ATTUALITÀ NEL CONTROLLO DELL'EMESI

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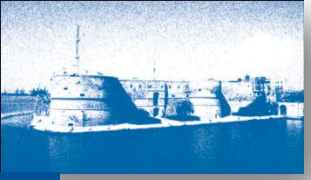
Types of CINV: Definitions

- Acute (post-treatment)
  - Occurs within first 24 hours after administration of cancer chemotherapy
- Delayed
  - CINV that begins after first 24 hours
  - May last for 120 hours
- Anticipatory
  - Learned or conditioned response from poorly controlled nausea and vomiting associated with previous chemotherapy



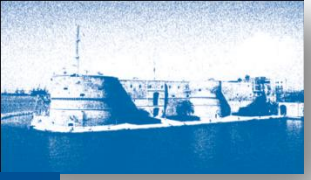
Risk Factors for CINV

Treatment-related Risk Factors

- Specific chemotherapeutic agents used
- Dosage of the agents
- Schedule and route of administration of the agents
- Target of the radiation therapy

Patients-specific Risk Factors

- Age <50 years
- Women > men
- History of light alcohol use
- History of vomiting with prior exposure to chemotherapeutic agents
- Other risks
  - History of motion sickness
  - History of nausea or vomiting during pregnancy
  - History of anxiety



Emetogenic Potential of Single Antineoplastic Agents

HIGH	**Risk in nearly all patients (> 90%)**
MODERATE	**Risk in 30% to 90% of patients**
LOW	**Risk in 10% to 30% of patients**
MINIMAL	**Fewer than 10% at risk**

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2012
Antiemesis

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Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT
High emetic risk (>90 % frequency of emesis)[q,r]	• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide[q] • Carmustine >250 mg/m^2 • Cisplatin ≥50 mg/m^2 • Cyclophosphamide >1,500 mg/m^2 • Dacarbazine • Doxorubicin >60 mg/m^2 • Epirubicin >90 mg/m^2 • Ifosfamide ≥10 g/m^2 • Mechlorethamine • Streptozocin
Moderate emetic risk (30% - 90% frequency of emesis)[q,s]	• Aldesleukin > 12-15 million international units/m^2 • Amifostine > 300 mg/m^2 • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin[s] • Carmustine[s] ≤250 mg/m^2 • Cisplatin[s] <50 mg/m^2 • Clofarabine • Cyclophosphamide ≤1500 mg/m^2 • Cytarabine >200 mg/m^2 • Dactinomycin[s] • Daunorubicin[s] • Doxorubicin[s] ≤60 mg/m^2 • Epirubicin[s] ≤90 mg/m^2 • Idarubicin • Ifosfamide[s] <10 g/m^2 • Interferon alfa ≥10 million international units/m^2 • Irinotecan[s] • Melphalan • Methotrexate[s] ≥ 250 mg/m^2 • Oxaliplatin • Temozolomide

Low Emetic Risk (See AE-8)
Minimal Emetic Risk (See AE-8)
Oral Chemotherapy (See AE-9)

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15: 103-109
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer. 2010 Oct 24. [Epub ahead of print].

[q]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[r]Continuous infusion may make this agent less emetogenic.
[s]These agents may be highly emetogenic in certain patients.
[t]Potential drug interactions between antineoplastic agents / antiemetic therapies and various other drugs should always be considered.

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Antiemesis

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EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT		
Low emetic risk (10% - 30% frequency of emesis)[q]	• Amifostine ≤300 mg • Aldesleukin ≤12 million international units/m^2 • Cabazitaxel Cytarabine (low dose) 100-200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil • Floxuridine • Gemcitabine • Interferon alfa >5 <10 million international units/m^2 • Ixabepilone	• Methotrexate >50 mg/m^2 <250 mg/m^2 • Mitomycin • Mitoxantrone • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Thiotepa • Topotecan	
Minimal emetic risk (<10% frequency of emesis)[q]	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine <100 mg/m^2 • Decitabine • Denileukin diftitox • Dexrazoxane • Fludarabine • Interferon alpha ≤5 million international units/m^2 • Ipilimumab	• Methotrexate ≤50 mg/m^2 • Nelarabine • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Rituximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vinorelbine	High Emetic Risk (See AE-7) Moderate Emetic Risk (See AE-7) Oral Chemotherapy (See AE-9)

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15: 103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer. 2010 Oct 24. [Epub ahead of print].

[q]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

[t]Potential drug interactions between antineoplastic agents / antiemetic therapies and various other drugs should always be considered.

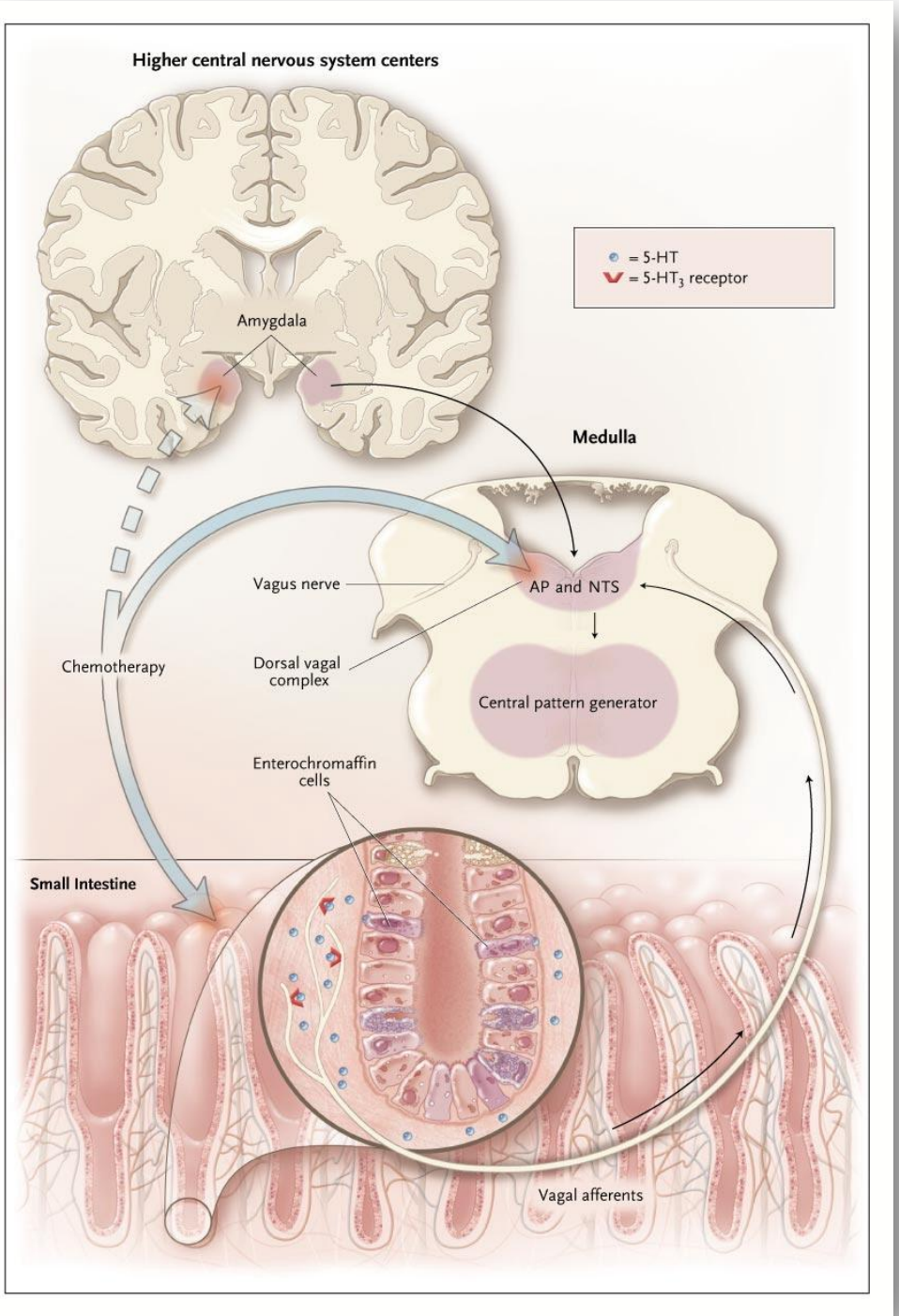
EMETOGENIC POTENTIAL OF ORAL ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT
Moderate to High	• Altretamine • Busulfan (≥4 mg/day) • Cyclophosphamide (≥100 mg/m^2/day) • Estramustine • Etoposide • Lomustine (single day) • Procarbazine • Temozolomide (>75 mg/m^2/day)
Minimal to Low	• Bexarotene • Busulfan (<4 mg/day) • Capecitabine • Chlorambucil • Cyclophosphamide (<100 mg/m^2/day) • Dasatinib • Erlotinib • Everolimus • Fludarabine • Gefitinib • Hydroxyurea • Imatinib • Lapatinib • Lenalidomide • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Pazopanib • Sorafenib • Sunitinib • Temozolomide (≤75 mg/m^2/day) • Thalidomide • Thioguanine • Topotecan • Tretinoin • Vandetanib • Vorinostat

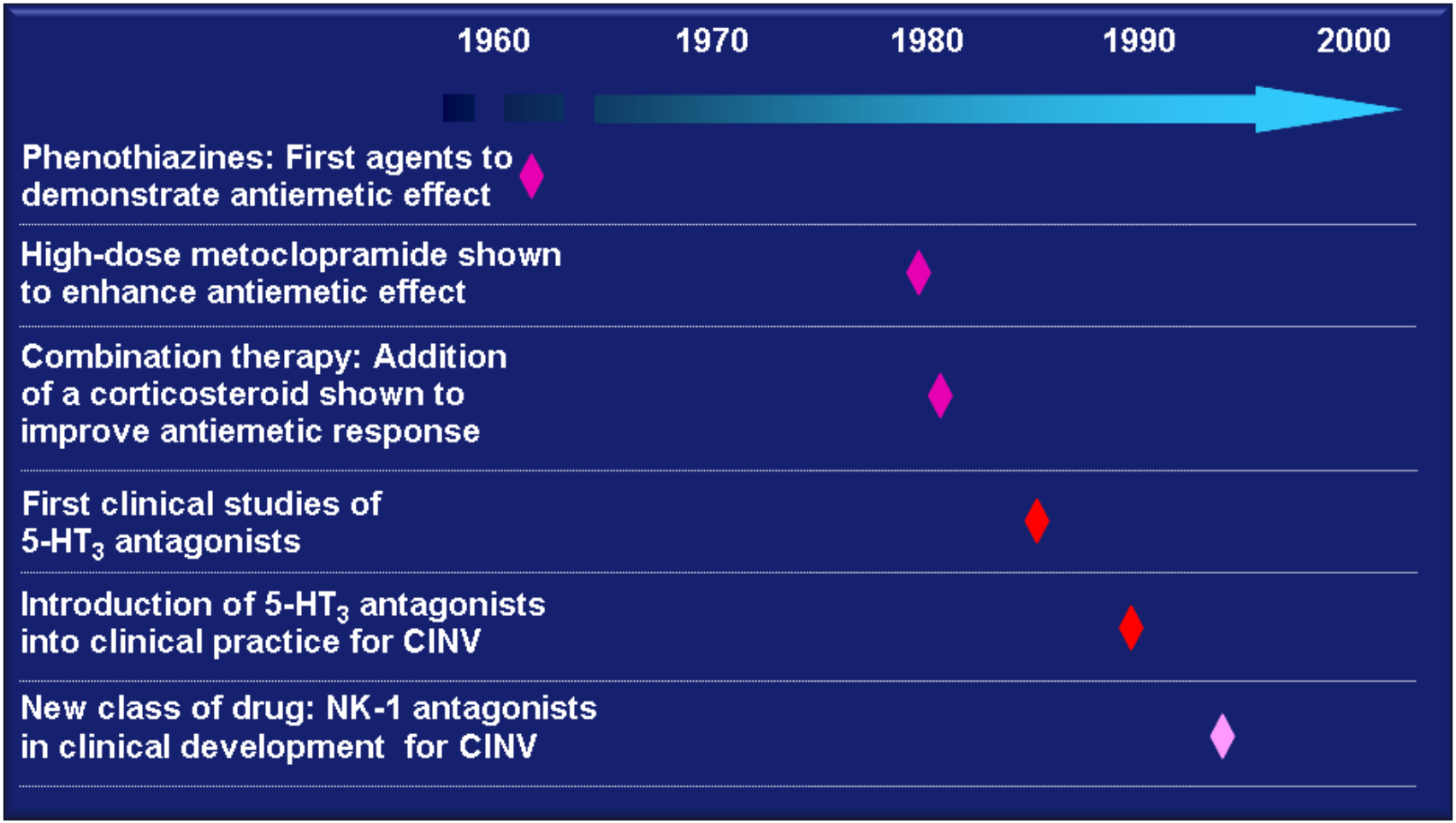
High Emetic Risk (See AE-7)
Moderate Emetic Risk (See AE-7)
Low Emetic Risk (See AE-8)
Minimal Emetic Risk (See AE-8)

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15: 103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer. 2010 Oct 24. [Epub ahead of print].

Pathways by Which Chemotherapeutic Agents May Produce an Emetic Response.



