

ASCO | Guidelines

Data Supplement

ANTIEMETICS GUIDELINE UPDATE

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Data Supplement DS1. MEDLINE Search Strategy

Population

(neoplasms[mh] OR neoplas*[tw] OR tumor*[tw] OR tumour*[tw] OR malignan*[tw] OR Cancer*[tw] OR Oncolog*[tw] OR Bone marrow diseases[mh] OR myelodysplas*[tw] OR Myeloproliferat*[tw] OR Sarcoma*[tw] OR Leukemi*[tw] OR Leukaemi*[tw] OR Lymphoma*[tw] OR (Hodgkin*[tw] AND (disease[tw] OR lymphoma[tw])) OR "NHL"[tw] OR Carcinom*[tw] OR adenocarcinom*[tw] OR antineoplastic agents[mh] OR antineoplastic protocols [mh] OR chemotherapy, adjuvant[mh] OR chemotherap*[tw] OR antineoplastic*[tw] OR drug therapy, combination[mh] OR stem cell transplantation[mh] OR (("bone marrow"[tw] OR "stem cell"[tw]) AND transplant*[tw]) OR "HSCT"[tw] OR "PBSCT"[tw] OR Radiotherapy[mh] OR Radiotherapy[tw] OR (Radiation[tw] AND (therapy[tw] OR therapeutic[tw] OR treatment[tw] OR treated[tw])) OR Combined modality therapy[mh]) AND (("Nausea"[Mesh] OR "Vomiting"[Mesh]) NOT ("Morning Sickness"[Mesh] AND "Postoperative Nausea and Vomiting"[Mesh] AND "Hematemesis"[Mesh])) AND

Intervention

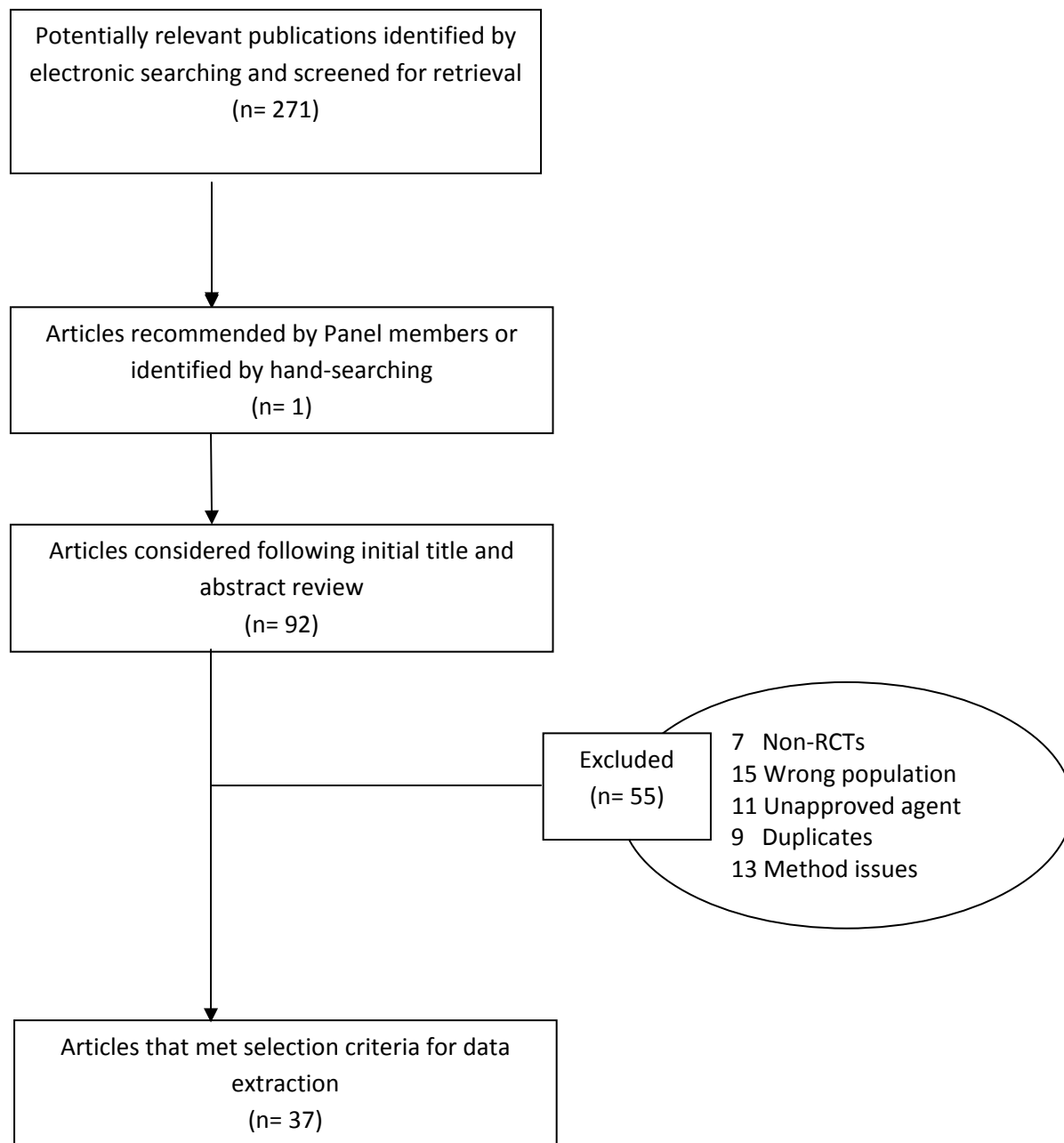
("Receptors, Serotonin, 5-HT₃/antagonists and inhibitors" [Mesh] OR Receptors, Serotonin, 5-HT₃[Mesh] OR "5-HT₃ serotonin receptor antagonists"[tiab] OR "5-hydroxytryptamine-3 (5-HT₃) serotonin antagonists"[tiab] OR "5-hydroxytryptamine-3 serotonin antagonists"[tiab] OR "5-HT₃ serotonin receptor antagonist"[tiab] OR "5-hydroxytryptamine-3 (5-HT₃) serotonin antagonist"[tiab] OR "5-hydroxytryptamine-3 serotonin antagonist"[tiab] OR "corticosteroids"[tiab] OR "corticosteroid"[tiab] OR Receptors, Neurokinin-1/antagonists and inhibitors[Mesh] OR "NK1 receptor antagonists"[tiab] OR "NK1 receptor antagonist"[tiab] OR "Ginger"[Mesh] and "Ginger"[tiab] OR "Serotonin Antagonists"[Mesh] OR "dolasetron mesylate "[Substance Name] OR "Granisetron"[Mesh] OR "Ondansetron"[Mesh] OR "palonosetron "[Substance Name] OR "tropisetron "[Substance Name] OR prednisone[mesh] OR "Dexamethasone"[Mesh] OR "Hydroxycorticosteroids"[Mesh] OR "dexamethasone 21-phosphate"[Substance Name] OR "Glucocorticoids" [Mesh] OR "Methylprednisolone Hemisuccinate"[Mesh] OR "methylprednisolone acetate "[Substance Name] OR "Methylprednisolone"[Mesh] OR "aprepitant "[Substance Name] OR "casopitant "[Substance Name] OR "dolasetron mesylate"[tiab] OR "Granisetron"[tiab] OR "granisetron transdermal system"[tiab] OR "Ondansetron" [tiab] OR "palonosetron "[tiab] OR "tropisetron"[tiab] OR "prednisone"[tiab] OR "Dexamethasone"[tiab] OR "Hydroxycorticosteroids"[tiab] OR "dexamethasone 21-phosphate"[tiab] OR "Glucocorticoids"[tiab] OR "Methylprednisolone Hemisuccinate"[tiab] OR "methylprednisolone acetate "[tiab] OR "Methylprednisolone"[tiab] OR "aprepitant "[tiab] OR "Fosaprepitant"[tiab] OR "casopitant"[tiab] OR "Anzemet"[tiab] OR "Kytril"[tiab] OR "sancuso"[tiab] OR "Zofran"[tiab] OR "Aloxi"[tiab] OR "Navoban"[tiab] OR "Emend"[tiab] OR "A-Methapred"[tiab] OR "Depo-Medrol"[tiab] OR "Medrol"[tiab] OR "Solu-Medrol"[tiab] OR

"Metoclopramide"[Mesh] OR "Butyrophenones"[Mesh] OR "Phenothiazines"[Mesh] OR "Cannabinoids"[Mesh] OR "Benzodiazepines"[Mesh] OR "Histamine Antagonists"[Mesh] OR "Metoclopramide"[tiab] OR "Butyrophenones"[tiab] OR "Phenothiazines"[tiab] OR "Cannabinoids"[tiab] OR "Benzodiazepines"[tiab] OR "Histamine Antagonists"[Mesh]) AND

