Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2016?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

2016: Novità in ambito di Terapia Antiemetica nel Carcinoma Mammario

Emilio Bria

Oncologia Medica, Dipartimento di Medicina, Università di Verona,

Azienda Ospedaliera Universitaria Integrata Verona

emilio.bria@univr.it

Pescantina (VR), 23 Aprile 2016

Disclosures

- Advisory Boards/Honoraria/Speakers' fee/Consultant for:
  - Astra-Zeneca, Celgene, Pfizer, Helsinn, MSD, Eli-Lilly, BMS, Novartis, Roche
- Research Support / Grants from:
  - A.I.R.C. (Associazione Italiana Ricerca sul Cancro)
  - I.A.S.L.C. (International Association for the Study of Lung Cancer)
  - Fondazione *Cariverona*

FONDAZIONE *Cariverona*

AIRC

IASLC
International Association for the Study of Lung Cancer

THE MULTIPLE ROLES FOR 'SUPPORTIVE CARE' IN CANCER

1. **Reduce or eliminate associated symptoms and side-effects**
2. **Preserve or improve quality of life**
3. **Permit safe out-patient treatment**
4. **Enhance the use of the most effective anti-neoplastic agents**

MASCC
MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER

Modified - Courtesy of Gralla R, 2009

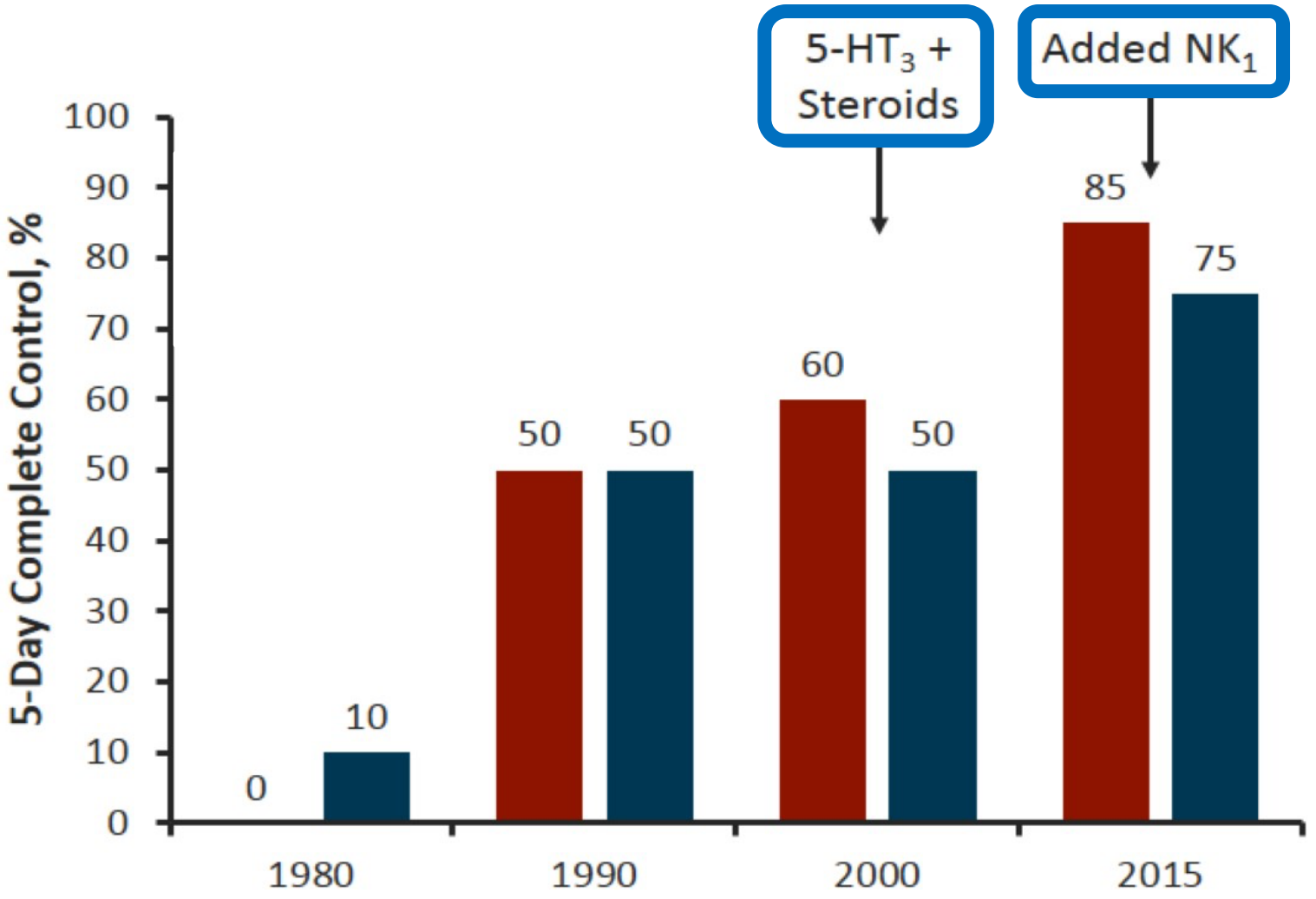
Patients' Top Concerns

Ranking	1983 [1]	1993 [2]	1995 [3]	1999 [4]	2003 [5]
1	**Vomiting**	**Nausea**	**Nausea**	**Nausea**	Fatigue
2	**Nausea**	Fatigue	Hair Loss	Hair Loss	**Nausea**
3	Hair Loss	Hair Loss	**Vomiting**	Fatigue	Sleep Problems
4	Anxiety	Family Issues	Fatigue	**Vomiting**	Weight Loss
5	Treatment duration	**Vomiting**	Injection Fear	Taste Issues	Hair Loss

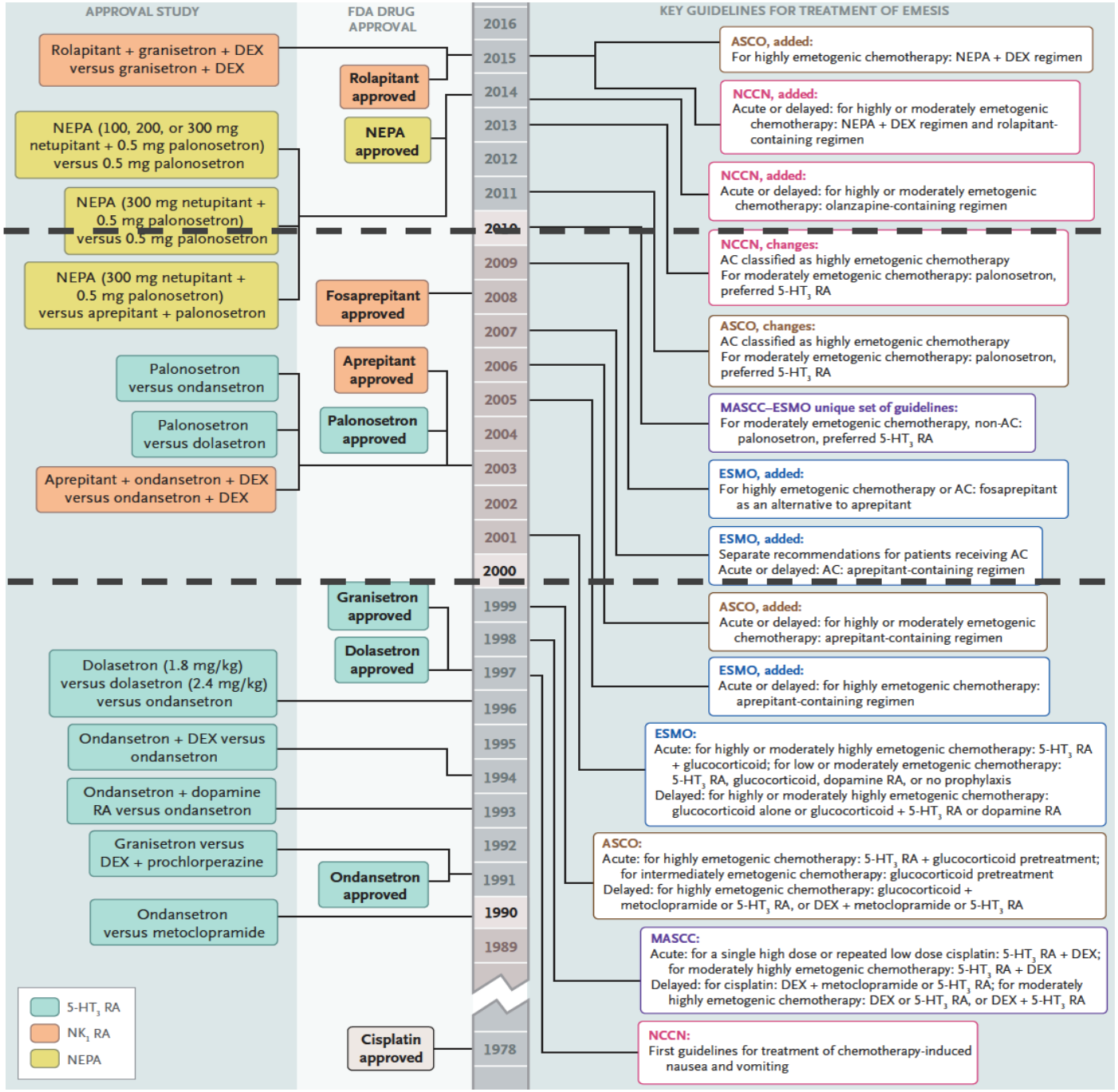
1. Coates *Eur J Cancer* 1983
2. Griffin, *Ann Oncol* 1996
3. de Boer-Dennert M, *Br J Cancer* 1997
4. Lindley *Cancer Pract 1999*
5. Hofman M, *Cancer 2004*

Modified by Di Maio M (2010) & Kris M (2012)

Improved Ability to Control Chemotherapy Induced Nausea & Vomiting (CINV)



