Triple-Negative Breast Cancer

Focus on Novel Immunotherapy Combinations and Implications for Pharmacists

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Type of Activity: Application

Faculty

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Chair, Pharmacy Practice
Associate Professor, Oncology
Touro College of Pharmacy
New York, NY

Dr. Adel serves as the academic and administrative leader of the Pharmacy Practice department at the Touro College of Pharmacy in New York City. In this role, she coordinates the long-term development of the clinical faculty, is responsible for promoting and supporting research, and oversees the Office of Practice Experience. Prior to joining the college, Dr. Adel served as director of the Oncology Residency Program and manager of Clinical Pharmacy Services at Memorial Sloan-Kettering Cancer Center. Dr. Adel obtained her Doctor of Pharmacy degree from the School of Pharmacy at Lebanese American University in Byblos, Lebanon. She has spoken at conferences and been published worldwide and worked on numerous special projects. She has made meaningful strides in the improvement of patient care in the field of oncology.

Faculty

Meagan S. Barbee, PharmD, BCOP

Chief Executive Officer
Barbee Oncology Consulting
Atlanta, GA

Dr. Barbee owns and operates an oncology consulting business. Prior to restarting her business, Dr. Barbee most recently served as the Clinical Coordinator of Oncology and the PGY2 Oncology Residency Program Director at Emory Healthcare/Winship Cancer Institute in Atlanta, GA where she practiced in breast oncology. Dr. Barbee received her bachelor's degree in Biochemistry from the Georgia Institute of Technology and her Doctor of Pharmacy degree from Mercer University. She completed both her PGY1 and PGY2 Oncology residencies at Emory. Prior to moving to Asia in 2015, Dr. Barbee was an Oncology Clinical Specialist at Memorial Sloan-Kettering Cancer Center in New York City. Dr. Barbee has served in the International Cancer Corps with the American Society of Clinical Oncology in Asia. She has held academic appointments with Mercer University in Atlanta, GA and Meiji Pharmaceutical University in Tokyo, Japan. Dr. Barbee has a passion for globally advancing the treatment and prevention of cancer.

Disclosures

Drs. Adel and Barbee have no relevant affiliations or financial relationships with a commercial interest to disclose.

The clinical reviewer, **Lisa Holle, PharmD, BCOP, FHOPA** has no actual or potential conflicts of interest in relation to this program.

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Learning Objectives

- **Discuss** the difficulties of treating triple-negative breast cancer (TNBC) and the rationale for the use of immunotherapy combinations in patients with TNBC
- **Identify** appropriate prognostic and predictive biomarkers in the treatment of TNBC with immunotherapy combinations
- **Examine** the emerging data for immunotherapy combination regimens in the treatment of advanced TNBC
- **Demonstrate** pharmacist-driven strategies to recognize and effectively prevent or manage immunotherapy combination-mediated toxicities

Outline

Overview of TNBC and the Immune System

Epidemiology and etiology | Standard approaches | Immunotherapeutic targets

Predictive and Prognostic Biomarkers

Tumor-infiltrating lymphocytes | PD-1 and PD-L1 | Emerging biomarkers

Emerging Immunotherapy Combinations

Pharmacology and rationale | ICI + chemo | ICI + targeted therapy | ICI + radiation

Management of Immune-Mediated Toxicities

Recognition | Prevention and management | Emerging combinations

Role of the Pharmacist

Patient education | Special populations | Practical and logistical considerations

Overview of TNBC and the Immune System

Epidemiology and Etiology of TNBC

Patient Case #1

ML is a 39-year-old premenopausal Caucasian woman who presents to a medical oncologist for a treatment plan for her newly diagnosed right breast cancer found on screening mammogram and confirmed with ultrasound and core needle biopsy as *invasive ductal carcinoma*.

The tumor is 3.8 cm × 3.2 cm, ER negative, PR negative, HER2 IHC 2+, and FISH negative (i.e., *TNBC disease*).

Pathology reveals a nuclear grade of 2 (*moderately differentiated*) and a Ki-67 of 55%.

She recently underwent a modified radical mastectomy (*MRM*) with negative LN and negative margins (> 1 mm).

ER, estrogen receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; LN, lymph node, PR, progesterone receptor.

Epidemiology and Etiology of TNBC

- Triple negative = ER negative, PR negative, HER2 negative
- Accounts for 10% to 17% of all breast carcinomas
- More aggressive than tumors with other molecular subtypes
- Usually presents with high-grade disease
- More commonly diagnosed in women younger than 40 years old
- Weak relationship between tumor size and nodal status

Reis-Filho JS, Tutt AN. *Histopathology*. 2008;52(1):108-18.

Epidemiology and Etiology of TNBC

Disease Course

- Rapid risk of recurrence after diagnosis
- Peak risk of recurrence within 1-3 years
- Distant recurrence is not preceded by local recurrence
- Local recurrence is not predictive of distant recurrence

Prognosis

- Worse than other subtypes
- Increased mortality rate within first 5 years
- Rapid progression from distant recurrence to death

Dent R, et al. *Clin Cancer Res.* 2007;13(15 Pt 1):4429-34.

Epidemiology and Etiology of TNBC

- **TNBC = ER–, PR–, HER2–**
- **Disease heterogenicity**

AR, androgen receptor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog protein; BRCA, breast cancer gene

Metzger-Filho O, et al. *J Clin Oncol.* 2012;30(15):1879-87.

Epidemiology and Etiology of TNBC

No targets? Are there any other means?

- Androgen receptor (AR) targeting
- Poly ADP ribose polymerase (PARP) inhibitors

- Vascular endothelial growth factor receptor (VEGFR) inhibitors
- Epidermal growth factor receptor (EGFR) inhibitors

- Death receptor and ligand (PD-1 and PD-L1) inhibitors

Standard Therapies for TNBC

Standard Chemotherapy Regimens: Neoadjuvant/Adjuvant Disease

Abbreviation	Chemotherapy
AC	Doxorubicin + cyclophosphamide Dose-dense therapy followed by paclitaxel every 2 weeks Dose-dense therapy followed by paclitaxel weekly
TC	Docetaxel + cyclophosphamide
CMF	Cyclophosphamide + methotrexate + fluorouracil
EC	Epirubicin + cyclophosphamide
TAC	Docetaxel + doxorubicin + cyclophosphamide

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 6, 2019.

Standard Therapies for TNBC

Standard Chemotherapy Regimens: Metastatic Disease

Class	Chemotherapy	Target Specific
Anthracyclines	Doxorubicin or liposomal doxorubicin	
Taxanes	Paclitaxel	
Anti-metabolites	Capecitabine Gemcitabine	
Microtubule inhibitors	Vinorelbine Eribulin	
PARP inhibitors	Olaparib Talazoparib	BRCA1/2 mutation
Platinums	Carboplatin Cisplatin	
Immunotherapy	Atezolizumab + nab-paclitaxel	PD-L1 positive

National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published September 6, 2019.

ARS Question #1

Patient Case #1

ML is a 39-year-old premenopausal Caucasian woman who presents to a medical oncologist for a treatment plan for her newly diagnosed right breast cancer found on screening mammogram and confirmed with ultrasound and core needle biopsy as *invasive ductal carcinoma*.

The tumor is 3.8 cm × 3.2 cm, ER negative, PR negative, HER2 IHC 2+, and FISH negative (i.e., *TNBC disease*).

Pathology reveals a nuclear grade of 2 (*moderately differentiated*) and a Ki-67 of 55%.

She recently underwent a modified radical mastectomy (*MRM*) with negative LN and negative margins (> 1 mm).

What do you recommend for this patient?

1. AC every 3 weeks
2. No adjuvant therapy is needed
3. TC regimen
4. CMF regimen

Immunotherapeutic Targets in TNBC

- Higher expression of PD-L1 in TNBC than in HR+ breast cancers
  - 26% of primary TNBCs expressed PD-L1 on cancer cell surface
- Higher tumor mutational load in TNBC than in other subtypes
- Higher level of tumor-infiltrating lymphocytes (TILs)
  - Suggests an immune response to tumor-associated antigens
  - Prognostic significance
- Genomic instability and high rates of genetic mutations
  - Production of more neoantigens and increased immunogenicity

HR, hormone receptor.

Adams S, et al. *J Clin Oncol*. 2014;32(27):2959-66.; Loi S, et al. *Ann Oncol*. 2014;25(8):1544-50.; Mittendorf EA, et al. *Cancer Immunol Res.* 2014;2(4):361-70.; Tung N, et al. *NPJ Breast Cancer*. 2016;2:16002.