Chemotherapy-Induced Emesis: Key Treatment Milestones



Palonosetron July, 2003

Aprepitant, March 2003

Pharmacologic Agents

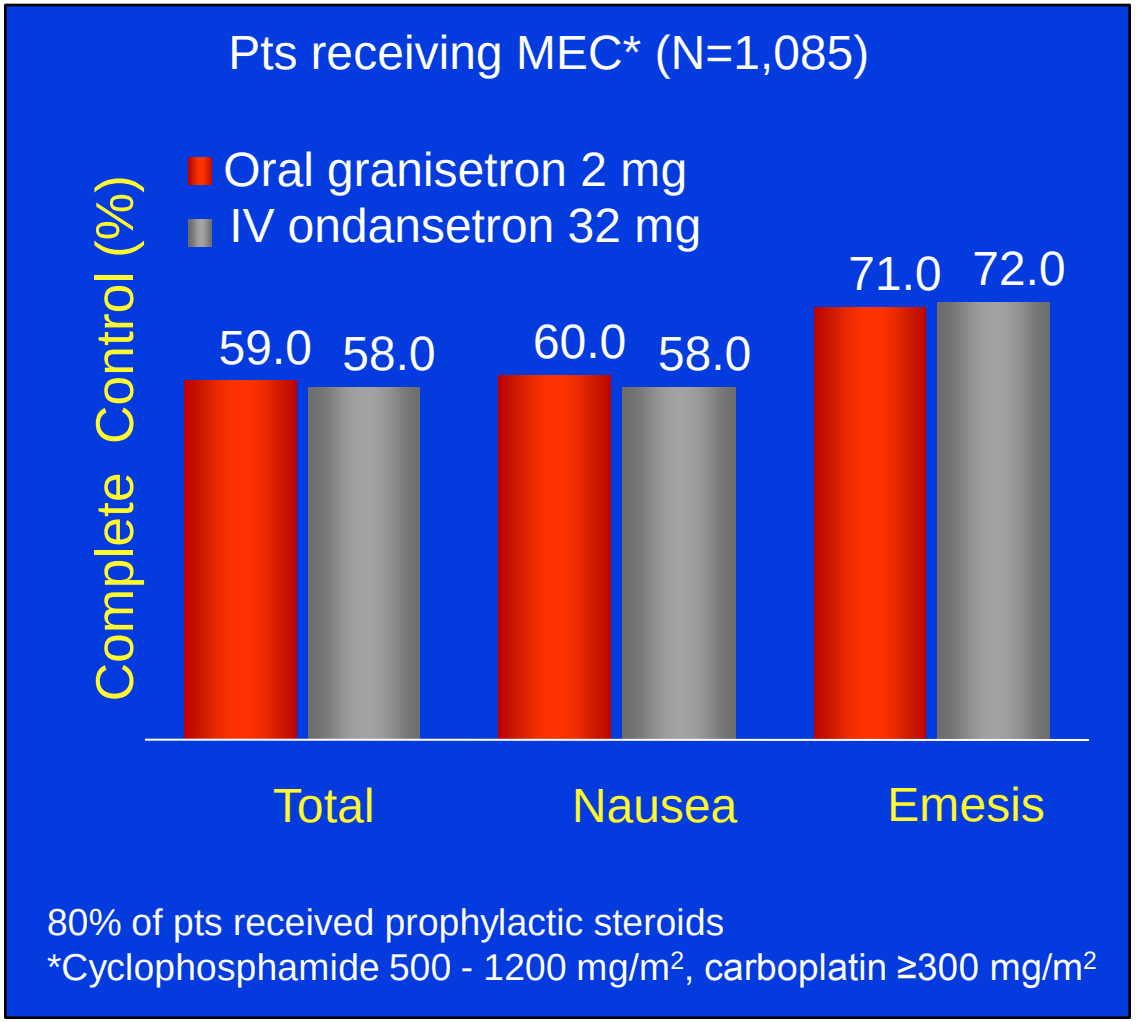
- Corticosteroids
- Dopamine antagonists
- Serotonin (5-HT3) antagonists
- NK-1 receptor antagonists
- Cannabinoids

1st Generation $5HT_3$ Receptors Antagonost Dose and Schedules

Drug	Dose	
	Before Chemotherapy (day 1)	**After Chemotherapy**
Dolasetron (Anzemet®)	Intravenous dose: 100 mg or 1.8mg/kg of body weight; oral dose: 100 mg	Oral dose: 100 mg on days 2 and 3 for MEC with potential for delayed emesis
Granisetron (Kytril®)	Intravenous dose: 1 mg or 0.01 mg/kg; oral dose: 2 mg	Oral dose: 1 mg twice daily on days 2 and 3 for MEC with potential for delayed emesis
Ondansetron (Zofran®)	Intravenous dose: 8 mg or 0.15 mg/kg; oral dose: 24 mg for HEC, 8 mg twice daily for MEC	Oral dose: 8 mg twice daily on days 2 and 3 for MEC with potential for delayed emesis
Tropisetron (Navoban®)	Intravenous dose: 5 mg; oral dose: 5 mg	Oral dose: 5 mg on days 2 and 3 for MEC with potential for delayed emesis

1st Generation $5HT_3$ RAs are Therapeutically Equivalent

- 1st Generation Agents are Therapeutically Equivalent
  - Dolasetron
  - Ondansetron
  - Granisetron
- 1st Generation oral and IV doses equally effective
- Complete control CINV
  - HEC: 50-70%
  - MEC: 70-80%



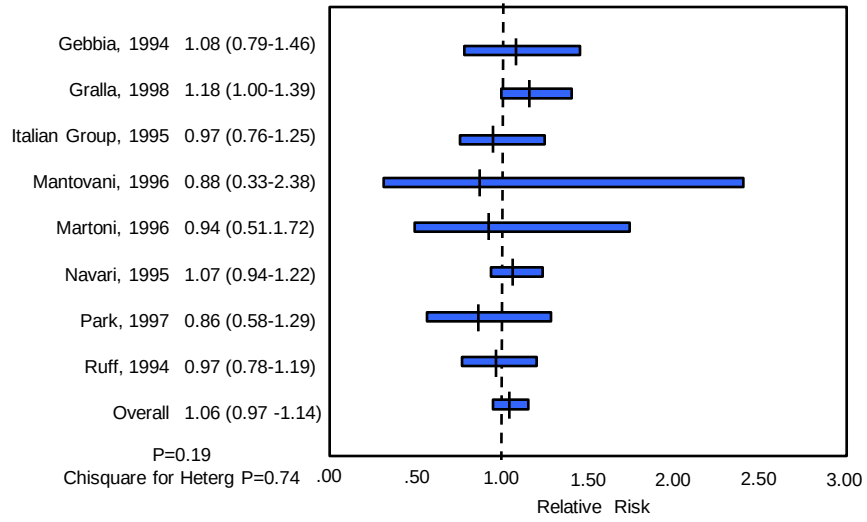
Perez et al. J Clin Oncol 1998;16:754

Granisetron Is Equivalent to Ondansetron for Prophylaxis of Chemotherapy-Induced Nausea and Vomiting

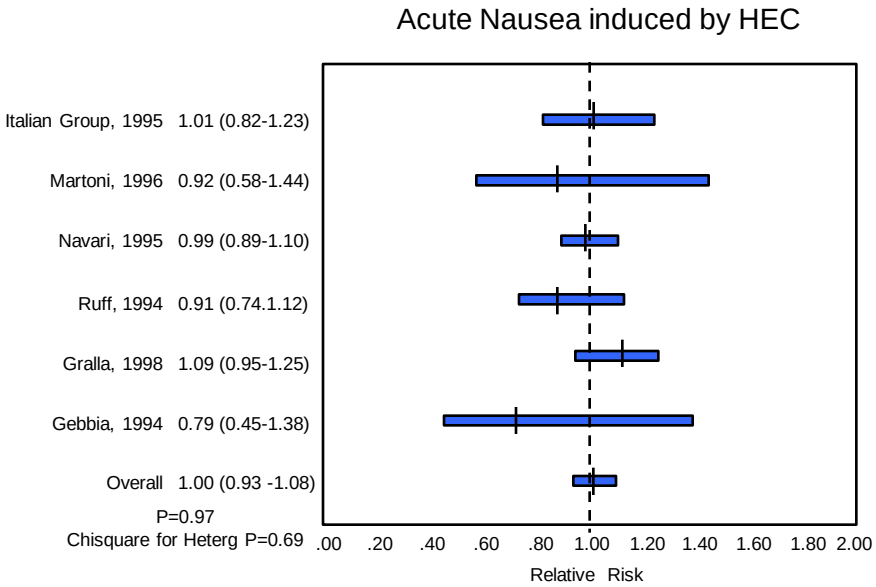
Results of a Meta-Analysis of Randomized Controlled Trials

Del Giglio A. *et al.;*
Cancer 2000
89: 2301-8

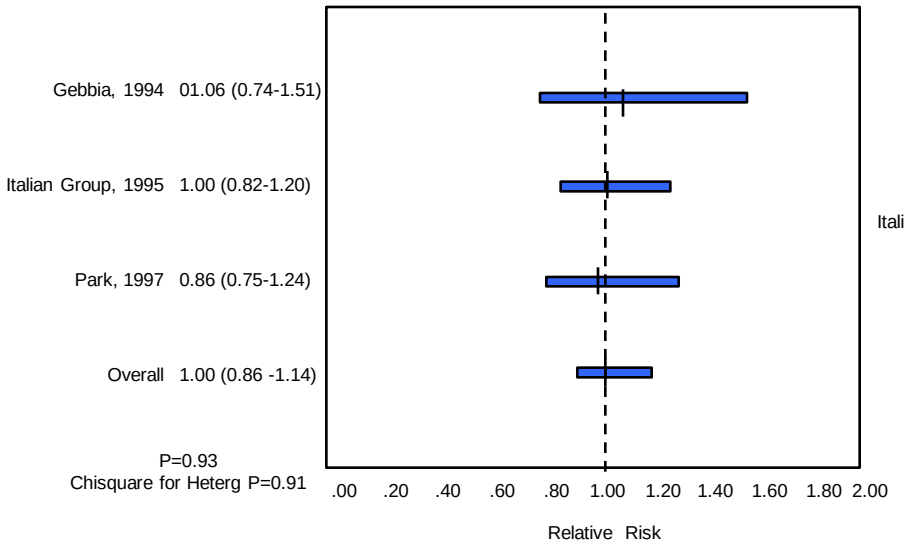
Acute Vomiting induced by HEC



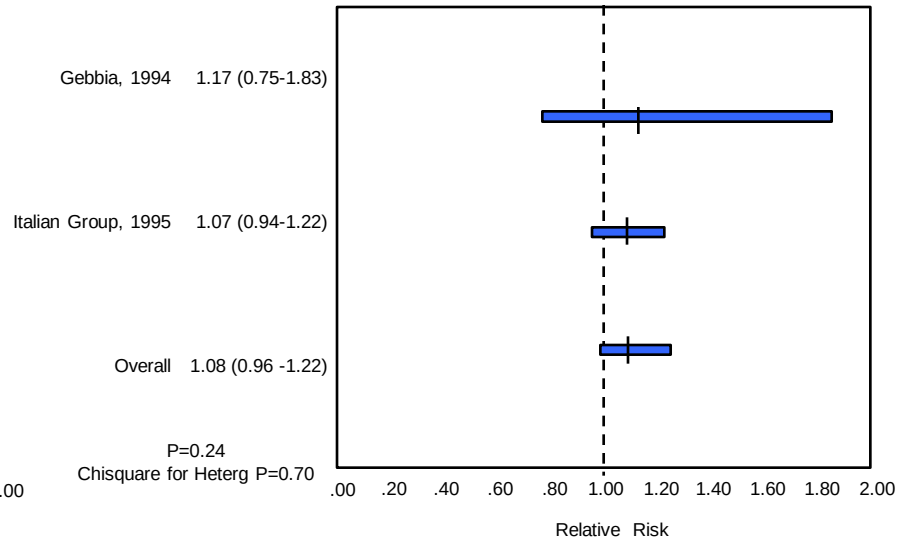
Acute Nausea induced by HEC

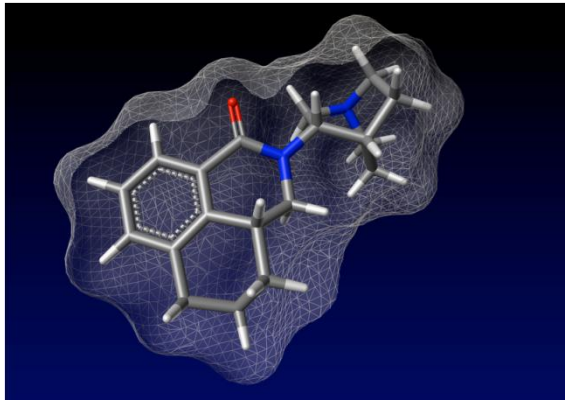


Delayed Vomiting induced by HEC



Delayed Nausea induced by HEC



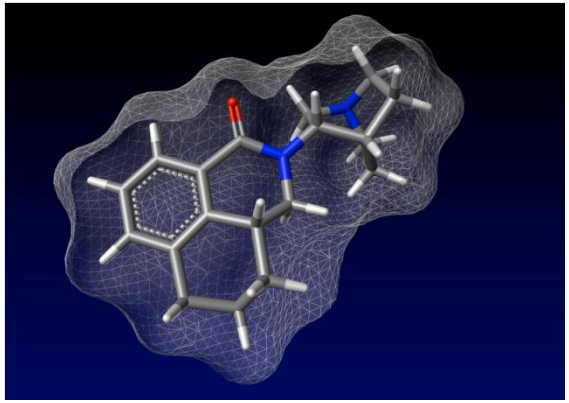


Palonosetron (Aloxi®)

- Second generation 5-HT_3 antagonist

- Pharmacologic differences from older 5-HT_3 antagonists
  - prolonged half-life (~40 hours)
  - enhanced receptor binding affinity (~100-fold)

- FDA approved
  - IV formulation July 25, 2003
- Regimens
  - IV 0.25 mg pre chemotherapy acute/delayed HEC/MEC

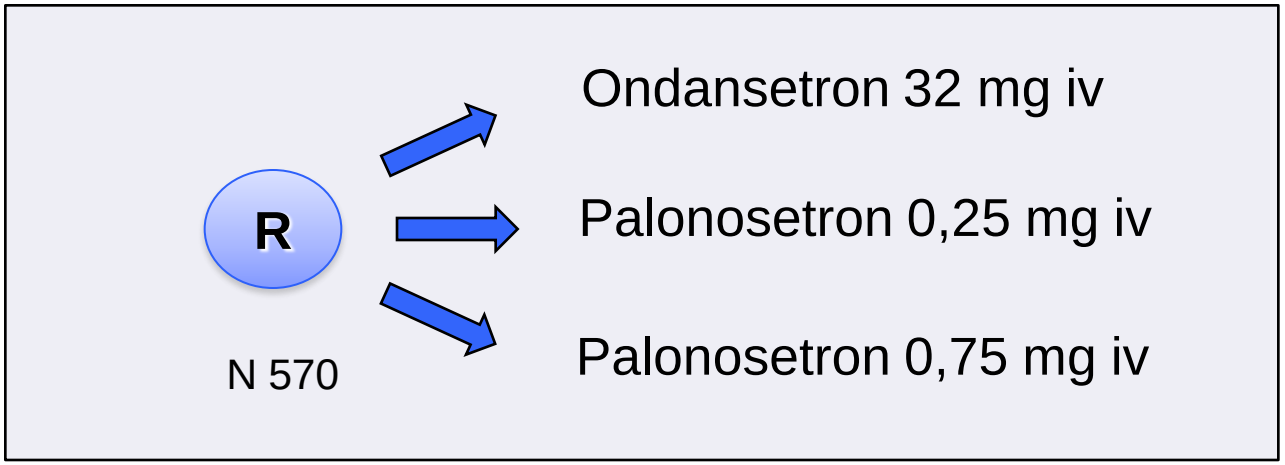


Palonosetron Phase III Trial

- Moderately emetogenic trials (MEC)
  - PALO 99-03 (vs ondansetron); N=563
  - PALO 99-04 (vs dolasetron); N = 569
- Highly emetogenic trials (HEC)
  - PALO 99-05 (vs ondansetron); N = 667

