ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO PRECEPTORSHIP PROGRAMME

SUPPORTIVE AND PALLIATIVE CARE

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Zurich, Switzerland
20-21 February 2017

Anticancer treatment toxicity assessment in clinical oncology routine

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DISCLOSURE SLIDE

Consultant / Advisory Boards / Speaker : Sanofi, Roche, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, AMGEN, Pierre Fabre Oncologie, Vifor pharma.

Associations: ESMO, ASCO, MASCC, AFSOS, AESCO.

WHAT WE WANT TO ASSESS ?

- Anti-Cancer Treatment Toxicity ?
- Anti-Cancer Treatment Efficacy ?
- Individualized Patient’s Safety ?

WHAT WE WANT TO ASSESS ?

- **Anti-Cancer Treatment Toxicity ?**

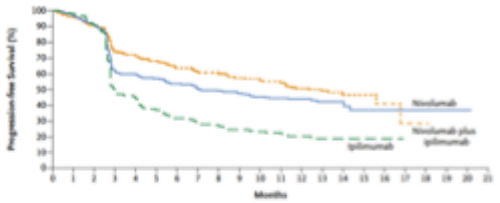


Table 3. **Adverse Events.**°

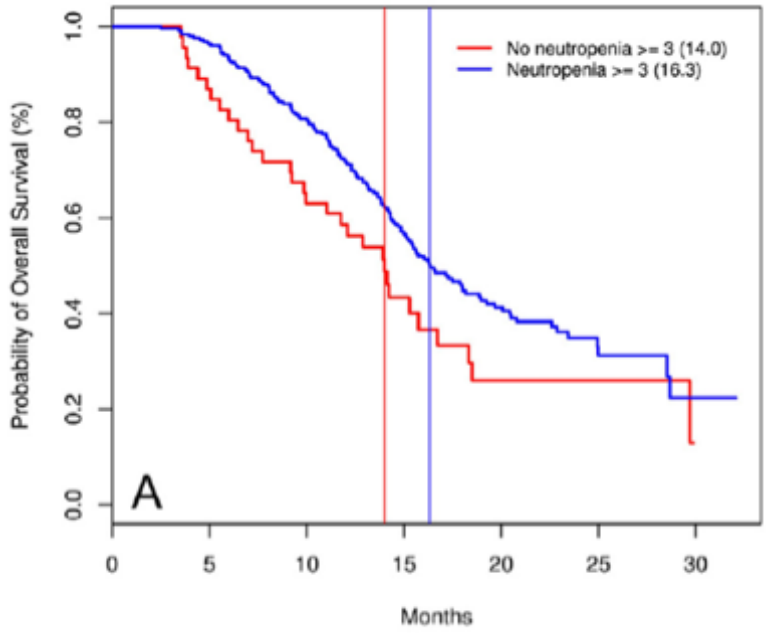
Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

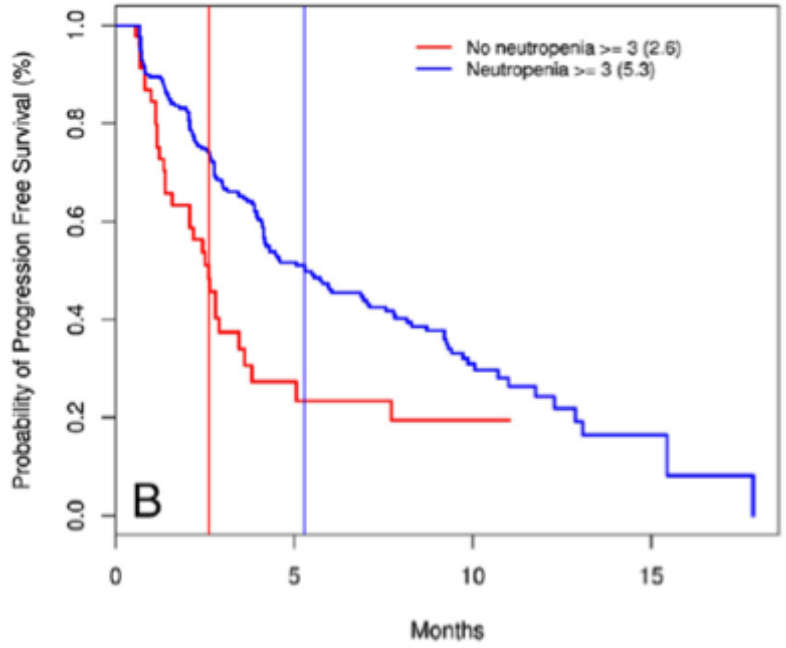
Larkin J et al. N Engl J Med 2015;373:23-34.

WHAT WE WANT TO ASSESS ?

