INSTITUT JULES BORDET

Management of side effects of immunotherapy and targeted therapies

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

AFSOS Association Francophone des Soins Oncologiques de Support

MASCC MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER

Florian Scotté, MD.PhD

Hôpital Foch

Suresnes, France

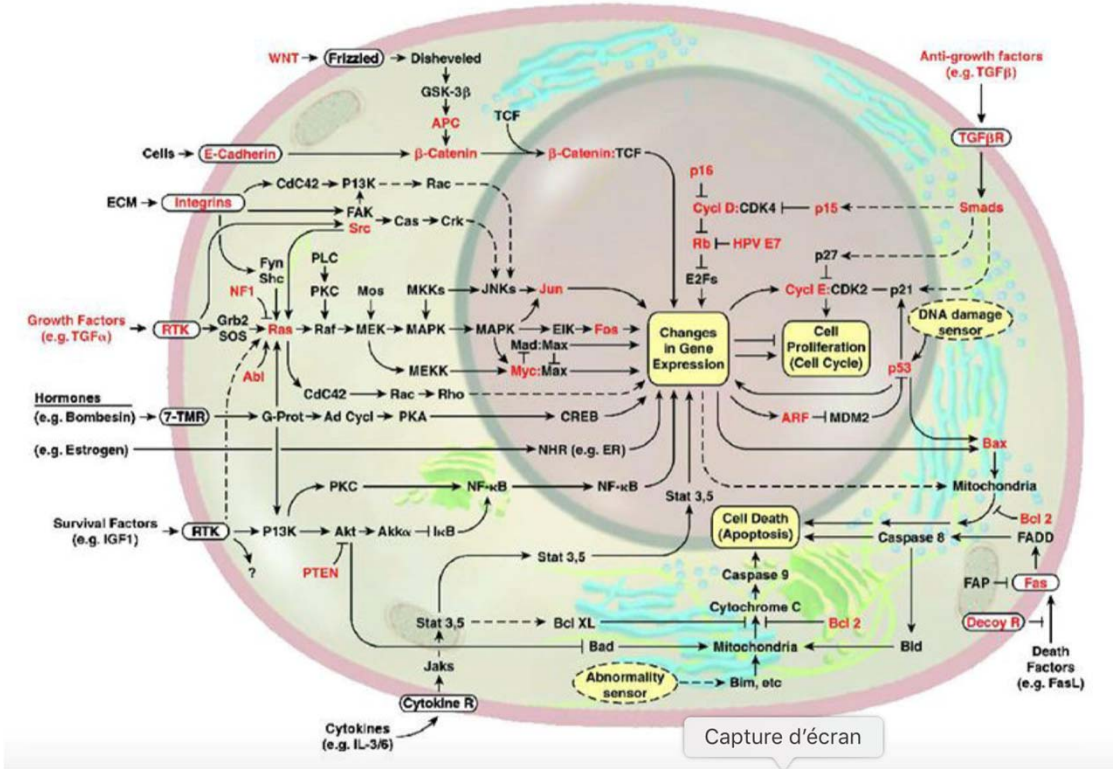
HOPITAL FOCH

DISCLOSURE SLIDE

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

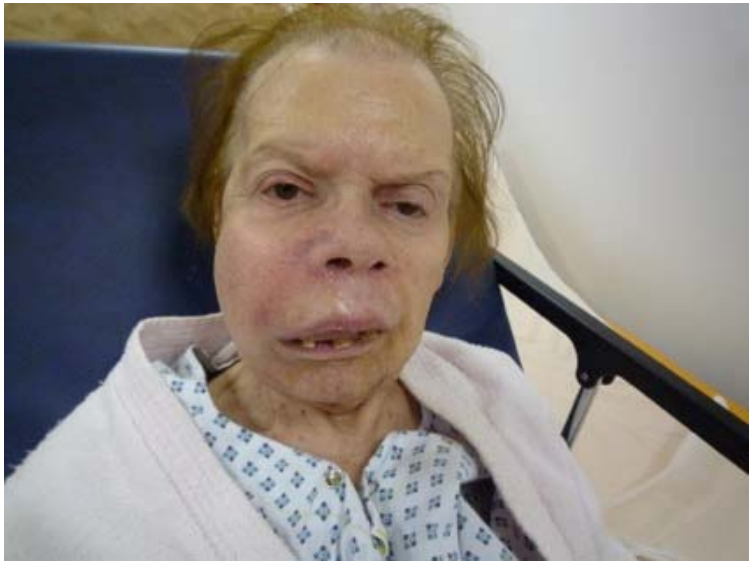
- Associations: ESMO, ASCO, MASCC, AFSOS, AESCO

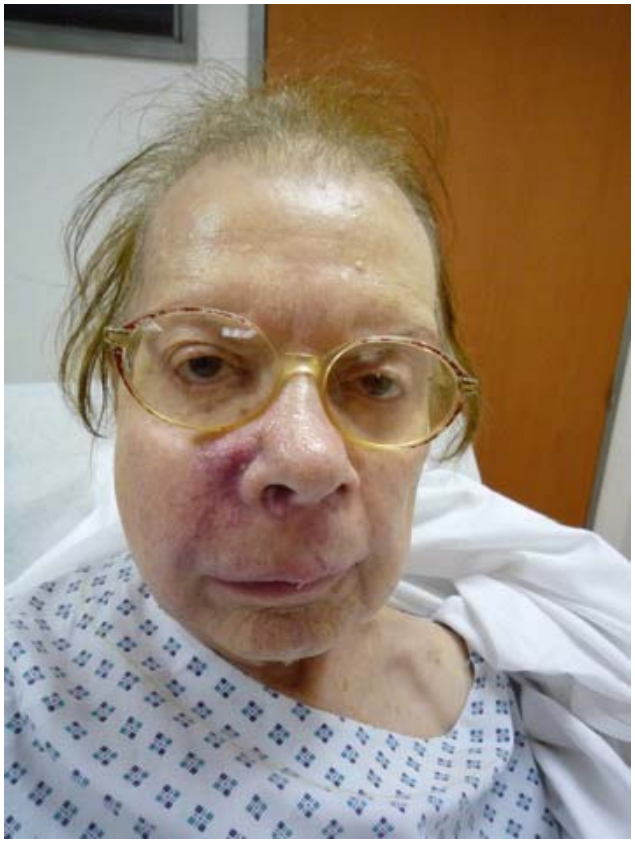
Targeted Therapies



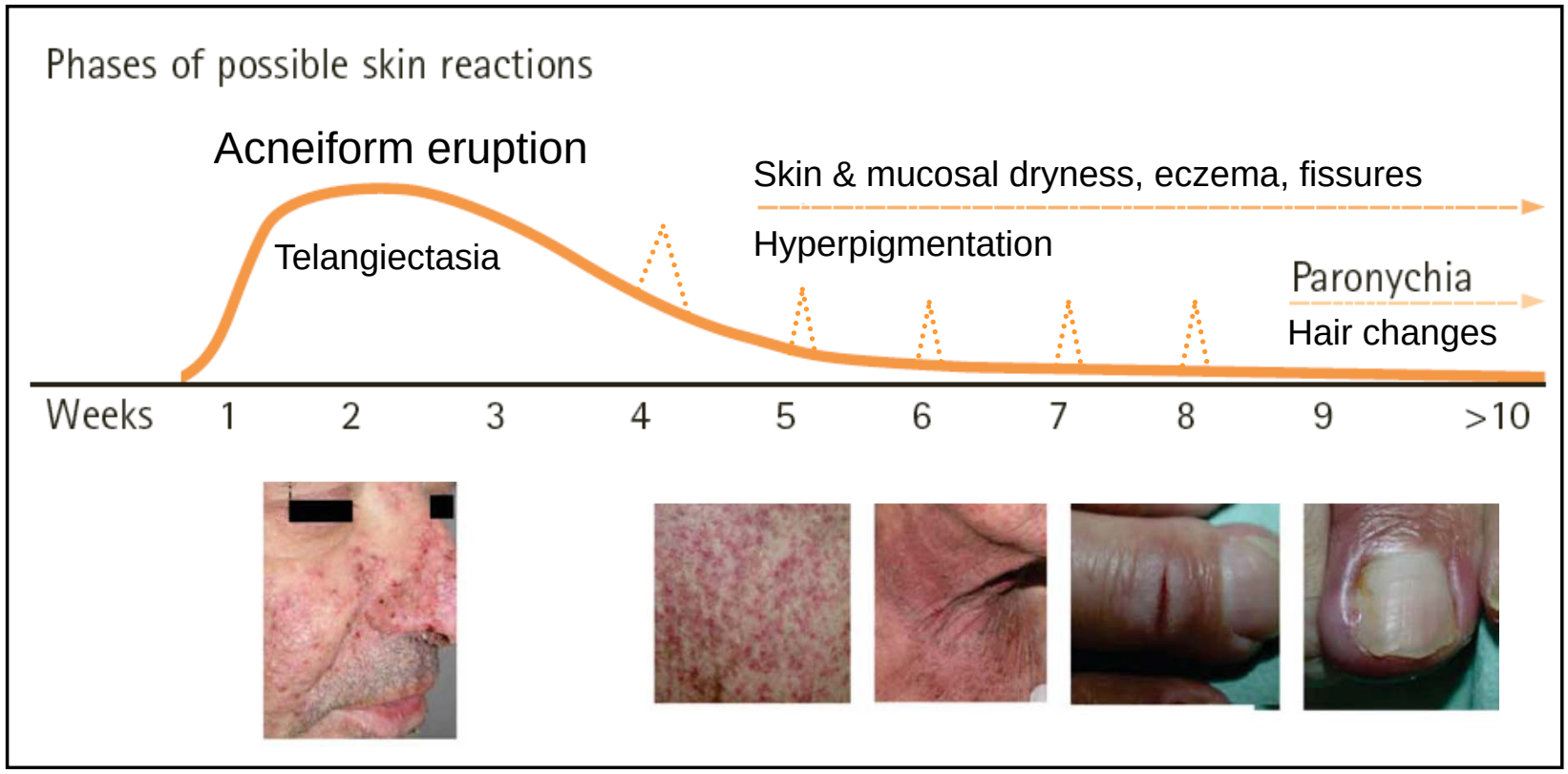
Capture d'écran

« Denise » : Efficacy – Real Life





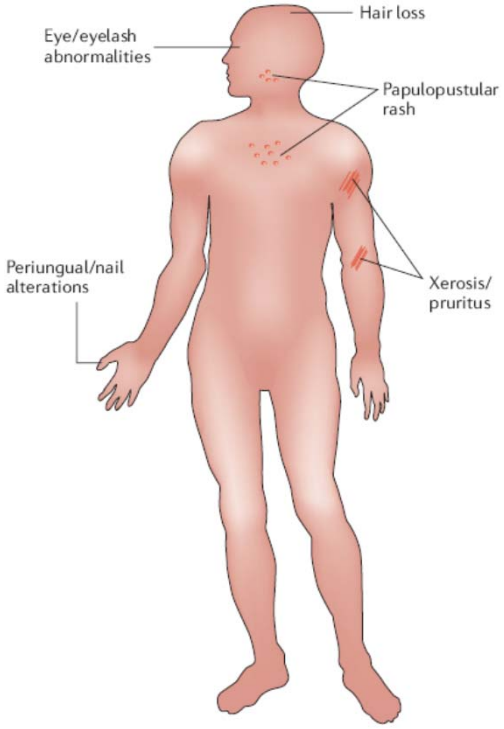
Skin Toxicity and EGFR inhibitors



from Segaert S, Van Cutsem E. Ann Oncol 2005; 16:1425-33.

PRIDE Syndrome

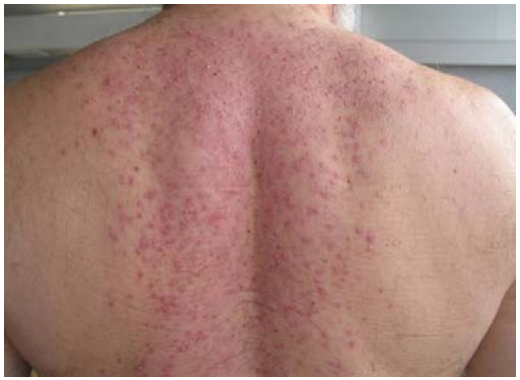
Papulopustules and/or ***p***aronychia, ***r***egulatory abnormalities of hair growth, ***i***tching, and ***d***ryness due to ***e***pidermal growth factor receptor inhibitors

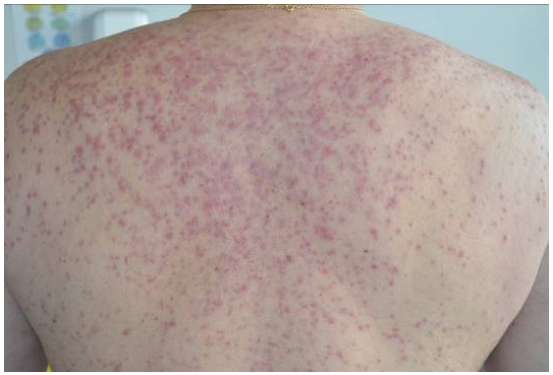


Anti EGFR, anti MEK, pan HER….Cetuximab, erlotinib, gefitinib, panitumumab, afatinib, lapatinib, pertuzumab, cobimetinib, selumetinib…..

