FAKULTAS KEDOKTERAN
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Advancing Antiemetic Therapy for Optimal Control of Chemotherapy

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Disclaimer

- All information presented in these slides are intended for scientific exchange.
- This content may not reflect local approvals.
- Please refer to local prescribing information before use.
- Disclaimer Indication of Akynzeo in Indonesia[1]
  - Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy
  - Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy

Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022.

Outline

- Understanding CINV
- Major Antiemetic Guidelines and Goals
- Is non-adherence of antiemetic guidelines a risk factor for CINV?
- What is the Solution for CINV?
- NEPA vs APR in cisplatin-based chemotherapy setting
- Head-to-Head Comparison: NEPA vs APR AC/MEC chemotherapy

Understanding CINV*

*Chemotherapy Induced Nausea and Vomiting

Introduction: Chemotherapy Induced Nausea and Vomiting (CINV)

- **Chemotherapy-induced nausea and vomiting (CINV) is a frequent complication of chemotherapy.[1]**
- Nausea and vomiting is a life saving mechanism that has a protective role against toxins:[2]

Avoiding ingestion (nausea)

Eliminating them (vomiting)[2,3]

- Multiple patient risk factors (eg, age, gender, alcohol consumption) have been identified along with the emetogenic potential of individual or combination chemotherapeutic agents.[4]

Why is it important to address CINV?

CINV decreases compliance with cancer therapies & decreases QoL[3]

1. Aapro M, *et al*. Ann Oncol. 2012;23(8):1986-1992. 2. Horn CC. Appetite. 2008;50(2-3):430–434.
3. Janelsins MC, *et al*. Expert Opin Pharmacother. 2013;14(6):757–766. 4. Cada DJ et al. Hosp Pharm 2015;50(4):310-325.

Incidence of CINV in patients receiving emetogenic chemotherapy

Acute
32.8%[1]

of acute CINV occurs within 24 hours of chemotherapy administration[1]

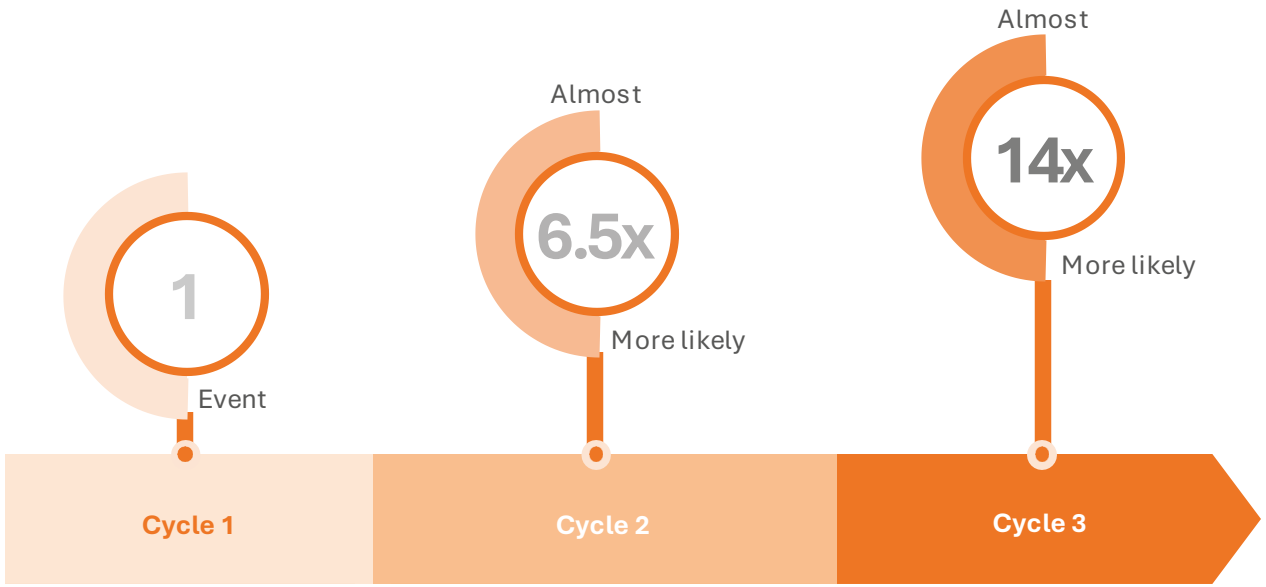
Delayed
60.7%[1]

of delayed CINV occurs from 25 to 120 hours after chemotherapy administration[1]

More than 90% of patients receiving highly emetogenic chemotherapy (HEC) will have episodes of vomiting if they don't receive an adequate anti-emetic prophylactic treatment.[2]

1. Navari and Aapro. N Engl J Med 2016;374:1356-67. 2. NCCN Guidelines Antiemesis, Version 2.2025

Risk Alert: Uncontrolled CINV from previous cycles



A retrospective observational study of 991 patients receving highly or moderately chemotherapy[1]

- CINV in the first cycle chemotherapy is a strong predictor of CINV in subsequent cycles.
- Uncontrolled CINV in the previous cycle is the **key factor for CINV in the subsequent cycle**, increasing the likelihood of CINV by 6.5 times in Cycle 2 and 14 times in Cycle 3[1]

Therefore, the best available anti-emetic prophylaxis should be administered starting from the first course of chemotherapy to maximize **prevention of CINV from the start**.

1. Molassiotis A et al. J Pain Symptom Manage 2016; 51(6):987-9

Understanding Risk Factors Helps in Determining Antiemesis Strategy

Patient-related risk factors[1]:

- Younger age (<50 years)
- Female gender
- No/minimal prior history of alcohol and tobacco use
- Susceptibility to motion sickness
- Prior CINV
- Anxiety
- Emesis during pregnancy
- Impaired performance status
- Previous exposure to chemotherapy

+

Treatment-related risk factors:[2]

- Emetogenic potential of chemotherapy agents or regimens (Hesketh classification)[3]
- Chemotherapy dose and schedule [1]
- Use of multiple chemotherapy agents[3]

Tailoring CINV treatments to the patient based on individual risk factors will greatly enhance the potential of antiemetics and to eliminate CINV

