UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

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Checking In with the Immune Checkpoint Inhibitors

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PollEverywhere Audience Response

- ACPE requires active learning and most prefer real-time participation rather than a graded post-test
- We are utilizing PollEverywhere software for this process.
- You may join to participate by 3 different ways:
  - **Web Browser: Go to PollEv.com/ushp**
  - **PollEverywhere app: Download app and join ushp presentation**
  - **Text Messaging: Text ushp to 22333**
- We recommend the PollEverywhere app or web browser as they are easier to respond
- For each question, you can click on the correct answer in Web Browser or App or text correct answer to 22333

Disclosure

- Relevant Financial Conflicts of Interest
  - CE Presenter, Danielle Rustem: No relevant conflicts of interest
  - CE Mentor, Jordan McPherson: No relevant conflicts of interest
  - CE Mentor, Dan Sageser: No relevant conflicts of interest
- Off-Label Uses of Medications
  - This presentation will not include off-label uses of medications

Learning Objectives - Pharmacists

At the conclusion of this activity, participants should be able to successfully:

- Describe new first-line and novel indications for immune checkpoint inhibitors and their current impact on health care costs in the US.
- Develop an immune checkpoint inhibitor-containing treatment regimen based on a patient's diagnosis, FDA-approved indications, and toxicity profile.
- Assess appropriateness of immune checkpoint inhibitor therapy based on oncologic history, genetic testing, and immunotherapy biomarkers.

Learning Objectives - Technicians

At the conclusion of this activity, participants should be able to successfully:

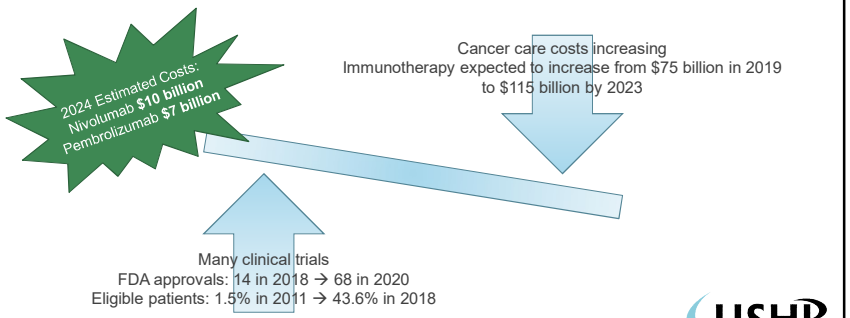
- Recognize the current impact of increased immune checkpoint inhibitor utilization on health care costs in the US.
- Compare and contrast the toxicities expected with chemotherapy-based, immunotherapy-based, and combined regimens.
- Discuss immunotherapy biomarkers used to predict response to immune checkpoint inhibitors.

Presentation Checkpoints

- ✓ The Immunotherapy Renaissance
- ✓ New Practice-Changing Indications
  - ✓ Tumor Agnostic
  - ✓ Melanoma
  - ✓ Small Cell Lung Cancer
  - ✓ Triple-Negative Breast Cancer
- ✓ Checking Out

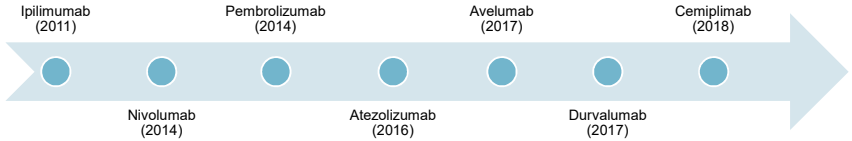
The Immunotherapy Renaissance

Growing in Utility…And Cost



Haslam A, Prasad V. JAMA. 2019;2(5):e192535
PRNewswire. [Internet]. 2019 Dec. Available from: https://www.prnewswire.com/news-releases/global-cancer-immunotherapy-market-report-2020-market-accounted-for-50-o-the-overall-oncology-drugs-market-generating-75-billion-in-2019-and-115-billion-by-2023-300969196.html
European Pharmaceutical Review. [Internet]. 2016 Apr. Available from: https://www.europeanpharmaceuticalreview.com/news/40547/immuno-oncology-globaldata/

The Immune Checkpoint Inhibitors (ICIs)



68 Total FDA Approved Indications as of September 2020

Lexi-Comp Online, Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc. Accessed 2020 Sep.