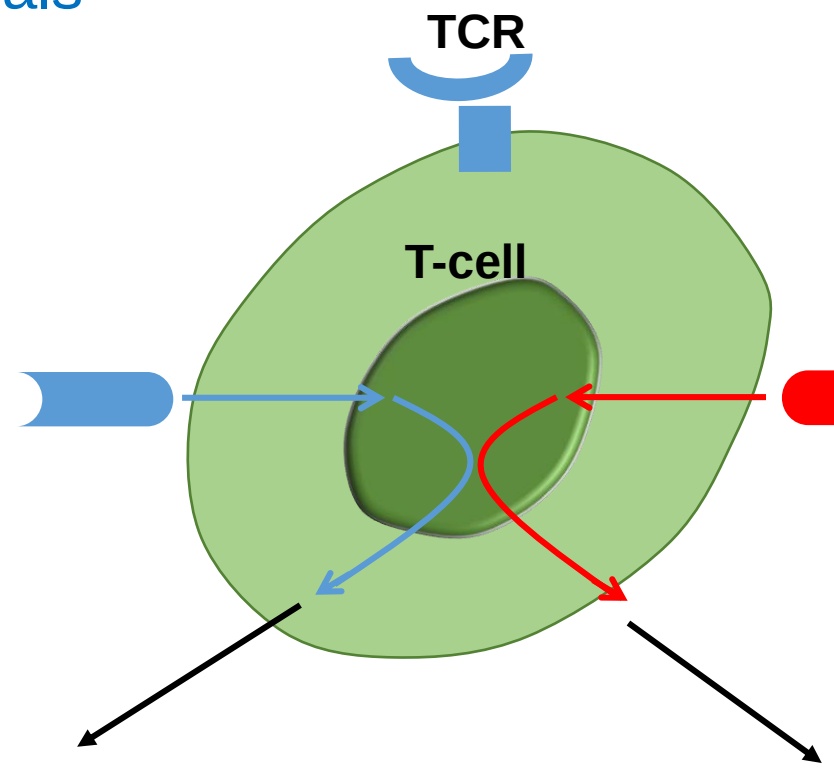
Predictive and Prognostic Biomarkers

PD-1 and PD-L1

Coactivation signals

- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Agonistic mAbs to ↑ activation



PD-1 and PD-L1

Inhibitory signals

- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Blocking mAbs to ↑ activation

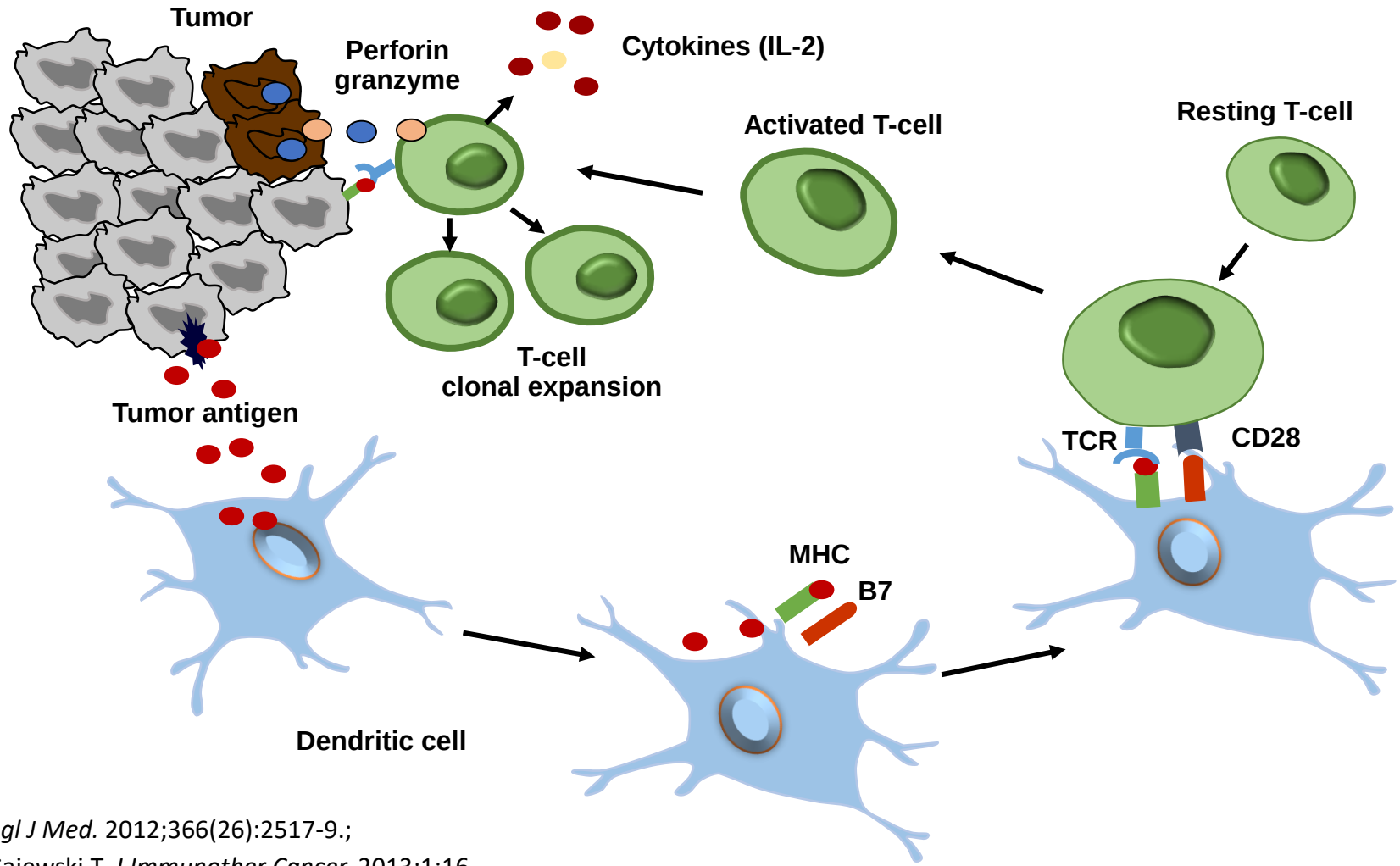
T-cell stimulation

T-cell inhibition

mAbs, monoclonal antibodies.

Mellman I, et al. *Nature*. 2011;480(7378):480-9.

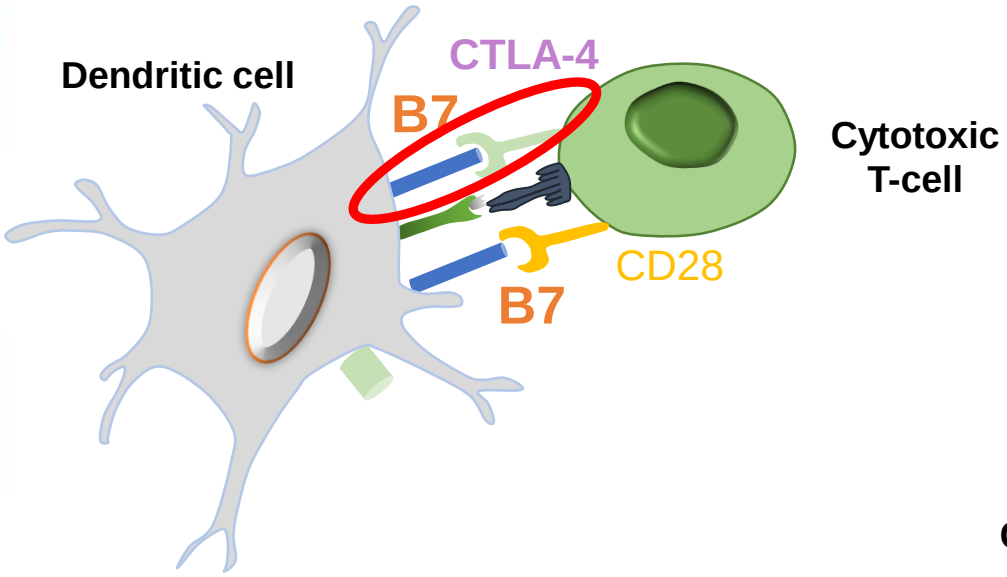
Tumor Immunology: Overview



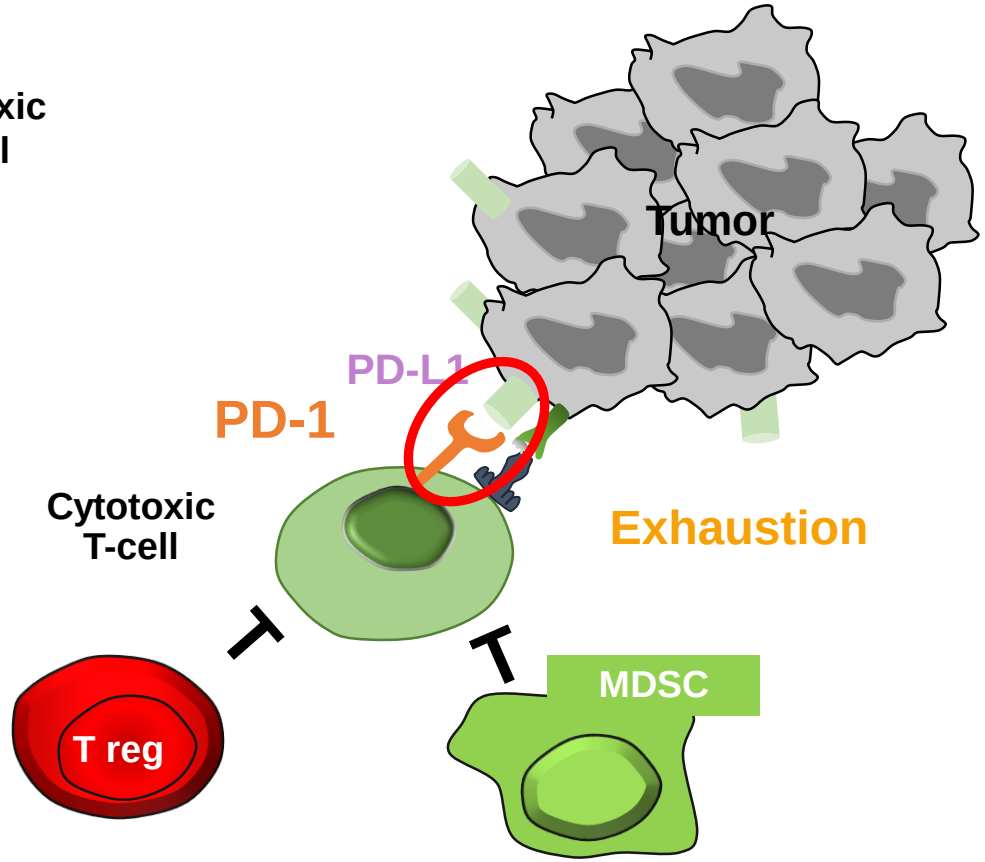
Ribas A. *N Engl J Med.* 2012;366(26):2517-9.;
Spranger S, Gajewski T. *J Immunother Cancer.* 2013;1:16.

