
Article:
Sterrantino, Carmelo, Miroddi, Marco, Phillips, Bob orcid.org/0000-0002-4938-9673 et al. (1 more author) (2016) Letter to the Editor. International Journal of Cancer. pp. 2763-2770. ISSN 1097-0215

https://doi.org/10.1002/ijc.30005

Letter to the Editor

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/ijc.30005

Dear Editor,

We are writing to bring serious concerns about the validity of the paper ***"Hematologic toxicity assessment in solid tumor patients treated with cetuximab: A pooled analysis of 18 randomized controlled trials[1]"*** **authored by Ran Cui and colleagues"** recently published by the International Journal of Cancer to your attention. After careful reading, we firmly believe that the review uses inappropriate methods and incorrect data and therefore that the conclusions are misleading.

We should be clear that the reason that we have been able to consider the data so carefully is that our group is conducting a systematic review on serious thromboembolic adverse events which has a very similar design (PROSPERO registration number CRD42014009165[2]), although our systematic review also includes RCTs in which panitumumab (another approved anti-EGFR monoclonal antibody) is tested as an add-on to standard regimens.

We detail the many shortcomings of the research reported by Cui and colleagues below.

(1) Search strategy and missing trials

We were surprised by the small number of records (511) returned by the authors' initial search, the number of RCTS identified (18) and by the small number of articles that were excluded on grounds of lack of data (2). In contrast our own search, yielded a total of 6777 records of which 45[3-5,7-48] were RCTs. Of the 37[3-16,19-20,22-28,30-34,36-38,40-41,43,45,47-48] trials of cetuximab, 32[3-6,8-12,14-16,19-20,22-28,30-34,36-38,40-41,43,45,47-48] reported data on hematologic toxicities.

Cui and colleagues do not report their search strategies in full, making it difficult to have confidence in their quality. From the information given, it would seem that, although there are several rigorous search filters that can be used to identify RCTs, none of these were used in either MEDLINE or Embase. It also seems that

the Cochrane Central Register of Controlled Trials was not used. The impact of these choices would be to restrict the number of papers identified by the literature searching.

As of October 31st, 2013, the time at which the literature search by Cui and colleagues was done, six of the additional sixteen RCTs that we identified were already published. These six trials (including over 1,700 participants) should therefore have been identified and added to the 18 trials they included (see Table 1).

To date, further data from more than 5,000 patients are available, as compared to the analysis of Cui and colleagues; around one third of these data were already published at the time of their search and therefore have been missed from the review.

(2) Inclusion of an ineligible trial

The authors included a trial reported by Cunningham et al.[49] in which both treatment and control groups received cetuximab. This does not match their stated inclusion criteria and should have been excluded from the review (for the same reason as they did exclude 3 trials - see flow-chart)[1].

(3) Quality assessment

The Authors assessed the quality of the evidence using the Jadad scale[50]. The use of this scale is explicitly discouraged by Cochrane[51]. As well as suffering from the generic problems of scales, it has a strong emphasis on reporting rather than conduct, and does not cover one of the most important potential biases in randomized trials, namely allocation concealment. The PRISMA statement[52], which Authors declare their paper to be compliant with, describes scales that numerically summarise multiple components into a single number as misleading

and unhelpful. In addition, the reported quality evaluation does not reflect the content of the articles reviewed. The Jadad Scale assigns up to two points out of a possible 5 score for blinding procedures[50]. Although all the studies included in the analysis are open label, reducing the maximum score to 3 points, four studies received scores higher than 3 [5,10,31,49].

(4) Inappropriate combination of neutropenia and leukopenia events

The authors have combined neutropenic events with broader leukopenic events (which include both neutropenia and lymphocytopenia) in the analyses. This is both inappropriate clinically, and unnecessary. In all the trials included in this study, neutropenia and leukopenia adverse events are listed separately, with the only exception being the trial reported by Ye and colleagues[47]. Besides the clinical incoherence, potential double-counting and combination of overlapping outcomes may lead to analytical issues.

The issue of double counting is illustrated in the trial conducted by Lynch and colleagues[25], where the sum of neutropenic and leukopenic adverse events exceeds the denominator in the experimental arm. In their letter, Cui and colleagues responded to this by changing the denominator, but they did not provide any justification or description of the method used to calculate the new number.

Furthermore, summing leukopenic and neutropenic events is not applied consistently across trials. In at least one case only leukopenic events have been extracted and analysed[12]. For the articles by Rosell and colleagues[34] it is not clear what has been done, as this trial, although listed in the summary table of included studies, does not appear in the forest plot of relative risk[1].