- **Anti-Cancer Treatment Efficacy ?**

The TROPIC Study case: cabazitaxel / FN / GCSF use



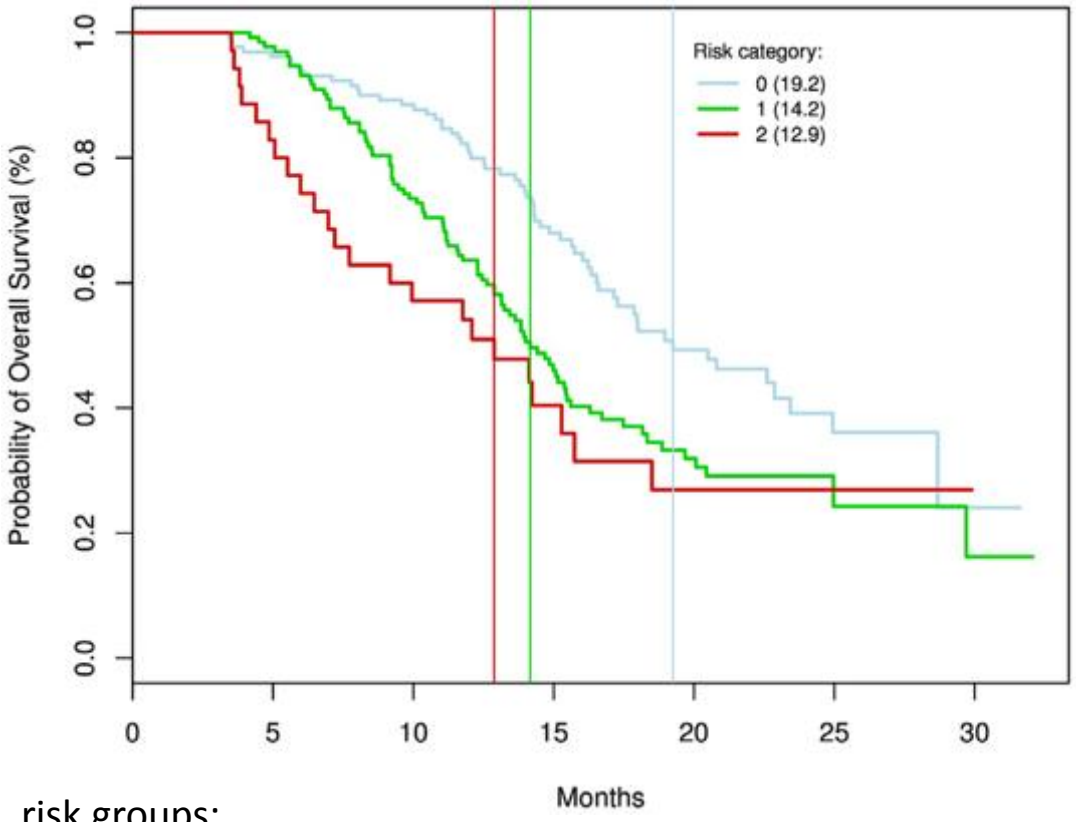


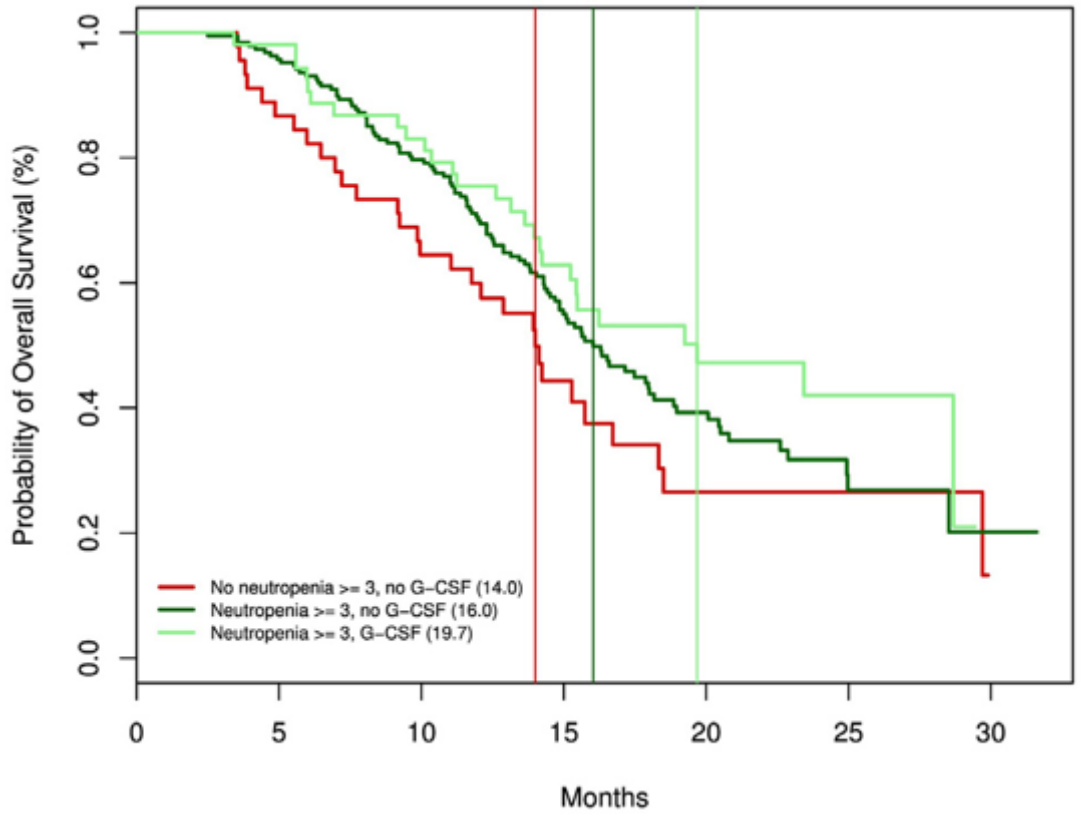
Meisel A. et al. / Eur J Cancer 2016; 56; 93-100

WHAT WE WANT TO ASSESS ?

- **Individualized Patient's Safety ?**

The TROPIC Study case: cabazitaxel / FN / GCSF use





risk groups:
0 = one grade 3 neutropenia during cabazitaxel therapy and low NLR
1 = high NLR or no grade 3 neutropenia during cabazitaxel therapy
2 = high NLR and no grade 3 neutropenia during cabazitaxel therapy

Meisel A. et al. / Eur J Cancer 2016; 56; 93-100

WHAT WE WANT TO ASSESS ?

- **Individualized Patient's Safety ?**

?

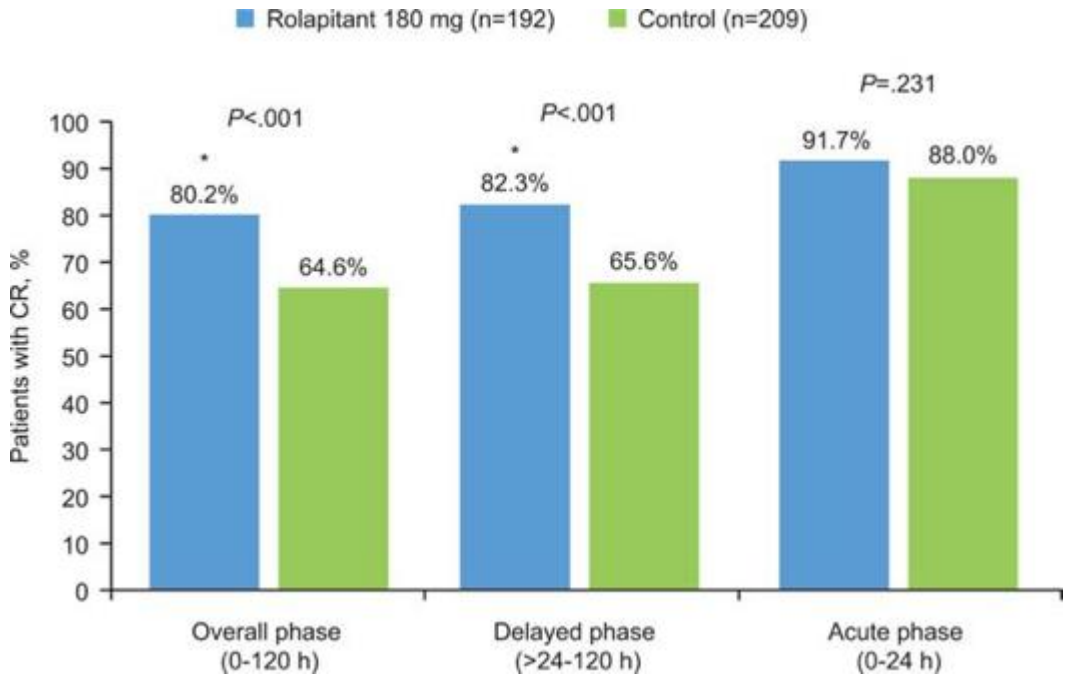
- Fatigue
- Nausea and Vomiting
- Neutropenia
- Hepatitis
- Pain
- Sexual Disorders
- Psychological Disorders
- Social Burden

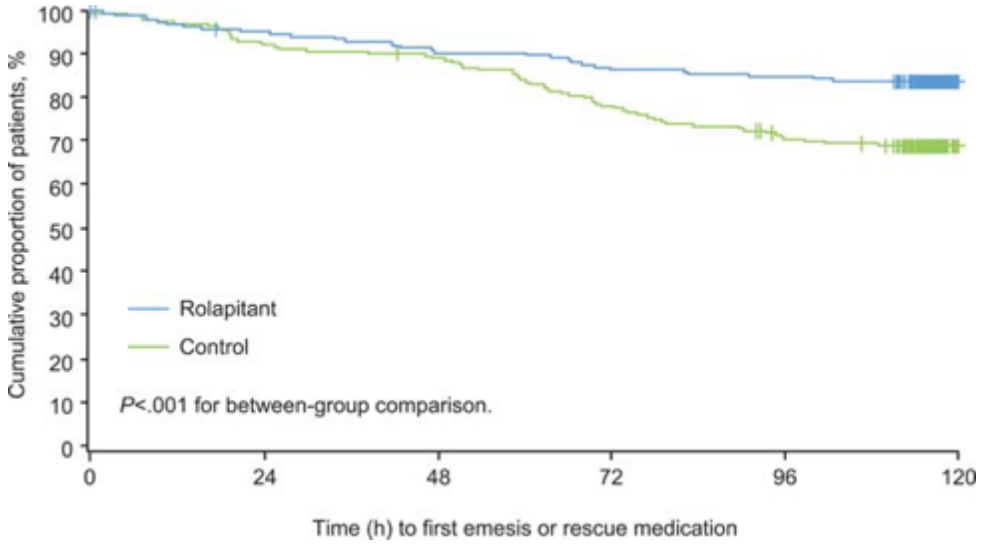
WHY WE WANT TO ASSESS ?

- Toxicity Management ?
- Dose Intensity Optimization ?
- Toxicity Impact on Survival ?

WHY WE WANT TO ASSESS ?

- Toxicity Management ?



