First-line biological agents plus chemotherapy in older patients with metastatic colorectal cancer: a retrospective pooled analysis

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## Supplementary materials

### Table S1. Studies included in this analysis

| Study name  | Design                              | Patients      | Median follow up, months (range) | Intervention                                                                 | N   | Primary endpoint |
|-------------|-------------------------------------|---------------|----------------------------------|-------------------------------------------------------------------------------|-----|------------------|
| MACRO [9]   | Multicentre, randomized, open-label, phase 3 | ≥18 years, ECOG PS ≤2 | 29 (0–53.2)                      | Bevacizumab + XELOX (6 cycles) then Bevacizumab + XELOX (maintenance) Bevacizumab + XELOX (6 cycles) then Bevacizumab monotherapy (maintenance) | 239 | PFS              |
| AVAXIRI [6] | Multicentre, single-arm, open-label, phase 2 | ≥18 years, ECOG PS ≤2 | 23.3 (0.4–39.6)                   | Bevacizumab + Irinotecan + Capecitabine* | 77  | PFS at 9 months  |
| PLANET [8]  | Multicentre, randomized, open-label, phase 2 | ≥18 years, wild-type KRAS, liver-only metastases | 33 (1.4–64.0)                    | Panitumumab + FOLFOX 4                                                     | 38  | ORR              |
| SETICC [10] | Multicentre, randomized, open-label, phase 2 | ≥18 years, ECOG PS ≤2 | 18 (1.1–41.7)                     | Bevacizumab + XELOX                                                          | 65  | PFS              |

*a*Capecitabine

*b*FUOX or FUIRI
| MACRO2 [7] | Study Design | Age | Median Age Range | Treatment | Duration | PFS at 9 months |
|------------|--------------|-----|------------------|-----------|----------|----------------|
| Multicentre, randomized, open-label, phase 2 | 18-70 years, 23 (0-54) | Cetuximab + mFOLFOX-6 (8 cycles) then Cetuximab monotherapy (maintenance) | 129 | 64 |
| ECOG PS ≤2, wild-type KRAS | | | | |

*aCapecitabine dose was lower in patients aged >65 years (800 vs 1000 mg/m²).

*bTreatment tailored according to TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T polymorphisms.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; FUIRI, 5-fluorouracil + irinotecan; FUOX, 5-fluorouracil + oxaliplatin; mCRC, metastatic colorectal cancer; mFOLFOX, modified FOLFOX; ORR, objective response rate; PFS, progression-free survival; XELIRI, capecitabine + irinotecan; XELOX, capecitabine + oxaliplatin.
**Supplementary Table S2.** Most common (>5% of patients) adverse events by age group