Tumor Immunology: Overview

Priming phase



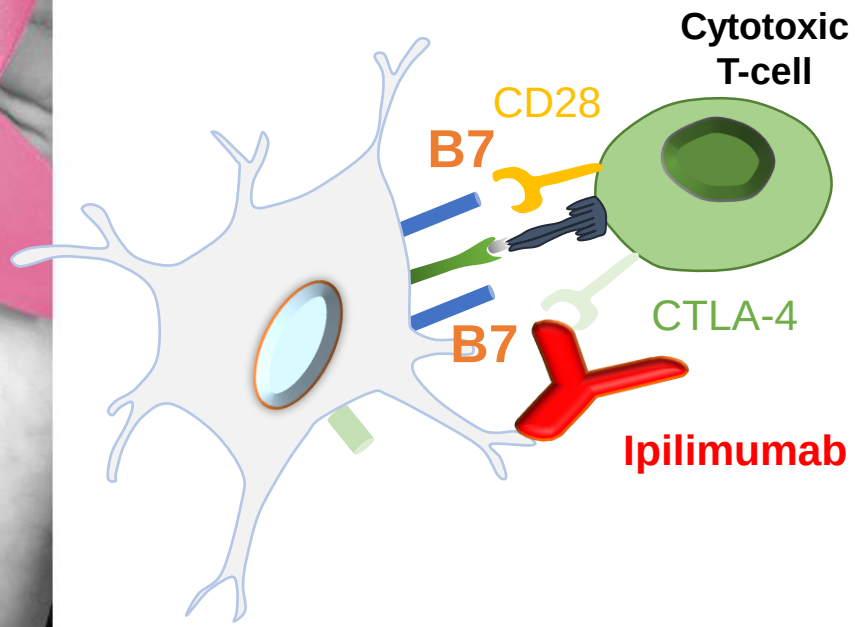
Effector phase



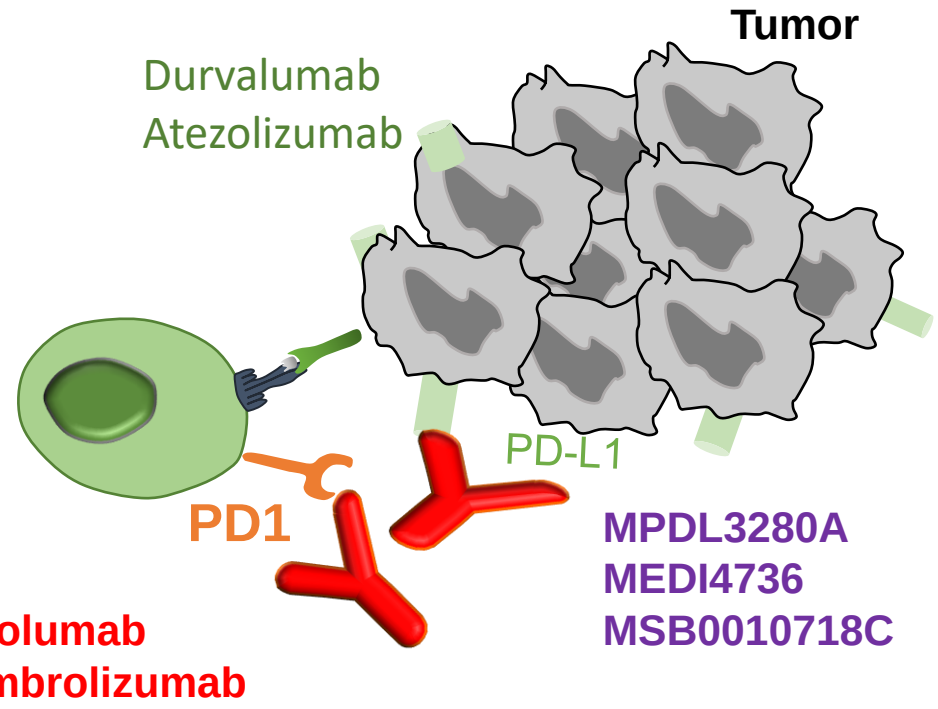
Ribas A. *N Engl J Med.* 2012;366(26):2517-9.;
Spranger S, Gajewski T. *J Immunother Cancer.* 2013;1:16.

Tumor Immunology: Overview

Priming: T-cell activation in the lymph node



Effector phase: peripheral tissues



Ribas A. *N Engl J Med.* 2012;366(26):2517-9.;
Spranger S, Gajewski T. *J Immunother Cancer.* 2013;1:16.

Emerging Biomarkers

- **Tumor-infiltrating lymphocytes**
  - Present intramurally and in adjacent stromal tissues
  - Have predictive and prognostic roles
  - Increased TILs have been associated with high pathologic complete response (pCR)
  - Associated with higher overall survival (OS) in patients with HER2+ disease

Emerging Biomarkers

- **Tumor mutational burden (TMB)**
  - High TMB is an emerging predictive biomarker for checkpoint inhibitor therapy
  - Higher TMB in TNBC than in other subtypes
  - TAPUR: a phase II basket study evaluating targeted agents in patients with advanced cancers that have specific genomic alterations
    - ASCO 2019: authors reported on a cohort of 28 metastatic TNBC patients
    - Heavily pretreated: 93% of patients had 3+ lines of prior therapy in stage IV setting
    - All patients had high TMB (≥ 9 mutations per megabase)
    - Received pembrolizumab IV every 3 weeks until progression
    - Disease control rate (DCR): 37%
    - Objective response rate (ORR): 21%

ASCO, American Society of Clinical Oncology; IV, intravenously.

Alva AS, et al. *J Clin Oncol.* 2019;37(15_suppl):abstract 1014.; Banerji S, et al. *Nature*. 2012;486(7403):405-9.; Budczies J, et al. *J Pathol Clin Res*. 2015;1(4):225-38.

