PREVENTION AND MANAGEMENT OF FEBRILE NEUTROPENIA

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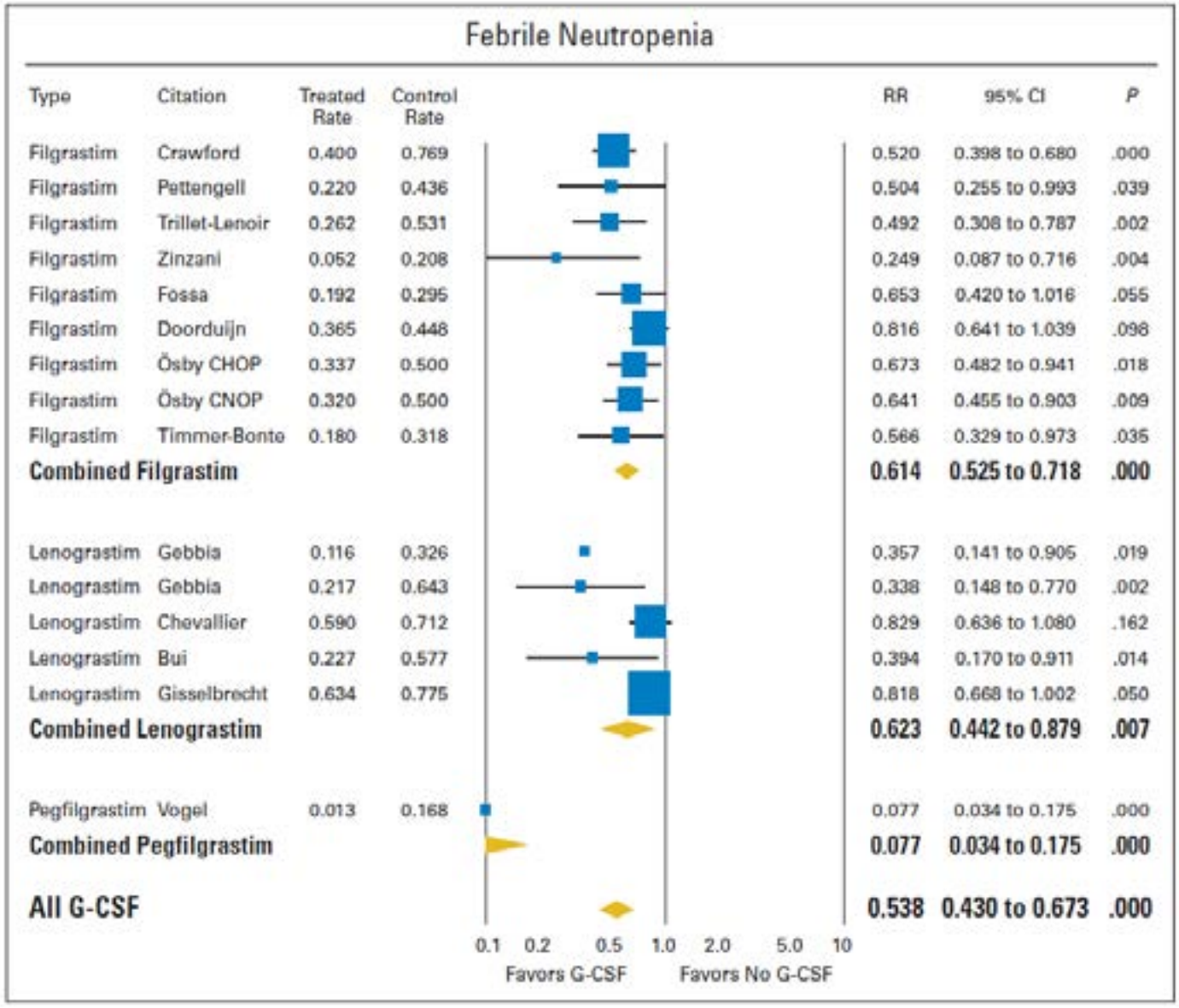
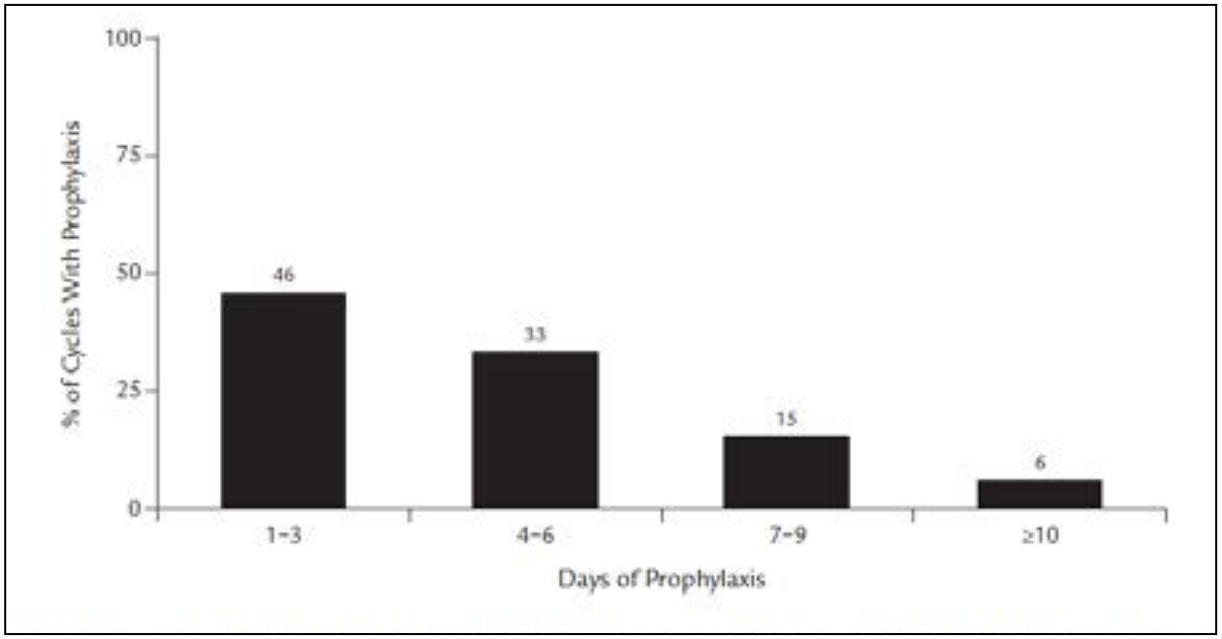
PREVENTION

FEBRILE NEUTROPENIA RISK



Kuderer et al, JCO, 2007

DURATION OF PROPHYLAXIS FOR NEUTROPENIC COMPLICATIONS OF CHEMOTHERAPY IN PATIENTS WITH PRIMARY SOLID TUMORS RECEIVING FILGRASTIM



