SINGAPORE 2015 ESMO ASIA

ESMO ASIA 2015

18-21 DECEMBER, SINGAPORE

MONDAY 21.12 Hall 405 11:00 - 12:30

Special Symposium

Assuring that the treatment is acceptable: Managing side-effects in practice

Chairs: A. Molassiotis and C.J. Henry

11:00 - 11:05 Introduction A. Molassiotis
11:05 - 11:25 Cardiac toxicities T. Suter
11:25 - 11:45 Nutrition / cachexia / anorexia C.J. Henry
11:45 - 12:05 Anti-emetics M. Aapro
12:05 - 12:25 Peripheral neuropathy A. Molassiotis
12:25 - 12:30 Conclusions and (clinical) perspectives C.J. Henry

Antiemetics

Matti Aapro, MD

Multidisciplinary Oncology Institute

Genolier, Switzerland

Thanks to K Jordan, A. Molasiotis

and all members of MASCC/ESMO guidelines committee

COI

Dr Aapro is/was a consultant for

Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro,Teva, Vifor

and has received honoraria for lectures at symposia of

Amgen, Bayer Schering, Cephalon, Chugai, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Kyowa, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor

No responsibility accepted for
involuntary errors or omissions.
The list may be incomplete, and does not reflect consultancy for NGOs, Universities, Governmental agencies, and others

