Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

ESMO
Designated Centers of Integrated Oncology and Palliative Care

Con il Patrocinio di

AIOM
Associazione Italiana di Oncologia Medica

SIAPEC - IAP

SICO

AIRO
Associazione Italiana Radioterapia Oncologica

SIRM

CORSO DI IMMUNOTERAPIA IN ONCOLOGIA

"CARCINOMA DEL RENE E DELLA VESCICA"

NEGRAR (VR)
28/29 Novembre 2017

Cancer Care Center
"Sacro Cuore - Don Calabria"
Centro Formazione - Aula 1

La gestione della tossicità: carcinoma della vescica

Veronica Prati
Oncologia Medica
ASLCN2 Alba-Bra

BRA ALBA
ASL CN2

Currently Approved Immuno-Oncology Agents in Advanced Urothelial Carcinoma

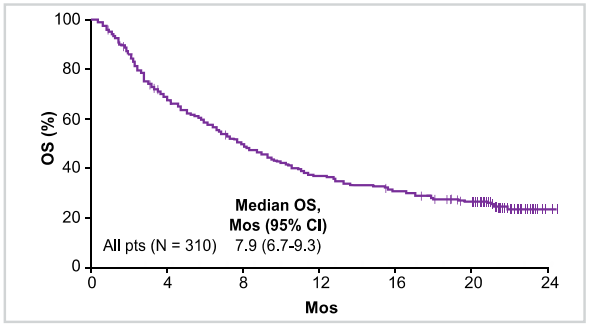
Atezolizumab: Anti–PD-L1 Antibody

First-line approval for patients not eligible for cisplatin-containing chemo[1]

ORR: 23%; median OS: 15.9 months

Second-line approval on or after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant chemo[2,3]

ORR: 15%; median OS: 7.9 months



Dosing: 1200 mg IV ***every 3 weeks,*** infuse over 1 hour; continue until PD or unacceptable AE

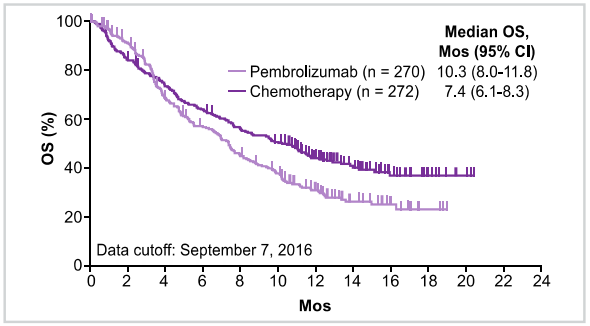
Pembrolizumab: Anti–PD-1 Antibody

First-line approval for patients not eligible for cisplatin-containing chemo[4]

ORR: 24%; OS data not yet mature

Second-line approval on or after platinum-based chemo or within 12 months of neoadjuvant or adjuvant chemo[5]

ORR: 21%; median OS: 10.3 months



Dosing: 200 mg IV ***every 3 weeks,*** infuse over 30 minutes; continue until PD or unacceptable AE for up to 24 months

3-5% pts discontinued for AE

General Immune-Related AE (irAE) Management

Grade	General Guidelines*
1 (mild)	• Supportive care; may or may not withhold tx
2 (moderate)	• Withhold therapy (except with certain endocrine AEs) • Consider restarting tx if AE resolves to grade ≤ 1 • Begin low-dose corticosteroids if AE does not resolve in 1 wk (except with certain endocrine AEs)
3/4 (severe)	• Grade 3: consider hospital admission • Grade 4: hospitalization recommended • Discontinue tx (consider resuming for some grade 3 irAE if resolves to grade ≤ 1) • Begin IV or oral corticosteroid (depending on severity and type of irAE) followed by taper over at least 1 month • If symptoms persist > 3 days or recur, add noncorticosteroid immunosuppressive

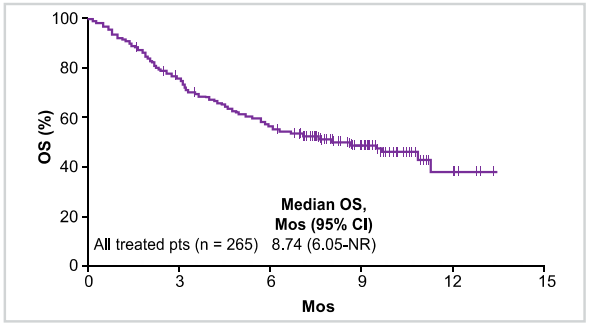
*For specific guidance on managing irAEs, please use online resources such as CCO's **"Managing Immune-Related Adverse Events: An Interactive Algorithm Tool"** or other online AE management algorithms

http://clinicaloptions.com/immuneAEtool

Nivolumab: Anti–PD-1 Antibody

Second-line approval on or after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant chemo[6]

ORR: 20%; median OS: 8.7 months

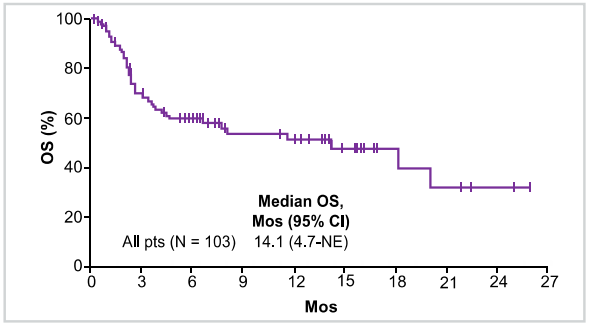


Dosing: 240 mg IV ***every 2 weeks,*** infuse over 1 hour; continue until PD or unacceptable AE

Durvalumab: Anti–PD-L1 antibody

Second-line approval on or after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant chemo[7]

ORR: 20%; median OS: 14.1 months



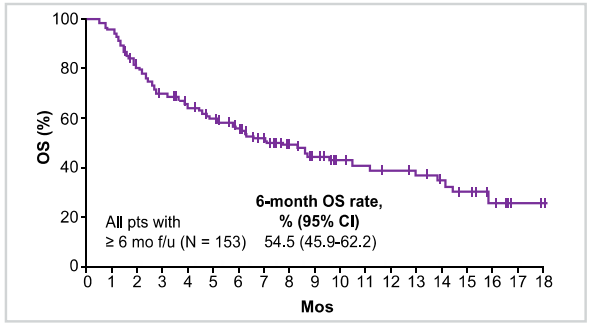
NOTE: Approval includes a complementary diagnostic assay for PD-L1 expression

Dosing: 10 mg/kg IV ***every 2 weeks,*** infuse over 1 hour; continue until PD or unacceptable AE

Avelumab: Anti–PD-L1 antibody

Second-line approval on or after platinum-based chemo or within 12 months of neoadjuvant or adjuvant chemo[8]

ORR: 18%; median OS: NR (6-Mo OS rate: 54.5%)



Dosing: 10 mg/kg IV ***every 2 weeks,*** infuse over 1 hour; continue until PD or unacceptable AE

References:

1. Balar AV, et al. Lancet. 2017;389:67-76. 2. Rosenberg JE, et al. Lancet. 2016;387:1909-1920. 3. Loriot Y, et al. ESMO 2016. Abstract 783P. 4.Balar AV, et al. ASCO GU 2017. Abstract 284. 5. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026. 6. Sharma P, et al. Lancet Oncol. 2017;18:312-322. 7. Powles T, et al. ASCO GU 2017. Abstract 286. 8. Patel MR, et al. ASCO GU 2017. Abstract 330.

