| Study or Subgroup       | Experimental | Control | Odds Ratio | Odds Ratio |
|------------------------|--------------|---------|------------|------------|
|                        | Events       | Total   | Events     | Total      | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Abou-Alfa2018          | 137          | 467     | 14         | 237        | 2.5%        | 6.61 [3.72, 11.76] |
| Ahn2013                | 13           | 75      | 0          | 42         | 0.5%        | 18.36 [1.06, 317.23] |
| Arnold2007             | 11           | 52      | 1          | 53         | 0.9%        | 13.95 [1.73, 112.53] |
| Baggstrom2017          | 27           | 99      | 9          | 99         | 2.2%        | 3.75 [1.66, 8.48] |
| Brose2014              | 84           | 207     | 26         | 209        | 2.6%        | 4.81 [2.93, 7.89] |
| Bruix2015              | 108          | 559     | 35         | 548        | 2.8%        | 3.51 [2.35, 5.24] |
| Bruix2017              | 87           | 374     | 9          | 193        | 2.3%        | 6.20 [3.04, 12.62] |
| Cheng2009              | 28           | 149     | 1          | 75         | 0.9%        | 17.12 [2.28, 128.51] |
| Cheng2013              | 110          | 526     | 95         | 542        | 2.9%        | 1.24 [0.92, 1.69] |
| Chouei2017             | 63           | 78      | 49         | 72         | 2.3%        | 1.97 [0.93, 4.17] |
| Demetri2006            | 21           | 202     | 4          | 102        | 1.8%        | 2.84 [0.95, 8.52] |
| Demetri2013            | 64           | 132     | 11         | 66         | 2.3%        | 4.71 [2.26, 9.78] |
| Du Bois2014            | 275          | 477     | 91         | 461        | 2.9%        | 5.54 [4.13, 7.42] |
| Eisen2015              | 7            | 64      | 5          | 32         | 1.6%        | 0.66 [0.19, 2.28] |
| Elisei2013             | 70           | 214     | 5          | 109        | 2.0%        | 10.11 [3.94, 25.93] |
| Escudier2007           | 76           | 451     | 8          | 451        | 2.3%        | 11.22 [5.35, 23.56] |
| Gounder2018            | 31           | 49      | 14         | 36         | 2.1%        | 2.71 [1.11, 6.57] |
| Gross-Goupil2018       | 229          | 356     | 88         | 359        | 2.8%        | 5.55 [4.02, 7.68] |
| Grothey2013            | 152          | 500     | 20         | 253        | 2.6%        | 5.09 [3.10, 8.35] |
| Haas2016               | 102          | 628     | 26         | 626        | 2.7%        | 4.47 [2.86, 6.99] |
| Haas2016               | 105          | 625     | 102        | 628        | 2.9%        | 1.94 [0.77, 4.40] |
| Haas2016               | 105          | 625     | 26         | 626        | 2.7%        | 4.66 [2.99, 7.27] |
| Herzog2013             | 45           | 123     | 7          | 123        | 2.1%        | 9.56 [4.28, 22.29] |
| Huston2013             | 92           | 189     | 28         | 96         | 2.6%        | 2.30 [1.36, 3.89] |
| Kang2015               | 72           | 133     | 9          | 68         | 2.2%        | 7.74 [3.55, 16.88] |
| Kudo2011               | 31           | 229     | 7          | 227        | 2.1%        | 4.92 [2.12, 11.42] |
| Kudo2018               | 201          | 476     | 111        | 475        | 2.9%        | 2.40 [1.81, 3.17] |
| Leboulleux2012         | 25           | 73      | 4          | 72         | 1.8%        | 8.85 [2.89, 27.09] |
| Ledermann2011          | 2            | 43      | 0          | 40         | 0.5%        | 4.88 [0.23, 104.81] |
| Lee2012                | 164          | 619     | 9          | 303        | 2.4%        | 11.77 [5.92, 23.40] |
| Li2015                 | 34           | 136     | 4          | 68         | 1.8%        | 5.33 [1.81, 15.74] |
| Llovet2008             | 15           | 297     | 6          | 302        | 2.0%        | 2.62 [1.00, 6.86] |
| Mir2016                | 32           | 89      | 10         | 92         | 2.2%        | 4.60 [2.10, 10.11] |
| O’ Brien2015           | 40           | 50      | 30         | 50         | 2.1%        | 2.67 [1.09, 6.52] |
| Palmer2018             | 9            | 62      | 3          | 31         | 1.4%        | 1.58 [0.40, 6.33] |
| Pavlikis2015           | 10           | 97      | 1          | 50         | 0.9%        | 5.63 [0.70, 45.32] |
| Paz-Ares2015           | 68           | 346     | 16         | 351        | 2.5%        | 5.12 [2.90, 9.03] |
| Ravaud2016             | 110          | 309     | 29         | 306        | 2.7%        | 5.28 [3.37, 8.26] |
| Raymond2011            | 24           | 83      | 6          | 82         | 2.0%        | 5.15 [1.98, 13.42] |
| Rini2011               | 149          | 359     | 107        | 355        | 2.8%        | 1.64 [1.21, 2.24] |
| Schlumberger2015       | 177          | 261     | 12         | 131        | 2.4%        | 20.90 [10.93, 39.94] |
| Sterberg2013           | 116          | 290     | 15         | 145        | 2.5%        | 5.78 [3.22, 10.36] |
| Sun2018                | 8            | 48      | 1          | 47         | 0.8%        | 9.20 [1.10, 76.77] |
| Van Cutsem2015         | 42           | 384     | 17         | 381        | 2.5%        | 2.63 [1.47, 4.71] |
| Van Der Graaf2012      | 99           | 239     | 8          | 123        | 2.3%        | 10.17 [4.76, 21.77] |
| Wells2012              | 73           | 231     | 5          | 99         | 2.0%        | 8.69 [3.39, 22.27] |
| Yen2018                | 10           | 63      | 7          | 32         | 1.8%        | 0.87 [0.23, 2.98] |

| Total (95% CI)         | 12138        | 9868    | 100.0%     | 4.32 [3.43, 5.44] |
| Total events           | 3553         | 1091    |             |             |

Heterogeneity: Tau² = 0.46; Chi² = 291.62, df = 46 (P < 0.00001); I² = 84%
Test for overall effect: Z = 12.43 (P < 0.00001)