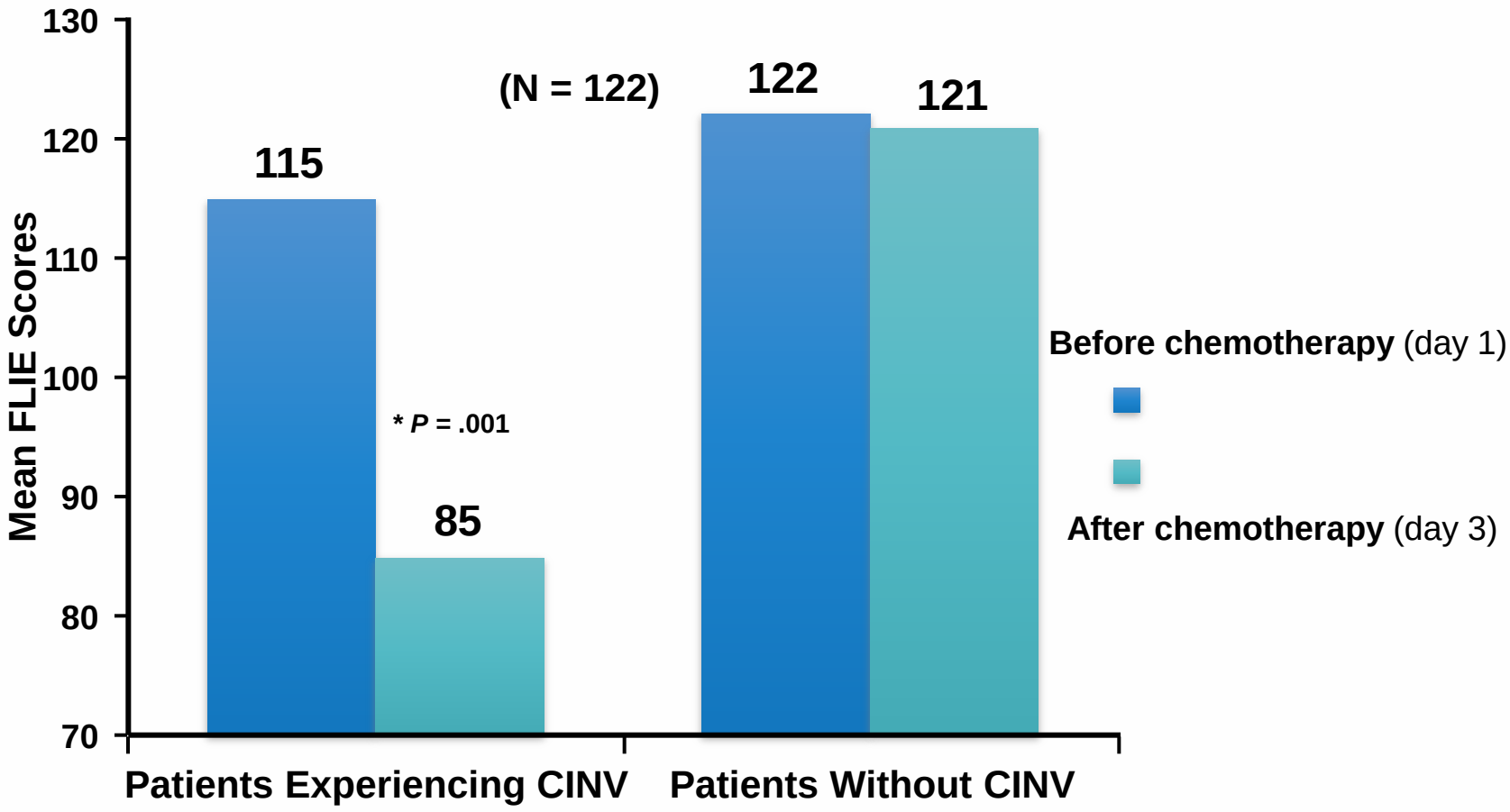
MASCC/ESMO Antiemetic Guidelines

Will Soon Be Updated

and Available at

www.mascc.org

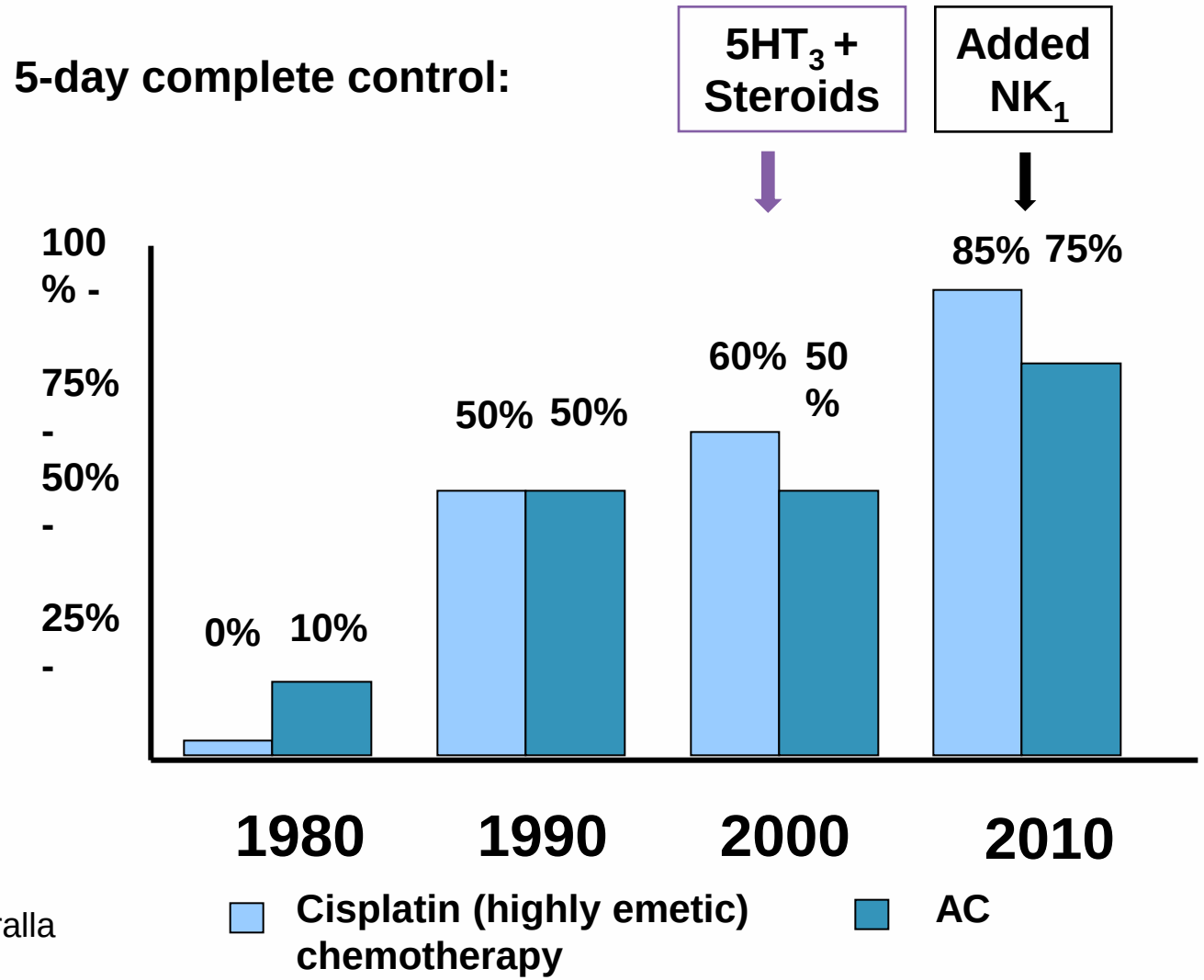
Chemotherapy-Induced Nausea and Vomiting (CINV): Impact on Quality of Life