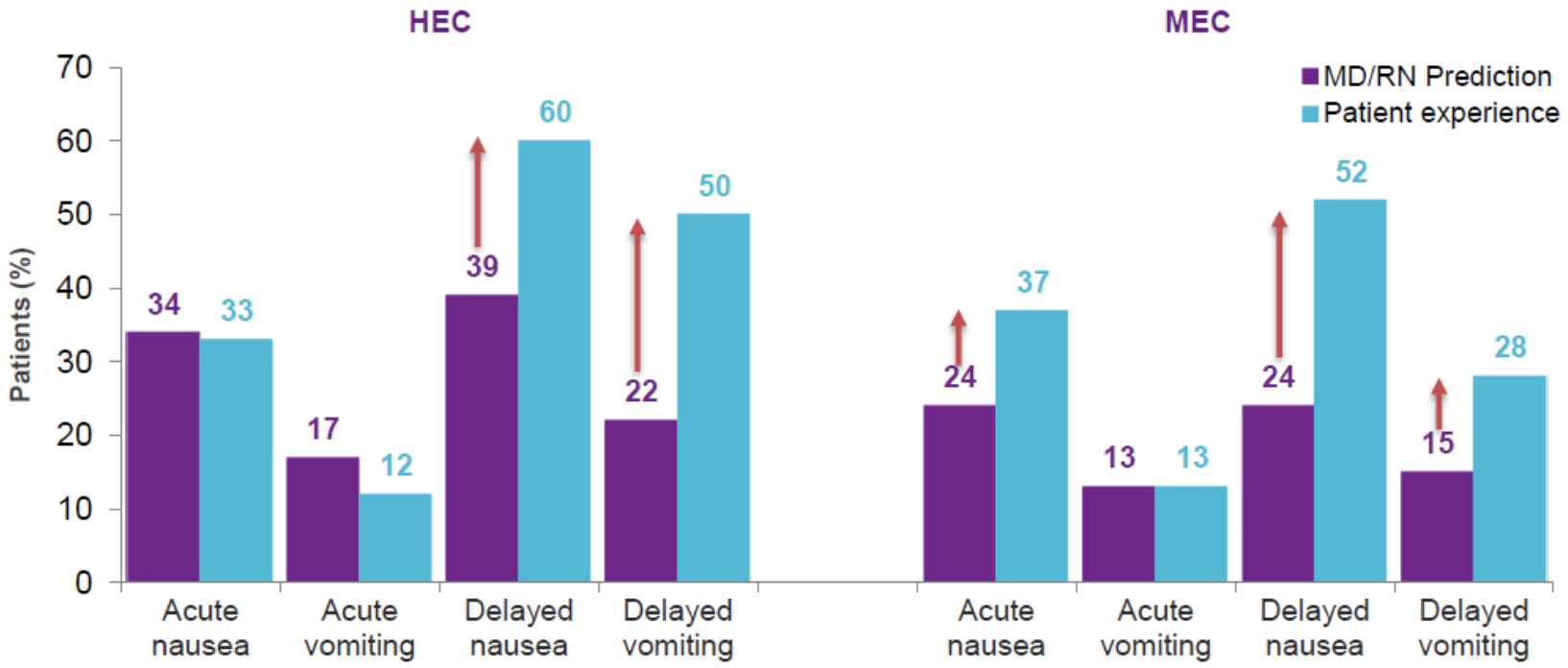
Actual probability of developing CINV

1. Mosa ASM, et al. *Front Pharmacol*. 2020;11:329. 2. Hesketh PJ, et al. *J Clin Oncol*. 1997;15(1):103-109.

HCP underestimate the incidence of CINV in HEC & MEC

Perception vs Reality

Healthcare providers' predictions of incidence rates of nausea and emesis



Physicians and nurses from 14 oncology practices in 6 countries
Patients: 72% women; 78% MEC; 49% breast cancer; 18% lung cancer

MEC = Moderately emetogenic chemotherapy, MD = Medical doctor, RN = Registered nurse

1. Grunberg SM, et al. Cancer. 2004; 100:2261-2268.

CINV leads to medical complications and affects patients' QoL

Medical complications[1]

- Significant morbidity
- Poor nutrition
- Muscle wasting
- Dehydration
- Anxiety
- Physical damage to the stomach
- Discontinuation of anticancer therapy
- **Compromised survival outcomes**

Impact of CINV[3-6]

- **Decreased compliance** with chemotherapy
- Delays or refusal of future chemotherapy
- Unplanned visits and hospitalizations
- **Increased healthcare costs**

These side effects can interfere with treatment compliance; patients sometimes delay chemotherapy cycles and contemplate refusing future treatments because of fear of further CINV – **thus impacting survival outcomes**

1. Rao KV, et al. Am Health Drug Benefits 2012;5(4):232-240. 2. Aapro M, et al. Ann Oncol. 2012;23:1986-1992. 3. Feyer P. Jordan K. Ann Oncol 2011; 22:30-28. 4. Dibble SL, et al. Oncol Nurs Forum. 2003;30:E40-E47. 5. Turini M. et al. Drugs Contex 2015; 4:212285.

Major Antiemetic Guidelines and Goals

Initiatives to achieve better control of CINV

CINV = Chemotherapy-Induced Nausea and Vomiting

M. Aapro, R. Tarricone. EMJ Oncol. 2020;8[Suppl 1]:2-13.

International Antiemetic Guidelines – an overview

- Treatment recommendations are regularly updated
- New clinical trials are studied and worked up into recommendations that are consistent, easy to use, and based on compelling clinical data

- There are 4 principal sets of internationally recognized guideline recommendations with regard to antiemetic treatment:
  - Multinational Association of Supportive Care in Cancer (MASCC)[1*]
  - European Society for Medical Oncology (ESMO)[1*]
  - National Comprehensive Cancer Network (NCCN)[2]
  - American Society of Clinical Oncology (ASCO)[3]

1. Herrstedt et al, 2024. ESMO Open Feb;9(2):102195 2. NCCN Antiemesis Guideline, 2005. 3. Hesketh, PJ. 2020 Aug 20;38(24):2782-2797.

Antiemetic treatment goals with chemotherapy: all major guideline groups

The MAIN OBJECTIVE is to *prevent nausea and vomiting, rather than treat it*

- Complete control in all settings
- No side-effects
- Convenient and easy to use

Jordan K, et al. Eur J Pharmacol. 2014;722:197-202.

Classifying chemotherapy based on emetogenic potential

Frequency of emesis (%)	Antiemesis guidelines
> 90	High (HEC)
30-90	Moderate (MEC)
10-30	Low
< 10	Minimal

- The moderate class includes a broad range of emetogenic agents
- AC has been classified as HEC in ASCO, NCCN, and MASCC/ESMO guidelines[1-3]
- Carboplatin is considered as "high MEC" by ASCO (only when AUC ≥ 4) and MASCC/ESMO (all doses), and reclassified as HEC (when AUC ≥ 4) by NCCN: the use of NK_1 RAs is recommended in all cases.[1-3] Studies had shown the benefit of the NK_1 RA- containing regimens in patients receiving carboplatin[4]
- NCCN recommends the inclusion of NK_1 RAs in MEC for selected patients with additional risk factors or previous treatment failure with a steroid plus 5-HT_3 RA alone[2]

5-HT_3RA, 5-hydroxytryptamine type 3 receptor antagonist; AC, anthracycline, cyclophosphamide; ASCO, American Society of Clinical Oncology; AUC, area under the curve; ESMO, European Society for Medical Oncology; HEC, highly emetogenic chemotherapy; MASCC, Multinational Association of Supportive Care in Cancer; MEC, moderately emetogenic chemotherapy; NCCN, National Comprehensive Cancer Network; NK_1 RA, neurokinin-1 receptor antagonist.

1. Herrstedt et al, 2024. ESMO Open Feb;9(2):102195 2. NCCN Antiemesis Guideline, 2005. 3. Hesketh, PJ. 2020 Aug 20;38(24):2782-2797. 4. Jordan K, et al. Support Care Cancer. 2016;24:4617-25.

Overall conclusions: NK1 RA inclusion recommendations

NK_1 RA recommendations for acute nausea and vomiting

	ASCO	MASCC/ESMO	NCCN
HEC (including cisplatin)	✓	✓	✓
AC	✓	✓	✓
Carboplatin[a]	✓	✓	✓
MEC			✓ [b]

[a] Carboplatin is considered as "high MEC" by ASCO (only when AUC ≥ 4 mg/mL per minute) and MASCC/ESMO, and reclassified as HEC (when AUC ≥4) by NCCN: an NK1 RA should be added in all cases b Selected patients with additional risk factors or previous treatment failure with a steroid plus 5-HT3 RA alone

- NK_1 RA is a recommended option by ASCO, MASCC/ESMO, and NCCN for **HEC** and **AC-based** regimens[1–3]
- NK_1 RA is a recommended option by ASCO, MASCC/ESMO, and NCCN for **carboplatin-based** chemotherapy[1–3]
- NK_1 RA is a recommended option by NCCN in **MEC for selected patients** with **additional risk factors** or **previous treatment failure** with a steroid plus 5-HT_3 RA alone[2]