Palonosetron and MEC

PALO 99-03
Moderate Emetogenic Chemotherapy



Non Inferiority Trial

No Corticosteroids

Gralla R. et al.; Ann Oncol 2003 (14): 1570–1577,

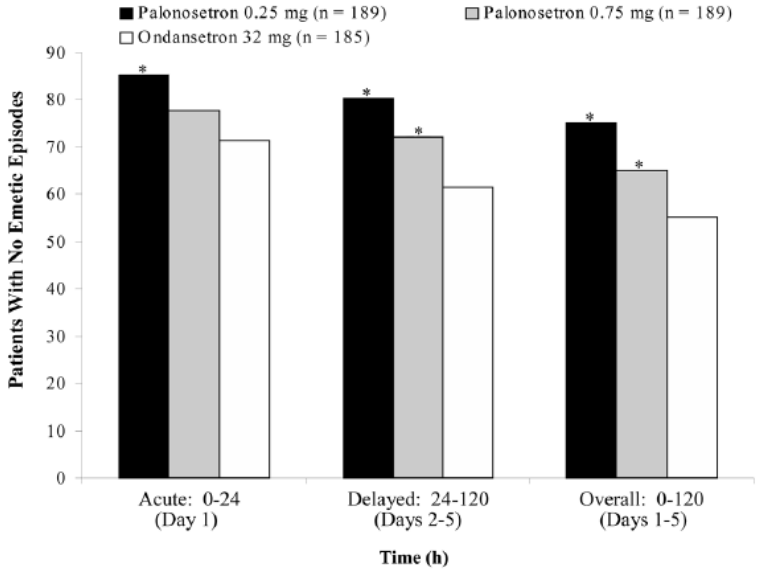
Palonosetron and MEC

PALO 99-03 Trials

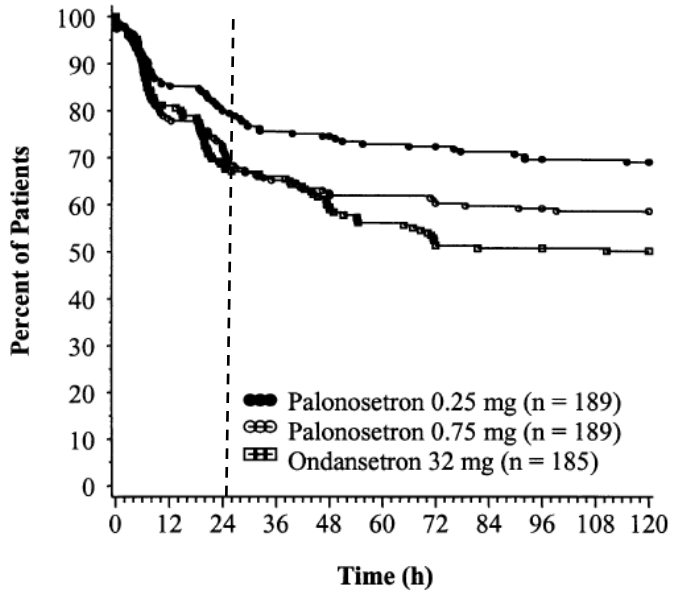
Complete Response Rates in ITT Cohorts

	PALO 0.25 mg (n=189)	PALO 0.75 mg (n=189)	OND 32mg (n=185)
Acute (0-24 h)	81%*	73.5%	68.6%
Delayed (24-120 h)	74.1%*	64.6%	55.1%
Overall (0-120 h)	69.3%*	58.7%	46.0%

* *P* ≤.025 for paolonsetron versus ondansetron (Fisher's exacr test)



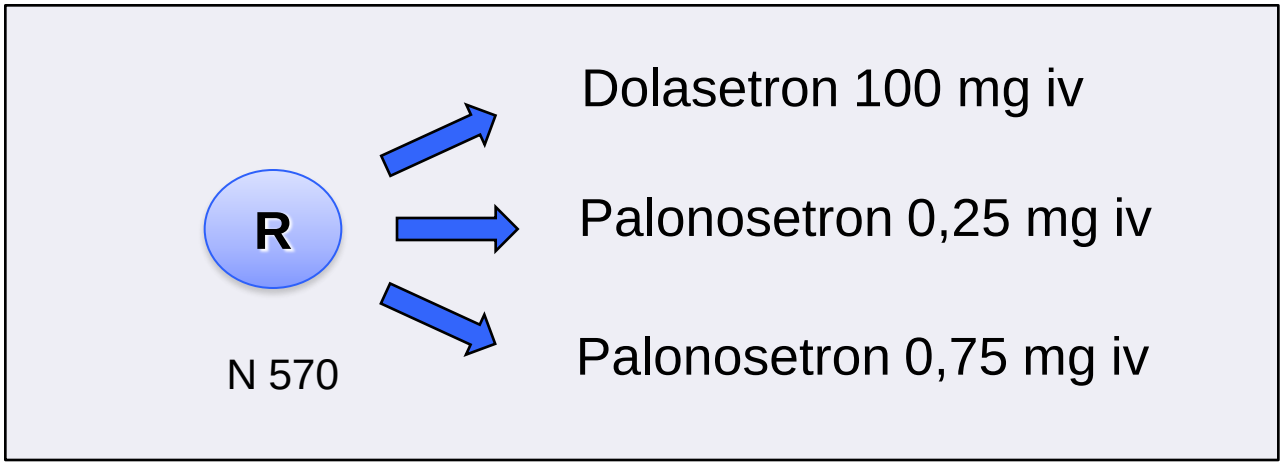
P ≤0.05 for palonosetron *vs* ondansetron



Gralla R. et al.; Ann Oncol 2003 (14): 1570–1577,

Palonosetron and MEC

PALO 99-04
Moderate Emetogenic Chemotherapy



Non- Inferiority Trial

Corticosteroids administrated in 5% of patients (by a late protocol amendment)

Elsenberg P. et al.; Cancer 2003 (98): 2473–2482

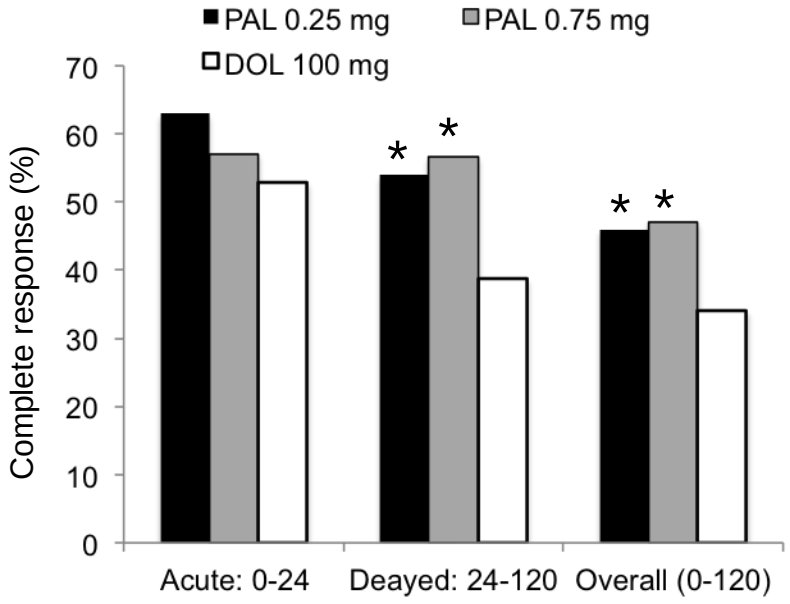
Palonosetron and MEC

PALO 99-04 Trials

Complete Response Rates in ITT Cohorts

	PALO 0.25 mg (n=189)	PALO 0.75 mg (n=189)	OND 32mg (n=185)
Acute (0-24 h)	63%	57%	52.9%
Delayed (24-120 h)	54%*	56.6%°	38.7%
Overall (0-120 h)	46%*	47.1%*	34%

* *P* ≤.025 for paolonsetron versus ondansetron (Fisher's exacr test)

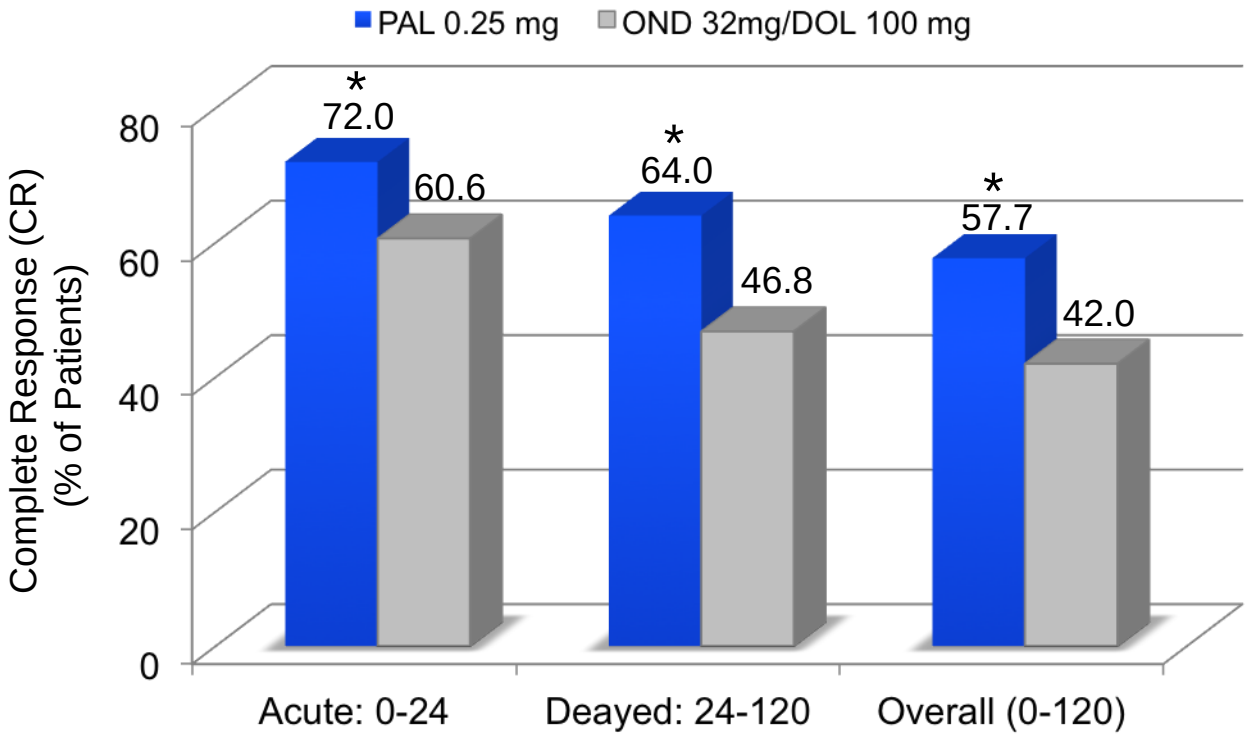


*P ≤0.25 for palonosetron *vs* ondansetron

Elsenberg P. et al.; Cancer 2003 (98): 2473–2482

Palonosetron and MEC

Pooled results from studies 99-03 and 99-04



CR = no emetic episodes or use of rescue medications

*p<0.025 for pairwise difference (2-sided Fisher's exact test) between palonosetron and ondansetron/dolasetron.

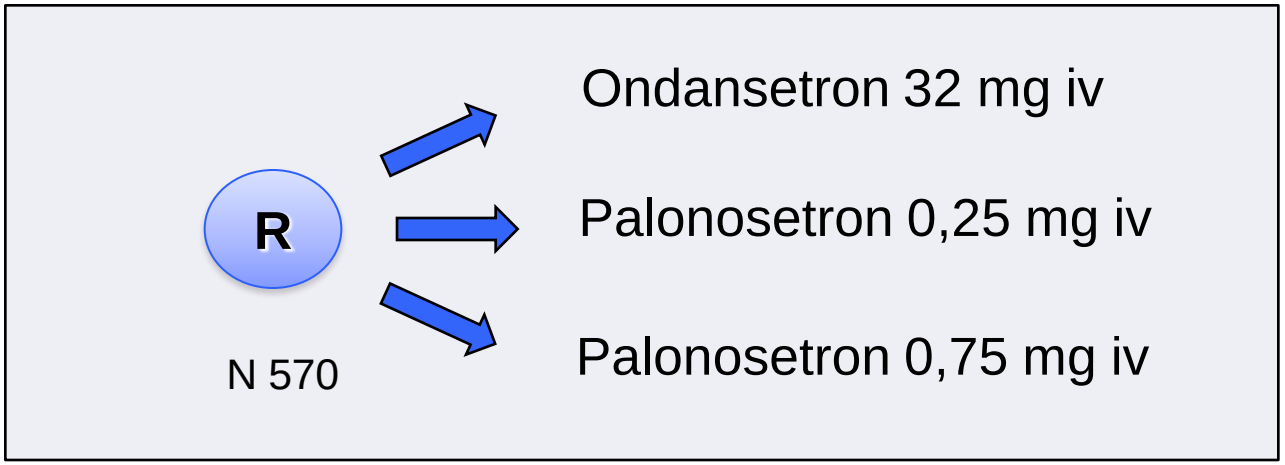
Gralla R et al. *Ann Oncol*. 2003; Eisenberg P et al. *Cancer*. 2003.
Rubenstein EB et al. *Proc Am Soc Clin Oncol.* 2003. Abstract 2932.

