Supplemental Online Content

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eFigure 1. Liver-Related Toxic Effects in Placebo-Controlled Trials and Trials With Active Comparator

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This supplemental material has been provided by the authors to give readers additional information about their work.
eFigure 1. Liver-Related Toxic Effects in Placebo-Controlled Trials and Trials With Active Comparator

A. Placebo-Controlled Trials

| Study or Subgroup | Experimental Events | Total Events | Total Control | Total Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|------------------|---------------------|-------------|--------------|-------------|-------------------------------|-------------------------------|
| Abou-Alla et al., #11 2018 | 94 | 467 | 25 | 237 | 12.3% | 1.94 [1.26, 2.88] |
| Brule et al., #10 2017 | 59 | 374 | 27 | 193 | 12.1% | 1.13 [0.74, 1.73] |
| Rapp et al., #2 2015 | 94 | 133 | 40 | 68 | 16.1% | 1.20 [0.86, 1.65] |
| Kudo et al., #3 2011 | 20 | 229 | 5 | 22 | 4.8% | 3.97 [1.51, 10.38] |
| Hiejri et al., #4 2013 | 42 | 263 | 16 | 132 | 9.9% | 1.32 [0.77, 2.25] |
| Hiejri et al., #3 2008 | 1 | 299 | 0 | 303 | 0.8% | 3.04 [0.12, 74.33] |
| Rinaldi et al., #5 2018 | 19 | 225 | 11 | 114 | 7.3% | 0.98 [0.43, 2.27] |
| Santoro et al., #7 2013 | 8 | 71 | 1 | 36 | 1.3% | 4.06 [0.53, 31.19] |
| Zhu et al., #8 2014 | 50 | 362 | 12 | 184 | 8.9% | 2.12 [1.16, 3.88] |
| Zhu et al., #9 2015 (a) | 56 | 277 | 66 | 276 | 14.3% | 0.95 [0.62, 1.46] |
| Zhu et al., #6 2019 | 4 | 187 | 0 | 95 | 0.7% | 4.38 [0.24, 80.23] |
| Subtotal (95% CI) | 2897 | 1805 | 88.2% | | | 1.38 [1.06, 1.79] |
| Total events | 447 | 203 |

B. Trials With Active Comparator

| Study or Subgroup | Experimental Events | Total Events | Total Control | Total Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|------------------|---------------------|-------------|--------------|-------------|-------------------------------|-------------------------------|
| Lee et al., 2019 compares atezolizumab + bevacizumab to atezolizumab. The remaining comparators are Soraениb. |

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eFigure 2. Serious Adverse Events in Placebo Controlled Trials and in Trials With Active Comparator

### A. Placebo-Controlled Trials

| Study or Subgroup | Treatment Events | Control Events | Total | Weight | M-H Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI |
|-------------------|------------------|----------------|-------|--------|-----------------------------------|-------------------------------|
| 2.1.1 TKI vs Placebo |
| Bruck et al. 2017 | 166 347 | 90 123 | 11.7% | 0.95 [0.79, 1.13] |
| Cheng et al. 2009 | 71 149 | 34 75 | 8.8% | 1.05 [0.78, 1.42] |
| Kang et al. 2015 | 63 134 | 17 68 | 5.8% | 1.68 [1.26, 2.25] |
| Kudo et al. 2013 | 42 228 | 25 227 | 5.4% | 1.67 [1.09, 2.54] |
| Uther et al. 2013 | 185 261 | 75 131 | 12.0% | 1.10 [0.93, 1.31] |
| Ramnasa et al. 2018 | 103 225 | 51 114 | 10.1% | 1.02 [0.80, 1.31] |
| Santoro et al. 2013 | 24 69 | 14 56 | 4.8% | 0.88 [0.55, 1.41] |
| Zhu et al. 2014 | 173 362 | 65 164 | 10.7% | 1.35 [0.88, 2.07] |
| Zhu et al. 2015 (1) | 100 277 | 79 276 | 10.2% | 1.24 [0.91, 1.71] |
| Zhu et al. 2015 (2) | 210 362 | 186 538 | 12.5% | 1.58 [1.38, 1.84] |
| Zhu et al. 2019 | 68 187 | 28 95 | 7.3% | 1.17 [0.81, 1.70] |
| Subgroup Total (95% CI) | 2639 1957 | 100.0% | 1.22 [1.06, 1.40] |
| Total events 1185 | 674 |
| Heterogeneity: Tau² = 0.03; Ch² = 31.82, df = 10 (P = 0.0004); I² = 69%
| Test for overall effect: Z = 2.83 (P = 0.005) |
| Total (95% CI) 2639 | 1937 | 100.0% | 1.22 [1.06, 1.40] |

