New Drug Update

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Financial Disclosures

- I currently do not have any relevant financial relations to disclose

Objectives

- Describe the therapeutic classifications and indications for select new oncologic agents approved in last year
- Discuss dosing, administration, and appropriate role for each new agent
- List major adverse effects, contraindications, and precautions for each new agent
- Discuss special considerations in regards to storage, preparation, dispensing, and monitoring each new agent

New Drugs Since October 2016

Brand	Generic	Date Approved
Lartruvo™	Olaratumab	October 19, 2016
Rubraca®	Rucaparib	December 19, 2016
Kisqali®	Ribociclib	March 13, 2017
Bavencio®	Avelumab	March 23, 2017
Zejula™	Niraparib	March 27, 2017
Rydapt®	Midostaurin	April 28, 2017
Alunbrig™	Brigatinib	April 28, 2017
Imfinzi™	Durvalumab	May 1, 2017
Nerlynx™	Neratinib	July 17, 2017
IDHIFA®	enasidenib	August 3, 2017

Olaratumab (Lartruvo™)

Olaratumab

- Indication
  - Treatment of patients with soft tissue sarcomas (STS) not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which anthracycline-containing regimen is appropriate

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

Olaratumab

- Mechanism of Action
  - Olaratumab is a human (recombinant) IgG1 antibody which expressly binds to platelet-derived growth receptor alpha (PDGFR-α) to prevent binding of PDGF-AA, PDGF-BB, and PDGF-CC and block receptor activation and disrupt PDGF receptor signaling

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

Olaratumab

- Dose - 15 mg/kg IV over 60 minutes on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity
  - For first eight cycles given with doxorubicin
  - Premedication with diphenhydramine and dexamethasone is recommended
  - Infusion must be completed within 28 hours of dilution
- NCCN
  - Recommend combination therapy with doxorubicin for use in STS histologies in which an anthracycline-containing regimen is appropriate

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

Olaratumab

- Dosage Adjustments for Toxicity
  - Hematologic
    - Neutropenic fever/infection or grade 4 neutropenia lasting longer than 1 week
      - Withhold olaratumab until ANC is ≥ 1,000/mm^3, then resume with dose permanently reduced to 12 mg/kg
  - Infusion reaction
    - Grade 1 or 2 – interrupt infusion; after resolution, resume with 50% reduced rate
    - Grade 3 or 4 – Discontinue permanently

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

Olaratumab

- Adverse Effects
  - Nausea (73%), fatigue (69%), neutropenia (65%), musculoskeletal pain (64%), mucositis (53%), alopecia (52%), vomiting (45%), diarrhea (34%), neuropathy (22%)
  - Infusion-related reactions were seen in 13% of patients
    - Most infusion reactions occurred with first or second cycle
    - Symptoms include flushing, dyspnea, bronchospasm, and/or fever/chills
    - Severe cases included hypotension, anaphylactic shock, or cardiac arrest

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

Olaratumab

- Storage – Vials stored in refrigerator
  - Solutions diluted for infusion may be stored for up to 24 hours refrigerated and for an additional 4 hours at room temperature
- Dosage Forms
  - 190 mg/9 mL; 500 mg/50 mL

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

Olaratumab

- Preparation – Normal Saline to total volume 250 mL
  - If refrigerated, allow prepared infusion to come to room temperature prior to administration
- Monitoring
  - CBC with differential
  - Signs and symptoms of infusion reactions

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

Olaratumab

- Open-label, Phase 1b, Randomized, active-controlled trial
- 133 patients with metastatic STS
  - Randomized 1:1 olaratumab + doxorubicin or doxorubicin as single agent

Regimen	Median OS (months)	Median PFS (months)	Overall Response Rate
Doxorubicin + olaratumab	26.5	8.2	18%
Doxorubicin single agent	14.7	4.4	8%

Tap WD, et al. Lancet.2016;388(10043):388-99.

