Update on Use of Immune CheckPoint Inhibitors in Cancer and Management of Immune-Mediated Side Effects

Kellye Aschmeyer, PharmD, BCOP

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BUILT TO BEAT CANCER | NORTHSIDE HOSPITAL CANCER INSTITUTE

1

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Faculty: Kellye Aschmeyer, PharmD, BCOP

No relevant financial relationships exist.

2

Objectives

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At the conclusion of this presentation pharmacists should be able to:

- Discuss the mechanism of action of Immune Checkpoint Inhibitors (ICIs)
- Describe the disease states where ICIs are commonly used
- Identify newer approvals and indications of ICIs
- Review potential irAEs (immune-related adverse events) of ICIs

At the conclusion of this presentation pharmacy technicians should be able to:

- Name the Immune Checkpoint Inhibitor (ICI) used for second line treatment of cervical cancer
- Recall examples of irAEs (immune-related adverse events)
- List one endocrine disorder caused by ICIs

3

Immune Checkpoint Inhibitors

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- Modern era of immune therapy began in 1985 with first studies of interferon in melanoma, approved 1995
- Approval of first Immune Checkpoint Inhibitors (ICIs) targeting CTLA-4 in 2011 for metastatic melanoma (ipilimumab)
- Two approvals in 2014 of PD-1 inhibitors (pembrolizumab and nivolumab)
- These therapies result in lasting tumor responses

4

Targets of Immune Checkpoint Inhibitors

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- CTLA-4 –cytotoxic T lymphocyte-associated antigen
- Programmed cell death protein-1(PD-1) on T-cell
- Programmed cell death protein-1 ligand (PD-L1) on tumor cell

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5

Mechanism of Immune Checkpoint Inhibitors:

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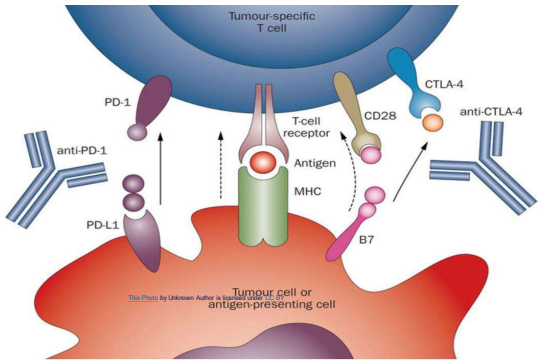

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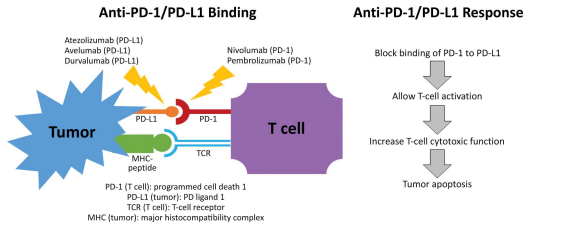

Figure 1a. Illustrations show the mechanisms of action (left) of ICIs and the downstream tumor effects (right) for PD-1 and PD-L1 **(a)** and CTLA-4 **(b)** inhibitors. *APC* = antigen-presenting cell, *B7-1/2* = ligands B7-1 and B7-2.

Kalisz KR. Published Online: October 04, 2019
https://doi.org/10.1148/rg.2019190036

7

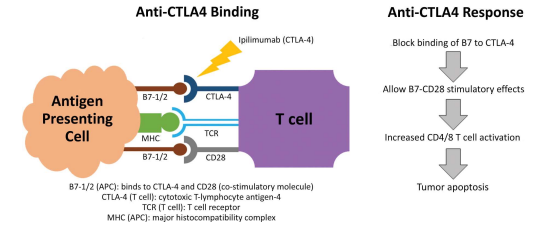

Figure 1b. Illustrations show the mechanisms of action (left) of ICIs and the downstream tumor effects (right) for PD-1 and PD-L1 **(a)** and CTLA-4 **(b)** inhibitors. *APC* = antigen-presenting cell, *B7-1/2* = ligands B7-1 and B7-2.