Study Design

((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR clinical trials as topic[mh] OR controlled clinical trials as topic[mh] OR randomized controlled trials as topic[mh] OR clinical trials, phase II as topic[mh] OR clinical trials, phase III as topic[mh] OR clinical trials, phase IV as topic[mh] OR clinical trial, phase II[pt] OR clinical trial, phase III[pt] OR clinical trial, phase IV[pt] OR random allocation[mh] OR "random allocation"[tiab] OR "randomly allocated"[tiab] OR double-blind method[mh] OR single-blind method[mh]) OR ((random[tiab] OR randomly[tiab] OR randomized [tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab]) AND (clinical[tiab] OR control[tiab] OR controlled[tiab] or control groups[mh])) OR ((single[tiab] OR single-[tiab] OR double[tiab] OR double-[tiab] OR triple[tiab] OR triple-[tiab] OR multi[tiab] OR multi-[tiab] OR evaluator[tiab] OR assessor[tiab] OR interviewer[tiab]) AND (mask[tiab] OR masked[tiab] OR masking[tiab] OR blind[tiab] OR blinded[tiab] OR blinding[tiab])) OR ((placebos[mh] OR placebo[tiab] OR placebos[tiab] OR random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomization[tiab]) AND (research design[mh] OR "comparative study"[tiab] OR comparative study[pt] OR evaluation studies as topic[mh:noexp] OR evaluation studies[pt] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR validation studies as topic[mh] OR follow-up studies[mh] OR "follow-up study"[tiab] OR "follow up study"[tiab] OR "follow-up studies"[tiab] OR "follow up studies"[tiab] OR prospective studies[mh] OR prospective[tiab] OR epidemiologic research design[mh] OR epidemiologic methods[mh] OR epidemiologic study characteristics as topic[mh] OR epidemiologic studies[mh] OR intervention studies[mh] OR cross-over studies[mh] OR Meta-Analysis[pt]))) NOT (clinical trial, phase I[pt] OR clinical trials, phase I as topic[mh]) NOT (animals[mh] NOT humans[mh])) AND English[la] AND ("2008/09/01"[PDAT] : "2009/12/02"[PDAT])

Data Supplement DS2. QUOROM Diagram



Abbreviation: RCTs, randomized controlled trial

**Data Supplement DS3. Summary of Cochrane Review Meta-Analysis Comparing
Granisetron vs. Ondansetron**

Outcome	# Studies Included	# Patients Included	Odds Ratio (95% CI)
Acute Vomiting	8	4256	0.89 (0.78 to 1.02)
Acute Nausea	7	4160	0.97 (0.85 to 1.10)
Delayed Vomiting	3	1119	1.00 (0.74 to 1.34)
Delayed Nausea	2	1024	0.96 (0.75 to 1.24)

CI: confidence interval

From Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No. CD006272. DOI:

10.1002/14651858.CD006272.pub2. <http://www2.cochrane.org/reviews/en/ab006272.html>

Data Supplement Table 4a. Study Characteristics

Author	Primary Endpoint	Secondary Endpoint(s)	Intervention	Other Meds	Stratification Factors
Highly Emetogenic Chemotherapy					
Herrington 2008 ¹	Proportion w/ emesis in acute (d1) and delayed (d2-5)	1- Use of rescue meds, 2- severity of nausea d1-5	3 arms: (1) 3-day aprepitant vs. (2) 1-day aprepitant vs. (3) placebo. (<i>Placebo arm halted after 50 patients</i>)	Palonosetron 0.25mg IV, d2-4: Dexamethasone	NOTE: pilot study
Yeo, 2009 ²	Efficacy	Patient reported QOL	2 arms: (1) d1- aprepitant 125mg, and dex 12mg, d2,3- aprep 80mg vs. (2) d1- placebo, dex 20mg d2,3- ondans 8mg bid, placebo	D1- Ondansetron 8mg pre chemo and 8mg 8h s/p chemo	No concomitant XRT
Hoshi, MASCC 2007 ³	Percent of patients with complete response (No emesis, no rescue meds)	1- Percent of patients with complete protection (no emesis, rescue meds, or significant nausea; 2- Percent of pts with no significant nausea	3 arms: (1) Aprepitant d1: 125mg, d2-5: 80mg vs (2) Aprepitant d1: 40mg, d2-5: 25 mg vs (3) Placebo	Granisetron and dexamethasone doses not reported	NR
Grunberg, 2011 ⁴	Overall complete response (no emesis, no rescue meds); fosaprepitant non-inferiority (<i>margin -7%</i>)	1- Complete response during the delayed phase (hours 24-120 s/p chemotherapy, 2- no emesis throughout study period	2 arms: (1) Aprepitant d1- 125mg, days 2 and 3- 80 mg vs. (2) Fosaprepitant 115 mg d1 only	Ondansetron 32 mg, dexamethasone 8mg (d1 only)	Stratification by patient sex
Navari, MASCC 2010 ⁵	Complete acute response (no emesis, no rescue meds) during overall period	Complete response during delayed period and no emesis during overall period	2 arms: (1) d1-4: Olanzapine 10mg po vs (2) d1 Aprepitant 125 mg po, d2,3: 80 mg	D1: Palo 0.25 mg IV, Dex (20mg IV- Olan arm, 12 mg IV Aprep arm), d2-4: Dex (20mg IV Olanzapine arm;4mg po bid – Aprepitant arm)	NR
Navari, personal communication	Complete acute response (no emesis, no rescue meds) during overall period	Complete response during delayed period and no emesis during overall period; nausea control	2 arms: (1) d1-4: Olanzapine; Dexamethasone 20 mg vs (2) d1: Aprepitant 125 mg po, d2-3: Aprepitant 80 mg	D1: Palo 0.25 mg IV, Dex (20mg IV- Olan arm, 12 mg IV-Aprep arm), d2-4: Dex (20mg IV Olan arm; 4mg po bid – Aprep arm)	NR

d: day; IV: intravenous; QOL: Quality of life; dex: dexamethasone; aprep: aprepitant; ondans: ondansetron; bid: twice daily; h: hour; s/p: after; XRT: radiation therapy; NR: not reported; po: by mouth; Olan: olanzapine

Data Supplement 4b. Study Characteristics

Author	Primary Endpoint	Secondary Endpoint(s)	Intervention	Other Meds	Stratification Factors
Moderately Emetogenic Chemotherapy					
Rapaport 2010 ⁶	Proportion of patients with no emesis overall	Overall complete response (no emesis, rescue meds)	2 arms: (1) Aprepitant 125mg po d1; d2,3: 80mg po vs. (2) Placebo d1-3	Ondan 8mg po bid; Dex-20mg Aprep arm, 12mg placebo arm	gender
Aapro 2010 ⁷	Overall Complete Response (no emesis, no rescue meds)	1- Acute, delayed Complete Response, 2- rate of no emesis, 3- rate of no nausea, 4- FLIE scores, 5- complete control (no emesis or rescue meds, minimal nausea), 6- safety, 7- maximum nausea severity	2 arms: (1) d2, 3: placebo vs. (2) d2, 3: dexamethasone, 4mg po bid	D1: palonosetron 0.25mg (route NR) and dexamethasone 8mg IV	All patients were chemotherapy naïve
Celio, Supp Ca Care 2010 ⁸	Complete Response (no emesis, no rescue meds) during overall period (120hours)	Proportion with no emesis throughout study period	2 arms: (1) 1-day dexamethasone, 8mg IV. vs. (2) 3-day dex, d1: 8mg IV, d2-3 dex 8mg po	Palonosetron 0.25mg IV, d1 only	By chemo especially AC; non-inferiority
5-HT₃ Antagonist Equivalency					
Aapro 2006 ⁹	At least one dose of palonosetron not inferior to ondansetron dose using a max delta of 15% at 24 hours	1- Response rate comparisons thru d5, 2- complete control, 3- number of emesis episodes, 4- time to rescue meds, 5- time to treatment failure, 6- nausea severity	3 arms: (1) palonosetron 0.25mg IV vs. (2) palonosetron 0.75mg IV vs. (3) ondansetron 32mg IV	Single prophylactic corticosteroid at physician discretion	
Yu 2009 ¹⁰	Complete Response rate for acute vomiting (non-inferior in acute phase)	Complete Response Rate for delayed vomiting	2 arms: (1) palonosetron 0.25mg IV vs. (2) granisetron 3mg IV	Rescue meds ok	NR
Saito 2009 ¹¹	Proportion of pts with Complete Response during acute (10% non-inferiority), delayed (superior) phases	1- Overall Complete Response, 2- proportion with complete control, 3- number of emetic episodes, 4- time to first emesis and rescue meds, 5- time to failure, 6- nausea severity	2 arms: (1) palonosetron 0.75mg vs. (2) granisetron 40 µg/kg	d1: Dex 16 mg IV, d2-3: Dex 16mg IV (cisplatin) or 4mg po (AC/EC)	NOTE: margin for superiority not defined, inferiority at 10%

Po: by mouth; d: day; ondan: ondansetron; bid: twice daily; Dex: dexamethasone; Aprep: aprepitant; FLIE: Functional Living Index-Emesis questionnaire; po: by mouth; IV: intravenous; AC: adriamycin + cyclophosphamide; NR: not reported; EC: epirubicin+ cyclophosphamide;

