New Drug Update

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Disclosures

- Nothing to disclose

Objectives

- Identify notable drug approvals over the last year
- Discuss mechanisms of action
- Summarize pertinent clinical studies
- Review indications, doses, adverse events, drug interactions and pertinent patient counseling points
- Highlight clinical impact and potential role in therapy

Since TOPA 2017…

- Ivosidenib (Tibsovo®)
- Gemtuzumab ozogamicin (Mylotarg™)
- Copanlisib (Aliqopa™)
- Inotuzumab ozogamicin (Besponsa™)
- Acalabrutinib (Calquence®)
- Axicabtagene ciloleucel (Yescarta®)
- Abemaciclib (Verzenio™)
- Encorafenib (Braftovi™)
- Binimetinib (Mektovi®)
- Apalutamide (Erleada™)
- Lutetium 177 dotatae (Lutathera®)

Ivosidenib (Tibsovo®)

- Approved July 2018
- Treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test

Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Ivosidenib (Tibsovo®)

- Mechanism of Action
  - Reversible, small molecule inhibitor of mutant IDH1
  - Inhibition of IDH1 decreases abnormal production of 2-hydroxyglutarate (2-HG), an oncometabolite
    - Restoring myeloid differentiation and oncogene regulation
- Dosing
  - 500 mg PO once daily until disease progression or unacceptable toxicity
- Dosage Forms/Administration
  - 250 mg tablets; taken without regard to food

Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Ivosidenib (Tibsovo®)

- Clinical Trial Data
  - AG120-C-001
    - Open-label, single-arm study
    - 174 adults with relapsed or refractory AML with an IDH1 mutation
      - Median number of prior therapies: 2
    - 24.7% of patients had complete remission (CR) and 8.0% had complete remission with partial hematologic improvement (CRh)
      - Median time to CR/CRh (months): 2.0 (0.9 – 5.6)
      - Median duration of CR/CRh (month): 8.2 (5.6-12)

DiNardo, CD et al. NEJM. 2018; 378:2386-2398.
Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Ivosidenib (Tibsovo®)

- Adverse Events
  - *Differentiation syndrome
  - QTc prolongation
  - Leukocytosis
  - Guillain-Barré syndrome
  - Fatigue
  - Arthralgia
  - Diarrhea
  - Dyspnea
  - Edema
  - Nausea
  - Mucositis
  - Rash
  - Pyrexia
  - Cough
  - Constipation

DiNardo, CD et al. NEJM. 2018; 378:2386-2398.
Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Ivosidenib (Tibsovo®)

- Differentiation Syndrome
  - Median onset: 29 days (range 5-59)
  - Neutrophil-predominant leukocytosis
  - Symptoms are generally non specific
    - Fever, edema, hypotension, malaise and pleural and/or pericardial effusions
  - Treatment
    - Systemic corticosteroids
    - Interrupt treatment if necessary

DiNardo, CD et al. NEJM. 2018; 378:2386-2398.
Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Ivosidenib (Tibsovo®)

- Monitoring parameters
  - Blood counts/chemistries
    - Weekly for the 1st month
    - Every other week for the 2nd month
    - Monthly thereafter
  - Creatine phosphokinase (CPK) weekly for the 1st month
  - EKGs weekly for the first three weeks, then monthly
  - Signs/symptoms differentiation syndrome

Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Ivosidenib (Tibsovo®)

- Clinical Pearls
  - First in class option for patients with relapsed or refractory AML with IDH1 mutation
    - Treat for a minimum of 6 months to allow time for response
  - CYP 3A4 substrate
  - Mutational testing with Abbott RealTime IDH1 assay
  - Cost: ~$31,000 (30 day supply)
  - myAgios Patient Support Services
    - Quick Start Program
    - Co-Pay program
    - Patient Assistance Program

Tibsovo®[package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc.; 2018.