Ribociclib (Kisqali®)

Ribociclib

- Indication
  - Treatment of postmenopausal women with hormone receptor positive, HER-2 negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy
- Mechanism of Action
  - Cyclin-dependent kinase 4/6 inhibitor

TOPA

KISQALI [package insert].East Hanover, NJ:Novartis Pharmaceutical Corp.;2017

Ribociclib

- Dose
  - 600 mg PO once daily with or without food x 21 days
- Adverse Effects (observed in 20% or more patients)
  - Neutropenia, leukopenia, N/V/D, fatigue, diarrhea, alopecia, constipation, headache, back pain
  - Grade 3 or 4 adverse reactions
    - Leukopenia, neutropenia, abnormal LFTs, lymphopenia, vomiting
  - QT prolongation – concentration dependent

KISQALI [package insert].East Hanover, NJ:Novartis Pharmaceutical Corp.;2017

Ribociclib

- Dosage forms
  - 200, 400, and 600 mg tablet
- Storage
  - Store tablets at room temperature
- Administration
  - May be given with or without food at approximately same time daily (and letrozole or other aromatase inhibitors)
  - Do not crush, chew, or split tablets

KISQALI [package insert].East Hanover, NJ:Novartis Pharmaceutical Corp.;2017

Ribociclib

- Monitoring Parameters
  - CBC (baseline and every 2 weeks) for 1st 2 cycles, then at beginning of each subsequent 4 cycles
  - Serum electrolytes prior to treatment and at the beginning of each cycle
  - ECG prior to treatment and repeat on Day14 of cycle1 and beginning of cycle 2

KISQALI [package insert].East Hanover, NJ:Novartis Pharmaceutical Corp.;2017

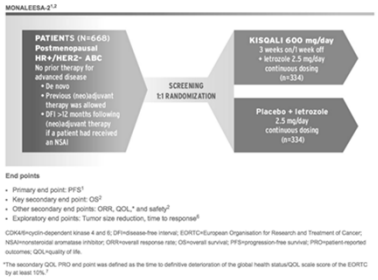
Ribociclib

- Drug Interactions
  - Levels/effects of ribociclib may be **decreased** by Bosentan; CYP3A4 inducers (moderate and strong); Dabrefenib; deferasirox; tocilizumab
  - Levels/effects of ribociclib may be increased by CYP3A4 inhibitors (moderate and strong); denosumab; fosaprepitant; trastuzumab

KISQALI [package insert].East Hanover, NJ:Novartis Pharmaceutical Corp.;2017

MONALEESA-2

- International randomized, double-blind, placebo-controlled, phase 3 trial



KISQALI [package insert].East Hanover, NJ:Novartis Pharmaceutical Corp.;2017

MONALEESA-2

- Regimens
  - Ribociclib or placebo PO daily X 21 days, 7 days off + letrozole 2.5 mg PO once daily X 28 days
- Pre-planned interim efficacy analysis
  - Hazard ratio = 0.556 (95% CI: 0.429,0.720; p<0.0001)

Regimen	Progression-Free Survival (months)	Objective Response Rate
Ribociclib-containing arm	Not reached	52.7% (95% CI: 46.6,58.9)
Placebo-containing arm	14.7	37.1% (95% CI: 31.1, 43.2)

Hortobagyi GN, et al. N Engl J Med.2016;375:1738-48

Avelumab (Bavencio®)

Avelumab

- Indication – treatment of locally advanced or metastatic urothelial carcinoma
  - Disease progressed during or following platinum containing chemotherapy

OR

  - Within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Avelumab

- Mechanism of Action
  - Avelumab is a fully human monoclonal antibody that binds programmed death ligand 1 (PD-L1) to selectively prevent the interaction between programmed cell death-1 (PD-1) and B7.1 receptors, while still allowing interaction between PD-L2 and PD-1

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Avelumab

- Dose
  - 10 mg/kg IV over 60 minutes every 2 weeks
  - Pre-medicate with antihistamine and acetaminophen prior to 1st four infusions
- Dosage form
  - Solution for injection
    - 200 mg/10 ml vial

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Avelumab

- Adverse Reactions
  - Death – 6%
  - Serious (reported in 2% or more)
    - Infection/urosepsis, abdominal pain, musculoskeletal pain, increased SCr/renal failure, hematuria, intestinal obstruction, pyrexia
  - Most common
    - Fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, urinary tract infection