Adverse Reactions Reported in Treatment Group (Phase II and Phase III Comparator Trials, N=1,237)

Adverse Reaction, n (%)	Palonosetron 0.25 mg (n=633) n (%)	Ondansetron 32 mg (n=410) n (%)	Dolasetron 100 mg (n=194) n (%)
Headache	60 (9)	34 (8)	32 (16)
Constipation	29 (5)	8 (2)	12 (6)
Diarrhea	8 (1)	7 (2)	4 (2)
Dizziness	8 (1)	9 (2)	9 (2)
Fatigue	3 (<1)	4 (1)	4 (2)
Abdominal pain	3 (<1)	2 (<1)	3 (2)
Insomnia	3 (<1)	3 (1)	3 (2)

Palonosetron and HEC

PALO 99-05
High Emetogenic Chemotherapy



Non- Inferiority Trial

Corticosteroid use allowed at physician discretion:
67.3% of pts PAL groups
66.5% of pts OND groups

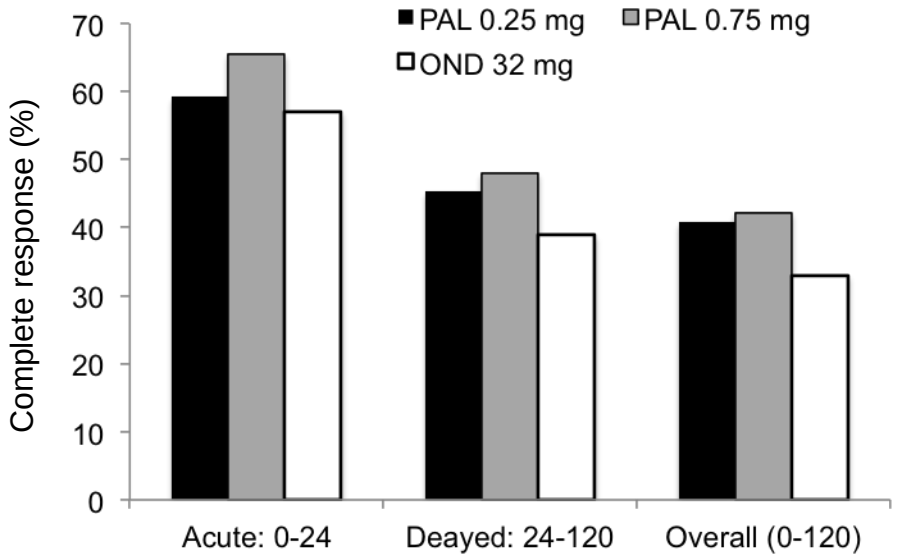
Appro MS et al.; Ann Oncol 2006 (17): 1441–1449

PALO 99-05 Trials
HEC: Palonosetron vs Ondansetron

Complete Response Rates in ITT Cohorts

	PALO 0.25 mg (n=223)		PALO 0.75 mg (n=223)		OND 32mg (n=221)
	%	p	%	p	%
Acute (0-24 h)	59.2	0.701	65.5	0.079	57.0
Delayed (24-120 h)	45.3	0.8	48.0	0.056	38.9
Overall (0-120 h)	40.8	0.095	42.2	0.051	33.0

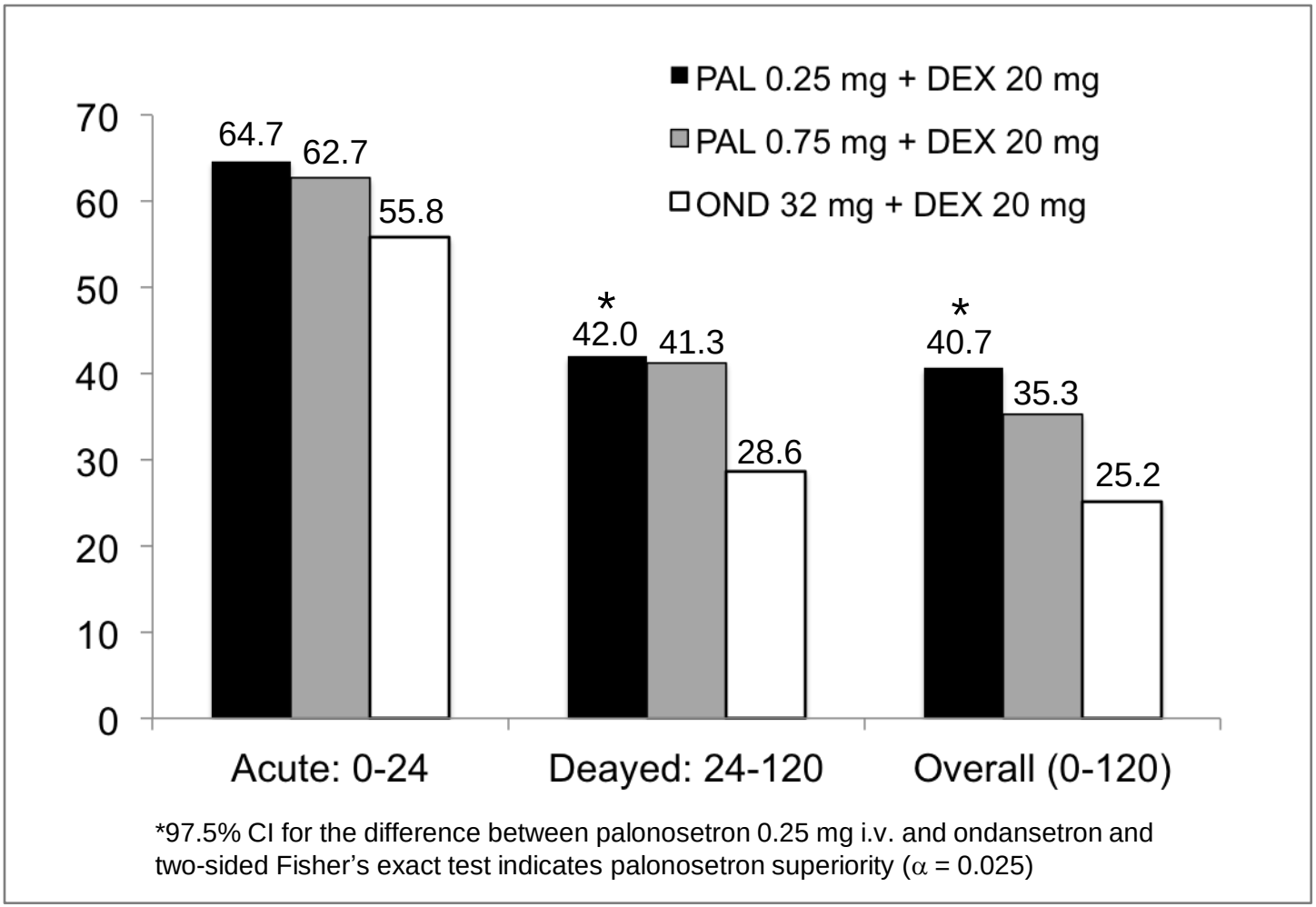
Fisher's exact test comparisons of palonosetron with ondansetron, significance level = 0.025.



Appro MS et al.; Ann Oncol 2006 (17): 1441–1449

HEC: Palonosetron vs Ondansetron
PALO 99-05 Trials

Complete Response Rates in Patients Taking Desamethasone



*97.5% CI for the difference between palonosetron 0.25 mg i.v. and ondansetron and two-sided Fisher's exact test indicates palonosetron superiority ($\alpha = 0.025$)

Phase III Trial of IV Palonosetron vs. IV Granisetron with Cisplatin or AC-Based Chemotherapy

- 1114 patients
- Cisplatin (57%) or anthracycline/cyclophosphamide (43%)
- Single 0.75 mg dose of palo vs. single 40 µg/kg dose of granisetron
- Dexamethasone 16 mg d1; 4mg/d d 2-3 (AC/EC); 8 mg/d d 2-3 CDDP
- Objective: demonstrate non-inferiority d1 and superiority d 2-5 of palo
- Primary endpoint complete response (no emesis/no rescue)

Saito M et al. Lancet Oncol. 2009;10(2):115-24

Phase III Trial Palonosetron vs. Granisetron both with Dexamethasone in HEC

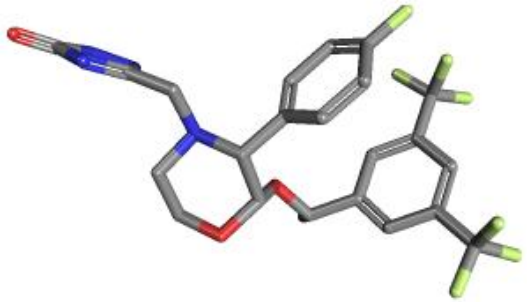
	Palo+ Dex (n=555) %	Grani+ Dex (n=558) %	*P*
Acute (0-24h)	73.7	72.1	ND
Delayed (24-120h)	53.0	42.4	0.0003
Overall (0-120h)	47.9	38.1	0.0007
No Nausea: 0-120 hours	32	25	0.01
No Emesis: 0-120 hours	58	49	0.006

Saito M et al. Lancet Oncol. 2009;10(2):115-24

Palonosetron: 5-HT_3 Antagonist of Choice?

- Palonosetron is a 5-HT_3 antagonist with strong receptor binding affinity and an extended half-life
- In 2 MEC trials, IV palonosetron (single dose) was superior to dolasetron and ondansetron (single dose) in the prevention of acute and delayed emesis in a post-hoc analysis
- In 1 HEC trial, emetic control was comparable between IV palonosetron and ondansetron; better control with palonosetron in the subset receiving dexamethasone
- In large phase III trial with cisplatin or AC, palonosetron was equivalent to granisetron in acute control and superior during the delayed phase
- Comparable tolerability
- Ease of use and trends towards superiority favor palonosetron as the preferred 5-HT_3 antagonist
- Definitive proof of superiority to first generation 5-HT_3 antagonists would require trials with control arms utilizing corticosteroids, NK_1 antagonists and repetitive dosing of the first generation agents

Aprepitant
(Emend®, Ivemend®)

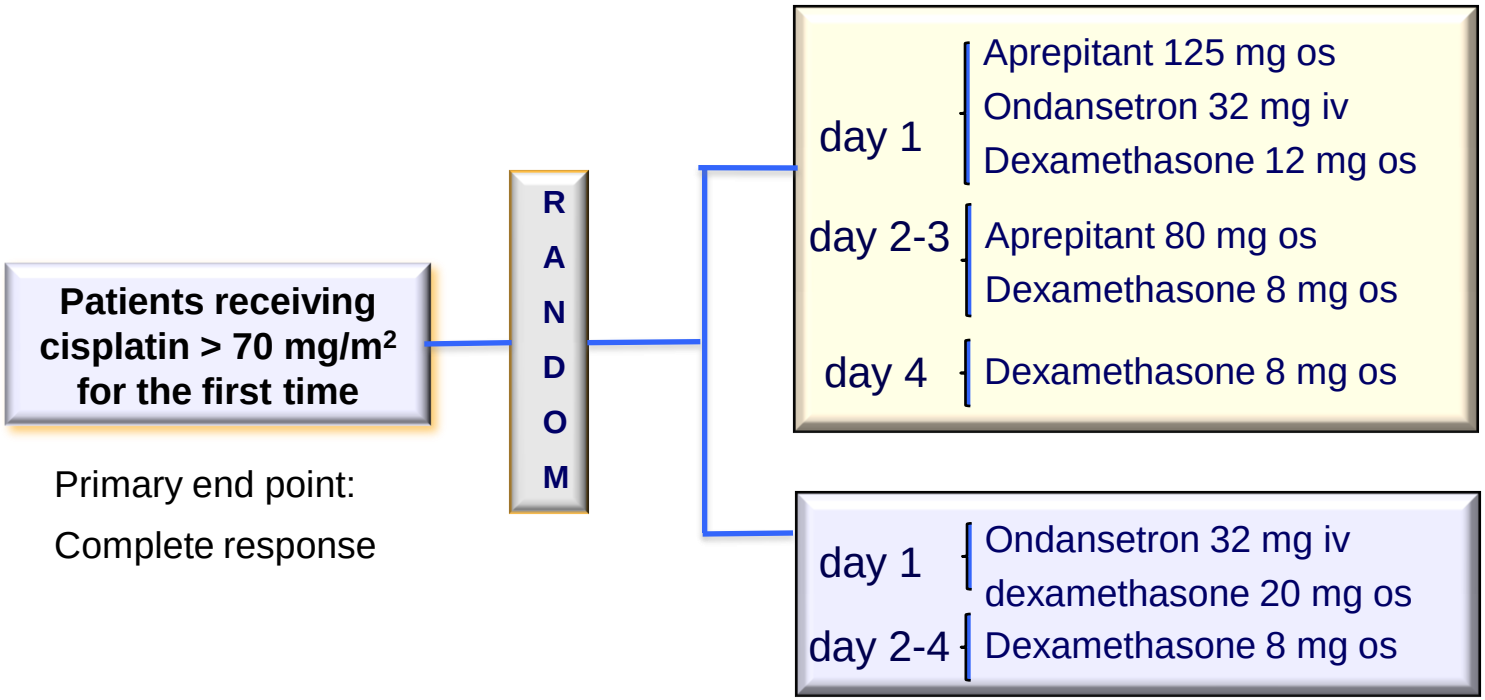


- Selective antagonist of the binding of Substance P to the neurokinin 1 (NK1) receptor
- FDA approved
  - Oral formulation: March 26, 2003
  - IV formulation (fosaprepitant): January 31, 2008
- Regimen
  - 125 mg PO day 1, 80 mg PO days 2-3
    acute/delayed HEC/MEC
  - 115 mg IV day 1, 80 mg PO days 2-3
    acute/delayed HEC/MEC

