Changes in Cancer Care: Practicing Pharmacy in the Era of COVID-19

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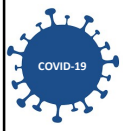
Educational Objectives

After completion of this activity, participants will be able to:

- Recognize the impact that COVID-19 has had on the treatment and management of patients with cancer
- Discuss the evolving guidelines and recommendations for cancer treatment during the COVID-19 pandemic
- Outline strategies for pharmacists that improve disease and treatment-related management in patients with cancer during the COVID-19 pandemic

Cancer and COVID-19



Location	Design	Population	Notable
China	Multicenter, observational	n = 1590 (cancer, n = 18)	• Patients with cancer at higher risk of severe event 39% vs 8% (*P* = 0.0003)
Europe	Multicenter, observational	n = 890	• Overall 8.6% rate of mortality • Complicated COVID-19 associated with male gender, advanced age, comorbidities
USA	Multicenter, cohort study	n = 928	• Race/ethnicity, obesity, cancer type, type of anticancer therapy, and recent surgery were ***NOT*** associated with mortality

Liang W, et al. *Lancet Oncol*. 2020;21(3):335-337; Pinato DJ, et al. *Cancer Discov*. Published online July 31, 2020. doi: 10.1158/2159-8290.CD-20-0773; Kuderer NM, et al. *Lancet*. 2020;395(10241):1907-1918.

CCC19: 30-Day All Cause Mortality

Characteristic	pAOR*	95%CI
Older age, risk per decade	1.84	1.53-2.21
Male gender	1.63	1.07-2.48
Former vs never smoker	1.60	1.03-2.47
ECOG PS 2 vs 0/1	3.89	2.11-7.18
Cancer present, stable	1.79	1.09-2.95
Cancer present, progressing	5.20	2.77-9.77
HCQ + azithromycin vs neither	2.93	1.79-4.97

HCQ, hydroxychloroquine; pAOR, partially adjusted odds ratio.
*Adjusted for age, sex, smoking status, and obesity.

Kuderer NM, et al. *Lancet*. 2020;395(10241):1907-1918.

The COVID-19 & Cancer Consortium

TERAVOLT: Thoracic Malignancies

- Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry: multicenter observational study
- Updated analysis (n = 400)
  - Thoracic tumors have a higher risk of death compared with general population or other malignancies
  - Of the fatalities: 47% received chemotherapy, 22% received immune checkpoint inhibitors (ICIs), 12% received targeted therapy
  - Prior use of steroids or anticoagulants increased mortality
  - Multivariate analysis: age older than 65 years increased risk of COVID-19 mortality (HR, 1.70; 95% CI, 1.09-2.63; *P* = 0.018)
  - ICU admission lower compared with other tumor types

Garassino MC, et al. *Lancet Oncol*. 2020;21(7):914-922;
Garassino MC. COVID -19 in thoracic malignancies. Oral presentation. 2020 World Conference on Lung Cancer; August 8, 2020.

Disease Severity in Patients with Cancer

Memorial Sloan Kettering Cancer Center (MSKCC)

- Retrospective analysis (March 10-April 7, 2020)
- n = 423 symptomatic COVID (N = 2035 tested)
- 40% hospitalized, 20% developed severe respiratory illness, 12% died within 30 days

	Multivariate	
	HR (95% CI)	*P* value
Age (>65 years)	1.67 (1.07-2.60)	0.024
Smoking (current/former)	1.39 (0.89-2.17)	0.148
Asthma/COPD	1.24 (0.72-2.13)	0.436
Cancer (nonmetastatic)	1.00 (Ref)	--
Cancer (metastatic solid)	0.75 (0.40-1.41)	0.371
Cancer (hematologic)	1.79 (0.97-3.32)	0.063
Cardiac disorder	1.18 (0.73-1.89)	0.505
Lymphopenia or corticosteroids	1.42 (0.86-2.34)	0.165
ICI	2.74 (1.37-5.46)	0.004

Predictors of severe respiratory illness, by COX proportional hazard (n = 423).

COPD, chronic obstructive pulmonary disease.

Robilotti EV, et al. *Nat Med*. 2020;26(8):1218-1223.

Hematological Malignancies

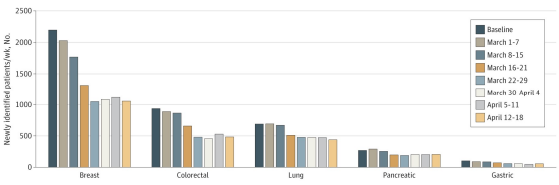
Italian Hematology Alliance

- Multicenter, retrospective, cohort study
- WHO confirmed hematologic malignancy with confirmed and symptomatic COVID-19
- Standard mortality ratios (study cohort vs Italian cohort without COVID-19)
- N = 536; 37% died
- Independent predictors of mortality
  - Severe/critical 4.08 (2.73-6.09)

	Deaths/patients	HR (95% CI)
Malignancy status: progressive disease	48/81	2.10 (1.41 -3.12)
Type of malignancy		
Myeloproliferative disease	27/83	1 (Ref)
Myelodysplastic syndromes	20/41	1.58 (0.69-3.62)
Acute myeloid leukemias	22/51	3.49 (1.56-7.81)
Acute lymphoblastic leukemias	3/16	1.65 (0.46-5.94)
Chronic lymphoproliferative neoplasms	22/69	1.64 (0.77-3.51)
Aggressive lymphomas	41/99	2.56 (1.34-4.89)
Plasma cell neoplasms	39/106	2.48 (1.31-4.69)

Passamonti F, et al. *Lancet Haematol*. Published online August 13, 2020. doi: 10.1016/S2352-3026(20)30251-9

Another Reason for Concern



Kaufman HW, et al. *JAMA Netw Open*. 2020;3(8):e2017267.

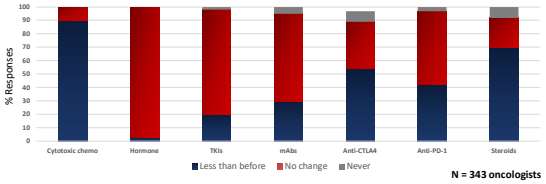
Impact of COVID-19

Delayed diagnosis	• ↓Visits based on patient observations • ↓ Compliance to national screening recommendations	↑ Mortality
Deferred care	• Postponed surgery, radiation, chemotherapy	↑ Mortality
Reduced care	• Less intensive chemotherapy • Neo-adjuvant chemotherapy instead of surgery	↓ Response ↑ Mortality

Bin Han Ong M. Sharpless: COVID expected to increase mortality by at least 10,000 deaths from breast and colorectal cancers over 10 years. *The Cancer Letter*. Published June 19, 2020. Accessed August 15, 2020. cancerletter.com/articles/20200619_1/

Impact of COVID-19 Decision Making

Question: *Comparing with your previous practice, would you recommend the following during the COVID-19 outbreak?*

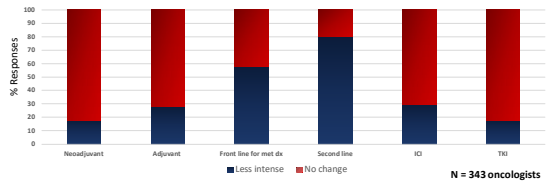


N = 343 oncologists

Uren Y, et al. *JCO Glob Oncol*. 2020;6:1248-1257.

Impact of COVID-19 Decision Making

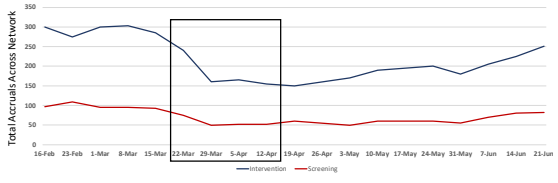
Question: *Comparing your previous practice, would you change dose intensity for the following settings during the COVID-19 outbreak?*



N = 343 oncologists

Uren Y, et al. *JCO Glob Oncol*. 2020;6:1248-1257.

NCI National Clinical Trials Network (NCTN) Trial Activity



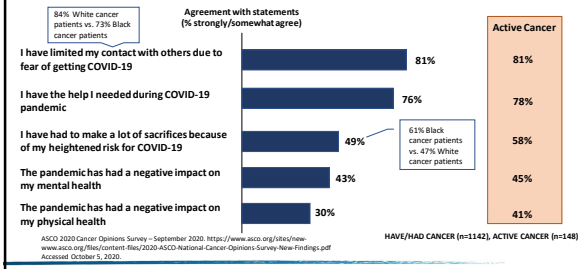
Sharpless, N. NRG General Session. Oral presentation at NRG Virtual Summer Meeting. July 17, 2020.

Clinical Research/Investigational Drug Services

- Develop COVID-19 standard operating procedures (SOPs)
- Communicate to participants about changes
- E-signatures for informed consent and other study documents
- Promote telehealth
- Implement patient review of symptoms and adverse effects
- Remote labs
- Remote study initiation visits and monitoring
- Staff working remotely
- Ship oral agents to home
- Communicate changes to institutional review boards (IRBs)
- Use technology for trial recruitment

Waterhouse DM, et al. *JCO Oncol Pract*. 2020;16(7):417-421.

The Cancer Patient Voice – ASCO Survey



ASCO 2020 Cancer Opinions Survey – September 2020. https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-National-Cancer-Opinions-Survey-New-Findings.pdf Accessed October 5, 2020.

Potential Changes in Cancer Care

Impact on Profession

PERSONAL

Communication
- The 4Ps (patients, peers, pharma, parents)

Professional Development
- Trainees
- Meetings
- Interviews

Economic
- Furloughs
- Unemployment

PRACTICE

Virtual care/telemedicine
- Ambulatory outpatient specialists

Treatment changes
- IV -> PO
- De-intensification (protocol ΔS)

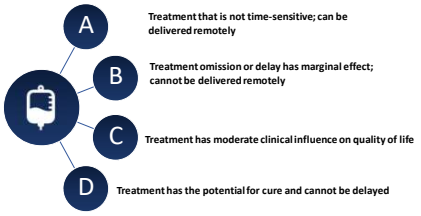
Health care worker safety
- PPE
- Staff shortage to limit exposure

Inpatient and Outpatient Pharmacy Practice

Distribution of Services	
INPATIENT	**OUTPATIENT**
Onsite	**Onsite**
Emergent needs (rapid response)	Emergent needs (rapid response)
Interdisciplinary collaboration	Maintain clinic workflow
Discharge counseling	Interdisciplinary collaboration
Offsite	**Offsite**
Medication education and reconciliation	Medication education and reconciliation
Patient own medication identification	Oral chemotherapy education and follow-up
Therapeutic drug monitoring	Transplant/oncology education
Order verification	Lab follow-ups
Medication adjustments (renal/hepatic)	Therapeutic drug monitoring
Drug-drug interactions	Order verification/chemo order preparation

Mahmoudjafari Z et al. Bio Blood Marrow Transplant. 2020 Jun;26(6):1043-1049.

Framework to Modify Cancer Treatments



Schrag D, et al. JAMA. 2020;323(20):2005-2006.

ASCO: Choosing Wisely®

Don't…

1. Use cancer directed therapies for solid tumor patients with ECOG ≥3
2. Perform PET, CT, or bone scans for staging of early prostate cancer
3. Perform PET, CT, or bone scans for staging of early breast cancer
4. Perform surveillance testing (biomarkers) or imaging for asymptomatic individuals who have been treated for breast cancer
5. Use G-CSFs for primary prevention of febrile neutropenia with <20% risk
6. Undertreat CINV
7. Use combination chemotherapy instead of one-drug when treating metastatic breast cancer unless the patient needs a rapid response
8. Use PET or PET-CT as a part of routine follow-up to monitor for recurrence in asymptomatic patients who have finished initial therapy
9. Perform PSA testing with no symptoms when patients are expected to live <10 years
10. Use a targeted therapy unless a patient's tumor cells have a specific biomarker that predicts an effective response to the targeted therapy

CINV, chemotherapy-induced nausea and vomiting; G-CSF, granulocyte colony-stimulating factor; PSA, prostate-specific antigen;

American Society of Clinical Oncology (ASCO). Ten things physicians and patients should question. Released April 4, 2012; October 29, 2013. Last reviewed 2019. Accessed August 15, 2020. choosingwisely.org/societies/american-society-of-clinical-oncology

ASCO Recommendations: Neutropenic Fever (NF)

- Prophylaxis: "***may be reasonable***" for patients at risk for NF at a lower expected risk (>10% risk)*
- Acute Care for Potential NF: Reasonable to evaluate the febrile patient by telemedicine
- Acute Care for Known NF: follow standard guidelines for NF including isolation, regardless of COVID-19 status

*NCCN short-term recommendations – expand use of G-CSF to intermediate (10%-20%) neutropenia risk.
Cautionary statement – avoid or discontinue use in confirmed or suspected COVID-19 to avoid ↑ risk of pulmonary inflammatory cytokines

Cancer treatment & supportive care. ASCO. Updated September 3, 2020. Accessed September 9, 2020. asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care; Tapitz RA, et al. *J Clin Oncol.* 2018;36(14):1443-1453; NCCN hematopoietic growth factors: short-term recommendations specific to issues with COVID-19 (SARS-CoV-2). NCCN. Accessed August 15, 2020. nccn.org/covid-19/pdf/HGF_COVID-19.pdf

GI Cancers: Modifications of Care

Condition	Proposed Modification
Low-risk chemotherapy (single or doublet +/- biologic)	Explore the possibility of in-home disconnection
High-risk chemotherapy	Decrease intensity (FOLFIRINOX → FOLFOX of FOLFIRI)
Heavily pretreated patients	Reevaluate risk/benefit
Oral chemotherapy	Transition to telehealth
5-FU-based regimens	Switch from 5-FU infusions to capecitabine
Oral targeted agents (regorafenib, sorafenib)	Transition to telehealth, consider a break from therapy, or reduction in frequency labs

Lou E, et al. *JCO Oncol Pract.* 2020;16(7):383-388.

Treatment Adaptations

- Modify regimen to reduce patient visits
  - Examples: (Colon): Adjuvant CAPOX rather than infusional 5-FU, (Ovarian): q21d carboplatin/paclitaxel rather than weekly paclitaxel, (Multiple): immune checkpoint inhibitor intervals, (Prostate): leuprolide intervals (q6mo), (Breast): neo-adjuvant hormonal therapy for ER+/HER2 negative
- Reduce treatment duration
  - Example: (Breast): Short-HER trial – 9 weeks of trastuzumab vs 12 months (5-year DFS: 85% vs 88%)
- Not initiating therapy
  - Lack of benefit in 2nd or later lines of therapies (advanced cervical, glioblastoma)

Waisberg F, et al. *JCO Oncol Pract.* 2020;16(6):305-307.

Extending Interval Dosing ICI

- Possible dosing strategies
  - Pembrolizumab 400 mg IV q6wk
  - Nivolumab 480 mg IV q4wk
  - Atezolizumab 1680 IV q4wk
  - Durvalumab 1500 mg IV q3-4wk
- Payers? Every indication?
- Potential pitfalls

Sehgal K, et al. *Front Oncol.* 2020;10:1193.

The New Infusion Center?

"In the context of anticancer therapy, home infusion benefit policies from public and commercial payers should be strictly limited to exceptional circumstances where the benefits of home infusion outweigh the risks."

American Society of Clinical Oncology Position Statement Home Infusion of Anticancer Therapy. ASCO. Published June 23, 2020. Accessed August 15, 2020. asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2020_Home-Infusion-Position-Statement.pdf?cid=DM5714&bid=53107298

Cancer Care at Home

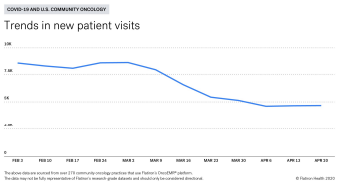
- Penn Center for Cancer Care Innovation
  - Cancer Care at Home (CC@H) launched November 2019
- CC@H provided a foundation for rapid COVID response
- Prior to launch
  - 5-Fluorouracil infusions, hydration, supportive care
- Mid-March to mid-June referrals
  - 13 new cancer agents (39-430 patients participating in program)

Select Cancer Treatments

- Bortezomib
- EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone)
- Pembrolizumab maintenance
- Rituximab maintenance
- Leuprolide

Laughlin AI, et al. *N Engl J Med Catalyst*. Published online July 7, 2020.

Trends in New Patient Visits



Other Notables

- Patient visits involving chemotherapy were reduced by up to 17% in the Northeast
- Non-chemo visits ↓ across the country up to 37%
- Cancellations and no-shows doubled, up to 80%

Bin Han Ding M. COVID-19 vs. community oncology: Flatiron's data provides first damage assessment. *The Cancer Letter*. Published May 1, 2020. Accessed June 30, 2020. cancerletter.com/articles/20200501_1/

Telehealth

- Medicare primary care visits (0.1% February 2020 vs 43.5% April 2020)
- Joint Commission of Pharmacy Practitioners (JCPP) Joint Policy Recommendations to Combat the COVID-19 pandemic
- Oncology pharmacy: oral oncolytic adherence, adverse effect management, supportive care, post-transplant medication management
- Billing/reimbursement
- CALL TO PUBLISH – pharmacy telehealth activities!

https://www.hhs.gov/about/news/2020/07/28/hhs-issues-new-report-highlighting-dramatic-trends-in-medicare-beneficiary-telehealth-utilization-amid-covid-19.html Accessed August 15,2020. ; COVID-19 Joint Pharmacy Organization Statement on Coronavirus Policy Recommendations Update. Updated April 3, 2020. https://www.aacp.org/sites/default/files/JCPP_COVID19_Joint_Pharmacy_Organization_Statement_on_Coronavirus_Policy_Recommendations_Update.pdf Accessed August 15, 2020.

Disparities in Digital Access

- Medicare temporarily expanded its coverage of telemedicine to all beneficiaries
  - Audio-only visits paid at same rate as video and in-person
- Cross-sectional study analyzing data from 2018 American Community Survey
  - Sample surveyed (n=638,830)
  - Assessment of those who did NOT have: 1) desktop or laptop computer with high-speed internet, 2) smartphone, 3) either means of digital access
  - Results: 41.4% (95% CI, 40.4%-42.4%) of Medicare beneficiaries lacked access to computer (26.3% either form of digital access)
    - Digital access lower – ≥ 85 yo, widowed, high-school education or less, Black or Hispanic, received Medicaid, or had disability

Roberts ET and Mehrotra A. JAMA Intern Med. 2020 Aug 3;e202666

Strategies for Pharmacists: Take Home Points

- Increase pharmacist involvement in ambulatory patients
- Prepare for staffing shortages and quarantining
- Ensure patient follow-up to prevent readmissions (or additional visits to clinic)
  - Initial comprehensive education
  - Telehealth follow-up
- Confirm pharmacist input into patient triage/treatment
  - Alternative dosing schedules?
  - Appropriate supportive care
  - Informatics/clinical decision support

Kjerengtroen S et al. Am J Health-Syst Pharm. 2020;77:1250-1257

Conclusion

- COVID-19 has significantly impacted cancer patient outcomes and oncology care delivery
- Ongoing cancer registries will provide tremendous insight into future care
- Mobilize pharmacy organizational efforts: telehealth future
- Don't practice in a pharmacy "bubble;" extend/expand pharmacy services in the ambulatory setting

Recommendation Guidance

- American Society of Clinical Oncology (ASCO) – A Guide to Cancer Care Delivery During the COVID-19 Pandemic
- American Society of Hematology (ASH) – COVID-19 Resources
- Association of Community Cancer Centers (ACCC)
  - Implementing telehealth, clinical trial administration
- National Comprehensive Cancer Network (NCCN) – COVID-19 Resources

https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf; www.accc-cancer.org Accessed August 15, 2020; https://www.hematology.org/covid-19. Accessed August 15, 2020; https://www.nccn.org/covid-19/ Accessed August 15, 2020

Ongoing COVID + Cancer Registries

- American College of Surgeons (ACS)
- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH) Research Collaborative
- Center for International Blood and Marrow Transplant Research (CIBMTR)
- COVID-19 & Cancer Consortium (CCC19)
- European Society for Medical Society (ESMO) CoCARE
- NCI COVID-19 in Cancer Patients Study (NCCAPS)
- TERAVOLT

Additional Resources

COVID-19 & Cancer Consortium	ccc19.org/publications
ASCO special report: a guide to cancer care delivery during the COVID-19 pandemic. 2020.	www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf
National Comprehensive Cancer Network (NCCN) Free Webinar Series on COVID-19 and Cancer	www.nccn.org

B-Cell Malignancies: Exploring the Influence of BTK Inhibitors and Pharmacist-Led Interventions on Patient Outcomes

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Oncology Pharmacy Manager
M Health Fairview

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Mayo Clinic College of Medicine
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Educational Objectives

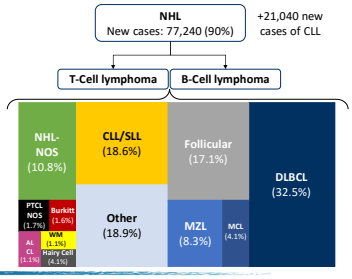
After completion of this activity, participants will be able to:

- Describe the relationship between Bruton's tyrosine kinase (BTK) and the BCR pathway in B-cell malignancies
- Review guideline recommendations for the use of BTK inhibitors in the management of mantle cell lymphoma, chronic lymphocytic leukemia/small cell leukemia, Waldenström macroglobulinemia, and marginal zone lymphoma
- Outline a strategy to improve medication adherence among patients receiving a BTK inhibitor

Overview of B-Cell Malignancies

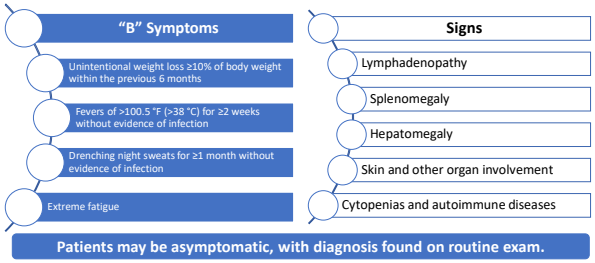
Select Subtypes of B-Cell Malignancies

- **Heterogeneous group of hematologic malignancies**
  - Non-Hodgkin lymphomas (NHLs)
  - Some lymphomas/leukemias
- **Select subtypes require aggressive treatment and others may never require therapy**



Siegel RL, et al. *CA Cancer J Clin.* 2020;70(1):7-30;
Al-Hamadani M, et al. *Am J Hematol.* 2015;90(9):790-795.

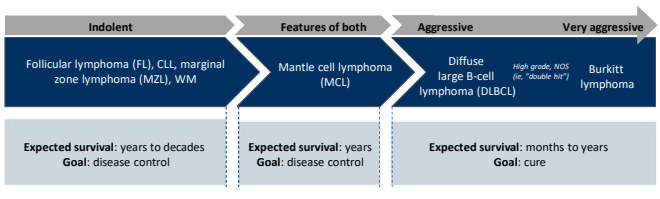
Patient Presentation



Patients may be asymptomatic, with diagnosis found on routine exam.

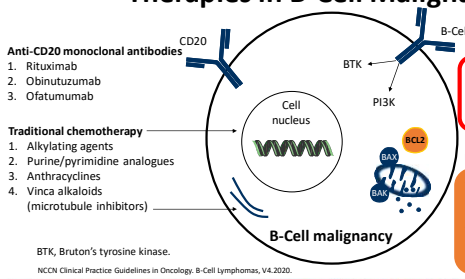
Hallek M, et al. *Blood.* 2018;131(25):2745-2760; NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas, V4.2020.

Features of Select B-Cell NHLs



Siegel RL, et al. *CA Cancer J Clin.* 2020;70(1):7-30; Al-Hamadani M, et al. *Am J Hematol.* 2015;90(9):790-795.

Therapies in B-Cell Malignancies



Anti-CD20 monoclonal antibodies
1. Rituximab
2. Obinutuzumab
3. Ofatumumab

Traditional chemotherapy
1. Alkylating agents
2. Purine/pyrimidine analogues
3. Anthracyclines
4. Vinca alkaloids (microtubule inhibitors)

BTK inhibitors
1. Ibrutinib
2. Acalabrutinib
3. Zanubrutinib

PI3K inhibitors
1. Idelalisib
2. Duvelisib
3. Copanlisib

BCL2 inhibitor: venetoclax

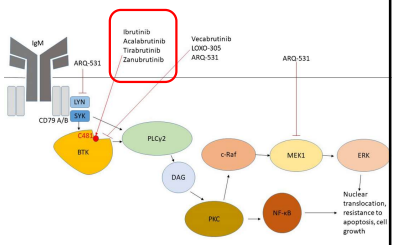
- Variety of standard combinations (eg, FCR, BR, CHOP, PI3Ki + anti-CD20)
- Ongoing studies to determine optimal sequence or combinations

BTK, Bruton's tyrosine kinase.

NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas, V4.2020.

Targeting BTK

- **BTK**
  - Downstream Tec family non-receptor protein
  - Involved in upstream BCR pathway transduction
- **BTK plays a role in:**
  - Survival and proliferation of leukemic B-cells
  - Interaction between cells in tumor microenvironment
- **BCR activation**
  - BTK activated by tyrosine protein kinases LYN and SYK
  - PLCγ2 activation
  - Increased activation of NF-κB resulting in inhibition of apoptosis of the B cell



Kim HO. *Arch Pharm Res.* 2019;42(2):171-181; Zhang Z, et al. *Arch Pharm (Weinheim).* 2018;351(7):e1700369.

CLL/SLL

Most common form of adult leukemia in Western countries

21,040 new cases and 4060 deaths in 2020

- Diagnosis median age 70 y
- Death median age 81 y
- 1.2% of all new cancer cases in the United States

Death rates falling on average 2.9% each year over 2008-2017

5-year overall survival (OS): 86.1%

Key prognostic factors:

- Del(17p)/TP53 mutation
- Unmutated IGHV
- ZAP-70 expression
- Presence of del(11q)
- Complex karyotype
- Patient age and comorbidities

IGHV, immunoglobulin heavy-chain variable region gene.

NCCN Clinical Practice Guidelines in Oncology. CLL/SLL, V4.2020; Siegel RL, et al. *CA Cancer J Clin.* 2020;70(1):7-30; SEER Cancer Stat Facts: leukemia - chronic lymphocytic leukemia (CLL). National Cancer Institute. Accessed August 20, 2020. seer.cancer.gov/statfacts/html/clyl.html

CLL/SLL Management

Variable	Adverse prognosis	Grading
Age	>65 years	1
Clinical stage	Binet B or C Rai I-IV	1
Del(17p) and/or TP53 mutation	Deleted and/or mutated	4
IGHV mutation	Unmutated	2
Beta-2-microglobulin	>3.5 mg/L	2

Risk	Score	5-year OS	Treatment
Low	0-1	93.2%	Watch/wait
Intermediate	2-3	79.3%	Treat only if symptomatic
High	4-6	63.3%	Treat, unless asymptomatic
Very high	7-10	23.3%	Non-cytotoxic protocol, if possible

Some patients with CLL survive for many years without therapy.

International CLL-IPI Working Group. *Lancet Oncol.* 2016;17(6):779-790.

NCCN Guidelines: First-Line CLL/SLL Treatment

Without del(17p)			With del(17p)		
Patient factors	**Preferred**	**Other**	**Patient factors**	**Preferred**	**Other**
Frail with significant comorbidities OR **≥65 y/younger with significant comorbidities**	1. Ibrutinib (category 1) 2. Acalabrutinib ± obinutuzumab 3. Venetoclax + obinutuzumab	1. Bendamustine + anti-CD20 monoclonal antibody (mAb) (not for frail patients)* 2. Chlorambucil + obinutuzumab	Any	1. Ibrutinib 2. Acalabrutinib ± obinutuzumab 3. Venetoclax + obinutuzumab	1. Alemtuzumab ± rituximab 2. High-dose methylprednisolone + rituximab 3. Obinutuzumab
Young/fit (<65 y without significant comorbidities)		1. Bendamustine + anti-CD20 mAb 2. FCR (preferred for IGHV-mutated CLL) 3. Fludarabine + rituximab			

FCR, fludarabine, cyclophosphamide, rituximab.
*Bendamustine 70 mg/m² for cycle 1 (escalate to 90 mg/m² if tolerated). All recommendations are category 2A unless otherwise indicated. This table does not include NCCN category 2B/3 recommendations.
NCCN Clinical Practice Guidelines in Oncology. CLL/SLL, V4.2020.

Ibrutinib: First-Line Treatment

Trial	Study details	Summary
Single agent		
RESONATE-2	• >65 years, without del(17p); n = 269 • Ibrutinib vs chlorambucil	• 5-year PFS for ibrutinib versus chlorambucil: • 70% vs 12%; HR [95% CI], 0.146 [0.098-0.218] • 5-year OS: 83% vs 68%; HR [95% CI], 0.450 [0.266-0.761] • Established efficacy of ibrutinib as first-line choice for patients ≥65 years without del(17p)
Combination therapy		

Alliance A041202	• Older patients; ± del(17p); n = 547
	• Ibrutinib vs ibrutinib + rituximab vs bendamustine + rituximab (BR)
		• Longer overall response and improved PFS regardless of del(17p) status with ibrutinib arm
		  • No difference in PFS with ibrutinib + rituximab vs ibrutinib
		  • Benefit especially in patients with unmutated IGHV
		• Confirmed results from RESONATE-2 trial, specifically in older patients regardless of del(17p) status

E1912	• Younger patients, excluded those with del(17p); n = 529
	• Ibrutinib + rituximab vs FCR
		• 3-year PFS and 3-year OS ibrutinib + rituximab vs FCR
		  • 89.4% vs 72.9%; *P* <0.001
		  • 98.8% vs 91.5%; *P* <0.001
		• Established efficacy of ibrutinib + rituximab as first-line choice for younger patients, especially if unmutated IGHV

- **Led to FDA approval for front-line setting**
- **NCCN Category 1 recommendation for older patients, frail patients, *OR* younger patients with comorbidities**

Led to change in NCCN Category 2A (other recommended regimen) ➔Category 1 (preferred) in patients <65 years *without* del(17p)

Burger JA, et al. *Leukemia.* 2020;34(3):787-798; Barr PM, et al. *Blood.* 2016:Abstract 642; Woyach JA, et al. *N Engl J Med.* 2018;379(26):2517-2528; Shanafelt TD, et al. *Blood.* 2018;132: Abstract LBA-4.

PFS, progression-free survival.

Acalabrutinib: First-Line Treatment

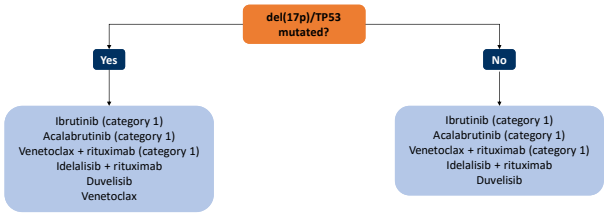
Trial name	Study details	Summary

ELEVATE TN	• Untreated CLL ± del(17p); n = 526
	• Acalabrutinib vs acalabrutinib + obinutuzumab vs obinutuzumab + oral chlorambucil
		• PFS: acalabrutinib ± obinutuzumab vs obinutuzumab
		  • Not reached (NR) vs 22.6 mo; HR, 0.10; 95% CI, 0.06-0.17; *P* <0.0001 at a median follow-up of 28 mo
		  • Benefit seen across different subgroups, including del(17p) mutation
		  • Longer follow-up needed to evaluate OS
		• Acalabrutinib/obinutuzumab well tolerated
		  • Atrial fibrillation any grade: 3% or 4% vs 1%
		  • Bleeding any grade/grade ≥3: 43%/2% or 39%/2% vs 12%/0%
		  • Hypertension grade ≥3: 3% or 2% vs 3%

Along with results from the ASCEND trial, led to FDA approval of acalabrutinib for CLL in November 2019.

Sharman JP, et al. *Blood.* 2019;134:Abstract 31; Sharman JP, et al. *Lancet.* 2020:395(10232):1278-1291.

Relapsed/Refractory CLL/SLL



*Select therapies shown. Refer to NCCN for full list of options.

NCCN Clinical Practice Guidelines in Oncology. CLL/SLL, V4.2020.

BTK Inhibitors in Relapsed/Refractory CLL

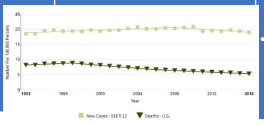
Trial name	Study details	Summary	
RESONATE-1	Relapsed/refractory (R/R) CLL, high risk; n = 391 Ibrutinib vs ofatumumab	Results: ibrutinib vs ofatumumab • Median PFS at 74 months: 44 months vs 8 months; *P* <0.0001 • Median OS favored ibrutinib (HR, 0.64); confirmed at 6-year follow-up • Grade ≥3 atrial fibrillation and hypertension in 9% and 6%, respectively • Conclusion: ibrutinib effective, well tolerated in R/R CLL	**Led to initial FDA approval for ibrutinib in CLL and NCCN Category 1 recommendation in R/R setting**
ASCEND	R/R CLL; n = 310 Acalabrutinib vs idelalisib + rituximab vs bendamustine + rituximab	Results at median follow-up of 16.1 months: • Median PFS was significantly longer with acalabrutinib vs investigator's choice (NR vs 16.5 mo [HR, 0.31; 95% CI, 0.20-0.49; *P* <0.0001]) • Median OS not different between groups	**Led to NCCN Category 1 recommendation in R/R setting regardless of age, comorbidities**

Byrd JC, et al. *N Engl J Med.* 2014;371(3):213-223; Munir T, et al. *Am J Hematol.* 2019;94(12):1353-1363; Ghia P, et al. *J Clin Oncol.* 2020;38(25):2849-2861; Awan FT, et al. *Blood Adv.* 2019;3(9):1553-1562.

MCL and MZL

Aggressive subtypes of NHL
- 72,240 new cases and 19,940 deaths in 2020
  - Diagnosis median age 67 years
  - Death median age 76 years
- MCL: 3%-6% of cases
- MZL: 5%-17% of cases

Death rates falling on average 2.2% each year over 2008-2017
5-year OS = 72%



Hallmark characteristics
- **MCL**
  - t(11;14) translocation
  - SOX11 transcription
  - Strong expression and Y223-phosphorylation of BTK
- **MZL**
  - Originate in marginal zone
  - Spleen- and mucosa-associated lymphoid tissues
  - Overexpression of IGHV 1-2 gene and low mutation rates

NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas, V4. 2020; Hoster E, et al. *Blood.* 2008;111(2):558-565; SEER Cancer Stat Facts: non-Hodgkin lymphoma. National Cancer Institute. Accessed August 20, 2020. seer.cancer.gov/statfacts/html/nhl.html; Al-hamadani M, et al. *Am J Hematol.* 2015;90(9):790-795; Cheah CY, et al. *J Clin Oncol.* 2016;34(11):1256-1269; Herrmann A, et al. *J Clin Oncol.* 2009;27(4):511-518; Martin P, et al. *Ann Oncol.* 2008;19(7):1327-1330.

MCL and MZL Management

- Incurable with conventional chemotherapy
- Observation limited to select patients (eg, MCL in situ, smoldering MCL)
- Stage I-II: radiation ± chemoimmunotherapy
- Stage II (bulky) and Stage III-IV: chemotherapy ± autologous hematopoietic cell transplantation (HCT)

MZL shares similar treatment modality based on prognostic risk factors, patient comorbidities, and subtype of less aggressive lymphomas.

NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas, V4.2020; Hoster E, et al. *Blood.* 2008;111(2):558-565.

NCCN Guidelines: R/R MCL and MZL

MCL Second-line Therapy

Short Response Duration to Prior Chemoimmunotherapy
- BTK inhibitors (acalabrutinb, ibrutinib ± rituximab, zanubrutinib)
- Lenalidomide ± rituximab
- Venetoclax

Other Recommended Regimens
- Ibrutinib, lenalidomide, rituximab (2B)
- Venetoclax + ibrutinib (2B)

Extended Response Duration to Prior Chemoimmunotherapy
- Bendamustine ± rituximab (if not previously given)
- Bortezomib ± rituximab
- BTK inhibitors (acalabrutinb, ibrutinib ± rituximab, zanubrutinib)
- Lenalidomide ± rituximab

Other Recommended Regimens
- Venetoclax
- Bendamustine, bortezomib, and rituximab (2B)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab (2B)
- R-CHOP or VRCAP (if not previously given) (2B)

MZL Second-line and Subsequent Therapy

Preferred Regimens
- Bendamustine + obinutuzumab
- Bendamustine + rituximab
- Ibrutinib
- Lenalidomide + rituximab
- RCHOP
- RCVP

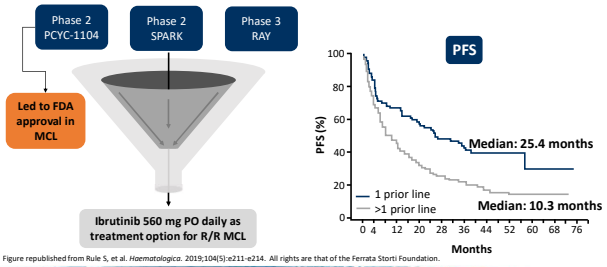
Other Recommended Regimens
- Ibritumomab tiuxetan
- PI3K inhibitors (copanlisib, duvelisib, idelalisib)
- Rituximab

Elderly or Infirm
- Ibrutinib
- Lenalidomide + rituximab
- Rituximab

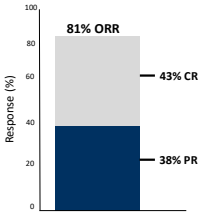
R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; VRCAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.

