Achieving control of CINV with NK_1 receptor antagonists: making the most of available medications

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- Speakers bureau
  - Helsinn Healthcare SA
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- Consultant/advisor
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Approved NK_1 RAs: CINV prevention

- Aprepitant (APR) and fosaprepitant (FOS; i.v. pro-drug)
- Rolapitant (ROL)
- Netupitant (with PALO in a fixed-combination in NEPA)
- NK_1 RAs are recommended:[1–3]
  - In combination with other antiemetics
  - Single-day CT, multiple-day cisplatin (APR), high-dose CT (APR)
  - Not for the treatment of established nausea and vomiting

CT, chemotherapy; i.v., intravenous;
NEPA, fixed-combination of netupitant (300 mg) and palonosetron (0.50 mg);
NK_1, neurokinin 1; PALO, palonosetron; RA, receptor antagonist.

1. MASCC/ESMO Antiemetic Guideline 2016 v1.2. Available from: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_v.1.2.1.pdf. Accessed May 2018.
2. Hesketh PJ, et al. J Clin Oncol. 2017;35:3240-61.
3. Einhorn LH, et al. Support Care Cancer. 2017;25:303-8.

MASCC/ESMO 2016 antiemetic guidelines summary: acute CINV prevention

Emetic risk group	Antiemetics
High non-AC	5-HT$_3$ + DEX + NK$_1$
High AC	5-HT$_3$ + DEX + NK$_1$
Carboplatin	5-HT$_3$ + DEX + NK$_1$
Moderate (other than carboplatin)	5-HT$_3$ + DEX
Low	5-HT$_3$ or DEX or DOP
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist

DEX = dexamethasone

NK$_1$ = neurokinin$_1$ receptor antagonist such as aprepitant or fosaprepitant or rolapitant or NEPA (fixed combination of netupitant and palonosetron)