Gralla R, Medscape Feb 2016

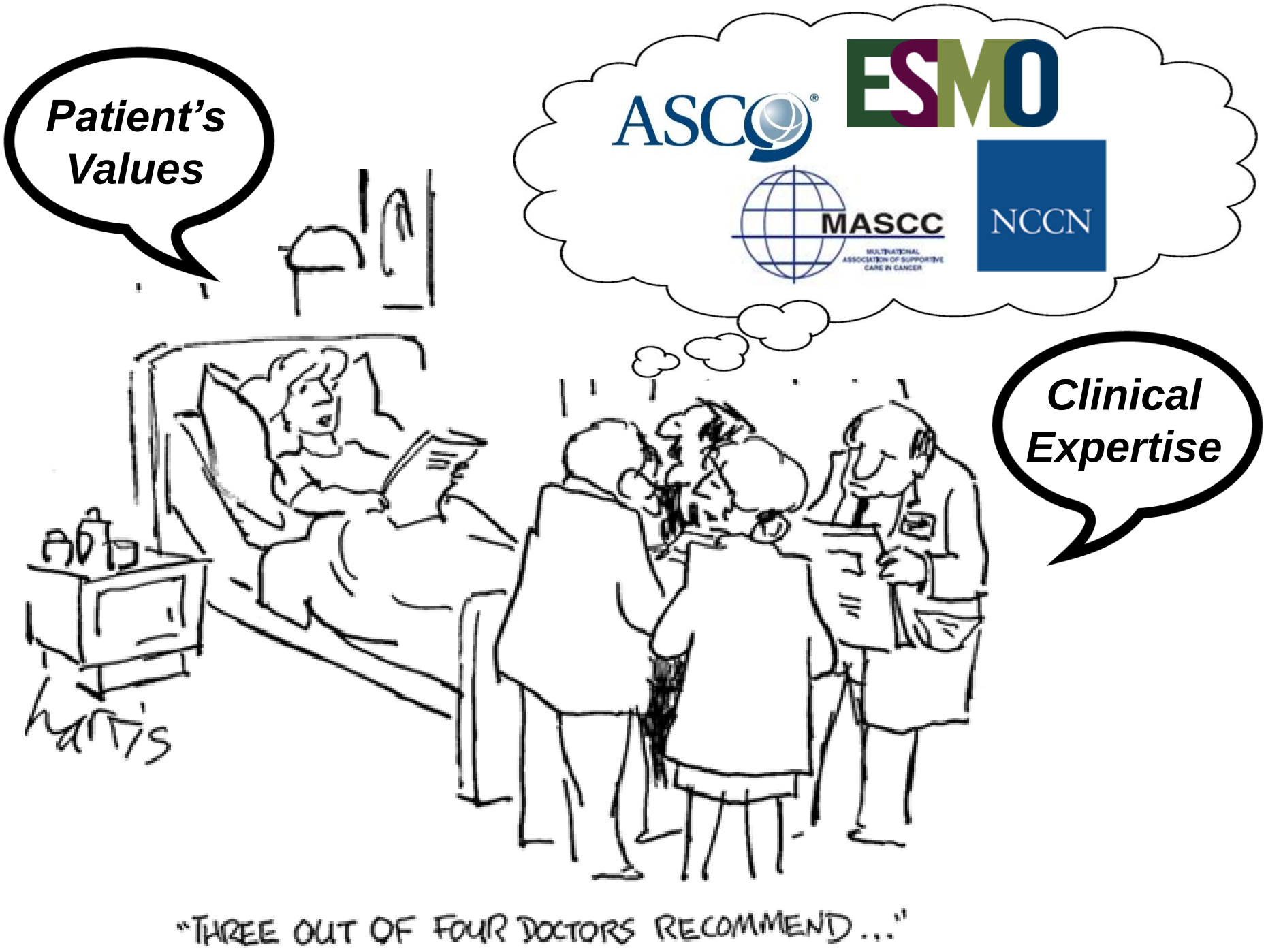


New Drugs
Combos
Strategies

NK1 &
***Newer* 5HT3**

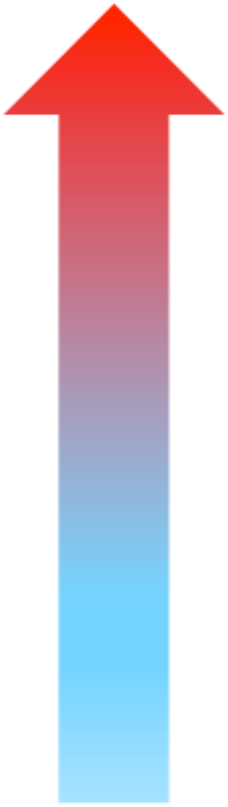
DEX &
***Older* 5HT3**

Navari R, Aapro M, NEJM 2016


Patient's Values
ASCO
ESMO
MASCC
MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER
NCCN
Clinical Expertise
harris
"THREE OUT OF FOUR DOCTORS RECOMMEND..."

EMETOGENIC POTENTIAL of I.V. Agents

(MASCC / ASCO / ESMO Guidelines)



Chemotherapy	Risk	Examples
High	> 90%	Cisplatin, streptozocin, carmustine, dacarbazine
Moderate	30–90%	Carboplatin, cyclophosphamide, doxorubicin, ifosfamide, oxaliplatin, irinotecan, alemtuzumab, azacitidine, bendamustine
Low	10–30%	Etoposide, gemcitabine, 5-FU, docetaxel, paclitaxel, cetuximab, catumaxomab, panitumumab
Minimal	< 10%	Vinca alkaloids, bleomycin, bevacizumab

Basch E et al. J Clin Oncol. 2911; 29:4198-4198 (ASCO Guideline).
Roila, F. et al Ann Oncol. 2010;21:v232–v243.

Courtesy of Jordan J, 2014

EMETOGENIC POTENTIAL of Agents

……..is evolving!

Forty new agents identified

The reported **incidence of vomiting varied** across studies for many agents, but there was adequate evidence to allow **37 new agents to be classified** according to emetogenic risk:

No **highly emetogenic** agents identified

6 **moderately emetogenic:**
IV : peg-lipo doxorubicin, romidepsin, temozolomide, trabectedin
PO: bosutinib, crizotinib

31 agents were identified as **low (23) or minimally (8)** emetogenic

Hesketh P, MASCC 2015

2013: MASCC & ESMO Guidelines

HEC

a. Hesketh PJ, et al. *J Clin Oncol.* 2003;21:4112-4119; b. Poli-Bigeli S, et al *Cancer.* 2003;97:3090-3098.

AC

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

Non-AC MEC

a. Schwartzberg L, et al. *Support Care Cancer.* 2013 Oct 19. [Epub ahead of print]; b. Gralla R, et al. *Ann Oncol.* 2003;14:1570-1577; c. Eisenberg P, et al. *Cancer.* 2003;98:2473-2482; d. Aapro MS, et al. *Ann Oncol.* 2006;17:1441-1449; e. Saito M, et al. *Lancet Oncol.* 2009;10:115-124.

Gralla RJ, Medscape 2013

2016: ASCO & NCCN Guidelines

ASCO guidelines[6]		
High (including AC)	5-HT_3–receptor antagonist, dexamethasone, and aprepitant	Dexamethasone and aprepitant
	NEPA and dexamethasone	Dexamethasone
Moderate	Either palonosetron and dexamethasone or 5-HT_3–receptor antagonist, dexamethasone, and aprepitant	5-HT_3–receptor antagonist, dexamethasone, or aprepitant
Low	Dexamethasone	—
NCCN guidelines[11]		
High (including AC)	5-HT_3–receptor antagonist and dexamethasone, plus one of the following agents: aprepitant, fosaprepitant, or rolapitant§	Aprepitant plus dexamethasone¶
	NEPA and dexamethasone§	Dexamethasone
	Olanzapine, palonosetron, and dexamethasone§	Olanzapine
Moderate	5-HT_3–receptor antagonist and dexamethasone, with or without aprepitant, fosaprepitant, or rolapitant§	5-HT_3–receptor antagonist,‖ dexamethasone, or aprepitant with or without dexamethasone**
	NEPA and dexamethasone§	Dexamethasone may be used
	Olanzapine, palonosetron, and dexamethasone§	Olanzapine
Low	Dexamethasone§, metoclopramide§, prochlorperazine§, or 5-HT_3–receptor antagonist§ (ondansetron, granisetron, or dolasetron)	—

Navari R, Aapro M, NEJM 2016

NEPA + DEX *vs.* PALO + DEX

AC

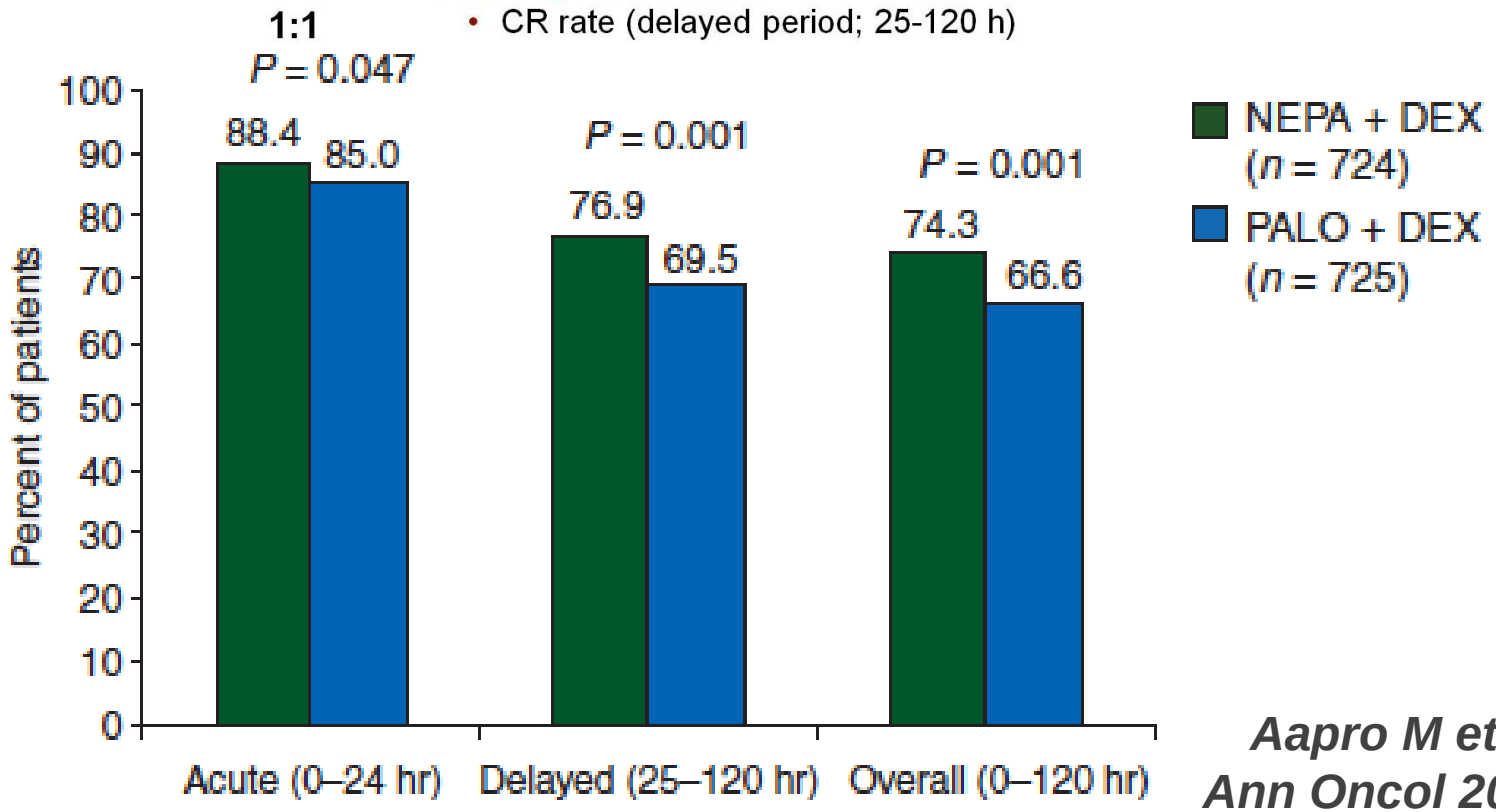
Chemotherapy-naive patients scheduled to receive AC-based MEC
N = 1455

→ RANDOMIZE 1:1

- Oral NEPA (netupitant 300 mg + oral palonosetron 0.50 mg) + oral dexamethasone 12 mg -- d 1 only
  N = 724 → **NEPA + DEX 12**
- Oral palonosetron 0.50 mg + oral dexamethasone 20 mg -- d 1 only
  N = 725 → **PALO + DEX 20**

Primary End Point:

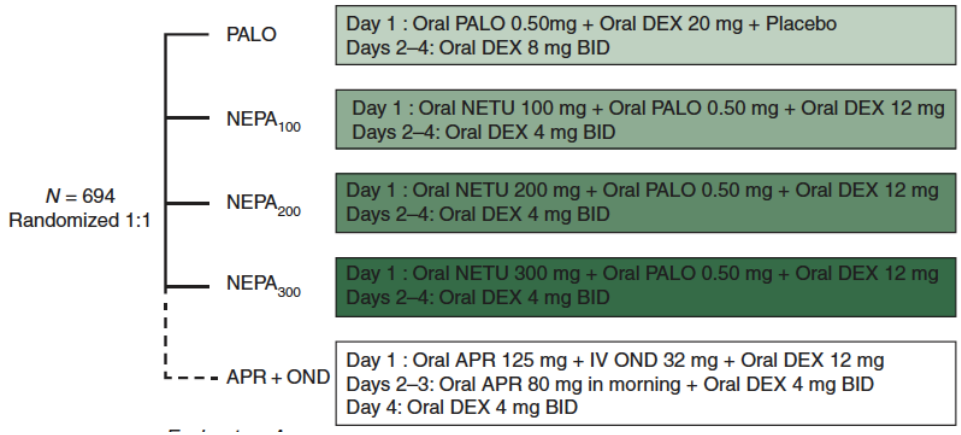
- CR rate (delayed period; 25-120 h)

