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

Prevention, assessment & management of oral and gastrointestinal mucosal injury; ESMO CPGs

Cancer- and anticancer treatment related diarrhoea & constipation

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GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v139–v151, 2015
doi:10.1093/annonc/mdv202
Published online 4 July 2015

Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up†

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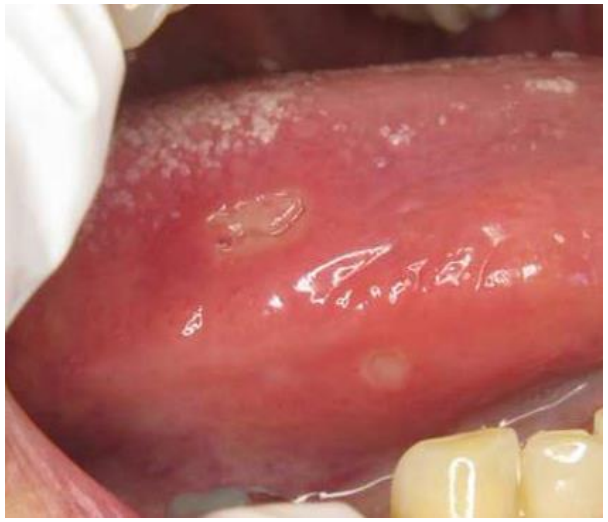
DEFINITIONS:

- Mucositis :
  - inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract
  - resulting from chemotherapeutic agents or ionising radiation.
- Stomatitis:
  - any inflammatory condition of oral tissues
  - Targeted therapies
  - include altered taste, oral sensitivity and pain without oral lesions, and xerostomia
  - mTOR inhibitor-associated stomatitis, specific term (mIAS)

Presentation

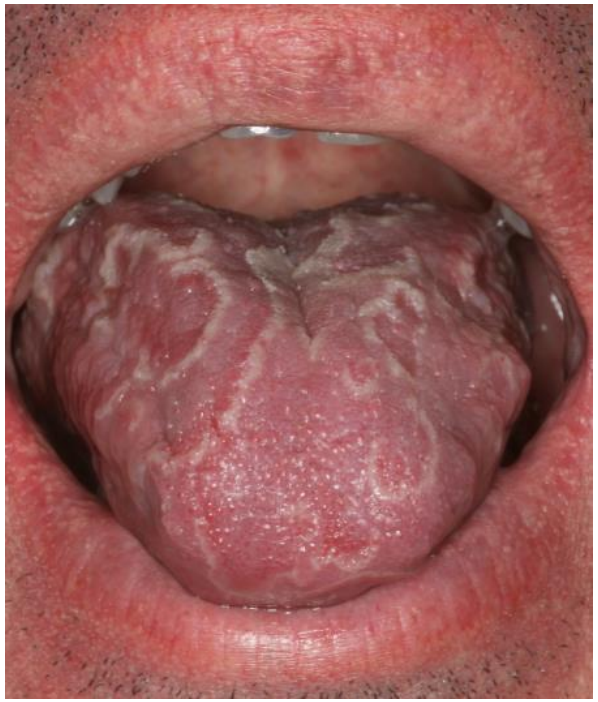
- Stomatitis with Targeted Therapy :
  - bevacizumab, erlotinib, sorafenib, sunitinib (same as CT)
  - mTOR inhibitors 75%



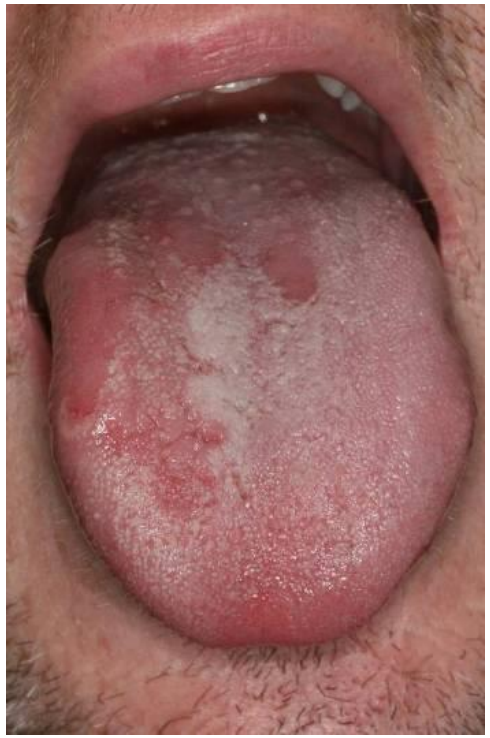
Aphtoide lesion

PRESENTATION

- Stomatitis with Targeted Therapy : antiangiogenics
  - bevacizumab, pazopanib, axitinib, sunitinib
  - mTOR inhibitors 75%



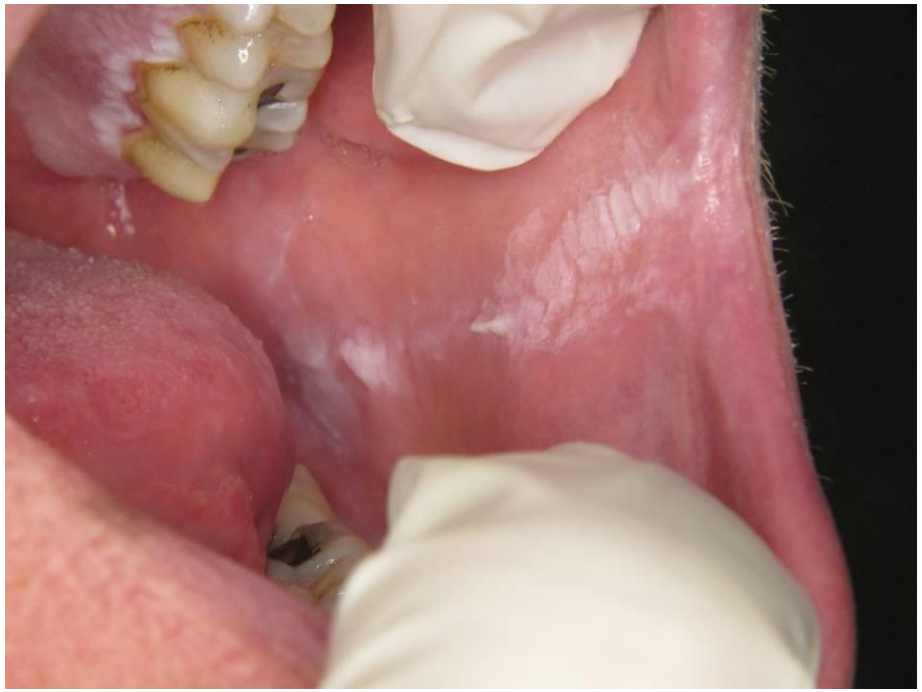
Geographic Tongue



Hubiche T, Valenza B, Chevreau C, Fricain JC, Del Giudice P, Sibaud V. Geographic tongue induced by angiogenesis inhibitors. Oncologist 2013; 18: e16-7.

PRESENTATION

- Stomatitis with BRAF inhibitors



Hyperkeratotic Lesion

Vigarios E, Lamant L, delord JP, Sibaud V. Oral squamous cell carcinoma and hyperkeratotic lesions with BRAF inhibitors Br J Dermatol 2015; 172: 1680-2.

INCIDENCE

- Head Neck Irradiation (60-70 Gy) : 85%
- Haematopoietic stem cell transplantation : 75%
- Chemotherapy : 15 – 25%
  - cyclophosphamide, doxorubicin, vincristine,
  - etoposide, ifosfamide, methotrexate, docetaxel, paclitaxel,
  - cisplatin, carboplatin, oxaliplatin, irinotecan, 5-fluorouracil (5-FU),
  - leucovorin, and vinorelbine.

INCIDENCE

- GI mucositis under targeted therapy :
  - Diarrhea most common side effects of targeted therapy
  - Risk X 2-8 compared to conventional therapy
  - erlotinib, gefitinib, **lapatinib**, sorafenib, sunitinib

Elting LS, Chang YC, Parelkar P et al. Support Care Cancer 2013; 21: 3243–3254.

