The combination of NK₁ receptor antagonist, palonosetron and dexamethasone compared to palonosetron and/or dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis of randomized controlled trials

Ronald Chow, Marko Popovic, Leonard Chiu, Wayne Fu, Stephanie Cheon, Henry Lam, Milica Milakovic, Mark Pasetka, Sherlyn Vuong, Edward Chow, Carlo DeAngelis



Sunnybrook Odette Cancer Centre, Toronto, Canada



Objective

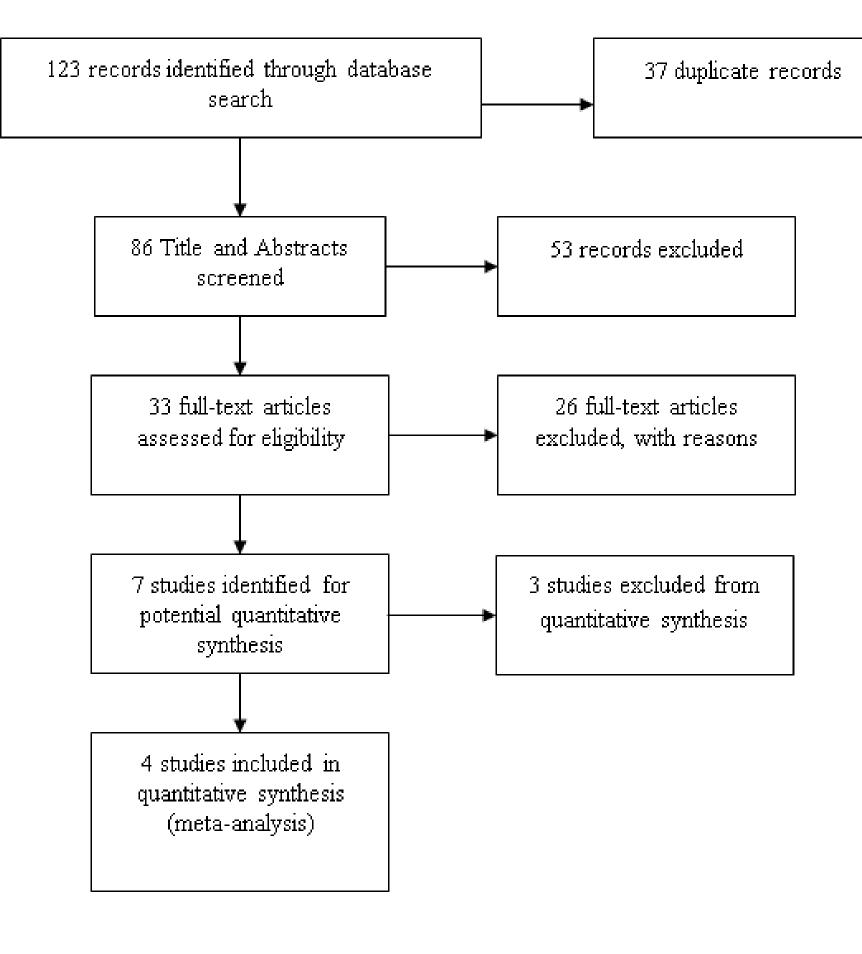
Investigate the efficacy of combined NK₁ receptor antagonist (RA), palonosetron (PALO) and dexamethasone compared to PALO and/or dexamethasone in the prophylaxis of CINV

Methods

- A literature search was conducted in Ovid MEDLINE from 1946 to April Week 5 2015, EMBASE Classic and EMBASE from 1947 to 2015 Week 18, and the Cochrane Central Register of Controlled Trials up until March 2015
- Articles were included if they reported on both (1) combination of NK₁RA and PALO, and (2) PALO and/or dexamethasone for prophylaxis of CINV
- Studies needed to report on at least one endpoint: complete response (CR), complete control (CC), no nausea and no vomiting in the acute (0-24 hr), delayed (24-120 hr) and overall (0-120 hr) phases
- Primary endpoint was the proportion of patients achieving CR in acute/delayed/overall phase
- Secondary endpoints were proportion of patients achieving CC, no nausea and no vomiting