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Avelumab

- Warnings/Precautions
  - Adrenal insufficiency
  - Diabetes mellitus (Type 1 has occurred)
  - Gastrointestinal toxicity
    - Immune-mediated colitis
  - Hepatotoxicity
    - Immune-mediated hepatitis
  - Infusion-related reactions
  - Nephrotoxicity
  - Pulmonary toxicity
  - Thyroid disorders

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Avelumab

- Storage/Stability
  - Vials are stored in refrigerator; protect from light (store in original packaging)
  - Do not shake
  - Prepared infusions may be stored at room temperature for 4 hours or refrigerated for 24 hours
- Preparation
  - Add required volume for dose to NS 250 mL or ½ NS
  - Prepared infusions must be protected from light

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Avelumab

- Monitoring Parameters
  - AST, ALT, total bilirubin
  - Blood glucose
  - Renal and thyroid tests at baseline and periodically during treatment
  - Monitor for signs and symptoms of colitis, thyroid disorders, pneumonitis, adrenal insufficiency, hyperglycemia

BAVENCIO[package insert].EMD Seronon, Inc. Rockland, MD:2017.

Metastatic Merkel Cell Carcinoma

- JAVELIN Merkel 200
- Open-label, single arm, multi-center, phase 2 study
- 88 patients enrolled
- Patients received 10 mg/kg IV every 2 weeks
  - Until radiographic or clinical progression or unacceptable toxicity

Kaufman H, et al. J Clin Oncol.2016;34 (suppl;abstr 9508).

Metastatic Merkel Cell Carcinoma

Results of JAVELIN Merkel 200

Efficacy Endpoints	Results (n=88)
Overall Response Rate (ORR)	
Overall response rate, (95% CI)	33.0% (23.3%, 43.8%)
Complete response (CR) rate, (95% CI)	11.4% (6.6%, 19.9%)
Partial response (PR) rate, (95% CI)	21.6% (13.5%, 31.7%
Duration of Response (DOR)	N=29
Range in months	2.8 to 23.3+
Patients with DOR ≥ 6 months, n(%)	25 (86%)
Patients with DOR ≥ 12 months, n(%)	13 (45%)

Kaufman H, et al. J Clin Oncol.2016;34 (suppl;abstr 9508).

Locally Advanced or Metastatic Urothelial Carcinoma (UC)

- UC Cohorts of the JAVELIN Solid Tumor trail
  - Open-label, single-arm, multi-center, phase 1b study
  - Included 242 patients
    - Regardless of PD-L1 status
  - Received avelumab 10 mg/kg IV every 2 weeks until radiographic or clinical progression or unacceptable toxicity

Gulley JL, et al. Lancet Oncol. 2017;18(5):599-610.

Locally Advanced or Metastatic Urothelial Carcinoma

Results of UC Cohorts

Efficacy Endpoints	≥ 13 Weeks Follow-up (n=226)	≥ 6 months Follow-up (n=161)
Confirmed Overall Response Rate (ORR)		
Overall Response Rate n (%)	30 (13.3%)	26 (16.1%)
(95% CI)	(9.1, 18.4)	(10.8, 22.8)
Complete Response (CR) n (%)	9 (4.0%)	9 (5.6%)
Partial Response (PR) n (%)	21 (9.3%)	17 (10.6%)
Duration of Response (DOR)		
Median, months (range)	Not estimable (1.4+ to 17.4+)	Not estimable (1.4+ to 17.4+)

Gulley JL, et al. Lancet Oncol. 2017;18(5):599-610.

Midostaurin (Rydapt™)

Midostaurin

- Indications
  - Treatment of newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive (FLT3+) in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
  - Treatment of aggressive systemic mastocytosis (SM), SM with associated hematological neoplasms, or mast cell leukemia

RYDAPT [package insert]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; 2017.

Midostaurin

- Mechanism of Action
  - Tyrosine kinase inhibitor which inhibits wild type FLT3, FLT3 mutant kinases ITD and TKD, KIT (wild type and D816V mutant), PDGFRα/β, VEGFR2, and members of the serine/threonine protein kinase C (PKC) family

RYDAPT [package insert]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; 2017.