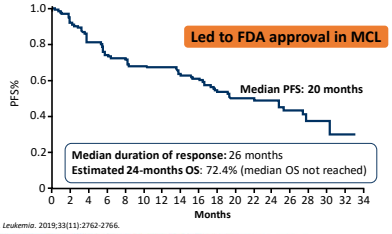
NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas, V4.2020.

Ibrutinib Pooled Analysis: R/R MCL



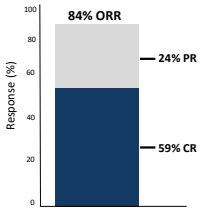
ACE-LY-004 Trial: Acalabrutinib in R/R MCL





Wang M, et al. *Lancet*. 2018;391(10121):659-667; Wang M, et al. *Leukemia*. 2019;33(11):2762-2766.

BCG-3111-206 Trial: Zanubrutinib in R/R MCL



Conclusions

Median PFS: 16.7 months

Median duration of response (DOR): 19.5 months

Led to FDA approval in MCL

Song Y, et al. *Hematol Oncol*. 2019;37:45-4; Brukinsa. Prescribing information. BeiGene USA, Inc; November 2019.

PCYC-1112: Ibrutinib in R/R MZL

Patients with R/R MZL with ≥1 prior therapy including ≥1 anti-CD20-directed regimen, ECOG PS 0-2 (N = 63)

→ **Ibrutinib 560 mg PO once daily** →

Primary end point

- **ORR** per IRC assessment: 48%
  - ORR concordance rate (IRC and investigator assessment): 84%

Secondary end points

- **Median PFS:** 14 months
- **OS rate** using 18-month estimate: 81% OS
- **DOR** at 18 months: 62%
- **Median time to response:** 4.5 months; best: 5.2 months
- **Clinical benefit rate** (CR + PR + SD) per IRC assessment: 83%
  - Tumor shrinkage in 79% of patients (all 3 MZL subtypes)

Conclusion: ibrutinib provides a treatment option in patients with R/R MZL

IRC, independent review committee; IWG, International Working Group.
Noy A, et al. ASH 2016. Abstract 1213; Noy A, et al. *Blood*. 2017;129(16):2224-2232.

Waldenström Macroglobulinemia (WM)

Subtype of NHL

Bone marrow infiltration by lymphoplasmacytic cells and IgM

- Rare and indolent
- 1000–1500 new cases per year
- ≈2% of hematologic malignancies
- MyD88^{L265P} expression

ISSWM risk group	5-year survival rate	Median survival
Low	87%	12 y
Intermediate	68%	8 y
High	36%	3.5 y

Poor prognostic factors:

- Age >65 years
- Hemoglobin (Hgb) <10 g/dL
- Albumin level <4 g/dL
- Elevated β_2-microglobulin level

NCCN Clinical Practice Guidelines in Oncology. Waldenström Macroglobulinemia/lymphoplasmacytic Lymphoma, V1.2021; Morel P, et al. *Blood*. 2009;113(18):4163-4170; American Cancer Society. Key statistics about Waldenström macroglobulinemia. Accessed August 20, 2020. cancer.org/cancer/waldenstrom-macroglobulinemia/about/key-statistics.html

WM Management

Treatment initiated for patients who are symptomatic
Hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, presence of cytopenia

Plasmapheresis for immediate disease control

Agents limiting future treatment options should be avoided during initial therapy

NCCN Clinical Practice Guidelines in Oncology. Waldenström Macroglobulinemia/lymphoplasmacytic Lymphoma, V1.2021.

iNNOVATE: Ibrutinib + R vs R in WM

Randomized phase 3 study

Patients with WM and serum IgM >0.5 g/dL; not refractory to rituximab or no rituximab in 12 months before study (n = 150)

- **Ibrutinib** 420 mg PO daily + **Rituximab** 375 mg/m² IV on day 1 of weeks 1-4 and 17-20 (n = 75)
- **Rituximab** 375 mg/m² IV day 1 of weeks 1-4 and 17-20 + placebo (n = 75)

Primary end point
- **30-month PFS:** 82% vs 28%, *P* <0.001

Secondary end points
- **ORR:** 92% vs 47%, *P* <0.001
- **Major response:** 72% vs 32%, *P* <0.001
- 30-month OS: 94% vs 92%
- Rate of sustained Hgb improvement higher with ibrutinib/rituximab in all patients and in patients with baseline Hgb ≤11 mg/dL

Conclusion: ibrutinib + rituximab showed significant improvement in PFS in patients with WM

Dimopoulos MA, et al. *N Engl J Med*. 2018;378(25):2399-2410; Owen RG, et al. *Semin Oncol*. 2003;30:110-115; Kyle RA, et al. *Semin Oncol* 2003;30:116-120.

ASPEN: Ibrutinib vs Zanubrutinib Head-to-Head

Randomized, open-label, multicenter phase 3 study

- Cohort 1: MYD88 mutation
- Cohort 2: MYD88 wildtype

→ **Ibrutinib** 420 mg PO daily
→ **Zanubrutinib** 160 mg PO BID
→ **Zanubrutinib** 160 mg PO BID

Tx until PD, unacceptable AE, death, withdrawal of consent

Cohort 1
- No patient achieved CR
- Ibrutinib vs zanubrutinib
  - **VGPR:** 19 (19%), 29 (28%); *P* = 0.09
  - **Major response rate:** 78%, 77%
  - **Median DOR and PFS:** NR
  - **18-month PFS**: 84%, 85%

Conclusion: ibrutinib and zanubrutinib are both efficacious in treating WM

Tam CS, et al. *Blood*. Published online July 30, 2020. doi: 10.1182/blood.2020006844

Acalabrutinib and Zanubrutinib in WM

Acalabrutinib: ACE-WM-001
International, open-label, single-arm phase 2 trial

Response Based on 6th IWWM Criteria	Treatment naïve (n = 14)	R/R (n = 92)
ORR (≥MR), % (95% CI)	94 (66-100)	93 (86-98)
MRR (≥PR), % (95% CI)	79 (49-95)	78 (68-86)
Best response, n (%)		
▪ CR	0	0
▪ VGPR	1 (7)	29 (32)
▪ PR	10 (71)	43 (47)
▪ MR	2 (14)	14 (15)
Median time to best response, mo (range)	4.9 (1.8-16.6)	1.9 (0.9-23.2)
24-mo DOR	90.0 (47-99)	84.0 (73-90)
24-mo PFS	90.0 (47-99)	82 (72-88)
24-mo OS	92 (54-99)	89 (80-94)

Zanubrutinib phase 1 trial
Different subtypes of B-cell malignancies, including WM

Outcome	Overall (n = 73)
Median follow-up	22.5 mo
Response criteria	Mod. 6th IWWM (IgM and lymph node reduction)
ORR	92%
MRR	82%
VGPR	41%
PR/PR-L	41%
Median IgM reduction (g/L)	32.7 → 8.2 g/L
Median Hgb change (g/dL) n = 32	8.85 → 13.4 g/L

Owen R, et al. ASCO 2018. Abstract 7501. ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.7501; Tam CS, et al. International Workshop for Waldenstrom's Macroglobulinemia Meeting 2018. Accessed September 10, 2020. wmworkshop.org/images/NYC-2018/Abstracts/Session-10/2-Tam-10.pdf; BeiGene announces updated results from phase 1 clinical trial of zanubrutinib in patients with Waldenström's macroglobulinemia. News release. BeiGene Ltd; October 12, 2018. Accessed September 10, 2020. beigeneltd.gcs-web.com/news-releases/news-release-details/beigene-announces-updated-results-phase-1-clinical-trial?loc=US

The Role of the Pharmacist

Multidisciplinary Collaboration

- **Coordination of care**
  - Supportive care and lab monitoring
  - Cost considerations
- **Pharmacy-led oral chemotherapy management programs improved**
  - Adherence to national oral chemotherapy prescribing standards
  - Time to medication access
- **Identification of clinically significant issues**
  - Most common: adverse drug reactions, 40%; modification of laboratory monitoring, 25%
  - Provider and patient satisfaction

Multidisciplinary collaboration → **Drug considerations: interactions, administration** → **Antimicrobial prophylaxis, infectious concerns** → **Adverse effect management** → **Patient activation and communication** → **Financial barriers and medication access**

Hansen EA, et al. *J Pharm Pract*. 2016;29(3):206-211; Holle LM, et al. *J Oncol Pharm Pract*. 2016;22(3):511-516; Lam MS, et al. *J Oncol Pharm Pract*. 2016;22(6):741-748; Muluneh B, et al. *J Oncol Pract*. 2018;14(6):e324-e334; Perez A, et al. *J Hematol Oncol Pharm*. 2015;5:99-108; Mancini R, et al. *J Clin Oncol*. 2012;30(suppl):Abstract 44; Koselke E, et al. *J Hematol Oncol Pharm*. 2015;5:62-68; Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355.

BTK Inhibitors: Drug Interactions

Agent	Metabolism and transport	Concurrent CYP3A inhibitor dose adjustment	Concurrent CYP3A inducer dose adjustment	Other
Acalabrutinib	Substrate: CYP3A4 (major), P-gp, BCRP/ABCG2	Strong: Avoid Moderate: Reduce to 100 mg PO daily	Strong: Increase to 200 mg PO BID	Separate antacids by 2 h; take acalabrutinib 2 h prior to H2RAs; avoid PPIs
Ibrutinib	Substrate: CYP2D6 (minor), CYP3A4 (major)	Moderate: Reduce to 280 mg PO daily Strong (posaconazole): Reduce to 70 mg PO daily Strong (other): Avoid	Strong: Avoid	N/A
Zanubrutinib	Substrate: CYP3A4 (major)	Strong: Reduce to 80 mg PO daily Moderate: Reduce to 80 mg PO twice daily	Moderate or strong: Avoid	N/A

BCRP, breast cancer resistance protein; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor.

Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019.

BTK Inhibitors: Administration

Agent	Pill burden	Dosing frequency	Administration	Missed dose recommendations
Acalabrutinib	1 capsule (100 mg)	BID	• Administer with ***OR*** without food • High-fat, high-calorie meal decreases C_{max} by 73%; T_{max} delayed 1-2 h	Within 3 hours, otherwise skip
Ibrutinib	1 tablet	Daily	• Administer with ***OR*** without food; • High-fat, high-calorie meal increases C_{max} 2- to 4-fold and AUC by ≈2-fold	Same day ASAP
Zanubrutinib	2-4 capsules (80 mg)	Daily or BID	Administer with ***OR*** without food	Same day ASAP

Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019.

Infection Prophylaxis: No Standard for BTK Inhibitor

Agent	*Pneumocystis jirovecii* pneumonia (PJP)	Herpes simplex virus (HSV)	Cytomegalovirus (CMV)	Hepatitis B (HepB)
Agent for prophylaxis or monitoring	Sulfamethoxazole/ trimethoprim or equivalent	Acyclovir or equivalent	CMV PCR Q2-3W	High-risk: prophylaxis and monitoring
Acalabrutinib				
Ibrutinib				
Zanubrutinib				
Duvelisib	X		X	
Idelalisib	X		X	
Purine analog	X	X	X	
Venetoclax				
Bendamustine	X	X	X	
Alemtuzumab	X	X	X	
Anti-CD20				X

Consider prophylaxis with BTK inhibitor for "high-risk" patients

HepB
Fungal PNA
PJP
EBV
CMV

NCCN Clinical Practice Guidelines in Oncology. CLL/SLL, V4.2020; Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019; Copiktra. Prescribing information. Verastem Oncology; July 2019; Zydelig. Prescribing information. Gilead Sciences Inc; October 2018; Venclexta. Prescribing information. AbbVie Inc; May 2020.

EBV, Epstein-Barr virus; PNA, pneumonia.

BTK Inhibitors: Inhibition Differences

IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

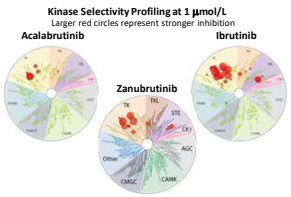


Figure used with permission of American Society of Hematology, from "Potency and selectivity of BTK inhibitors in clinical development for B-cell malignancies," Kaptein A, et al; 132(suppl 1) © 2018; permission conveyed through Copyright Clearance Center, Inc.

Off-Target Effects

TEC	Platelet effects, T-cell priming
EGFR	Rash, cardiac toxicity, diarrhea
SRC	Platelet effects
BMX	Cardiac toxicity
ITK	Antibody-dependent cellular cytotoxicity, migration of PMN
JAK3	Immune effects
ERBB4	Cardiac toxicity

PMN, polymorphonuclear leukocyte.

Berglöf A, et al. *Scand J Immunol*. 2015;82(3):208; Shatzel JJ, et al. *J Thromb Haemost*. 2017;15(5):835-847; Bye AP, et al. *Blood Adv*. 2017;1(26):2610-2623; Ghez D, et al. *Blood*. 2018;131(17):1955-1959; Woyach JA. *Blood*. 2018;132(18):1869-1870; Rogers K. *Blood*. 2018;131(17):1882-1884; Ruchlemer R, et al. *Mycoses*. 2019;62(12):1140-1147; Rogers KA, et al. *Leukemia*. 2019;33(10):2527-2530; Bose P, et al. *Expert Opin Drug Metab Toxicol*. 2016;12(11):1381-1392.

BTK Receptor Occupancy Challenges

- BTK is continuously synthesized, requiring 100% drug inhibition
- Maintaining BTK inhibitor concentrations across disease-relevant tissues may help prevent areas of unchecked disease
- Selective targeting to potentially mitigate adverse effects

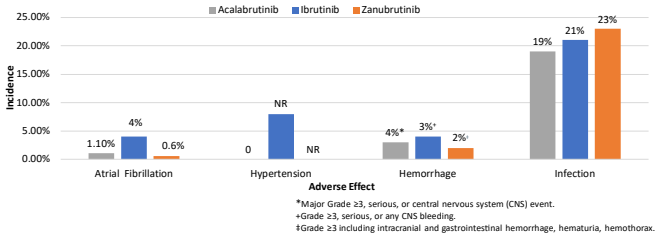
Acalabrutinib
≥95% occupancy of the BTK active site in peripheral blood maintained up to 12 hours

Ibrutinib
>90% occupancy of the BTK active site in peripheral blood observed up to 24 hours

Zanubrutinib
100% occupancy over 24 hours in peripheral blood and 94%-100% in lymph nodes

Daryaee F, et al. *Chem Sci*. 2017;8(5):3434-3443.; Woyach JA, et al. *Blood*. 2012;120(6):1175-1184; LeBien TW, et al. *Blood*. 2008;112(5):1570-1580; Stephens DM, Spurgeon SE. *Ther Adv Hematol*. 2015;6(5):242–252; Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019.

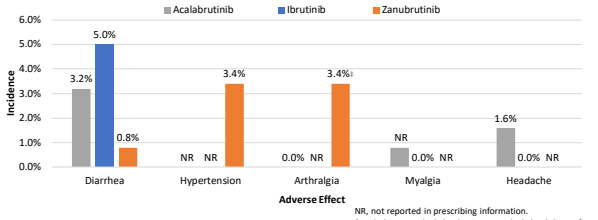
Toxicity Comparison: Select Grade ≥3 AEs



*Major Grade ≥3, serious, or central nervous system (CNS) event.
†Grade ≥3, serious, or any CNS bleeding.
‡Grade ≥3 including intracranial and gastrointestinal hemorrhage, hematuria, hemothorax.

Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019.

Toxicity Comparison: Select Grade ≥3 AEs



NR, not reported in prescribing information.
‡ Includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019.

Acalabrutinib AE Management

- Headaches
  - Acetaminophen, caffeine, hydration
- Arm skin thickening/lymphedema
  - Discontinue
- Hypertension
  - Standard management
  - Discontinue if 2-3 medications required
- Grade 3/4 nonhematologic AEs:
  - **HOLD** until resolution to baseline or grade 1
  - Once resolved: restart at **starting dose (100 mg twice daily) for the 1st or 2nd recurrence** or can be resumed **at 100 mg once daily after the 3rd recurrence**
  - **Discontinue** if 4th recurrence
- Most commonly seen in ≥20% of patients: anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising

Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019.

Ibrutinib AE Management

- Muscle cramps
  - Magnesium and calcium tablets
- Hypertension
  - Standard management; discontinue if 2-3 medications required
  - Median time to onset, 5.9 mo (range, 0.03-24.0 mo)
- Arthralgias/myalgias
  - Acetaminophen, prednisone, quinine/tonic water, discontinue
- Leg lymphedema
  - Discontinue
- Fatigue
  - Reduce dose/discontinue
- Grade 3/4 nonhematologic AEs:
  - **HOLD** until resolution to baseline or grade 1
  - Once resolved, ibrutinib can be restarted at the **starting dose (420 mg daily for CLL or WM; 560 mg daily for MCL and MZL) for the 1st occurrence**
    - **Dose reduce** by 140 mg per recurrence
    - **Discontinue** for 4th recurrence
- Most commonly seen in ≥30% of patients: thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising

Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020.

Zanubrutinib AE Management

- Rash
  - Topical emollients or corticosteroids can help alleviate symptoms
- Diarrhea
  - If no evidence of infection, antidiarrheals as needed
- Infection
  - Monitor and treat as needed
- Hypertension
  - Standard management; discontinue if 2-3 medications required
- Grade 3/4 nonhematologic AEs:
  - **HOLD** until resolution to baseline or grade 1
  - Once resolved, restart at:
    - **320 mg once daily (or 160 mg BID) for the 1st recurrence**
    - **160 mg once daily (or 80 mg BID) after the 2nd recurrence**
    - **80 mg once daily after the 2nd recurrence**
    - Discontinue if 4th recurrence
- Most commonly seen in ≥20% of patients: neutrophil, white blood cell, platelet, Hgb, decrease; upper respiratory tract infection; rash; bruising; diarrhea; cough

Brukinsa. Prescribing information. BeiGene, Ltd; November 2019.

Atrial Fibrillation

Ibrutinib (8.4%) > Acalabrutinib (4.1%) > Zanubrutinib (2%)
All Grades

Prevention: monitor for signs and symptoms
- Palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort

Management
- CHA_2DS_2-VASc score ≥2: guidelines recommend anticoagulation
- Consider non-warfarin anticoagulation
  - In combination with ibrutinib, prefer rivaroxaban or apixaban
- Monitor carefully; if uncontrolled, consider switching to alternative therapy

Weerdt I, et al. *Haematologica*. 2017;102(10):1629-39; Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Chai LK, et al. *Leuk Lymphoma*. 2017;58(12):2811-2814; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019; Jones JA, et al. *Br J Haematol*. 2017;178(2):286-291; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019.

Major Bleeding

Ibrutinib (4%) > Acalabrutinib (3%) > Zanubrutinib (2%)

Prevention
- Impact of platelet aggregation reversible within 1 week of discontinuation
- Clinical trials excluded patients receiving warfarin
- Consider risks and benefits with antiplatelet and anticoagulation therapy
- Monitor for signs of bleeding
- Surgery: evaluate risk and benefit
  - Consider hold for 3-7 days pre and post surgery

Weerdt I, et al. *Haematologica*. 2017;102(10):1629-39; Imbruvica. Prescribing information. Pharmacyclics LLC; August 2020; Chai LK, et al. *Leuk Lymphoma*. 2017;58(12):2811-2814; Calquence. Prescribing information. AstraZeneca Pharmaceuticals LP; November 2019; Jones JA, et al. *Br J Haematol*. 2017;178(2):286-291; Brukinsa. Prescribing information. BeiGene, Ltd; November 2019.

Treatment-Related Lymphocytosis

Does NOT indicate progressive disease.

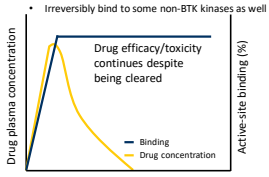
- Occurs with many therapies used to treat B-cell malignancies
- BTK inhibitors lead to transient lymphocytosis due to redistribution or release of cells from lymph nodes to peripheral blood
- Often resolves within 8 months from treatment initiation, but prolonged durations have been reported

Chanan-Khan A, et al. *Cancer*. 2011;117(10):2127-2135; Woyach JA, et al. *Blood*. 2014;123(12):1810-1817; Brown JR, et al. *Blood*. 2014;123(22):3390-3397; NCCN Clinical Practice Guidelines in Oncology. CLL/SLL. V4.2020.

BTK Inhibitor Reversibility

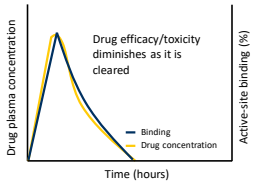
Irreversible inhibitor

- Most drugs not irreversible due to toxicity
- Acalabrutinib, ibrutinib, tirabrutinib, zanubrutinib
  - Irreversibly bind to some non-BTK kinases as well



Reversible inhibitor

- Being developed to increase BTK selectivity, have fewer off-target effects, and allow for persistent binding to mutated BTK/different BTK binding site to overcome resistance
- ARQ-531, LOXO-305, ICP-022, SNS-062



Berglöf A, et al. *Scand J Immunol*. 2015;82(3):208-217.

Patient Education: The Role of the Pharmacist

Impact of Adherence on Efficacy: CLL/SLL

Study design	Retrospective sub-analysis from RESONATE trial evaluating effect of ibrutinib dose adherence on patient outcomes

Methods	• Treatment adherence measured by overall dose intensity ($DI_{overall}$) and 8-week DI ($DI_{8\text{-week}}$)
	  • DI defined as proportion of administered vs planned doses
	  • Patients with DI below mean considered "low DI"

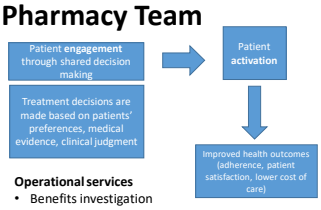
Results	• Fewer PFS events in patients with high $DI_{overall}$ vs low $DI_{overall}$ (12% vs 33%) • Patients who missed ≥8 consecutive days experienced more PFS events (30% vs 12%) with decrease in PFS (10.9 months vs NR, $P = 0.0151$) than those who missed <8 days

Barr PM, et al. *Blood*. 2017;129(19):2612-2615.

Role of the Pharmacy Team

Clinical services

- Adherence
- Education/counseling
  - Disease state
  - Medication
  - Storage, handling, administration, and disposal
  - When and whom to contact with questions/concerns
- Comprehensive medication review (ie, DDIs, concurrent CLL therapies)
- Monitoring
  - Efficacy
  - Safety: toxicity management



Operational services

- Benefits investigation
- Patient assistance programs
- Dispensing and shipping
- Refills and renewals

DDI, drug-drug interaction.

Hibbard JH, et al. *Health Aff (Millwood)*. 2013;32(2):207-214; Hibbard JH, et al. *Health Aff (Millwood)*. 2013;32(2):216-222; Carman KL, et al. *Health Aff (Millwood)*. 2013;32(2):223-231.

Patient Education Checklist

Administration

- With or without food, number of times per day, etc
- Refer to food–drug interaction chart
- DDI education (including over the counter medications)

Monitoring/labs

- Frequency and type of labs that will be collected during treatment course

Adherence

- Concern of missing even 1 dose
- Missed dose instructions

Hazardous handling

- "Just as strong" as IV chemotherapy
- No splitting/crushing/chewing
- Do not expose others to the medication/body fluids
- Wash hands; store in original container

Adverse effects

- Common AE management
- Serious AEs requiring immediate attention

Access

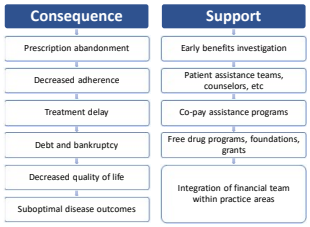
- Specialty pharmacy contact information/workflow
- Refill instructions; encourage early refills
- Insurance authorization and potential high cost

Checklist recreated from Initiation checklist for a new start oral chemotherapy. HOPA Oral Chemotherapy Resources. Accessed February 24, 2020. hopanx.org/images/hopa/membership/Initiation-Checklist-for-a-New-Start-Oral-Chemotherapy.pdf; Oral adherence toolkit. Oncology Nursing Society. Published 2016. Accessed February 24, 2020. www.ons.org/sites/default/files/ONS_Toolkit_ONLINE.pdf

Financial Burden

Agent	AWP for 30 days of therapy
Acalabrutinib (100 mg PO bid)	$16,876.80
Ibrutinib (420 mg PO daily)	$14,616.00
Zanubrutinib (320 mg PO daily)	$15,522.00

AWP, average wholesale price.



Acalabrutinib: drug information. Lexicomp database. Accessed August 24, 2020; Zanubrutinib: drug information. Lexicomp database. Accessed August 24, 2020; Ibrutinib: drug information. Lexicomp database. Accessed August 24, 2020; Doshi JA, et al. *J Clin Oncol*. 2018;36(5):476-482; Doshi JA, et al. *J Clin Oncol.* 2018;36(5):476-482; Niccolai JL, et al. *J Oncol Pract*. 2017;13(1):e29-e36; Tran G, et al. *Ann Transl Med*. 2018;6(9):166.

Conclusion

- **Treatment of B-cell malignancies, including MCL, CLL/SLL, WM, and MZL differ greatly**
  - CLL/SLL may never require treatment, but some patients require aggressive therapy up front
  - MCL and MZL often require treatment at diagnosis with intensive therapies ± stem cell transplant
  - WM, a rare subtype, is often treated when patients become symptomatic
- **BTK inhibitors play a key role in profile in the management of B-cell malignancies**
  - Treatment with acalabrutinib, ibrutinib, and zanubrutinib should be tailored based on patient and disease specifics
  - In select scenarios, BTK inhibitors may be combined with other agents, such as anti-CD20 mAbs
- **Pharmacists are integral in the management of patients with B-cell malignancies through education of patients and the medical team, management of AEs and DDIs, and patient adherence**

Additional Resources

NCCN Guidelines	www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf www.nccn.org/professionals/physician_gls/pdf/cll.pdf www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf
Non-Hodgkin lymphoma	Armitage JO, et al. *Lancet*. 2017;390(10091):298-310.
Where do the new drugs fit in for relapsed/refractory Hodgkin lymphoma?	Khan N, et al. *Curr Hematol Malig Rep*. 2017;12(3):227-233.
Interventions for adherence with oral chemotherapy in hematological malignancies	Kavookjian J, et al. *Res Social Admin Pharm*. 2015;11(3):303-314.
Medication education materials	www.chemocare.com

Breast Cancer: A Focus on Oral Chemotherapeutic Formulations for Pharmacists in the Ambulatory Care Setting

Jason Bergsbaken, PharmD, BCOP
Pharmacy Coordinator, Regional Oncology Services
UW Health
Madison, Wisconsin

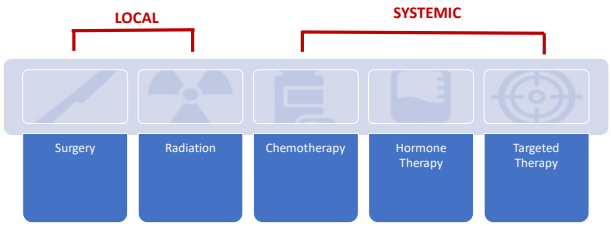
PTce

Educational Objectives

After completion of this activity, participants will be able to:

- Describe current and emerging oral chemotherapy agents for the treatment of breast cancer by their mechanisms of action
- Discuss the results of recent clinical trials with recently approved and emerging treatment options to inform the appropriate management of adverse effects and adherence for patients with breast cancer
- Define the benefits of the pharmacist on the multidisciplinary team for patients with breast cancer to optimize patient outcomes

Breast Cancer Treatment Strategies



NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 6.2020. Accessed September 21, 2020.

Pharmacologic Therapy for Breast Cancer

Cytotoxic Chemotherapy

Hormonal Therapies
- Tamoxifen
- Aromatase inhibitors (AIs)
- Fulvestrant
- LHRH agonists

Targeted Therapies
- HER2-targeted
- CDK 4/6 inhibitors
- mTOR inhibitors
- PD-1/PD-L1 inhibitors
- PARP inhibitors

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 6.2020. Accessed September 21, 2020.

Possible Routes of Administration

- Intravenous
  - Most utilized approach for traditional cytotoxic chemotherapy
  - 100% bioavailability
  - Infusion appointments allow patient evaluation but require patient coordination
- Subcutaneous
  - May reduce administration time and hypersensitivity reactions
  - Generally relies on proper administration technique by medical professional
  - Body habitus considerations
- Oral

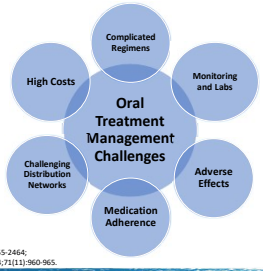
NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 6.2020. Accessed September 21, 2020.

Oral Route of Administration: Advantages

- Patient convenience
- Home treatment
- Removes need for IV access and possible related complications

Ciruelos EM, et al. *Eur J Cancer Care.* 2019;28:e13164.

Oral Route of Administration: Challenges



Weingart SN, et al. *Cancer*. 2010;116(10):2455-2464;
Wong SF, et al. *Am J Health Syst Pharm*. 2014;71(11):960-965.

Adherence in Patients With Breast Cancer

- Systematic review of 29 studies of patients with breast cancer receiving adjuvant hormonal therapy
- Prevalence of adherence ranged from 41% to 72% measured at the end of 5 years of treatment
  - Adherence most often defined as a medication possession ratio (MPR) of ≥80%

Factors associated with adherence

Negative Association	Positive Association
Adverse effects	More medications at baseline
Age (older or younger)	Referral to an oncologist
Increasing out-of-pocket costs	Earlier year at diagnosis

Murphy C, et al. *Breast Cancer Res Treat*. 2012;134(2):459-478.

Pharmacist Role in Adherence

- **Recommendations**
  - Identify patient factors that may increase risk for nonadherence
    - Focus on modifiable risk factors
  - Support adverse effect identification and management
  - Implement a consistent process with standardized tools for monitoring and follow-up
  - Incorporate intervention strategies if necessary
    - Patient outreach

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355.

Barriers to Development of Oral Formulations

- Active excretion of drug by efflux transporters
  - P-glycoprotein (P-gp) in the intestinal cells
  - Breast cancer-resistant protein (BCRP)
- Limited aqueous solubility
- Acid hydrolysis in the stomach
- Susceptibility to cytochrome P450
- Poor permeability across the gastrointestinal (GI) tract

Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:25-34; Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:93-98.
Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:99-104.

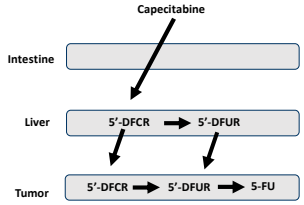
Circumventing Barriers

- Drug delivery systems
  - Addition of micelles, liposomes, micro- and nanocapsules, dendrimers, emulsions, microemulsions, nanoemulsions, and cyclodextrins
  - Use of mucoadhesive drug delivery system
- Prodrugs
- Coadministration with inhibitors (eg, CYP450, P-gp)

Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:25-34; Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:93-98.
Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:99-104.

Circumventing Barriers: Prodrugs

- Inactive compounds that are converted in vivo to active cytotoxic compounds
- Benefits of the prodrug design
  - Improve solubility and chemical stability
  - Increase oral or local absorption and brain permeability
  - Modify pre-systemic metabolism
  - Reduce toxicity

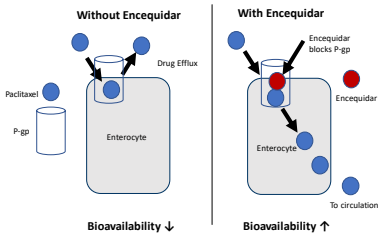


Mazzaferro S, et al. *Drug Discovery Today*. 2013;18:93-98.
Delahousse J, et al. *Cancer Chemother Pharmacol*. 2019;84:937-958.
Yasuno H, et al. *Oncol Rep*. 2013;29(2):451-458.

Caroxyl Esterase, Cytidine Deaminase, Thymidine Phosphorylase involved in capecitabine to 5-FU

Circumventing Barriers: P-gp Inhibitor Coadministration

- P-glycoprotein (P-gp) is an efflux membrane transporter
- P-gp inhibitors may allow for oral absorption of chemotherapy agents
- Benefits of P-gp inhibitor coadministration
  - Minimal systemic absorption
  - Localized P-gp inhibitory activity
  - Minimal/no systemic adverse effects
  - May expect fewer severe toxicities than with IV route



Amin ML. *Drug Target Insights*. 2013;7:27-34.
Umanzor G, et al. Presented at the San Antonio Breast Cancer Symposium; December 10-14. 2019. Abstract: GS6-01.

Common Oral Targeted Agents in Breast Cancer

ER/PR/HER2 (Triple-negative)	PARP inhibitors*
HER2+	Tyrosine kinase inhibitors
ER/PR+	PI3K inhibitor mTOR inhibitor CDK4/6 inhibitors PARP inhibitors*

*BRCA mutation

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 6.2020. Accessed September 21, 2020.

Select Oral Cytotoxic Agents in Breast Cancer

Agent	NCCN Place in Therapy
Capecitabine	• Monotherapy: adjuvant; metastatic • Combination: metastatic
Cyclophosphamide	• Monotherapy: metastatic • Combination: neoadjuvant, adjuvant, or metastatic
Etoposide	• Monotherapy: metastatic
Methotrexate	• Combination: neoadjuvant, adjuvant, or metastatic

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 6.2020. Accessed September 21, 2020.

Criteria for Treatment Selection

- Extent and site of disease (symptomatic versus asymptomatic)
- Pathology
- Targetable mutations (HER2, ER/PR, BRCA, etc)
- Comorbidities
- Performance status
- Response to prior treatments
- Tolerability of prior treatments
- Demonstrated adherence

Treatment Selection: Site of Disease
Tucatinib

HER2CLIMB Study

- International, randomized, double-blind trial in HER2 positive disease
  - Tucatinib (versus placebo) plus trastuzumab and capecitabine

	Total population (N = 320)		(+) Brain metastases (N = 148)	
	TUCATINIB	PLACEBO	TUCATINIB	PLACEBO
1-year PFS	**33.1%** 95% CI, 26.6 to 39.7	**12.3%** 95% CI, 6.0 to 20.9	**24.9%** 95% CI, 16.5 to 34.3	**0%**
Median PFS	**7.8 months** 95% CI, 7.5 to 9.6	**5.6 months** 95% CI, 4.2 to 7.1	**7.6 months** 95% CI, 6.2 to 9.5	**5.4 months** 95% CI, 4.1 to 5.7
Median OS	**21.9 months** 95% CI, 18.3 to 31.0	**17.4 months** 95% CI, 13.6 to 19.9		

- Tucatinib was FDA approved in 2020 in combination with trastuzumab and capecitabine for patients with unresectable or metastatic HER2+ breast cancer, including brain metastases, who have received ≥1 prior anti-HER2 regimen in the metastatic setting
- **Efficacy in patients with brain metastases (site of disease) may impact its place in therapy**

Murthy RK, et al. *N Engl J Med*. 2020;382(7):597-609.
FDA approval. April 20, 2020. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tucatinib-patients-her2-positive-metastatic-breast-cancer

Tucatinib: Dosing and Administration

Mechanism of Action	Tyrosine kinase inhibitor of HER2
Dosing	• 300 mg taken orally twice daily • Supplied as 50-mg and 150-mg tablets
Administration	With or without food
Drug Interactions	• Avoid strong CYP3A inducers or strong CYP2C8 inhibitors • Avoid concomitant use with CYP3A4 substrates • Consider reducing dosage of P-gp substrates

Tukysa. Prescribing information. Seattle Genetics. 2020.

Tucatinib: Safety and Monitoring

Adverse Effect Summary Any Grade (grade 3 or 4) %	Tucatinib + Trastuzumab + Capecitabine (N = 404)	Trastuzumab + Capecitabine (N = 197)
Diarrhea	81 (13)	53 (9)
Hepatotoxicity	42 (9)	24 (4)

Diarrhea
- Administer antidiarrheal treatment (ie, loperamide) as needed
- Grade 3
  - Hold until recovery to ≤ grade 1; then resume at lower dose level (may consider to resume at same dose level if occurred without antidiarrheal treatment)

Hepatotoxicity
- Hold for grade 2 elevated bilirubin
- Hold for grade 3 ALT or AST elevation OR grade 3 bilirubin elevation and reduce dose

Tukysa. Prescribing information. Seattle Genetics. 2020.

Treatment Selection: Pathology
Neratinib in Adjuvant Setting

ExteNET Study
- International, randomized, double-blind trial
- Neratinib (versus placebo) in patients with HER2+ disease in extended adjuvant setting

	Neratinib (N = 1420)			Placebo (N = 1420)		
	Total population	HR+	HR-	Total population	HR+	HR-
2-year IDFS	93.9%	95.4%	92%	91.6%	91.2%	92.2%
2-year DDFS	95.1%			93.7%		

Neratinib was FDA approved in 2017 for the extended adjuvant treatment of patients with early-stage HER2+ breast cancer, following adjuvant trastuzumab-based therapy

Chan A, et al. *Lancet Oncol.* 2016;17(3):367-377; FDA approval. July 17, 2017. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neratinib-extended-adjuvant-treatment-early-stage-her2-positive-breast-cancer; Chan A, et al. *Clinical Breast Cancer.* 2020. Accepted for publication Sept 28, 2020.