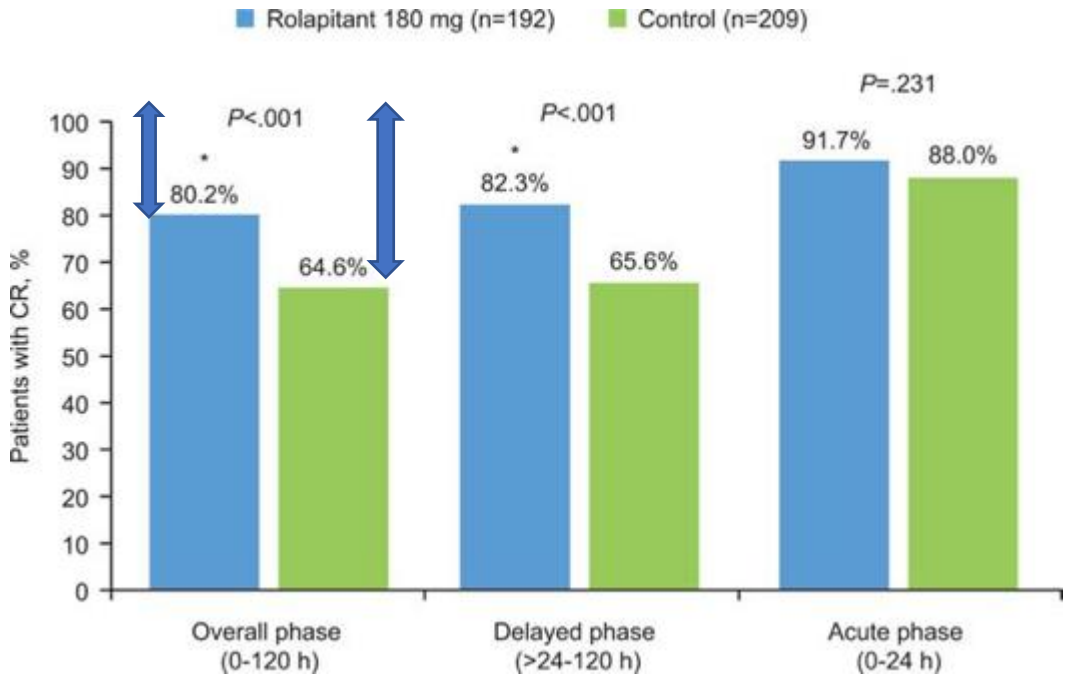


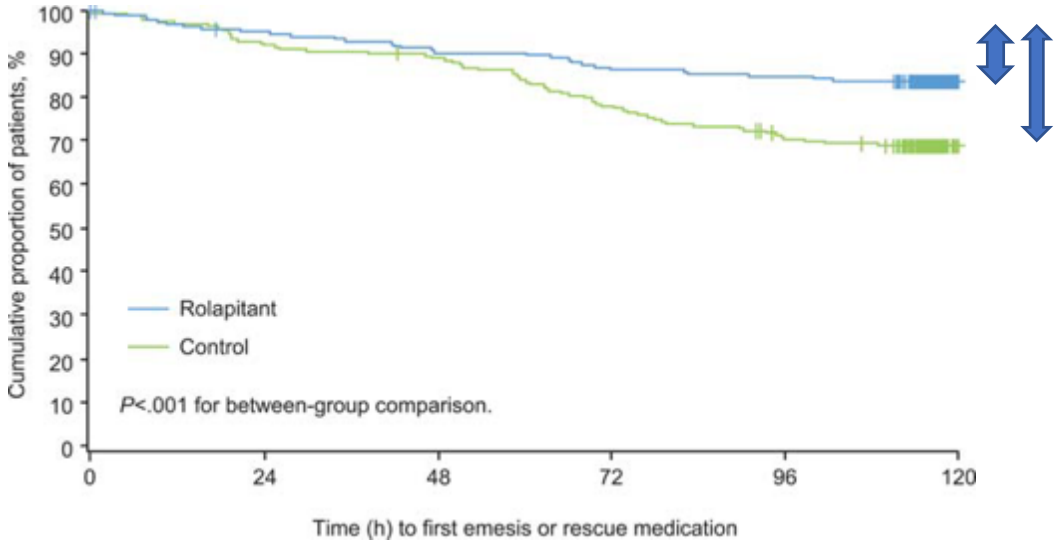
Hesketh PJ. Et al. Cancer. 2016

WHY WE WANT TO ASSESS ?

- Toxicity Management ?

Daily Impact ?
Rescue Treatment ?





Hesketh PJ. Et al. Cancer. 2016

WHY WE WANT TO ASSESS ?

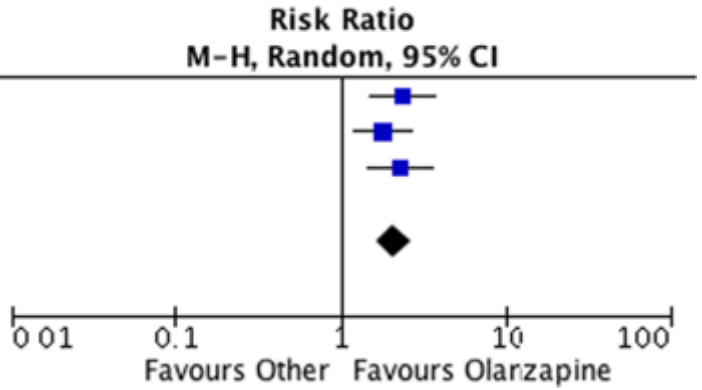
- Toxicity Management ?

Daily Impact ?
Rescue Treatment ?

a

Study or Subgroup	Olanzapine Events	Total	Other Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Navari et al 2009	21	32	19	68	29.7%	2.35 [1.49, 3.71]
Navari et al 2010	21	32	25	68	38.7%	1.78 [1.20, 2.66]
Navari et al 2013	39	56	16	52	31.6%	2.26 [1.45, 3.52]
Total (95% CI)		**120**		**188**	**100.0%**	**2.09 [1.63, 2.68]**
Total events	81		60			

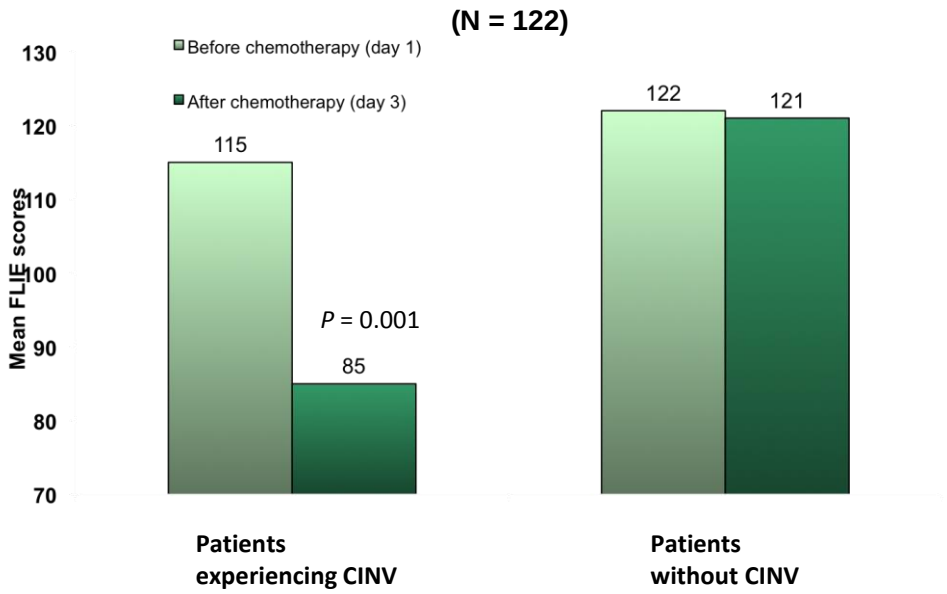
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.98$, df = 2 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 5.80 (P < 0.00001)

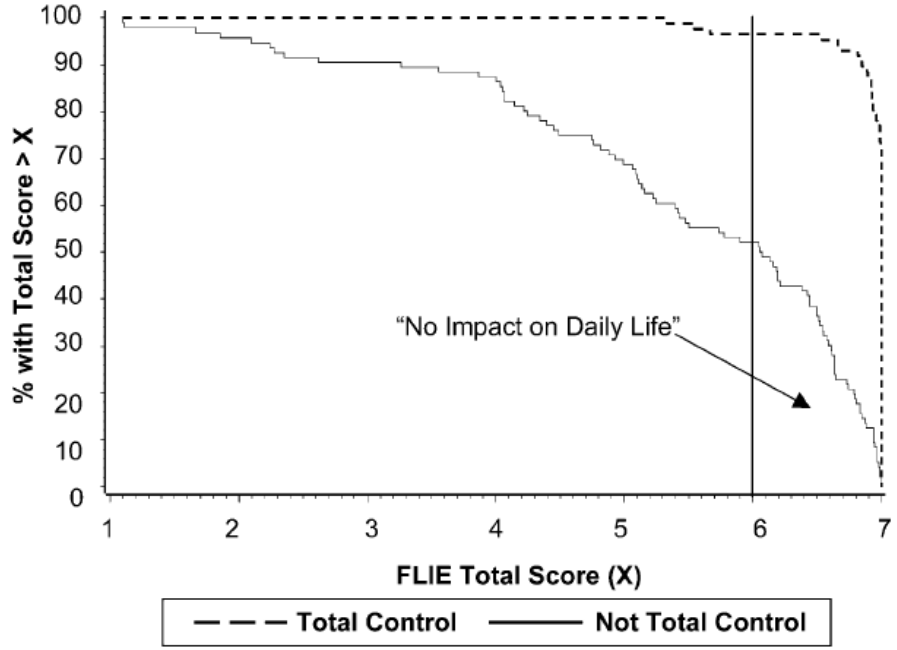


Chiu L. et al. Support Care Cancer 2016

WHY WE WANT TO ASSESS ?

- Toxicity Management ?





