EFFICACY AND SECURITY OF CETUXIMAB IN THE TREATMENT OF METASTATIC COLORECTAL CANCER

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BACKGROUND

- Cetuximab has already been authorized for commercialization in Uruguay.
- It is prescribed for the treatment of metastatic colorectal cancer and for head and neck tumors.
- It has not yet been included in the uruguayan National Therapeutic Formulary (NTF).

BACKGROUND

- Currently the Ministry of Public Health is in charge of the technical assessment of the drugs to be included in the NTF.
- The final decision is taken by a group of stakeholders related to the health system.

OBJECTIVE

- The objective of this systematic review is to assess the efficacy and safety of Cetuximab-based therapy vs. non Cetuximab therapy in patients with metastatic colorectal cancer in order to decide the inclusion of the drug in the NTF.

METHODS

- A systematic search of literture was performed in electronic database with no languages restrictions. The last update of the search was done in April 2011.
- Key words included were:

cetuximab, metastatic OR secondarism, colorectal cancer OR neoplasm

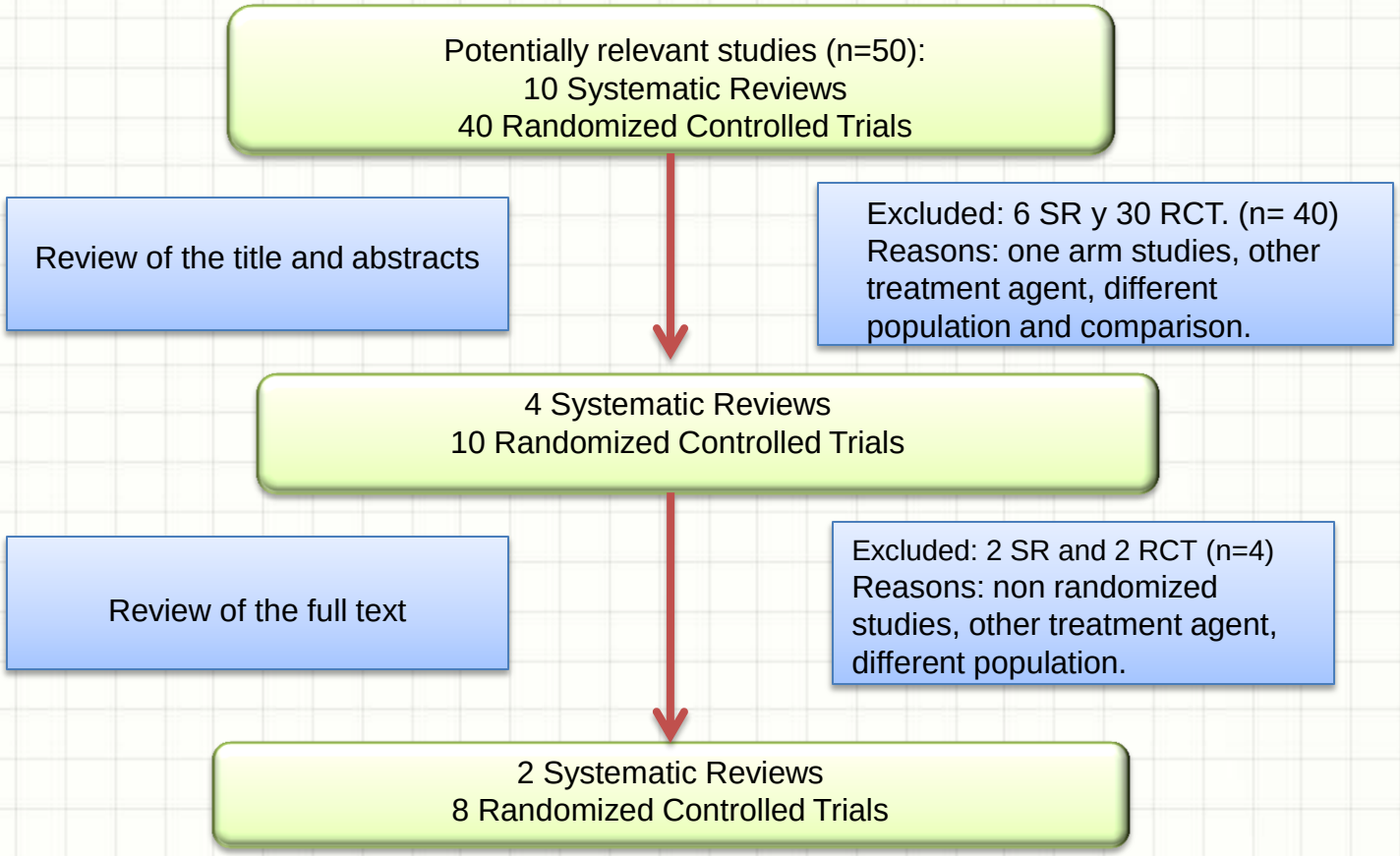
METHODS, cont

- Limits were: meta-analysis, clinical trial and randomized controlled trial (RCT).
- All studies comparing combined chemotherapy with Cetuximab vs. non Cetuximab chemotherapy were included.
- Critical appraisal of the papers was done by two independent reviewers.

METHODS, cont

- If a systematic review (SR) of high quality was found, the authors searched for RCT published after the most recent study included in the review.
- Statistical analysis was performed with Review Manager 5.0
- Sensitivity analysis and subgroup analysis for KRAS mutation status were performed.