### B. Trials With Active Comparator

| Study or Subgroup | Experimental Events | Control Events | Total | Weight | M-H Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI |
|-------------------|---------------------|----------------|-------|--------|-----------------------------------|-------------------------------|
| 4.2.1 TKI vs Sorafenib |
| Calisap et al. 2015 | 267 510 | 200 519 | 17.6% | 1.36 [1.18, 1.56] |
| Cheng et al. 2013 | 0 526 | 0 542 | 0% | Not estimable |
| Cheng et al. 2015 (1) | 25 63 | 18 32 | 5.1% | 0.82 [0.55, 1.23] |
| Cheng et al. 2016 | 40 71 | 34 83 | 7.1% | 1.38 [0.89, 2.11] |
| Johnson et al. 2013 | 510 575 | 276 575 | 19.4% | 1.13 [1.00, 1.28] |
| Kudo et al. 2018 | 208 476 | 144 475 | 14.9% | 1.42 [1.20, 1.68] |
| Zhu et al. 2015 (2) | 0 0 | 0 0 | Not estimable |
| Subtotal (95% CI) 2221 | 2262 | 64.1% | 1.24 [1.07, 1.44] |
| Total events 851 | 672 |
| Heterogeneity: Tau² = 0.02; Ch² = 11.55, df = 4 (P = 0.03); I² = 65%
| Test for overall effect: Z = 2.93 (P = 0.003) |
| 4.2.2 ICIs vs Sorafenib |
| Hett et al. 2020 (MMRAVE150) | 129 329 | 48 196 | 5.1% | 1.23 [0.94, 1.62] |
| Yau et al. 2021 | 43 371 | 39 372 | 5.1% | 1.11 [0.73, 1.66] |
| Subtotal (95% CI) 700 | 528 | 14.2% | 1.19 [0.95, 1.50] |
| Total events 169 | 87 |
| Heterogeneity: Tau² = 0.00; Ch² = 0.20, df = 1 (P = 0.66); I² = 0%
| Test for overall effect: Z = 1.53 (P = 0.13) |
| 4.2.3 TKI + Sorafenib vs Sorafenib |
| Koebeler et al. 2016 | 28 60 | 14 46 | 3.5% | 1.53 [0.92, 2.56] |
| Zhu et al. 2015 (2) | 210 362 | 195 358 | 16.2% | 1.07 [0.84, 1.35] |
| Subtotal (95% CI) 422 | 404 | 21.6% | 1.17 [0.85, 1.61] |
| Total events 239 | 209 |
| Heterogeneity: Tau² = 0.03; Ch² = 1.85, df = 1 (P = 0.17); I² = 46%
| Test for overall effect: Z = 0.98 (P = 0.33) |
| Total (95% CI) 3343 | 3158 | 100.0% | 1.21 [1.09, 1.34] |
| Total events 1257 | 968 |
| Heterogeneity: Tau² = 0.01; Ch² = 16.82, df = 8 (P = 0.03); I² = 52%
| Test for overall effect: Z = 3.64 (P = 0.0003) |
| Test for subgroup differences: Ch² = 0.16, df = 2 (P = 0.92), I² = 0% |
**Figure 3. Grade 3 or Higher Adverse Events in Placebo-Controlled Trials and Trials With Active Comparator**