Midostaurin Dosage

Indication	Dosage	Dosage adjustment for toxicity
AML, FLT3-positive	Induction: 50 mg PO BID on days 8 to 21 in induction (with daunorubicin and cytarabine Consolidation: 50 mg PO BID on days 8 to 21 (with high-dose cytarabine)	HEMATOLOGIC Low ANC/platelets/hemoglobin – interrupt therapy Persistent low ANC/platelets/Hemoglobin(> 21 days) – discontinue
Mast cell leukemia and Systemic mastocytosis	100 mg PO BID until disease progression or unacceptable toxicity	NON-HEMATOLOGIC Nausea/Vomiting - Grade 3 or 4 and other Grade 3 or 4 toxicities - interrupt Pulmonary - discontinue

*All doses to be taken with food
**If a dose is missed or vomited, do not make up dose; take next dose at scheduled time

RYDAPT [package insert]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; 2017.

Midostaurin

- Dosage Form
  - 25 mg capsule
  - Not to be crushed or chewed
- Adverse Effects
  - Common (>/= 20% of patients)
    - Febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, epistaxis, hyperglycemia, upper respiratory infection, musculoskeletal pain
  - Serious
    - Febrile neutropenia

RYDAPT [package insert]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; 2017.

Midostaurin

- Storage
  - Room temperature and in original container if possible to protect from moisture
- Warnings/Precautions
  - Bone marrow suppression
  - GI toxicity
  - Hypersensitivity reactions
  - Pulmonary toxicity

RYDAPT [package insert]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; 2017.

Midostaurin

- Monitoring Parameters
  - CBC with differential
  - Signs and symptoms of pulmonary toxicity
  - ECG if also taking concomitant medications that may prolong QT interval
- Drug Interactions
  - Avoid use with CTP3A4 inducers, highest risk QTc-prolonging agents
  - Midostaurin levels may be increased by aprepitant, dasatinib, grapefruit juice

RYDAPT [package insert]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; 2017.

FLT3+ AML Approval

- RATIFY study
- Randomized, double-blind, placebo-controlled, phase 3 trial
  - 717 patients randomized
    - 360 patients = midostaurin group
    - 359 patients = placebo group

Stone RM, et al. N Engl J Med.2017;377:454-464.

RATIFY Study Results

	Midostaurin Group	Placebo Group	P-value (Hazard ratio)
Overall Survival (OS)	74.7 months (95% CI, 31.5-not reached)	25.6 months (95% CI, 18.6-42.9)	0.009 (0.78)
Median Event-Free Survival (EFS)	8.2 months (95% CI, 5.4-10.7)	3 (95% CI, 1.9-5.9)	0.002 (0.78)
Complete Remission Rate	58.9%	53.5%	0.15

Stone RM, et al. N Engl J Med.2017;377:454-464.

Aggressive Systemic Mastocytosis and Mast Cell Leukemia Approval

- International, multicenter, single-arm, open-label
- Midostaurin 100 mg PO BID in 4 week continuous cycles

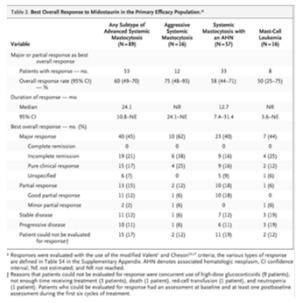


Table 2. Best Overall Response to Midostaurin in the Primary Efficacy Population.*

Variable	Any Subtype of Advanced Systemic Mastocytosis (N=89)	Aggressive Systemic Mastocytosis (N=16)	Systemic Mastocytosis with an AHN (N=57)	Mast-Cell Leukemia (N=16)
Major or partial response as best overall response				
Patients with response — no.	53	12	33	8
Overall response rate (95% CI) — %	60 (49–70)	75 (48–93)	58 (44–71)	50 (25–75)
Duration of response — mo				
Median	24.1	NR	12.7	NR
95% CI	10.8–NE	24.1–NE	7.4–31.4	3.6–NE
Best overall response — no. (%)				
Major response	40 (45)	10 (62)	23 (40)	7 (44)
Complete remission	0	0	0	0
Incomplete remission	19 (21)	6 (38)	9 (16)	4 (25)
Pure clinical response	15 (17)	4 (25)	9 (16)	2 (12)
Unspecified	6 (7)	0	5 (9)	1 (6)
Partial response	13 (15)	2 (12)	10 (18)	1 (6)
Good partial response	11 (12)	1 (6)	10 (18)	0
Minor partial response	2 (2)	1 (6)	0	1 (6)
Stable disease	11 (12)	1 (6)	7 (12)	3 (19)
Progressive disease	10 (11)	1 (6)	6 (11)	3 (19)
Patient could not be evaluated for response†	15 (17)	2 (12)	11 (19)	2 (12)