May 2017

Atezolizumab: Anti–PD-L1 Antibody

IMvigor210: Cohort 1

Safety: Adverse Event Profile

Treatment-Related AEs

AE (N = 119)[a]	All Grade	Grade 3-4
Fatigue	30%	3%
Diarrhea	11%	1%
Pruritus	11%	1%
Decreased appetite	9%	1%
Hypothyroidism	6%	0%
Anemia	5%	1%
Chills	5%	0%
Nausea	5%	0%
Pyrexia	5%	0%
Rash	5%	1%
Vomiting	5%	0%
ALT increased	4%	3%
AST increased	3%	2%
Blood bilirubin increased	3%	2%
Hypophosphatemia	3%	2%
Renal Failure	2%	2%

IMvigor210: Cohort 2

Safety: Adverse Event Profile

Treatment-Related AEs

AE (N = 310)[a]	All Grade	Grade 3-4
Fatigue	31%	2%
Nausea	14%	0%
Decreased appetite	11%	1%
Pruritus	11%	< 1%
Pyrexia	9%	< 1%
Diarrhea	8%	< 1%
Rash	7%	< 1%
Vomiting	7%	< 1%
Arthralgia	7%	1%
AST increased	4%	1%
ALT increased	3%	1%
Hypertension	1%	1%

Immune-Mediated AEs Requiring Use of Systemic Corticosteroids

AE (N = 119)[a]	All Grade	Grade 3-4
Rash	3%	1%
Pruritus	3%	1%
ALT increased	2%	2%
Blood bilirubin increased	2%	2%
Rhabdomyolysis	2%	1%
AST increased	1%	1%
Autoimmune colitis	1%	1%
Colitis	1%	1%
Hyperglycemia	1%	1%
Liver disorder	1%	1%

No pts received systemic non corticosteroid immuno-modulatory drug (eg infliximab)

AE (N = 310)[a]	All Grade	Grade 3-4
Pneumonitis	2%	1%
AST increased	2%	1%
Dyspnea	1%	1%
ALT increased	1%	< 1%
Blood bilirubin increased	1%	< 1%
Rash	1%	< 1%
Hyperglycemia	1%	0%
Colitis	1%	1%
Diarrhea	1%	< 1%
Transaminases increased	1%	< 1%
Dry skin	1%	0%
Pruritus	1%	0%
Pyrexia	1%	0%

Pembrolizumab: anti-PD1 Antibody

KEYNOTE-052

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	171 (46%)	52 (14%)	5 (1%)	1 (<1%)
Fatigue	54 (15%)	8 (2%)	0	0
Pruritus	51 (14%)	1 (<1%)	0	0
Rash	35 (9%)	1 (<1%)	0	0
Appetite decrease	29 (8%)	1 (<1%)	1 (<1%)	0
Diarrhoea	26 (7%)	2 (1%)	0	0
Nausea	27 (7%)	1 (<1%)	0	0
Asthenia	13 (4%)	2 (1%)	1 (<1%)	0
Pyrexia	13 (4%)	1 (<1%)	0	0
AST increase	10 (3%)	3 (1%)	0	0
ALT increase	8 (2%)	3 (1%)	0	0
Maculopapular rash	9 (2%)	1 (<1%)	0	0
Arthralgia	8 (2%)	1 (<1%)	0	0
Anaemia	7 (2%)	1 (<1%)	0	0
Colitis	3 (1%)	3 (1%)	1 (<1%)	0
Alkaline phosphatase increase	2 (1%)	5 (1%)	0	0
Creatinine increase	6 (2%)	1 (<1%)	0	0
Muscle weakness	1 (<1%)	4 (1%)	0	0
Pneumonitis	3 (1%)	2 (1%)	0	0
Arthritis	3 (1%)	2 (1%)	0	0
Dizziness	4 (1%)	1 (<1%)	0	0
Bilirubin increase	4 (1%)	1 (<1%)	0	0
Hyperglycaemia	3 (1%)	1 (<1%)	0	0
Hepatitis	0	2 (1%)	0	0

KEYNOTE-045

Table 2. Adverse Events in the As-Treated Population.*

Event	Pembrolizumab Group (N=266)		Chemotherapy Group (N=255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group‡				
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0	27 (10.6)	2 (0.8)
Neutropenia	0	0	39 (15.3)	34 (13.3)
Alopecia	0	0	96 (37.6)	2 (0.8)
Event of interest§				
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0
Infusion reaction	2 (0.8)	0	10 (3.9)	0
Nephritis	2 (0.8)	2 (0.8)	0	0
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0
Myositis	0	0	1 (0.4)	1 (0.4)

Nivolumab: Anti–PD-1 Antibody
CheckMate 275

	Grade 1–2	Grade 3	Grade 4
All treatment-related adverse events			
Fatigue	40 (15%)	5 (2%)	0
Pruritus	25 (9%)	0	0
Diarrhoea	19 (7%)	5 (2%)	0
Decreased appetite	22 (8%)	0	0
Hypothyroidism	21 (8%)	0	0
Nausea	18 (7%)	1 (<1%)	0
Rash	13 (5%)	3 (1%)	0
Asthenia	12 (4%)	4 (1%)	0
Pyrexia	15 (6%)	0	0
Select treatment-related adverse events			
Skin	43 (16%)	4 (1%)	0
Endocrine	38 (14%)	1 (<1%)	0
Gastrointestinal	19 (7%)	6 (2%)	0
Pulmonary	7 (3%)	3 (1%)	0
Hepatic	5 (2%)	5 (2%)	0
Renal	2 (1%)	1 (<1%)	0

Sharma P, et al. Lancet Oncol. 2017

Durvalumab: Anti–PD-L1 antibody

A phase 1/2 multicenter, open-label study

	No. (%)	
	UC Cohort (As-Treated Population) (n = 191)	
Adverse Event	All Grades[c]	Grade 3/4
Any	116 (60.7)	13 (6.8)
Occurring in ≥5% of patients in either population or with grade ≥3 severity in ≥1 patient in the UC cohort		
Fatigue	37 (19.4)	0
Decreased appetite	18 (9.4)	0
Diarrhea	16 (8.4)	1 (0.5)
Rash	14 (7.3)	0
Nausea	13 (6.8)	0
Arthralgia	11 (5.8)	0
Pyrexia	11 (5.8)	0
Pruritus	10 (5.2)	0
Increased ALT level	8 (4.2)	2 (1.0)
Increased AST level	6 (3.1)	3 (1.6)
Increased GGT level	6 (3.1)	2 (1.0)
Increased blood ALP level	4 (2.1)	1 (0.5)
Hypertension	3 (1.6)	2 (1.0)
Anemia	2 (1.0)	1 (0.5)
Maculopapular rash	2 (1.0)	1 (0.5)
Infusion-related reaction	2 (1.0)	1 (0.5)
Increased transaminases	2 (1.0)	1 (0.5)
Autoimmune hepatitis	2 (1.0)	1 (0.5)
Tumor flare	2 (1.0)	1 (0.5)
Acute kidney injury	1 (0.5)	1 (0.5)
Atrial fibrillation	1 (0.5)	1 (0.5)