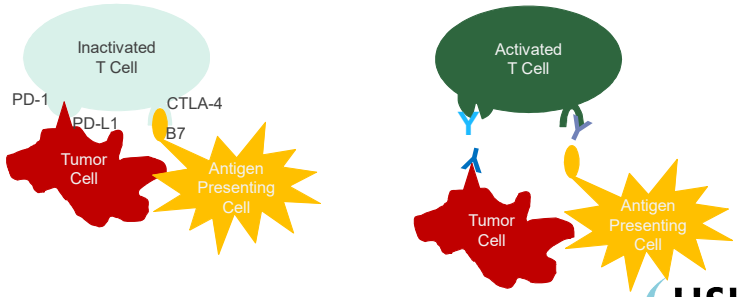
Immune Checkpoint Physiology

- T cells recognize tumor specific antigens presented by MHC and activate
- Inhibitory pathways in the immune system
  - Minimize unwanted targeting of "self" tissues (autoimmunity)
  - CTLA-4 and PD-1 are immune checkpoint receptors on T cells
    - Bound to ligands: negative feedback to de-activate T cells
- Cancer cells hijack immune pathways to escape immune system
  - Express ligands found on normal tissue (ex: PD-L1)

Li B, et al. Curr Med Chem. 2019;26:3009-25

Mechanism of ICIs

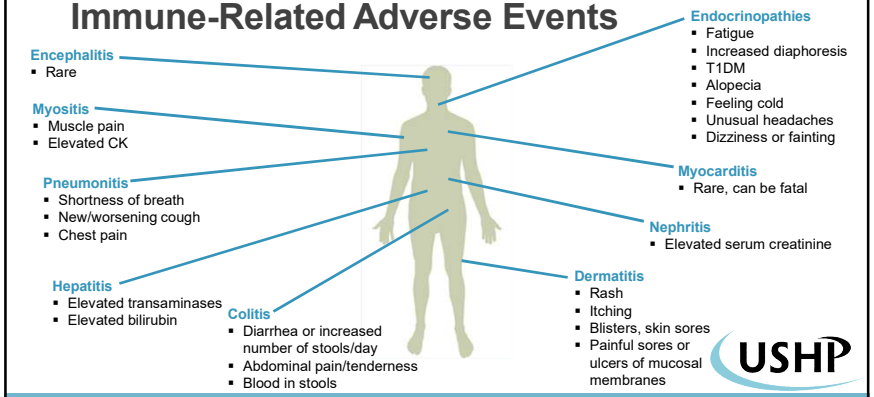
*Illustrations not drawn to scale (or morphologically accurate)



ICIs: Taking the Foot off the Brakes of the Immune System

Li B, et al. Curr Med Chem. 2019;26:3009-25
Wei SC, et al. Cancer Discov. 2018 Sep;8(9):1069-86

Immune-Related Adverse Events



Adapted from: Bristol-Myers Squibb Opdivo (nivolumab) Safety Tool
https://www.opdivosafetytool.com/#/superhome

Why Immunotherapy?

- Durable treatment responses
- Success in patients who have failed multiple other lines of treatment
- Less toxic than chemotherapeutic agents
- Accumulation of somatic mutations → neoantigens

- **BUT** single agent immunotherapy gives limited response
  - Melanoma: 40% ORR
  - NSCLC: 25% ORR
  - RCC: 19% ORR

Dudley, JC, et al. Clin Cancer Res. 2016 Feb;22(4):813-20
Goodman AM, et al. Mol Cancer Ther. 2017 Nov;16(11):2598-608