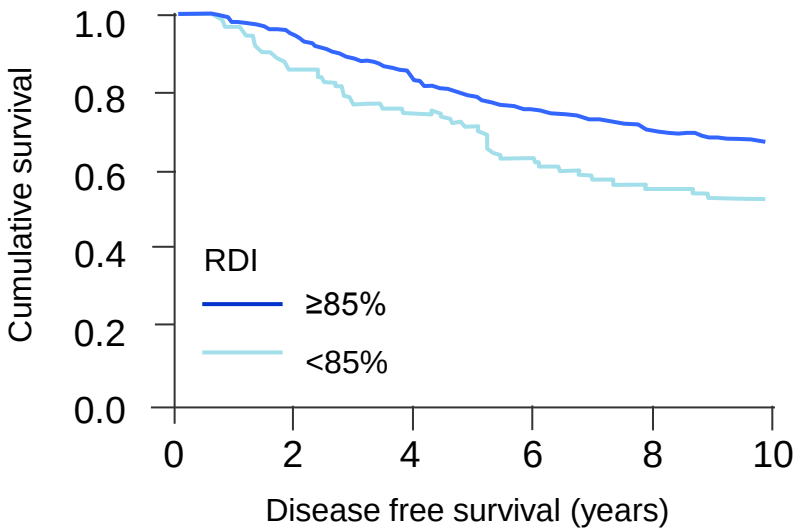
Functional Living Index–Emesis (FLIE):
Adapted from CM Lindley et al.
Qual Life Res. 1992;1:331–340

Martin AR et al. Support Care Cancer 2003.

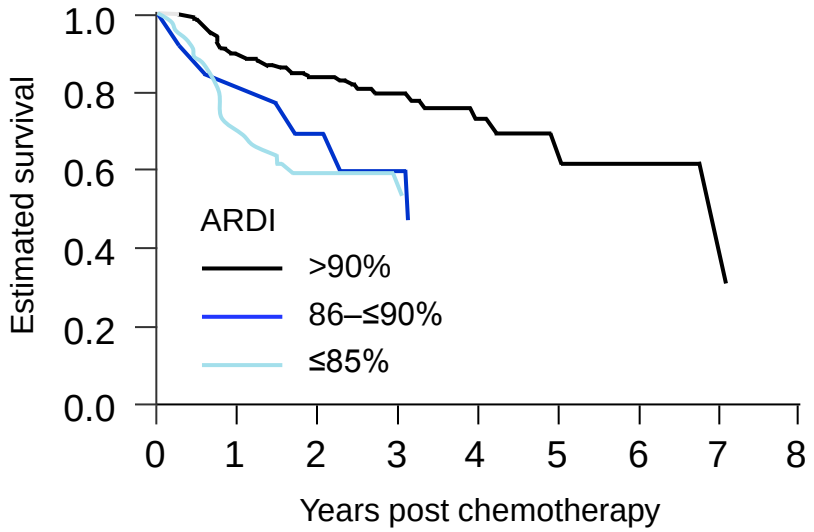
WHY WE WANT TO ASSESS ?

- Dose Intensity Optimization ?

Breast cancer



NHL



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

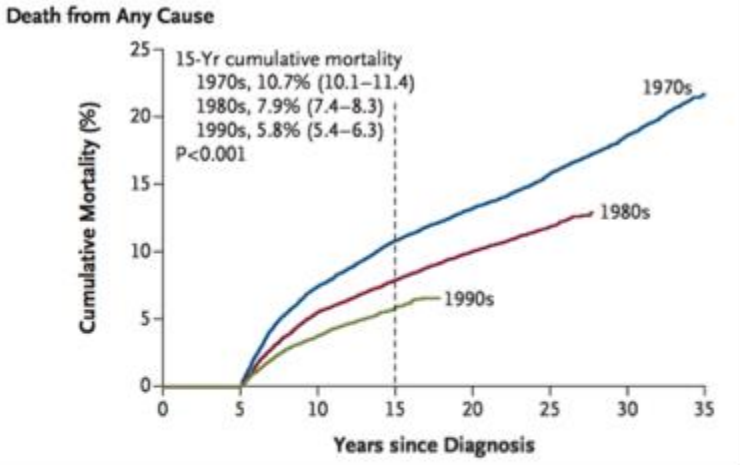
A reduced dose intensity results in reduced overall survival in DLBCL-patients with CHOP-21 chemotherapy[2]

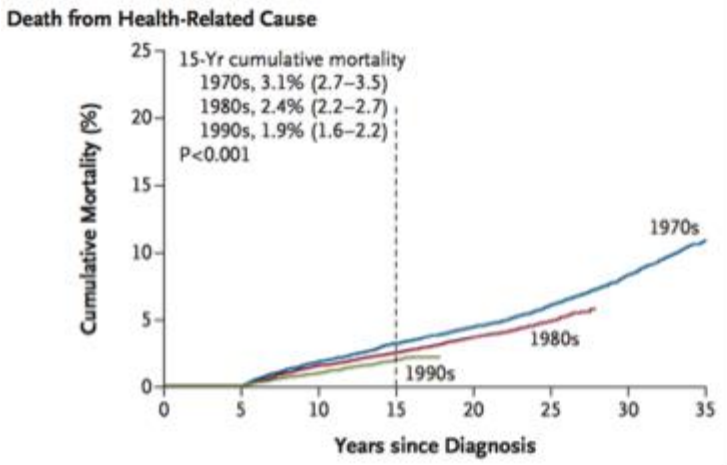
OS, overall survival; (A)RDI, (average) relative dose intensity; DLBCL, diffuse large B-cell lymphoma

[1]Chirivella I, et al. *Breast Cancer Res Treat.* 2009;114:479-484
[2]Bosly A, et al. *Ann Hematol.* 2008;87:277–283

WHY WE WANT TO ASSESS ?

- Toxicity Impact on Survival ?





Anti Cancer Treatment innovation
Radiotherapy adaptation
Chemotherapy optimization

More Survival Benefit
Less Second Neoplasm
Less Late Toxicity

Armstrong GT et al., N Engl J Med 2016;374:833-42

WHEN WE WANT TO ASSESS ?

- Before Treatment Start ?
- Before Each Cycle ?
- After Treatment Completion ?
- During and After Treatment Course ?

WHEN WE WANT TO ASSESS ?

- Before Treatment Start

PREDICTIVE RISK FACTORS AND PREDICTION TOOL FOR CINV

Predictive Factor		Odds Ratio	Impact on CINV Risk	Scoring Algorithm
Patient age	If patient aged < 60	1.41	↑ by 41%	+ 1
Expectation	If patient expects to have CINV	1.41	↑ by 41%	+ 1
Sleep	If patient slept less than 7 hours the night before chemo	1.34	↑ by 34%	+ 1
Morning sickness	If patient has positive history of morning sickness	1.30	↑ by 30%	+ 1
Chemotherapy	If patient is about to receive platinum or anthracyclines	1.94	↑ by 94%	+ 2
Prior CINV	If patient had nausea or vomiting in the prior cycle	5.17	↑ by 5.17 times	+ 5
Antiemetic use at home	If non-Rx antiemetics are used at home	2.70	↑ by 2.7 times	+ 3
Cycle	If 2nd cycle of chemotherapy If ≥ 3rd cycle	0.17 0.15	↓ by 83% ↓ by 85%	– 5 – 6

Start at base score of 10

Total score

ESMO 2016. Dranitsaris G et al. Abs. 1438 PD

WHEN WE WANT TO ASSESS ?