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8

FDA-Approved ICI Therapy Agents

Drug	Target	Indications
Ipilimumab	CTLA-4	Melanoma, RCC (with nivo), colorectal (with nivo)
Nivolumab	PD-1	Melanoma, small cell CA, NSCLC, RCC, Hodgkin lymphoma, head/neck CA, SCC, urothelial carcinoma, colorectal, Hepatoceullar carcinoma
Pembrolizumab	PD-1	Melanoma, NSCLC, Hodgkin, head/neck CA, urothelial carcinoma, colorectal cancer, HCC, gastric CA, cervical CA, Merkel cell

 9

9

FDA-Approved ICI Therapy Agents

Drug	Target	Indications
Cemiplimab	PD-1	Cutaneous Squamous cell CA
Durvalumab	PD-L1	Urothelial CA, NSCLC
Atezolizumab	PD-L1	Urothelial CA, NSCLC, HCC
Avelumab	PD-L1	Merkel cell CA, Urothelial CA
Dostarlimab	PD-1	Endometrial CA, recurrent dMMR disease

 10

10

Evolution of Use in Cancer

- First used in metastatic setting, Stage IV melanoma, Non-Small Cell Lung Cancer
- Applications for use as consolidation therapy (durvalumab)
- Now being used in adjuvant setting (after surgery)
- Studies underway in neoadjuvant setting (before surgery)
- Estimated 45% of cancer patients will now be treated with ICIs

 11

11

Dostarlimab-gxly

- Humanized monoclonal Ab that binds to PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, resulting in improved T-cell response to tumor, increasing T-cell proliferation and cytokine production
- Indicated in endometrial cancer, recurrent or advanced, dMMR disease, that has progressed on or following treatment with a platinum containing compound
- Indicated in solid tumors with dMMR disease, recurrent or advanced, that have progressed on or following prior treatment

 12

12

Dostarlimab-gxly

- Dose 1-4: 500mg IV over 30 mins every 3 weeks
- Subsequent doses: 1000mg IV over 30 mins every 6 weeks (begin 3 weeks after dose 4)
- Duration of therapy: continue until disease progression or unacceptable toxicity

13

Outcomes in Non-Small Cell Lung Cancer

- Historically, patients with Stage IV NSCLC were treated with cisplatin-based chemotherapy, median survival 8-10 months
- Data from 4 pivotal trials (2015-2017) provided basis for use of ICI as single agent therapy after progression on platinum-based therapies (pembrolizumab, nivolumab, atezolizumab)
- Subsequent studies demonstrated survival benefits using ICIs alone or combined with chemotherapy in first line setting

14

Outcomes in Non-Small Cell Lung Cancer

- KEYNOTE -024 demonstrated overall survival benefit for pembrolizumab vs platinum-based chemotherapy as first line therapy in patients whose tumors expressed a high level of PD-L1 on the cell surface (PD-L1 >/= 50%)
- Median survival at 3 years of follow-up: 26.3 months (pembrolizumab) compared with 14.2 months in the platinum-based chemotherapy group. 36-month overall survival 43.7% (pembrolizumab) vs 24.9% (chemotherapy arm)
- KEYNOTE-189 trial demonstrated a similar doubling of survival for patients receiving pembrolizumab with chemotherapy compared with chemotherapy alone.
- Benefits seen in squamous and non-squamous forms of NSCLC. Anti-PD-1/PD-L1 now a mainstay of treatment

15

Outcomes in Melanoma

- Ipilimumab, inhibitor of CTLA4 checkpoint, first drug to improve overall survival in patients with advanced melanoma.
- Potential for durable disease control in a minority of patients
- In a pooled analysis of 12 phase II and III studies there was a plateau in overall survival curve at 3 years at 20% which was maintained for 10 years.