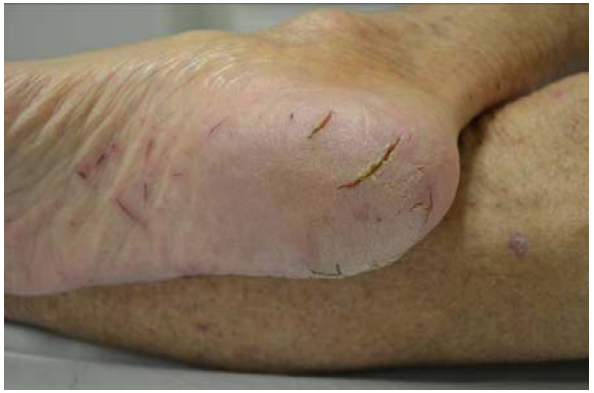
Lacouture ME. The PRIDE syndrome. *Br J Dermatol, 2006.*

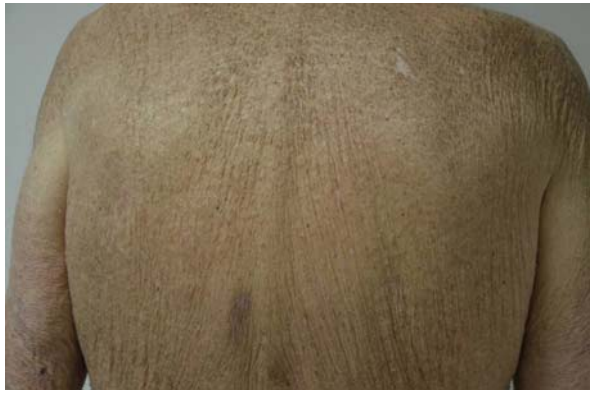
Rash

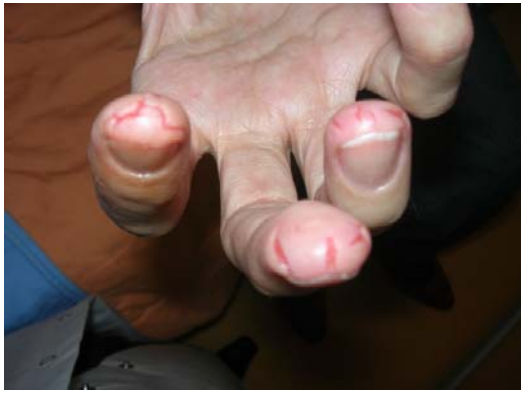




Dry skin





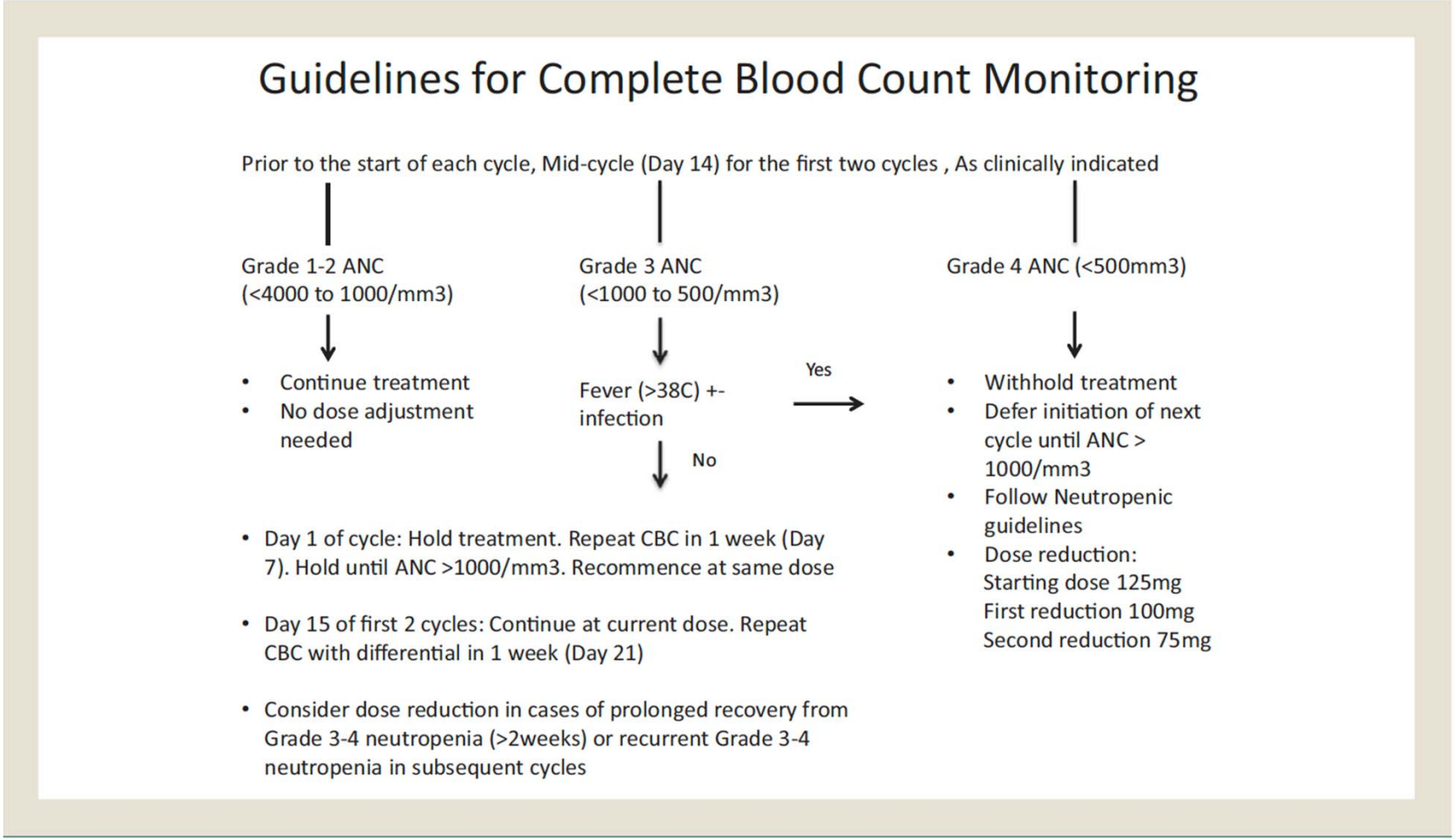


Solutions

- Information
- Education: « Don’t touch the spot »
- Topical Antibiotics : erythromycin, metronidazol, tetracyclins
- Topical Steroids
- Make up
  - Daily Emollient Cream Application
  - Sun protection
  - Avoid fragrance

Paradise corner…

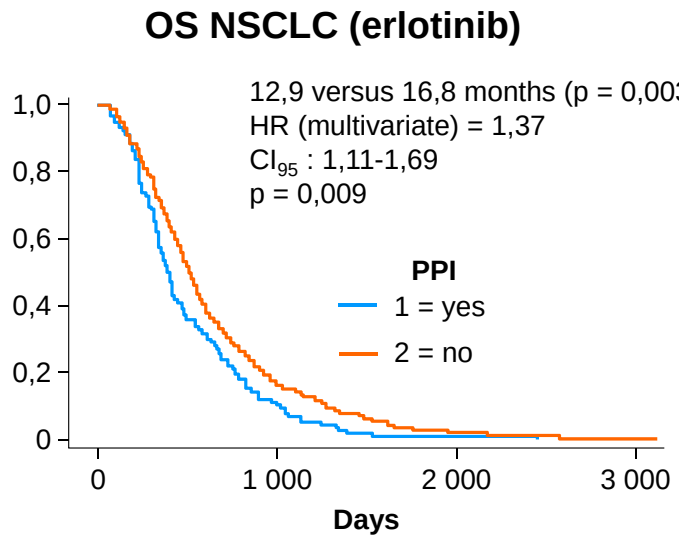
Monitoring Guidelines and Management of Neutropenia

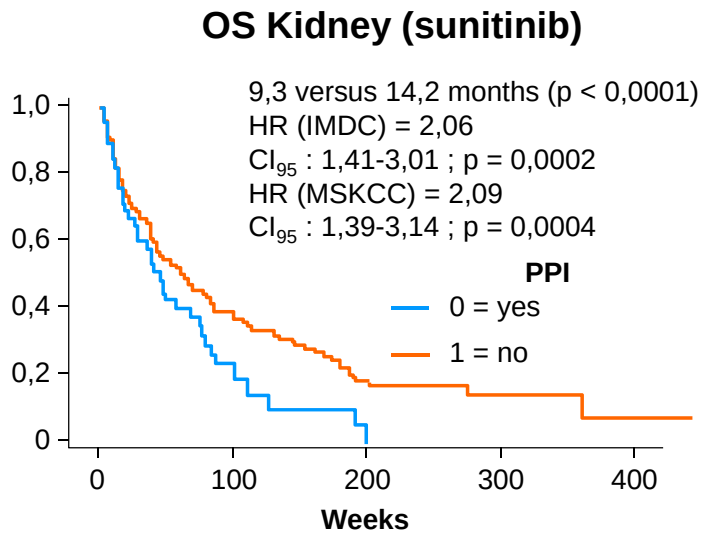


Spring L et al. Oncologist 2017; 22: 1039-48.

Pyrosis

- Incidence unknown: 0 - 50% ?
- Pre-existing ?
- Coping +++
- Be aware PPI and drug drug interactions → Anti-H2





ASCO 2014 - Chu MP, abstr. 2594,

ENDOCRINOPATHIES

- Dysthyroïdies (10 - 80%)
  - Pre Treatment assessment / monitoring TSH +/- T4 (/15 d 1st month then each cycle)
  - Hormonal substitution if symptoms (objective TSH = 0,5 to 4)
  - If thyrotoxicosis, beta blockers + steroids
  - Endocrinologist advice

- Hyperglycemia : mTOR inhibitors (20 – 60%) > TKI (10 – 40%)
  - Pre Treatment assessment / monitoring (/15d 1st month then each cycle)
  - Endocrinologist advice

- Dyslipidemia : mTOR inhibitors (20 – 80%)
  - Hypercholestérolemia, hypertriglyceridemia
  - Pre Treatment assessment / monitoring (/15d 1st month then each cycle)
  - Daily living rules
  - Statines better if cardiovascular risk factors

Questions To Cardiologist…

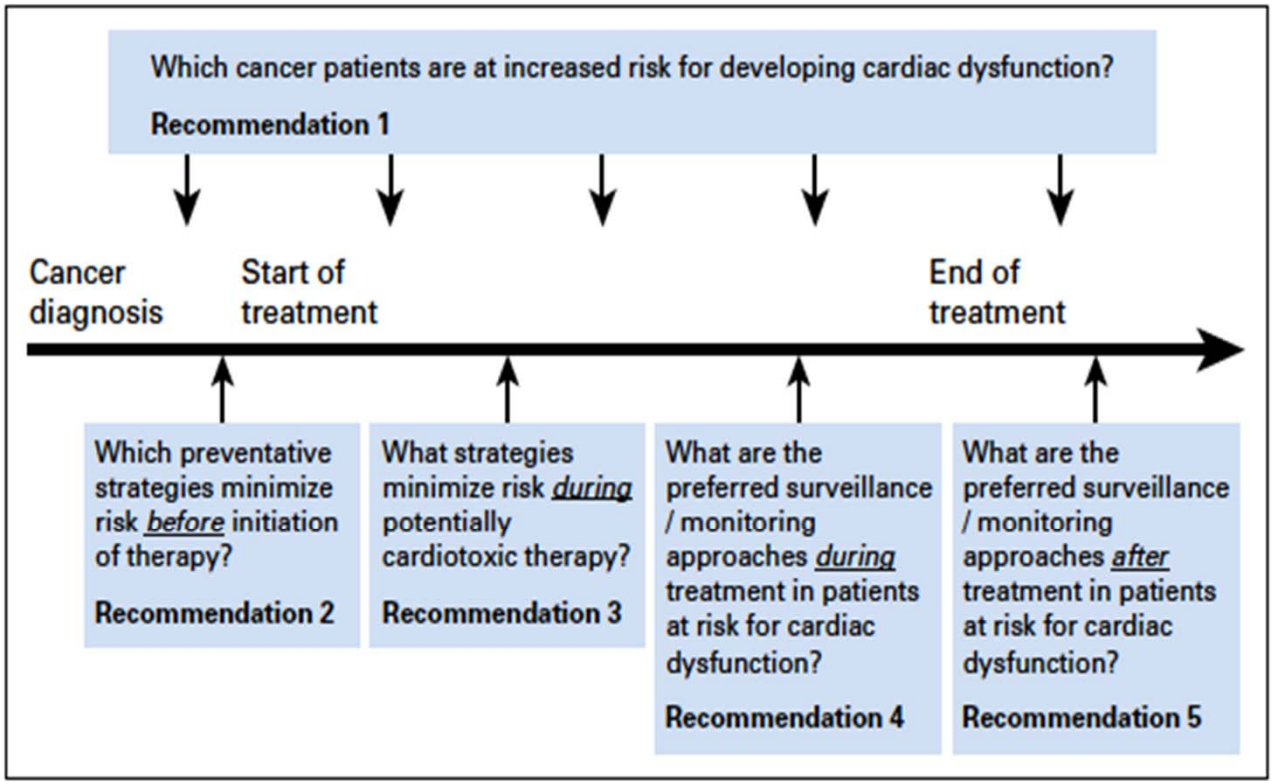
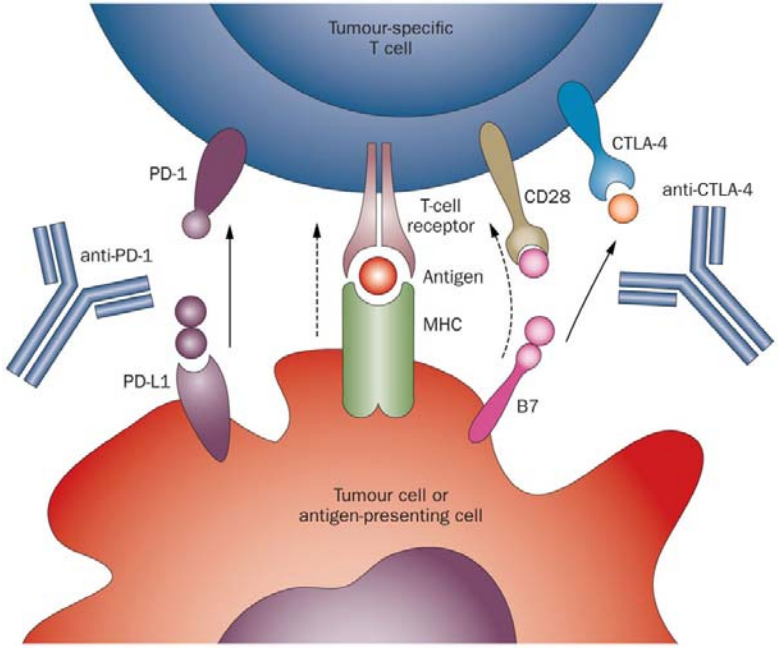


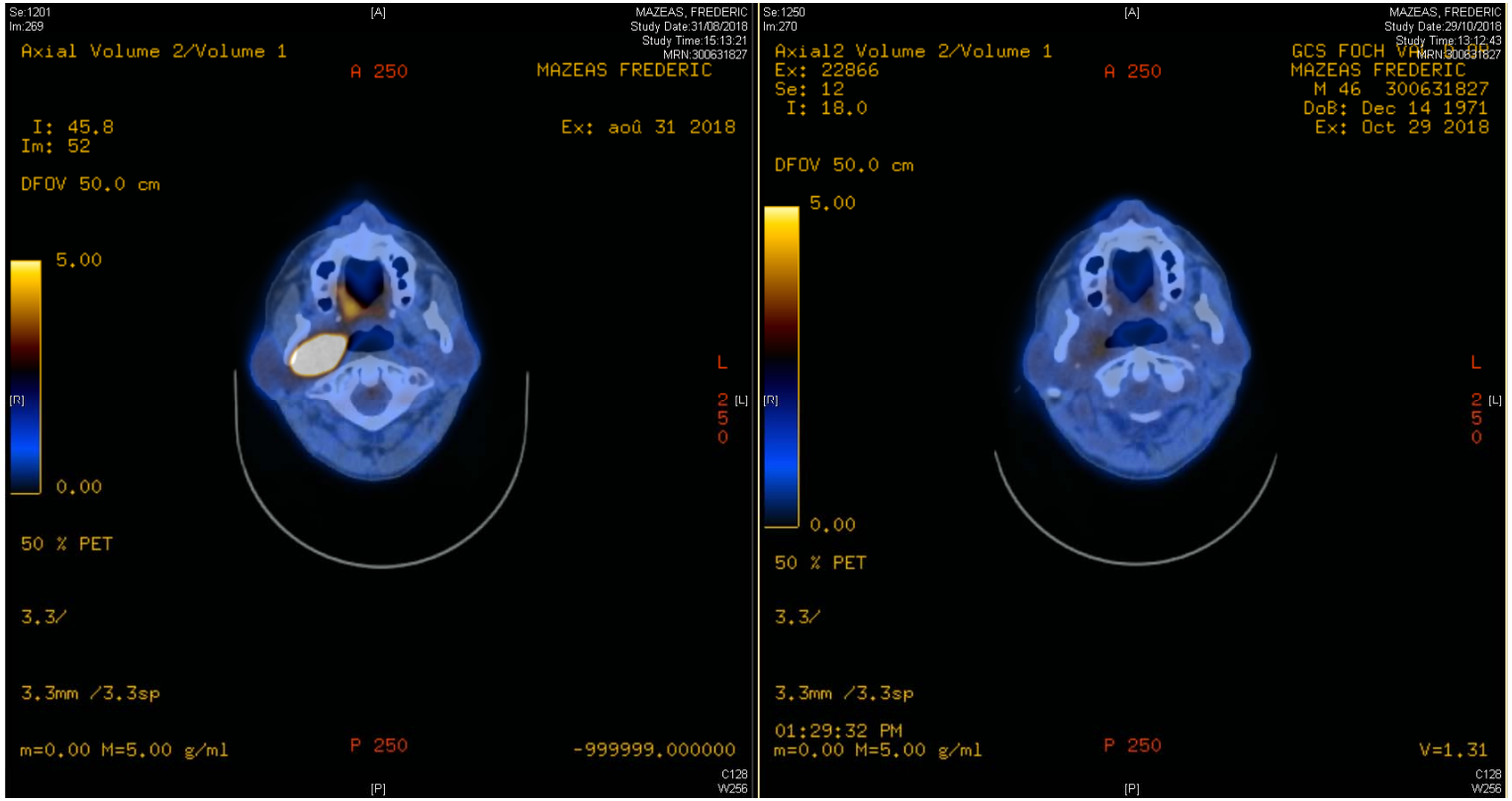
Fig 1. Overarching clinical questions addressed in the clinical practice guideline.