EVALUATION

- WHO Scale
- NCI-CTCAE

- More useful with targeted therapy :
  - Vanderbilt Head Neck Symptom Survey V2.0 (VHNSS2.0)
  - mIAS scale

- **AND PRO programs !**

EVALUATION - Oral mucositis

WHO Scale :

- Grade 0 = no oral mucositis
- Grade 1 = erythema and soreness
- Grade 2 = ulcers, able to eat solids
- Grade 3 = ulcers, requires liquid diet (due to mucositis)
- Grade 4 = ulcers, alimentation not possible (due to mucositis)

NCI-CTCAE V4.03 :

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					

National Cancer Institute CTCAE; http://evs.nci.nih.gov/ftp1/CTCAE/About.html

EVALUATION - Diarrhea

Boers-Doets and Lalla scale (mIAS) :

Subjective :

- Grade 0 = no oropharyngeal pain attributed to mIAS
- Grade 1 = oropharyngeal pain attributed to mIAS, with average oropharyngeal pain score (over the last 24 h) reported as 2 or less on a 0–10 scale
- Grade 2 = oropharyngeal pain attributed to mIAS, with average oropharyngeal pain score (over the last 24 h) reported as 5 or less on a 0–10 scale
- Grade 3 = oropharyngeal pain attributed to mIAS, with average oropharyngeal pain score (over the last 24 h) reported as 6 or more on a 0–10 scale

Objective :

- Grade 0 = no visible mIAS (i.e. no erythema and no ulceration, attributed to mIAS, in the oropharyngeal area)
- Grade 1 = oral and/or pharyngeal erythema, attributed to mIAS, but no ulceration
- Grade 2 = visible oral and/or pharyngeal ulceration(s), attributed to mIAS, of duration <7 days
- Grade 3 = visible oral and/or pharyngeal ulceration(s), attributed to mIAS, with at least one ulceration persisting for ≥ 7 days

Boers-Doets CB, Lalla RV. Support Care Cancer 2013; 21: S140

EVALUATION - Diarrhea

NCI-CTCAE V4.03 :

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

National Cancer Institute CTCAE; http://evs.nci.nih.gov/ftp1/CTCAE/About.html

EVALUATION - Global

NCI-CTCAE V4.03 :

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Useful with targeted therapy

National Cancer Institute CTCAE; http://evs.nci.nih.gov/ftp1/CTCAE/About.html

PREVENTIVE MEASURES

BASIC ORAL CARE

- Maintenance of optimal nutritional support throughout the entire period of cancer therapy
- Daily oral hygiene routine, including brushing teeth and the gums four times a day with a soft brush and using mouth rinses.

NO RECOMMENDATION

- normal saline, sodium bicarbonate, mixed medication, mouthwash, chlorhexidine

SPECIFIC / TARGETED THERAPY

- saline-containing mouthwashes (higher risk of infection)

Table 1. Example of a Basic Oral Care Protocol (expert opinion)

Two key strategies for mitigation of oral mucosal injury before and during treatment are

- Maintenance of optimal nutritional support throughout the entire period of cancer therapy.
- Developing a daily oral hygiene routine, including brushing teeth and the gums four times a day with a soft brush and using mouth rinses. This approach can contribute to the reduction and, ideally, prevention of oral tissue injury and associated pain, nutritional compromise, and related adverse outcomes.

The following information is presented as a portfolio of patient-based instructions for which health professional guidance is recommended

General measures	• Inspect your oral mucosa daily. • Have your dental team eliminate sources of trauma (e.g. ill-fitting prostheses; fractured teeth). • Lubricate lips with (sterile) vaseline/white paraffin (petrolatum), lip balm, or lip cream. Be aware that vaseline/white paraffin (petrolatum) should not be used chronically on the lips, as this promotes mucosal cell dehydration and is occlusive leading to risk of secondary infection. • Drink ample amount of fluids to keep the mouth moist.
Brushing teeth and gums	• Use a soft toothbrush or swab (as tolerated) after meals and before sleep. Brushing with a soft toothbrush reduces risk of bleeding. Each month you should utilise a new soft toothbrush. • Clean the dentition and gingiva with a mild fluoride-containing, non-foaming toothpaste. • Brush teeth twice a day (after meals and at bedtime) according to the Bass or modified Bass method. If using an electric toothbrush, utilise the techniques cited in the product description instead. • Rinse the brush thoroughly after use with water and store the toothbrush in a cup with the brush head facing upward. • If you are used to do so, clean the area between the teeth once a day. Consult a dental hygienist/dentist about the most appropriate interdental cleaner (floss, toothpick, brushes). In case you are not used to use interdental cleaners on a regular base, do not start with it while on cancer therapy, since it can break the epithelial barrier, visible through gingival bleeding.
Rinse mouth	• Rinse mouth with an alcohol-free mouthwash upon awakening and at least four times a day after brushing, for ~1 min with 15 ml mouthwash; gargle; and then spit out. During the first half hour after rinsing, avoid eating and drinking.
Denture care	• Remove dentures before performing oral care. Brush dentures with toothpaste and rinse with water; clean the gums. • Defer wearing dental prostheses as much as possible until the lining tissues of your mouth are healed. If in the hospital, soak the denture for 10 min in an antimicrobial solution (e.g. chlorhexidine 0.2% if available) before inserting in your mouth.
Avoid painful stimuli	• Smoking • Alcohol • Certain foods such as tomatoes, citrus fruits, hot drinks and spicy, hot, raw, or crusty foods.

ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

PREVENTION

- Bolus 5-fluorouracil chemotherapy: 30 min of oral cryotherapy (II).
- high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy:
  - Recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) (60 µg/kg per day for 3 days before conditioning treatment and for 3 days after transplant) (II).
- Head and neck cancer with moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy:
  - benzydamine mouthwash (I).

ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

TREATMENT

- HSCT conditioned with high-dose chemotherapy, with or without total body irradiation:
  - Low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm2), (II).
- HSCT:
  - controlled analgesia with morphine (II).

ORAL MUCOSITIS - GUIDELINES

SUGGESTION IN FAVOR OF AN INTERVENTION

PREVENTION

- All age groups and across all cancer treatment modalities :
  - Oral care protocols (III).
- High-dose melphalan, with or without total body irradiation, as conditioning for HSCT :
  - Oral cryotherapy (III).
- Radiotherapy, without concomitant chemotherapy, for head and neck cancer :
  - Low-level laser therapy (wavelength ~632.8 nm) (III).
- Oral cancer patients receiving radiation therapy or chemoradiation :
  - Systemic zinc supplements administered orally (III).

ORAL MUCOSITIS - GUIDELINES

SUGGESTION IN FAVOR OF AN INTERVENTION

TREATMENT

- Conventional or high-dose chemotherapy, with or without total body irradiation :
  - Transdermal fentanyl to treat pain (III).
- Chemoradiation therapy for head and neck cancer :
  - 0.2% morphine mouthwash to treat pain (III).
- Pain due to oral mucositis :
  - 0.5% doxepin mouthwash (IV).

ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS AGAINST AN INTERVENTION

PREVENTION not be used

- Radiation therapy for head and neck cancer :
  - PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste (II).
- High-dose chemotherapy, with or without total body irradiation, for HSCT or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer :
  - Iseganan antimicrobial mouthwash (II),
- Chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head and neck cancer :
  - Sucralfate mouthwash

ORAL MUCOSITIS - GUIDELINES

RECOMMENDATIONS AGAINST AN INTERVENTION

TREATMENT not be used

- Chemotherapy for cancer (I), or radiation therapy (II) for head and neck cancer :
  - sucralfate mouthwash.

ORAL MUCOSITIS - GUIDELINES

SUGGESTIONS AGAINST AN INTERVENTION

PREVENTION not be used

- Radiation therapy for head and neck cancer:
  - Chlorhexidine mouthwash (III).
- High-dose chemotherapy, for autologous or allogeneic stem cell transplantation :
  - Granulocyte–macrophage colony-stimulating factor (GM-CSF) mouthwash (II).
- Radiation therapy for head and neck cancer :
  - Misoprostol mouthwash (III).
- Bone marrow transplantation :
  - Systemic pentoxifylline, administered orally, (III).
- Radiation therapy for head and neck cancer (III), or in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II):
  - Systemic pilocarpine, administered orally,

ORAL MUCOSITIS - GUIDELINES

SUGGESTIONS AGAINST AN INTERVENTION

TREATMENT not be used

- Chemotherapy for cancer (I), or radiation therapy (II) for head and neck cancer :
  - sucralfate mouthwash.

GI MUCOSITIS - GUIDELINES

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

PREVENTION

- Radiation therapy :
  - i.v. amifostine be used, at a dose of ≥340 mg/m2, to prevent radiation proctitis (II).

GI MUCOSITIS - GUIDELINES

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION

TREATMENT

- Standard- or high-dose chemotherapy associated with HSCT, if loperamide is ineffective :
  - Octreotide, at a dose of ≥100 µg s.c. twice daily, be used to treat diarrhea induced (II).

GI MUCOSITIS - GUIDELINES

SUGGESTION IN FAVOR OF AN INTERVENTION

PREVENTION

- Concomitant chemotherapy and radiation therapy in patients with nonsmall-cell lung carcinoma :
  - i.v. amifostine be used to prevent esophagitis (III).
- Radiation therapy to the pelvis :
  - Systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to prevent radiation-induced enteropathy (II).
- Chemotherapy and/or radiation therapy for a pelvic malignancy :
  - Probiotics containing Lactobacillus species be used to prevent diarrhea (III).

