4% | 64.7% / 45.0% | 31.5% / 16.2% |
| PPC subgroup | 56.1% / 40.2% | 20.1% / 17.0% | 31.7% / 28.2% | 10.1% / 5.5% |
| | Age <65 years | | Age ≥65 years | |
| GPC subgroup | 72.6% / 54.8% | 38.8% / 26.8% | 70.7% / 52.6% | 36.2% / 23.2% |
| PPC subgroup | 44.3% / 36.7% | 14.0% / 9.8% | 44.9% / 31.1% | 16.6% / 11.5% |
| | KRAS wild type | | KRAS mutant | |
| GPC subgroup | 71.7% / 53.5% | 33.0% / 19.5% | 71.9% / 54.4% | 43.1% / 29.7% |
| PPC subgroup | 51.9% / 37.6% | 18.5% / 10.7% | 38.6% / 30.8% | 12.9% / 11.8% |

ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; ITT, intent to treat; OS, overall survival; PPC, poor prognostic characteristics.

GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

Table S3 The effect of various prognostic factors on PFS at 3, 6 and 9 months

| | 3 month PFS FTD/TPI/Placebo | 6 month PFS FTD/TPI/Placebo | 9 month PFS FTD/TPI/Placebo | 3 month PFS FTD/TPI/Placebo | 6 month PFS FTD/TPI /Placebo | 9 month PFS FTD-TPI /Placebo |
|--------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|
| ITT RECOURSE | | | | | | |
| Overall | 40.9% / 13.0% | 15.1% / 1.4% | 7.7% / 1.4% | | | |
| GPC subgroup | 51.1% / 14.5% | 22.4% / 1.9% | 12.1% / 1.9% | | | |
| PPC subgroup | 31.0% / 11.6% | 7.9% / 0.9% | 3.3% / NE | | | |
| No liver metastases | | | | Liver metastases | | |
| GPC subgroup | 66.9% / 26.2% | 35.9% / 4.3% | 20.7% / 4.3% | 41.9% / 4.7% | 14.5% / 0.0% | 7.1% / 0.0% |
| PPC subgroup | 37.6% / 30.6% | 17.6% / 0.0% | 6.6% / 0.0% | 30.1% / 8.2% | 6.6% / 1.1% | 2.8% / NE |
| No lung metastases | | | | Lung metastases | | |
| GPC subgroup | 47.5% / 20.0% | 18.4% / 4.0% | 11.9% / 4.0% | 53.0% / 13.1% | 24.5% / 1.3% | 12.3% / 1.3% |
| PPC subgroup | 20.4% / 13.0% | 4.7% / 0.0% | 2.3% / 0.0% | 33.6% / 11.3% | 8.8% / 0.9% | 3.5% / NE |
| No lymph metastases | | | | Lymph metastases | | |
| GPC subgroup | 49.9% / 13.6% | 21.3% / 1.4% | 12.8% / 1.4% | 55.9% / 17.4% | 26.6% / 3.5% | 9.2% / 3.5% |
| PPC subgroup | 34.9% / 7.7% | 9.0% / 0.0% | 2.3% / 0.0% | 28.0% / 14.2% | 7.3% / 1.3% | 4.4% / NE |
| No peritoneal metastases | | | | Peritoneal metastases | | |
| GPC subgroup | 49.5% / 15.3% | 21.7% / 2.0% | 11.7% / 2.0% | 73.0% / 0.0% | 32.7% / 0.0% | 17.5% / 0.0% |
| PPC subgroup | 32.6% / 12.2% | 8.8% / 0.0% | 3.4% / 0.0% | 26.5% / 10.3% | 5.9% / 2.6% | 2.9% / NE |
| ECOG PS = 0 | | | | ECOG PS = 1 | | |
| GPC subgroup | 53.7% / 13.7% | 22.2% / 2.7% | 12.2% / 2.7% | 47.2% / 15.7% | 22.7% / 0.0% | 11.9% / 0.0% |
| PPC subgroup | 35.8% / 16.4% | 9.6% / 0.0% | 4.7% / 0.0% | 25.8% / 7.2% | 6.2% / 1.4% | 1.7% / NE |
| Age <65 years | | | | Age ≥65 years | | |
| GPC subgroup | 50.1% / 16.3% | 18.6% / 1.8% | 7.0% / 1.8% | 52.2% / 12.1% | 26.9% / 2.0% | 18.3% / 2.0% |
| PPC subgroup | 26.1% / 13.6% | 7.1% / 2.0% | 2.1% / NE | 38.1% / 9.6% | 9.1% / 0.0% | 4.6% / 0.0% |
| KRAS wild type | | | | KRAS mutant | | |
| GPC subgroup | 51.1% / 16.8% | 20.3% / 1.9% | 13.4% / 1.9% | 51.2% / 12.5% | 25.1% / 2.1% | 10.5% / 2.1% |
| PPC subgroup | 33.3% / 16.5% | 8.8% / 2.5% | 2.9% / NE | 29.2% / 7.3% | 7.2% / 0.0% | 3.9% / 0.0% |

ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; ITT, intent to treat; NE, not evaluable; PFS, progression-free survival.

GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

Table S4 Baseline patient demographics and clinical characteristics in RECURSE patients in the GPC subgroup (number of metastatic sites <3 and time since 1st metastasis ≥18 months) with no liver metastasis at randomisation (n=153).

| | Trifluridine/tipiracil | | Placebo | |
|-------------------------------------------|-------------------------|----------------------------------------|-------------------------|----------------------------------------|
| | GPC subgroup (n=261) | GPC no liver met subgroup (n=97) | GPC subgroup (n=125) | GPC no liver met subgroup (n=56) |
| Median age, years | 64.0 | 64.0 | 63.0 | 61.0 |
| Patient age, n (%) | | | | |
| <65 years | 137 (52.5) | 52(53.6) | 72 (57.6) | 36(64.3) |
| 65 to <75 years | 105 (40.2) | 37(38.1) | 43 (34.4) | 16(28.6) |
| ≥75 years | 19 (7.3) | 8(8.2) | 10 (8.0) | 4(7.1) |
| Gender, n (%) | | | | |
| Females | 97 (37.2) | 38(39.2) | 47 (37.6) | 22(39.3) |
| Male | 164 (62.8) | 59(60.8) | 78 (62.4) | 34(60.7) |
| Race, n (%) | | | | |
| Asian | 91 (34.9) | 35(36.1) | 43 (34.4) | 26(46.4) |
| Other | 170 (65.1) | 62 (63.9) | 82 (65.6) | 30 (53.6) |
| ECOG PS, n (%) | | | | |
| 0 | 158 (60.5) | 59(60.8) | 77 (61.6) | 32(57.1) |
| 1 | 103 (39.5) | 38(39.2) | 48 (38.4) | 24(42.9) |
| KRAS status, n (%) | | | | |
| Mutant | 119 (45.6) | 49(50.5) | 64 (51.2) | 26(46.4) |
| Wild type | 142 (54.4) | 48(49.5) | 61 (48.8) | 30(53.6) |
| Time since diagnosis of metastasis, n (%) | | | | |
| <18 months | 0 | 0 | 0 | 0 |
| ≥18 months | 261 (100.0) | 97(100.0) | 125 (100.0) | 56(100.0) |
| Number of prior regimens, n (%) | | | | |
| 2 | 26 (10.0) | 7(7.2) | 15 (12.0) | 6(10.7) |
| 3 | 50 (19.2) | 11(11.3) | 18 (14.4) | 6(10.7) |
| ≥4 | 185 (70.9) | 79(81.4) | 92 (73.6) | 44(78.6) |
| Number of metastatic sites, n (%) | | | | |
| 1–2 | 261 (100.0) | 97(100.0) | 125 (100.0) | 56(100.0) |
| ≥3 | 0 | 0 | 0 | 0 |
| Site of Lesion | | | | |
| Liver | 164(62.8) | 0 | 69(55.2) | 0 |
| Lung | 172(65.9) | 74(76.3) | 100(80.0) | 47(83.9) |
| Lymph | 53(20.3) | 37(38.1) | 32(25.6) | 24(42.9) |

| | | | | |
|--------------------------------|------------|----------|-----------|----------|
| Peritoneum | 19(7.3) | 14(14.4) | 6(4.8) | 6(10.7) |
| Primary site of disease, n (%) | | | | |
| Colon | 171 (65.5) | 57(58.8) | 63 (50.4) | 25(44.6) |
| Rectum | 90 (34.5) | 40(41.2) | 62 (49.6) | 31(55.4) |

ECOG PS, Eastern Cooperative Oncology Group performance status; GPC, good prognostic characteristics