| Disorder                              | <65 years | ≥65 years | p-valuea | <65 years | ≥65 years | p-valuea | <65 years | ≥65 years | p-valuea |
|---------------------------------------|-----------|-----------|----------|-----------|-----------|----------|-----------|-----------|----------|
| Blood and lymphatic system disorders  |           |           |          |           |           |          |           |           |          |
| Anaemia                               | 66 (12.72)| 42 (8.75) | **0.0437**| 64 (12.33)| 42 (8.75) | 0.0663   | 6 (1.16)  | 2 (0.42)  | 0.1902   |
| Leukopenia                            | 51 (9.83) | 47 (9.79) | 0.9852   | 50 (9.63) | 47 (9.79) | 0.9329   | 3 (0.58)  | 1 (0.21)  | 0.3552   |
| Neutropenia                           | 110 (21.19)| 86 (17.92)| 0.1924   | 101 (19.46)| 66 (13.75)| **0.0157**| 50 (9.63) | 48 (10.00)| 0.8459   |
| Thrombocytopenia                      | 83 (15.99)| 85 (17.71)| 0.4687   | 83 (15.99)| 82 (17.08)| 0.6427   | 5 (0.96)  | 12 (2.50) | 0.0606   |
| Gastrointestinal disorders            |           |           |          |           |           |          |           |           |          |
| Abdominal pain                        | 128 (24.66)| 135 (28.13)| 0.2144   | 119 (22.93)| 126 (26.25)| 0.2228   | 19 (3.66) | 12 (2.50) | 0.2904   |
| Constipation                          | 126 (24.28)| 106 (22.08)| 0.4119   | 126 (24.28)| 105 (21.88)| 0.3682   | 1 (0.19)  | 2 (0.42)  | 0.5180   |
| Diarrhoea                             | 328 (63.20)| 306 (63.75)| 0.8565   | 318 (61.27)| 282 (58.75)| 0.4162   | 51 (9.83) | 82 (17.08)| **0.0007**|
| Dry mouth                             | 27 (5.20) | 22 (4.58) | 0.6508   | 26 (5.01) | 22 (4.58) | 0.7529   | 1 (0.19)  | 2 (0.42)  | 0.5180   |
| Nausea                                | 220 (42.39)| 194 (40.42)| 0.5272   | 219 (42.20)| 187 (38.96)| 0.2978   | 5 (0.96)  | 18 (3.75) | **0.0033**|
| Proctalgia                            | 25 (4.82) | 27 (5.63) | 0.5657   | 23 (4.43) | 26 (5.42) | 0.4714   | 2 (0.39)  | 2 (0.42)  | 0.9376   |
| Rectal haemorrhage                    | 31 (5.97) | 31 (6.46) | 0.7508   | 31 (5.97) | 29 (6.04) | 0.9636   | 0         | 4 (0.83)  | **0.0372**|
| Upper abdominal pain                  | 40 (7.71) | 25 (5.21) | 0.1096   | 39 (7.51) | 24 (5.00) | 0.1024   | 2 (0.39)  | 3 (0.63)  | 0.5918   |
| Vomiting                              | 190 (36.61)| 168 (35.00)| 0.5962   | 186 (35.84)| 155 (32.29)| 0.2376   | 16 (3.08) | 29 (6.04) | **0.0243**|
| General disorders and administration site conditions |           |           |          |           |           |          |           |           |          |
| Asthenia                              | 205 (39.50)| 157 (32.71)| 0.0257   | 202 (38.92)| 151 (31.46)| **0.0137**| 23 (4.43) | 35 (7.29) | 0.0534   |
| Fatigue                               | 137 (26.40)| 171 (35.63)| **0.0016**| 136 (26.20)| 162 (33.75)| **0.0092**| 9 (1.73)  | 34 (7.08) | <**0.0001**|
| Mucosal                               | 202 (38.92)| 168 (35.00)| 0.1998   | 200 (38.54)| 165 (34.38)| 0.1724   | 13 (2.50) | 15 (3.13) | 0.5529   |
| Peripheral oedema                     | 17 (3.28) | 25 (5.21) | 0.1283   | 17 (3.28) | 25 (5.21) | 0.1283   | 0         | 0         | –        |
| Condition                          | Count (Percentage) | Control (Percentage) | p Value | Count (Percentage) | Control (Percentage) | p Value | Count (Percentage) | Control (Percentage) | p Value |
|-----------------------------------|--------------------|----------------------|---------|--------------------|----------------------|---------|--------------------|----------------------|---------|
| **Pyrexia**                       |                    |                      |         |                    |                      |         |                    |                      |         |
| Infections and infestations       |                    |                      |         |                    |                      |         |                    |                      |         |
| Conjunctivitis                    | 28 (5.39)          | 30 (6.25)            | 0.5637  | 28 (5.39)          | 30 (6.25)            | 0.5637  | 3 (0.58)           | 2 (0.42)             | 0.7180  |
| Paronychia                        | 34 (6.55)          | 28 (5.83)            | 0.6385  | 33 (6.36)          | 28 (5.83)            | 0.7291  | 6 (1.16)           | 1 (0.21)             | 0.0728  |
| Upper respiratory infection       | 22 (4.24)          | 48 (10.00)           | 0.0004  | 22 (4.24)          | 45 (9.38)            | 0.0012  | 1 (0.19)           | 3 (0.63)             | 0.2797  |
| Urinary tract infection           | 28 (5.39)          | 32 (6.67)            | 0.3980  | 27 (5.20)          | 31 (6.46)            | 0.3964  | 3 (0.58)           | 2 (0.42)             | 0.7180  |