FLIE, Functional Living Index-Emesis

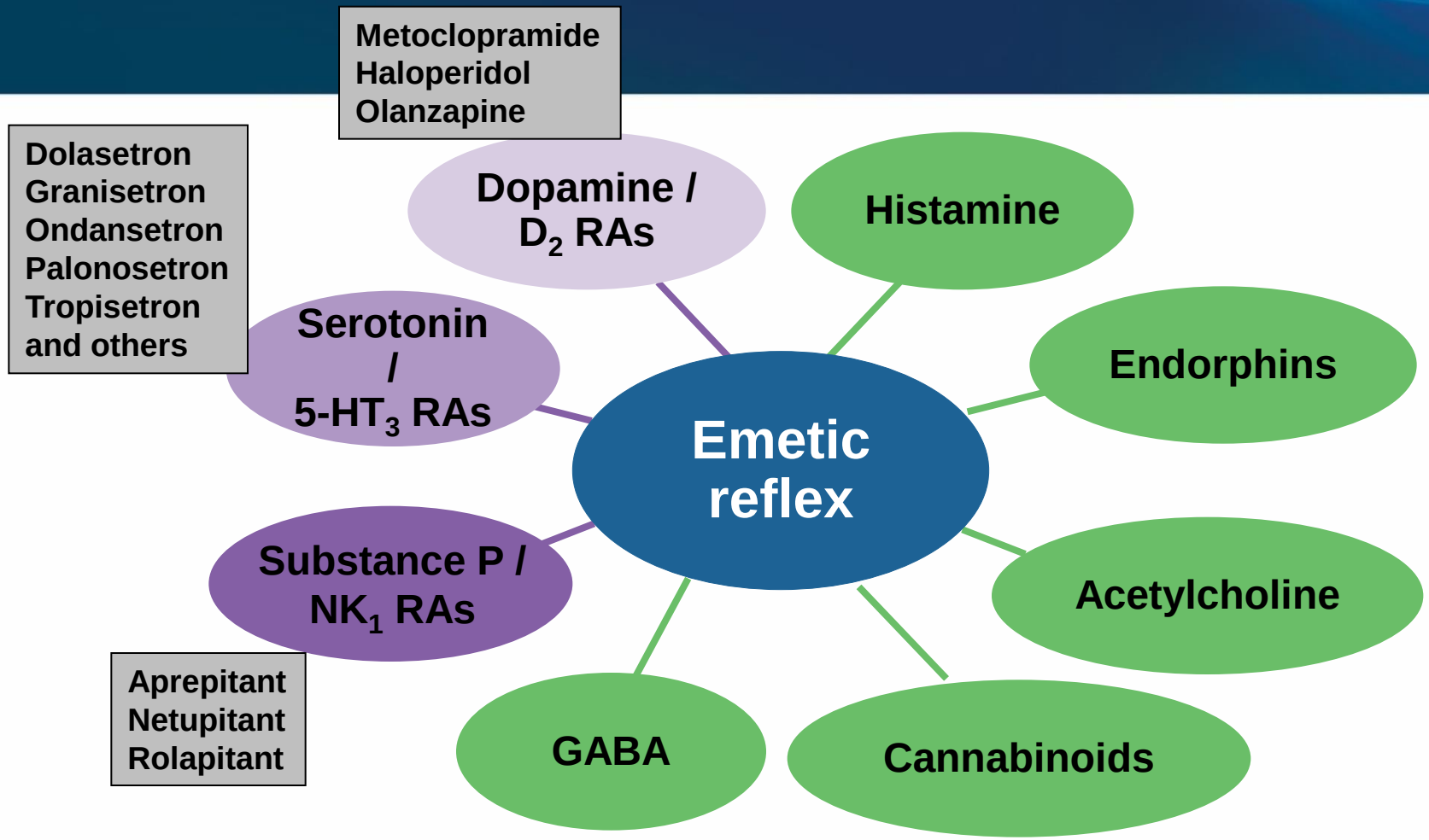
Lindley CM, et al. *Qual Life Res.* 1992;1(5):331-340.

Controlling Chemotherapy-Induced Emesis: Progress Over the Past 30 Years: Efficacy



Courtesy R Gralla

Neurotransmitters and Antiemetics



D_2, dopamine; GABA, gamma-aminobutyric acid; NK, neurokinin; Ras, receptor antagonists

Gralla RJ, et al. *J Clin Oncol.* 1999;17(9):2971-2994. Grunberg SM, et al. *N Engl J Med.* 1993;329(24):1790-1796. Hesketh PJ. *Support Care Cancer*. 2001;9(5):350-354.

MASCC/ESMO Antiemetic Guidelines

Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Ritternberg C, Saito M, Tonato M, Warr D; on behalf of the ESMO/MASCC Guidelines Group

Guideline Update for MASCC and ESMO in the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting: Results of the Perugia Consensus Conference

Roila F, et al. *Ann Oncol.* 2010;21(Suppl 5):v232-v243.

Summary Acute Nausea and Vomiting

Emetic risk group	Antiemetics		
High	5-HT_3	DEX	APR or FOS
Anthracycline + cyclophosphamide (AC)	5-HT_3	DEX	APR or FOS
Moderate (other than AC)	PALO	DEX	
Low	DEX	5-HT_3	DRA
Minimal	No routine prophylaxis		

5-HT_3 = Serotonin Receptor Antagonist	DEX = Dexamethasone	APR = Aprepitant FOS = Fosaprepitant	PALO = Palonosetron	DRA = Dopamine Receptor Antagonist

NOTE: If the NK_1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.

Roila F, et al. *Ann Oncol.* 2010;21(Suppl 5):v232-v243.

Summary Delayed Nausea and Vomiting

Emetic risk group	Antiemetics
High	DEX* + APR*
Anthracycline + cyclophosphamide (AC)	APR or none**
Moderate (other than AC)	DEX
Low	No routine prophylaxis
Minimal	No routine prophylaxis

DEX = DEXAMETHASONE

APR = APREPITANT

*DEX only, if fosaprepitant used on day 1

**If fosaprepitant used on day 1

Roila F, et al. *Ann Oncol.* 2010;21(Suppl 5):v232-v243.

ASCO Recommendations

AC has been reclassified as HEC in the ASCO recommendations, which is different to the MASCC/ESMO recommendations

Emetic Risk Group	Risk (% Patients)	Acute Prevention	Delayed Prevention
High & AC combinations	>90%	5-HT_3 RA + DEX + NK_1 RA	DEX + aprepitant*
Moderate	30% to 90%	PALO + DEX	DEX
Low	10% to 30%	5-HT_3 RA or DEX or DRA	No routine prophylaxis
Minimal	<10%	No routine prophylaxis	No routine prophylaxis

*** When aprepitant administered on day 1**

AC, anthracycline and cyclophosphamide; HEC, highly emetogenic chemotherapy; RA, receptor antagonist; DEX, dexamethasone; PALO, palonosetron; DRA, dopamine receptor antagonist

Basch E, et al. *J Clin Oncol.* 2011;29(31):4198-4198. www.asco.org UPDATED Hesketh et al JCO.2015 64:3635-7

“Moderate” Emetogenic Risk

- Moderate emetogenic chemotherapy:
  - Risk of emesis: 30% to 90%
  - Broad range of chemotherapeutic agents

Guidelines Should be Evidence-based

www.medscape.com

The Virtues and Vices of the NCCN Guidelines

Nick Mulcahy | March 16, 2015

HOLLYWOOD, Florida — Now in their 20th year, the National Comprehensive Cancer Network (NCCN) guidelines have greatly evolved from early efforts and continue to add new wrinkles, according to participants in a roundtable discussion at the group's annual meeting here.