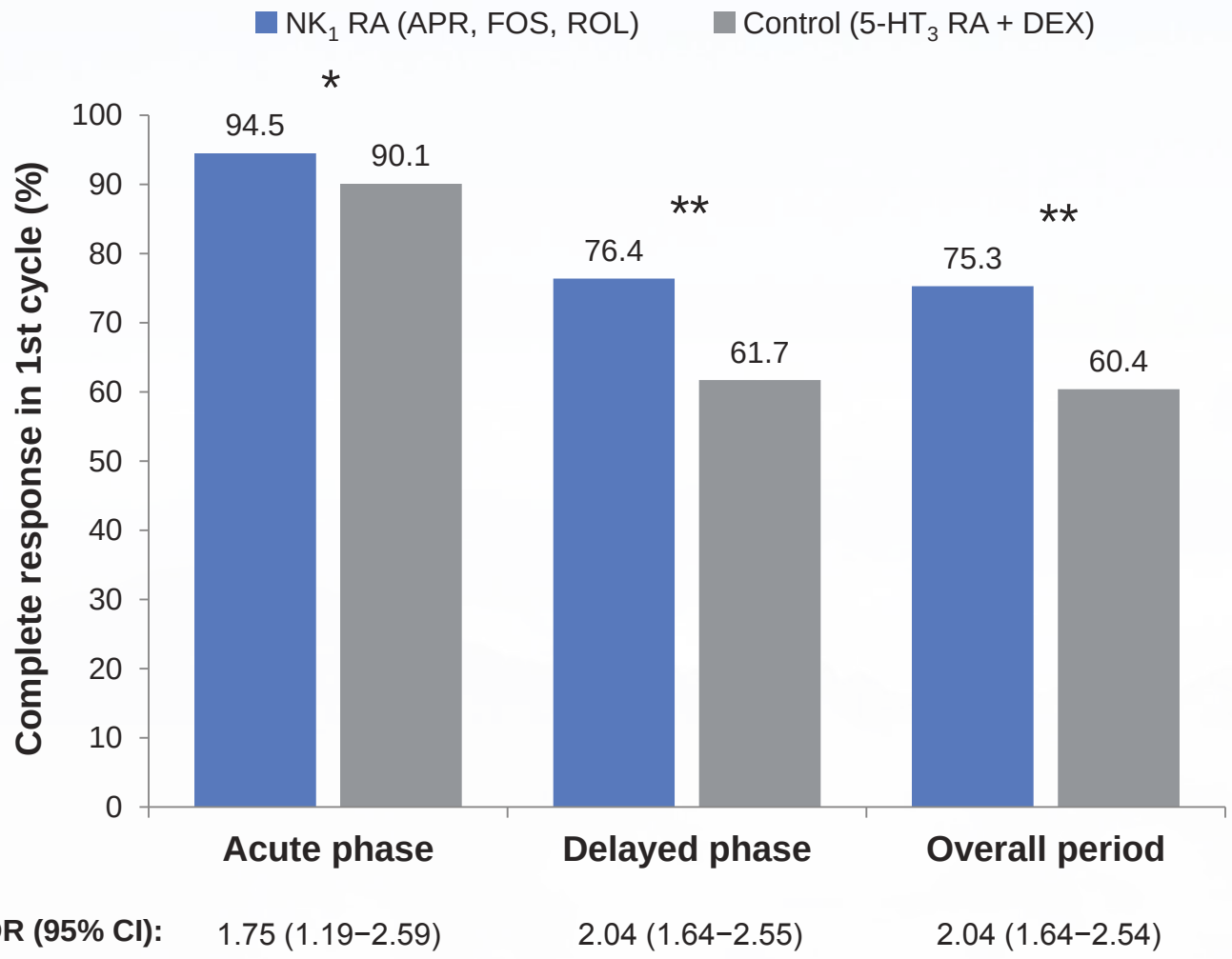
DOP = dopamine receptor antagonist

NOTE: If the NK$_1$ RA is not available for AC chemotherapy, PALO is the preferred 5-HT$_3$ RA.

5-HT, 5-hydroxytryptamine; AC, chemotherapy containing anthracyclines and cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting; DEX, dexamethasone; DOP, dopamine receptor antagonist; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer.

MASCC/ESMO Antiemetic Guideline 2016 v1.2. Available from: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_v.1.2.1.pdf. Accessed May 2018.

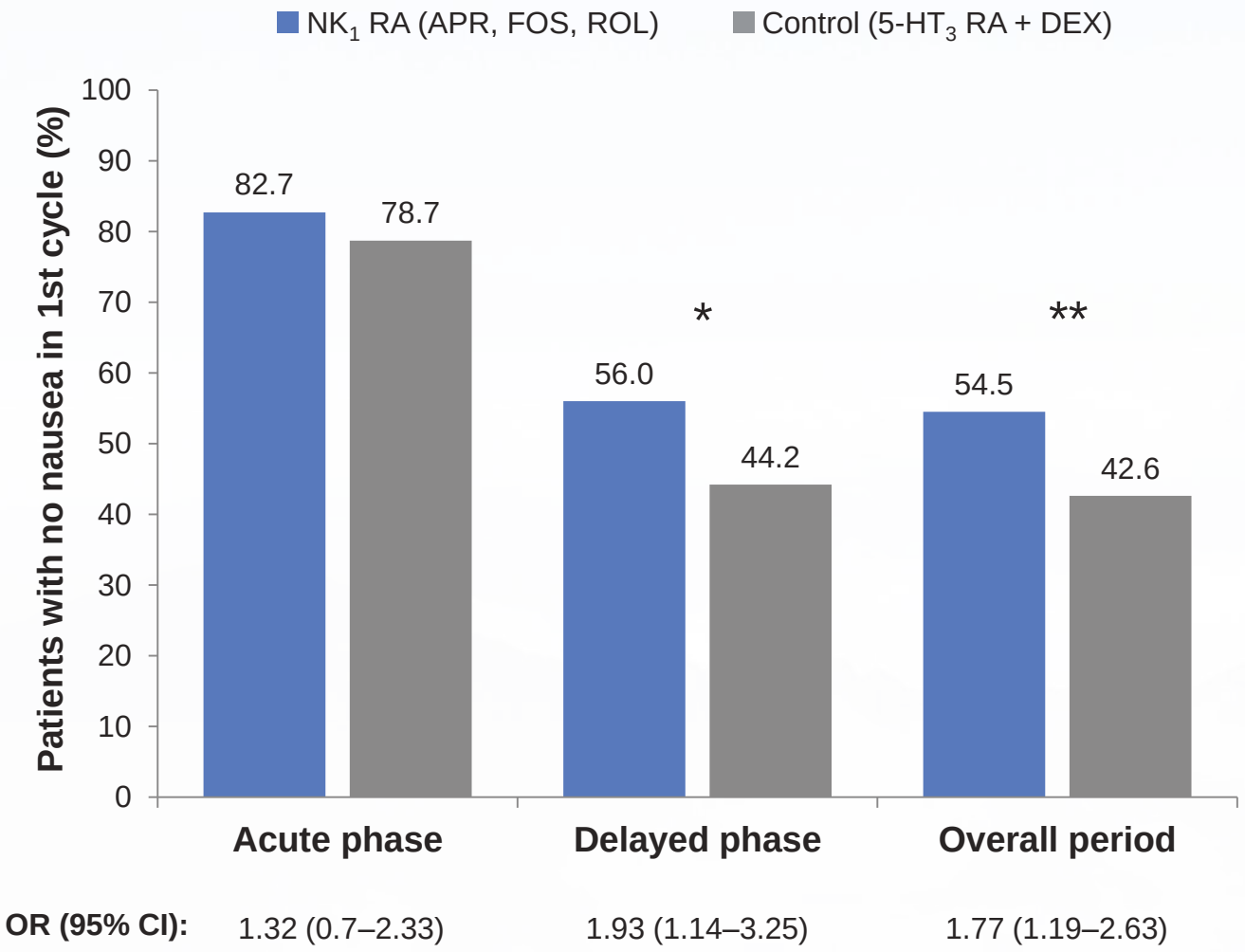
Benefit of adding NK_1 RAs with carboplatin: complete response (no vomiting and no rescue)