IDFS, invasive disease-free survival; DDFS, distant disease-free survival.

Treatment Selection: Pathology
Neratinib in Metastatic Setting

NALA Study
- International, randomized, double-blind trial
- Neratinib + capecitabine versus lapatinib + capecitabine in HER+ advanced breast cancer

	NERATINIB + capecitabine N = 307	LAPATINIB + capecitabine N = 314	*P* value
Mean PFS	8.8 months	6.6 months	0.0059
Mean OS	24.0 months	22.2 months	0.2086

Neratinib was FDA approved in 2020 for patients with advanced or metastatic HER2+ breast cancer who received ≥2 prior anti-HER2–based regimens in the metastatic setting
According to a subgroup analysis, statistically significant reductions in risk, favoring neratinib, were observed in patients with nonvisceral metastases (HR, 0.44) and hormone receptor–negative tumors (HR, 0.42)

Saura C, et al. *J Clin Oncol.* 2020 Jul 17;JCO2000147.
FDA approval. February 26, 2020. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neratinib-metastatic-her2-positive-breast-cancer

Neratinib: Dosing and Administration

Mechanism of Action	Tyrosine kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4
Dosing	• 240 mg by mouth once daily continuously (in metastatic HER2+ setting is given continuously with capecitabine 750 mg/m^2 by mouth BID on days 1-14 of 21-day cycle) • Available as 40-mg tablet
Administration	With food
Drug Interactions	Avoid concomitant use with strong or moderate CYP3A4 inhibitors, strong or moderate CYP3A4 inducers, and P-gp dual inhibitors Gastric acid-reducing agents • Avoid concomitant proton pump inhibitors (PPIs) • Take neratinib at least 2 hours before the next dose of the H2-receptor antagonist or 10 hours after the H2-receptor antagonist • Separate dosing of neratinib by 3 hours after antacids

Nerlynx. Prescribing information. Puma Biotechnology, Inc. 2020.

Neratinib: Safety and Monitoring

Adverse Effect Summary Any Grade (grade 3 or 4) %	Neratinib (N = 1408)	Placebo (N = 1408)
Diarrhea	95 (40)	35 (2)
Nausea	43 (2)	22 (0.1)
Vomiting	26 (3)	8 (0.4)
Stomatitis	14 (1)	6 (0.1)

Chan A, et al. *Lancet Oncol.* 2016;17(3):367-377.
Nerlynx. Prescribing information. Puma Biotechnology, Inc. 2020.

Neratinib: Safety and Monitoring

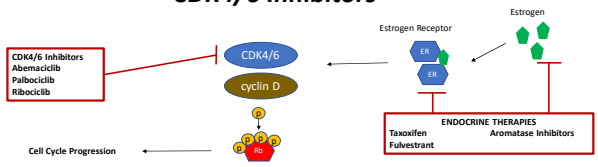
- **Diarrhea**
  - Administer antidiarrheal prophylaxis during the first 56 days of treatment

Time on Neratinib	Loperamide Dose and Frequency
Weeks 1-2 (days 1-14)	4 mg TID
Weeks 3-8 (days 15-56)	4 mg BID
Weeks 9-52 (days 57-365)	4 mg as needed, not to exceed 16 mg per day (titrate dosing to 1-2 bowel movements daily)

  - **Dose escalation** management and prevention strategy an option in extended adjuvant setting
    - 120 mg PO once daily x 1 week, 160 mg PO once daily x 1 week, then 240 mg PO once daily
  - Diet modification and fluids
- **Hepatoxicity**
  - Monitor LFTs monthly for first 3 months, then at least every 3 months
  - Hold for grade 3 LFT elevation and reduce dose

Nerlynx. Prescribing information. Puma Biotechnology, Inc. 2020.
Barcenas CH. *J Clin Oncol* 2019;37:15_suppl 548.

Treatment Selection: Pathology
CDK4/6 Inhibitors



CDK4/6 inhibitors with approval in HR-positive, HER2-negative advanced breast cancer

Portman N. *Endocr Relat Cancer*. 2019;26(1):R15-R30.

CDK4/6 Inhibitors: FDA Approval Summary

All CDK4/6 inhibitors approved for **HR-positive, HER2-negative advanced or metastatic breast cancer**:

FDA Approvals	Abemaciclib	Palbociclib	Ribociclib
In combination with an aromatase inhibitor (AI) as initial endocrine-based therapy in postmenopausal women	✓	✓ FDA approval also in men	✓ FDA approval also in pre/peri menopausal
In combination with fulvestrant as initial endocrine-based therapy following disease progression			✓
In combination with fulvestrant as patients with disease progression following endocrine therapy	✓	✓	✓ FDA approval specifies post-menopausal women
Monotherapy for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting	✓		

Ibrance. Prescribing information. Pfizer Inc. 2020; Kisqali. Prescribing information. Novartis. 2020; Verzenio. Prescribing Information. Eli Lilly and Company. 2020.

CDK4/6 Inhibitors: Dosing and Administration

	Abemaciclib	Palbociclib	Ribociclib
Dosing	• 200 mg PO BID continuously (**monotherapy**) • 150 mg PO BID continuously (**combination**) • Available in 50-, 100-, 150-, and 200-mg tablets	• 125 mg PO daily days 1-21 every 28 days • Available in 75-, 100-, and 125-mg tablets	• 600 mg PO daily days 1-21 every 28 days • Available in 200-mg tablets
Administration	With or without food	With or without food	With or without food
Drug-Drug Interactions	Minor substrate of CYP3A4	Major substrate of CYP3A4	Avoid grapefruit and grapefruit juice

Ibrance. Prescribing information. Pfizer Inc. 2020; Kisqali. Prescribing information. Novartis. 2020; Verzenio. Prescribing Information. Eli Lilly and Company. 2020.

CDK4/6 Inhibitors: Safety and Monitoring

Adverse Effect Summary Any Grade (grade 3 or 4) %	Abemaciclib (with AI) [MONARCH 3]	Palbociclib (with AI) [PALOMA-2]	Ribociclib (with AI) [MONALEESA-2]
Neutropenia	41 (22)	80 (66)	75 (60)
Anemia	28 (6)	24 (5)	18 (1)
Thrombocytopenia	10 (2)	16 (1)	NR
Diarrhea	81 (9)	26 (1)	35 (1)
Nausea	39 (<1)	35 (<1)	52 (2)
ALT elevation	16 (6)	43 (2)	46 (10)
AST elevation	15 (3)	52 (3)	44 (7)

AI, aromatase inhibitor.

Ibrance. Prescribing information. Pfizer Inc. 2020; Kisqali. Prescribing information. Novartis. 2020; Verzenio. Prescribing Information. Eli Lilly and Company. 2020.

CDK4/6 Inhibitors: Safety and Monitoring

- **Abemaciclib**
  - Diarrhea
    - Administer antidiarrheal treatment (ie, loperamide) as needed
    - Hold for grade ≥3, or grade 2 that does not resolve within 24 hours
  - Neutropenia
    - CBC at baseline, every 2 weeks for initial 2 months, monthly for 2 months, then as clinically indicated
  - Hepatotoxicity
    - LFTs prior to initiation, every 2 weeks for initial 2 months, monthly for 2 months, then as clinically indicated

Verzenio. Prescribing Information. Eli Lilly and Company. 2020.

CDK4/6 Inhibitors: Safety and Monitoring

- **Palbociclib**
  - Neutropenia
    - CBC at baseline, every 2 weeks for initial 2 cycles, then at the beginning of each cycle
- **Ribociclib**
  - Neutropenia
    - CBC at baseline, every 2 weeks for initial 2 cycles, then at the beginning of subsequent 4 cycles
  - QT prolongation
    - Electrocardiogram at baseline, repeat at day 14 of initial cycle and beginning of cycle 2
    - Only initiate in patients with QTcF values <450 ms; interrupt treatment for QTcF >480 ms
    - Monitor serum electrolytes prior to initiation and at the beginning of first 6 cycles
  - Hepatobiliary toxicity
    - LFTs at baseline, every 2 weeks for initial 2 cycles, then at the beginning of subsequent 4 cycles

Ibrance. Prescribing information. Pfizer Inc. 2020; Kisqali. Prescribing information. Novartis. 2020.

Treatment Selection: Comorbidities
Alpelisib

	PIK3CA-mutated		PIK3CA-wildtype	
	Fulvestrant + ALPELISIB (N = 169)	Fulvestrant + PLACEBO (N = 172)	Fulvestrant + ALPELISIB (N = 115)	Fulvestrant + PLACEBO (N = 116)
Median PFS	11.0 months	5.7 months	7.4 months	5.6 months
ORR	26.6%	12.8%		
Dose interruptions	74.0%	32.2%		
Grade 3 Hyperglycemia	32.7%		0.3%	

- Alpelisib was FDA approved in 2019 for patients with HR+/HER2-, PIK3CA-mutated advanced or metastatic breast cancer following progression on an endocrine-based regimen
- **Patients with type 1 diabetes and uncontrolled type 2 diabetes were excluded from the trial**

Andre F, et al. *N Engl J Med.* 2019;380(20):1929-1940.
FDA approval. May 28, 2019. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer

Alpelisib: Dosing and Administration

Mechanism of Action	Phosphatidylinositol 3-kinase (PI3K) inhibitor
Dosing	• 300 mg by mouth once daily continuously **Supplied as** • 200 mg daily dose (1 blister pack, with 28-day supply of 200-mg tablets) • 250 mg daily dose (2 blister packs, each with 14-day supply of 200-mg and 50-mg tablets • 300 mg daily dose (2 blister packs, each with 14-day supply of 150-mg tablets)
Administration	With food
Drug Interactions	• Avoid concomitant use with strong CYP3A4 inducers • Avoid concomitant use with BCRP inhibitors • Closely monitor when coadministered with CYP2C9 substrates

Piqray. Prescribing information. Novartis. 2020.

Alpelisib: Safety and Monitoring

Adverse Effect Summary Any Grade (grade 3 or 4) %	Alpelisib + Fulvestrant (N = 284)	Fulvestrant + Placebo (N = 287)
Increased glucose	**79 (39)**	**34 (1)**
Diarrhea	**58 (7)**	**16 (0.3)**
Rash	**53 (20)**	**7 (0.3)**

- **Rash**
  - Grade 1-2
    - Topical corticosteroid treatment; for grade 2 oral antihistamine and consider systemic corticosteroid
  - Grade ≥3
    - Interrupt alpelisib; initiate or intensify topical/systemic corticosteroid and oral antihistamine
- **Diarrhea**
  - Grade 1
    - Initiate antidiarrheal treatment (ie, loperamide) as clinically indicated
  - Grade ≥2
    - Interrupt alpelisib; initiate or intensify antidiarrheal treatment
    - May resume alpelisib after recover to grade ≤1 (at lower dose level if grade 3 or 4 reaction)

Piqray. Prescribing information. Novartis. 2020.

Alpelisib: Hyperglycemia

- Monitor fasting plasma glucose (FPG) at minimum weekly for first 2 weeks, then every 4 weeks
- Monitor HbA1C every 3 months

Blood glucose value	Initial management	Subsequent management
Grade 1 FPG > ULN-160 mg/dL	Initiate or intensify antihyerglycemic	None
Grade 2 FPG >160-250 mg/dL	Initiate or further intensify antihyperglycemic	If not reduced to grade 1 within 21 days, reduce alpelisib dose by 1 dose level
Grade 3 FPG >250-500 mg/dL	- Interrupt alpelisib - Initiate or further intensify antihyperglycemic - Administer IV hydration and consider additional treatment	- If FPG decreases to grade 1 within **3-5 days**, reduce alpelisib dose - If FPG does not decrease to grade 1 within **3-5 days**, consult a specialist for further glucose management - If FPG does not decrease to grade 1 within **21 days**, permanently discontinue
Grade 4 FPG >500 mg/dL		- If FPG ≤500 in **1 day**, follow grade 3 recommendations - If FPG remains >500 in **1 day**, permanently discontinue

Piqray. Prescribing information. Novartis. 2020.

Treatment Selection: Targetable Mutations
PARP Inhibitors in gBRCAm

OlympiAD Trial: Olaparib vs chemotherapy treatment of physician's choice (TPC) capecitabine, vinorelbine, or eribulin

	OLAPARIB N = 205	Chemotherapy treatment of physician's choice (TPC) N = 97
Mean PFS	7.0 months	4.2 months
Response Rate	59.9%	28.8%

- Olaparib was FDA approved in 2018 for treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting
- **Patients possessing a germline BRCA mutation may benefit from PARP inhibitor, particularly in metastatic setting for patients with fewer previous treatments**

Robson M, et al. *N Engl J Med.* 2017;377:523-533; Kaufman B, et al. *J Clin Oncol.* 2015;33:244-250; FDA Oncology Center of Excellence. October 23, 2018.
www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-olaparib-gbrcam-her2-negative-metastatic-breast-cancer

Treatment Selection: Targetable Mutations
PARP Inhibitors in gBRCAm

EMBRACA Trial: Talazoparib vs chemotherapy treatment of physician's choice (TPC) capecitabine, vinorelbine, gemcitabine, or eribulin

	TALAZOPARIB N = 287	Chemotherapy treatment of physician's choice (TPC) N = 144
Mean PFS	8.6 months	5.6 months
Objective Response Rate (ORR)	62.6%	27.2%

- Talazoparib was FDA approved in 2018 for patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative locally advanced or metastatic breast cancer
- **Patients possessing a germline BRCA mutation may benefit from PARP inhibitor**

Litton J, et al. *N Engl J Med.* 2018;379:753-763; FDA approval. December 14, 2018.
www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-talazoparib-gbrcam-her2-negative-locally-advanced-or-metastatic-breast-cancer

PARP Inhibitors: Safety and Monitoring

Adverse Effect Summary Any Grade (grade 3 or 4) %	Olaparib [OlympiAD]	Talazoparib [EMBRACA]
Anemia	40 (16)	53 (39)
Thrombocytopenia	NR	27 (15)
Neutropenia	27 (9)	35 (21)
Nausea	58 (0)	49 (<1)
Vomiting	30 (0)	25 (2)
Fatigue	37 (4)	62 (3)

- **Bone marrow suppression**
  - Interrupt PARP **inhibitor** and monitor blood counts weekly until grade 1 or less
  - If hematologic profile recovers, consider restarting drug at a reduced dose
  - Monitor CBC at baseline, then monthly
- **Nausea and/or vomiting**
  - Olaparib considered moderate to high emetic risk by NCCN; talazoparib low to minimal risk
  - In practice, we typically opt for PRN antiemetics for olaparib (may consider scheduling if issues tolerating)

Lynparza. Prescribing information. AstraZeneca. 2020; Talzenna Prescribing Information. Pfizer. 2020.

Oral Drugs in the Pipeline: Taxanes

Taxane	Formulation	Half-life (hours)	Major toxicity
Paclitaxel (DHP107)	Oral	15.3	Diarrhea, neutropenia
Tesetaxel	Oral	167	Leukopenia, GI
Docetaxel (ModraDoc001)	Oral	Not reported	Diarrhea, fatigue, dehydration
Docetaxel (ModraDoc006)	Oral	Not reported	Diarrhea, fatigue, dehydration
Ortataxel	IV and oral	6.9	Leukopenia, GI
Milataxel	IV and oral	178	Leukopenia
BMS-275183	Oral	26	Peripheral neuropathy, leukopenia

Flores JP, Saif MW. *Clin Investig.* 2013;3(4):333-341; De Weger VA, et al. *Eur J Cancer.* 2017;86:217-225.

Phase 1: Oral Paclitaxel + P-gp Inhibitor

Multicenter, single-arm, open-label
N = 28 patients
- MBC
- 26 patients received multiple previous chemotherapy regimens

→ HM30181A (encequidar) 15 mg PO
Paclitaxel 205 mg/m² PO (oraxol)
Given 3 consecutive days weekly for up to 16 weeks

→ Pharmacokinetics (PK) assessed at weeks 1 and 4

→ Tumor response measured at weeks 8 and 16

- *Achieved paclitaxel exposure similar to that of weekly*
- *IV paclitaxel 80 mg/m², with lower peak exposure*
- *26 evaluable patients*
- *42.3% partial response*
- *46.2% stable disease*
- *3 patients experienced treatment-related AEs (grade ≥3 neutropenia)*

Dai MS, et al. *J Clin Oncol.* 2019;37(suppl 15):abstr 1084.

Phase 3: Oral vs IV Paclitaxel

Open-label
N = 360
- MBC
- ECOG 0-1
- CNS mets were excluded
- Allowed prior taxane if >1 year prior

→ 2:1 RANDOMIZE

→ N = 265
OPE:
Paclitaxel 205 mg/m² PO x 3 consecutive days every week x 3 weeks (each capsule = 30 mg solubilized paclitaxel)
Encequidar 15 mg PO prior to each dose of paclitaxel
6 cycles

→ N = 137
Paclitaxel 175 mg/m² IV every x 3 weeks
6 cycles

ECOG, Eastern Cooperative Oncology Group.

- *OPE regimen: fast for 4 hours before taking encequidar followed 1 hour later by paclitaxel (≈11 capsules) followed by 4 hours of fasting*
- *Primary end points: response rate by week 19 and safety and tolerability*
- *Secondary end points: PFS and OS*

Umanzor G, et al. San Antonio Breast Cancer Symposium 2019. Abstract G26-01. Accessed April 20, 2020. www.abstractsonline.com/pp8/#!/7946/presentation/2050; DePolo J. Accessed March 23, 2020. breastcancer.org/research-news/oral-vs-iv-paclitaxel-for-mbc

Results: Oral vs IV Paclitaxel

Efficacy end points	OPE (N = 235)	IV paclitaxel (N = 125)	
Response rate	40.4%	25.6%	*P* = 0.005
PFS	9.3 months	8.3 months	*P* = 0.077
OS	27.9 months	16.9 months	*P* = 0.035

- **Summary**
  - Oral paclitaxel may be a promising alternative to the IV formulation in terms of both efficacy and tolerability for patients with breast cancer
  - Adherence and patient acceptance are concerns based on complicated administration

Umanzor G, et al. San Antonio Breast Cancer Symposium 2019. Abstract G26-01. Accessed August 20, 2020. www.abstractsonline.com/pp8/#!/7946/presentation/2050; DePolo J. Accessed March 23, 2020. breastcancer.org/research-news/oral-vs-iv-paclitaxel-for-mbc

Phase 2 and 3 Trials: Oral Tesetaxel

- Phase 2
  - Single-arm, open-label trial (N = 38) in (HR+/HER2- metastatic breast cancer)
  - Tesetaxel 27 mg/m² day every 3 weeks (escalated to 35 mg/m²)
  - ORR: 45%
    - 44% in patients who did not have prior taxane exposure
    - 45% in patients who received prior taxane
  - Median PFS: 5.4 months
  - Most common AE: neutropenia (grade 3 or 4 in 13%)
- Phase 3
  - Planned 600 patients (HR+/HER2- metastatic breast cancer)
  - Includes patients with prior (neo)adjuvant taxane and CNS metastases
  - Randomized to oral tasetaxel +/- capecitabine
  - Primary end point: PFS
  - Enrollment began in December 2017 (enrollment closed for CONTESSA)

Seidman AD, et al. *J Clin Oncol.* 2018;36(suppl); abstr 10442; O'Shaughnessy J, et al. *J Clin Oncol.* 2019;37(suppl; abstr TPS1107).

Select Oral Drugs in the Pipeline for Breast Cancer

Drug class	Agents
VEGF Inhibitors	Apatinib Sorafenib Lucitanib
HDAC Inhibitors	Panobinostat Vorinostat
mTOR Inhibitors	Ridaforolimus/deforolimus
Antimicrotubules	Vinorelbine
Antimetabolites	Azacitidine
Antiprogesterone	Telapristone
PI3K Inhibitor	Pictilisib Buparlisib
Others	PMD-026 Reparixin Mesupron

Clinicaltrials.gov. Accessed August 13, 2020.

Pharmacists' Roles in Oral Oncolytic Management

- **Prescribing**
  - Pharmacists should provide comprehensive review and help determine place in therapy
  - Support oral oncolytic prescribing on individual patient level
  - Comprehensive medication review at time of prescription
- **Education**
  - Pharmacist involvement in patient education materials
  - Education provided with focus on management of adverse effects and adherence
- **Distribution**
  - Medication assistance support (preferably non-pharmacist)
  - Coordination with internal or external specialty pharmacies
- **Monitoring and follow-up**
  - Initial monitoring of symptoms and adherence within initial 1-2 weeks of treatment
  - Ongoing monitoring of symptoms and adherence with each clinical encounter

Mackler E, et al. *J Oncol Pract*. 2019;15(4):e346-e355.

Conclusion

- Breast cancer treatment strategies have been bolstered by the recent approvals of oral chemotherapy agents
- Robust patient management strategies are required to manage current and emerging oral chemotherapy agents with unique adverse effect profiles
- Numerous oral chemotherapeutic agents in development aim to capitalize on some of the advantages of the oral treatment route
- Pharmacists are uniquely positioned to help patients optimize outcomes of current and emerging oral chemotherapy agents

Additional Resources

Oral Chemotherapy Education Sheets www.oralchemoedsheets.com

Mackler E, et al. 2018 Hematology/Oncology Pharmacist Association best practices for the management of oral oncolytic therapy: pharmacy practice standard. *J Oncol Pract*. 2019;15(4):e346-e355.

Dillmon M, et al. Patient-centered standards for medically integrated dispensing: ASCO/NCODA standards. *J Clin Oncol*. 2020;38(6):633-644.

Neuss MN, et al. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology. *J Oncol Pract*. 2016;12(12):1262-1271.

HER2-Directed Therapy in Metastatic Breast Cancer: Pharmacist Involvement to Optimize Care

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PTce

Educational Objectives

After completion of this activity, participants will be able to:

- Recognize the role and usage of biomarker testing for HER2+ breast cancer and how testing results impact therapy
- Review approved and emerging HER2-targeted agents and combination treatment strategies and their roles in evolving guideline recommendations in the treatment of HER2+ metastatic breast cancer
- Discuss the adverse effects and appropriate management strategies associated with HER2-targeted agents and combination treatment strategies to optimize therapy and patient outcomes

Hallmarks of HER2+ Breast Cancer

- Accounts for 20% to 25% of breast cancers
- High-grade tumors
- Rapid growth rates
- Frequent lymph node spread
- Early distant metastases
- Reduced disease-free and overall survival

Slamon D, et al. *N Engl J Med*. 2001;344(11):783-792.

Biomarker Testing in HER2+ Breast Cancer

History of HER2+ Breast Cancer

1982-1984:

HER2 Receptor Identified

Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J*. 2015;15(1):e34-e38.

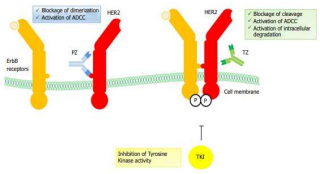
The HER2 Receptor

- Receptor tyrosine kinase within the ErbB or EGFR family, discovered in the early 1980s
  - HER2 (ErbB2) is the most potent oncoprotein within the receptor family
  - Activated upon ligand-dependent dimerization with another ErbB receptor
  - Oncogenic when a mutation leads to constitutively active receptor signaling (HER2/neu)
  - Shared co-receptor for several stromal ligands, which lead to activation of multiple mitogenic pathways
- Gene is located on the long arm of chromosome 17 (17q12)

Yarden Y, Sliwkowski MX. *Nat Rev Mol Cell Biol*. 2001;2(2):127-137.
Iqbal N, Iqbal N. *Mol Biol Int*. 2014;2014:1-9.

The HER2 Receptor

- Ubiquitous receptor found on the epithelium of the breast, stomach, ovaries, colon, bladder, endometrium, lung, cervix, esophagus, and skin as well as cardiac myocytes
- HER2 pathway mediates growth, differentiation, invasion, and downstream survival pathways in normal and malignant epithelial cells
  - Mitogen-activated protein kinase (MAPK)
  - Phosphatidylinositol-4,5-bisphosphonate 3-kinase (PI3K)
  - Protein kinase C (PKC)



Iqbal N, Iqbal N. *Mol Biol Int.* 2014;2014:1-9. Image from: Mazzucchelli S. *World J Pharmacol* 2014;3(4):72-85.

HER2 Testing Methods

Immunohistochemistry (IHC)	Fluorescence in situ hybridization (FISH)	HER2 copy number
• Measures intensity and completeness of membrane staining • Reported as 3+, 2+, 1+ or 0	• Measures the ratio of HER2 gene copies per chromosome 17 • Reported HER2/CEP17 ratio	• Measures the number of gene copy signals per cell • Reported as copies/cell

Wolff AC, et al. *J Clin Oncol.* 2018;36(20):2105-2122.

HER2 Testing Methods

IHC		FISH		Copy Number
3+	Complete, intense staining in >10% of tumor cells	HER2/CEP17 ratio ≥2.0	Average copy number ≥4.0	Average copy number ≥6.0
2+	Complete, weak to moderate staining in >10% of tumor cells	HER2/CEP17 ratio ≥2.0	Average copy number <4.0	
1+	Incomplete staining that is faint in >10% of tumor cells	HER2/CEP17 ratio <2.0	Average copy number ≥6.0	Average copy number ≥4.0 and <6.0
0	No staining or incomplete, faint staining in ≤10% of tumor cells	HER2/CEP17 ratio <2.0	Average copy number ≥4.0 and <6.0	
		HER2/CEP17 ratio <2.0	Average copy number <4.0	Average copy number <4.0

Anti-HER2 therapy indicated **Anti-HER2 therapy NOT indicated** **Further workup needed**

Wolff AC, et al. *J Clin Oncol.* 2018;36(20):2105-2122.

Why do biomarker results matter?

History of HER2+ Breast Cancer

1982-1984
HER2 Receptor Identified

1998
Trastuzumab FDA Approved

Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J.* 2015;15(1):e34-e38.
Herceptin. Prescribing information. Genentech. November 2018. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5345lbl.pdf

Trastuzumab

- Anti-HER2 monoclonal antibody that binds to the extracellular region of the HER2 receptor
- Blocks HER2 receptor signaling and triggers antibody-dependent cellular cytotoxicity
- Effectively inhibits tumor growth as monotherapy, but has synergistic activity when combined with additional agents
- **Place in therapy:** 1st line for neoadjuvant, adjuvant, and metastatic disease
  - Should be continued upon progression in the metastatic setting
  - FDA-approved biosimilar may be substituted for the reference product

Slamon D, et al. *N Engl J Med.* 2001;344(11):783-792; NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V6.2020.
FDA: Biosimilar product information. Accessed August 15, 2020. www.fda.gov/drugs/biosimilars/biosimilar-product-information

Trastuzumab in HER2 Amplified Breast Cancer

Trial	Population	HER2+ Status	Intervention	Primary Outcome
Slamon, et al. 2001	1st line metastatic HER2+ (n = 469)	2+ or 3+ by IHC	Chemotherapy ± trastuzumab	**Median PFS:** 7.4 vs 4.6 months (*P* <0.001)
Romond, et al. 2005 (B-31/N9831)	Node (+) or high-risk node (–) HER2+ (n = 3351)	3+ by IHC or FISH ratio ≥ 2.0	Chemotherapy ± trastuzumab x 1 year	**Recurrence, second primary, or death:** HR, 0.48 (*P* <0.0001) **4-year DFS:** 85.3% vs 67.1%

Slamon D, et al. *N Engl J Med*. 2001;344(11):783-792.
Romond E, et al. *N Engl J Med*. 2005;353(16):1673-1684.

Trastuzumab in HER2-Low Expressing Breast Cancer

Trial	Population	HER2 Status	Intervention	Primary Outcome
Mass, et al. 2005	Metastatic HER2+ (n = 799)	2-3+ by IHC; FISH ratio ≥2.0 (pos) FISH ratio <2.0 (neg)	Chemotherapy + trastuzumab	Clinical benefit limited to patients with FISH+ cancer
Paik, et al. 2008	Node (+) or high-risk node (–) HER2+ (n = 174)	IHC <3+ (neg) and FISH ratio <2.0 (neg)	Chemotherapy ± trastuzumab x 1 year	**DFS:** HR, 0.34 (*P* = 0.014)
Fehrenbacher, et al. 2019 (B-47)	Node (+) or high-risk node (-) HER2- (n = 3270)	1+ by IHC 2+ with FISH ≤2.0 HER2 copies <4.0	Chemotherapy ± trastuzumab x 1 year	**IDFS:** HR, 0.98 (*P* = 0.85)

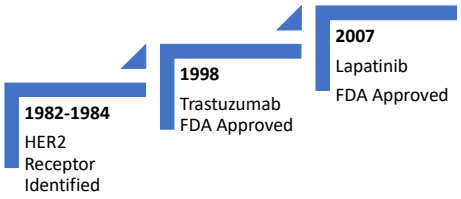
Mass RD, et al. *Clin Breast Cancer*. 2005;6:240-246; Paik S, et al. *N Engl J Med*. 2008;358(13):1409-1411.
Fehrenbacher L, et al. *J Clin Oncol*. 2019;38(5):444-453.

Summary of the Role and Usage of Biomarker Testing for HER2+ Breast Cancer

- Multiple methods of HER2 testing are available and utilized in practice
- Although there is sometimes discordance among the testing methods, accurate detection of HER2 amplification is critical to identify patients expected to derive a significant benefit from anti-HER2 therapies, such as trastuzumab

The Evolving Landscape of Metastatic HER2+ Breast Cancer

History of HER2+ Breast Cancer



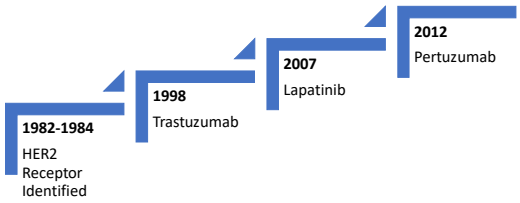
Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J*. 2015;15(1):e34-e38.
Tykerb. Prescribing information. Novartis Pharmaceuticals. December 2018. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2018/022059s024lbl.pdf

Lapatinib

- Oral inhibitor of intracellular tyrosine kinases of HER2
- Combined with capecitabine alone, lapatinib + capecitabine significantly improves progression-free survival (PFS) in patients previously treated with an anthracycline, taxane, and trastuzumab
  - 8.4 vs 4.4 months (*P* <0.001)
- Addition of lapatinib increases the risk of diarrhea, dyspepsia, and rash
- **Place in therapy:** 3rd line and beyond

Geyer CE, et al. *N Engl J Med*. 2006;355(26):2733-2743.

History of HER2+ Breast Cancer



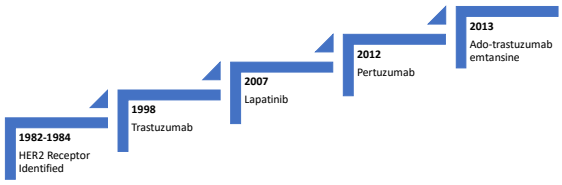
Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J.* 2015;15(1):e34-e38.
Perjeta. Prescribing information. Genentech. January 2020. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf

Pertuzumab

- Anti-HER2 monoclonal antibody with a complementary mechanism to trastuzumab, leading to synergistic activity
- Combined with docetaxel and trastuzumab, pertuzumab significantly increases PFS in the 1st line metastatic setting
  - 18.5 vs 12.4 months (*P* <0.001)
- Addition of pertuzumab increases the risk of febrile neutropenia and diarrhea, without increasing cardiotoxicity
- Unlike trastuzumab, there is not sufficient evidence to continue pertuzumab beyond progression
- **Place in therapy:** 1st line metastatic setting in combination with a taxane + trastuzumab

Baselga J, et al. *N Engl J Med.* 2012;366(2):109-119; NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V6.2020.

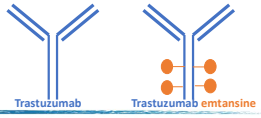
History of HER2+ Breast Cancer



Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J.* 2015;15(1):e34-e38.
Kadcyla. Prescribing information. Genentech. May 2019. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf

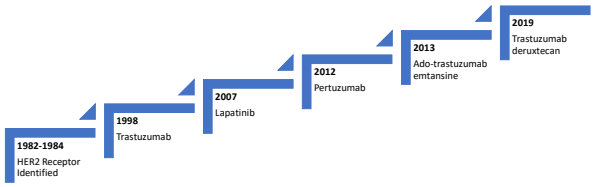
Ado-trastuzumab emtansine (T-DM1)

- Antibody-drug conjugate: trastuzumab + microtubule-inhibitor
- Significantly improves PFS compared with lapatinib/capecitabine in metastatic patients previously treated with a taxane/trastuzumab
  - 9.6 vs 6.4 months (*P* <0.001)
- Adverse drug reactions include thrombocytopenia and increased liver enzymes
- **Place in therapy:** Standard of care for 2nd line metastatic HER2+ breast cancer



Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791.
Krop IE, et al. *Lancet Oncol.* 2017;18:743-754.

History of HER2+ Breast Cancer



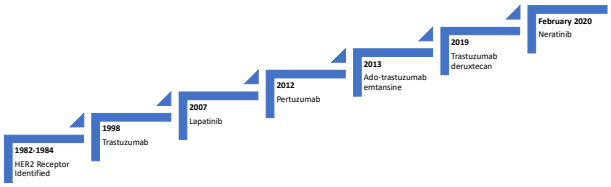
Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J.* 2015;15(1):e34-e38.
Enhertu. Prescribing information. Daiichi Sankyo; December 2019. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf

Trastuzumab deruxtecan (T-DXd)

- Antibody-drug conjugate: trastuzumab + topoisomerase I inhibitor
- Significantly improved PFS in a heavily pretreated population
  - All patients previously received trastuzumab and trastuzumab emtansine (median of 6 prior lines of therapy in the study population)
  - Median PFS of 16.4 months
- ADRs include neutropenia, anemia, nausea, and interstitial lung disease
- **Place in therapy:** 3rd line or beyond
  - Additional trials ongoing comparing T-DXd to:
    - Capecitabine/lapatinib or capecitabine/trastuzumab in HER2+ metastatic patients after T-DM1 (DESTINY-Breast02)
    - T-DM1 in 2nd line HER2+ metastatic patients (DESTINY-Breast03)
    - Investigator's choice chemotherapy for HER2-low metastatic patients (DESTINY-Breast04)
    - T-DM1 in high-risk HER2+ patients with residual invasive disease after neoadjuvant therapy (DESTINY-Breast05)

Modi S, et al. *N Engl J Med.* 2020;382:610-621.
Enhertu. Prescribing information. Daiichi Sankyo; December 2019. Accessed August 2, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf

History of HER2+ Breast Cancer



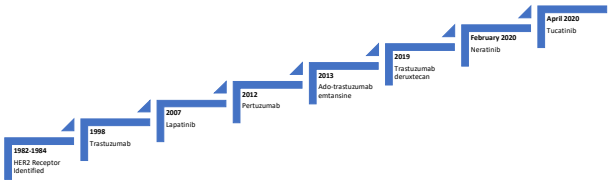
Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J*. 2015;15(1):e34-e38.
Nerlynx. Prescribing information. Puma Biotechnology. July 2020. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/208051s007lbl.pdf

Neratinib

- Oral inhibitor of intracellular tyrosine kinases of HER2
- Compared with lapatinib + capecitabine, neratinib + capecitabine significantly improves PFS in patients previously treated with two or more lines of therapy
  - 8.8 vs 6.6 months (*P* = 0.003)
- Neratinib increases the risk of diarrhea
- **Place in therapy:** 3rd line and beyond

Saura C, et al. *J Clin Oncol*. 2020; 38:3138-49.
Nerlynx. Prescribing information. Puma Biotechnology. July 2020. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/208051s007lbl.pdf

History of HER2+ Breast Cancer



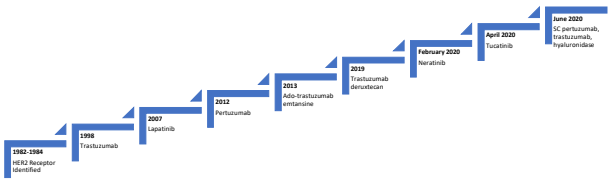
Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J*. 2015;15(1):e34-e38.
Tukysa. Prescribing information. Seattle Genetics. April 2020. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf

Tucatinib

- Oral inhibitor of intracellular tyrosine kinases of HER2
- In combination with trastuzumab and capecitabine, tucatinib significantly improves PFS in patients previously treated with trastuzumab, pertuzumab, and ado-trastuzumab compared with trastuzumab + capecitabine + placebo
  - 7.8 vs 5.6 months (*P* <0.001)
  - In patients with brain metastases, 1-year PFS was improved from 0% to 24.9%
- Tucatinib increases the risk of diarrhea and elevated liver enzymes compared with placebo
- **Place in therapy:** 2nd line and beyond. May be more strongly considered in patients with brain metastases.