16

Outcomes in Melanoma

- In Phase III clinical trials both pembrolizumab and nivolumab had superior efficacy in treatment-naive patients compared to ipilimumab. Five-year landmark overall survival of 43% for pembrolizumab and 44% for nivolumab compared to 26% for ipilimumab
- Combining ipilimumab with nivolumab results in superior PFS and overall survival. There is also a higher risk of toxicity with the combination, so focus on identifying subgroups most likely to benefit from the combination
- Studies demonstrate that patients with negative PD-L1 expression, liver or brain metastases, elevated LDH and high burden of disease benefit most with combined ipilimumab plus nivolumab therapy

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17

Outcomes in Urothelial Cancer

- For use after surgery (cystectomy) for early-stage tumors: nivolumab has shown benefit in the Checkmate 274 trial
- 709 patients with muscle invasive urothelial carcinoma treated with radical surgery treated with nivolumab vs placebo. DFS 20.8 months with nivolumab vs 10.8 months w placebo (HR, 0.70, CI: 0.55-0.90, P<.001)
- For patients with a PD-L1 expression of 1% or more, DFS was 74.5% for nivolumab vs 55.7% for placebo (HR 0.55; CI 0.35-0.85, P<.001)
- Treatment related AE of grade 3 or greater occurred in 17.9% of nivolumab patients vs 7.2% of placebo patients

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18

Outcomes in Urothelial Cancer

- For patients with Stage IV (metastatic) disease who are ineligible to receive cisplatin-based therapy, Pembrolizumab may be considered as first line therapy based on PD-L1 testing results
- Pembrolizumab, Nivolumab, and Avelumab are approved for treatment of locally advanced or metastatic urothelial carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 testing
- Avelumab has been approved as “maintenance” therapy for locally advanced or metastatic urothelial carcinoma that has not progressed after cisplatin-based therapy

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19

Role in Breast Cancer
High Risk Triple-Negative Breast Cancer (TNBC)

- Pembrolizumab has been approved for treatment of triple negative breast cancer, combined with standard first line chemotherapy (**earlier stage disease**)
- Preoperative pembrolizumab with carboplatin/paclitaxel, followed by pembrolizumab with cyclophosphamide and doxorubicin, followed by adjuvant pembrolizumab OR same combinations given after surgery for TNBC
- KEYNOTE 522: 1174 patients were studied. Pembrolizumab + chemo vs chemo alone. Median follow-up 39 months. Event-free survival at 36 months 84.5% (pembro + chemo) vs 76.8% in the chemo alone group. HR 0.63, CI 0.48-0.82 (P <0.001)
- For TNBC **recurrent or unresectable** or Stage IV with PD-L1 expression, the combination of Pembrolizumab + chemotherapy (Abraxane, paclitaxel, or gemcitabine plus carboplatin) is a preferred combination

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20

Role in Breast Cancer
High-Risk Triple-Negative Breast Cancer (TNBC)

- Addition of pembrolizumab in early stage disease improves pathologic complete response
- Why give chemotherapy before surgery? Improves breast conservation

21

Role in Hodgkin Lymphoma

- For relapsed or refractory Hodgkin Lymphoma: after treatment with stem cell transplant and/or brentuximab vedotin, or if patient is transplant ineligible
- Pembrolizumab or ICE (Ifosfamide/Cisplatin/Etoposide) + nivolumab are both options in these settings

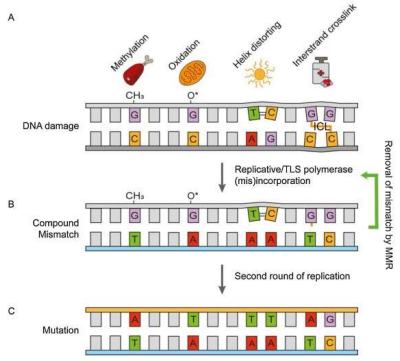
22

Deficient Mismatch Repair and Microsatellite Instability (high)