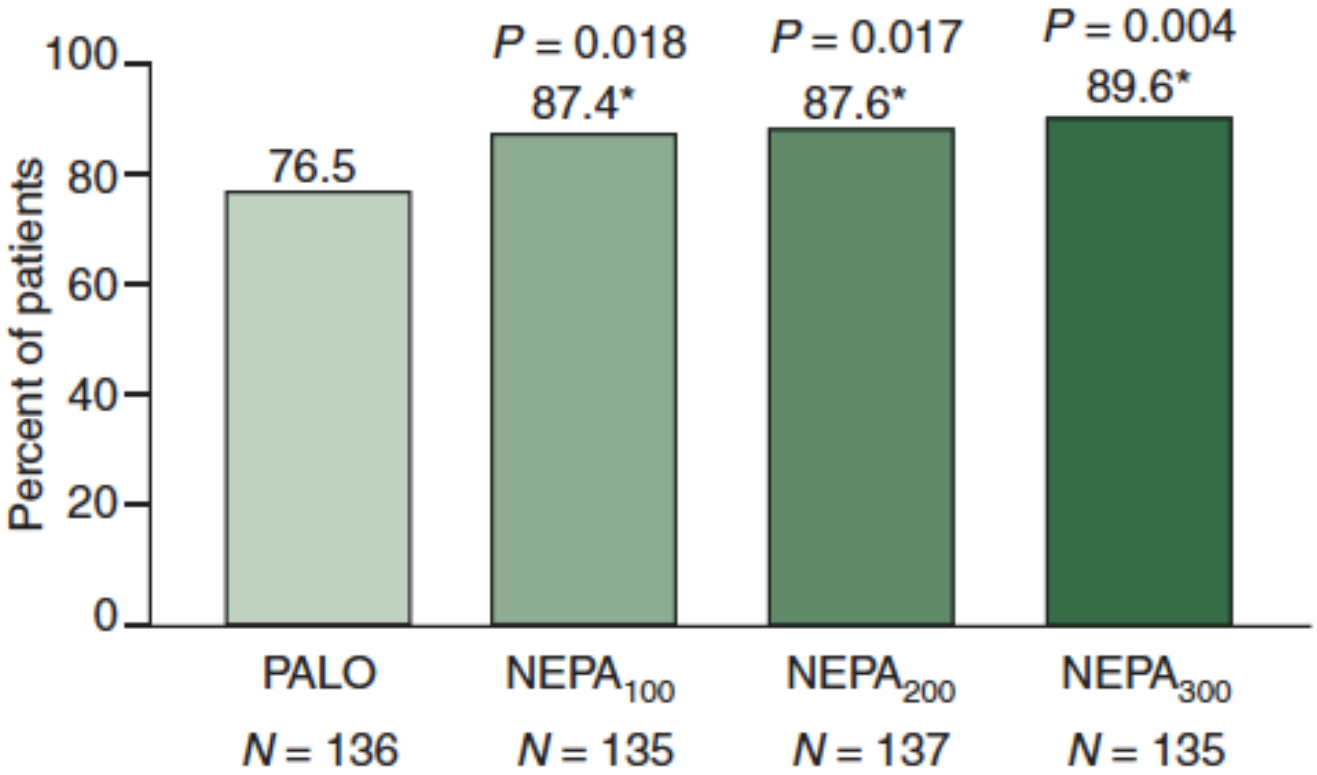


Aapro M et al, Ann Oncol 2014

NEPA + DEX *vs.* PALO + DEX

HEC



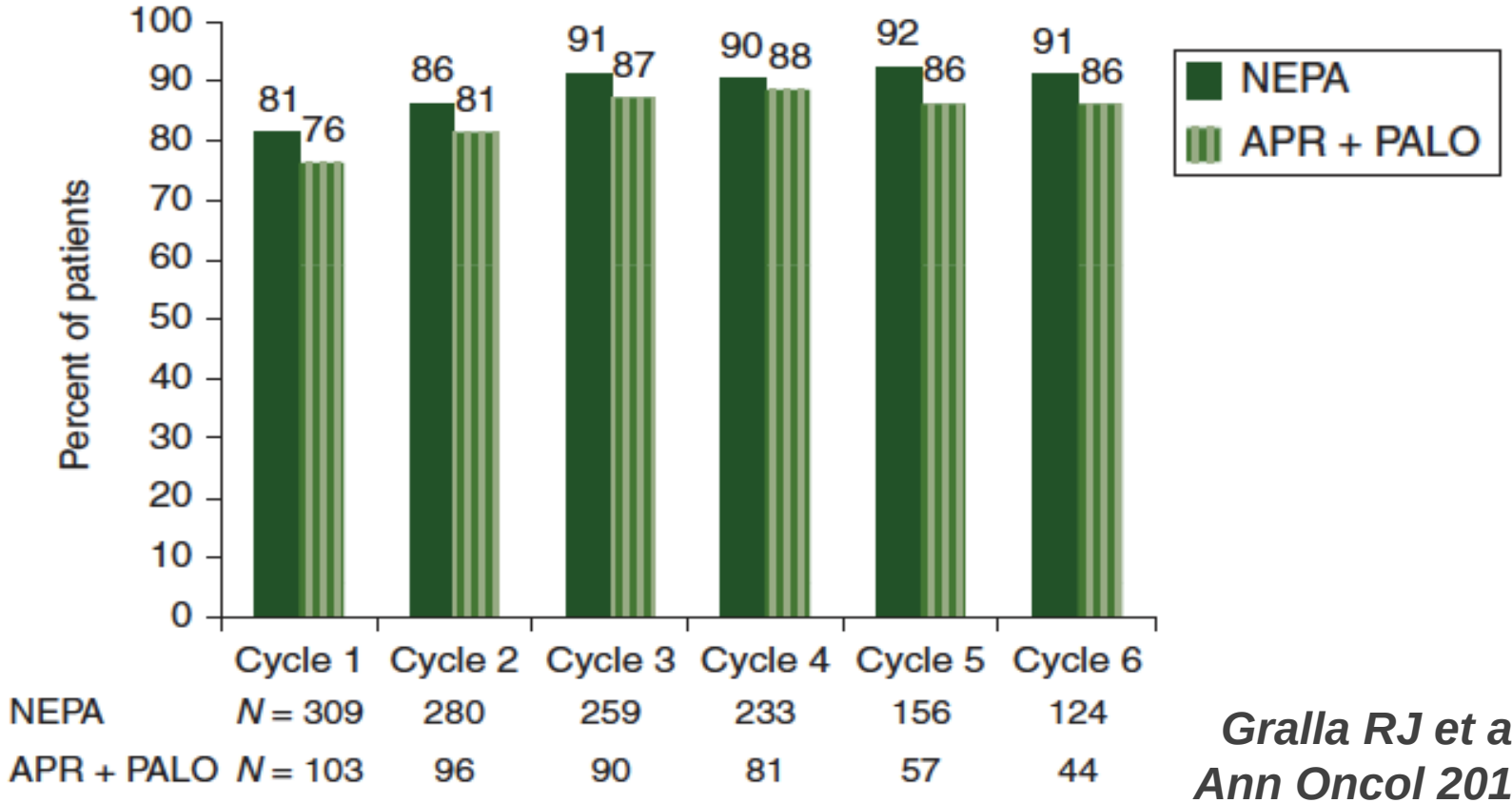


Hesketh P et al, Ann Oncol 2014

NEPA + DEX *vs.* APR/PALO + DEX

MEC
HEC

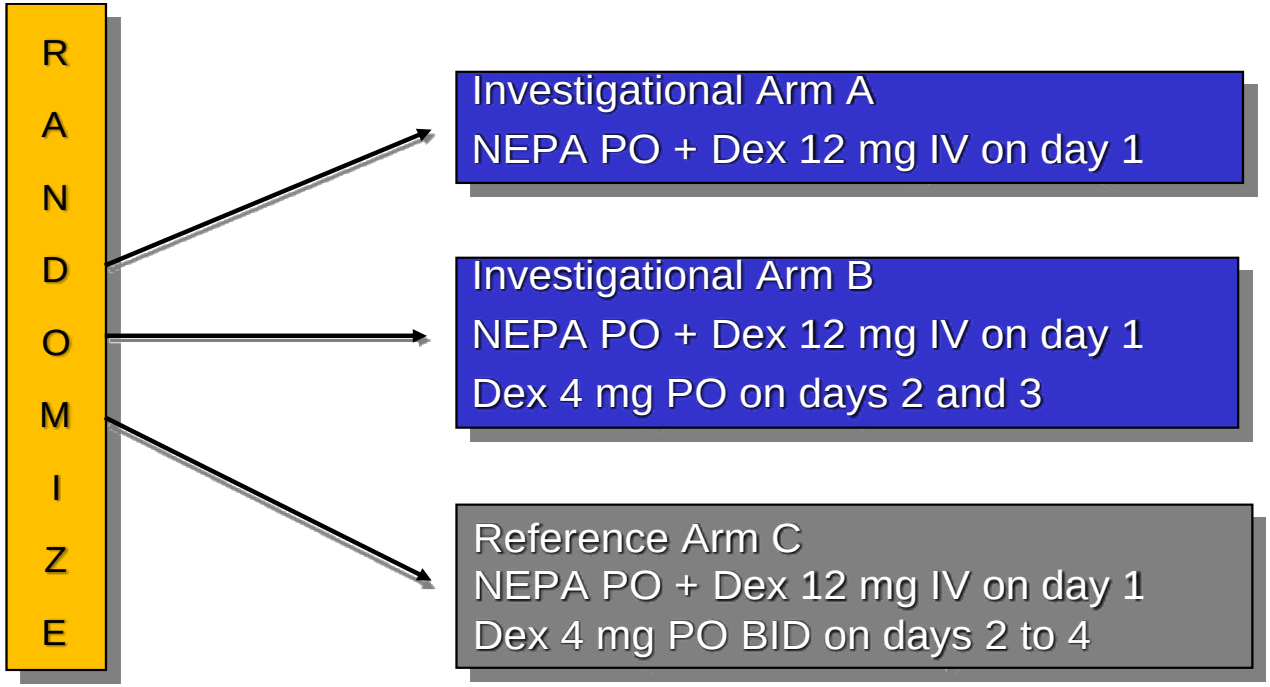
Randomized 3:1	Group	Day 1	Days 2 and 3	Day 4	
75/25% Naive to MEC/HEC	NEPA	NEPA (NETU 300 mg + PALO 0.5 mg) + DEX 12 mg (HEC & MEC)	HEC: DEX 8 mg MEC: none	HEC: DEX 8 mg MEC: none	**NEPA + DEX 12**
	APR + PALO	APR 125 mg + PALO 0.5 mg + DEX 12 mg (HEC & MEC)	HEC: APR 80 mg + DEX 8 mg MEC: APR 80 mg	HEC: DEX 8 mg MEC: none	**APR / PALO + DEX 12**



Gralla RJ et al, Ann Oncol 2014

NEPA w/o DEX (DEX-Sparing Strategy) for CIS-based CINV in NSCLC

Phase III, randomized, multicenter, open-label, parallel-group, active-comparator, three-arm, non-inferiority study