Powels et al JAMA 2017

Avelumab: Anti–PD-L1 antibody

	1 mg/kg dose (n=4)			3 mg/kg dose (n=13)			10 mg/kg dose (n=15)			20 mg/kg dose (n=21)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fatigue	0	0	0	5 (39%)	0	0	10 (67%)	1 (7%)	0	5 (24%)	0	0
Influenza-like illness	1 (25%)	0	0	1 (8%)	0	0	3 (20%)	0	0	6 (29%)	0	0
Pyrexia	2 (50%)	0	0	2 (15%)	0	0	4 (27%)	0	0	0	0	0
Chills	2 (50%)	0	0	0	0	0	2 (13%)	0	0	2 (10%)	0	0
Allergic rhinitis	0	0	0	2 (15%)	0	0	1 (7%)	0	0	1 (5%)	0	0
Increased blood creatine phosphokinase	0	0	0	0	0	0	1 (7%)	0	0	1 (5%)	1 (5%)	1 (5%)
Diarrhoea	1 (25%)	0	0	0	0	0	2 (13%)	0	0	1 (5%)	0	0
Infusion-related reaction	0	0	0	0	0	0	1 (7%)	0	0	3 (14%)	0	0
Lymphopenia	0	0	0	2 (15%)	0	0	2 (13%)	0	0	0	0	0
Decreased lymphocyte count	0	0	0	2 (15%)	0	0	1 (7%)	1 (7%)	0	0	0	0
Myalgia	1 (25%)	0	0	1 (8%)	0	0	0	0	0	2 (10%)	0	0
Increased aspartate aminotransferase	1 (25%)	1 (25%)	0	0	0	0	0	1 (7%)	0	0	0	0
Autoimmune disorder	0	0	0	0	0	0	0	1 (7%)	1 (7%)	0	1 (5%)	0
Hyperglycaemia	1 (25%)	0	0	0	0	0	2 (13%)	0	0	0	0	0
Increased lipase	0	0	0	0	0	0	0	0	0	2 (10%)	1 (5%)	0
Nausea	0	0	0	0	0	0	2 (13%)	0	0	1 (5%)	0	0
Rash	1 (25%)	0	0	0	0	0	1 (7%)	0	0	1 (5%)	0	0
Increased alanine aminotransferase	1 (25%)	0	0	0	0	0	0	1 (7%)	0	0	0	0
Increased amylase	0	0	0	0	0	0	0	0	0	1 (5%)	1 (5%)	0
Hypotension	0	0	0	0	0	0	0	0	0	2 (10%)	0	0
Malaise	1 (25%)	0	0	0	0	0	0	0	0	1 (5%)	0	0
Increased blood alkaline phosphatase	0	1 (25%)	0	0	0	0	0	0	0	0	0	0
Lower abdominal pain	0	0	0	0	0	0	0	1 (7%)	0	0	0	0
Hypocalcaemia	1 (25%)	0	0	0	0	0	0	0	0	0	0	0
Insomnia	1 (25%)	0	0	0	0	0	0	0	0	0	0	0

Data are n (%). No grade 5 treatment-related adverse events occurred.

Table 2: **Treatment-related adverse events occurring at any grade in ≥10% of patients in any cohort or at grade ≥3 in any patient**

General aspects of irAEs

- Depending on the immune checkpoint that is targeted, the incidence of toxicity varies.

- Toxicities from immune checkpoint inhibitors (ICPis) can be divided into
  → infusion reactions
  → immune-related adverse events (irAEs)

- The incidence of irAEs with IPI and PEMBRO is dose-dependent

- The exact pathogenesis of immunotoxicity is not clear

- Any organ or tissue can be involved, although some irAEs occur much more commonly than others

- The role of tissue biopsy in the diagnosis of immune-therapy related toxicity is not established.

Some recommendations suggest tissue biopsy in higher grade (3 and 4) toxicity [skin, gastro-instestinal (GI), liver, kidney, lung] where there is diagnostic doubt about the aetiology of the complication and management would be altered by the outcome of the biopsy procedure.

Naidoo J, et sl Ann Oncol 2015
Puzanov et al J for Immunotherapy of Cancer 2017

General aspects of irAEs

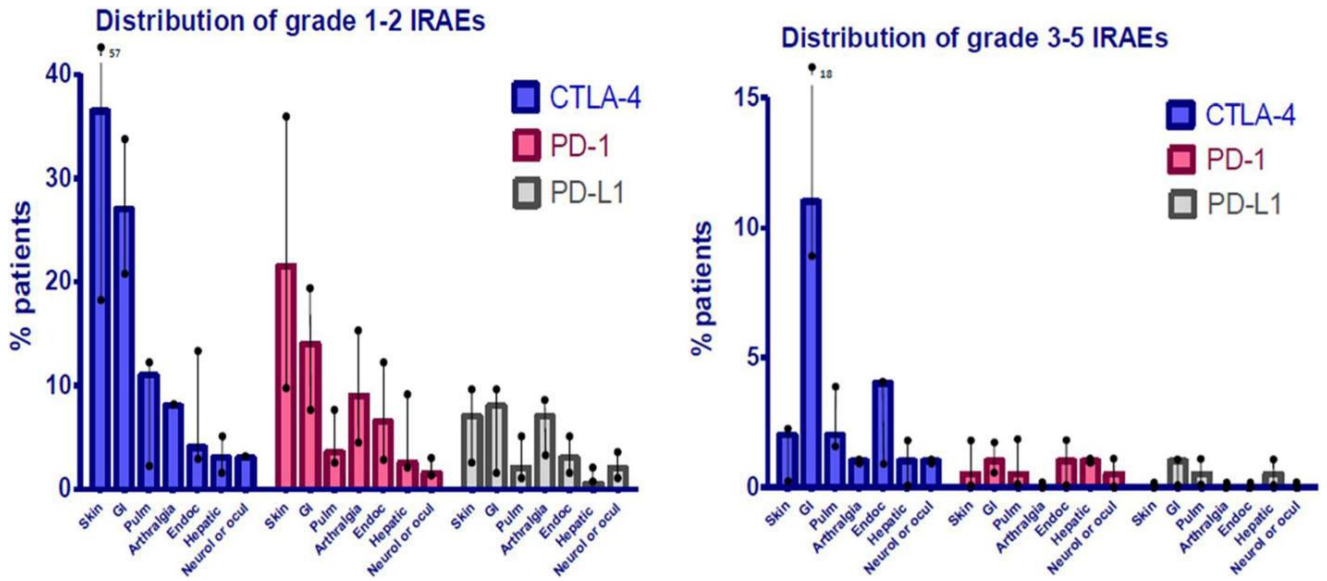


Fig. 1 Distribution of mild and severe immune-related adverse events (irAEs) associated with immune checkpoint inhibitor therapy. [Adapted from [88]]

- The most frequently occurring irAEs affect skin, colon, endocrine organs, liver, lungs and musculoskeletal.

Others are very infrequent, but may be very serious, even lethal, such as neurological disorders and myocarditis.

Naidoo J, et sl Ann Oncol 2015
Puzanov et al J for Immunotherapy of Cancer 2017

General aspects of irAEs

- In general, irAEs occur quite early, mostly within weeks to 3 months after initiation of immune checkpoint blockers.