- Mismatch repair refers to a DNA process involved in maintaining genomic stability
- Involves recognizing and repairing base-base mismatches and insertion/deletion errors during DNA replication
- When there are defects in MMR, results in genomic instability and progressive accumulation of mutations, especially in regions of simple repetitive DNA sequences known as microsatellites
- Microsatellite instability high reflects a hypermetabolic phenotype that allows mutations to accumulate rapidly, resulting in tumor development
- Next-generation sequencing tests used to detect dMMR/MSIh within tumor samples

23

Deficient Mismatch repair



24

MSI-H or dMMR Disease "Tumor-Agnostic therapy"

- Pembrolizumab approved May 2017 for unresectable or metastatic solid tumors that have been identified as possessing either of these biomarkers
- Dostarlimab gained similar approval in 2021 for patients with dMMR disease
- Microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR)
- ICIs may be used in any tumor with this biomarker after progression on first line therapies. Includes colon, gastric and endometrial cancer

25

Role in Cervical Cancer

- Pembrolizumab approved June 2018 approved for previously treated patients with recurrent or metastatic cervical cancer whose tumors express PD-L1 (≥1%) can be used as second-line therapy.

26

Ipilimumab as Part of Combination Therapy with Nivolumab

- For unresectable or metastatic melanoma (off-label) 3mg/kg Q3 weeks for 4 doses in combination
- For advanced renal cancer, ipilimumab 1mg/kg Q3 weeks for 4 doses, in combination
- For colorectal cancer, metastatic, MSI-H or dMMR, 1mg/kg Q3 weeks in combination
- For small cell lung cancer (off-label) 3mg/kg Q3 weeks for 4 doses, in combination

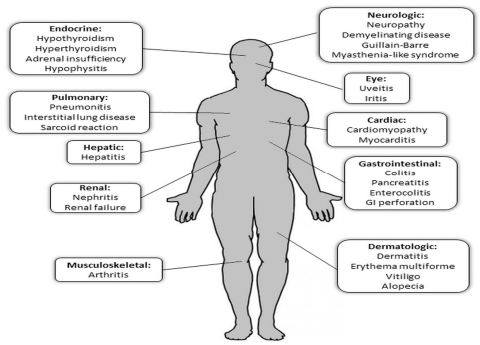
27

Side Effects of Immune Checkpoint Inhibitors

- Boosting innate immune system may lead to inflammatory toxicities known as irAEs (immune-related adverse events). Commonly involve skin, gastrointestinal, hepatic and endocrine systems
- Overall rate of severe irAEs requiring immunosuppression and withdrawal of immunotherapy estimated to be 0.5-13%
- Toxicities appear to be dose-related with ipilimumab; not dose-dependent with anti-PD-1 or anti-PD-L1

28

Targets of Immune-Mediated Toxicity



29

General Principles of Management

- Follow package insert guidelines
- Severity graded using Common Terminology Criteria for Adverse Events (CTCAE). Scale 1-5, with 1=mild, 2=moderate, 3=severe, 4=life threatening, 5=death
- Regardless of affected organ system, same general approach applies

30

Common Terminology Criteria for Adverse Events (CTCAE), Version 5

Grade	1	2	3	4	5
Diarrhea Colitis	Increase of < 4 stools per day over baseline (or mild increase in ostomy output compared with baseline) without colitis symptoms	Increase of 4–6 stools per day over baseline (or moderate increase in ostomy output compared with baseline) and/or colitis symptoms limiting instrumental ADLs	Increase of > = 7 stools per day over baseline (or severe increase in ostomy output compared to baseline), colitis symptoms interfering with ADLs; incontinence; hospitalization indicated; limiting self-care ADL	Life-threatening consequences (e.g., perforation, hemodynamic instability); urgent intervention indicated	Death