But the guides are not solely evidence-based and, as a result, are subject to the biases of the authors, which can result in a variety of negative consequences, including questionable advice and excessive care, said critics at the meeting.

And Guidelines Decrease Costs

Kosimbei *et al. Health Research Policy and Systems* 2011, **9**:24
http://www.health-policy-systems.com/content/9/1/24

HEALTH RESEARCH POLICY AND SYSTEMS

REVIEW **Open Access**

Do clinical guidelines reduce clinician dependent costs?

George Kosimbei[1*], Kara Hanson[2] and Mike English[3]

Kosimbei G, et al. *Health Res Policy Syst.* 2011 Jun 16;9:24

Relevant Studies on Guideline Adherence Benefit

- The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER)[1]
- Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE Study[2]
- Antiemetic therapy in Asia Pacific countries for patients receiving moderately and highly emetogenic chemotherapy – a descriptive analysis of practice patterns, antiemetic quality of care, and use of antiemetic guidelines[3]

1. Aapro M, et al. *Ann Oncol.* 2012;23(8):1986-1992; 2. Gilmore JW, et al. *J Oncol Pract.* 2014;10(1):68-74; 3. Yu S, et al. *Support Care Cancer.* 2015;23(1):273-282

Guideline-Consistent Antiemetic Therapy in CINV: CINV Outcomes

- Percentage of patients with complete response (no emesis and no use of rescue therapy) was significantly higher in the guideline-consistent (GCCP) cohort than in the guideline-inconsistent (GICP) cohort
- Incidence of all other desirable CINV outcomes (no emesis, no nausea, no CINV) was also higher in the GCCP cohort than the GICP cohort

	GCCP (n=287)	GICP (n=704)	P value[a]	Multivariate model[b]	
				Odds ratio	*P* value
Complete response	172 (59.9%)	357 (50.7%)	0.008	1.43 (1.04-1.97)	.027
No emesis	182 (63.4%)	412 (58.5%)	0.154	1.18 (0.86-1.63)	.301
No nausea	138 (48.1%)	286 (40.6%)	0.031	1.37 (0.99-1.90)	.056
No CINV	122 (42.5%)	242 (34.4%)	0.016	1.41 (1.01-1.96)	.041

[b]Model adjusted for age, sex, pre-chemotherapy nausea, pre-chemotherapy anxiety, expectation of nausea, use of primary antiemetic therapy not recommended by guidelines, underdosing of primary antiemetic therapy, and use of secondary antiemetic agents

Aapro M, et al. Ann Oncol. 2012;23(8):1986-1992

BUT SINCE THEN…

Emetic Risk Groups – Single IV Agents

HIGH	**Anthracycline/cyclophosphamide combination*** Carmustine Cisplatin Cyclophosphamide ≥ 1500 mg/m² Dacarbazine Mechlorethamine Streptozocin	
MODERATE	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide < 1500 mg/m² Cytarabine > 1000 mg/m² Daunorubicin Doxorubicin	Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin **Romidepsin** **Temozolomide[b]** **Thiotepa** **Trabectedin**

*The combination of an anthracycline and cyclophosphamide in patients with breast cancer should be considered highly emetogenic

[b]No direct evidence found for temozolomide IV; as all sources indicate a similar safety profile to the oral formulation, the classification was based on oral temozolomide.

Emetic Risk Groups – Single IV Agents

Low	**Aflibercept** **Belinostat** **Blinatumomab** Bortezomib **Brentuximab** **Cabazitaxel** **Carfilzomib** Catumaxumab Cetuximab Cytarabine $\leq$ 1000 mg/m^2 Docetaxel **Eribulin** Etoposide 5-Fluorouracil Gemcitabine	**Ipilimumab** Ixabepilone Methotrexate Mitomycin Mitoxantrone **Nab- paclitaxel** Paclitaxel Panitumumab Pemetrexed **Pegylated liposomal doxorubicin** **Pertuzumab** Temsirolimus Topotecan **Trastuzumab-emtansine** **Vinflunine**

Emetic Risk Groups – Single IV Agents

MINIMAL	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Cladribine Fludarabine **Nivolumab** **Ofatumumab** **Pembrolizumab** **Pixantrone**	Pralatrexate Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine
Classification not yet possible[a]	**Obinutuzumab**	

[a]The information was insufficient or inadequate to determine a classification.