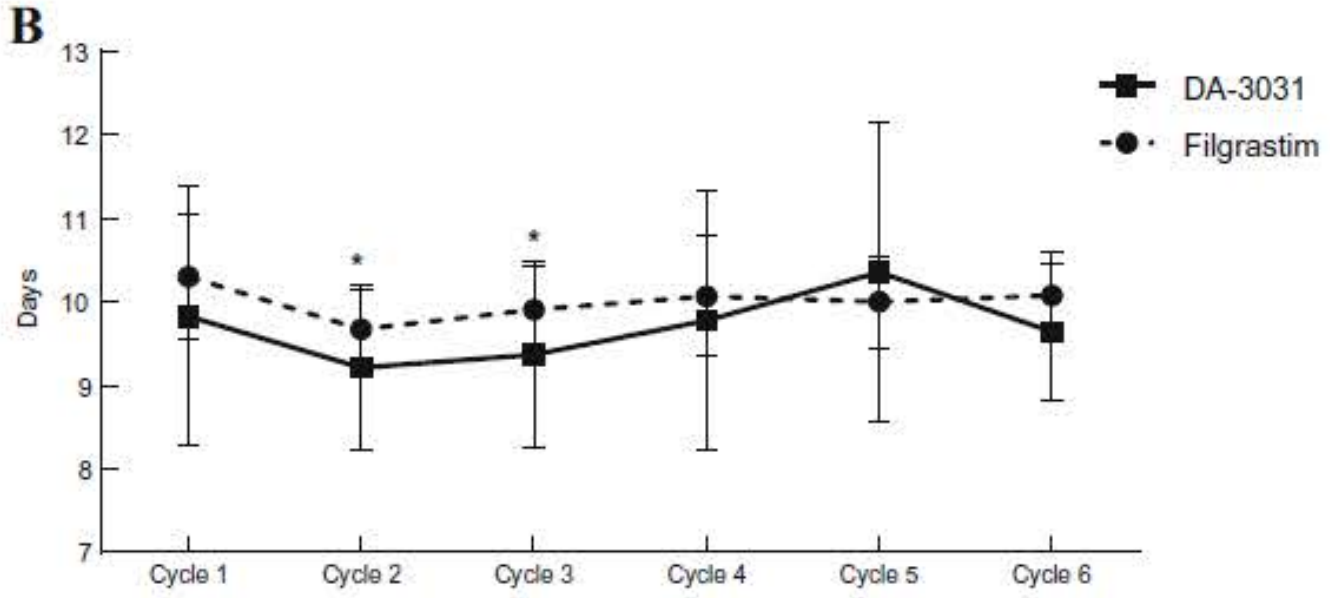
Weycker et al.,J Clin Ther ,2009

Patients receiving filgrastrim for a solid tumor in US (12/2003-01/2015), n=1193

Patients receiving pegfilgrastim, n=14570

Risk of hospitalization for neutropenic complications : 2.1% versus 1.2%, $p<0.05$

TIME TO RECOVERY OF ANC



Breast cancer patients receiving TAC chemotherapy (docetaxel, doxorubicin, cyclophosphamide)

74 patients

Non significant difference between arms

Patients who were randomized to filgrastim received daily subcutaneous injections of filgrastim 100 μg/m^2/day beginning approximately 24h after chemotherapy and continued until ANC was documented to be 5 x 10^9/L after nadir, or for up to 10 days. Patients who were randomized to the DA-3031 group received a single subcutaneous injection of DA-3031 at fixed doses of 6 mg on day 2 of each chemotherapy cycle approximately 24h after completion of chemotherapy.

Park et al., Support Care Cancer (2017) 25:505-511

PEGFILGRASTIM VS FILGRASTIM

Study or Subgroup	Pegfilgrastim Events	Total	Filgrastim Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Green 2003 (breast)	10	77	15	75	30.5%	0.65 [0.31, 1.35]
Holmes 2002 (breast, ph3)	14	149	27	147	45.1%	0.51 [0.28, 0.94]
Holmes 2002 (breast, ph2)	5	46	2	25	6.7%	1.36 [0.28, 6.50]
Grigg 2003* (NHL)	0	14	1	13	1.7%	0.31 [0.01, 7.02]
Vose 2003 (NHL, HL)	6	29	6	31	16.1%	1.07 [0.39, 2.94]
Total (95% CI)		**315**		**291**	**100.0%**	**0.66 [0.44, 0.98]**
Total events	35		51			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.60$, df = 4 (P = 0.63); $I^2 = 0\%$

Test for overall effect: Z = 2.04 (P = 0.04)

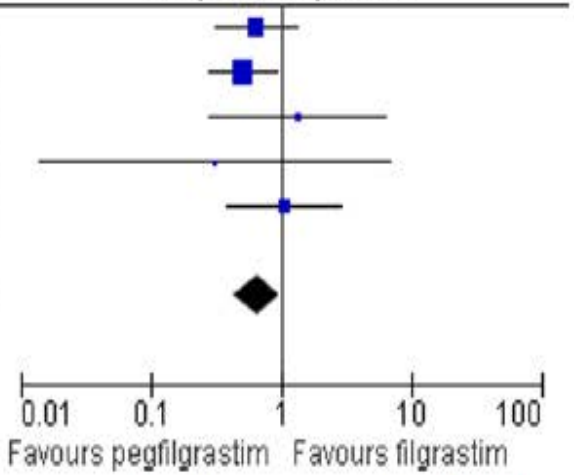
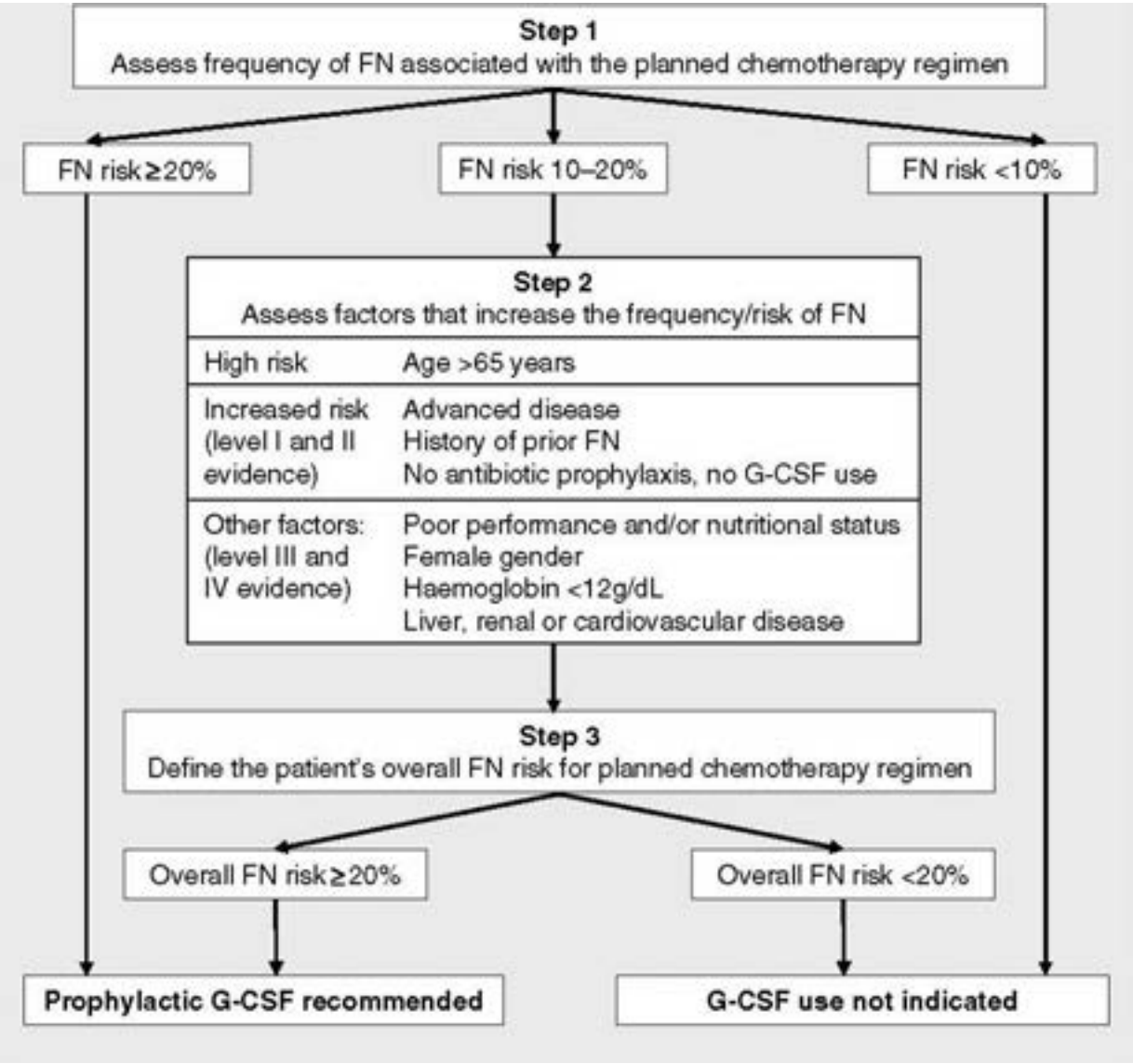