Table S5 Adverse events occurring in ≥10% of patients in any group

| AEs, n (%) | FTD/TPI | | | | Placebo | | | |
|-----------------------------------------------------|----------------------|------------|----------------------|------------|----------------------|-----------|----------------------|-----------|
| | GPC subgroup (n=261) | | PPC subgroup (n=272) | | GPC subgroup (n=125) | | PPC subgroup (n=140) | |
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any AE | 257 (98.5) | 171 (65.5) | 267 (98.2) | 199 (73.2) | 115 (92.0) | 57 (45.6) | 132 (94.3) | 80 (57.1) |
| Blood disorders or laboratory investigations | | | | | | | | |
| Anaemia | 109 (41.8) | 46 (17.6) | 105 (38.6) | 40 (14.7) | 9 (7.2) | 2 (1.6) | 13 (9.3) | 5 (3.6) |
| Neutrophil count decrease | 87 (33.3) | 56 (21.5) | 61 (22.4) | 29 (10.7) | 1 (0.8) | 0 | 0 | 0 |
| Neutropenia | 85 (32.6) | 62 (23.8) | 71 (26.1) | 45 (16.5) | 0 | 0 | 0 | 0 |
| WBC decrease | 82 (31.4) | 32 (12.3) | 64 (23.5) | 23 (8.5) | 1 (0.8) | 0 | 0 | 0 |
| Platelet count decrease | 47 (18.0) | 7 (2.7) | 34 (12.5) | 6 (2.2) | 2 (1.6) | 0 | 4 (2.9) | 0 |
| Blood ALP increase | 22 (8.4) | 4 (1.5) | 25 (9.2) | 14 (5.1) | 9 (7.2) | 5 (4.0) | 17 (12.1) | 8 (5.7) |
| Weight loss | 20 (7.7) | 0 | 21 (7.7) | 1 (0.4) | 9 (7.2) | 0 | 18 (12.9) | 0 |
| Gastrointestinal disorders | | | | | | | | |
| Nausea | 130 (49.8) | 4 (1.5) | 128 (47.1) | 6 (2.2) | 29 (23.2) | 1 (0.8) | 34 (24.3) | 2 (1.4) |
| Diarrhoea | 86 (33.0) | 7 (2.7) | 84 (30.9) | 9 (3.3) | 13 (10.4) | 0 | 20 (14.3) | 1 (0.7) |
| Vomiting | 73 (28.0) | 6 (2.3) | 75 (27.6) | 5 (1.8) | 14 (11.2) | 1 (0.8) | 24 (17.1) | 0 |
| Constipation | 39 (14.9) | 1 (0.4) | 42 (15.4) | 0 | 18 (14.4) | 1 (0.8) | 22 (15.7) | 2 (1.4) |
| Abdominal pain | 36 (13.8) | 1 (0.4) | 43 (15.8) | 10 (3.7) | 10 (8.0) | 3 (2.4) | 26 (18.6) | 7 (5.0) |

| AEs, n (%) | FTD/TPI | | | | Placebo | | | |
|----------------------------------------|----------------------|----------|----------------------|----------|----------------------|----------|----------------------|----------|
| | GPC subgroup (n=261) | | PPC subgroup (n=272) | | GPC subgroup (n=125) | | PPC subgroup (n=140) | |
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Metabolism and nutrition disorders | | | | | | | | |
| Decreased appetite | 91 (34.9) | 9 (3.4) | 117 (43.0) | 10 (3.7) | 28 (22.4) | 6 (4.8) | 50 (35.7) | 7 (5.0) |
| General disorders | | | | | | | | |
| Fatigue | 90 (34.5) | 9 (3.4) | 98 (36.0) | 12 (4.4) | 22 (17.6) | 3 (2.4) | 40 (28.6) | 12 (8.6) |
| Asthenia | 50 (19.2) | 9 (3.4) | 47 (17.3) | 9 (3.3) | 17 (13.6) | 4 (3.2) | 13 (9.3) | 4 (2.9) |
| Pyrexia | 42 (16.1) | 1 (0.4) | 56 (20.6) | 5 (1.8) | 11 (8.8) | 0 | 26 (18.6) | 1 (0.7) |
| Peripheral oedema | 26 (10.0) | 0 | 27 (9.9) | 1 (0.4) | 8 (6.4) | 0 | 19 (13.6) | 2 (1.4) |
| Respiratory or thoracic disorders | | | | | | | | |
| Cough | 32 (12.3) | 2 (0.8) | 25 (9.2) | 0 | 18 (14.4) | 0 | 12 (8.6) | 2 (1.4) |
| Dyspnoea | 25 (9.6) | 5 (1.9) | 31 (11.4) | 9 (3.3) | 17 (13.6) | 4 (3.2) | 17 (12.1) | 6 (4.3) |
| Skin and subcutaneous tissue disorders | | | | | | | | |
| Alopecia | 27 (10.3) | 0 | 9 (3.3) | 0 | 0 | 0 | 3 (2.1) | 0 |

AE, adverse event; ALP, alkaline phosphatase; FTD/TPI, trifluridine/tipiracil; GPC, good prognostic characteristics; PPC, poor prognostic characteristics; WBC, white blood cell.

GPC was defined as <3 metastatic sites and ≥18 months since first metastasis.

Figure S1 Overall survival in RECURSE patients in the GPC subgroup (number of metastatic sites <3 and time since first metastasis ≥18 months) with no liver metastasis at randomisation (n=153) receiving trifluridine/tipiracil (blue) or placebo (red).