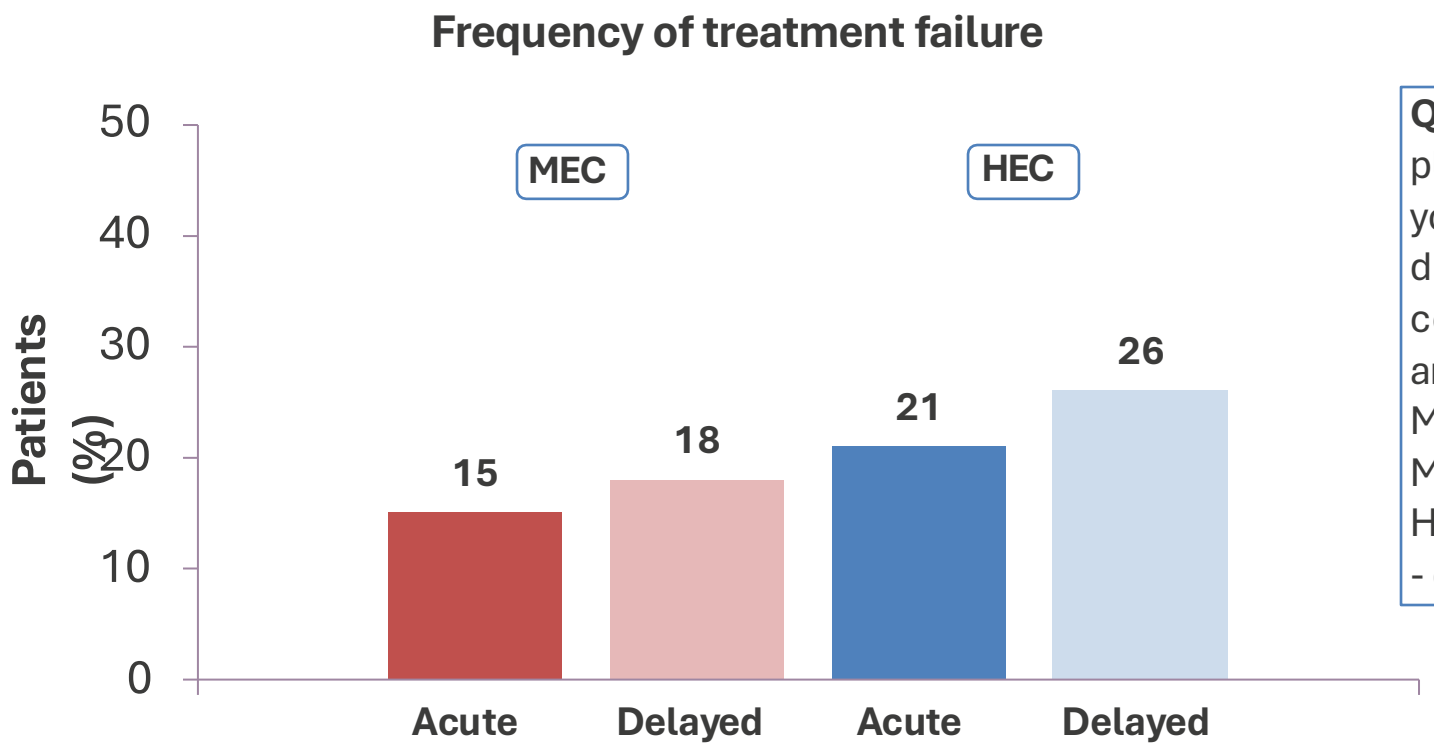
Oncology; AUC, area under the curve; ESMO, European Society for Medical Oncology; HEC, highly emetogenic chemotherapy; ASCC, Multinational Association of Supportive Care in Cancer; MEC, moderately emetogenic chemotherapy; NCCN, National Comprehensive Cancer Network; NK1 RA, neurokinin-1 receptor antagonist.

1. Herrstedt et al, 2024. ESMO Open Feb;9(2):102195 2. NCCN Antiemesis Guideline, 2005. 3. Hesketh, PJ. 2020 Aug 20;38(24):2782-2797.

Is non-adherence of antiemetic guidelines a risk factor for CINV?

Survey shows high incidence of CINV despite use of antiemetics

- Following HEC: 21% of patients in the acute phase and 26% in the delayed phase
- Following MEC: 15% of patients in the acute phase and 18% in the delayed phase



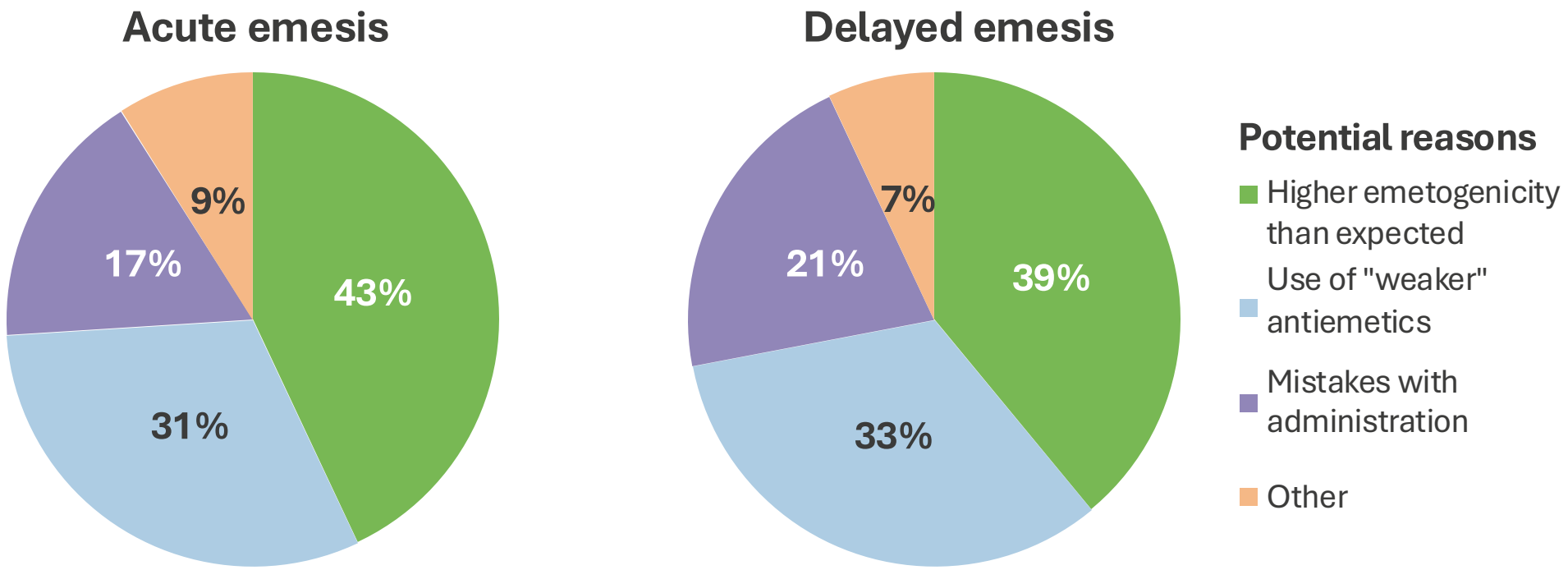
Question: For the categories below, please indicate what percentages of your patients who receive antiemetic drugs report emesis, hence you consider as non-responders to current antiemetic treatments:
MEC - acute emesis
MEC - delayed emesis
HEC - acute emesis HEC
- delayed emesis.

CINV, chemotherapy-induced nausea and vomiting;
HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

Aapro M, et al. Cancer Reports. 2018; e1127.