| **Metabolism and nutrition disorders** |                |                      |         |                    |                      |         |                    |                      |         |
| Decreased appetite                | 123 (23.70)        | 166 (34.58)          | **0.0002** | 116 (22.35)        | 160 (33.33)          | **0.0001** | 10 (1.93)          | 18 (3.75)            | 0.0811  |
| Hypomagnesaemia                   | 39 (7.51)          | 22 (4.58)            | 0.0532  | 38 (7.32)          | 22 (4.58)            | 0.0688  | 2 (0.39)           | 5 (1.04)             | 0.2141  |
| **Musculoskeletal and connective tissue disorders** |                |                      |         |                    |                      |         |                    |                      |         |
| Arthralgia                        | 27 (5.20)          | 21 (4.38)            | 0.5413  | 27 (5.20)          | 21 (4.38)            | 0.5413  | 0                  | 0                    | –       |
| Back pain                         | 47 (9.06)          | 32 (6.67)            | 0.1621  | 46 (8.86)          | 30 (6.25)            | 0.1196  | 5 (0.96)           | 4 (0.83)             | 0.8279  |
| **Nervous system disorders**      |                    |                      |         |                    |                      |         |                    |                      |         |
| Dizziness                         | 21 (4.05)          | 30 (6.25)            | 0.1139  | 21 (4.05)          | 30 (6.25)            | 0.1139  | 0                  | 0                    | –       |
| Dysgeusia                         | 62 (11.95)         | 56 (11.67)           | 0.8913  | 62 (11.95)         | 55 (11.46)           | 0.8107  | 0                  | 2 (0.42)             | 0.1410  |
| Headache                          | 27 (5.20)          | 28 (5.83)            | 0.6622  | 26 (5.01)          | 28 (5.83)            | 0.5651  | 1 (0.19)           | 0                    | 0.3360  |
| Peripheral sensory neuropathy b   | 344 (66.28)        | 305 (63.54)          | 0.3884  | 341 (65.70)        | 302 (62.92)          | 0.3901  | 52 (10.02)         | 58 (12.08)           | 0.3129  |
| **Psychiatric disorders**         |                    |                      |         |                    |                      |         |                    |                      |         |
| Insomnia                          | 29 (5.59)          | 26 (5.42)            | 0.9058  | 29 (5.59)          | 26 (5.42)            | 0.9058  | 0                  | 0                    | –       |
| **Renal and urinary disorders**   |                    |                      |         |                    |                      |         |                    |                      |         |
| Proteinuria                       | 13 (2.50)          | 24 (5.00)            | **0.0369** | 12 (2.31)          | 21 (4.38)            | 0.0684  | 2 (0.39)           | 5 (1.04)             | 0.2141  |
| **Respiratory, thoracic and mediastinal disorders** |                |                      |         |                    |                      |         |                    |                      |         |
| Cough                             | 41 (7.90)          | 28 (5.83)            | 0.1981  | 41 (7.90)          | 28 (5.83)            | 0.1981  | 0                  | 0                    | –       |
| Condition                          | Count 1 | Count 2 | p-value | Count 1 | Count 2 | p-value | Count 1 | Count 2 | p-value |
|-----------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Dyspnoea                          | 25 (4.82) | 34 (7.08) | 0.1290 | 23 (4.43) | 29 (6.04) | 0.2524 | 2 (0.39) | 6 (1.25) | 0.1255 |
| Epistaxis                         | 79 (15.22) | 62 (12.92) | 0.2958 | 79 (15.22) | 62 (12.92) | 0.2958 | 0 | 0 | – |
| **Skin and subcutaneous tissue disorders** |         |         |         |         |         |         |         |         |         |
| Alopecia                          | 44 (8.48) | 36 (7.50) | 0.5694 | 42 (8.09) | 36 (7.50) | 0.7273 | 2 (0.39) | 2 (0.42) | 0.9376 |
| Palmar-plantar erythrodysaesthesia syndrome | 126 (24.28) | 117 (24.38) | 0.9714 | 124 (23.89) | 109 (22.71) | 0.6585 | 30 (5.78) | 28 (5.83) | 0.9715 |
| Pruritus                          | 30 (5.78) | 19 (3.96) | 0.1828 | 30 (5.78) | 17 (3.54) | 0.0950 | 2 (0.39) | 2 (0.42) | 0.9376 |
| Skin toxicity dermatitis
c          | 152 (29.29) | 85 (17.71) | 0.00101 | 152 (29.29) | 84 (17.50) | 0.00101 | 29 (5.59) | 14 (2.92) | 0.0425 |
| Skin fissures                     | 28 (5.39) | 12 (2.50) | 0.0197 | 27 (5.20) | 11 (2.29) | 0.0163 | 2 (0.39) | 4 (0.83) | 0.3599 |
| **Vascular disorders**            |         |         |         |         |         |         |         |         |         |
| Hypertension                      | 78 (15.03) | 97 (20.21) | **0.0314** | 72 (13.87) | 87 (18.13) | 0.0664 | 14 (2.70) | 22 (4.58) | 0.1101 |