- Before Treatment Start

Table 1. Immune checkpoint blockade (ICB) toxicities

Frequent (>10%) ICB toxicities
- Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain
- Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea
- Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue

Rare (<10%) life-threatening ICB toxicities
- Colitis and risk of gastrointestinal perforation
- Pneumonitis including acute interstitial pneumonia/acute respiratory distress syndrome
- Infusion reaction and anaphylactic shock
- Type 1 diabetes and risk of diabetic ketoacidosis
- Severe skin reactions, DRESS, Stevens Johnson syndrome
- Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk
- Neutropenia and sepsis risk
- Encephalopathy and neurological sequelae
- Guillain–Barré syndrome and respiratory risk
- Myelitis and motor sequelae
- Myocarditis and cardiac insufficiency
- Acute adrenal insufficiency and hypovolemic shock
- Pleural and pericardial effusion
- Nephritis

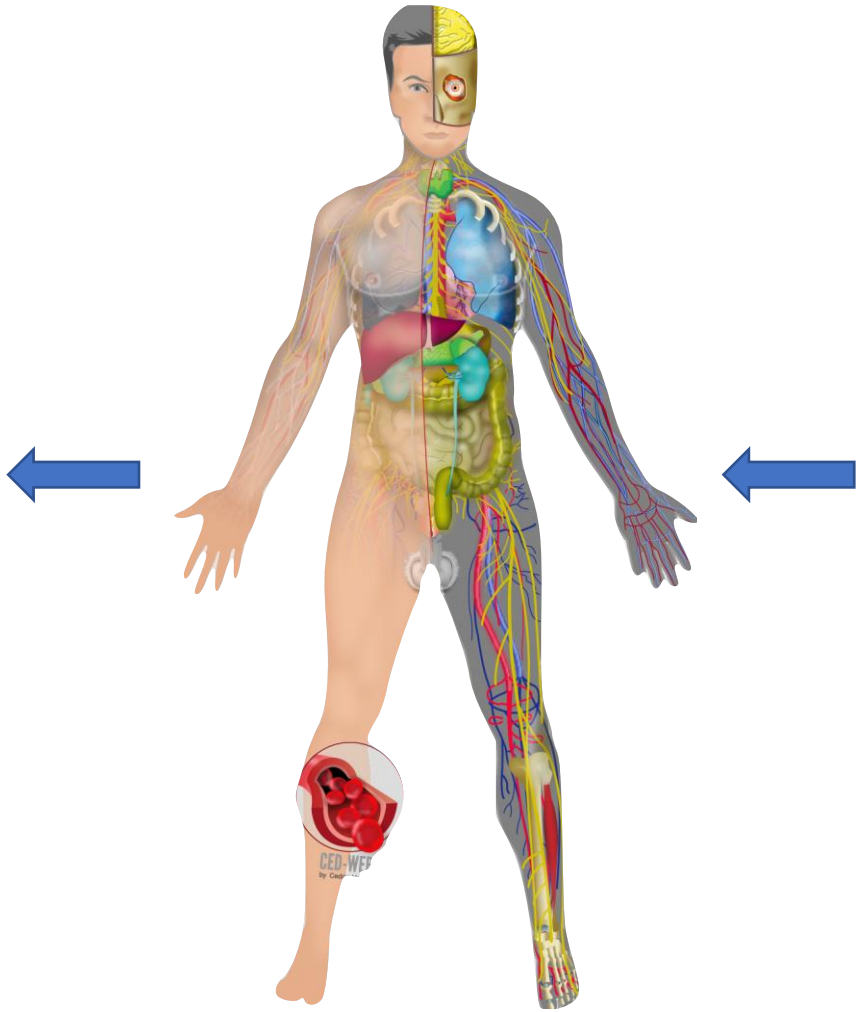


Table 2. Immunotherapy baseline checklist

Physical examination
- Performance status
- Weight, size, body mass index
- Heart rate and blood pressure
- General symptoms such as asthenia or appetite should be evaluated as they are frequently affected
- Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia
- History of fever or recent infection must be checked and investigated appropriately
- Baseline electrocardiogram
- Ongoing treatment

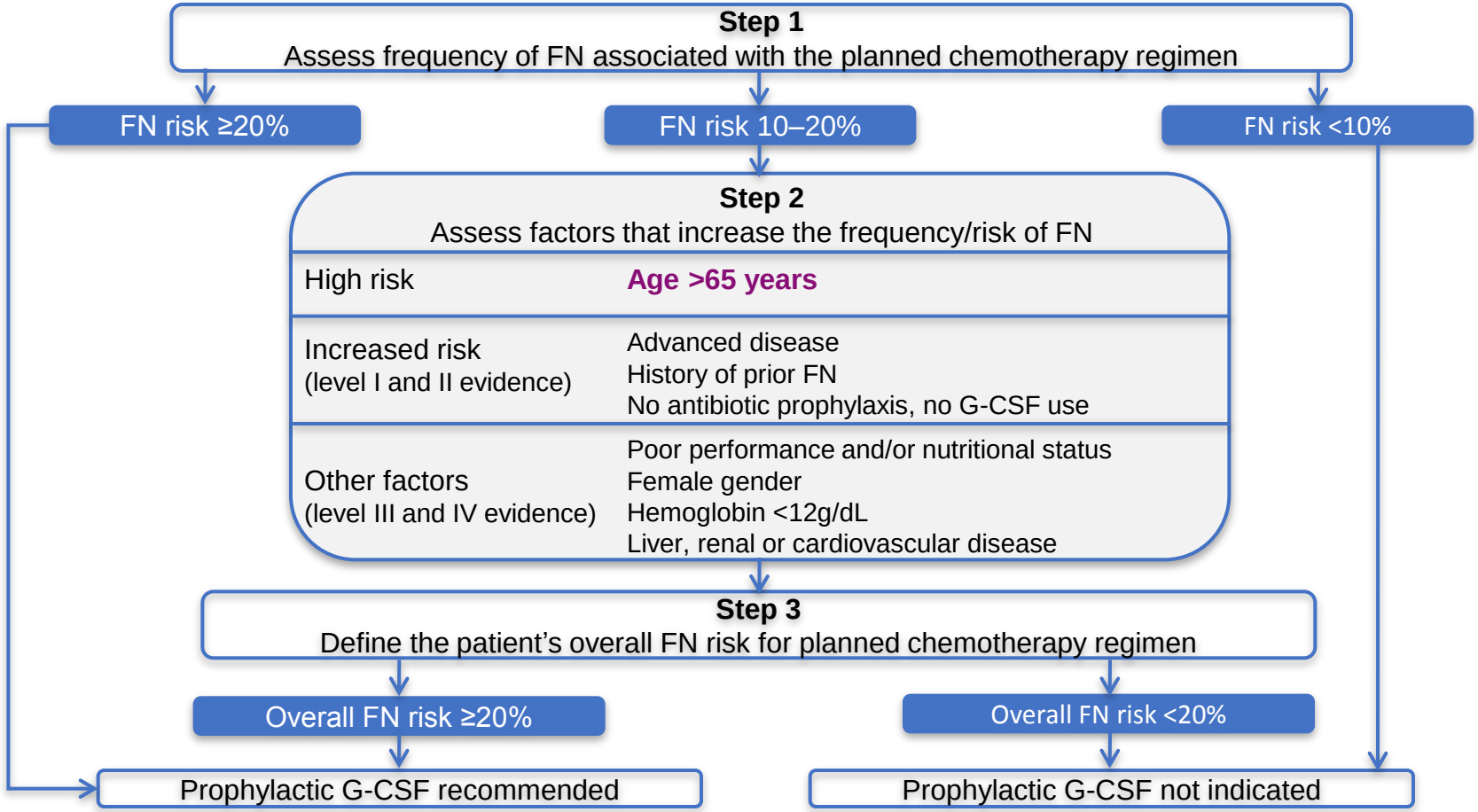
Laboratory test
- Complete CBC
- Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)
- Glycemia
- Total bilirubin, AST, ALT, GGT, PAL
- Albuminemia, CRP
- TSH, T4
- Cortisol and ACTH at 8 am
- LH FSH estradiol testosterone
- Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria
- Urinary sediment
- Quantiferon tuberculosis or TST in case of anterior exposure
- Virology: HIV, HCV and HBV serology
- Antibody: ANA, TPO Ab, Tg Ab
- If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker.

Imaging
- X-ray chest imaging reference is recommended at baseline
- The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs.

Any other evaluation may also be necessary before starting immunotherapy depending on patient's history, symptoms or diseases detected at baseline.

WHEN WE WANT TO ASSESS ?

- Before Treatment Start ?

