UNIVERSITÀ DEGLI STUDI DI MESSINA

TESI DI DOTTORATO DI RICERCA IN BIOLOGIA APPLICATA E MEDICINA SPERIMENTALE
CURRICULUM IN MEDICINA SPERIMENTALE

XXX CICLO

SSD BIO/14

Risk of severe and life-threatening diarrhea and mucositis in cancer patients receiving anti-EGFR monoclonal antibodies: a systematic review and meta-analysis of published and unpublished data

Candidato:
DOTT. MARCO MIRODDI

Relatore:

Ch.mo Prof.
GIOACCHINO CALAPAI

Coordinatore:
Ch.mo Prof. SALVATORE CUZZOCREA

ANNO ACCADEMICO 2016-2017

Table of Contents

1. Background 3
1.1. Epidemiology of diarrhea and mucositis induced by anti-cancer regimens 5
1.2. Diarrhea and mucositis clinical aspects 5
1.3. Anti-tumoral drugs as factor favouring diarrhea and mucositis 7
1.4. Anti-epidermal Growth Factor monoclonal antibodies 7
1.5. Current evidence and risk of diarrhea and mucositis associated to molecularly targeted agents 8
1.6. Research question 10

2. Methods 11
2.1. Aims and objective 11
2.2. Searching 11
2.3. Inclusion criteria 13
2.4. Review procedures 14
2.5. Strategy for data collection and data Synthesis 14
2.6. Dealing with aggregate data and unpuplished data 15
2.7. Quality assessment 16
2.8. Statistical analysis 16

3. Results (Overview of the evidence) 19
3.1. Studies identification and selection 19
3.2. Study characteristics 21
3.3. Study quality 25
3.4. Outcomes 25

4. Discussion 37
4.1. Quality of the evidence 41
4.2. Limitations 41
As in other meta-analyses, our study has potential limitations. 41

5. Conclusion 42

6. References 43

7. Appendices 50
7.1. Appendix 1: Search strategy 50
7.2. Appendix 2: Common Terminology Criteria for Adverse Events v 3.0 (CTCAE) 53

1. Background

Gastrointestinal toxicity, including diarrhoea and mucositis, is one of the most common complications caused by systemic cytotoxic chemotherapy (Gibson 2009). Chemotherapy induced diarrhea (CID) can occur in 50–80% of patients depending on the chemotherapy regimen (Benson et al. 2004; Gibson et al. 2009).

A review of early toxic deaths occurring in two National Cancer Institute-sponsored cooperative group trials of irinotecan plus high-dose fluorouracil and leucovorin for advanced colorectal cancer has led to the recognition of a life-threatening gastrointestinal syndrome and highlighted the need for vigilant monitoring and aggressive therapy for this serious complication (Conti et al. 1996; Arbuckle et al. 2000; Saltz et al. 2000).

Diarrhea caused by chemotherapy regimens is a multifactorial process whereby acute damage of the intestinal mucosa is due to loss of intestinal epithelium, superficial necrosis and inflammation of the bowel wall. Prolonged or profound oral and gastrointestinal mucositis can lead to painful ulcerations, bleeding, risk of infections, dysphagia, bloatedness and increase of diarrhoea.

CID can cause depletion of fluids and electrolytes, malnutrition, dehydration and hospitalization, all of which can lead to cardiovascular compromise and death. In addition, diarrhea can interfere with and detract from cancer treatment by causing

dosing delays or reductions which may have an impact on survival (Engelking et al. 1998; Ippoliti, 1998).

Therapeutic agents commonly causing diarrhea include 5-fluorouracil (5-FU), capecitabine and irinotecan (CPT-11) (Benson et al. 2004; Keefe et al. 2004). Usually it is a dose-related adverse effect and may be associated with other features of toxicity. CID appears to be a multifactorial process whereby acute damage to the intestinal mucosa (including loss of intestinal epithelium, superficial necrosis and inflammation of the bowel wall) causes an imbalance between absorption and secretion in the small bowel (Keefe et al. 2000; Keefe, 2007; Gibson and Stringer, 2009; Stein 2010)

Although in many cases diarrhea and mucositis are clinically manageable, in some cases they are life-threatening or even fatal events. The rapid extension of available anti-neoplastic drugs, including targeted therapies used in combination with traditional back-bone chemo-therapy, emphasized the urgent need for clinicians to better understand and detect the risk of gastrointestinal toxicities associated with these regimens.

Anti-EGFR monoclocanal anti-bodies are widely used in the treatment of several cancers, as other anti-cancer agents they are characterized by an increased risk of causing various toxicities including diarrhea and mucositis.

Thus, it appears relevant to quantify the magnitude of the risk of life-threatening and fatal diarrhea and mucositis with the aim to optimize clinical outcomes in cancer patients.

1.1. Epidemiology of diarrhea and mucositis induced by anti-cancer regimens

Diarrhea is caused by a wide range of of different chemotherapy regimens to varying degrees. In particular, fluoropyrimidines and irinotecan seem to initiate extensive diarrhoea with incidences restimated to be as high as 50–80% in treatment regimens containing these agents (Viele et al. 2003; Saltz et al. 2000). Although there is uncertainty on the absolute number of cancer patients that suffer from chemotherapy-induced diarrhoea a recent epidemiological investigation indicates that up to 40% of patients receiving combination chemotherapy can develop severe diarrhoea.

Oral and gastrointestinal (GI) mucositis can affect up to 100% of patients undergoing high-dose chemotherapy, 80% of patients with malignancies of the head and neck receiving radiotherapy, and a wide range of patients receiving chemotherapy (Stein 2010).

1.2. Diarrhea and mucositis clinical aspects

Diarrhea induced by chemotherapy can be debilitating and, in some cases, life threatening. Findings in such patients include volume depletion, renal failure, and electrolyte disorders such as metabolic acidosis and depending upon water intake,

hyponatremia (increased water intake that cannot be excreted because of the hypovolemic stimulus to the release of antidiuretic hormone) or hypernatremia (insufficient water intake to replace losses) (Benson et al. 2004; Maroun et al. 2007).

Severe treatment-related diarrhoea significantly affects patient's morbidity and mortality favouring life-threatening dehydration, loss of electrolytes, renal failure, cardiac disorders, and in general a deterioration of the patient's mental and physical condition. It should also be considered that other factors can contribute to diarrhea in cancer patients treated with chemotherapeutic regimen. These include intestinal infection (e.g. Clostridium difficile), radiation, and a history of prior intestinal resection (Davila and Bresalier, 2008; Vincenzi et al. 2008).

Diarrhea and mucositis can interfere with and detract from cancer treatment by causing dosing delays or reductions which may have an impact on survival (Engelking et al. 1998; Ippoliti, 1998). Prolonged or profound oral and gastrointestinal mucositis can lead to painful ulcerations, bleeding, risk of infections, dysphagia, bloatedness and diarrhoea (Davila and Bresalier, 2008).

Diagnosis of diarrhea and mucositis begins with a history to determine the severity according to the NCI CTC grades (National Cancer Institute Common Toxicity Criteria (Trotti 2003).

1.3. Anti-tumoral drugs as factor favouring diarrhea and mucositis

Irinotecan-induced diarrhea

Regardless of irinotecan schedule of administration, myelosuppression and delayed-type diarrhea are the most common side effects (Davila and Bresalier, 2008).

Irinotecan can cause acute diarrhea (immediately after drug administration) or delayed diarrhea. Immediate-onset diarrhea is caused by acute cholinergic properties and is often accompanied by other symptoms of cholinergic excess, including abdominal cramping, rhinitis, lacrimation, and salivation. The mean duration of symptoms is 30 minutes and they usually respond rapidly to atropine. Delayed-type diarrhea is defined as diarrhea occurring more than 24 hours after administration of irinotecan and is noncumulative and occurs at all dose levels (Stein 2010).

Fluoropyrimidines (5-FU, capecitabine, tegafur/uracil)

The severity and prevalence of diarrhea caused by 5-FU treatment is increased by the addition of leucovorin (LV) to the treatment regimen. Diarrhea is reported in up to 50% of patients receiving weekly 5-FU/LV combined treatment. Moreover, the severity of the diarrhea can increase when 5-FU is administered by bolus injection as opposed to intravenous infusion Clinical factors predictive for fluoropyrimidine-induced diarrhea are female sex, caucasian race and presence of diabetes. The gender- and race-related differences are possibly influenced by the variable activity of dihydropyrimidine-dehydrogenase (DPD) (Stein 2010).

1.4. Anti-epidermal Growth Factor monoclonal antibodies

Endotelial Growth Factor Receptor (EGFR), a member of the ErbB family including four structurally related tyrosine kinases receptor, is often constitutively expressed in many normal epithelial tissues and frequently over-expressed in

approximately 30% of cancers. It is considered as a prominent therapeutic target for tumour antigen targeted monoclonal antibody (MoAbs)-based immunotherapy **(Yang 2010; Giannopoulou 2009).**

Anti-EGFR MoAbs, binding the EGFR, block interaction of EGF with its specific receptor in both tumour and normal cells, inhibiting receptor phosphorylation **(Jorissen 2003; Vale 2012).** This results in down-regulation of EGF receptors and modulation of processes which are critical to tumour growth and progression such as angiogenesis, induction of apoptosis, tumour invasiveness and metastatic spread **(Keating 2010; Vale 2012).**

Cetuximab and Panitumumab, a chimeric monoclonal and a fully human monoclonal antibody, respectively, are two anti-EGFR agents. Both these MoAbs have been proven to be effective, either as mono-therapy or as add-on to standard therapies, in several randomised clinical trials (RCTs) and thus they are now incorporated into several anti-cancer treatment regimens **(Vale 2012).**

1.5. Current evidence and risk of diarrhea and mucositis associated to molecularly targeted agents

Epidermal growth factor receptor-targeted therapies

The rate of severe diarrhea (grade 3/4) with epidermal growth factor receptor (EGFR) targeting therapies is less than 10%. For monoclonal antibodies (mAb), such as the chimeric IgG1 mAb cetuximab or the fully human IgG2 mAb panitumumab, rates of grade 2 diarrhea are up to 21% and for grade 3 (ie greater than 7 stools per day or requiring intravenous fluids) between 1 and 2% (Van

Cutsem et al. 2007; Davila and Bresalier, 2008). Diarrhea is more common in patients receiving small molecule EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib or lapatinib. Occurrence of diarrhea is up to 60% for all grades. Grade 3 diarrhea develops in about 6–9%. However, dose reduction due to EGFR-targeting therapy induced diarrhea is seldom necessary. In combination with radiotherapy diarrhea could be a more serious problem for EGFR-targeting drugs (Stein 20010).

Multitargeting tyrosine kinase inhibitors

Sorafenib and sunitinib cause diarrhea in 30–50% of patients (all grades) with a rate of less than 10% of grade 3 diarrhea (Llovet et al. 2008; Gore et al. 2009; Motzer et al. 2009). Imatinib, an inhibitor of the Bcr-Abl protein tyrosine kinase, causes diarrhea in about 30% of the patients, but severe diarrhea is also rare.

m-TOR inhibitors

Everolimus and temsirolimus (inhibitors of the mammalian target of rapamycin [m-TOR]) were both recently approved for treatment of renal cell cancer, causing diarrhea in up to 40% with a rate of severe diarrhea in less than 5% of patients (Hudes et al. 2007; Motzer et al. 2008; Hess et al. 2009).

The mechanisms of targeted agent-induced diarrhea are not adequately investigated yet. The antitumor activity is based on apoptosis induction, antiangiogenesis and tyrosine kinase inhibition by targeting receptors or signaling pathways that are present in normal cells as well, including the mucosa. Increased levels of EGFR are

found in inflamed mucosa, particulary in goblet cells, which seem to play a role in CID (Threadgill et al. 1995).