*Significant p-values are shown in **bold**

bIncludes dysaesthesia, neurotoxicity, paraesthesia and peripheral neuropathy.

*Includes dermatitis acneiform, exfoliative rash and rash.
### Supplementary Table S3. Most common (>5% of patients) adverse events by detailed age group

|                  | <65 years | ≥65 to 70 years | ≥70 to 75 years | ≥75 years | <65 years | ≥65 to 70 years | ≥70 to 75 years | ≥75 years | <65 years | ≥65 to 70 years | ≥70 to 75 years | ≥75 years |
|------------------|----------|----------------|---------------|---------|----------|----------------|---------------|---------|----------|----------------|---------------|---------|
| **Blood and lymphatic system disorders** |          |                |               |         |          |                |               |         |          |                |               |         |
| Anaemia          | 66       | 20             | 12            | 10      | 64       | 20            | 12            | 10      | 6        | 1              | 1             | 0       |
| (12.72)          | (10.31)  | (7.10)         | (8.55)        | (12.33) | (10.31)  | (7.10)        | (8.55)        | (1.16)  | (0.52)   | (0.59)         |               |         |
| Leukopenia       | 51       | 17             | 17            | 13      | 50       | 17            | 17            | 13      | 3        | 0              | 1             | 0       |
| (9.83)           | (8.76)   | (10.06)        | (11.11)       | (9.63)  | (8.76)   | (10.06)       | (11.11)       | (0.58)  | (0.59)   |               |               |         |
| Neutropenia      | 110      | 39             | 29            | 18      | 101      | 32            | 23            | 11      | 50       | 24             | 13            | 11     |
| (21.19)          | (20.10)  | (17.16)        | (15.38)       | (19.46) | (16.49)  | (13.61)       | (9.40)        | (9.63)  | (12.37)  | (7.69)         | (9.40)        |         |
| Thrombocytopenia | 83       | 30             | 35            | 20      | 83       | 30            | 35            | 17      | 5        | 6              | 2             | 4       |
| (15.99)          | (15.46)  | (20.71)        | (17.09)       | (15.99) | (15.46)  | (20.71)       | (14.53)       | (0.96)  | (3.09)   | (1.18)         | (3.42)        |         |
| **Gastrointestinal disorders** |          |                |               |         |          |                |               |         |          |                |               |         |
| Abdominal pain   | 128      | 50             | 51            | 34      | 119      | 45            | 48            | 33      | 19       | 6              | 4             | 2       |
| (24.66)          | (25.77)  | (30.18)        | (29.06)       | (22.93) | (23.20)  | (28.40)       | (28.21)       | (3.66)  | (3.09)   | (2.37)         | (1.71)        |         |
| Constipation     | 126      | 42             | 42            | 22      | 126      | 42            | 41            | 22      | 1        | 1              | 1             | 0       |
| (24.28)          | (21.65)  | (24.85)        | (18.80)       | (24.28) | (21.65)  | (24.26)       | (18.80)       | (0.19)  | (0.52)   | (0.59)         |               |         |
| Diarrhoea        | 328      | 120            | 100           | 86      | 318      | 112           | 93            | 77      | 51       | 32             | 25            | 25     |
| (63.20)          | (61.86)  | (59.17)        | (73.50)       | (61.27) | (57.73)  | (55.03)       | (65.81)       | (9.83)  | (16.49)  | (14.79)        | (21.37)        |         |
| Dry mouth        | 27       | 5              | 5             | 12      | 26       | 5             | 5             | 12      | 1        | 0              | 1             | 1       |
| (5.20)           | (2.58)   | (2.96)         | (10.26)       | (5.01)  | (2.58)   | (2.96)        | (10.26)       | (0.19)  | (0.59)   | (0.85)         |               |         |
| Gastrointestinal disorder | 7       | 1               | 6             | 7       | 6        | 1             | 4             | 5       | 1        | 0              | 2             | 2       |
| (1.35)           | (0.52)   | (3.55)         | (5.98)        | (1.16)  | (0.52)   | (2.37)        | (4.27)        | (0.19)  | (1.18)   | (1.71)         |               |         |