Saro H. Armenian, Christina Lacchetti, Ana Barac, et al. J Clin Oncol 2017 ; 35:893-911

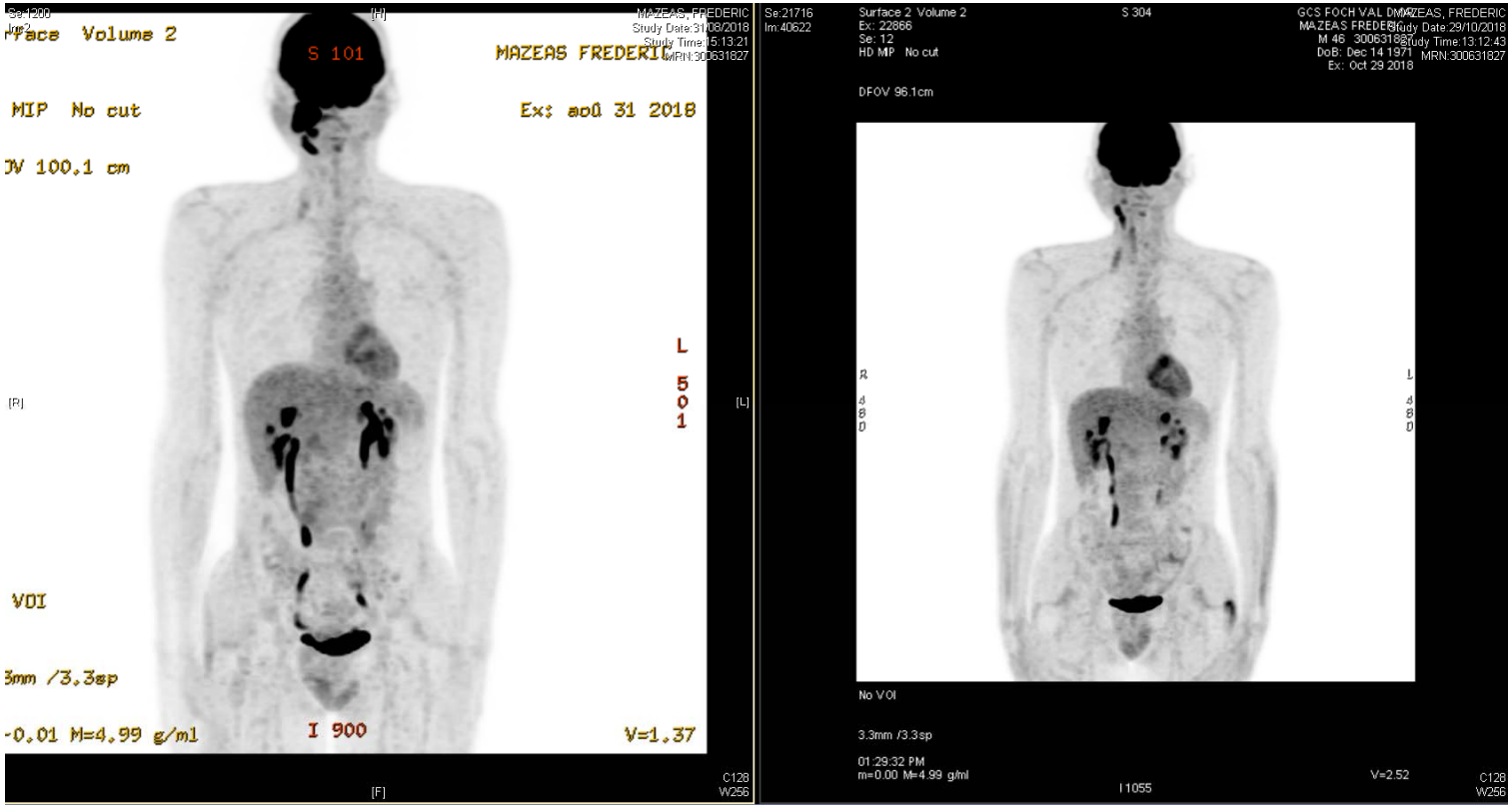
Checkpoint Inhibitors



« Thierry » : Efficacy – real life



« Thierry » : Efficacy – real life



Safety – Anticipation - Management

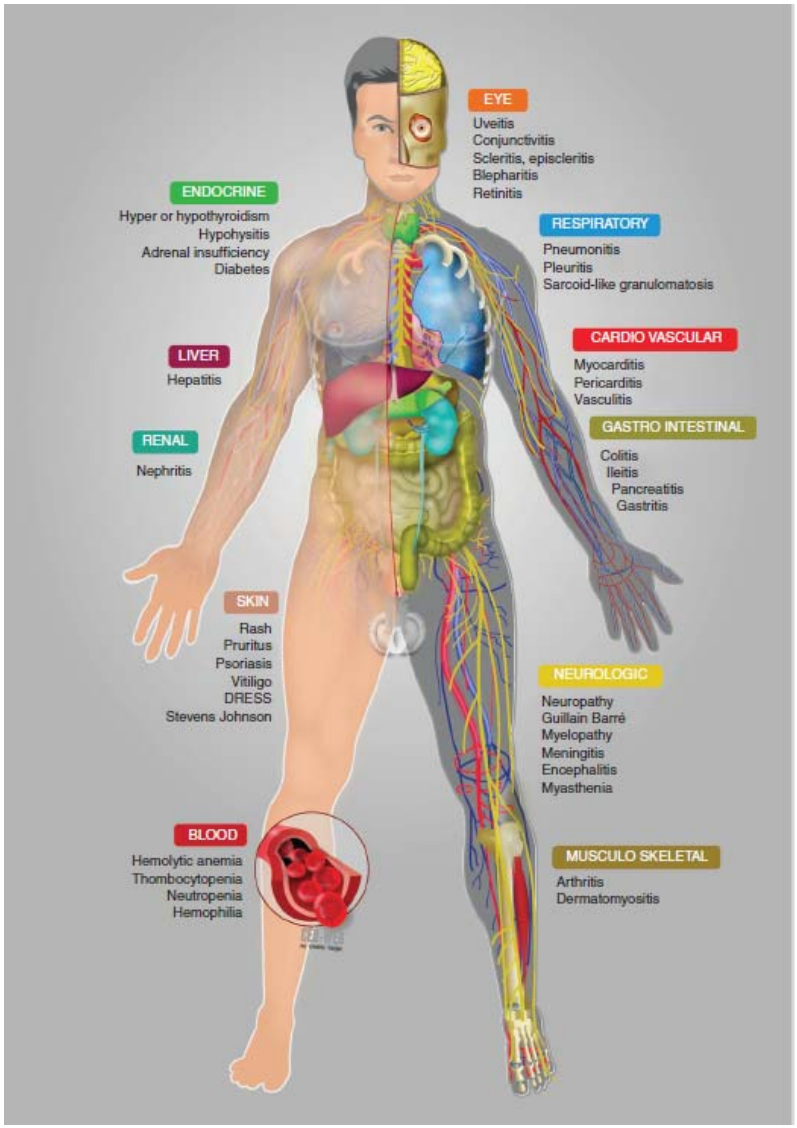
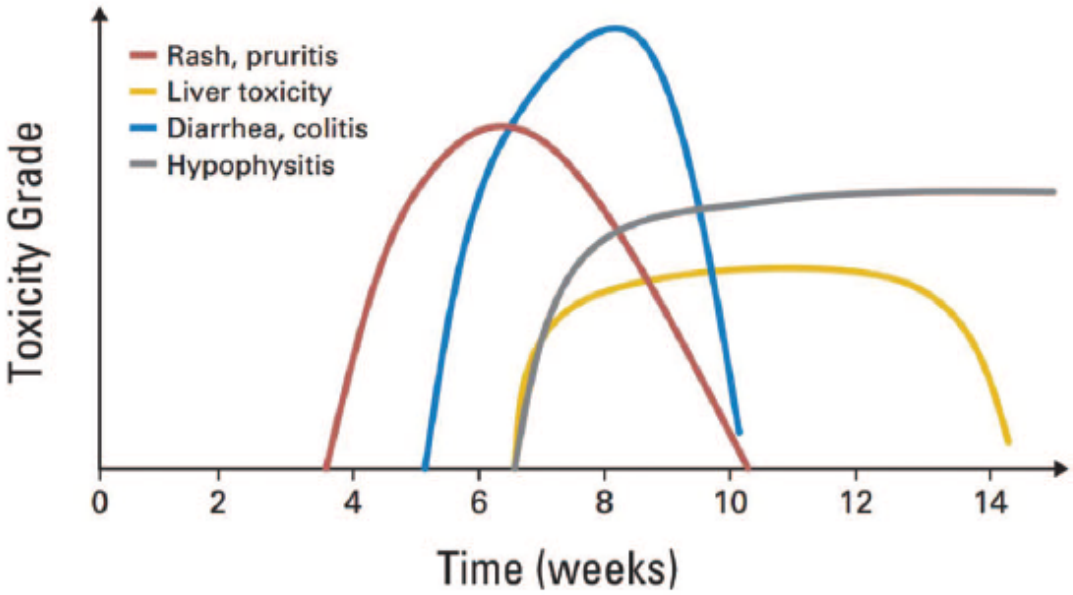
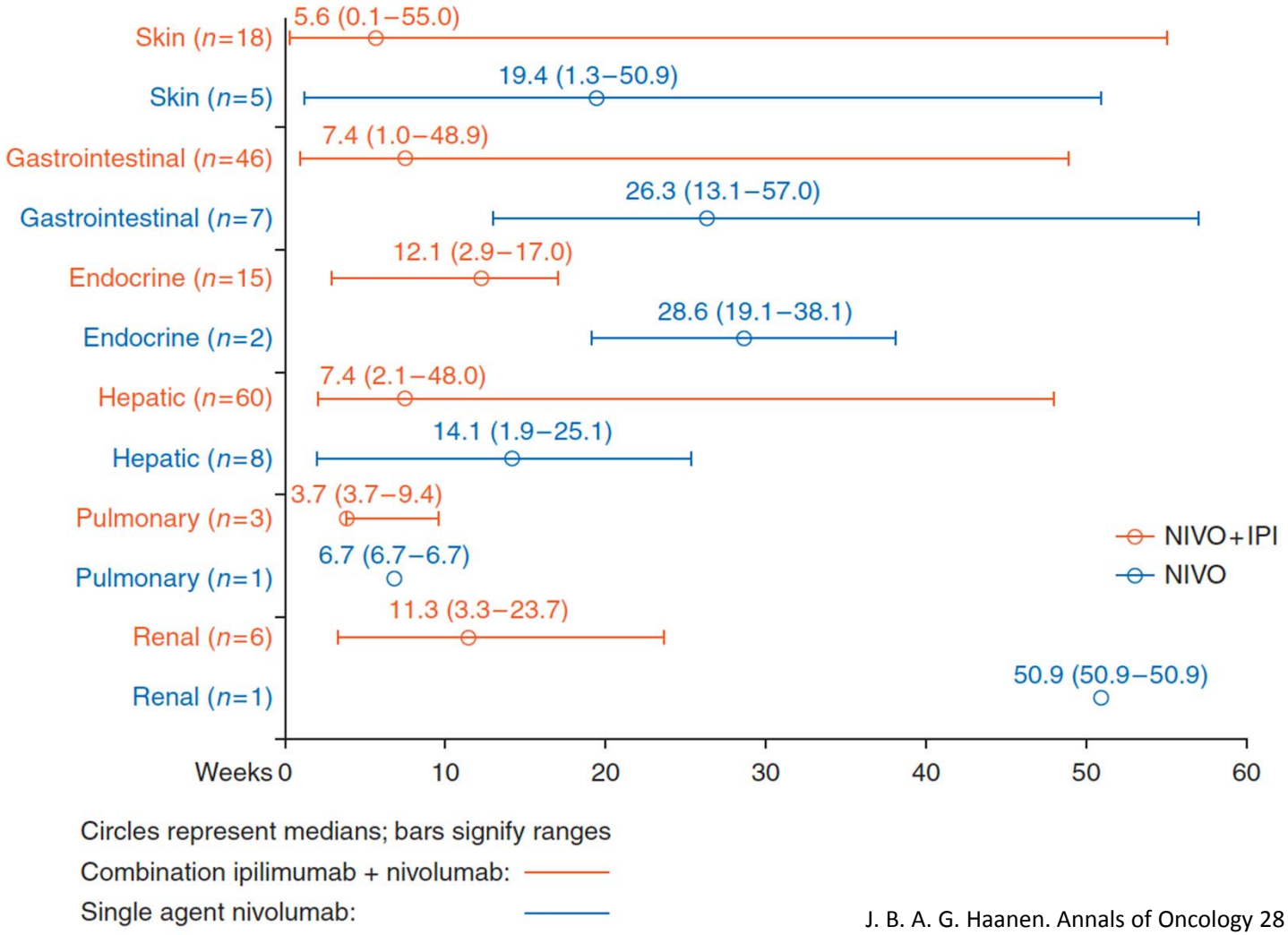