* Responses were evaluated with the use of the modified Valent and Cheson criteria; the various types of response are defined in Table S4 in the Supplementary Appendix. AHN denotes associated hematologic neoplasm, CI confidence interval, NE not estimated, and NR not reached.
† Reasons that patients could not be evaluated for response were concurrent use of high-dose glucocorticoids (9 patients), not enough time receiving treatment (9 patients), death (1 patient), red-cell transfusion (1 patient), and neutropenia (1 patient). Patients who could be evaluated for response had an assessment at baseline and at least one postbaseline assessment during the first six cycles of treatment.

Gotlib J, et al. N Engl J Med.2016;374(26):2530-41.

Brigatinib (Alunbrig™)

Brigatinib

- Indication
  - Treatment of metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) in patients who progressed on or are intolerant to crizotinib

TOPA

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA; 2017.

Brigatinib – Mechanism of Action

- Multi-kinase inhibitor with activity against ALK, ROS1, insulin-like growth factor-1 (IGF-1R), and FLT3, as well as EGFR deletion and point mutations
- ALK autophosphorylation and ALK-mediated phosphorylation of downstream signaling proteins STAT3, AKT, ERK1/2, and S6 are inhibited by brigatinib
- Clinically, brigatinib showed anti-tumor activity against EML4-ALK mutant forms

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA; 2017.

Brigatinib

- Dose
  - 90 mg PO once daily for 7 days; if tolerated, increase to 180 mg once daily with or without food
    - Continue until disease progression or unacceptable toxicity
    - If therapy is interrupted for ≥ 14 days (reasons not due to toxicity), resume at 90 mg PO once daily for 7 days, then escalate
  - Dose adjustments are necessary when given with concomitant strong CYP3A4 inhibitors
    - Reduce brigatinib by 50%

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA; 2017.

Brigatinib

- Dosage adjustments for toxicity are required
  - Toxicities include hypertension, bradycardia, creatine phosphokinase (CPK) elevations, hyperglycemia, pancreatic enzyme elevations, ocular toxicity, and pulmonary toxicity

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA; 2017.

Brigatinib

- Adverse Effects
  - Nausea, diarrhea, fatigue, headache, and cough
  - Pneumonitis and pneumonia – most common to lead to discontinuation of brigatinib

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA: 2017.

Brigatinib

- Dosage form
  - 30 mg tablet
  - Not to be crushed or chewed
- Storage
  - Stored at room temperature

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA: 2017.

Brigatinib

- Monitoring parameters
  - CPK
  - Pancreatic enzymes periodically
  - Fasting blood glucose (baseline and thereafter)
  - Heart rate and blood pressure
  - Signs and symptoms of visual disturbances and interstitial lung disease

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA: 2017.

Brigatinib

- Drug Interactions
  - Avoid concomitant use with CYP3A4 inducers and grapefruit juice
  - Brigatinib levels may be increased by CYP3A4 inhibitors, aprepitant, fosaprepitant
  - Brigatinib is a substrate of BCRP, CYP2C8, CYP3A4, P-glycoprotein

ALUNBRIG [package insert]. Ariad Pharmaceuticals: Cambridge, MA: 2017.

ALTA Trial - Brigatinib

- Non-comparative, two-arm, open-label, multicenter clinical trial (n=222)
  - Brigatinib 90 mg PO once daily (n=112)
  - 180 mg PO once daily following a 7 day lead in at 90 mg PO once daily (n=110)

Kim DW, et al. Journal of Clinical Oncology.2017;35(22):2490-98.