However, there was no increase in toxicity of head and neck radiation by addition of cetuximab in a phase III trial despite a possible correlation between EGFR targeting and maturation of squamous eptithelium of the tongue and nasal cavity (Bonner et al. 2006; Keefe and Gibson, 2007).

The high expression of Kit in the interstitial cells of Cajal, which function as pacemaker cells of the intestinal motility, might be a potential mechanism for diarrhea induced by imatinib or sunitinib (Deininger et al. 2003).

Regarding the increasing utilization of targeted therapies further research to gain the ability to prevent diarrhea is urgently warranted (Keefe and Anthony, 2008).

1.6. Research question

Do anti-Epidermal Growth Factor Receptor monoclonal antibodies (cetuximab or panitumumab), administered along with standard antitumoural regimens, increase the risk of severe vascular thromboembolic adverse events in patients with cancer?

2. Methods

2.1. Aims and objective

To undertake a systematic review of the potential risk of developing serious thromboembolic adverse events (AEs) in cancer patients treated with cetuximab or panitumumab along with standard therapeutic regimens. To evaluate risk factor associated to kind of anti-EGFR agent administered and underlying malignancies. The information we provide will be relevant for clinical and regulatory decision-making processes.

2.2. Searching

An information specialist developed the search strategy and searched the following databases: Medline, Embase, Central and Web of Science. The base search strategy for studies comparing the effects of anti-EGFR monoclonal antibody + standard regimen VS standard regimen alone was constructed using MEDLINE and then adapted to the other resources searched.

Search strategy

The search included the following components:

1. cancer

AND

2. anti-EGFR monoclonal antibody

AND

3. clinical trials

Full search strategies are shown in Appendix 1. References of identified clinical studies were checked in an iterative process. Moreover, to identify other undetected published papers, we carried out a manual search of the bibliographies of relevant studies.

In the case a trial was considered eligible, but did not report data on diarrhea and mucositis adverse events an enquire was delivered to the corresponding author of the publication, the principal investigator or the sponsor/institution to collect unpublished data or to have the confirmation that these adverse events did not occur.

Table 1: Resources searched

Databases searched for randomized controlled trials comparing anti-EGFR monoclonal+standard regimen VS standard regimen alone
• Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and <1946 to Present> (via Ovid, 1946 to present) searched 15th September 2014 • EMBASE (Excerpta Medical Database) (via OVID SP <1974 to 2014 September 11>1st October 2014 • CENTRAL 1st October 2014 • Web of Science (SCI-EXPANDED, CPCI-S) 1st October 2014
Databases searched for systematic reviews on thromboembolism and anti-EGFR agents
• CDSR (Cochrane Database of Systematic Reviews) (via Cochrane Library. Searched 1st/Ocotober/2014) • DARE - Datase of Abstracts of Reviews of Effects (via CRD website http://www.crd.york.ac.uk/CRDWeb/ Searched 4th November 2014).

2.3. Inclusion criteria

The way to assess thromboembolism risk has been to collect RCTs comparing these MoAbs plus backbone therapy with backbone therapy alone. Pre-specified inclusion criteria are shown in Table 2.

Table 2. Study inclusion criteria

Participants	Inclusion: Adults (>18 years) with solid tumours treated with anti-EGFR monoclonal antibodies. Exclusion: Adolescents and children with solid tumors.
Interventions	Standard therapeutic anti-tumoral regimen containing Anti-EGFR MoAbs (Cetuximab or Panitumumab)
Comparators	Therapeutic anti-tumoral regimen without Anti-EGFR MoAbs (Cetuximab or Panitumumab)
Outcomes	Primary outcome Incidence of Grade 3-4 diarrhea adverse events Incidence of Grade 3-4 mucositis adverse events
Study design	1. randomised clinical trial reporting phase II or III trials comparing anti-EGFR MoAbs-containing regimens versus the same regimens without anti-EGFR MoAbs; 2. available data on the number of cases of diarrhea or mucositis adverse events; 3. articles written in English Phase I trials, single-arm phase II or III trials, trials comparing different backbone regimens for anti-EGFR MoAbs were also omitted from the analysis.

Phase I trials, single-arm phase II or III trials, all trials using anti-EGFR MoAbs in both arms of treatment will be omitted from analysis, because they do not provide a comparison between therapeutic regimens containing anti-EGFR MoAbs and the

same regimens without anti-EGFR MoAbs. The study selection process was summarised in a flow diagram according to the PRISMA statement **(Liberati 2008; Moher 2015).**

2.4. Review procedures

Studies were assessed for inclusion at both abstract and full text stages and appraised for quality by two independent reviewers; data were extracted by one reviewer and checked by a second. A third reviewer was consulted where necessary. Selection procedure of records provided by literature search was performed using EndNote X5 Thomson Reuters Software. Data were collected using a pre-specified form. Data extraction records for the included studies are available on request from the authors.

2.5. Strategy for data collection and data Synthesis

We provided a narrative synthesis of the findings from the considered studies, structured around the type of exposure, target population characteristics, type of solid tumours and outcomes of interest. We reported in a table from each eligible clinical trial the first author's name or name of the trial, publication year, study design, sample size (total and for each arm of treatment), safety population analysed, patient characteristics, underlying malignancies, therapeutic regimens administered, time to exposure to treatment, time-point of AEs assessment.

The considered outcomes for quantitative analyses were the incidence of VTE and PE defined according to the National Cancer Institute's Common Terminology

Criteria for Adverse Events (CTCAE), version 2 or 3 (See Appendix 2) **(Trotti 2000; Trotti 2003).**

The number of grade 3-4 diarrhea and mucositis AEs in both arms of treatment was collected and was used to perform meta-analysis for dichotomous outcomes. The number of patients evaluable for toxicity was used as the number analysed, unless this was not indicated, in which case the number of patients enrolled was considered. In the case the results of a particular study were reported in more than one publication, only the most recent and complete data were included in the analysis. Patients assigned to anti-EGFR MoAbs in combination with standard chemotherapy or other therapeutic regimen were compared with those assigned to chemotherapy or other therapeutic regimen without anti-EGFR MoAbs in the same trial. Multiple papers reporting the results of the same cohort were handled by considering only the one reporting the larger population.

2.6. Dealing with aggregate data and unpuplished data

It was decided to ask principal investigators of included studies for not aggregate data in the case an eligible article reported diarrhea and mucositis events without providing more details on their nature. In addition it was asked investigators, corresponding authors and representitive of sponsor or institution for unpublished data.

2.7. Quality assessment

Two authors independently evaluated the risk of bias by using Cochrane Collaboration Risk of Bias tool for included studies by considering the following characteristics:

- Randomisation sequence generation: was the allocation sequence adequately generated?
- Treatment allocation concealment: was the allocated treatment adequately concealed from study participants and clinicians and other healthcare or research staff at the enrolment stage?
- Blinding: were the personnel assessing outcomes and analysing data sufficiently blinded to the intervention allocation throughout the trial?
- Completeness of outcome data: were participant exclusions, attrition and incomplete outcome data adequately addressed in the published report? **(Higgins 2003)**.

2.8. Statistical analysis

Relative risk (RR), the ratio of the risk of an event in the two arms of treatment, has been used as effect size. For the RR, patients assigned to anti-EGFR MoAbs in combination with chemotherapy or chemotherapy plus radiotherapy or best supportive care (BSC) were compared with those assigned to chemotherapy or chemotherapy plus radiotherapy or BSC alone in the same trial. In case of multiple

arms studies, reporting results of two or more different treatment comparisons. Since the clinical heterogeneity among studies (i.e. cancer site differs between trials), the overall estimate of RR was obtained using a random-effects model **(DerSimonian 1986).** However, statistical heterogeneity was investigated using Cochran Q test (with $p<0.10$ considered statistically significant) and I-squared statistic (I^2), the latter describing the percentage of total variation across studies due to heterogeneity rather than chance **(Higgins 2003).** The following techniques were used to explain the possible causes of identified heterogeneity, where sufficient trials were available: subgroup analysis; sensitivity analysis performed by excluding the trials that potentially biased the results and meta-regression to evaluate the impact of covariates on overall heterogeneity **(Schutz 2012).**

The incidence of Grade 3-4 AEs was calculated by using the number of patients experiencing AEs divided by the total number of patients in each arm and calculated the 95% confidence interval for each proportion.

Various sensitivity analyses were planned to explore the influence of the following factors on the size of the effect and heterogeneity. Statistical analyses were conducted using appropriate software, including R and Review Manager version 5.2 and Microsoft Excel version 14.1.0 (Microsoft Corporation).

Other subgroups analyses according to anti-EGFR MoAb administered and cancer type for both outcomes were also conducted. Sensitivity analyses were performed to assess the influence of the following factors on the size of the effect and

heterogeneity: co-administration of anti-angiogenic drugs (excluding trials with regimens containing bevacizumab) and not standard dose of drug.

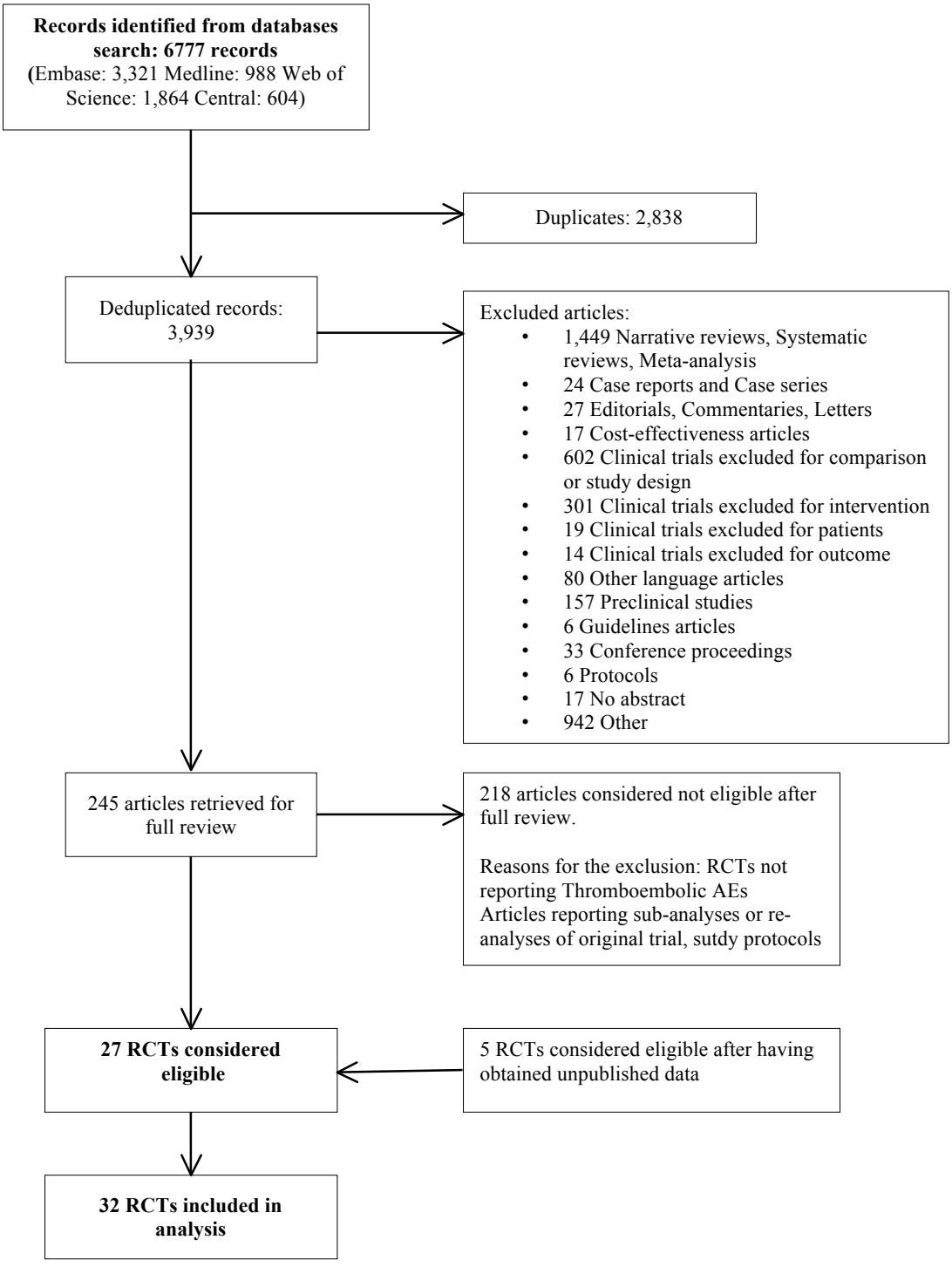
3. Results (Overview of the evidence)

3.1. Studies identification and selection

The systematic search provided 6,777 records, after de-duplication we obtained 3,939 records. After a first screening, we included 245 records that underwent a full text evaluation and 27 randomized clinical trials fulfilled all inclusion criteria and were selected for the systematic review and meta-analysis. As previously explained in the section regarding methods, we delivered a direct enquire to the corresponding author of the publication, the principal investigator or the sponsor/institution to collect unpublished data on trials considered eligible, but not reporting data on diarrhea and mucositis in the article published. We received unpublished data from 6 trials.