Figure 3 Pegfilgrastim versus filgrastim: FN incidence. Cancer types for each study are shown after the author and date. HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma. *Indicates studies in patients aged ≥ 60 or ≥ 65 years. In the Holmes 2002 (phase II) study,[37] FN incidence in the filgrastim arm was reported as 2/25, which was incorrectly converted to 12%. The absolute numbers (2/25) have been used in this analysis. Therefore the resulting relative risk differs slightly from that reported in the previous systematic review by Pinto (2007),[19] which used the 12% figure.

Cooper et al., BMC Cancer, 2011

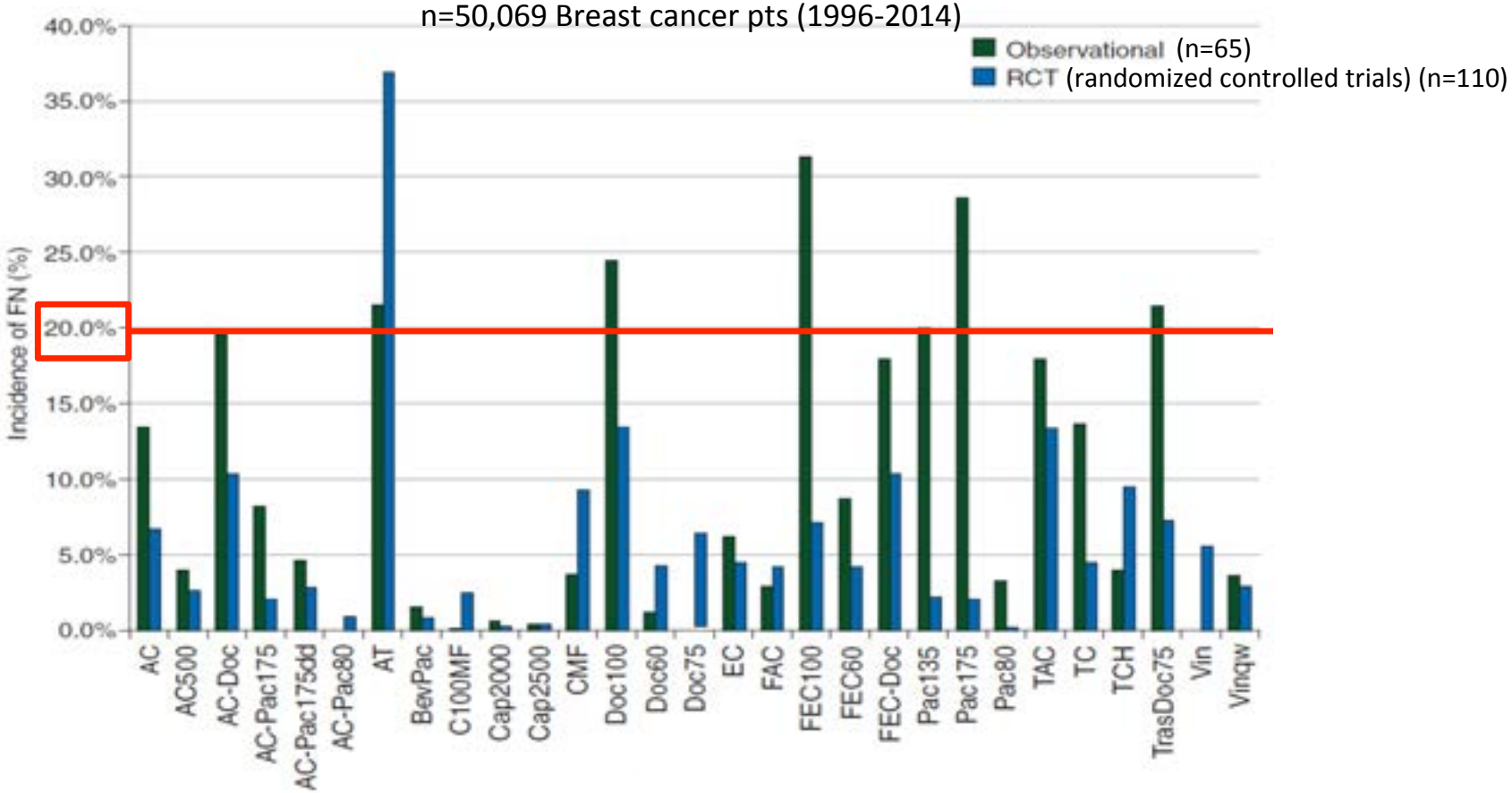
PATIENT ASSESSMENT ALGORITHM TO DECIDE PROPHYLACTIC G-CSF USAGE



Aapro MS et al., Eur J Cancer, 2011

FN Incidence
Gap Between Clinical Trials and Real Life Practice

n=50,069 Breast cancer pts (1996-2014)