Murthy RK, et al. *N Engl J Med*. 2020;382:597-609.
Tukysa. Prescribing information. Seattle Genetics. April 2020. Accessed August 2, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf

History of HER2+ Breast Cancer



Lakhtakia R, Burney I. *Sultan Qaboos Univ Med J*. 2015;15(1):e34-e38.
Phesgo. Prescribing information. Genentech. June 2020. Accessed August 28, 2020. www.gene.com/download/pdf/phesgo_prescribing.pdf

Trastuzumab/Pertuzumab/Hyaluronidase

- SC formulation of trastuzumab and pertuzumab combined with recombinant human hyaluronidase
- Primary objective: Noninferiority of pre-cycle 8 pertuzumab trough concentrations of IV vs SC regimen
  - Found to produce similar concentrations of trastuzumab and pertuzumab
  - Also produced similar response rates and safety profiles
  - Significantly lower rates of hypersensitivity reactions
- **Place in therapy:** 1st line in combination with a taxane

Phesgo. Prescribing information. Genentech. June 2020. Accessed August 2, 2020. www.gene.com/download/pdf/phesgo_prescribing.pdf
Tan AR, et al. *Cancer Res*. 2020;80(4 suppl):Abstract nr PD4-07.

Emerging Therapies

Drug	Mechanism
Margetuximab	Anti-HER2 antibody engineered to increase innate and adaptive immune response
Pyrotinib	Pan-ErbB inhibitor
Taselisib and ipatasertib	PI3K inhibitors
TVB-2640	FASN inhibitor
Palbociclib, ribociclib, abemaciclib	CDK 4/6 inhibitors (for ER+/HER2+ breast cancer)
Avelumab, atezolizumab	PD-L1 inhibitors
huMNC2-CAR44	Autologous CAR-T cells

ClinicalTrials.gov. Accessed July 6, 2020.

Dosing and Administration

Agent	Dosing	Route and Frequency	Administration Pearls
Trastuzumab	mg/kg (loading dose)	IV every 3 weeks	90 min load; 30 min maintenance
Pertuzumab	Flat dose (loading dose)	IV every 3 weeks	60 min load; 30 min maintenance
Ado-trastuzumab emtansine	mg/kg	IV every 3 weeks	90 min load; 30 min maintenance
Trastuzumab deruxtecan	mg/kg	IV every 3 weeks	90 min load; 30 min maintenance Moderate emetic potential
SC Trastuzumab	Flat dose	SC every 3 weeks	2-5 minutes
SC Trastuzumab/Pertuzumab	Flat dose (loading dose)	SC every 3 weeks	8 min load; 5 min maintenance
Lapatinib	Flat dose	PO once daily	Take on an empty stomach
Neratinib	Flat dose	PO once daily	Take with food
Tucatinib	Flat dose	PO twice daily	Take with or without food

Perjeta. Prescribing information. Genentech. January 2020. Accessed August 2, 2020; Kadcyla. Prescribing information. Genentech. May 2019. Accessed August 2, 2020. Modi S, et al. *N Engl J Med*. 2020;382:610-621; Herceptin Hylecta. Prescribing information. Genentech. February 2019. Accessed August 28, 2020; Accessed August 2, 2020. Tykerb. Prescribing information. Novartis Pharmaceuticals. December 2018. Accessed August 28, 2020; Phesgo. Prescribing information. Genentech. June 2020. Accessed August 28, 2020; Nerlynx. Prescribing information. Puma Biotechnology. July 2020. Accessed August 28, 2020; Tukysa. Prescribing information. Seattle Genetics. April 2020. Accessed August 2, 2020.

Summary of HER2-Targeted Agents and Their Places in Therapy

- Trastuzumab has been a mainstay in the management of HER2+ breast cancer for over 20 years
- Additional agents have been developed to optimize metastatic treatment options, significantly improving outcomes
- Several drugs are being investigated to identify complementary targets in HER2+ breast cancer

Preferred 1st Line Regimens	2nd Line and Beyond Regimens
Taxane + trastuzumab + pertuzumab	Ado-trastuzumab emtansine Tucatinib + trastuzumab + pertuzumab Trastuzumab deruxtecan Neratinib + capecitabine Lapatinib + capecitabine Lapatinib + trastuzumab Trastuzumab + chemotherapy

NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V6.2020.

Adverse Effect Management

Common Adverse Effects Observed in Anti-HER2 Therapies

- Hypersensitivity Reactions
- Cardiotoxicity
- Rash
- Diarrhea

Barroso-Sousa R, et al. *Breast*. 2013.22:1009-1018.

Hypersensitivity Reactions

- Overall incidence of ≈16% with trastuzumab
- Highest risk with first dose (91%), and low risk for subsequent reactions
- Symptoms include fever, chills, hypotension, dyspnea, and rigors
  - Generally mild-moderate severity
  - Anaphylaxis and pulmonary toxicity in <1% of cases
- Management
  - Hold infusion
  - Administer supportive medications (eg, antihistamines, corticosteroid, acetaminophen)
  - Rechallenge
  - Premedicate!
    - Shown to reduce the incidence by 9% with first dose
    - Antipyretic (eg, acetaminophen) and antihistamine (eg, diphenhydramine)

Thompson L, et al. *Oncologist*. 2014;19:228-234.

Hypersensitivity Reactions

Agent	Infusion Reaction Rate
Trastuzumab	16%
Pertuzumab	13%
Ado-trastuzumab emtansine	1.4%
Trastuzumab deruxtecan	2.2%
SC trastuzumab	4.2-9%
SC trastuzumab/pertuzumab	1.2%

Thompson L, et al. *Oncologist*. 2014;19:228-234.; Perjeta. Prescribing information. Genentech. January 2020. Accessed August 2, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf; Kadcyla. Prescribing information. Genentech. May 2019. Accessed August 2, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf Modi S, et al. *N Engl J Med*. 2020;382:610-621.; Herceptin Hylecta. Prescribing information. Genentech. February 2019. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/761106s000lbl.pdf

Cardiotoxicity

- HER2 signaling is involved in cardiac myocyte survival pathways and heart development during embryogenesis
- Typically an asymptomatic drop in ejection fraction that is reversible with treatment interruption
  - Occurs while on treatment with an anti-HER2 therapy and delayed cardiomyopathy is uncommon

Drug	Incidence of LVEF Drop
Trastuzumab	2%-25%
Pertuzumab	6%
Lapatinib	1%-3%
Ado-trastuzumab emtansine	1%-2%
Trastuzumab deruxtecan	1.6%
Neratinib	0-0.3%
Tucatinib	NR

Ponde N, et al. *ESMO Open*. 2016;1:e000073.
Murthy RK, et al. *N Engl J Med*. 2020;382:597-609.
Modi S, et al. *N Engl J Med*. 2019;382:610-621.

Cardiotoxicity

- Management
  - Avoid concomitant cardiotoxic therapy (eg, anthracyclines)
  - Patient selection
    - Advanced age
    - Obesity
    - Hypertension
    - Baseline reduced ejection fraction
  - Cardiac surveillance
    - Functional imaging (echocardiogram or multigated acquisition [MUGA] scan) at baseline and every 3-6 months
    - Biomarkers???
  - Cardioprotection (eg, ACE inhibitors or beta blockers)???
  - Treatment interruption (monitor EF at 4-week intervals) if ejection fraction drops below 50%

Ponde N, et al. *ESMO Open*. 2016;1:e000073.

Rash

- An acneiform rash on the face, chest, and back that presents within the first weeks-months on therapy
- Most commonly seen with pertuzumab (24%) and lapatinib (28%)
- Management
  - **Topical antibiotics** (eg, clindamycin 1% gel)
  - **Topical corticosteroids** (eg, hydrocortisone 1% cream)
  - **Oral antibiotics** (eg, doxycycline 100 mg bid)
    - Typically continued for 6 weeks
  - **Oral corticosteroids** (eg, methylprednisolone dose pack)
  - **Dose interruption**
  - **Topical skin moisturizer** and **broad-spectrum sunscreen**

Barroso-Sousa R, et al. *Breast*. 2013.22:1009-1018; Lacouture M, et al. *Support Care Cancer*. 2011;19(8):1079-1095.
Lacouture ME. *The ASCO Post*. May 15, 2013. Accessed August 2, 2020. ascopost.com/issues/may-15-2013/prevention-and-treatment-of-acneiform-rash-caused-by-egfr-inhibitors/

Diarrhea

- Most commonly occurs with pertuzumab (46%) and the oral tyrosine kinase inhibitors (TKIs) (60% with lapatinib, 80.9% with tucatinib, and 95% with neratinib)
- Leads to frequent dose reductions, interruptions, and discontinuation of therapy
- Management
  - **Diet modification:** lactose-free and small portioned meals
  - **Increased fluid intake**
  - **Antidiarrheals**: loperamide 4 mg followed by 2 mg after every unformed stool AND/OR atropine/diphenoxylate 5 mg 4 times daily until controlled
  - **Dose interruption and/or reduction**

Barroso-Sousa R, et al. *Breast*. 2013.22:1009-1018; Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119.
Murthy RK, et al. *N Engl J Med*. 2020;382:597-609; Geyer CE, et al. *N Engl J Med*. 2006;355(26):2733-2743.
Nerlynx. Prescribing information. Puma Biotechnology. July 2020. Accessed August 2, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/208051s007lbl.pdf

Antidiarrheal Prophylaxis

- Recommended to initiate prophylaxis with neratinib therapy in all patients:

Time on Therapy	Dose of Loperamide	Frequency
Weeks 1-2	4 mg	Three times daily
Weeks 3-8	4 mg	Twice daily
Weeks 9-52	4 mg	As needed

- Addition of budesonide and colestipol to loperamide has been shown to further reduce the incidence of severe diarrhea, hospitalization, and subsequent treatment discontinuation
- While not required with other TKIs, a similar regimen can be considered in patients at higher risk or those who are not adequately controlled with PRN antidiarrheal use

Nerlynx. Prescribing information. Puma Biotechnology. July 2020. Accessed August 28, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/208051s007lbl.pdf
Barcenas CH, et al. *J Clin Oncol*. 2019;37(5_suppl):548.

Summary of Common Adverse Effects and Appropriate Management Strategies

- Adverse effects associated with anti-HER2 therapies are generally mild and reversible in comparison with other antineoplastic agents
- However, these AEs can significantly impact quality of life and must be addressed

Conclusion

- Management of HER2+ breast cancer has changed significantly in the past 20 years, with resulting improvements in patient outcomes
- Biomarker testing must be accurately performed in order to identify patients who are expected to benefit from targeted therapies
- Several targeted agents have been FDA approved in recent years, with additional antibody-drug conjugates and therapies with complementary targets under development
- Patients must be monitored for potentially serious toxicities such as cardiomyopathy. While most adverse effects are mild, they can have a significant impact on quality of life and adherence.

Additional Resources

Loibl S , Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389(10087):2415-2429.	dx.doi.org/10.1016/S0140-6736(16)32417-5.
NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V6.2020.	www.nccn.org/professionals/physician_gls/pdf/breast.pdf
NCCN Guidelines for Patients 2020: Breast Cancer Metastatic	www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf
Oral Chemotherapy Education Sheets	www.oralchemoedsheets.com/

Cervical and Endometrial Cancers: A Pharmacist's Review of the New and Emerging Treatment Paradigm for Patients With Advanced or Metastatic Disease

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McGovern Medical School at The University of Texas Health Sciences Center at Houston
Houston, Texas

PTce

Educational Objectives

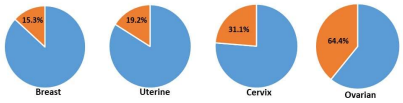
After completion of this activity, participants will be able to:

- Recognize the role of the pharmacist in disease prevention based on the risk factors for cervical and endometrial cancers
- Recall clinical data supporting the use of approved and pipeline agents and their place within treatment paradigms of advanced or metastatic cervical and endometrial cancers
- Describe strategies for managing adverse effects associated with targeted therapy or immunotherapies for advanced or metastatic cervical and endometrial cancers

Overview of Cervical and Endometrial Cancers

Gynecologic Cancers

- Cervical cancer is the most common gynecologic cancer worldwide
- Endometrial cancer is the most common gynecologic cancer in well-developed countries
  - Most common gynecologic cancer in the United States
- Ovarian cancer has the highest mortality rate of all gynecologic malignancies



Orange color represents the percent mortality for each female cancer

American Cancer Society. Cancer Facts & Figures 2020.

Overview of Cervical Cancer

Cervical Cancer

Risk Factors

- Increased HPV exposure
  - First intercourse at early age
  - Multiple partners
  - History of other sexually transmitted diseases
  - Intercourse with uncircumcised males
- Decreased screening
  - Low socioeconomic status
  - Poor access to health care
- Smoking
- HIV/AIDS or other immunosuppressive conditions
- Oral contraceptive use/multiple pregnancies

Patient Presentation

- Stage 0/stage I: often asymptomatic; incidental finding
- Advanced disease:
  - Abnormal bleeding/discharge
  - Pelvic pain
  - Lower extremity swelling
  - Difficulty urinating/bowel movements

Morris BJ, Hankins CA. *Lancet*. 2017;5:e1054-e1055; American Cancer Society: Cervical Cancer. Accessed August 3, 2020. cancer.org/cancer/cervical-cancer.html; NCCN Guidelines: Cervical Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf

Cervical Cancer Pathology

- 75% squamous cell, 25% adenocarcinoma
- Noninvasive squamous lesions
  - Cervical intraepithelial neoplasia (CIN)
    - CIN grade 2 = moderate lesion
    - CIN grade 3 = carcinoma in situ (CIS)
- Invasive, malignant cells
  - Penetrate basement membrane
  - Infiltrate stroma
  - Potential vascular/lymphatic invasion
- Common gene mutations:
  - PI3K/MAPK
  - TGF-β
- Gene mutations associated with coding for targets for immunotherapy
  - CD274
  - PDCDILG2
  - PDL-1
- Other future actionable targets
  - MED1, ERBB3, CASP8, HLA-A, TGFBR-2, BCA44, NTRK

Adegoke O, et al. *J Womens Health.* 2012;21(10):1031-1037; Cancer Genome Atlas Research Network. *Nature.* 2017;543(7645):378-384; Dooley KE, et al. *mBio.* 2016;7(5):301446-16; NCCN Guidelines: Cervical Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf

Treatment: Recurrent or Persistent Cervical Cancer

Pelvic Disease

- Radiation if not used in primary treatment
- If recurrence is central after radiotherapy, consider exenteration
- If previously radiated and sidewall involved, consider chemotherapy

Extrapelvic Disease

- Chemotherapy
- Immunotherapy
- Palliative radiotherapy
- Surgical resection (rare)

Bermann T, Smith JA. Cervical Cancer, Chapter 33, *Women's Health Across the Lifespan*, 2E, November 2018. NCCN Guidelines: Cervical Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf

Treatment: Recurrent or Persistent Cervical Cancer

- Chemotherapy associated with poor response rates in recurrent cervical cancer
  - Palliative role
  - Single-agent regimen response rates 15% to 30%
  - Combination regimen response rates 30% to 46%
- Immunotherapy associated with improved response rates
- New directions with combination therapy and molecularly targeted agents

Bermann T, Smith JA. Cervical Cancer, Chapter 33, *Women's Health Across the Lifespan*, 2E, November 2018. NCCN Guidelines: Cervical Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf

Metastatic Cervical Cancer Systemic Therapies

First-line Combination Regimens	Possible First-line Single Agent	Second Line
• Paclitaxel/cisplatin/bevacizumab • Paclitaxel/carboplatin/bevacizumab **Other Recommended Regimens** • Paclitaxel/cisplatin • Paclitaxel/carboplatin • Paclitaxel/topotecan/bevacizumab • Paclitaxel/topotecan • Topotecan/cisplatin	• Cisplatin **Other Recommended Regimens** • Carboplatin • Paclitaxel	• Pembrolizumab if PD-L1 positive or MSI-H/dMMR **Other Recommended Regimens** • Bevacizumab • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Mitomycin • Pemetrexed • Topotecan • Vinorelbine **Useful in certain circumstances** Larotrectinib or entrectinib (NTRK gene fusion-positive tumors)

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

NCCN Guidelines: Cervical Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf

Overview of Endometrial Cancer

Endometrial Cancer

- Adenocarcinoma of the endometrium is also known as uterine cancer, carcinoma of the uterine corpus
- Most common malignancy of the female genital tract in the United States
  - 67% of patients with adenocarcinoma of the endometrium diagnosed with disease confined to the uterus
  - 10% of endometrial cancer diagnoses: uterine papillary serous carcinoma (UPSC)

NCCN Guidelines: Uterine Neoplasms V 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/uterine.pdf; Boruta DM, et al. *Gynecologic Oncol.* 2009;115:142-152.

Endometrial Cancer Risk Factors

- Obesity
- Increased estrogen exposure/unopposed estrogen exposure over a lifetime
  - Early menarche, nulliparity, late menopause
  - Exogenous hormone replacement or tamoxifen
- Poor diet and lack of exercise
- Type 2 diabetes/insulin resistance
- Family history: endometrial, colorectal cancer
- History of breast or ovarian cancer
- History of endometrial hyperplasia
- Past treatment with pelvic radiation therapy

NCCN Guidelines: Uterine Neoplasms V 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/uterine.pdf; Centers for Disease Control and Prevention: Uterine Cancer. Accessed August 17, 2020. cdc.gov/cancer/uterine/basic_info/risk_factors.htm; Constantine GD, et al. *J Womens Health.* 2019;28(2):237-243.

Endometrial/Uterine Cancer

- **Symptoms**
  - Irregular bleeding
    - Bleeding between periods
    - Postmenopausal bleeding
  - Abnormal, watery, or blood-tinged discharge
  - Pelvic pain
  - Fatigue
- **Diagnosis**
  - Pelvic examination
  - Transvaginal ultrasound
  - Exam with hysteroscope
  - Endometrial biopsy (EMB) of uterus
- **Primary treatment**
  - Total hysterectomy with bilateral salpingo-oophorectomy
    - Tumor de-bulking
    - Pelvic washings
    - Lymph node dissection
    - Staging

NCCN Guidelines: Uterine Neoplasms V 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/uterine.pdf; Constantine GD, et al. *J Womens Health.* 2019;28(2):237-243. National Cancer Institute: Uterine Cancer. Accessed August 17, 2020. training.seer.cancer.gov/cervical-uterine/uterus/intro/symptoms.html

Genetic Mutations: Endometrial/Uterine Cancers

Endometrial Carcinoma

- Inactivation of the PTEN tumor-suppressor gene
- Defects in DNA mismatch repair leading to microsatellite instability
- Mutations in β-catenin and K-ras among others
- Preceded by hormonally induced atypical endometrial hyperplasia
- PD-L1 expression

Uterine Papillary Serous Carcinoma

- Frequent p53 gene mutations
- HER2/neu gene amplification
- May arise within atrophic endometrium
- Endometrial intraepithelial carcinoma may be a precursor lesion

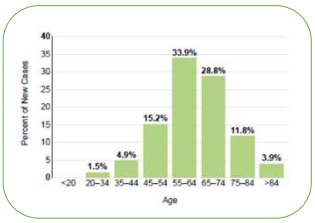
Boruta DM, et al. *Gynecologic Oncol.* 2009;115:14; Ott PA, et al. *J Clin Oncol.* 2017;35(22):2535-2541.

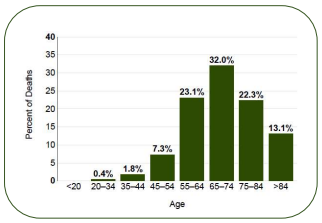
Types I and 2 Endometrial Cancer

	Type I: Endometrial Adenocarcinoma	Type II: Non-endometrial
Histology	Endometrioid	Non-endometrioid (eg, clear cell, serous)
Primary risk factor	Unopposed estrogen	Numerous; not related to estrogen
Menopausal status	Perimenopausal	Postmenopausal
Race	White	No differentiation
Stage at diagnosis	I/II	III/IV
Behavior	Indolent	Aggressive
Prognosis	Favorable	Not favorable
Molecular features	Diploid K-ras overexpression PTEN mutations Microsatellite instability (MSI)	Aneuploid K-ras overexpression HER2 overexpression P53 overexpression

Setiawan VW, et al. *J Clin Oncol.* 2013;31:2607-2618; Buza et al. *Arch Pathol Lab Med.* 2014;138(3):343-350. Singh et al. *J Pathol.* 2020;250(3):336-345.

Endometrial Cancer Prognosis





NIH Cancer Stat Facts: Uterine Cancer. Accessed July 21, 2020. seer.cancer.gov/statfacts/html/corp.html

Endometrial Cancer Treatment: Recurrent Disease

Patient Assessment

- Tumor genetic testing
- Residual toxicity
- Comorbidities

Treatment Options

- Chemotherapy
  - Platinum resistance
- Radiation
  - History of radiation
  - Location of recurrence
- Hormone therapy
- Immunotherapy
- Targeted therapies

NCCN Guidelines: Uterine Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/uterine.pdf

Endometrial Cancer Systemic Therapies

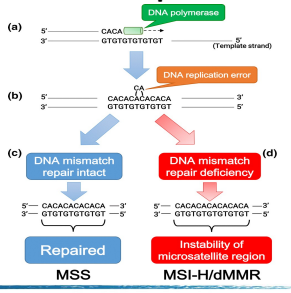
Used in High-Risk, Recurrent, or Metastatic Disease

Preferred	Other Recommended Regimens	Hormone Therapy Examples
• Carboplatin, paclitaxel (for carcinosarcoma) • Carboplatin, paclitaxel, trastuzumab (for stage III/IV or recurrent HER2+ uterine serous carcinoma)	• Carboplatin, docetaxel • Cisplatin, doxorubicin ± paclitaxel • Carboplatin, paclitaxel, bevacizumab • Doxorubicin or liposomal doxorubicin • Cisplatin or carboplatin alone • Paclitaxel or albumin-bound paclitaxel • Temsirolimus • Topotecan • Bevacizumab • Lenvatinib/pembrolizumab	• Medroxyprogesterone ± tamoxifen • Megestrol acetate ± tamoxifen • Levonorgestrel intrauterine device • Aromatase inhibitors (eg, anastrozole, letrozole) • Tamoxifen • Fulvestrant • Everolimus/letrozole
Useful in Certain Circumstances • Pembrolizumab (MSI-high/dMMR tumors) • Larotrectinib or entrectinib (NTRK gene fusion-positive tumors)		

NCCN Guidelines: Uterine Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/uterine.pdf

Molecular Testing in Cervical and Endometrial Cancers

DNA Mismatch Repair Deficiency



Eso Y, et al. *J Gastroenterol.* 2020;55:15-26.

Molecular Profiles

MSI –High/dMMR

Biomarker Findings
Microsatellite status - MSI-High
Tumor Mutational Burden - 32 Muts/Mb

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.

PIK3CA H1047Y
PTCH1 E703*
PTEN G251V, R130*
ARID1A L2119fs*30, Q1631*
KEAP1 R169C
KRAS G12V
BCORL1 P1681fs*20
CDK12 splice site 1047-2A>G
JAK1 K860fs*16
STAG2 N277fs*5
TP53 W91*

POLE Mutations

Biomarker Findings
Tumor Mutational Burden - TMB-High (223 Muts/Mb)
Microsatellite status - Cannot Be Determined

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.

CTNNB1 D32G
EGFR T354M
FBXW7 R278*
NF1 R440*, R2637*
PIK3CA T1025A, R88Q
PTEN E173C, Y177*, V222fs*21
ARID1A R1989*
CBL R149Q
EZH2 A25ST
FANCA W171*
RNF43 S607L
ATRX R907*, E1547*
CASP8 E448*
CD22 R802C
CDC73 R139Q, R91Q
CDKN2A/B p14ARF G83R
CHEK2 W485*
CIC R1319W
CTCF splice site 1015+1G>A
DDR2 D661Y
EP300 R580Q, R86*, R1312*
ESR1 R256Q, E247K
GNAQ R183*
HGF R181*
HSD3B1 T353M, R186*
INPP4B R252*, R297*
IRF2 A79V
KEL V550A
KLHL6 D104N
KMT2A (MLL) L1423S
LTK R669*
MAP3K1 G914*
PBRM1 G1206R
POLE V419L
PTPRD R963*
RB1 splice site 540-1G>A
SMAD4 R97H
SPEN E417*
TP53 R273C, R282W

De-identified patient molecular profile.

Molecular Profile: MSI-High Disease

Biomarker Findings
Microsatellite status - MSI-High
Tumor Mutational Burden - 32 Muts/Mb

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.

PIK3CA H1047Y
PTCH1 E703*
PTEN G251V, R130*
ARID1A L2119fs*30, Q1631*
KEAP1 R169C
KRAS G12V
BCORL1 P1681fs*20
CDK12 splice site 1047-2A>G
JAK1 K860fs*16
STAG2 N277fs*5
TP53 W91*

Biomarker Findings
Microsatellite status - MSI-High
Tumor Mutational Burden - 20 Muts/Mb

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.

CTNNB1 S45P
HRAS G13S
PTCH1 E539fs*3
PTEN R130*
ARID1A D1850fs*33
PIK3R1 splice site 1746-2A>G
CD79A R131fs*61
MAP3K1 P512fs*45
MLL2 Y2199fs*65
PRKAR1A R16*
PTPRO N238fs*36
SMARCA4 P263fs*40
SPEN splice site 882-2A>G
WT1 R462W

De-identified patient molecular profile.

Immunotherapies and Targeted Therapies for Cervical Cancer

Bevacizumab in Advanced Cervical Cancer: GOG 240

Study Design	• Randomized, controlled, open-label, phase 3 trial; 452 patients with advanced cervical cancer • Bevacizumab 15 mg/kg IV once every 21 days ± one of the following: • Paclitaxel 135-175 mg/m^2 + cisplatin 50 mg/m^2 • Paclitaxel 175 mg/m^2 topotecan 0.75 mg/m^2 days 1 to day 3
Response	• Overall survival (OS) • Paclitaxel + topotecan not superior to paclitaxel + cisplatin • Addition of bevacizumab to either chemotherapy regimen improved OS: 16.8 vs 13.3 months (P = 0.007) • Progression-free survival (PFS) favored addition of bevacizumab (8.2 vs 5.9 months; HR, 0.67)
Adverse effects	Bevacizumab + chemotherapy versus chemotherapy alone: • Any grade hypertension (25% vs 2%, P <0.001); no patients discontinued therapy • Adverse effects ≥ grade 3: • Thromboembolic events (8% vs 1%, P <0.001) • Gastrointestinal or genitourinary fistulas (6% vs 0%, P = 0.002)

August 2014: FDA granted bevacizumab approval for the treatment of patients with **persistent, recurrent, or metastatic cervical cancer.**

Tewari KS, et al. *N Engl J Med*. 2014;370(8):734-743; Tewari KS, et al. *Lancet*. 2017;390(10103):1654-1663.

Pembrolizumab in Cervical Cancer: KEYNOTE-158

Study Design	• Multicenter, open-label phase 2 basket study in 27 cancer types • 98 patients with previously treated advanced cervical cancer • Pembrolizumab 200 mg IV every 3 weeks
Response	• Overall response rate (ORR): 12 (14.6%), **all in PD-L1+ tumors** • 3 complete responses (CRs), 9 partial responses (PRs) • Disease control rate (DCR): **30.6%,** 18 patients with stable disease (SD) • Median PFS and OS: 2.1 months and 9.4 months
Adverse effects	Any grade: 65.3% • Hypothyroidism (10.2%), decreased appetite (9.2%), fatigue (9.2%), diarrhea (8.2%) • 12.2% with grade 3/4 • 4.1% discontinued therapy

June 2018: FDA granted pembrolizumab accelerated approval for the treatment of patients with **advanced, PD-L1–positive cervical cancer with disease progression on or after chemotherapy**. The approval defined PD-L1 positivity as a combined positive score (CPS) of ≥1 as measured by an FDA-approved test.

Chung CH, et al. *J Clin Oncol*. 2019;37(17):1470-1478; Marabelle A, et al. *J Clin Oncol*. 2019;38(1):1-10.

Immunotherapies and Targeted Therapies for Endometrial Cancer

Trastuzumab in Uterine Serous Carcinoma

Study Design	• Randomized phase 2 study at 11 institutions • 58 patients with HER2+ uterine serous carcinoma (28 control, 30 in experimental arm) • Paclitaxel 175 mg/m^2 + carboplatin AUC 5 ± trastuzumab 8 mg/kg load, then 6 mg/kg q 21 days
Response	PFS: control versus trastuzumab • All patients: 8 months vs 12.6 months • Primary treatment for stage III/IV disease: 9.3 months vs 17.9 months (n = 41) • Recurrent disease 6 months versus 9.2 months
Adverse effects	Any grade: 27 events vs 51 events (control vs trastuzumab) • No significant difference between arms • Largest difference: incidence of hypertension 0% control vs 16% trastuzumab

Fader AN, et al. *J Clin Oncol*. 2018;36(20):2044-2051.

Pembrolizumab in Endometrial Cancer: KEYNOTE-158

Study Design	• Multicenter, open-label phase 2 basket study in 27 cancer types • 49 patients with MSI-H advanced endometrial cancer • Pembrolizumab 200 mg IV every 3 weeks
Response	• ORR: 12 (57%), **all in PD-L1+ tumors** • 8 CRs, 20 PRs • DCR: **73%** • 8 patients with stable disease (SD) • Median duration of response (DOR): not reached
Adverse effects	Any grade: 80% • Fatigue (26%), diarrhea (24%) • 16% grade 3/4 adverse effects

May 2017: FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with **unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed** following prior treatment and who have no satisfactory alternative treatment options.

Marabelle A, et al. *J Clin Oncol*. 2019;38(1):1-10; O'Malley D, et al. *Ann Oncol*. 2019;30(suppl 5):V425 #1044P; FDA. News release. Accessed August 24, 2020. www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication

Pembrolizumab + Lenvatinib in MSI-Stable Endometrial Cancer

Study Design	• Open-label, single-arm phase 2 in 11 centers • 53 patients with advanced endometrial carcinoma • Pembrolizumab 200 mg IV every 3 weeks + lenvatinib 10 mg PO BID
Response	• Median follow-up: 13.3 months (6.7 to 20.1 months) • 21 (39.6%) with objective response at 24 weeks • Overall: 1 complete response, 20 partial responses, 25 with stable disease
Adverse effects	• Any grade: • Hypertension (58%) • Fatigue (55%) • Diarrhea (51%) • 5 patients discontinued therapy due to AEs

September 2019: FDA approved **pembrolizumab + lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR and who have disease progression** following prior systemic therapy but are not candidates for curative surgery or radiation.

Makker V, et al. *Lancet*. 2019;20:711-718; FDA. News release. Accessed August 24, 2020. www.fda.gov/drugs/resources-information-approved-drugs/simultaneous-review-decisions-pembrolizumab-plus-lenvatinib-australia-canada-and-us

Bevacizumab in Advanced Endometrial Cancer: MITO END-2

Study Design	• Phase 2 trial in patients with advanced or recurrent endometrial cancer; n = 108 • Randomized to paclitaxel 175 mg/m^2 + carboplatin AUC 5 IV ± bevacizumab 15 mg/kg IV every 21 days
Response	Paclitaxel + carboplatin versus paclitaxel + carboplatin + bevacizumab: • PFS: 10.5 vs 13.7 months • ORR: 53.1 vs 74.4% • OS: 29.7 months vs 40 months • Not statistically significant
Adverse effects	Paclitaxel + carboplatin versus paclitaxel + carboplatin + bevacizumab: • Grade >2 hypertension 0% vs 21% • Grade >2 thromboembolic events 2% vs 11% • Incidence of discontinuation: 4% vs 19%

Addition of bevacizumab to paclitaxel + carboplatin in advanced or recurrent endometrial cancer did not have a significant impact on results and had an increased incidence of adverse effects.

Lorusso D, et al. *Gynecol Oncol.* 2019;155(3):406-412.

In the Pipeline*

Cervical Cancer

- LN-145: tumor-infiltrating lymphocytes; breakthrough therapy designation
- GOG 3016: human monoclonal anti-programmed death cell-1 therapy cemiplimab
- Nivolumab + radiation followed by nivolumab alone for primary treatment

Endometrial Cancer

- Prevention: metformin
- Treatment
  - Everolimus + letrozole with or without metformin for treatment
  - Paclitaxel/carboplatin + temsirolimus for treatment
  - Dostarlimab (PD-L1/PD-L2 inhibitor) with paclitaxel/carboplatin followed by dostarlimab maintenance for primary treatment
  - Selinexor (selective inhibitor of nuclear export) monotherapy or in combination with taxane/platinum regimens

***Note: not all-inclusive.**

Guo J. *Oncotarget.* 2017;8(39):66169-66177; Slomovitz BM, et al. *J Clin Oncol.* 2015;33(8):930-936; Soliman PT, et al. *Clin Cancer Res.* 2020;26:581-587;ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT03981796; Vergote I, et al. *J Clin Oncol.* 2020;38(15_suppl):TPS6105-TPS6105; *Am J Manag Care.* ajmc.com/view/cemiplimab-in-gog-3016-looks-to-break-new-ground-for-immunotherapy-in-cervical-cancer; Center for Cancer Research. ccr.cancer.gov/news/article/fda-grants-breakthrough-therapy-designation-of-new-til-therapy-for-advanced-cervical-cancer; ClinicalTrials.gov. clinicaltrials.gov/ct2/show/NCT02257528

Pharmacist Role in Managing Patients With Gynecologic Malignancies

Pharmacist Role: Cervical Cancer Prevention

- Cervical Cancer Screening
  - Pap smears
  - HPV testing
    - After age 25; not helpful in younger patients
- HPV vaccine
  - Recommended in males and females aged 11 to 12 years
  - Vaccine series can begin as young as age 9
    - Two injections before age 15; thereafter, 3-shot series
  - Now approved in patients up to age of 45

NCCN Guidelines: Cervical Cancer V. 2. 2020. Accessed August 20, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf;CDC HPV Vaccine Schedules and Dosing. Accessed August 20, 2020. cdc.gov/hpv/hcp/schedules-recommendations.html; NCCN Guidelines: Bermann T, Smith JA. Cervical Cancer, Chapter 33, *Women's Health Across the Lifespan*, 2E, November 2018.

Pharmacist Role: General Education for Patients With Cervical Cancer

- Patients often have residual radiation toxicity
  - Vaginal dilators
  - Bowel regimens
  - Bone health support
  - Pain control
- Address menopausal symptoms, difficulties with sexual function/health
- Smoking cessation resources
- Bone marrow reserve is less due to prior radiation
  - Difficulty tolerating myelosuppressive regimens

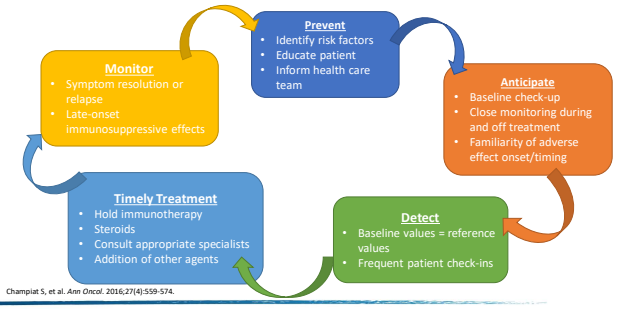
Bermann T, Smith JA. Cervical Cancer, Chapter 33, *Women's Health Across the Lifespan*, 2E, November 2018. NCCN Guidelines: Cervical Cancer V. 2. 2020. Accessed August 20, 2020. nccn.org/professionals/physician_gls/pdf/cervical.pdf

Pharmacist Role: General Education for Patients With Endometrial Cancer

- Encourage family genetic screening
- Offer resources for healthy, sustainable weight loss
- Address menopausal symptoms, difficulties with sexual function/health
- If prior radiation
  - Vaginal dilators
  - Bowel regimens
  - Bone health support
  - Pain control

Mach CM, Hall TR. Endometrial Cancer, Chapter 31, *Women's Health Across the Lifespan*, 2E, November 2018. NCCN Guidelines: Uterine Cancer V. 2.2020. Accessed August 17, 2020. nccn.org/professionals/physician_gls/pdf/uterine.pdf

Immunotherapy Adverse Effect Management



Champiat S, et al. *Ann Oncol*. 2016;27(4):559-574.

Pembrolizumab

Adverse Effects

- Fatigue
- Diarrhea/abdominal pain
- Decreased appetite
- Immune-mediated reactions
  - Colitis
  - Pneumonitis
  - Endocrinopathies
  - Hepatitis
  - Dermatologic

Pearls/Monitoring

- Early intervention for ADRs
- Baseline and routine thyroid panel
- Caution on photosensitivity

Keytruda. Prescribing information. Merck Sharp & Dohme Corp; June 2020. Accessed August 24, 2020. merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Select Immunotherapy Toxicity Management

Symptom	Grade/Intervention	Management
Dermatologic Maculopapular rash	• Grade 1/2: continue therapy • Grade 3: hold therapy • Grade 4: N/A	• Grade 1/2: oral antihistamines (eg, loratadine 10 mg PO) • Topical corticosteroid (eg, clobetasol) • Grade 3: systemic steroids (prednisone 0.5-1 mg/kg PO) until resolution
Dermatologic Pruritus	• Grade 1: continue therapy • Grade 2/3: dermatology referral • Grade 4: N/A	• Grade 1: topical treatment • Grade 2: topical treatment and oral antihistamines, steroids • Grade 3: GABA agonist; oral steroids (prednisone 0.5-1 mg/kg, taper over 2 weeks) • Grade 4: N/A

Pneumonitis	• Grade 1: consider holding; resume when symptoms resolve with close monitoring
	• Grade 2: hold therapy; consider hospitalization; consider re-challenge if resolve
	• Grade 3/4: discontinue therapy; hospitalization (consider ICU); pulmonary consult
		• Grade 1: self-monitor symptoms/oxygenation
		• Grade 2: IV methylprednisolone 1 mg/kg/d, slow taper over 1 month after symptoms improve
		• Grade 3/4: initiate IV methylprednisolone 2 mg/kg/d
		  • Improvement: decrease to 1 mg/kg/d, slow taper over 2 months
		  • No improvement: add alternative agent (eg, infliximab, cyclophosphamide, mycophenolate, IVIG)

Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95.