- However irAEs resulting from immunotherapy can have a delayed onset and prolonged duration compared to adverse events resulting from chemotherapy, in part due to pharmacodynamic differences

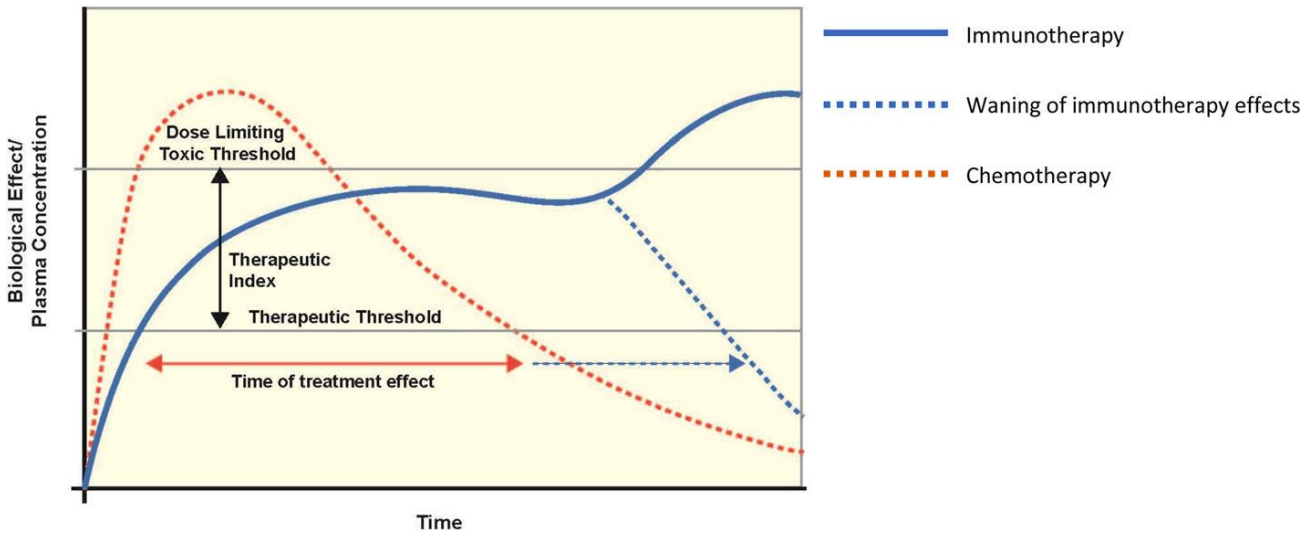


Fig. 2 Pharmacokinetic/pharmacodynamic differences between chemotherapy and immunotherapy. Reproduced with permission from [25]. Dotted blue line represents waning of the biological effects of immunotherapy over time, and solid blue line represents early or late toxic effects. Horizontal dotted blue arrow therefore represents duration of immunotherapy treatment benefit

EigentlerTK et al Cancer Treat Rev 2016
Puzanov et al J for Immunotherapy of Cancer 2017

General aspects of irAEs

- Once irAEs have developed, prompt work-up is required and action should be taken to prevent further aggravation of AEs.
  In many cases immunotherapy should be discontinued and immunosuppressive or immune modulating drugs are needed to overcome these toxicities.

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

- Long-term (> 6 weeks) treatment with immunosuppressive drugs or use of infliximab increases the chance of opportunistic infections; therefore, pneumocystis prophylaxis should be considered according to local guidelines.

EigentlerTK et al Cancer Treat Rev 2016
Puzanov et al J for Immunotherapy of Cancer 2017

Table 1 Pre-treatment evaluation and diagnostic tests to consider in all patients prior to initiating checkpoint inhibitor therapy

Routine pre-treatment screening

History
- ♦ Detailed questioning for autoimmune, infectious disease, endocrine and organ-specific disease history
- ♦ History of base line bowel habit (frequency of bowel movements, usual stool consistency)

Blood tests
- ♦ CBC
- ♦ CMP
- ♦ TSH
- ♦ HbA1c
- ♦ Free T4
- ♦ Total CK
- ♦ Infectious disease screen: HBsAg, HBsAb, HBcAb, hCAb, CMV antibody, T-spot test, HIV antibody, HIV antigen (p24)[a]
- ♦ Fasting lipid profile

Dermatologic examination
- ♦ Full skin and mucosal exam, taking note of the extent and type of lesions present

Pulmonary tests
- ♦ Baseline oxygen saturation on room air and during ambulation

Cardiac tests
- ♦ ECG
- ♦ Troponin I or T: baseline and weekly for 6 weeks[b]

Additional screening tests recommended in patients with pre-existing organ disease/at risk of organ-specific toxicity

Endocrine tests
- ♦ 8 am cortisol
- ♦ 8 am ACTH

Cardiac tests
- ♦ Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)

Pulmonary tests
- ♦ PFTs[c]
- ♦ 6MWT[c]

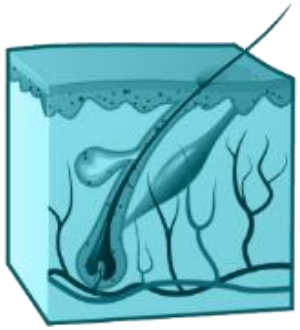
Before starting treatment

Patient selection

Baseline assessments

Patient education

Puzanov et al J for Immunotherapy of Cancer 2017



Skin toxicity

Dermatologic toxicity (all grades) is reported in 30-40% of pts taking PD1/PDL1 inhibitors

The most frequent skin AEs are rash, pruritus and vitiligo

- **Rash**

  24% of the patients treated with ipilimumab,
  15% of those receiving anti-PD-1 MoAbs
  40% with the combination of ipilimumab and nivolumab.

Grade 3 or 4 rashes are rare, with an incidence of<3% with monotherapy ipilimumab or anti-PD-1 and<5% with the combination

- **Pruritus**

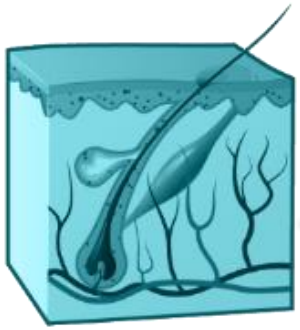
  25%–35% of the cases with ipilimumab
  13%– 20% with anti-PD-1
  33% with the combination

Grade 3 and 4 in<2.5%

- **Vitiligo** in about 8% of patients with melanoma treated with anti- PD-1 MoAbs or with the combination of checkpoint in- hibitors, but is more rarely reported with ipilimumab alone. In a small prospective study, vitiligo was found in up to 25% of patients treated with pembrolizumab

Vitiligo seems to be associated with good clinical responses to anti-PD-1 MoAbs in patients treated for melanoma

Haanen J et al Annals of Oncol 2017



Skin toxicity

Histopathologically, skin reactions may be categorised into four broad groups

- Inflammatory skin disorders

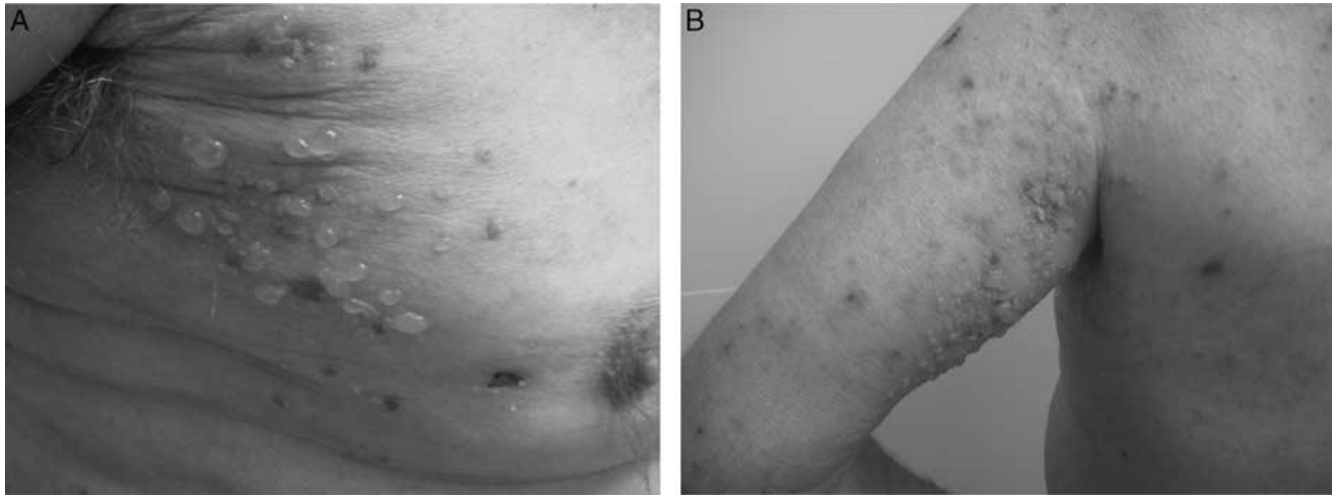
→acute, subacute or chronic inflammation of various patterns