FIGURE 1. Kinetics of Appearance of Immune-Related Adverse Events

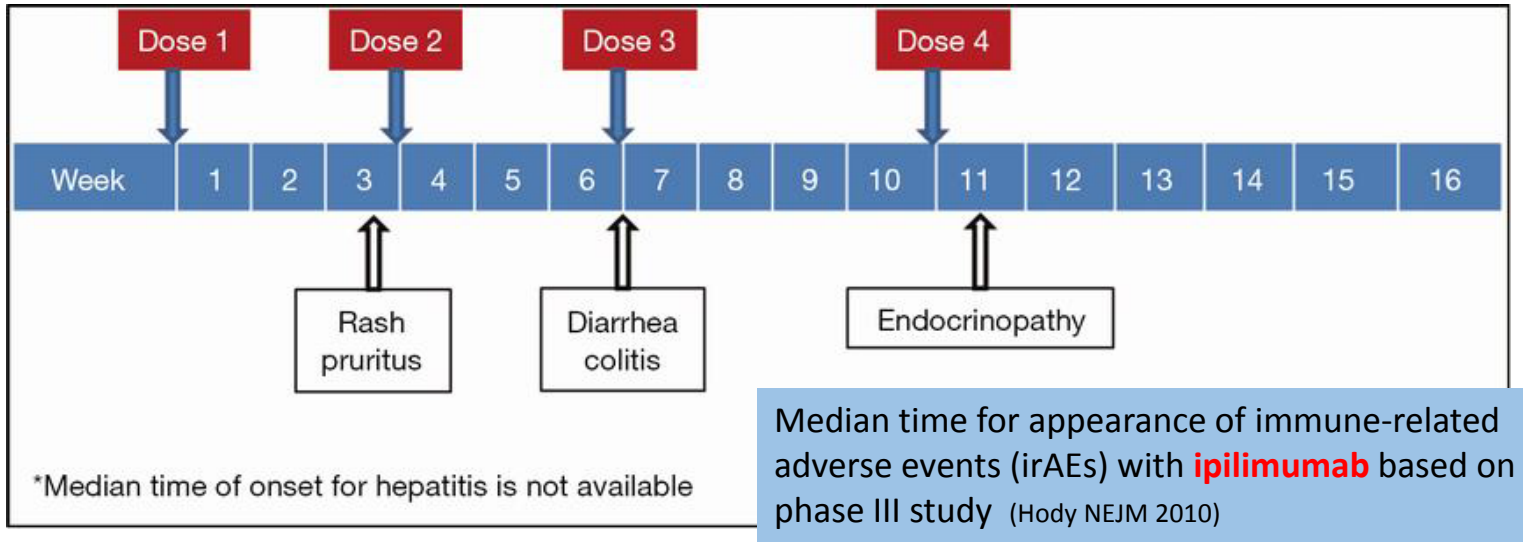


S.Champiat, ann oncol 2016

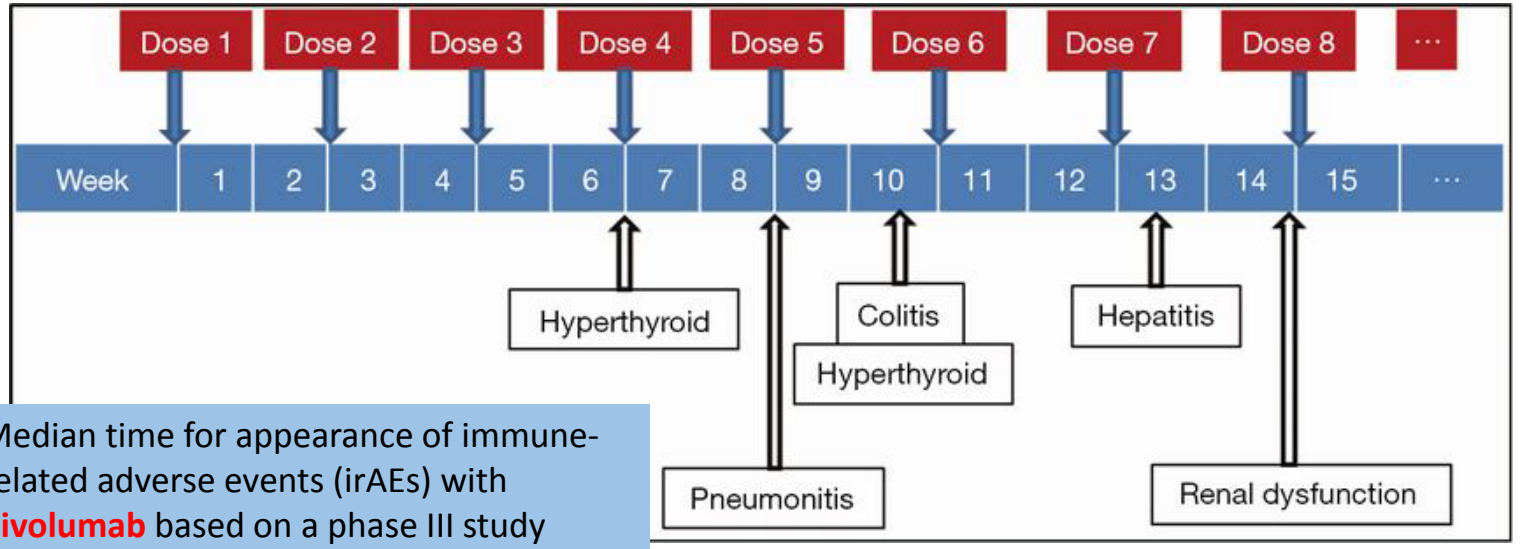
Time to onset of grade 3–4 treatment-related select AEs



J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017

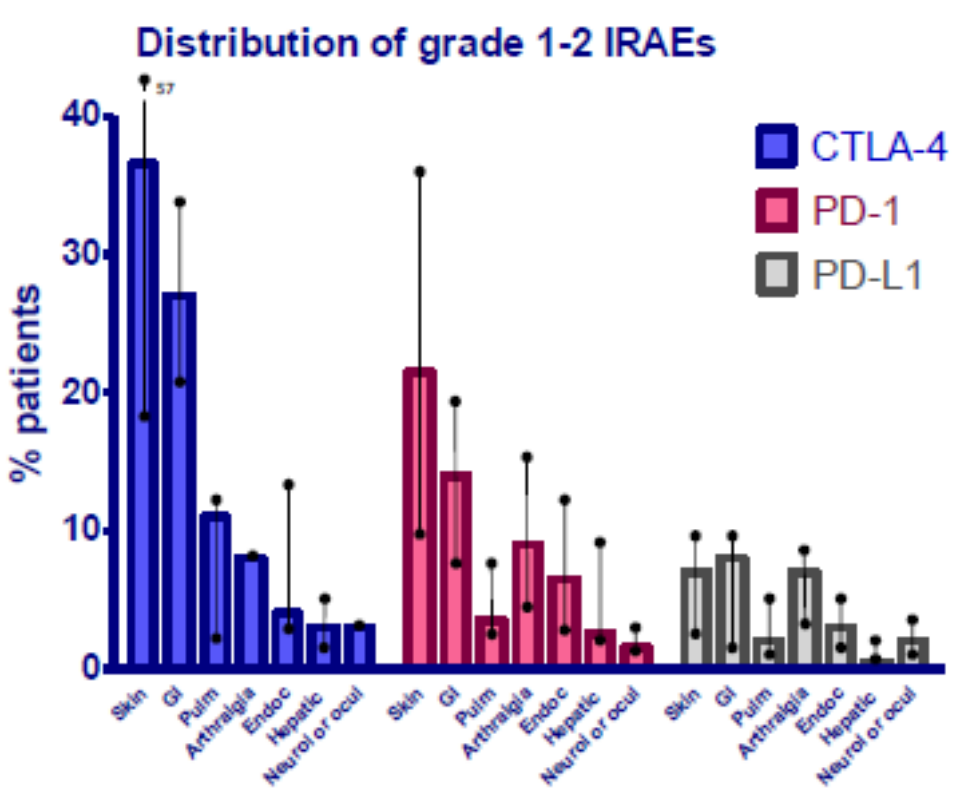


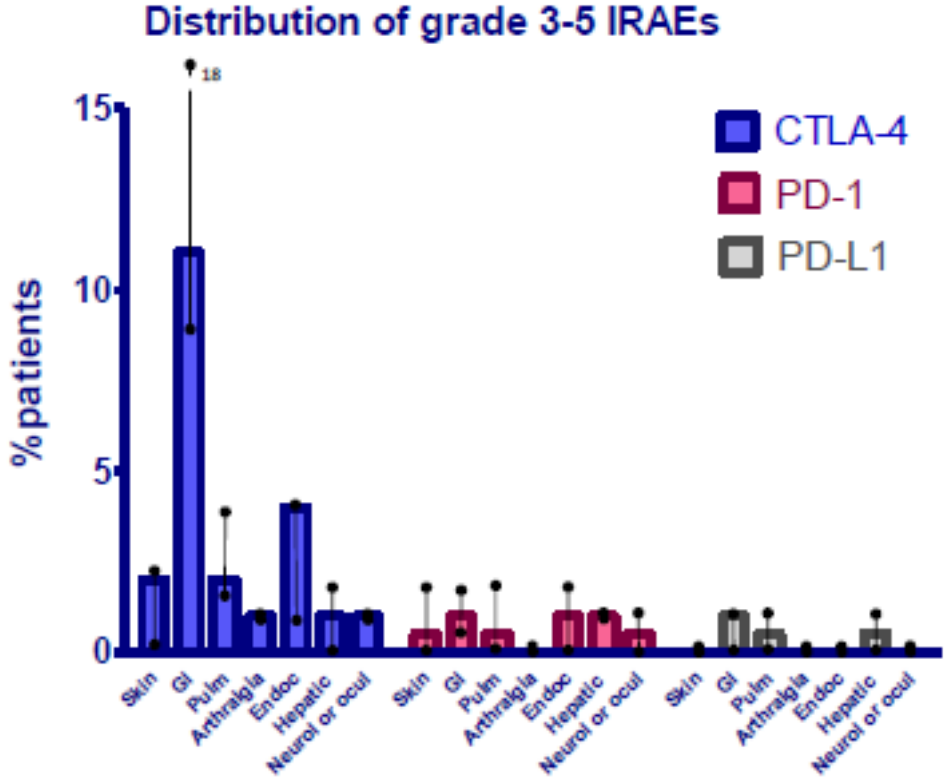
Median time for appearance of immune-related adverse events (irAEs) with **ipilimumab** based on a phase III study (Hody NEJM 2010)



Median time for appearance of immune-related adverse events (irAEs) with **nivolumab** based on a phase III study
(Weber Lancet oncol 2015)

AE Distribution





Michot, EJ cancer 2016

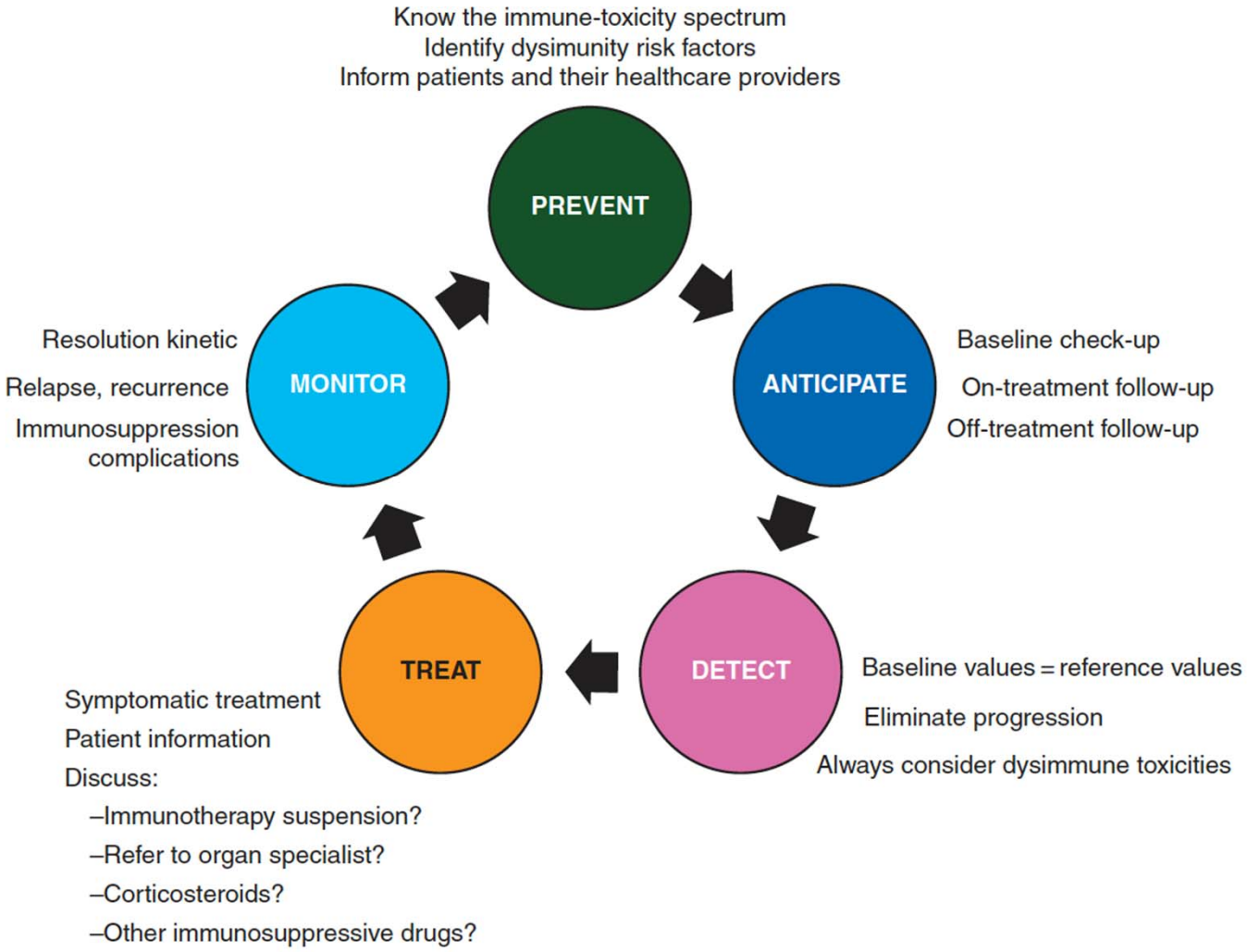
special article

Annals of Oncology 27: 559–574, 2016
doi:10.1093/annonc/mdv623
Published online 28 December 2015

Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper

S. Champiat[1,2], O. Lambotte[3,4,5,6], E. Barreau[7], R. Belkhir[8], A. Berdelou[9], F. Carbonnel[10], C. Cauquil[11], P. Chanson[12,13,14], M. Collins[10], A. Durrbach[15], S. Ederhy[16], S. Feuillet[17,18], H. François[15], J. Lazarovici[19], J. Le Pavec[17,18,20], E. De Martin[21,22], C. Mateus[23], J.-M. Michot[1], D. Samuel[21,22], J.-C. Soria[1,2], C. Robert[2,23], A. Eggermont[24] & A. Marabelle[1,24,25*]

The five pillars of immunotherapy toxicity management



Champiat S. et al. Annals of Oncology 27: 559–574, 2016

General Management of IrAEs

Table 4. Typical management of irAEs

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.
[a]Outside skin or endocrine disorders where immunotherapy can be maintained.