* p = 0.005; ** p < 0.00001.
Data were available from 8 trials: NK_1 RA group (n = 793), control (n = 805).
CI, confidence interval; OR, odds ratio.

Di Maio M, et al. Crit Rev Oncol Hematol. 2018;124:21-8.

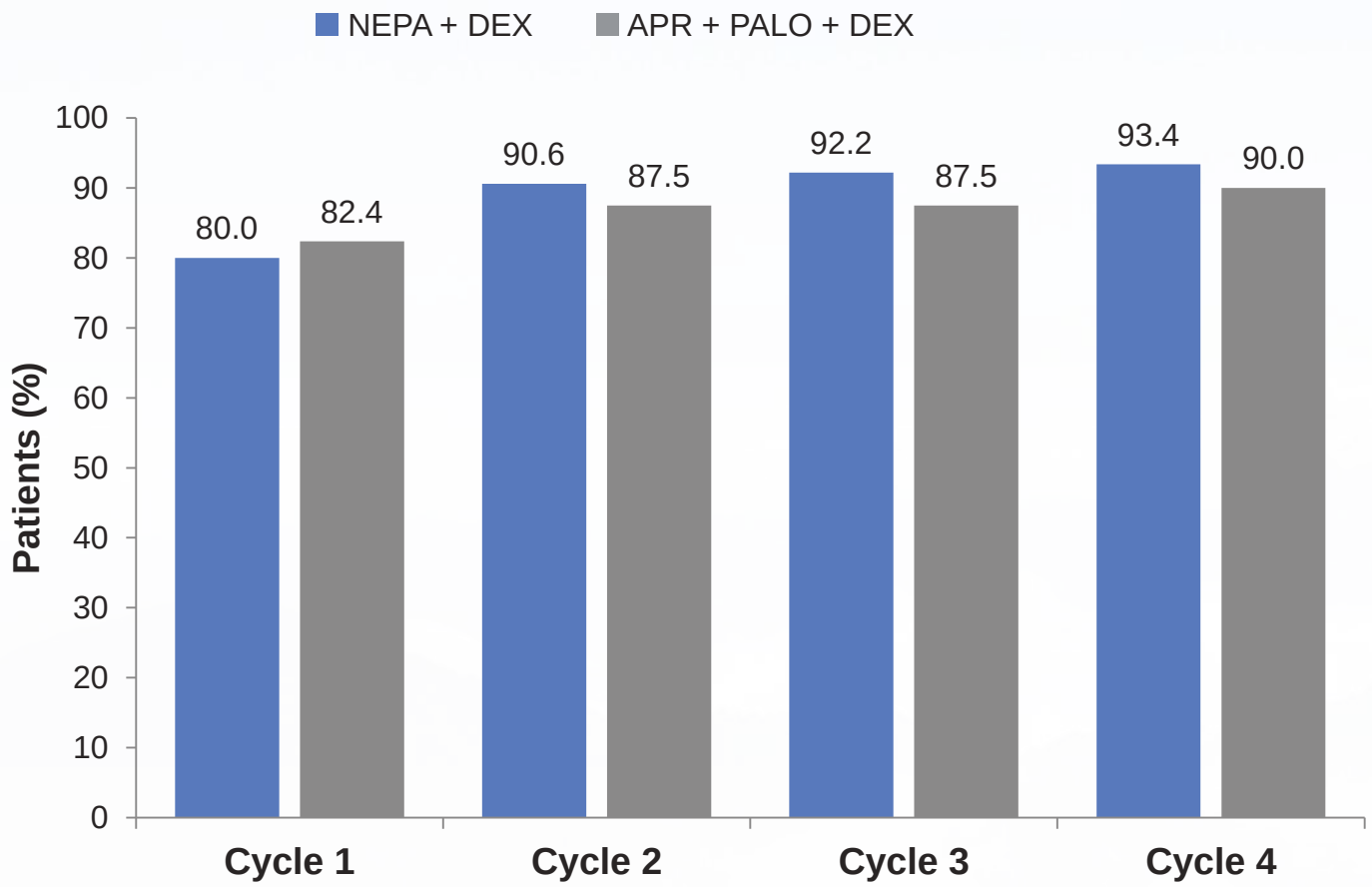
Benefit of adding NK_1 RAs with carboplatin: no nausea



* p = 0.01; ** p < 0.004.
Data were available from 6 trials for overall phase (N = 1,005) and from 5 trials (N = 914) for acute and delayed phases.