Survey identified potential reasons for antiemetic treatment failure

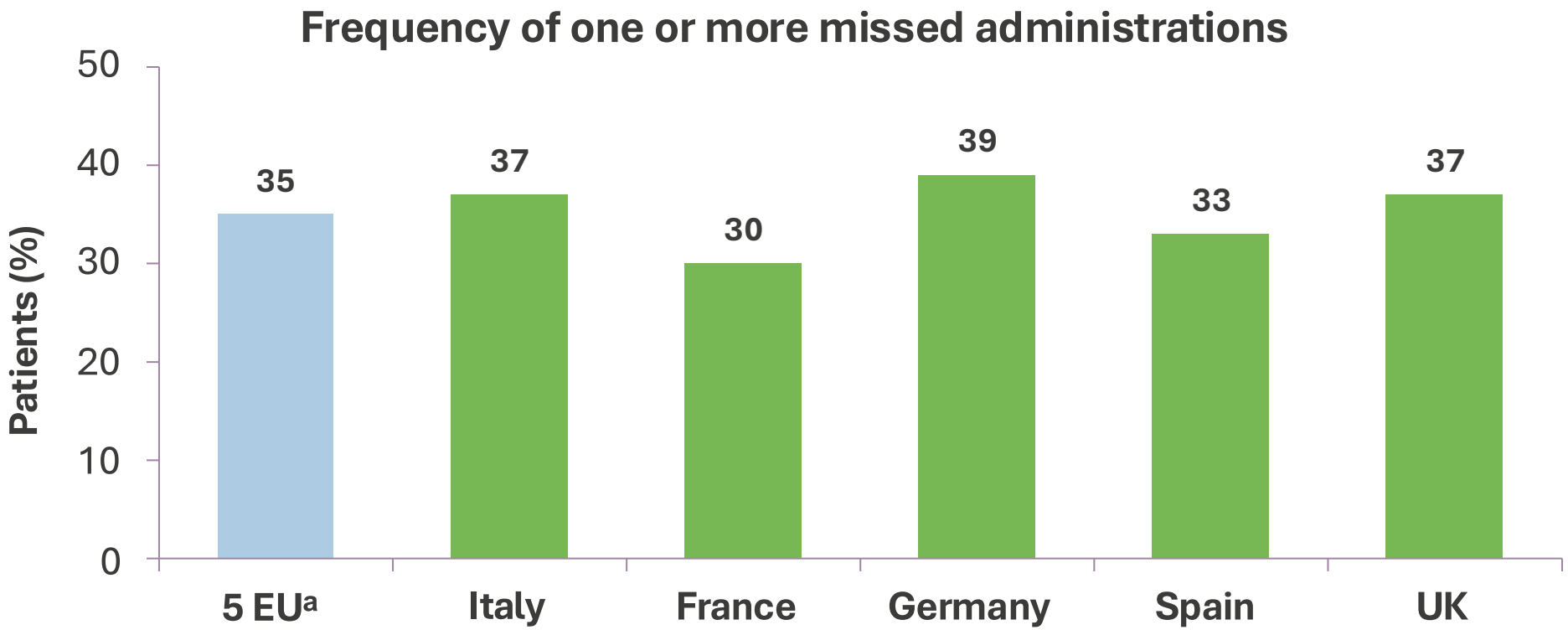
- Underestimating the emetogenic potential of chemotherapy
- Utilizing weaker antiemetics than required
- Non-adherence to antiemetics due to mistakes in administration by patients



Aapro M, et al. Cancer Reports. 2018; e1127.

Survey identified that approximately one third of patients are non-adherent with home administration of antiemetics

- 30-39% of patients made administration mistakes or missed/delayed one or more doses during home administration of antiemetics

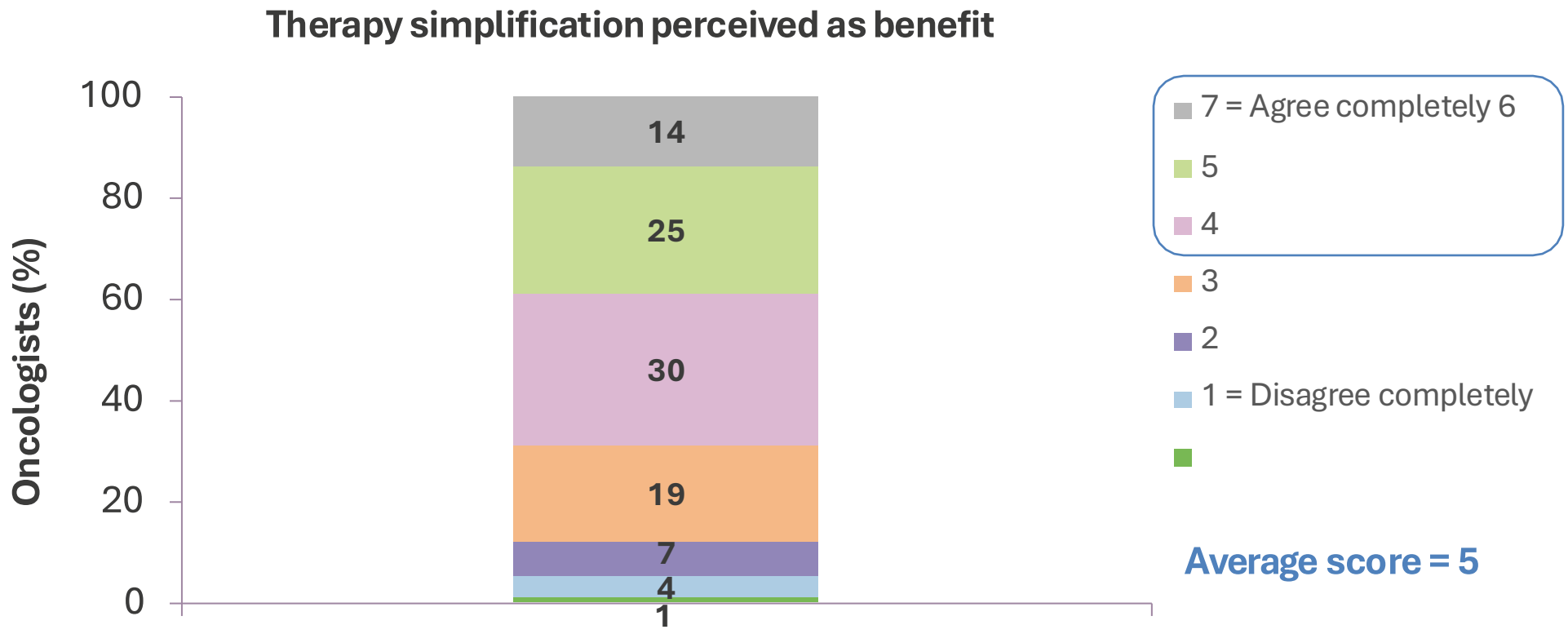


[a] Combined responses from oncologists from Italy, France, Germany, Spain, and the UK.

Aapro M, et al. Cancer Reports. 2018; e1127.