New FDA Indications 2019-2020

- Pembrolizumab: adjuvant treatment of high risk, stage III melanoma
- Atezolizumab (+ chemotherapy): first line treatment of unresectable or metastatic triple-negative breast cancer that expresses PD-L1
- Atezolizumab (+ chemotherapy): first line treatment of extensive-stage small cell lung cancer
- Pembrolizumab: first line treatment of stage III non-small cell lung cancer that is PD-L1 positive and not amenable to surgery or chemo-radiation
- Avelumab (+ axitinib): first line treatment of advanced renal cell carcinoma
- Pembrolizumab: first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma

Cancer Research Institute. [Internet]. Immunotherapy timeline of progress. Accessed: 2020 Sep. Available from:
https://www.cancerresearch.org/immunotherapy/timeline-of-progress

New FDA Indications 2019-2020

- Pembrolizumab: treatment of metastatic lung cancer after progression on or after platinum-based chemotherapy and at least one other prior therapy
- Pembrolizumab: treatment of metastatic lung cancer after progression on or after platinum-based chemotherapy and at least one other prior therapy
- Pembrolizumab: treatment of advanced esophageal squamous cell cancer
- Pembrolizumab: treatment of advanced endometrial carcinoma after progression following prior systemic therapy and ineligible for surgery or radiation
- Atezolizumab (+ chemo): first line treatment of metastatic nonsquamous non-small cell lung cancer without EGFR or ALK mutations
- Pembrolizumab: treatment of high risk, non-muscle invasive bladder cancer not responsive to BCG treatment and not undergoing cystectomy

Cancer Research Institute. [Internet]. Immunotherapy timeline of progress. Accessed: 2020 Sep. Available from:
https://www.cancerresearch.org/immunotherapy/timeline-of-progress

New FDA Indications 2019-2020

- Nivolumab + ipilimumab: treatment of advanced hepatocellular carcinoma after treatment with sorafenib
- Durvalumab: first line treatment of extensive small cell lung cancer in combination with standard of care chemotherapy
- Nivolumab + ipilimumab: first line treatment of metastatic non-small cell lung cancer that expresses PD-L1 and without EGFR or ALK mutations
- Nivolumab + ipilimumab (+ platinum doublet): first line treatment of metastatic or recurrent non-small cell lung cancer without EGFR or ALK mutations
- Atezolizumab (+ bevacizumab): treatment of previously untreated hepatocellular carcinoma
- Nivolumab: treatment of unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after fluoropyrimidine and platinum-based chemotherapy

New FDA Indications 2019-2020

- Pembrolizumab: treatment of unresectable or metastatic tumor mutational burden-high solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- Pembrolizumab: treatment of recurrent or metastatic cutaneous squamous cell carcinoma not curable by surgery or radiation
- Pembrolizumab: first line treatment of unresectable or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer
- Avelumab: maintenance treatment of locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-based chemotherapy
- Atezolizumab (+ cobimetinib and vemurafenib): treatment of BRAF V600 mutation-positive advanced melanoma

Cancer Research Institute. [Internet]. Immunotherapy timeline of progress. Accessed: 2020 Sep. Available from: https://www.cancerresearch.org/immunotherapy/timeline-of-progress
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Knowledge Checkpoint - Pharmacists

- Which of the following best describes the number of FDA-approved indications for ICIs in the past 9 years?
  - Most new indications for immune checkpoint inhibitors are in 3rd line or greater settings
  - The number of FDA-approved indications has more than tripled in 9 years
  - Most new indications for immune checkpoint inhibitors are for melanoma
  - Due to increased toxicity, the FDA is no longer approving chemo-immunotherapy combinations

Knowledge Checkpoint - Technicians

- What impact do the ICIs have on the cost of cancer care in the US?
  - The cost of ICIs is decreasing, lowering the cost of cancer care
  - The cost of ICIs is remaining relatively the same
  - The cost of ICIs is increasing, raising the cost of cancer care
  - The cost of ICIs has no impact on the cost of cancer care

Practice Changing Indications

Tumor Agnostic

Mutations, Mutations

Deficient mismatch repair (dMMR)

- MMR targets base pair mismatches in DNA for correction
- Frameshift mutations can cause truncated protein products (dysfunctional MMR)
- Found in several advanced cancers: colorectal (4%), endometrial (18%), ovarian (11%)