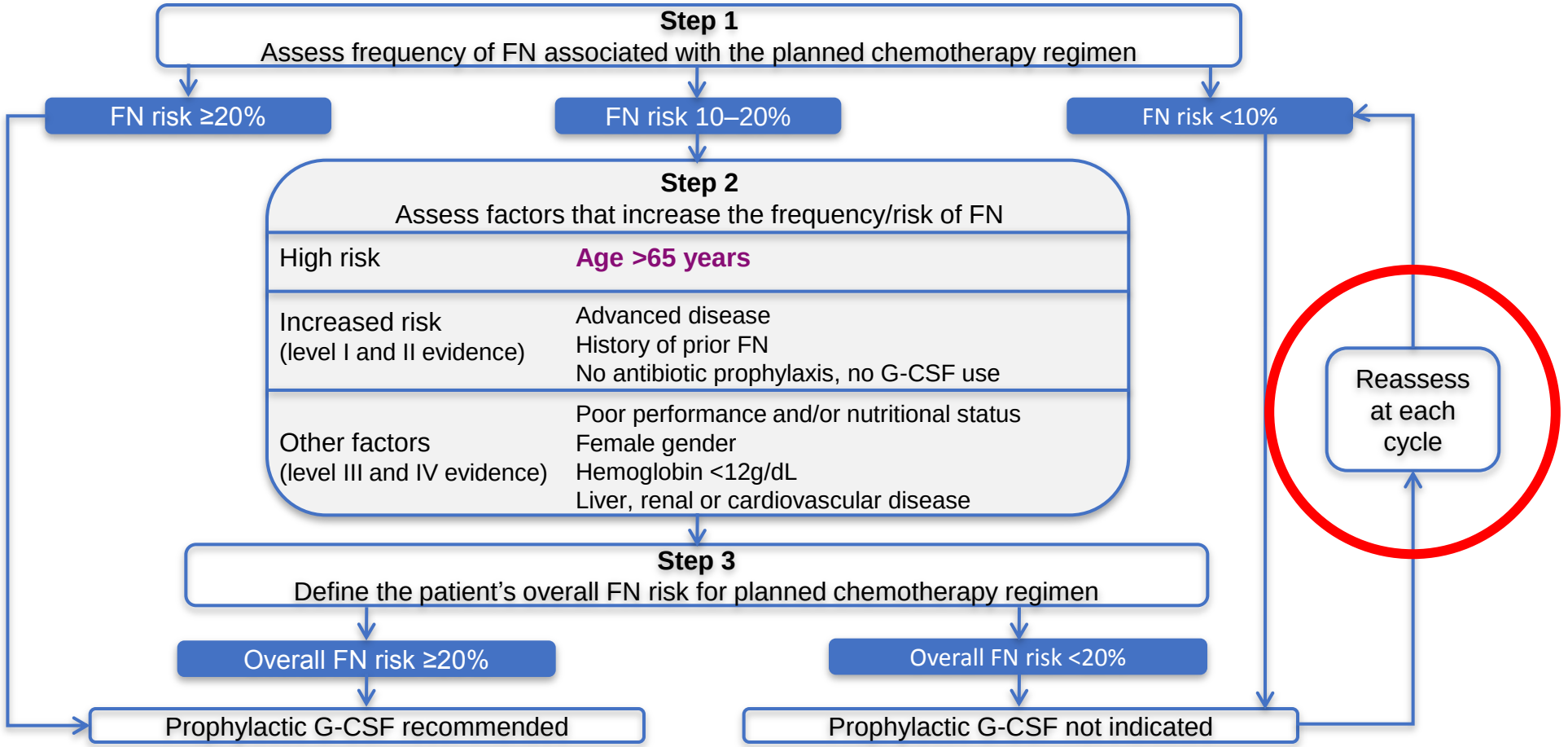


FN: Febrile neutropenia

Aapro MS, et al. EORTC guidelines. *Eur J Cancer* 2011;47:8-32
Updated by Flowers CR, et al. *J Clin Oncol.* 2013;31(6):794-810

WHEN WE WANT TO ASSESS ?

- Before Each Cycle ?



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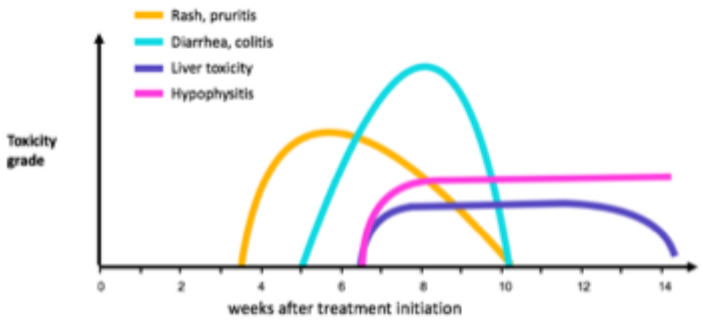
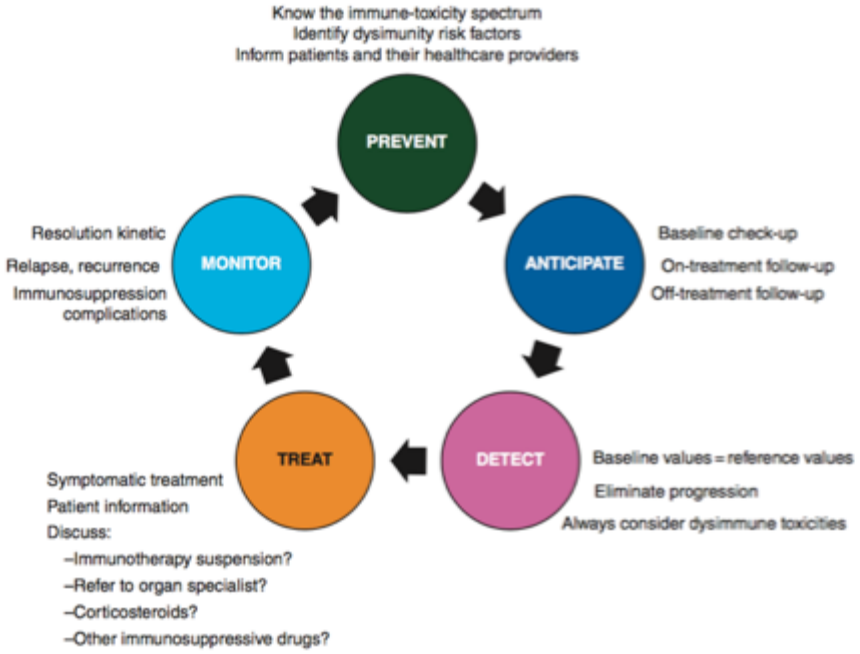
WHEN WE WANT TO ASSESS ?

- Before and At Each Cycle.





adapted from Weber, et al., Management of immune-related adverse events and kinetics of response with ipilimumab. Journal of Clinical Oncology, 2012.

WHEN WE WANT TO ASSESS ?

- After Treatment Completion.

SURVIVOR CARE

HOW TO ASSESS ?

- NCI CTC-AE.
- Patient Reported Outcomes Programs.
- New Digital Technology

HOW TO ASSESS ?

- NCI CTC-AE.

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

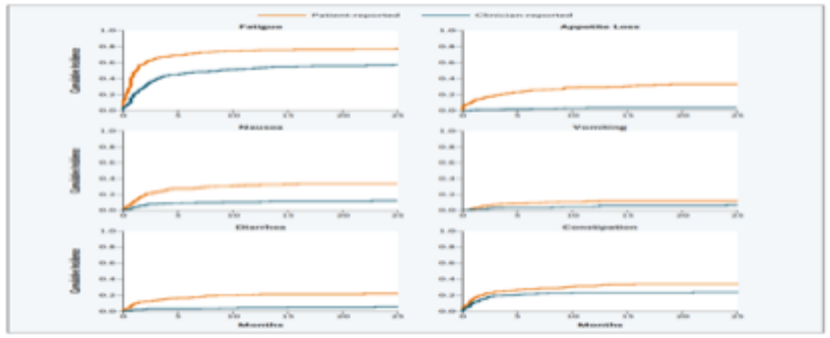
Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					

HOW TO ASSESS ?

- Patient Reported Outcomes Programs.



Toxicity	Toxicity reported by patients (%cycles)	Toxicity reported by pts and by physicians (%cycles)	% of under reporting
Anorexia	46.2	9.2	80.2
Nausea	45.3	20.8	54.2
Vomiting	16.8	7.2	57.4
Constipation	37.5	7.8	79.2
Diarrhea	22.7	8.9	61.0
Hair loss	42.7	13.9	67.4