Di Maio M, et al. Crit Rev Oncol Hematol. 2018;124:21-8.

NEPA and APR/PALO in carboplatin subset: overall complete response

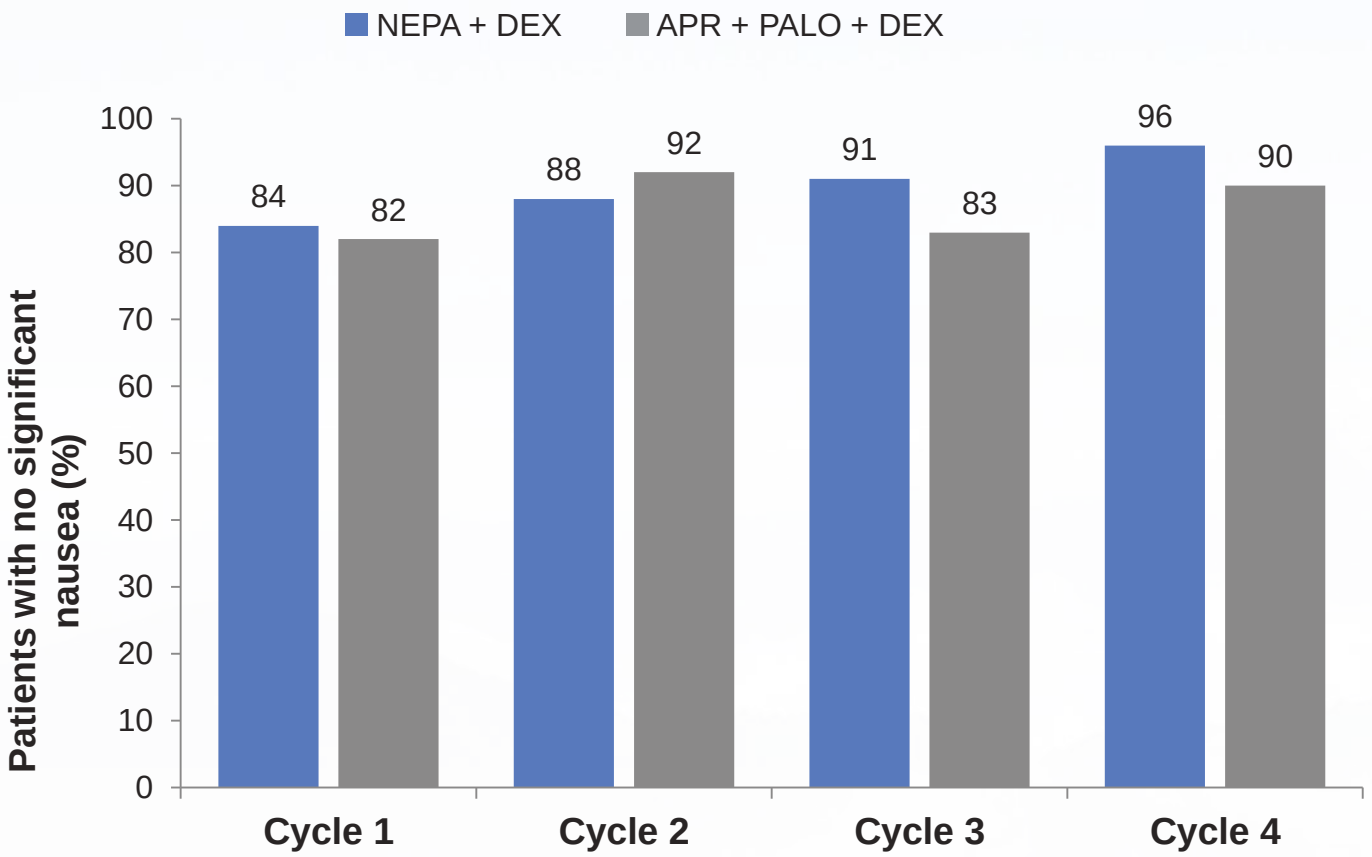


	Cycle 1	Cycle 2	Cycle 3	Cycle 4
NEPA + DEX: N =	145	128	116	106
APR + PALO + DEX: N =	51	48	48	40

Overall CR rate 0−120 hours.
CR, complete response.

Jordan K, et al. Support Care Cancer. 2016;24:4617-25.