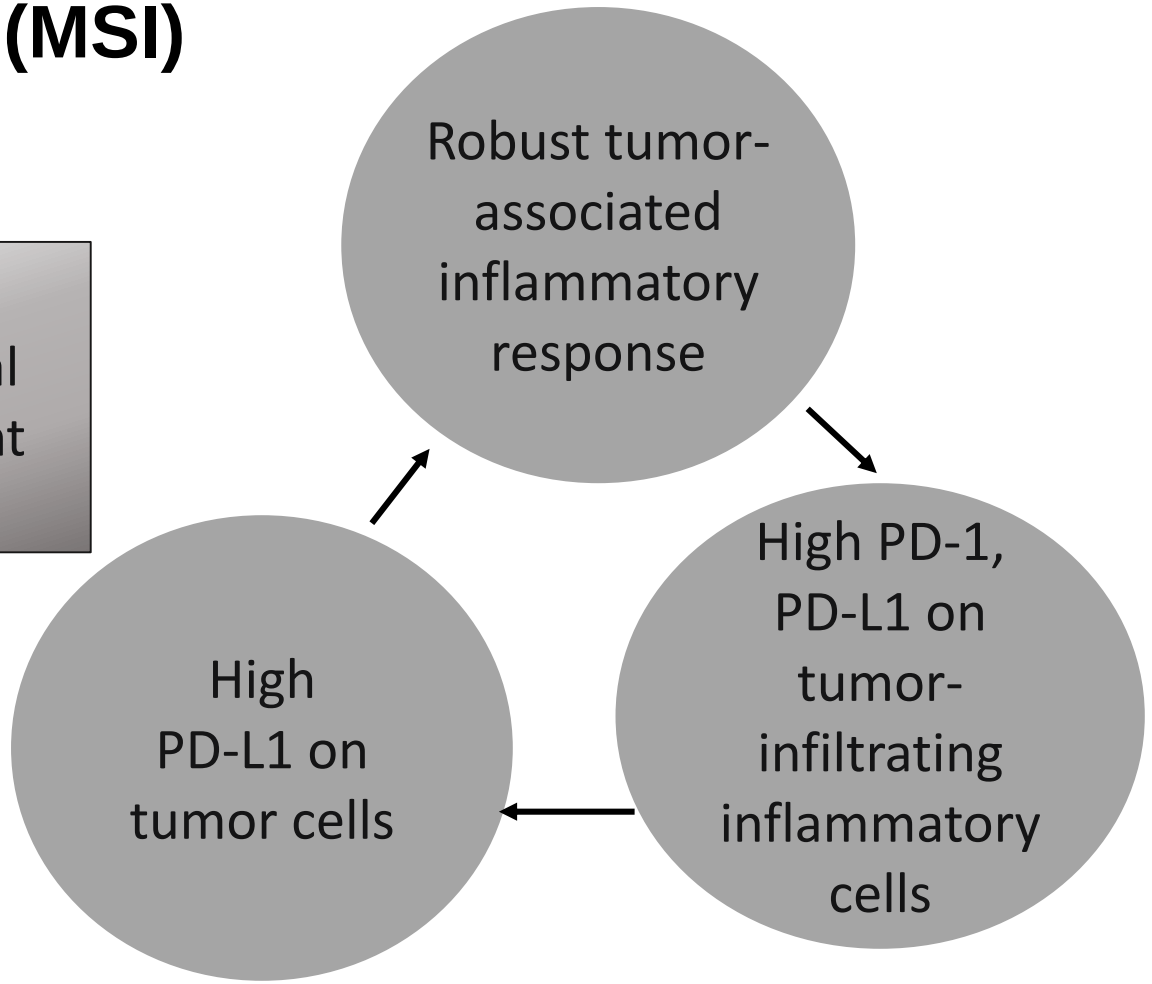
Emerging Biomarkers

- **Microsatellite instability (MSI)**

MSI-H

Hypermutation
(10× to 100× increase in mutational load with dMMR vs. MMR-proficient tumors)

High number of neoantigens expressed on tumor cells



dMMR, deficient mismatch repair; MMR, mismatch repair; MSI-H, microsatellite instability-high.

Le DT, et al. *N Engl J Med.* 2015;372(26):2509-20.

Emerging Immunotherapy Combinations

Neoadjuvant

Patient Case #2

SG is a 42-year-old premenopausal woman of Ashkenazi Jewish descent. She presents to a medical oncologist for a treatment plan for her newly diagnosed left breast cancer found on screening mammogram and confirmed with ultrasound and core needle biopsy as *invasive ductal carcinoma*.

The tumor is 4.4 cm × 4.2 cm, ER negative, PR negative, HER2 IHC 1+, and FISH negative (i.e., *TNBC disease*).

Pathology reveals a nuclear grade of 3 (*moderately differentiated*) and a Ki-67 of 62%.

Upon physical exam, there are no palpable lymph nodes.

Neoadjuvant and pCR

- pCR is a key outcome in neoadjuvant trials
  - Successful surgery: complete resection with negative margins
  - No residual disease
  - Better prognosis
  - Occurs in 30%-40% of patients with TNBC treated with neoadjuvant therapy
    - Opportunity for changes in practice
  - High risk of recurrence in patients who do not achieve pCR
- Chemotherapy has become the standard of care for tumors that are > 2 cm

Symmans WF, et al. *J Clin Oncol*. 2017;35(1):1049-60.

Rationale for ICIs + Chemotherapy

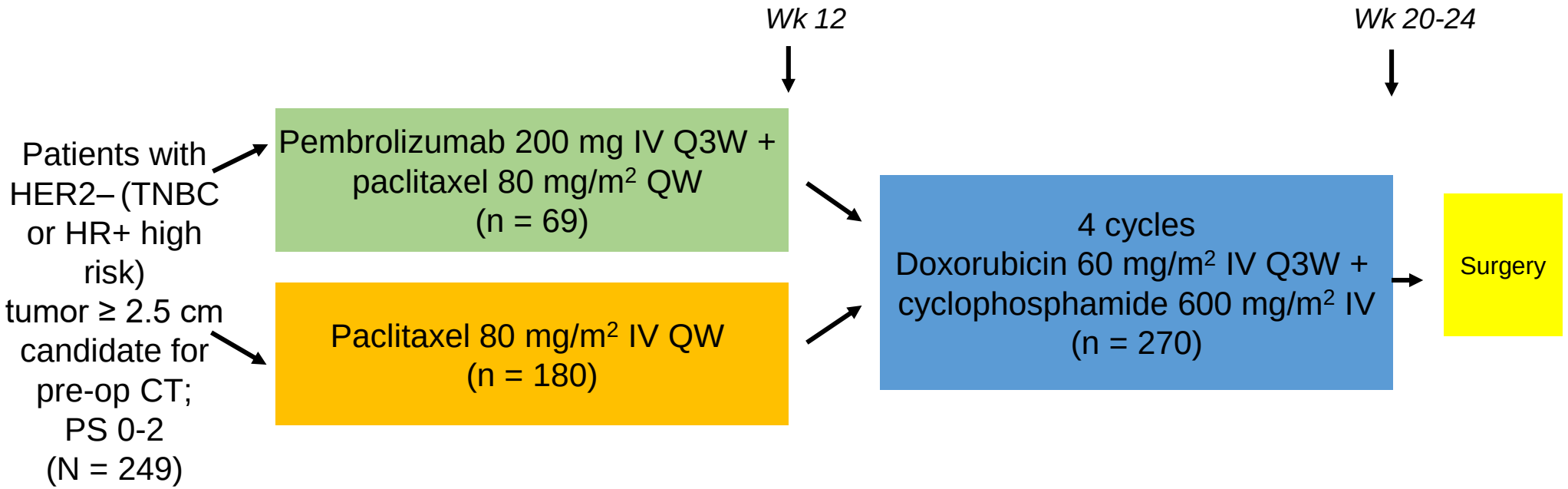
- Do they really complement each other?
  - The theory is that chemotherapy can increase neoantigens and increases apoptosis when given prior to ICIs

- Neoadjuvant trials
- Adjuvant trials
- Metastatic trials

ICI, immune checkpoint inhibitor.

I-SPY-2: Pembrolizumab + Chemo

Randomized, double-blind, phase III trial



Primary endpoint: pCR

CT, computed tomography; IV, intravenous; PS, performance status; Q3W, every 3 weeks; QW, every week.

Nanda R, et al. *J Clin Oncol*. 2017;35(15_suppl):abstract 506.

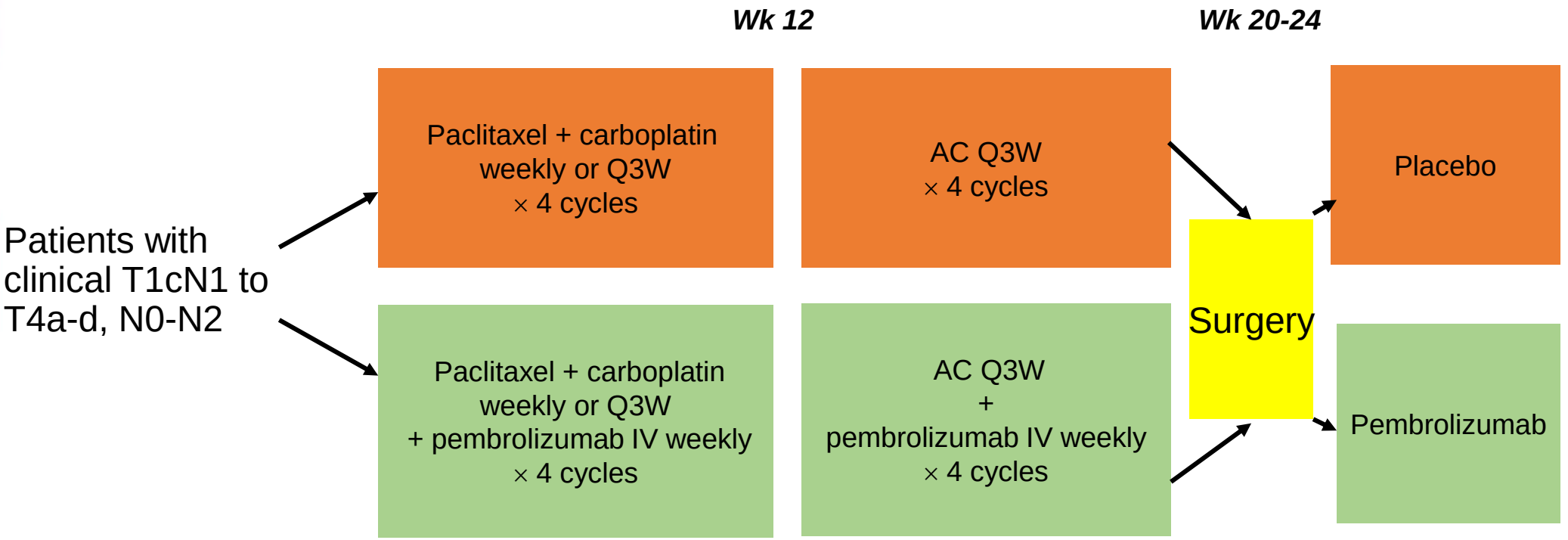
I-SPY-2: Pembrolizumab + Chemo

- Pembrolizumab predicted to augment activity of paclitaxel in neoadjuvant T → AC for HER2-negative patients with early-stage disease
  - High pCR rate in TNBC signature (60% vs. 20%)
  - High pCR rate in HR+/HER2– signature (34% vs. 13%)
- More adrenal insufficiency with pembrolizumab + paclitaxel than in previous studies of pembrolizumab in advanced cancer
- More data to come regarding several arms of prior trial

Nanda R, et al. *J Clin Oncol*. 2017;35(15_suppl):abstract 506.

