**Supplementary material**

### Appendix 1. Unpublished data series

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Ota2018 | Andersen2018 |
| Country |  | Japan | Denmark |
| N |  | 17 | 21 |
| Age   | Median | 68 | 62 |
| Lower range | 40 | 38 |
| Upper range | 86 | 75 |
| Gender | Male | 7 | 17 |
| Female | 10 | 4 |
| ECOG    | 0 | 3 | 7 |
| 1 | 4 | 11 |
| 2 | 7 | 3 |
|  > 2 | 3 | 0 |
| Primary site of tumor | Colon | 8 | 14 |
| Rectum | 9 | 7 |
| RAS mutation   | No | 9 | 10 |
| Yes | 6 | 11 |
| Unknown | 2 | 0 |
| Time from diagnose of metastatic disease | <18 months | 2 | 9 |
| ≥ 18 months | 15 | 10 |
| Unknown | 0 | 2 |
| Number of prior regimens | 1 | 1 | 0 |
| 2 | 2 | 0 |
| 3 | 4 | 21 |
| ≥ 4 | 10 | 0 |
| Prior anticancer agents for metastatic disease | Fluorpyrimidines | 13 | 21 |
| Oxaliplatin | 16 | 21 |
| Irinotecan | 8 | 21 |
| Bevacizumab/ramucirumab | 13 | 21 |
| Anti-EGFR monoclonal antibody | 13 | 9 |
| Aflibercept | 0 | 0 |
| Regorafenib | 4 | 0 |
|  |  |  |
|  |  |  |

Kaplan Meier curves Ota 2018



Kaplan Meier curves Andersen 2018



## Appendix 2. Appraisal of study quality

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***No*** | ***Question*** | Cremolini 2018 | Kwakman 2018 | Moriwaki2018 | Masuishi2017 | Sueda2016 | Arita2016 | Kotani2016 |  |  |
| 1 | Were the two groups similar and recruited from the same population? | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant |  | **Yes** |
| 2 | Were the exposures measured similarly to assign people to both exposed and unexposed groups? | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant |  | **Unclear** |
| 3 | Was the exposure measured in a valid and reliable way? | No details on actualdose intensity | No details on actualdose intensity | No details on actualdose intensity | No details on actualdose intensity |   |   |   |  | **No** |
| 4 | Were confounding factors identified? |   |   |   |   |   |   |   |  |  |
| 5 | Were strategies to deal with confounding factors stated? | Multivariableregression | Multivariableregression | Multivariableregression | Multivariableregression |   | Multivariableregression |   |  |  |
| 6 | Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? |   |   |   |   |   |   |   |  |  |
| 7 | Were the outcomes measured in a valid and reliable way? | RadiologicalRECIST | Assessment ofprogression not described | Assessment ofprogression not described | RadiologicalRECIST | RadiologicalRECIST | RadiologicalRECIST | RadiologicalRECIST |  |  |
| 8 | Was the follow up time reported and sufficient to be long enough for outcomes to occur? |   |   |   |   |   | Medianfollow-up time not described |   |  |  |
| 9 | Was follow up complete, and if not, were the reasons to loss to follow up described and explored? |   |   |   |   |   |   |   |  |  |
| 10 | Were strategies to address incomplete follow up utilized? | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant | Not relevant |  |  |
| 11 | Was appropriate statistical analysis used? |   |   |   |   |   |   |   |  |  |

Appendix 3.

Search history PubMed

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