Survey shows that simplified antiemetic regimens may improve CINV control

- 69% of oncologists indicated that an orally administered antiemetic drug on Day 1 would be beneficial for them and their patients[a]



[a] Includes oncologists who responded 5, 6, or 7. CINV, chemotherapy-induced nausea and vomiting

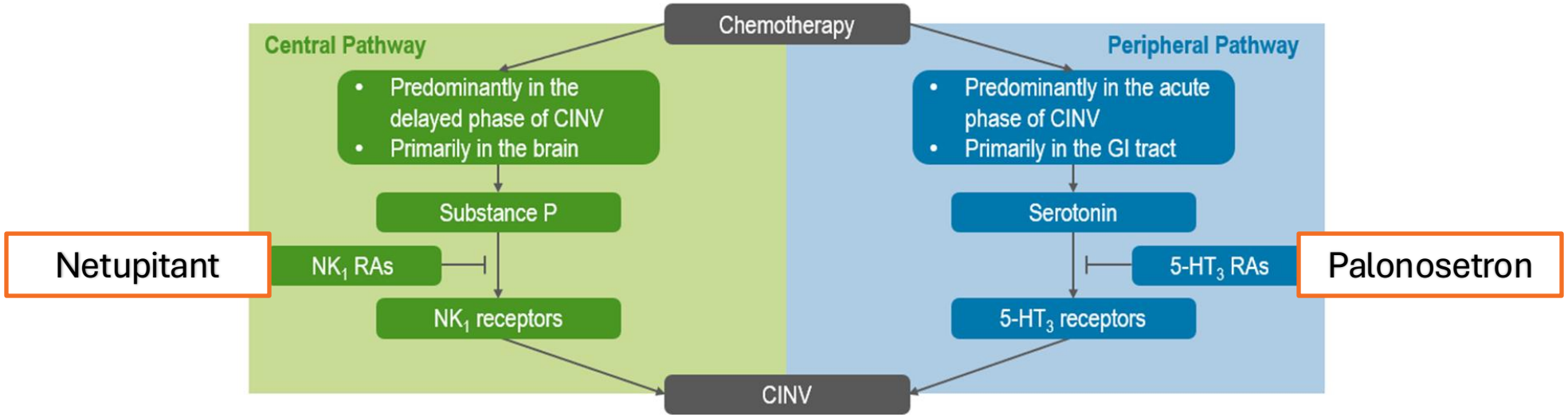
Aapro M, et al. Cancer Reports. 2018; e1127.

What is the Solution for CINV?

Netupitant / Palonosetron (NEPA)

- **What is NEPA?[1]**
  - NEPA is an oral fixed combination of netupitant and palonosetron for prevention of chemotherapy-induced nausea and vomiting.
  - Each capsule contains 300 mg of netupitant and 0.5 mg of palonosetron.

- **How does NEPA works?[2]**
  - Netupitant and palonosetron synergistically block two key CINV pathways in one dose.



1. Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022 2. Hesketh PJ et al. Ann Oncol. 2014 Jul;25(7):1340-6.

Netupitant / Palonosetron (NEPA)

- **Indications:**

NEPA is indicated in adults for the:

  - prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy;
  - prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

- **Dosage:**

Adults: One 300 mg/0.5 mg capsule should be administered approximately one hour prior to the start of each chemotherapy cycle.

- **Method of Administration:**
  - For oral use.
  - The hard capsule should be swallowed whole.
  - It can be taken with or without food.

1. Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022.

Mode of Action of NEPA

***Synergy*[1]**

- When used separately, both netupitant and PALO can trigger **NK_1 receptor internalization**
- When used in combination, the effect is **synergistic**

Best friend

- Netupitant and palonosetron exhibit **complementary pharmacokinetic profiles**[2]
  - **No interaction** observed between the two drugs
- The **half-life** of netupitant (96 h) is **longer** than that of aprepitant (9–13 h)[3,4]
  - Optimal CINV prevention in the **delayed phase** with a single dose
  - A **reduced need** for rescue medication
- PALO has distinct pharmacologic and clinical properties from other 5-HT_3 RAs
  - PALO is **more effective than first-generation 5-HT_3 RAs** in controlling CINV in the delayed and overall phases in MEC/HEC[5]
- Pharmacologic rationale for NEPA as an **optimal fixed combination** of antiemetic agents[2]

***Drug-drug interactions*[3,4]**

- In contrast with aprepitant, netupitant has **no drug-drug-interactions** with **oral contraceptives** or CYP2C9 substrates such as **warfarin**

5-HT_3: 5-hydroxytryptamine-3; CINV: chemotherapy-induced nausea and vomiting; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; NK_1: neurokinin-1; oral NEPA: fixed combination of netupitant (300 mg) and palonosetron (0.50 mg); PALO: palonosetron; RA: receptor antagonist. NEPA: fixed combination of netupitant(300 mg) and palonosetron (0.50 mg).

1. Stathis M, et al. Eur J Pharmacol 2012;689:25-30. 2. Gilmore J and Bernareggi A. J Clin Pharmacol 2019;59:1007-1012. 3. Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022 4. Hesketh PJ et al. Ann Oncol. 2014 Jul;25(7):1340-6. 4. Emend (Aprepitant). Product Information. BPOM RI, 2023. 5. Schwartzberg L, et al. Support Care Cancer 2014;22:469-477.

NEPA: Safety and Tolerability

- NEPA was well tolerated with a low incidence of serious adverse events.[1-3]
- There were no cardiac safety concerns for either NEPA or palonosetron based on cardiac AEs/ECGs.[2-5]
- NEPA has a similar safety profile to aprepitant/granisetron.[6]

- Common adverse reaction reported with NEPA:[1]

Headache	**3.6%**
Constipation	**3.0%**
Fatigue	**1.2%**

None of these events were serious.[1]

1. Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022. 2. Aapro M et al. Ann Oncol. 2014 Jul;25(7):1328-33. 3. Hesketh PJ et al. Ann Oncol. 2014 Jul;25(7):1340-6. 4. Gralla RJ et al. Ann Oncol. 2014 Jul;25(7):1333-9. 5. Aapro M et al. Oncologist 2016;21(4):494-502. 6. Zhang L et al. Ann Oncol. 2018 Feb 1;29(2):452-458.

NEPA: Akynzeo in Special Patients[1]

Renal Impairment	Hepatic impairment	Elderly patients
• Dosage adjustment is not considered necessary in patients with mild to severe renal impairment. • The pharmacokinetics of palonosetron or netupitant has • not been studied in subjects with end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of NEPA in these patients are available. • Therefore use in these patients should be avoided.	• No dosage adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score 5-8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥9). • As use in patients with severe hepatic impairment may be associated with increased exposure of netupitant, NEPA should be used with caution in these patients.	• No dosage adjustment is necessary for elderly patients. • Caution should be exercised when using this product in patients over 75 years, due to the long half-life of the active substances and the limited experience in this population.

1. Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022.

NEPA vs APR in cisplatin-based chemotherapy setting

Head-to-Head Comparison: NEPA vs APR cisplatin-based chemotherapy

Single-Dose Netupitant/Palonosetron Versus 3-Day Aprepitant for Preventing Chemotherapy-Induced Nausea and Vomiting: A Pooled Analysis

Navari RM, et al. Future Oncol 2021 Aug;17(23):3027-3035

Post-hoc analysis of 3 pivotal NEPA phase II/III studies[1-3] in patients receiving cisplatin-based HEC to evaluate pooled efficacy results with oral NEPA vs aprepitant regimens

228 Chemotherapy-naïve patients (76 each arm) diagnosed with NSCLCs scheduled to receive first course of high-dose (≥70mg/m^2) **cisplatin-based chemotherapy**

Objective: To evaluate the pooled efficacy from three cisplatin registration trials, each with arms containing netupitant/palonosetron (NEPA), a fixed neurokinin 1 RA (netupitant)/serotonin Type 3 (5-HT3) RA (palonosetron) combination, and an aprepitant (APR) regimen.

1. Hesketh PJ, et al. Ann Oncol 2014;25:1340-1346. 2. Gralla R, et al. Ann Oncol 2014;25:1333-1339. 3. Zhang L, et al. Ann Oncol 2018;29:452-458.