Hesketh P.J. et al., J Clin Oncol 2003 (21): 4112-4119

Aprepitant and HEC

052 Study Group (521 pts)
054 Study Group (569 pts)



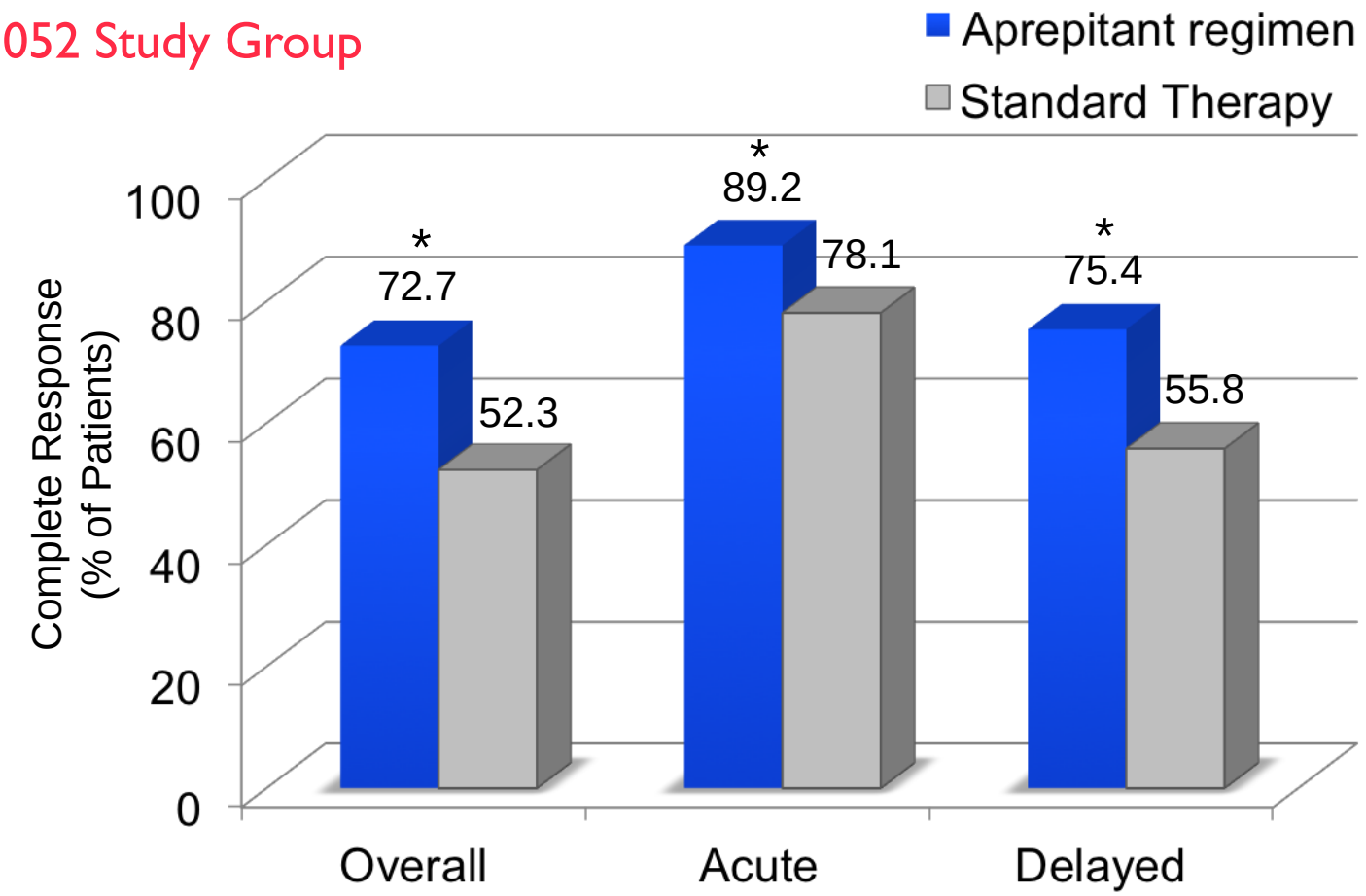
Primary end point:

Complete response

Hesketh P.J. et al., J Clin Oncol 2003 (21): 4112-4119
Poli-Bigelli S. et al.; Cancer 2003 (97): 3090-3098

Aprepitant and HEC

052 Study Group

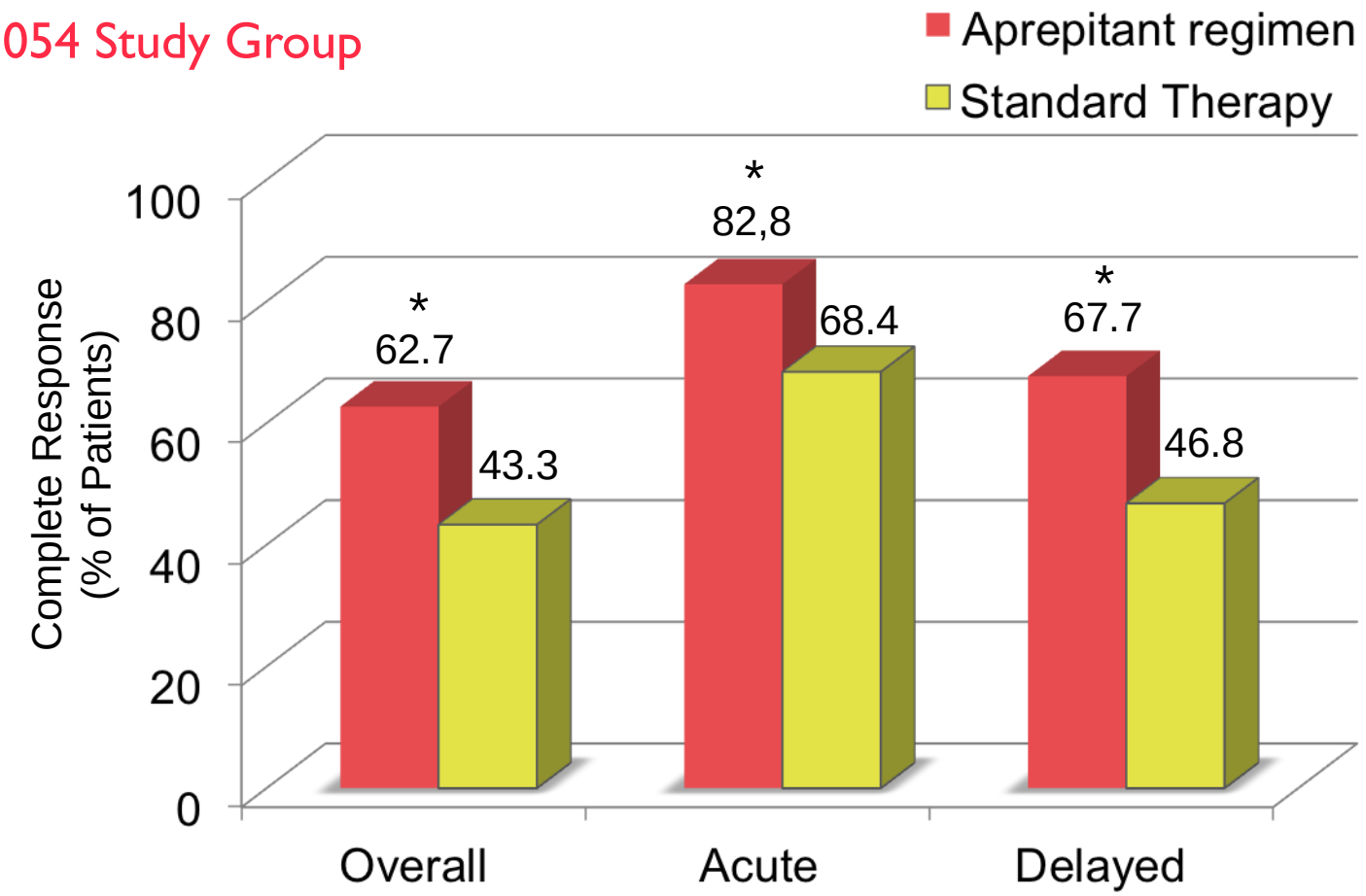


*P < .001 versus standard therapy.

Hesketh P.J. et al., J Clin Oncol 2003 (21): 4112-4119

Aprepitant and HEC

054 Study Group

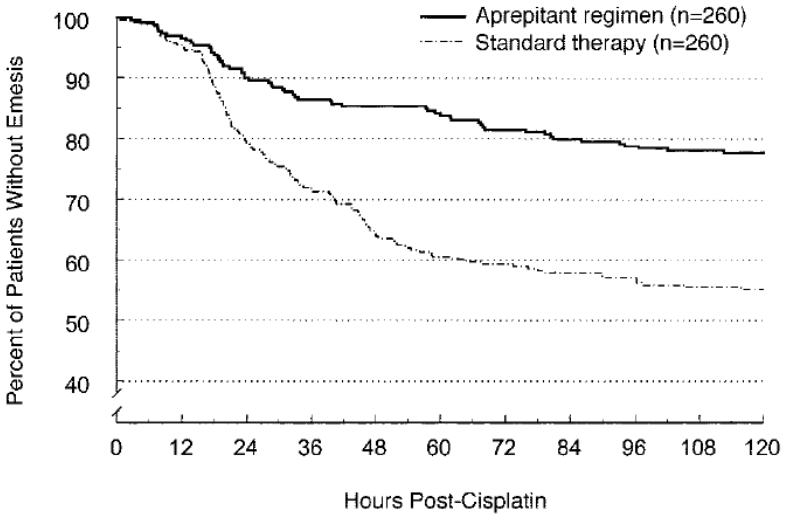


*P < .001 versus standard therapy.

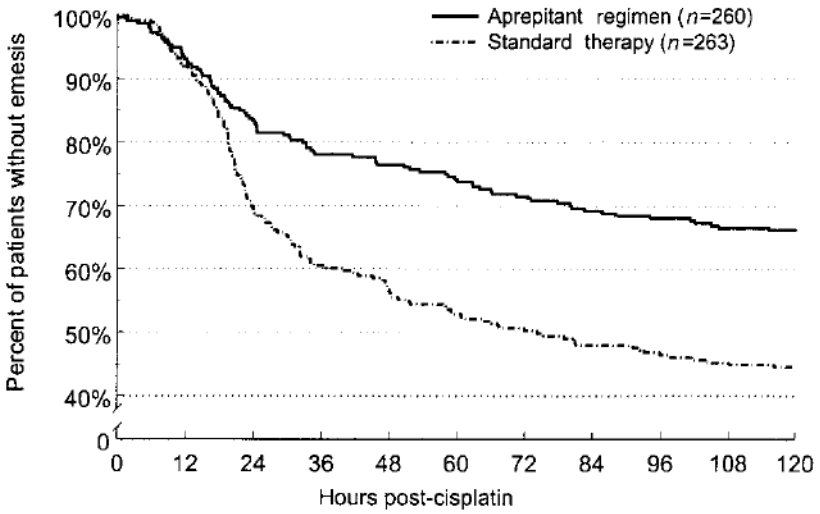
Poli-Bigelli S. et al.; Cancer 2003 (97): 3090-3098

Aprepitant and HEC

052 Study Group



054 Study Group



Hesketh P.J. et al., J Clin Oncol 2003 (21): 4112-4119
Poli-Bigelli S. et al.; Cancer 2003 (97): 3090-3098

Aprepitant and HEC

original article

Annals of Oncology 17: 1000–1006, 2006
doi:10.1093/annonc/mdl019
Published online 8 March 2006

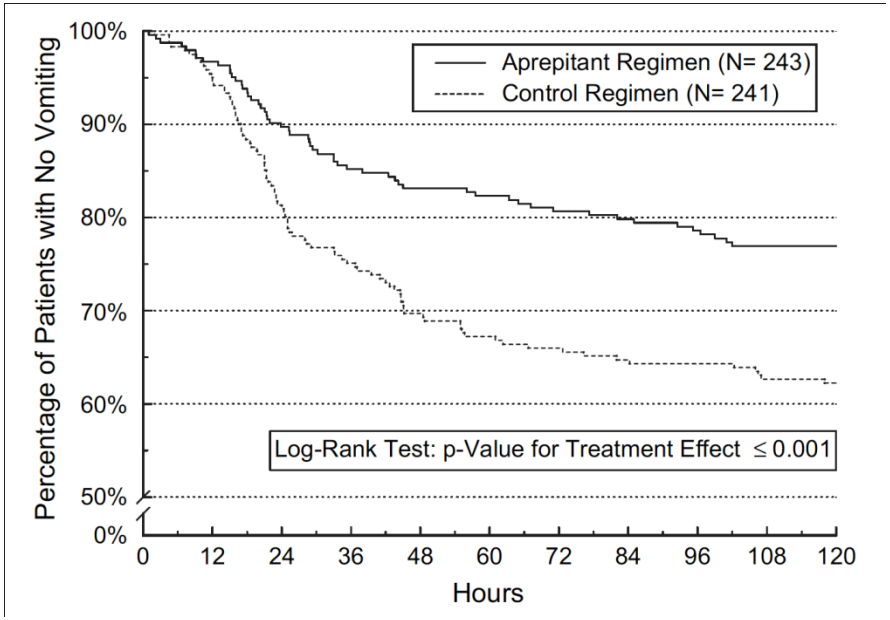
Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment

H. J. Schmoll[1]*, M. S. Aapro[2], S. Poli-Bigelli[3], H.-K. Kim[4], K. Park[5], K. Jordan[1], J. von Pawel[6], H. Giezek[7], T. Ahmed[8] & C. Y. Chan[9]

Group	day 1			days 2-3		Day 4
Aprepitant (n = 244)	OND 32 mg iv	DEX 12 mg os	APR 125 mg os	DEX 12 mg os	APR 80 mg os	DEX 12 mg os
Standard (n = 245)	OND 32 mg iv	DEX 12 mg os	Placebo	DEX 12 mg os		OND 8 mg os bid

Primary end point: CR

Schmoll et al: Ann Oncol 17:1000-6, 2006



	Aprepitant regimen (N = 243) % of patients	Control regimen (N = 241) % of patients	Odds ratio	95% CI	P value for odds ratio[a]
Complete response[b]					
0–120 h	72.0	60.6	1.80	1.21–2.66	0.003
0–24 h	87.7	79.3	2.10	1.25–3.52	0.005
>24–120 h	74.1	63.1	1.78	1.20–2.65	0.004
No vomiting					
0–120 h	76.5	62.2	2.14	1.43–3.22	≤0.001
0–24 h	88.9	80.5	2.17	1.27–3.69	0.004
>24–120 h	79.0	64.3	2.24	1.48–3.40	≤0.001
No use of rescue therapy					
0–120 h	82.3	79.7	1.23	0.78–1.96	0.373
0–24 h	94.2	92.9	1.32	0.63–2.77	0.468
>24–120 h	83.5	81.7	1.17	0.73–1.88	0.517
No significant nausea[c]					
0–120 h	73.1	69.7	1.24	0.83–1.87	0.290
0–24 h	92.1	89.5	1.45	0.77–2.76	0.254
>24–120 h	75.9	72.1	1.28	0.84–1.94	0.248

[a]P value of logistic model including terms for treatment, gender, use of concomitant emetogenic chemotherapy and geographic region.
[b]Complete response = no vomiting and no use of rescue therapy.
[c]For No significant nausea, the Ns varied from 237 to 242. No significant nausea = score of <25 mm on 100-mm visual analog scale.

