New Drug Updates in Solid Tumors: PARP Inhibitors in Ovarian Cancer, Immunotherapeutics, and Other Agents

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2017 JADPRO Live at APSHO

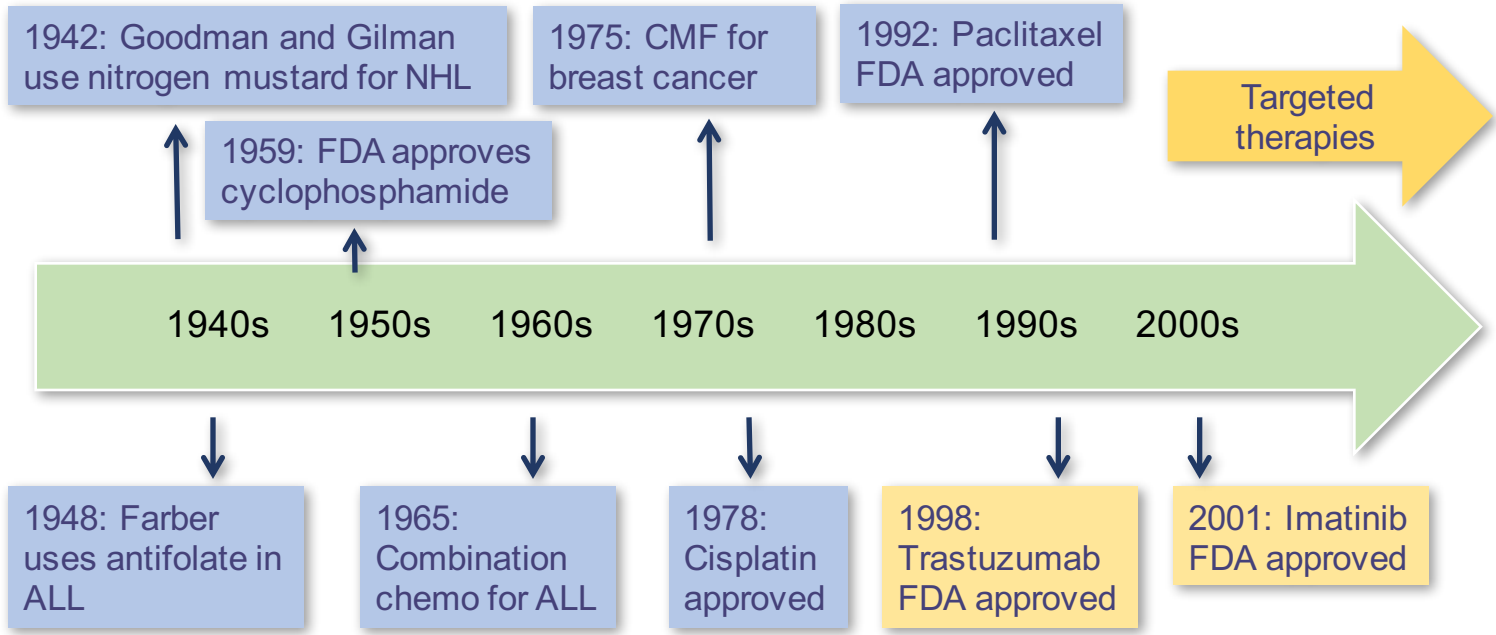
Learning Objectives

1. Discuss the pharmacology and indications of medications approved in the year 2016–2017 for the management of patients with solid tumors
2. Recall the pivotal clinical trial data considered by the FDA when approving new oncologics
3. Identify the signs and symptoms of serious or life-threatening adverse effects of newly approved oncology drugs
4. Describe the impact of these agents in advanced practice

Financial Disclosure

- Edward Li, PharmD, MPH, BCOP, declares that he has served on the speakers bureau for Pfizer and ApoBiologix and on advisory boards for Pfizer, Eli Lilly, and Mylan.

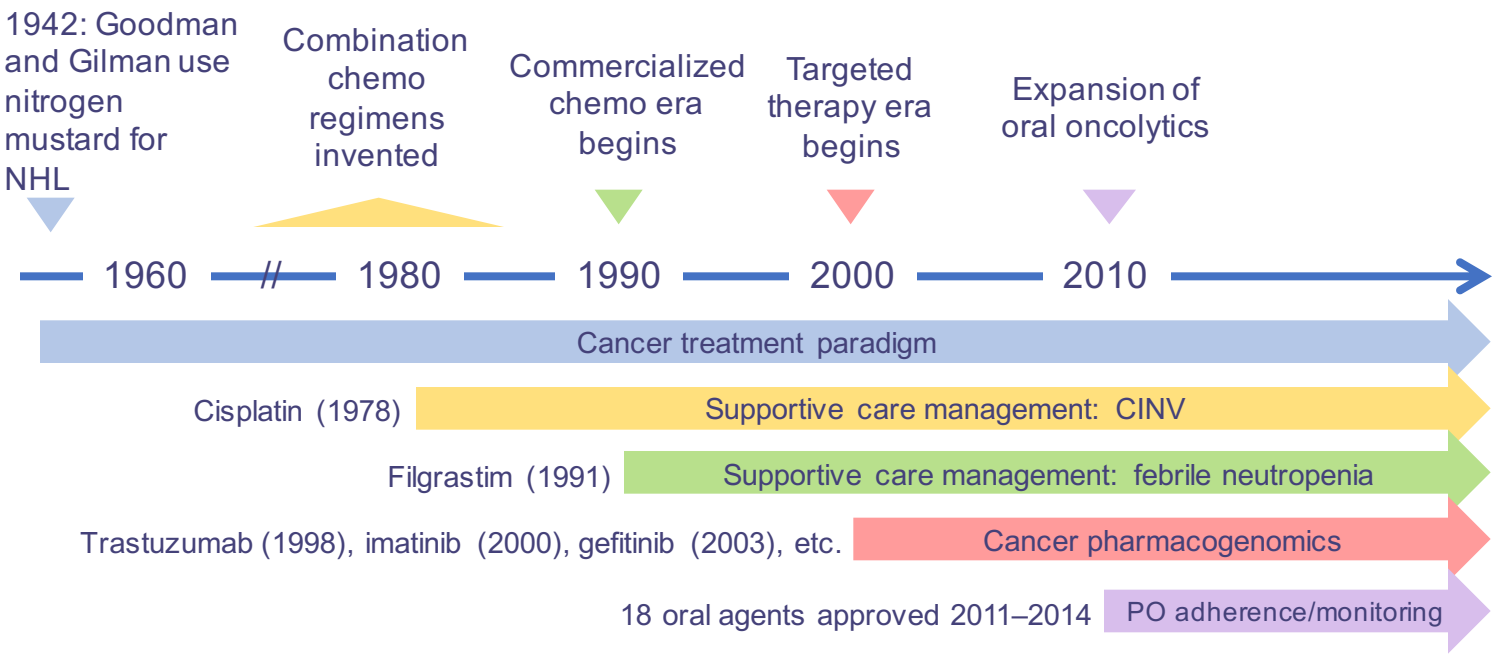
History of Cancer Drug Approvals in the United States



ALL = acute lymphoblastic leukemia; CMF = cyclophosphamide, methotrexate and fluorouracil; FDA = US Food and Drug Administration; NHL = non-Hodgkin lymphoma.