NEPA and APR/PALO in carboplatin subset: overall no significant nausea



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NEPA vs APR/GRAN regimen: HEC cisplatin

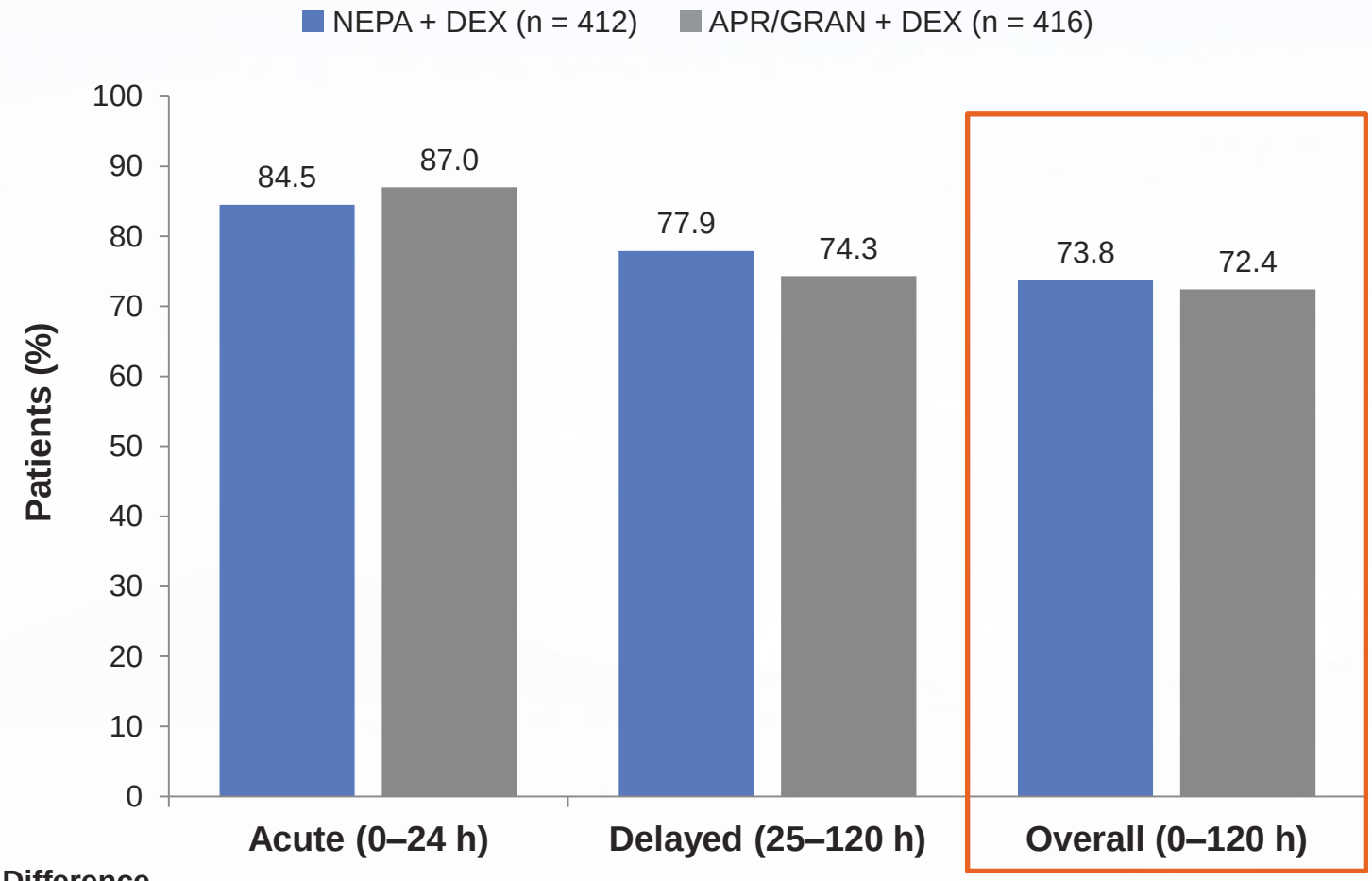
- Phase 3, multicentre, randomized, double-blind/double-dummy, parallel group international study conducted in Asia

	NEPA regimen		APR/GRAN regimen		
	Oral NEPA	**Oral DEX**	**Oral APR**	**i.v. GRAN**	**Oral DEX**
Day 1	NETU 300 mg/ PALO 0.50 mg	12 mg	125 mg	3 mg	12 mg
Day 2		8 mg	80 mg		8 mg
Day 3		8 mg	80 mg		8 mg
Day 4		8 mg			8 mg

GRAN, granisetron; HEC, highly emetogenic chemotherapy; NETU, netupitant.

Zhang L, et al. Ann Oncol. 2018;29:452-58.