Study Design and Treatment

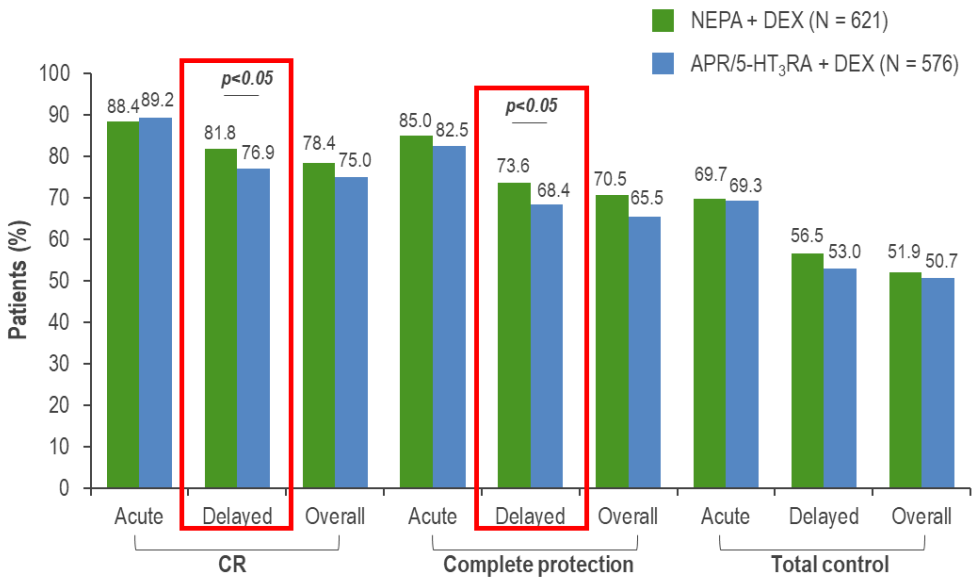
- Post hoc analysis of three similarly designed **cisplatin-based** HEC phase II/III, randomized, oral NEPA registration studies[1–3]
  - Patients who received ≥70 mg/m^2 cisplatin (the highest dose) were analyzed as a separate subgroup
- All patients included in the analysis received oral NEPA or a 3-day aprepitant comparator/control regimen

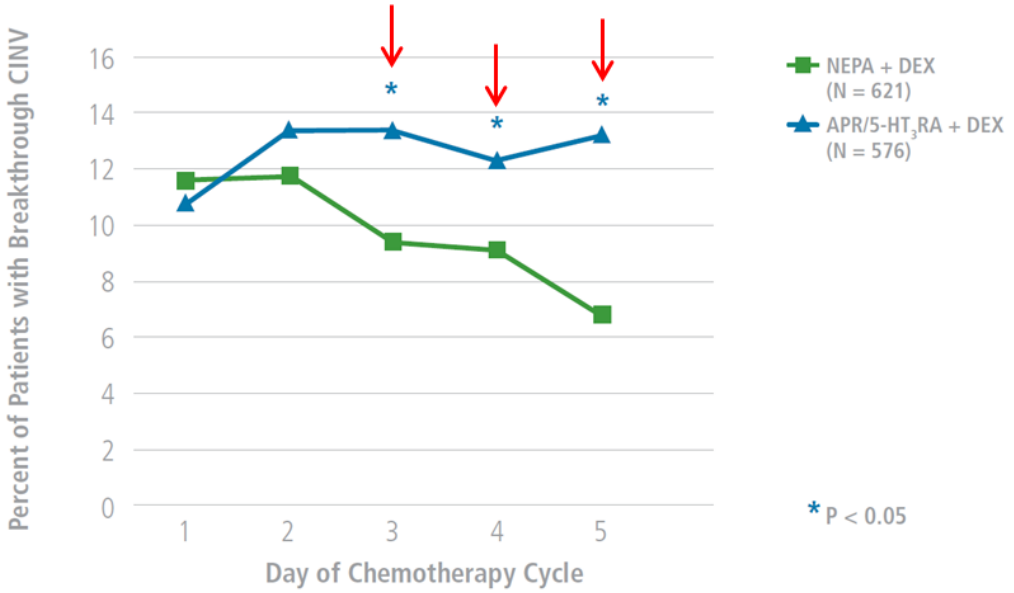
Treatment groups					
	Oral NEPA regimen		APR regimen		
	Oral NEPA	DEX	Oral APR	5-HT$_3$ RA	DEX
Day 1	Single, oral capsule of NEPA (300 mg NETU/0.50 mg PALO) administered ~1 h prior to chemotherapy	12 mg	125 mg administered ~1 h prior to chemotherapy	3 mg IV GRAN *or* 32 mg IV OND *or* 0.50 mg oral PALO	12 mg
Day 2	-	8 mg	80 mg (once daily)	-	8 mg
Day 3	-	8 mg	80 mg (once daily)	-	8 mg
Day 4	-	8 mg	-	-	8 mg

5-HT$_3$: 5-hydroxytryptamine-3; APR: aprepitant; DEX: dexamethasone; GRAN: granisetron; HEC: highly emetogenic chemotherapy; IV: intravenous; NETU: netupitant; OND: ondansetron; oral NEPA: fixed combination of netupitant (300 mg) and palonosetron (0.50 mg); PALO: palonosetron; RA: receptor antagonist

1. Hesketh PJ, et al. Ann Oncol 2014;25:1340-1346. 2. Gralla R, et al. Ann Oncol 2014;25:1333-1339. 3. Zhang L, et al. Ann Oncol 2018;29:452-458.

Results from overall population



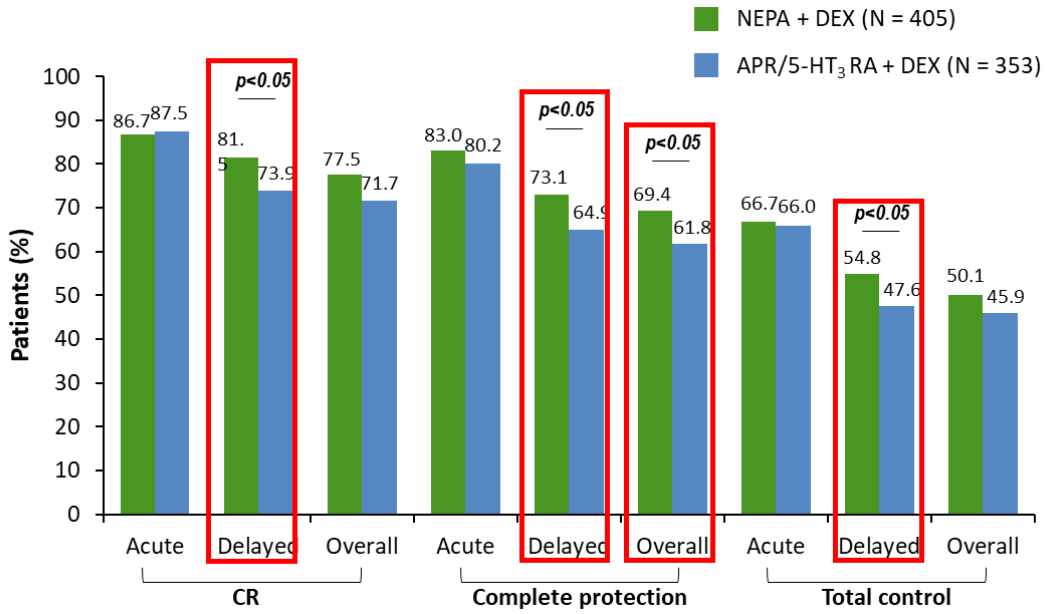


- Significantly higher response rates with oral NEPA vs aprepitant during the **delayed phase**
- The **NSN rates** during the delayed (79.8 vs 73.7%; *p = 0.049*) and overall (78.3 vs 71.4%; *p = 0.031*) phases were significantly higher for oral NEPA
- The rates of **breakthrough CINV** or **breakthrough significant nausea** were significantly **lower with oral NEPA** on individual days 3–5

5-HT_3: 5-hydroxytryptamine-3; APR: aprepitant; CINV: chemotherapy-induced nausea and vomiting; CR: complete response; DEX: dexamethasone; NSN: no significant nausea; oral NEPA: fixed combination of netupitant (300 mg) and palonosetron (0.50 mg); RA: receptor antagonist

Navari RM, et al. Future Oncol 2021;17:3027-3035.