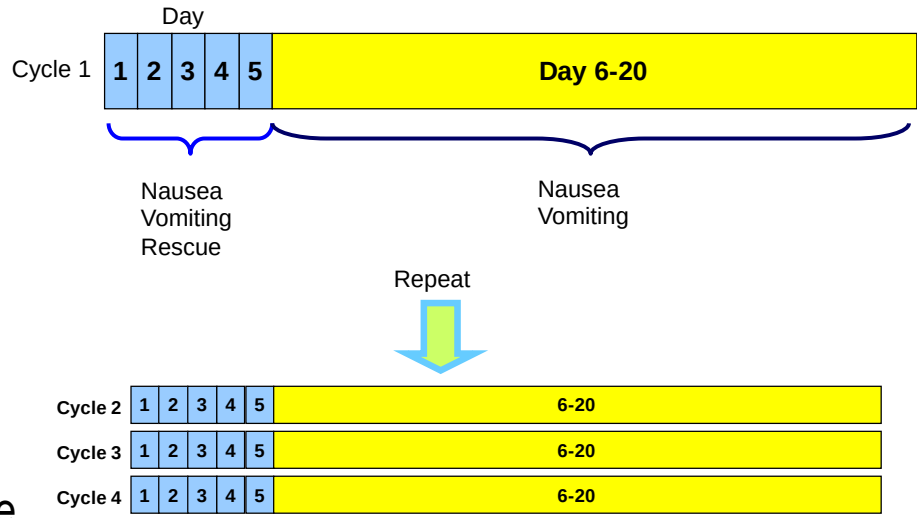


Sponsor	**Consorzio ONCOTECH**
Principal Investigator	**Emilio Bria, Verona**
Study Protocol	**Luigi Celio, Milan**
Cancer-associated weight loss study	**Augusto Caraceni, Milan**
Statistician	**Erminio Bonizzoni, Milan**

- **Arms A, B and C**: NEPA will be given 60 min before chemotherapy on day 1 Dex will be given 30 min before chemotherapy on day 1
- **Arm B**: Dex will be given in the morning on days 2 and 3
- **Arm C**: Dex will be given in the morning and in the evening on days 2 to 4

GIM 15: NEPA plus DEX for AC-based regimens

Study coordinator: Dr Michele De Laurentiis



- Open-label, 1 arm trial (non-comparative)
- AC-based chemotherapy multicycles (up to a maximum of 4 cycles): the time between two consecutive cycles is 21 days
- Prevention with NEPA: one dose on Day 1 before each CT administration
- Dexamethasone IV, 12 mg, on Day 1
- Conducted in 35 centres
- Number of patients: 150, to have 135 evaluable (10% lost to follow up), according to a Fleming design)
- Enrolment time: 12 months

To evaluate whether the efficacy on CINV of a single dose NEPA (co-administered with dexamethasone) on Day 1 of each AC-based chemotherapy is maintained throughout the duration of the whole chemotherapy treatment (up to 4 cycles)

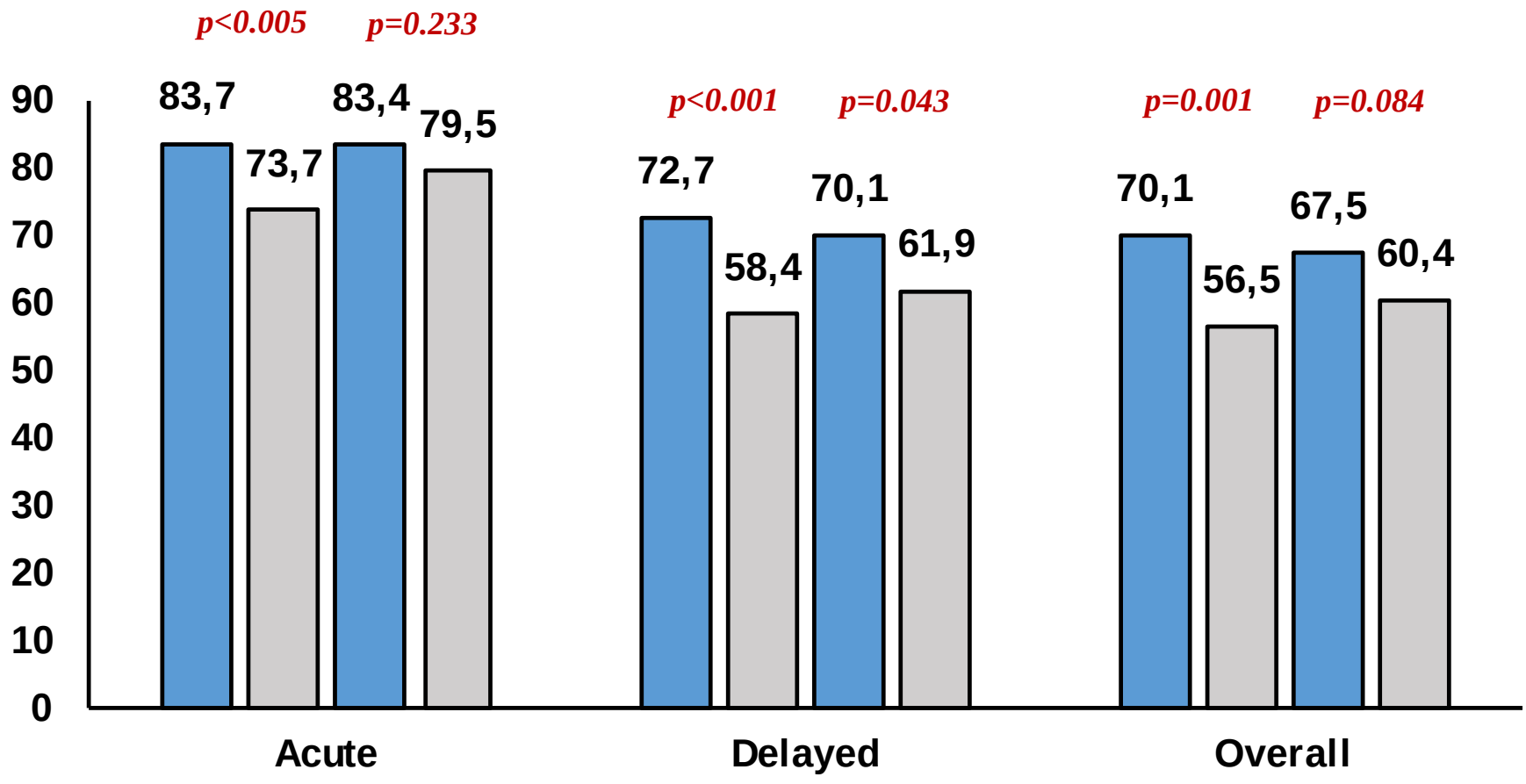
Safety evaluation throughout the whole observation period

NB: Advanced/Metastatic Breast Cancer EXCLUDED

ROLA + GRAN/DEX *vs.* GRAN/DEX

2 RCTs: 526 & 544 pts

HEC



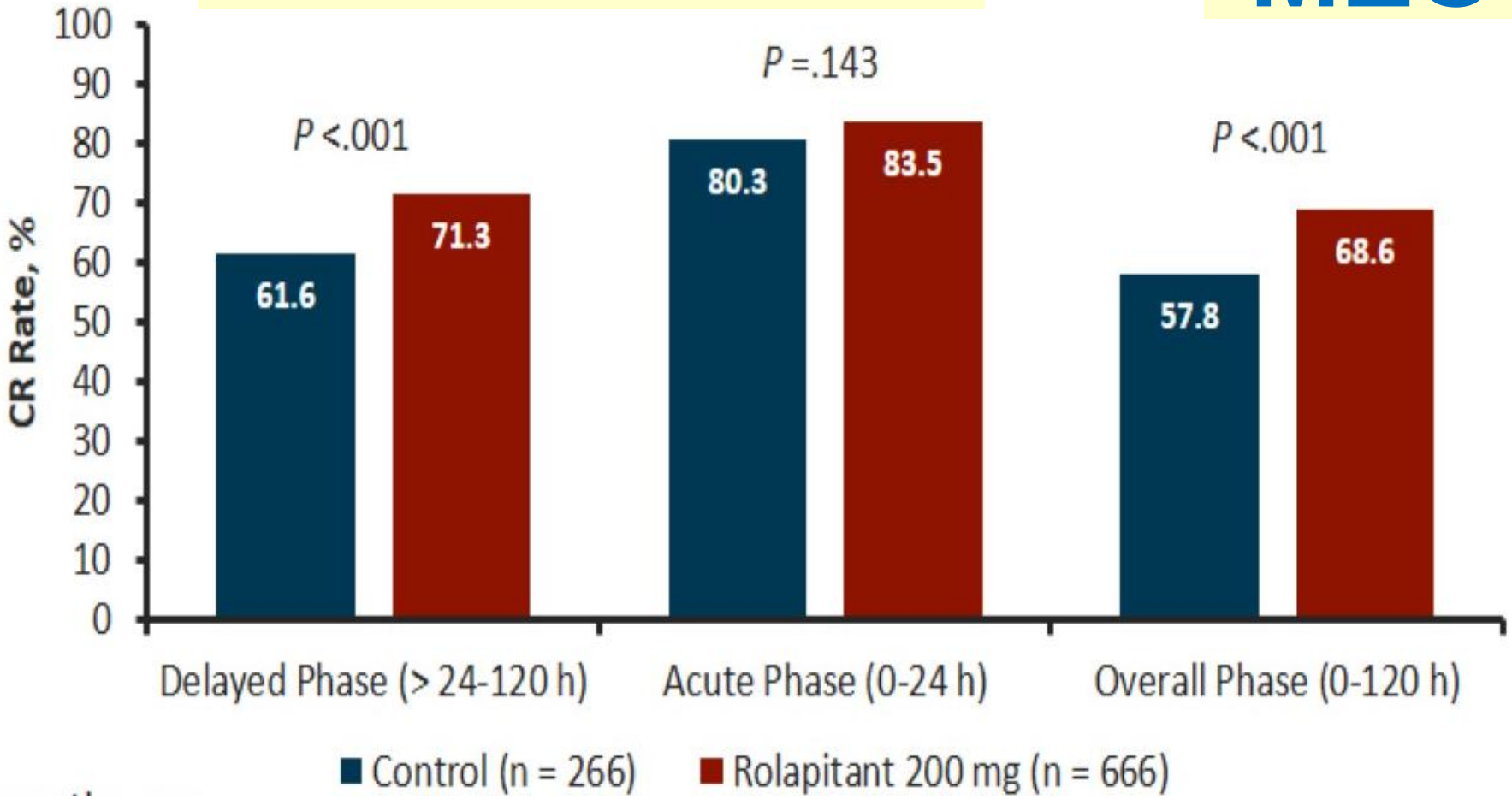
End-Point: Complete Response (%) at cycle 1