KEYNOTE-522: Pembrolizumab + Chemo

Randomized, double-blind, placebo-controlled, phase III trial



Primary endpoints (dual): pCR and EFS

EFS, event free survival

Schmid P, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934. DOI 10.1093/annonc/mdz394

KEYNOTE-522: Pembrolizumab + Chemo

Outcome	Pembrolizumab + Chemo n=784	Placebo + Chemo n=390
pCR (ypT0/Tis ypN0)	64.8% (95% CI, 59.9-69.5)	51.2% (95% CI, 44.1-58.3)
	p = 0.00055	
PD-L1+	68.9%	54.9%
PD-L1-negative	45.3%	30.3%
pCR (ypT0 ypN0)	59.9%	45.3%
pCR (ypT0/Tis)	68.6%	53.7%
EFS	HR 0.63 (95% CI, 0.43-0.93), favoring pembrolizumab	
Grade 3 or higher adverse events	78%	73%

Schmid P, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934. DOI 10.1093/annonc/mdz394

SWOG S1418

Randomized, phase III trial of TNBC with residual disease

Patients with
TNBC
≥ 1 cm
N(+/-)
PD-L1 (+/-)

Neoadjuvant chemo → pCR not achieved

- Observation
- Pembrolizumab 200 mg IV Q3W × 1 year

Primary endpoint: disease-free survival in PD-L1+

Pusztai L, et al. *Cancer Res.* 2018;78(4 supplement):OT1-02-04.

ARS Question #2

Patient Case #2

SG is a 42-year-old premenopausal woman of Ashkenazi Jewish descent. She presents to a medical oncologist for a treatment plan for her newly diagnosed left breast cancer found on screening mammogram and confirmed with ultrasound and core needle biopsy as *invasive ductal carcinoma*.

The tumor is 4.4 cm × 4.2 cm, ER negative, PR negative, HER2 IHC 1+, and FISH negative (i.e., *TNBC disease*).

Pathology reveals a nuclear grade of 3 (*moderately differentiated*) and a Ki-67 of 62%.

Upon physical exam there are no palpable lymph nodes.

What would you recommend for this patient as a valid clinical trial?

1. Neoadjuvant therapy with chemotherapy alone
2. Neoadjuvant chemotherapy + radiation
3. Neoadjuvant ICI only
4. Neoadjuvant ICI + chemotherapy

Metastatic Disease

Patient Case #3

RK is a 49-year-old premenopausal African American woman who came back to the clinic for *new* findings on her CT scans.

The patient was diagnosed *3 years ago* with early-stage TNBC. She underwent a double mastectomy with breast reconstruction. She received *standard treatment* with chemotherapy and radiation.

RK received *dose-dense AC* followed by weekly paclitaxel. She completed her regimen with some mild episodes of emesis despite proper treatment.

Lately, she has not been feeling well: she went to her family doctor who advised her to undergo an abdominal and chest CT.

CT of abdomen and chest revealed several nodules in the liver. A biopsy was done and pathology revealed metastatic disease with a tumor that is still *negative for all conventional markers (ER, PR, HER2).*

IMpassion 130: Atezolizumab + Chemo

Randomized, double-blind, placebo-controlled, phase III trial

Patients with mTNBC, no prior therapy for advanced setting, RECIST v1.1 measurable disease; ECOG PS 0/1; tumor evaluable for PD-L1 (N = 902)

- Atezolizumab 840 mg IV Q2W + nab-paclitaxel 100 mg/m^2 IV on D1, 8, and 15 28-day cycles (n = 451)
- Placebo IV Q2W + nab-paclitaxel 100 mg/m^2 IV on D1, 8, and 15 28-day cycles (n = 451)

→ Treatment until PD per RECIST v1.1 or intolerable toxicity

Primary endpoint: PFS and OS (ITT population and PD-L1+ subgroup)

ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; mTNBC, metastatic triple-negative breast cancer; PD, progressive disease; Q2W, every 2 weeks; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Schmid P, et al. *J Clin Oncol.* 2019;37(15_suppl):abstract 1003.;
Schmid P, et al. *N Engl J Med.* 2018;379(22):2108-21.

IMpassion 130: Atezolizumab + Chemo

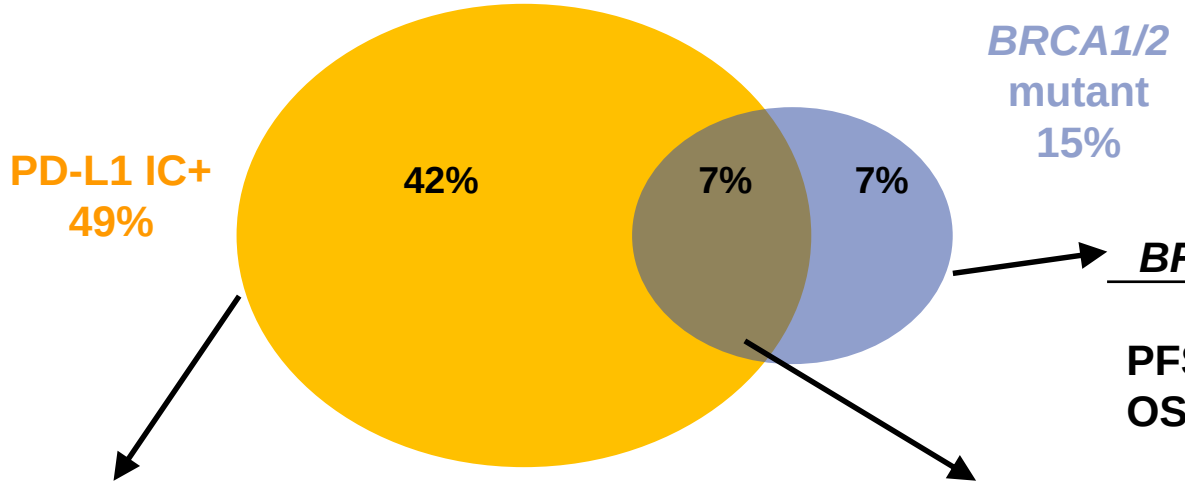
Outcome	Atezolizumab + nab-paclitaxel n=451	Placebo + nab-paclitaxel n=451
mPFS overall cohort*	7.2 months	5.5 months
	HR 0.80, 95% CI 0.69-0.92, p=0.002	
mPFS PD-L1+ subgroup	**7.5 months**	**5.0 months**
	HR 0.62, 95% CI 0.49-0.78, p<0.001	
mOS overall cohort	21.3 months	17.6 months
	HR 0.84, 95% CI 0.69-1.02, p=0.08 (interim)	
mOS PD-L1+ subgroup	**25.0 months**	**15.5 months**
	HR0.62, 95% CI 0.45-0.86	
ORR overall/PDL1+ subgroup	56.0%/58.9%	45.9%/42.6%
mDoR overall/PD-L1+ subgroup	7.4 months/8.5 months	5.6 months/5.5 months
Rate of grade 3-4 AEs	48.7%	42.2%

*HR for mPFS crossed line of unity in multiple subgroups, namely in patients who were PD-L1 negative (mPFS = 5.6 months for both arms)

Schmid P, et al. *J Clin Oncol.* 2019;37(15_suppl):abstract 1003.;
Schmid P, et al. *N Engl J Med.* 2018;379(22):2108-21.

IMpassion 130: Benefit in PD-L1 IC+ Independent of *BRCA1/2*

- Updates from SABCS 2018



***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

Emens LA, et al. *Cancer Res.* 2019;79(4 Suppl):abstract GS1-04. DOI: 10.1158/1538-7445.SABCS18-GS1-04

CI, confidence interval; HR, hazard ratio; IC, immune cells.

IMpassion 130: Atezolizumab + Chemo

- Updates from ASCO 2019

Patient: n (%)	Atezolizumab + nab-paclitaxel (n = 451)	Placebo + nab-paclitaxel (n = 451)
Patients on study		
▪ Active on treatment	39 (9)	13 (3)
▪ Active in survival follow-up	133 (30)	135 (30)
Patients who discontinued		
▪ Dead	255 (57)	279 (62)
▪ Lost to follow-up	24 (5)	24 (5)

Schmid P, et al. *J Clin Oncol.* 2019;37(15_suppl):abstract 1003.;
Schmid P, et al. *N Engl J Med.* 2018;379(22):2108-21.