Figure 1 shows the flow-chart of study selection procedure from their identification through final inclusion in the meta-analysis.

Fig. 1. Flow-chart of the studies through the literature selection



3.2. Study characteristics

3.2.1. *Patients and treatment*

Overall, 32 studies, carrying out 34 comparisons, were included in the analysis. Of these, 26 (27 comparisons) reported data on cetuximab and 6 (7 comparisons) on panitumumab (Table 1). Taken together, all the included RCTs reported data on a total population of 19.379 patients affected by colorectal cancer, non-small cell lung cancer, gastro-oesophageal cancer, squamous cell head and neck cancer, pancreatic cancer, breast cancer or biliary tract cancer.

3.2.2. *Intervention, dose administered and safety follow-up*

Most of the considered trials used doses of 400 mg/m2 on day one followed by 250 mg/m2 weekly for cetuximab and 6.0 mg/kg every 2 weeks for panitumumab.

Five studies reported different cetuximab doses: BINGO trial (Cet 500mg/m2 biweekly), PETACC-8 (1,400mg/m2 on day one and 250mg/m2 weekly), PICCOLO trial (Pan 9 mg/kg /3 weeks) and SAAK trial (500mg/m2 on day 1 and bee-weekly). In the SPECTRUM trial scheduled dose of panitumumab 9 mg/Kg every three weeks.

Twenty five studies out of the 32 included studies reported the duration of follow-up for the safety analysis, which ranged between 28 and 30 days after the last dose. Only in one study adverse events have been assessed within 12 weeks after the first administration. All the relevant data for each study is summarised in the following .

Table 1 – Summary of the features of included studies

Study name	Trial phase	Underlying malignancy	Number randomized	Safety population	Treatment arm A	Treatment arm B	Anti-egfr dose per week or biweekly for Panitumumab	Duration of follow-up median in months and range	Time-point of AEs assessment
Alberts 2012	3	Colorectalcancer	1863	1825	mFOLFOX6 + Cet	mFOLFOX6	Cet 400mg/m2; Cet 250mg/m2	28 (0-68)	NR
Baselga	2	Breast cancer	181	171	Cisplatin + Cet	Cisplatin	Cet 400mg/m2; Cet 250mg/m2	NR	NR
BINGO	2	Biliary tract cancer	150	144	Gemcitabine + Oxaliplatin + Cet	Gemcitabine + Oxaliplatin +	Cet 500mg/m2 biweekly	23 weeks [range 4–83] (median treatment duration*)	NR
Bonner 2006	3	SCHNC	213 vs 211	212 vs 208	Radiot + Cet	Radiot	Cet 400mg/m2; Cet 250mg/m2	54.0 months	NR
BSM09	3	NSCLC	338 vs 338	325 vs 320	Carboplatin + Taxane + Cet	Taxane+ Carboplatin	Cet 400mg/m2; Cet 250mg/m2	NR	NR
Butts 2007	2	NSCLC	65 vs 66	64 vs 66	Gemcitabine + Cispatin (or Carboplatin) + Cet	Gemcitabine + Cispatin (or Carboplatin)	Cet 400mg/m2; Cet 250mg/m2	NR	30 days ALDR
CAIRO2	3	mCRC	378 vs 377	366 vs 366	Capecitabine + bevacizumab + cetuximab	Capecitabine + bevacizumab	Cet 400mg/m2; Cet 250mg/m2	23 months	NR
Cascinu 2009	2	Pancreatic cancer	42 vs 42	42 vs 42	Gemcitabine + Cispatin + Cet	Gemcitabine + Cispatin	Cet 400mg/m2; Cet 250mg/m2	11.8 months (2.5-18.5)	NR
COIN a,b	3	Untreated advanced colorectal	1,630	815 vs 805	Cet + Fluorouracil or Cet + Capecitabine	Fluorouracil or Capecitabine	Cet400mg/m2; Cet250mg/m2	23 vs 21 months (IQR 17-29 vs 18-29)	NR
CRYSTAL	3	Colorectal cancer	1217	1202	FOLFIRI + Cet	FOLFIRI	Cet 400mg/m2; Cet 250mg/m2	29.9 vs 29.4 months (29.1-30.5 vs 28.8-30.4)	NR

EXPAND	3	Gastric cancer	445 vs 449	446 vs 436	Capec+Cisplatin + Cet	Capec+Cisplatin	Cet 400mg/m2; Cet 250mg/m2	24.4 vs 21.0 months (20·0–24·9)	30 days ALDR
EXPERT-C	3	Rectal cancer	83 vs 81	83 vs 81	Capec-Oxaliplatin + Cet	Capec-Oxaliplatin	Cet 400mg/m2; Cet 250mg/m2	37 vs 32	NR
EXTREME	3	SCHNC	442	434	Platinum+ Fluorouracil + Cet	Platinum+ Fluorouracil +	Cet 400mg/m2; Cet 250mg/m2	12.9 – 26.0 months	NR
FLEX	3	NSCLC	557 vs 568	548 vs 562	Cisplatin + Vinorelbine + Cet	Cisplatin + Vinorelbine	Cet 400mg/m2; Cet 250mg/m2	23.8 months (22·1–24·9 vs 22·4–24)	NWS
Kim 2013	3	NSCLC	468 vs 470	451 vs 448	Docetaxel or pemetrexed + Cet	Docetaxel or pemetrexed	Cet 400mg/m2; Cet 250mg/m2	NR	NR
Lorenzen 2009	2	Esophagus carcinoma	904	446 vs 436	Cisplatin + 5-Fluorouracil + Cet	Cisplatin + 5-Fluorouracil	Cet 400mg/m2; Cet 250mg/m2	22.4 vs 21.0 months (21.3–24.0vs 20.0–24.9)	30 days ALDR
NEW EPOC	2	Colorectal liver metastasis	137 vs 134	137 vs 134	Oxaliplatin + Flurouracil + Cet or Oxaliplatin + Capecitabine + Cet	Oxaliplatin + Flurouracil or Oxaliplatin + Capecitabine	Cet 400mg/m2; Cet 250mg/m2	21.1 vs 19.8 months (12.6–33.8 vs 12.2–28.7)	NR
OPUS trial	2	Colorectal cancer	169 vs 168	170 vs 168	Cet+FOLFOX4	Cet+FOLFOX4	Cet 400mg/m2; Cet 250mg/m2	NR	30 days ALDR
PACCEa and b	3b	Colorectal cancer	413 vs 410 115 vs 115	407 vs 397 111 vs 113	Pan+BevOx Pan+BevIri	BevOx BevIri	Pan 6 mg/kg	12.3 months for the Ox-CT cohort vs9.0 for the Iri-CT cohort (0.2 to 26.2vs 0.2 to 18.6)	30 days ALDR
Peeters 2010	3	Colorectal cancer	591 vs 595	541 vs 542	Pan+FOLFIRI	FOLFIRI	Pan 6 mg/kg	13.3 vs 10.2 months (0.2-31.7 vs 0.5-32.9)	30 days ALDR
PETACC-8	3	Colorectal cancer	1280 vs 1279	1149 vs 1179	Cet+FOLFOX4	FOLFOX4	Cet 1,400mg/m2; Cet 250mg/m2	3.3 years (3.2–3.4)	30 days ALDR
PICCOLO	3	Colorectal cancer	230 vs 230	223 vs 224	Irinotecan + Pan	Irinotecan	Pan 9 mg/kg /3 weeks	NR	NR
PRIME	3	Colorectal cancer	593 vs 590	539 vs 545	Pan+FOLFOX4	FOLFOX4	Pan 6 mg/kg	13.2 vs 12.5 months (0-25.2 vs 0 to 24.7)	30 days ALDR

Richards 2013	2	Gastroesophageal cancer	75 vs 75	72 vs 68	Docetaxel + Oxaliplatin + Cet	Docetaxel + Oxaliplatin	Cet 400mg/m2; Cet 250mg/m2	NR	NR
Rosell 2008	2	NSCLC	43 vs 43	42 vs 43	Cisplatin+Vinorelbin+ Cet	Cisplatin+Vinorelbin	Cet 400mg/m2; Cet 250mg/m2	NR	NR
S0205 trial	3	Pancreatic cancer	372 vs 371	361 vs 355	Gemcitabine + Cet	Gemcitabine	Cet 400mg/m2; Cet 250mg/m2	NR	12 weeks AFA
SAAK 41/07	2	CRC	40 vs 28	39 vs 27	Cap + Radiot +Pan	Cap + Radiot	Pan 9 mg/kg /3 weeks	9.1 months	NS
SCOPE-1	2/3	Esophagus carcinoma	129 vs 129	129 vs 129	Cisplatin + Capecitabine + Radiot + Cet	Cisplatin + Capecitabine + Radiot	Cet 400mg/m2; Cet 250mg/m2	16.8 months (11.2–24.5)	12 weeks AFA
Siena 2010	2	Colorectal cancer	21 vs 21	21 vs 21	Cet+Lenalidomide	Lenalidomide	Cet 400mg/m2; Cet 250mg/m2	NR	28 days ADLR
Sobrero 2008	3	mCRC	1298	638 vs 629	Cet + Irinotecan	Irinotecan	Cet 400mg/m2; Cet 250mg/m2	14.0 weeks (range, 0.7 to 97.9) vs13.1 weeks (range, 0.7 to 89.1)	6 weeks ALDR
SPECTRUM	3	SCHNC	327 vs 330	325 vs 325	Pan+Cis+FU	Cis+FU	Pan 9 mg/kg 3 weeks	44.0 vs 35.0 weeks (21.0–75.0 vs 16·0–66·0)	30 day ADLR
Ye 2013	3	mCRC	138	70 vs 68	Cet+ mFOLFOX6 (or FOLFIRI)	mFOLFOX6 (or FOLFIRI)	Cet 400mg/m2; Cet 250mg/m2	37 months	NR

LEGENDA: NR: Not Reported; NSCLC: Non Small Cell LungCancer; ALDR: After Last Dose Received; NWS: Not Well Specified; AFA: After First Administration; AT: Acute toxicity; LT: Late Toxicity;

3.3. Study quality

Our evaluation of study quality based on Cochrane Risk of Bias Assessment Tool (Higgins 2011) revealed that the most RCTs clearly reported appropriate methods to generate random sequences (18 out of 32), most of the studies were multicenter and it is expected that the randomization sequence was c generated by interactive voice/web computer-based system as current regulation requires. Thus, it is plausible that this is a matter of selective reporting in the published article, instead of a methodological deficiency. The same issue of selective reporting could have determined that in seven studies concealment methods were not adequately reported. Only in one study an unclear risk of attrition bias was found, which was low for all the others. Given the open label design of all studies, all the studies are at high risk of performance bias (32 out of 32). For the same reason more than half of the studies (20 out of 32) are at high risk of detection bias, while for the 12 remaining the risk is unclear (Figures 2-3). The results are depicted in Figure 2-3.