Gemtuzumab ozogamicin (Mylotarg™)

- Approved September 2017
- Treatment of newly-diagnosed CD33 positive AML in adults and treatment of relapsed or refractory CD33 positive AML in patients ≥ 2 years old
  - May be used in combination with daunorubicin and cytarabine for adults with newly-diagnosed AML

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Gemtuzumab ozogamicin (Mylotarg™)

- Mechanism of Action
  - CD33 directed antibody-drug conjugate (ADC)
  - Cytotoxic agent, N-acetyl gamma calicheamicin induces double-strand DNA breaks once ADC internalized and N-acetyl gamma calicheamicin released intracellularly
    - Leading to cell cycle arrest and apoptotic cell death

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Gemtuzumab ozogamicin (Mylotarg™)

- Dosing
  - Newly Diagnosed CD33-positive AML
    - Combination (with daunorubicin and cytarabine)
      - Induction: 3 mg/m^2 (up to 4.5 mg) IV days 1, 4 and 7
      - Consolidation: 3 mg/m^2 (up to 4.5 mg) IV day 1
    - Single-agent
      - Induction: 6 mg/m^2 IV on day 1 followed by 3 mg/mg^2 IV on day 8
      - Continuation (up to 8 cycles): 2 mg/m^2 IV day 1 Relapsed or refractory CD33-positive AML (single agent)
  - Relapsed/refractory CD33-positive AML
    - 3 mg/m^2 (up to 4.5 mg) IV days 1, 4 and 7

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Gemtuzumab ozogamicin (Mylotarg™)

- Administration
  - Pre-medicate with acetaminophen, diphenhydramine and methylprednisolone
  - Infused over 2 hours through 0.2-micron polyethersulfone filter

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Gemtuzumab ozogamicin (Mylotarg™)

- Clinical Trial Data
  - ALFA-0701
    - Open-label, phase 3 study
    - 271 patients with newly diagnosed, de novo AML
    - Randomized 1:1 to 7+3d with or without gemtuzumab
    - Event-free survival 17.3 vs. 9.5 months
  - AML-19
    - Open-label, phase 3 study
    - 237 patients with newly diagnosed AML
    - Randomized to gemtuzumab vs. best supportive care
    - Median overall survival 4.9 vs. 3.6 months

Castaigne S, et al. Lancet. 2012; 379(9825):1508-16.
Amadori S, et al. J Clin Oncol. 2016; 34(9): 972-9.
Taksin AL, et al. Leukemia. 2007; 21(1): 66-71.

Gemtuzumab ozogamicin (Mylotarg™)

- Clinical Trial Data
  - MyloFrance-1
    - Open-label, single arm phase 2 study
    - 57 patients with AML in first relapse
    - 26% of patients achieved CR following single course of gemtuzumab
    - Median relapse-free survival 11.6 months

Castaigne S, et al. Lancet. 2012; 379(9825):1508-16.
Amadori S, et al. J Clin Oncol. 2016; 34(9): 972-9.
Taksin AL, et al. Leukemia. 2007; 21(1): 66-71.

Gemtuzumab ozogamicin (Mylotarg™)

- Adverse Events
  - *Veno-occlusive disease (VOD)
  - Infusion reaction
  - QTc prolongation
  - Increased AST and ALT
  - Hemorrhage
  - Infection
  - Fever
  - Nausea
  - Vomiting
  - Constipation
  - Rash
  - Mucositis

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Gemtuzumab ozogamicin (Mylotarg™)

- Monitoring Parameters
  - Liver function tests prior to each dose and at least 3 times per week through recovery
  - Serum chemistries
    - At least three times per week
  - EKG
    - Prior to therapy and as indicated
  - Infusion related reactions
    - Monitor during infusion and for at least 1 hour after end of infusion
  - Signs/symptoms of VOD
  - Signs/symptoms of tumor lysis syndrome
  - Signs/symptoms of bleeding

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Gemtuzumab ozogamicin (Mylotarg™)

- Clinical Pearls
  - First ADC approved for CD33 positive AML; consider in newly diagnosed patients with favorable and intermediate cytogenetic-risk disease
  - Cost: ~$9,800 (per 4.5 mg)

Mylotarg™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Copanlisib (Aliqopa™)

- Approved September 2017
- Treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies

Aliqopa™ [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; 2017.