- Immunobullous skin lesions akin to dermatitis herpetiformis or bullous pemphigoid

- Keratinocyte alteration—Grover's disease/acantholytic dyskeratosis

- Immune-reaction mediated by alteration of melanocytes

→regression of nevi, prurigo nodularis, tumoural melanosis and vitiligo



Acute flare of bullos Pemphigus with pembro

dermatologic assessments are warranted in patients with a known history of immune-related skin disorders such as psoriasis, bullous pemphigoid or lupus

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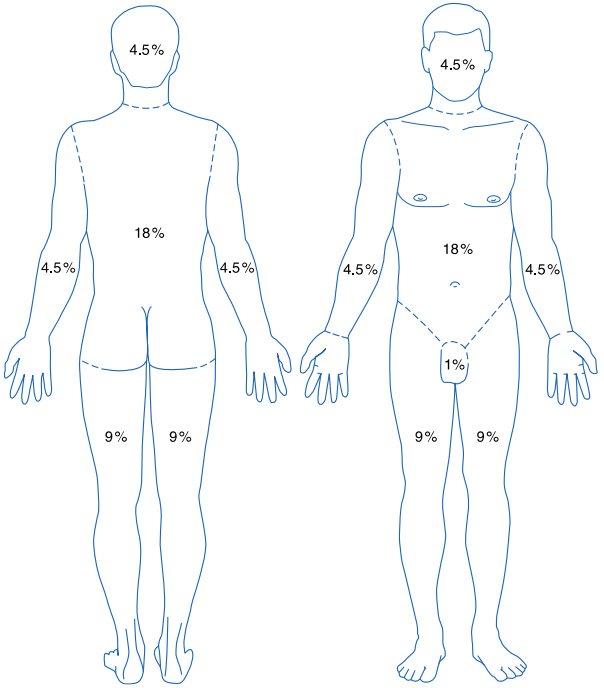
Garje R et al J Immunotherapy 2017

Skin toxicity

Most dermatologic irAEs are low-grade and manageable, although rare, potentially life-threatening exfoliative dermatological conditions such as Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported

Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 1: skin rash, with or without symptoms, < 10% BSA (see Figure 4)	Avoid skin irritants, avoid sun exposure, topical emollients recommended Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch Proceed with treatment	Physical examination Exclude other causes, e.g. viral illness, infection, other drug rash
Grade 2: rash covers 10%-30% of BSA (see Figure 4) With or without symptoms Limiting instrumental activities of daily living (ADL)	Supportive management, as above Topical steroids (moderate strength) cream od or(potent) cream bd +/- oral or topical antihistamines for itch Proceed with ICPi treatment	As above Consider dermatology referral and skin biopsy *If not resolved, treatment should be Interrupted until the skin AE has reverted to G 1*
Grade 3: rash covers > 30% BSA (see Figure 4) or grade 2 with substantial symptoms Limiting selfcare ADL	Withhold ICPi Topical treatments as above (potent) Initiate steroids: if mild to moderate 0.5-1 mg/kg prednisolone od for 3 days then wean over 1-2 weeks; or if severe i.v. (methyl)prednisolone 0.5 -1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks Recommence ICPi at G1/mild G2 after discussion with patient and consultant	As for Grade 1 Dermatology review Consider punch biopsy and clinical photography
Grade 4: skin sloughing > 30% BSA (see Figure 4) with associated symptoms (e.g. erythema, purpura, epidermal detachment)	i.v. (methyl)prednisolone 1-2 mg/kg **Seek urgent dermatology review** Discontinue ICPi treatment	As for Grade 1 Dermatology review Punch biopsy Clinical photography



Schematic of body surface area (BSA).

• If worsens in 48 hours, consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil) or supportive measures#

Figure 3. ICPi-related toxicity: management of skin rash/toxicity.

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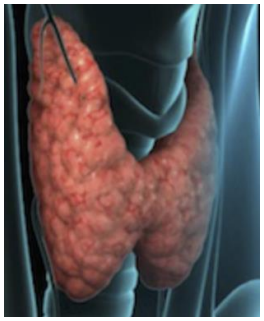

Endocrine Toxicities

- Hypophysitis is most commonly seen with anti CTLA-4 antibody and with combination ipi/nivo
- With anti-PD-1 (either pembrolizumab or nivolumab) or anti- PD-L1 (atezolizumab) therapy, the reported thyroid dysfunction rate varies from 5% to 10% (irrespective of tumour type).
  With combination immunotherapy the frequency of thyroid disorders icreases to 20%
- Little is known about the pathogenesis of thyroid disorders following ICPis.
  It is thought to be mediated by T cells and not by B cell autoimmunity.
- **Hypothyroidism** is more common.
  Symptoms: unexplained fatigue, weight gain, hair loss, cold intolerance, constipation, depression

Lab. high TSH and low free T4

- **Thyroiditis** is the most frequent cause of thyrotoxicosis and is seen more commonly with anti-PD1/ PD-L1 drugs than with anti-CTLA-4 agents
  Symptoms: weight loss, palpitations, heat intolerance, tremors, anxiety, diarrhea and other symptoms of hypermetabolic activity

Lab: high free T4 or triiodothyronine (T3) levels, with low/normal TSH

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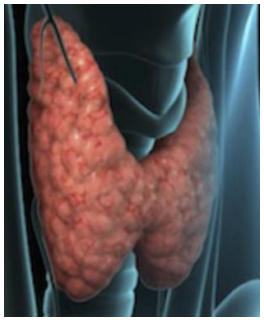


Endocrine Toxicities

Baseline Endocrine Panel:
TSH, FT4, T3* TFTs

Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertain
*when indicated

Monitoring during treatment:
Anti-CTLA4 (including combination with anti-PD-1
· TFTs every cycle
· TFTs 4–6 weeks after cycle 4 (i.e. with restaging
Late endocrine dysfunction can occur

Anti-PD-1/Anti-PD-L1
· TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
· Cortisol as indicated by symptoms/falling TSH

Anti-PD-1/Anti-PD-L1
- TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
- Cortisol as indicated by symptoms/falling TSH

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed (see also Figure 6)

If TSH is abnormal, refer to algorithm below. Iodine from CT scans may impact TFTs

Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4

Treatment: Thyroxine 0.5–1.5 µg/kg (start low in elderly, if cardiac history)