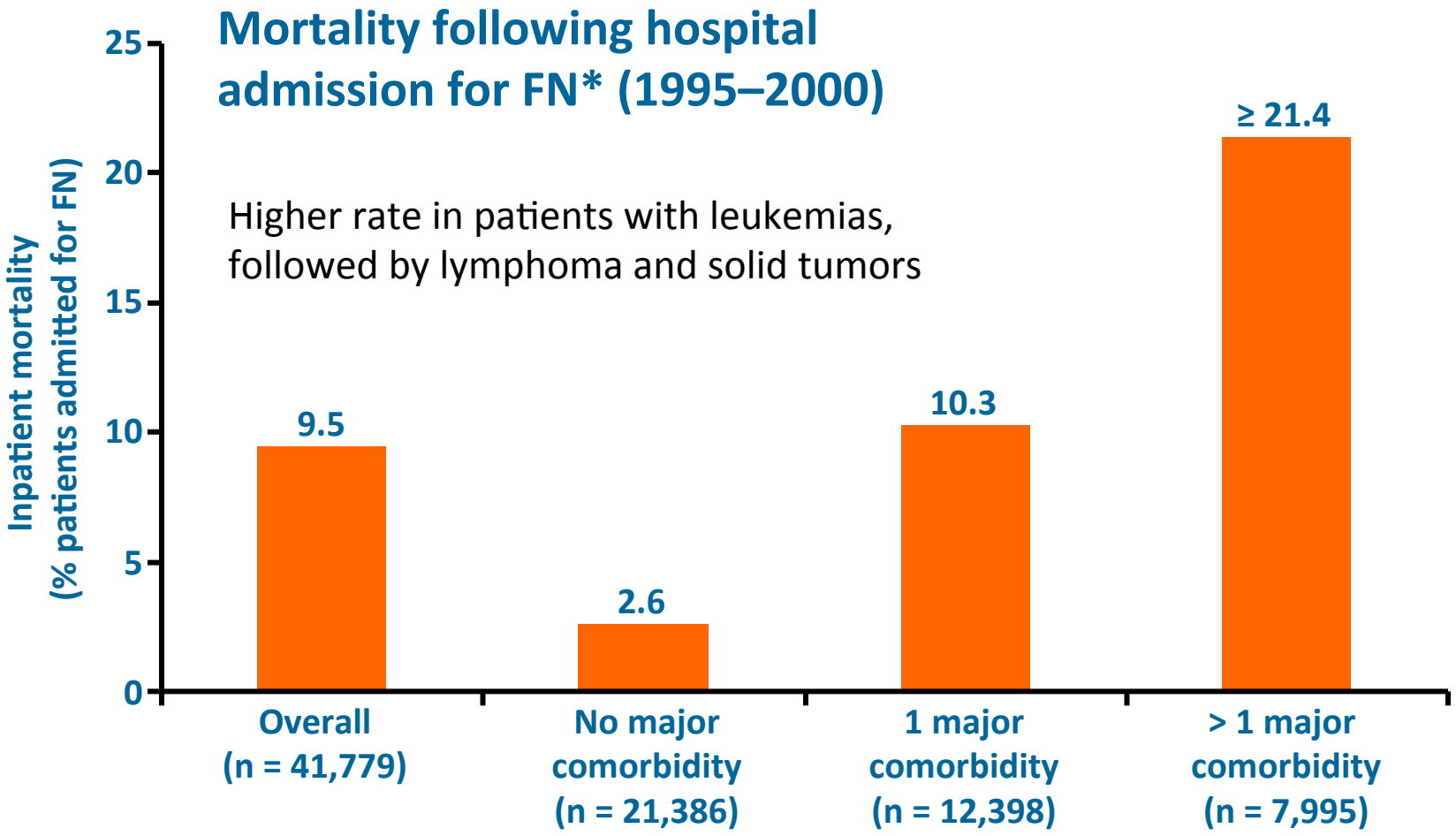
FN rates: significantly higher in the observational study compared with RCT cohorts (OR = 1.74; 95% CI 1.15–2.62; p = 0.012).

This meant that a 13% (95% CI 8.7% to 17.9%) FN rate in RCT would translate into 20% FN rate in observational study.

Truong J et al. Ann Oncol. 2016

MANAGEMENT

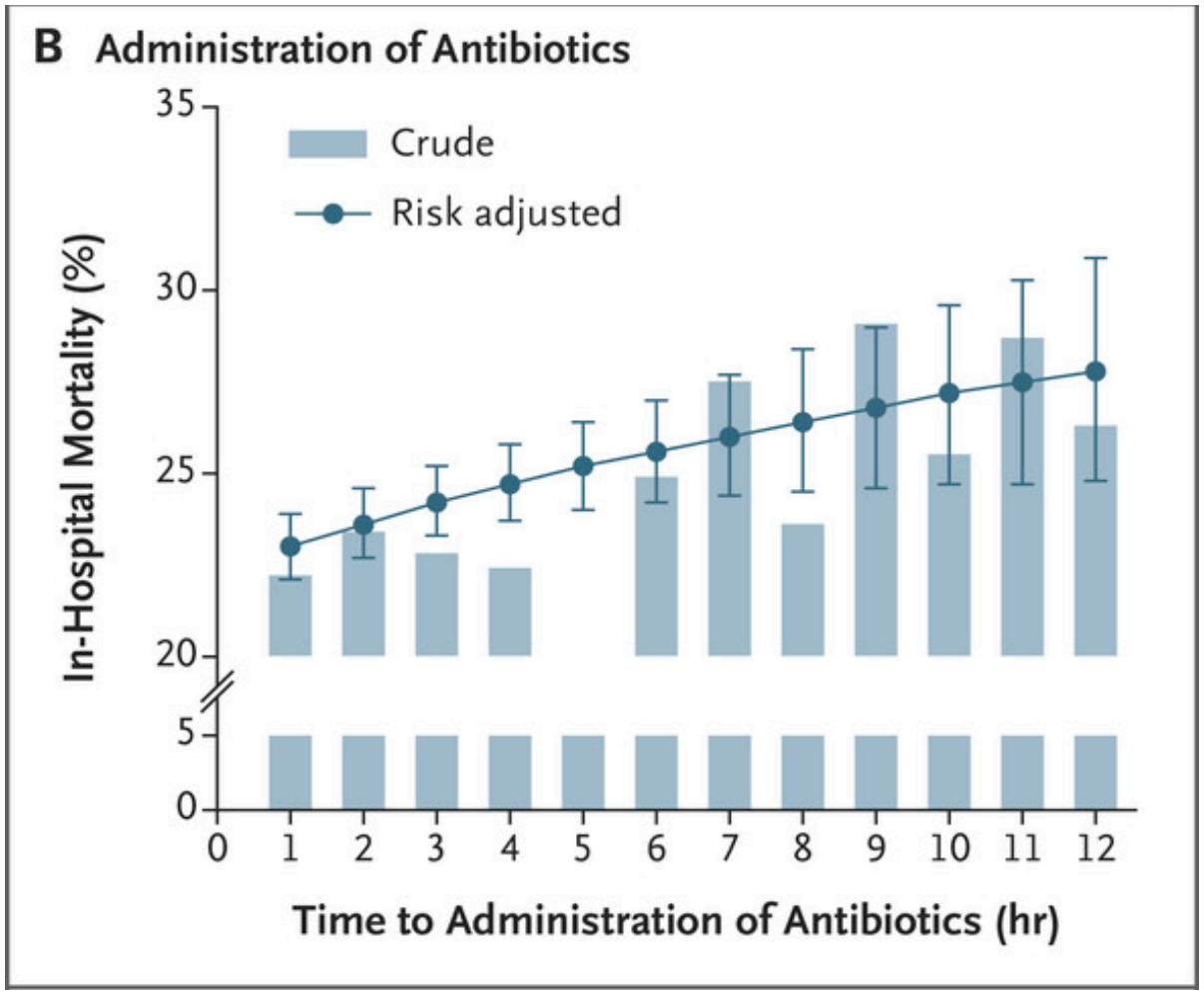
RELATIONSHIP BETWEEN FN, RISK OF MORTALITY AND COMORBIDITIES – US discharge data base – 155 academic centres