Emetic Risk Groups – Single Oral Agents

HIGH	Hexamethylmelamine	Procarbazine
MODERATE	**Bosutinib** **Ceritinib** **Crizotinib** Cyclophosphamide	Imatinib Temozolomide Vinorelbine
LOW	**Afatinib** **Axatinib** Capecitabine **Dabrafenib** **Dasatinib** Everolimus Etoposide Fludarabine **Ibrutinib** **Idelalisib** Lapatinib Lenalidomide	**Olaparib** **Nilotinib** **Pazopanib** **Ponatinib** **Regorafenib** Sunitinib Tegafur Uracil Thalidomide **Vandetanib** **Vorinostat**
MINIMAL	Chlorambucil Erlotinib Gefitinib Hydroxyurea Melphalan Methotrexate L-Phenylalanine mustard	**Pomalidomide** **Ruxolitinib** Sorafenib 6-Thioguanine **Vemurafenib** **Vismodegib**

Next Steps….

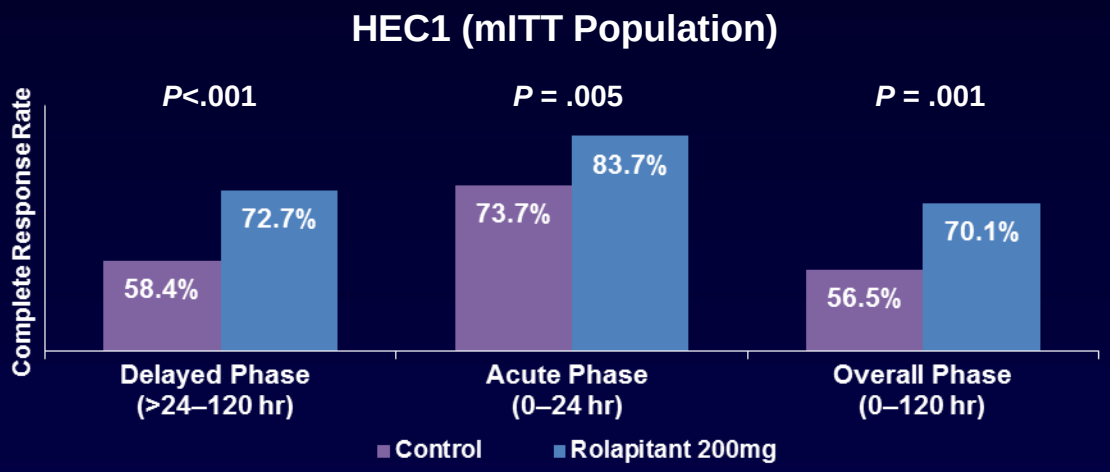
Rolapitant

- Rolapitant is a potent, selective, NK-1 receptor antagonist, with a half-life of approximately 180 hours
- A 200-mg dose of rolapitant could provide over 90% NK-1 brain receptor occupancy
- Rolapitant is not an inducer or inhibitor of CYP-3A4

Rolapitant HEC Studies

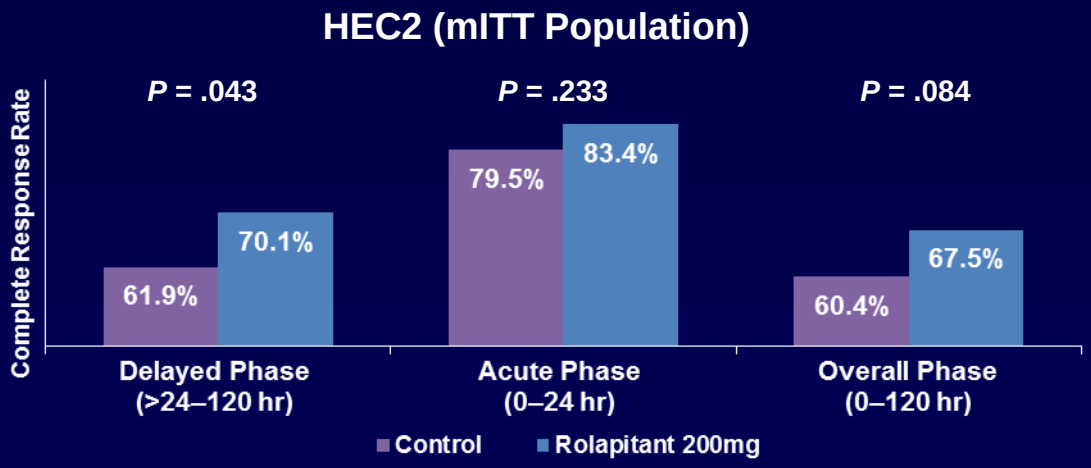
HEC1

- Complete response (CR) rate is superior in rolapitant vs the control arm in the delayed phase
- CR rate is superior in rolapitant vs the control arm in the acute and overall phases



HEC2

- CR rate is superior in rolapitant vs the control arm in the delayed phase
- CR rate is numerically greater in rolapitant vs the control arm in the acute and overall phases