GI MUCOSITIS - GUIDELINES

SUGGESTION IN FAVOR OF AN INTERVENTION

TREATMENT

- Rectal bleeding :
  - Sucralfate enemas be used to treat chronic radiation-induced proctitis (III).
- Radiation therapy for a solid tumor :
  - Hyperbaric oxygen be used to treat radiation-induced proctitis (IV).

GI MUCOSITIS - GUIDELINES

RECOMMENDATIONS AGAINST AN INTERVENTION

PREVENTION not be used

- Radiation therapy for a pelvic malignancy :
  - 5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, not be used to prevent acute radiation-induced diarrhea (I).
- Radiation therapy for prostate cancer :
  - Misoprostol suppositories not be used to prevent acute radiation-induced proctitis (I).

GI MUCOSITIS - GUIDELINES

RECOMMENDATIONS AGAINST AN INTERVENTION

TREATMENT not be used

- Radiation therapy for a solid tumor :
  - Systemic sucralfate, administered orally, not be used to treat gastrointestinal mucositis (I).

GI MUCOSITIS - GUIDELINES

SUGGESTIONS AGAINST AN INTERVENTION

PREVENTION not be used

- NONE

DIARRHEA - TREATMENT

- **UNCOMPLICATED**:
  - Grade 1-2 with no complications
- **COMPLICATED**:
  - Grade 3-4 with one or more complicating signs or symptoms
- **EARLY ONSET** : < 24h after administration
- **LATE ONSET** : > 24h after administration
- **NON PERSISTENT** : present for < 4 weeks
- **PERSISTENT** : present for > 4 weeks

DIARRHEA - TREATMENTS

- Hygieno – dietetics rules
- Loperamide :
  - Non analgesic agonist μ opioid receptor
  - Standard first line therapy for CID
- Octreotide:
  - Synthetic somatostatin analog that promote absorption (inhibits specific gut hormone to increase intestinal transit time)
  - Indicated in loperamide refractory diarrhea after 48 h.
- Deodorised tincture of opium
  - Similar to loperamide (no litterature support)
  - Contains 10 mg/ml of morphine

McQuade et al. Frontiers in Pharmacology 2016; 7
Stein A et al. *Ther Adv.Med.Oncol. 2010;* 2, 51–63

DIARRHEA - NCCN

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Palliative Care

NCCN Guidelines Index
Palliative Care TOC
Discussion

DIARRHEA

ESTIMATED LIFE EXPECTANCY

Years

Year to months

Months to weeks

SCREENING

Determine Diarrhea Grade[m] (Increase over Baseline)

- Grade 1: Increase of <4 stools/day over baseline; mild increase in ostomy output compared with baseline
- Grade 2: Increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared with baseline
- Grade 3: Increase of >7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care; interferes with ADLs
- Grade 4: Life-threatening consequences; urgent intervention indicated

→

ASSESSMENT

Provide immediate antidiarrheal therapy indicated by grade.
- If chemotherapy induced, decrease or delay the next dose of chemotherapy

Assess for cause:
- Recent antibiotic use
- Chemotherapy regimen side effects
- Drugs that frequently induce diarrhea
- Dietary changes
- Infection
  - Screen for C. diff
- If fecal impaction is suspected:
  - Confirm with rectal examination or x-ray,
  - Premedicate patient with opiods or anxiolytics,
  - Treat with digital disimpaction, and
  - Administer enemas until clear

→ See Anti-Diarrheal Interventions, Grades 1-4 (PAL-19)

ANTIDIARRHEAL INTERVENTIONS

ESTIMATED LIFE EXPECTANCY	SCREENING	INTERVENTION
Years	GRADE 1 →	• Provide oral hydration and electrolyte replacement • Initiate antidiarrheal: ▸ Loperamide 4 mg PO x 1, then 2 mg PO after each loose stool, up to 16 mg/d • If patient not already on opioids: ▸ Diphenoxylate/atropine 1–2 tabs PO q 6 h PRN, Maximum 8 tabs/d • Bland/BRAT diet (Bananas, Rice, Applesauce, Toast) • Continue oral hydration and electrolyte replacement • If chemotherapy-induced: ▸ Decrease dose or discontinue chemotherapy
Year to months Months to weeks	GRADE 2 →	• Provide IV fluids if patient is unable to tolerate oral fluids • Initiate/continue antidiarrheal--as above • Bland/BRAT diet (Bananas, Rice, Applesauce, Toast) • Continue oral hydration and electrolyte replacement • Consider anticholinergic agents ▸ Hyoscyamine 0.125 mg PO/ODT/SL q 4 h PRN, Max: 1.5 mg/d ▸ Atropine 0.5–1 mg subcut; IM; IV; SL q 4–6 h prn • If infection-induced (C. diff): ▸ Metronidazole 500 mg PO/IV QID x 10–14 days ▸ Vancomycin 125–500 mg PO QID x 10–14 days • If infection-induced and not C.diff ▸ Treat with appropriate antibiotics • If chemotherapy-induced: ▸ Delay or discontinue chemotherapy • If ipilimumab-related diarrhea, consider ▸ Corticosteroids for 0.1–1 mg/kg/d ▸ Infliximab 5 mg/kg q 2–6 weeks
	Persistent GRADES 2, 3, 4 →	Inpatient hospitalization (intensive care for Grade 4) • Provide IV fluids and use antidiarrheal agents and anticholinergics as mentioned above • Consider Octreotide 100–500 mcg/d subcut or IV, q 8 h or by continuous infusion
Weeks to days (Dying patient) →		• Ensure that the above interventions are consistent with the goals of care • Consider IV hydration at home • Start on around-the-clock opioids or increase dose of current opioid • Consider Scopolamine 0.4 mg subcut every 4 h prn • Consider Octreotide 100–200 microgram subcut q 8 h • Consider glycopyrrolate 0.2–0.4 mg IV q 4 h prn