Champiat S. et al. Annals of Oncology 27: 559–574, 2016

Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

Frank Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Charles Lance Cowey, Christopher D Lao, Dirk Schadendorf, John Wagstaff, Reinhard Dummer, Pier Francesco Ferrucci, Michael Smylie, Andrew Hill, David Hogg, Ivan Marquez-Rodas, Joel Jiang, Jasmine Rizzo, James Larkin, Jedd D Wolchok**

Lancet Oncol 2018; 19: 1480–92

Summary

Background Previously reported results from the phase 3 CheckMate 067 trial showed a significant improvement in

	Nivolumab plus ipilimumab group (n=313)			Nivolumab group (n=313)			Ipilimumab group (n=311)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	115 (37%)	151 (48%)	34 (11%)	200 (64%)	54 (17%)	16 (5%)	181 (58%)	74 (24%)	12 (4%)
Diarrhoea	112 (36%)	29 (9%)	1 (<1%)	60 (19%)	9 (3%)	0	87 (28%)	18 (6%)	0
Fatigue	107 (34%)	13 (4%)	0	111 (36%)	3 (1%)	0	86 (28%)	3 (1%)	0
Pruritus	106 (34%)	6 (2%)	0	68 (22%)	1 (<1%)	0	112 (36%)	1 (<1%)	0
Rash	83 (27%)	10 (3%)	0	73 (23%)	1 (<1%)	0	64 (21%)	5 (2%)	0
Nausea	81 (26%)	7 (2%)	0	41 (13%)	0	0	49 (16%)	2 (1%)	0
Pyrexia	58 (19%)	1 (<1%)	1 (<1%)	21 (7%)	0	0	20 (6%)	1 (<1%)	0
Decreased appetite	56 (18%)	4 (1%)	0	35 (11%)	0	0	40 (13%)	1 (<1%)	0
Hypothyroidism	53 (17%)	1 (<1%)	0	32 (10%)	0	0	14 (5%)	0	0
Vomiting	41 (13%)	7 (2%)	0	21 (7%)	1 (<1%)	0	23 (7%)	1 (<1%)	0
Arthralgia	41 (13%)	2 (1%)	0	31 (10%)	1 (<1%)	0	22 (7%)	0	0
Headache	33 (11%)	2 (1%)	0	24 (8%)	0	0	25 (8%)	1 (<1%)	0
Increased aspartate aminotransferase	33 (11%)	18 (6%)	1 (<1%)	11 (4%)	3 (1%)	0	10 (3%)	2 (1%)	0
Increased alanine aminotransferase	33 (11%)	25 (8%)	2 (1%)	9 (3%)	3 (1%)	1 (<1%)	7 (2%)	4 (1%)	1 (<1%)
Dyspnoea	33 (11%)	3 (1%)	0	18 (6%)	1 (<1%)	0	12 (4%)	0	0
Maculopapular rash	32 (10%)	6 (2%)	0	14 (5%)	2 (1%)	0	37 (12%)	1 (<1%)	0
Hyperthyroidism	32 (10%)	3 (1%)	0	14 (5%)	0 (0%)	0	3 (1%)	0	0
Vitiligo	28 (9%)	0	0	30 (10%)	1 (<1%)	0	16 (5%)	0	0
Hypophysitis	19 (6%)	5 (2%)	0	1 (<1%)	1 (<1%)	0	7 (2%)	5 (2%)	0
Increased amylase	17 (5%)	9 (3%)	0	14 (5%)	7 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Colitis	14 (5%)	25 (8%)	1 (<1%)	5 (2%)	3 (1%)	0	11 (4%)	23 (7%)	1 (<1%)
Increased lipase	11 (4%)	19 (6%)	15 (5%)	13 (4%)	6 (2%)	10 (3%)	6 (2%)	8 (3%)	4 (1%)
Dehydration	9 (3%)	5 (2%)	0	1 (<1%)	0	0	3 (1%)	2 (1%)	0
Adrenal insufficiency	5 (2%)	5 (2%)	1 (<1%)	2 (1%)	2 (1%)	0	3 (1%)	1 (<1%)	0
Increased transaminases	2 (1%)	9 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	0	3 (1%)	0	0
Hepatotoxicity	2 (1%)	8 (3%)	0	0	1 (<1%)	0	1 (<1%)	0	0
Hepatitis	2 (1%)	5 (2%)	0	0	0	0	0	0	0

Data are n (%). The table shows grade 1–2 adverse events occurring in at least 10% of patients in any treatment group and all grade 3 and 4 adverse events occurring in at least 2% of patients in any treatment group. A complete table of adverse events showing grade 1–2 events occurring in at least 5% of patients in any group and all grade 3 and 4 events is in the appendix (pp 5–8).

Table 2: **Treatment-related adverse events**

The “1% toxicities”

Event	Nivolumab n = 287		Docetaxel n = 268	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	Number of patients with an event (%)			
Any event	21 (7)	15 (5)	53 (20)	48 (18)
Pneumonitis	4 (1)	3 (1)	0	0
Interstitial lung disease	2 (1)	1 (<1)	0	0
Infusion related reaction	2 (1)	0	0	0
Nausea	2 (1)	1 (<1)	1 (<1)	1 (<1)
Colitis	2 (1)	1 (<1)	0	0
Diarrhea	1 (<1)	1 (<1)	1 (<1)	0
Dyspnea	1 (<1)	1 (<1)	0	0
Hypoxia	1 (<1)	1 (<1)	0	0
Pulmonary embolism	1 (<1)	1 (<1)	0	0
Cardiac tamponade	1 (<1)	1 (<1)	0	0
Pericardial effusion	1 (<1)	1 (<1)	0	0
Blood creatinine increased	1 (<1)	0	0	0
Transaminases increased	1 (<1)	1 (<1)	0	0
Osteonecrosis	1 (<1)	1 (<1)	0	0
Polymyalgia rheumatica	1 (<1)	1 (<1)	0	0
Hepatotoxicity	1 (<1)	0	0	0
Cerebrovascular accident	1 (<1)	1 (<1)	0	0
Encephalitis	1 (<1)	1 (<1)	0	0

Borghaei et al. *NEJM 2015*

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.

Champiat et al Annals Oncol 2016

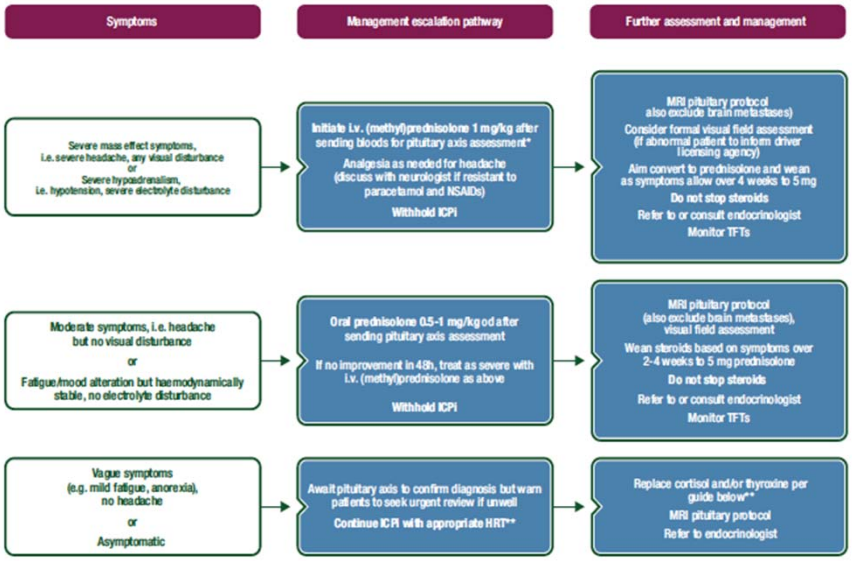
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

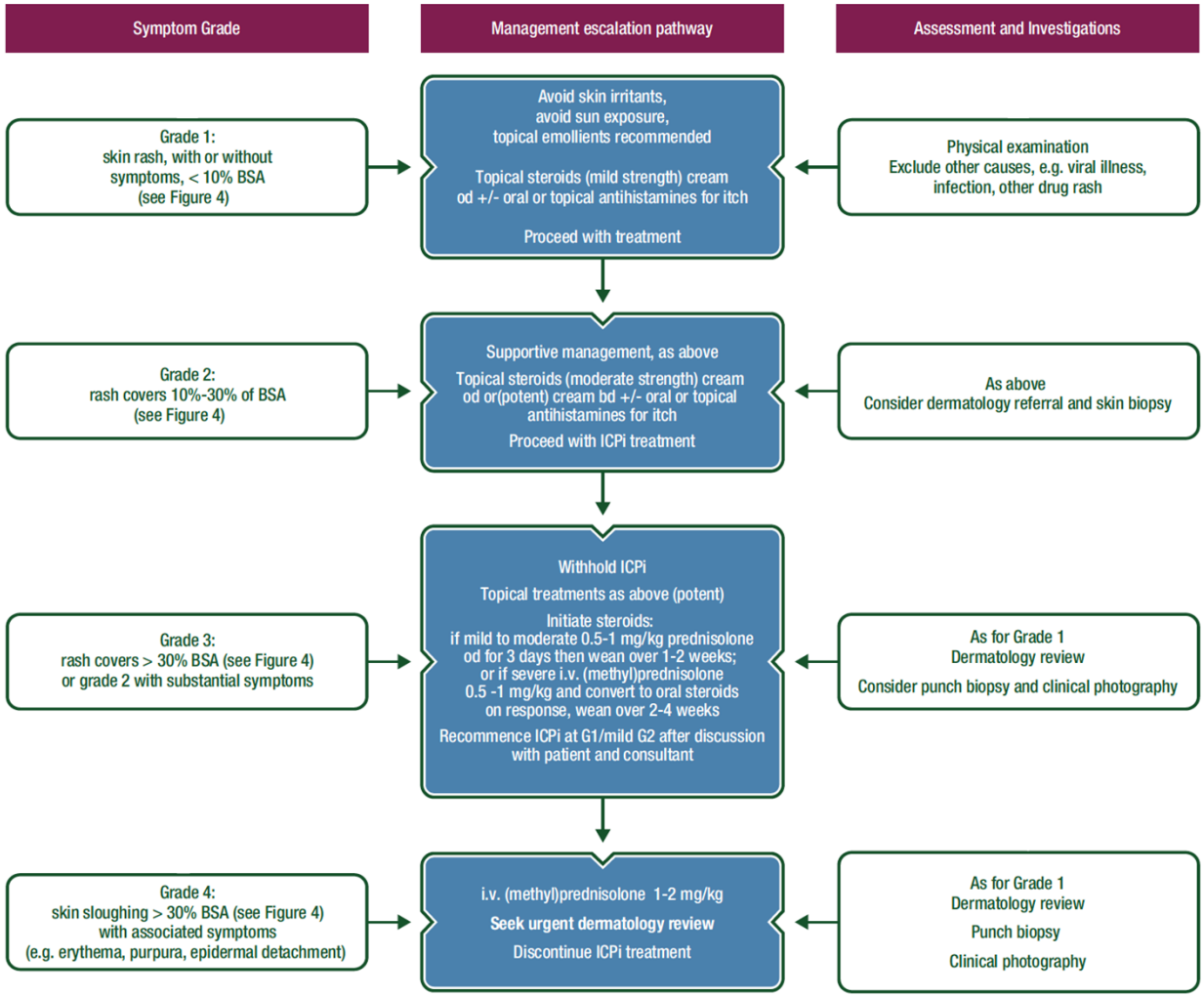
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*



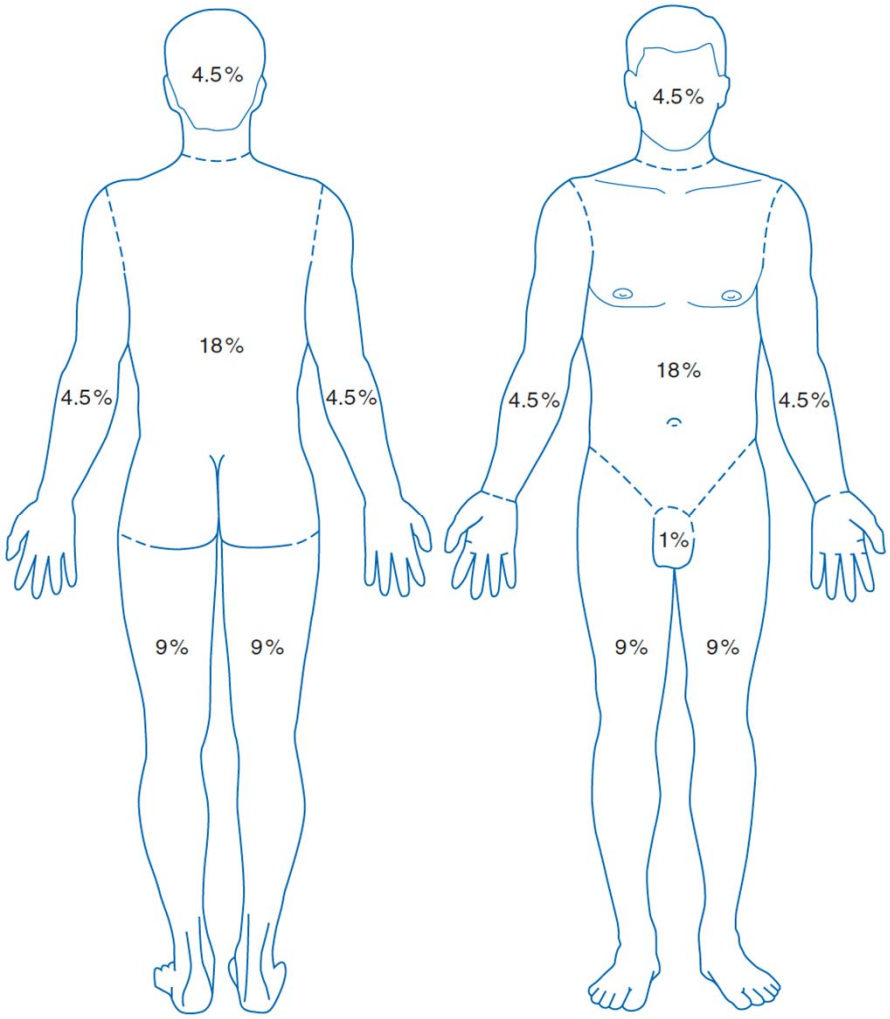
J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017