Select Immunotherapy Toxicity Management

Symptom	Grade/Intervention	Grade/Management

Gastrointestinal Diarrhea/colitis	• Grade 1: continue therapy
	• Great 2/3: hold therapy; abdominal x-ray + consider sigmoidoscopy to rule out colitis
	• Grade 4: discontinue therapy, rule out colitis; potential imaging + surgical referral if concerns with megacolon
		• Grade 1: initiate antimotility agent (eg, loperamide)
		• Grade 2: antimotility agents
		  • If no improvement: start prednisone 1 mg/kg PO daily
		  • If still no improvement in 72 hours, manage as grade 3
		  • If improves within 72 hours, gradual taper of steroids
		• Grade 3/4:
		  • Systemic steroids (prednisone 0.5-1 mg/kg PO once daily or methylprednisolone 1-2 mg IV once daily)
		  • Reassess in 24 hours; if no improvement, add infliximab 5 mg/kg IV at week 1, 2, and 6 and continue steroids; add mycophenolate if needed
		  • Once ≤ grade 1, taper steroids over 4 to 6 weeks

Gastrointestinal Hepatitis	Grade 1: continue therapy; monitor LFTs Grade 2/3: hold therapy Grade 4: discontinue therapy	• Grade 2-4: prednisone 1-2 mg/kg PO daily; taper gradually after symptoms improve • Resume once taper less than 10 mg/day and ≤ grade 1 • Can consider mycophenolate, liver biopsy if refractory

Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95; DeSouza K, et al. *J Cancer Prev Curr Res*. 2016;6(1):00187.

Example Steroid Taper

- Taper initiated once symptoms improve
  - Variable time to initiation: 10 days to up to 6 weeks before taper begins
- Prednisone 60 mg PO once daily (starting dose)
  - Prednisone 60 mg by mouth once daily x 10 days *then reduce to*
  - Prednisone 50 mg by mouth once daily x 3 days *then reduce to*
    - Prednisone 40 mg by mouth once daily x 3 days *then reduce to*
      - Prednisone 30 mg by mouth once daily x 3 days *then reduce to*
        - Prednisone 20 mg by mouth once daily x 3 days *then reduce to*
          - Prednisone 10 mg by mouth once daily x 5 days *then reduce to*
            - Prednisone 5 mg by mouth once daily x 5 days then STOP

William KJ, et al. *J Oncol Pharm Prac*. 2019;25(3):544-550.

Bevacizumab

Adverse Effects

- Gastrointestinal perforation
- Wound healing
- Hemorrhage
- Arterial/venous thrombosis
- Proteinuria
- Hypertension

Pearls/Monitoring

- Hold 28 days pre-/post-surgery
- Blood pressure
  - If elevated, hold therapy and initiate antihypertensive
  - Can resume once normal
- Urine protein
  - Urine protein:creatinine ratio less than 2
  - Urine protein less than 2+
- Signs/symptoms of clots or bleeding

Avastin. Prescribing information. Genentech; May 2020. Accessed August 21, 2020. gene.com/download/pdf/avastin_prescribing.pdf

Lenvatinib

Adverse Effects

- Diarrhea
- Hypertension
- Fatigue
- Nausea/vomiting
- Stomatitis
- Peripheral edema
- Arthralgia/myalgia
- Hypothyroidism
- Rash

Pearls/Monitoring

- Baseline thyroid panel
  - Monthly thereafter
- Urine protein monitoring at baseline and periodically
  - Hold if ≥2+ grams/proteinuria in 24 hours
- Blood pressure monitoring at baseline; periodically thereafter
- Antidiarrheals/antiemetics recommended as needed

Lenvima. Prescribing information. Eisai Inc. July 2020. Accessed August 24, 2020. lenvima.com/pdfs/prescribing-information.pdf

Trastuzumab

Adverse Effects

- Headache
- Arthralgia
- Diarrhea
- Nausea/vomiting
- Edema
- Hypertension
- Cardiac failure/cardiomyopathy
- Anaphylaxis

Pearls/Monitoring

- Baseline cardiac assessment
  - Echocardiogram
  - Repeat every 3 months
- Signs/symptoms of infusion reaction
- Loading dose, followed by maintenance dosing
  - Repeat loading dose if significant interruption in therapy
- Consideration of biosimiliars
  - Prior authorization with insurance

Herceptin Prescribing information. Genetech September 2020. Accessed September 14, 2020. https://www.gene.com/download/pdf/herceptin_prescribing.pdf

Role of the Pharmacist

- Patient care
  - Medication education, adherence strategies
  - Supportive care recommendations
  - Telehealth visits, phone calls, in-clinic visits
  - Routine follow-up
- Coordination of care
  - Medication education for oncology team
  - Recommended dosing of chemotherapy, supportive care
  - Communication with patients, caregivers, team
- Dispensing practices
  - Order verification
  - Specialty pharmacy resources

Neuss M, et al. *Oncol Nurs Forum*. 2017;44(1):31-43; Weingart SN, et al. *J Natl Compr Canc Netw*. 2008;6 suppl 3:S1-S14; Mackler E, et al. *JOP*. 2019;15:4:e346-e355.

Conclusion

- Advanced or recurrent cervical and endometrial cancers have historically been associated with poor prognosis
- Immunotherapies and targeted therapies have shown improvement in both progression-free and overall survival in patients with advanced cervical or endometrial cancer
- Pharmacists have potential impact on the prevention and management of adverse effects associated with immunotherapies and targeted therapies
- Pharmacists can assist with education for patients, caregivers, and the medical team

Additional Resources

National Comprehensive Cancer Network: Cervical Cancer	nccn.org/professionals/physician_gls/pdf/cervical.pdf
National Comprehensive Cancer Network: Uterine Neoplasms	nccn.org/professionals/physician_gls/pdf/uterine.pdf
National Comprehensive Cancer Network: Management of Immunotherapy-Related Toxicities	nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
Purple Book for Biological Interchangeability	www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or
Manufacturer Patient Assistance Program Information	cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/PAPData

Acute Graft-Versus-Host Disease: Innovative Strategies in Risk Assessment, Prevention, and Treatment

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Stem Cell Transplant & Cellular Therapy Clinical Pharmacist Specialist
Vanderbilt University Medical Center
Nashville, Tennessee

PTce

Educational Objectives

After completion of this activity, participants will be able to:

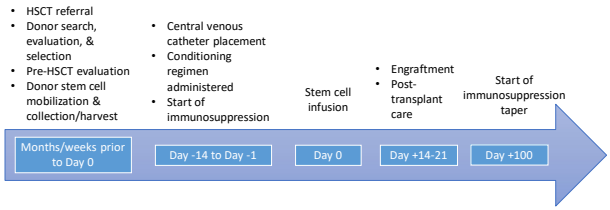
- Recognize grading and staging of acute graft-versus-host disease (aGVHD) in patients with allogeneic hematopoietic stem cell transplantation (HSCT) using updated risk scoring tools
- Outline emerging therapeutic agents and treatment strategies in the prevention and treatment of aGVHD
- Discuss the role of the pharmacist on the HSCT team

Definitions in Transplant

- Autologous: receiving own stem cells
- Allogeneic: receiving stem cells from a donor
  - Haploidentical: use of donor cells that are a half match
- Preparative/conditioning regimen: use of chemotherapy ± radiation prior to transplant
- Reduced intensity: less aggressive chemotherapy administered in preparative regimen
- Day zero: day of stem cell infusion
- Engraftment: infused stem cells begin to form new blood cells in the bone marrow

Stem cell transplantation. Leukemia and Lymphoma Society. Accessed September 16, 2020. lls.org/treatment/types-of-treatment/stem-cell-transplantation; Be the Match. Accessed September 16, 2020. bethematch.org/patients-and-families/about-transplant/what-is-a-bone-marrow-transplant/haploidentical-transplant/

Example HSCT Timeline



Acute Graft-Versus-Host Disease (aGVHD): Pathophysiology, Diagnosis, and Grading

Immune Interaction Post-Allogeneic HSCT

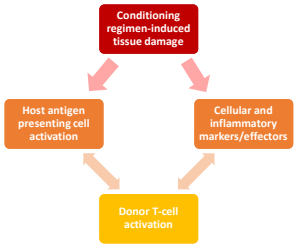
- Donor lymphocytes encounter many immunogenic recipient antigens
- GVHD results from immune responses directed at recipient antigens
  - Interaction also facilitates graft-versus-leukemia/tumor effect (GVL/GVT)
  - The separation of GVHD from GVL has yet to be achieved in clinical practice
- Risk of developing GVHD is dependent on several factors:
  - **Degree of human leukocyte antigen (HLA) mismatch**
  - Age older than 40 years
  - Sex and parity, if female
  - Graft source: peripheral blood > bone marrow > cord blood
  - Conditioning regimen intensity: ablative > reduced intensity > nonmyeloablative

HSCT, hematopoietic stem cell transplantation.
Flowers ME, et al. *Blood.* 2011;117(11):3214-3219.

GVHD Pathophysiology

Billingham criteria

1. Graft must contain immunologically competent cells
2. Recipient must express tissue antigens not present in the donor
3. Recipient must be incapable of mounting an effective response to eliminate the graft



Ferrara JLM, et al. *Lancet*. 2009;373(9674):1550-1561; Zeiser R, et al. *Br J Haematol*. 2016;175(2):191-207.

aGVHD Incidence

- Incidence of grade 2-4 aGVHD: 20%-85%, depending on risk factors and stem cell source
  - Incidence 22%-31% with matched sibling donor (MSD) vs 37%-52% with matched unrelated donor (MUD)
  - ≈15% develop severe (grade 3-4) disease
- Skin is the most commonly affected organ system; usually first
  - ≈80% of patients first present with skin involvement
- One of the leading causes of nonrelapse mortality (NRM)
  - 10%-15% mortality rate within first 3 years posttransplant

Flowers ME, et al. *Blood*. 2011;117(11):3214-3219; Zeiser R, Blazar BR. *N Engl J Med*. 2017;377(22):2167-2179.

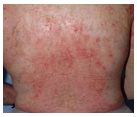
Features of aGVHD

- Mediated by mature donor T-cells in stem cell product
- Classic aGVHD: occurring early posttransplant, less than day +100
  - Usually first presents within 30-60 days posttransplant
  - Can occur/persist after day +100: late-onset
  - Can overlap with chronic GVHD: "overlap syndrome"
- Restricted to skin, gut, and liver

Ferrara JLM, et al. *Lancet*. 2009;373(9674):1550-1561; Zeiser R, Blazar BR. *N Engl J Med*. 2017;377(22):2167-2179.

Presentation of aGVHD

- Skin
  - Maculopapular rash ± pruritus
  - Blistering and desquamation in severe cases
- Gut
  - Lower GI: secretory diarrhea, abdominal pain/cramping
  - Upper GI: N/V, anorexia, abdominal pain
  - Severe cases: GI bleeding, ileus
- Liver
  - Hyperbilirubinemia



GI, gastrointestinal; N/V, nausea/vomiting.

Ferrara JLM, et al. *Lancet*. 2009;373(9674):1550-1561.

Image source National Cancer Institute. www.cancer.gov/news-events/cancer-currents-blog/2017/ibrutinib-fda-gvhd

Diagnosis of aGVHD

- Diagnosis made from clinical assessment ± tissue biopsy

Differential diagnoses		
Skin	**Gut**	**Liver**

• Drug allergy
• Contact dermatitis
• Sunburn
	• Chemotherapy toxicity, mucositis
	• Gastroenteritis (eg, viral infection, food poisoning)
	• *Clostridium difficile* infection
	• Drug toxicity
		• Veno-occlusive disease (VOD)
		• Drug toxicity
		  • Azole antifungals
		  • Total parental nutrition
		  • Immunosuppressants
		• Infection
		  • Viral reactivation
		  • Sepsis
		• Iron overload

Ferrara JLM, et al. *Lancet*. 2009;373(9674):1550-1561; Dignan FL, et al. *Br J Haematol*. 2012;158(1):30-45.

aGVHD Grading and Staging

- Severity staged in each organ system involved and then combined to assign an overall GVHD grade
  - Modified Glucksberg criteria most common
- Limitations with current grading systems as no system demonstrates superiority over the other

Stage	Skin (rash)	Liver (total bilirubin)	Gut (stool output)
0	None	<2 mg/dL	<500 mL/day
1	<25% BSA	2-3 mg/dL	500-999 mL/day
2	25%-50% BSA	3.1-6 mg/dL	1000-1500 mL/day
3	>50% BSA	6.1-15 mg/dL	>1500 mL/day
4	Generalized erythroderma + bullae or desquamation	>15 mg/dL	Severe abdominal pain +/- ileus or grossly bloody diarrhea

Overall clinical grade

Grade 1: Stage 1-2 skin, no liver or gut involvement
Grade 2: Stage 3 skin and/or stage 1 liver and/or stage 1 gut
Grade 3: Stage 1-3 skin and stage 2-3 liver and/or stage 2-4 gut
Grade 4: Stage 4 skin and/or stage 4 liver

Martino R, et al. *Bone Marrow Transplant*. 1999;24(3):283-287; Przepiorka D, et al. *Bone Marrow Transplant*. 1995;15(6):835-838; Zeiser R, et al. *N Engl J Med*. 2017;377(1):2167-2179.

BSA, body surface area.

Minnesota aGVHD Risk Score

- Developed to help better predict response to therapy, survival, and transplant-related mortality (TRM)

Risk score	1 organ	2 organs	3 organs
Standard	• Stage 1-3 skin • Stage 1-2 gut	• Stage 1-3 skin + stage 1 gut • Stage 1-3 skin + stage 1-4 liver	N/A
High	• Stage 4 skin • Stage 3-4 gut • Stage 1-4 liver	• Stage 1-3 skin + stage 2 gut • Stage 1-2 lower gut + stage 1-3 liver • Stage 1-3 skin + stage 3-4 gut • Stage 3-4 gut + stage 1-4 liver	• Stage 1-3 skin + stage 1-2 gut + stage 1-3 liver • Stage 1-3 skin + stage 3-4 gut + stage 1-4 liver

- Patients with high-risk aGVHD:
  - Less likely to respond to corticosteroid treatment
  - 2-fold higher TRM risk than those with standard risk

MacMillan ML, et al. *Biol Blood Marrow Transplant*. 2015;21(4):761-767; MacMillan ML, et al. *Biol Blood Marrow Transplant*. 2020;105:519-24.

Use of Biomarkers in aGVHD

- Routine biomarker testing could allow for tailored prophylaxis, treatment approaches, and improved grading systems
- Biomarkers have the potential to predict:
  - Those at higher risk of aGVHD
  - Likelihood of response to front-line therapy
  - Risk of death from aGVHD
- Biomarkers showing promise in clinical trials:
  - **Suppressor of tumorigenicity 2 (ST2)**
  - **Regenerating islet-derived protein 3α (REG3 α)**
  - Tumor necrosis factor-α receptor type 1 (TNFR1)
  - Interleukin-2α (IL-2)

Hartwell MJ, et al. *JCI Insight*. 2017;2(3):e89798.; Srinagesh HK, et al. Blood Adv. 2019;3:4034-42.

Biomarkers in aGVHD Grading: Ann Arbor Score

- What does the Ann Arbor score tell us?
  - Response to treatment
    - Patients with Ann Arbor 1: more likely to respond to front-line corticosteroid therapy and achieve a durable response
    - Patients with Ann Arbor 3: twice as likely to develop steroid-refractory (SR) aGVHD as compared with Ann Arbor 1
  - Outcomes
    - Patients with Ann Arbor 3 at diagnosis of aGVHD: twice as likely to develop gut aGVHD than those with Ann Arbor 1
    - Patients with Ann Arbor 3 have a higher risk of TRM

Levine JE, et al. *Lancet Haematol*. 2015;2(1):e21-e29; Major-Monfried H, et al. *Blood*. 2018;131(25):2846-2855; Srinagesh HK, et al. *Blood Adv*. 2019;3(23):4034-4042.

Biomarkers in aGVHD: Putting It All Together

Response	Minnesota risk score	Biomarker value	Positive predictive value of biomarkers for predicting 1-year no-relapse mortality
Present	Standard	Low	0.06
		High	0.29
Absent	Standard	Low	0.12
		High	0.46
	High	Low	0.22
		High	0.84

Major-Monfried H, et al. *Blood*. 2018;131(25):2846-2855.

aGVHD: Prevention and Treatment

aGVHD Prevention: Historical Approach

- Calcineurin inhibitor (CNI): tacrolimus, cyclosporine

PLUS 1 of the following:

- Methotrexate (MTX)
- Mycophenolate mofetil (MMF)
- Sirolimus
- Antithymocyte globulin (ATG)

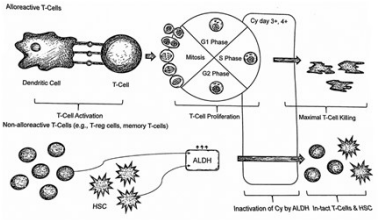
- Choice dictated by underlying disease, degree of HLA mismatch, and conditioning regimen intensity
  - Unrelated/HLA-mismatched donor: ATG for T-cell depletion
  - Myeloablative conditioning: CNI + MTX
  - Reduced intensity conditioning: CNI + MMF or low-dose/mini MTX

Ruutu T, et al. *Bone Marrow Transplant*. 2014;49(2):168-173; Khoury HJ, et al. *Haematologica*. 2017;102(5):958-966.

The Era of Posttransplant Cyclophosphamide (PTCy)

Cyclophosphamide

- Nitrogen mustard alkylating agent
- Potent immunosuppressive effects
- Able to successfully induce immune tolerance in haploidentical transplantation



ALDH, aldehyde dehygrogenase; HSC, hematopoietic stem cells.

Fuchs EJ. *Biol Blood Marrow Transplant*. 2015;50(2):531-36.; Kanakry CG, et al. *Sci Transl Med*. 2013;5(211):211ra157;
Figure republished from Patel DA, et al. *Hematol Oncol Stem Cell Ther*. 2020;13(2):91-97, under the terms of Elsevier's COVID-19 resource center.

PTCy in Haploidentical HSCT

Study	GVHD prophylaxis	Patients	Grade 2-4 aGVHD	Chronic GVHD (cGVHD)	Overall survival (OS)
Brustein CG, et al	PTCy 50 mg/kg days +3/4 + FK + MMF	n = 50 BM	32%	13%	84%
Castagna L, et al	PTCy 50 mg/kg days +3/4 + FK + MMF	n = 69 46 BM, 23 PB	25% (BM) vs 33% (PB) *P* = NS	13%	68%
Kanate AS, et al	PTCy 50 mg/kg days +3/4 + FK + MMF	n = 185 Haploidentical	27%	13%	60%
	CNI ± ATG	491 MUD (+ATG) 241 MUD (-ATG)	49% 40% *P* = NS	33% 51% *P* <0.0001	50% 62% *P* = NS at 3 years

BM, bone marrow; FK, tacrolimus; NS, nonsignificant; PB, peripheral blood.

Brustein CG, et al. *Blood*. 2011;118(2):282-288; Castagna L, et al. *Biol Blood Marrow Transplant*. 2014;20(5):724-729; Kanate AS, et al. *Blood*. 2016;127(7):938-947.

Taking PTCy Beyond Haploidentical HSCT

- Success in haploidentical HSCT fueled PTCy studies
  - Matched related donor (MRD)
  - MUD HSCT
  - Goal: to improve incidence of GVHD and reduce overall immunosuppression use
- Potential for CNI-free GVHD regimens
  - Improved immune reconstitution and GVL effects
  - Decreased toxicity
  - Decreased monitoring and drug interaction issues

Al-Homsi AS, et al. *Biol Blood Marrow Transplant*. 2015;21(4):604-611.

PTCy in MRD and MUD HSCT

Study	Conditioning	Patients	GVHD PPX	aGVHD, day +100	cGVHD, 2 y	NRM, 2 y	Relapse, 2 y	OS, 2 y
Luznik L, et al. *Blood*. 2010;155(16):3224-3230.	BuCy (MAC)	n = 117, MRD/MUD BM	PTCy	2-4: 43% 3-4: 10%	10%	17%	44%	55%
Kanakry CG, et al. *J Clin Oncol*. 2014;32(31):2497-3505.	BuFlu (MAC)	n = 92, MRD/MUD BM	PTCy	2-4: 51% 3-4: 15%	14%	16% (1 y)	22%	67%
Moiseev IS, et al. *Biol Blood Marrow Transplant*. 2016;22(6):1037-1042.	BuCy/BuFlu (MAC)	n = 86, MUD/MMUD PB	PTCy + FK/MMF	2-4: 19% 3-4: 4%	16% (1 y)	16%	19%	69%
Carneval-Schianca F, et al. *Biol Blood Marrow Transplant*. 2017;23(3):459-466.	Variety (MAC/RIC)	n = 35, MRD/MUD/ MMUD PB	PTCy + FK/MMF	2-4: 12% 3-4: 0%	7%	3%	46%	77%

Bu, busulfan; BM, bone marrow; FK, tacrolimus; Flu, fludarabine; MAC, myeloablative conditioning; MMUD, mismatched unrelated donor; PB, peripheral blood; PPX, prophylaxis; RIC, reduced intensity conditioning.

PTCy in MRD and MUD HSCT

European Society for Blood and Marrow Transplantation Registry Study

- Patients with AML or ALL undergoing MRD or MUD allogeneic HSCT from 2007-2015 at 150 centers
- PTCy-based GVHD prophylaxis (n = 423)
  - **Group 1:** PTCy single agent (n=78)
  - **Group 2:** PTCy + 1 additional IST: CSA, MTX, MMF (n = 204)
  - **Group 3:** PTCy + 2 additional IST: CSA + MTX, CSA + MMF (n = 141)
  - 143 patients across the study also received ATG with PTCy

CSA, cyclosporine; IST, immunosuppressive therapy.

Ruggeri A, et al. *J Hematol Oncol*. 2018;11(1):40.

PTCy in MRD and MUD HSCT

Outcomes at median follow-up of 20 months	Group 1 (PTCy alone)	Group 2 (PTCy + 1 IST)	Group 3 (PTCy + 2 IST)	*P* value
aGVHD (grade 2-4), day +100	27.9% (cumulative incidence)			NS
cGVHD, 1 year	31%	34%	33%	0.92
Relapse, 2 year	32%	36%	28%	0.47
NRM, 2 year	19%	20%	14%	0.47
Leukemia-free survival, 2 year	49%	43%	57%	0.08
GVHD-free, relapse-free survival, 2 year	24%	28%	44%	<0.001
OS, 2 year	50%	52%	62%	0.06

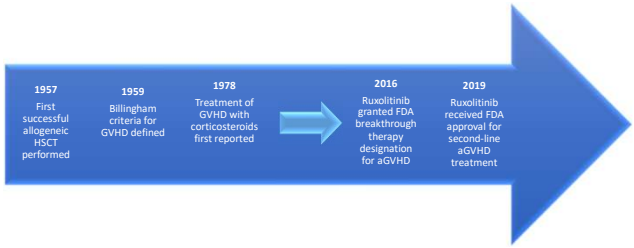
Ruggeri A, et al. *J Hematol Oncol*. 2018;11(1):40.

Taking PTCy Beyond Haploidentical HSCT: Where Do We Stand?

PTCy single agent		PTCy + additional IST
BM source	PB source	
• **Acceptable** aGVHD rates • **Low** chronic GVHD rates • **Mixed** TRM results	• Increased aGVHD rates • Increased TRM	• **Acceptable** aGVHD rates • **Low** cGVHD rates • Preferred in myeloablative regimens and PB source • Some improved outcomes with PTCy + 2 IST

Conclusion: Use of PTCy is associated with a positive impact on incidence of aGVHD and cGVHD, although results vary based on stem cell source and additional immunosuppression.

Evolution of aGVHD Treatment



Thomas ED. *Br J Haematol*. 1999;105(2):330-339; Martin PI. *Blood*. 2020;135(19):1630-1638; Jakafi. Prescribing information. Incyte Corporation; January 2020.

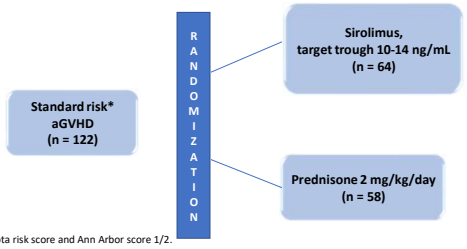
Front-Line Treatment: Corticosteroids

- **Topical steroids** for low grade (1-2) GVHD
  - Skin: triamcinolone and/or hydrocortisone creams
  - GI: beclomethasone 1 mg PO QID (upper GI) and/or budesonide 3 mg PO BID-TID (lower GI)
- **High-dose systemic corticosteroids:** prednisone, methylprednisolone equivalent
  - Recommended in high grade (3-4) or grade 2 GVHD refractory to topicals
    - IV therapy usually preferred for initial treatment of GI and liver GVHD
  - More likely to require second-line therapy and more frequent progression to grade 3 or 4 GVHD if treated initially with prednisone 1 mg/kg/day
  - **Grade 1-2 skin and upper GI**: prednisone 0.5 mg/kg/day
  - **Grade ≥3 skin or grade ≥2 GI/liver**: prednisone 2 mg/kg/day
    - **Taper** after 5-10 days of therapy, **regardless of response**
      - No standard taper schedule, usually ≈10%-20% decrease every 3-7 days

IV, intravenous.

Hockenbery DM, et al. *Blood*. 2007;109(10):4557-4563; Martin PI, et al. *Biol Blood Marrow Transplant*. 2012;18(8):1150-1163; Mielcarek M, et al. *Haematologica*. 2015:100(6);842-848; Fraira C, et al. *Biol Blood Marrow Transplant*. 2020;26(7):1303-1311.

Challenging the Steroid Standard: BMT CTN 1501



*Per Minnesota risk score and Ann Arbor score 1/2.

Pidala J, et al. *Blood*. 2020;135(2):97-107.

BMT CTN 1501 Results

	Day 28				Day 56	
	Prednisone	Sirolimus	Prednisone ≤0.25 mg/kg	Sirolimus	Prednisone	Sirolimus
CR (%)	62	56	30	57	76	57
PR (%)	11	9	<8	9	<8	8
Treatment failure (%)	27	35	68	33	21	36
***P* value**	0.68		<0.01		0.07	

- Higher rate of thrombotic microangiopathy with sirolimus (10.3% vs 1.6%)
- Lower rate of hyperglycemia with sirolimus
- No difference in incidence of serious infection between groups
  - Higher rate of CMV reactivation requiring treatment with sirolimus (9.1% vs 2.2%)

CMV, cytomegalovirus.

Pidala J, et al. *Blood*. 2020;135(2):97-107.

Response to Front-Line Treatment

- Fewer than 50% of patients treated with steroids will achieve a complete response, and second-line therapy is often required
  - Severe aGVHD is also less likely to respond to steroid treatment
  - 6-month survival is 49% in patients with steroid-refractory (SR) aGVHD
- Toxicity of steroids limit long-term use, even in patients responding
- Definitions:
  - SR: progression of GVHD symptoms within first 72 hours of treatment, lack of response after 5-7 days of treatment, or incomplete response after 14 days of treatment
  - Steroid-dependent (SD): inability to taper steroids below a certain threshold dose without provoking a GVHD flare

Martin PI, et al. *Biol Blood Marrow Transplant*. 2012;18(8):1150-1163; Dignan FL, et al. *Br J Haematol*. 2014;158(1):30-45.

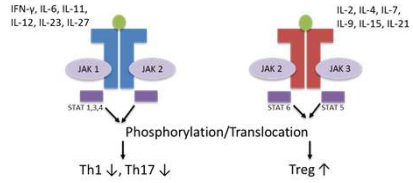
Second-Line Treatment Options

Treatment	Mechanism of action	Response rate, organ(s) likely to respond	Toxicity
α$_1$-antitrypsin	Protease inhibitor	30%-65%, all	Limited
Alemtuzumab	Anti-CD52 mAb	50%-94%, gut/liver	Infusion reactions, infection
ATG	Depletion of T-cells	19%-57%, skin	Infusion reactions, infection
Basiliximab	Anti-CD25 mAb	70%-83%, gut	Hypersensitivity reactions, infection
Etanercept	Anti-TNFα	46%, gut	Infection
ECP	Leukocyte apoptosis	67%-75%, skin/liver	Limited, catheter-related blood stream infections
Infliximab	Anti-TNF	40%-67%, skin/gut	Infection
MMF	Inhibits B/T-lymphocytes	31%-60%, gut	N/V, diarrhea, myelosuppression
Pentostatin	Purine analog	77%-83%, skin/gut	Myelosuppression, infection, hepatotoxicity
Ruxolitinib	JAK-2 inhibitor	40%-80%, skin/gut	Myelosuppression, hepatotoxicity
Sirolimus	mTOR inhibitor	57%-91%, gut/liver	Dyslipidemia, TMA, hepatotoxicity
Tocilizumab	Anti-IL-6 mAb	44%-67%, all	Infusion reactions, hepatotoxicity, infection

N/V, nausea/vomiting; TMA, thrombotic microangiopathy.

Pidala J, et al. *Biol Blood Marrow Transplant*. 2010;16(11):1504-1518; Martin PJ, et al. *Biol Blood Marrow Transplant*. 2012;18(8):1150-1163; Martin PJ. *Blood*. 2020;135(19):1630-1538; Kekre N, Antin JH. *Expert Opin Emerg Drugs*. 2016;21(2):209-218.

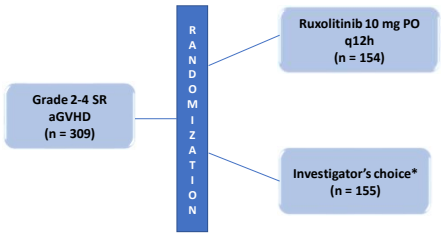
The Role of Janus Associated Kinase (JAK) in GVHD



IFN, interferon; IL, interleukin; Th, helper T-cell; Treg, regulatory T-cell.

Spoerl S, et al. *Blood*. 2014;123(24):3832-3842; Teshima T. *Blood*. 2014;123(24):3691-3693.

REACH2: Ruxolitinib for SR aGVHD



*Investigator's choice:
- Low-dose MTX
- ECP
- ATG
- MMF
- Mesenchymal stromal cells
- Sirolimus or everolimus
- Etanercept
- Infliximab

Zeiser R, et al. *N Engl J Med*. 2020;382(19):1800-1810.

REACH2 Outcomes

Outcome	Ruxolitinib (n = 154)	Control (n = 155)	*P* value/hazard ratio
PR (%)	27.9	20	NR
CR (%)	34.4	19.4	NR
Overall response at day 28 (%)	62.3	39.4	<0.001
Failure-free survival, median	5 months	1 month	0.46; 95% CI, 0.35-0.60
OS, median	11.1 months	6.5 months	0.83; 95% CI, 0.60-1.15

Zeiser R, et al. *N Engl J Med*. 2020;382(19):1800-1810.

REACH2: Adverse Effects

	Ruxolitinib		Control	
Adverse effect	Any grade	Grade ≥3	Any grade	Grade ≥3
Thrombocytopenia	50 (33%)	41 (27%)	27 (18%)	23 (15%)
Anemia	46 (30%)	33 (22%)	42 (28%)	28 (19%)
CMV infection	39 (26%)	11 (7%)	31 (21%)	12 (8%)
Peripheral edema	28 (18%)	2 (1%)	26 (17%)	1 (1%)
Neutropenia	24 (16%)	20 (13%)	19 (13%)	14 (9%)
Hypokalemia	20 (13%)	9 (6%)	25 (17%)	9 (6%)

Adverse effects led to treatment discontinuation in 11% of patients treated with ruxolitinib, compared with 5% with control.

Zeiser R, et al. *N Engl J Med*. 2020;382(19):1800-1810.

Ruxolitinib Dosing

- Initial dose: 5 mg orally twice daily, titrated up to a maximum of 10 mg twice daily
  - Recommend taper by 1 dose level (≈5 mg) every 8 weeks in patients responding after 6 months of therapy
- Only available as oral tablet, but can be crushed and mixed with water for administration

Dose adjustments	
ANC <1000 cells/mm^3	Interrupt treatment for up to 14 days, then resume at 1 dose level lower (≈5 mg) when ANC recovers
Clinically significant/refractory thrombocytopenia	Reduce by 1 dose level; when platelets recover, may increase back to prior dose level
Concomitant CYP3A4 inhibitor administration	Consider dose adjustment; recommend usual starting dose and adjusting dose if toxicity occurs

Jakafi. Prescribing information. Incyte Corporation; January 2020; Jagasia M, et al. *Blood*. 2020;135(20):1739-1749.

Future Directions: Gut Microbiome and aGVHD

- Intestinal microbiota influences regulatory T-cells, Th17, and cytokine production
- Gut microbiome + development of aGVHD
  - Loss of intestinal microbiota diversity associated with increased aGVHD incidence
  - Potential use of microbiota constitution at neutrophil engraftment as a predictive biomarker for aGVHD development and severity
- Interventions to improve the gut microbiome and prevent/treat aGVHD
  - **Reduce broad-spectrum antibiotic exposure**
  - Probiotics
    - Few strains tested, unknown which are responsible for modulating aGVHD
    - Safety concerns: infection, possible transfer of drug resistance from probiotic bacteria strains to native strains
  - Fecal microbiota transplant
    - Some small promising trials to-date in treating SR aGVHD

Poutsiaka DD, et al. *Clin Infect Dis*. 2015;61:358-60.; Bilinski J, et al. *Blood*. 2019;134(51):5667.; Han L, et al. *Biol Blood Marrow Transplant*. 2019;25(10):1944-55.; van Lier YF, et al. *Biol Blood Marrow Transplant*. 2020;25(3)S241; Image: https://www.genengnews.com/news/novel-approach-can-determine-the-sources-of-the-guts-microbiome/

aGVHD: Supportive Care Considerations

GVHD Prophylaxis Management Pearls

Drug	Toxicity	Drug interactions	Monitoring
Cyclosporine	Neurotoxicity, nephrotoxicity, hypertension, hypomagnesemia, hyperkalemia, dyslipidemia, hirsutism, gingival hyperplasia, TMA, PRES	CYP3A4, P-glycoprotein, OATP1B1	Trough level 150-450 ng/mL
Tacrolimus	Neurotoxicity, nephrotoxicity, hypertension, hypomagnesemia, hyperkalemia, dyslipidemia, TMA, PRES	CYP3A4, P-glycoprotein	Trough level 5-20 ng/mL (5-10 ng/mL with sirolimus due to TMA)
Sirolimus	Dyslipidemia, hypertension, hyperglycemia, rash, stomatitis, hepatotoxicity, TMA	CYP3A4, P-glycoprotein	Trough level 3-12 ng/mL
MTX	Mucositis, hepatotoxicity, myelosuppression	OATP1B1, P-glycoprotein	Reduce dose or hold in renal or hepatic dysfunction, fluid collections or third spacing, and severe mucositis
Mycophenolate	N/V, diarrhea, myelosuppression	OATP1B1	Not routinely recommended, limited data

PRES, posterior reversible encephalopathy syndrome.

Chao NJ, Sullivan KM. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantion,* 5th edition. John Wiley & Sons; 2016. Accessed August 10, 2020. doi: 10.1002/9781118416426; Glotzbecker B, et al. *Biol Blood Marrow Transplant*. 2012;18(7):989-1006.

GVHD Prophylaxis: PTCy

- Traditional adverse effects of cyclophosphamide:
  - N/V (delayed), cardiotoxicity, hemorrhagic cystitis
- Additional PTCy-associated adverse effects:
  - Infections (viral), delayed engraftment, syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Cytokine release syndrome

Toxicity	Management pearls
N/V	• Steroid premedication should be avoided; may affect PTCy efficacy • 5-HT_3 antagonist + NK-1 antagonist + olanzapine recommended
Cytokine release syndrome	• Occurs between day 0 and day +5, usually mild • More frequent in haploidentical HSCT (77% vs 18%) • Supportive care: fluids, antipyretics, antibiotics if neutropenic • Refractory or severe cases: consider tocilizumab
Cardiotoxicity	• Cardiomyopathy and arrhythmias more common during periods of infection/neutropenic fever • Age and diabetes increase risk

Andersson B, et al. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantion,* 5th edition, John Wiley & Sons; 2016. Accessed August 10, 2020. doi: 10.1002/9781118416426

GVHD Treatment: Corticosteroid Toxicity

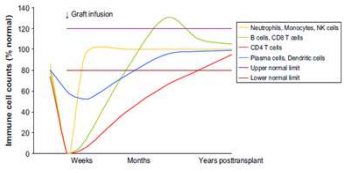
Short-term use	Long-term use
Hyperglycemia	Muscle atrophy
Hypertension	Bone mineral density loss and osteonecrosis
Psychological disturbances (eg, insomnia, agitation/mood swings, psychosis)	HPA axis suppression/adrenal insufficiency
Increased appetite	Increased ocular pressure, glaucoma, and cataracts
Fluid retention	Cushing syndrome (eg, weight gain/fatty deposits around face, upper back, and midsection, thinning skin, muscle wasting, fatigue, cognitive difficulties/depression, menstrual irregularity, hirsutism, acne)
Infection risk (particularly fungal, viral, and opportunistic infections)	
Impaired wound healing	
GI bleeding/ulcers	

Schäcke H, et al. *Pharmacol Ther*. 2002;96:23-43.