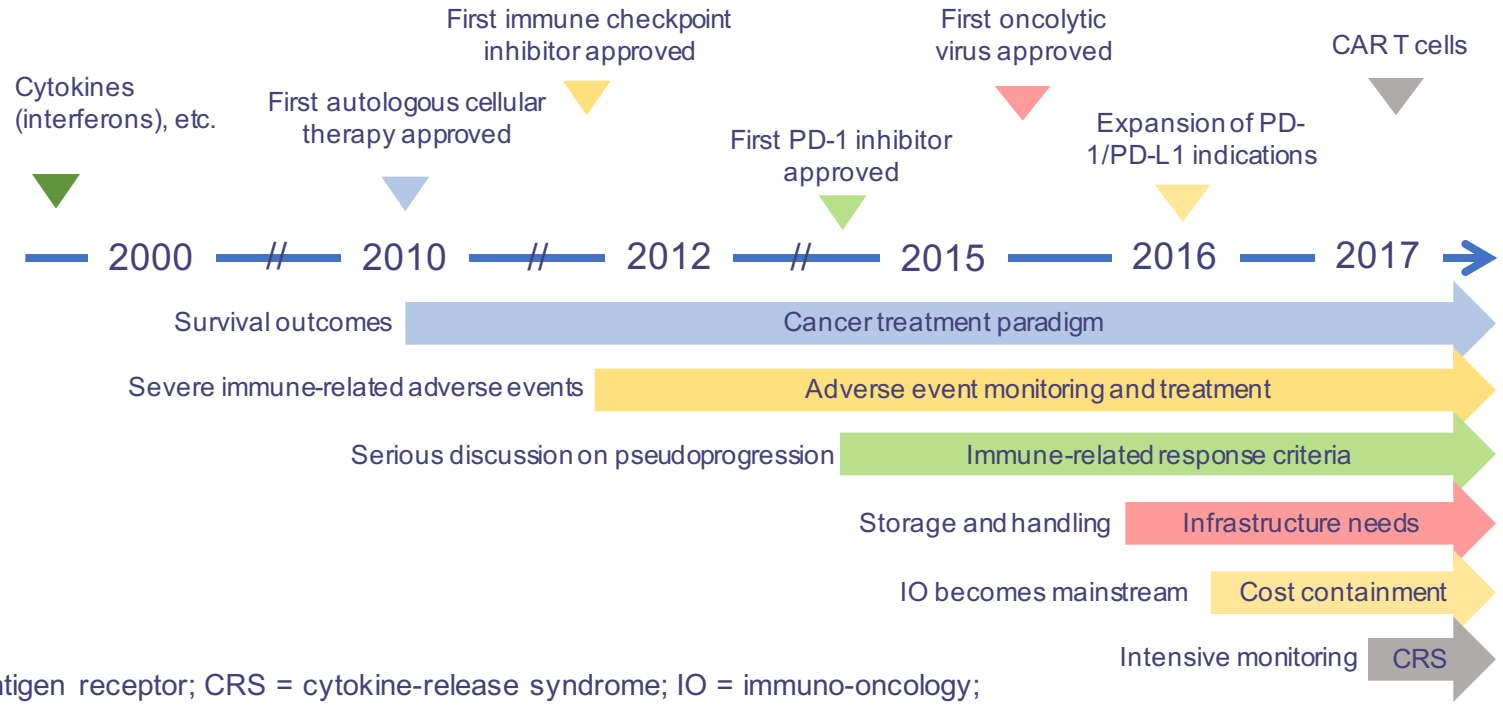
Adapted from Chabner BA, et al. *Nat Rev Cancer* 2005;5:65-72.

Drug Approvals Impact the Practice Paradigm



CINV = chemotherapy-induced nausea and vomiting.

Era of Immuno-Oncology



CAR = chimeric antigen receptor; CRS = cytokine-release syndrome; IO = immuno-oncology; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

New Drug Approvals: December 2016 to September 2017

Novel Mechanism

Generic	Brand	Approval Date
Olaratumab	Lartruvo	October 20, 2016

Established Mechanism

Generic	Brand	Approval Date
Rucaparib	Rubraca	December 19, 2016
Ribociclib	Kisqali	March 13, 2017
Avelumab	Bavencio	March 23, 2017
Niraparib	Zejula	March 27, 2017
Brigatinib	Alunbrig	April 28, 2017
Durvalumab	Imfinzi	May 1, 2017
Neratinib	Nerlynx	July 17, 2017
Olaparib tabs	Lynparza	August 17, 2017*
Abemaciclib	Verzenio	September 28, 2017

*Original FDA approval date: Dec. 19, 2014

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Nivolumab	Opdivo	Expanded indication	Urothelial carcinoma	Feb. 2, 2017
Osimertinib	Tagrisso	Acc → Reg approval	T790M+ NSCLC	Mar. 30, 2017
Palbociclib	Ibrance	Acc → Reg approval	HR+, *HER2*-, initial advanced/metastatic breast cancer with AI	Mar. 31, 2017
Regorafenib	Stivarga	Expanded indication	Hepatocellular carcinoma	Apr. 27, 2017
Pembrolizumab	Keytruda	Accelerated approval	Metastatic nonsquamous NSCLC with carboplatin/pembrolizumab	May 10, 2017
Pembrolizumab	Keytruda	Regular approval	Urothelial carcinoma	May 18, 2017
Pembrolizumab	Keytruda	Accelerated approval	MSI-H or dMMR solid tumors	May 23, 2017
Ceritinib	Zykadia	Acc → Reg approval	*ALK*+ NSCLC	May 26, 2017

AI = aromatase inhibitor; ALK = anaplastic lymphoma kinase; dMMR = mismatch repair deficient; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; MSI-H = microsatellite instability high; NSCLC = non–small call lung cancer.

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Dabrafenib + trametinib	Tafinlar + Mekinist	Regular approval	*BRAF* V600E mutated NSCLC	June 22, 2017
Nivolumab	Opdivo	Accelerated approval	MSI-H or dMMR met colorectal cancer	Aug. 1, 2017
Bevacizumab-awwb	Mvasi	Biosimilar approval	CRC, NSCLC, GBM, RCC, cervical	Sep. 14, 2017
Cabazitaxel	Jevtana	Lower dose	CRPC in combination with prednisone	Sep. 14, 2017
Pembrolizumab	Keytruda	Accelerated approval	PD-L1+, advanced/metastatic gastric/GE junction adenocarcinoma	Sep. 22, 2017
Nivolumab	Opdivo	Accelerated approval	Hepatocellular carcinoma	Sep. 22, 2017

CRC = colorectal cancer; CRPC = castration-resistant prostate cancer; GBM = glioblastoma; GE = gastroesophageal; RCC = renal cell carcinoma.