ICPi-related toxicity: management of skin rash/toxicity

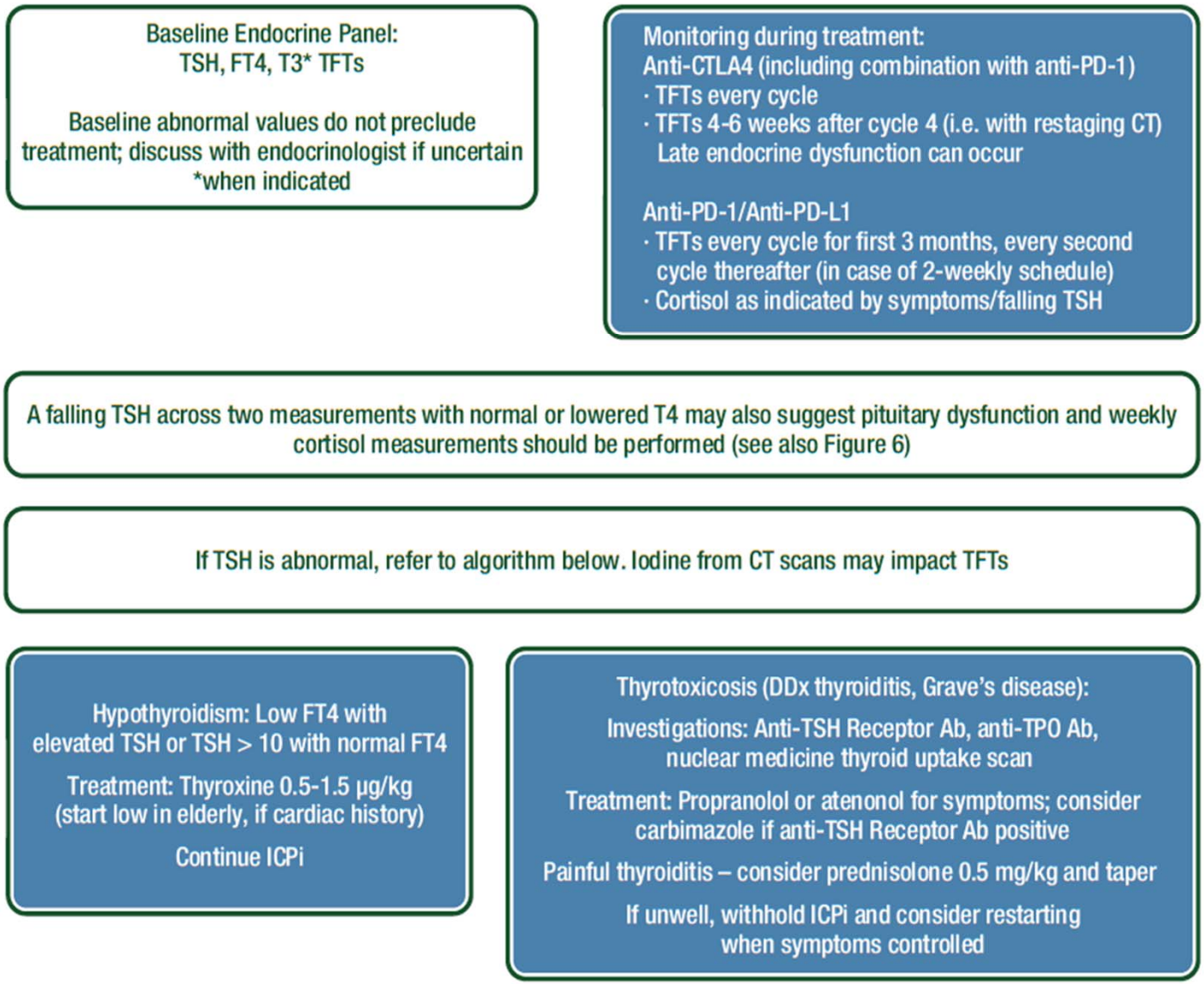


J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017

ICPi-related toxicity: management of skin rash/toxicity



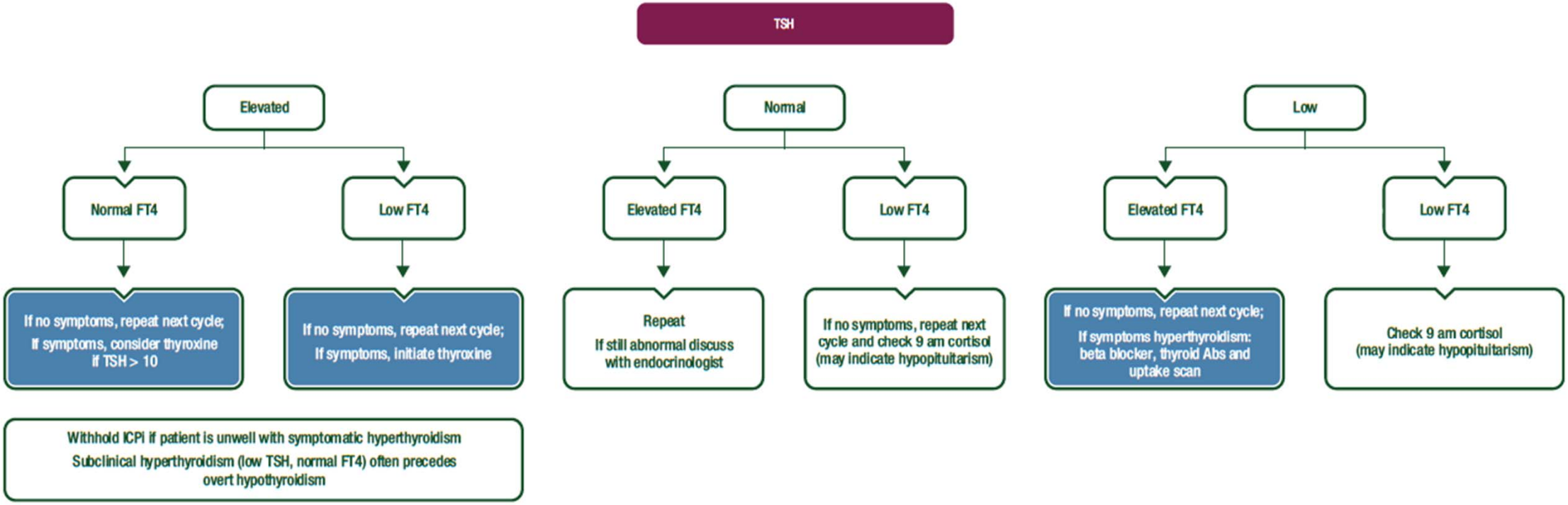
J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017



ICPi monitoring and management: thyroid function

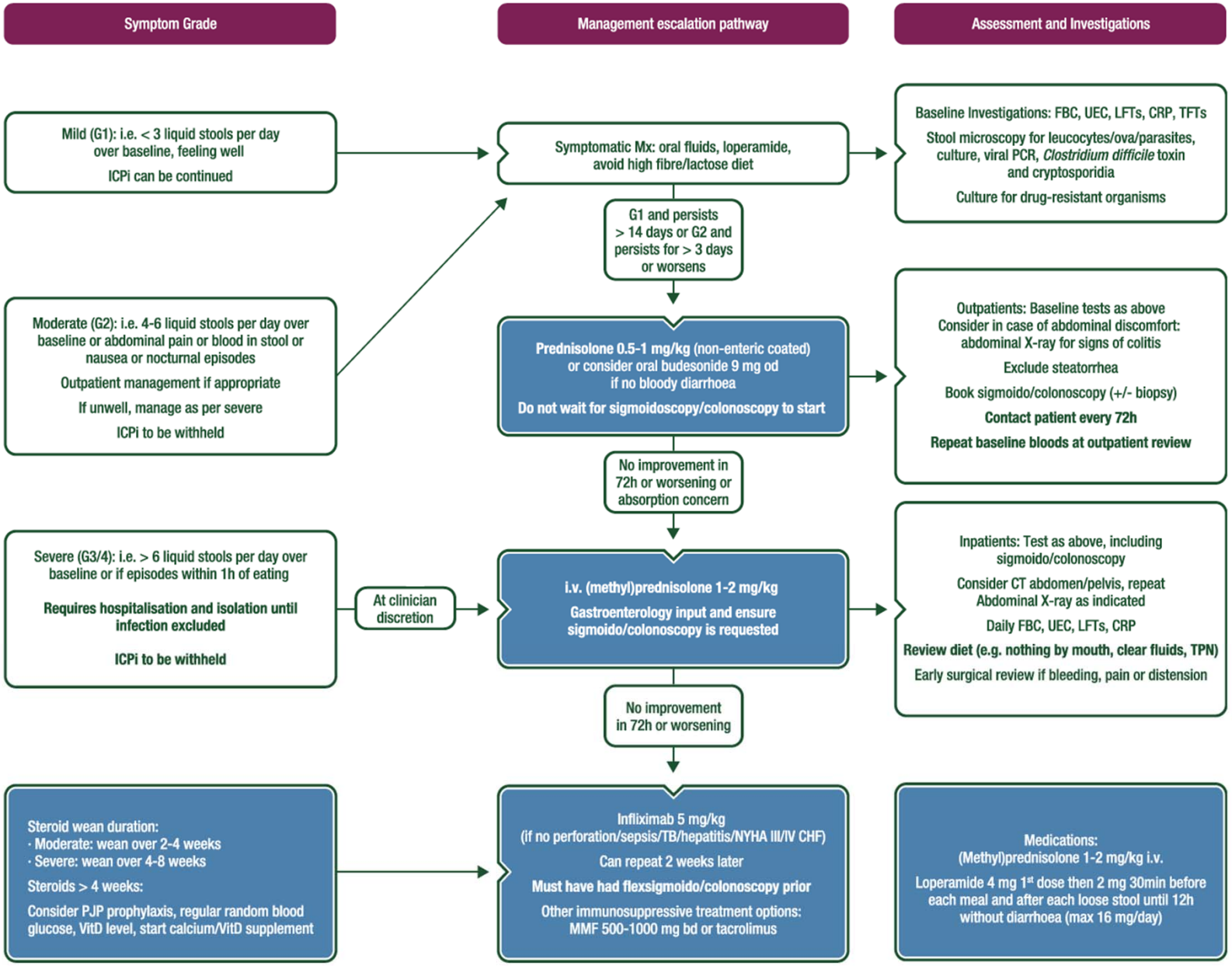
J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017

ICPi monitoring and management: thyroid function



J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017

ICPi-related toxicity: management of diarrhoea and colitis



J. B. A. G. Haanen. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017

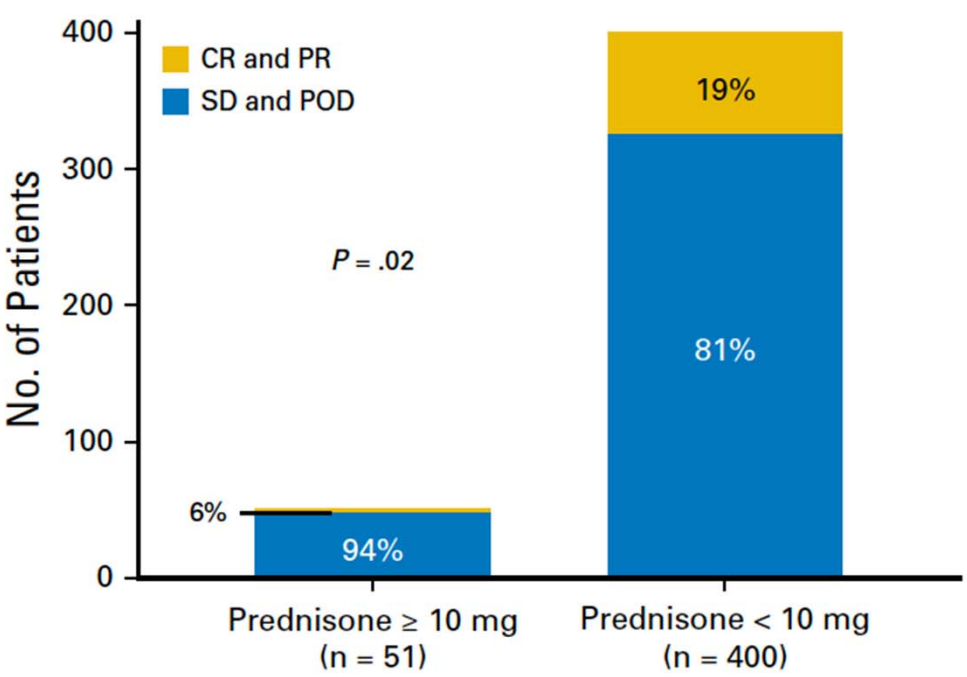
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

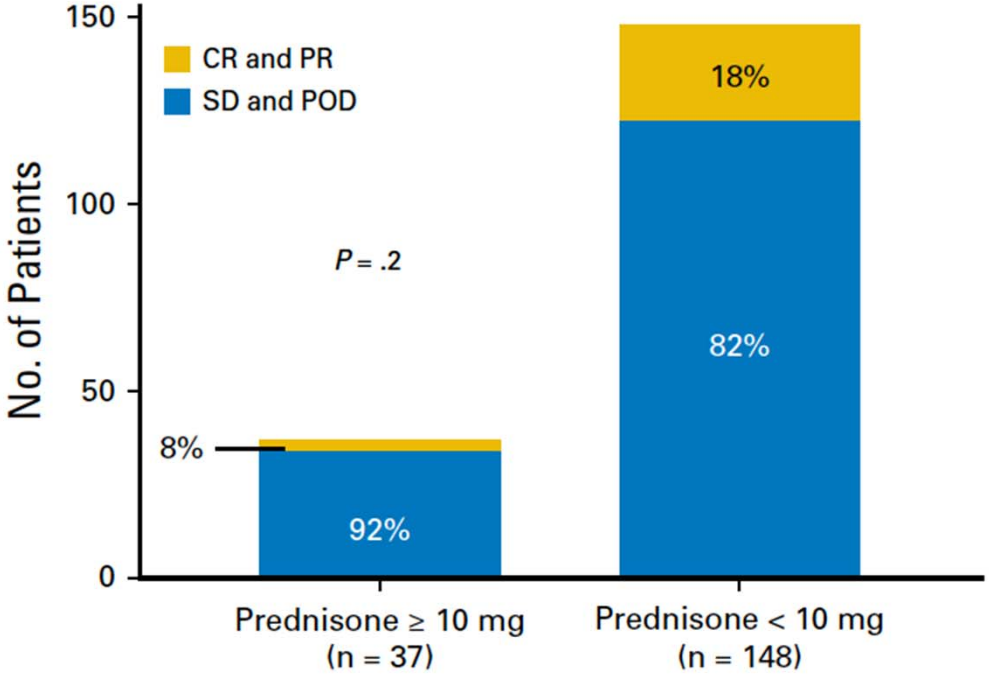
Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