3.4. Outcomes

3.4.1. *Incidences and RRs of diarrhea*

Data on grade 3 and 4 diarrhea AEs were reported in all of the 32 included studies. There were 1,361 cases of diarrhea out of 9,757 patients in the anti-EGFR MoAbs group and 786 out of 9,613 patients in the control group. The incidence observed was 11.8% (9.1 to 14.5%) in the experimental arm and 6.3% (4.8 to 7.9%) in the control arm (Table 2). Using the fixed-effect model we found that the anti-EGFR regimens were associated with a higher risk of severe venous thromboembolism

compared with the control arm (RR of 1.68; 95% CI 1.55 to 1.83). It has been observed absence of heterogeneity (I^2 3%; p=0.42) (Table 5, Figure 4).

3.4.2. *Incidences and RRs of mucositis*

Data on grade 3 and 4 mucositis events were provided by 16 studies (including 17 comparisons as the four-arm COIN trial was considered as two double-arm studies) including a total population of 13,124 patients. There were 456 cases of mucositis out of 6,572 patients in the anti-EGFR MoAbs group and 262 out of 6,552 patients in the control group. The incidence was 6.9% (95% CI 4.7 to 9.2%) in the experimental arm and 3.6% (95% CI 2.3 to 4.8%) in the control arm (Table 6). Using the random-effect model we found that the anti-EGFR regimens were associated with a higher risk of severe mucositis compared with the control arm RR 2.22 (95% CI 1.45 to 3.39). It has been observed heterogeneity (I^2 82%; p<0.0001) (Table 3, Figure 5).

3.4.3. *Subgroups Analyses*

To better understand the relationship between anti-EGFR MoAbs and diarrhea and mucositis, subgroups analyses stratifying patients by anti-EGFR agent used, anti-EGFR dose, therapeutic regimen co-administered and underlying malignancy were performed.

3.4.4. *Influence of Anti-EGFR Dose on RR of diarrhea and mucositis*

The most of the studies adopted the same standard doses of anti-EGFR MoAbs. Only four (Burtness et al.', Hussain et al.', PETACC-8 and SPECTRUM trials) adopted different doses. We investigated if the use of non-standard schedule of cetuximab or panitumumab may influence the risk of thromboembolism. We categorized anti-EGFR MoAbs dosing as:

- "standard" 400mg/m2-250mg/m2 weekly for cetuximab and 6 mg/kg bi-weekly for panitumumab,
- "non-standard" 1,400mg/m2 and 250mg/m2 for cetuximab or 500mg/m2 biweekly for cetuximab, and 9 mg/kg every 3 weeks.

The highest RR for diarrhea was observed in those patients receiving a standard doses, no subgroups difference was observed. The RR for mucositis according to doses does not change in a statistically significant manner among subgroups.

3.4.5. *Influence of kind of anti-EGFR agent*

We hypothesized that the risk of diarrhea and mucositis could be influenced by the kind of anti-EGFR MoAbs administered, thus we divided the studies in two subgroups (cetuximab and panitumumab). In the cetuximab subgroup we found a diarrhea incidence of 10.6% % (95% CI 7.7 to 13.6%) in the experimental arm and 5.8% (95% CI 4.1 to 7.5 %) in the control arm; in the panitumumab subgroup incidence was 16.2% (95% CI 10.4 to 22.1%) in the experimental arm and 8.5% % (95% CI 4.4 to 12.6 %) in the control arm.

Using the random-effect model the RR of diarrhea was 1.66 (95% CI 1.52 to 1.83) in cetuximab subgroup and 1.98 (95% CI 1.38 to 2.82) in the panitumumab subgroup (Table 5). No statistically significant differences between subgroups were detected (Figure 4).

In the cetuximab subgroup it was found a mucositis incidence of 6.7% (95% CI 4.3 to 9.2 %) VS 3.9% (95% CI 2.5 to 5.4 %) (Table 6). Using the random-effect model the RR of mucositis was 2.22 (95 CI % 1.45 to 3.39) in cetuximab subgroup and 1.98 (95% CI 1.25, 3.13). In the panitumumab subgroup the incidence was 8.0% (95% CI 6.4 to 9.6 %) VS 2.2% (95% CI 0.9 to 3.5 %) (Table 6, Figure 5). No statistically significant differences between subgroups were detected (Figure 5).

3.4.6. *Influence of Underlying Tumour Type*

Given the potentially differing risks of diarrhea among patients with different tumour types, an exploratory analysis stratifying patients by underlying tumour was performed (Table 3). Using random effects-model, the effect sizes on both mucositis and diarrhea varied, but the differences among tumour types were not statistically significant (Figure 7; Tables 5 and 6).

3.4.7. *Sensitivity analyses*

Sensitivity analyses were carried out to define whether co-administration of Bevacizumab or different exposure might have affected heterogeneity however, no significant change was noted to be due to these factors on diarrhea and mucositis

relative risks. The abscence of RCTs evaluating BSC prevented a sensitivity analysis (Results not showed).

3.4.8. *Publication bias*

We found no evidence of bias related to small study size, such as publication biases. Visual inspection of funnel plots for both outcomes diarrhea and mucositis did not reveal asymmetry (Figures 8 and 9).

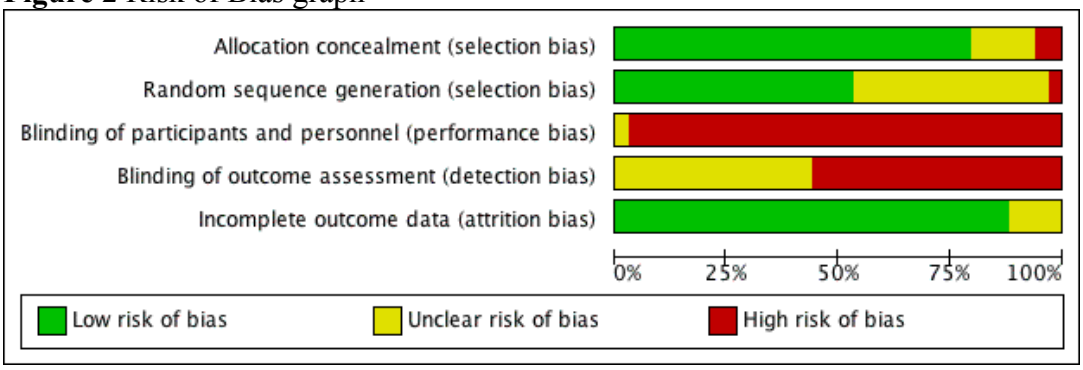
Table 5: Diarrhea RRs, Incidences

Diarrhea		**No of Grade 3-4 AEs/ total**		**Incidence [CI 95%]**		
	Number of studies	**Anti-EGFR arm**	**Control arm**	**Anti-EGFR arm**	**Control arm**	**Relative risk [CI 95%]**
Overall	32	1,361/9,757	786/9,613	11.8% (9.1 to 14.5%)	6.3% (4.8 to 7.9%)	1.68 [1.55, 1.83]
Cetuximab	26	1,020/7,577	600/7,447	10.6% (7.7 to 13.6%)	5.8% (4.1 to 7.5%)	1.66 [1.52, 1.83]
Panitumumab	6	341/2,180	186/2,166	16.2% (10.4 to 22.1%)	8.5% (4.4 to 12.6%)	1.98 [1.38, 2.82]
Colorectal cancer	17	1,203/6,458	709/6,400	17.6% (14.5 to 20.8%)	10.1% (8.0 to 12.3%)	1.67 [1.49, 1.88]
Gastric and esophageal cancer	4	64/679	33/663	10.1% (6.4 to 13.7%)	4.8% (2.0 to 7.6%)	1.79 [1.19, 2.69]
SCHNC	3	26/756	8/748	3.0% (0.4 to 5.6%)	0.9% (0.2 to 1.5%)	3.20 [1.46, 7.04]
Breast cancer	1	2/114	0/57	1.8% (0.0 to 4.2)	NA	2.52 [0.12, 51.67]
NSCLC	5	48/1,271	23/1,280	3.4% (0.9 to 5.9%)	1.5% (0.6 to 2.4%)	2.02 [1.24, 3.28]
Biliary tract cancer	1	6/76	3/68	7.9% (1.8 to 14.0%)	4.4 (0.00 to 9.4%)	1.79 [0.47, 6.88]
Pancreatic cancer	2	12/403	10/397	1.3% (0.00 to 5.6%)	1.9% (0.4 to 14.0%)	1.18 [0.51, 2.71

Table 6: Mucositis RRs, Incidences

Mucositis		**No of Grade 3-4 AEs/ total**		**Incidence (CI 95%)**		
	Number of studies	**Anti-EGFR arm**	**Control arm**	**Anti-EGFR arm**	**Control arm**	**Relative risk [CI 95%]**
Overall	16	456/6,572	262/6,552	6.9% (4.7 to 9.2%)	3.6% (2.3 to 4.8%)	2.22 [1.45, 3.39]
Cetuximab	13	368/5,473	237/5,446	6.7% (4.3 to 9.2%)	3.9% (2.5 to 5.4%)	1.98 [1.25, 3.13]
Panitumumab	3	88/1,099	25/1,106	8.0% (6.4 to 9.6%)	2.2% (0.9 to 3.5%)	3.40 [2.16, 5.36]
Colorectal cancer	7	273/4,449	78/4,426	5.6% (4.0 to 7.2%)	1.6% (1.1 to 2.0%)	3.33 [2.59, 4.27]
Gastric and esophageal cancer	1	17/446	8/436	3.8% (2.0 to 5.6%)	1.8% (0.6 to 3.1%)	2.08 [0.91, 4.76]
SCHNC	3	124/448	143/448	20.1% (0.00 to 47.0%)	23.1%(0.00 to 51.0%)	0.78 [0.37, 1.64]
NSCLC	4	42/1,229	33/1,242	3.0% (0.5 to 5.5%)	1.7% (0.2 to 3.2%)	1.39 [0.69, 2.81]

Figure 2 Risk of Bias graph



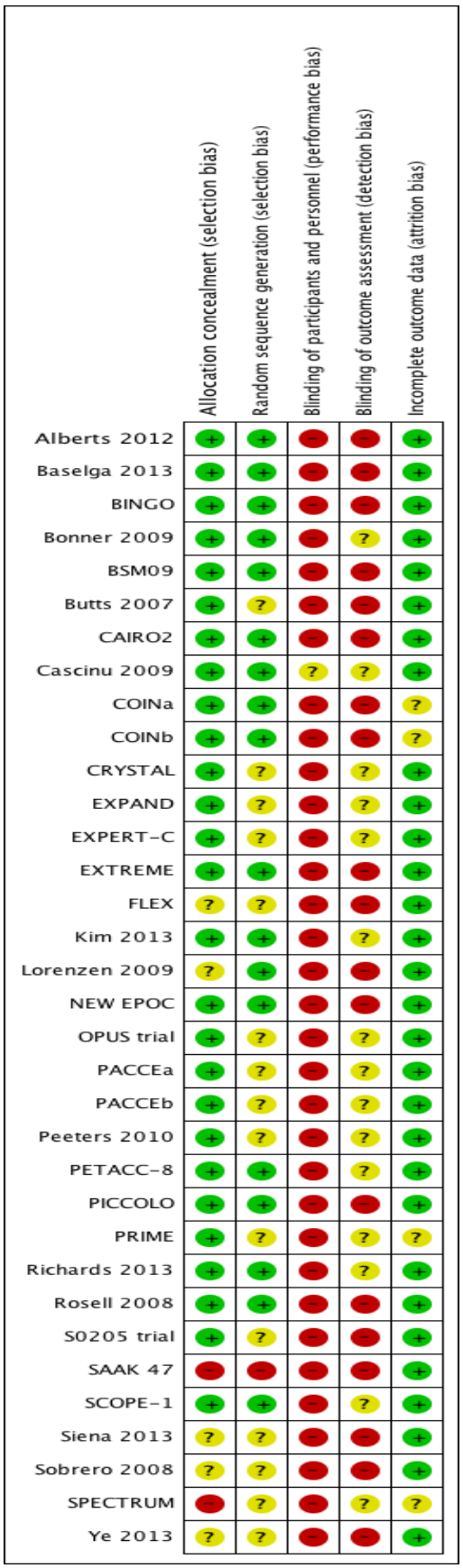


Figure 3 Risk of Bias summary

Figure 4 Forest plot of relative risk of severe diarrhea associated with kind of anti-EFGR monoclonal antibody