Results

Fig 1. Flow of information diagram for RCTs included in review

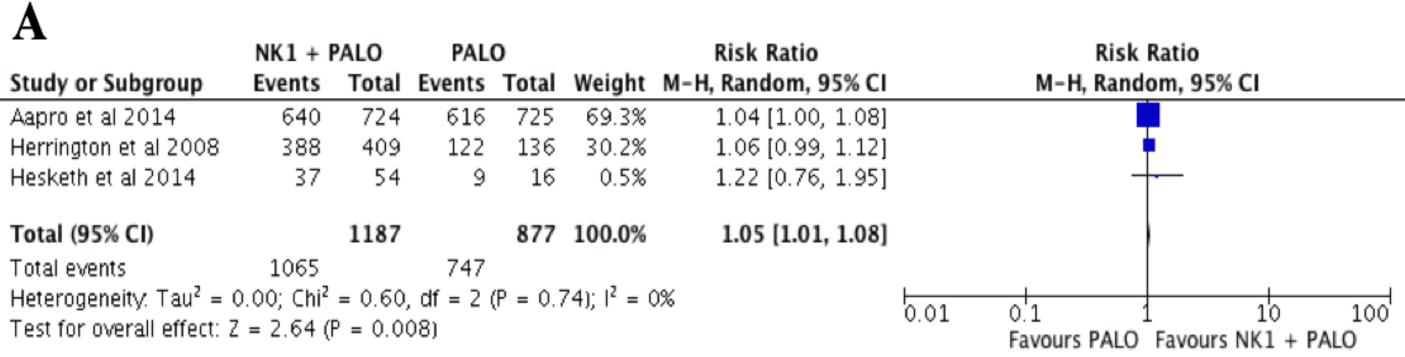


Absolute risk difference for all CINV endpoints

A

Endpoints	Absolute risk	95%	Test for	Heteroge	Satisfies MASCC/ESMO
	difference	confidence	overall	neity test	antiemetic guidelines
	(%)	interval (%)	effect		requirement
CR, acute phase	4	1-7	p=0.007	p=0.73	No
CR, delayed phase	9	5-13	p<0.00001	p=0.40	Approaching requirement
CR, overall phase	9	5-13	p<0.00001	p=0.61	Approaching requirement
CC, acute phase	2	-1 to +6	p=0.18	p=0.32	No
CC, delayed phase	8	4-12	p=0.0002	p=0.46	Approaching requirement
CC, overall phase	7	3-11	p=0.002	p=0.41	Approaching requirement
No nausea, acute phase	3	0-6	p=0.02	p=0.63	No
No nausea, delayed	7	3-11	p=0.001	p=0.85	Approaching requirement
phase					
No nausea, overall	6	2-10	p=0.006	p=0.99	Approaching requirement
phase					
No vomiting, acute	4	1-7	p=0.004	p=0.89	No
phase					
No vomiting, delayed	13	2-24	p=0.02	p=0.008	Yes
phase					
No vomiting, overall	14	4-24	p=0.008	p=0.02	Yes
phase					

A Efficacy of palonosetron compared with NK₁ RA and palonosetron in the prophylaxis of chemotherapy-induced-nausea and vomiting – complete response in the acute phase **B** Complete response in the delayed phase **C** Complete response in the overall phase



Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%

Test for overall effect: Z = 2.64 (P = 0.008)

NK1 + PALO PALO Risk Ratio Favours PALO Favours NK1 + PALO

Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI

Aapro et al 2014 560 724 504 725 65.7% 1.11 [1.05, 1.18]

Herrington et al 2008 33 54 5 16 0.4% 1.96 [0.92, 4.17]

