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

Authors: Josep Tabernero, Guillem Argilés, Alberto Sobrero, Christophe Borg, Atsushi Ohtsu, Robert J. Mayer, Loick Vidot, Shanti R. Moreno Vera, Eric Van Cutsem

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    | 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.

*A 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 | 12 month OS | 6 month OS | 12 month OS |
|----------------------|------------|-------------|------------|-------------|
|                      | FTD/TPI /Placebo | FTD/TPI /Placebo | FTD/TPI /Placebo | FTD/TPI /Placebo |
| Overall              | 57.8% / 43.5% | 26.6% / 17.6% | 57.8% / 43.5% | 26.6% / 17.6% |
| GPC subgroup         | 71.7% / 53.9% | 37.5% / 25.2% | 71.7% / 53.9% | 37.5% / 25.2% |
| PPC subgroup         | 44.4% / 34.1% | 15.3% / 10.7% | 44.4% / 34.1% | 15.3% / 10.7% |

|                      | Overall | GPC subgroup | PPC subgroup | GPC subgroup | PPC subgroup | GPC subgroup | PPC subgroup | GPC subgroup | PPC subgroup | GPC subgroup | PPC subgroup | GPC subgroup | PPC subgroup | GPC subgroup | PPC subgroup |
|----------------------|---------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
|                      | 83.4% / 71.0% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% | 65.1% / 34.8% |
|                      | 62.7% / 52.4% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% | 36.1% / 22.2% |
|                      | 73.8% / 60.0% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% | 30.8% / 19.5% |
|                      | 38.5% / 37.5% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% | 11.9% / 16.7% |

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 | 6 month PFS | 9 month PFS | 3 month PFS | 6 month PFS | 9 month PFS |
| FTD/TPI /Placebo | FTD/TPI/Placebo | FTD/TPI/Placebo | FTD/TPI/Placebo | FTD/TPI/Placebo | FTD-TPI/Placebo |
| ITT RECURSE | Liver metastases | Lung metastases | Lymph metastases | Peritoneal metastases | ECOG PS = 0 | ECOG PS = 1 |
| 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 | | | | | | |
| 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 | | | | | | |
| 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 | | | | | | |
| 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 | | | | | | |
| 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 | | | | | | |
| 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 | | | | | | |
| 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 | | | | | | |
| 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 | 28.2% / 7.3% | 2.7% / 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 RECOURSE 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) |
| Primary site of disease, n (%) | 19(7.3) | 14(14.4) | 6(4.8) | 6(10.7) |
|-------------------------------|---------|----------|--------|---------|
| Peritoneum                    |         |          |        |         |
| 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**
  - Any grade: 109 (41.8), 46 (17.6), 105 (38.6), 40 (14.7), 9 (7.2), 2 (1.6), 13 (9.3), 5 (3.6)
  - Grade ≥3: 46 (17.6), 29 (10.7), 1 (0.8), 0, 0, 0

- **Neutrophil count decrease**
  - Any grade: 87 (33.3), 61 (22.4), 29 (10.7), 1 (0.8), 0, 0, 0

- **Neutropenia**
  - Any grade: 85 (32.6), 71 (26.1), 45 (16.5), 1 (0.8), 0, 0, 0

- **WBC decrease**
  - Any grade: 82 (31.4), 64 (23.5), 23 (8.5), 1 (0.8), 0, 0, 0

- **Platelet count decrease**
  - Any grade: 47 (18.0), 34 (12.5), 6 (2.2), 2 (1.6), 0, 4 (2.9), 0

- **Blood ALP increase**
  - Any grade: 22 (8.4), 25 (9.2), 14 (15.1), 9 (7.2), 5 (4.0), 17 (12.1), 8 (5.7)

- **Weight loss**
  - Any grade: 20 (7.7), 21 (7.7), 1 (0.4), 9 (7.2), 0, 18 (12.9), 0

#### Gastrointestinal disorders

- **Nausea**
  - Any grade: 130 (49.8), 128 (47.1), 6 (2.2), 29 (23.2), 1 (0.8), 34 (24.3), 2 (1.4)

- **Diarrhoea**
  - Any grade: 86 (33.0), 84 (30.9), 9 (3.3), 13 (10.4), 0, 20 (14.3), 1 (0.7)

- **Vomiting**
  - Any grade: 73 (28.0), 75 (27.6), 5 (1.8), 14 (11.2), 1 (0.8), 24 (17.1), 0

- **Constipation**
  - Any grade: 39 (14.9), 42 (15.4), 0, 18 (14.4), 1 (0.8), 22 (15.7), 2 (1.4)

- **Abdominal pain**
  - Any grade: 36 (13.8), 43 (15.8), 10 (3.7), 10 (8.0), 3 (2.4), 26 (18.6), 7 (5.0)
| AE, 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).