Continue ICPi

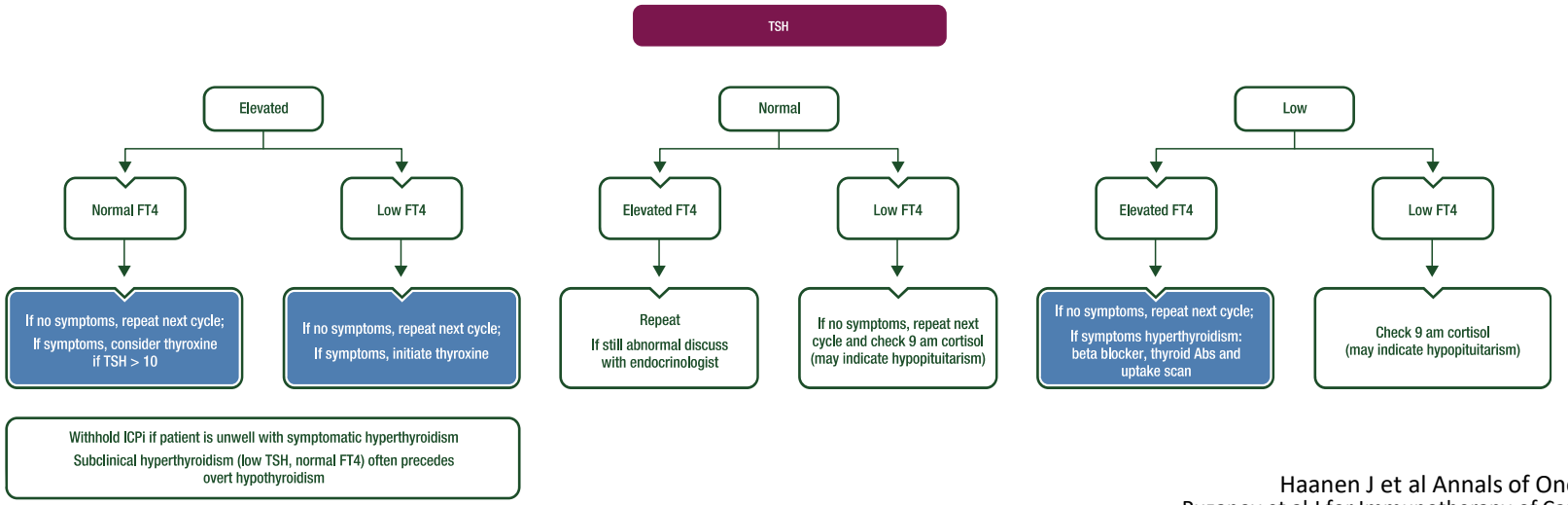
Thyrotoxicosis (DDx thyroiditis, Grave's disease):

Investigations: Anti-TSH Receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan

Treatment: Propranolol or atenonol for symptoms; consider carbimazole if anti-TSH Receptor Ab positive

Painful thyroiditis – consider prednisolone 0.5 mg/kg and taper

If unwell, withhold ICPi and consider restarting when symptoms controlled



Withhold ICPi if patient is unwell with symptomatic hyperthyroidism

Subclinical hyperthyroidism (low TSH, normal FT4) often precedes overt hypothyroidism

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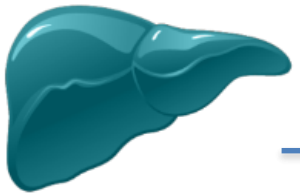

Hepatotoxicity

- Hepatitis occurs in

  5%–10% (of which 1%–2% is grade 3) of patients during therapy with ipilimumab, nivolumab and pembrolizumab
  25%–30% (of which 15% is grade 3) of those treated with the combination of ipilimumab 3 mg/kg and nivolumab 1 mg/kg

- Hepatitis is usually asymptomatic and detected on such routine blood monitoring. If hepatitis develops, disease-related causes, concomitant drug administration (including alcohol) and infectious causes, particularly viral hepatitis, should be ruled out.

- Liver biopsy may be considered in assisting in the differential diagnosis of more severe hepatitic reactions. Lobular hepatitis indistinguishable from autoimmune hepatitis is most commonly reported

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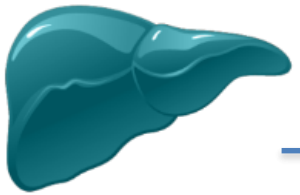
Hepatotoxicity



Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 1: ALT or AST > ULN-3x ULN	Continue treatment	If > ULN–3x ULN repeat in 1 week
Grade 2: ALT or AST 3-5x ULN	Withhold ICPi treatment If rising ALT/AST when re-checked start oral prednisolone 1 mg/kg	Re-check LFTs/INR/albumin every 3 days Review medications, e.g. statins, antibiotics and alcohol history Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies Consider imaging for metastases/clot
Grade 3: ALT or AST 5-20x ULN	Cease treatment ALT/AST < 400 and normal bilirubin/INR/albumin: oral prednisolone 1 mg/kg ALT/AST > 400 or raised bilirubin/INR/low albumin: i.v. (methyl)prednisolone 2 mg/kg	As above; daily LFTs/INR/albumin Perform US with Doppler Low threshold to admit if clinical concern
Grade 4: ALT or AST > 20x ULN	i.v. (methyl)prednisolone 2 mg/kg Permanently discontinue treatment	As above; hepatology consult Consider liver biopsy

Steroid wean:
- G2: once G1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- G3/4: once improved to G2, can change to oral prednisolone and wean over 4 weeks; for G3, rechallenge only at consultant discretion

Worsening despite steroids:
- If on oral change to i.v. (methyl)prednisolone
- If on i.v. add MMF 500-1000 mg bd
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis [31]

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Fatigue

Cancer-Related Fatigue

Version 2.2017 — April 10, 2017

NCCN.org

NCCN National Comprehensive Cancer Network®

- The most frequently reported AE with anti-PD-1/PD-L1 is fatigue.
- Incidence of fatigue, of which the pathogenesis is poorly understood, across single drug studies, is 16%-37% for anti-PD-1 and 12%-24% for anti-PD-L1.
- Only in a minority of patients fatigue can be attributed to hypothyroidism
- **Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.**
- **Fatigue is a subjective experience**
- Fatigue is rarely an isolated symptom and most commonly occurs with other symptoms, such as pain, emotional distress, anemia, and sleep disturbances, in symptom clusters. Therefore, patients should be screened for multiple symptoms that may vary according to diagnosis, treatment, and stage of disease.
- Patients and families should be informed that management of fatigue is an integral part of total health care
- **Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner.**

Fatigue

Cancer-Related Fatigue

Version 2.2017 — April 10, 2017

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INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT[f,h]

Patient/Family Education and Counseling

Information about known pattern of fatigue during and following treatment
- Reassurance that treatment-related fatigue is not necessarily an indicator of disease progression

General Strategies for Management of Fatigue

- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities and realistic expectations
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
  - Assistive devices[g]
  - Postpone nonessential activities
  - Limit naps to <1 hour to not interfere with night-time sleep quality
  - Structured daily routine
  - Attend to one activity at a time
- Use distraction (eg, games, music, reading, socializing)
- Find meaning in current situation
  - Emphasis on meaningful interactions
  - Promote dignity of patient
- Consider referral to appropriate specialist or supportive care provider

SPECIFIC INTERVENTIONS

Nonpharmacologic[h]