Jordan K, Ann Oncol 2015

ROLA + GRAN/DEX *vs.* GRAN/DEX

63% Breast Cancer; 53% AC

MEC

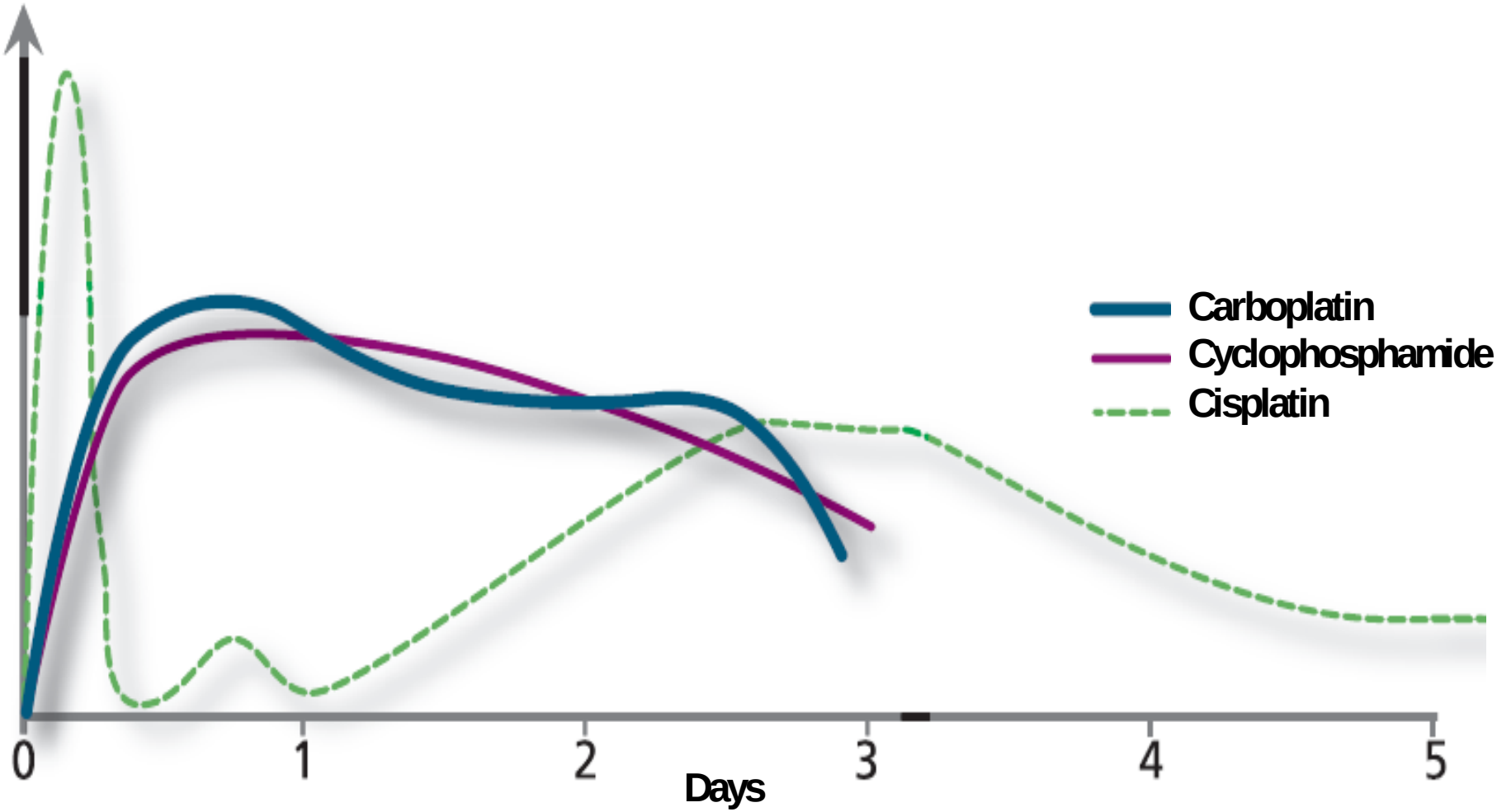


End-Point: Complete Response (%) at cycle 1

Schwarzberg LS et al, Lancet Oncol 2015

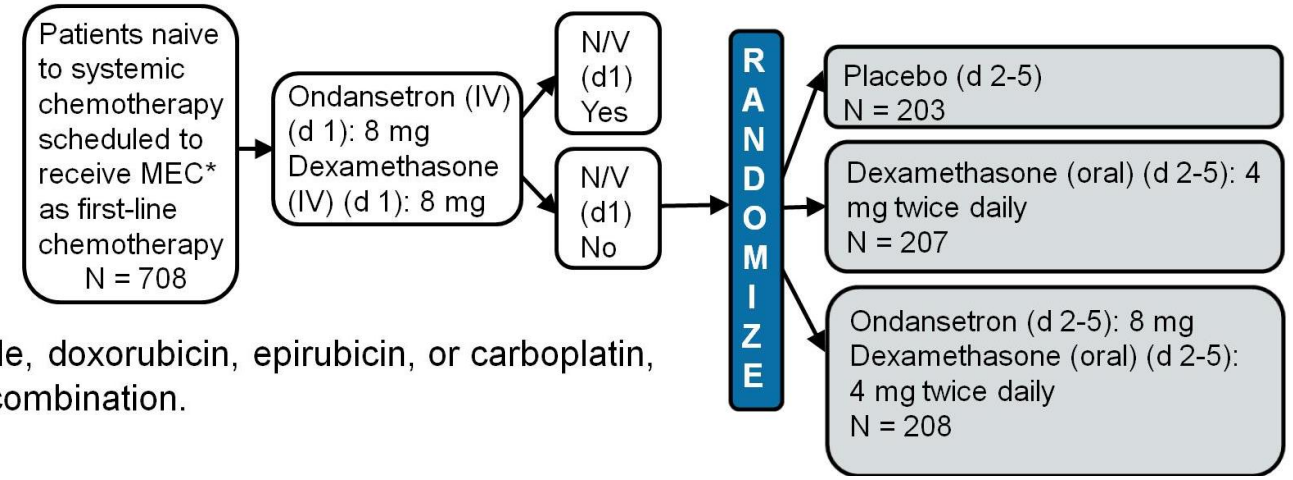
DELAYED EMESIS

- Do we use Agents in these Classes Optimally? -



Aapro et al. Oncology 2005

The Italian Group for Antiemetic Research 2000



*Cyclophosphamide, doxorubicin, epirubicin, or carboplatin, either alone or in combination.

	Placebo	Dexamethsone (d 2-5)	Ondansetron + Dexamethasone (d 2-5)	*P* Value for Overall Comparison Between 3 Groups
No emesis (delayed period)	87.3%	92.3%	95.2%	.02
No moderate or severe nausea (delayed period)	81.8%	89.4%	93.3%	.002

The Italian Group for Antiemetic Research. *N Engl J Med.* 2000;342:1554-1559.

- Conclusion: Dexamethasone alone is an optimal approach for the prevention of CINV during the delayed period in this patient population.

Raftopoulos H, Medscape 2013

Issues for Delayed Emesis Control

The '*Dex-Sparing*' Strategy

Author (year)	N	Type of chemo	Anti-emetic regimens	Overall CR
Aapro (2010)	300	**AC**	**Palo + Dex d1** vs. Palo + Dex d1-3	**53.6%** *vs.* **53.7%**
Celio (2011)	332	**MEC**	**Palo + Dex d1** vs. Palo + Dex d1-3	**67.5%** *vs.* **71.1%**
Komatsu (2015)	305	**nonAC-MEC**	**Palo + Dex d1** vs. Palo + Dex d1-3	**68.2%** *vs.* **64.7%**

All non inferiority trials; Primary endpoint: Complete Response

Aapro M et al. Ann Oncol 2010
Celio L et al. Support Care Cancer 2011
Komatsu Y et al. Cancer Sci 2015

Issues for Delayed Emesis Control

What is the best Strategy?

Day 1 (before chemo): PALO i.v. 0.25 + DEX (8 or 12) mg + APR 125 mg

Author (year)	N	Type of chemo	Anti-emetic regimens	Overall CR
Roila (2014)	508	**AC**	**DEX** ***vs.*** **APR**	**79.5%** *vs.* **79.5%**
Roila (2015)	332	**HEC**	**APR + DEX** ***vs.*** **MTC + DEX**	**80.3%** *vs.* **82.5%**

Both superiority (DEX > APR and APR > MTC);
Primary endpoint: Complete Response

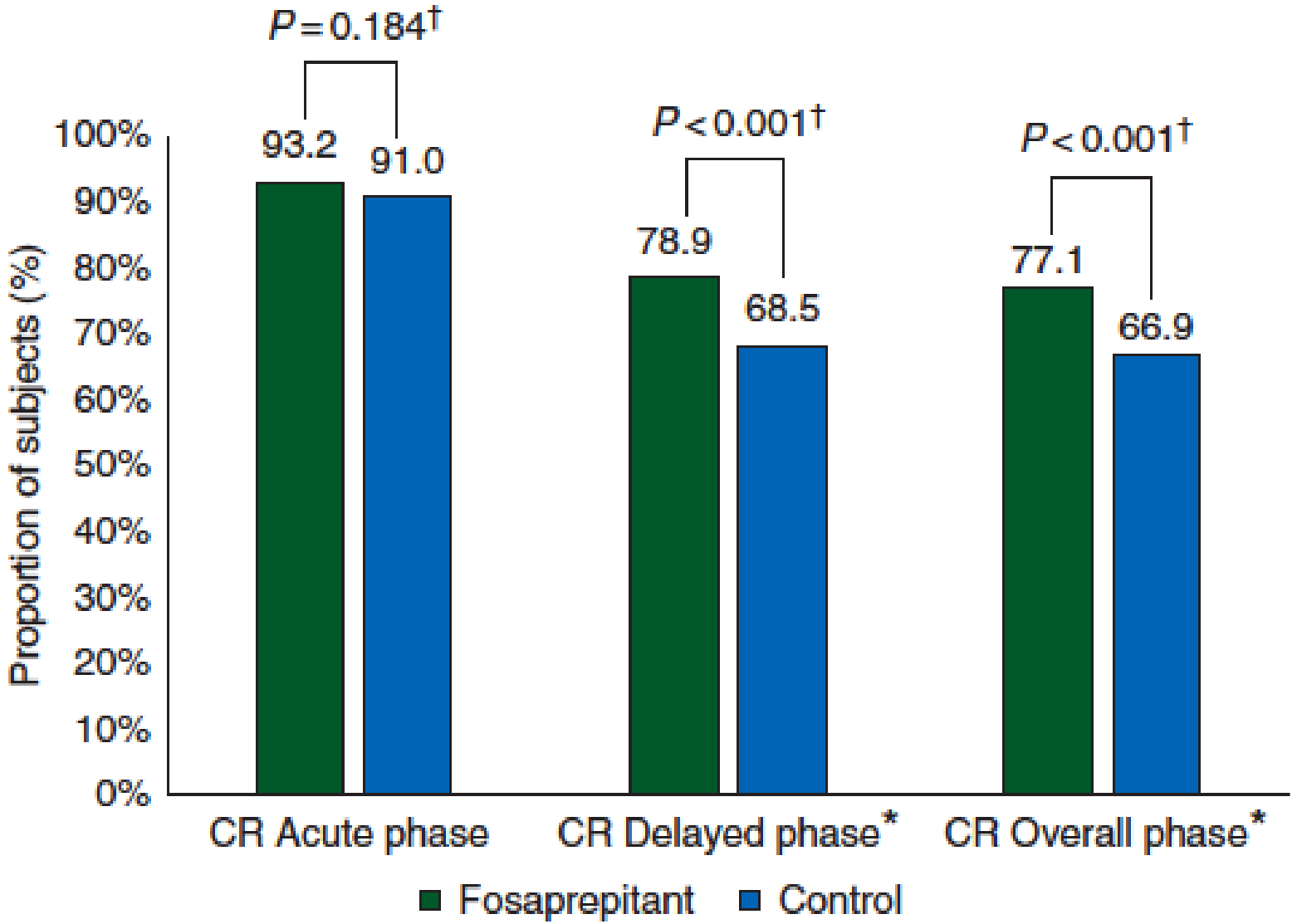
Roila F et al, JCO 2014
Roila F et al, Ann Oncol 2015