Kathryn C. Arbour, Laura Mezquita, Niamh Long, Hira Rizvi, Edouard Auclin, Andy Ni, Gala Martínez-Bernal, Roberto Ferrara, W. Victoria Lai, Lizza E.L. Hendriks, Joshua K. Sabari, Caroline Caramella, Andrew J. Plodkowski, Darragh Halpenny, Jamie E. Chaft, David Planchard, Gregory J. Riely, Benjamin Besse, and Matthew D. Hellmann

Memorial Sloan Kettering

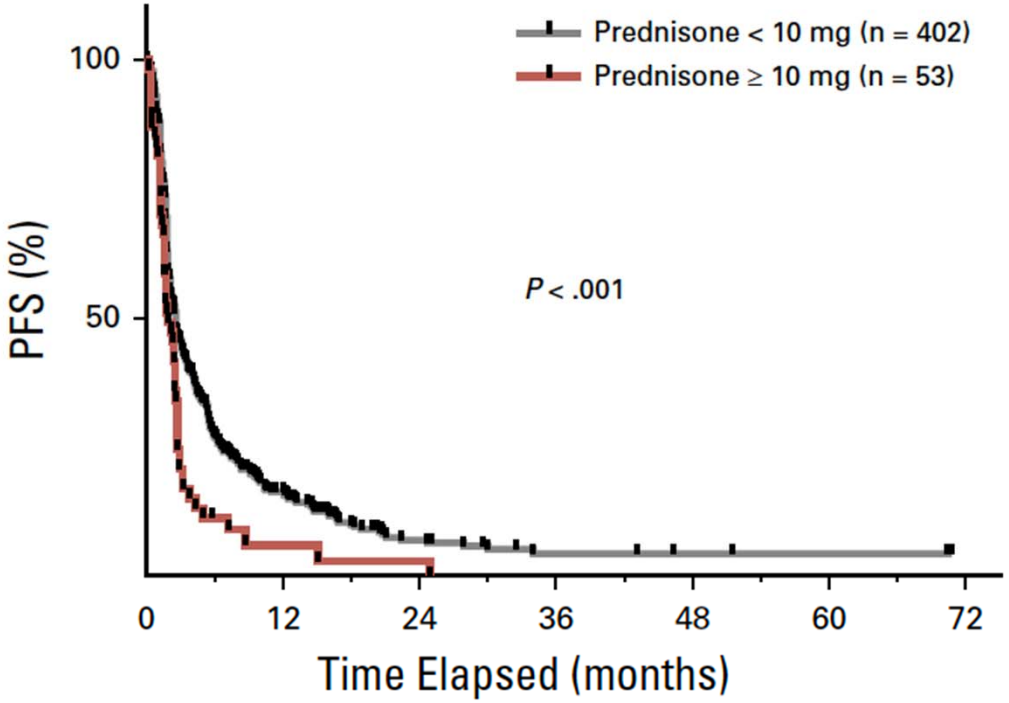


Gustave Roussy



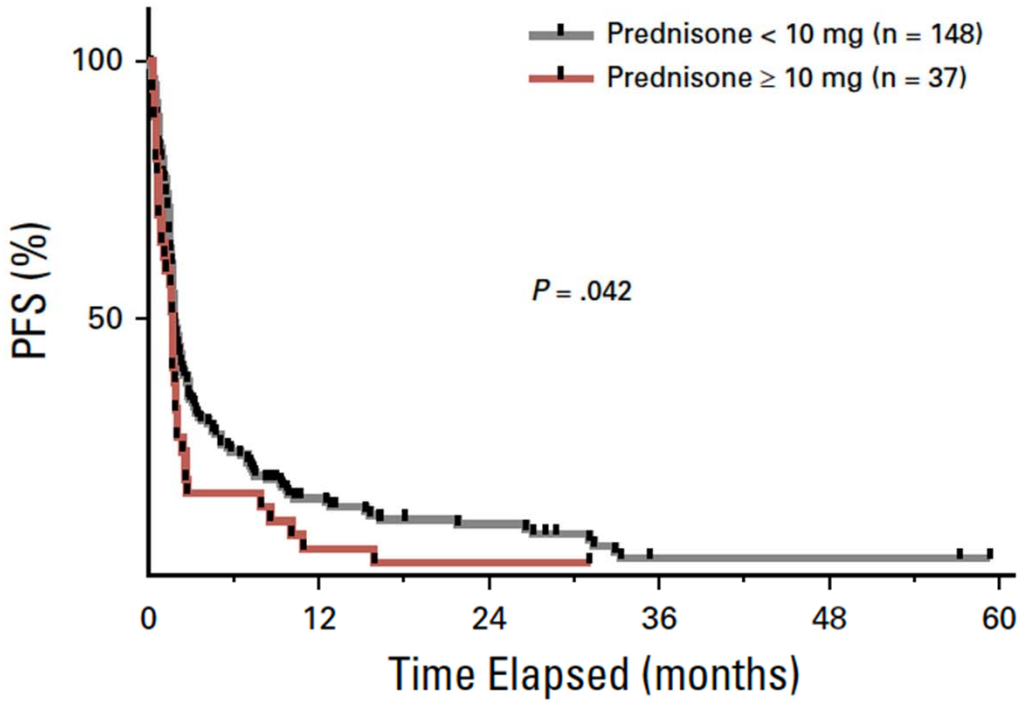
Kathryn C. Arbour .J Clin Oncol 2018; 36

PROGRESSION FREE SURVIVAL



No. at risk:

< 10 mg:	402	50	13	5	3	2	0
≥ 10 mg:	53	2	1	0	0	0	0

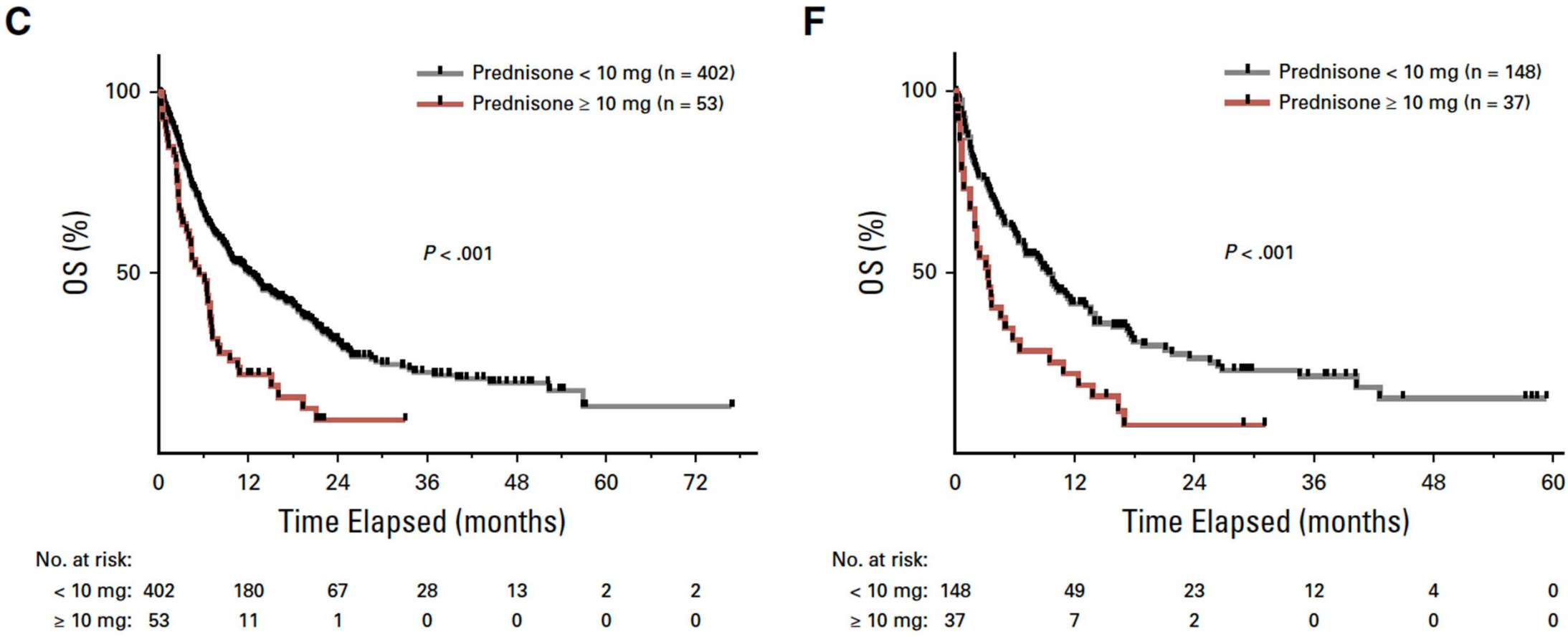


No. at risk:

< 10 mg:	148	19	11	2	2	0	
≥ 10 mg:	37	2	1	0	0	0	

Kathryn C. Arbour .J Clin Oncol 2018; 36

OVERALL SURVIVAL



Kathryn C. Arbour .J Clin Oncol 2018; 36

VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

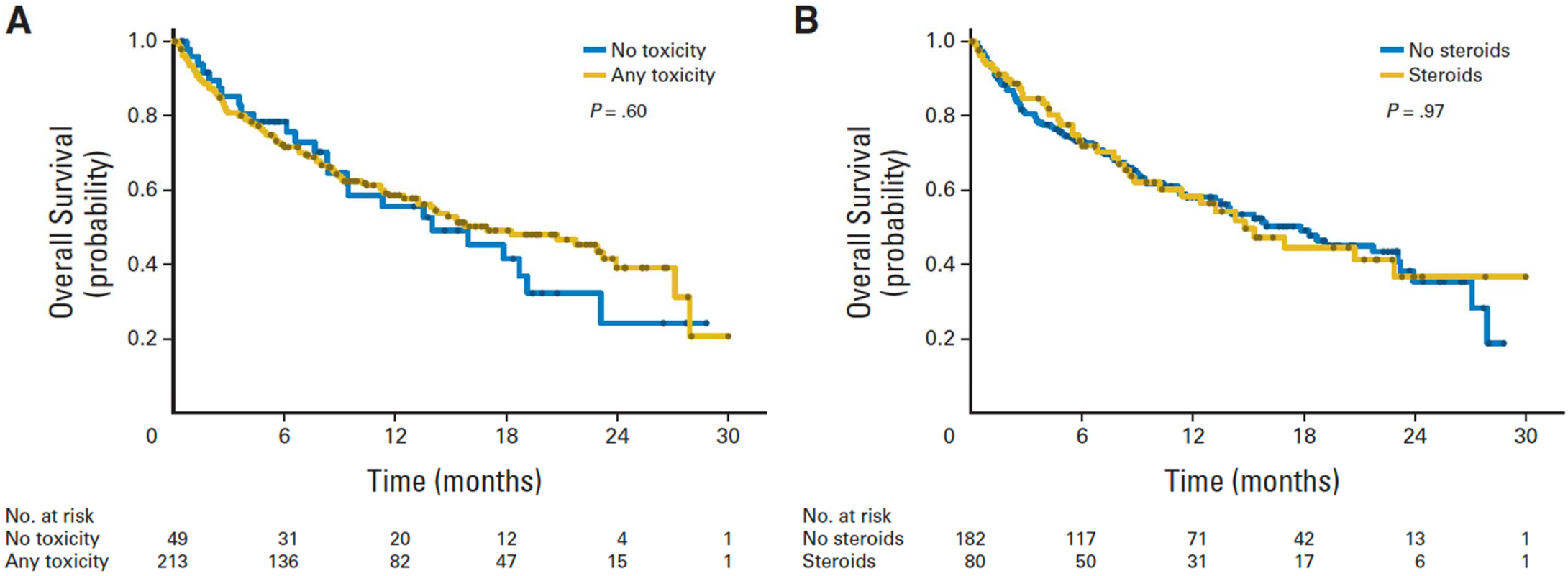
Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center

Troy Z. Horvat, Nelly G. Adel, Thu-Oanh Dang, Parisa Momtaz, Michael A. Postow, Margaret K. Callahan, Richard D. Carvajal, Mark A. Dickson, Sandra P. D'Angelo, Kaitlin M. Woo, Katherine S. Panageas, Jedd D. Wolchok, and Paul B. Chapman

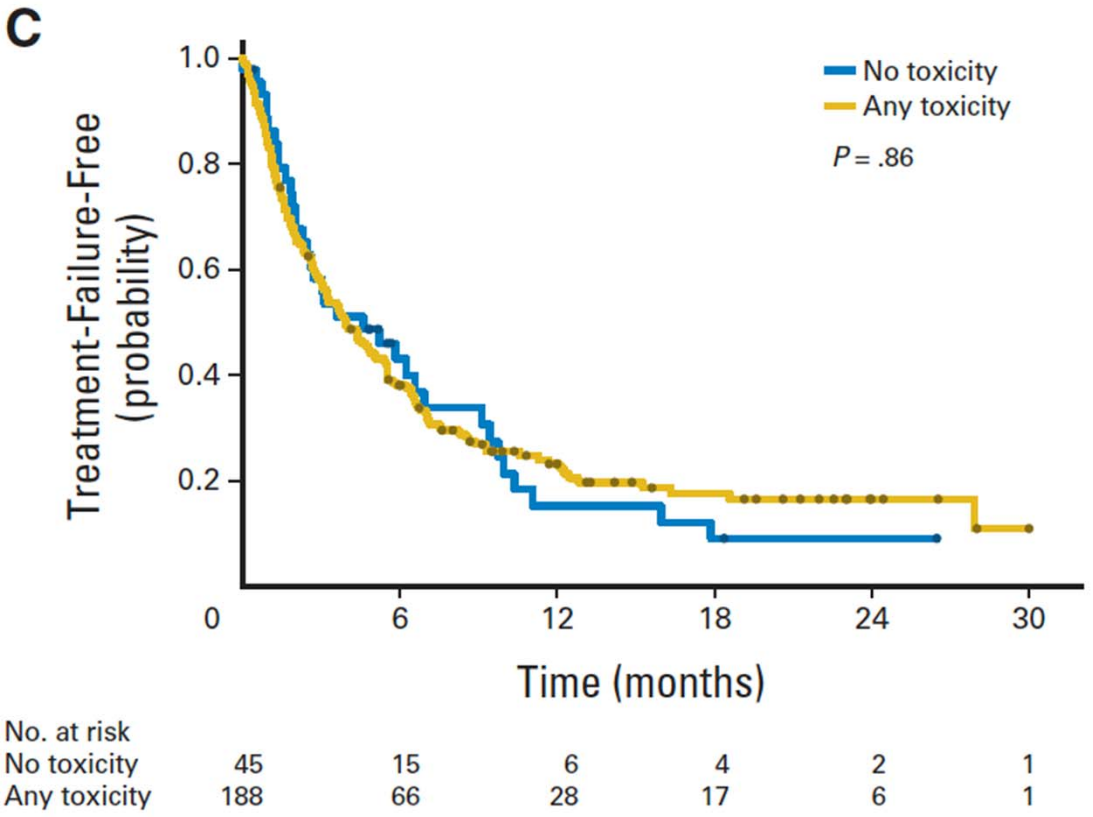
Table 2. irAEs by Grade

irAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hepatotoxicity	135	23	32	7	0	197
Dermatitis	69	36	18	0	0	123
Diarrhea	25	20	29	12	1	87
Hypophysitis	1	6	10	0	0	17
Uveitis	1	5	1	1	0	8
Other	1	6	8	0	0	15
Total*	232	96	98	20	1	447