### A. Placebo-Controlled Trials

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------------|----------------|--------------|--------------|--------------------------------|--------------------------------|
| **2.2.1 TKI vs Placebo** |                     |                |              |              |                                |                                |
| Abou-Alla et al. 2018 | 320                | 470            | 69            | 237          | 18.3% 1.88 [1.57, 2.25]          |                                |
| Iovet et al. 2008  | 45                 | 237            | 63            | 302          | 12.9% 1.43 [0.94, 2.18]          |                                |
| Iovet et al. 2013  | 178                | 261            | 349           | 131          | 15.0% 2.75 [2.04, 3.62]          |                                |
| Ramli et al. 2018  | 155                | 225            | 380           | 114          | 18.1% 1.25 [1.03, 1.50]          |                                |
| Zhu et al. 2014    | 257                | 362            | 619           | 184          | 18.9% 1.36 [1.17, 1.59]          |                                |
| Subtotal (95%) CI  | 1615               | 2968           | 4583          | 968          | 82.5% 1.65 [1.27, 2.14]          |                                |
| **Total events**   | 955                | 308            | 1263          |              |                                |                                |
| **Heterogeneity:** |                    |                |              |              |                                |                                |
| Tau²: 0.07; Chi²: 27.74, df = 4 (P < 0.0001); I² = 86% |                                |                                |
| Test for overall effect: Z = 3.75 (P = 0.0001) |                                |                                |

### B. Trials With Active Comparator

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------------|----------------|--------------|--------------|--------------------------------|--------------------------------|
| **4.3.1 TKI vs Sorafenib** |                     |                |              |              |                                |                                |
| Cai et al. 2013    | 435                | 510            | 945          | 512          | 14.2% 1.51 [1.39, 1.64]          |                                |
| Cheng et al. 2013  | 432                | 526            | 958          | 542          | 14.6% 1.11 [1.04, 1.18]          |                                |
| Cheng et al. 2015 (1) | 35             | 63             | 98            | 27          | 8.7% 0.70 [0.53, 0.93]           |                                |
| Kudo et al. 2018   | 357                | 476            | 833          | 475          | 14.2% 1.13 [1.04, 1.22]          |                                |
| Palmer et al. 2018 | 42                 | 62             | 104          | 28           | 10.7% 0.75 [0.61, 0.92]          |                                |
| Zhu et al. 2015 (2) | 315               | 362            | 677          | 258          | 14.4% 1.20 [1.11, 1.29]          |                                |
| Subtotal (95%) CI  | 1999               | 1949           | 3948         | 76.8%        | 1.07 [0.92, 1.24]               |                                |
| **Total events**   | 1816               | 1320           | 3136         |              |                                |                                |
| **Heterogeneity:** |                    |                |              |              |                                |                                |
| Tau²: 0.03; Chi²: 70.97, df = 5 (P < 0.000001); I² = 93% |                                |                                |
| Test for overall effect: Z = 3.68 (P = 0.000021) |                                |                                |

| **4.3.2 ICI vs Sorafenib** |                     |                |              |              |                                |                                |
| Himm et al. 2020 (IMRAVE150) | 201             | 329            | 530          | 156          | 12.4% 1.00 [0.86, 1.17]          |                                |
| Subtotal (95%) CI | 329                 | 156            |              |              |                                |                                |
| **Total events**   | 201                | 95             |              |              |                                |                                |
| **Heterogeneity:** |                    |                |              |              |                                |                                |
| Tau²: 0.04 (P = 0.977) |                                |                                |

| **4.3.3 TKI + Sorafenib vs Sorafenib** |                     |                |              |              |                                |                                |
| Koebel et al. 2016  | 53                 | 60             | 113          | 33           | 10.9% 1.23 [1.00, 1.51]          |                                |
| Subtotal (95%) CI  | 60                  | 46             |              |              |                                |                                |
| **Total events**   | 53                 | 33             |              |              |                                |                                |
| **Heterogeneity:** |                    |                |              |              |                                |                                |
| Tau²: 0.03 (P = 0.917) |                                |                                |