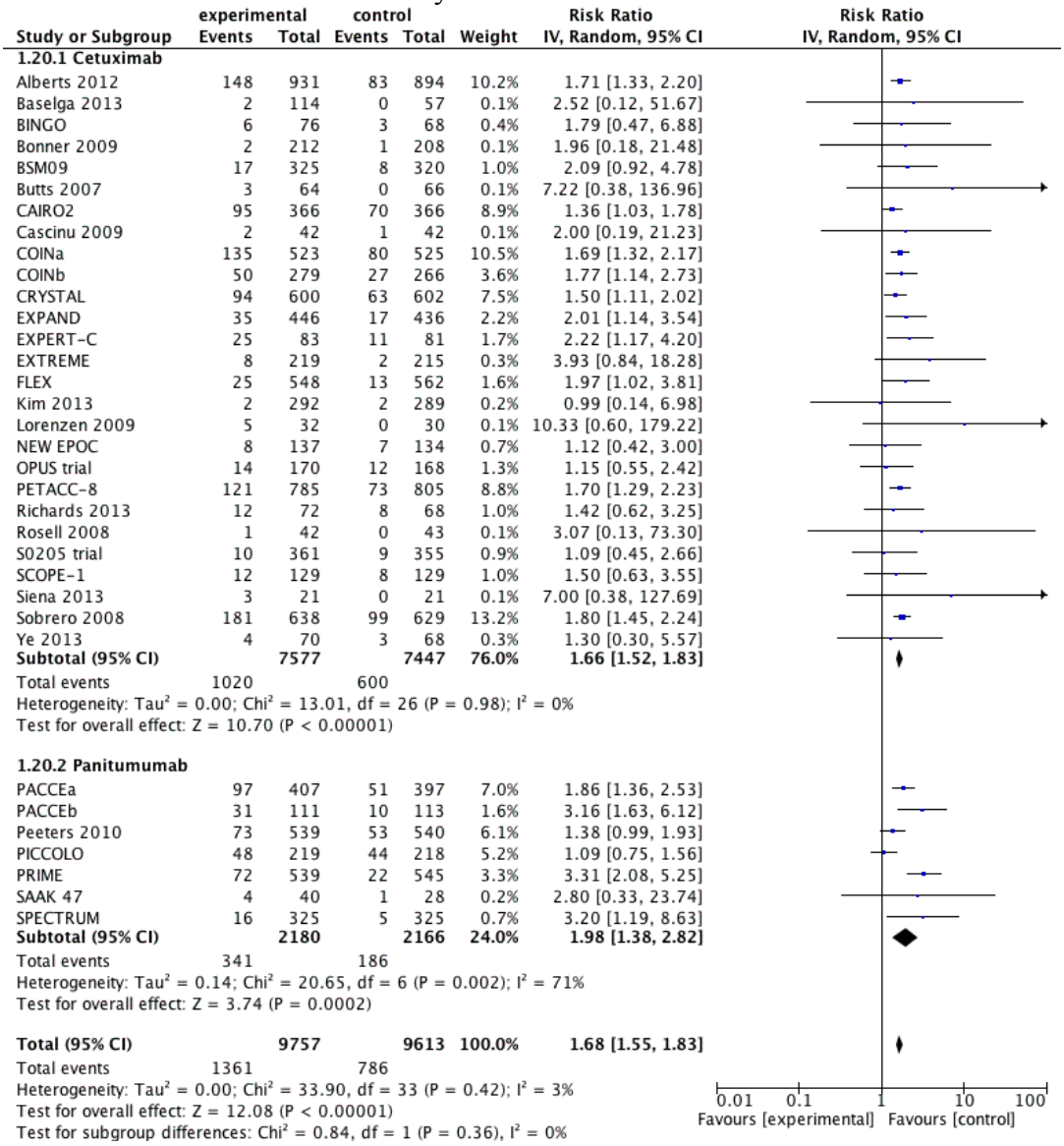


Figure 5 Forest plot of relative risk of mucositis associated with kind of anti-EFGR monoclonal antibody

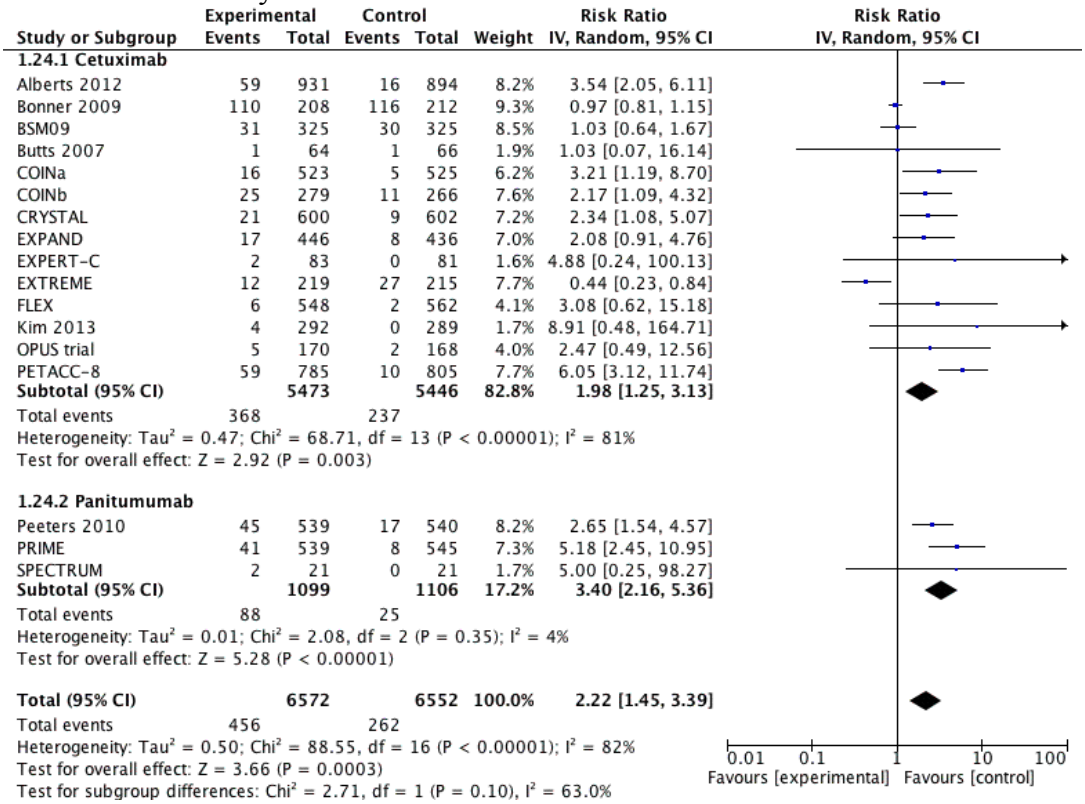


Figure 6 Forest plot of relative risk of severe diarrhea associated with underlying cancer

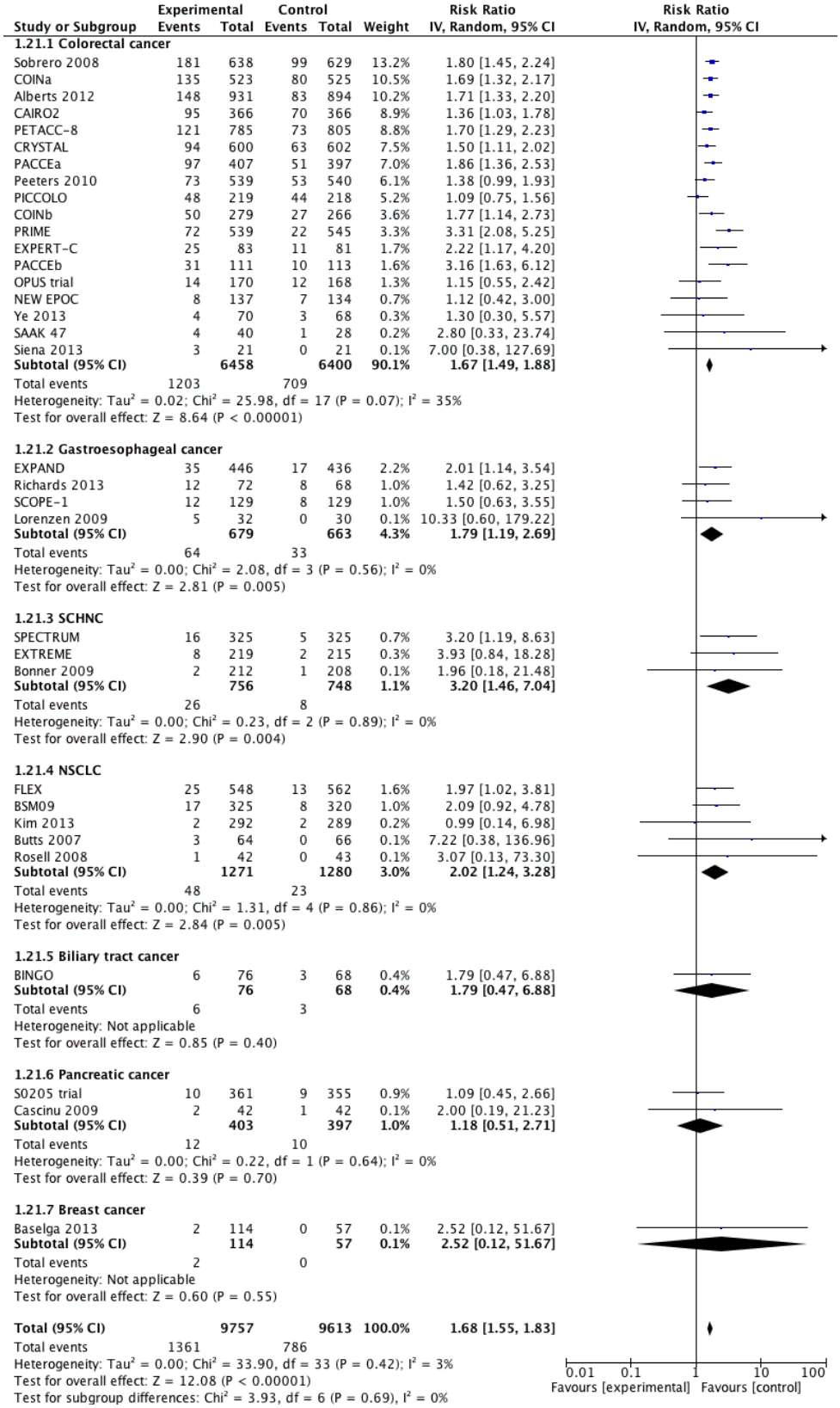


Figure 7 Forest plot of relative risk of severe mucositis associated with underlying cancer