| Nausea           | 220      | 77             | 71            | 46      | 219      | 75            | 69            | 43      | 5        | 5              | 5             | 8       |
| (42.39)          | (39.69)  | (42.01)        | (39.32)       | (42.20) | (38.66)  | (40.83)       | (36.75)       | (0.96)  | (2.58)   | (2.96)         | (6.84)        |         |
| Proctalgia       | 25       | 16             | 10            | 1       | 23       | 16            | 9             | 1       | 2        | 0              | 2             | 0       |
| (4.82)           | (8.25)   | (5.92)         | (0.85)        | (4.43)  | (8.25)   | (5.33)        | (0.85)        | (0.39)  | (1.18)   |               |               |         |
| Rectal haemorrhage | 31     | 15             | 11            | 5       | 31       | 14            | 11            | 4       | 0        | 3              | 0             | 1       |
| (5.97)           | (7.73)   | (6.51)         | (4.27)        | (5.97)  | (7.22)   | (6.51)        | (3.42)        | (1.55)  | (0.85)   |               |               |         |
| Upper abdominal pain | 40    | 9              | 8             | 8       | 39       | 9             | 8             | 7       | 2        | 0              | 3             | 0       |
| (7.71)           | (4.64)   | (4.73)         | (6.84)        | (7.51)  | (4.64)   | (4.73)        | (5.98)        | (0.39)  | (2.56)   |               |               |         |
| Stomatitis       | 18       | 10             | 7             | 5       | 17       | 9             | 7             | 5       | 2        | 1              | 1             | 0       |
| (3.47)           | (5.15)   | (4.14)         | (4.27)        | (3.28)  | (4.64)   | (4.14)        | (4.27)        | (0.39)  | (0.52)   | (0.59)         |               |         |
| Vomiting         | 190      | 59             | 62            | 47      | 186      | 55            | 57            | 43      | 16       | 10             | 9             | 10      |
| (36.61)          | (30.41)  | (36.69)        | (40.17)       | (35.84) | (28.35)  | (33.73)       | (36.75)       | (3.08)  | (5.15)   | (5.33)         | (8.55)        |         |
| Disorder                                           | Cases | Controls | Odds Ratio | 95% CI | p-value |
|---------------------------------------------------|-------|----------|------------|--------|---------|
| Arthralgia                                        | 11    | 10       | 0.9         | 0.3    | 0.08    |
| Mucosal inflammation                              | 127   | 136      | 0.9         | 0.6    | 0.18    |
| Palpitations                                      | 127   | 136      | 0.9         | 0.6    | 0.18    |
| Fatigue                                           | 127   | 136      | 0.9         | 0.6    | 0.18    |
| Urinary tract infection                           | 127   | 136      | 0.9         | 0.6    | 0.18    |
| Immune system disorders                           | 127   | 136      | 0.9         | 0.6    | 0.18    |
| Hypersensitivity                                  | 127   | 136      | 0.9         | 0.6    | 0.18    |
| Infections and infestations                       |       |          |            |        |         |
| Conjunctivitis                                    | 28    | 34       | 0.8         | 0.5    | 0.21    |
| Paronychia                                        | 28    | 34       | 0.8         | 0.5    | 0.21    |
| Upper respiratory infection                       | 28    | 34       | 0.8         | 0.5    | 0.21    |
| Urinary tract infection                           | 28    | 34       | 0.8         | 0.5    | 0.21    |
| Metabolism and nutrition disorders                |       |          |            |        |         |
| Decreased appetite                                | 123   | 136      | 0.9         | 0.6    | 0.18    |
| Hyperglycaemia                                    | 123   | 136      | 0.9         | 0.6    | 0.18    |
| Hypomagnesemia                                    | 123   | 136      | 0.9         | 0.6    | 0.18    |
| Musculoskeletal and connective tissue disorders   |       |          |            |        |         |