Data Supplement Table 4c. Study Characteristics

Author	Primary Endpoint	Secondary Endpoint(s)	Intervention	Other Meds	Stratification Factors
Palonosetron Dosing					
Raftopoulos ASCO 2009 ¹²	Complete Response (no emesis, no rescue meds): overall, acute, and delayed	Grades 3-4 toxicities, reported in at least 50% of trials	Meta-Analysis (per study) of 8 trials, both HEC and MEC which included palonosetron 0.25 or 0.75 mg arms	Studies must include dexamethasone	MEC and HEC, results pooled
Maemondo 2009 ¹³	Proportion of patients with Complete Response (CR) during acute phase	1- proportion with CR during delayed and overall phases, 2- daily Complete Response rates, 3- proportion of patients with complete control, 4- time to treatment failure	3 arms: (1) palonosetron 0.075mg vs. (2) palonosetron 0.25mg vs. (3) palonosetron 0.75mg IV single bolus	Dexamethasone d1: 12-16mg, d2: 8mg, d3: 4-8mg (dose increased for pts receiving paclitaxel)	gender, paclitaxel; NOTE stratification inconsistent w/ HEC
Segawa 2009 ¹⁴	Proportion of patients with Complete Response (CR) during acute phase	1- proportion with CR during delayed and overall phases, 2- complete control rates, 3- time to treatment failure, 4- severity of nausea, 5- patient global satisfaction	3 arms: (1) palonosetron 0.075mg vs. (2) palonosetron 0.25mg vs. (3) palonosetron 0.75mg IV single bolus	Dexamethasone 8mg (20mg for paclitaxel)	gender, paclitaxel
Formulation Equivalency					
Grunberg ECCO 2007 ¹⁵	Complete Response (CR) during the acute phase	1- Daily and overall CR, 2- proportion of patients without emesis, 3- nausea severity, 4- patient satisfaction	4 arms: (1) oral palo 0.25mg vs. (2) oral palo 0.50mg vs. (3) oral palo 0.75mg vs. (4) IV palo 0.25mg	Within each arm, randomized 1:1 – dex (8mg IV) vs. placebo	Gender, chemo naivety
Pectasides 2007 ¹⁶	Compare the major emesis control rates in the 2 treatment arms	Comparison of complete emesis and nausea control	2 arms: (1) ondansetron 8mg OT vs. (2) ondansetron 8mg ODT, both bid d1-3	Rescue meds allowed	
Boccia 2010 ¹⁷	Non-inferiority (15%) of granisetron transdermal patch (GTDS) compared to oral granisetron in MEC, HEC with respect to complete control (no vomiting, rescue meds; mild nausea)	1- Complete Response (no emesis, rescue meds), 2- Total Control (no emesis, rescue meds, or nausea), 3- Assessment of safety and tolerability, adhesive property	2 arms: (1) GTDS, applied 24-48 h pre chemo worn for 7d vs. (2) 2mg granisetron po 1hour before chemotherapy start	Dex at investigator discretion, rescue meds	Gender, cisplatin or not, duration, chemo naivety
Multi-day Chemotherapy					
Herrstedt 2007 ¹⁸	Emetic control (no failure, > 5 emetic episodes, patient satisfaction with treatment)	1- Complete Response (no emesis), 2- Nausea Severity, 3- Appetite, 4- Satisfaction with emetic treatment	2 arms: (1) Metopimazine 30mg d1 tid, d2-6: qid, vs. (2) placebo	Tropisetron 5mg IV d1-5	Study center, cisplatin dose (20 vs. 40 mg)

HEC: highly emetogenic chemotherapy; MEC: moderate emetogenic chemotherapy; IV: intravenous; d: day; palo: palonosetron; dex: dexamethasone; OT: conventional oral tablet; ODT: orally disintegrating tablet; bid: twice daily; h: hour(s); po: by mouth; tid: three times daily; qid: four times daily

Data Supplement Table 4d. Study Characteristics

Author	Primary Endpoint	Secondary Endpoint(s)	Intervention	Other Meds	Stratification Factors
High Dose Chemotherapy prior to SCT/ BMT					
Stiff, ASH 2009 ¹⁹	“Response Rates”; Complete Response (no emesis, minimal nausea)	1- Major Response (1 emetic episode or moderate nausea), 2- Failure (>4 emetic episodes)	2 arms: (1) Aprepitant, d1: 125mg po, 80mg throughout regimen and 3 days post treatment vs. (2) placebo	Ondan 8mg po q8h and dex (10mg ondan and 7.5mg aprep arm) IV during regimen and day +1	gender
Giralt, ASCO 2008 ²⁰	Complete Protection (no emesis throughout 7d study)	Emetic episodes	3 arms (all palonosetron 0.25mg IV): (1) palo d -2 (1d) vs. (2) palo d -2, -1 (2d) vs. (3) palo d -2, -1, 0 (3d)	dex 20mg days -2 and -1	
Walsh, BMT, 2004 ²¹	Acute (24h s/p chemotherapy) efficacy and safety	Overall control of emesis Safety assessments using SWOG toxicity grading	2 arm: (1) ondansetron 0.15mg/kg IV q8h vs (2) granisetron 10ug/kg IV qD;	Dex 10mg IV daily and lorazepam 1mg IV q8h	
Pediatrics					
Sepulveda - Vildosola 2008 ²²	Safety and efficacy of palonosetron in children	NR	2 arms: (1) ondansetron 8mg/m ² IV vs. (2) palonosetron 0.25mg IV	No other meds	NOTE: Acute: d1-3, delayed: d4-7
Gore 2009 ²³	Difference in drug-related AEs during and 14d following treatment	1- Efficacy, 2- pharmacokinetics	2 arms: (1) aprepitant (125/80/80mg) vs. (2) placebo	D1-4: ondan 0.15mg/ kg tid; Control arm- d1: dex 8mg po ; Aprep arm- d2-4: dex 4mg	2:1 enrollment (aprep vs. control), (Pts age 11-19)
Delayed Emesis					
Fabi 2008 ²⁴	Proportion of patients with no emesis after receiving rescue meds	Tolerability of the two ondansetron formulations, personal satisfaction with rescue medicine	2 arms: (1) 8mg ondan IM vs. (2) 16mg orodispersible ondansetron (orally disintegrating, ODT) 16 mg po	CINV Prophylaxis- d1: ondan 8mg IV, dex 8mg IV. D2-4: dex 8mg po	
Lajolo 2009 ²⁵	Effect of tachyphylaxis to 5-HT ₃ antagonists as a strategy to improve delayed CINV protection	Function Living Index-Emesis (FLIE)	2 arms: (1) granisetron 0.5mg po d2, 3 vs. (2) placebo	Ondan: 16 mg (d1), Ranit: 50mg (d1), 150mg q 12h (d2,3); Dex: 20mg (d1), 8mg po (d2, 3); Meto: 10mg po q 8h (d2-4)	

D: day; po: by mouth; ondan: ondansetron; q: every; h: hour(s); dex: dexamethasone; aprep: aprepitant; IV: intravenous; palo: palonosetron; s/p: after; SWOG: Southwest Oncology Group; NR: not reported; AEs: adverse events; tid: three times daily; pts: patients; IM: intramuscular; CINV: chemotherapy-induced nausea and vomiting; FLIE: Functional Living Index-Emesis questionnaire; ranit: ranitidine; meto: metoclopramide;

Data Supplement Table 4e. Study Characteristics

Author	Primary Endpoint	Secondary Endpoint(s)	Intervention	Other Meds	Stratification Factors
Complementary Therapy					
Tan, 2009 ²⁶	Complete response: acute, delayed, overall	Quality of Life (EORTC QLQ-C30), drug safety	2 arms: (1) olanzapine 10mg po qD d1-5 vs. (2) placebo	Azaseteron d1: 10 mg IV and Dex d1: 10 mg IV qD	
Ginger					
Ryan 2009 ²⁸	Effectiveness of ginger for nausea among patients receiving a 5-HT ₃ receptor antagonist	NR	2 arms: (1)Ginger day minus 3 thru d +3 (no d0, 6d of treatment) vs. (2) placebo	Any of the 5HT ₃ receptor antagonists	NOTE: three doses of ginger
Zick 2009 ²⁷	Effect of low vs. high dose ginger vs. placebo in reducing prevalence, severity of delayed N/V	1- Reducing prevalence and severity of N/V in acute period, 2- safety of ginger doses, 3- efficacy of blinding	3 arms: (1) 1.0g ginger bid vs. (2) 2.0g ginger bid vs. (3) placebo for 3 days	Pts also received either aprepitant (31.6%) or 5-HT ₃ receptor antagonist for remainder	Aprepitant vs. 5HT ₃ antagonist
Pillai 2011 ²⁹	Incidence and severity of acute – (w/in 24h of starting chemo [days 1-4]) and delayed (days 5-10) CINV	NR	4 arms: <i>Pts ≥ 20 kg and < 40kg:</i> (1) 6,000mg/d ginger root vs. (2) placebo <i>Pts ≥40kg and 60kg:</i> (3) 10,000 mg/d ginger root vs. (4) placebo	Ondansetron and dexamethasone	Cycle of chemo; weight
Radiation Therapy					
Wong 2006 ³⁰	1: Complete Control of RINV during fractions 1-5, 2: days 1-15	1- Average nausea score, 2- use of rescue meds, 3- AEs, 4- QOL	2 arms: (1) dexamethasone 8mg po qD vs. (2) placebo days 1-5	All received ondansetron 8mg bid days 1-5	Degree of emetic risk

EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; po: by mouth; q: every; d/D: day; IV: intravenous; dex: dexamethasone; NR: not reported; N/V: nausea and vomiting; bid: twice daily; Pts: patients; w/in: within; h: hours; CINV: chemotherapy-induced nausea and vomiting; RINV: Radiation-Induced Nausea and Vomiting; AEs: Adverse events; QOL: Quality of Life; Ondansetron: ondansetron; ODT: orally disintegrating formula

Data Supplement Table 5a. Patient Characteristics

Author, Yr	Design		Sample Size	Age ± SD (in years)	Gender	Quality					Chemotherapy	Emetic Risk Category	Disease
	RCT	Double Blind				Random Method Allocation	Conceal	Groups similar	Eligibility Defined	Outcomes Defined			
Highly Emetogenic Chemotherapy (HEC)													
Herrington 2008¹ Arm A: 3d Aprep Arm C 1d Aprep	X		75 29 16	59.6 ± 10.7 56.1 ± 12.6	31% male 12.5% male	x	x		x	x	HEC (cisplatin ≥ 50 mg/m ² , AC combos for breast cancer)	HEC	45% breast, 21% lung, 14% H/N, 21% other
Yeo 2009² Arm A: Aprep Arm B: Placebo	X	X	124 mITT 62 62	46.5 48.5	100% female	x	x		x	x	Anthracycline-cyclophosphamide (AC) regimens for breast cancer	HEC	100% breast cancer
Hoshi MASCC 2007³ Arm A: Aprep 125 Arm B: Aprep 40 Arm C: Placebo	X	X	440 mITT 146 144 150	60.5 63.3 62.2	76.0% male 75.0% male 74.7% male			x	x	x	High dose cisplatin (≥ 70 mg/m ²)	HEC	NR
Grunberg, 2011⁴ Arm A: Aprep Arm B: Fosaprep	X	X	2,247 mITT 1,175 1,147	60 57	64% male 63% male	x	x	x	x	x	Cisplatin (≥70 mg/m ²) among chemo naive patients	HEC	Lung, GI, reproductive/GU, renal & urinary
Navari, 2010⁵ Arm A: Olan Arm B: Aprep	X	NR	61 mITT 31 30	58	70% female NR NR						Cisplatin, doxorubicin, or cyclophosphamide	MEC HEC	Bladder, Breast, Lymphoma, Lung
Navari, unpublished Arm A: Olan Arm B: Aprep	X	X	121 61 60	39-77 42-81	34% female 35% female	x	x	x	x	x	Cisplatin, doxorubicin or cyclophosphamide.	MEC HEC	Bladder, Breast, Lymphoma, Lung

SD: standard deviation; Aprep: Aprepitant; HEC: highly emetogenic chemotherapy; AC: anthracycline-cyclophosphamide; H/N: head and neck; mITT: modified intent-to-treat analysis; NR: Not reported; Fosaprep: Fosaprepitant; GI: gastrointestinal; GU: genitourinary; MEC: moderately emetogenic chemotherapy; Olan: Olanzapine

Data Supplement Table 5b. Patient Characteristics

Author, Yr	Design		Sample Size	Age ± SD (in years)	Gender	Quality						Chemotherapy	Emetic Risk Category	Disease			
	RCT	Double Blind				Random Method Allocation	Conceal	Groups similar	Eligibility Defined	Outcomes Defined							
Moderately Emetogenic Chemotherapy																	
Rapoport 2010⁶	X	X	832 mITT	57 years	77% female	x	x	x	x	x		48% AC regimens, 52% non-AC regimens	MEC, HEC	52% Breast, 20% colon, 13% lung, 5% ovarian			
Arm A: Aprep			430	57.1 (11.8)	76% female												
Arm B: Placebo			418	55.9 (12.6)	78% female												
Aapro, 2010⁷	X	X	300	51.6	100% female			x	x	x		MEC, including AC	MEC, HEC	Breast cancer			
Arm A: 1d Dex			151	52.1													
Arm B: 3d Dex			149	51.2													
Celio, 2010⁸	X		324 mITT	57.5	65% female				x	x		MEC (65%) regimens and including AC (35%)	MEC, HEC	Breast, colon, lung			
Arm A: 1d Dex			166	56.9	62% female												
Arm B: 3d Dex			166	57.2	68% female												
5-HT₃ Antagonist Equivalency																	
Aapro 2006⁹	X	X	667	51.63	49% male					x	x	low to moderate emetogenic chemotherapy	HEC	17% ovarian, 15% lung, 8% Hodgkins 5% Gastric, 5% Breast			
Arm A: Palo 0.25 IV			223	53.4 (13.7)	48% male												
Arm B: Palo 0.75 IV			223	50.6 (14.1)	49% male												
C: Ondan 0.35mg IV			221	50.9 (14.2)	49% male												
Yu 2009¹⁰	X	X	208 (ITT)					x	x	x		Epirubicin or cisplatin	HEC/MEC	32% H/N, 18% NSCLC, 10% gastric			
Arm A: Palo 0.25mg			104	52.6 ± 11.0	63.5% male												
Arm B: Gran 3mg			104	50.3± 9.5	63.5% male												
Saito 2009¹¹	X	X	1114 (ITT)		42% male	x	x		x	x		Cisplatin (57%) or AC/EC (43%)	HEC	45% lung, 43% breast			
Arm A: Palo 0.75mg			555	58.4 (10.4)	41% male												
Arm B: Gran 40 µg/kg			559	58.0 (10.5)	42% male												

SD: standard deviation; Aprep: Aprepitant; mITT: modified intent-to-treat analysis; AC: anthracycline-cyclophosphamide; MEC: moderately emetogenic chemotherapy; HEC: Highly emetogenic chemotherap; Dex: Dexamethasone; Palo: palonosetron; Ondan: ondansetron; Gran: granisetron; ITT: intent-to-treat analysis; H/N: Head and Neck; NSCLC: Non Small Cell Lung Cancer; EC: epirubicin-cyclophosphamide

Data Supplement Table 5c. Patient Characteristics

Author, Yr	Design		Sample Size	Age ± SD (in years)	Gender	Quality						Chemotherapy	Emetic Risk Category	Disease
	RCT	Double Blind				Random Method Allocation	Conceal	Groups similar	Eligibility Defined	Outcomes Defined				
Palonosetron Dosing														
Raftopoulos, 2009¹²	x		1926	8 trials included	NR							NR	MEC, HEC	NR
Maemondo 2009¹³	x	x	231			x		x	x	x		cisplatin, cy ≥ 1500 mg, dacarbazine	HEC	~95% lung cancer
Arm A: Palo 0.075			76	61.7 ± 8.9	56 (74%) male									
Arm B: Palo 0.25			77	62.1 ± 8.8	56 (73%) male									
Arm C: Palo 0.75			78	62.0 ± 9.8	57 (73%) male									
Segawa 2009¹⁴	x	x	204			x		x	x	x		Carboplatin (55%), paclitaxel (47%), Cy (41%), Epi (22%), Doxorubicin (18%); 39% of pts rec'd AC regimens	MEC/ HEC	53% NSCLC, 41% breast,
Arm A: Palo 0.075			67	57.0 ± 11.2	31 (46%) male									
Arm B: Palo 0.25			68	58.2 ± 11.4	28 (41%) male									
Arm C: Palo 0.75			69	59.3 ± 10.2	29 (42%) male									
Formulation Equivalency														
Grunberg, 2007¹⁵	x	x	635					x		x		Naïve/non similar in groups	NR	50% breast cancer
A: Palo 0.25mg po			155	57.1	74% female									
B: Palo 0.50mg po			160	56.1	74% female									
C: Palo 0.75mg po			158	55.8	72% female									
D: Palo 0.25mg IV			162	57.7	72% female									
Pectasides 2007¹⁶	x		134	53	NR					x	x	High-dose epirubicin	MEC	separated into early and advanced disease
Arm A: Ondan ODT			66	53 (29-78)										
Arm B: Ondan OT			68	53 (25-78)										
Boccia 2010¹⁷	x	x	641			x	x	x	x	x		Cisplatin (71, 72%)	HEC, MEC	NR, 68% treated with ≤ 3d chemo
Arm A: GTDS			318	54 ± 13	52% female									
Arm B: Gran po			323	55 ± 14	51% female									
Multi-day Chemotherapy														
Herrstedt 2007¹⁸	x	x	82 mITT					x	x	x		Cisplatin, either 20 or 40 mg/m ²		Germ cell tumors
Arm A: Metopim			42	34	98% male									
Arm B: Placebo			40	34	90.5% male									

SD: standard deviation; NR: not reported; MEC: moderately emetogenic chemotherapy; HEC: highly emetogenic chemotherapy; Palo: Palonosetron; Cy: cyclophosphamide; Epi: epirubicin; AC: anthracycline-cyclophosphamide; NSCLC: Non Small Cell Lung Cancer; po: oral; IV: intravenous; Ondan: ondansetron; ODT: oral disintegrating tablets; OT: conventional oral tablet; GTDS: granisetron transdermal system; gran: granisetron; d: day; Metopim: metopimazine; mITT: modified intent-to-treat