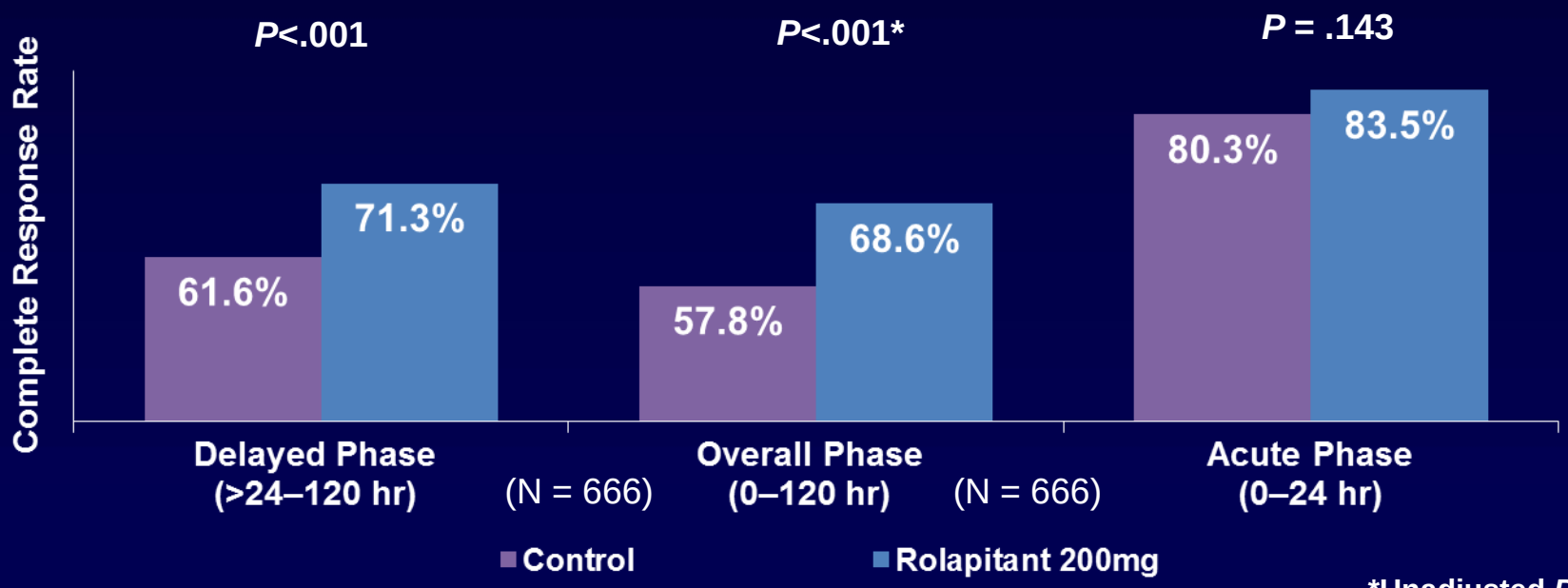


Rapoport B, et al. *Support Care Cancer.* 2014;22(Suppl 1): Abstract 0387. Lancet Oncology 2015

Rolapitant MEC

- Rolapitant group achieved statistically significant higher CR rates in the primary endpoint of delayed phase (>24 hrs - 120 hrs) compared to the control group

mITT Population



*Unadjusted *P* value

Presented by Lee Schwartzberg on behalf of Schnadig I, et al. *Support Care Cancer.* 2014;22(Suppl 1): Abstract 0384.

Lancet Oncology 2015

NEPA: A Combination of Netupitant and Palonosetron

- An oral fixed-dose combination of netupitant, a new highly selective NK1 receptor antagonist and palonosetron (PALO), a pharmacologically distinct and clinically superior agent compared to the older 5-HT_3 receptor antagonist[1-5]
- Developed to provide a convenient treatment, consistent with treatment guidelines for antiemetic prophylaxis
- NEPA targets two critical pathways associated with acute and delayed CINV, the serotonin and substance P-mediated pathways

NK1, neurokinin 1

1. Gralla R, et al. *Eur J Cancer.* 2013;49 (suppl 2): Abstract 1301. 2. Aapro M, et al. *Eur J Cancer.* 2013; 49(suppl 2): Abstract 1300. 3. Gralla RJ, et al. *Eur J Cancer.* 2013;49(suppl 2): Abstract 1302. 4. Feyer P, et al. *Ann Oncol.* 2011;22(1):30-38. 5. Rojas C, et al. *Eur J Pharmacol.* 2012;684(1-3):1-7.

CR in Registration Studies

Cycle 1 overall (0-120 h) CR	NEPA + DEX	Oral PALO + DEX	APR + 5-HT_3 RA‡ + DEX
Phase II Dose-ranging **HEC** Study	90%* (N = 136)	77% (N = 136)	87% (N = 134)
Phase III **AC MEC** Study†	74%* (N = 724)	67% (N = 725)	NA
Phase III Multiple Cycle **Non-AC MEC + HEC** Study	81% (N = 309)	NA	76% (N = 104)

* *P*<.01 vs Oral PALO
† Primary endpoint delayed (25-120h) phase – NEPA 77% vs Oral PALO 70% (*P* = .001)
‡ 5-HT_3 RA = ondansetron in phase II and palonosetron in phase III

- CR = No emesis and no use of rescue medication
- All patients were chemotherapy naïve with solid tumors
- No formal (efficacy) comparisons with APR + 5-HT_3 RA + DEX
  - Included as exploratory and to help interpret results

APR, aprepitant; PALO, palonosetron, DEX, dexamethasone

Aapro M, et al. *Ann Oncol.* 2014;25(7):1328-1333. Gralla R, et al. *Ann Oncol.* 2014;25(7):1333-1339. Hesketh P, et al. *Ann Oncol.* 2014;25(7):1340-1346.