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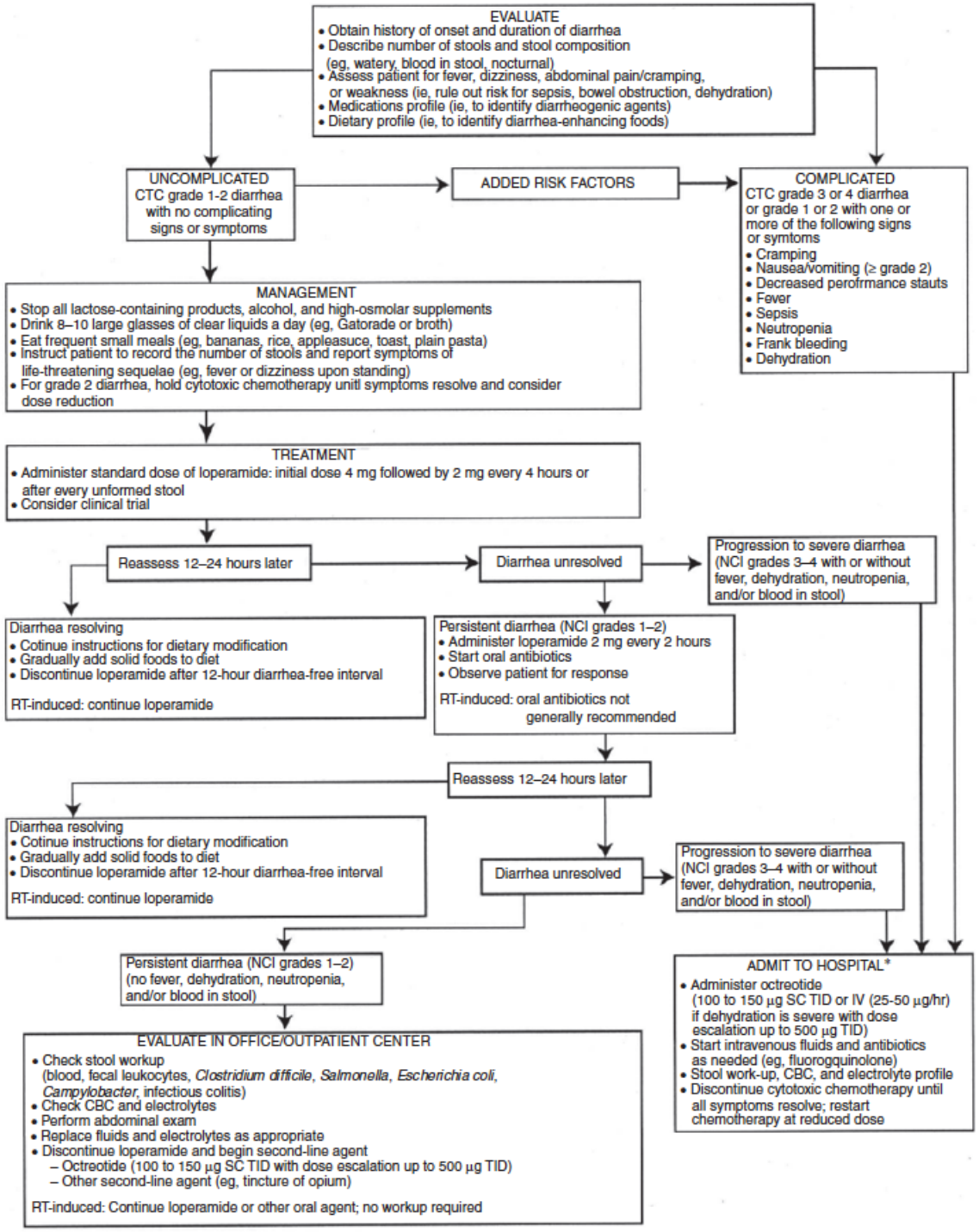
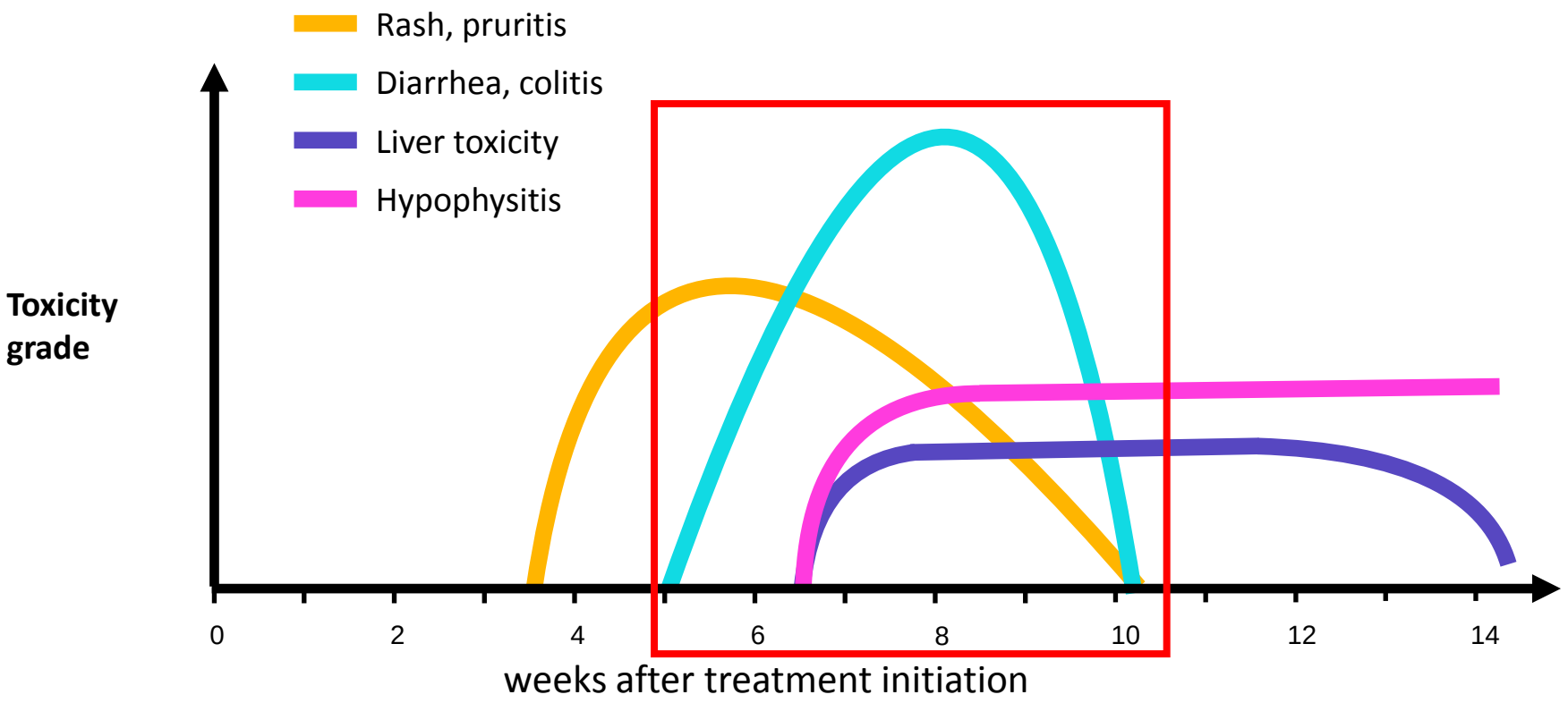


Stein A. Et al. Ther Adv Med Oncol. 2010; 2(1) 5163

IMMUNOTHERAPY SPECIFICITIES

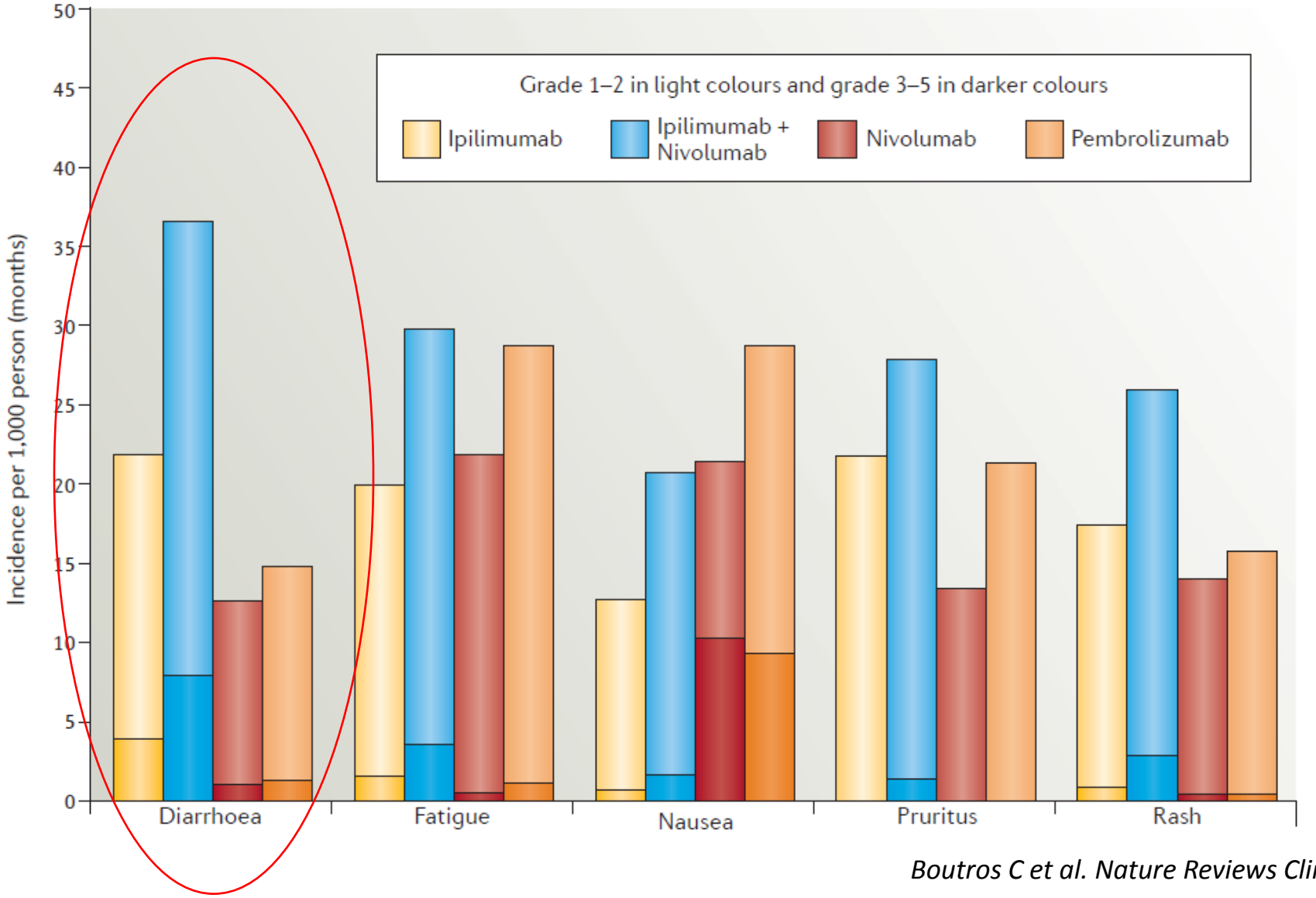
Kinetics of appearance of immune-related adverse events