| Arthralgia                                        | 27    | 34       | 0.8         | 0.5    | 0.21    |
| Back pain                                         | 27    | 34       | 0.8         | 0.5    | 0.21    |
| Condition                              | Count 1 | Count 2 | Count 3 | Count 4 | Count 5 | Count 6 | Count 7 | Count 8 | Count 9 |
|----------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Bone pain                              | 13      | 9       | 9       | 12      | 9       | 9       | 3       | 1       | 0       |
|                                        | (2.50)  | (4.64)  | (5.33)  | (2.31)  | (4.64)  | (5.33)  | (2.56)  | (0.19)  | (0.59)  |
| Myalgia                                | 12      | 6       | 4       | 6       | 12      | 6       | 4       | 6       | 0       |
|                                        | (2.31)  | (3.09)  | (2.37)  | (5.13)  | (2.31)  | (3.09)  | (2.37)  | (5.13)  | 0       |
| Nervous system disorders               |         |         |         |         |         |         |         |         |         |
| Dizziness                              | 21      | 10      | 12      | 8       | 21      | 10      | 12      | 8       | 0       |
|                                        | (4.05)  | (5.15)  | (7.10)  | (6.84)  | (4.05)  | (5.15)  | (7.10)  | (6.84)  | 0       |
| Dysgeusia                              | 62      | 28      | 14      | 14      | 62      | 28      | 13      | 14      | 0       |
|                                        | (11.95) | (14.43) | (8.28)  | (11.97) | (11.95) | (14.43) | (7.69)  | (11.97) | (0.59)  |
| Headache                               | 27      | 11      | 10      | 7       | 26      | 11      | 10      | 7       | 1       |
|                                        | (5.20)  | (5.67)  | (5.92)  | (5.98)  | (5.01)  | (5.67)  | (5.92)  | (5.98)  | (0.19)  |
| Peripheral sensory neuropathy\(a\)     | 344     | 123     | 103     | 79      | 341     | 122     | 103     | 77      | 52      |
|                                        | (66.28) | (63.40) | (60.95) | (67.52) | (65.70) | (62.89) | (60.95) | (65.81) | (10.02) |
| Psychiatric disorders                  |         |         |         |         |         |         |         |         |         |
| Insomnia                               | 29      | 11      | 8       | 7       | 29      | 11      | 11      | 8       | 7       |
|                                        | (5.59)  | (5.67)  | (4.73)  | (5.98)  | (5.59)  | (5.67)  | (4.73)  | (5.98)  | 0       |
| Renal and urinary disorders            |         |         |         |         |         |         |         |         |         |
| Proteinuria                            | 13      | 6       | 10      | 8       | 12      | 5       | 9       | 7       | 2       |
|                                        | (2.50)  | (3.09)  | (5.92)  | (6.84)  | (2.31)  | (2.58)  | (5.33)  | (5.98)  | (0.39)  |
| Renal failure                          | 3 (0.58)| 3 (1.55)| 4 (2.37)| 7 (5.98)| 1 (0.19)| 1 (0.52)| 3 (1.78)| 4 (3.42)| 2 (0.39)| 2 (1.03)| 2 (1.18)| 4 (3.42) |
| Respiratory, thoracic and mediastinal disorders |         |         |         |         |         |         |         |         |         |
| Cough                                  | 41      | 16      | 11      | 11      | 41      | 16      | 11      | 11      | 0       |
|                                        | (7.90)  | (3.09)  | (6.51)  | (9.40)  | (7.90)  | (3.09)  | (6.51)  | (9.40)  | 0       |
| Dysphonia                              | 9 (1.73)| 4 (2.06)| 3 (1.78)| 8 (6.84)| 9 (1.73)| 4 (2.06)| 3 (1.78)| 8 (6.84)| 0       |
|                                        | (2.50)  | (3.09)  | (5.92)  | (6.84)  | (2.31)  | (2.58)  | (5.33)  | (5.98)  | (0.39)  |
| Dyspnnoa                               | 25      | 11      | 10      | 10      | 23      | 12      | 8       | 9       | 2       |
|                                        | (4.82)  | (6.70)  | (6.51)  | (8.55)  | (4.43)  | (6.19)  | (4.73)  | (7.69)  | (0.39)  |
| Epistaxis                              | 79      | 20      | 29      | 13      | 79      | 20      | 29      | 13      | 0       |
|                                        | (15.22) | (10.31)| (17.16)| (11.11)| (15.22)| (10.31)| (17.16)| (11.11)| 0       |