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

New Drug Approvals: December 2016 to September 2017

Route of Administration

Generic	Brand	Approval Date	Route
Rucaparib	Rubraca	December 19, 2016	Oral
Ribociclib	Kisqali	March 13, 2017	Oral
Avelumab	Bavencio	March 23, 2017	Parenteral (IV)
Niraparib	Zejula	March 27, 2017	Oral
Brigatinib	Alunbrig	April 28, 2017	Oral
Durvalumab	Imfinzi	May 1, 2017	Parenteral (IV)
Neratinib	Nerlynx	July 17, 2017	Oral
Olaparib tabs	Lynparza	August 17, 2017*	Oral
Abemaciclib	Verzenio	September 28, 2017	Oral

Parenteral (IV) administration

Oral administration

*Original FDA approval date: Dec. 19, 2014

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

New Drug Approvals: December 2016 to September 2017

FDA-Approved Indications

Monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer; treated with two or more chemotherapies

Maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy

PARP Inhibitors

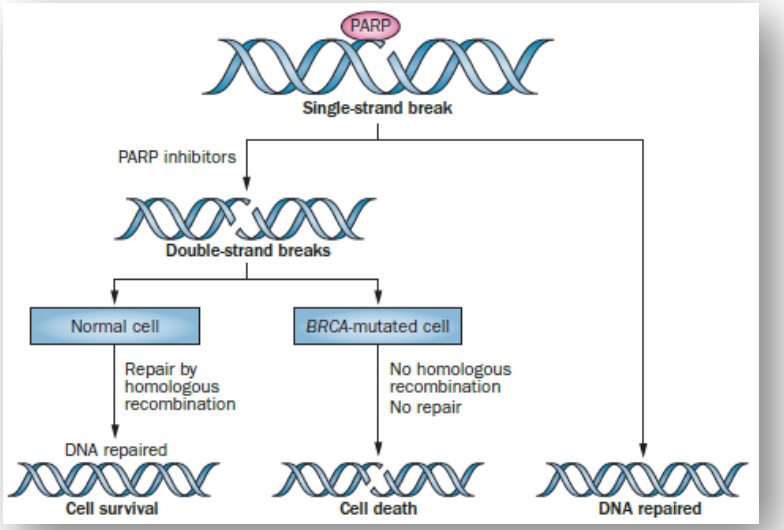
Generic	Brand	Approval Date
Rucaparib	Rubraca	December 19, 2016
Ribociclib	Kisqali	March 13, 2017
Avelumab	Bavencio	March 23, 2017
Niraparib	Zejula	March 27, 2017
Brigatinib	Alunbrig	April 28, 2017
Durvalumab	Imfinzi	May 1, 2017
Neratinib	Nerlynx	July 17, 2017
Olaparib tabs	Lynparza	August 17, 2017*
Abemaciclib	Verzenio	September 28, 2017

*Original FDA approval date: Dec. 19, 2014
PARP = poly (ADP-ribose) polymerase.

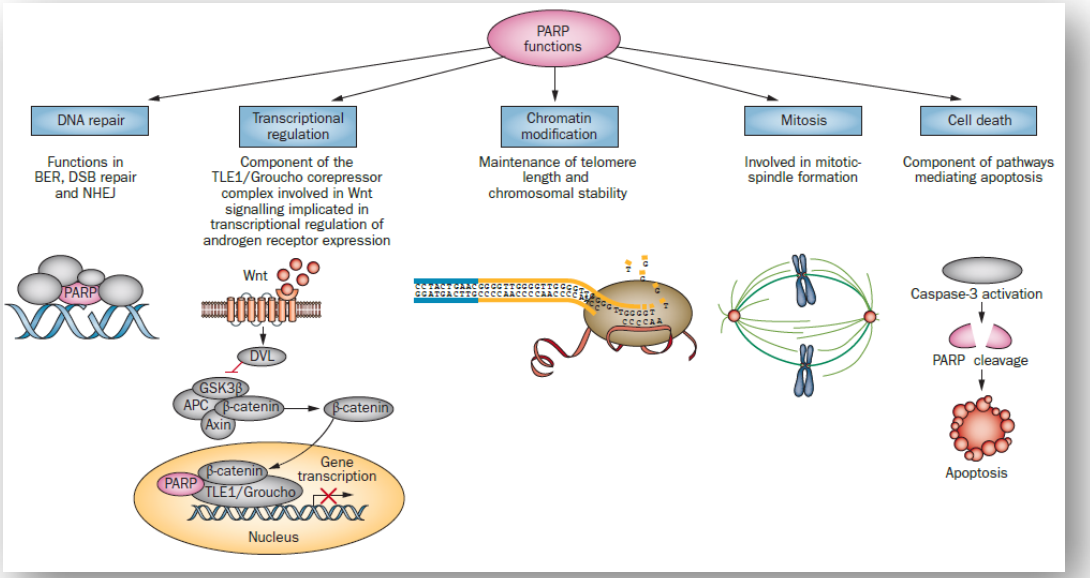
US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Pharmacology of PARP Inhibition

Role in Synthetic Lethality



Other Functions of PARP



PARP Inhibitor Clinical Trials (Landmark)

Agent (Activity)	Study Design	Dosing	Reference
Rucaparib (PARP 1/2)	Phase 2 open-label study of rucaparib in recurrent platinum-sensitive disease (3+ lines of chemo) stratified according to homologous recombination deficiency (n = 206)	600 mg orally twice daily continuously as monotherapy	NCT01891344[1]
Niraparib (PARP 1/2)	Randomized phase 3 study of niraparib vs. placebo for maintenance in recurrent, platinum-sensitive disease (n = 553)	Niraparib 300 mg orally daily within 8 weeks after completing last dose of platinum-based chemotherapy	NCT01847274[2]
Olaparib (PARP 1/2/3)	Randomized phase 2 study of olaparib vs. placebo for maintenance in recurrent, platinum-sensitive disease (n = 265)	Olaparib 400 mg orally twice daily within 8 weeks after completing last dose of platinum-based chemotherapy	NCT00753545[3]

1. Swisher EM, et al. *Lancet Oncol* 2017;18:75-87; 2. Mirza MR, et al. *N Engl J Med* 2016;375:2154-64; 3. Ledermann JA, et al. *Lancet Oncol* 2016;17:1579-89.

Rucaparib for Recurrence: ARIEL2

Outcome	BRCA Mutation+ n = 40	BRCA Wild-Type and LOH High n = 82	BRCA Wild-Type and LOH Low n = 70
ORR, %	80%	29%	10%
Progression-free survival Median HR (vs. LOH-low) (95% CI) p value	 12.8 months 0.27 (0.16–0.44) < .0001	 5.7 months 0.62 (0.42–0.90) .011	 5.2 months -- -- --
Duration of response Median (95% CI) p value (vs. LOH-low)	9.2 months 6.4–12.9 .013	10.8 months 5.7–NR .022	5.6 months 4.6–8.5

CI = confidence interval; HR = hazard ratio; LOH = loss of heterozygosity; ORR = objective response rate.