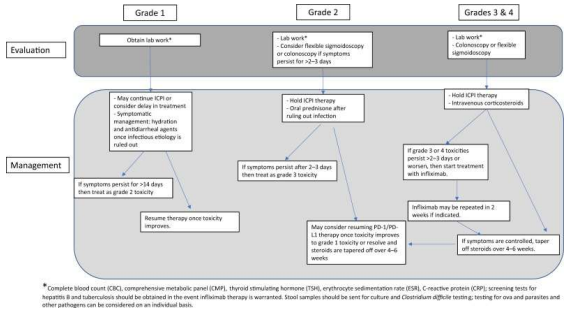
31

Common Terminology Criteria for Adverse Events (CTCAE), Version 5

Grade	1	2	3	4	5
Hepatitis	AST/ALT < 3x ULN and/or total bilirubin <1.5x ULN	AST/ALT 3–5x ULN and/or total bilirubin >1.5 to ≤ 3x ULN	AST/ALT > 5–20x ULN and/or total bilirubin 3–10x ULN	Decompensated liver function, AST/ALT > 20x ULN, and/or total bilirubin >10x ULN	Death

32

Management of ICI-induced Colitis



*Complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid stimulating hormone (TSH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP); screening tests for hepatitis B and tuberculosis should be obtained in the event infliximab therapy is warranted. Stool samples should be sent for culture and *Clostridium difficile* testing; testing for ova and parasites and other pathogens can be considered on an individual basis.

33

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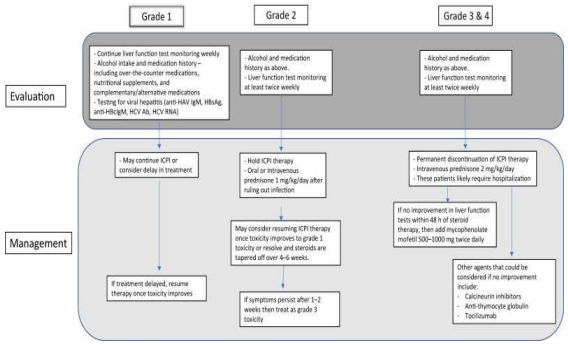
Management of ICI-induced Hepatitis



34

Dermatologic Side Effects

- Most common and occurs earliest. 47-68% of patients on CTLA-4 inhibitors, 30-60% of patients on anti-PD-1/anti-PD-L1 antibodies. Within 2-5 weeks may appear
- Rash/pruritus and mucositis. Characteristic rash is erythematous and maculopapular, involves trunk and extremities, most mild
- Vitiligo has delayed appearance after several months. Topical glucocorticoids or urea-containing creams and oral anti-pruritic agents

35

Endocrine Side Effects

- Presents at the ninth week and later and involves inflammation of the pituitary (hypophysitis), thyroid and adrenal glands (adrenal failure), pancreas (DM)
- Seen in up to 10% of patients
- Non-specific symptoms such as nausea, headache, fatigue
- Routine monitoring of thyroid function tests (TSH and free T4) determine hypothyroidism and hyperthyroidism
- Hypophysitis requires thyroid testing, serum cortisol, ACTH, Growth Hormone, prolactin, LH, and FSH in women, testosterone in men

36

Gastrointestinal Toxicities

- Occurs from 5-6 weeks and later. Diarrhea is common, greater with CTLA-4 antibodies compared to antibodies to PD-1/PD-L1
- Important to differentiate symptoms of colitis (abdominal pain, radiographic or endoscopic evaluation)
- Higher grades of diarrhea/colitis up to 5% with ipilimumab, 1-2% with anti-PD-1/anti-PD-L1
- Severe cases may require IV corticosteroids, hospitalization, hydration, electrolyte replacement. If 2mg/kg methylprednisolone twice daily does not lead to symptom resolution within 3 days, start infliximab at dose of 5mg/kg
- Rare cases of bowel perforation, death