Data Supplement Table 5d. Patient Characteristics

Author, Yr	Design		Sample Size	Age ± SD (in years)	Gender	Quality					Chemotherapy	Emetic Risk Category	Disease
	RCT	Double Blind				Random Method	Allocation Conceal	Groups similar	Eligibility Defined	Outcomes Defined			
High Dose Chemotherapy prior to SCT/ BMT													
Stiff 2009¹⁹ Arm A: Aprep Arm B: Placebo	x	x	90 89	50 51	33% female 32% female	x					TBI/VP/CY, TBI/CY, BU/CY, CBV	NR	HD, NHL, ALL, AML, CML, MM, MDS, and others
Giralt, ASCO 2008²⁰ Arm A: 1 day palo Arm B: 2 days palo Arm C: 3 days palo	x	x	24 24 25	59- 61 58.2 (8.4) 57.9 (10.8) 59.3 (7.6)	54-71% male 54.2% male 71% male 68% male			x		x	Melphalan (100 mg/m ² /d) followed by SCT on day 0	NR	Multiple Myeloma
Walsh, 2004²¹ Arm A: Ondansetron Arm B: Granisetron	x	x	110 50 46	52.3± 11.4 50.8± 12	47% male 38% male	x	x	x	x	x	Busulfan, Cyclophosphamide, Melphalan, CBV	HEC	NHL, Hodgkin's Disease, Myeloma, breast
Pediatrics													
Sepulveda-Vildosola, 2008²²	x		100	11	69% male			x					
Gore 2009²³	x		46	15 (range: 11-19)	72% male	x		x	x	x	NR, "emetogenic chemotherapy"	NR	bone sarcoma
Delayed Emesis													
Fabi 2008²⁴ Arm A: Ondan IM Arm B: Ondan po	x		89 44 45	58 61	14.6% male 16% male 13% male	x			x		MEC; including AC/EC regimens (57-68%)	MEC, HEC	72% breast, 11% GYN, 8% lung,
Lajolo 2009²⁵ Arm A: Granisetron Arm B: Placebo	x	x	36 37	52.44 ± 10.3 50.3 ± 11.7	1/36 male 4/37 male	??			x		Cisplatin, doxorubicin, epirubicin	HEC	89.0% breast

SD: standard deviation; Aprep: aprepitant; TBI: total Body Irradiation; VP: etoposide (VP-16) ;Cy: cyclophosphamide; Bu: busulfan; CBV: cyclophosphamide, carmustine, etoposide; NR: not reported; HD: Hodgkin's Disease; NHL: Non-Hodgkin's lymphoma; ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; CML: chronic myelogenous leukemia; MM: multiple myeloma; MDS: myelodysplastic syndrome; palo: palonosetron; SCT: stem cell transplant; Ondan: ondansetron; IM: intramuscular; po: by mouth; MEC: moderate emetogenic chemotherapy; AC: anthracycline + cyclophosphamide; EC: epirubicin + cyclophosphamide; GYN: gynecologic;

Data Supplement Table 5e. Patient Characteristics

Author, Yr	Design		Age \pm SD (in years)	Gender	Quality						Chemotherapy	Emetic Risk Category	Disease
	RCT	Double Blind			Random Method	Allocation Conceal	Groups similar	Eligibility Defined	Outcomes Defined				
Complementary Therapy													
Tan, 2009 ²⁶	x	x	229										
Arm A: Olanzipine			121	54 (male)	59.5% male	x		x	x	x	cisplatin, dacarbazine, oxaliplatin, carboplatin, epirubicin, adriamycin	HEC MEC	Lung, breast, colon, lymphoma, and others
Arm B: Azasetron			108	54.5 (male)	60.2% male								
Ginger													
Ryan 2009 ²⁸			644	53	10% male				x				66% breast, 6.5% alimentary, 6.1% lung
Zick 2009 ²⁷	x	x		53.3 - 58.3	24.7% male	x	x	x	x	x	All pts had N/V with previous chemo, all treated with same regimen. 17.5% HEC, 63.2% MEC, 19.3% low emetic risk	all (low- high)	NR
Arm A: ginger 1.0			53										
Arm B: ginger 2.0g			52										
Arm C: placebo			57										
Pillai 2011 ²⁹	x	x	60	ages 16-21: 66.7%		x		x	x	x	Cisplatin and dexamethasone	HEC	Bone sarcoma
Arm A: Placebo			30	ages 16-21: 50%									
Arm B: Ginger			30										
Radiation Therapy													
Wong 2006 ³⁰	x	x		50-51	58-59% male	x	x	x	x	x	XRT to the upper abdomen (between L3- T11), \geq 20Gy, at least 15 fractions	Mod- erate	38% GU, 30% Lymphoma, 28% GYN,
			101										
			103										

SD: standard deviation; HE C: HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; N/V: nausea and vomiting; NR: not reported; XRT: radiation therapy; Gy: gray; GU: genitourinary; GYN: gynecologic

Data Supplement Table 6a. Efficacy Outcomes

Author	Complete Response (CR)		Emetic Episodes		Nausea Control		Rescue Anti-Emetics	
	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)
Highly Emetogenic Chemotherapy								
Herrington¹ 3d Aprep (n=29) vs. 1d Aprep (n=30)	Complete Response 67% vs. 70%, NS 63% vs. 59%, NR Overall: 55.6% vs. 51.9%, NS		No Emesis 96% vs. 100%, p= 1.00 d2-5: 93% vs. 93%, p= 1.00 Overall: 92.9% vs. 92.6%, p= 1.00		Nausea Severity (VAS) 12.6 vs. 8.7, NS d2-5 (each calculated separately): NS		No Rescue Meds 82% vs. 85%, p= 1.00 days 2-5: 56% vs. 70%, p= 0.26	
Yeo² Aprep vs. Placebo, (both n=62)	Complete Protection (no vomiting or rescue meds, only mild nausea): 38% vs. 42%, NS Total Control: 26% vs. 31%, NS		No Emesis: 55% vs. 50%, NS CR (no vomiting or rescue meds): 47% vs. 42%, NS Vomiting Domain (FLIE): 3.40 vs. 23.99, p< 0.01, favors aprepitant		No significant Nausea: 66% vs. 63%, NS Nausea Domain (FLIE): 26.7 vs. 31.75, NS		No Rescue Meds: 82% vs. 68%, NS Note: acute, delayed reported for all outcomes, none significant	
Hoshi³ Aprep 125 (n=146) vs. Aprep 40 (n=144) vs. pla (n=150)	Complete Response- Overall 70.5% vs. 67% vs. 50%, p< 0.01 (high vs. placebo) Complete Protection – Overall Aprep 125 mg vs. Pla, p< 0.01		No Emesis- Overall Aprep 125mg vs. Placebo, p< 0.001 Aprep 40 mg vs. Placebo, p< 0.001		No Significant Nausea Aprep 125 mg vs. Placebo, p< 0.05			
Grunberg⁴ Fosaprep (n=1,109) vs. Aprepitant (n=1,138)	Complete Response Delayed: 74% vs. 74%, Difference: 0.1% (95% CI, -3.5 to 3.7) Overall: 72% vs. 72%, Difference: -0.4% (95%CI, -4.1 to 3.3)		No Emesis- Overall 73% vs 75%, Difference -1.7% (95% CI, -5.3,3.2)		Nausea, Rate 7% vs. 6%			
Navari⁵ Olan (n=31) vs Aprep (n=30)	Complete Response 100% vs. 90% 77% vs. 73% Overall: 77% vs. 73%, p>0.05				No Nausea 90% vs. 87%, p> 0.05 68% vs. 37%, p< 0.01 68% vs. 37%, p<0.01			
Navari unpublished Olan (n=61) vs Aprep (n=60)	Complete Response 97% vs. 87% 77% vs. 73% Overall: 77% vs. 73%, p>0.05				No Nausea 87% vs. 87%, p > 0.05 69% vs. 38% p< 0.01 Overall: 69% vs. 38%, p< 0.01			

d: day; Aprep: aprepitant; n: number of patients; NS: not significant; NR: not reported; d: day; VAS: visual analog scale; FLIE: Function Living Index-Emesis; pla: placebo; fosaprep: fosaprepitant; CI: confidence interval; Olan: Olanzapine