ALTA Trial

- Overall Response Rate (ORR) assessed by independent review committee according to Response Evaluation Criteria in Solid Tumors (RECIST)
  - 48% (95% CI:39-58%) in 90 mg arm
  - 53% (95% CI:43-62%) in 180 mg arm
- Median duration follow-up of eight months, median duration of response (DOR)
  - 13.8% in both arms

Kim DW, et al. Journal of Clinical Oncology.2017;35(22):2490-98.

Durvalumab (Imfinzi™)

Durvalumab

- Indication – treatment of locally advanced or metastatic urothelial carcinoma in patients
  - With disease progression during or following platinum containing therapy

OR

  - With disease progression within 12 months of neoadjuvant or adjuvant treatment of platinum-containing therapy

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

Durvalumab

- Mechanism of Action
  - Human immunoglobulin G1 kappa which blocks PD-L1 binding to PD-1 and CD-80; PD-L1 blockage leads to increased T-cell activation, allowing T-cells to kill tumor cells
- Dose
  - 10 mg/kg IV over 60 minutes every 2 weeks until disease progression or unacceptable toxicity

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

Durvalumab

- Adverse Effects
  - Fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, urinary tract infection
- Dosage Form
  - Solution, intravenous
    - 120 mg/2.4 mL; 500 mg/10 mL
  - Vials stored in refrigerator
- Availability of drug is currently undetermined (8/18/2017)

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

Durvalumab

- Preparation
  - May be added to D5W or NS to a final concentration between 1 and 15 mg/mL
- Stability
  - 4 hours room temperature and 24 hours refrigerated
- Monitoring Parameters
  - Liver function, renal function, thyroid function, blood glucose

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

Durvalumab

- Randomized, open-label, single-arm, phase 3 trial
  - 182 patients with locally advanced or metastatic urothelial carcinoma with disease progression after prior platinum-containing therapy
  - Dose of 10 mg/kg IV once every 2 weeks
- ORR determined by RECIST
  - 17% (95% CI: 11.9-23.3)
  - Median response duration was not reached

Powles T, et al. Journal of Clinical Oncology.2017;34, no 15-suppl-published online

Neratinib (Nerlynx™)

Neratinib

- Indication
  - Extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy
- Mechanism of Action
  - Irreversible tyrosine kinase inhibitor of HER1, HER2, HER4, as well as, EGFR
    - Reduces EGFR and HER2 autophosphorylation and downstream MAPK and AKT signaling pathways

NERLYNX [package insert]. Puma Biotechnology, Inc: Los Angeles, CA; 2017.

Neratinib

- Dose – 240 mg (6 tablets) PO once daily with food continuously for 1 year
  - Antidiarrheal prophylaxis should be initiated with first dose and continued during first 2 cycles and PRN thereafter
    - Days 1-14: Loperamide 4 mg PO 3 times a day
    - Days 15-56: Loperamide 4 mg PO twice daily
    - Days 57-365: Loperamide 4 mg PO as needed (max 16 mg/day)

NERLYNX [package insert]. Puma Biotechnology, Inc: Los Angeles, CA; 2017.

Neratinib

- Dosage adjustments maybe necessary for toxicity
- Dosage Forms
  - 40 mg tablet
- Adverse Effects
  - Diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, muscle spasms, increase in AST or ALT, dry skin

NERLYNX [package insert]. Puma Biotechnology, Inc: Los Angeles, CA; 2017.

Neratinib

- Storage
  - Room temperature
- Monitoring Parameters
  - Liver function (AST, ALT, bilirubin, Alk Phos) prior to treatment then monthly for 3 months, then every 3 months
  - Pregnancy test for women

NERLYNX [package insert]. Puma Biotechnology, Inc: Los Angeles, CA; 2017.

Neratinib

- ExteNET Trial
  - Multi-center, randomized, double-blind, placebo-controlled, phase 3 trial of neratinib following adjuvant trastuzumab
  - Women (n=2,840) with early stage HER2 positive breast cancer + within 2 years of completing adjuvant trastuzumab
    - Randomized to neratinib (n=1420) or placebo (n=1420)

Chan A, et al. Lancet. 2016; 17(3): 367-377.