(5) **Errors in data extraction/analysis**

We found several inconsistencies between the data reported in the original articles and the data analysed in the review:

- the analysis of wild type patients did not include the data presented by Bokemeyer[5] and colleagues (see Figure 2 in the paper[1]); while Cui and his group, reviewed the article published in 2009, the results were presented in a more recent report[6], which was published by Annals of Oncology in 2011;

- although data on neutropenia from the report by Rosell and colleagues[34] and data on anemia, from the EXPERT[45] trial reported by Vermorken et al. were presented in the articles reviewed, these trials do not appear in the analysis of relative risk (Figure 3[1] and Supporting information table s1 respectively); moreover data on anemia were available for the OPUS trial from the more recent report[6] published in 2011;

- in one case grade 4 adverse events were counted twice (Vermorken et al[45], see Table 2), while, in another, those of grade 3 were neglected **(**Rosell et al[34], see Table 3**);**

- In at least one case, the proportion of adverse events, expressed as a percentage, was used as the actual number of events, without being converted[37].

Hematologic toxicities are one of the main concerns in patients exposed to cancer treatments. Considering the relevance of synthesized evidence in clinical practice as well as in regulatory decision-making processes, we strongly believe that the publication of misleading analyses, based on poor methods and incorrect data, in an important journal may have important consequences on public health and future research.

We believe that the extent of the errors in the Cui et al. article are substantial and that it may affect not only the estimates but even the direction of the effect. Readers of the journal and article need to be made aware of its potential to mislead.