Copanlisib (Aliqopa™)

- Mechanism of Action
  - Phosphatidylinositol-3-kinase (PI3K) inhibitor with activity predominantly against PI3K-alpha and PI3K-delta (expressed in malignant B cells)
    - Induces tumor cell death by apoptosis and inhibition of proliferation of primary malignant B cell lines
- Dosing
  - 60 mg IV days 1, 8, 15 of a 28-day treatment cycle
    - Continued until disease progression or unacceptable toxicity
- Administration
  - Infused over 1 hour

Aliqopa™ [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; 2017.

Copanlisib (Aliqopa™)

- Clinical Trial Data
  - CHRONOS-1
    - Single-arm, multicenter, phase 2 clinical trial
    - 104 patients with relapsed FL
      - Must have received rituximab and an alkylating agent
      - 36% of patients received three prior lines of therapy
    - Copanlisib dosing: 0.8 mg/kg or 60 mg fixed dose
    - Overall response rate 59%
      - CR 14%; PR 44.2%
    - Median duration of response 12.2 months
      - Median time to response 1.7 months

Dreyling MH, et al. JCO. 2017;35:15. Abstr 7535.

Copanlisib (Aliqopa™)

- Adverse Events
  - Hyperglycemia
  - Cutaneous reactions
  - Diarrhea
  - Fatigue
  - Hypertension
  - Leukopenia
  - Neutropenia
  - Thrombocytopenia
  - Lower respiratory tract infections

Dreyling MH, et al. JCO. 2017;35:15. Abstr 7535
Aliqopa™ [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; 2017.

Copanlisib (Aliqopa™)

- Monitoring Parameters
  - CBC weekly during treatment
  - Blood glucose
  - Blood pressure
  - Signs/symptoms of infection, pneumonitis and dermatologic toxicity

Aliqopa™ [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; 2017.

Copanlisib (Aliqopa™)

- Clinical Pearls
  - Third line option for FL
    - Manageable and distinct safety profile
    - Idelalisib (Zydelig) oral PI3K-delta inhibitor
  - CYP 3A4 substrate
  - Cost: ~$5,500 (per 60 mg)
  - Aliqopa™ Resource connections
    - Copay assistance
    - Patient Assistance Program

Aliqopa™ [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Approved August 2017
- Treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Mechanism of Action
  - CD22 directed ADC
  - Cytotoxic agent, N-acetyl gamma calicheamicin induces double-strand DNA breaks
- Dosing
  - Initial cycle: 1.8 mg/m^2 per cycle
    - 0.8 mg/m^2 day 1 followed by 0.5 mg/m^2 days 8 and 15
  - Subsequent cycles:
    - CR or CRi achieved: 1.5 mg/m^2 per cycle
      - 0.5 mg/m^2 days 1, 8, and 15

Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Administration
  - Pre-medicate with corticosteroid, antipyretic and antihistamine
  - Infused over 1 hour

Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Clinical Trial Data
  - INO-VATE ALL
    - Phase 3, open label trial
    - 326 patients with Philadelphia (Ph) chromosome positive or negative relapsed/refractory B-cell ALL
    - Randomized to inotuzumab vs. standard intensive chemotherapy
    - CR 80.7% vs. 29.4%
      - MRD negativity 78.4% vs. 28.2%

Kantarjian HM, et al. NJEM. 2016; 375:740-53.
Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Adverse Events
  - *Hepatotoxicity, including VOD
  - *Increased post-HSCT non-relapse mortality
  - Hyperbilirubinemia
  - Increased transaminases
  - Thrombocytopenia
  - Neutropenia
  - Infection
  - Anemia
  - Leukopenia
  - Fatigue
  - Hemorrhage
  - Pyrexia
  - Nausea
  - Headache
  - Febrile neutropenia
  - Abdominal pain

