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Supplemental Appendix for:
BRAF mutations as predictive biomarker for response to anti-EGFR monoclonal antibodies
Jan Schellens et al.

Appendix S1

METHODS

A PubMed search was performed to collect meta-analyses that included data of *BRAF* mutated (mt) patients and *BRAF* wildtype (wt) patients and survival outcome of treatment with the anti-EGFR mAbs cetuximab or panitumumab using the following terms (molecular testing OR mutation) AND (BRAF OR RAF) AND survival AND EGFR AND 'colorectal cancer' AND meta-analysis. Of the 12 articles, 10 were selected for review and 2 were excluded based on incomplete results or irrelevance. The same search without the term “meta-analysis” was performed to check if relevant randomized clinical trials were recently published and not included in the selected meta-analysis, focusing on publications after 2014. This was not the case.

The quality of evidence was considered high if included articles in the meta-analyses were mainly randomized controlled trials (RCTs) and the results included survival outcome of *BRAF*mt vs. *BRAF*wt patients. Furthermore, the overlap of included trials in the selected meta-analyses was assessed (Appendix 1) and taken into consideration in the quality assessment. As a comparison, the evidence for *KRAS* and *NRAS* mutations was extracted from the American Society of Clinical Oncology (ASCO) guidelines of 2009 and 2016 [1,2] and from the European Society for Medical Oncology (ESMO) guideline of 2016[3].

Statistical analyses were performed in R. The confidence interval for *BRAF*mt versus *BRAF*wt was calculated using the HR of 0.86 and 0.62 as provided by Rowland *et al.* using properties of two normal distributions and the following calculation:

```
a <- log(0.86)
b <- log(0.62)
a.low <- log(0.61)
b.low <- log(0.50)
se.a <- (a - a.low)/1.96
se.b <- (b - b.low)/1.96

logQ <- a - b
se.logQ <- sqrt(se.a ^ 2 + se.b ^ 2)
logQ.low <- logQ - 1.96 * se.logQ
logQ.high <- logQ + 1.96 * se.logQ

exp(logQ.low)
exp(logQ.high)
```

The required sample size to detect a significant interaction effect between *BRAF*wt and *BRAF*mt with a power of 80% was calculated with the PowerSurvEpi package assuming a hazard rate (HR) of 1.4 as a clinically relevant effect of *BRAF*mt[4], indicating a 40% increased risk of death during treatment with anti-

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EGFR mAbs in presence of a *BRAF* mutation, an event rate (death) of 50% during clinical studies[5], and 10% incidence of *BRAF* mutations[6].

References

1 Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol 2016;34:179–85.

2 Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol 2009;27:2091–6.

3 Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;:mdw235.

4 Rowland a, Dias MM, Wiese MD, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. Br J Cancer 2015;112:1888–1894.

5 Douillard J-Y, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023–34.

6 R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. 2014.Available at http://www.r-project.org/.