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

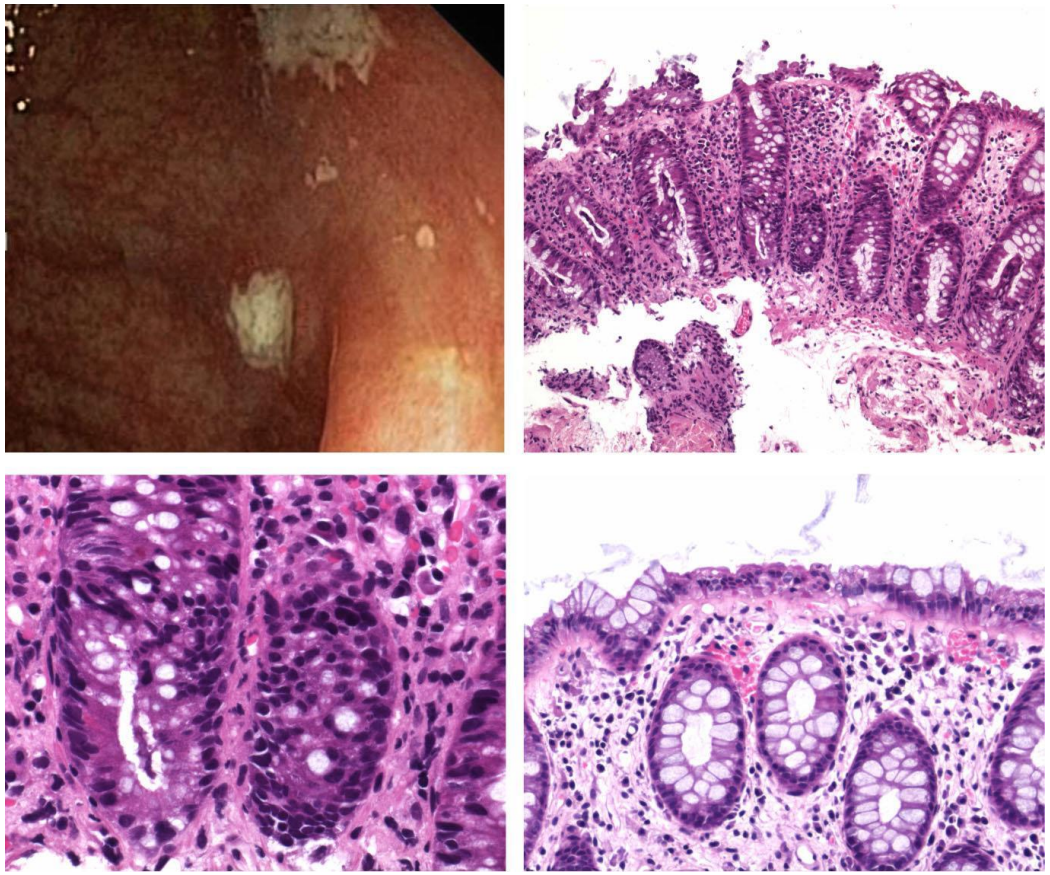
IMMUNOTHERAPY SPECIFICITIES

Inform patients of the most frequent toxicities



Boutros C et al. Nature Reviews Clinical Oncology 2016

IMMUNOTHERAPY SPECIFICITIES



A) Colonoscopy: patches of ulcerated mucosa in sigmoid colon;
B) Active colonic inflammation, with an inflammatory cell infiltrate in lamina propria, crypt injury, and surface erosion;
C,D) Crypt injury and surface regeneration;

Cheng R et al. Ipilimumab-induced toxicities and the gastroenterologist. Journal of Gastroenterology and Hepatology30 (2015) 657–666

IMMUNOTHERAPY SPECIFICITIES

Grade	Toxicity Management
Any	◆Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) ◆Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) ◆Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event ◆Use analgesics carefully; they can mask symptoms of perforation and peritonitis

	Grade				
Adverse Event	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

IMMUNOTHERAPY SPECIFICITIES

Grade	Dose Modification	Toxicity Management
1	No dose modification	◆ Close monitoring for worsening symptoms ◆ Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.

	Grade				
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Definition: A disorder characterized by frequent and watery bowel movements.					

IMMUNOTHERAPY SPECIFICITIES

Grade	Dose Modification	Toxicity Management
2	◆Hold study drug/study regimen until resolution to ≤ Grade 1 ◆If toxicity worsens then treat as Grade 3 or Grade 4 ◆If toxicity improves to baseline then treat at next scheduled treatment date	◆Consider symptomatic treatment (hydration, electrolyte replacement, dietary changes, and loperamide and/or budesonide ◆Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent ◆If not responsive within 3-5 days or worsens: ✓ GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation; ✓ Prompt treatment with IV methylprednisolone 2-4mg/kg/day started. ◆If still no improvement within 3-5 days, promptly start immunosuppressives (infliximab at 5mg/kg once every 2 weeks). Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab ◆Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment

	Grade				
Adverse Event	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
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Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

IMMUNOTHERAPY SPECIFICITIES

Grade	Dose Modification	Toxicity Management
3 or 4	Permanently discontinue study drug/study regimen	◆Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent ◆Monitor stool frequency and volume and maintain hydration ◆Urgent GI consult and imaging and/or colonoscopy as appropriate ◆If still no improvement within 3-5 days of IV methylprednisolone 1 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (infliximab at 5mg/kg once every 2 weeks). ◆Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. ◆Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment

	Grade				
Adverse Event	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

IMMUNOTHERAPY SPECIFICITIES

Patient card

Name, Family name:
Immunotherapy drug(s):
I am currently receiving an immunotherapy which may increase the risk of occurrence of autoimmune diseases and in particular:

- pneumonitis (inflammation of the lungs)
- colitis (inflammation of the gut)
- hepatitis (inflammation of the liver)
- nephritis (inflammation of the kidneys)
- endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,… **The management of these dysimmune adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team which has prescribed the treatment:**

Prescriber Contact Information

Medical information letter

Dear Colleague,

Mr/Mrs *Name, Family name*:

has been put under the following Immunotherapy drug(s):

.
.

I wanted to raise your attention on the fact that this immunotherapy may increase the risk of occurrence of autoimmune symptoms such as:

- ✓ pneumonitis (inflammation of the lungs)
- ✓ colitis (inflammation of the gut)
- ✓ hepatitis (inflammation of the liver)
- ✓ nephritis (inflammation of the kidneys)
- ✓ endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- ✓ cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,…

The management of these dysimmune toxicities requires specific care and can be organ or life threatening. It absolutely necessitates coordination with the health care team which has prescribed the therapy.

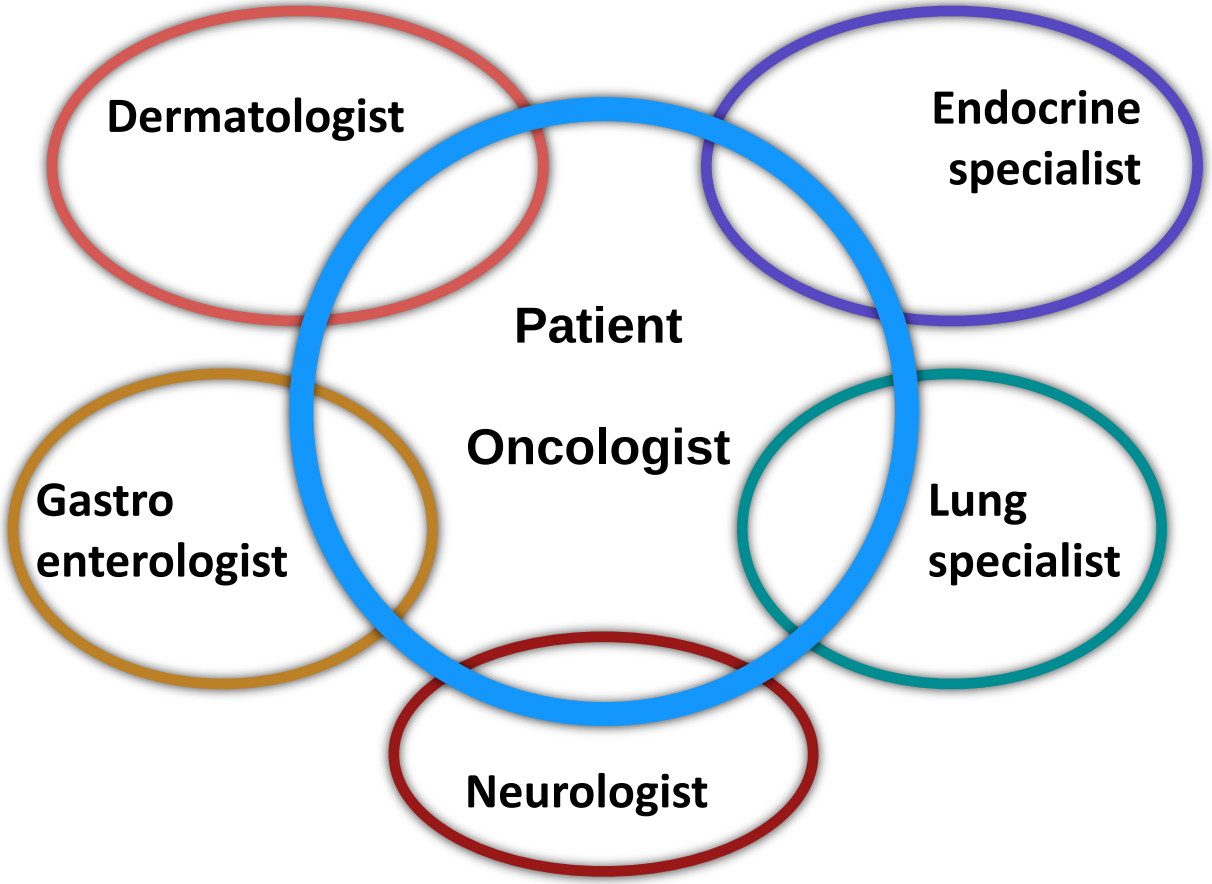
Please contact the following contact for any further information you may need or in case of emergence of symptoms which may be related to an organ inflammation:

Prescriber ID:
Contact information :

IMMUNOTHERAPY SPECIFICITIES

Define **your** dream team

A Multidisciplinary Approach



Home Care monitoring and management

PRO programs

IMMUNOTHERAPY SPECIFICITIES

Application mobile Gustave Roussy

IMMUNOTHERAPIE

Disponible sur App Store

Available on the Android App Store

Une aide au diagnostic et à la prise en charge des toxicités des immunothérapies

Actualité publications sur les toxicités des immunothérapies :

@iTOXreport

stephane.champiat@gustaveroussy.fr

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

CONSTIPATION

ETIOLOGY

- Mechanical :
  - GI cancer
  - External Obstruction
  - Peritoneal Carcinosis
- Neurological :
  - Medullar disorders
- **Iatrogenic** :
- Psychological
  - History of transit / anxiety / depression
- Metabolic disorders:
  - Hypokaliemia, hypercalcemia
  - Hypothyroidism
- Pain – Fatigue - EOL

- Opioids
- Antiemetics and other supportive treatment
- Antidepressant, antiepileptics
- Iron
- Chemotherapy
  - Vinorelbin…
  - Taxanes
  - Temozolomide
  - Thalidomide
  - Platinum salts

EVALUATION

NCI-CTCAE V4.03 :

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.					

National Cancer Institute CTCAE; http://evs.nci.nih.gov/ftp1/CTCAE/About.html

CONSTIPATION

ESTIMATED LIFE EXPECTANCY

- Years
- Year to months
- Months to weeks
- Weeks to days (Dying patient)

INTERVENTIONS

Preventive measures
- Increase fluids
- Increase dietary fiber if patient has adequate fluid intake and physical activity
- Exercise, if appropriate
- Administer prophylactic medications
  - Stimulant laxative ± stool softener (senna ± docusate, 2 tablets every night)
  - Increase dose of laxative ± stool softener (senna ± docusate, 2–3 tablets BID-TID) with goal of 1 non-forced BM every 1–2 days

If constipation is present:
- Assess for cause and severity of constipation
  - Discontinue any non-essential constipating medication
- Rule out impaction, especially if diarrhea accompanies constipation (overflow around impaction)
- Rule out obstruction (physical exam, abdominal x-ray/consider GI consult)
- Treat other causes (eg, hypercalcemia, hypokalemia, hypothyroidism, diabetes mellitus, medications)
- Add and titrate bisacodyl 10–15 mg daily-TID with a goal of 1 non-forced bowel movement (BM) every 1–2 days

If impacted:
- Administer glycerine suppository ± mineral oil retention enema
- Perform manual disimpaction following pre-medication with analgesic ± anxiolytic

If constipation persists:
- Reassess for cause and severity of constipation
- Recheck for impaction or obstruction
- Consider adding other laxatives, such as bisacodyl suppository (one rectally daily-BID); polyethelene glycol (1 capful/8 oz water BID); lactulose, 30–60 mL BID-QID; sorbitol, 30 mL every 2 h x 3, then prn; magnesium hydroxide, 30–60 mL daily-BID; or magnesium citrate, 8 oz daily
- Consider methylnaltrexone for opioid-induced constipation, except for post-op ileus and mechanical bowel obstruction, 0.15 mg/kg subcut every other day, no more than once a day
- Administer tap water enema until clear
- Consider use of a prokinetic agent (eg, metoclopramide, 10–20 mg PO QID)

REASSESSMENT

Acceptable:
- Adequate constipation symptom management
- Reduction of patient/family distress
- Acceptable sense of control
- Relief of caregiver burden
- Strengthened relationships
- Optimized quality of life

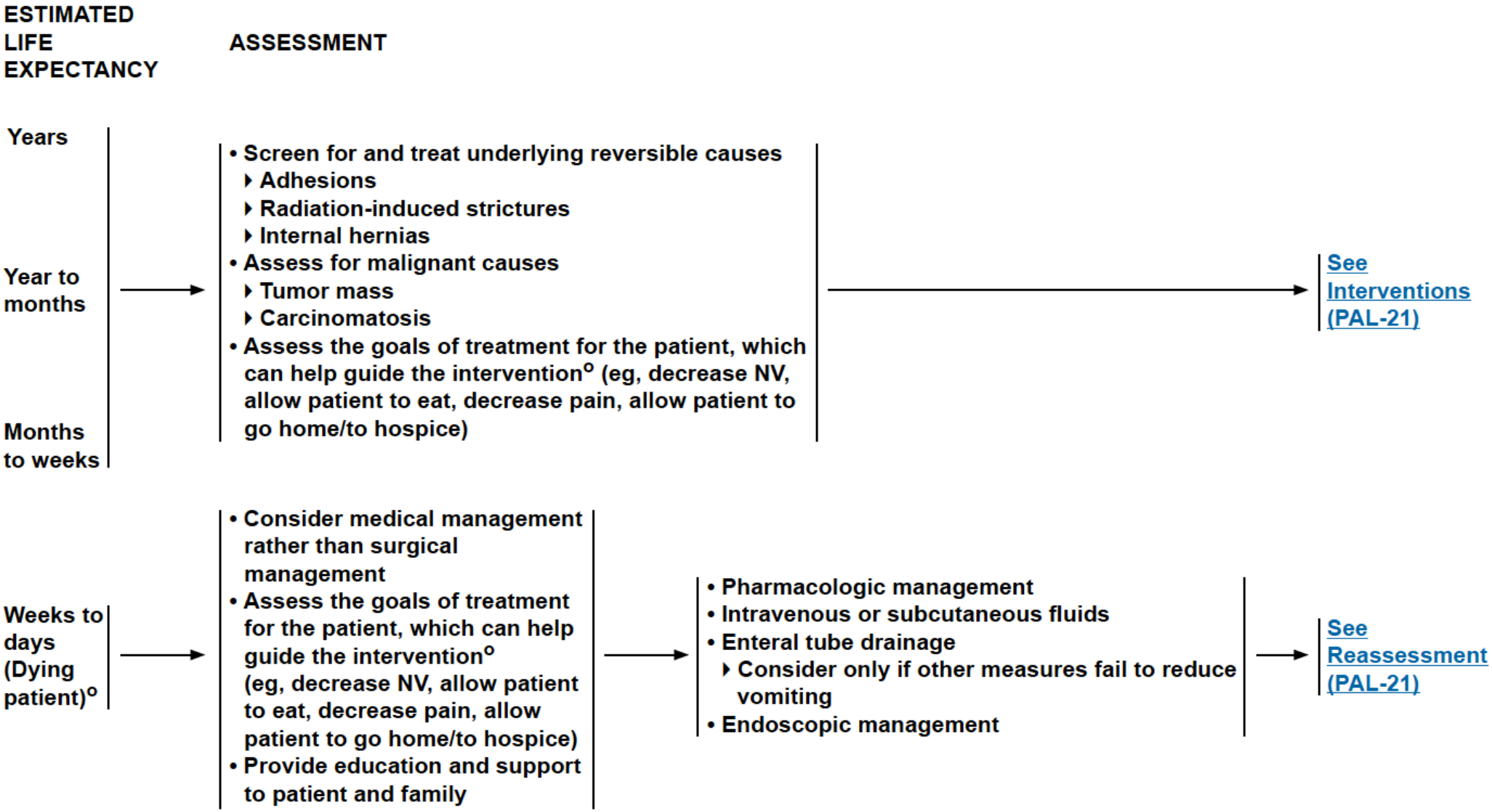
→ Continue to treat and monitor symptoms and quality of life

→ Ongoing reassessment

Unacceptable →
- Intensify palliative care interventions
- Consult or refer to specialized palliative care services or hospice

→ Ongoing reassessment

MALIGNANT BOWEL OBSTRUCTION[n]



OPIOID INDUCED CONSTIPATION

- Incidence 50 - 87% in terminally ill patients
- μ -receptors widely distributed ileum, stomach proximal colon
  - Control of fluid and electrolyte transport
  - Motility
- First laxative
- Second selective μ - opioid receptors antagonists

→ Methylnaltrexone
Naldemedine

(Abernethy et al., 2009; Abramowitz et al., 2013)

GENERAL INTERVENTIONS

- Physical Activity
- Fluid Intake
- Fiber Consumption
- Privacy and convenience during defecation
- Iatrogenic impact limitation

(Mancini and Bruera, 1998)