Table 1. Published RCTs of anti-EGFR monoclonal antibodies

Author /Year (Study Name)	Trial phase	Underlying malignancy	Number randomized	Safety population	Treatment arm MoAbs	Treatment arm Controls	Anti-EGFr MoAbs	Follow up	Time-point of AEs assemment	Jadad score
Baselga 2013 (4)	2	Breastcancer	120 vs 61	114 vs 57	Cisplatin+ Cet	Cisplatin	Cet 400mg/m2; Cet 250mg/m2	NR	NR	3
BMS099 (25)	3	NSCLC	338 vs 338	325 vs 320	Cet+Taxane+carb	Taxane+ Carboplatin	Cet 400mg/m2; Cet 250mg/m2	NR	NR	3
Butts 2007 (10)	2	NSCLC	65 vs 66	64 vs 66	Gemcitabine + Cispatin (or Carboplatin) + Cet	Gemcitabine + Cispatin (or Carboplatin)	Cet 400mg/m2; Cet 250mg/m2	NR	30d ALDR	3
CALG B (16)	2	NSCLC	53 vs 48	53 vs 50	Pemetrexed + Carboplatin + Radiother + Cetuximab	Pemetrexed + Carboplatin + Radiother	Cet 400mg/m2; Cet 250mg/m2	32 months (11.7-48.4)	Unclear	2
Cascinu 2009 (11)	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	3
COIN (26)	3	mCRC	815 vs 815	815 vs 815	Fluorouracil or Capecitabine + Cet	Fluorouracil or Capecitabine	Cet400mg/m2; Cet250mg/m2	23 vs 21 months	NR	3
CRYSTAL (42)	3	mCRC	1217	600 vs 602	FOLFIRI + Cet	FOLFIRI	Cet 400mg/m2; Cet 250mg/m2	29.9 vs 29.4 months	NR	2
EXTREME (45)	3	SCHNC	222 vs 220	219 vs 215	Platinum + Fluorouracile + Cet	Platinum Fluorouracile	Cet 400mg/m2; Cet 250mg/m2	12.9 – 26.0 months	NR	3
FLEX (31)	3	NSCLC	557 vs 568	548 vs 562	Cisplatin + Vinorelbine + Cet	Cisplatin + Vinorelbine	Cet 400mg/m2; Cet 250mg/m2	23.8 months	Unclear	3
NCCTG N0147 (Alberts) (3)	3	Colorectal Cancer	954 vs 909 40 vs 106	894 vs 931 40 vs 106	mFOLFOX6 + Cet	mFOLFOX6	Cet 400mg/m2; Cet 250mg/m2	28 (0-68)	NR	2
Lorenzen 2009 (24)	2	Esophagus carcinoma	33 vs 33	32 vs 30	Cisplatin + 5-Fluorouracil + Cet	Cisplatin + 5-Fluorouracil	Cet 400mg/m2; Cet 250mg/m2	22.4 vs 21.0 months	30d ALDR	2
OPUS trial (6)	2	mCRC	169 vs 168	170 vs 168	Cet+FOLFOX4	Cet+FOLFOX4	Cet 400mg/m2; Cet 250mg/m2	NR	30d ALDR	2
Rosell 2008 (34)	2	NSCLC	43 vs 43	42 vs 43	Cisplatin + Vinorelbine + Cet	Cisplatin + Vinorelbine	Cet 400mg/m2; Cet 250mg/m2	NR	NR	3
S0205 trial (30)	3	Pancreatic cancer	372 vs 371	361 vs 355	Cet + Gemcitabine	Gemcitabine	Cet 400mg/m2; Cet 250mg/m2	NR	12 weeks AFA	2
SCOPE-1 (12)	2/3	Esophageal carcinoma	129 vs 129	129 vs 129	Cet+CRT	CRT	Cet 400mg/m2; Cet 250mg/m2	16.8 months	12w AFA	3
Siena 2010 (36)	2	mCRC	21 vs 21	21 vs 21	Cet+Lenalidomide	Lenalidomide	Cet 400mg/m2; Cet 250mg/m2	NR	28d ADLR	2
Sobrero 2008 (37)	3	mCRC	648 vs 650	638 vs 629	Cet + Irinotecan	Irinotecan	Cet 400mg/m2; Cet 250mg/m2	14.0 weeks	6w ALDR	2
Ye 2013 (47)	3	mCRC	70 vs 68	70 vs 68	Cet+ mFOLFOX6 (or FOLFIRI)	mFOLFOX6 (or FOLFIRI)	Cet 400mg/m2; Cet 250mg/m2	37 months	NR	2
Borner 2008 (8)	2	mCRC	37 vs 37	37 vs 37	XELOX + Cet	XELOX	Cet 400mg/m2; Cet 250mg/m2	17.2 months	NR	2
Burtness 2006 (9)	3	SCHNC	57 vs 60	58 vs 58	Cisplatin + Cetuximab	Cisplatin	Cet 200mg/m2; Cet 125mg/m2	NR	NR	2
EXPAND (23)	3	Gastric cancer	445 vs 449	446 vs 436	Capecitabine + Cisplatin + Cet	Capecitbine + Cisplatin	Cet 400mg/m2; Cet 250mg/m2	24.4 vs 21.0 months	30d ALDR	3
Fleming 2012 (15)	2	Prostate cancer	75 vs 40	75 vs 39	Cetuximab + Mitoxantrone	Mitoxantrone	Cet 400mg/m2; Cet 250mg/m2	NR	NR	2
NORDIC VII (40)	3	mCRC	194 vs 185	194 vs 185	FLOX + Cet	FLOX	Cet 400mg/m2; Cet 250mg/m2	NR	NR	2
Richards 2013 (33)	2	Gastroesophagealcancer	75 vs 75	72 vs 68	Docetaxel + Oxaliplatin + Cet	Docetaxel + Oxaliplatin	Cet 400mg/m2; Cet 250mg/m2	NR	NR	2
Hussain 2014 (20)	2	Urothelial Carcinoma	60 vs 29	59 vs 28	Gemcitabine + Cisplatin + Cet	Gemcitabine + Cisplatin	500 mg/m2, days 1 and 15	NR	NR	2
Kim 2013 (22)	3	NSCLC	468 vs 470	451 vs 448	Docetaxel or pemetrexed + Cet	Docetaxel or pemetrexed	Cet 400mg/m2; Cet 250mg/m2	NR	NR	3
FOCUS3 (28)	2	Advanced CRC	47 vs 82	47 vs 82	Cet + FOLFIRI	FOLFIRI	Cet 500mg/m2 (bolus)	15.2 months (IQR 1⁄4 12.6-18.8)	NR	3
NCCTG N0147 (Huang) (19)	3	Colorectal cancer	40 vs 106	40 vs 106	FOLFIRI + Cet	FOLFIRI	Cet 400mg/m2; Cet 250mg/m2	28 months	NR	2
Malka 2014 (BINGO) (26)	2	Biliary tract cancer	76 vs 74	76 vs 68	Gemcitabine + Oxaliplatin + Cet	Gemcitabine + Oxaliplatin +	Cet 500mg/m2 biweekly	23 weeks (4–83)	NR	3
NEW EPOC (32)	2	mCRC	137 vs 134	137 vs 134	FU + OX + Cet or XELOX + Cet	FU + OX or XELOX	Cet 400mg/m2; Cet 250mg/m2	21.1 vs 19.8 months	NR	3
PETACC-8 (38)	3	Colorectal cancer	1,280 vs 1,279	1,149 vs 1,179	Cet+FOLFOX4	FOLFOX4	Cet 1,400mg/m2; Cet 250mg/m2	3.3 years (3.2–3.4)	30d ALDR	3
van den Heuvel 2014 (43)	2	NSCLC	51 vs 51	51 vs 51	Cet+Cis+RT	Cis+RT	Cet 400mg/m2; Cet 250mg/m2	29 months	12w AFA for AT; >12w for LT	2
Zhang 2014 (48)	NR	Advanced Urothelial Carcinoma	30 vs 26	30 vs 26	Cet + SOX	SOX	Cet 400mg/m2; Cet 250mg/m2	NR	NR	2
PACCE (17)	3b	mCRC	528 vs 525	407 vs 397	Pan+Bev-Ox/IRI	Bev-Ox/IRI	Pan 6 mg/kg	12.3/9.0 months	30d ALDR	2
Peeters 2010 (29)	3	mCRC	591 vs 595	541 vs 542	Pan+FOLFIRI	FOLFIRI	Pan 6 mg/kg	13.3 vs 10.2 months	30d ALDR	2
PICCOLO (35)	3	Colorectal cancer	230 vs 230	223 vs 224	Irinotecan + Pan	Irinotecan	Pan 9 mg/kg /3 weeks	NR	NR	3
PRIME (14)	3	mCRC	593 vs 590	539 vs 545	Pan+FOLFOX4	FOLFOX4	Pan 6 mg/kg	13.2 vs 12.5 months	30d ALDR	3
SPECTRUM (46)	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	30d ADLR	3