HPA, hypothalamic-pituitary-adrenal axis.

Infection Prophylaxis

- aGVHD and immunosuppressive agents used in treatment cause immune dysregulation, delayed immune reconstitution, and increased infection risk
- Patients with aGVHD have been shown to develop ≈60% more infections than those who never develop aGVHD
  - 2-fold higher risk of life-threatening and fatal infections



Miller HK, et al. *Biol Blood Marrow Transplant*. 2017;23(3):522-528.
Figure republished from Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238, under the terms of Elsevier's COVID-19 resource center.

Infection Prophylaxis for Patients With aGVHD

Infection type	Management
Bacterial infections	• Penicillin prophylaxis due to functional asplenia • Fluoroquinolone prophylaxis considered in patients on high-dose corticosteroids with aGVHD of the gut due to risk of bacterial translocation
Fungal infections	• Mold prophylaxis should be given to patients receiving high-dose corticosteroids
Viral infections	• Increased risk with high-dose corticosteroids, PTCy, ATG, ruxolitinib • Letermovir for CMV prophylaxis should be given to patients who are CMV-positive • Routine CMV and EBV surveillance • Symptom-driven monitoring for other viral pathogens
Opportunistic infections	• PJP prophylaxis should be given to patients on high-dose steroids • Symptom-driven monitoring of other pathogens

EBV, Epstein-Barr virus; PJP, *Pneumocystis jirovecii* pneumonia.

Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238;
Ullmann AJ, et al. *Ann Hematol*. 2016;95(9):1435-1455; Marty FM, et al. *N Engl J Med*. 2017;377(25):2433-2444.

Conclusions

- aGVHD is a leading cause of NRM after HSCT
- Novel grading systems for aGVHD are used in practice to better inform front-line treatment decisions
- Corticosteroids remain the mainstay of front-line treatment for aGVHD but cause significant toxicity
- Approximately 50% of patients with aGVHD will become SR or SD
- Several agents are available for second-line treatment of SR/SD aGVHD, with no single agent superior to another
- Pharmacists can assist in treatment decisions for aGVHD, as well as an infection prophylaxis

Additional Resources

National Marrow Donor Program	bethematchclinical.org/resources-and-education/education-courses-and-events/curriculum/curriculum-modules-and-videos/
Acute graft-versus-host disease: biologic process, prevention, and therapy	Zeiser R, Blazar BR. *N Engl J Med*. 2017;377(22):2167-2179. doi: 10.1056/NEJMra1609337
Graft-versus-host disease	Ferrara JLM, et al. *Lancet*. 2009;373(9674):1550-1561. doi: 10.1016/S0140-6736(09)60237-3
How I treat steroid-refractory acute graft-versus-host disease	Martin PJ. *Blood*. 2020;135(19):1630-1638. doi: 10.1182/blood.2019000960
EBMT-NIH-CIBMTR Task Force Position Statement on Standardized Terminology & Guidance for Graft-Versus-Host Disease Assessment	Schoemans HM, et al. *Bone Marrow Transplant*. 2018;53(11):1401-1415. doi: 10.1038/s41409-018-0204-7

The Relationship Between Anemia and Cancer: Opportunities for Pharmacists to Improve Patient Outcomes

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PTce

Educational Objectives

After completion of this activity, participants will be able to:

- Outline the prevalence of cancer-related anemia and iron deficiency anemia as well as the associated complications for patients with cancer
- Review evidence-based treatment recommendations for the management of anemia in patients with cancer
- Recognize the treatments to ensure safe and appropriate management of anemia in patients with cancer
- Describe the pharmacist's role in improving clinical outcomes for patients with cancer-related anemia

The Relationship Between Anemia and Cancer

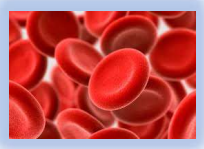
Prevalence

- 30%-90% of patients with cancer
  - Different cutoff values (9 g/dL vs 11 g/dL)
  - Type of cancer: hematological > solid
  - Stage of cancer
  - Age, gender (M 77%, F 68%)
  - Type of treatment

Madeddu C, et al. *Front Physiol.* 2018;9:1294; Knight K, et al. *Am J Med.* 2004;116(suppl 7A):115-265; Busti F, et al. *Pharmaceuticals (Basel).* 2018;11(4):94.

Symptoms

- Fatigue
- Impaired mental capacity, lethargy, confusion
- Nausea, loss of appetite, dyspnea, syncope



Madeddu C, et al. *Front Physiol.* 2018;9:1294; Knight K, et al. *Am J Med.* 2004;116(suppl 7A):115-265; Busti F, et al. *Pharmaceuticals (Basel).* 2018;11(4):94.

Clinical Significance

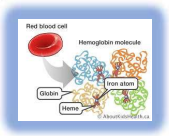
- Decline in PS and QOL
- Negative prognostic factor for disease progression
- Poor survival outcomes
- Increased risk of mortality
  - Caro et al (2001): meta-analysis (60 trials)
    - 65% overall increase in mortality in patients with cancer with anemia vs without anemia
    - 19% lung, 65% lymphoma, 75% head and neck carcinoma
- Decreased efficacy of chemotherapy/radiation
  - Poor local tumor control

PS, performance status; QOL, quality of life.

Madeddu C, et al. *Front Physiol.* 2018;9:1294; Caro JJ, et al. *Cancer.* 2001;91(12):2214–2221.

What Is Anemia?

- Clinical diagnosis of decreased erythrocyte mass with decreased hemoglobin (Hgb) and hematocrit (Hct) counts
- WHO defines it as Hgb <11.9 g/dL in women and <12.9 g/dL in men
- NCCN: Hgb <11 or Hgb decrease >2 g/dL below baseline
- NCI grading (g/dL)
  - Mild: 10 to lower normal
  - Moderate: 8-9.9
  - Severe: 6.5-7.9
  - Life threatening: <6.5



Madeddu C, et al. *Front Physiol*. 2018;9:1294; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

Cancer-related Anemia

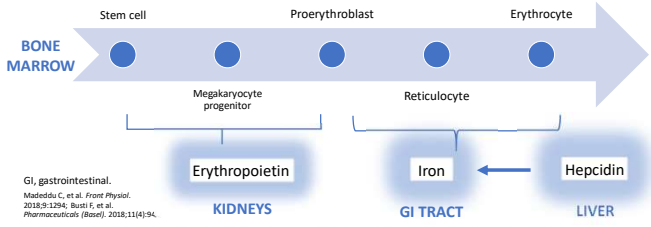
- **Chronic inflammation**
- Impaired hematopoiesis
- Reduction of erythropoietin (EPO)
- Hemolysis
- Blood loss
- Nutritional deficiency
- Hormone dysfunction

Treatment-related Anemia

- Chemotherapy
- Radiation

Madeddu C, et al. *Front Physiol*. 2018;9:1294; Busti F, et al. *Pharmaceuticals (Basel)*. 2018;11(4):94; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

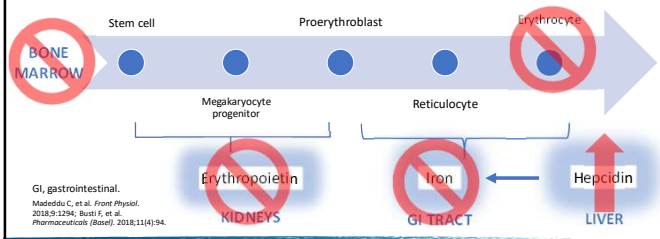
Back to the Basics



GI, gastrointestinal.

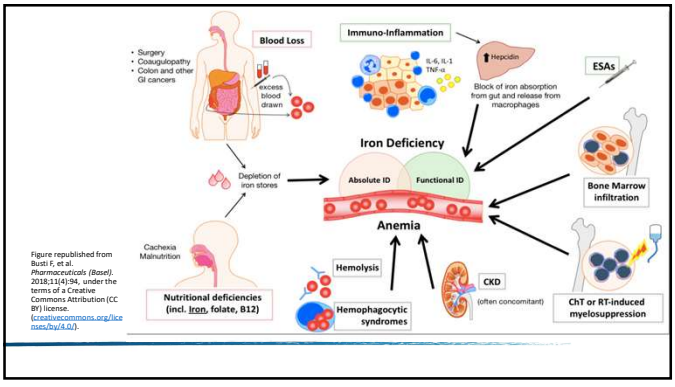
Madeddu C, et al. *Front Physiol*. 2018;9:1294; Busti F, et al. *Pharmaceuticals (Basel)*. 2018;11(4):94.

Back to the Basics



GI, gastrointestinal.

Madeddu C, et al. *Front Physiol*. 2018;9:1294; Busti F, et al. *Pharmaceuticals (Basel)*. 2018;11(4):94.



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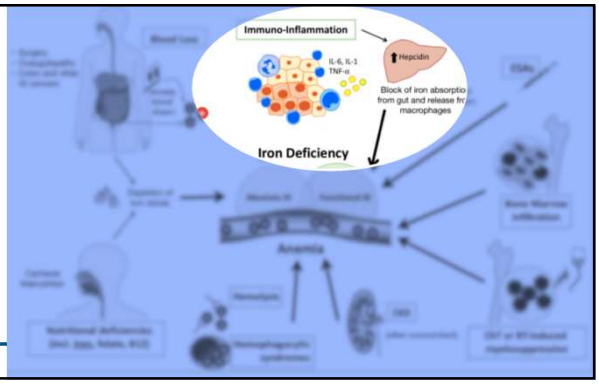

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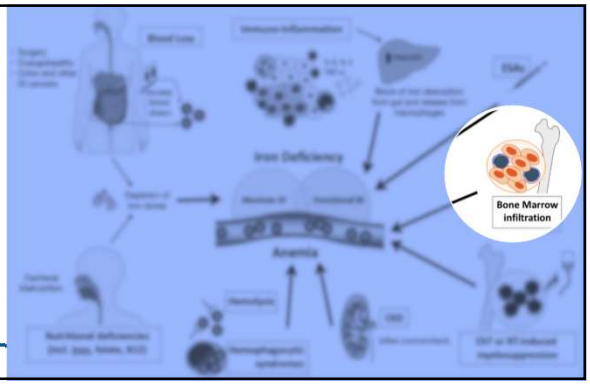


Figure republished from Busti F, et al. *Pharmaceuticals (Basel).* 2018;11(4):94, under the terms of a Creative Commons Attribution (CC BY) license. (creativecommons.org/licenses/by/4.0/).

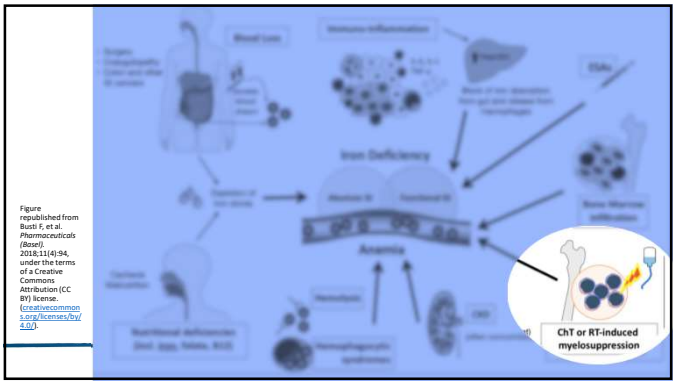


Figure republished from Busti F, et al. *Pharmaceuticals (Basel).* 2018;11(4):94, under the terms of a Creative Commons Attribution (CC BY) license. (creativecommons.org/licenses/by/4.0/).

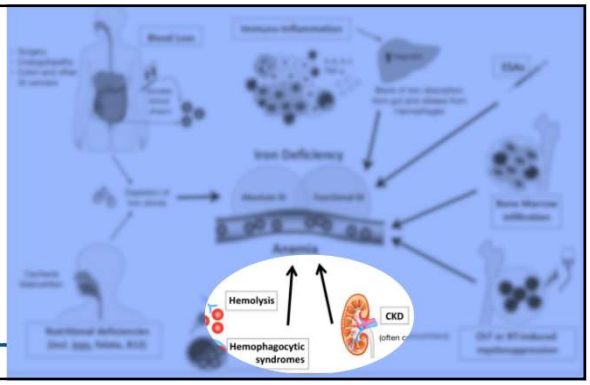


Figure republished from Busti F, et al. *Pharmaceuticals (Basel).* 2018;11(4):94, under the terms of a Creative Commons Attribution (CC BY) license. (creativecommons.org/licenses/by/4.0/).

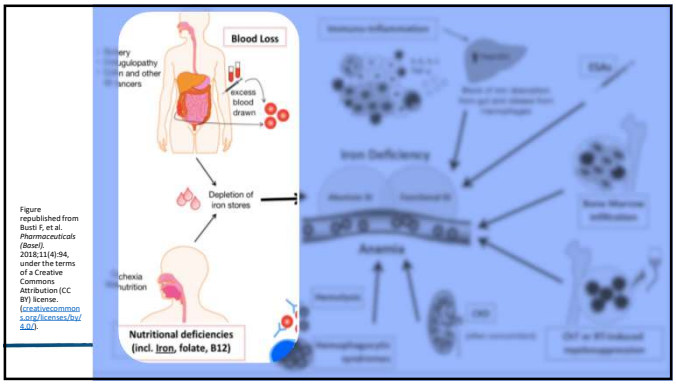


Figure republished from Busti F, et al. *Pharmaceuticals (Basel).* 2018;11(4):94, under the terms of a Creative Commons Attribution (CC BY) license. (creativecommons.org/licenses/by/4.0/).

Lab Work-up

- CBC
  - **Hgb**
  - Hct
- Iron studies
  - Total iron binding capacity (TIBC)
  - Serum iron
  - **Transferrin saturation (TSAT) %** $(serum\ iron/TIBC) * 100$
  - **Serum ferritin**

- Nutritional – vitamin B_{12} levels, folate
- Reticulocyte count
- Mean corpuscular volume
- Disseminated intravascular coagulation panel, haptogloblin, lactate dehydrogenase, total bilirubin
- C-reactive protein and erythrocyte sedimentation rate

Gilreath J, Rodgers G. *Blood.* 2020;136(7):801-813; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

Absolute iron deficiency

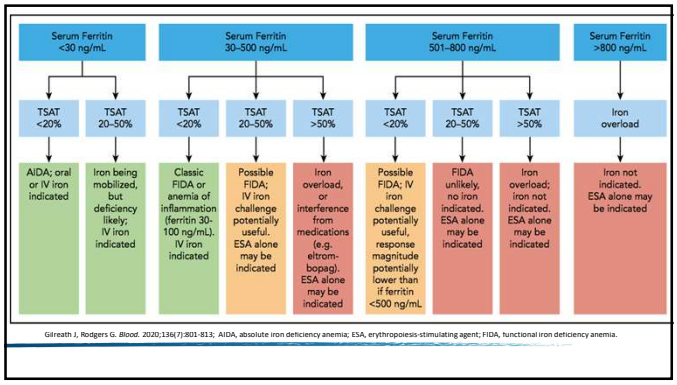
- Low iron stores
- ↓ Hgb, ↓ ferritin ↓ TSAT
- Nutritional deficiencies
- Malabsorption
- Blood loss

Reference values:
Ferritin: 30-500 ng/mL
TSAT: 20%-50%

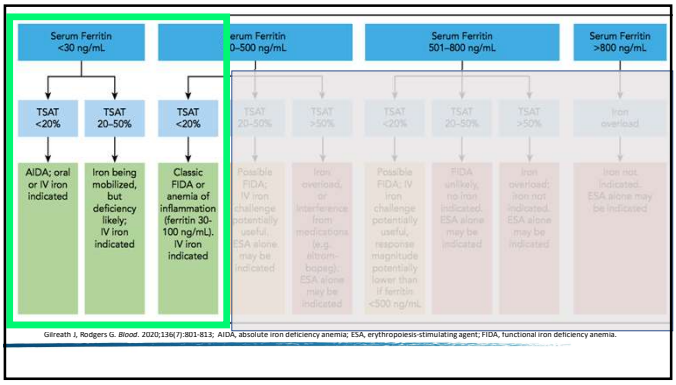
Functional iron deficiency

- Adequate iron store
- ↓ Hgb, normal ferritin ↓ TSAT
- Proinflammatory cytokines
- Hepcidin mediated

Madeddu C, et al. *Front Physiol.* 2018;9:1294; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.



Gilreath J, Rodgers G. *Blood.* 2020;136(7):801-813; AIDA, absolute iron deficiency anemia; ESA, erythropoiesis-stimulating agent; FIDA, functional iron deficiency anemia.



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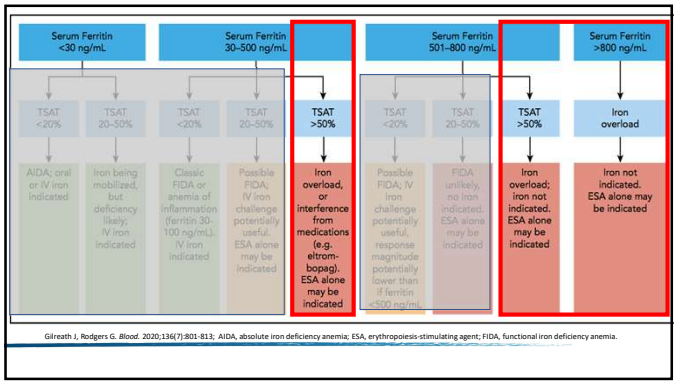
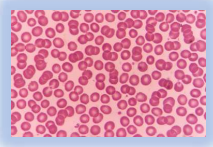


Gilreath J, Rodgers G. *Blood.* 2020;136(7):801-813; AIDA, absolute iron deficiency anemia; ESA, erythropoiesis-stimulating agent; FIDA, functional iron deficiency anemia.

Management of Anemia

- Transfusions
- Erythropoiesis-stimulating agents (ESAs)
- Iron supplementation
  - Oral
  - IV



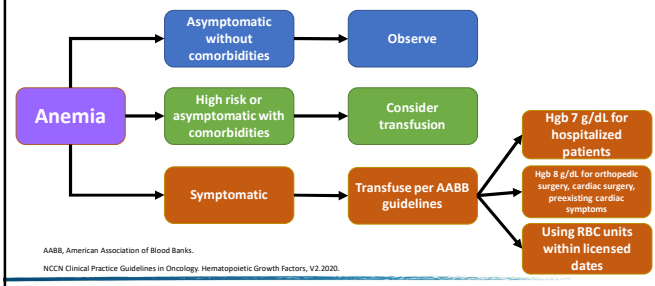
NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

Transfusions

- Packed red blood cells (PRBC)
- Goal of therapy: rapid and effective increase in levels
- Transfusion-related reactions
- Iron or volume overload
- Pathogen transmission
- Alloimmunization
- Cancer recurrence and decreased survival

Gilreath J, Rodgers G. *Blood.* 2020;136(7):801-813; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020; Iqbal N, et al. *Transfus Apheresis Sci.* 2017;56(3):287-290.

Transfusions



AABB, American Association of Blood Banks.

NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

Erythropoiesis-Stimulating Agents (ESAs)

- Recombinant human EPO
  - Initially approved in 1989 for CKD, 1993 for cancer
- REMS mandate issued in 2010 and ended in 2017
- Indicated for chemotherapy-induced anemia, not cancer-induced anemia

CKD, chronic kidney disease; REMS, Risk Evaluation and Mitigation Strategy.

Madeddu C, et al. *Front Physiol.* 2018;9:1294; Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

	Epoetin α (Procrit, Epogen) Epoetin α-epbx (Retacrit)	Darbapoetin α (Aranesp)
Route	SC/IV	SC/IV
Pharmacokinetics	$T_{1/2}$ (SC) 16-67 h	24-144 h
Pharmacodynamics	Reticulocyte count: 10 d RBC, Hgb/Hct: 2-6 wk	Hgb: 2-6 wk
Initial dosing	150 units/kg SC TIW ***OR*** 40,000 units SC weekly	2.25 ug/kg SC weekly ***OR*** 500 ug/SC 3 wk
Alternate dosing	80,000 units SC 2 wk 120,000 units SC 3 wk	100 ug SC weekly 200 ug SC 2 wk 300-500 ug SC 3 wk
Dose increase	If Hgb increases <1 g/dL and remains below 10 g/dL after 4 wk	If Hgb increases <1 g/dL and remains below 10 g/dL after 6 wk
Dose reduction	Decrease dose by 25%	Decrease dose by 40%
	Hgb reaches a level needed to avoid transfusion or Hgb >1 g/dL in 2 wk	
Discontinue	Following discontinuation of chemo or if no response after 8 wk of therapy	

Epogen. Prescribing information. Amgen Inc; 2018; Aranesp. Prescribing information. Amgen Inc; 2019; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020; Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351.

ESAs: Mortality

Glasby et al (2010): No effect
- 60 trials (N = 15,323)
- From 1993-2008
- Epoetin or darbopoetin vs placebo/standard of care
- Cancer-related and treatment-related anemia
- Solid and heme malignancies

Overall OR	• **1.06**; 95% CI, 0.97-1.15
Hgb <10	• **0.99** [0.8-1.22]
Hgb 10-12	• **0.91** [0.77-1.08]
Hgb >12	• **1.13** [0.94-1.36]

Tonia T, et al. *Cochrane Database Syst Rev.* 2012;12:CD003407; Glasby J, et al. *Br J Cancer.* 2010;102(2):301-315; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

OR: Odds ratio

ESAs: Mortality

Tonia et al (2012): increased mortality
- 78 trials (N = 15,935)
- From 1993-2010
- Epoetin or darbopoetin vs placebo/standard of care
- Cancer-related and treatment-related anemia
- Solid and heme malignancies

Overall HR	• **1.17** [1.06 -1.29] ***P* = 0.0022**
Hgb <10	• **1.12** [0.96, 1.32] ***P* = 0.15**
Hgb 10-12	• **1.09** [0.91, 1.29] ***P* = 0.35**
Hgb >12	• **1.37** [1.12, 1.68] ***P* = 0.0026**

Tonia T, et al. *Cochrane Database Syst Rev.* 2012;12:CD003407; Glasby J, et al. *Br J Cancer.* 2010;102(2):301-315; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020.

HR: Hazard ratio

ESAs: Thromboembolism

- Black Box Warning: increased risk MI, stroke, VTE, vascular access thrombosis
- Increased risk irrespective of Hgb status
- Tonia et al (2012) – epoetin or darbopoetin vs placebo/standard of care
  - 78 trials (N = 15,935)
  - Increased thromboembolic complications RR, 1.52 (95% CI, 1.34-1.74)

MI, myocardial infarction; VTE, venous thromboembolism; RR, Relative Risk

Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351; Tonia T, et al. *Cochrane Database Syst Rev.* 2012;12:CD003407; Bennett CL, et al. *JAMA.* 2008;299(8):914-924; Epogen. Prescribing information. Amgen Inc; 2018; Aranesp. Prescribing information. Amgen Inc; 2019.

ESAs: Adverse Effects

- No data for adding prophylactic medications, such as aspirin or anticoagulants
- Concomitant use of high-risk medications: steroids, IMIDs (lenalidomide, pomalidomide)
- Hypertension, thrombocytopenia, hemorrhage, pure red cell aplasia

IMID, immunomodulatory drug.

NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020; Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351.

ESAs: Guidelines

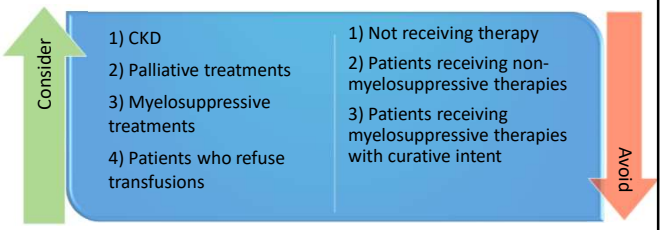
- ASCO/ASH – 2019
  - Initiate when Hgb <10 g/dL
  - There is similar efficacy between the different agents—availability, cost, convenience, personal choice
  - No target Hgb recommended – depends on ability to reduce transfusion need, patient condition

ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology

Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351.

Goals of Therapy

Improvement of anemia symptoms and avoidance of transfusions



NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020; Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351.

Iron Supplementation

- Route is dependent upon multiple factors
  - Formulation availability, cost
  - Patient characteristics, comorbidities
  - Consider IV if no response to oral

Oral iron supplementation	IV iron supplementation
• Inexpensive, convenient • Poor bioavailability • GI adverse effects; intolerance	• High bioavailability • Fast acting • Potential adverse reactions

DeLoughery TG. *Acta Haematol.* 2019;142(1):8-12; NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020; Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351.

Iron Supplementation: Oral

- Bioavailability of 10%-15% for ferrous salts
  - Sulfate, fumerate, gluconate
  - Even lower in ferric compounds
- Administration: food can decrease absorption
- Up to 30%-70% GI adverse effects: can lead to decreased tolerance and compliance
- DDI: antibiotics (tetracyclines and fluoroquinolones), PPI, antacids
- Alternate dosing: every-other-day dosing increased iron absorption
  - Stoffel et al (2020) : 200 mg given on alternate days was twice that of 100 mg on consecutive days

DDI, drug-drug interaction; PPI, proton pump inhibitors.

DeLoughery TG. *Acta Haematol.* 2019;142(1):8-12; Gómez-Ramírez S, et al. *Pharmaceuticals (Basel).* 2018;11(4):97; Campbell N, Hasinoff B. *Br J Clin Pharmacol.* 1991;31(3)251-2555; Stoffel NU et al *Haematologica.* 2020;105(5):1232-1239.

Considerations for Selecting an IV Iron Product

- Equally effective in treating iron deficiency
- Administration
  - Time
  - Length of course and number of doses (single vs multiple)
  - Premedication
- Adverse effects
  - Risk of hypersensitivity/infusion reaction vs allergic reaction (anaphylaxis)
  - Risk of hypophosphatemia
- Cost
  - Cost of formulation
  - Contracts and formulary preferences

Roger SD. *Clin Kidney J.* 2017;10(Suppl 1):i9-i15.

Iron Supplementation…With ESAs?

- Iron supplementation in conjunction with ESAs
  - Auerbach et al (2004)
    - Hematopoietic responses: IV iron (68%), oral iron (36%), no iron (25%) (P <0.01)
  - Mhaskar et al (2016) – 8 studies (ESA + iron vs ESA alone)
    - Hematopoietic response: RR, 1.17 (95% CI, 1.09-1.26)
    - RBC transfusions: RR, 0.74 (95% CI, 0.60-0.92)
- Concurrent use is recommended by ASCO/ASH Clinical Practice Guideline Update

RR, Risk Ratio

Auerbach M, et al. *J Clin Oncol.* 2004;22(7):1301-1307; Mhaskar R, et al. *JAMA Oncol.* 2016;2(11):1499-1500; Bohlius J, et al. *J Clin Oncol.* 2019;37(15):1336-1351.

The Role of the Pharmacist

Key Aspects of Managing Patients

Identify	• Different management strategies based on clinical characteristics and laboratory values
Optimize	• Indication, pharmacokinetics, and dosing of different agents
Monitor	• Response to therapy and adverse effects
Educate	• Risk and benefits of different management strategies
Develop	• Institutional ESAs and transfusion policies • Pharmacist-managed anemia programs

Hinkel JM, et al. *J Natl Compr Canc Netw.* 2010;8(suppl 7):S38-S55; Gebara SN, Moubayed H. *J Oncol Pharm Pract.* 2010;16(1):33-37.

Conclusion

- Anemia in patients with cancer may be cancer-related or treatment-related and can be associated with reduced survival and decreased therapy efficacy
- Management of iron deficiency anemia can be based on iron studies
- There are multiple guideline recommendations for using ESAs in patients with cancer
- The pharmacist's role is critical in treatment of patients with cancer with anemia to improve clinical outcomes

Additional Resources

NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors, V2.2020. www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf

Bohlius J, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH Clinical Practice Guideline Update. *J Clin Oncol.* 2019;37:1336-1351.

Gilreath J, Rodgers G. How I treat cancer-associated anemia. *Blood*. 2020;136(7):801-813.

PARP Inhibition: Current and Emerging Indications for Use in Ovarian, Breast, Pancreatic, and Prostate Cancers

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PTce

Educational Objectives

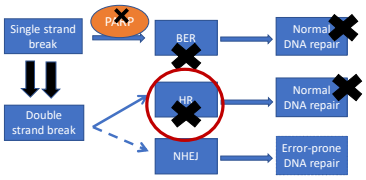
After completion of this activity, participants will be able to:

- Define the role of biomarkers and genetic testing in the selection of patients who may benefit from treatment with a PARP inhibitor
- Review efficacy and safety data supporting the emerging use of PARP inhibitors in breast, ovarian, prostate, and pancreatic cancers
- Outline the roles of pharmacists within the collaborative care team for effective initiation of therapy and management of patients being treated with PARP inhibitors

Review of PARP Inhibitors

PARP Inhibitors Mechanism of Action

- Impairs cellular DNA repair by inhibiting base excision repair and trapping PARP1 on damaged DNA leading to obstruction at replication fork



BER = base excision repair (preferred method of repair of single strand DNA breaks)
HR = homologous recombination (preferred method of repair for double stranded DNA breaks)
NHEJ = non-homologous end joining

Ohmoto A, Yachida S. *OncoTargets and Therapy.* 2017;10:5195–5208.

Biomarkers and Genetic Testing: Brief Review of Mutations

Therapeutically important mutations can be germline (g) or somatic (s)

Germline mutations

- Present in **all cells** of the body
- **Inherited** and can be passed to offspring (via germ cells: egg/sperm)
- Relatively **rare** in the general population and most tumors
- Familial implications for tumor risk
- Usually test blood/saliva
- Eg, pathogenic gBRCA mutation

Somatic mutations

- Present in the **tumor cells only**
- **Not inherited** and not passed to offspring
- Relatively **common in tumors**, results from tumor-causing DNA damaging events (UV light, radiation, etc) and increased cell proliferation over time
- Usually test tumor tissue
- Eg, actionable mutations in BRCA, PI3K, EGFR, ALK, BRAF, etc

Oncology Nursing Society. January 14, 2020. Accessed September 15, 2020. voice.ons.org/news-and-views/germline-and-somatic-mutations-what-is-the-difference

Biomarkers and Genetic Testing: BRCA and Beyond

- Genetic mutations that interfere with DNA repair and the homologous recombination pathway are important targets for PARP inhibitors, most notably BRCA
- BUT…there are other somatic mutations in this pathway, called homologous recombination deficiencies (HRD)/noted as HRD-positive status
  - Loss of heterozygosity (LOH) of tumor suppressor genes (noted as high genomic expression of LOH)
  - RAD51, PALB2, ATM, CHEK2 mutations (and others)
- Important to have patients tested for somatic or germline mutations with advanced/metastatic disease in ovarian, breast, pancreatic, and prostate cancers to guide therapy decisions
  - Current indications for PARP inhibitors include both germline and somatic mutations, depending on the disease state

Ryland GL, et al. *BMC Medical Genomics.* 2015;8:45-57; Swisher EM, et al. *Lancet Oncol.* 2017;18(1):75-87; NCCN Guidelines Version 6.2020 Invasive Breast Cancer; NCCN Guidelines Version 1.2020 Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer; NCCN Guidelines Version 1.2020 Pancreatic Adenocarcinoma; NCCN Guidelines Version 2.2020 Prostate Cancer.

Biomarkers and Genetic Testing: Examples of Tests and Results

Examples of approved genetic tests for PARP inhibitors (companion diagnostics)

- FoundationOne CDx
- myChoice CDx (Myriad)
- BRCAnalysis CDx (Myriad)
- Many others are also available for testing somatic and germline mutations
- Test chosen depends on what the team is looking for (germline or somatic mutation) based on the patient, disease, line of therapy, etc

Example interpretation of test results

- Somatic BRCA mutation in ovarian or metastatic prostate cancer indicates utility of PARP inhibitor
- Germline BRCA mutation in metastatic breast or prostate cancer indicates utility of PARP inhibitor

FDA. Medical Devices. September 10, 2020. Accessed September 15, 2020. www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Biomarkers and Genetic Testing: Rates of Mutations by Disease

- Ovarian cancer
  - ≈15% gBRCAm, ≈6% sBRCAm, 20% likely harbor another somatic HRD mutation
- Breast cancer
  - ≈5% gBRCAm (up to 10% in high-risk groups, such as Ashkenazi Jewish families)
  - More likely in patients with strong family history of breast cancer, younger patients, triple-negative disease
- Pancreatic cancer
  - ≈4-7% gBRCAm
- Prostate cancer
  - ≈10% gBRCAm, ≈20%-30% harbor germline or somatic HRD mutations

Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87; Robson, et al. *N Engl J Med*. 2017; 377:523-533; Malone KM, et al. *Cancer Res*. 2006;66(16):8297-8308; Golan T, et al. *N Engl J Med*. 2019;381:317-327; Abida W, et al. *JCO Precis Oncol*. 2017 May 31 (Epub ahead of print); DeBono, et al. *N Engl J Med*. 2020;382:2091-2102.

FDA-Approved PARP Inhibitors

- Approvals vary
  - Based on disease state
  - Based on indications within each disease
  - May correspond to specific companion diagnostics, but many validated tests available
- Although all have same mechanism, nuances involve
  - Potency/hematologic adverse effects (PARP-1 trapping)
  - Pharmacokinetic properties (metabolism, transporter effects)

Niraparib | Olaparib | Rucaparib | Talazoparib

PARP Inhibitors in Specific Diseases

PARP Inhibitors in Ovarian Cancer

Maintenance in first-line setting (with response to platinum-based therapy)	Maintenance in recurrent/metastatic disease (with response to platinum-based therapy)	Treatment of recurrent/metastatic disease after multiple prior lines of therapy
Olaparib: germline or somatic BRCAm *(SOLO1)*	**Olaparib: all-comers *(SOLO2)***	**Olaparib: germline BRCAm and >3 prior lines of therapy *(SOLO3)***
-improved PFS ≈36 months with BRCAm	*-improved PFS ≈14 months with BRCAm*	*-improved PFS ≈4 months with gBRCAm*
Olaparib + bevacizumab: HRD-positive status *(PAOLA1)*	**Rucaparib: all-comers *(ARIEL3)***	**Rucaparib: BRCAm and >2 prior lines of therapy *(ARIEL2)***
-improved PFS ≈6 months in all-comers; ≈20 months with HRD/BRCAm; ≈12 months in HRD (no BRCAm)	*-improved PFS ≈11 months with BRCAm; ≈5 months in all-comers*	*-improved PFS ≈8 months with BRCAm*
Niraparib: all-comers *(PRIMA)*	**Niraparib: all-comers *(NOVA)***	**Niraparib: HRD-positive status and >3 prior lines of therapy *(QUADRA)***
-improved PFS ≈6 months in all-comers; ≈12 months in HRD	*-improved PFS ≈16 months with gBRCAm; ≈5 months in all comers (w/o gBRCAm)*	*-28% response rate with HRD*

BRCAm = BRCA mutation, HRD = homologous recombination deficiency, PFS = progression-free survival; Maintenance = post-remission therapy.
Phase 3 studies noted in parentheses.
Moore KN, et al. *N Engl J Med*. 2018;379(26):2495-2505; Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428; Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-2402; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;9:1274-1284; Coleman RL, et al. *Lancet*. 2017;390(10106):1949-1961; Mirza MR, et al. *N Engl J Med*. 2016; 375(22):2154-2164; Penson RT, et al. *J Clin Oncol*. 2020;38(11):1164-1174; Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87; Moore KN, et al. *Lancet Oncol*. 2019;20(5):636-648.

Clinical Use in Ovarian Cancer

- BRCA mutations have better outcomes even compared with other HRD mutations
- Use in earlier lines of therapy in the maintenance setting (ie, remission of disease after good response to chemotherapy) is more effective than later use
  - Poorer responses if patients are platinum resistant and after multiple lines of therapy

The takeaway: Category 1 recommendation to use PARP inhibitors (olaparib or niraparib) in the up-front maintenance (post-remission) setting with BRCA mutation

- Although niraparib or olaparib/bevacizumab are category 2 recommendations for patients with other HRD mutations or no mutations, patients with no mutations have much less benefit and use in this subset of patients (≈50%) is still up for clinical debate
- Category 2 recommendation for PARP inhibitors (olaparib/rucaparib/niraparib) in recurrent maintenance setting if have not previously received a PARP inhibitor

Moore KN, et al. *N Engl J Med*. 2018;379(26):2495-2505; Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428; Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-2402; Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;9:1274-1284; Coleman RL, et al. *Lancet*. 2017;390(10106):1949-1961; Mirza MR, et al. *N Engl J Med*. 2016; 375(22):2154-2164; Penson RT, et al. *J Clin Oncol*. 2020;38(11):1164-1174; Swisher EM, et al. *Lancet Oncol*. 2017;18(1):75-87; Moore KN, et al. *Lancet Oncol*. 2019;20(5):636-648; NCCN Guidelines Version 1.2020 Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.