LAXATIVES

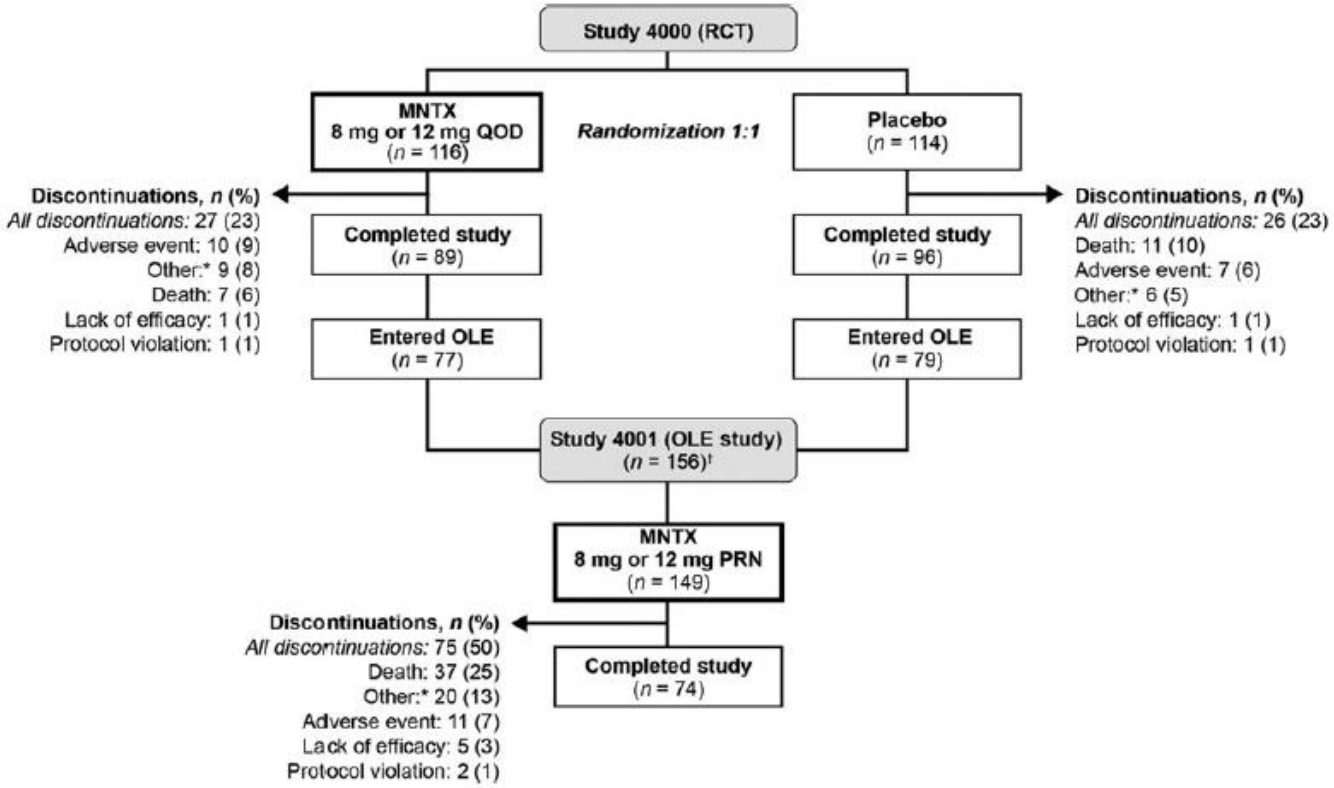
- Bulk Forming Laxatives : promote GI evacuation
  - Delayed action, risk of obstruction aggravation : not ideal in cancer patients
- Osmotic Laxatives : attract and retain fluid
  - Lactulose, sorbitol, polyethylene glycol
  - Action 24h – 72h, risk og metabolic complication, pain, dyscomfort
- Emollient Laxatives : stool softeners
  - Action 24-48h ; liver caution
- Stimulant Laxatives : stimulate myenteric neurons to increase peristalsis
  - Senna, Cascara, Castor oil, phenolphtaleine
- Lubricant Laxatives
- Rectal Laxatives

Methylnaltrexone

JOURNAL OF PALLIATIVE MEDICINE
Volume 18, Number 7, 2015
Mary Ann Liebert, Inc.
DOI: 10.1089/jpm.2014.0362

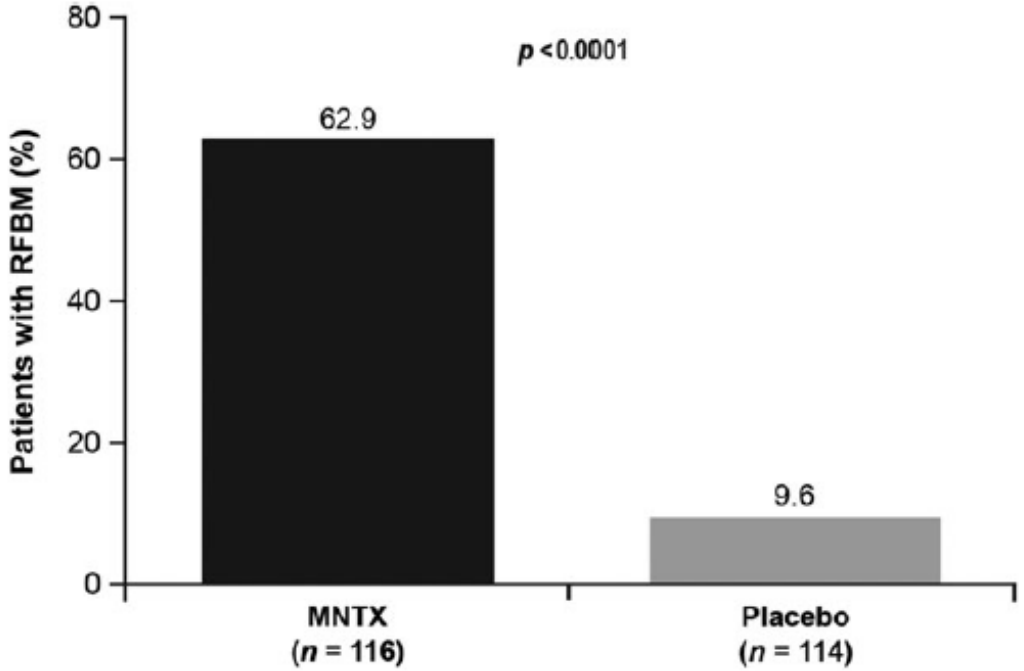
Fixed-Dose Subcutaneous Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation: Results of a Randomized, Placebo-Controlled Study and Open-Label Extension

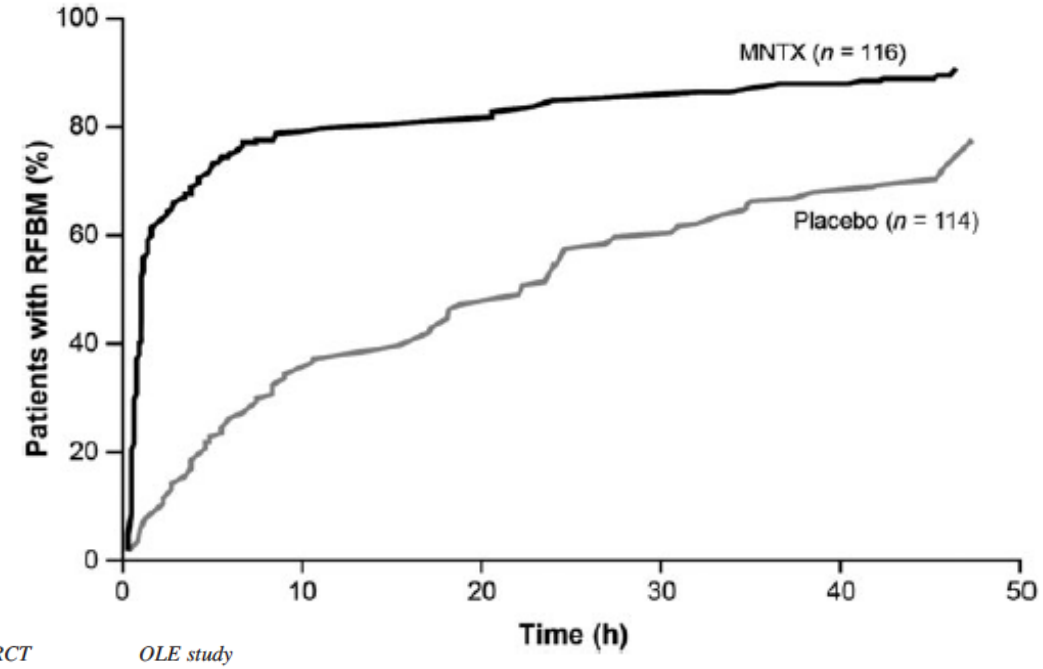
Janet Bull, MD,[1] Charles V. Wellman, MD,[2] Robert J. Israel, MD,[3] Andrew C. Barrett, PhD,[4] Craig Paterson, MD,[4] and William P. Forbes, PharmD[4]