* Data based on a single admission per patient

Kuderer NM et al., Cancer, 2006

In patients with sepsis



Seymour CW et al. N Engl J Med 2017;376:2235-2244.

Risk of complication : low risk prediction

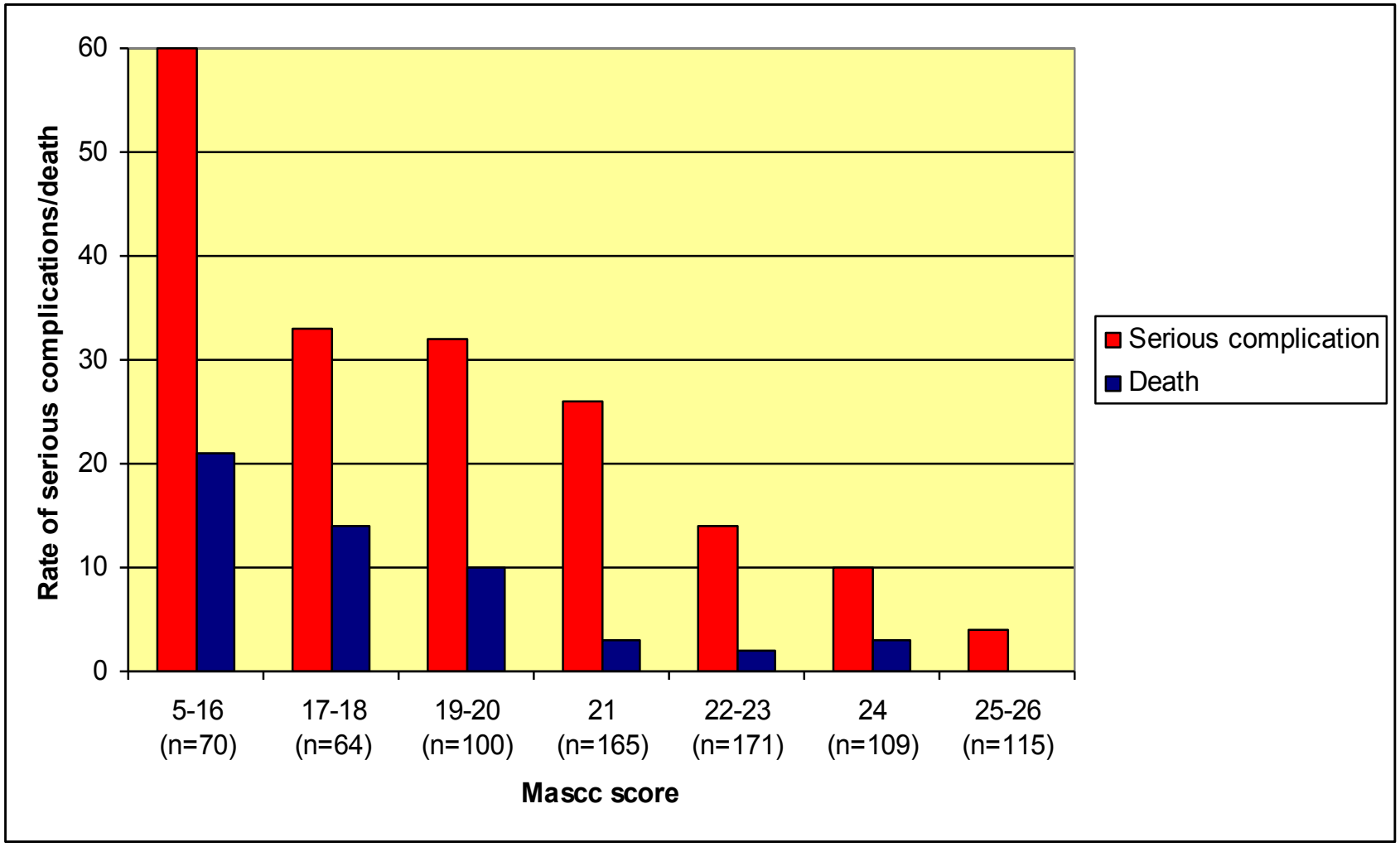
Multinational Association of Supportive Cancer Care scoring system

Characteristic	Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age <60 years	2