37

Hepatitis

- Usually presents as elevated AST/ALT, sometimes bilirubin, fever less common. Incidence 2-9%. Routine monitoring recommended
- Onset 8-12 weeks. If no other causes explain, treat with corticosteroids. If elevated transaminases are refractory to steroids, treatment with mycophenolate 500mg Q12H recommended
- Hepatitis may persist, require prolonged or repeated corticosteroid tapers

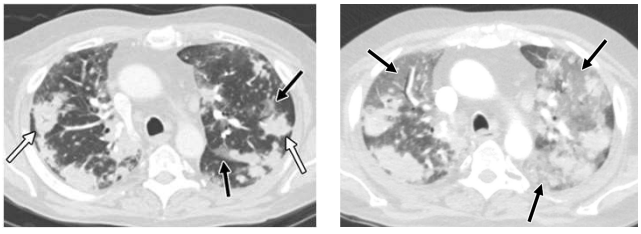
38

Immune Mediated Pneumonitis with PD-1 Inhibitors

- Meta-analysis has evaluated total of 20 clinical trials. Included patients with melanoma, renal cell carcinoma, non-small cell lung cancer
  - Overall incidence of pneumonitis all grades was 2.7% and 0.8% for Grade 3 or higher in patients treated with monotherapy
  - With combination therapy (melanoma patients) incidence is higher: 6.6% for all grades and 1.5 % for Grade 3 or higher
- Incidence higher in NSCLC and RCC than in melanoma. Onset 8-14 weeks, presents as cough, SOB, fever
- NSCLC may have a higher incidence due to exposure to smoking and underlying lung conditions. Also may be due to underlying tumor burden in lung

39

Case report: Pneumonitis



Case: 57 yo man treated with nivolumab for stage IV lung cancer. Six weeks after starting nivo patient presents w worsening dyspnea. Started high dose steroid therapy, still developed ARDS pattern of pneumonitis; died one week later.

40

Less Common Toxicities

- Eye: symptoms include photophobia, pain, dry eye, blurry vision. Consult with ophthalmologist, steroid eye drops. Infrequent, less than 1%
- Kidney: acute granulomatous interstitial nephritis, presents at 13 weeks
- Neurologic syndromes: posterior reverse encephalopathy syndrome, aseptic meningitis, enteric neuropathy, transverse myelitis, Guillain-Barre syndrome

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41

Less Common Toxicities

- Pancreatitis: Routine monitoring of amylase, lipase not recommended. Elevations seen commonly, not sure of clinical significance
- Hematologic: Rarely seen red cell aplasia, neutropenia, acquired hemophilia A, and thrombocytopenia
- Myocarditis: Rare, less than 1%. High mortality

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42

Recommendations for Grades of Toxicity

- Grade 2: interrupt therapy; begin corticosteroids (prednisone 0.5-1mg/kg per day) if symptoms persist > 1 week
- Grade 3 or 4: higher doses of corticosteroids (prednisone 1-2mg/kg/day). Taper steroids gradually until symptoms subside to Grade 1 or less
- Grade 4: stop ICIs permanently. See organ-specific guidelines
- Immunotherapies can be continued in setting of endocrinopathies controlled with hormone replacement

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43

Key Points with Immune-Related AEs

- If appropriately managed with immunosuppressive therapy, patients generally recover from AEs
- Efficacy of immunotherapy not impaired by immunosuppressive treatments
- Appears to be a correlation to immune-mediated AE and long-term outcomes with immunotherapy
- Patients who stop immunotherapy because of AEs can still have excellent outcomes

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44

Assessment Questions

Which ICI was approved for use in triple negative breast cancer and for second-line treatment of cervical cancer?

A. nivolumab
B. atezolizumab
C. pembrolizumab
D. avelumab

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Assessment Questions

Are irAEs (immune-related adverse events) correlated to a worse or better disease response to ICIs?

A. Worse

B. Better

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Assessment Questions

Endocrine disorders cause by ICIs (immune checkpoint inhibitors) are treated with supplementation of the gland in most cases, for example, hypothyroidism treated with levothyroxine.

A. True

B. False

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50

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