- Physical activity (category 1)
  - Maintain optimal level of activity
  - Cautions in determining level of activity:
    - ◊ Bone metastases
    - ◊ Thrombocytopenia
    - ◊ Anemia
    - ◊ Fever or active infection
    - ◊ Limitations secondary to metastases or other comorbid illnesses
    - ◊ Safety issues (ie, assessment of risk of falls)
  - Consider starting and maintaining an exercise program, as appropriate per health care provider, of both endurance (walking, jogging, or swimming) and resistance (light weights) exercises[i]
  - Yoga (category 1)
  - Consider referral to rehabilitation: physical therapy, occupational therapy, and physical medicine
- Physically based therapies
  - Massage therapy (category 1)
- Psychosocial interventions
  - Cognitive behavioral therapy (CBT)[j]/Behavioral therapy (BT) (category 1)[k]
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies[l]
- Nutrition consultation
- CBT[j] for sleep
  - Stimulus control/Sleep restriction/Sleep hygiene
- Bright white light therapy[n]

Pharmacologic

- Consider psychostimulants[m] (methylphenidate) after ruling out other causes of fatigue
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines (See appropriate NCCN Guidelines for Supportive Care)
- Optimize treatment for sleep dysfunction, nutritional deficit/imbalance, and comorbidities

Repeat screening and evaluation See (FT-3) and (FT-4)

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JOURNAL OF CLINICAL ONCOLOGY

THE ART OF ONCOLOGY

Integrating Supportive and Palliative Care in the Trajectory of Cancer: Establishing Goals and Models of Care

Eduardo Bruera and David Hui

Patients with advanced cancer frequently develop devastating physical and psychosocial symptoms . These symptoms require individualized assessment and management.

Table 1. Frequency of Common Symptoms in Patients With Advanced Cancer

Symptom	Frequency (%)
Anorexia	30-92
Pain	35-96
Fatigue	32-90
Dyspnea	10-70
Delirium	6-93
Depression	3-77

NOTE. Data adapted.[1]

A

Hopeful and unrealistic attitude: Nothing bad will happen!!

No Supportive / Palliative Care

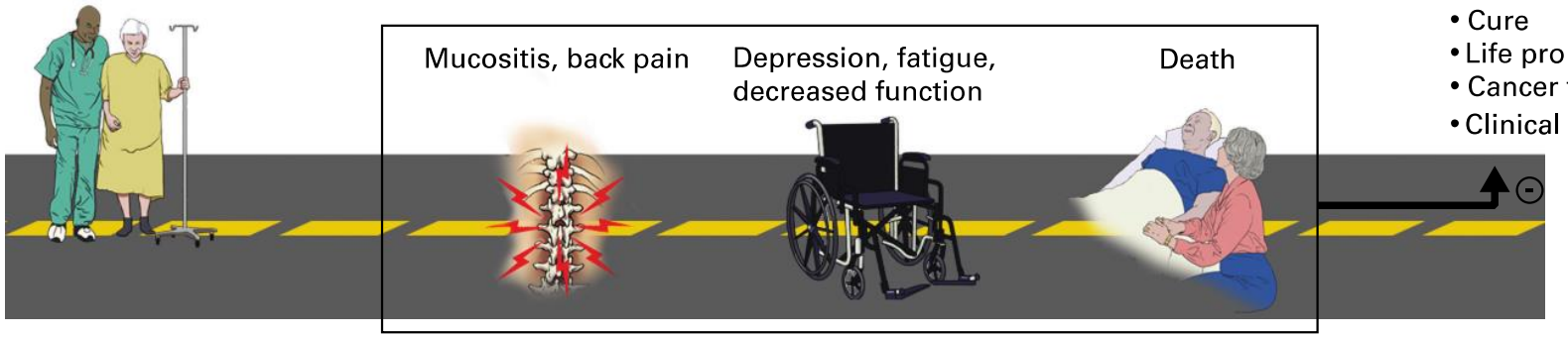
- **No comfort measures** (e.g. treatment of pain, depression)
- **No safety features** (e.g. advance planning for living arrangements, transportation / mobility, bedroom / bathroom aids, family knowledge and support, advance directives, resuscitation status)

- Suboptimal symptom control, increased distress, poor quality of life
- Frequent ER / hospital visits, CPR, intubation, ICU stay, distressed patient and family.

⊖

Goals

- Cure
- Life prologation
- Cancer treatments
- Clinical trials



B

Hopeful and realistic attitude: I want to ensure maximal comfort during my cancer journey. I also want to be prepared in case things do not go as planned.

Supportive / Palliative Care

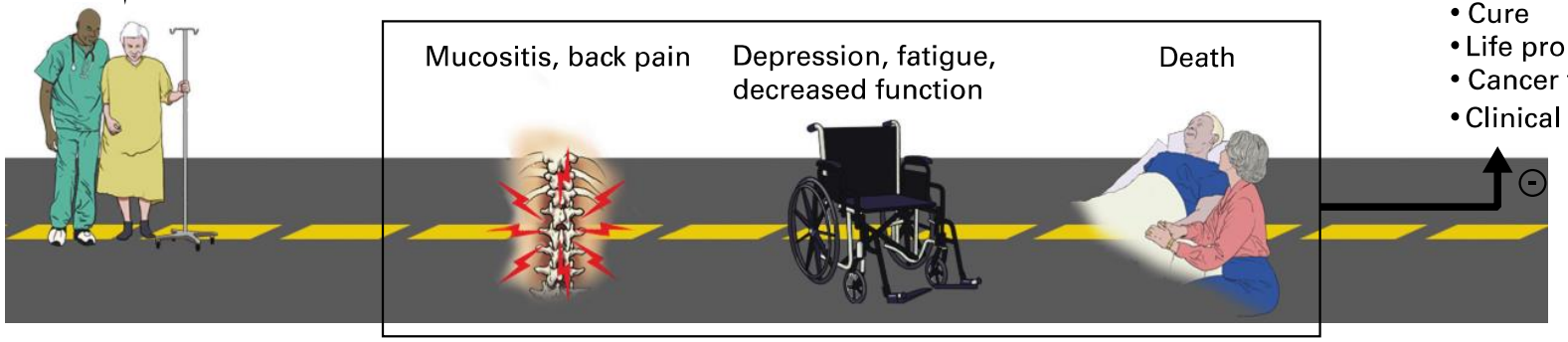
- **Comfort measures**
- **Safety features**

- Less distress, improved quality of life, increased adherence to cancer treatments.
- Minimizes patient and family distress at the end of life.