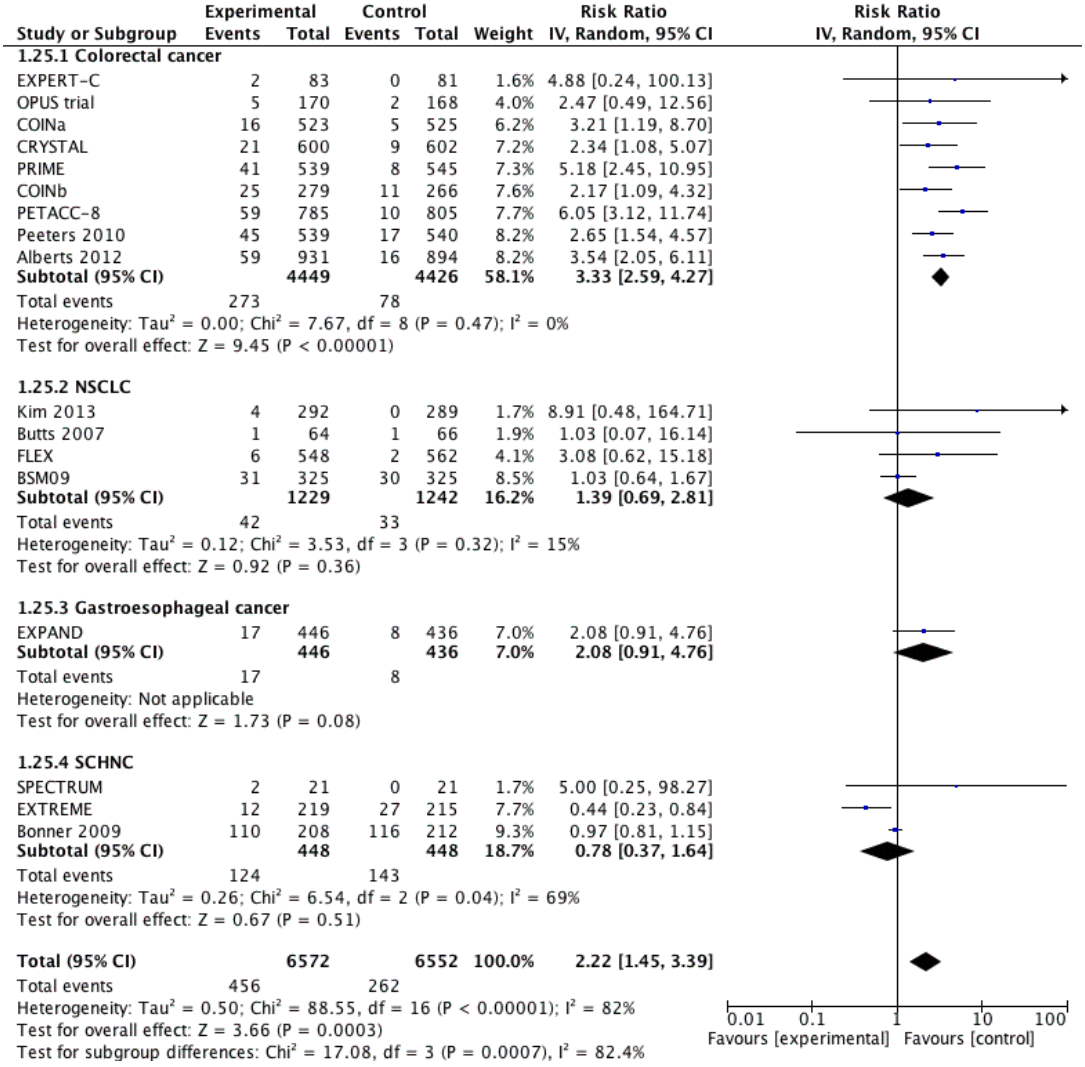


Figure 8: Funnel plot on publication bias regarding studies reporting diarrhea

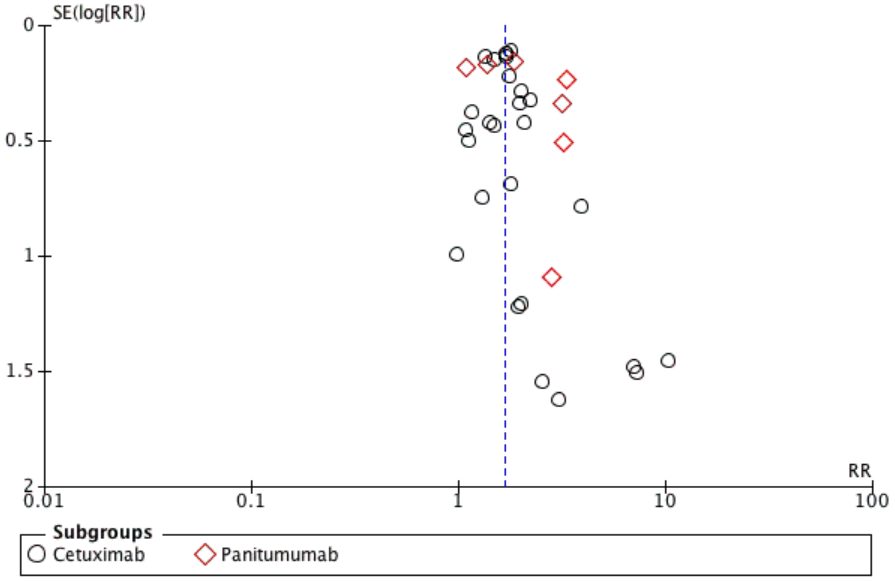
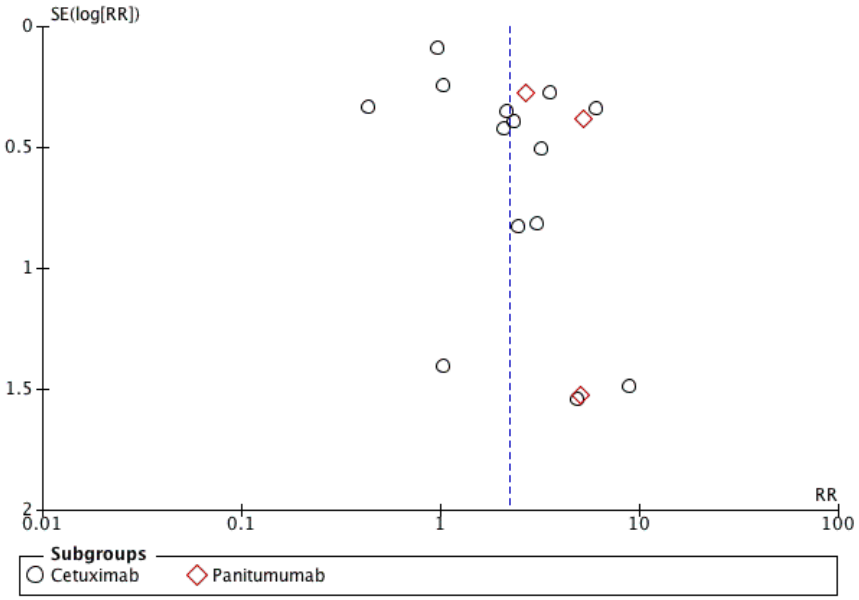


Figure 9 Funnel plot on publication bias regarding studies reporting mucositis



4. Discussion

Severe and life-threatening gastrointestinal AEs in cancer therapy remain a significant burden to patients, producing morbidity and impacting on optimal dosing for effective treatment (Lee 2014). To the best of the knowledge, this is the most comprehensive systematic review and meta-analysis investigating on the association between anti-EGFR MoAbs and the risk of high grade diarrhoea, and the first demonstrating an increased risk of severe mucositis.

The present analyses, based on an overall population of twenty thousand patients, have shown that the addition of cetuximab or panitumumab to standard treatments increases by 68% the risk of grade 3-4 diarrhea and by 122% the risk of grade 3-4 severe mucositis (Fig 2; Fig. 4 and Table 2).

These results regarding diarrhea did not differ importantly in accordance to underlying cancer, kind of anti-EGFR agent administered and scheduled doses. While, there is a higher risk of mucositis among patients suffering from colorectal cancer compared to the overall RR and the other RRs for different malignancies. The type of anti-EGFR moAbs and scheduled dose seemed to not impact on the RR of mucositis as well.

Diarrhea and mucositis are some of the most commonly encountered side effects during systemic chemotherapy (Jones 1999). The lack of interaction between chemotherapy backbone regimens and anti-EGFR agents resulting from our analysis is interesting, as the risk of chemotherapy-induced diarrhea, generally, seems to be influenced by the choice of chemotherapeutic agents, combination schemes and administration routes (Lee 2014). These findings suggest that the

administration of anti-EGFR MoAbs poses an additional risk of experiencing these AEs, independently of any overlapping toxicity due to chemotherapy, or anti-VEGF, such as bevacizumab, co-administered.

The mechanism of induction of diarrhea caused by targeted agents remains unclear. A plausible explanation could be directly related to the inhibition of EGFR pathway in enterocytes. EGFR works as a negative regulator of chloride secretion in the normal colon mucosa cells, in which sodium chloride exchange is stimulated by intracellular messengers (Uribe 1996). EGFR inhibitors might cause secretory diarrhea as a result of excessive chloride secretion and deficient sodium absorption by blocking this pathway (Loriot 2008). EGF, in fact, has been proved to decrease chloride secretion in T84 human cells through protein kinase C (PKC) and phosphatidylinositol 3-kinase (PI3K) (Barrett 1998). Such data are not available for intestinal and colonic cells but this mechanism might be a possible explanation for some cases of anti EGFR MoAbs-associated diarrhea.

A partial overlapping of diarrhea and mucositis, moreover, is extremely likely. Damage to intestinal epithelium caused by cytotoxic agents, with superficial necrosis and inflammation of the bowel wall, results in loss of absorption surface and thus imbalance between absorption and secretion in the small bowel (Keefe 2000; Gibson 2006).

The pathogenesis of mucositis could be caused by sequential steps starting from a cellular DNA direct damage which, amplified by inflammatory pathways, progressively leads to ulceration and finally to the healing process. EGFR seems to play a major role in the last process (Sonis 2004). After gastric mucosal injury, for

example, tyrosine kinase activity associated with EGFR significantly increases (Relan 1995, Majumdar 1996). EGF and other growth factors, furthermore, promote cell migration and increase blood flow allowing repair of the denuded basal membrane (Pai 1998; Blay 1985).

Preclinical experiments demonstrated that EGF is involved also in colonic mucosal repair (Procaccino 1994). The importance of the EGF pathway in this process has been shown in human conditions as well. Necrotizing enterocolitis seems more frequent in infants fed with formula (lacking of EGF) than in newborns fed with breast milk (Lucas 1990). Other clinical evidence supports the role of EGF in increasing crypt-cell mitotic activity with a rapid recovery of the villous architecture when administered to children with congenital microvillous atrophy or necrotising enteritis (Fagbemi 2001).

Besides the regenerative effects, it has been hypothesized that EGF could exert a protective effect on gastrointestinal mucosa. It may stimulate the synthesis and secretion of mucin glycoprotein, enhancing mucosal defences by creating a dilutional barrier which protects epithelium from caustic agents and toxic oxygen metabolites (Gibson 2013). Therefore, the addition of anti-EGFR MoAbs to chemotherapy could inhibit both regenerative and protective effects, enhancing chemotherapeutic agents toxicity by delaying or impeding a complete healing process. This results in reduction of intestinal villous area, crypt length and crypt proliferation (Keefe 2000), which cause painful ulcerations and disphagia, abdominal cramps, bloatedness and diarrhea (Logan 2008). This mechanism could

partially explain the additional risk associated with the use of cetuximab and panitumumab which resulted from our analyses.

Several sensitivity analyses were performed to assess if the findings were affected by confounding factors or potential sources of bias detected while examining the articles and supplementary material published online only.

In the first analysis regarding the risk of mucositis, the studies on patients affected by colorectal cancer were excluded. The symptoms of such a malignancy could be erroneously considered as AEs, in some cases. This hypothesis is supported by the lower risk of mucositis found with this sensitivity analysis (RR 1.12; 95% CI 0.82 to 1.52)

On the contrary, the increase in the risk of this AE was higher by excluding patients with head and neck cancer (RR 2.90; 95% CI 1.86 to 4.51). Patients with head and neck cancer undergoing radiotherapy treatment are prone to develop radiation-induced stomatitis, which can not be distinguished by stomatitis induced by other agents (Fekrazad 2014). Although patients in both arms are exposed to radiotherapy, differences in the incidence of this AE between the two arms of a study could be found due to an unbalanced distribution of tumour characteristics, in particular position or dimension.