IMpassion130: Atezolizumab + Chemo

Outcomes and Subgroups

- PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1%
- A treatment effect was not seen when adding atezolizumab to chemotherapy in the PD-L1-negative subgroup

Biomarkers and Targets in Study Population

- PD-L1 IC expression was the best predictor of clinical benefit
- Patients with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T-cells (CD8+) derived clinical benefit with atezolizumab + nab-paclitaxel if their tumors were also PD-L1 IC+
- PFS and OS results were consistent regardless of BRCA1/2 mutation status

Conclusions

- PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + nab-paclitaxel treatment for mTNBC
- Atezolizumab + nab-paclitaxel sets new benchmark in first-line setting for patients with PD-L1+ metastatic TNBC
- First therapy to cross 2-year landmark OS benefit in this setting (24-month OS: 51% vs. 37%)
- FDA approved and guideline recommended

Schmid P, et al. *J Clin Oncol.* 2019;37(15_suppl):abstract 1003. Schmid P, et al. *N Engl J Med.* 2018;379(22):2108-21.
Emens LA, et al. *Cancer Res.* 2019;79(4 Suppl):abstract GS1-04. DOI: 10.1158/1538-7445.SABCS18-GS1-04

FDA, United States Food and Drug Administration.

KEYNOTE-355: Pembrolizumab + Chemo

Phase III trial

Patients with
mTNBC
PD-L1(+/-)
First Line

Placebo
+
chemotherapy

Pembrolizumab
+
chemotherapy

Progression of disease

Chemotherapy:
Nab-paclitaxel
Paclitaxel
Gemcitabine/carboplatin

U.S. National Library of Medicine. https://clinicaltrials.gov. Accessed September 9, 2019.

ICI + Targeted Therapy

PARP inhibitors: clinical trials to watch

- Olaparib + durvalumab phase II studies
  - MEDIOLA: BRCA-***mutated***, any PD-L1 status, metastatic disease
    - Preliminary results
      - ORR: 10%
      - mDOR: 11.1 months
  - NCT03801369: BRCA ***wild-type***, any PD-L1 status, metastatic disease
  - DORA: platinum treated, ***any BRCA status***, any PD-L1 status, advanced/metastatic disease
- Niraparib + pembrolizumab
  - TOPACIO (Keynote-162)

Domchek SM, et al. *Cancer Res.* 2019;79(4 supplement):abstract PD5-04.; Mitri Z, et al. *J Clin Oncol.* 2019;37(15_suppl):abstract TPS1111.; U.S. National Library of Medicine. https://clinicaltrials.gov. Accessed September 9, 2019.; Vinayak S, et al. *JAMA Oncol*. 2019;5(8):1132-40.

TOPACIO: Pembrolizumab + Niraparib

Study Design and Intervention

- Open-label, single-arm, phase II study with a phase I lead-in
- 200 mg oral niraparib once daily and 200 mg IV pembrolizumab every 3 weeks

Patients

- Metastatic TNBC
- **Any BRCA status, any PD-L1 status, any platinum status**
- Median of 1 previous line of therapy (range, 0-3)

Endpoints and Outcomes

- Primary endpoint, ORR: 21% in the efficacy-evaluable patients
  - 47% in BRCA-mutated and 11% in BRCA wild-type
  - 32% in PD-L1+ and 8% in PD-L1–
  - Higher in platinum-naïve patients
- DCR (at least stable disease): 49%
- mPFS: 2.3 months (95% CI: 2.1-3.9)
- mDOR, OS: immature
- Safety events: anemia, thrombocytopenia, fatigue, nausea, constipation

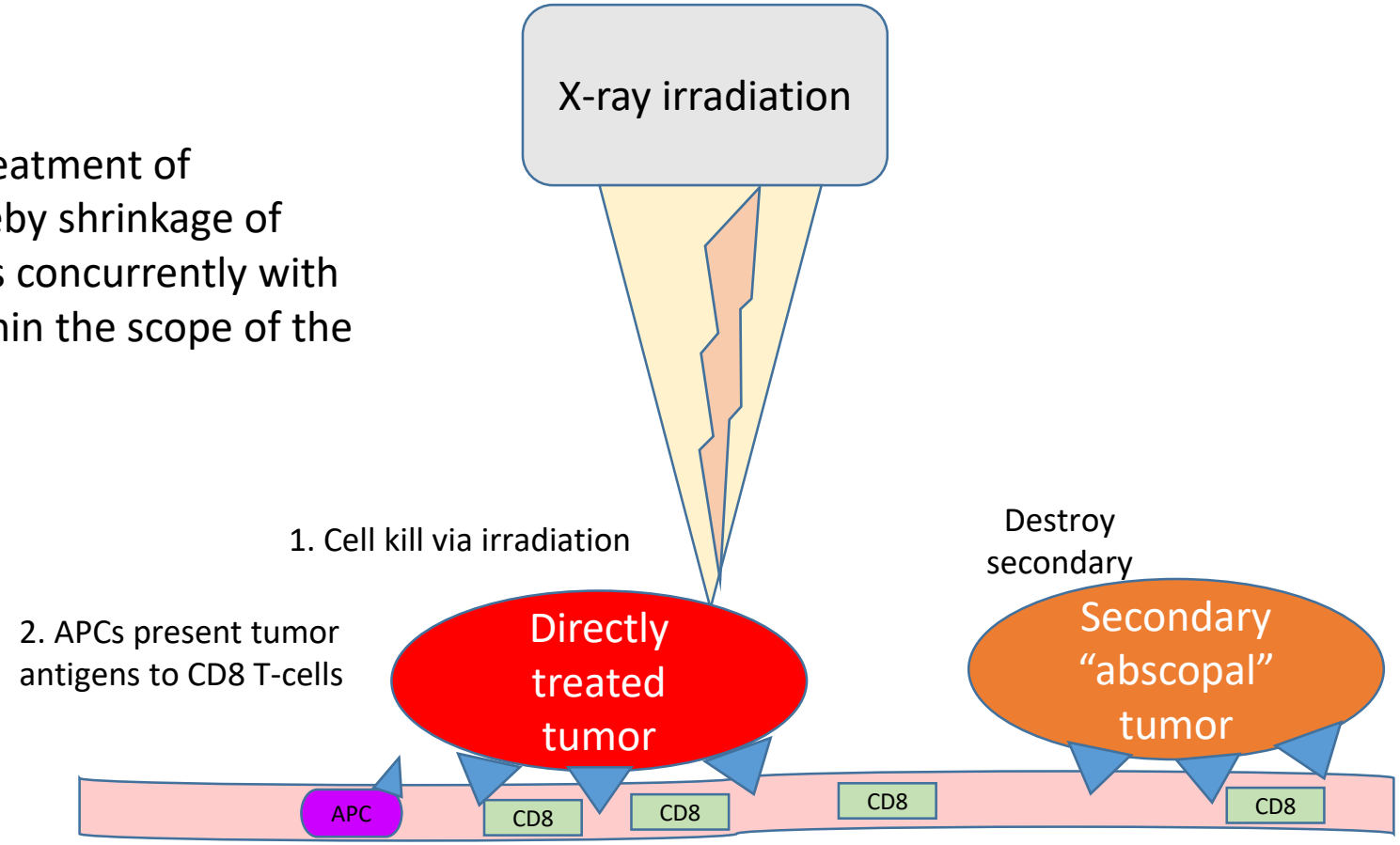
mDOR: median duration of response; mPFS: median progression-free survival.

Vinayak S, et al. *JAMA Oncol*. 2019;5(8):1132-40.

Rational for ICI + Radiation

- Abscopal Effect

The hypothesis in the treatment of metastatic cancer whereby shrinkage of untreated tumors occurs concurrently with shrinkage of tumors within the scope of the localized treatment



3. CD8 T-cells circulate through the body destroying both directly irradiated and "abscopal" tumors

APC, antigen-presenting cell.

Mole RH. *Br J Radiol.* 1953;26(305): 234-41.

TONIC Trial: ICI + Radiation

Adaptive, non-randomized phase II trial

Patients with mTNBC, ≤ 3 lines of palliative chemotherapy

	ORR
No Induction	17%
8 Gy irradiation of 1 metastatic lesion 3 cycles over 2 weeks	8%
Cisplatin 40 mg/m² IV weekly × 2 weeks	23%
Cyclophosphamide PO 50 mg/day × 2 weeks	8%
Doxorubicin 15 mg IV weekly × 2 weeks	35%

Nivolumab 3 mg/kg IV Q2W until disease progression

Primary endpoint: PFS

PO, by mouth.

Kok MH, et al. *J Clin Oncol*. 2018;36(15_suppl):abstract 1012.; Voorwerk L, et al. *Nat Med*. 2019;25(6):920-8.

ARS Question #3

Patient Case #3

RK is a 49-year-old *premenopausal* African American woman who came back to the clinic for new findings on her CT scans.

The patient was diagnosed *3 years ago* with early stage TNBC. She underwent a double mastectomy with breast reconstruction. She received standard treatment with chemotherapy and radiation.

RK received dose-dense AC followed by weekly paclitaxel. She completed her regimen with some mild episodes of emesis despite proper treatment.