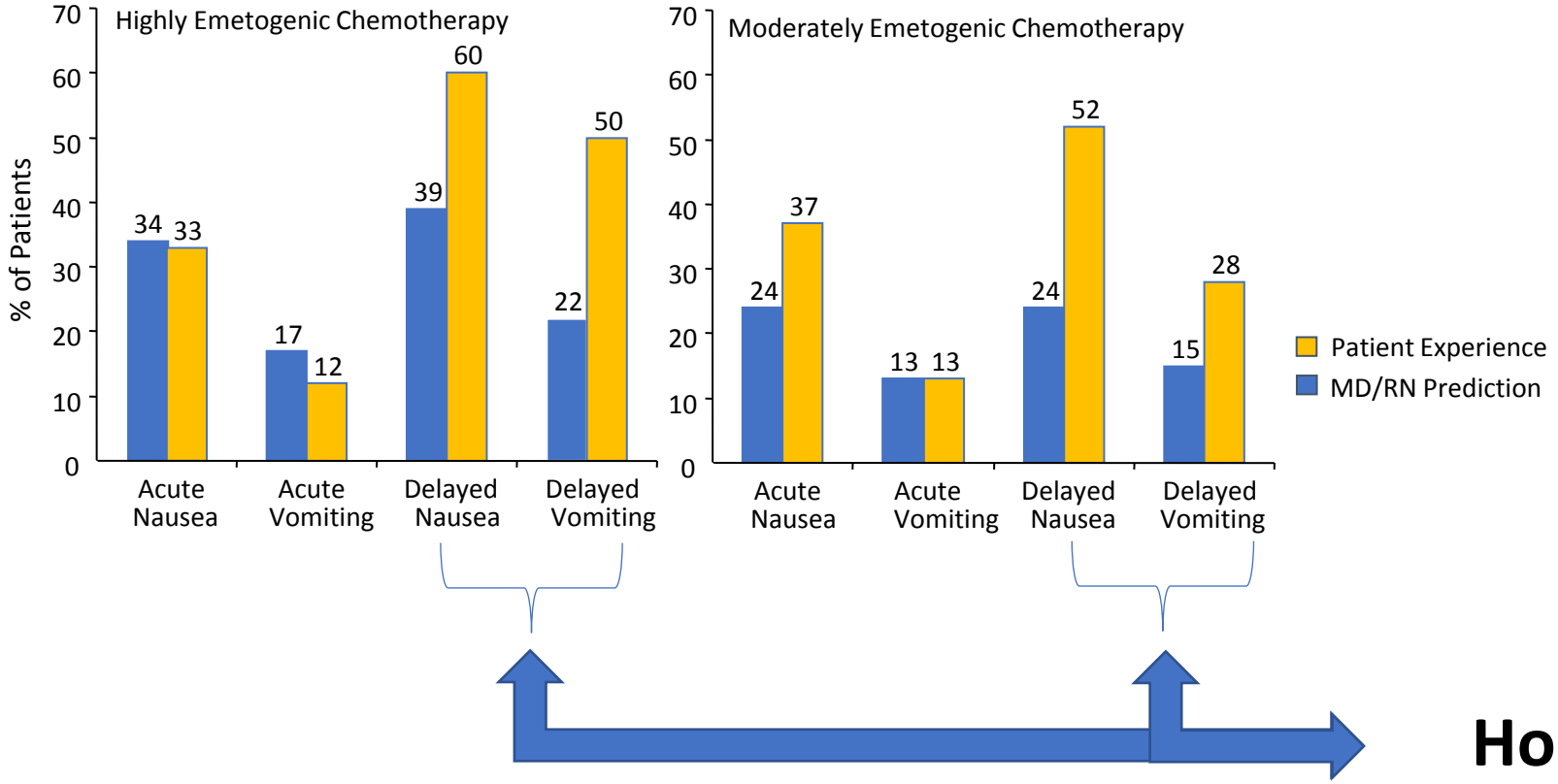
Physician under-reporting
Patient over-reporting

From daily practice to clinical trials

Basch E. et al, NEJM 2010
Di Maio M et al, J Clin Oncol 33:910-915

HOW TO ASSESS ?

- Patient Reported Outcomes Programs.



Home assessment

Grunberg SM, et al. Cancer. 2004;100:2261-8

HOW TO ASSESS ?

- Patient Reported Outcomes Programs.

STAR Program:

- Randomized trial PRO vs SOC : 766 patients 12 +/- 4 weeks
- Quality of Life EQ-5D: $p < 0.001$
- Longer Time to Chemotherapy Completion: $p = 0.002$
- Better Survival : 0.7 months, $p = 0.004$
- Better benefit to patients digital naive
- Less Emergency Visits

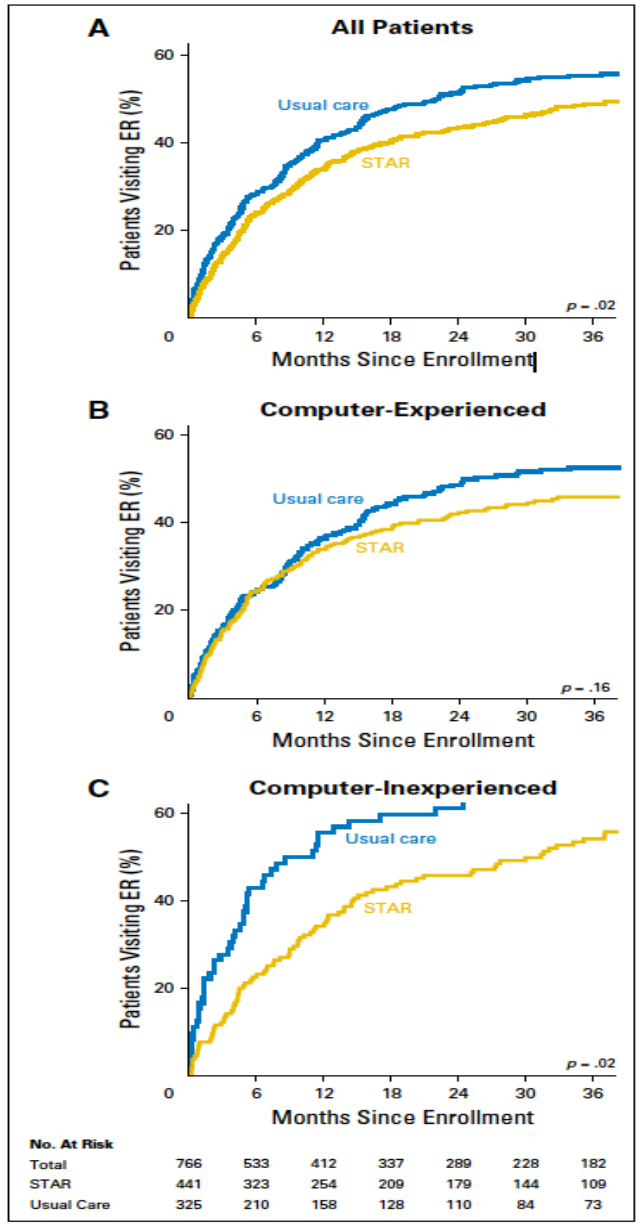
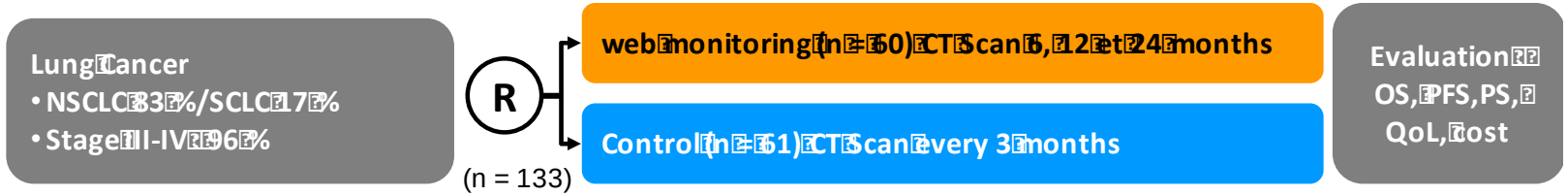


Fig 3. Cumulative incidence of emergency room (ER) visits. The incidence of patients visiting the ER is shown, with death as a competing event. (A) All patients; (B) computer-experienced patients; (C) computer-inexperienced patients. STAR, Symptom Tracking and Reporting web-based self-reporting system (study intervention).

Basch E, et al. J Clin Oncol 2016 ; 34(6) : 557-65

HOW TO ASSESS ?