Results from High-dose Cisplatin Subset



- The increased benefit with oral NEPA vs aprepitant regimens is more pronounced for patients receiving high-dose cisplatin (≥70 mg/m2)

Navari RM, et al. Future Oncol 2021;17:3027-3035.

Conclusion – Efficacy outcomes (I):

- **A single dose of oral NEPA administered on day 1 of chemotherapy only was more effective than a 3-day aprepitant regimen in preventing delayed CINV associated with cisplatin-based HEC**
- Oral NEPA was superior to the aprepitant regimen in terms of CR and complete protection in the delayed phase and for no significant nausea in the delayed and overall phases
- The rates of breakthrough CINV or breakthrough significant nausea were significantly lower with oral NEPA on individual days 3–5
- The increased benefit with oral NEPA vs aprepitant regimens is more pronounced for patients receiving high-dose cisplatin (≥70 mg/m2)
- The favorable results with oral NEPA in the **delayed phase** and for **NSN**, **two challenging unmet needs** that can greatly impact QoL, were particularly encouraging and suggest that oral NEPA may provide an advantage in limiting CINV duration

Navari RM, et al. Future Oncol 2021;17:3027-3035.

Head-to-Head Comparison: NEPA vs APR AC/MEC chemotherapy

Head-to-Head Comparison: NEPA vs APR AC/MEC chemotherapy

A Pragmatic Study Evaluating Oral NEPA vs Aprepitant for Prevention of CINV in Patients Receiving AC/MEC

Zelek L et al. Oncologist 2021;26(10):e1870-e1879

Pragmatic, multicenter, randomized, single cycle, open-label, parallel group prospective study, 30 enrolling sites in France

430 Chemotherapy-naïve patients scheduled to receive first course of **AC or MEC chemotherapy**

Objective: To demonstrate noninferiority of single dose oral NEPA to a 3-day aprepitant SoC regimen in patients receiving AC/MEC in a real-world setting

Study Design, Treatment, and Patient Eligibility Criteria

- Patients were randomly assigned (1:1) to receive **either oral NEPA** or an **aprepitant regimen (SoC in France)**
- Randomization was stratified by chemotherapy (AC and MEC)

Treatment					
	Administration	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Oral NEPA + DEX					
Oral NEPA	Single oral capsule, ~1 hour prior to chemotherapy	1 capsule			
DEX	Daily	8 mg	8 mg	8 mg	8 mg
Aprepitant + ondansetron + DEX					
Aprepitant	Oral dose, ~1 hour prior to chemotherapy and once daily on days 2 and 3	125 mg	80 mg	80 mg	
Ondansetron	IV, in conjunction with aprepitant on day 1	8 mg			
DEX	Daily	8 mg	8 mg	8 mg	8 mg

Key inclusion criteria

- ✓ Adult males and females (≥18 years)
- ✓ Diagnosed with a malignant solid tumor
- ✓ Chemotherapy-naive
- ✓ ECOG PS of 0–2
- ✓ Scheduled to receive the first course of AC or MEC
- ✓ Scheduled to receive CINV prophylaxis with oral NEPA or an aprepitant regimen

AC subset: mainly women with breast cancer

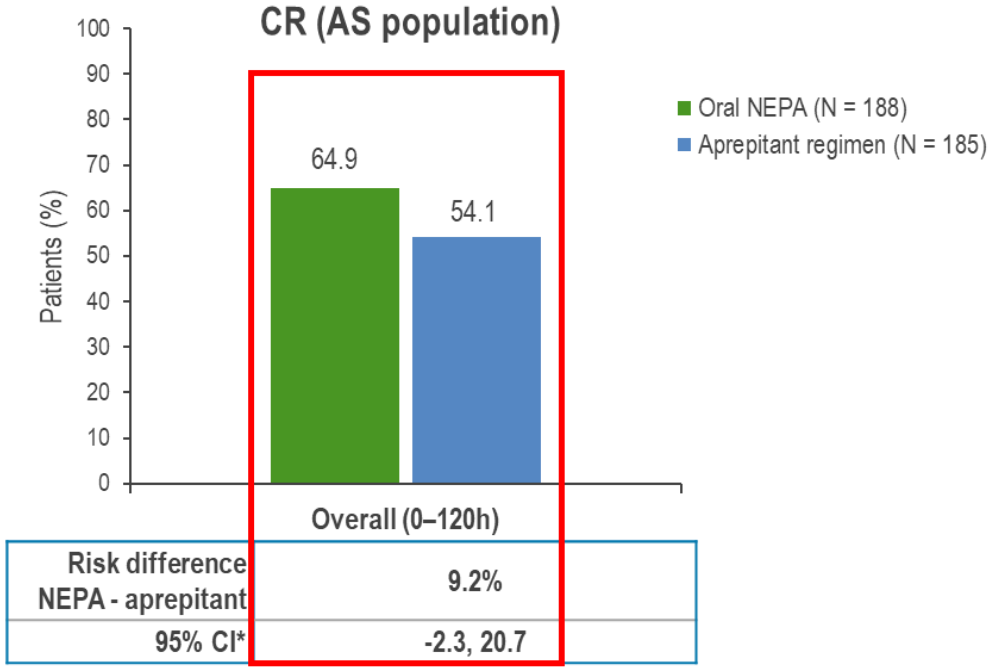
MEC subset: mostly male and the most common cancer types were gastric and lung cancer

Oxaliplatin and carboplatin were the most administered MEC

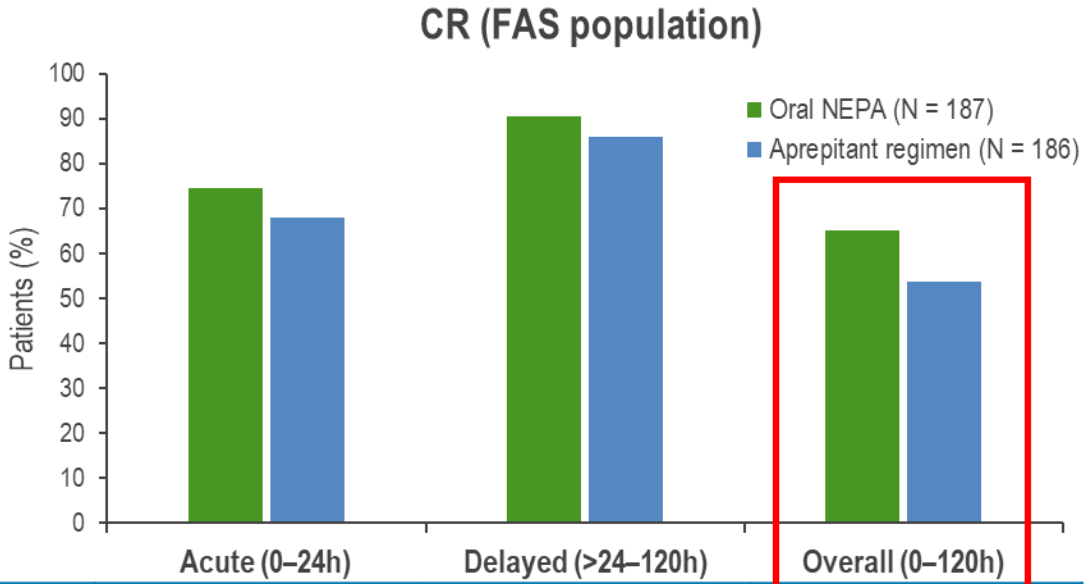
AC: anthracycline/cyclophosphamide; DEX: dexamethasone; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IV: intravenous; MEC: moderately emetogenic chemotherapy; oral NEPA: fixed combination of netupitant (300 mg) and palonosetron (0.50 mg); SoC: standard of care

Zelek L, et al. Oncologist 2021;26(10):e1870-e1879

Results, Efficacy - Overall Population



	Overall (0–120h)
Risk difference NEPA - aprepitant	9.2%
95% CI*	-2.3, 20.7



	Acute (0–24h)	Delayed (>24–120h)	Overall (0–120h)
Risk difference NEPA - aprepitant	5.4%	2.6%	9.7%
95% CI*	-5.5, 16.3	-3.4, 8.6	-1.6, 21.0

- Non-inferiority between oral NEPA and the aprepitant regimen was established for CR in the overall phase in both populations
- CR rates were numerically higher for oral NEPA than the aprepitant regimen during the acute, delayed, and overall phases
- The rates of no emesis, no rescue medication, and NSN were also numerically higher for oral NEPA, with the greatest difference being for no rescue medication and NSN (6%) during the overall phase

*Non-inferiority margin set at -10%.