High microsatellite instability (MSI-H)

- Short tandem repeats
- DNA polymerase is more likely to make mistake in repeat regions
- Found in >10% of following cancers: colorectal, endometrial, gastric, hepatocellular, thyroid, melanoma
- Significant predictor of response to immunotherapy

High tumor mutational burden (TMB-H)

- Number of genetic mutations in malignant cells
- Independent of dMMR/MSI-H
- High TMB associated with higher response rates, longer PFS and OS
- Tumors with high TMB: non-small cell lung cancer, melanoma

Dudley, JC, et al. Clin Cancer Res. 2016 Feb;22(4):813-20
Goodman AM, et al. Mol Cancer Ther. 2017 Nov;16(11):2598-608

KEYNOTE-177 (Ongoing)

Randomized Controlled Trial

- Open-label, phase III
- Metastatic MSI-H or dMMR colorectal cancer
- Previously untreated patients

Interim Analysis Cutoff:
February 19, 2020
- 307 patients
- Median 32.4mo follow up

Treatment Arms

- Pembrolizumab 200mg every 3 weeks (up to 2 years)
- Standard of care (SOC): FOLFOX6 or FOLFIRI every 2 weeks (until progression or toxicity)
  - +/- bevacizumab or cetuximab

Helwick, C. [Internet]. The ASCO Post. 2020 Jun [Accessed 2020 Sep]. Available from: https://ascopost.com/issues/june-10-2020/pembrolizumab-doubles-progression-free-survival-in-msi-hdmmr-metastatic-colorectal-cancer/

KEYNOTE-177 Interim Analysis Results

Primary Outcomes

- Progression Free Survival (PFS)

	Pembrolizumab	SOC	
Median PFS	16.5 mos	8.2 mos	p=0.0002
PFS at 12 mos	55%	37%	
PFS at 24 mos	48%	19%	

- Overall Survival
  - Will be evaluated at study completion

KEYNOTE-177 Interim Analysis Results

Other Outcomes

	Pembrolizumab	SOC
Objective response rate	43.8%	33.1%
Median duration of response	Not Reached	10.6 mos
Complete response	11.1%	3.9%
Partial response	32.7%	29.2%
Response at 24 mos	83%	35%
Grade 3-5 toxicities	22%	66%

FDA approved indication: For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer

Knowledge Checkpoint - Technicians

- Which of the following biomarkers would be most useful in determining if a patient was a candidate for therapy with pembrolizumab?
  - High microsatellite instability (MSI-H)
  - Endothelial growth factor receptor (EGFR) mutated
  - BRAF V600E mutated
  - Functioning mismatch repair (MMR)

Melanoma

BRAF Melanoma

- Historically, metastatic melanoma uniformly fatal
  - BRAF-targeted and immunotherapy have improved OS

BRAF/MEK-targeted therapy

- BRAF mutated in 50% of tumors
  - BRAF V600E most common
- MEK downstream of BRAF
- Median OS >25mos in BRAF/MEK inhibitor trials
- Became standard of care for BRAF-mutated melanoma

+?

Immunotherapy

- High burden of somatic mutations
- 10-15% of patients responded to ipilimumab
- 20-40% of patients responded to anti-PD-1 agents
- Durable responses

Luke JJ, et al. Nat Rev Clin Oncol. 2017 Aug;14(8):463-482

IMspire150

Randomized Controlled Trial

- Double-blind, phase III
- Unresectable, stage III-IV BRAFV600 positive melanoma

514 patients enrolled
- 256 atezolizumab
- 258 placebo
- Median 18.9mo follow-up

Treatment Arms

- Atezolizumab arm
  - Vemurafenib 720mg BID D1-28, cobimetinib 60mg QD D1-21, atezolizumab 840mg D1 and D15
- Placebo arm
  - Vemurafenib 960mg BID D1-28, cobimetinib 60mg QD D1-21, placebo D1 and D15

Gutzmer R, et al. Lancet. 2020;395:1835-44

IMspire150 Results

Primary Outcome

- Progression Free Survival (PFS)