NEPA vs APR/GRAN in HEC cisplatin: complete response



Risk Difference
NEPA – APR/GRAN
(95% CI)

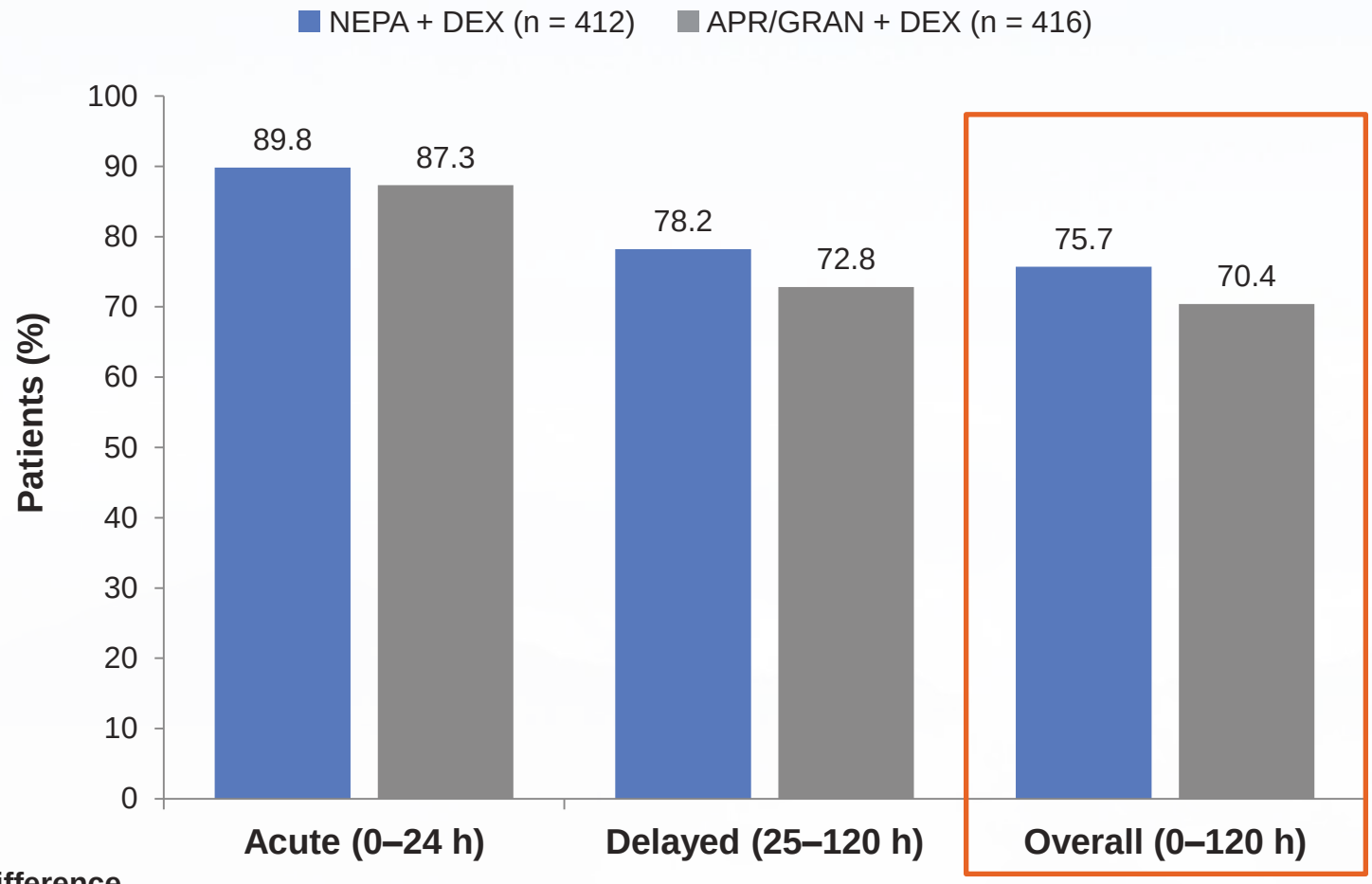
Acute (0–24 h)	Delayed (25–120 h)	Overall (0–120 h)
−2.5% (−7.2–2.3)	3.7% (−2.1–9.5)	1.5% (−4.5–7.5)

Non-inferiority margin set at −10%

h, hours.

Zhang L, et al. Ann Oncol. 2018;29:452-58.