Included
Missed
Published After October 31st 2013
Panitumumab

NR: Not Reported; NSCLC: Non Small Cell Lung Cancer; SCHNC: squamous cell head and neck cancer; mCRC: metastatic colorectal cancer; ALDR: After Last Dose Received; d: days; w: weeks; AFA: After First Administration; AT: Acute toxicity; LT: Late Toxicity

Table 2. Neutropenia and Leukopenia AEs in the RCTs included by Cui et al. as reported in the original articles.

	Leukopenia AEs as reported in RCTs				Neutropenia AEs as reported in RCTs				Neutropenia AEs in Cui et al.			
	Cetuximab Arm		Control Arm		Cetuximab Arm		Control Arm		Cetuximab Arm		Control Arm	
Study ID	Events	Total Pts	Events	Total Pts	Events	Total Pts	Events	Total Pts	Events	Total Pts	Events	Total Pts
Alberts (3)					156	1273	132	1261	156	1273	132	1261
Baselga (4)					11	114	3	57	11	114	3	57
Bokemeyer* (5,6)	12	170	10	168	51	170	57	168	63	170	67	168
Butts (10)					31	64	32	66	31	64	32	66
Cascinu (11)					10	42	6	42	10	42	6	42
Crosby (12)	14	129	21	129	15	129	24	129	14	129	21	129
Govindan (16)					25	53	21	50	25	53	21	50
Lorenzen (24)					7	32	4	30	7	32	4	30
Lynch (25)	139	325	97	320	198	325	177	320	337	634	274	632
Maughan (27)					101	815	107	815	101	815	107	815
Philip (30)	40	361	50	355	84	361	85	355	124	361	135	355
Pirker (31)	139	548	109	562	289	548	289	562	428	548	398	562
Rosell° (34)	21	42	16	43	35	42	23	43				
Sobrero (37)					196	617	151	595	196	638	151	629
Van Cutsem (41)	43	600	32	602	169	600	150	602	212	600	182	602
Vermorken (45)	19	219	19	215	49	219	50	215	81	219	92	215
Ye^ (47)					8	70	6	68	8	70	6	68
Cunningham§ (49)	Cetuximab		Cetuximab		20	212	0	115	20	212	0	115

*2009 instead of 2011 (no data on anemia)
°does not appear in any forrest plot
^Ye et al. reported neutropenia/Leukopenia as one outcome
§Ineligible
Leukopenia only
Unclear
safety population instead of actually tested
grade 3/4 + grade 4

Table 3. Anemia AEs in the RCTs included by Ran Cui et al. as reported in the original articles and main mistakes in data extraction

	Anemia AEs as reported in RCTs				Anemia AEs in Ran Cui et al.			
	Cetuximab Arm		Control Arm		Cetuximab Arm		Control Arm	
Study ID	Events	Total Pts	Events	Total Pts	Events	Total Pts	Events	Total Pts
Bokemeyer* (5,6)	7	170	4	168				
Butts (10)	17	64	13	66	17	64	13	66
Cascinu (11)	0	42	3	42	0	42	3	42
Crosby (12)	3	129	3	129	3	129	3	129
Govindan (16)	7	53	9	50	7	53	9	50
Lorenzen (24)	2	32	0	30	2	32	0	30
Lynch (25)	17	325	15	320	17	325	15	320
Maughan (27)	38	815	13	815	38	815	13	815
Philip (30)	35	361	22	355	35	361	22	355
Pirker (31)	76	548	94	562	76	548	94	562
Rosell (34)	6	42	6	43	0	42	1	43
Sobrero (37)	16	618	19	596	16	638	19	629
Vermorken* (45)	29	219	41	215				
Cunningham° (49)	Cetuximab		Cetuximab		10	212	3	115

*not found in forrest plots

°Ineligible

grade 4 only (not converted from %)

safety population instead of actually tested

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