1. Bull J. *et al.* Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation : results of a randomized, placebo-controlled study and open-label extension. *J Palliat Med.* 2015 ; 18(7):593-600

Methylnaltrexone





Adverse event, n (%)	RCT: MNTX 8 mg or 12 mg QOD (n = 116)	RCT: Placebo (n = 114)	OLE study: MNTX 8 mg or 12 mg PRN (n = 149)
SAE	14 (12.1)	24 (21.1)	59 (39.6)
Any AE	95 (81.9)	84 (73.7)	135 (90.6)
Drug-related AEs	49 (42.2)	21 (18.4)	38 (25.5)
Most common AEs[a]			
Abdominal pain	39 (33.6)	19 (16.7)	40 (26.8)
Nausea	13 (11.2)	18 (15.8)	21 (14.1)
Back pain	9 (7.8)	3 (2.6)	7 (4.7)
Diarrhea	9 (7.8)	15 (13.2)	24 (16.1)
Fall	9 (7.8)	4 (3.5)	21 (14.1)
Flatulence	8 (6.9)	5 (4.4)	7 (4.7)
Confusional state	7 (6.0)	9 (7.9)	23 (15.4)
Peripheral edema	7 (6.0)	4 (3.5)	26 (17.4)
Vomiting	5 (4.3)	10 (8.8)	10 (6.7)

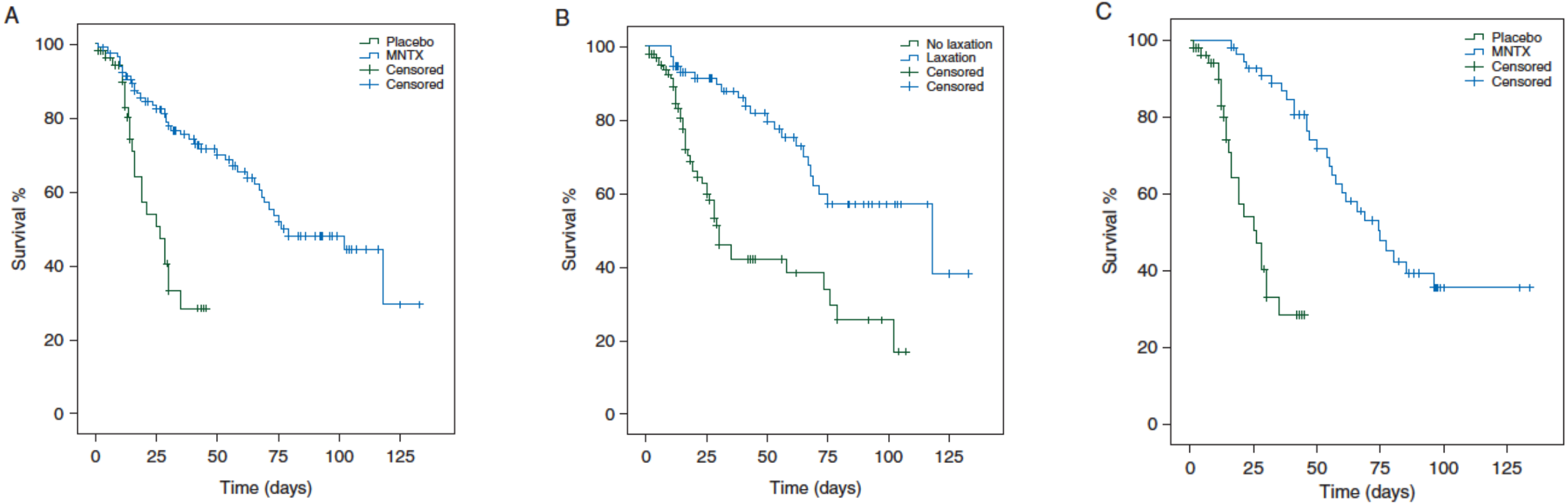
1. Bull J. *et al.*. *J Palliat Med.* 2015 ; 18(7):593-600

Methylnaltrexone

Annals of Oncology 27: 2032–2038, 2016
doi:10.1093/annonc/mdw317
Published online 29 August 2016

Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer

F. Janku[1], L. K. Johnson[2], D. D. Karp[1], J. T. Atkins[1], P. A. Singleton[3,4] & J. Moss[4*]



(A) Patients (n = 117, blue) treated with methylnaltrexone (MNTX) had a longer median overall survival (OS) compared with patients (n = 56, red) treated with placebo without subsequent crossover to MNTX (76 days, 95% CI 43–109 versus 26 days, 95% CI 17–35; P < 0.001). (B) Patients (n = 73, blue) with a response to treatment (laxation within 4 h after the first administration) had a longer median OS compared with patients (n = 100, red) without a response and crossover to MNTX (118 days, 95% CI 46–190 versus 30 days, 95% CI 23–37; P < 0.001). (C) Patients (n = 56, blue) who crossed over from placebo to MNTX had a longer median OS compared with patients (n = 56, red) treated with placebo without subsequent crossover to MNTX (75 days, 95% CI 59–91 versus 26 days, 95% CI 17–35; P < 0.001).

A PHASE 3 STUDY: NALDEMEDINE TO TREAT OPIOID INDUCED CONSTIPATION

Peripheral Acting μ opioid receptor antagonist

- Cancer patients
- Stable opioids > 2 w
- Laxative insufficient

N=190

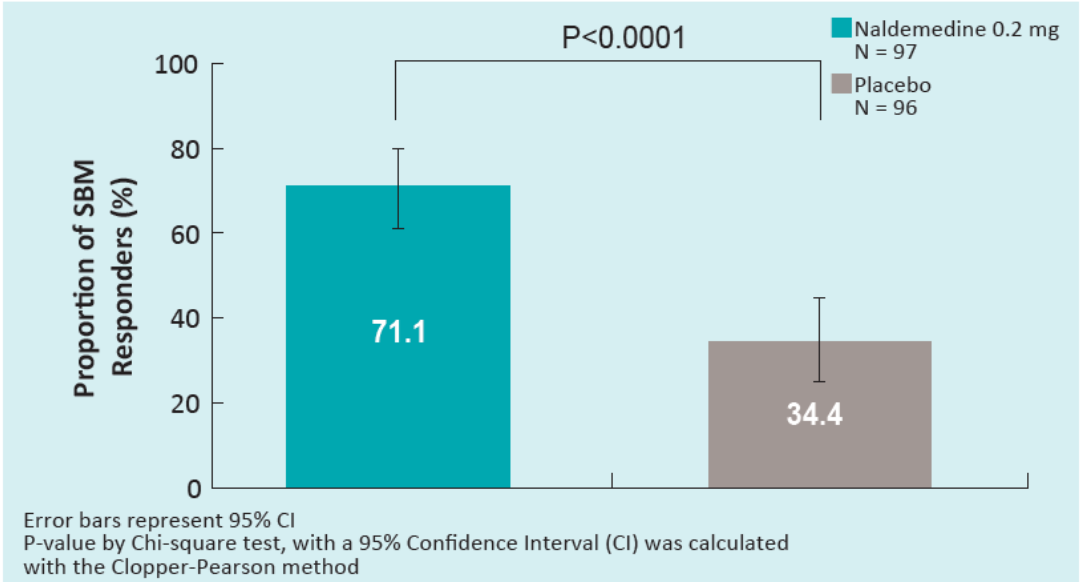
R

1:1

NALDEMEDINE 0.2 mg QD n=83

2w treatment + 4w follow up

PLACEBO QD n=88



	SBM		CSBM	
	Naldemedine 0.2 mg N=97	Placebo N=96	Naldemedine 0.2 mg N=97	Placebo N=96
Median time to BM after the initial dose (hour, 95% CI)	4.67 (3.00, 7.58)	26.58 (19.65, 58.17)	24.00 (9.00, 43.25)	218.50 (117.75, -)
P value	< 0.0001		< 0.0001	

SBM=Spontaneous Bowel Movement
CSBM=SBM + complete evacuation feeling

ESMO 2016. Toru Murata et al. Abs 1466P

Others …

- Cannabinoid Receptor
  - CB1 activation : transit inhibition
  - Dronabinol
- Chloride Channel Receptors
  - Activation : limit constipation
  - Inhibition : efficacy in diarrhea
- Probiotics – Antibiotics
  - Lactobacillus Rhamnosus reduces 5FU diarrhea
  - Fluoroquinolone
  - Selective inhibition of bacterial b-glucuronidase

Esfandyari et al., 2006
Österlund,P et al. *Br. J.Cancer 2007;* 97, 1028–1034
Maroun,J.A et al. *Curr. Oncol.* 2007 14, 13–20
Wallace,B.D.,et al. *Science* 2010 330, 831–835.

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