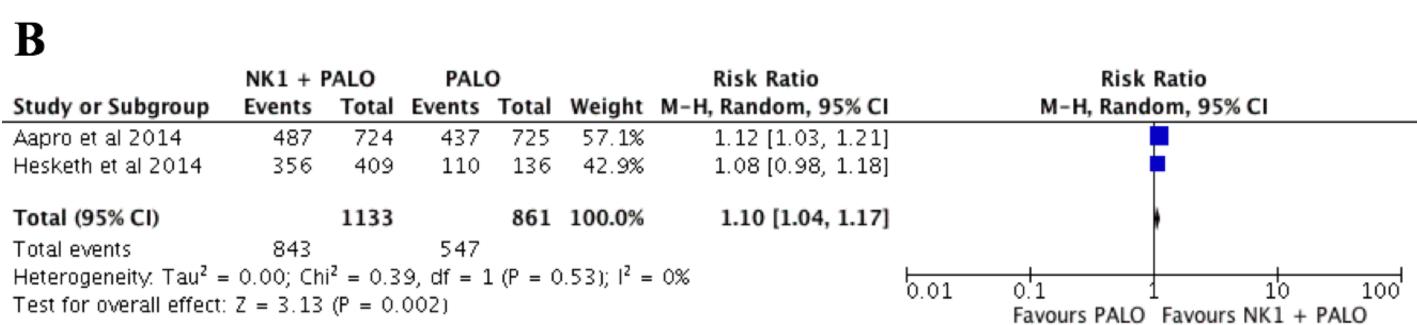
Hesketh et al 2014 371 409 109 136 32.0% 1.13 [1.04, 1.24]

409 109 136 32.0% 1.13 [1.04, 1.24] Hesketh et al 2014 1.21 [0.83, 1.76] 1.8% Ozaki et al 2013 21 Total (95% CI) 1208 916 100.0% 1.12 [1.07, 1.18] 641 Total events Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.37$, df = 3 (P = 0.50); $I^2 = 0\%$ Test for overall effect: Z = 4.51 (P < 0.00001) Favours PALO Favours NK1 + PALO

	NK1 +	PALO	PAL	0		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Aapro et al 2014	538	724	483	725	67.2%	1.12 [1.04, 1.19]		
Herrington et al 2008	29	54	5	16	0.5%	1.72 [0.80, 3.70]		
Hesketh et al 2014	361	409	104	136	30.4%	1.15 [1.04, 1.28]		
Ozaki et al 2013	14	21	23	39	1.9%	1.13 [0.76, 1.69]		
Total (95% CI)		1208		916	100.0%	1.13 [1.07, 1.19]	•	
Total events	942		615					
Heterogeneity: $Tau^2 = 0$	0.00; Chi ²	= 1.47	df = 3	P = 0.6	59); I ² = 0	0%		100
Test for overall effect: 2	? = 4.36 (P < 0.0	001)	_			Favours PALO Favours NK1 + PALO	100

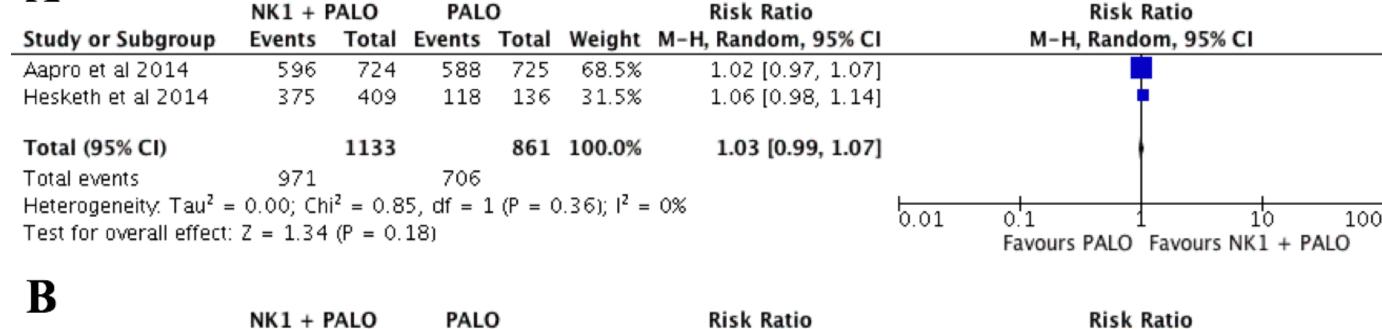
A Efficacy of palonosetron compared with NK₁ RA and palonosetron in the prophylaxis of chemotherapy-induced-nausea and vomiting – no nausea response in the acute phase **B** No nausea in the delayed phase **C** No nausea in the overall phase