Niraparib, Olaparib for Maintenance

	Mirza et al., 2016 Phase 3			Ledermann et al., 2016 Phase 2	
Outcome (BRCA mutations vs. wild-type)	**Niraparib BRCA mut(+)**	**Niraparib BRCA wt and HRD**	**Niraparib BRCA wt**	**Olaparib BRCA mut(+)**	**Olaparib BRCA wt**
Progression-free survival HR (95% CI) Median, mo (vs. placebo) p-value	0.27 (0.17–0.41) 21.0 vs. 5.5 $p < .001$	0.38 (0.24–0.59) 12.9 vs. 3.8 $p < .001$	0.45 (0.34–0.61) 9.3 vs. 3.9 $p < .001$	0.18 (0.10–0.31) 11.2 vs. 4.3 $p < .0001$	0.54 (0.34–0.85) 7.4 vs. 5.5 $p = .0075$
Overall Survival HR (95% CI) Median, mo (vs. placebo) p-value	Not available	Not available	Not available	0.62 (0.41–0.94) 34.9 vs. 30.2 $p = .025$*	0.83 (0.55–1.24) 24.5 vs. 26.6 $p = .37$

* Did not reach the threshold for statistical significance

1. Mirza MR, et al. *N Engl J Med* 2016;375:2154-64; 2. Ledermann JA, et al. *Lancet Oncol* 2016;17:1579-89; Ledermann J, et al. *Lancet Oncol* 2014;15:852-61.

PARP Inhibitor Safety: General

Adverse Reaction	Rucaparib		Niraparib		Olaparib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Fatigue/Asthenia	77%	11%	57%	8%	66%	8%
Nausea	77%	5%	74%	3%	64%	3%
Abdominal Pain	32%	3%	33%	2%	43%	4%
Diarrhea	34%	3%	20%	< 1%	31%	1%
URI	10%		NR		26%	
UTI	18%	2%	13%	< 1%	NR	
Headache	17%		26%	< 1%	21%	< 1%
Myalgia	7%	< 1%	19%	< 1%	22%	
Dysgeusia	39%	3%	10%		16%	
Dyspnea	21%	0.5%	20%	1%	NR	

HR = not reported; URI = upper respiratory infection; UTI = urinary tract infection.

Ledermann J, et al. *Lancet Oncol* 2014;15:852-61; Mirza MR, et al. *N Engl J Med* 2016;375:2154-64; Swisher EM, et al. *Lancet Oncol* 2017;18:75-87; Rubraca (rucaparib) prescribing information, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf; Lynparza (olaparib) prescribing information, 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf; Zejula (niraparib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf.

PARP Inhibitor Safety: Vitals and Lab Abnormalities

	Rucaparib		Niraparib		Olaparib	
Adverse Reaction	**Grades 1-4**	**Grades 3-4**	**Grades 1-4**	**Grades 3-4**	**Grades 1-4**	**Grades 3-4**
Neutropenia	35%	10%	53%	21%	32%	8%
Anemia	67%	23%	85%	25%	85%	8%
Thrombocytopenia	39%	6%	72%	35%	26%	6%
Increased SCr	92%	1%	< 10%		26%	
Increased ALT	74%	13%	28%	1%	NR	
Increased AST	73%	5%	36%	1%	NR	
Hypertension	NR		20%	9%	< 10%	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SCr = serum creatinine.

Ledermann J, et al. *Lancet Oncol* 2014;15:852-61; Mirza MR, et al. *N Engl J Med* 2016;375:2154-64; Swisher EM, et al. *Lancet Oncol* 2017;18:75-87; Rubraca (rucaparib) prescribing information, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf; Lynparza (olaparib) prescribing information, 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf; Zejula (niraparib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf.

PARP Inhibitor Safety: Special Monitoring

Adverse Reaction	Rucaparib	Niraparib	Olaparib
MDS/AML	X	X	X
Bone marrow suppression		X	
Cardiovascular effects		X	
Pneumonitis			X

Pneumonitis: If patients present with new or worsening respiratory symptoms such as dyspnea, fever, cough, wheezing, or a radiological abnormality occurs, interrupt treatment and initiate prompt investigation. If pneumonitis is confirmed, discontinue.

MDS/AML occurred in patients exposed to drug, and some cases were fatal. Monitor patients for hematologic toxicity and discontinue if MDS/AML is confirmed.

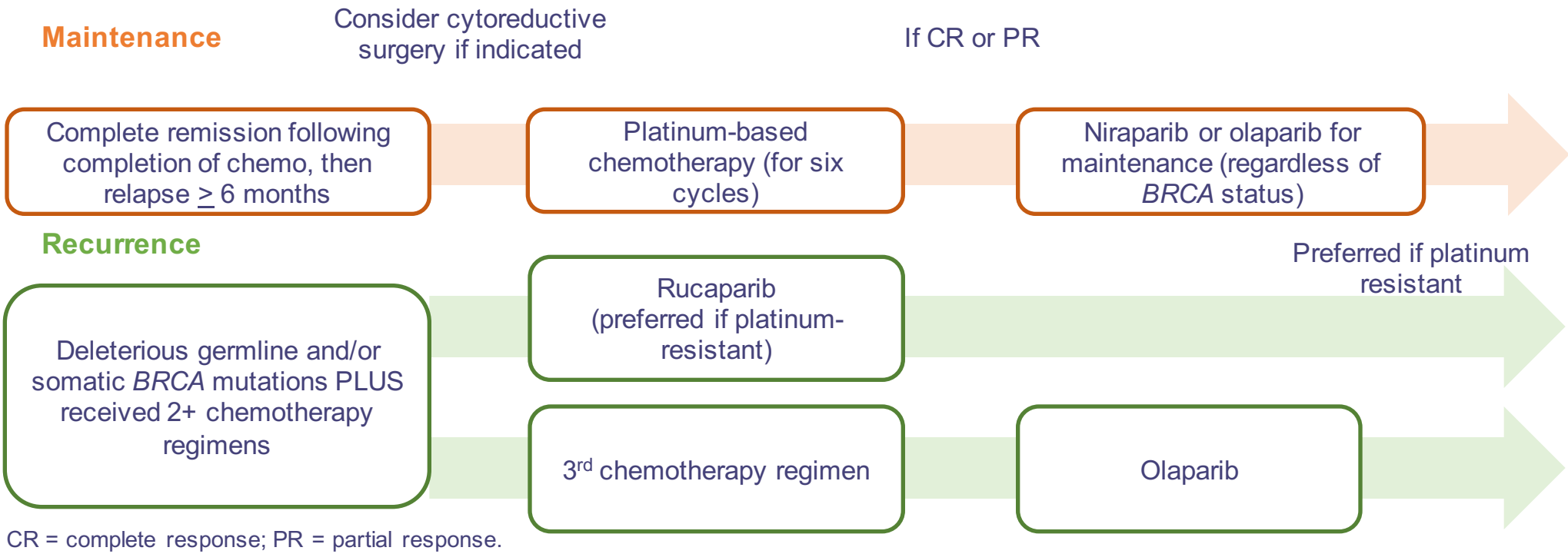
Bone Marrow Suppression: Test complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter for clinically significant changes.