ExteNET Trial

- Major efficacy outcome measure
  - Invasive disease-free survival (iDFS)
    - Defined as time between the randomization date to first occurrence of invasive recurrence, distant recurrence, or death from any cause within 2 years and 28 days of follow-up
- iDFS (HR 0.66, 95% CI: 0.49, 0.90, p=0.008)
  - Neratinib – 94.2%
  - Placebo – 91.9%

Chan A, et al. Lancet. 2016; 17(3): 367-377.

Enasidenib (IDHIFA®)

Enasidenib

- Indication
  - Relapsed or refractory AML specifically with an isocitrate dehydrogenase 2 (IDH2) mutation

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Enasidenib

- Mechanism of Action
  - Small molecule inhibitor of the enzyme IDH2
  - Targets mutant IDH2 variants R140Q, R172S, and R172K at ~40-fold lower concentrations than wild-type enzyme
  - Inhibition of IDH2 results in decreased 2-hydroxyglutarate (2-HG) levels, reduced abnormal histone hypermethylation, and restored myeloid differentiation

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Enasidenib

- Dose
  - 100 mg PO once daily until disease progression or unacceptable toxicity
- No dosage adjustments necessary for renal impairment or hepatic impairment prior to treatment
- Hepatotoxicity during treatment
  - Bilirubin >3 times ULN for ≥ 2 weeks without elevated transaminases or other hepatic disorders
  - Reduce dose to 50 mg PO once daily
    - May increase to 100 mg PO once daily if bilirubin elevation resolves

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Enasidenib

- Dosage Adjustments for Toxicity
  - Differentiation syndrome
    - If suspected, initiate systemic corticosteroids
      - Dexamethasone 10 mg IV or PO 2 times daily
      - Monitor hemodynamics
      - Interrupt enasidenib for severe pulmonary symptoms requiring intubation or ventilator support and/or renal dysfunction persisting > 48 hours after initiation of corticosteroids

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Enasidenib

- Dosage Adjustments for Toxicity
  - Noninfectious leukocytosis (WBC > 30,000/mm^3)
    - Initiate hydroxyurea
    - Interrupt enasidenib if leukocytosis is not improved with hydroxyurea
    - Enasidenib may be resumed at 100 mg PO once daily once WBC < 30,000/mm^3
  - Tumor Lysis Syndrome (TLS) – Grade 3 or higher
    - Interrupt enasidenib until toxicity improves to ≤ Grade 2, then resume at 50 mg PO once daily
    - Once toxicity resolves to ≤ Grade 1, may increase to 100 mg PO once daily

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Enasidenib

- Dosage Forms
  - 50 and 100 mg tablets
- Adverse Effects (occurring in > 20% patients)
  - Nausea, vomiting, diarrhea, elevated bilirubin, and decreased appetite
  - Differentiation syndrome occurred in 14% of patients in trial (AG221-C-001)

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Enasidenib

- Black Box Warning
  - Differentiation syndrome, electrolyte imbalance, noninfectious leukocytosis, hepatotoxicity, GI toxicity, and TLS

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Study AF221-C-001

- Phase 1/2, open-label, single-arm, multicenter clinical trial
  - 199 patients with relapsed or refractory AML with IDH2 mutation as detected by RealTime IDH2 Assay
  - Patients were treated with enasidenib 100 mg PO once daily

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Study AF221-C-001

Table 5: Efficacy Results in Patients with Relapsed or Refractory AML

Endpoint	IDHIFA (100 mg daily) N=199
CR[a] n (%)	37 (19)
95% CI	(13, 25)
Median DOR[b] (months)	8.2
95% CI	(4.7, 19.4)
CRh[c] n (%)	9 (4)
95% CI	(2, 8)
Median DOR (months)	9.6
95% CI	(0.7, NA)
CR/CRh n (%)	46 (23)
95% CI	(18, 30)
Median DOR (months)	8.2
95% CI	(4.3, 19.4)

CI: confidence interval, NA: not available.
[a] CR (complete remission) was defined as <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).
[b] DOR (duration of response) was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.
[c] CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

IDHIFA [package insert]. Celgene Pharmaceuticals: Summit, NJ;2017.

Summary

- Several new medications have been FDA approved in the last year
- Of the medications discussed in this presentation, avelumab, brigatinib, durvalumab received accelerated FDA approval

Questions???

TOPA