With the aim to reduce confounding factors associated with therapeutic control regimens, only studies that administered cetuximab or panitumumab as add-on agent with exactly the same regimen in control arm were included. It is retained that these more strict inclusion criteria that can reduce the introduction of additional

biases related to different agents administered in the backbone therapeutic schemes. Unfortunately, the data reported in the considered RCTs did not permit to clearly establish if a dose-response relationship exists and if a threshold effect can be ruled out.

4.1. Quality of the evidence

The risk of bias of the included studies varied from low to high (Figures 2 and 3). Every study has a high risk of performance bias related to the lack blinding. We found no evidence of bias related to small study size, such as publication biases, in fact a visual inspection of the funnel plots and formal analysis of asymmetry did not indicate asymmetry for both outcomes diarrhea and mucositis.

4.2. Limitations

As in other meta-analyses, our study has potential limitations.

Our study has different limitations:

1. several included primary studies did not report Grade 4 AEs separately from Grade 3 AEs, precluding an independent analysis based on different grade of severity;
2. the considered studies were conducted by evaluating patients with adequate major organ function, which might not reflect “real world” patients;
3. the present study was designed as a meta-analysis of aggregate data reported in scientific articles, thus confounding factors at the individual patient level could not be assessed.

5. Conclusion

The present work yielded a wider perspective including more additional studies providing data on wider population compared to a previously published meta-analysis (Miroddi 2015). In addition this study implemented unpuslished data from five clinical trials.

In conclusion, the present meta-analysis of puplished and unpulished data shows that the addition of cetuximab or panitumumab to any therapeutic regimens for cancer is associated with an increased risk of severe diarrhea and mucositis. Prevention, early recognition and appropriate clinical management of severe diarrhea and mucositis are considered essential in order to develop risk reduction strategies for limiting incidence, duration, and severity of these AEs. These strategies may differ from approaches directed at preventing other forms of chemotherapy-induced gastrointestinal side effects.

6. References

Arbuckle R.B., Huber S.L., Zacker C. (2000) The consequences of diarrhea occurring during chemotherapy for colorectal cancer: a retrospective study. Oncologist 5: 250–259

Barrett KE, Smitham J, Traynor-Kaplan A, et al: Inhibition of Ca(2+)-dependent Cl-secretion in T84 cells: membrane target(s) of inhibition is agonist specific. Am J Physiol 274:C958-65, 1998

Benson A.B., 3rd,, Ajani J.A., Catalano R.B., Engelking C., Kornblau S.M., Martenson J.A., Jr,, et al. (2004) Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol22: 2918–2926

Blay J, Brown KD: Epidermal growth factor promotes the chemotactic migration of cultured rat intestinal epithelial cells. J Cell Physiol 124:107-12, 1985

Bonner J.A., Harari P.M., Giralt J., Azarnia N., Shin D.M., Cohen R.B., et al. (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354: 567–578

Caraglia M, Santini D, Bronte G, Rizzo S, Sortino G, Rini GB, et al. Predicting efficacy and toxicity in the era of targeted therapy: focus on anti-EGFR and anti-VEGF molecules. Curr Drug Metab. 2011 Dec;12(10):944-55.

Clin Oncol. 2007 May 1;25(13):1658-64. PubMed PMID: 17470858

Conti J.A., Kemeny N.E., Saltz L.B., Huang Y., Tong W.P., Chou T.C., et al. (1996) Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J Clin Oncol 14: 709–715

Davila M., Bresalier R.S. (2008) Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastroenterol Hepatol 5: 682–696

Deininger M.W., O'Brien S.G., Ford J.M., Druker B.J. (2003) Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol 21: 1637–1647

DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88.

Engelking C., Rutledge D.N., Ippoliti C., Neumann J., Hogan C.M. (1998) Cancer-related diarrhea: a neglected cause of cancer-related symptom distress. Oncol Nurs Forum 25: 859–860

Fagbemi AO, Wright N, Lakhoo K, et al: Immunoreactive epidermal growth factor receptors are present in gastrointestinal epithelial cells of preterm infants with necrotising enterocolitis. Early Hum Dev 65:1-9, 2001

Fekrazad R, Chiniforush N. Oral mucositis prevention and management by therapeutic laser in head and neck cancers. J Lasers Med Sci. 2014

frequency and guideline-based management. Ther Adv Med Oncol. 2010

Giannopoulou E, Antonacopoulou A, Floratou K, et al: Dual targeting of EGFR and HER-2 in colon cancer cell lines. Cancer Chemother Pharmacol 63:973-81, 2009

Gibson R.J., Stringer A.M. (2009) Chemotherapy-induced diarrhea. Curr Opin Support Palliat Care 3: 31–35

Gore M.E., Szczylik C., Porta C., Bracarda S., Bjarnason G.A., Oudard S., et al. (2009) Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 10: 757–763
Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor receptor-positive tumors: a new paradigm for cancer therapy. Cancer. 2002 Mar 1;94(5):1593-611.
Higgins JP, Thompson SG, Deeks JJ, et al: Measuring inconsistency in meta-analyses. BMJ 327:557-60, 2003
Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.
Ippoliti C. (1998) Antidiarrheal agents for the management of treatment-related diarrhea in cancer patients.Am J Health Syst Pharm 55: 1573–1580
Jan;2(1):51-63. doi: 10.1177/1758834009355164. PubMed PMID: 21789126; PubMed Central PMCID: PMC3126005.
Jones MK, Tomikawa M, Mohajer B, et al: Gastrointestinal mucosal regeneration: role of growth factors. Front Biosci 4:D303-9, 1999
Jorissen RN, Walker F, Pouliot N, Garrett TP, Ward CW, Burgess AW. Epidermal growth factor receptor: mechanisms of activation and signalling. Exp Cell Res. 2003 Mar 10;284(1):31-53.
Keating GM: Panitumumab: a review of its use in metastatic colorectal cancer. Drugs 70:1059-78, 2010
Keefe D.M., Brealey J., Goland G.J., Cummins A.G. (2000) Chemotherapy for cancer causes apoptosis that precedes hypoplasia in crypts of the small intestine in humans. Gut 47: 632–637
Keefe D.M., Gibson R.J. (2007) Mucosal injury from targeted anti-cancer therapy. Support Care Cancer15: 483–490
Keefe D.M., Gibson R.J., Hauer-Jensen M. (2004) Gastrointestinal mucositis. Semin Oncol Nurs 20: 38–47
Lee CS, Ryan EJ, Doherty GA: Gastro-intestinal toxicity of chemotherapeutics in colorectal cancer: the role of inflammation. World J Gastroenterol 20:3751-61, 2014
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
Llovet J.M., Ricci S., Mazzaferro V., Hilgard P., Gane E., Blanc J.F., et al. (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359: 378–390
Loriot Y, Perlemuter G, Malka D, et al: Drug insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy. Nat Clin Pract Oncol 5:268-78, 2008
Lucas A, Cole TJ: Breast milk and neonatal necrotising enterocolitis. Lancet 336:1519-23, 1990
Majumdar AP, Fligiel SE, Jaszewski R, et al: Inhibition of gastric mucosal regeneration by tyrphostin: evaluation of the role of epidermal growth factor receptor tyrosine kinase. J Lab Clin Med 128:173-80, 1996

Maroun J.A., Anthony L.B., Blais N., Burkes R., Dowden S.D., Dranitsaris G., et al. (2007) Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the canadian working group on chemotherapy-induced diarrhea. Curr Oncol 14: 13–20
Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. J Clin Oncol. 2003 Jul 15;21(14):2787-99.
Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
Motzer R.J., Hutson T.E., Tomczak P., Michaelson M.D., Bukowski R.M., Oudard S., et al. (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 27: 3584–3590
Pai R, Tarnawski A: Signal transduction cascades triggered by EGF receptor activation: relevance to gastric injury repair and ulcer healing. Dig Dis Sci 43:14S-22S, 1998
Perrotte P, Matsumoto T, Inoue K, Kuniyasu H, Eve BY, Hicklin DJ, et al. Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. Clin Cancer Res. 1999 Feb;5(2):257-65.
Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Ann Oncol. 2012 Jul;23(7):1672-9.
Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. Lancet Oncol. 2005 Jun;6(6):401-10.
Procaccino F, Reinshagen M, Hoffmann P, et al: Protective effect of epidermal growth factor in an experimental model of colitis in rats. Gastroenterology 107:12-7, 1994
Relan NK, Fligiel SE, Dutta S, et al: Induction of EGF-receptor tyrosine kinase during early reparative phase of gastric mucosa and effects of aging. Lab Invest 73:717-26, 1995
Saltz L.B., Cox J.V., Blanke C., Rosen L.S., Fehrenbacher L., Moore M.J., et al. (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med343: 905–914
Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res. 2006 Sep 15;12(18):5268-72.
Seng S, Liu Z, Chiu SK, Proverbs-Singh T, Sonpavde G, Choueiri TK, et al. Risk of venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. J Clin Oncol. 2012 Dec 10;30(35):4416-26.
Simmonds MC, Higgins JP. A general framework for the use of logistic regression models in meta-analysis. Stat Methods Med Res. 2014 May 12.
Sonis ST, O'Donnell KE, Popat R, et al: The relationship between mucosal cyclooxygenase-2 (COX-2) expression and experimental radiation-induced mucositis. Oral Oncol 40:170-6, 2004
Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology,

Stringer A.M., Gibson R.J., Logan R.M., Bowen J.M., Yeoh A.S., Laurence J., et al. (2009) Irinotecan-induced mucositis is associated with changes in intestinal mucins. Cancer Chemother Pharmacol 64: 123–132
Threadgill D.W., Dlugosz A.A., Hansen L.A., Tennenbaum T., Lichti U., Yee D., et al. (1995) Targeted disruption of mouse EGF receptor: effect of genetic background on mutant phenotype. Science 269: 230–234
Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013 Sep 5;122(10):1712-23.
Toffoli G, De Mattia E, Cecchin E, Biason P, Masier S, Corona G. Pharmacology of epidermal growth factor inhibitors. Int J Biol Markers. 2007 Jan-Mar;22(1 Suppl 4):S24-39.
Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys. 2000 Apr 1;47(1):13-47.
Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003 Jul;13(3):176-81.
Uribe JM, Gelbmann CM, Traynor-Kaplan AE, et al: Epidermal growth factor inhibits Ca(2+)-dependent Cl- transport in T84 human colonic epithelial cells. Am J Physiol 271:C914-22, 1996
Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M, Amado RG. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J
Viele CS. Overview of chemotherapy-induced diarrhea. Semin Oncol Nurs 2003; 19 (4 Suppl 3):2–5.
Winter;5(1):1-7. Review. PubMed PMID: 25606332; PubMed Central PMCID: PMC4290523.
Woo J, Palmisiano N, Tester W, Leighton JC, Jr. Controversies in antiepidermal growth factor receptor therapy in metastatic colorectal cancer. Cancer. 2013 Jun 1;119(11):1941-50.
Yang BB, Lum P, Chen A, et al: Pharmacokinetic and pharmacodynamic perspectives on the clinical drug development of panitumumab. Clin Pharmacokinet 49:729-40, 2010