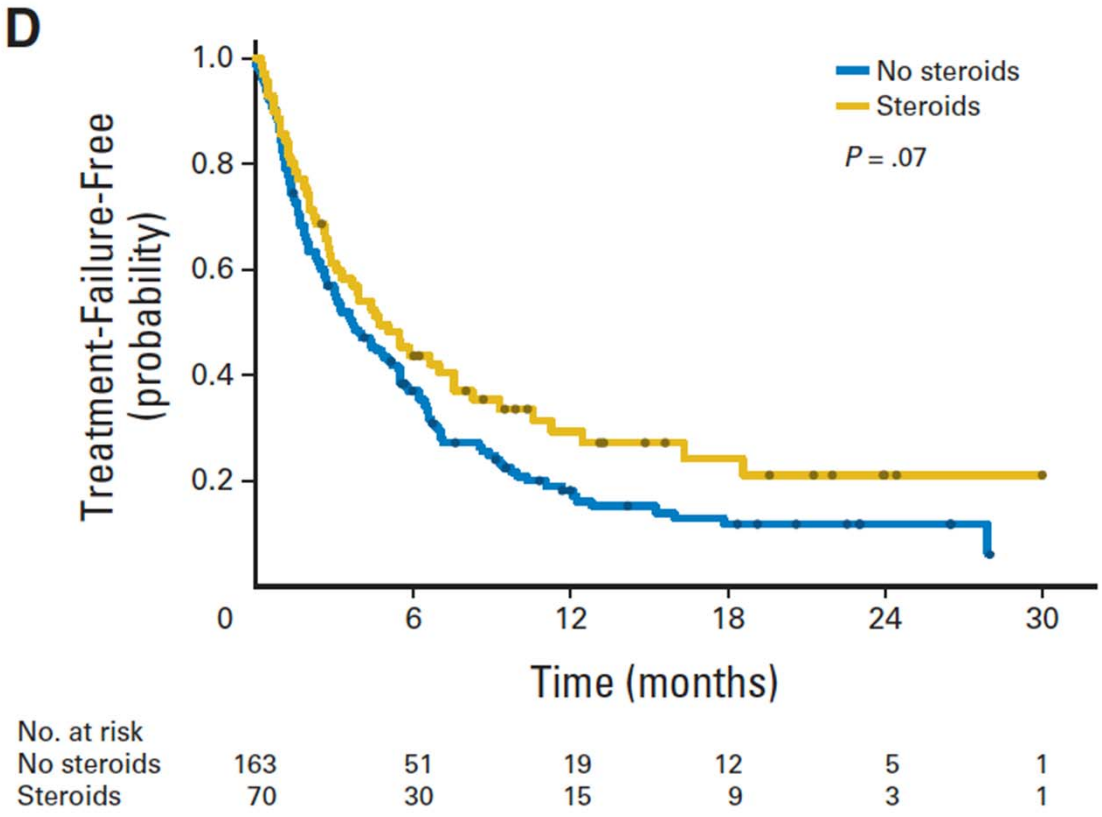
Abbreviation: irAEs, immune-related adverse events.
*Patients could have experienced more than one irAE. Therefore, the total number of irAEs is more than the total number of patients.



Troy Z. Horvat et al. J Clin Oncol 2015; 33:3193-3198



No. at risk						
No toxicity	45	15	6	4	2	1
Any toxicity	188	66	28	17	6	1

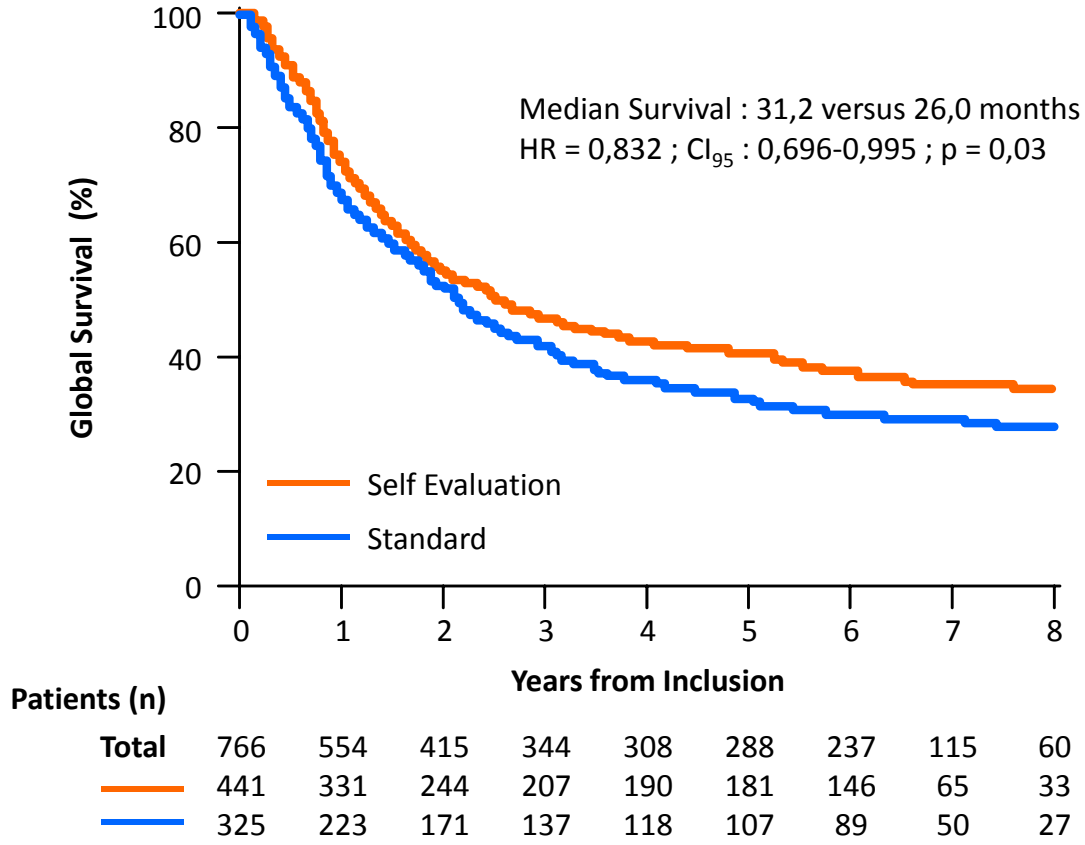


No. at risk						
No steroids	163	51	19	12	5	1
Steroids	70	30	15	9	3	1

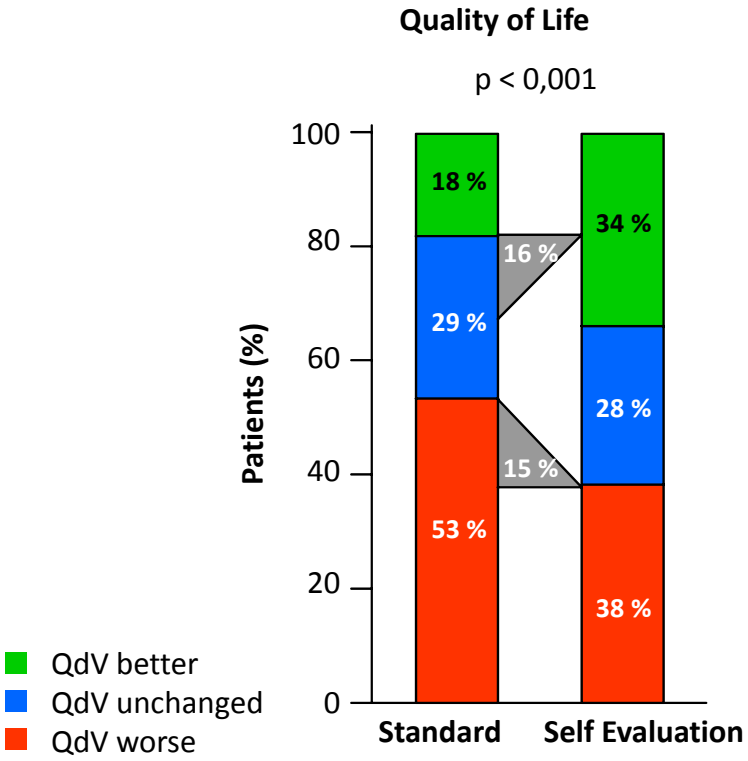
Troy Z. Horvat et al. J Clin Oncol 2015; 33:3193-3198

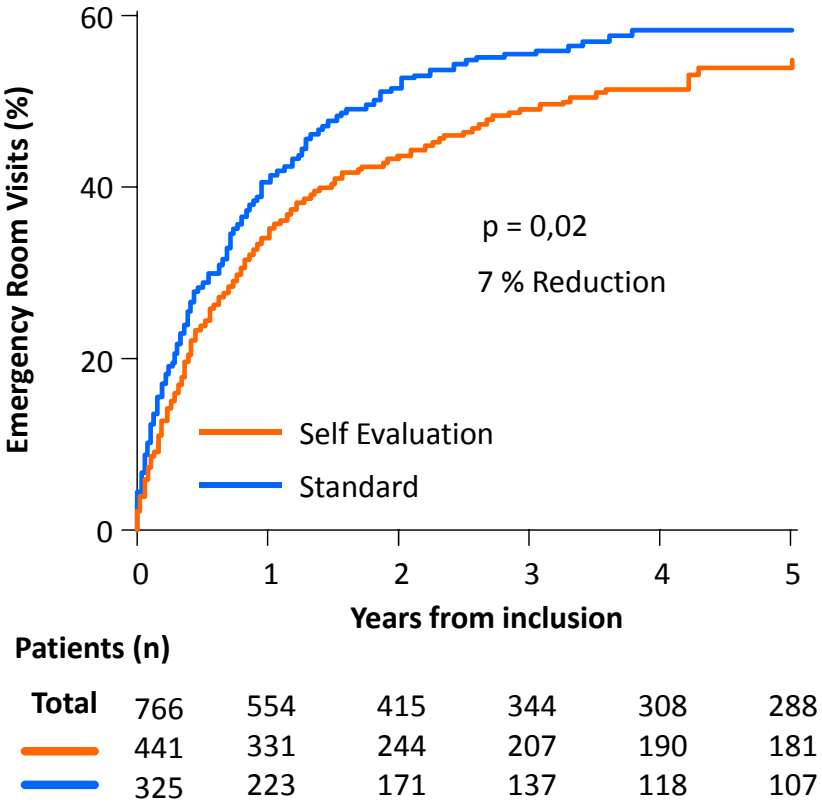
Monitoring Safety

Patient Reported Outcome …



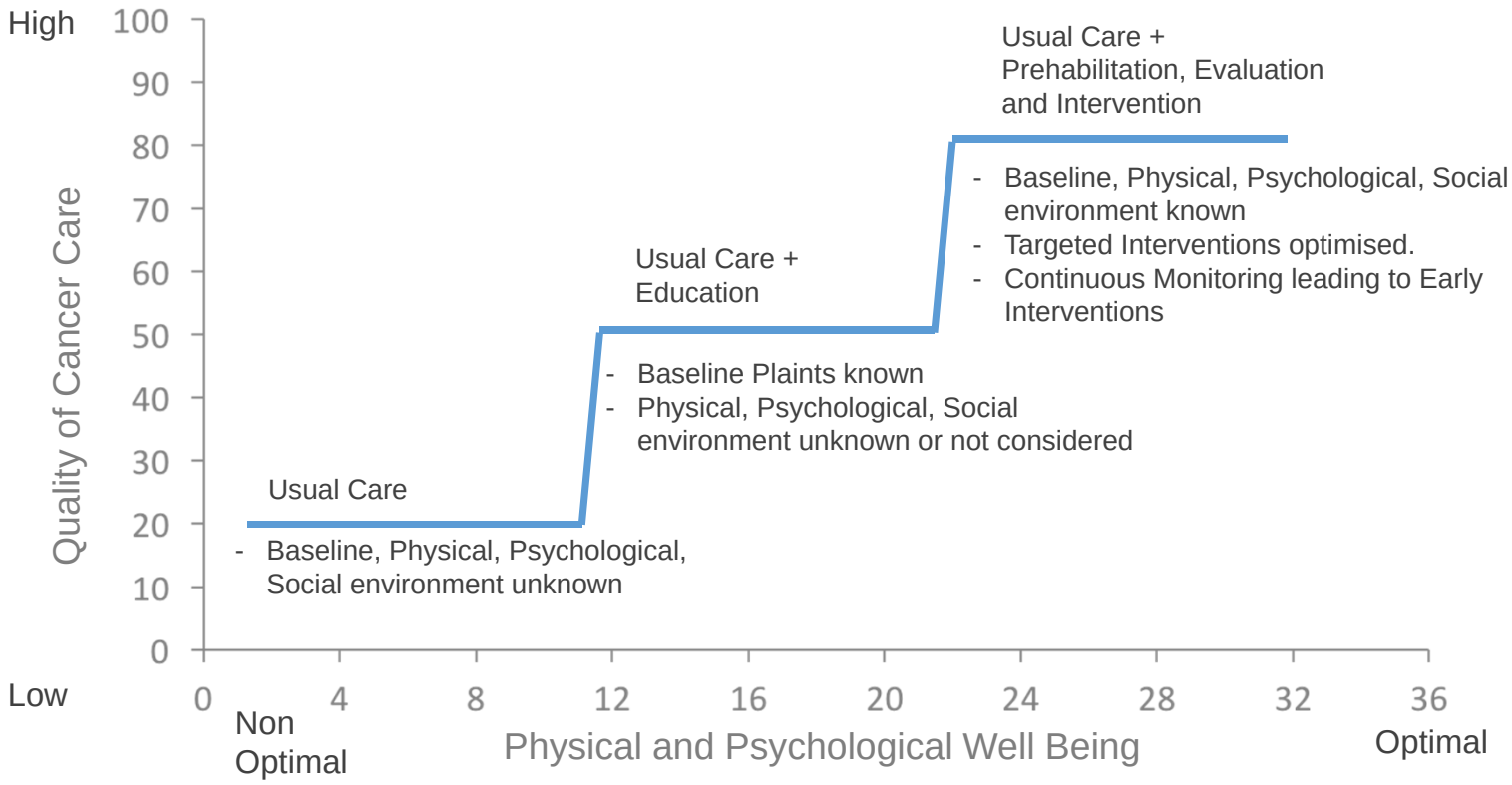
Basch EM et al., ASCO 2017 - abstr. LBA2, / JAMA 2017





Basch EM et al., ASCO 2017 - abstr. LBA2, / JAMA 2017

The way to improve cancer care



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"Supportive care makes excellent cancer care possible"

Dorothy M.K. Keefe,
past-President of MASCC

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