Cardiovascular Effects: Monitor blood pressure and heart rate monthly for the first year and periodically thereafter during treatment. Manage with antihypertensive medications as well as adjustment of the dose, if necessary.

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.

Ledermann J, et al. *Lancet Oncol* 2014;15:852-61; Mirza MR, et al. *N Engl J Med* 2016;375:2154-64; Swisher EM, et al. *Lancet Oncol* 2017;18:75-87; Rubraca (rucaparib) prescribing information, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf; Lynparza (olaparib) prescribing information, 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf; Zejula (niraparib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf.

PARP Inhibitors' Place in Therapy



CR = complete response; PR = partial response.

NCCN Clinical Practice Guidelines in Oncology, Ovarian Cancer, v3.2017, https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.

PARP Inhibitor Summary

- New advances in treating patients with ovarian cancer; there are now three drugs with the same mechanism of action
- Olaparib and niraparib are utilized in similar situations (maintenance), while rucaparib is used for patients with *BRCA* mutation
- Increases in PFS seen, but the clinical significance of OS benefit is debatable

PFS = progression-free-survival; OS = overall survival.

New Drug Approvals: December 2016 to September 2017

CDK4/6 Inhibitor

Generic	Brand	Approval Date
Rucaparib	Rubraca	December 19, 2016
Ribociclib	Kisqali	March 13, 2017
Avelumab	Bavencio	March 23, 2017
Niraparib	Zejula	March 27, 2017
Brigatinib	Alunbrig	April 28, 2017
Durvalumab	Imfinzi	May 1, 2017
Neratinib	Nerlynx	July 17, 2017
Olaparib tabs	Lynparza	August 17, 2017*
Abemaciclib	Verzenio	September 28, 2017

FDA-Approved Indications

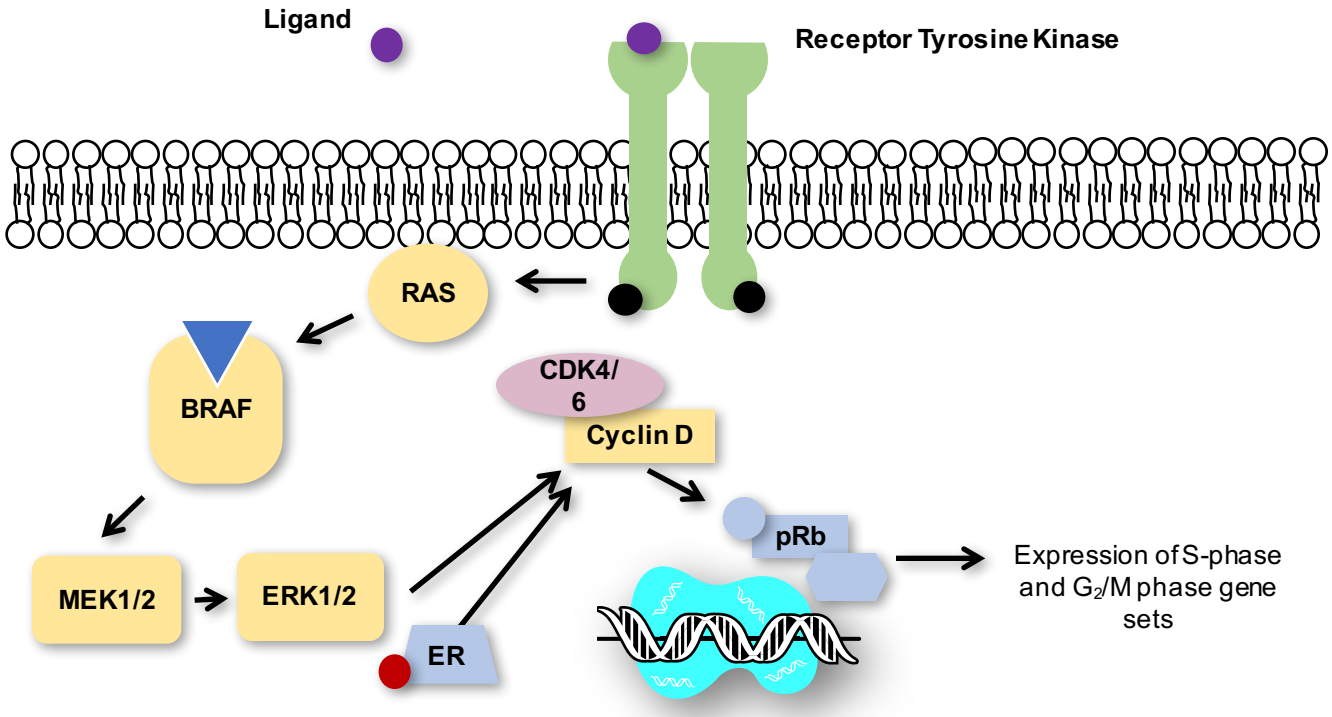
- In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with HR-positive, *HER2*-negative advanced or metastatic breast cancer

- In combination with fulvestrant for HR-positive, *HER2*-negative advanced/metastatic breast cancer after disease progression with endocrine therapy
- Monotherapy for HR-positive, *HER2*-negative advanced/metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