Kantarjian HM, et al. NJEM. 2016; 375:740-53.
Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Monitoring Parameters
  - CBC
    - Prior to each dose
  - LFTs
    - Prior to and following each dose
  - Electrolytes
  - EKG
    - Baseline and after initiation of any concomitant medications that are known to prolong QTc
    - Periodically as clinically indicated
  - Signs/symptoms of VOD
  - Infusion related reactions
    - Monitor during infusion and for at least 1 hour after end of infusion

Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Inotuzumab ozogamicin (Besponsa™)

- Clinical Pearls
  - First ADC for Ph-positive or Ph- negative ALL
    - Degree of CD22 expression did not affect remission rates
  - Cytoreduction recommended prior to first dose for patients with circulating lymphoblasts
    - Hydroxyurea, steroids, and/or vincrisine
  - Cost: ~$22,400 (per 0.9 mg)
  - Pfizer Oncology Together
    - Access and reimbursement support

Besponsa™ [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2017.

Acalabrutinib (Calquence®)

- Approved October 2017
- Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy

Calquence® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP.; 2017.

Acalabrutinib (Calquence®)

- Mechanism of Action
  - Selective and irreversible inhibitor of Bruton tyrosine kinase (BTK)
    - BTK is a critical effector molecule for B cell development and plays a major role in lymphoma genesis
- Dosing
  - 100 mg PO twice daily until disease progression or unacceptable toxicity
- Dosage Forms/Administration
  - 100 mg capsules; taken without regard to food
  - Avoid proton pump inhibitors (PPIs), separate antacids by at least 2 hours

Calquence® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP.; 2017.

Acalabrutinib (Calquence®)

- Clinical Trial Data
  - LY-004
    - Open label, phase 2 trial
    - 124 patients with MCL receiving at least 1 prior therapy (range 1-5 prior therapies)
    - Overall response rate 81%
    - Complete response rate 40%
    - Median time to response 1.9 months

Calquence® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP.; 2017.

Acalabrutinib (Calquence®)

- Adverse Events
  - Anemia
  - Thrombocytopenia
  - Neutropenia
  - Headache
  - Diarrhea
  - Fatigue
  - Myalgia
  - Bruising

Calquence® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP.; 2017.

Acalabrutinib (Calquence®)

- Monitoring Parameters
  - CBC monthly
  - Signs/symptoms of atrial flutter and fibrillation, bleeding, infection and secondary malignancies
    - Hepatitis B reactivation
    - Skin cancer reported most frequently (7%)

Calquence® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP.; 2017.

Acalabrutinib (Calquence®)

- Clinical Pearls
  - Second line option for patients with MCL
    - Second generation BTK inhibitor- more potent and selective than ibrutinib
    - ↑ neutropenia, ↑ secondary malignancy, ↓ bleeding, ↓ atrial fibrillation/flutter
  - Lymphocytosis (31.5% of patients)
    - Within 7 days of initiation, lasting for 6-7 weeks
  - Restricted to certain specialty pharmacies
  - CYP3A4 substrate
  - Cost: ~$16,900 (30 day supply)
  - AstraZeneca Patient Savings Program

Calquence® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, LP.; 2017.

Axicabtagene ciloleucel (Yescarta®)

- Approved October 2017
- Treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of therapy

Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

Axicabtagene ciloleucel (Yescarta®)

- Mechanism of Action
  - CD19 directed, genetically modified autologous T-cell immunotherapy
- Dosing
  - Target dose: 2 x 10^6 CAR-positive viable T cells per kg of body weight
  - Maximum dose: 2 x 10^8 CAR-positive viable T cells per kg of body weight
- Administration
  - Pre-medicate with acetaminophen and diphenhydramine
  - Infused over 30 minutes

Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

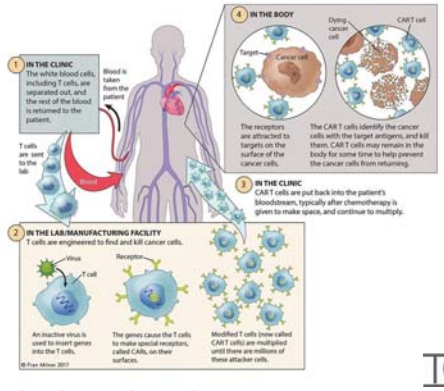


Image: http://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Axicabtagene ciloleucel (Yescarta®)

- Clinical Trial Data
  - ZUMA
    - Phase 2 multi-center study; single arm
    - 101 patients
      - 69% of patients received 3 prior lines of treatment
    - Low-dose conditioning chemotherapy with fludarabine and cyclophosphamide followed by infusion of CAR-T cells
    - ORR 82% (CR 54%)
    - Median time to respose 1 month (range 0.8-6)

Neelapu SS, et al. NEJM. 2017; 377:2351-44.
Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

Axicabtagene ciloleucel (Yescarta®)

- Adverse Events
  - *Cytokine release syndrome (CRS)
    - Fever, hypoxia, hypotension
    - Occurred in 94% of patients
      - Grade 3: 13%
  - *Neurologic toxicities
    - Encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, anxiety
    - Occurred in 87% of patients
      - Grade 3: 31%
    - Majority occur within first 8 weeks of infusion
      - Median onset 4 days (range 1-43)
      - Median duration 17 days

Neelapu SS, et al. NEJM. 2017; 377:2351-44.
Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

Axicabtagene ciloleucel (Yescarta®)

- Adverse Events
  - Prolonged cytopenias
  - Febrile neutropenia
  - Infections
  - Fever
  - Hypotension
  - Hypoxia

Neelapu SS, et al. NEJM. 2017; 377:2351-44.
Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

Axicabtagene ciloleucel (Yescarta®)

- Monitoring Parameters
  - Signs/symptoms CRS and neurologic toxicities daily for at least 7 days following infusion
  - Blood counts
  - Chemistries
  - Immunoglobulin levels

Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

Axicabtagene ciloleucel (Yescarta®)

- Clinical Pearls
  - Third line treatment option
  - Supportive care considerations
    - CRS
    - Hypogammaglobulinemia
    - Myeloid growth factor support
    - Seizure prophylaxis
    - Tumor lysis syndrome prophylaxis
  - Available at authorized treatment centers
  - Yescarta REMS Program
  - Cost: ~$373,000
  - Kite Konnect

Yescarta® [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017.

Since TOPA 2017…

- Ivosidenib (Tibsovo®)
- Gemtuzumab ozogamicin (Mylotarg™)
- Copanlisib (Aliqopa™)
- Inotuzumab ozogamicin (Besponsa™)
- Acalabrutinib (Calquence®)
- Axicabtagene ciloleucel (Yescarta®)

- Abemaciclib (Verzenio™)
- Encorafenib (Braftovi™)
- Binimetinib (Mektovi®)
- Apalutamide (Erleada™)
- Lutetium 177 dotatae (Lutathera®)

Abemaciclib (Verzenio™)

- Approved September 2017
- Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (MBC)
  - With disease progression following endocrine therapy (in combination with fulvestrant)
  - Initial endocrine-based therapy (in combination with an aromatase inhibitor[AI])
  - With disease progression following endocrine therapy and prior chemotherapy in the metastatic setting (monotherapy)

Verzenio™ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

Abemaciclib (Verzenio™)

- Mechanism of Action
  - Cyclin-dependent kinase (CDK) 4/6 inhibitor
    - CDK4/6 promote phosphorylation of the retinoblastoma protein, cell cycle progression and cell proliferation
    - CDK 4/6 inhibition blocks progression from G1→S phase of cell cycle
- Dosing
  - Combination: 150 mg PO twice daily until disease progression or toxicity
  - Monotherapy: 200 mg PO twice daily until disease progression or toxicity
- Dosage Forms/Administration
  - 50, 100, 150 and 200 mg tablets; taken without regard to food