Data Supplement Table 6b. Efficacy Outcomes

Author	Complete Response		Emetic Episodes		Nausea Control		Rescue Anti-Emetics	
	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)
Moderately Emetogenic Chemotherapy								
Rapoport⁶ Aprep vs. Placebo	Complete Response 89.2% vs. 80.3%, p (nom) < 0.001 70.8% vs. 60.9%, p (nom) < 0.01 Overall: 68.7% vs. 56.3%, p< 0.001		No Vomiting 92.0% vs. 83.7%, p (nom) < 0.001 77.9% vs. 66.8%, p (nom) < 0.001 Overall: 76.2% vs. 62.1%, p< 0.001		No Significant Nausea- VAS Score: 73.6% vs. 66.4%, p< 0.05		Time to First Emesis p (nominal)< 0.001, favors aprepitant	
AC Pts only Aprep (n=199), PLA (n=204)	84.3% vs. 72.5%, p< 0.05 64.8% vs. 52.9%, p< 0.05 Overall: 62.8% vs. 47.1%, p< 0.05		86.9% vs. 76.0%, p< 0.05 70.4% vs. 59.8%, p< 0.05 Overall: 68.3% vs. 52.9%, p< 0.05					
Non-AC pts Aprep (n= 226) PLA (n= 203)	93.4% vs. 88.1%, NS 76.1% vs. 69.0%, NS Overall: 73.9% vs. 65.5%, NS		96.5% vs. 91.6%, p< 0.05 84.5% vs. 73.9%, p< 0.05 Overall: 83.2% vs. 71.3%, p< 0.05					
Aapro⁷ 1d dex (n=151) vs. 3d dex (n=149)	Complete Response- Overall 53.6% vs. 53.7%, (95% CI: -11.7, +11.6)*		No Emesis- Overall 71.5% vs. 72%, NS		No Nausea- Overall NS No Nausea- Acute 47.0% vs. 49.7%, NS		FLIE QOL- Overall Nausea 48.7% vs. 50.3%, NS FLIE QOL- Overall Vomiting 56.5% vs. 55.7%, NS	
Celio⁸ 1d dex vs. 3d dex (n=166, both arms)	Complete Response- MEC 69% vs. 72%, NS Complete Response- AC 56% vs. 61%, NS		No Emesis- MEC 84% vs. 90%, NS No Emesis- AC 79% vs. 74%, NS		No Nausea- MEC 59% vs. 64%, NS No Nausea- AC 39% vs. 44%, NS			
5-HT₃ Antagonist Equivalency (continued on subsequent page)								
Yu¹⁰ Palo(n=104) vs. gran (n=104)	Complete Response 82.69% vs. 72.1%, p = 0.0682 Days 2- 5: NS							

Aprep: aprepitant; nom: nominal; VAS: visual analog scale; AC: anthracycline-cyclophosphamide; pla: placebo; n: number of patients; NS: not significant; dex: dexamethasone; CI: confidence interval; FLIE: Function Living Index-Emesis; QOL: quality of life; d: day; MEC: moderate emetogenic chemotherapy; palo: palonosetron; gran: granisetron

* CR rates favored 3d dex on days 2, 3; statistically significant for day 3 only (p< 0.01);

Data Supplement Table 6c. Efficacy Outcomes

Author	Complete Response		Emetic Episodes		Nausea Control		Rescue Anti-Emetics	
	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)
5-HT₃ Antagonist Equivalency (cont'd)								
Aapro⁹ Palo 0.25 (n=223) vs. palo 0.75 (n=223) vs. ondansetron (n=221)	<i>Complete Response Rate</i> 59.2% vs 65.5% vs. 57.0%, NS 45.3% vs 48.0% vs. 38.9%, NS Overall: 40.8% vs 42.2% vs 33.0%, NS		<i>Pts Emesis Free (subgroup with dex)*</i> 75.3% vs. 71.3% vs. 59.2% ^a 55.3% vs 50.7% vs. 39.5% (p<0.05 palo 0.25 vs. ondansetron)				<i>Time to Treatment Failure</i> 48.2 h vs. 42.2 h vs. 27.4 h, p (log-rank) = 0.032 <i>Use of Rescue Meds (Acute Phase):</i> 19.7% vs. 17.0% vs. 22.6%	
Saito¹¹ Palo (n=555) vs. Gran (n=559)	<i>Complete Response</i> 75.3% vs. 73.3%, p= not done 56.8% vs. 44.5%, p < 0.01 ^b Overall: 51.5% vs. 40.4%, p= 0.0001		<i>No Emetic Episodes</i> 77.5% vs. 76.4%, p=NS 63.2% vs. 54.2%, p= 0.0023 Overall: 57.5% vs. 49.2%, p= 0.0058		<i>No Nausea</i> 58.7% vs. 59.9%, p=NS 37.8% vs. 27.2%, p< 0.001 Overall: 31.9% vs. 25.0%, p< 0.01		<i>Time to Treatment Failure: HR 1.3</i> (1.106 - 1.526), p= NR <i>Time to First Use of Rescue Meds:</i> HR 1.387 (1.141 - 1.685), p=NR	
Palonosetron Dosing (continued on subsequent page)								
Raftopoulos, ASCO 2009 ¹²	<i>Complete Response- Acute</i> RR 1.002 (0.914 – 1.099), p= 0.960 <i>HEC Complete Response- Acute</i> RR 1.075 (0.875 – 1.321), p=0.492 <i>MEC-Only Complete Response- Acute</i> RR 0.985 (0.889 – 1.092) p= 0.774		<i>Heterogeneity (acute)</i> Overall= 0.032, MEC= 0.06, HEC= 0.075 Significant interaction 0.027, random effects model		<i>Complete Response- Delayed</i> RR 1.003 (0.920 – 1.093), p= 0.950 <i>HEC Complete Response- Delayed</i> RR 1.065 (0.909 – 1.248), p= 0.436 <i>MEC Complete Response- Delayed</i> RR 0.978 (0.882 – 1.084) p= 0.667		<i>Heterogeneity (delayed)</i> Overall= 0.52, MEC= 0.25, HEC= 0.81 No significant interaction	
Maemondo, 2009¹³ Palo 0.075 (n=76) vs. 0.25 (n=77) vs. 0.75 (n=78)	<i>Complete Response</i> 77.6% vs. 81.8% vs. 79.5%, p= NS 40.8% vs. 53.2% vs. 56.4%, p= 0.0142 Overall: 38.2% vs. 49.4% vs. 56.4%, p= 0.0108				Dose Response: statistically significant difference between two high groups and 0.075 mg		<i>Time to Treatment Failure</i> 82.0 vs. 117 vs. > 120 hours	

Palo: palonosetron; n: number of patients; ondansetron; NS: Not significant; pts: patients; dex: dexamethasone; h: hour; gran: granisetron; HR: hazard ratio; NR: not reported; RR: relative risk; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy;

* palo 0.25mg n= 150, palo 0.75mg n= 150, ondansetron 32mg n= 147, ^a p< 0.05 for *both comparisons*,

^b analysis stratified by type of chemotherapy, age, and sex

Data Supplement Table 6d. Efficacy Outcomes

	<i>Acute (day 1)</i>	<i>Delayed (d 2-5)</i>	<i>Acute (day 1)</i>	<i>Delayed (d 2-5)</i>	<i>Acute (day 1)</i>	<i>Delayed (d 2-5)</i>	<i>Acute (day 1)</i>	<i>Delayed (d 2-5)</i>
Palonosetron Dosing (continued)								
Segawa, 2009¹⁴ Palo 0.075 (n=67) vs. 0.25 (n=68) vs. 0.75 (n=69) AC/EC pts (n= 26, 27, 27) Non-AC (n= 41, 41, 42)	<i>Complete Response</i>						<i>Time to Treatment Failure</i> > 120 h in all three treatment groups first quartile: 41.8 vs. 44.3 vs. 72.2 hours, p=NS	
	85.1% vs. 82.4% vs. 92.8%	62.7% vs. 66.2% vs. 71.0%					36.2 vs. 55.8 vs. >120 hours	
	Overall: 59.7% vs. 64.7% vs. 69.6%							
	61.5% vs. 63.0% vs. 85.2%	38.5% vs. 48.1% vs. 63.0%						
	Overall: 30.8% vs. 44.4% vs. 59.3%							
	100% vs. 95.1% vs. 97.6%	78.0% vs. 78.0% vs. 76.2%						
	Overall: 78.0% vs. 78.0% vs. 76.2%							
Formulation Equivalency (continued on subsequent page)								
Grunberg 2007¹⁵ palo 0.25mg po (n= 155) vs. 0.50mg po (n= 160) vs. 0.75 mg po (n= 158) vs. 0.25mg IV (n= 162)	<i>Complete Response</i>		<i>No Emesis</i>		<i>No Nausea</i>			
	74% vs. 76% vs. 74% vs. 70%	59% vs. 63% vs. 60% vs. 65%	79% vs. 83% vs. 79% vs. 77%	68% vs. 74% vs. 67% vs. 75%	59% vs. 59% vs. 63% vs. 57%	42% vs. 49% vs. 46% vs. 48%		
	Overall: 54% vs. 59% vs. 53% vs. 59%		Overall: 61% vs. 71% vs. 61% vs. 67%		Overall: 38% vs. 46% vs. 42% vs. 43%			
Pectasides, 2007¹⁶ ODT (n=66) vs. OT (n= 68)	<i>Complete Control (d1-3)</i>		<i>Proportion with No Emesis (d1-3)</i>		<i>Complete Nausea Control</i>		<i>Rescue Meds (d1-3)</i>	
	70% vs. 76%, p=0.28		52% vs. 72%, NR		d1: 39% vs. 50%, NS d2: 42% vs. 42%, NS d3: 45% vs. 54%, NS		20% vs. 9%, NR	

Palo: palonosetron; n= number of patients; AC: adriamycin-cyclophosphamide; EC: epirubicin- cyclophosphamide; pts: patients; h: hour; NS: not significant; po: by mouth; IV: intravenous; ODT: orally disintegrating tablet; OT: standard oral tablet; d: day; NR: not reported