Aprepitant and MEC

VOLUME 23 · NUMBER 12 · APRIL 20 2005

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

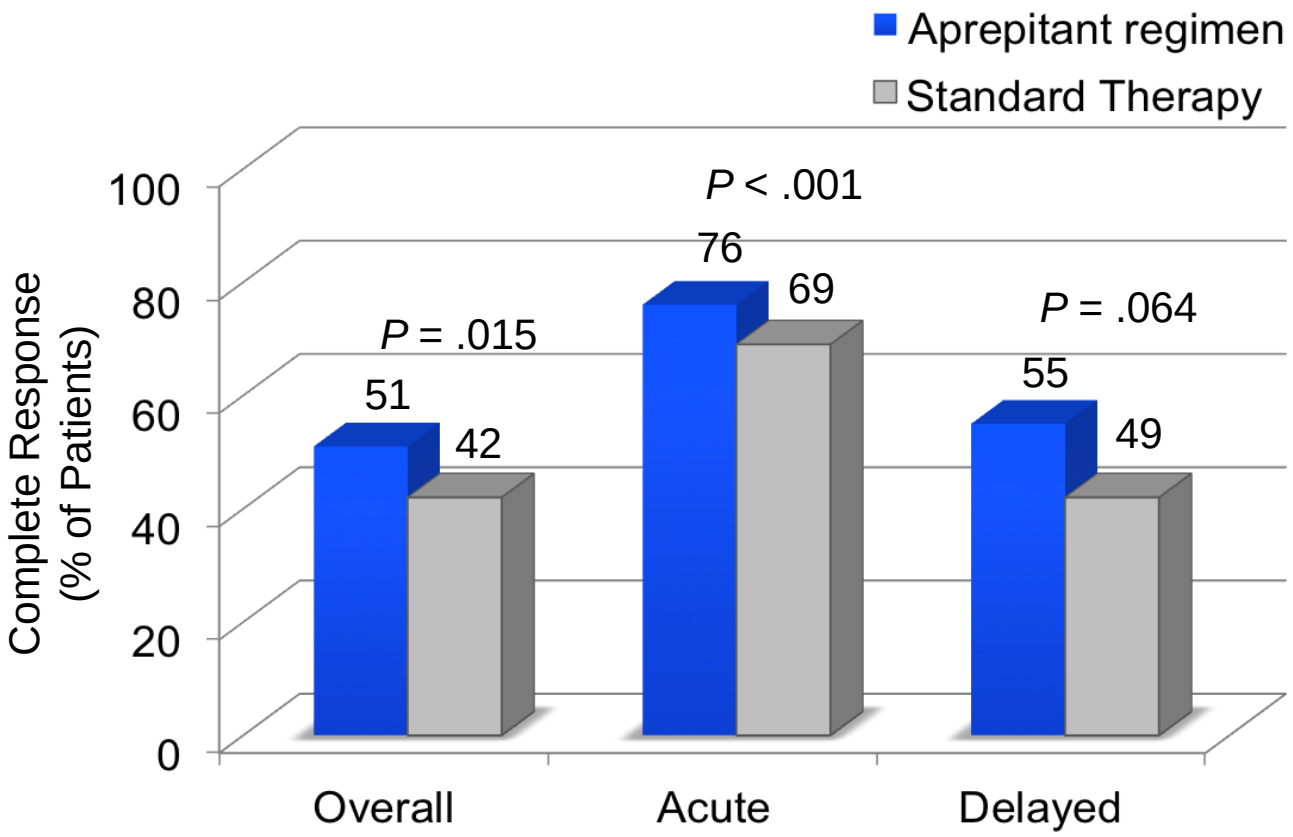
Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer After Moderately Emetogenic Chemotherapy

David G. Warr, Paul J. Hesketh, Richard J. Gralla, Hyman B. Muss, Jørn Herrstedt, Peter D. Eisenberg, Harry Raftopoulos, Steven M. Grunberg, Munir Gabriel, Anthony Rodgers, Norman Bohidar, George Klinger, Carolyn M. Hustad, Kevin J. Horgan, and Franck Skobieranda

Group	day 1			days 2-3	
Aprepitant (n = 438)	APR 125 mg os	OND 8 mg os bid	DEX 12 mg os	APR 80 mg os	Placebo
Standard (n = 428)	OND 8 mg os bid	DEX 20 mg os		OND 8 mg os bid	Placebo

Warr DG et al. *J Clin Oncol* 2005; 23:2822-2830

Aprepitant and MEC



Warr DG et al. *J Clin Oncol* 2005; 23:2822-2830

Palonosetron + Aprepitant + Dexamethasone Phase II Study Design

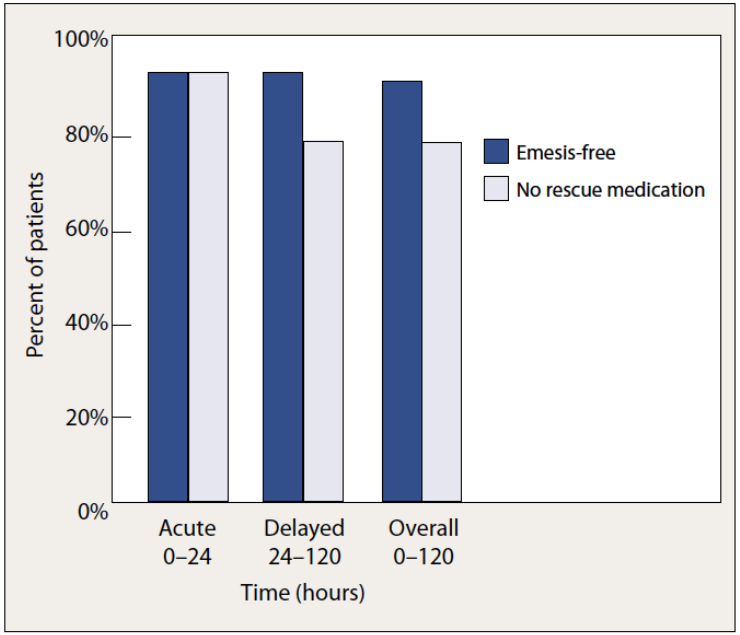
- Multicenter, phase II, open-label study
- Naïve and non-naïve patients receiving moderately to moderately-highly emetogenic chemotherapy
- Treatment:

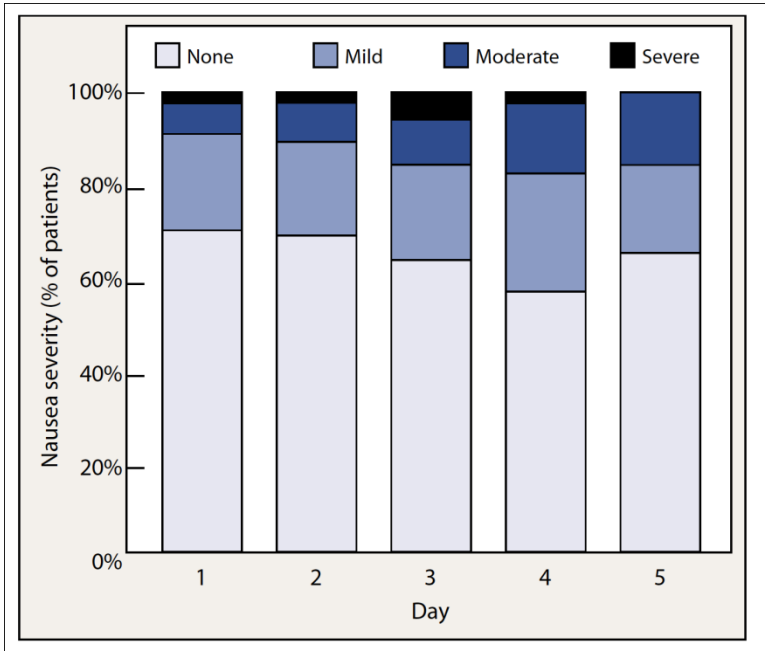
day 1			days 2-3	
APR 125 mg os	PAL 0,25 mg iv	DEX 12 mg os	APR 80 mg os	DEX 8 mg os

ITT Cohort, n = 58

Grote T. et al; J Support Oncol. 2006 Sep;4(8):403-8

Palonosetron + Aprepitant + Dexamethasone Phase II Study Design





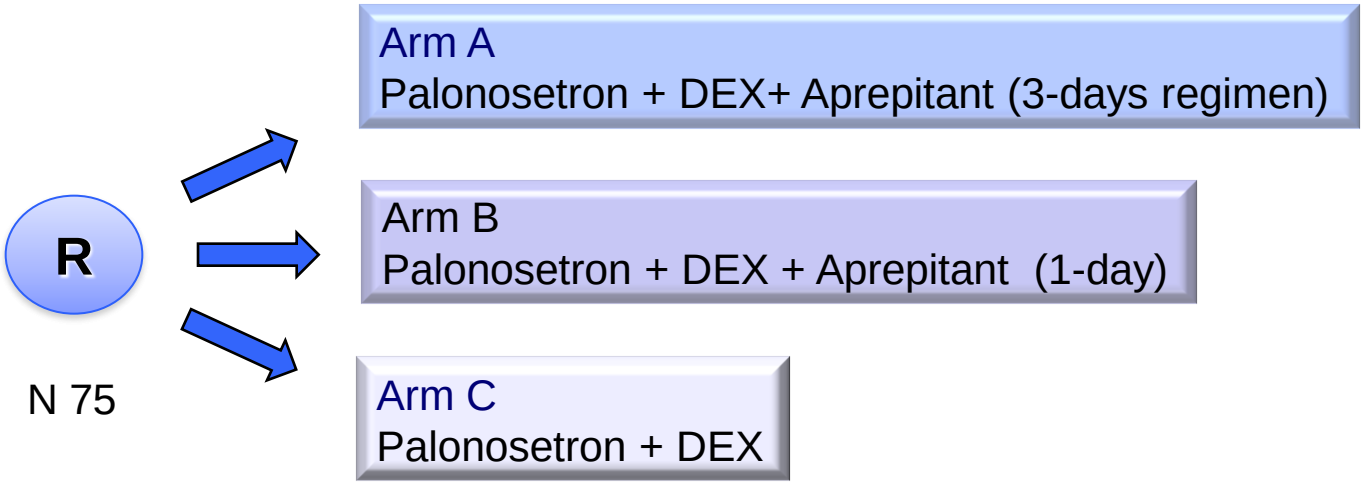
Adverse Reactions Possibly Related to Treatment (Safety Cohort, n = 58)

	n (% OF PATIENTS)		
ADVERSE EVENT	PALONOSETRON	APREPITANT	DEXAMETHASONE
Insomnia	0	0	6 (10.3)
Convulsion	1 (1.7)	1 (1.7)	1 (1.7)
Diarrhea	1 (1.7)	2 (3.4)	0
Constipation	2 (3.4)	0	0
Headache	1 (1.7)	0	1 (1.7)
Fatigue	0	0	1 (1.7)
Abdominal pain	0	0	1 (1.7)
Feeling abnormal	0	0	1 (1.7)
Anxiety	0	0	1 (1.7)

Grote T. et al; J Support Oncol. 2006

Palonosetron + Aprepitant + Dexamethasone and HEC

Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting

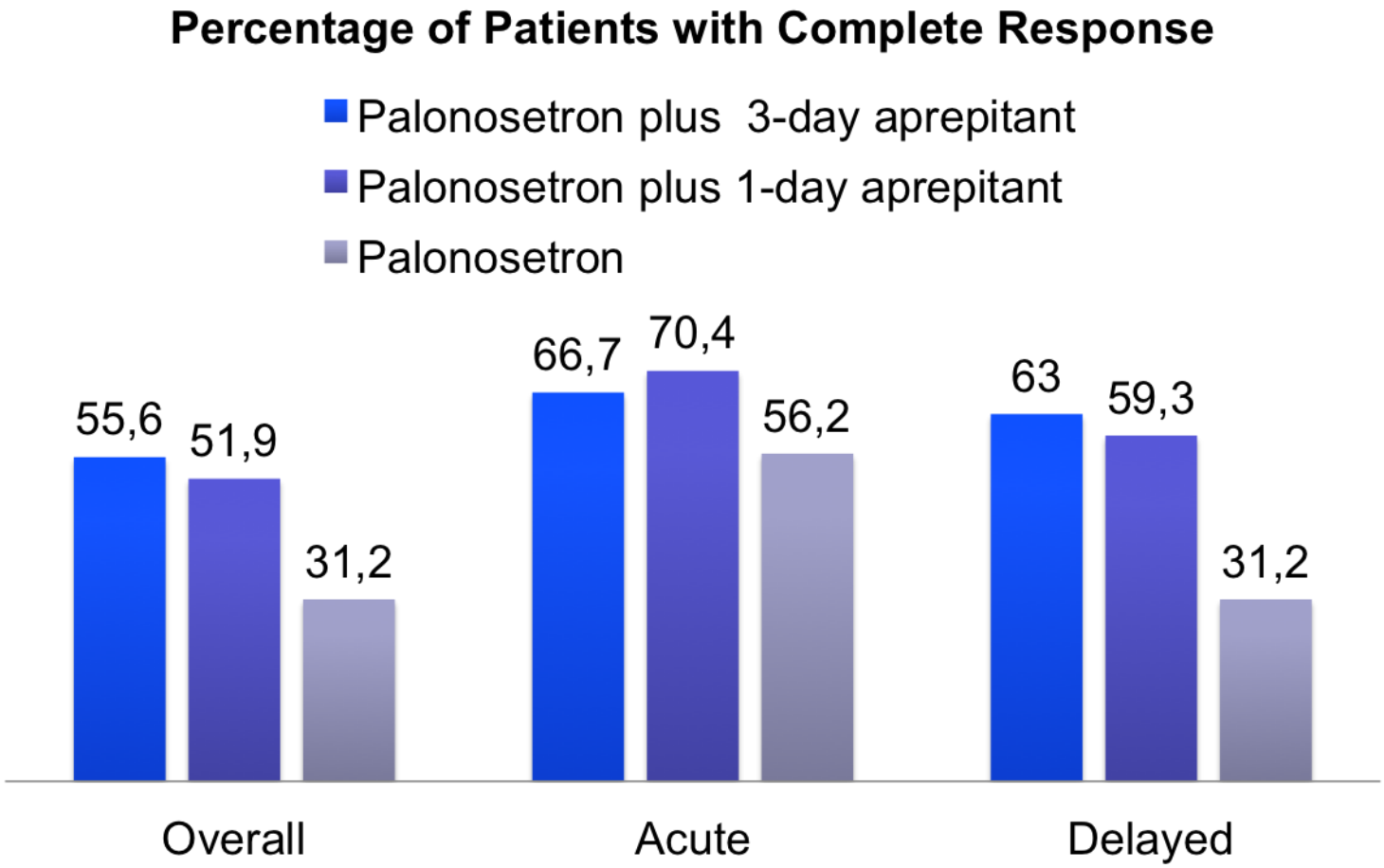


DEX: dexamethasone

- day 1: 12 mg day 1 in arm A and arm B; 20 mg in arm C
- days 2-4: 8 mg

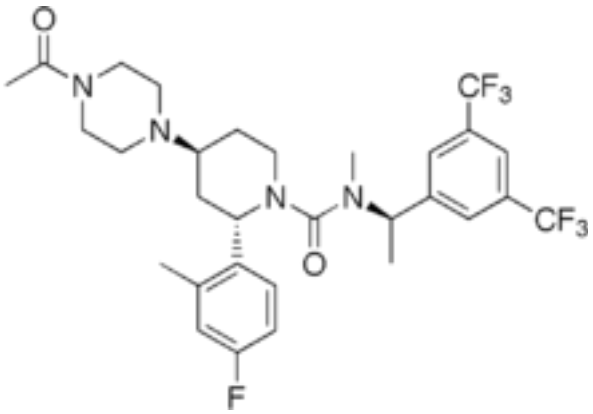
Herrington JD et al.; Cancer 112:2080-2087, 2008