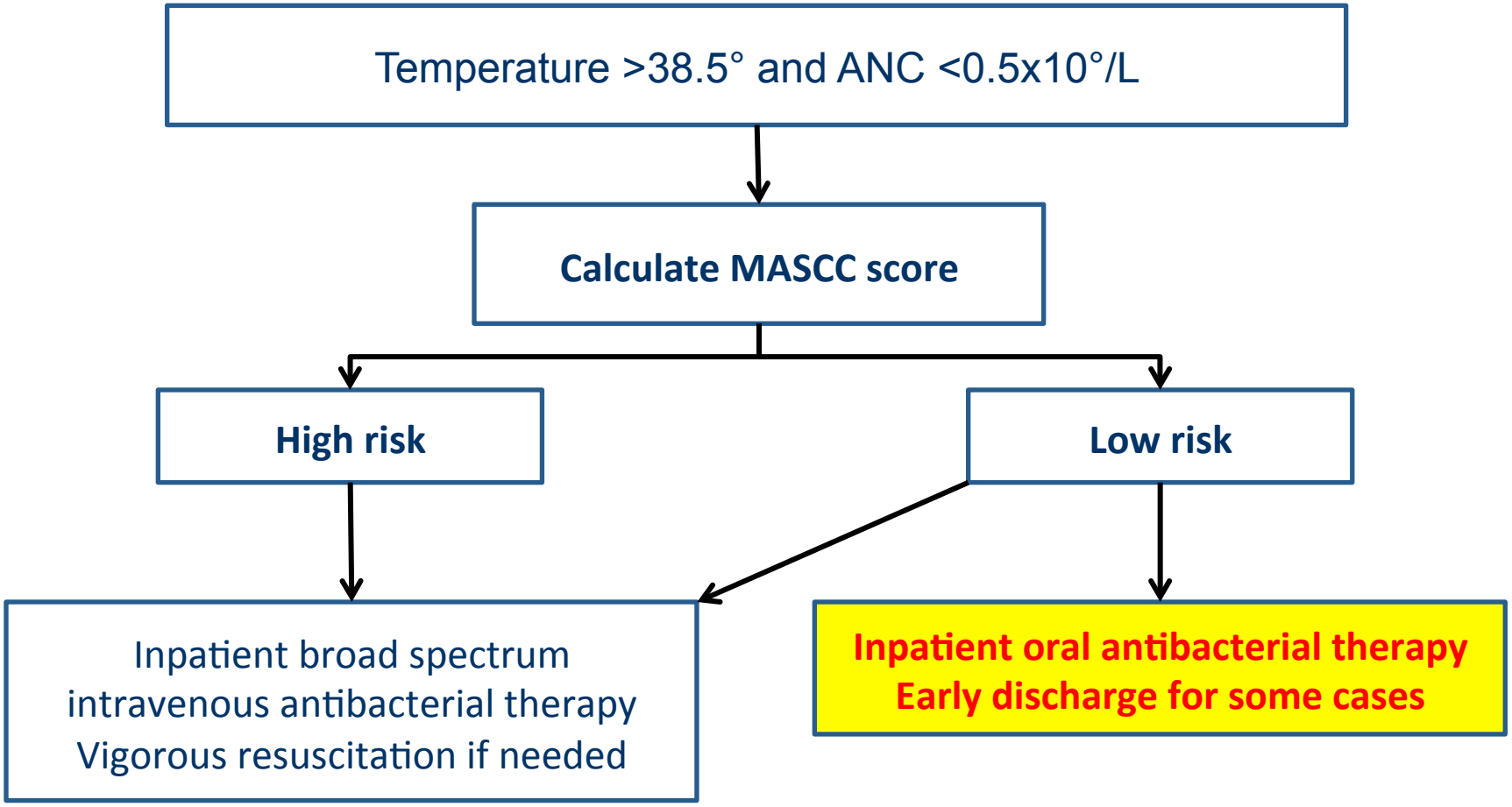
A MASCC score index ≥ 21 predicts

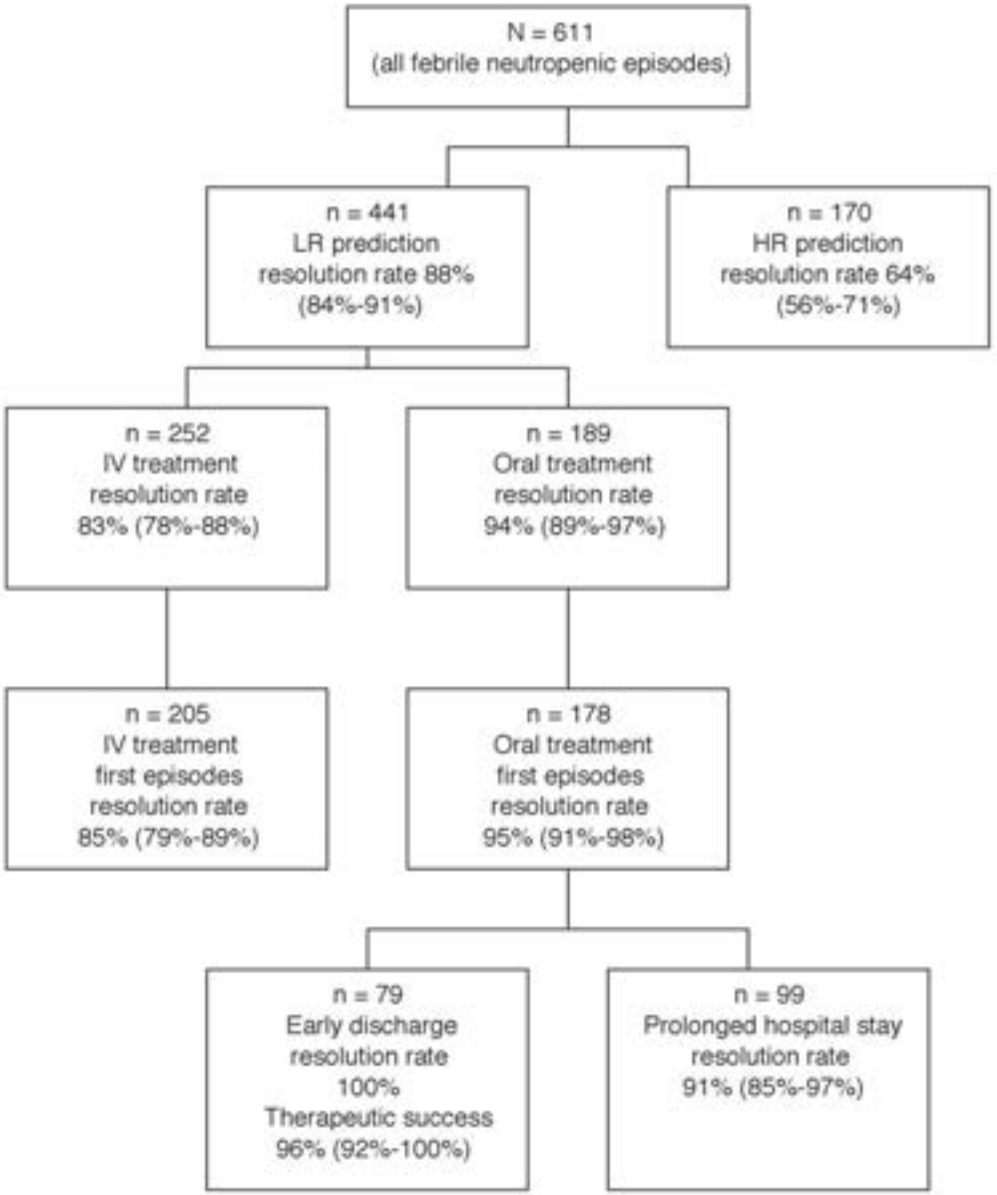
a low (5-10%) risk of complications and death (<2%)

Predicting high risk ?