Data Supplement Table 6e. Efficacy Outcomes

Author	Complete Response		Emetic Episodes		Nausea Control		Rescue Anti-Emetics	
	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)
Formulation Equivalency (continued)								
Boccia, 2010 ¹⁷ GTDS (n=284) vs. oral (n=298)	<i>Complete Control (per protocol pop)</i> 60% vs. 65%, diff -4.9% (95% CI: -12.9, +13.1) <i>Complete Response (per protocol pop)</i> 62% vs. 68%, diff -6.6% (95% CI: -14.4, +1.3)		<i>Total Control (per protocol)</i> 56% vs. 59%, diff -3.8 (95% CI: -11.8, +4.3) <i>Complete Control (ITT)</i> 60% vs. 65%, diff -5.8% (95% CI: -13.5, +2.0)				<i>Note: per protocol outcomes favored over ITT for non-inferiority studies</i>	
Multi-day Chemotherapy								
Herrstedt, 2007 ¹⁸ Meto (n=42) vs. placebo (n=40)	<i>Complete Protection</i> d1-5: 42.9% vs. 22.5%; d6-9: 86.2% vs. 64.3%; d1-9: 40.5% vs. 17.5%, p= 0.029				<i>No Nausea</i> d1-5: 26.2% vs. 12.5%; d6-9: 44.8% vs. 39.3%; d1-9: 23.8% vs. 10.0%, p= 0.027		<i>Treatment Failures</i> d1-5: 26.2% vs. 25.0%; d6-9: 0% vs. 10.3%, p= 0.043; d1-9: 26.2% vs. 32.5%, p= 0.031	
High Dose Chemotherapy prior to SCT/ BMT								
Stiff 2009 ¹⁹ Aprep (n=90) vs. placebo (n=89)	<i>Complete Response (no emesis, < gr 3 nausea) – Overall</i> 48.9% vs. 14.6%, p< 0.001 <i>Composite Major Efficacy</i> 97.9% vs. 87.4%, p< 0.001		<i>No Emesis- Overall</i> 73.3% vs. 22.5%, p< 0.001 <i>Composite Failure</i> 0.1% vs. 2.2%, p= 0.001		<i>Average VAS Scores</i> 16.5 vs. 16.9, p= 0.892			
Giralt 2008 ²⁰ Palo 1d (n=24) vs. 2d (n=24) vs. 3d (n=25)	<i>Complete Response</i> <i>Day 0 of chemo</i> 41.7% vs. 66.7% vs. 60%, p=NR	<i>Overall</i> 8.3% vs. 20.8% vs. 20%, p=NR	<i>No Emesis</i> <i>Day 0 of chemo</i> 66.7% vs. 75.0% vs. 76.0%	<i>Overall</i> 41.7% vs. 41.7% vs. 44.0%, p= 0.4347	<i>No Nausea</i> <i>Day 0 of chemo</i> 29.2% vs. 58.3% vs. 44%, p=0.157	<i>Overall</i> 8.3% vs. 29.2% vs. 16%, p=0.253	<i>No Rescue Meds</i> <i>Day 0 of chemo</i> 41.7% vs. 66.7% vs. 60%, p=0.104	<i>Overall</i> 8.3% vs. 33.3% vs. 24.0%, p= 0.099
Walsh, 2004 ²¹ Ondan vs. Gran	<i>Complete Response– NS</i>		<i>CR- 1d n=50 vs n=46; 90% vs. 83%,</i>	<i>CR- 6d n=13 vs n=14; 46% vs. 50%</i>	<i>Nausea Rates</i> NS difference in the degrees of nausea and distress		Overall emesis control was similar between treatment groups 8% vs. 10.9% had treatment failure	

GTDS: granisetron transdermal system; n= number of patients; pop: population; diff: difference; CI: confidence interval; ITT: intent-to-treat; d: day; SCT: stem cell transplant; BMT: bone marrow transplant; gr: grade; VAS: visual analog scale; palo: palonosetron; chemo: chemotherapy; NR: not reported; ondan: ondansetron; gran: granisetron; NS: not statistically significant; CR: complete response;

Data Supplement Table 6f. Efficacy Outcomes

Author	Complete Response		Emetic Episodes		Nausea Control		Rescue Anti-Emetics	
	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)
Pediatrics								
Sepulveda-Vildosola, 2008²² Palo (n=50) vs. Ondan (n=50)	<i>Complete Control</i> D1: 92% vs. 72% D2: 72% vs. 46%, D3: 78% vs. 54%, D4: 88% vs. 84%, D5: 98% vs. 90%, D6: 100% vs. 94%, D7: 100% vs. 96%		<i>Median Emetic Events (Min-Max)</i> D1: 0 (0-2) vs. 0 (0-5), NS D2: 0 (0-5) vs. 1 (0-5), d3: 0 (0-7) vs. 0 (0-6), d4: 0 (0-3) vs. 0 (0-6), d5: 0 (0) vs. 0 (0-5), d6: 0 (0) vs. 0 (0-6), d7: 0 (0) vs. 0 (0-5); all NS		<i>Nausea Absent</i> D 1: 74% vs. 38% D2: 62% vs. 18%, D3: 72% vs. 30%, D4: 88% vs. 58%, D5: 98% vs. 88%, D6: 98% vs. 92%, Day 7: 98% vs. 94%		**Nausea Intensity data collected from self-report questionnaire. Nausea assessment: absent, mild (decrease in oral intake), intense (no oral intake)	
Gore, 2009²³ Aprep (n=28) vs. Ondan (n=18)	<i>Complete Response</i> 60.7% vs. 38.9% 35.7% vs. 5.6% <i>Overall: 28.6% vs. 5.6%</i>		<i>No Nausea (Overall)</i> 44.4% vs. 17.6%		<i>No Vomiting</i> 64.3% vs. 44.4% 39.3% vs. 5.6% <i>Overall: 32.1% vs. 5.6%</i>		<i>No Use of Rescue Meds</i> 71.4% vs. 61.1% 50% vs. 27.8% <i>Overall: 42.9% vs. 22.2%</i>	
Delayed Emesis								
Fabi 2008²⁴ Ondan IM (n=44) vs. Ondan po (n=45)			<i>CR- Vomiting (s/p rescue meds)</i> 31.8% vs. 81.8%, p= 0.01		<i>CR- Nausea (s/p rescue meds)</i> 40.9% vs. 77.3%, p= 0.001		Pts randomized before chemo; tx'ed w/ 2 ondansetron formulations were those who had CINV (50% from IM arm and 48.8% in po arm)	
Formulation Equivalency (continued on subsequent page)								
Lajolo, 2009²⁵ Gran d2,3 (n=36) vs. Placebo d2/Gran d3, d4 (n= 37)	<i>Complete Protection from both N/V</i> D2-5 30% vs. 32%, p=0.5 <i>Only pts with CR, acute phase</i>		<i>Complete Protection- Vomiting, d2-5</i> 69.5% vs. 70.3%, p=0.94 <i>Only pts with CR, acute phase</i>					

Palo: palonosetron; n: number of patients; ondansetron; d: day; min: minimum; max: maximum; NS: not statistically significant; aprep: aprepitant; ondansetron; IM: intramuscular; po: by mouth; CR: complete response; s/p: following; pts: patients; tx'ed: treated; w/: with; CINV: chemotherapy-induced nausea and vomiting; gran: granisetron; N/V: nausea and vomiting

Data Supplement Table 6g. Efficacy Outcomes

Author	Complete Response		Emetic Episodes		Nausea Control		Rescue Anti-Emetics	
	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)	Acute (day 1)	Delayed (d 2-5)
Formulation Equivalency (continued)								
Tan, 2009 ²⁶ Olanzapine (n=121) vs. Placebo (n=108)	No difference		HEC: 91.07% vs. 89.13%, MEC: 96.92% vs. 96.77%	HEC: 78.57 vs. 56.52%, MEC: 89.23% vs. 75.80%	HEC: 94.64% vs. 86.96%, MEC: 98.46% vs. 93.54%	HEC: 69.4% vs. 30% MEC: 78.57% vs. 56.62%		
Ginger								
Ryan ²⁸ Gin 0.5g vs. Gin 1g vs. Gin 1.5g vs. pla (N=644)	No significant effects on vomiting noted				<i>Pt-reported Nausea Scores, Cycle 2:</i> decrease w/ Ginger, p< 0.01	<i>Pt-reported Nausea Scores, Cycle 3:</i> decrease w/ Ginger, p< 0.01		
Zick 2009 ²⁷ Gin 1g (n=53) vs. Gin 2g (n=52) vs. Placebo (n=57)			<i>Vomiting Prevalence</i> No Aprep: 26.4% vs. 27.5% vs. 23.9%, NS Aprep: 11.6% vs. 15% vs. 6.5%		No Aprep: 32.6% vs. 17.5% vs. 52.6%, NS Aprep: 11.6% vs. 12.5% vs. 2.2%	<i>Nausea Prevalence</i> No Aprep: 48.8% vs. 50% vs. 50%, NS Aprep: 27.9% vs. 25% vs. 17.4%		<i>Higher score= more severe delayed nausea</i> All pts: 2.9 ± 1.1 vs. 3.4 ± 1.1 vs. 2.8 ± 1.2, p=0.03
Pillai, 2011 ²⁹ Placebo (n= 30) vs. Ginger (n= 27)			<i>Days 1-4</i> None: 3.3% vs. 14.8%, Severe: 43.3% vs. 11.1%	<i>Days 5-9</i> None: 10% vs. 33.3%, Severe: 20% vs. 3.7%	<i>Days 1-4</i> Mild: 6.7% vs. 44.4%, Severe: 73.3% vs. 14.8%	<i>Days 5-9</i> None: 0% vs. 22.2% Severe: 40% vs. 11.1%		
Radiation Therapy								
Wong, 2006 ³⁰ Ondan + Dex (n=101) vs. Ondan (n=103)			<i>Complete Emesis Control</i> <i>Fractions 1-5</i> 78% vs. 71%, p= 0.14		<i>Fractions 1-15</i> 23% vs. 12%, p= 0.02	<i>Complete Nausea Control</i> <i>Fractions 1-5</i> 50% vs. 38%, p= 0.06		<i>Fractions 1-15</i> 15% vs. 9%, p=0.14
							<i>No Rescue Meds</i> <i>Fractions 1-5</i> 91% vs. 88%, p=0.2	
							<i>Fractions 1-15</i> 30% vs. 21%, p=0.09	