RESULTS


Potentially relevant studies (n=50):
10 Systematic Reviews
40 Randomized Controlled Trials
Review of the title and abstracts
Excluded: 6 SR y 30 RCT. (n= 40)
Reasons: one arm studies, other treatment agent, different population and comparison.
4 Systematic Reviews
10 Randomized Controlled Trials
Review of the full text
Excluded: 2 SR and 2 RCT (n=4)
Reasons: non randomized studies, other treatment agent, different population.
2 Systematic Reviews
8 Randomized Controlled Trials

RESULTS, cont

The analyzed outcomes were:

- Overall Survival
- Progression Free Survival
- Median Survival
- Grade 3-4 Adverse Events
- Skin reactions

RESULTS, cont

Overall Survival

Study or Subgroup	Hazard Ratio	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Maughan 2009	1.04	0.09	21.2%	1.04 [0.86, 1.22]
Sobrero 2008	0.975	0.066	39.4%	0.97 [0.85, 1.10]
Van Cutsem 2009	0.93	0.066	39.4%	0.93 [0.80, 1.06]
Total (95% CI)			**100.0%**	**0.97 [0.89, 1.05]**

Heterogeneity: $Chi^2 = 0.98$, $df = 2$ ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 23.44$ ($P < 0.00001$)

There is no significant difference between the Cetuximab and control group.

RESULTS, cont

Progression free survival

Study or Subgroup	Hazard Ratio	SE	Weight	Hazard Ratio IV, Random, 95% CI
Bokemayer 2008	0.931	0.134	16.2%	0.93 [0.67, 1.19]
Maughan 2009	0.96	0.077	25.3%	0.96 [0.81, 1.11]
Sobrero 2008	0.692	0.04	31.7%	0.69 [0.61, 0.77]
Van Cutsem 2009	0.85	0.068	26.9%	0.85 [0.72, 0.98]
Total (95% CI)			**100.0%**	**0.84 [0.70, 0.98]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.63$, df = 3 (P = 0.006); $I^2 = 76\%$

Test for overall effect: Z = 11.46 (P < 0.00001)

Cetuximab increase the Progression Free Survival

RESULTS, cont

Median Survival in months

Study	Median Cetuximab group*	CI 95%	Median control group*	CI 95%
Borner 2008	20.5	[15,5- 27,2]	16.5	[14,4- 27,0+]
Sobrero 2008	10.7	[9.6- 11,3]	10.0	[9,1- 11,3]
Tol 2009	19.4	[17.5- 21,4]	20.3	[17,8- 24,7]
Van Cutsem 2009	19.9	[18.5- 21,3]	18.6	[16,6- 19,8]

There is no significant difference between the two groups.

RESULTS, cont

Grade 3- 4 Adverse Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Adam 2009 a	64	102	72	203	5.8%	3.06 [1.87, 5.02]
Adam 2009 b	95	166	118	333	10.9%	2.44 [1.67, 3.57]
Bokemayer 2008	129	170	117	168	9.2%	1.37 [0.85, 2.22]
Sobrero 2008	396	638	274	629	33.8%	2.12 [1.69, 2.65]
Tol 2009	299	366	268	366	15.9%	1.63 [1.15, 2.32]
Van Cutsem 2009	476	600	367	602	24.5%	2.46 [1.90, 3.18]
Total (95% CI)		**2042**		**2301**	**100.0%**	**2.15 [1.88, 2.45]**
Total events	1459		1216			

Heterogeneity: $Chi^2 = 9.17$, df = 5 (P = 0.10); $I^2 = 45\%$

Test for overall effect: Z = 11.46 (P < 0.00001)

Cetuximab group shows a significant increase of Adverse Events

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RESULTS, cont

Skin reactions

	Experimental		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Adam 2009 a	12	102	0	203	4.5%	56.22 [3.29, 959.79]
Adam 2009 b	16	166	2	333	18.3%	17.65 [4.01, 77.75]
Bokemayer 2008	19	170	1	168	13.6%	21.01 [2.78, 158.86]
Borner 2008	8	37	0	37	5.9%	21.61 [1.20, 389.88]
Jonker 2007	34	288	1	274	13.8%	36.54 [4.97, 268.92]
Sobrero 2008	52	638	1	629	14.1%	55.73 [7.68, 404.39]
Tol 2009	93	366	2	366	22.7%	62.00 [15.14, 253.82]
Van Cutsem 2009	49	600	0	602	7.0%	108.16 [6.66, 1757.65]
Total (95% CI)		**2367**		**2612**	**100.0%**	**44.46 [22.09, 89.51]**
Total events	283		7			

Heterogeneity: $Chi^2 = 2.98$, $df = 7$ ($P = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 10.63$ ($P < 0.00001$)

Cetuximab group shows a significant increase in skin reactions

RESULTS, cont

- KRAS wild type population showed a greater increase in the **Progression Free Survival** (Bokemeyer, 2008 and Van Cutsem, 2009) but not significant difference in **Overall Survival** in the treated group.

- In May 20th 2011 a new paper was published. It was an update analysis of Overall Survival according to tumor KRAS mutation status (Van Cutsem 2011)

RESULTS

- This report included a higher number of participants with the KRAS wild type (n= 666)

- The combination Cetuximab + FOLFIRI (fluorouracil+irinotecan+leucovorin) showed a significant increase in **Overall Survival** (HR 0.796 p= 0.0093), **Median survival time** (23.5 month vs. 20.0 month) in KRAS wild type population.

CONCLUSION

- According to this global analysis there is not enough scientific evidence to assure that the inclusion of Cetuximab to the treatment of metastatic colorectal cancer in **general population** can improve Overall Survival.
- Adverse effects increase with Cetuximab.
- KRAS wild type population appears to benefits with the use of Cetuximab in terms of Overall Survival

CONCLUSION, cont

- Further research is needed to determine risk/benefits and cost-effectiveness of the inclusion of Cetuximab in the treatment of metastatic colorectal cancer in KRAS wild type population in order to include this drug in the NTF in Uruguay.

THANK YOU
MUCHAS GRACIAS