**Figure legend:**

- **Favours [experimental]**
- **Favours [control]**

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## eFigure 4. Risk of Bias 2 Assessment

| Study ID | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall |
|----------|------------|---------|--------|----|----|----|----|----|---------|
| C1       | Amelitamib | Placebo | Adverse Events | Low risk | | | | | |
| C2       | Braux      | Placebo | Adverse Events | Some concerns | | | | | |
| C3       | Carney     | Placebo | Adverse Events | High risk | | | | | |
| C4       | Cheng2009  | Placebo | Adverse Events | | | | | | |
| C5       | Cheng2011  | Placebo | Adverse Events | | | | | | |
| C6       | Cheng2015  | Placebo | Adverse Events | | | | | | |
| C7       | Cheng2015  | Placebo | Adverse Events | | | | | | |
| C8       | Cheng2015  | Placebo | Adverse Events | | | | | | |
| C9       | Cheng2016  | Placebo | Adverse Events | | | | | | |

D1: Randomization process  
D2: Deviations from the intended interventions  
D3: Missing outcome data  
D4: Measurement of the outcome  
D5: Selection of the reported result
### eTable. MINORS Assessment

| Criteria                                           | Marron et al., 2022 | Finn et al., 2020 (iii) |
|----------------------------------------------------|----------------------|-------------------------|
| A clearly stated aim                               | 2                    | 2                       |
| Inclusion of consecutive patients                  | 0                    | 2                       |
| Prospective collection of data                     | 2                    | 2                       |
| Appropriate endpoints                              | 2                    | 2                       |
| Unbiased assessment of endpoints                   | 2                    | 2                       |
| Appropriate follow up                              | 2                    | 2                       |
| Loss to follow up <5%                              | 2                    | 2                       |
| Prospective calculation of sample size             | 2                    | 2                       |
| **Total**                                          | **14/16**            | **16/16**               |
eFigure 5. GRADE of Evidence Assessment

| N. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | TKIs | ICIs | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---------------|-------------|--------------|---------------|--------------|-------------|---------------------|------|------|------------------|------------------|-----------|------------|
| **IV Liver**  |             |              |               |              |             |                     |      |      |                  |                  |           |            |
| 23            | randomised trials | not serious | not serious | serious* | not serious | none                | 1668/6040 (21.0%) | 301/1075 (28.0%) | Proportion 0.23 (0.18 to 0.28) | -- per 1,000 (from - to -) | 🗝️ 🗝️ 🗝️ 🗝️ | Moderate   |
|               |              |              |               |              |             |                     |      |      |                  |                  |           |            |
| **IV serious AEs** |            |              |               |              |             |                     |      |      |                  |                  |           |            |
| 23            | randomised trials | not serious | not serious | serious | not serious | none                | 2998/6517 (40.0%) | 304/1266 (24.0%) | Proportion 0.41 (0.34 to 0.48) | -- per 1,000 (from - to -) | 🗝️ 🗝️ 🗝️ 🗝️ | Moderate   |
|               |              |              |               |              |             |                     |      |      |                  |                  |           |            |
| **IV grade 3+** |           |              |               |              |             |                     |      |      |                  |                  |           |            |
| 20            | randomised trials | not serious | not serious | serious* | not serious | none                | 3968/5645 (69.0%) | 555/1587 (35.0%) | Proportion 0.56 (0.46 to 0.67) | -- per 1,000 (from - to -) | 🗝️ 🗝️ 🗝️ 🗝️ | Moderate   |

CI: confidence interval

Explanations:

a. Proportions largely compared between different studies.