Lately, she has not been feeling well: she went to her family doctor who advised her to undergo an abdominal and chest CT.

CT of abdomen and chest revealed several nodules in the liver. A biopsy was done and pathology revealed *metastatic disease with a tumor that is still negative for all conventional markers (ER, PR, HER2)*. The patient tested positive for PD-L1.

What do you recommend as first-line therapy on the basis of the *latest data*?

1. Atezolizumab + nab-paclitaxel
2. Atezolizumab + paclitaxel
3. Pembrolizumab + atezolizumab
4. Pembrolizumab + paclitaxel

Management of Immune-Mediated Adverse Events (imAEs) and Toxicities

Recognition of ImAEs

Commonly Affected Organ Systems	Patient Education	Laboratory Monitoring	Qualitative Monitoring
• Skin • Gastrointestinal • Endocrine • Pulmonary • Renal	• Helpful handouts • When to call office • Timing of onset	• CBC w/ diff • CMP – liver, renal, glucose • HbA1C • ACTH • TSH, Free T4	• Neurologic changes • Mood • Libido • Diarrhea • Rash • Fatigue • Pulmonary dysfunction

ACTH, adrenocorticotropic hormone; CBC, complete blood count; CMP, comprehensive metabolic panel; HbA1C, hemoglobin A1C; TSH, thyroid-stimulating hormone.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Onset and Incidence of Select ImAEs

ImAE	Onset	Incidence (any grade)
Dermatologic reactions	4-6 weeks (1-2 cycles)	30%-50%
Colitis	5-10 weeks	8%-27%
Hepatitis	6-12 weeks	2%-10%
Pneumonitis	12 weeks (range, 2-24 months)	0%-10%
Hypothyroidism	10 weeks (range, 4-68)	6.5%
Hyperthyroidism	6.7 weeks (range, 2-68)	2.5%
Nephritis	13 weeks (range, 3-35)	1%-2%
Hypophysitis	10 weeks	1.2%
Adrenal insufficiency	10-17 weeks	0.7%
Insulin-deficient diabetes	varies widely	0.2%

Barroso-Sousa R, et al. *JAMA Oncol*. 2018;4(2):173-82.; Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.; Haissaguerre M, et al. *Ann Endocrinol (Paris).* 2018;79(5):539-44.; Lee H, et al. *Cancer Immunol Res.* 2017;5(12):1133-40.; Solinas C, et al. *Semin Oncol*. 2018;45(3):181-6.

Rare ImAEs

Musculoskeletal	Neurologic	Hematologic
• Inflammatory arthritis • Myositis • Polymyalgia-like syndrome • Myocarditis	• Myasthenia gravis • Guillain-Barre syndrome • Peripheral neuropathy • Autonomic neuropathy • Aseptic meningitis • Encephalitis • Transverse myelitis	• Autoimmune hemolytic anemia • Acquired thrombocytopenic purpura • Hemolytic uremic syndrome • Aplastic anemia • Lymphopenia • Immune thrombocytopenia • Acquired hemophilia

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Overlapping Toxicities: Future Considerations in TNBC

Peripheral neuropathy	• Vinorelbine, taxanes, eribulin, platinums
Cardiotoxicity	• Anthracyclines
Autonomic neuropathy	• Vinorelbine
Hemolytic uremic syndrome	• Gemcitabine
Lymphopenia	• Cytotoxic chemotherapy, PARP inhibitors
Rash	• Taxanes, radiation
Diarrhea	• Taxanes, PARP inhibitors

Toxicities: due to individual drug, combination therapy, or progression of disease?

Prevention and Management of ImAEs

- NCCN and ASCO guidelines
  - Predate data in TNBC
- No routine prophylaxis recommended
- Early detection and intervention is paramount
- Dose modifications
  - Hold or discontinue ICI, do not dose reduce
  - Identify whether ICI, other therapy, or progression is responsible
- Supportive care + increased monitoring
  - First line
  - Continue even if steroids are necessary
- Steroids
- Steroid-refractory adjuncts
- Consider specialist consultation for grade 3+ or refractory cases

NCCN, National Comprehensive Cancer Network.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.;
National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Published April 8, 2019.

Management of ImAEs: Dermatologic Reactions

Grade	Definition	Treatment	ICI Modulation
Grade 1	• Covering < 10% BSA • Pruritus only • Symptoms do not affect QOL or are controlled with topical/oral antipruritic regimen	• Topical emollient • Moderate-to-high-potency topical steroid • Oral antihistamine	• Continue ICI for rash/pruritus • Hold ICI for bullous dermatitis until resolved
Grade 2	• Covering 10%-30% BSA • Intense or widespread or intermittent skin changes from scratching • Limiting instrumental ADLs	• High-potency topical steroid • Oral antihistamine • Prednisone 0.5-1 mg/kg/day for bullous dermatitis	• Consider holding ICI • Hold ICI for bullous dermatitis
Grade 3 or 4	• Covering > 30% BSA • Limiting self-care ADLs	• High-potency topical steroid • Prednisone 0.5-1 mg/kg/day	• Hold ICI
Permanently discontinue ICI for Grade3-4 bullous dermatitis, Stevens-Johnson Syndrome, or toxic epidermal necrolysis			

ADLs, activities of daily living; BSA, body surface area; QOL, quality of life.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Management of ImAEs: Diarrhea/Colitis

Grade	Definition	Treatment	ICI Modulation
Grade 1	• < 4 bowel movements/day above baseline • No colitis symptoms	• Loperamide • Diphenoxylate/ atropine	Consider holding ICI
Grade 2	• 4-6 bowel movements/day above baseline • Colitis symptoms not interfering with ADLs	• Methylprednisolone 1 mg/kg/day	Hold ICI
Grade 3 or 4	• > 6 bowel movements/day above baseline • Colitis symptoms interfering with ADLs • Hemodynamic instability • Ischemic bowel, perforation, or toxic megacolon	• Methylprednisolone 2 mg/kg/day	Grade 3: hold ICI Grade 4: discontinue ICI

Risk factor: non-steroidal anti-inflammatory drugs (NSAIDs)

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Management of ImAEs: Hepatitis

Grade	Definition	Treatment	ICI Modulation
Grade 1	• Transaminitis > ULN to 3 × ULN • Bilirubin > ULN to 1.5 × ULN	--	Consider holding ICI
Grade 2	• Transaminitis > 3 × ULN to ≤ 5 × ULN • Bilirubin > 1.5 to ≥ 3 × ULN	• Prednisone 0.5-1 mg/kg/day	Hold ICI
Grade 3	• Transaminitis 5-20 × ULN • Bilirubin 3-10 × ULN • Symptomatic • Fibrosis on biopsy	• Consider hospitalization • Methylprednisolone 1-2 mg/kg/day	Discontinue ICI
Grade 4	• Transaminitis > 20 × ULN • Bilirubin > 10 × ULN • Decompensated liver function/symptomatic	• Hospitalization • Methylprednisolone 2 mg/kg/day	Discontinue ICI

ULN, upper limit of normal.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Management of ImAEs: Pneumonitis

Grade	Definition	Treatment/ICI Modulation
Grade 1	• Asymptomatic • Confined to 1 lobe of the lung • < 25% of lung parenchyma • Clinical/diagnostic observations only	• Increase monitoring • Hold ICI
Grade 2	• Symptomatic • Involves more than 1 lobe of lung • 25%-50% of lung parenchyma • Limiting instrumental ADLs	• Prednisone 1-2 mg/kg/day • Consider bronchoscopy with BAL • Hold ICI
Grade 3 or 4	• Severe symptoms • Hospitalization required, oxygen indicated • Involves all lung lobes • > 50% of lung parenchyma • Limiting self-care ADLs	• Methylprednisolone 1-2 mg/kg/day • Consider bronchoscopy with BAL • Discontinue ICI

BAL, bronchoalveolar lavage.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Management of ImAEs: Nephritis

Grade	Definition	Treatment/ICI Modulation
Grade 1	• Creatinine level increase by +0.3 mg/dL • Creatinine 1.5-2 × baseline	• Rule out other etiologies • Consider holding ICI
Grade 2	• Creatinine 2-3 × baseline	• Prednisone 0.5-1 mg/kg/day • Hold ICI
Grade 3	• Creatinine > 3 × baseline • Creatinine > 4.0 mg/dL • Hospitalization indicated	• Discontinue ICI • Prednisone 1-2 mg/kg/day
Grade 4	• Life-threatening consequences • Dialysis indicated	• Prednisone 1-2 mg/kg/day • Discontinue ICI • Consult nephrology

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Management of ImAEs: Endocrinopathies

Grade	Definition	Treatment/ICI Modulation
Grade 1	• TSH < 10 mIU/L • Asymptomatic or mild symptoms • Fasting glucose > ULN – 160 mg/dL	• Continue ICI • Supplementation/replacement as indicated if symptomatic: mineralocorticoid, levothyroxine, estrogen, testosterone • Metformin
Grade 2	• TSH > 10 mIU/L • Moderate symptoms, able to perform ADLs • Fasting glucose 160-250 mg/dL	• Consider holding ICI • Supplementation as above • Betablocker + methimazole for hyperthyroid • Metformin +/- insulin
Grade 3 or 4	• Severely symptomatic • Life-threatening • Unable to perform ADLs • Fasting glucose 250-500 mg/dL	• Hold ICI • Supplementation as above • Beta-blocker + methimazole for hyperthyroid and prednisone 1-2 mg/kg/day for thyroid storm • Insulin

Note: data are for single-ICI therapy, not dual-ICI therapy.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

Steroid-Refractory ImAEs

- Steroid adjuncts if not improving on maximum-dose steroids (specialist referral)

ImAE	Adjunctive Therapy
Dermatologic reaction	Omalizumab, aprepitant, gabapentin, pregabalin, IVIG, cyclosporine
Colitis	Infliximab
Hepatitis	MMF, azathioprine
Pneumonitis	Infliximab, MMF, IVIG, cyclophosphamide
Inflammatory arthritis	Infliximab, methotrexate, leflunomide, azathioprine, sulfasalazine, tocilizumab, IVIG
Myositis	Plasmapheresis, IVIG, methotrexate, azathioprine, MMF
Neurologic	Pulse dose steroids, IVIG, plasmapheresis, rituximab
Nephrological	Azathioprine, cyclophosphamide, cyclosporine, infliximab, MMF

- Long steroid taper: 4-6 weeks

IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil.