N: number of patients; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; Gin: ginger; pla: placebo; w/: with; Aprep: Aprepitant; NS: not statistically significant; Ondan: Ondansetron; Dex: Dexamethasone;

Data Supplement Table 7a. Adverse Events

Author	Constipation	Diarrhea	Headache	Other Adverse Events
Highly Emetogenic Chemotherapy (HEC)				
Herrington, 2008¹	AEs not reported			
Yeo, 2009² (aprepitant vs. placebo)	11.3% vs. 22.6%, p= 0.09	16.3% vs. 9.7%, p= 0.28	3.2% vs. 4.8%, p= 0.65	<i>Fatigue: 25.8% vs. 21.0%, p= 0.52</i> <i>Anorexia: 16.1% vs. 21.0%, p= 0.49</i>
Hoshi (aprepitant 125 vs. aprepitant 40 vs. placebo)	2.0% vs. 2.7% vs. 4.0%	2.0% vs. 2.7% vs. 0.7%	1.3% vs. 1.4% vs. 0.7%	<i>Somnolence: 1.3% vs. 0.7% vs. 0%</i> <i>Increased ALT: 4.0% vs. 7.5% vs. 2.0%</i>
Grunberg 2011⁴ (fosaprepitant vs. aprepitant)	10.6% vs 9.6%	7.8% vs 8.7%	NR	<i>Anorexia 6.6% vs 9.1%</i> <i>Infusion site pain 1.4% vs 0.1%</i>
Navari , 2010⁵ (olanzapine vs. aprepitant)	NR	NR	NR	<i>No Grade 3 or 4 toxicities</i>
Navari, 2010 (manuscript) (olanzapine vs. aprepitant)	No Grade 3 or 4 toxicities			
Moderately Emetogenic Chemotherapy				
Rapoport, 2010⁶ (aprepitant vs. placebo)	8.6% vs. 13.4%	9.8% vs. 11.2%	10.0% vs. 12.2%	<i>Fatigue: 10.9% vs. 9.8%</i> <i>Anorexia: 8.1% vs. 8.9%</i>
Aapro 2006⁹				
Celio 2010⁸ (1d dexamethasone vs. 3d dexamethasone)				
5-HT₃ Antagonist Equivalency				
Aapro 2006⁹ (palonosetron 0.25 vs. palonosetron 0.75 vs. ondansetron)	4.4% vs. 7.6% vs. 2.2%	1.3% vs. 0.4% vs. 2.2%	8.0% vs. 12.4% vs. 10.8%	
Yu, 2009¹⁰ (palonosetron vs. granisetron)	0.96% both groups		0.96% both groups	<i>Hypokalemia: 1.92% vs. 0.96%</i>
Saito, 2009¹¹ (palonosetron vs. granisetron)	17.4% vs. 15.7%		3.2% vs. 3.8%	<i>Increased ALT: 4.4% vs. 6.0%</i> <i>Increased Bilirubin: 1.8% vs. 3.2%</i>
Palonosetron Dosing				
Raftopoulos 2009¹²				
Maemondo, 2009¹³ (palonosetron 0.075 vs. 0.25 vs. 0.75)	6.6% vs. 11.7% vs. 14.1%	1.3%, all groups	3.9% vs. 6.5% vs. 2.6%	<i>Cold Sweat: 0 vs. 2.6% vs. 0</i> <i>Rash: 1.3% vs. 1.3% vs. 2.6%</i>
Segawa, 2009¹⁴ (palonosetron 0.075 vs. 0.25 vs. 0.75)	12.0% vs. 7.3% vs. 10.1%		4.5% vs. 4.4% vs. 4.3%	<i>Increased ALT: 6.0% vs. 2.9% vs. 2.9%</i> <i>Increased Bili: 3.0% vs. 4.4% vs. 2.9%</i> <i>Rash: 3.0% vs. 8.8% vs. 0</i>

AEs: adverse events; ALT: alanine aminotransferase; NR: Not reported

Data Supplement Table 7b. Adverse Events

Author	Constipation	Diarrhea	Headache	Other Adverse Events
Formulation Equivalency				
Grunberg 2007 ¹⁵ (palonosetron 0.25 mg po vs. 0.40 mg po vs. 0.75 mg po vs. 0.25 mg IV)	0.6% vs. 0.6% vs. 3.2% vs. 3.1%		3.8% vs. 3.7% vs. 3.8% vs. 8.6%	
Pectasides, 2007 ¹⁶ (ondansetron ODT vs. ondansetron OT)	3% vs. 6%		4.5% vs. 4%	
Boccia 2010 ¹⁷ (GTDS vs. granisetron po)	7% vs. 3%		2.5% vs. 0.3%	15 deaths, 1 related to study (toxic megacolon)
Multi-day Chemotherapy				
Herrstedt 2007 ¹⁸ (metopimazine vs. placebo)	11.9% vs. 13.5%	NR	38.1% vs. 32.5%	<i>Dizziness: 11.9% vs. 7.5%</i> <i>Tiredness: 4.8% vs. 5%</i>
High Dose Chemotherapy prior to SCT/ BMT				
Stiff, ASH 2009 ¹⁹ (aprepitant vs. placebo)	28% vs. 21%	59% vs. 52%	44% vs. 46%	<i>Fatigue 37% vs. 34%</i> <i>Fever 22% vs. 19%</i> <i>Heartburn 12% vs. 6%</i> <i>Weakness 6% vs. 1%</i>
Giralt, 2008 ²⁰ (palonosetron 1d vs. 2d vs. 3d)	12.5% vs. 16.7% vs. 8.0%	0 vs. 25% vs. 24%	4.2% vs. 16.7% vs. 12.0%	<i>Insomnia: 4.2% vs. 12.5% vs. 8.0%</i>
Walsh, 2004 ²¹	4% vs. 2% P =1.00	12% vs. 8.7 % P=0.596	10% vs. 2 % P=0.206	<i>Most common adverse event was hiccups 34% vs 26% P=0.399</i>
Pediatrics				
Sepulveda-Vildosola, 2008 ²² (palonosetron vs. ondansetron)	None Reported			
Gore, 2009 ²³ (palonosetron vs. ondansetron)				<i>Hypokalemia: 3.1% vs. 11.1%</i>
Delayed Emesis				
Fabi, 2008 ²⁴ (ondansetron IM vs. ondansetron po)	4.5% vs. 4.5%		4.5% vs. 4.5%	<i>Hypertransaminasemia: 4.% per arm</i> <i>Gastritis: 0 vs. 4.5%</i> <i>Skin reaction: 4.5% vs. 0</i>
Lajolo, 2009 ²⁵ (granisetron vs. placebo)	N= 8 vs. n= 9	N= 4 vs. n= 7	N= 24 vs. n= 20	<i>Rash: n= 4 vs. n= 0</i> <i>Insomnia: n= 8 vs. n= 13</i>

po: by mouth; IV: intravenous; ODT: orally disintegrating tablet; OT: oral formulation; GTDS: granisetron transdermal delivery system; NR: not reported; d: day; IM: intramuscular

Data Supplement Table 7c. Adverse Events

Author	Constipation	Diarrhea	Headache	Other Adverse Events
Complementary Data				
Tan, 2009 ²⁶	NR	NR	NR	Common AEs included fatigue, headache, dry mouth, diarrhea; but no grade 3 or 4 toxicities
Ginger				
Ryan, 2009 ²⁸ (ginger vs. placebo)				
Zick, 2009 ²⁷ (ginger 1.0g vs. 2.0g vs. placebo)				<i>Fatigue: 5 vs. 1 vs. 0, p= 0.03</i>
Pillai 2011 ²⁹	Well-tolerated, no significant adverse effects with either ginger powder or placebo.			
Radiation Therapy				
Wong, 2006 ³⁰ (dexamethasone vs. placebo)	27% vs. 20%		18% vs. 12%	<i>Dyspepsia: 16% vs. 17%</i> <i>Fatigue: 11% vs. 12%</i>

AEs: adverse events

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