Initial management of febrile neutropenia





Klastersky et al., J Clin Oncol, 2006

Reasons for not administering oral treatment to patients predicted at low-risk of serious complication development (MASCC score ≥ 21)*

Reason	N° of patients	%
Antibacterial prophylaxis and/or treatment	179	71
Inability to swallow	27	11
Contraindication(s) to oral therapy	17	6
Protocol violation	16	6
Refusal (by patient or physician)	11	5
Allergy to penicillin or quinolones	2	1

* A study of 611 consecutive patients with FN at the Institut Jules Bordet

Klastersky et al, J Clin Oncol, 2000

Reasons for prolonged hospitalization more than 24 hours in predicted low-risk patients receiving oral empiric treatment*

Reason	N° of patients	% of complications
Persistent fever and need for treatment change	19	21
Objective medical reason	42	9
Reason not related to a medical event	38	2

* A study of 611 consecutive patients with FN at the Institut Jules Bordet

Klastersky et al, J Clin Oncol, 2006

Remaining issues about the acceptance of orally administered antibiotics and early discharge for low-risk cancer patients with febrile neutropenia

Predictive factors for discharge

Standardized surveillance system

Education of physician and patient anxiety about safety

Demonstration of a quality-of-life benefit

Applicability to low income countries and rural areas

Definition of the cost effectiveness

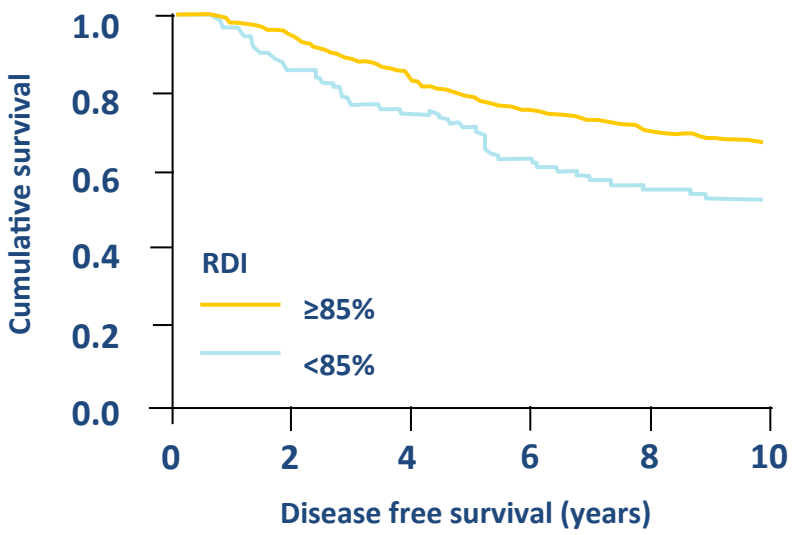
Patients' preferences

SECONDARY PREVENTION OF SUBSEQUENT FN IN PATIENTS WHO HAD A FIRST EPISODE

	CRAWFORD (1991) (n=59 SCLC)	LALAMI (2001) (n=48 breast ca)
Incidence of FN after the first cycle of chemotherapy (without CSF)	100%	100%
Incidence of FN after the second cycle of chemotherapy (with CSF)	23%	6%

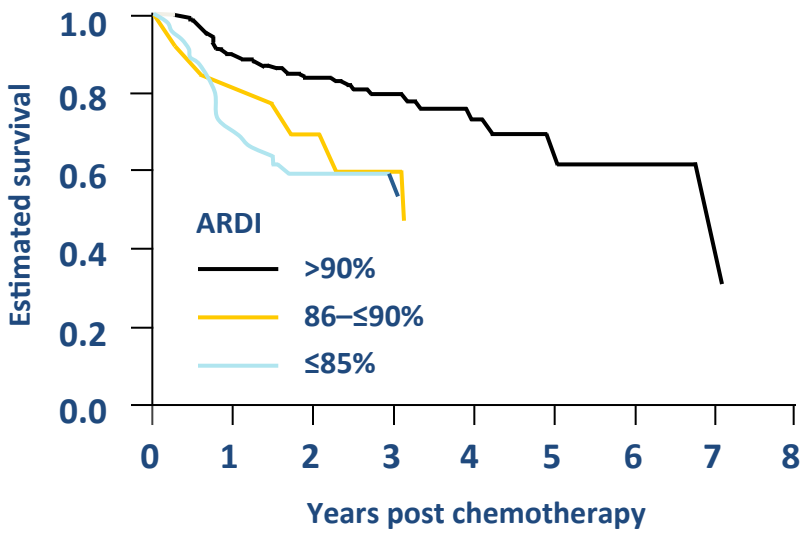
REDUCED DOSE INTENSITY AND IMPACT ON SURVIVAL

Breast cancer



A reduced dose intensity results in reduced overall survival in patients with primary breast cancer and anthracycline containing chemotherapy[1]

NHL



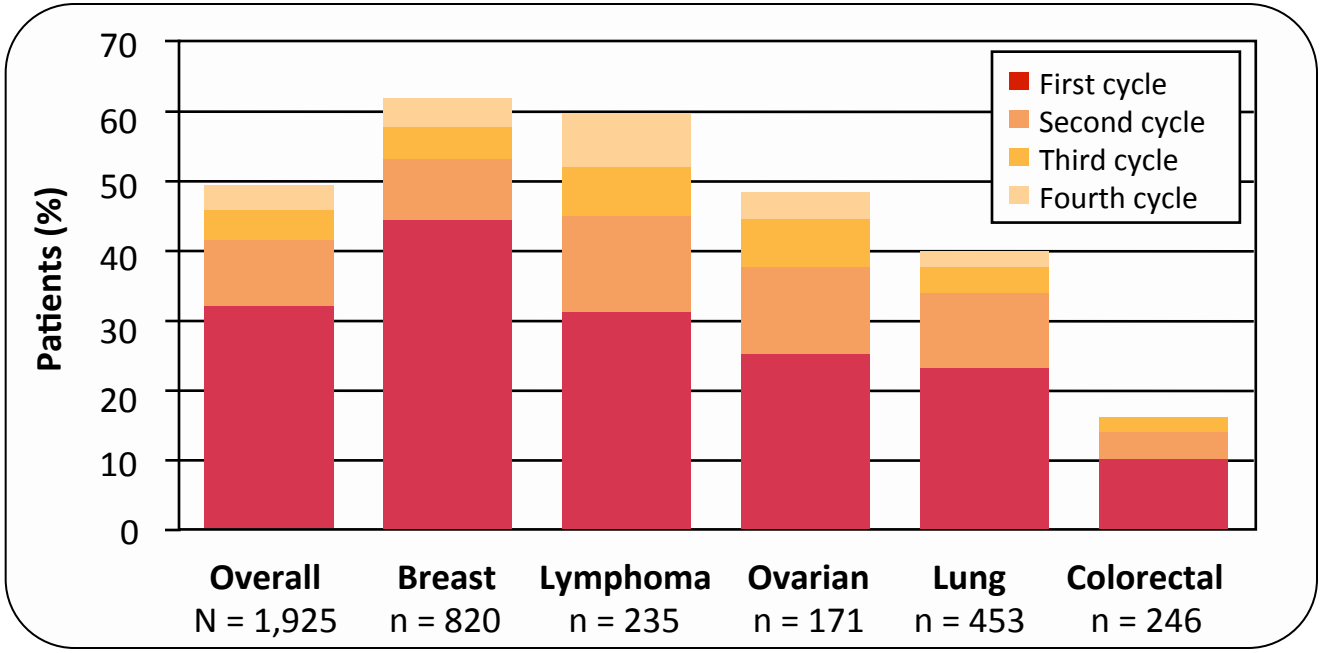
A reduced dose intensity results in reduced overall survival in DLBCL-patients with CHOP-21 chemotherapy[2]