AND FURTHER CHANGES

- Olanzapine
- Carboplatin
- Patient risk factors

NCCN Guideline Version 1.2015

MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[a,b]

DAY 1: Select option A, B, or C (order does not imply preference) Start before chemotherapy:[c]	DAYS 2 and 3:
A: Serotonin (5-HT3) antagonist + steroid (category 1) ± NK-1 antagonist[d] • Serotonin (5-HT3) antagonist (Select one):[e] ‣ Dolasetron 100 mg PO once ‣ Granisetron 2 mg PO once, or 1 mg PO BID, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h prior to first dose of chemotherapy ‣ Ondansetron 16-24 mg PO once or 8-16 mg IV once[f] ‣ Palonosetron 0.25 mg IV once[g] (preferred) AND • Steroid:[h] ‣ Dexamethasone 12 mg PO/IV once WITH/WITHOUT • Neurokinin-1 (NK1) antagonist:[m] ‣ Aprepitant 125 mg PO once ‣ Fosaprepitant 150 mg IV once	**A:** • Serotonin (5-HT3) antagonist monotherapy[o] (Select one):[e] ‣ Dolasetron 100 mg PO daily on days 2, 3 ‣ Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily on days 2, 3 ‣ Ondansetron 8 mg PO BID or 16 mg PO daily or 8-16 mg IV daily on days 2, 3[f] OR • Steroid monotherapy:[h] ‣ Dexamethasone 8 mg PO/IV daily on days 2, 3 OR • NK1 antagonist ± steroid: [h,m,l] ‣ Aprepitant used day 1: Aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV daily on days 2, 3 ‣ Fosaprepitant used day 1: ± dexamethasone 8 mg PO or IV daily on days 2, 3
B: Netupitant-containing regimen:[d,n] ‣ Netupitant 300 mg/palonosetron 0.5 mg PO once ‣ Dexamethasone 12 mg PO/IV once	**B:** ‣ ± Dexamethasone 8 mg PO/IV daily on days 2, 3
C: Olanzapine-containing regimen:[d,j] ‣ Olanzapine 10 mg PO once ‣ Palonosetron 0.25 mg IV once ‣ Dexamethasone 20 mg IV once	**C:** ‣ Olanzapine 10 mg PO daily days 2, 3

NCCN Guideline Version 1.2015

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[a,b]

DAY 1: Select option A, B, or C (order does not imply preference) Start before chemotherapy:[c]	DAYS 2, 3, 4:
A: Aprepitant-containing regimen:[d] select one agent from each of the following groups (category 1): • Neurokinin-1 (NK1) antagonist: ▸ Aprepitant 125 mg PO once ▸ Fosaprepitant 150 mg IV once AND • Serotonin (5-HT3) antagonist:[e] ▸ Dolasetron 100 mg PO once ▸ Granisetron 2 mg PO once, or 1 mg PO BID, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h prior to first dose of chemotherapy ▸ Ondansetron 16-24 mg PO once or 8-16 mg IV once[f] ▸ Palonosetron 0.25 mg IV once[g] AND • Steroid:[h,l] ▸ Dexamethasone 12 mg PO/IV once	**A:**[k] ▸ If aprepitant PO given day 1, aprepitant 80 mg PO daily on days 2, 3 ▸ If fosaprepitant IV given on day 1, no further aprepitant is needed on days 2, 3 AND ▸ If aprepitant PO given day 1, dexamethasone 8 mg PO/IV daily days 2, 3, 4[l] ▸ If fosaprepitant IV given on day 1, dexamethasone 8 mg PO/IV once on day 2, then 8 mg PO/IV BID days 3, 4[l]
B: Netupitant-containing regimen:[d,i] ▸ Netupitant 300 mg/palonosetron 0.5 mg PO once ▸ Dexamethasone 12 mg PO/IV once	**B:** ▸ Dexamethasone 8 mg PO/IV daily on days 2, 3, 4
C: Olanzapine-containing regimen:[d,j] ▸ Olanzapine 10 mg PO once ▸ Palonosetron 0.25 mg IV once ▸ Dexamethasone 20 mg IV once	**C:** ▸ Olanzapine 10 mg PO daily on days 2, 3, 4

Carboplatin

What Do The Guidelines Tell Us?