Verzenio™ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

Abemaciclib (Verzenio™)

- Clinical Trial Data

Trial	Patient Population	Treatment	Results
MONARCH-1	3rd line; n= 132	Abemaciclib	Median PFS 6 months ORR 19.7%
MONARCH-2	1st and 2nd line; n= 223 Pre/peri and postmenopausal women with HR+, HER2- MBC	Fulvestrant ± abemaciclib	Median PFS 16.4 vs. 9.3 months ORR 48.1% vs. 21.3%
MONARCH-3	1st line; n= 493 Postmenopausal women with HR+, HER2- MBC	AI ± abemaciclib	Median PFS 28.2 vs. 14.8 months ORR 59% vs. 44%

Dickler MN, et al. Clin Cancer Res. 2017; 23(17):5218-5224.
Sledge Jr GW, et al. J Clin Oncol. 2017;35:2875-2884.
Goetz MP, et al. J Clin Oncol. 2017;35(32):3638-3646.

Abemaciclib (Verzenio™)

- Adverse Events
  - Diarrhea
  - Neutropenia
  - Leukopenia
  - Thrombocytopenia
  - Infections
  - Nausea
  - Vomiting
  - Decreased appetite
  - Abdominal pain
  - Fatigue
  - Anemia
  - Headache

Verzenio™ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

Abemaciclib (Verzenio™)

- Monitoring Parameters
  - CBC
    - Baseline
    - Every 2 weeks for the first 2 months
    - Monthly for the next two months, then as clinically indicated
  - Liver function tests
    - Baseline
    - Every 2 weeks for the first 2 months
    - Monthly for the next two months, then as clinically indicated

Verzenio™ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

Abemaciclib (Verzenio™)

- Clinical Pearls
  - An additional CDK4/6 inhibitor with a unique side effect profile; available for use as monotherapy
    - ↑Diarrhea, ↓ hematologic toxicity
    - Creatinine elevations
  - CYP3A4 substrate
  - Crosses blood brain barrier
  - Cost: ~$14,500
  - Verzenio Savings Card

Verzenio™ [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

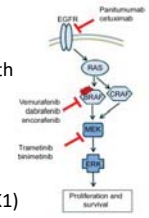
Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Approved June 2018
- Treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutation

Braftovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Mektovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.

Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Mechanisms of Action
  - Encorafenib
    - Tyrosine kinase inhibitor targeting BRAF with V600 mutations as well as wild type BRAF and CRAF
  - Binimetinib
    - Reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2



Braftovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Mektovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Image: https://www.researchgate.net/figure/Targeted-therapy-approaches-in-clinical-trials-for-BRAF-V600E-mutant-CRC-Abbreviation_fig1_323936283

Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Dosing
  - Encorafenib
    - 450 mg PO once daily until disease progression or toxicity
  - Binimetinib
    - 45 mg PO twice daily until disease progression or toxicity
- Dosage forms/Administration
  - Encorafenib: 50 and 75 mg capsules; taken without regard to food
  - Binimetinib: 15 mg tablet; taken without regard to food

Braftovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Mektovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.

Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Clinical Trial Data
  - COLUMBUS
    - Open-label, phase 3 study
    - 577 patients
    - Compared encorafenib + binimetinib, encorafenib monotherapy, and vemurafemib monotherapy
    - Median PFS 14.9 months (encorafenib and binimetinib) vs. 9.6 months (encorafenib) vs. 7.3 months (vemurafenib)

Dummer R, et al. Lancet Oncol. 2018; 19:603-15.

Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Adverse Events
  - QTc prolongation†
  - Hemorrhage†‡
  - Uveitis†
  - New primary malignancies†
  - Ocular toxicities (retinopathy, retinal vein occlusion)‡
  - Cardiomyopathy ‡
  - Venous thromboemolism‡
  - Hepatotoxicity‡
  - Nausea
  - Diarrhea
  - Vomiting
  - Fatigue
  - Arthralgia
  - Constipation
  - Headache

†: Encorafenib
‡: Binimetinib

Braftovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Mektovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.

Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Monitoring parameters
  - EKG†
    - Baseline and during treatment
  - Dermatologic evaluations†
    - Baseline and every 2 months during therapy
  - Electrolytes†
  - Liver function tests‡
  - CPK as indicated‡
  - Echocardiogram to assess left ventricular ejection fraction‡
    - Baseline, after 1st month, then every 2-3 months thereafter

†: Encorafenib
‡: Binimetinib

Braftovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Mektovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.

Encorafenib (Braftovi™)/Binimetinib (Mektovi®)

- Clinical Pearls
  - First line option for metastatic or unresectable melanoma
    - ↓ pyrexia, ↓ photosensitivity
  - Dose reduce encorafenib to 300 mg daily if holding or discontinuing binimetinib
  - Encorafenib has longer $t_{1/2}$ and more potent BRAF V600E inhibition
    - CYP3A4 substrate
  - Cost: ~$19,800 (encorafenib), ~$6,600 (binimetinib)
  - Array Co-Pay Savings Program
  - ArrayACTS Patient Assistance Program

Braftovi™ [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.
Mektovi® [package insert]. Boulder, CO: Array BioPharma, Inc.; 2018.

Apalutamide (Erleada™)

- Approved February 2018
- Treatment of non-metastatic castration-resistant prostate cancer (M0-CRPC)

Erleada™ [package insert]. Horsham, PA: Janssen Biotchen, Inc.; 2018.

Apalutamide (Erleada™)

- Mechanism of Action
  - Androgen receptor inhibitor, resulting in decreased tumor cell proliferation and increased apoptosis
- Dosing
  - 240 mg by mouth once daily continued until disease progression or toxicity
- Dosage forms/administration
  - 60 mg tablets; taken without regard to food

Erleada™ [package insert]. Horsham, PA: Janssen Biotchen, Inc.; 2018.

Apalutamide (Erleada™)

- Clinical Trial Data
  - SPARTAN
    - Double-blind, placebo-controlled, phase 3 study
    - 1207 patients
    - Randomized 2:1 to androgen deprivation therapy +/- apalutamide
    - Median metastasis-free survival 40.5 vs. 16.2 months
    - Patients receiving apalutamide had 72% lower risk of metastasis or death

Smith MR, et al. NEJM. 2018;378:1408-18.

Apalutamide (Erleada™)

- Adverse Events
  - Rash
  - Hypertension
  - Nausea
  - Hypothyroidism
  - Fall
  - Fracture
  - Fatigue
  - Diarrhea
  - Weight decrease
  - Arthralgia
  - Hot flash
  - Decreased appetite

Erleada™ [package insert]. Horsham, PA: Janssen Biotchen, Inc.; 2018.

Apalutamide (Erleada™)

- Monitoring Parameters
  - Thyroid function
  - Signs/symptoms of seizure
  - Signs/symptoms of dermatologic toxicity
  - Fall/fracture risk

Erleada™ [package insert]. Horsham, PA: Janssen Biotchen, Inc.; 2018.

Apalutamide (Erleada™)

- Clinical Pearls
  - First FDA-approved option for M0-CRPC with a PSA doubling time ≤ 10 months
  - Restricted to certain specialty pharmacies
  - CYP2C8 and CYP3A4 substrate
  - CYP3A4 inducer
  - Patients should concurrently receive a gonadotropin-releasing hormone analog unless they have had a documented bilateral orchiectomy
  - Cost: ~$13,000
  - Janssen CarePath

Erleada™ [package insert]. Horsham, PA: Janssen Biotchen, Inc.; 2018.

New Drug Update

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