(FOS)Aprepitant for nonAC-MEC

Regimen	Study Medication	Day 1 Dose	Day 2 Dose	Day 3 Dose
Fosaprepitant	Fosaprepitant	150 mg IV	None	None
	Ondansetron 8 mg	1 capsule 30-60 min prior to MEC; 1 capsule 8 h after first dose	1 placebo capsule q12h	1 placebo capsule q12h
	Dexamethasone 12 mg[a,b]	3 capsules of 4 mg each + 2 placebo capsules[b]	None	None
Control	Placebo	150 mL normal saline IV	None	None
	Ondansetron 8 mg	1 capsule 30-60 min prior to MEC; 1 capsule 8 h after first dose	1 capsule q12h	1 capsule q12h
	Dexamethasone 20 mg[a]	5 capsules of 4 mg each	None	None

Weinstein C et al, Ann Oncol 2016

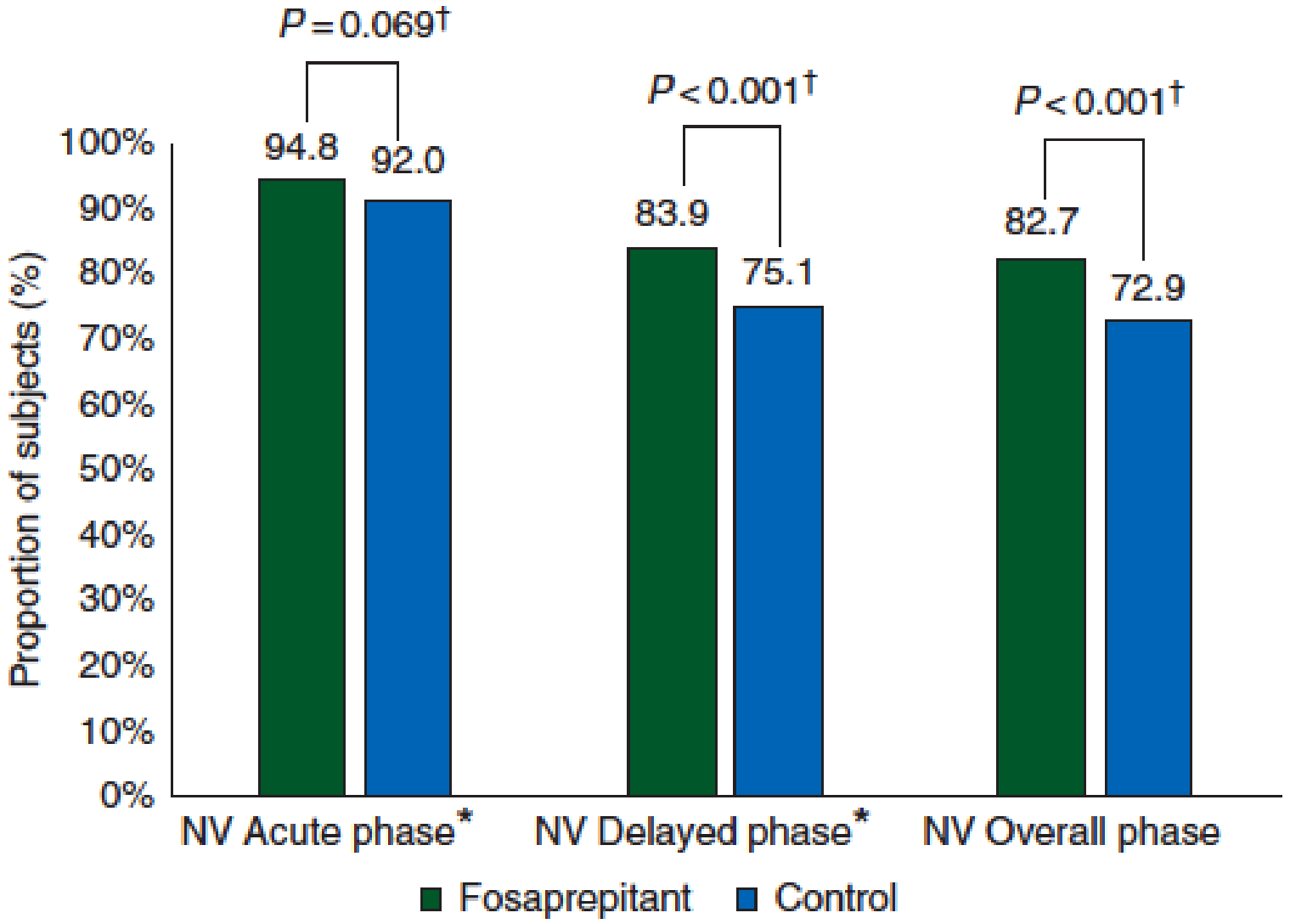
(FOS)Aprepitant for nonAC-MEC



COMPLETE RESPONSE

Weinstein C et al, Ann Oncol 2016

(FOS)Aprepitant for nonAC-MEC



NO VOMITING

Weinstein C et al, Ann Oncol 2016

Do Guidelines Improve Emetic Control?
- Adherence to Guidelines -

- **Adherence to (MASCC) guidelines significantly improves CINV control**
- **Utilization effects of adopting MASCC guidelines:**
  - Marked ***decrease of 5-HT3*** in the delayed emesis period
  - ***Increased*** use of ***corticosteroids***
  - ***Increased*** use of ***aprepitant***
  - *Estimated* ***equal*** or ***decreased total costs***

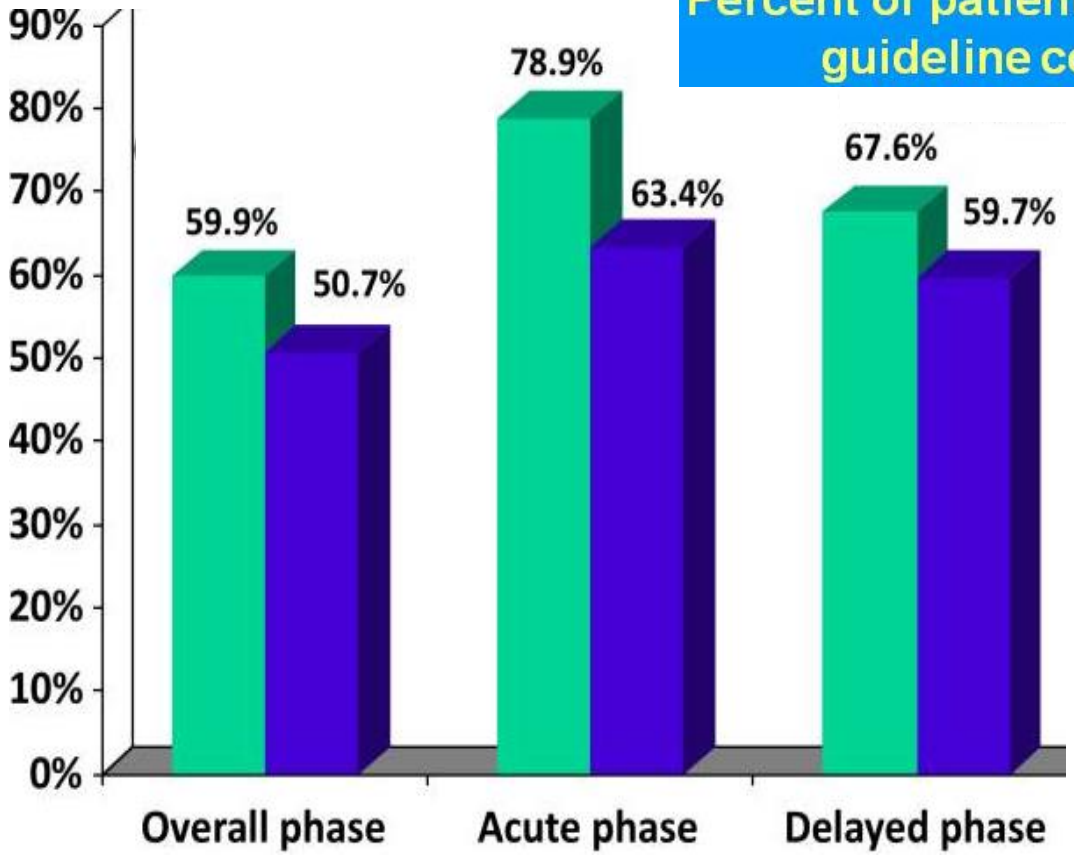
- ***PEER Investigators, Ann Oncol 2012***
- ***INSPIRE Investigators, J Oncol Practice 2013***
- ***Molassotis et al, JPSM 2013***
- ***O'Kane et al. Proc. MASCC 2009***
- ***De Moor et al. Proc. ASCO 2013***

The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER)

M. Aapro[1*], A. Molassiotis[2], M. Dicato[3], I. Peláez[4], Á. Rodríguez-Lescure[5], D. Pastorelli[6], L. Ma[7], T. Burke[7], A. Gu[7], P. Gascon[8] & F. Roila[9]; on behalf of the PEER investigators

Chemotherapy	Acute phase (day 1) GCCP	Delayed phase (days 2–4) GCCP
HEC	Corticosteroid + NK1-RA + 5HT3-RA[a]	Corticosteroid days 2–4 + NK1-RA days 2–3
Female AC	Corticosteroid + NK1-RA + 5HT3-RA[a]	Corticosteroid +/or NK1-RA days 2–3[c]
MEC	Corticosteroid + 5HT3-RA[a,b]	Corticosteroid +/or 5HT3-RA days 2–3[c]

Percent of patients with Complete Response among guideline consistency groups, by phase

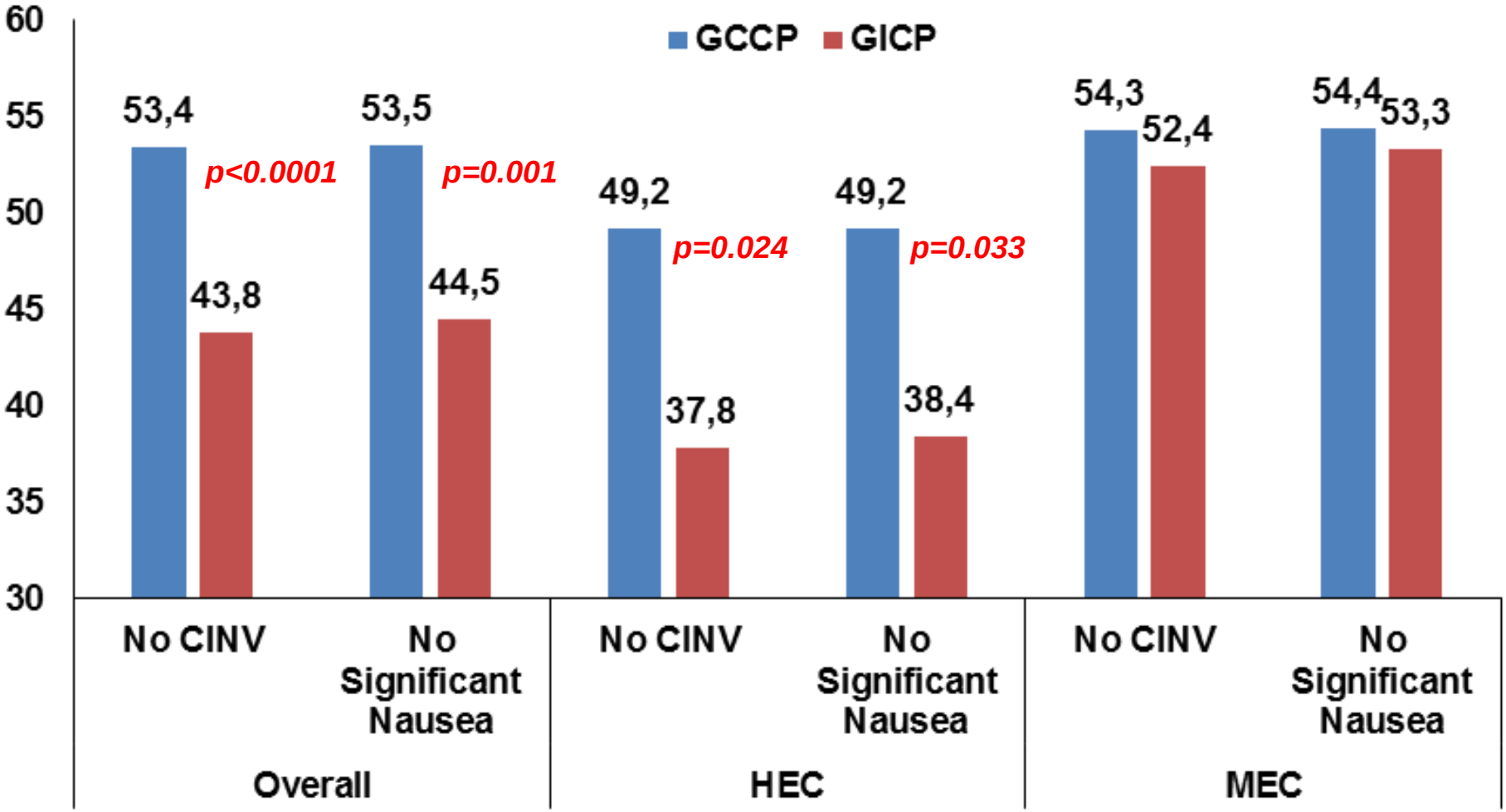


Annals of Oncology
doi:10.1093/annonc/mds021

Antiemetic Guideline Consistency and Incidence of Chemotherapy-Induced Nausea and Vomiting in US Community Oncology Practice: INSPIRE Study