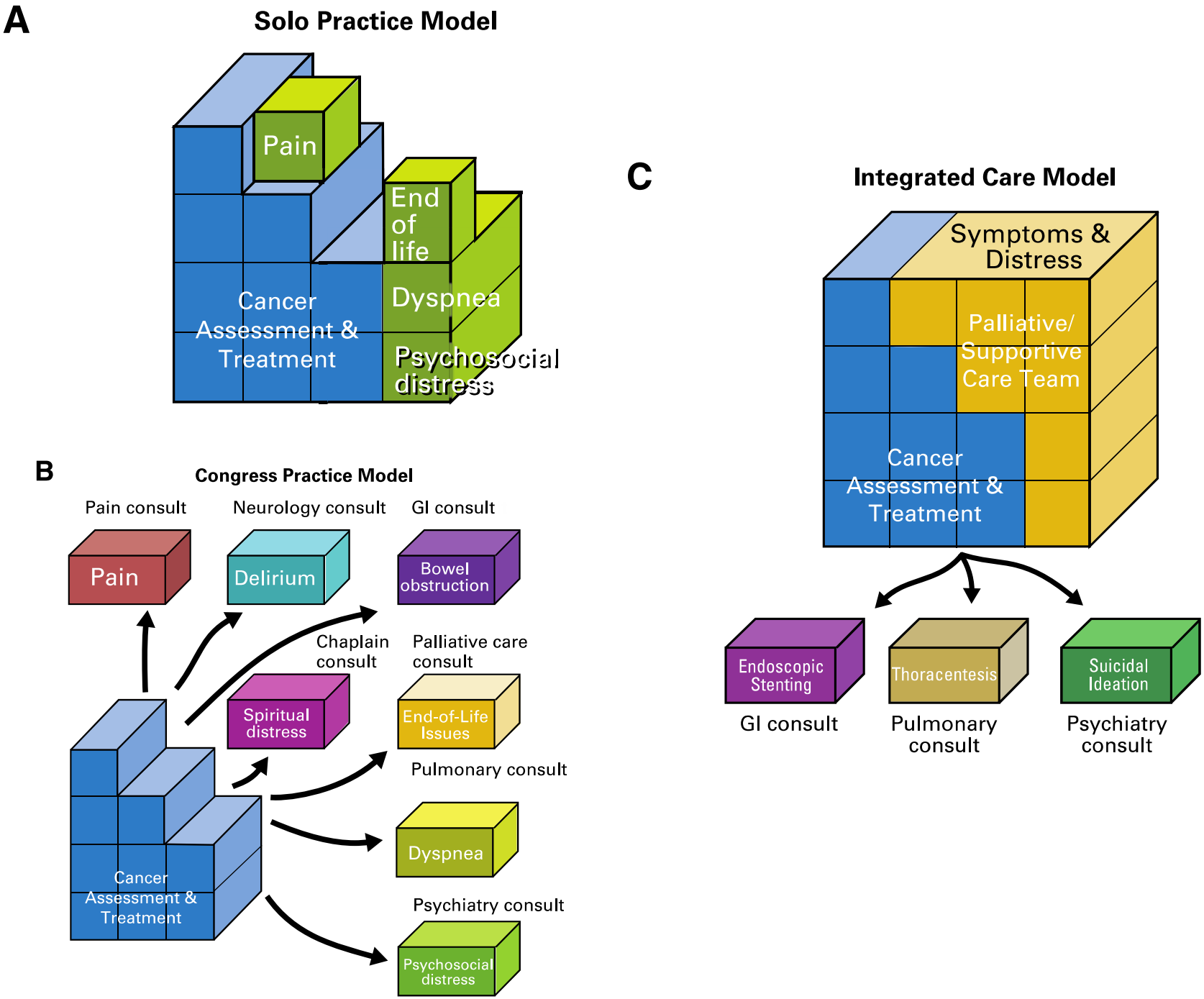
⊕

Goals

- Cure
- Life prologation
- Cancer treatments
- Clinical trials



Bruera JCO 2010

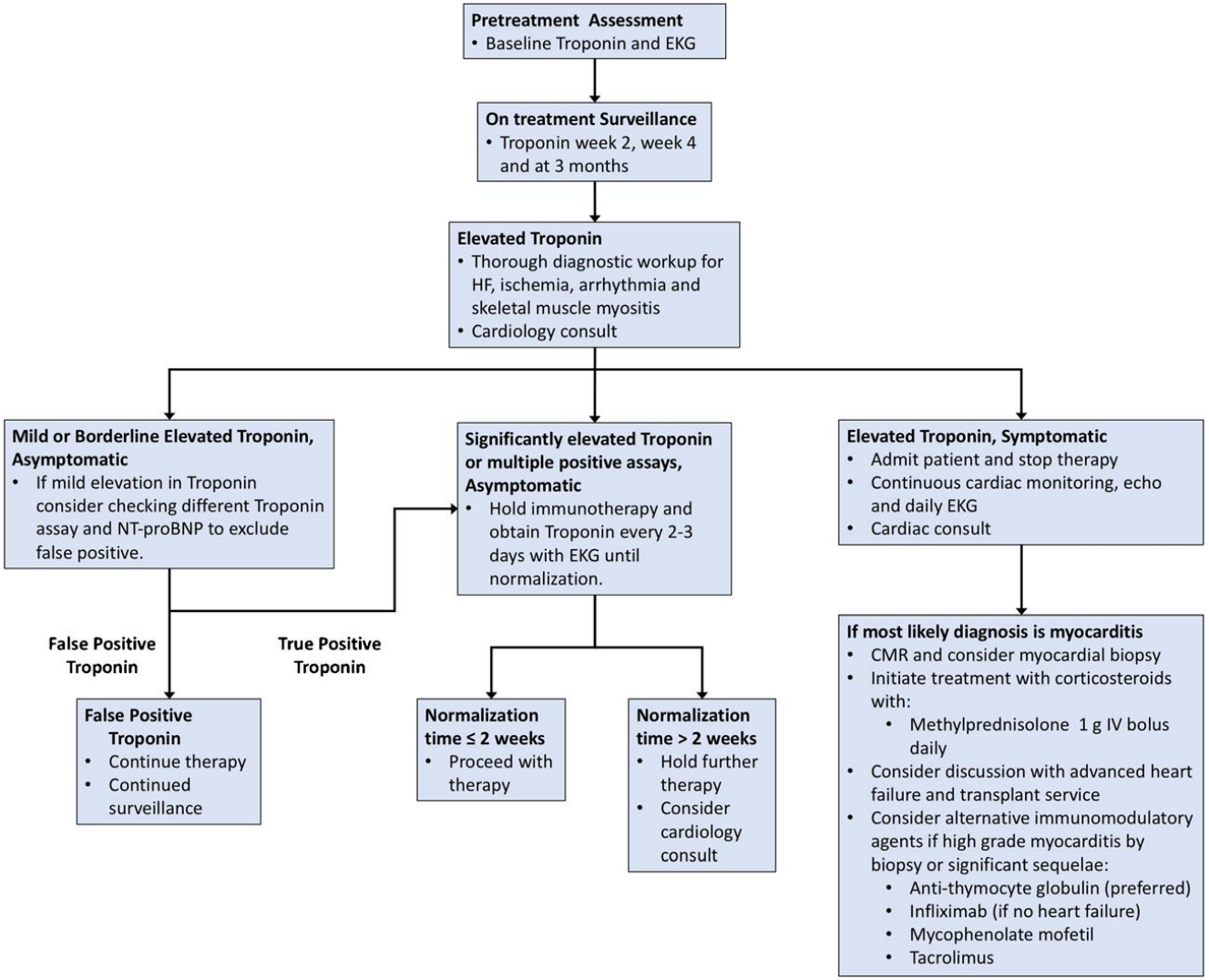


Bruera JCO 2010

ESMO Open
Cancer Horizons

Cardiotoxicity of immune checkpoint inhibitors

Gilda Varricchi,[1,2,3] Maria Rosaria Galdiero,[1,2,3] Giancarlo Marone,[4,5] Gjada Criscuolo,[1] Maria Triassi,[4] Domenico Bonaduce,[1,2,3] Gianni Marone,[1,2,3,6] Carlo Gabriele Tocchetti[1,2,3]



Immune-related Adverse Event Management
SUMMARY

- Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events

- Toxicity is often low (grade 1-2) in anti-PD1/PDL-1 antibodies; is higher in anti-CTLA4 antibodies and combined terapies

- For Grade >2 ieAE, treatment should be discontinued

→ Remember the durability of response

- Toxicity can be managed with supportive treatment.

- Early diagnosis, patient education, rapid and aggressive intervention

Immune-related Adverse Event Management
SUMMARY