A	NK1 + I	PALO	PAL	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aapro et al 2014	658	724	633	725	65.1%	1.04 [1.00, 1.08]	
Hesketh et al 2014	391	409	127	136	34.9%	1.02 [0.97, 1.08]	•
Total (95% CI)		1133		861	100.0%	1.03 [1.01, 1.07]	
Total events	1049		760				
Heterogeneity. Tau ² =	= 0.00; Ch	$i^2 = 0.3$	0, df = 3	1 (P = 0)).58); I ² =	: 0%	0.01 0.1 1 10 100
Test for overall effect	Z = 2.31	(P = 0.	02)				Favours PALO Favours NK1 + PALO
_							



C							
	NK1 +	PALO	PAL	o		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aapro et al 2014	462	724	420	725	56.6%	1.10 [1.01, 1.20]]
Hesketh et al 2014	349	409	108	136	43.4%	1.07 [0.98, 1.18]] 📍
Total (95% CI)		1133		861	100.0%	1.09 [1.02, 1.16]	1
Total events	811		528				
Heterogeneity. Tau2 =	= 0.00; Ch	$i^2 = 0.1$.6, df = 3	1 (P = 0)).68); I ² =	: 0%	0.01 0.1 1 10 100
Test for overall effect	Z = 2.70	(P = 0.	007)				Favours PALO Favours NK1 + PALO

A Efficacy of palonosetron compared with NK₁ RA and palonosetron in the prophylaxis of chemotherapy-induced-nausea and vomiting – complete control in the acute phase **B** Complete control in the delayed phase **C** Complete control in the overall phase