*Original FDA approval date: Dec. 19, 2014

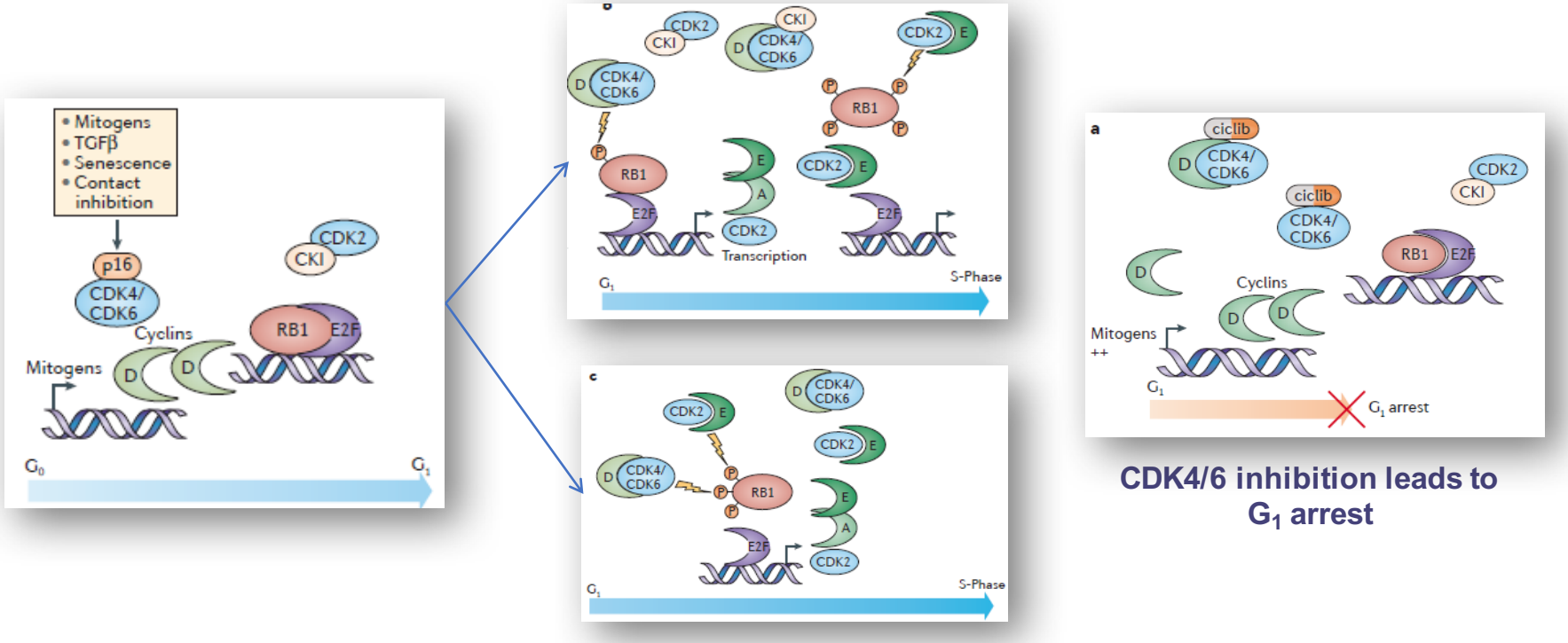
US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

Role of CDK4/6 in the Cell Cycle



Adapted from VanArsdale T, et al. *Clin Cancer Res* 2015;21:2905-10.

Role of CDK4/6 in the Cell Cycle



CDK4/6 inhibition leads to G_1 arrest

Comparison of CDK4/6 Inhibitors

	Abemaciclib	Palbociclib	Ribociclib
CDK activity	4, 6, and 9	4 and 6	4 and 6
CDK selectivity	CDK4: 9-fold	Equal	CDK4: 5-fold
Cycle	Continuous	3 week on, 1 week off	3 week on, 1 week off
Frequency	Twice daily	Once daily	Once daily
Dose	150–200 mg	125 mg	600 mg
Toxicity profile Bone marrow Gastrointestinal	 ++ +++	 +++ +	 +++ ++
Drug interactions	CYP3A	CYP3A	CYP3A

Ibrance (palbociclib) prescribing information, 2015, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf; Kisqali (ribociclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf; Chen P, et al. *Mol Cancer Ther* 2016;15:2273-81.

Abemaciclib and Ribociclib Clinical Trials: HR+, *HER2*-, Advanced Breast Cancer

Agent	Indication	Study Name	Description
Ribociclib	• With letrozole • Initial endocrine-based therapy in postmenopausal women	MONALEESA-2 NCT01958021[1]	Phase 3, randomized, double-blind, placebo-controlled, global
Abemaciclib	• Single agent • Refractory to prior endocrine therapy and one to two chemotherapy regimens	MONARCH 1 NCT02102490[2]	Phase 2, single arm, open-label, multicenter
Abemaciclib	• With fulvestrant • Progressed on adjuvant or first-line (metastatic) endocrine therapy	MONARCH 2 NCT02107703[3]	Phase 3, randomized, double-blind, placebo-controlled, global

1. Hortobagyi GN, et al. *N Engl J Med* 2016;375:1738-48; 2. Dickler MN, et al. *Clin Cancer Res* 2017;23:5218-24; 3. Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875-84.

Ribociclib Clinical Trial: MONALEESA-2 First Line for HR+/*HER2*- Metastatic Breast Cancer with AI vs. AI Alone

Outcome	Ribociclib (n=668) (Hortobagyi et al., 2016)	Palbociclib (n=165) (Finn et al, 2015)
Progression-free survival		
Median	Not reached vs. 14.7 mo	20.2 vs. 10.2 mo
p-value	$p < 0.0001$	$p = 0.004$
HR	0.56	0.49
95% CI	(0.43–0.72)	(0.319–0.748)
Overall survival		
Median	Not available	37.5 vs. 33.3 mo
p-value		$p = 0.42$*
HR		0.81
95% CI		(0.492–1.345)

*Larger sample size needed to draw conclusions

1. Hortobagyi GN, et al. *N Engl J Med* 2016;375:1738-48; 2. Finn RS, et al. *Lancet Oncol* 2015;16:25-35.

Abemaciclib Clinical Trials

Outcome	MONARCH 1 (n = 132)	MONARCH 2 (n = 669)
Indication	Last line for HR+/*HER2*- metastatic breast cancer, single agent, no control arm	Second-line for HR+/*HER2*- metastatic breast cancer, with fulvestrant (vs. fulvestrant alone)
ORR (CR + PR), %	19.7%	35.2% vs. 16.1% ($p < .001$)
Progression-free survival Median HR	6 months (95% CI, 4.2–7.5)	16.4 vs. 9.3 months, $p < .001$ 0.553 (95% CI, 0.449–0.681)
Overall survival Median HR	17.7 months (95% CI,16–NR)	Not available

Dickler MN, et al. *Clin Cancer Res* 2017;23:5218-24; Sledge GW Jr., et al. *J Clin Oncol* 2017;35:2875-84.

Safety: Abemaciclib vs. Ribociclib vs. Palbociclib General

	Ribociclib			Abemaciclib			Palbociclib		
Adverse Reaction	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Fatigue	37%	2%		37%	3%		36%	2%	
Nausea	29%			42%	3%		29%		
URI	19%	< 1%		11%			19%	< 1%	
Diarrhea	19%			73%	13%		19%		
Arthralgia	13%	< 1%		11%	< 1%		13%	< 1%	
Stomatitis	11%	< 1%		15%	< 1%		12%	< 1%	
Abdominal pain	7%	1%		33%	3%				
Decreased appetite	12%	1%		25%	1%		13%	< 1%	
With:	Letrozole			Fulvestrant			Fulvestrant		

Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875-84; Cristofanilli M, et al. *Lancet Oncol* 2016;17:425-39; Turner NC, et al. *N Engl J Med* 2015;373:209-19.