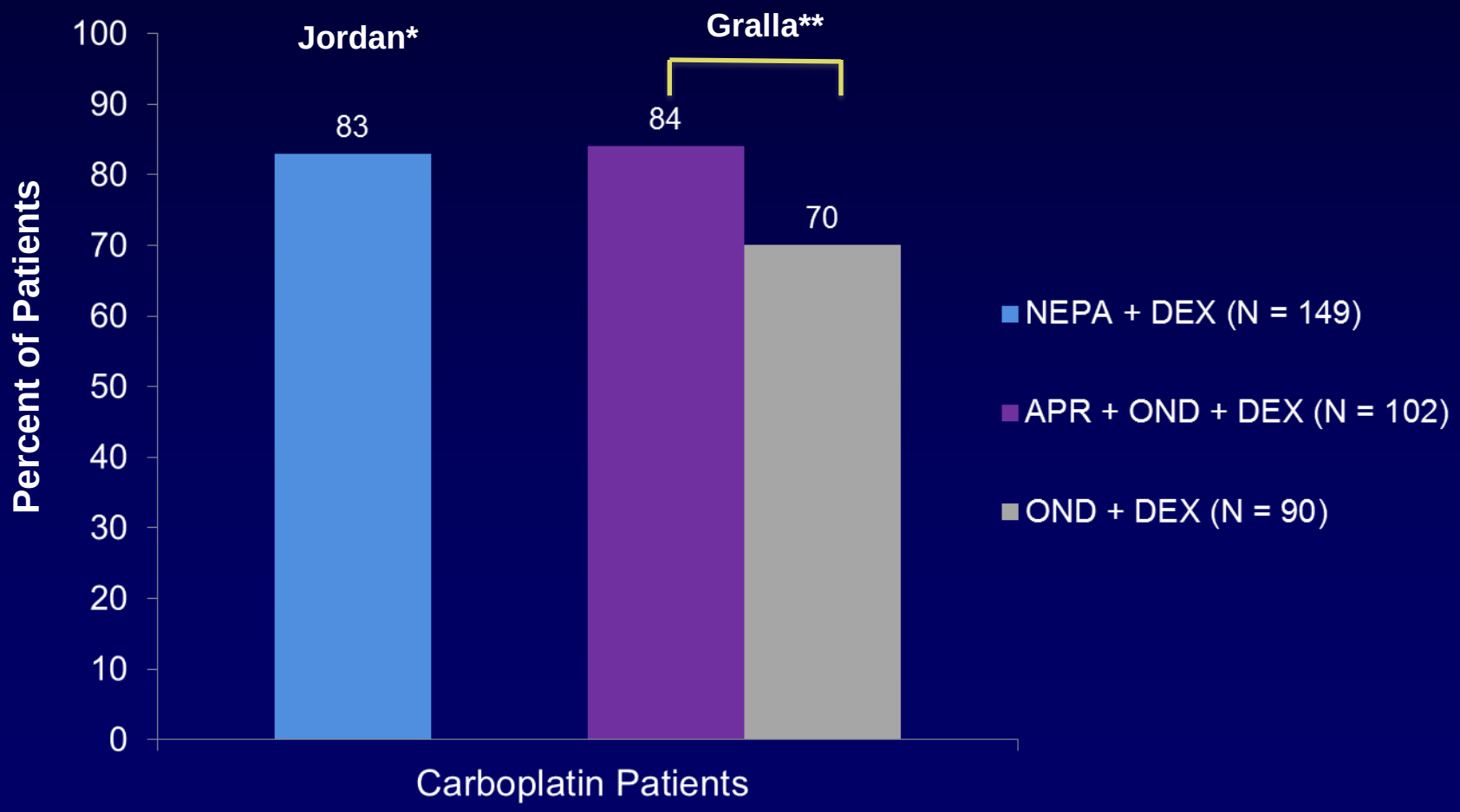
CTX	Emetic Risk	Examples	Prophylaxis	MASCC/ ESMO	ASCO	NCCN
High	> 90%	Cisplatin Carmustine Dacarbazine	NK_1 RA	+	+	+
			$5\text{-}HT_3$ RA	+	+	+
			DEX	+	+	+
Moderate	30% to 90%	Carboplatin Cyclophosphamide Doxorubicin Ifosfamide Oxaliplatin Irinotecan	NK_1 RA	-	*	**
			Palonosetron	+	+	+
			DEX	+	+	+

* "may consider"
** in "selected patients" where appropriate (ie, receiving carboplatin, cyclophosphamide, and doxorubicin)

CTX, chemotherapy treatment; NK_1, neurokinin-1; RA, receptor antagonist; DEX, dexamethasone

Basch E, et al. *J Clin Oncol.* 2011;29(31):4198-4198 (ASCO Guideline). Roila F, et al. *Ann Oncol.* 2010;21(Suppl 5):v232-v243.

Post Hoc Analyses: Overall (0-120 h) Cycle 1 No Emesis Rates in Carboplatin Setting (NEPA and Historical Aprepitant and Control)



*** Jordan KJ, et al. Presented at the MASCC/ISOO International Symposium on Supportive Care in Cancer; June 26-28, 2014: Miami, Florida. Abstract PS03.**

****Gralla RJ, et al. *Eur J Cancer Suppl.* 2009;7(2): Abstract 9048.**

Randomized Trials: NK_1 Receptor Antagonists in Carboplatin Based Chemotherapy

Complete Response (No Emesis/Rescue Medication) (0-120 h)

APR study	APR + 5 HT_3-RA + DEX	5 HT_3-RA + DEX	Absolute Difference
Tanioka[1] (N = 91*)	62%	52%	10%
Ito[2] (n = 134)	80%	67%	13%
Yahata[3] (n = 324 §)	85%	62%	23%

- 98% of patients receiving carboplatin-based chemotherapy
- § All patients received paclitaxel and carboplatin

APR, aprepitant; DEX, dexamethasone

1. Tanioka M, et al. *Br J Cancer.* 2013;109(4):859-865. 2. Ito Y, et al. *Lung Cancer.* 2014;84(3):259-264. 3. Yahata H, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1481PD.

Individual Risk Factor

- Female gender
- Young age
- Anxious personal
- Minimal alco ≥5 drinks week is protectiv
- His during pregnancy
- otion sickness
- y of chemotherapy

Although important to acknowledge, individual risk factors are not involved in the primary treatment algorithm

Roila F, et al. *J Clin Oncol.* 1991;9(4):675-678. Morrow GR, et al. *Support Care Cancer*. 2002;10(2):96-105.

TAKE HOME MESSAGE

Evidence-based guidelines improve outcomes

And will soon be updated...

www.mascc.org


MASCC/ISOO 2016
International Symposium on Supportive Care in Cancer
Save The Date...Adelaide, Australia - June 23-25 2016
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SOUTH AUSTRALIA