By James W. Gilmore, PharmD, Nancy W. Peacock, MD, Anna Gu, MD, PhD, Stephen Szabo, MD, Melissa Rammage, PharmD, MS, Joyce Sharpe, RN, OCN, Sally T. Haislip, RPh, Toni Perry, RN, Tim L. Boozan, RN, Katherine Meador, RN, Xiting Cao, PhD, and Thomas A. Burke, PharmD, PhD

N (pts) = 1,295



Evaluation of Risk Factors Predicting Chemotherapy-Related Nausea and Vomiting: Results From a European Prospective Observational Study

Alexander Molassiotis, RN, PhD, Matti Aapro, MD, Mario Dicato, MD, FRCP, Pere Gascon, MD, PhD, Sylvia A. Novoa, MD, Nicolas Isambert, MD, Thomas A. Burke, PhD, Anna Gu, MD, PhD, and Fausto Roila, MD

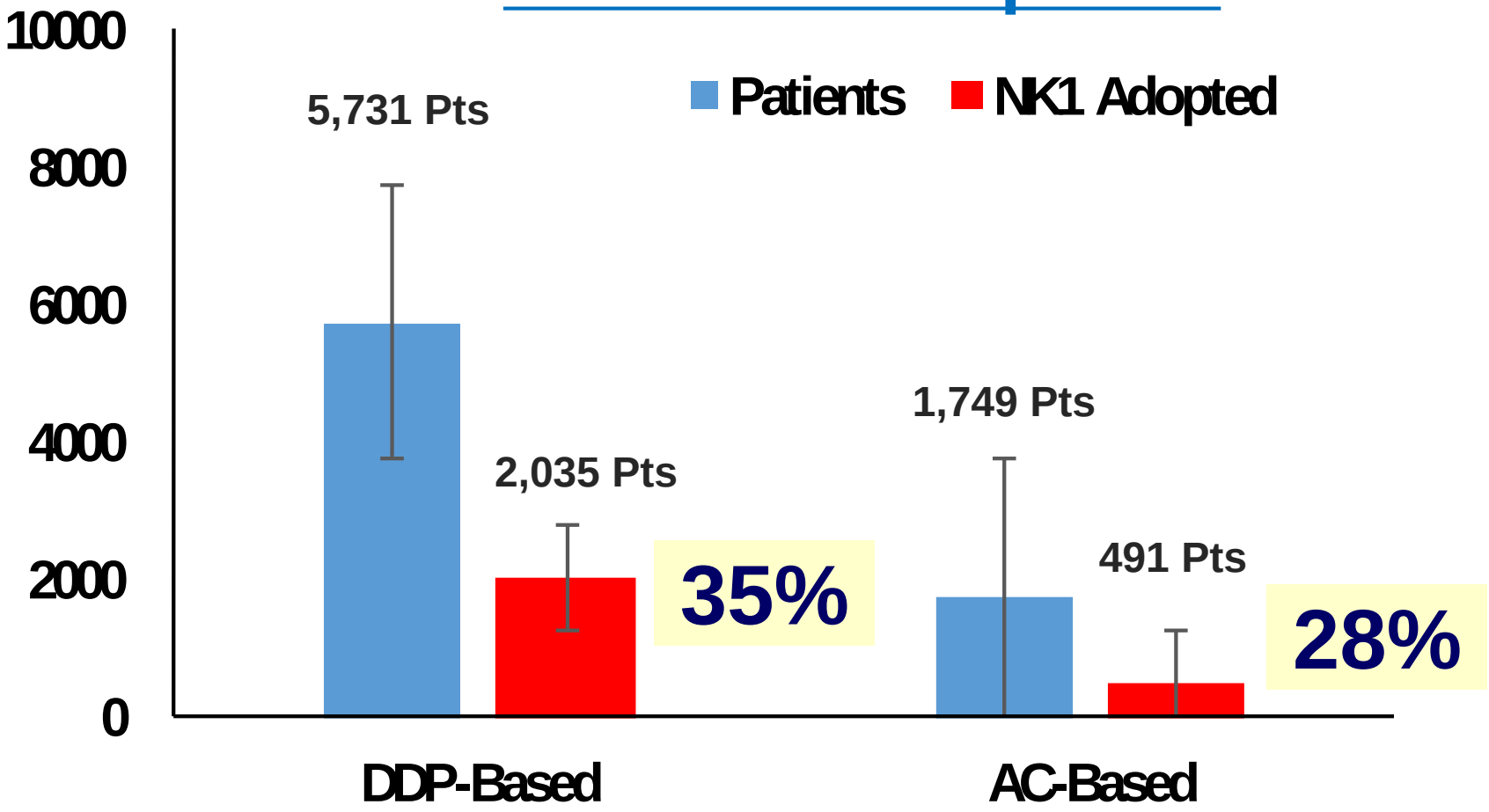
N (pts) = 991

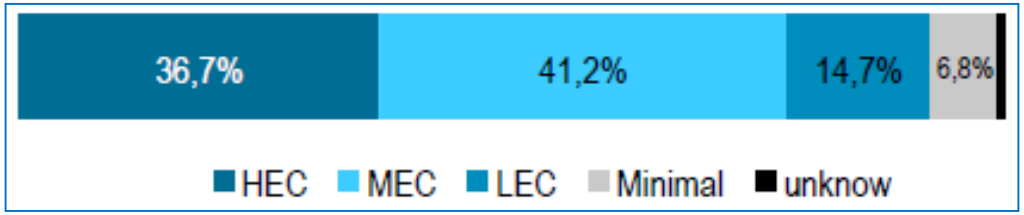
	OR (95% CI)	*P-value*
Guidelines Consistency	**1.56 (1.09-2.24)**	***<0.0001***
Age		
<50	0.40 (0.25-0.64)	*<0.0001*
50-64	0.54 (0.36-0.81)	*0.0029*
Sex	0.65 (0.42-0.98)	*0.0409*
Previous N/V	0.51 (0.34-0.76)	*0.0164*
Pre-chemo anxiety (>50)	0.37 (0.20-0.68)	*0.0015*
CR 1° course	6.63 (4.80-9.17)	*<0.0001*

Overall Phase, N (pts) = 517

2013 *Journal of Pain and Symptom Management*

Adherence to Guidelines in the '*Real World*' remains Suboptimal

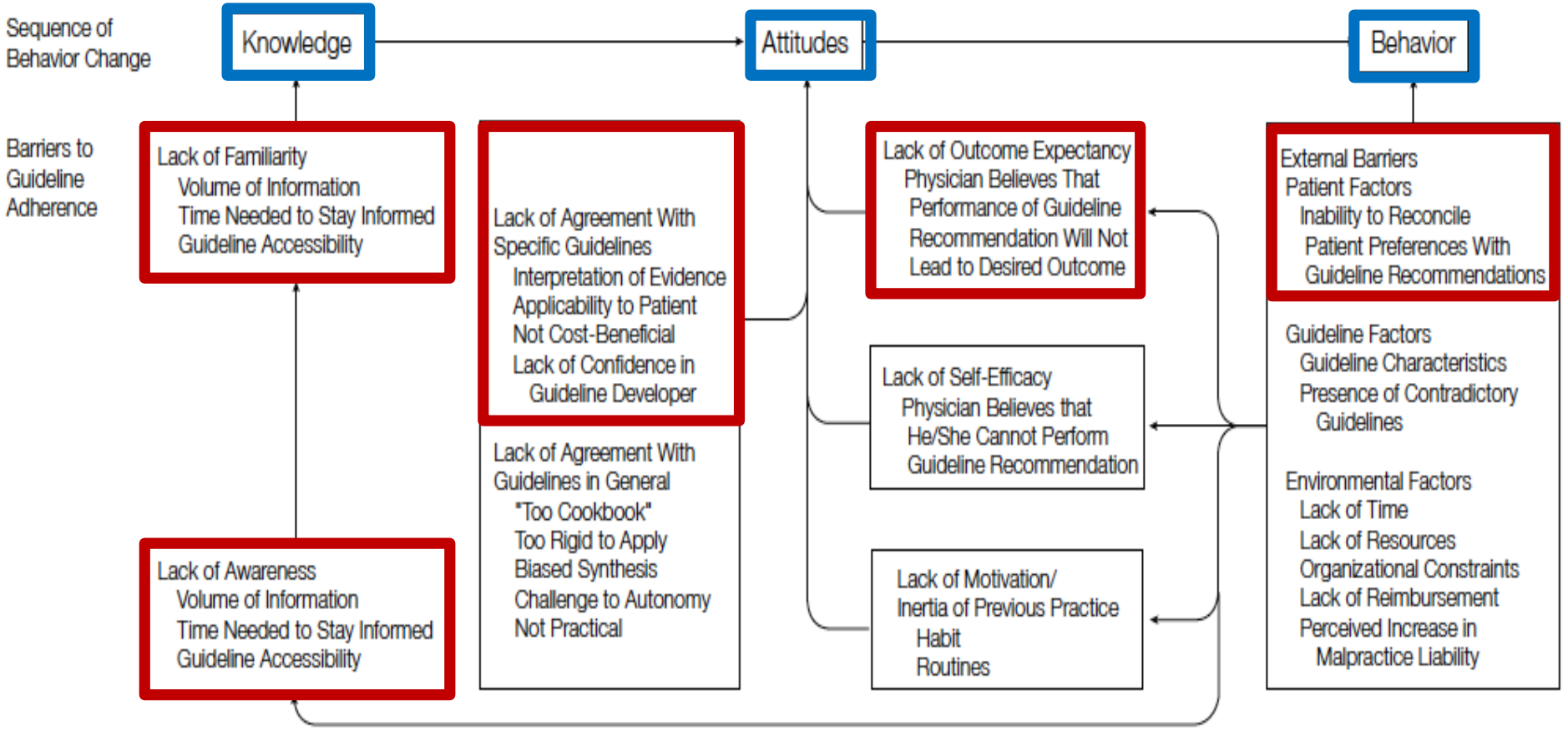




European Survey (>12,000 Pts)