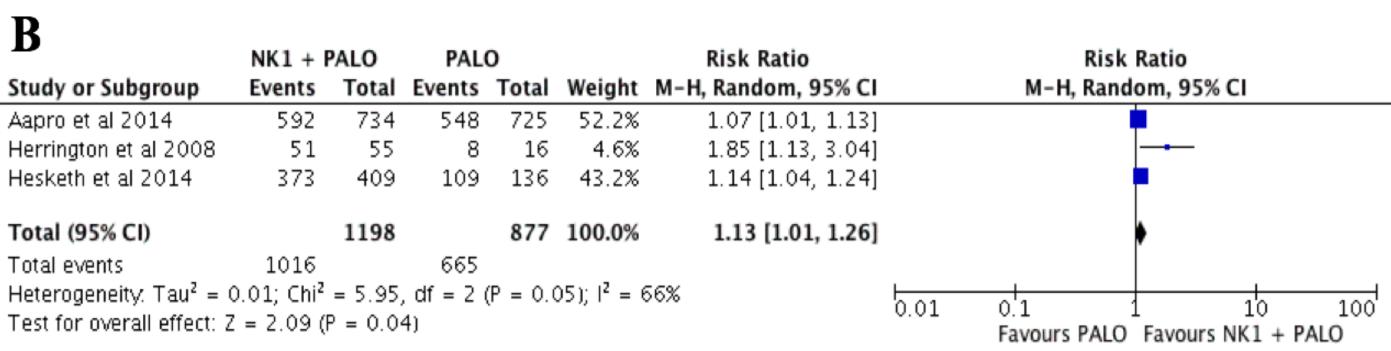


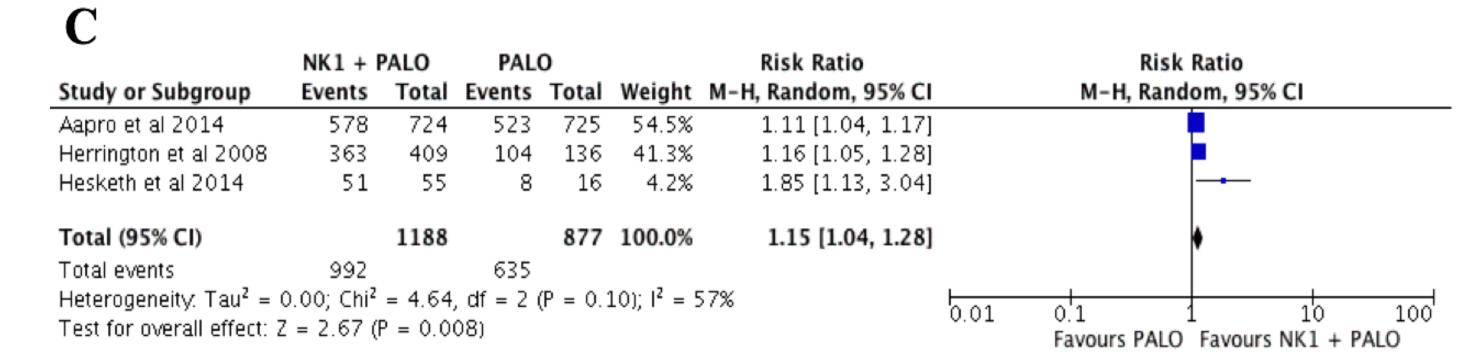
D	NK1 + I	PALO	PAL	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aapro et al 2014	487	724	437	725	66.3%	1.12 [1.03, 1.21]	
Hesketh et al 2014	344	409	100	136	33.7%	1.14 [1.03, 1.28]	•
Total (95% CI)		1133		861	100.0%	1.13 [1.06, 1.20]	•
Total events	831		537				
Heterogeneity: Tau² =	0.00; Ch	$i^2 = 0.1$	3, df = 3	1 (P = 0)).71); l² =	: 0%	0.01 0.1 1 10 100
Test for overall effect:	Z = 3.65	(P = 0.	0003)			·	Favours PALO Favours NK1 + PALO

C	NK1 + F	PALO.	PAL	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% CI	
Study of Subgroup	LVEIICS	Total	LVCIICS	Total	Weight	M-11, Kandoni, 55% Ci	M-11, Kandoni, 55% Ci
Aapro et al 2014	462	724	420	725	68.0%	1.10 [1.01, 1.20]	
Hesketh et al 2014	327	409	95	136	32.0%	1.14 [1.01, 1.29]	
Total (95% CI)		1133		861	100.0%	1.12 [1.04, 1.19]	
10tal (95% CI)		1133		801	100.0/0	1.12 [1.04, 1.15]	·
Total events	789		5 1 5				
Heterogeneity: Tau ² =	0.00; Ch	$i^2 = 0.2$	7, df = 3	L(P = 0)).60); I ² =	0%	
Test for overall effect:	Z = 3.13	(P = 0.	002)				0.01 0.1 1 10 100 Favours PALO Favours NK1 + PALO

A No vomiting response in the acute phase **B** No vomiting in the delayed phase **C** No vomiting in the overall phase

\mathbf{A}	NK1 + I	PALO	PAL	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aapro et al 2014	658	724	633	725	70.3%	1.04 [1.00, 1.08]	
Herrington et al 2008	54	55	15	16	5.3%	1.05 [0.92, 1.19]	+
Hesketh et al 2014	388	409	122	136	24.4%	1.06 [0.99, 1.12]	•
Total (95% CI)		1188		877	100.0%	1.05 [1.01, 1.08]	
Total events	1100		770				
Heterogeneity: Tau ² = ().00; Chi²	= 0.19	df = 2	(P = 0.9)	91); I ² = (0%	0.01 0.1 1 10 100
Test for overall effect: Z	= 2.87 (P = 0.00	04)				Favours PALO Favours NK1 + PALO





Conclusions

NK₁RA in combination with PALO is statistically more efficacious than PALO alone

We thank the generous support of Bratty Family Fund, Michael and Karyn Goldstein Cancer Research Fund, Joey and Mary Furfari Cancer Research Fund, Pulenzas Cancer Research Fund, Joseph and Silvana Melara Cancer Research Fund, and Ofelia Cancer Research Fund.