PARP Inhibitors in Metastatic Breast Cancer

PARP Inhibitor	Indication	Clinical Efficacy
Olaparib *(OlympiAD)*	Germline BRCAm, HER2-, metastatic disease with prior chemotherapy; if ER/PR+, prior endocrine therapy	Improved PFS ≈3 months, higher response rate and lower rate of serious (grade 3+) adverse effects vs chemotherapy group
Talazoparib *(EMBRACA)*	Germline BRCAm, HER2-, locally advanced or metastatic disease	Improved PFS ≈3 months, higher rates of response, no difference in OS (≈19 months for talazoparib vs chemotherapy group)

BRCAm = BRCA mutation, PFS = progression-free survival, OS = overall survival. Phase 3 studies noted in parentheses.
Patient-reported outcomes favor the PARP inhibitor from these studies.

The takeaway: All patients with metastatic breast cancer should be tested for germline BRCA mutations for use of PARP inhibitor. Category 1 recommendation for olaparib or talazoparib for this patient population

Robson M, et al. *N Engl J Med*. 2017;377:523-533; Litton JK, et al. *N Engl J Med*. 2018;379:753-763; Litton JK, et al. *Ann Oncol*. 2020 Aug 20 (online ahead of print); NCCN Guidelines Version 6.2020 Invasive Breast Cancer.

PARP Inhibitors in Metastatic Pancreatic Cancer

- Olaparib *(POLO)*: maintenance therapy in patients with metastatic pancreatic cancer and gBRCA mutation who have not progressed on first-line platinum-based regimen
- Designed as maintenance regimen trial (unique in metastatic pancreatic cancer)
- 154 patients randomized to olaparib or placebo after at least 16 weeks of platinum-based chemotherapy with at least stable disease
  - Regimens: FOLFIRINOX/gemcitabine-cisplatin/other platinum regimen
  - At progression, proceeded to another chemotherapy regimen (did not cross over to olaparib)
- Increased PFS ≈4 months vs placebo (7.4 months vs 3.8 months)
  - No difference in OS (19 vs 18 months) or quality-of-life scores

Golan T, et al. *N Engl J Med*. 2019;381(4):317-327.

Clinical Use in Metastatic Pancreatic Cancer

The takeaway: Category 2 recommendation to use olaparib for patients with germline BRCA mutations with good performance status after response to first-line therapy.

- Germline testing is recommended for all patients with pancreatic cancer to identify familial risk/syndromes
- Tumor/somatic testing is recommended for patients with advanced/metastatic disease to identity uncommon therapeutic targets

NCCN Guidelines Version 1.2020 Pancreatic Adenocarcinoma.

PARP Inhibitors in Metastatic Prostate Cancer

PARP Inhibitor	Indication	Clinical Efficacy
Olaparib *(PROfound)*	metastatic CRPC with germline or somatic HRD-positive disease following progression on either abiraterone or enzalutamide	-improved PFS ≈4 months in patients with BRCA or ATM mutation (vs enzalutamide or abiraterone as control group)
Rucaparib *(TRITON2)*	metastatic CRPC with germline or somatic BRCAm who have been treated with androgen receptor-directed therapy and taxane-based chemotherapy	-confirmed radiographic or PSA responses of 44%-51% (with BRCA mutation, 0-15% with other HRD mutations)

BRCAm = BRCA mutation, HRD = homologous recombination deficiency, also called homologous recombination repair (HRR) mutation, PFS = progression-free survival, CRPC = castrate-resistant prostate cancer.
Phase 3 studies noted in parentheses. TRITON2 was a phase 2 study with no control group.

The takeaway: Category 1 recommendation for olaparib use as subsequent (beyond 2nd line) therapy in HRD-positive disease (category 2B for 2nd line therapy). Category 2A for rucaparib as subsequent line therapy with BRCA mutation

De Bono J, et al. *N Engl J Med*. 2020;382(22):2091-2102; Abida W, et al. *J Clin Oncol*. 2020 (online ahead of print); Abida, et al. *Clin Cancer Res*. 2020;26(11):2487-2496; NCCN Guidelines Version 2.2020 Prostate Cancer.

PARP Inhibitors and Their Place in Therapy

Drug	Ovarian cancer 1st line maintenance (after platinum)	Recurrent ovarian cancer 2nd line maintenance (after platinum)	Recurrent/ metastatic ovarian cancer	Recurrent, metastatic breast cancer	Metastatic pancreatic cancer maintenance after chemotherapy	Recurrent, metastatic castrate-resistant prostate cancer
Niraparib 300 mg PO daily	✓	✓	✓			
Olaparib 300 mg PO BID	✓	✓	✓	✓	✓	✓
Rucaparib 600 mg PO BID		✓	✓			✓
Talazoparib 1 mg PO daily				✓		

NCCN Guidelines Version 6.2020 Invasive Breast Cancer, NCCN Guidelines Version 1.2020 Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, NCCN Guidelines Version 1.2020 Pancreatic Adenocarcinoma; NCCN Guidelines Version 2.2020 Prostate Cancer; Lynparza. Prescribing information. AstraZeneca; 2020, Rubraca. Prescribing information. Clovis Oncology; 2020; Zejula. Prescribing information. GlaxoSmithKline; 2020. Talzenna. Prescribing information. Pfizer Inc; 2020.

Adverse Effects Across Diseases

- Most common adverse effects across diseases
  - Fatigue, nausea/vomiting, anemia
- May differ slightly based on disease and specific PARP inhibitor

Example for olaparib across diseases

Adverse Effect (any grade)	Ovarian	Breast	Pancreatic	Prostate
Fatigue	60.1%	48.4%	73.9%	12.5%
Nausea	61.7%	53.2%	47.8%	37.5%
Vomiting	38.9%	33.9%	39.1%	0
Anemia	32.1%	25.8%	39.1%	62.5%

Adapted from: Moore KN, Monk BJ. *Oncologist* 2016;21:954-963.

Adverse Effect Comparison Within Class

- Notable differences in hematologic toxicities and laboratory abnormalities

Adverse Effect	Olaparib	Rucaparib	Niraparib	Talazoparib
	(Any grade %/>grade 3 %)			
Anemia	34/18	39/21	50/25	53/39
Neutropenia	27/9	20/8	30/20	35/21
Decrease in platelets	30/3	44/2	72/35	55/15
Fatigue	66/8	73/7	57/8	62/3
Nausea	66/3	76/4	74/3	49/<1
Insomnia (any grade)	1-10	15	27	NR
Alopecia	NR	NR	NR	25/0
Nasopharyngitis	26/0	29/0.3	23/0	NR
Hypertension	1-10	NR	20/9	NR
Hypocalcemia	NR	NR	NR	28/1
Increase in ALT	NR	73/7	28/1	33/1
Increase in creatinine	30/2	98/0.8	NR	NR
Hyperglycemia	NR	NR	NR	54/2

Adapted from: Hennes ER, et al. *J Oncol Pharm Pract.* 2020;26(3):718-729.

PARP Inhibitor Adverse Effect Statistics

Across studies and disease states

- ≈25%-60% of patients required dose reductions for adverse effects
- ≈10%-15% of patients discontinued for adverse effects

The takeaway: There is a huge role for pharmacists to help with adverse effect management/appropriate dosing recommendations to help patients stay on therapy

Moore KN, Monk BJ. *Oncologist.* 2016;21:954-963; Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;9:1274-1284; Coleman RL, et al. *Lancet.* 2017;390(10106):1949-1961; Mirza MR, et al. *N Engl J Med.* 2016;375:2154-2164; Hennes ER, et al. *J Oncol Pharm Pract.* 2020;26(3):718-729.

Role of the Pharmacist in the Collaborative Team

Pharmacist's Role in Management of PARP Inhibitors

- Treatment initiation
  - Chemotherapy education
  - Appropriate dosing based on patient factors
  - Drug interaction review
  - Medication access (facilitate with specialty pharmacy, refer for patient assistance)
- Treatment continuation
  - Adverse effect management
  - Dose reductions/tolerability check
  - Assessment of adherence
  - Coordination of follow-up (baseline labs, follow-up labs, provider/team visits)

Mackler E, et al. *J Oncol Pract.* 2019;15(4):e346-e355.

Treatment Initiation: Education and Dosing

- Chemotherapy education
  - Regimen, clinical rationale, common adverse effects, storage, safe handling, unused medications
- Dosing: Consider patient-specific factors
  - Genetic mutation status/approved indication
  - Baseline renal function
  - Others: baseline weight, platelets (and general CBC review)
- Drug interaction review
  - Especially CYP3A4 inhibitors and P-glycoprotein inhibitors

Lynparza. Prescribing information. AstraZeneca; 2020; Rubraca. Prescribing information. Clovis Oncology; 2020; Zejula. Prescribing information. GlaxoSmithKline; 2020. Talzenna. Prescribing information. Pfizer Inc; 2020.

Summary of Administration Pearls

Drug	Dose	Administration Pearls
Niraparib	300 mg PO daily	❑ Consider dose reduction to 200 mg daily if <77 kg or platelets <150,000 cells/mm^3
Olaparib	300 mg PO BID	❑ CYP3A4 dose adjustments (strong inhibitors, reduce to 100 mg PO BID; moderate inhibitors 150 mg PO BID; avoid strong inducers) ❑ Avoid grapefruit/Seville oranges ❑ Dose reduction for CrCL <50 mL/min to 200 mg BID ❑ Extensively metabolized in the liver (caution)
Rucaparib	600 mg PO BID	❑ Moderate CYP1A2 inhibitor, monitor for interactions
Talazoparib	1 mg PO daily	❑ Reduce dose to 0.75 mg daily for select P-gp inhibitors ❑ Dose reduction for CrCL 30-59 mL/min to 0.75 mg daily, for CrCL <30 mL/min to 0.5 mg daily

Generally: Take with/without food, store at room temperature in original container, swallow whole, wash hands, keep out of reach of children/pets, dispose of unused pills in drop box or in coffee grounds/sealed container

Lynparza. Prescribing information. AstraZeneca; 2020; Rubraca. Prescribing information. Clovis Oncology; 2020; Zejula. Prescribing information. GlaxoSmithKline; 2020. Talzenna. Prescribing information. Pfizer Inc; 2020.

Treatment Initiation: Medication Access

- Medication Access Facilitation
  - Provide information for prior authorization documentation to medication assistance team when needed
  - Provide resources to team and patient to help with completion of patient assistance program applications (available through manufacturers, including co-pay assistance, discount cards, free medication)
  - Communicate with specialty or other dispensing pharmacy to answer questions about treatment plan, laboratory assessments, etc

Mackler E, et al. *J Oncol Pract.* 2019;15(4):e346-e355; Felton MA, et al. *J Oncol Pharm Pract.* 2016;22(2):378-381.

Treatment Continuation: AE Management

Adverse Effect	Suggested Management (besides dose interruption for moderate or dose reduction for more severe grades)
Nausea/ vomiting	Moderate to high emetogenic risk in NCCN guidelines *(except talazoparib is minimal/low risk)*, can give antiemetic Rx for use if needed 30 min before dosing (5-HT_3 antagonist, prochlorperazine, metoclopramide, olanzapine, etc) and take with small meal/snack
Fatigue	Good sleep hygiene (not napping all day), planned activity/exercise, conserve energy/limit multitasking, stress reduction/psychosocial interventions; consider pharmacologic options if more severe grade
Diarrhea	Loperamide, etc and counseling about when to call health care team to rule out other issues
Constipation	Make sure it's not from the antiemetic! Senna or polyethylene glycol can help
Dyspepsia/ abdominal pain	Proton pump inhibitor may help; exclude other causes
Dysgeusia	Maintain hydration, using baking soda mouth rinses, adding sweet flavoring to food, diet changes, cooler temperature of foods, saliva substitutes, dental hygiene
Neurologic toxicities	Headache: offer OTC treatment Insomnia: if once-daily dosing, can take dose in morning

Madariaga A, et al. *Int J Gynecol Cancer.* 2020;30(7):903-915; LaFargue CJ, et al. *Lancet Oncol.* 2019;20(1):e15-e28; Moore KN, Monk BJ. *Oncologist* 2016;21:954–963; Moore KN, et al. *Gynecologic Oncology.* 2018;149:214-220.

AE Management: Hematologic Toxicity

- Occurs most often in the first 1-3 months
- Anemia
  - Most common hematologic toxicity
  - Usually stabilizes after 5-6 cycles
  - Can consider transfusion if symptomatic and Hgb <7 g/dL
- Neutropenia
  - Usually not associated with febrile neutropenia, growth factors not used
- Thrombocytopenia
  - Usually stabilizes after 2-3 cycles

General management = holding dose, lab reassessment and dose reduction if needed

Madariaga A, et al. *Int J Gynecol Cancer.* 2020;30(7):903-915; LaFargue CJ, et al. *Lancet Oncol.* 2019;20:e15-e28; Moore KN, Monk BJ. *Oncologist* 2016;21:954-963; Moore KN, et al. *Gynecologic Oncology.* 2018;149:214-220.

Other Less Common Adverse Effects (AEs)

- Niraparib
  - Cardiovascular (hypertension and palpitations): can treat with antihypertensives and monitoring of BP
  - Respiratory events, including nasopharyngitis: decongestants/antihistamines, rule out more serious issues
- Olaparib
  - Pneumonitis (new-onset cough/shortness of breath, wheezing): hold drug and give corticosteroids
  - Venous thromboembolic events (mCRPC): treat with anticoagulation
- Rucaparib: AST/ALT elevations, SCr elevations (due to MATE transporter effects)
  - Often do NOT require dose adjustment (if related to drug, often occurs between cycles 1 and 2)
  - Rule out true organ dysfunction
- Talazoparib: hyperglycemia, hypocalcemia, alopecia
- Secondary myelodysplastic syndrome/acute myeloid leukemia
  - Rare overall, <1%-2%, if ongoing myelosuppression despite holding dose (>28 days), refer to hematologist

Madariaga A, et al. *Int J Gynecol Cancer.* 2020;30(7):903-915; LaFargue CJ, et al. *Lancet Oncol.* 2019;20:e15-e28; Moore KN, Monk BJ. *Oncologist.* 2016;21:954-963; Moore KN, et al. *Gynecologic Oncology.* 2018;149:214-220; Hennes ER, et al. *J Oncol Pharm Pract.* 2020;26(3):718-729.

Other Pearls for Managing AEs

- Most AEs are more prominent in first 1-2 months and then improve over time on therapy
  - Usually grade 1/2, can continue PARPi, consider dose interruption
  - Usually grade 3/4, hold PARPi and consider dose reduction
- Common AEs, such as fatigue/gastrointestinal effects/anemia, occur often, but may vary within drug class and within specific diseases
- Dose interruption can be a good way to manage AEs and allow for resumption of prior dose
  - Especially with nonhematologic toxicities

Madariaga A, et al. *Int J Gynecol Cancer.* 2020;30(7):903-915; LaFargue CJ, et al. *Lancet Oncol.* 2019;20:e15-e28; Moore KN, Monk BJ. *Oncologist* 2016;21:954-963; Moore KN, et al. *Gynecologic Oncology.* 2018;149:214-220 .

Adherence and Follow-up

- Assessing adherence
  - Shown to affect outcomes across multiple oncology diseases (multiple different tools)
  - Phone follow-up/communication, adherence aids (alarms/calendar), technology
  - Refill assessment from dispensing pharmacy
- Coordination of follow-up
  - Laboratory assessments
    - CBC: Niraparib is weekly for first month, then monthly; others: monthly
    - Renal and liver function: as needed (usually monthly in clinical practice)
    - Patients may require more frequent follow-ups than what is stated in label
  - Other assessments (quality of life, stress/distress, cardiovascular, etc)
  - Provider return visits/clinic follow-up

Felton MA, et al. *J Oncol Pharm Pract.* 2016;22(2):378-381; Krikorian S, et al. *J Oncol Pharm Pract.* 2019;25(7):1590-1598, Lynparza. Prescribing information. AstraZeneca; 2020; Rubraca. Prescribing information. Clovis Oncology; 2020; Zejula. Prescribing information. GlaxoSmithKline; 2020; Talzenna. Prescribing information. Pfizer Inc; 2020.

Future of PARP Inhibitors

- Earlier lines of therapy (nonmetastatic setting)
- Combination with other agents (both with and without biomarker-positive disease)
  - + abiraterone or enzalutamide in metastatic prostate cancer
  - + immune checkpoint inhibitors (pembrolizumab, durvalumab in metastatic breast cancer)
  - + chemotherapy (veliparib + platinum and/or taxane in ovarian and metastatic breast cancer)
- PARP after PARP
  - DUETTE study: PARP inhibitor maintenance (+/- ceralasertib) for recurrent ovarian cancer after prior PARP inhibitor maintenance in first-line setting
- Increasing role of the pharmacist as more indications approved and increased use in the real-world setting
  - Likely more dose reductions/toxicity issues in practice than in clinical trials

McMullen M, et al. *Int J Gynecol Cancer*. 2020 Sep 2 (online ahead of print); Antonarakis ES. et al. *Eur Urol Oncol*. 2020 Aug 17 (online ahead of print), Eakin CM, et al. *Gynecol Oncol*. 2020 Aug 15 (online ahead of print); Domchek SM, et al. *Lancet Oncol*. 2020 Aug 6 (online ahead of print); Dieras V, et al. *Lancet Oncol*. 2020 Aug 27 (online ahead of print).

Conclusion

- Biomarkers for PARP inhibitor therapy include both germline and somatic BRCA mutations as well as other somatic mutations involving homologous recombination deficiencies
- PARP inhibitors have shown efficacy and have FDA approval now in multiple tumors, including advanced ovarian, breast, pancreatic, and prostate cancers
- PARP inhibitors have some common class-wide toxicities, but also demonstrate nuances related to toxicity, laboratory monitoring and assessment, and drug interactions
- A pharmacist is well-positioned in the team to help with treatment initiation of PARP inhibitors through medication teaching, therapy access, and review of dosing
- A pharmacist is also able to help with treatment continuation by offering supportive care management for AEs, assessing adherence, and helping with ongoing monitoring strategies

Additional Resources

NCCN Guidelines **Breast cancer** **Ovarian cancer** **Pancreatic cancer** **Prostate cancer**	nccn.org/professionals/physician_gls/default.aspx
Oral Chemotherapy Education Provides comprehensive and easy-to-understand patient counseling information for PARP inhibitors	oralchemoedsheets.com
PARP-inhibitor potpourri: A comparative review of class safety, efficacy, and cost Provides excellent tables and resources for PARP inhibitor toxicities and resources for patient medication access	Hennes ER, et al. *J Oncol Pharm Pract*. 2020;26(3):718-729.

Multiple Myeloma: Exploring the Rapidly Evolving Treatment Landscape for Relapsed or Refractory Disease

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Educational Objectives

After completion of this activity, participants will be able to:

- Recognize approved and pipeline medications used for the treatment of relapsed or refractory multiple myeloma based on mechanisms of action
- Discuss the rationale behind the use of combination therapies for the treatment of patients with relapsed or refractory multiple myeloma
- Describe ways pharmacists can assist in the supportive care of patients with relapsed or refractory multiple myeloma

Multiple Myeloma Background

Overview of Multiple Myeloma (MM)

- Malignancy of plasma cells
- Proliferation of monoclonal plasma cells in the bone marrow
  - Leads to bone destruction and bone marrow failure
- Abnormal plasma cells secrete proteins
  - Heavy chains: IgG, IgA, IgM; IgE/D at low levels
  - Light chains: kappa or lambda
  - None (non-secretors)

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).
Palumbo A, Anderson K. *N Engl J Med* 2011;364(11):1046-1060.

Epidemiology

- 32,270 new cases in 2020
  - 1.8% of all new cancer diagnoses
- 12,830 deaths in 2019
  - 2.1% of all cancer deaths
- Median age at diagnosis: 69 years
- 5-year relative survival: 53.9%
- Risk factors:
  - Male sex, African American race, monoclonal gammopathy of undetermined significance (MGUS), chemical exposure

Siegel RL, et al. *CA Cancer J Clin*. 2019;69 (1):7-34.
SEER Stat Fact Sheets: Myeloma. Accessed August 24, 2020. seer.cancer.gov/statfacts/html/mulmy.html

Revised IMWG Diagnostic Criteria

MGUS	Smoldering Myeloma	Multiple Myeloma
• M-protein <3 g/dL (serum) • Clonal plasma cells in marrow <10% • No SLiM-CRAB criteria	• M-protein ≥3 g/dL (serum) or ≥500 mg/24 h (urine) • Clonal plasma cells in marrow 10%-60% • No SLiM-CRAB criteria	• Clonal marrow plasma cells ≥10% or ≥1 biopsy-proven bony or extramedullary plasmacytoma • SLiM-CRAB criteria

SLiM	CRAB
S Clonal plasma cells in BM ≥60% Li Serum FLC ratio ≥100 M >1 focal lesion ≥5 mm on MRI	C Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN) R Renal insufficiency (CrCL <40 mL/min or SCr >2 mg/dL) A Anemia (Hgb <10 g/dL or 2 g/dL < normal) B Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar SV, et al. *Lancet Oncol*. 2014;15(12):e538-e554.
IMWG, International Myeloma Working Group.

Revised International Staging System (R-ISS)

Stage	Criteria	Genetics	5-year Overall Survival
I	B_2-microglobulin <3.5 mg/L and serum albumin ≥3.5 g/dL	No del (17p) No t(4;14) No t(14;16) Normal LDH	82%
II	Not stage I or III		62%
III	B_2-microglobulin ≥5.5 mg/L	Del(17p) t(4;14) t(14;16) High LDH	40%

Palumbo A, et al. *J Clin Oncol*. 2015;33(26):2863-2869.

Setting the Stage:
Available and Emerging Therapies in Relapsed/Refractory Multiple Myeloma

Criteria for Relapse

Biochemical relapse
- Increase in serum/urine M protein
- Increase in involved free light chain levels
- Increase in bone marrow plasma cell percentage

Clinical relapse
- Presence/worsening of CRAB criteria
- Development of new bone lesions or soft tissue plasmacytoma
- Hyperviscosity related to serum paraprotein

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).

Management of R/R MM

- Currently no universal standard for optimal therapy sequence in R/R disease
- Factors impacting treatment selection
  - Patient age and comorbidities
  - Disease cytogenetics
  - Timing and aggressiveness of relapse
  - Response to prior treatments, adverse affects
  - Drug cost/access

Moreau P. *Blood*. 2017;130(13):1507-1513.

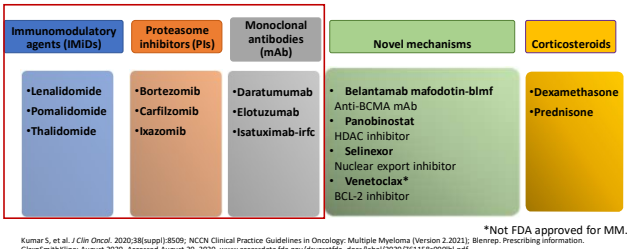
NCCN-Recommended First-Line Therapies

Transplant-eligible	Transplant-ineligible
Bortezomib/lenalidomide/dexamethasone **(category 1)**	Bortezomib/lenalidomide/dexamethasone **(category 1)**
Bortezomib/cyclophosphamide/dexamethasone	Daratumumab/lenalidomide/dexamethasone **(category 1)**
Carfilzomib/lenalidomide/dexamethasone	Lenalidomide/low-dose dexamethasone **(category 1)**
Ixazomib/lenalidomide/dexamethasone (category 2B)	Bortezomib/cyclophosphamide/dexamethasone
Bortezomib/thalidomide/dexamethasone **(category 1)**	Daratumumab/bortezomib/melphalan/prednisone **(category 1)**
Others: Daratumumab-VTD, Daratumumab-RVD, KCd	Others: IRD, KRD, Vd, KCd

Maintenance Therapy
Lenalidomide **(category 1)** Ixazomib **(category 1)** Bortezomib

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).

Treatment Options for R/R MM Overview



*Not FDA approved for MM.

Kumar S, et al. *J Clin Oncol*. 2020;38(suppl):8509; NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021); Blenrep. Prescribing information. GlaxoSmithKline; August 2020. Accessed August 20, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf

First Relapse Treatment Options

Carfilzomib-Based Regimens

Study/ Patient Population	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (grades 3-4)
ASPIRE: Carfilzomib lenalidomide dexamethasone (KRd) v. Rd **1-3 prior lines of therapy** **KRd (n = 396) vs Rd (n = 396)**	32.3 vs 31.5	26.3 vs 17.6	87.1% vs 66.7%	69.9% vs 40.4%	• Neutropenia (29.6% vs 26.5%) • Anemia (17.9% vs 17.2%) • Thrombocytopenia (16.6% vs 12.3%) • Diarrhea (3.8% vs 4.1%) • Hypertension (4.3% vs 1.8%) • Cardiac failure (3.8% vs 1.8%)
Phase 1: Carfilzomib Pomalidomide Dexamethasone (KPd) **≥1 prior line of therapy & lenalidomide refractory (n = 32)**	26.3	7.2	50%	16%	• Neutropenia (44%) • Thrombocytopenia (22%) • Anemia (19%) • Pneumonia (9%)

Stewart AK, et al. *N Engl J Med.* 2015;372:142-152; Shah JJ, et al. *Blood.* 2015;126(20):2284-2290.

A.R.R.O.W. – Carfilzomib

478 patients randomized 1:1 to once-weekly (n=240) or twice-weekly (n=238) dosing

↓

Once weekly: 70 mg/m² Days 1, 8, 15
Twice weekly: 27 mg/m² Days 1, 2, 8, 9, 15, 16

↓

Primary end point: PFS

Phase 3 Study	
Objective	To compare PFS for once- vs twice-weekly carfilzomib in patients with R/R MM after 2-3 treatments, including PI and IMiD
Results	Median PFS: 11.2 months with once-weekly versus 7.6 months with twice weekly (HR, 0.69; 95% CI, 0.54-0.83) **Adverse effects** • ≥Grade 3 higher with once weekly (68%) vs twice weekly (62%) • Anemia: 18% vs 18% • Pneumonia: 10% vs 7% • Thrombocytopenia: 7% vs 7% • Grade 3 or worse cardiac failure: 3% vs 4%
Conclusion	Once-weekly dosing yielded higher PFS with similar adverse effect profile

Moreau P, et al. *Lancet Oncol.* 2018;19:953-964.

Daratumumab-Based Regimens

Study/Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	SAEs (grades 3-4)
POLLUX 1+ prior lines of therapy	DaraRd (n = 286) vs Rd (n = 283)	44.3	44.5 vs 17.5	92.9% vs 76.4%	75.8% vs 44.2%	**Neutropenia** (51.9% vs 37.0%), anemia (12.4% vs 19.6%), thrombocytopenia (12.7% vs 13.5%), **fatigue** (6.4% vs 2.5%), diarrhea (5.3% vs 3.2%)
CASTOR 1+ prior lines of therapy	DaraVd (n = 251) vs Vd (n = 247)	40.0	16.7 vs 7.1	82.9% vs 63.2%	59.2% vs 29.1%	**Thrombocytopenia** (45.3% vs 32.9%), anemia (14.4% vs 16.0%), **neutropenia** (12.8% vs 4.2%), neuropathy (4.5% vs 6.8%), all-grade infusion reactions 45.3% (dara)
Phase 1b 2+ prior lines of therapy	DaraPd (n = 103)	13.1	8.8	60%	42%	**Neutropenia** (77%), anemia (28%), thrombocytopenia (19%), fatigue (12%)
CANDOR 1+ prior lines of therapy	DaraKd (n = 312) vs Kd (n = 154)	17	NR vs 15.8	84.3% vs 74.7%	-	Serious AEs (56.2% vs 45.8%), grade ≥ 3 cardiac failure (3.9% vs 8.5%)

Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331; Bahlis NJ, et al. *Leukemia.* 2020;34:1875-1884; Palumbo A, et al. *N Engl J Med.* 2016;375:754-766; Mateos MV, et al. *Clin Lymphoma Myeloma Leuk.* 2019;20(8):509-518. Chari A, et al. *Blood.* 2017;130:974-81.; Dimopoulos MA et al. *Lancet.* 2020;396:186-97.

Daratumumab-Pomalidomide-Dexamethasone

Cohorts	ORR	Median PFS
Daratumumab + pomalidomide naive	91.7%	Not reached at median follow-up of 41 months
Daratumumab or pomalidomide refractory	40.9%	3.2 months
Daratumumab and pomalidomide refractory	33.3%	Not reported

Conclusion: Earlier use of daratumumab + pomalidomide warranted due to significantly improved median PFS and ORR

Nooka AK, et al. *Cancer.* 2019;125:2991-3000.

Subcutaneous Daratumumab: Phase 3 Trial

522 patients randomized 1:1 to SC (n=263) or IV (n=259)

↓

SC: 1800 mg flat dose
IV: 16 mg/kg

↓

ORR and maximum trough concentration (Cycle 3, day 1 pre-dose)

Objective	Noninferiority study of subcutaneous (SC) versus intravenous (IV) daratumumab
Results	At a median follow-up of 7.5 months: • ORR 41% with SC vs 37% with IV (RR 1.11, 95% CI 0.89-1.37) • C_{trough} 593 ug/mL with SC vs 522 ug/mL with IV Most common adverse effects, SC vs IV: • Anemia (grade 3/4): 13% vs 14% • Neutropenia (grade 3/4): 13% vs 8% • Pneumonia (grade 3/4): 3% vs 4% • Infusion-related reactions (all grade): 13% vs 34%
Conclusion	SC daratumumab noninferior to IV in ORR, pharmacokinetics, and safety

Mateos MV, et al. *Lancet Haematol.* 2020;7:e370-e380.

SC versus IV Daratumumab

	SC Daratumumab	IV Daratumumab
FDA-Approved Indications	**Newly diagnosed MM:** • DaraRd, Dara-VMP **R/R MM:** • Dara monotherapy, DaraVd, DaraRd	**Newly diagnosed MM:** • Dara-VMP, DaraRd, Dara-VTD **R/R MM:** • Dara monotherapy, DaraVd, DaraRd, DaraPd, DaraKd
Dosing	1800 mg flat dose (15 mL)	16 mg/kg in 1000 mL (dose 1), then 500 mL
Administration	SC push over 3-5 minutes	Infusion rates vary based on dose; range from ≈1.5 to 8 hours
Pre-medications	Corticosteroid, antipyretic, antihistamine, montelukast (dose 1 only)	
Post-medications (often only given for high-risk)	Methylprednisone 20 mg (or equivalent) x 2 days after administration of dose, inhaled corticosteroids/bronchodilators in select patients	
Pearls	Observe after cycle 1, day 1; length of time will be institution specific	Can consider split dose for cycle 1 and give 8 mg/kg over days 1 and 2

Darzalex IV. Prescribing information. Janssen Biotech Inc; June 2020. Accessed August 24, 2020. janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf; Darzalex Faspro SC. Prescribing information. Janssen Biotech Inc; May 2020. Accessed August 24, 2020. janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf

Alternative PI + IMiD Combinations

Study/ Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (Grades 3-4)	Pearls
OPTIMISSM 1-3 prior therapies, including lenalidomide for 2+ cycles	Bortezomib, pomalidomide, dexamethasone (n=281) vs VD (n=278)	15.9	11.2 vs 7.1	82.2% vs 50.0%	52.7% vs 18.3%	• Neutropenia (42% vs 9%) • Infection (31% vs 18%), • Thrombocytopenia (27% vs 29%) • Peripheral neuropathy (8% vs 4%)	Alternative to KPD for a patient who cannot tolerate or has contraindication to carfilzomib
TOURMALINE -MM1 1-3 prior therapies	Ixazomib, lenalidomide, dexamethasone (n=360) vs Rd (n=362)	14.7	20.6 vs 14.7	78% vs 72%	48% vs 39%	• Neutropenia (23% vs 24%) • Thrombocytopenia (19% vs 9%) • Anemia (9% vs 13%), • Diarrhea (6% vs 3%) • Rash (5% vs 2%)	• All oral regimen • May not be ideal for a patient who progresses on ixazomib maintenance

Richardson PG, et al. *Lancet Oncol.* 2019;20:781-794; Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.

Elotuzumab + IMiD

Study/Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (Grades 3-4)	Pearls
ELOQUENT-2 1-3 prior therapies	EloRd (n=321) vs Rd (n=325)	48	19.4 vs 14.9	79% vs 66%	35% vs 29%	**Lymphopenia** (77% vs 49%), anemia (19% vs 21%), thrombocytopenia (19% vs 20%), neutropenia (34% vs 44%)	• Dosing: 10 mg/kg IV weekly cycles 1-2, then every other week for cycles 3+
ELOQUENT-3 At least 2 prior therapies, including lenalidomide and a PI	EloPd (n=60) vs Pd (n=57)	9.1	10.3 vs 4.7	53% vs 26%	20% vs 9%	Anemia (10% vs. 20%), neutropenia (13% vs. 27%), thrombocytopenia (8% vs. 5%), infections (13% vs. 22%)	• Dosing: 10 mg/kg IV weekly cycles 1-2, then 20 mg/kg monthly for cycles 3+

• Infusion time less than IV daratumumab
• Not to be used as monotherapy

Lonial S, et al. *N Engl J Med.* 2015;373:621-631; Dimopoulos MA et al. *Cancer.* 2018;124:4032-43.; Dimopoulos MA, et al. *N Engl J Med.* 2018;379:1811-1822

Isatuximab + IMiD

Study/Patient Population	Therapy	Median Follow-up (months)	Median PFS (months)	ORR	≥ VGPR	Adverse Effects (Grades 3-4)	Pearls
ICARIA-MM ≥2 prior therapies, including lenalidomide and a PI	IsaPd (n=154) vs Pd (n=153)	11.6	11.5 vs 6.5	60% vs 35%	32% vs 9%	**Infusion reactions** (38% vs 0%), upper respiratory tract infections (28% vs 17%), diarrhea (26% vs 20%)	• No data in patients who previously received dara • Dosing: 10 mg/kg IV weekly for cycle 1, then other week for cycles 2+ • Infusion time less than IV dara

Lonial S, et al. *N Engl J Med.* 2015;373:621-631; Dimopoulos MA, et al. *N Engl J Med.* 2018;379:1811-1822; Attal M, et al. *Lancet.* 2019;394:2096-2107.

Later Relapse Treatment Options

Selinexor: XPO Inhibitor

- First-in-class, oral, selective inhibitor of nuclear export compound exportin 1 (XPO1)
  - XPO1 overexpressed in myeloma cells
  - Inhibition of XPO1 leads to accumulation of tumor suppressor proteins, cell cycle arrest, and apoptosis
  - FDA approved with dexamethasone for R/R MM in patients previously treated with 2 PIs, 2 IMiDs, and a CD38-monoclonal antibody (triple-class refractory)
  - NCCN recommendation for "useful in certain circumstances"
- **STORM trial** (phase 2b)
  - Selinexor 80 mg PO twice weekly + dexamethasone 20 mg twice weekly
  - Outcomes: median PFS 3.7 months, median OS 8.6 months, ORR 26%
  - Most common grade 3/4 adverse effects: anemia (44%), thrombocytopenia (58%), fatigue (25%)
    - Nausea and decreased appetite occurred in 72% and 56% of patients, respectively

Chari A, et al. *N Engl J Med.* 2019;381:727-738.

Selinexor: Combination Therapy

- **BOSTON:** phase 3 study of patients exposed to 1 to 3 prior lines of therapy
  - Once-weekly selinexor 100 mg PO + bortezomib 1.3 mg/m^2 + dexamethasone 40 mg (SVd); n = 195 versus twice weekly VD; n = 207
  - Outcomes
    - SVd resulted in significantly longer median PFS: 13.9 months and 9.5 months
    - Median OS NR with SVd versus 25 months with Vd alone (P = 0.28)
  - ≥Grade 3 adverse effects: thrombocytopenia (35.9% vs 15.2%), fatigue (11.3% vs 0.5%), nausea (7.7% vs 0%)
- **STOMP**: phase 1b/2 study
  - Selinexor in combination with carfilzomib, lenalidomide, or pomalidomide
  - Ongoing

Dimopoulos MA, et al. *J Clin Oncol*. 2020;38:8501; Gasparetto C, et al. *J Clin Oncol*. 2020;38:8510; Gasparetto C, et al. *J Clin Oncol*. 2020;38:8530.

Panobinostat: Histone Deacetylase Inhibitor

- Oral agent blocking aggresome pathway
  - Dosed every other day for 3 doses/week weeks 1 and 2 of a 21-day cycle
- **PANORAMA-1**: phase 3 randomized trial of panobinostat + Vd (PanoVd) vs Vd
  - Patients received at least 2 prior lines of therapy, including bortezomib and IMiD
  - Outcomes: PanoVd vs Vd
    - Median PFS: 11.99 months vs 8.08 months
    - Median OS: 40.3 months vs 35.8 months
  - Adverse effects: PanoVd vs Vd
    - Thrombocytopenia (67% vs 31%), lymphopenia (53% vs 40%)
    - Diarrhea (26% vs 8%)
    - Fatigue (24% vs 12%)
  - Led to FDA approval in combination with bortezomib + dexamethasone
  - Recommended in NCCN guidelines; adverse effects may limit use

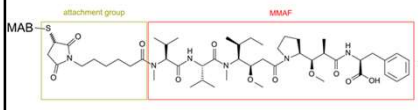
San-Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-1206; San-Miguel JF, et al. *Blood*. 2015;126(23):3026; Farydak. Prescribing information. Secura Bio. September 2019. Accessed August 18, 2020. us.farydak.com/assets/pdf/Farydak-SBI-USPI-201909.pdf

Venetoclax: BCL-2 Inhibitor

- Oral agent indicated in relapsed disease in patients with t(11;14)
  - 400 mg by mouth daily x 1 month, 800 mg by mouth daily thereafter + dexamethasone weekly
- **Phase 1 data**:
  - ORR with venetoclax monotherapy and in combination with Vd were 21% and 67%, respectively
  - ORR increased to 40% with venetoclax monotherapy and 65% with Vd in patients with t(11;14)
- **BELLINI trial**: Venetoclax + Vd (VenVd) vs Vd alone in patients with r/r MM with 1-3 prior lines of therapy; phase 3 trial
  - Median follow-up of 28.6 months
    - ORR 82% vs 68%
    - Minimal residual disease negativity rates were 13% vs 1%
  - Median PFS not reached for patients with t(11;14) (13% of total population) in the combination arm vs 9.3 months for Vd alone

Kumar S, et al. *Blood*. 2017;130:2401-2409; Moreau P, et al. *Blood*. 2017;130(22):2392-2400; Kaufman JL, et al. *Blood*. 2019;134(suppl_1):926. Kumar S, et al. *J Clin Oncol*. 2020:38(suppl):8509; Harrison S, et al. *Blood*. 2019;134(suppl_1):142.