Safety: Abemaciclib vs. Ribociclib vs. Palbociclib Laboratory Abnormalities

	Ribociclib			Abemaciclib			Palbociclib		
Adverse Reaction	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Neutropenia	14%	50%	10%	20%	24%	3%	16%	55%	10%
Anemia	17%	< 1%	< 1%	22%	7%	< 1%	25%	3%	
Thrombocytopenia	28%	1%	< 1%	14%	2%	1%	19%	2%	1%
QT prolongation	3%	< 1%						< 1%	
Increased ALT	36%	8%	2%	9%	4%	< 1%	4%	2%	
Increased creatinine	19%	1%		11%	1%				
Hypokalemia	9%	1%	1%	27%	7%	< 1%		< 1%	
Hyponatremia				31%			1%	1%	
Febrile neutropenia		< 1%			< 1%			1%	
With:	Letrozole			Fulvestrant			Fulvestrant		

Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875-84; Cristofanilli M, et al. *Lancet Oncol* 2016;17:425-39; Turner NC, et al. *N Engl J Med* 2015;373:209-19; Kisqali (ribociclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf; Ibrance (palbociclib) prescribing information, 2015, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf; Verzenio (abemaciclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716s000lbl.pdf.

CDK4/6 Inhibitor Special Monitoring

Adverse Reaction	Ribociclib	Abemaciclib	Palbociclib
QT interval prolongation	X		
Hepatic toxicity	X	X	X
Neutropenia	X	X	X
Infections			X
Diarrhea		X	
Venous thromboembolism		X	

Hepatotoxicity: Perform LFTs before initiating treatment, and monitor LFTs every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

Neutropenia: Monitor CBC prior to the start of therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

Venous Thromboembolism: Monitor for signs and symptoms of thrombosis and pulmonary embolism and treat as medically appropriate.

QT interval prolongation: Monitor ECGs and electrolytes prior to treatment initiation; repeat ECGs at around day 14 of cycle 1 and beginning of cycle 2 and as clinically indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles and as clinically indicated.

Infections: Monitor for signs and symptoms and withhold dosing as appropriate.

Diarrhea: Instruct patients at the first sign of loose stools to initiate antidiarrheal therapy, increase oral fluids, and notify their healthcare provider.

CBC = complete blood count; ECG = electrocardiography; LFTs = liver function tests.

Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875-84; Cristofanilli M, et al. *Lancet Oncol* 2016;17:425-39; Turner NC, et al. *N Engl J Med* 2015;373:209-19; Kisqali (ribociclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf; Ibrance (palbociclib) prescribing information, 2015, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf; Verzenio (abemaciclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716s000lbl.pdf.

CDK4/6 Inhibitors' Place in Therapy

	Newly Diagnosed, Metastatic, HR+ *HER2*-, Postmenopausal (No Chemo)	Previously Treated with Endocrine Therapies	Previously Treated with Endocrine Therapies and Chemotherapy
First Line	AI + palbociclib AI + ribociclib	AI	AI
Second Line	AI + everolimus	Fulvestrant + palbociclib Fulvestrant + abemaciclib	Fulvestrant Tamoxifen
Third Line	Tamoxifen/fulvestrant	AI + everolimus Tamoxifen	Abemaciclib (single agent)

NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, v2.2017, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

CDK4/6 Inhibitor Summary

- CDK4/6 inhibitors, in combination with established therapies now represent the standard of care in HR+, *HER2*- metastatic breast cancer
- Ribociclib is another option and is therapeutically equivalent to palbociclib
- Abemaciclib can be used as monotherapy for last-line therapy in patients who are naive to CDK4/6 inhibitors

New Drug Approvals: December 2016 to September 2017

FDA-Approved Indications

- Metastatic merkel cell carcinoma
- Locally advanced/metastatic urothelial carcinoma with disease progression during or following platinum-based chemotherapy (includes within 12 months of neoadjuvant/adjuvant)

PD-L1 Inhibitors

Generic	Brand	Approval Date
Rucaparib	Rubraca	December 19, 2016
Ribociclib	Kisqali	March 13, 2017
Avelumab	Bavencio	March 23, 2017
Niraparib	Zejula	March 27, 2017
Brigatinib	Alunbrig	April 28, 2017
Durvalumab	Imfinzi	May 1, 2017
Neratinib	Nerlynx	July 17, 2017
Olaparib tabs	Lynparza	August 17, 2017*
Abemaciclib	Verzenio	September 28, 2017

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

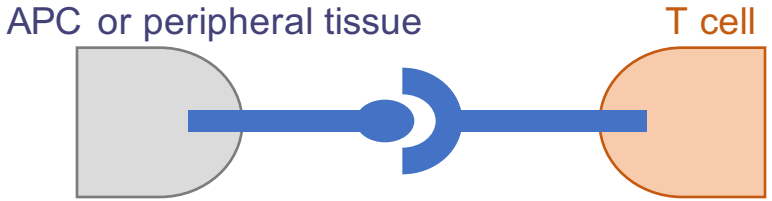
Immune Checkpoint: Mechanism

"Immune checkpoints refer to a plethora of inhibitory pathways hardwired into the immune system that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage." – Pardoll, 2012

Two immune checkpoints with current therapeutic applications

- CTLA-4
  - Downregulates T-cell function
  - Essential for normal immunologic homeostasis
- PD-1
  - Normal role is to limit autoimmunity during an inflammatory response via dampening T cells in peripheral tissues
  - Major immune resistance mechanism in tumors

- Many immune checkpoint receptors and ligands have been identified to be selectively upregulated in cancer



- Generally, receptors and ligands that regulate T-cell ***activation*** are typically ***NOT*** overexpressed in cancers
- Generally, receptors and ligands that regulate T-cell ***effector function*** (i.e., recognizing antigen in peripheral tissues) typically ***ARE*** overexpressed in cancers

APC = antigen-presenting cell; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4.

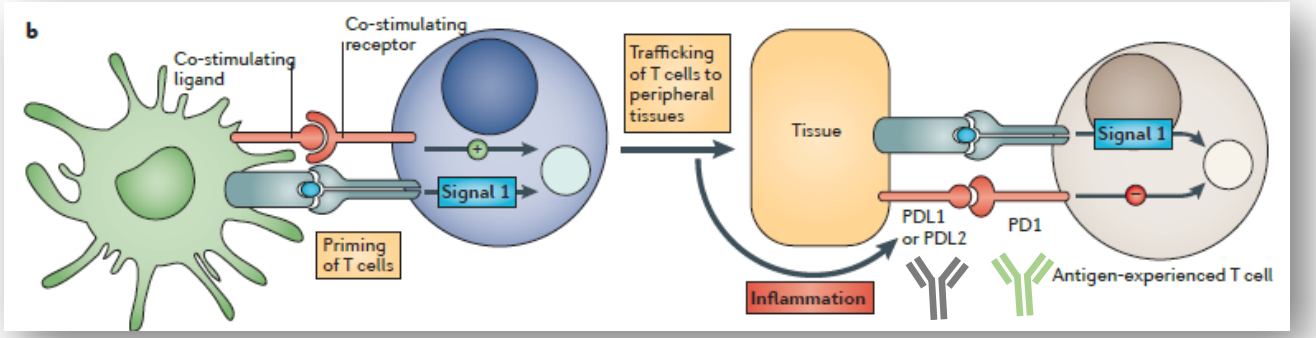
Pardoll DM. *Nat Rev Cancer* 2012;12:252-64.