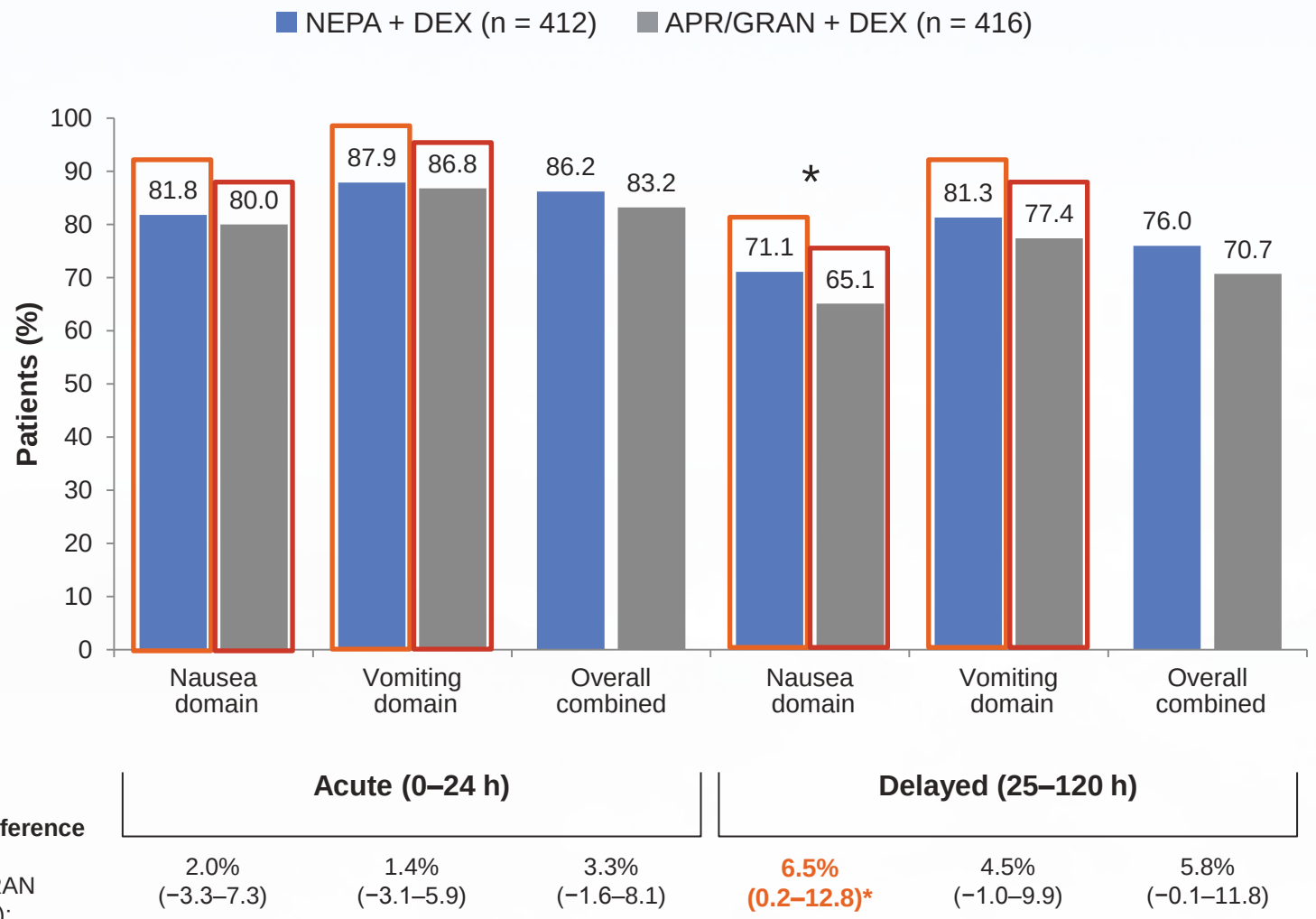
NEPA vs APR/GRAN in HEC cisplatin: no significant nausea



Risk Difference NEPA – APR/GRAN (95% CI)	Acute (0–24 h)	Delayed (25–120 h)	Overall (0–120 h)
	2.6% (−1.7–6.9)	5.4% (−0.4–11.2)	5.4% (−0.6–11.4)

Zhang L, et al. Ann Oncol. 2018;29:452-58.

NEPA vs APR/GRAN in HEC cisplatin: QoL, the impact of CINV on daily living



* Statistically significant difference.
QoL, quality of life, based on the functional living index–emesis.

Zhang L, et al. Ann Oncol. 2018;29:452-58.

NK_1 RAs: pharmacology

	APR[1]	NETU[2]	ROL[3]
Receptor binding	Selective NK_1	Selective NK_1	Selective NK_1
Metabolism[4]	CYP3A4 (extensive)	CYP3A4	CYP3A4
$T_{½}$ (hours)[4]	11.1 (125 mg) 11.6 (80 mg)	96	169–183
Regimen	3-day	1-day	1 day (≥ 2 wks)
Route of elimination	Hepatic	Hepatic	Hepatic
Route of administration	Oral, i.v. (FOS)	Oral, i.v.[a,b]	Oral, i.v. (suspended)[5]

[a] Registered in the USA only.
[b] Fosnetupitant (235 mg)/PALO (0.25 mg) fixed combination recently included in the NCCN v3.2018 guidelines.[6]

NCCN, National Comprehensive Cancer Network; $T_{1/2}$, half-life; wk, week.