B-Cell Maturation Antigen (BCMA) Target



- BCMA is expressed on normal plasma cells and MM cells
  - Normal cells:
    - Supports survival of plasma cells
    - Produces antibodies
    - Class switch of immunoglobulin
  - MM cells:
    - Promotes proliferation and survival of MM cells
    - Associated with immunosuppressive bone marrow microenvironment
    - Increased sBCMA level is associated with disease progression and worse outcomes

Cho SF, et al. *Front Immunol*. 2018;9:1821. Image entered into the public domain on March 16, 2014.

Belantamab mafodotin-blmf: DREAMM-2

- Fully humanized antibody-drug conjugate against BCMA conjugated to the microtubule-disrupting agent MMAF (monomethyl auristatin-F)

Open-label, phase 2, multinational study	
Patients	• Disease progression after 3 or more prior lines of therapy (IMiDs, PI, CD38 mAb) • 2.5 mg/kg (n=97) or 3.4 mg/kg (n=99) belantamab mafodotin-blmf IV day 1 every 3 weeks

Results	• ORR: 31% of patients in 2.5 mg/kg cohort and 34% in 3.4 mg/kg cohort
	• Grade 3/4 adverse effects 2.5 mg/kg versus 3.4 mg/kg:
	  • Keratopathy: 27% vs 21%
	  • Thrombocytopenia: 20% vs 33%
	  • Anemia: 20% vs 25%

Conclusion	• Single-agent belantamab mafodotin-blmf shows anti-myeloma activity with a manageable safety profile • Led to priority review with FDA August 2020 at 2.5 mg/kg dose

Lonial S, et al. *Lancet Oncol*. 2020;21:207-221. Blenrep. Prescribing information. GlaxoSmithKline; August 2020. Accessed August 20, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf

Belantamab mafodotin-blmf Supportive Care

- Baseline and subsequent ophthalmic exams required prior to each dose
- Eyecare
  - Preservative-free artificial tears: 2-4 drops in each eye 4 times daily
  - Cooling eye mask may be applied during infusion
  - Avoid contact lenses
- Platelet transfusions may be needed for thrombocytopenia

Lonial S, et al. *Lancet Oncol*. 2020;21:207-221. Blenrep. Prescribing information. GlaxoSmithKline; August 2020. Accessed August 20, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf

Other Emerging Investigational Drugs

- Melphalan flufenamide (Melflufen)
  - First-in-class peptide-drug conjugate
  - Targets aminopeptidases and rapidly releases alkylating agents into tumor cells
  - Phase 2 HORIZON (NCT02963493); phase 3 OCEAN trial (NCT03151811)
- Iberdomide (CC-220)
  - Orally bioavailable cereblon modulator (CELMoD), structurally similar to pomalidomide and lenalidomide but binds with higher affinity
  - Phase 1/2 (NCT02773030)
- CC-92480
  - Novel IMiD under investigation
  - Phase 1 (NCT03803644, NCT03374085)

NIH ClinicalTrials.gov. Accessed July 6, 2020. clinicaltrials.gov

Pharmacist Role in Managing Relapsed/Refractory Multiple Myeloma

Medication-Specific Monitoring

IMiDs	• VTE prophylaxis, pregnancy risk, secondary malignancies • Lenalidomide: rash and diarrhea
PIs	• Herpes reactivation, blepharitis/conjunctivitis • Bortezomib: peripheral neuropathy • Ixazomib: nausea/vomiting • Carfilzomib: heart failure, TMA
Monoclonal antibodies	• Infusion-related reactions, hepatitis B reactivation, interference with serological testing (obtain baseline type and screen)
Selinexor	• Nausea/vomiting, weight loss, appetite suppression
Venetoclax	• Tumor lysis syndrome monitoring
Belantamab mafodotin-blmf	• Keratopathy, dry eyes, blurry vision

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021); NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (Version 2.2020); Lonial S, et al. *Lancet Oncol*. 2020;21:207-221; Lee DW, et al. *Biol Blood Marrow Transpl*. 2019;35(4):625-638.

Supportive Care

- Bone-modifying agents
  - Zoledronic acid
  - Pamidronate
  - Denosumab
- Venous thromboembolism (VTE) prophylaxis
  - Aspirin 81 to 162 mg by mouth daily
  - Based on risk factors, consider oral rivaroxaban 10 mg daily or apixaban 2.5 mg BID
- VTE treatment
  - Enoxaparin or rivaroxaban/apixaban
- Peripheral neuropathy
  - Gabapentin, pregabalin, duloxetine

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).; NCCN Clinical Practice Guidelines for Cancer-Associated Venous Thromboembolic Disease (Version 1.2020), NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (Version 2.2020), Hershman DL, et al. *J Clin Oncol*. 2014;32(18):1941-1967; Anderson K, et al. *J Clin Oncol*. 2018;36(8):8128-8118.

Supportive Care

- Myelosuppression/Infection
  - Growth factor support and transfusions as needed
  - Erythropoietin-stimulating agents in select cases
  - Herpes simplex virus/varicella zoster prophylaxis (eg, acyclovir)
  - Bacterial prophylaxis (eg, levofloxacin) as needed for prolonged neutropenia
  - PJP prophylaxis (eg, sulfamethoxazole/trimethoprim) indicated based on steroid dose
- Endocrine monitoring
  - Thyroid-stimulating hormone (on IMiDs) and blood glucose
- Renal dysfunction
  - Renally adjustments
  - Dose after hemodialysis if needed

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (Version 2.2021).; NCCN Clinical Practice Guidelines for Cancer-Associated Venous Thromboembolic Disease (Version 1.2020), NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections (Version 2.2020), Hershman DL et al. *J Clin Oncol*. 2014;32(18):1941-67. Anderson K et al. *J Clin Oncol*. 2018;36(8):812-18.

Pharmacist-Led Communication

- Education of patients, caregivers, medical team
- Supportive care recommendations
- Chemotherapy dosing
  - Recommended dose modifications based on organ function or adverse effects
  - Management of drug–drug interactions
- Medication adherence techniques
  - Medication calendars, alarms, apps
  - Telehealth visits
  - Appropriate dosage form selection based on patient-specific factors
- Transitions of care
  - Multidisciplinary communication

Mackler E et al. *JOP*. 2019;15(4):203-e355 Sweiss K, et al. *JOP*. 2018 Nov;14(11):e674-e682. Segal E, et al. JOPP. 2019; 25(8):1945-67.

Conclusion

- Currently no universal standard for optimal sequencing of therapy in R/R MM
- Factors impacting treatment selection for R/R MM include patient specifics, disease cytogenetics, prior therapies, and timing of relapse
- Novel agents are emerging as treatment options for R/R disease
- Pharmacists have many opportunities to intervene with chemotherapy selection, education, dosing, and supportive care

Additional Resources

International Myeloma Foundation	www.myeloma.org
National Comprehensive Cancer Network: Multiple Myeloma Guidelines	www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
mSMART Stratification for Myeloma and Risk-Adapted Therapy	www.msmart.org/mm-treatment-guidelines
Management of Relapsed and Refractory Multiple Myeloma	Chim CS, et al. *Leukemia*. 2018;32:252-262.
B-cell maturation antigen (BCMA) in multiple myeloma	Shah N, et al. *Leukemia*. 2020;34:985-1005.
Medication Education Materials	www.chemocare.com

Supplemental Slides

Abbreviations

- ASCT: autologous stem cell transplant
- Dara-RVD: daratumumab, lenalidomide, bortezomib, dexamethasone
- DaraKd: daratumumab, carfilzomib, dexamethasone
- DaraPd: daratumumab, pomalidomide, dexamethasone
- DaraRd: daratumumab, lenalidomide, dexamethasone
- DaraVd: daratumumab, bortezomib, dexamethasone
- Dara-VMP: daratumumab, bortezomib, melphalan, prednisone
- EloPd: elotuzumab, pomalidomide, dexamethasone
- EloRd: elotuzumab, lenalidomide, dexamethasone
- HDT: high-dose therapy
- HSV: herpes simplex virus
- IRD: ixazomib, lenalidomide, dexamethasone
- IsaPd: isatuximab, pomalidomide, dexamethasone
- Kd: carfilzomib and dexamethasone
- KPD: carfilzomib, pomalidomide, dexamethasone
- KRD: carfilzomib, lenalidomide, dexamethasone
- MOA: mechanism of action
- ORR: overall response rate
- OS: overall survival
- PFS: progression-free survival
- Pd: pomalidomide and dexamethasone
- PJP: *Pneumocystis jiroveci* pneumonia
- Rd: lenalidomide and dexamethasone
- R/R MM: relapsed/refractory multiple myeloma
- RVD: lenalidomide, bortezomib, dexamethasone
- SAE: serious adverse effect
- TSH: thyroid-stimulating hormone
- Vd: bortezomib and dexamethasone
- VGPR: very good partial response
- VPD: bortezomib, pomalidomide, dexamethasone
- VZV: varicella zoster virus

Investigational BCMA-Targeted Therapies

Chimeric Antigen Receptor T-cell (CAR T-cell) Therapy		
Idecabtagene vicleucel (bb2121)	Genetically modified autologous T-cell immunotherapy (containing human cells modified with a lentiviral vector); patient's T cells are reprogrammed with a transgene encoding a CAR to identify and eliminate BCMA-expressing malignant and normal cells. After binding to BCMA-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the CAR T cells	Phase 1 (NCT03274219) Phase 2 (NCT03601078) Phase 3 (NCT03651128)
Bb21217		Phase 1 (NCT03274219)
JCARH125		Phase 1/2 (NCT03430011)
LCAR-B38M		Phase 1/2 (NCT03090659) Phase 2 (NCT03758417)
P-BCMA-101		Phase 1/2 (NCT03288493)
CT053		Phase 1b (NCT03915184)
Bi-specific T-cell engagers (BiTEs)		
AMG420	Binds to BCMA expressed on MM cells and CD3 expressed on T cells; activates endogenous T cells by connecting CD3 in the T-cell receptor complex with BCMA on MM cells, which causes MM cell death and T-cell proliferation	Phase 1b (NCT03836053)
AMG701		Phase 1/2 (NCT03287908)
CC-93269		Phase 1 (NCT03486067)

NIH ClinicalTrials.gov. Accessed July 6, 2020. clinicaltrials.gov/

Metastatic Non–Small Cell Lung Cancer in the Era of Immune Checkpoint Inhibitors

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Seattle, Washington

PTce

Educational Objectives

After completion of this activity, participants will be able to:

- Describe current therapy options in the treatment of metastatic non–small cell lung cancer (NSCLC), including emerging immune checkpoint inhibitors and the role of tumor genome testing
- Recognize adverse effects associated with immune checkpoint inhibitor therapy and identify applicable prevention and management strategies
- Discuss effective tools pharmacists can use to maximize therapeutic outcomes for patients with metastatic NSCLC

Incidence and Epidemiology

- Estimated 228,820 new cases of lung cancer in 2020
- 5-year relative survival rate of 20.5%

Lung Cancer: Incidence and Survival		
Stage	**Frequency of Diagnosis (%)**	**5-Year Survival (%)**
Localized	17	59
Regional	22	31.7
Distant	57	5.8
Unknown	4	8.3

SEER18 2010-2016, All Races, Both Sexes by SEER Summary Stage 2000. Accessed July 18, 2020. seer.cancer.gov/statfacts/html/lungb.html

Pathology of NSCLC

- NSCLC histology: 80% to 85% of all lung cancers
  - **Adenocarcinoma: ≈40% of NSCLC, most common type in nonsmokers**
  - Squamous cell carcinoma: 25%-30% of NSCLC
  - Large cell carcinoma: 10%-15% of NSCLC
- Small cell lung cancer (SCLC) histology: 10% to 15% of all lung cancers
  - Classic small cell carcinoma
  - Large cell neuroendocrine cancer
  - Combined small cell carcinoma
  - Typical carcinoid
  - Atypical carcinoid

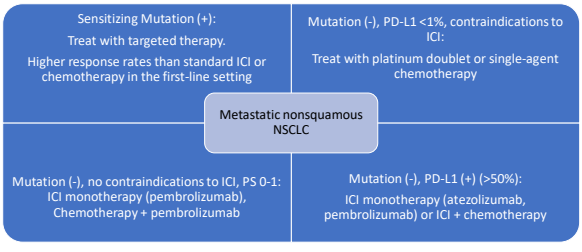
Govindan R, et al. *J Clin Oncol*. 2006;24(28):4539-4544.
Wahbah M, et al. *Ann Diagn Pathol*. 2007;11(2):89-96.

Determining Treatment for New Diagnosis of Metastatic NSCLC

- Assess patient performance status
- Molecular and biomarker testing
  - Molecular profiling for oncogenic driver variants/sensitizing mutations such as *EGFR*, *BRAF*, *ALK*, *MET*, *ROS1*
  - Immunohistochemistry (IHC) analysis testing for programmed death ligand 1 (PD-L1) expression
    - PD-L1 expression on tumor-infiltrating immune cells or tumor cells may be used as a biomarker to predict antitumor response
    - PD-L1 expression correlates to response rates up to 20%; may be imprecise
    - Shortcomings
      - Availability of assays to measure PD-L1
      - Variability of PD-L1 expression

NCCN Guidelines for Non-Small Cell Lung Cancer. V8.2020; Garinet S, et al. *J Clin Med*. 2018;7(6):144; Goldberg SB. *Am J Hematol/Oncol*. 2015;11(9):10-13; Davis AA, Patel VG. *J Immunother Cancer*. 2019;7:278.

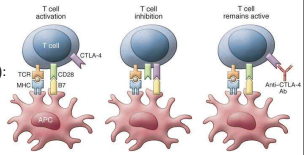
Initial Management: Nonsquamous NSCLC



NCCN Guidelines for Non-Small Cell Lung Cancer. V8.2020.

Immune Checkpoints and Cancer

- Immune homeostasis critical to survival
- Uncontrolled immune response can cause inflammation and autoimmune disease
- To prevent this, the immune system relies on checkpoints:
  - **Programmed cell death protein 1 (PD-1)**: regulates T-cell activity within tissues and tumors
    - Drug therapy: nivolumab
  - **Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)**: develops tolerance to self-proteins by neutralizing protein CD28
    - Drug therapy: ipilimumab
- Immune checkpoints help regulate immune homeostasis, chronic infections, and tumor antigens
  - Can be dysregulated by tumors leading to immune resistance

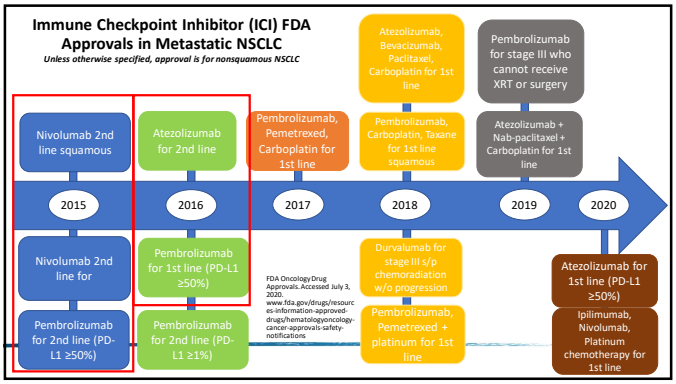


Republished with permission of American Society for Clinical Investigation, from "Cytotoxic T lymphocyte antigen-4 and immune checkpoint blockade," Buchbinder E, Hodi FS. Vol. 125, No. 9 © 2015; permission conveyed through Copyright Clearance Center, Inc.

Pardoll D. *Nat Rev Cancer*. 2012;12:252-264. Image: Buchbinder E, et al. *J Clin Invest*. 2015;125(9):3377-3383; NCCN Guidelines for Non-Small Cell Lung Cancer. V8.2020.

Immune Checkpoint Inhibitor (ICI) FDA Approvals in Metastatic NSCLC

Unless otherwise specified, approval is for nonsquamous NSCLC



FDA Oncology Drug Approvals. Accessed July 3, 2020. www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications

ICI in Pretreated NSCLC: Impact on Survival

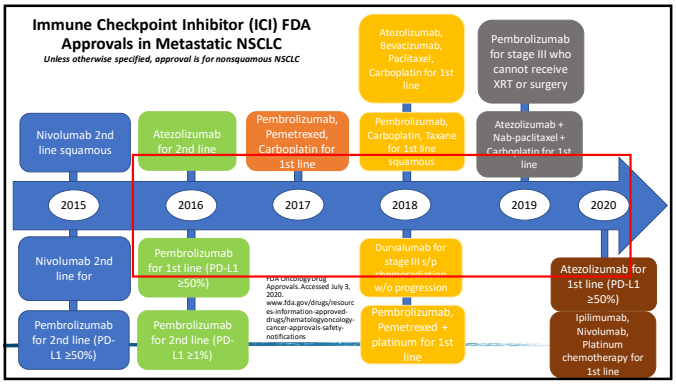
Study	Median Overall Survival (OS) (Months)	*P* Value	Median Progression-Free Survival (Months)
CheckMate 017 Nivolumab versus docetaxel	Nivolumab: 9.2 Docetaxel: 6	<0.001	Nivolumab: 3.5 Docetaxel: 2.8
CheckMate 057 Nivolumab versus docetaxel	Nivolumab: 12.2 Docetaxel: 9.4	0.002	Nivolumab: 2.3 Docetaxel: 4.2
Keynote-010 Pembrolizumab versus docetaxel	Pembrolizumab (PD-L1 >1%): 12.7 Pembrolizumab (PD-L1 >50%): 17.3 Docetaxel: 8.5	<0.001	Pembrolizumab (PD-L1 >1%): 3.9 Pembrolizumab (PD-L1 >50%): 5 Docetaxel: 4
OAK Atezolizumab versus docetaxel	Atezolizumab 13.8 Docetaxel: 9.6	0.0003	Atezolizumab: 2.8 Docetaxel: 4

ICI demonstrated superior overall survival advantages compared with chemotherapy in patients with **pretreated** advanced NSCLC.

Brahmer J, et al. *N Engl J Med*. 2015;373:123-135; Borghaei H, et al. *N Engl J Med*. 2015;373:1627-1639; Herbst RS, et al. *Lancet*. 2016;387:1540-1550; Rittmeyer A, et al. *Lancet*. 2017;389(10066):255-265.

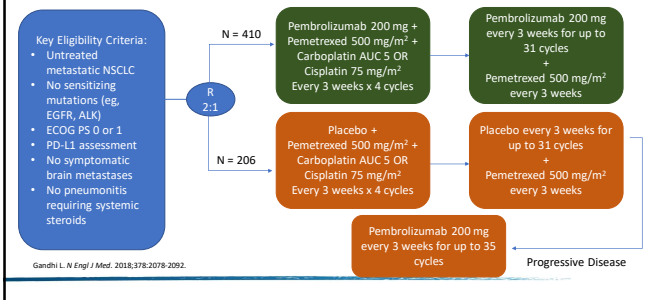
Immune Checkpoint Inhibitor (ICI) FDA Approvals in Metastatic NSCLC

Unless otherwise specified, approval is for nonsquamous NSCLC



FDA Oncology Drug Approvals. Accessed July 3, 2020. www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications

From the 2nd Line to Initial Treatment
Keynote-189: Pembrolizumab + Chemotherapy



Gandhi L. *N Engl J Med*. 2018;378:2078-2092.

Keynote-189: Pembrolizumab + Chemotherapy

Outcome	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy	Hazard Ratio (HR)
OS	12 months	11.3 months	0.49; 95% CI, 0.38-0.64
PFS	8.8 months	4.9 months	0.48; 95% CI, 0.40-0.58
ORR	48%	18.9%	95% CI, 13.8-25.0
Duration of response	11.2 months	7.8 months	N/A

Pembrolizumab + chemotherapy showed prolonged OS, PFS, ORR, and duration of response in the 1st line treatment setting in patients with metastatic NSCLC lacking EGFR or ALK mutations

Gandhi L. *N Engl J Med*. 2018;378:2078-2092.

First-Line Immunotherapies in Metastatic NSCLC

Study	Treatment	Median OS Survival	*P* Value
First-line: Immunotherapy versus chemotherapy			
Keynote-024	Pembrolizumab vs platinum doublet	HR, 0.60 (95% CI, 0.41-0.89)	0.005
Keynote-042	Pembrolizumab vs platinum doublet	16.7 months vs 12.1 months	0.0018
Checkmate-227	Nivolumab + ipilimumab vs platinum doublet	17.1 months vs 14.9 months	*P* = 0.007

Immunotherapy resulted in improved median OS compared to chemotherapy

Berghmans T, et al. Eur Respir J. 2020;55:01907-2019; Hellmann M, et all. *N Engl J Med.* 2019;381:2020-2031.

First-Line Immunotherapies in Metastatic NSCLC

Study	Treatment	Median OS Survival	*P* Value
First-line: Chemotherapy-immunotherapy versus chemotherapy			
Keynote-407	Carboplatin + nab-paclitaxel ± pembrolizumab	15.9 months vs 11.3 months	<0.001
IMpower150	Carboplatin + paclitaxel + bevacizumab ± atezolizumab	19.2 months vs 14.7 months	0.02
Checkmate-9LA	Nivolumab + ipilimumab + platinum doublet	14.1 months vs 10.7 months	Not significant

Immunotherapy + chemotherapy resulted in improved median OS compared to chemotherapy alone

Berghmans T, et al. Eur Respir J. 2020;55:01907-2019; Hellmann M, et all. *N Engl J Med.* 2019;381:2020-2031.

Adenocarcinoma NSCLC: 1st Line Treatment

PD-L1 expression over 1%, nonsquamous

First-line Systemic Therapy Options (PS 0-1)	First-line Systemic Therapy Options (PS 2)
Preferred: **Pembrolizumab**/carboplatin/pemetrexed **Pembrolizumab**/cisplatin/pemetrexed	Preferred: Carboplatin/pemetrexed
Other Recommended: **Atezolizumab**/carboplatin/(albumin-bound) paclitaxel/bevacizumab **Nivolumab + ipilimumab** **Nivolumab + ipilimumab** + pemetrexed + (carboplatin or cisplatin) **Pembrolizumab**	Other Recommended: Carboplatin/albumin-bound paclitaxel Carboplatin/docetaxel Carboplatin/etoposide Carboplatin/gemcitabine Carboplatin/paclitaxel
Contraindication to PD-1 or PD-L1 Inhibitors: Bevacizumab/carboplatin/paclitaxel Carboplatin/pemetrexed Cisplatin/pemetrexed Carboplatin/paclitaxel Carboplatin/etoposide Gemcitabine/docetaxel	Useful in Certain Circumstances: Albumin-bound paclitaxel Docetaxel Gemcitabine Gemcitabine/docetaxel Gemcitabine/vinorelbine Pemetrexed

NCCN Guidelines for Non-Small Cell Lung Cancer. V8. 2020.

*Atezolizumab monotherapy recommended in patients with PD-L1 expression less than 1%.

Review: New Diagnosis Metastatic NSCLC Treatment

- Patients with metastatic NSCLC and PD-L1 ≥1% with a targetable driver oncogene variant (eg, EGFR, ALK, ROS1) should receive first-line targetable treatment
- Common strategies; should be individualized to each patient:
  - PD-L1 ≥50% ICI monotherapy (eg, pembrolizumab) alone is recommended
  - PD-L1 ≤50% ICI + chemotherapy followed by ICI maintenance
  - Patients contraindicated to chemotherapy: nivolumab + ipilimumab

NCCN Guidelines for Non-Small Cell Lung Cancer. V8.2020.

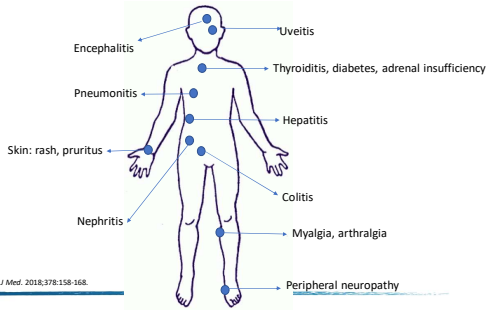
Management of Immune-Related Adverse Events (irAEs)

Immune-Related Adverse Events (irAEs)

- Adverse effect associated with oncology immunotherapies
  - CTLA-4 inhibitors: increased grade 3 adverse effects; 20% incidence overall
    - Associated with colitis
  - PD-1/PD-L1 inhibitors: 10% to 13% incidence of irAEs
    - Associated with thyroiditis and pneumonitis
- Mechanism: removal of activation of autoreactive T cells, increased inflammatory cytokines, or generation of autoreactive antibodies

Kennedy LC, et al. *JNCCN*. 2019;17(6):750-757; Medina PJ, Adams VR. *Pharmacotherapy*. 2016;36(3):317-334.
Postow MA, et al. *N Engl J Med*. 2018;378(2):158-168.

ICI Impact on Organ Systems



Postow MA, et al. *N Engl J Med*. 2018;378:158-168.

Pharmacist Involvement: irAE Management

- Early recognition
- Assess irAE severity: Common Terminology Criteria for Adverse Events (CTCAE)
- Consult specialists for complex management
- Use available guideline recommendations for management
  - National Comprehensive Cancer Network, European Society for Medical Oncology
  - Prescribing information
- Educate patients on potential adverse effects

Pustanov I, et al. *J Immunother Cancer*. 2017;5:95:1-28. Medina PI, et al. J Pharm Pract. 2020;33(3):338-49. US Department of Health and Human Services. Common terminology criteria for adverse events. V5.2017. Accessed July 18, 2020. ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Risk Factors and Onset of irAEs

- Risk factors
  - Combination therapy with PD-1/CTLA-4 (eg, nivolumab + ipilimumab)
  - Preexisting autoimmune disorders
  - Organ dysfunction
  - Chronic viral infections
- Most irAEs occur in the first 6 months of treatment

Organ	Onset (weeks)	Incidence (all grades) %
Lower GI tract	3	0.3 – 20
Endocrine	7	20
Skin	7	13-34
Renal	10.5	<5
Hepatic	15-18	2-10, 25-30 with combination ICI therapy
Pulmonary	15-18	1-5

Kennedy LC, et al. *JNCCN*. 2019;17(6):750-757; Martins F, et al. *Nat Rev*. 2019;16:563-580.
Medina PI, et al. J Pharm Pract. 2020;33(3):338-49

irAE Management

Grade	Management of irAE	Concomitant Treatment With ICI	Management of Persistent or Refractory irAE
1	Monitor	Continue	N/A
2	Begin systemic steroids*	Consider holding, if holding resume when < grade 1	Systemic steroids
3	Systemic steroids with prolonged taper >4 weeks	Hold or discontinue	Additional immunosuppression (eg, infliximab), d/c ICI
4	Systemic steroids with prolonged taper >4 weeks	Discontinue (except for endocrine irAE)	Add additional immunosuppression

***Immunosuppressive Systemic Steroid Regimens:**
- Methylprednisolone (IV) or prednisone (PO) 0.5 to 1 mg/kg/day
- Methylprednisolone (IV) or prednisone (PO) 1 to 2 mg/kg/day

Kennedy LC, et al. *JNCCN*. 2019;17(6):750-57. Postow MA, et al. *N Engl J Med*. 2018;378(2):158-168. Medina PI, et al. *J Pharm Pract*. 2020;33(3):338-49. National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2020). Accessed July 3, 2020. nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Pneumonitis

Background & Symptoms	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3-4)

• Incidence: <10%
  • Median onset: 3 months
  • Higher incidence in NSCLC
• Dyspnea
• Cough
• Exclude infection
	• Consider holding ICI
	• Reassess in 1-2 weeks
		• Hold ICI
		• Prednisone 1-2 mg/kg orally daily
		• Monitor every 3 to 7 days, if no improvement, treat as grade 3
			• Discontinue ICI
			• Inpatient care required
			• Methylprednisolone 1-2 mg/kg/day, taper over 6+ weeks
			• No improvement over 48 hours: consider adding infliximab, IVIG, or mycophenolate

Brahmer JE, et al. *J Clin Oncol*. 2018;36:1714-1768; National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2020). Accessed July 3, 2020. nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Dermatologic Reactions

Background & Symptoms	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)

• Incidence: 13%-34%
  • Median onset: 1-4 weeks
  • Can persist >20 weeks
• Maculopapular rash
• Blistering
• Redness
• Pruritus
• Pain
	• Continue ICI
	• Topical emollient
	• Oral antihistamines
	• Moderate-potency topical steroid to affected area
		• Continue ICI
		• Topical emollient
		• Oral antihistamine
		• Moderate- to high-potency topical steroid AND/OR prednisone 0.5-1 mg/kg/day
			• Hold ICI
			• High-potency topical steroids
			• Prednisone 0.5 to 1 mg/kg/day (max 2 mg/kg/day)
			• Urgent dermatology consult
			• Consider inpatient management

Brahmer JE, et al. *J Clin Oncol*. 2018; 36: 1714-1768; NCCN. Guidelines for Management of Immunotherapy-Related Toxicities (V1.2020). Accessed July 3, 2020. nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Colitis

Background & Symptoms	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3-4)

• Incidence: 0.3%-16%
  • Median onset: 4-10 weeks
  • CTLA-4 > PD-1
• Abdominal pain
• Diarrhea
• Black, tarry stools
• Blood or mucus in stools
• Rule out infection, medications
	• Consider holding ICI
	• Loperamide or diphenoxylate/atropine for 2-3 days
	• Hydration
	• MONITOR CLOSELY. If persistent, check lactoferrin; if positive, treat as G2. If negative, add mesalamine, cholestyramine
		• Hold ICI
		• Prednisone 1-2 mg/kg/day
		• No response in 2-3 days, continue steroids, add infliximab or vedolizumab within 2 weeks
			• Discontinue ICI
			• Consider inpatient management
			• IV methylprednisolone 1-2 mg/kg/day
			• No response in 2 days, continue steroids, add infliximab or vedolizumab within 2 weeks

Brahmer JE, et al. *J Clin Oncol*. 2018;36:1714-1768; NCCN. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2020). Accessed July 3, 2020. nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Hepatitis: Transaminitis Without Elevated Bilirubin

Background & Symptoms	Mild (Grade 1), Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)

• Incidence: 2%-10%, 25%-30% with combination ICI therapy
  • Median onset: 6-14 weeks
• Elevated LFTs with or without elevated bilirubin
• Abdominal pain
• Jaundice
• Bleeding/bruising
	• **Grade 1**
	  • Continue ICI
	  • Monitor frequently
	• **Grade 2**
	  • Hold ICI
	  • LFTs every 3-5 days
	  • Consider prednisone 0.5-1 mg/kg/day
		• Discontinue ICI
		• Prednisone 1-2 mg/kg/day
		• Consider inpatient care
		• Monitor LFTs every 1-2 days
		• No response after 3 days, consider adding mycophenolate
			• Discontinue ICI
			• Prednisone 2 mg/kg/day
			• Inpatient care
			• Monitor LFTs every 1-2 days
			• No response after 3 days, consider adding mycophenolate

Brahmer JE, et al. *J Clin Oncol*. 2018;36:1714-1768.
NCCN. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2020). Accessed July 3, 2020. nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Steroid-Refractory irAEs

- Patients with steroid-refractory irAEs require acute care management
- No preferred agent; doses and duration of therapy variable

ASCO/NCCN/SITC Clinical Guidelines	
Antithymocyte globulin (ATG)	Mycophenolate
Azathioprine	Plasmapheresis
Cyclophosphamide	Sulfasalazine
Cyclosporine	Rituximab
Infliximab	Thrombopoietin receptor agonists
Intravenous immune globulin (IVIG)	TNF-α inhibitors
Leflunomide	Tocilizumab
Methotrexate	Vedolizumab

Martins F, et al. *Lancet Oncol*. 2019;20(1):e56-e64; NCCN. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2020). Accessed July 3, 2020. nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; Brahmer JE, et al. *J Clin Oncol*. 2018;36:1714-1768; Puzanov I, et al. *J Immunother Cancer*. 2017;5:95

Pharmacist Involvement in irAE Management

- Ensure correct steroid dose and duration administered
- Severe irAEs/absorption concerns: consider use of IV steroids as first-line option
- Use of other immunomodulatory agents: dosing, duration, AE management
- Recommend steroid taper once irAE resolved
  - Do not discontinue steroids when adding other immunomodulatory agents
  - *Pneumocystis jiroveci* prophylaxis (eg, sulfamethoxazole/trimethoprim): considered in patients with more than 3 weeks of immunosuppression with over 30 mg of prednisone or equivalent/day
  - Gastrointestinal prophylaxis recommended (eg, omeprazole, rantitidine)
- Provide patients with education, including wallet card

Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. Medina PJ, et al. J Pharm Pract. 2020;33(3):338-49

Conclusions

- ICIs have demonstrated prolonged OS compared with platinum-based chemotherapy
- ICI + chemotherapy should be considered standard-of-care for patients with metastatic nonsquamous NSCLC with good PS without contraindications to ICI treatment
- Organ-related irAE is a diagnosis of exclusion; diagnosis may be challenging
  - Consider alternative causes such as infection, disease progression, and new medications in the differential diagnosis of an irAE
- Pharmacists play a key role in irAE management through therapy selection and education

Additional Resources

NCCN Guidelines for Lung Cancer	www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities	www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
American Society of Clinical Oncology Guidelines: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy	www.ascopubs.org/doi/10.1200/JCO.2017.77.6385
Society for Immunotherapy of Cancer Guidelines: Managing Toxicities Associated with Immune Checkpoint Inhibitors	https://doi.org/10.1186/s40425-017-0300-z
NCCN Understanding Immunotherapy Side Effects	www.nccn.org/images/pdf/Immunotherapy_Infographic.pdf

Supplemental Slide

First Line: Common ICI Regimens—Dosing and Administration

ICI	Indication	Dosing
Atezolizumab + bevacizumab + paclitaxel + carboplatin	1st line metastatic nonsquamous NSCLC no EGFR or ALK mutations	Q3W x 4-6 cycles: atezolizumab 1200 mg IV + paclitaxel 175 mg/m^2 IV on days 1, 8, 15 + carboplatin AUC 6 IV. Followed by atezolizumab 1200 mg IV + bevacizumab 15 mg/kg every Q3W
Atezolizumab + albumin-bound paclitaxel + carboplatin		Q3W x 4-6 cycles: atezolizumab 1200 mg IV + albumin-bound paclitaxel 100 mg/m^2 IV on days 1, 8, 15 + carboplatin AUC 6 IV. Followed by atezolizumab 840 mg IV Q2W, 1200 mg IV Q3W, or 1680 mg IV Q4W
Atezolizumab	1st line metastatic NSCLC with no EGFR or ALK mutations and PD-L1 ≥50%	840 mg IV Q2W, 1200 mg Q3W, or 1680 mg Q4W
Ipilimumab + nivolumab	1st line metastatic NSCLC with no EGFR or ALK mutations and PD-L1 ≥1%	Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg IV Q6W for a maximum of 2 years
Ipilimumab + nivolumab + platinum-based chemotherapy	1st line metastatic NSCLC with no EGFR or ALK mutations and PD-L1 ≥1%	Q3W x 2 cycles: platinum-based chemotherapy + nivolumab 360 mg IV Q3W+ ipilimumab 1 mg/kg Q6W. Followed by: Nivolumab 360 mg IV Q3W + Ipilimumab 1 mg/kg Q6W
Pembrolizumab + carboplatin + pemetrexed	1st line metastatic nonsquamous NSCLC with no EGFR or ALK mutations	Q3W x 4-6 cycles: Pembrolizumab 200 mg IV + pemetrexed 500 mg/m^2 IV + carboplatin AUC 5 IV. Followed by pembrolizumab 200 mg IV on day 1 or 400 mg IV on D1 every other cycle and pemetrexed 500 mg/m^2 IV on day 1 Q3W
Pembrolizumab + cisplatin + pemetrexed	1st line metastatic nonsquamous NSCLC with no EGFR or ALK mutations	Q3W x 4-6 cycles: pembrolizumab 200 mg IV + pemetrexed 500 mg/m^2 IV+ cisplatin 75 mg/m^2 IV. Followed by pembrolizumab 200 mg IV on day 1 or 400 mg IV on D1 every other cycle + pemetrexed 500 mg/m^2 IV on day 1 Q3W
Pembrolizumab	1st line metastatic NSCLC with no EGFR or ALK mutations and PD-L1 ≥50%	200 mg IV Q3W or 400 mg IV Q6W

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