Palonosetron + Aprepitant + Dexamethasone Phase III Study Design



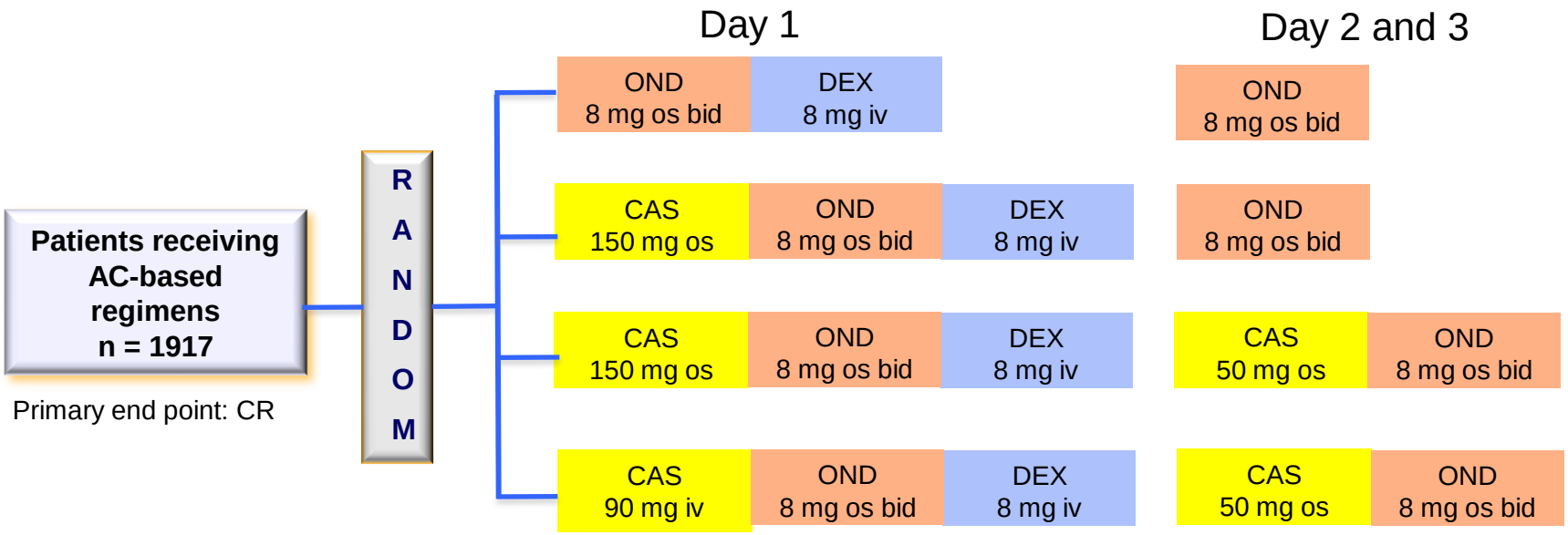
Herrington JD et al.; Cancer 112:2080-2087, 2008

Casopitant
(Zunrisa®)



Phase III Trial of Casopitant, a Novel Neurokinin-1 Receptor Antagonist, for the Prevention of Nausea and Vomiting in Patients Receiving Moderately Emetogenic Chemotherapy

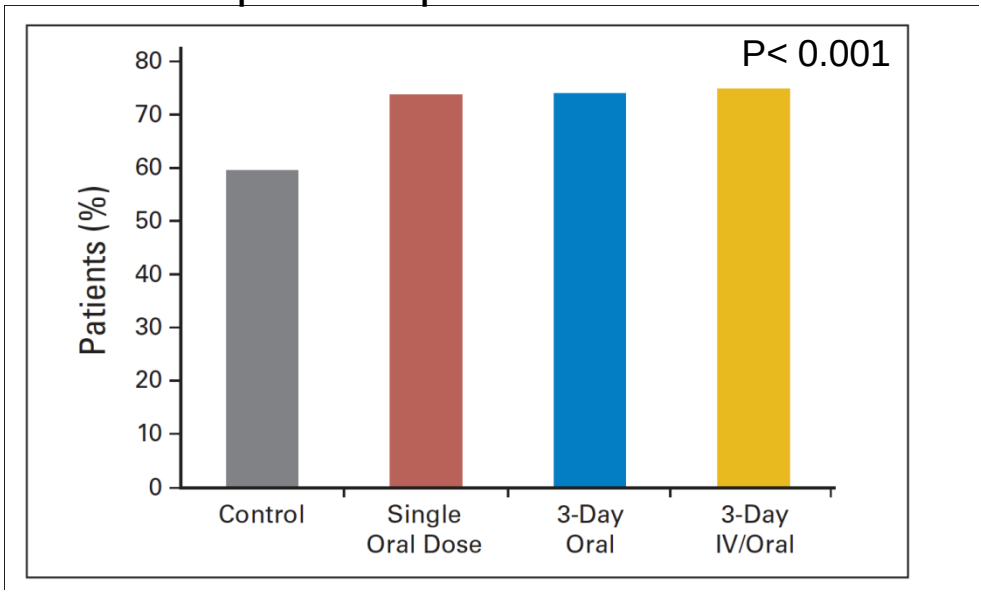
Jørn Herrstedt, Wichit Apornwirat, Ahmed Shaharyar, Zeba Aziz, Fausto Roila, Simon Van Belle, Mark W. Russo, Jeremey Levin, Salabha Ranganathan, Mary Guckert, and Steven M. Grunberg



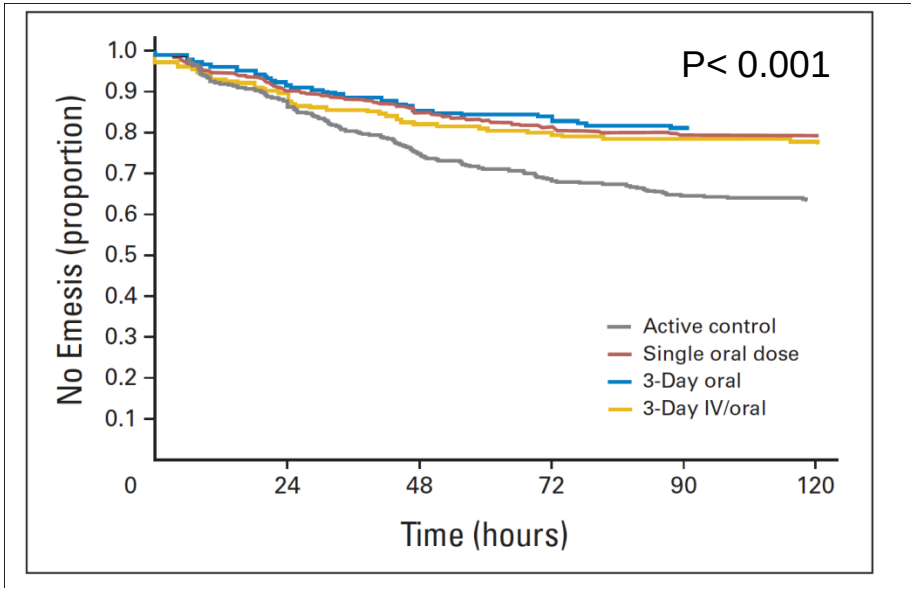
Herrstedt J. et al.; J Clin Oncol 2009 27(32):5363-9

Casopitant and AC-based regimens

Complete response at 120 hours



Kaplan-Meier estimate for time to first emetic event



Herrstedt J. et al.; J Clin Oncol 2009 27(32):5363-9

Fosaprepitant
(Ivemend®)

Single-Dose Fosaprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Cisplatin Therapy: Randomized, Double-Blind Study Protocol—EASE

Steven Grunberg, Daniel Chua, Anish Maru, José Dinis, Suzanne DeVandry, Judith A. Boice, James S. Hardwick, Elizabeth Beckford, Arlene Taylor, Alexandra Carides, Fausto Roila, and Jørn Herrstedt

A B S T R A C T

Patients receiving cisplatin > 70 mg/m² for the first time
N 2247

Group	day 1			days 2-3		Day 4
Fosprepitant (n = 1147)	FOS 150 mg iv	DEX 12 mg os	OND 32 mg iv	DEX 8 mg os bid		DEX 8 mg os bid
Aprepitant (n = 1175)	APR 125 mg os	DEX 12 mg os	OND 32 mg iv	APR 80 mg os	DEX 8 mg os bid	DEX 8 mg os bid

Grumberg S. et al.; J Clin Oncol 2011

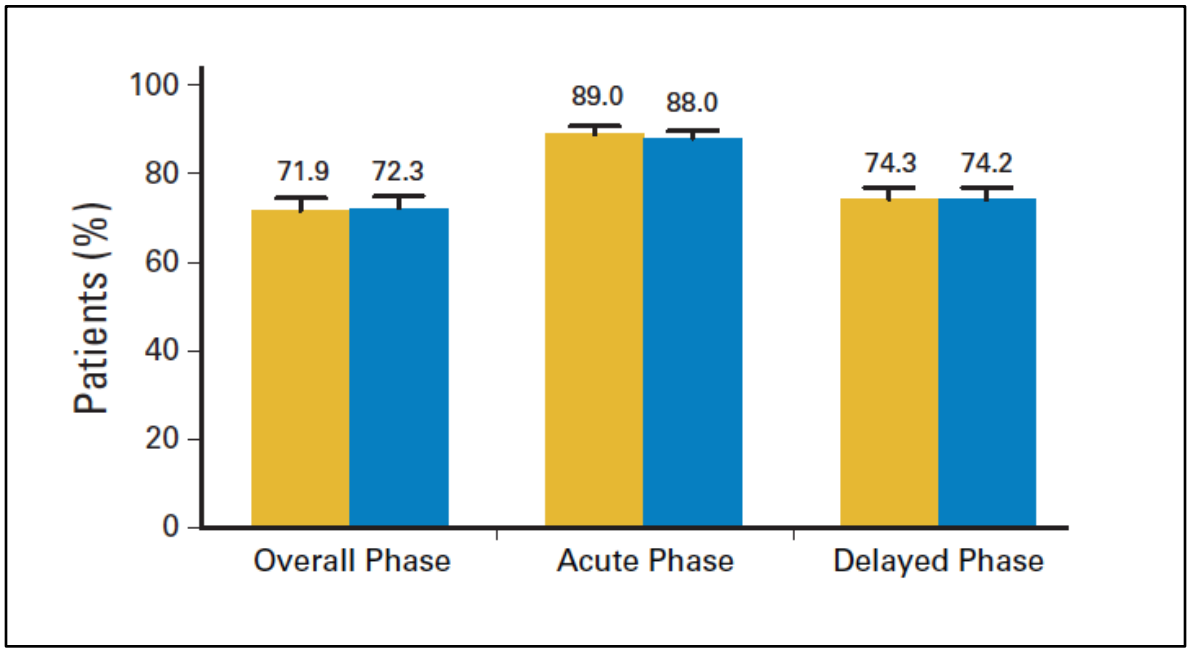
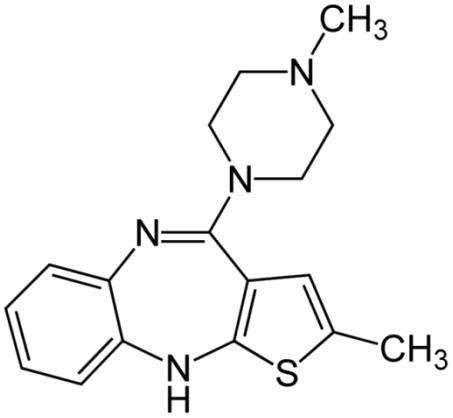


Table 3. Patients With Specific Clinical Adverse Events of Incidence ≥ 5% in at Least One Treatment Group

	Fosaprepitant Regimen (n = 1,143)		Aprepitant Regimen (n = 1,169)			
Adverse Event	No.	%	No.	%	Difference	95% CI*
Constipation	121	10.6	112	9.6	1.0	−1.5 to 3.5
Asthenia	98	8.6	136	11.6	−3.1	−5.5 to −0.6
Diarrhea	89	7.8	102	8.7	−0.9	−3.2 to 1.3
Vomiting	75	6.6	65	5.6	1.0	−1.0 to 3.0
Anorexia	76	6.6	106	9.1	−2.4	−4.6 to −0.2
Nausea	68	5.9	81	6.9	−1.0	−3.0 to 1.0
Hiccups	64	5.6	74	6.3	−0.7	−2.7 to 1.2

*For the difference, calculated by using the method of Miettinen and Nurminen.[16]

Grumberg S. et al.; J Clin Oncol 2011



Olanzapine (Zyprexa)

Olanzapine is a antipsychotic that blocks multiple neurotransmitters:

- dopamine: D1 , D2 , D3 , and D4
- serotonin: 5-HT2c , 5-HT3 , and 5-HT6
- receptors catecholamines: 1 -adrenergic receptors;
- acetylcholine: muscarinic receptors;
- histamine: H1 receptors

A phase II trial demonstrated that olanzapine, when combined with a single dose of dexamethasone and a single dose of palonosetron, was very effective at controlling acute and delayed CINV in patients receiving both HEC and MEC

Tan L, et al.; J Exp Clin Cancer Res 2009;28:1–7

ORIGINAL RESEARCH

Olanzapine Versus Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Randomized Phase III Trial