	Atezolizumab	Placebo	
Median PFS	15.1 mos	10.6 mos	p=0.025

- High discontinuation rate in both arms
  - 45% in atezo arm and 51% in placebo arm
  - Death most common reason for discontinuation in both arms (p=0.23)
  - Only 25% of all patients continuing study treatment at data cutoff
    - 28% in atezo arm and 21% in placebo arm

Gutzmer R, et al. Lancet. 2020;395:1835-44

IMspire150 Results

Other Outcomes

	Atezolizumab	Placebo
2yr event free survival	60%	53%
Objective response rate	66.3%	65%
Complete response rate	15.7%	17.1%
Stable disease	22.7%	22.8%
Median duration of response	21 mos	12.6 mos
Treatment related ADRs	99%	99%
Grade 3 or 4 reactions	79%	73%

FDA approved indication: In combination with cobimetinib and vemurafenib for the treatment of BRAFV600 mutation-positive unresectable or metastatic melanoma

Gutzmer R, et al. Lancet. 2020;395:1835-44

Knowledge Checkpoint - Technicians

- What is the likelihood of experiencing adverse events with the combination of cobimetinib + vemurafenib + atezolizumab?
  - 0-25%
  - 26-50%
  - 51-75%
  - 76-100%

Small Cell Lung Cancer

Effects on irAEs

- Conventional chemotherapy added to immunotherapy (CIT) for synergy
  - Significant improvements seen in OS, PFS, and response rates
- Incidence of irAEs increases with chemotherapy combinations
  - Dermatitis in 9-10% anti-PD-1 → 15% of anti-PD-1 + chemotherapy
  - Combination anti-PD-1 + chemotherapy increases hepatitis to 3-20%
  - Increased risk of endocrine irAEs with CIT

Yan Y, et al. Front Immunol. 2018 Jul;9:1739
Remon J, et al. J Thorac Dis. 2018;10(Suppl 13):S1516-33

IMpower133

Randomized Controlled Trial

- Double-blind, phase III
- Extensive-stage small cell lung cancer (SCLC)
- Previously untreated patients

403 patients enrolled
- 201 atezolizumab
- 202 placebo
- Median 13.9mo follow-up

Treatment Arms

- Carboplatin AUC 5 D1 + etoposide 100mg/m^2 D1-3 q21D x4 cycles PLUS
  - Atezolizumab 1200mg D1 OR
  - Placebo D1
- Maintenance atezo or placebo until progression or toxicity

Horn L, et al. N Engl J Med. 2018;379:2220-9

IMpower133 Results

Primary Outcomes

- Progression Free Survival (PFS) and Overall Survival (OS)

	Atezolizumab	Placebo	
Median PFS	5.2 mos	4.3 mos	p=0.02
Median OS	12.3 mos	10.3 mos	p=0.007
1yr OS rate	51.7%	38.2%	

IMpower133 Results

Safety Outcomes

	Atezolizumab	Placebo
Adverse events	94.9%	92.3%
Immune-related adverse events*	39.9%	24.5%

- *Immune-related adverse events ≠ immunotherapy-related adverse events

FDA approved indication: In combination with carboplatin and etoposide, for the first-line treatment extensive-stage small cell lung cancer

Knowledge Checkpoint - Pharmacists

- A 67 YOM patient was recently diagnosed with extensive stage small cell lung cancer. He returns for a follow-up appointment with his oncologist to discuss treatment options. Which of the following regimens would you recommend to the oncologist for this patient?
  - Cisplatin + etoposide because this patient is not a candidate with immunotherapy as his tumor is not deficient in MMR
  - Carboplatin + etoposide + ipilimumab because this regimen has a lower risk of immune-related adverse events
  - Carboplatin + etoposide + atezolizumab because this regimen has shown favorable outcomes in this patient population
  - Pembrolizumab monotherapy to avoid the risk of immune-related adverse events associated with chemo-immunotherapy