| Skin and subcutaneous tissue disorders |         |         |         |         |         |         |         |         |         |
| Acne                                   | 23      | 13      | 3       | 2       | 22      | 13      | 3       | 2       | 13      |
|                                        | (4.43)  | (6.70)  | (1.78)  | (1.71)  | (4.24)  | (6.70)  | (1.78)  | (1.71)  | (2.50)  |
| Alopecia                               | 44      | 16      | 15      | 5       | 42      | 16      | 15      | 5       | 2       |
|                                        | (8.48)  | (8.25)  | (8.88)  | (4.27)  | (8.09)  | (8.25)  | (8.88)  | (4.27)  | (2.50)  |
| Palmar-plantar erythrodysesthesia syndrome | 126     | 51      | 39      | 27      | 124     | 46      | 36      | 27      | 30      |
|                                        | (24.28) | (26.29)| (23.08)| (23.08)| (23.89)| (23.71)| (21.30)| (23.08)| (5.78)  |
| Pruritus                               | 30      | 7       | 5       | 7       | 30      | 5       | 5       | 7       | 2       |
|                                        | (5.78)  | (3.61)  | (2.96)  | (5.98)  | (5.78)  | (2.58)  | (2.96)  | (5.98)  | (0.39)  |
| Condition                        | Count | Percentage |
|----------------------------------|-------|------------|
| Skin toxicity dermatitis\(b\)    | 152   | (29.29)    |
|                                  | 44    | (22.68)    |
|                                  | 30    | (17.75)    |
|                                  | 11    | (9.40)     |
|                                  | 152   | (29.29)    |
|                                  | 44    | (22.68)    |
|                                  | 29    | (17.16)    |
|                                  | 11    | (9.40)     |
|                                  | 29    | (5.59)     |
|                                  | 8     | (4.12)     |
|                                  | 4     | (2.37)     |
|                                  | 2     | (1.71)     |
| Skin fissures                    | 28    | (5.39)     |
|                                  | 9     | (4.64)     |
|                                  | 3     | (1.78)     |
|                                  | 0     | (0.00)     |
|                                  | 27    | (5.20)     |
|                                  | 8     | (1.78)     |
|                                  | 3     | (0.60)     |
|                                  | 0     | (0.00)     |
|                                  | 2     | (0.40)     |
|                                  | 4     | (0.77)     |
|                                  | 0     | (0.00)     |
|                                  | 0     | (0.00)     |
| Skin hyperpigmentation           | 14    | (2.70)     |
|                                  | 11    | (2.22)     |
|                                  | 4     | (0.81)     |
|                                  | 2     | (0.40)     |
|                                  | 14    | (2.70)     |
|                                  | 11    | (2.22)     |
|                                  | 4     | (0.81)     |
|                                  | 2     | (0.40)     |
|                                  | 0     | (0.00)     |
|                                  | 0     | (0.00)     |
|                                  | 0     | (0.00)     |
| Vascular disorders               |       |            |
| Hypertension                     | 78    | (15.03)    |
|                                  | 35    | (18.04)    |
|                                  | 40    | (23.67)    |
|                                  | 22    | (18.80)    |
|                                  | 72    | (13.87)    |
|                                  | 32    | (16.49)    |
|                                  | 35    | (20.71)    |
|                                  | 20    | (17.09)    |
|                                  | 14    | (2.70)     |
|                                  | 10    | (5.15)     |
|                                  | 9     | (5.33)     |
|                                  | 3     | (2.56)     |

Data presented as N (%) unless otherwise specified

\(a\)Includes dysesthesia, neurotoxicity, paraesthesia and peripheral neuropathy.

\(b\)Includes dermatitis acneiform, exfoliative rash and rash.