Rudolph M. Navari, MD, PhD, Sarah E. Gray, BS, and Andrew C. Kerr, BS

Patients receiving HEC regimens n = 247

Primary end point: CR

R

OPD regime

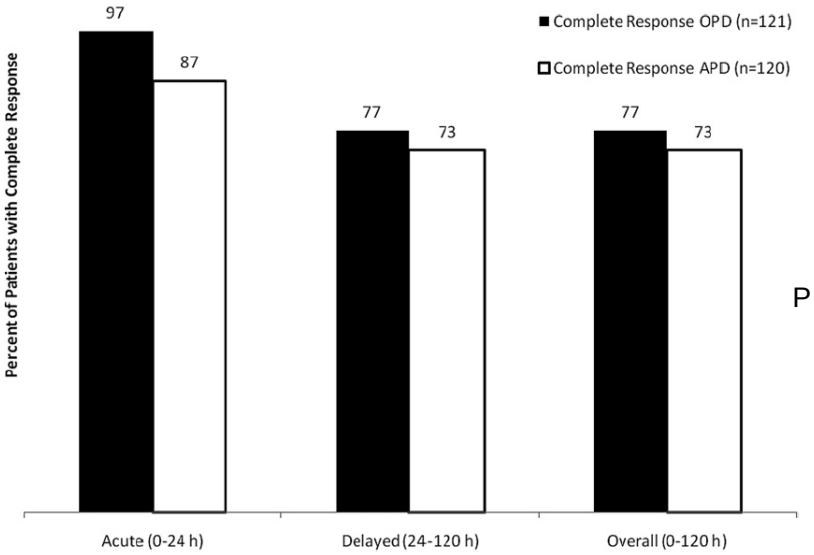
day 1			days 2-4
PAL 0,25 mg iv	DEX 20 mg iv	Olanzapine 10 mg os	Olanzapine 10 mg os

APD regime

day 1			days 2-4	
APR 125 mg os	PAL 0,25 mg iv	DEX 12 mg os	APR 80 mg os	DEX 8 mg os

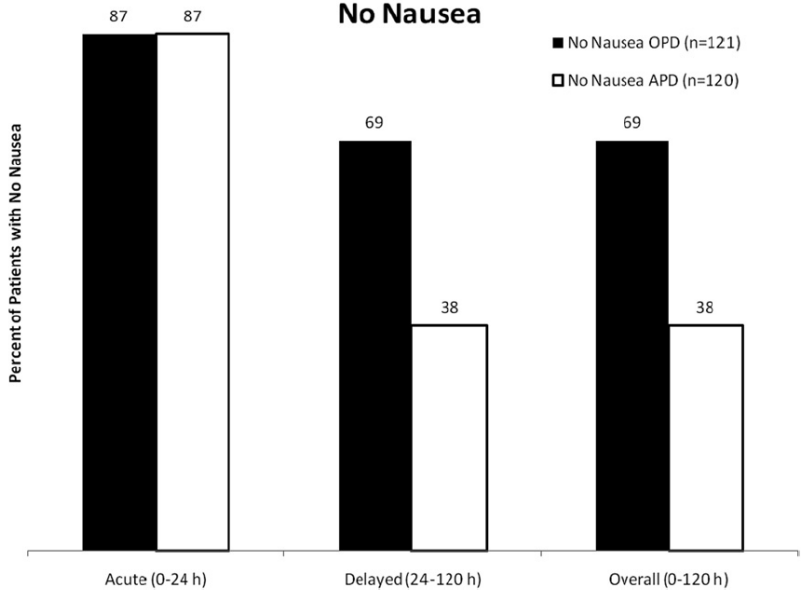
Navari RM et al.; J Support Oncol 2011; 9:188–195

OLN+PAL+DEX vs. APR+PAL+DEX
Complete Response



P > 0.05

OLN+PAL+DEX vs. APR+PAL+DEX
No Nausea



P < 0.01

Navari RM et al.; J Support Oncol 2011; 9:188–195

Olanzapine Versus Aprepitant in HEC

MDASI Scores (0–10) Over Days 1–5 in Patients Receiving Highly Emetogenic Chemotherapy in Chemotherapy Cycle 1

	OPD REGIMEN (N = 121)		APD REGIMEN (N = 120)	
SYMPTOM	DAY 1	DAY 5*	DAY 1	DAY 5**
Pain	1.5	1.2	1.1	1.6
Fatigue	4.1	4.2	3.0	3.5
Disturbed sleep	2.1	2.6	3.3	3.0
Distress	1.5	2.0	2.2	2.4
Problems remembering	1.5	1.6	2.1	2.2
Shortness of breath	1.9	2.2	2.5	2.3
Lack of appetite	1.9	1.8	2.2	1.9
Feeling drowsy	3.3	3.7	2.8	2.6
Dry mouth	3.5	3.8	3.3	3.5
Feeling sad	1.9	2.2	3.0	2.8
Numbness	0.9	1.2	2.1	1.7
General activity	2.1	2.2	2.1	2.3
Mood	0.5	1.3	2.0	1.7
Work	2.3	3.0	3.0	2.7
Relations	1.8	1.7	1.7	1.5
Walking	1.9	2.1	2.1	2.3
Enjoyment	1.5	2.1	3.1	2.8
Sedation	1.1	1.9	1.3	2.1

OPD, olanzapine + palonosetron + dexamethasone; APD, aprepitant + palonosetron + dexamethasone.

* $P > 0.05$ for all symptoms in OPD regimen, ** $P > 0.05$ for all symptoms in APD regimen.

Navari RM et al.; J Support Oncol 2011; 9:188–195

ASCO Guideline 2011

High emetic risk agents

NCCN National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2012
Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT	
High emetic risk (>90 % frequency of emesis)[q,r]	• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide[q] • Carmustine >250 mg/m^2 • Cisplatin ≥50 mg/m^2 • Cyclophosphamide >1,500 mg/m^2 • Dacarbazine	• Doxorubicin >60 mg/m^2 • Epirubicin >90 mg/m^2 • Ifosfamide ≥10 g/m^2 • Mechlorethamine • Streptozocin

The three-drug combination of

- Neurokinin 1 (NK1) receptor antagonist
  days 1 through 3 for aprepitant;
  day 1 only for fosaprepitant
- 5-HT3 receptor antagonist
  day 1 only
- Dexamethasone
  days 1 through 3 or 1 through 4

The Update Committee also recommended reclassification of the combined anthracycline and cyclophosphamide (AC) regimen as highly emetogenic

Basch et al.; J Clin Oncol 2011 29: 4189-4198

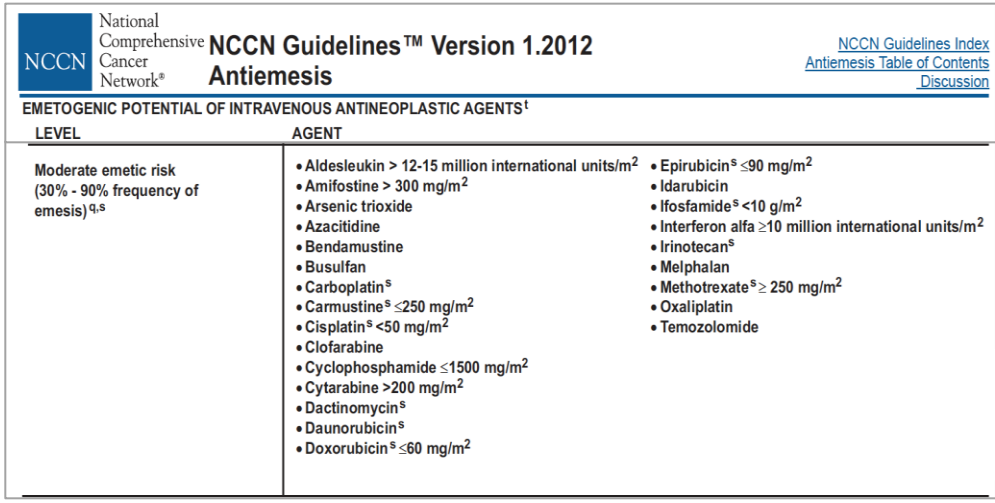
ASCO Guideline 2011

High emetic risk agents

	Dosing on Day of Chemotherapy	Dosing on Subsequent Days
NK1 antagonist		
Aprepitant (Emend®)	125 mg oral	80 mg oral; days 2 and 3
Fosaprepitant (Ivemend®)	150 mg iv	
5-HT3 antagonist		
Palonosetron (Aloxi®)	0.50 mg oral; 0.25 mg iv	
Granisetron	2 mg oral; 1 mg or 0.01 mg/kg iv	
Ondansetron	8 mg oral twice daily; 8 mg or 0.15 mg/kg iv	
Dolasetron	100 mg oral ONLY	
Tropisetron	5 mg oral; 5 mg IV	
Ramosetron	0.3 mg IV	
Corticosteroid		
Dexamethasone	12 mg os or iv	8 mg oral or IV; days 2-3 or days 2-4

Basch et al.; J Clin Oncol 2011 29: 4189-4198

ASCO Guideline 2011



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Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT
Moderate emetic risk (30% - 90% frequency of emesis)[q,s]	• Aldesleukin > 12-15 million international units/m^2 • Amifostine > 300 mg/m^2 • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin[s] • Carmustine[s] ≤250 mg/m^2 • Cisplatin[s] <50 mg/m^2 • Clofarabine • Cyclophosphamide ≤1500 mg/m^2 • Cytarabine >200 mg/m^2 • Dactinomycin[s] • Daunorubicin[s] • Doxorubicin[s] ≤60 mg/m^2 • Epirubicin[s] ≤90 mg/m^2 • Idarubicin • Ifosfamide[s] <10 g/m^2 • Interferon alfa ≥10 million international units/m^2 • Irinotecan[s] • Melphalan • Methotrexate[s] ≥ 250 mg/m^2 • Oxaliplatin • Temozolomide

Moderately emetogenic agents

The two-drug combination of:

- palonosetron (day 1 only)
- dexamethasone (days 1-3)

If palonosetron is not available, clinicians may substitute a first-generation 5-HT3 serotonin receptor antagonist, preferably granisetron or ondansetron.

Limited evidence also supports adding aprepitant to the combination.
Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT3 antagonists is appropriate

	Dosing on Day of Chemotherapy	Dosing on Subsequent Days
5-HT3 antagonist		
Palonosetron (Aloxi®)	0.50 mg oral; 0.25 mg iv	
Corticosteroid		
Dexamethasone	8 mg os or iv	8 mg; days2 and 3

Basch et al.; J Clin Oncol 2011 29: 4189-4198

ASCO Guideline 2011

Low emetic risk

NCCN National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2012
Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT	
Low emetic risk (10% - 30% frequency of emesis)[q]	• Amifostine ≤300 mg • Aldesleukin ≤12 million international units/m^2 • Cabazitaxel Cytarabine (low dose) 100-200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil • Floxuridine • Gemcitabine • Interferon alfa >5 <10 million international units/m^2 • Ixabepilone	• Methotrexate >50 mg/m^2 <250 mg/m^2 • Mitomycin • Mitoxantrone • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Thiotepa • Topotecan

A single 8-mg dose of dexamethasone before chemotherapy is suggested.

	Dosing on Day of Chemotherapy	Dosing on Subsequent Days
Corticosteroid		
Dexamethasone	8 mg os or iv	8 mg; Days 2 and 3

Basch et al.; J Clin Oncol 2011 29: 4189-4198

ASCO Guideline 2011

Minimal emetogenic antineoplastic agents

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2012
Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTINEOPLASTIC AGENTS[t]

LEVEL	AGENT	
Minimal emetic risk (<10% frequency of emesis)[q]	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine <100 mg/m^2 • Decitabine • Denileukin diftitox • Dexrazoxane • Fludarabine • Interferon alpha ≤5 million international units/m^2 • Ipilimumab	• Methotrexate ≤50 mg/m^2 • Nelarabine • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Rituximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vinorelbine

No antiemetic should be administered routinely before or after chemotherapy

Basch et al.; J Clin Oncol 29: 4189-4198

ASCO Guideline 2011

Clinical Situation	2011 Reccomendation
Combination chemotherapy	*Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. AC combinations are now classified as highly emetogenic*
Adjunctive drugs	*Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics.*
Role of complementary and alternative medicine therapies	*No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies*

Basch et al.; J Clin Oncol 29: 4189-4198

Principle of Managing Multiday Emetogenic Chemotherapy Regimens

ASCO Guideline 2011

It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate.

The Update Committee suggests, based on limited data, that patients receiving 5-day cisplatin regimens be treated with a 5-HT3 antagonist in combination with dexamethasone and aprepitant.

General Principles

- 5-HT3 antagonist before HEC and MEC
- DEX once daily for HEC and MEC and for 2-3 day after chemotherapy for delayed emesis
- Aprepitant for HEC and associated with significant risk for delayed CINV

Basch et al.; J Clin Oncol 29: 4189-4198

What is the optimal treatment to manage nausea and vomiting associated with radiation therapy?

Emetic Risk	Site of Radiation Therapy
High	Total-body irradiation Total nodal irradiation
Moderate	Upper abdomen Upper body irradiation Half-body irradiation
Low	Low Cranium Craniospinal Head and neck Lower thorax region Pelvis
Minimal	Extremities Breast

Basch et al.; J Clin Oncol 29: 4189-4198

Risk Category	Dose	Schedule
High emetic risk		
5-HT3 antagonist		5-HT3 antagonist before each fraction throughout XRT; continue for at least 24 hours after completion of XRT
Granisetron*	2 mg oral; 1 mg or 0.01 mg/kg iv	
Ondansetron*	8 mg oral twice daily; 8 mg or 0.15 mg/kg iv	
Palonosetron°	0.50 mg oral; 0.25 mg iv	
Dolasetron	100 mg oral only	
Tropisetron	5 mg oral; 5 mg IV	
Corticosteroid		
Dexamethasone	4 mg IV or oral	During fractions 1-5
Moderate emetic risk		
5-HT3 antagonist	Any of the above listed agents are acceptable;	5-HT3 antagonist before each fraction throughout XRT
Corticosteroid		
Dexamethasone	4 mg IV or oral	During fractions 1-5

* Preferred agents; ° No data are currently available on the appropriate dosing frequency with palonosetron in this setting; dosing every secondor third day may be appropriate for this agent

Risk Category	Dose	Schedule
Low emetic risk		
5-HT3 antagonist	Any of the above listed agents are acceptable;	5-HT3 either as rescue or prophylaxis; if rescue is used, then prophylactic therapy should be given until the end of XRT
Minimal emetic risk		
5-HT3 antagonist	Any of the above listed agents are acceptable;	Patients should be offered either class as rescue therapy; if rescue is used, then prophylactic therapy should be given until the end of XRT
Dopamine receptor		
Metoclopramide	20 mg oral	
Prochlorperazine	10 oral or IV	

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