AS: as treated; CI: confidence interval; CR: complete response; FAS: Full Analysis Set; NSN: no significant nausea; oral NEPA: fixed combination of netupitant (300 mg) and palonosetron (0.50 mg)

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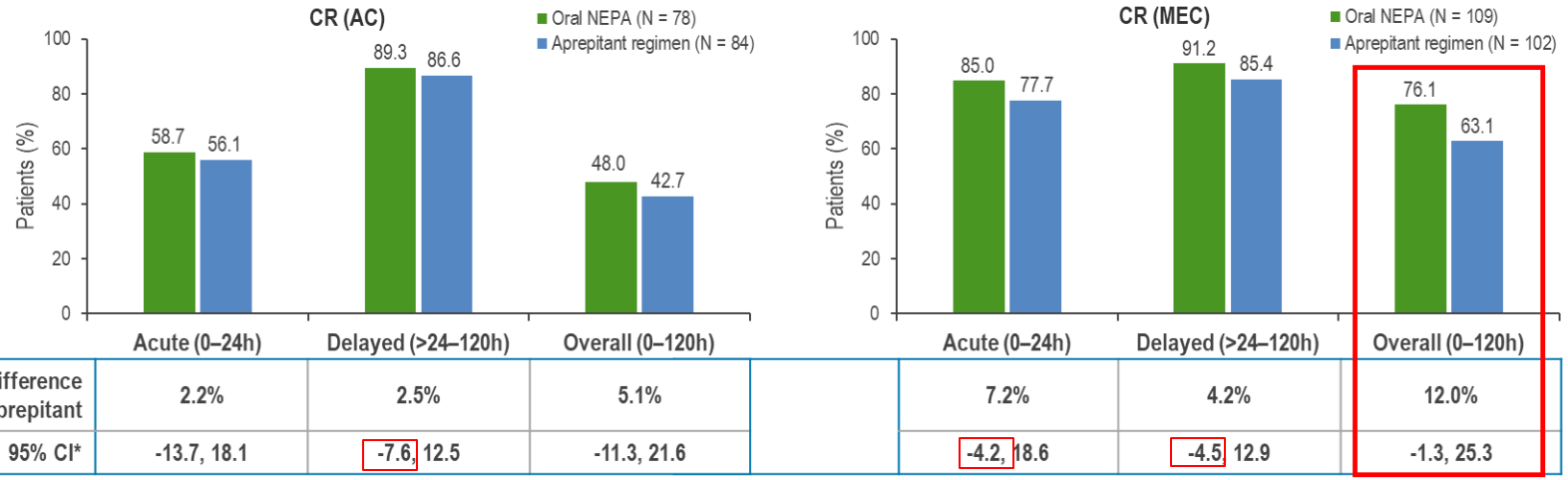
Results, Efficacy - AC and MEC Subsets



	Acute (0–24h)	Delayed (>24–120h)	Overall (0–120h)	Acute (0–24h)	Delayed (>24–120h)	Overall (0–120h)
Risk difference NEPA - aprepitant	2.2%	2.5%	5.1%	7.2%	4.2%	12.0%
95% CI*	-13.7, 18.1	-7.6, 12.5	-11.3, 21.6	-4.2, 18.6	-4.5, 12.9	-1.3, 25.3

- In both subsets, **CR rates were numerically higher with oral NEPA in <u>all phases</u>**; the **highest risk difference (12%)** was in MEC in the overall phase
- There was a 13% difference favoring oral NEPA for NSN rates during the delayed and overall phases in the AC subset, and an 8% difference favoring oral NEPA for no emesis rates during the overall phase in the MEC subset

*Non-inferiority margin set at -10%.

AC: anthracycline/cyclophosphamide; CI: confidence interval; CR: complete response; MEC: moderately emetogenic chemotherapy; NSN: no significant nausea; oral NEPA: fixed combination of netupitant (300 mg) and palonosetron (0.50 mg)

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Conclusion:

- **This real-world study in patients receiving AC or MEC showed that a single dose of oral NEPA plus DEX was at least as effective as a 3-day aprepitant SoC regimen**
- Efficacy outcomes: **oral NEPA was non-inferior** to the 3-day aprepitant regimen for overall CR rate
- The **overall CR rate was >10% greater for oral NEPA** than the aprepitant regimen, a **clinically significant difference**
- CR rate in the acute and delayed periods and all secondary efficacy endpoints were numerically higher for oral NEPA
- In the **AC subset**, oral NEPA was non-inferior in terms of CR in the **delayed phase**
- In the **MEC subset**, oral NEPA was non-inferior in terms of CR in the **acute, delayed, and overall phases**
- The effectiveness of oral NEPA in a real-world setting was in line with that seen for aprepitant- and rolapitant-based triple regimens in randomized double-blind phase 3 trials in a similar mixed AC/MEC population1,2
- **Safety outcomes:** The **safety profile of oral NEPA in real-world practice** was **similar** to that reported in the pivotal trials and the product label, and consistent with the general safety profile for the aprepitant regimen and the NK1 RA and 5-HT3 RA classes

Overall Conclusion

- NEPA different from aprepitant in terms of:
  - **Mode of action[1-4]:** Longer half-life, complementary pharmacokinetics and synergy between Netupitant and Palonosetron, lack of drug-drug interactions.
  - **Indirect comparison[5-8]:** Better nausea control during delayed phase (25-120 hrs), DEX-sparing advantage, real-world results consistent with pivotal trials.
  - **Head-to-head comparison against aprepitant:**
    - **Cisplatin-based setting[9]:** A single dose of oral NEPA administered on day 1 of chemotherapy only was more effective than a 3-day aprepitant regimen in preventing delayed CINV associated with cisplatin-based HEC.
    - **AC/MEC-based setting[10]:** patients receiving AC or MEC showed that a single dose of oral NEPA plus DEX was at least as effective as a 3-day aprepitant SoC regimen.

- Overall, NEPA is an effective and safe antiemetic that aligns with international antiemetic guidelines. The product provides the convenience of a single-dose regimen that specifically targets important pathways related to emesis. This makes it an appropriate option for preventing CINV in patients receiving chemotherapy.

1. Akynzeo® (netupitant/palonosetron). Product Information. BPOM RI, 2022. 2.Schwartzberg L, et al. Support Care Cancer 2014;22:469-477. 3.Gilmore J and Bernareggi A. J Clin Pharmacol 2019;59:1007-1012. 4. Stathis M, et al. Eur J Pharmacol 2012;689:25-30. 5. Karthaus M, et al. Future Oncol 2020;16:939-953. 6. Celio L, et al. Oncologist 2021;26:e1854-e1861. 7.Celio L, et al. J Geriatric Oncol 2021;21;S18-S19. 8. The National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: antiemesis, Version 2, 2025. 9. Navari RM, et al. Future Oncol 2021 Aug;17(23):3027-3035 10. Zelek L et al. Oncologist 2021;26(10):e1870-e1879

Thank You