Triple-Negative Breast Cancer

Limited Options in an Aggressive Disease

- Pathologic definition: lacks expression of ER/PR and HER2
  - Heterogeneous subtypes (basal and luminal most common)
- Higher overall rates of recurrence
  - Risk of recurrence peaks at 3 years, then declines
  - Median OS for metastatic disease: 10-13mos
- Chemotherapy options for advanced disease
  - Single agents preferred (taxanes, topoisomerase inhibitors, vinca alkyloids, etc.)
  - PARP inhibitors or platinum-based regimens if BRCA mutated
  - Next gen sequencing for other mutations

USHP

Waks AG, Winer EP. JAMA. 2019;321(3):288-300
Gadi VK, Davidson NE. J Oncol Pract. 2017 May;13(5):293-300

IMpassion130

Randomized Controlled Trial

- Double-blind, phase III
- Unresectable or metastatic triple negative breast cancer
- Previously untreated patients

902 patients enrolled
- 451 atezolizumab
- 451 placebo
- Median 12.9mo follow-up

Treatment Arms

- Nab-paclitaxel 100mg/m^2 D1, 8, 15 q28D PLUS
  - Atezolizumab 840mg D1, 15 OR
  - Placebo D1, 15

USHP

Schmid P, et al. N Engl J Med. 2018;379:2108-21

IMpassion130 Results

Primary Outcomes

- Progression Free Survival (PFS) and Overall Survival (OS)

	Atezolizumab	Placebo	
Median PFS	7.2 mos	5.5 mos	p=0.002
Progression or death	79.4%	83.8%	
PD-L1 positive progression or death	74.6%	85.3%	
PD-L1 positive PFS	7.5 mos	5 mos	p<0.001
Median OS	21.3 mos	17.6 mos	p=0.08
PD-L1 positive OS	25 mos	15.5 mos	

USHP

Schmid P, et al. N Engl J Med. 2018;379:2108-21

IMpassion130 Results

Other Outcomes

	Atezolizumab	Placebo
Objective response rate	56%	45.9%
PD-L1 positive subgroup	58.9%	42.6%
Median duration of response	7.4 mos	5.6 mos
PD-L1 positive subgroup	8.5 mos	5.5 mos
Adverse events	99.3%	97.9%
Grade 3 or 4	48.7%	42.2%
Potential immune-related	57.3%	41.8%

FDA approved indication: In combination with paclitaxel protein-bound for the treatment of unresectable locally advanced or metastatic TNBC whose tumors express PD-L1

USHP

Schmid P, et al. N Engl J Med. 2018;379:2108-21

But Not Every Combination Works…

- IMpassion131: double-blind, placebo-controlled, randomized phase III trial
  - Paclitaxel 90mg/m^2 + atezolizumab 840mg or placebo
  - Metastatic triple-negative breast cancer, previously untreated
- PFS: 6 mos atezo group vs. 5.7 mos placebo (p=0.2)
  - PD-L1 positive subgroup also had no difference
- OS: 19.2 mos atezo group vs. 22.8 mos placebo
  - PD-L1 positive subgroup also slight trend favoring placebo

Helwick C. The ASCO Post. [Internet]. 2020 Oct 2. Available from: https://ascopost.com/news/october-2020/impassion131-no-benefit-for-atezolizumab-plus-paclitaxel-in-triple-negative-breast-cancer/

Knowledge Checkpoint - Pharmacists

- Which of the following patients would be eligible for ICI therapy?
  - A patient with early stage triple-negative breast cancer whose tumor has <1% PD-L1 expression
  - A patient with early stage triple-negative breast cancer whose tumor has 85% PD-L1 expression
  - A patient with advanced triple-negative breast cancer whose tumor has 35% PD-L1 expression
  - A patient with advanced triple-negative breast cancer whose tumor has <1% PD-L1 expression

Checking Out

Summary

- ✓ ICIs rapidly gaining new indications
- ✓ Biomarkers help predict patients more likely to respond to ICIs
- ✓ ICIs create durable responses in patients
- ✓ Chemotherapy-immunotherapy combinations lead to higher rates of immune toxicities
- ✓ Increasing treatment options for patients who previously had few left

Questions?

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