ImAEs in ICI Combination Regimens

- Dual ICI
  - Studies terminated in breast cancer
    - Used in melanoma, renal cell, microsatellite-unstable colorectal cancer
  - In general, have additive toxicities
- ICI + chemotherapy
  - ICI does not appear to worsen chemotherapy-related toxicities in TNBC according to IMpassion130 results
  - Watch overlapping toxicities
- ICI + small-molecule inhibitor
  - Minimal overlapping toxicities w/ PARP inhibitors
- ICI + radiation
  - Insufficient data
  - Might be dependent on location of radiation field (e.g., pneumonitis)

Role of the Pharmacist

Patient Education

Treatment expectations

- Goals of therapy
- Average efficacy and duration of response dependent on line of therapy

Early detection of imAEs

- Printed education materials
- Websites
- Apps

Scheduling of combination regimen

- Patient calendar

Considerations in Special Populations

Autoimmune Disorders

- Severity, active/remissive, receipt of biologic therapy
- 10%-62.5% incidence of autoimmune exacerbation/flare on ICI
- Significantly higher incidence of imAEs (65.9% vs. 39.9%, p = 0.0162) but not grade 3/4
- Unknown how combinations of ICI + other therapy will affect

Pregnancy

- IgG crosses placenta and is excreted in breast milk
- May increase risk of fetus developing immune-mediated disorders
- Also an issue with most chemotherapy in breast cancer, but anthracyclines and cyclophosphamide have been used

Organ Transplantation

- Allograft rejection rates of 41% reported → 81% lost allograft and death in 46%
- Consider concomitant organ toxicities with combination chemotherapy

IgG, immunoglobulin G.

Abdel-Wahab N, et al. *J Immunother Cancer*. 2019;7(1):158.; Cortellini A, et al. *Oncologist.* 2019;24(6):e327-37.; Johnson DB, et al. *Oncology (Williston Park)*. 2018;32(4):190-4.; Pembrolizumab (Keytruda) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; 2019.

Practical and Logistical Considerations

Precertification and prior authorization

Denials, appeals, and peer-to-peer reviews

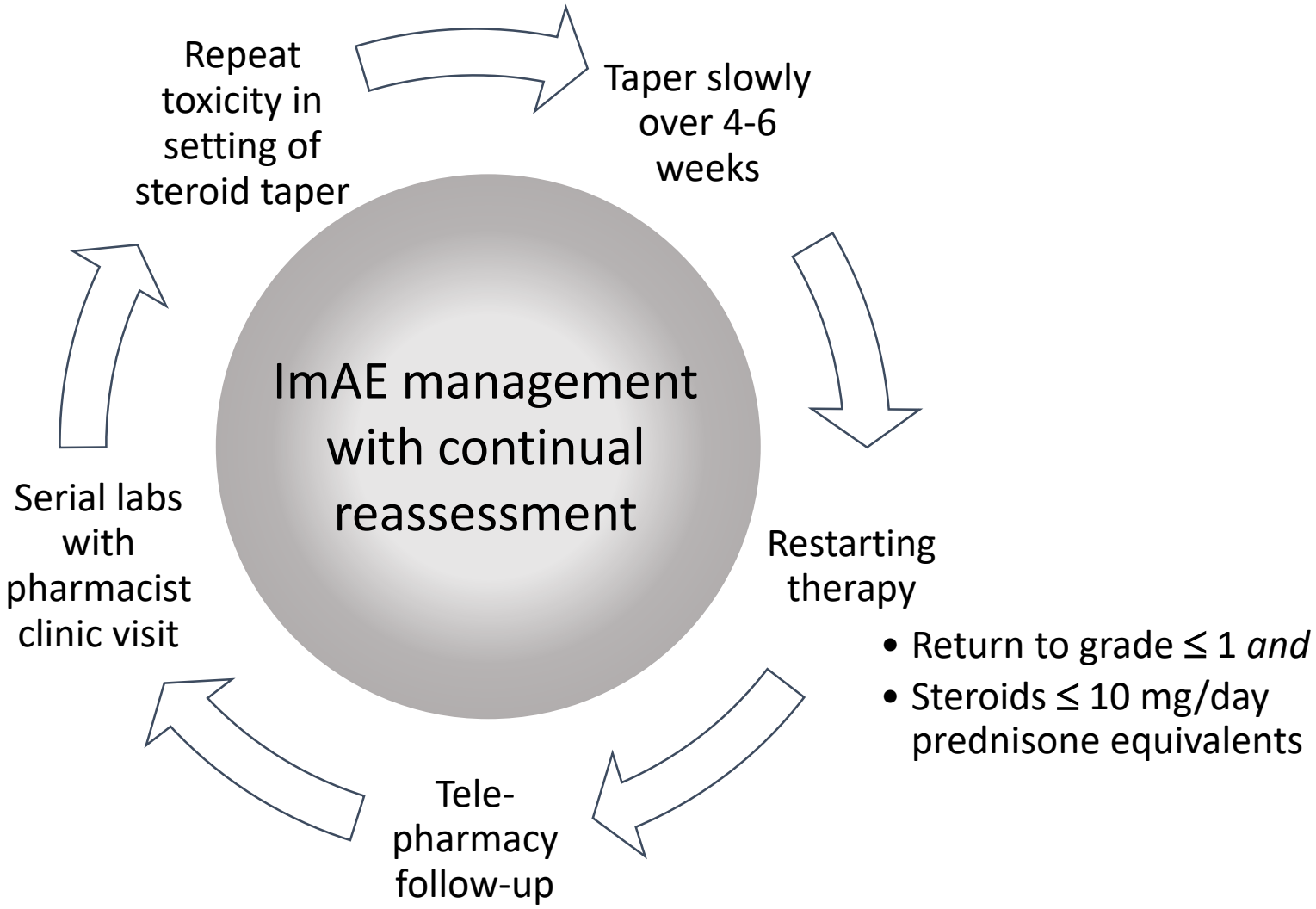
Off-label use

Compassionate use

Drug replacement programs

Pharmacist involvement in drug access and procurement

Practical and Logistical Considerations



- Return to grade ≤ 1 *and*
- Steroids ≤ 10 mg/day prednisone equivalents

Practical and Logistical Considerations

ImAE management

Long steroid tapers

PJP prophylaxis if ≥ 20 mg prednisone/day for ≥ 4 weeks

Fungal prophylaxis if ≥ 20 mg prednisone/day for ≥ 6 weeks

Consider HSV prophylaxis if seropositive

Stress ulcer prophylaxis

Supportive, preventive care

Calcium and vitamin D supplementation

HSV, herpes simplex virus; PJP, pneumocystis jeroveci pneumonia.

Practical and Logistical Considerations

Drug/drug interactions

- Steroid premedications:
  docetaxel, paclitaxel, emetogenic chemotherapy
- Medications that impair T-cell function
- Medications that impair the immune response

Practical and Logistical Considerations

FDA-approved companion diagnostics

- Atezolizumab in breast cancer: VENTANA PD-L1(SP142) Assay
- Pembrolizumab in other tumors: PD-L1 IHC 22C3 pharmDx
- Olaparib and talazoparib in breast cancer: BRACAnalysis CDx

Liquid/solid biopsies: common panels

- FoundationOne
- CGP+ (Caris)
- Guardant360

U.S. Food & Drug Administration. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed August 27, 2019.

Conclusions

- TNBC is still a disease associated with poor prognosis with tendency for relapse within 3 years after primary treatment
- TNBC has very high heterogenicity, which makes finding the optimal treatment options challenging
- PARP pathway is still a target with mild response to PARP inhibitors
- Immunotherapy is being studied in this disease due to more knowledge about tumor immunogenicity and the microenvironment
- Various immunotherapy trials are presenting promising data for combination with chemotherapy in all settings of TNBC
- The pharmacist is uniquely positioned to facilitate optimal patient selection and management of patients on ICI-based therapy

Thank you!