1. APR SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000527/WC500026537.pdf.
2. NEPA. SmPC. //www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003728/WC500188432.pdf.
3. ROL SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004196/WC500228742.pdf.
4. Rapoport B and Smit T. Expert Opin Drug Saf. 2017;16:697-710. 5. Tesaro Press Release. http://ir.tesarobio.com/news-releases/news-release-details/tesaro-announces-fourth-quarter-and-full-year-2017-operating. All accessed May 2018.
6. NCCN Clinical Practice Guidelines Oncology, Antiemesis Version 3, 2018. Available from: https://www.nccn.org. Accessed June 2018.

Convenience of dosing schedule: MASCC/ESMO HEC cisplatin

	Acute phase				Delayed phase
	D1				D2–D4
APR 125 mg	+	5-HT$_3$	+	DEX 12 mg	APR 80 mg × 1 (D2-D3) DEX 8 mg × 1 or MCP 20 mg × 4 DEX 8 mg × 2
FOS 150 mg	+	5-HT$_3$	+	DEX 12 mg	DEX 8 mg × 1; 8 mg × 2 (D3,D4)
ROL 180 mg	+	5-HT$_3$	+	DEX 20 mg	DEX 8 mg × 2
NEPA (NETU 300 mg/ PALO 0.5 mg)			+	DEX 12 mg	DEX 8 mg

5-HT$_3$ RA doses and dose of DEX in accordance with MASCC/ESMO and ASCO 2017 guidelines.
D, day; MCP, metoclopramide.

MASCC/ESMO Antiemetic Guideline 2016 v1.2. Available from: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_v.1.2.1.pdf. Accessed May 2018.
Hesketh PJ, et al. J Clin Oncol. 2017;35:3240-61.

NK_1 RAs: convenience of dosing schedule HEC cisplatin

Antiemetic drug	Day 1	Day 2	Day 3	Day 4	No. of antiemetic administrations
APR	X	X	X		8 (3 + 5)
5-HT_3 RA	X				
DEX	X	X	X	X	
FOS	X				6 (3 + 3)
5-HT_3 RA	X				
DEX	X	X	X	X	
ROL	X				6 (3 + 3)
GRAN	X				
DEX	X	X	X	X	
NEPA	X				5 (2 + 3)
DEX	X	X	X	X	

Based on Lorusso V. Ther Clin Risk Manag. 2016;12:917-25.
MASCC/ESMO Antiemetic Guideline 2016 v1.2.
Available from: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_v.1.2.1.pdf. Accessed May 2018.

Convenience of dosing schedule: MASCC/ESMO HEC cisplatin

Acute phase				Delayed phase	No. of antiemetic administrations
D1				D2–D3–D4	
APR 125 mg	+	5-HT$_3$	+ DEX 12 mg	APR 80 mg × 1 (D2, D3) DEX 8 mg or MCP 20 mg × 4 DEX 8 mg × 2	8
FOS 150 mg	+	5-HT$_3$	+ DEX 12 mg	DEX 8 mg; 8 mg × 2 (D3, D4)	6
ROL 2 × 90 mg	+	5-HT$_3$	+ DEX 20 mg	DEX 8 mg × 2	6
NEPA (NETU 300 mg/ PALO 0.5 mg)			+ DEX 12 mg	DEX 8 mg	5

5-HT$_3$ RA doses	Oral	i.v.
OND	• 8 mg × 2–3	8 mg/0.15 mg/kg (max. 16 mg)
GRAN	• 2 mg (1 mg)	1 mg/0.01 mg/kg

5-HT$_3$ RA doses and DEX dose in accordance with MASCC/ESMO and ASCO 2017 guidelines.
ASCO, American Society of Clinical Oncology; OND, ondansetron.

Adapted from: MASCC/ESMO Antiemetic Guideline 2016 v1.2. Available from: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_guidelines_english_v.1.2.1.pdf. Accessed May 2018.
Hesketh PJ, et al. J Clin Oncol. 2017;35:3240-61.

Conclusion: NK_1 RAs

- Guidelines consider all NK_1 RAs equally effective for CINV prevention
- No differences in efficacy/tolerability were identified between NEPA and APR/GRAN regimens in the first comparative study
- The choice of NK_1 RAs may be influenced by convenience of antiemetic schedule, availability of different routes of administration, drug–drug interactions, and cost