References of the included studies	
Alberts 2012	Alberts SR, Sargent DJ, Nair S et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA 2012; 307: 1383-1393.
Baselga	Baselga J, Gomez P, Greil R et al. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol 2013; 31: 2586-2592.
BINGO	Malka D, Cervera P, Foulon S et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol 2014; 15: 819-828.
Bonner 2006	Bonner J.A., Harari P.M., Giralt J., Azarnia N., Shin D.M., Cohen R.B., et al. (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354: 567–578
BSM09	Lynch TJ, Patel T, Dreisbach L, McCleod M, Heim WJ, Hermann RC, Paschold E, Iannotti NO, Dakhil S, Gorton S, Pautret V, Weber MR, Woytowitz D. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol. 2010 Feb 20;28(6):911-7. doi: 10.1200/JCO.2009.21.9618.
Butts 2007	Butts CA, Bodkin D, Middleman EL et al. Randomized phase II study of gemcitabine plus cisplatin or carboplatin [corrected], with or without cetuximab, as first-line therapy for patients with advanced or metastatic non small-cell lung cancer. J Clin Oncol 2007; 25: 5777-5784.
CAIRO2	Tol J, Koopman M, Rodenburg CJ, Cats A, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, Mol L, Antonini NF, Punt CJ. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. Ann Oncol. 2008 Apr;19(4):734-8.
Cascinu 2009	Cascinu S, Berardi R, Labianca R et al. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. Lancet Oncol 2008; 9: 39-44.
COIN a,b	Maughan TS, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011; 377: 2103-2114.
CRYSTAL	Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezínek I, Beier F, Stroh C, Rougier P, van Krieken JH, Ciardiello F. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol. 2015 Mar 1;33(7):692-700.
EXPAND	Lordick F, Kang YK, Chung HC et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14: 490-499.
EXPERT-C	Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, Tait D, Brown G, Wotherspoon A, Gonzalez de Castro D, Chua YJ, Wong R, Barbachano Y, Oates J, Chau I. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol. 2012

	May 10;30(14):1620-7.
EXTREME	Rivera F, García-Castaño A, Vega N, Vega-Villegas ME, Gutiérrez-Sanz L. Cetuximab in metastatic or recurrent head and neck cancer: the EXTREME trial. Expert Rev Anticancer Ther. 2009 Oct;9(10):1421-8.
FLEX	Pirker R, Pereira JR, Szczesna A et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009; 373: 1525-1531.
Kim 2013	Kim ES, Neubauer M, Cohn A et al. Docetaxel or pemetrexed with or without cetuximab in recurrent or progressive non-small-cell lung cancer after platinum-based therapy: a phase 3, open-label, randomised trial. Lancet Oncol 2013; 14: 1326-1336.
Lorenzen 2009	Lorenzen S, Schuster T, Porschen R et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009; 20: 1667-1673.
NEW EPOC	Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, Hornbuckle J, Peterson M, Rees M, Iveson T, Hickish T, Butler R, Stanton L, Dixon E, Little L, Bowers M, Pugh S, Garden OJ, Cunningham D, Maughan T, Bridgewater J. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol. 2014 May;15(6):601-11.
OPUS trial	Bokemeyer C, Bondarenko I, Hartmann JT et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011; 22: 1535-1546.
PACCEa and b	Hecht JR, Mitchell E, Chidiac T et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009; 27: 672-680.
Peeters 2010	Peeters M, Price TJ, Cervantes A et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28: 4706-4713.
PETACC-8	Taieb J, Tabernero J, Mini E et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 862-873.
PICCOLO	Seymour MT, Brown SR, Middleton G et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013; 14: 749-759.
PRIME	Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010 Nov 1;28(31):4697-705.
Richards 2013	Richards D, Kocs DM, Spira AI et al. Results of docetaxel plus oxaliplatin (DOCOX) +/- cetuximab in patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: results of a randomised Phase 2 study. Eur J Cancer 2013; 49: 2823-2831.

Rosell 2008	Rosell R, Robinet G, Szczesna A et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. Ann Oncol 2008; 19: 362-369.
S0205 trial	Philip PA, Benedetti J, Corless CL et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest oncology group-directed intergroup trial S0205. Journal of Clinical Oncology 2010; 28 (22): 3605-3610.
SAAK 41/07	Helbling D, Bodoky G, Gautschi O, Sun H, Bosman F, Gloor B, Burkhard R, Winterhalder R, Madlung A, Rauch D, Saletti P, Widmer L, Borner M, Baertschi D, Yan P, Benhattar J, Leibundgut EO, Bougel S, Koeberle D. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. Ann Oncol. 2013 Mar;24(3):718-25.
SCOPE-1	Crosby T, Hurt CN, Falk S et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013; 14: 627-637.
Siena 2010	Siena S, Van Cutsem E, Li M et al. Phase II open-label study to assess efficacy and safety of lenalidomide in combination with cetuximab in KRAS-mutant metastatic colorectal cancer. PLoS One 2013; 8: e62264.
Sobrero 2008	Sobrero AF, Maurel J, Fehrenbacher L et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26: 2311-2319.
SPECTRUM	Vermorken JB, Stohlmacher-Williams J, Davidenko I et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. Lancet Oncol 2013; 14: 697-710.
Ye 2013	Ye LC, Liu TS, Ren L et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol 2013; 31: 1931-1938.

7. Appendices

7.1. Appendix 1: Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp Neoplasms/ (2644015)

2 (cancer* or tumour* or tumor* or neoplas* or metasta* or oncol*).ab,ti. (2107982)

3 1 or 2 (3153974)

4 (cetuximab or "IMC C225" or IMC-C225 or "MAb C225" or C225 or Erbitux).ti,ab,rn. (4463)

5 (Panitumumab or ABX-EGF or Vectibix or anti-EGFR or "anti EGFR").ti,ab,rn. (2470)

6 4 or 5 (5795)

7 3 and 6 (5346)

8 randomized controlled trial.pt. (388379)

9 controlled clinical trial.pt. (89811)

10 randomi?ed.ab. (369707)

11 placebo.ab. (159551)

12 clinical trials as topic.sh. (173008)

13 randomly.ab. (222343)

14 trial.ti. (133603)

15 or/8-14 (958893)

16 exp animals/ not humans.sh. (4009228)

17 15 not 16 (886224)

18 7 and 17 (988)

****

Database: Embase <1974 to 2014 September 11>

Search Strategy:

1 exp *neoplasm/ (2674010)

2 (cancer* or tumour* or tumor* or neoplas* or metasta* or oncol*).ab,ti. (2604547)

3 1 or 2 (3483251)

4 cetuximab/ (17113)

5 (cetuximab or "IMC C225" or IMC-C225 or "MAb C225" or C225 or Erbitux).ti,ab,rn. (17647)

6 panitumumab/ (4900)

7 (Panitumumab or ABX-EGF or Vectibix or anti-EGFR or "anti EGFR").ti,ab,rn. (7313)

8 4 or 5 or 6 or 7 (20027)

9 3 and 8 (18024)

10 randomized controlled trial/ (352114)

11 random*.tw. (911453)

12 placebo.mp. (336367)

13 double-blind.tw. (140952)
14 single-blind.tw.
15 triple-blind.tw.

16 or/10-15 (1191053)

17 (animal/ or nonhuman/) not exp human/ (4659353)

18 16 not 17 (1066739)

17 9 and 18 (3321)

****

Database Web of Sciences (SCI-EXPANDED, CPCI-S):

#1 TOPIC: ((cancer* or tumour* or tumor* or neoplas* or metasta* or oncol*)) 2,348,265

#2 TOPIC: ((cetuximab or "IMC C225" or IMC-C225 or "MAb C225" or C225 or Erbitux or anti-EGFR or "anti EGFR")) 7,630

#3 TOPIC: ((Panitumumab or ABX-EGF or Vectibix or anti-EGFR or "anti EGFR")) 2,787

#4 #3 OR #2 8,032

#5 #4 AND #1 7,154

#6 TOPIC: (random* or placebo* or control* or "double blind" or "single blind" or "triple blind) 4,631,339

#7 #6 AND #5 1,864

****

CENTRAL:

Cetuximab or IMC C225 or IMC-C225 or MAb C225 or C225 or Erbitux or Panitumumab or ABX-EGF or Vectibix or anti-EGFR or antiEGFR

604 records

7.2. Appendix 2: Common Terminology Criteria for Adverse Events v 3.0 (CTCAE)

Quick Reference The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

Category

A Category is a broad classification of AEs based on anatomy and/or pathophysiology. Within each Category, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within Categories.

Short AE Name

The ‘SHORT NAME’ column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a Category and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word ‘Select’ and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

Remark

A ‘Remark’ is a clarification of an AE.

Also Consider

An ‘Also Consider’ indicates additional AEs that are to be graded if they are clinically significant.

Navigation Note

A ‘Navigation Note’ indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the ‘Navigation Note’ states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

An ‘Em dash’ (—) indicates a grade not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection **(Trotti 2003).**

Table - Effect sizes for all subgroups analyses performed

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Diarrhea	34	19370	Risk Ratio (IV, Random, 95% CI)	1.68 [1.55, 1.83]
Cetuximab	27	15024	Risk Ratio (IV, Random, 95% CI	1.66 [1.52, 1.83]
Panitumumab	7	4346	Risk Ratio (IV, Random, 95% CI)	1.98 [1.38, 2.82]
Diarrhea Cancer Subgroups	34	19370	Risk Ratio (IV, Random, 95% CI)	1.68 [1.55, 1.83]
Colorectal cancer	18	12858	Risk Ratio (IV, Random, 95% CI)	1.67 [1.49, 1.88]
Gastroesophageal cancer	4	1342	Risk Ratio (IV, Random, 95% CI)	1.79 [1.19, 2.69]
SCHNC	3	1504	Risk Ratio (IV, Random, 95% CI)	3.20 [1.46, 7.04]
NSCLC	5	2551	Risk Ratio (IV, Random, 95% CI)	2.02 [1.24, 3.28]
Biliary tract cancer	1	144	Risk Ratio (IV, Random, 95% CI)	1.79 [0.47, 6.88]
Pancreatic cancer	2	800	Risk Ratio (IV, Random, 95% CI)	1.18 [0.51, 2.71]
Breast cancer	1	171	Risk Ratio (IV, Random, 95% CI)	2.52 [0.12, 51.67]
Diarrhea - Treatment Exposure	27	15727	Risk Ratio (IV, Random, 95% CI)	1.73 [1.55, 1.92]
Diarrhea Doses Subgroups	34	19370	Risk Ratio (IV, Random, 95% CI)	1.68 [1.55, 1.83]
Standard Doses	29	16481	Risk Ratio (IV, Random, 95% CI)	1.71 [1.57, 1.87]
Non-standard Doses	5	2889	Risk Ratio (IV, Random, 95% CI)	1.56 [1.10, 2.22]
Mucositis	17	13124	Risk Ratio (IV, Random, 95% CI)	2.22 [1.45, 3.39]
Cetuximab	14	10919	Risk Ratio (IV, Random, 95% CI)	1.98 [1.25, 3.13]
Panitumumab	3	2205	Risk Ratio (IV, Random, 95% CI)	3.40 [2.16, 5.36]
Mucositis Cancer Subgroups	17	13124	Risk Ratio (IV, Random, 95% CI)	2.22 [1.45, 3.39]
Colorectal cancer	9	8875	Risk Ratio (IV, Random, 95% CI)	3.33 [2.59, 4.27]
NSCLC	4	2471	Risk Ratio (IV, Random, 95% CI)	1.39 [0.69, 2.81]
Gastroesophageal cancer	1	882	Risk Ratio (IV, Random, 95% CI)	2.08 [0.91, 4.76]

SCHNC	3	896	Risk Ratio (IV, Random, 95% CI)	0.78 [0.37, 1.64]
Mucositis Treatment exposure	11	6960	Risk Ratio (IV, Random, 95% CI)	2.42 [1.37, 4.27]
Mucositis Doses Subgroups	17	13124	Risk Ratio (IV, Random, 95% CI)	2.22 [1.45, 3.39]
Standard dose	15	11492	Risk Ratio (IV, Random, 95% CI)	1.98 [1.31, 3.00]
Non-standard dose	2	1632	Risk Ratio (IV, Random, 95% CI)	6.00 [3.14, 11.45]