- New Digital Technology



PS 0-1 at Cancer Relapse

Web cohort : 77%

Control 33%

p < 0,001

⇩

Earlier Relapse Detection

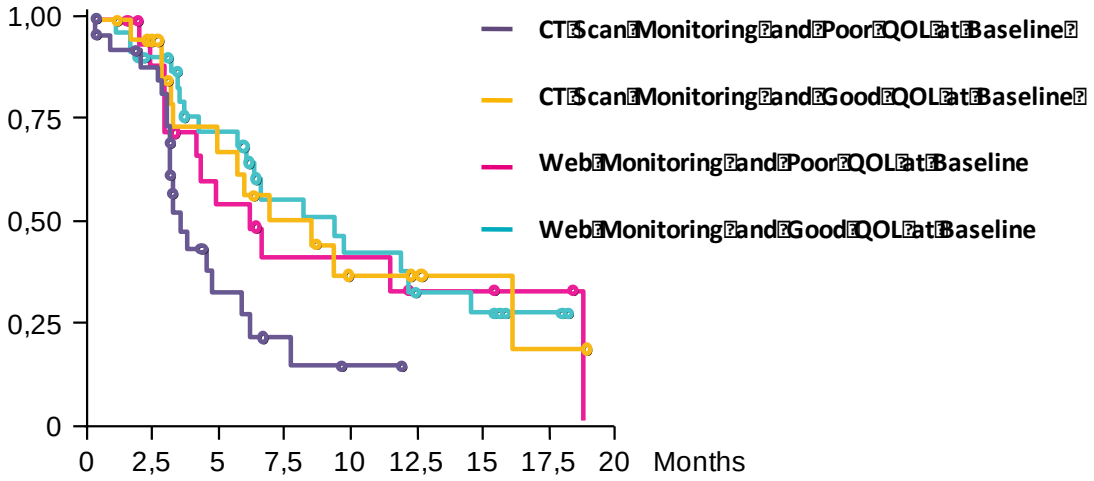
⇩

Earlier Treatment / Better PS

⇩

PFS IMPROVEMENT

PFS related to Baseline QOL en monitoring cohort



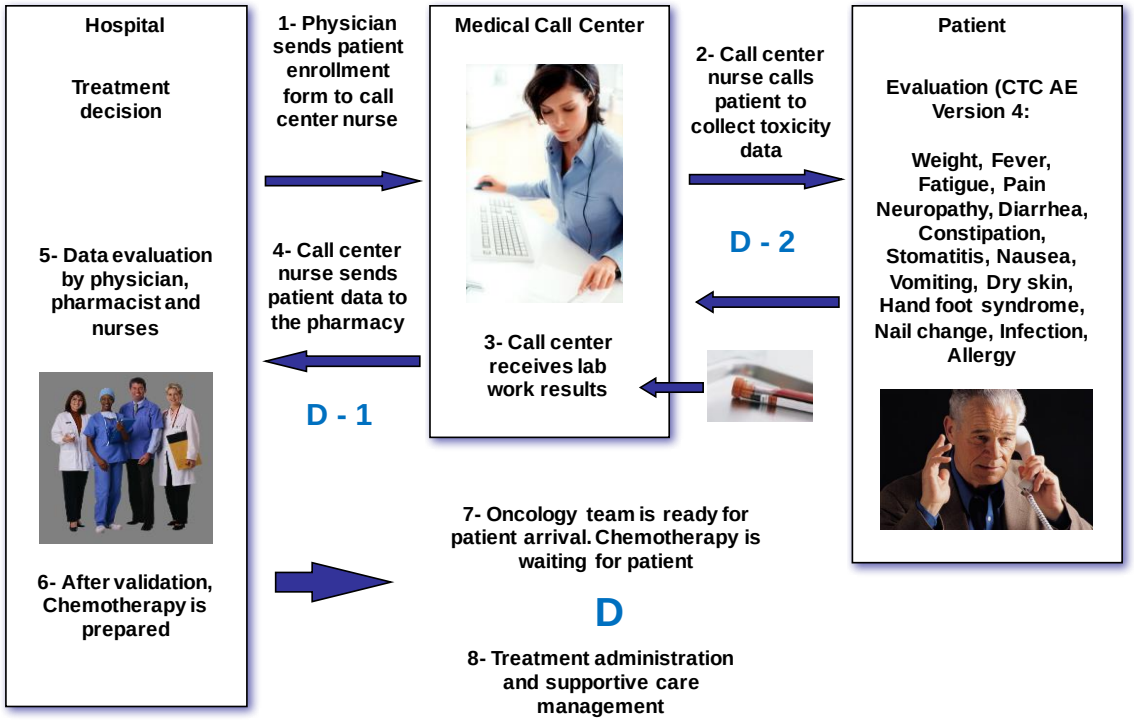
ASCO 2016 - Denis F et al., abstr. LBA 9006,

HOW TO ASSESS ?

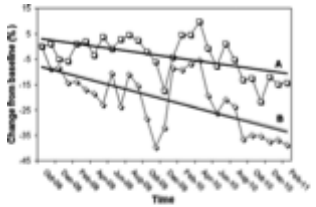
Period = **01.2009 – 02.2011**
1037 pts = prospective inclusion
513 pts = standard of care cohort

- New Digital Technology

PROCHE PROGRAM



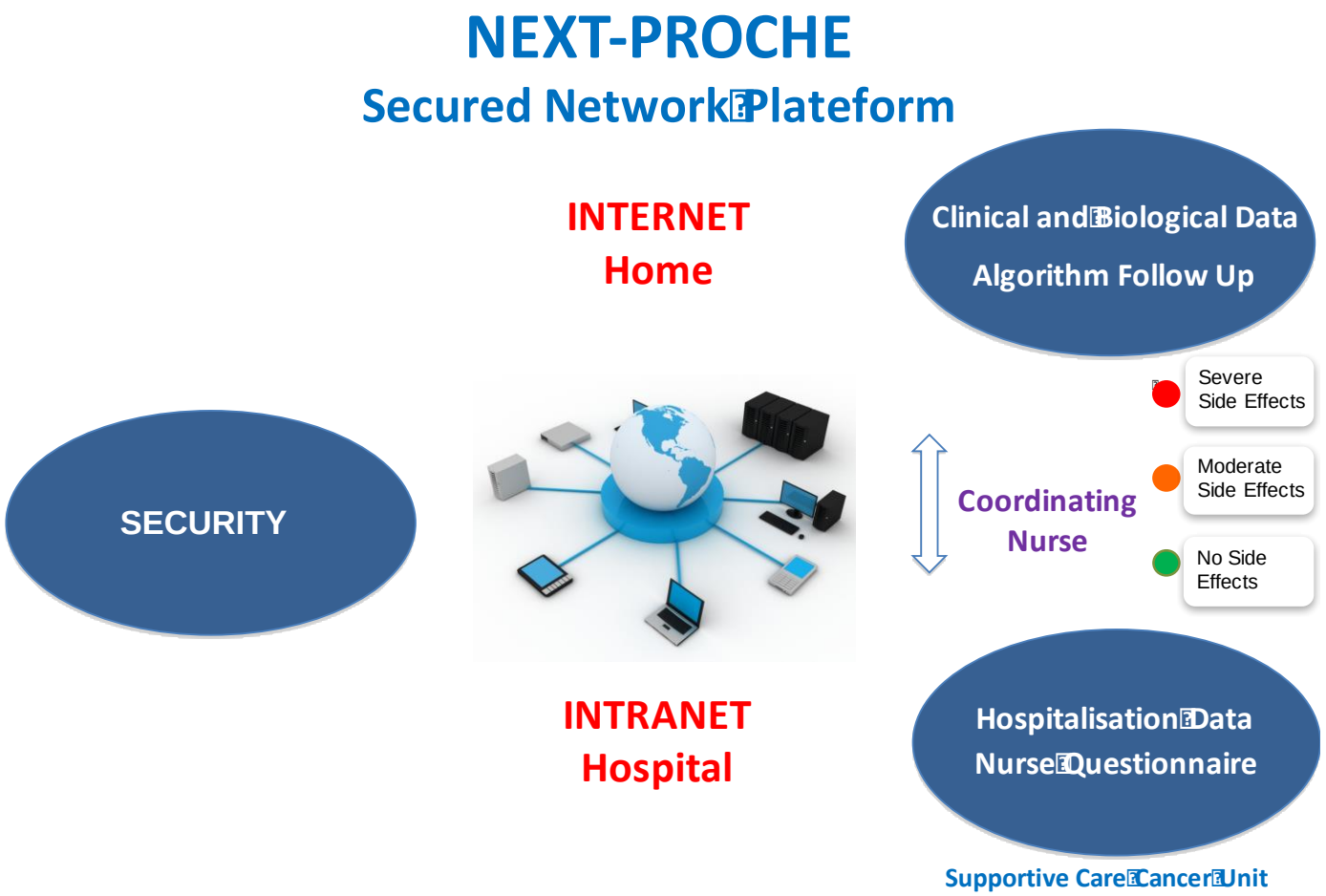
Evolution of incidence Fatigue (A) and Pain (B)



Scotte F. et al. Eur J Cancer 2013

HOW TO ASSESS ?

- New Digital Technology



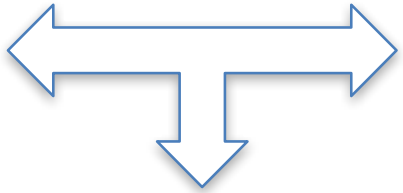
HOW TO ASSESS ?

- New Digital Technology

NEXT-PROCHE

Hospital

- Data-Sharing
- Home Monitoring



Home

- Toxicity Collection
- Safety Monitoring

Treatment Monitoring (IV / Oral)
Optimisation of Cancer Course

→ Personnalised medecine

PARIS 11 - 13 Octobre 2017
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