Ricarte C et al, ECCO-FECS 2013

Barriers to Physician Adherence to Practice Guidelines



Cabana MD et al, JAMA 1999

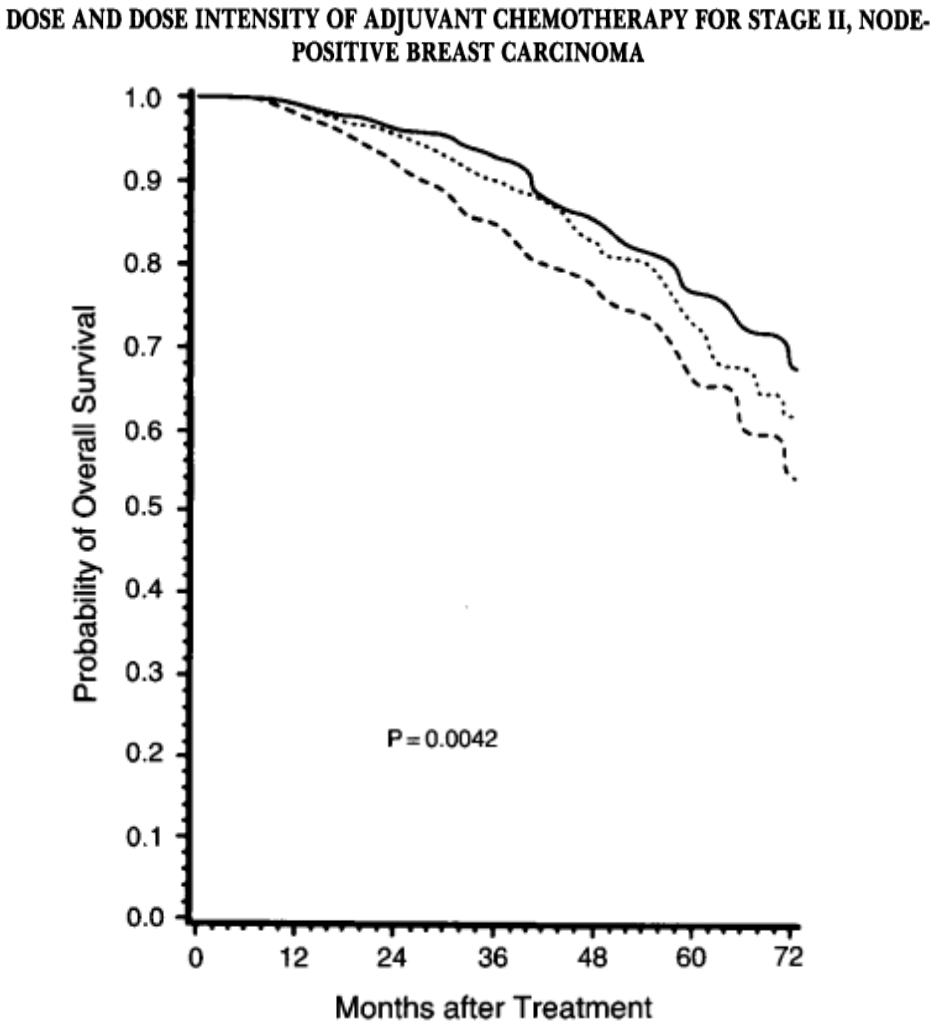
THE MULTIPLE ROLES FOR 'SUPPORTIVE CARE' IN CANCER

1. Reduce or eliminate associated symptoms and side-effects
2. Preserve or improve quality of life
3. Permit safe out-patient treatment
4. **Enhance the use of the most effective anti-neoplastic agents**

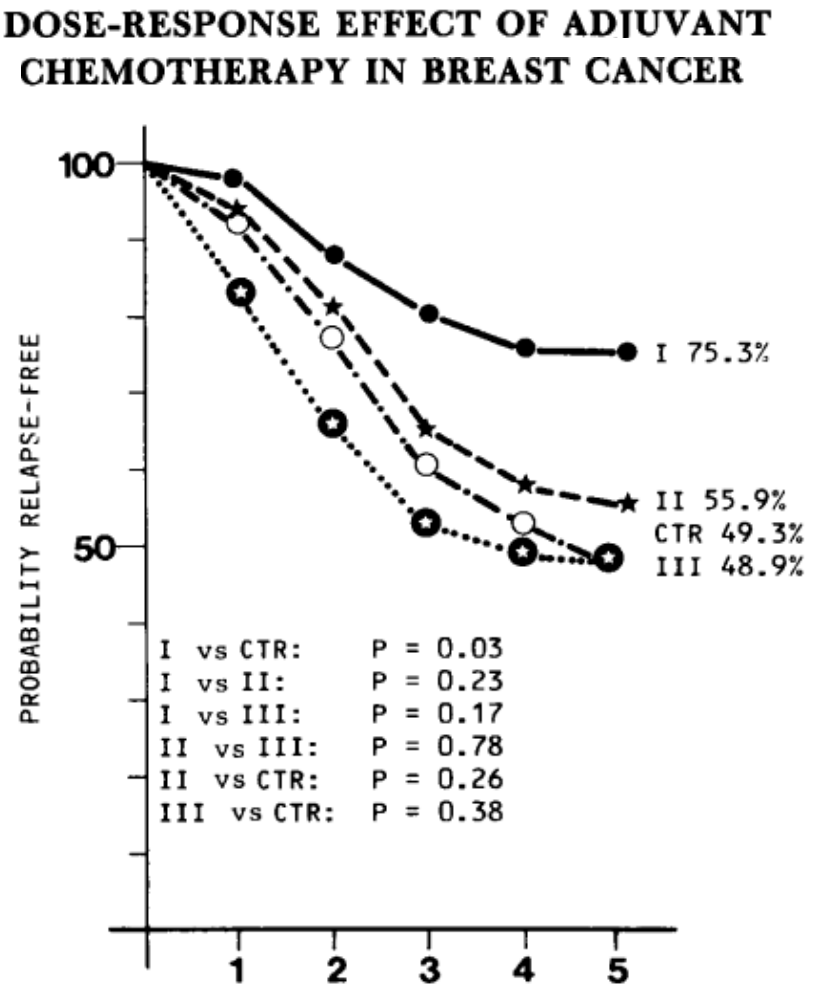
MASCC
MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER

Modified - Courtesy of Gralla R, 2009

Breast Cancer: RDI and outcome



Wood WC, NEJM 1994



Bonadonna G, NEJM 1994

Decreasing CINV may improve RDI and outcome?

Propensity score matching

Jan. 2008～Dec. 2012, 504 pts treated with A

AP group : 205 pts, nAP group 299 pts

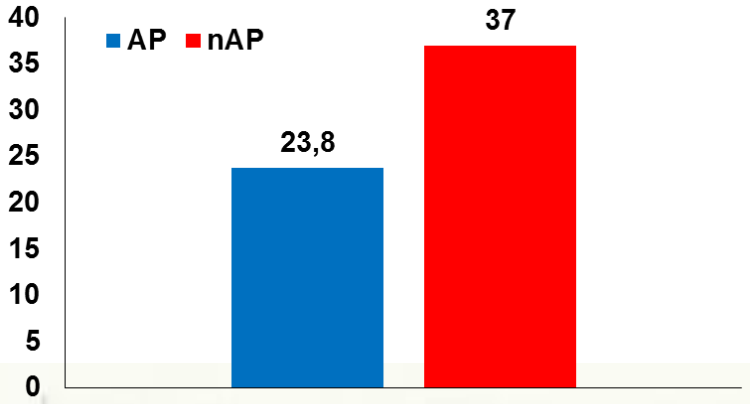
propensity score (PS)*

AP group : 181 pts, nAP group 181 pts

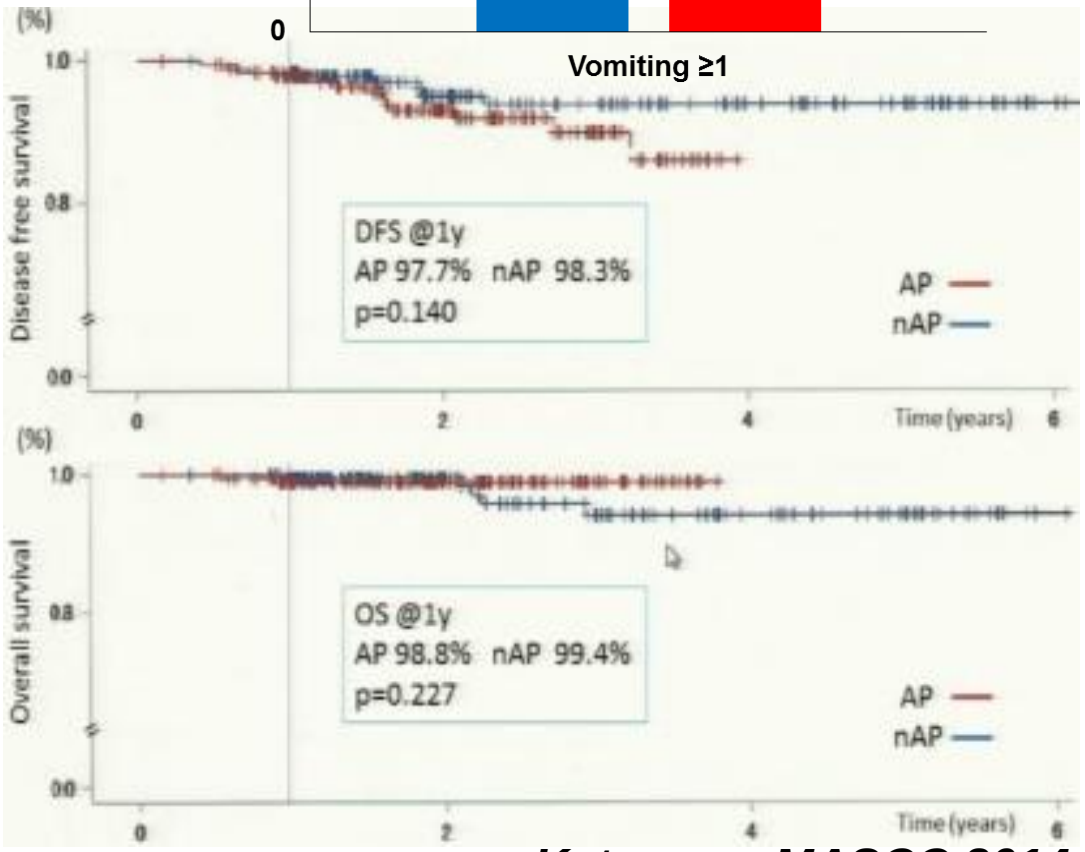
adjustment variables (age, BMI, use of taxanes, dose of corticosteroids and institute)

- **nAP group**
  - – Corticosteroid* on day 1 (iv) and day 2-4 or 5 (oral)
  - – 5HT3 receptor antagonist** on day 1 (iv)
- **AP group**
  - – oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3
  - – corticosteroid on day 1 (iv) and day 2-4 or 5 (oral)
  - – 5HT3 receptor antagonist on day 1 (iv)

* : dexamethasone, betamethasone ** : granisetron, palonosetron, ramosetron



Vomiting ≥1



Katayama MASCC 2014

Conclusions

- **AC-based chemotherapy is '*de facto*' to be considered as HEC**
  - True for ASCO, NCCN,
  - Under Consideration for MASCC, ESMO
- **Triple-drug approach (5HT3 + NK1 + DEX) is the standard in the majority of settings**
  - A two-drug strategy is now to be considered a under-treatment
  - A fully-i.v. strategy is currently available
- **Use guidelines to improve control!**
  - Clinical attitudes outside guidelines do not guarantee the best CINV prophylaxis and treatment!
- **New drugs & strategies upcoming:**
  - Newer NK1s with different profiles (*ex. Rolapitant*)
  - Newer fully-oral strategy (*ex. NEPA*)
  - New (add-on) drugs (*ex. Olanzapine*)
  - Decreasing steroids side-effects (*ex. DEX-sparing*)