OS, overall survival; (A)RDI, (average) relative dose intensity; DLBCL, diffuse large B-cell lymphoma

[1]*Chirivella I et al., Breast Cancer Res Treat, 2009*
[2]*Bosly A et al., Ann Hematol, 2008*

THE RISK OF NEUTROPENIC EVENTS IS GREATEST IN THE FIRST CYCLE

- **More than 50% of all initial Grade 3–4 neutropenia* occurs in the first cycle across many tumor types**



Grade 3-4 neutropenic events often lead to dose delays or dose reductions.[2]

1. *Adapted from Crawford J et al, for the ANC Study Group. Poster presented at: 46th Annual Meeting of the American Society of Hematology; December 4-7, 2004; San Diego, Calif. Poster 2210.*
2. *Dale DC et al., J Natl Compr Cancer Netw. 2003*

GENERAL CONCLUSIONS

- **The past two decades have witnessed major progress in the supportive management of cancer patients who develop fever and neutropenia. Morbidity and mortality have been dramatically reduced, and for many patients therapies are more simple, less toxic and more appropriately delineated according the patient's risk status.**

- **Primary prophylaxis with granulopoiesis colony-stimulating factors has proven to be a major tool for reducing infectious complications from febrile neutropenia and allowing the administration of optimal relative dose intensity of chemotherapy.**

CONCLUSIONS

Principles for the use of GCSF's for the prevention of chemotherapy-induced neutropenia (CIN)

- Use of G-CSF significantly reduces the mortality and morbidity associated with CIN
- Long-acting (pegylated) G-CSF offers a more convenient approach and might possibly be more effective than short-acting agents
- For short-acting agents, the optimal number of daily administrations is ≥7 for patients with a significant risk of developing CIN; the optimal strategy in lower risk patients is presently unknown.
- Other factors than the intensity of chemotherapy must be taken into account to evaluate the risk of CIN, namely age and the presence of co-morbidities

CONCLUSIONS

Principles for the use of GCSF's for the prevention of chemotherapy-induced neutropenia (CIN)

- G-CSF should be given as a primary prophylaxis, i.e. after cycle 1 of chemotherapy, in patients with significant risk of CIN
- Use of G-CSF is a good clinical practice in patients with significant risk of CIN, especially if chemotherapy is given with a curative intent (including neo-adjuvant and adjuvant situations)
- Future studies should concentrate on the definition of « significant » risk of CIN and on the optimal schedules of G-CSF corresponding to that risk
- Short-term side effects of G-CSF are rare and usually mild; long-term consequences in cancer survivors have to be evaluated

CONCLUSION

If FN hits

- FN is preventable in the majority of chemotherapy-treated patients
- Evaluate the risk of complications (MASCC score)
- Start antibiotics early (within 1 hour)
- For low risk: observe 12 to 24 hours before sending back home
- For non-low risk: evaluate for severe sepsis / septic shock and consider ICU
- Monotherapy is adequate in most cases
  (! consider local microbiological epidemiology)
- Critically re-evaluate after 48 hours
- Check with microbiological lab and ID specialist

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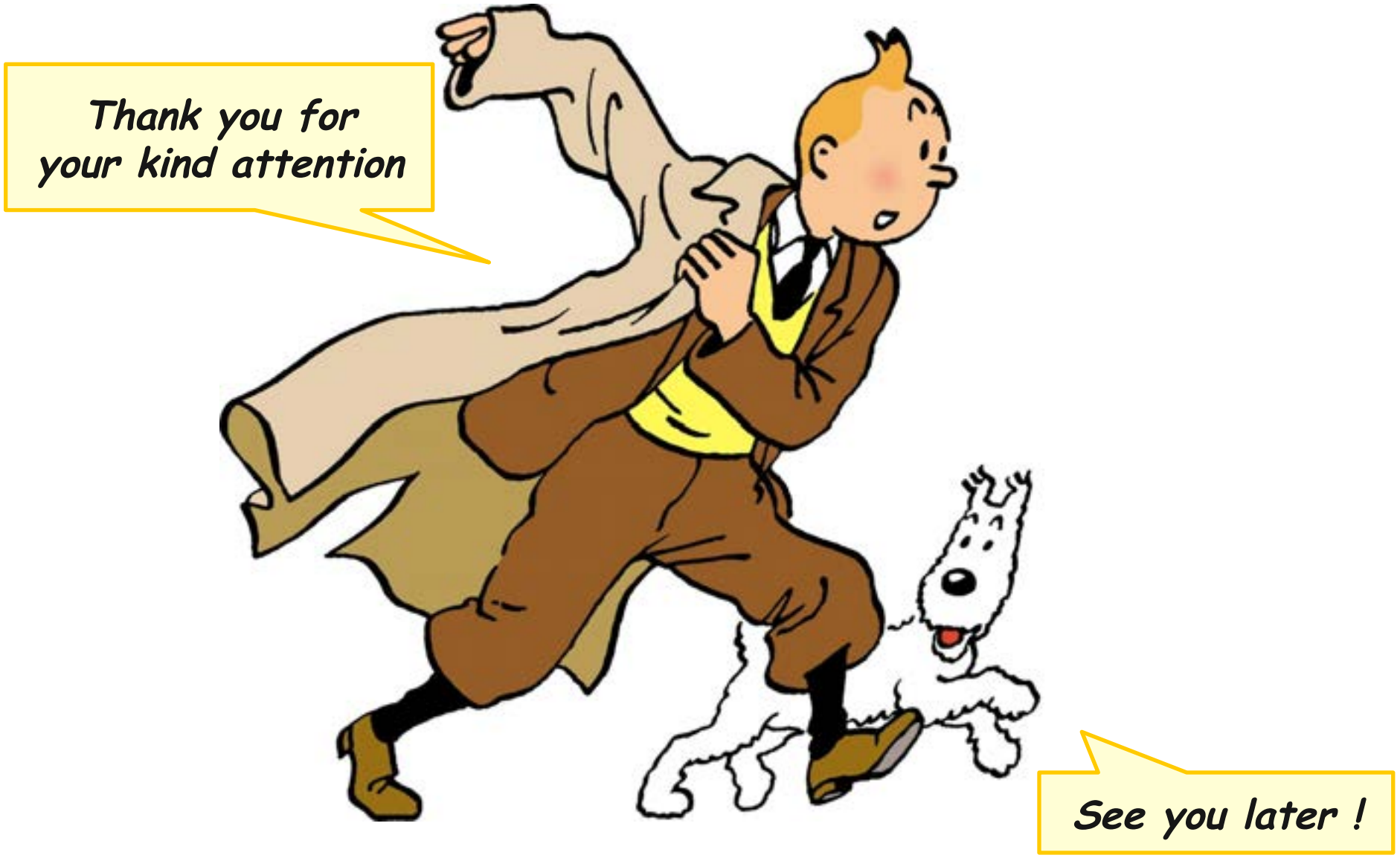
Thank you for your kind attention
See you later !