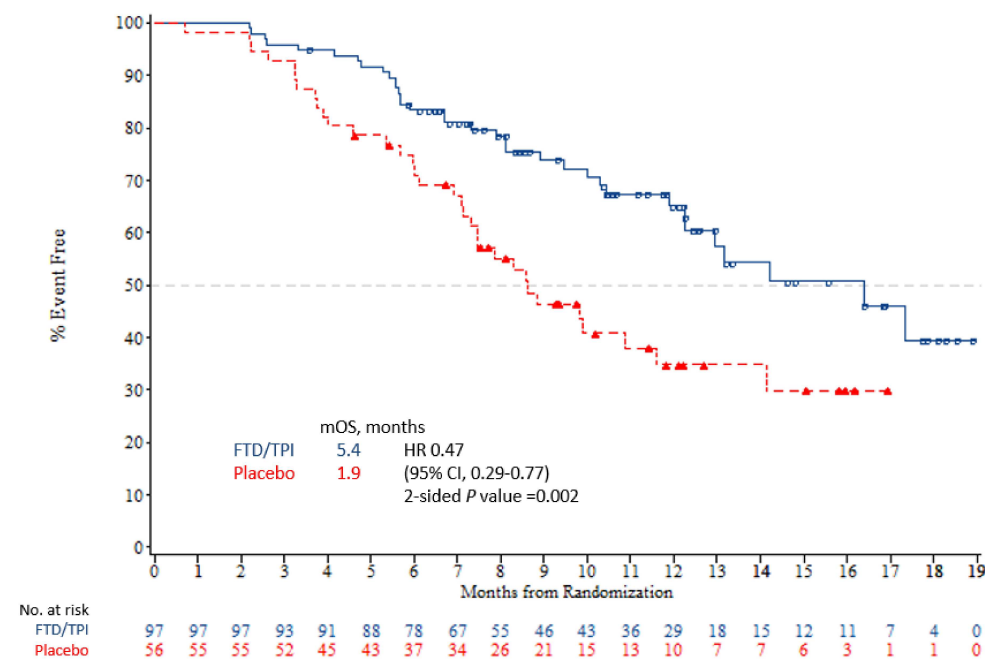


Figure S2 Progression-free survival in RECOURSE patients in the GPC subgroup (number of metastatic sites <3 and time since first metastasis ≥18 months) with no liver metastasis at randomisation (n=153) receiving trifluridine/tipiracil (blue) or placebo (red).

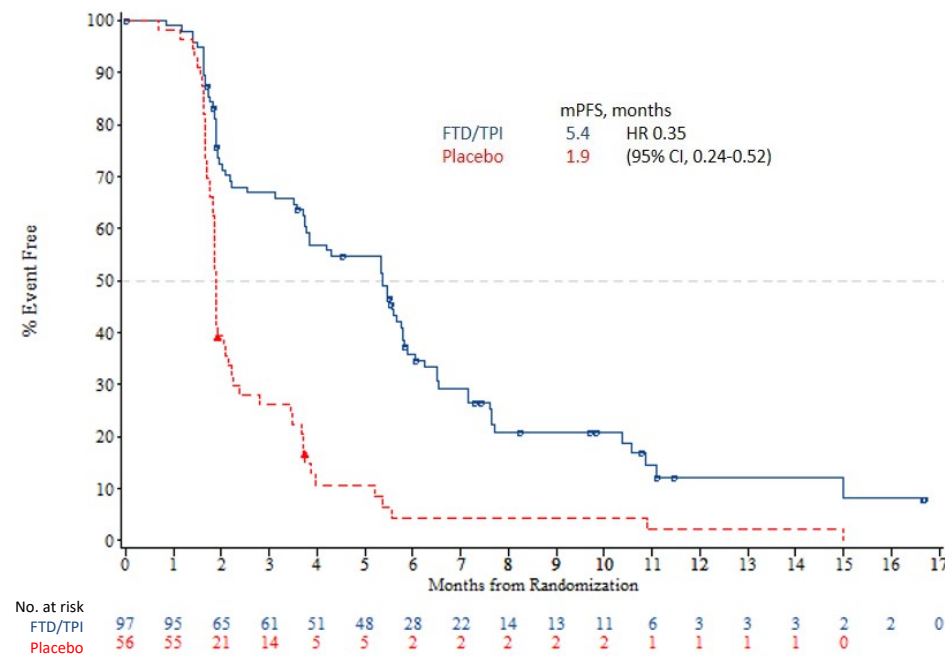


Figure S3 Time to Eastern Cooperative Oncology Group Performance Status ≥ 2 in RECOURSE patients in the GPC subgroup (number of metastatic sites <3 and time since first metastasis ≥ 18 months) with no liver metastasis at randomisation (n=153) receiving trifluridine/tipiracil (blue) or placebo (red).