Targeting Immune Checkpoints

- PD-1 is highly expressed on T-reg cells and interacts with a PD-ligand (e.g., PD-L1) to downregulate T cells
- Chronic antigen → high PD-1 expression and T-cell anergy
- Inhibition of PD-1 or PD-L1 enhances T-cell effector function in the tumor microenvironment

Downregulate T-cell activation

PD-1
PD-L1



PD-L1 Clinical Trials for MCC and UC

Drug/Indication	Study Design	NCT#
Avelumab MCC	• Multicenter, international, prospective, single-group, open-label, phase 2 trial • Stage IV chemotherapy-refractory, histologically confirmed MCC	NCT02155647[1]
Avelumab Advanced or metastatic UC	• Phase 1b, multicenter, expansion cohort, • UC progressing after platinum-based chemotherapy and unselected for PD-L1 expression	NCT01772004[2]
Durvalumab Advanced or metastatic UC	• Phase 1/2, multicenter, expansion cohort • UC progressing after platinum-based chemotherapy and unselected for PD-L1 expression	NCT01693562[3]

Both are dosed as a 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.
MCC = merkel cell carcinoma; UC = urothelial carcinoma.

1. Kaufman HL, et al. *Lancet Oncol* 2016;17:1374-85; 2. Apolo AB, et al. *J Clin Oncol* 2017;35:2117-24; 3. Powles T, et al. *JAMA Oncol* 2017;3:e172411.

Avelumab for MCC: Stage IV MCC Refractory to at Least 1 Chemo Regimen

Outcome	Avelumab[1] (n = 88)	Pembrolizumab[2] (n = 26)
ORR (CR + PR), % CR, % PR, % SD, %	31.8% 9% 23% 10%	56% 15% 38%
PFS at 6 months		67% (95% CI, 49–86)
OS Median		

SD = stable disease.

1. Kaufman HL, et al. *Lancet Oncol* 2016;17:1374-85; 2. Nghiem PT, et al. *N Engl J Med* 2016;374:2542-52.

Avelumab and Durvalumab for UC

Study Parameter	Avelumab	Durvalumab	Atezolizumab Nivolumab Pembrolizumab
Trial design	Phase 1b	Phase 1/2	Phase 1 to3
n	44	191	Range: 86 to 542
Study population	Advanced or metastatic UC with disease progression after platinum-based chemotherapy	Advanced or metastatic UC with disease progression after platinum-based chemotherapy	Advanced or metastatic UC with disease progression after platinum-based chemotherapy
Outcomes			(range for all studies)
Median OS, mo	13.7 mo	18.2 mo	7.9 to 10.3 mo
1-year survival rate	54%	55%	36 to 46%
Median PFS, mo	2.9 mo	1.5 mo	2.1 to 2.8 mo
ORR	18.2%	17.8%	15% to 24%
Grade 3+ AE	7%	7%	15% to 22%

AE = adverse events.

Sharma P, et al. *Lancet Oncol* 2016;17:1590-8; Rosenberg, JE et al. *Lancet* 2016;387:1909-20; Bellmunt J, et al. *N Engl J Med* 2017;376:1015-26; Powles T, et al. *JAMA Oncol* 2017;3:e172411; Apolo AB, et al. *J Clin Oncol* 2017;35:2117-24.

General Safety: PD-1/PD-L1 Comparison

	Avelumab		Durvalumab		Pembrolizumab		Nivolumab		Atezolizumab	
Adverse Reaction	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Fatigue	50%	2%	39%	6%	28%	< 1%	17%	2%	52%	6%
Infusion reaction	25%	< 1%	1.8%	< 1%	< 1%				1.7%	
Arthralgia	16%		6%		18%	< 1%			14%	1%
Diarrhea	23%		13%	1%	26%		9%	2%	18%	1%
Rash	22%		11%	1%	24%	< 1%	21%	< 1%	15%	< 1%
Decreased appetite	20%	2%	19%	1%	16%	< 1%	8%		26%	1%
Dyspnea	11%		13%	2%	11%	< 1%	4%	1%	16%	4%
Hypertension	13%	6%								

Bavencio (avelumab) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf; Keytruda (pembrolizumab) prescribing information, 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf; Opdivo (nivolumab) prescribing information, 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf; Imfinzi (durvalumab) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf; Tencentriq (atezolizumab) prescribing information, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761034s000lbl.pdf.

Avelumab and Durvalumab Special Monitoring

Immune-Mediated Adverse Reaction	Avelumab Rate	Durvalumab Rate
Pneumonitis	1.2%	2.3%
Hepatitis	0.9%	1.1%
Colitis	1.5%	1.3%
Endocrinopathies	6%	9.6%
Nephritis	0.1%	0.2%
Infusion reaction	25%*	1.8%

*Requires premedication with acetaminophen and an antihistamine for the first 4 infusions and subsequently as needed.

- **Immune-mediated pneumonitis:** Withhold for moderate pneumonitis; permanently discontinue for severe, life-threatening, or recurrent moderate pneumonitis.
- **Immune-mediated hepatitis:** Monitor for changes in liver function. Withhold for moderate hepatitis; permanently discontinue for severe or life-threatening hepatitis.
- **Immune-mediated colitis:** Withhold for moderate or severe colitis; permanently discontinue for life-threatening or recurrent severe colitis.
- **Immune-mediated endocrinopathies:** Withhold for severe or life-threatening endocrinopathies.
- **Immune-mediated nephritis and renal dysfunction:** Withhold for moderate or severe nephritis and renal dysfunction; permanently discontinue for life-threatening nephritis or renal dysfunction.
- **Infusion-related reactions:** Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue for severe or life-threatening infusion-related reactions.
- **Infection:** Withhold for severe or life-threatening infection.

Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875-84; Cristofanilli M, et al. *Lancet Oncol* 2016;17:425-39; Turner NC, et al. *N Engl J Med* 2015;373:209-19; Kisqali (ribociclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf; Ibrance (palbociclib) prescribing information, 2015, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf; Verzenio (abemaciclib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716s000lbl.pdf; Imfinzi (durvalumab) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf.

Avelumab and Durvalumab Place in Therapy

- Competes with other PD-1/PD-L1 therapies
  - MCC: Avelumab competes with pembrolizumab and nivolumab
  - UC: All five PD-1/PD-L1 inhibitors have this indication
- Toxicity profile includes typical immune-mediated adverse reactions
  - Avelumab requires premedication to prevent infusion-related reactions

NCCN Clinical Practice Guidelines in Oncology, Merkel Cell Carcinoma, v1.2018, https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf.

New Drug Approvals: December 2016 to September 2017

FDA-Approved Indications

ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib

Extended adjuvant treatment in early-stage *HER2*-positive breast cancer, following adjuvant trastuzumab-based therapy

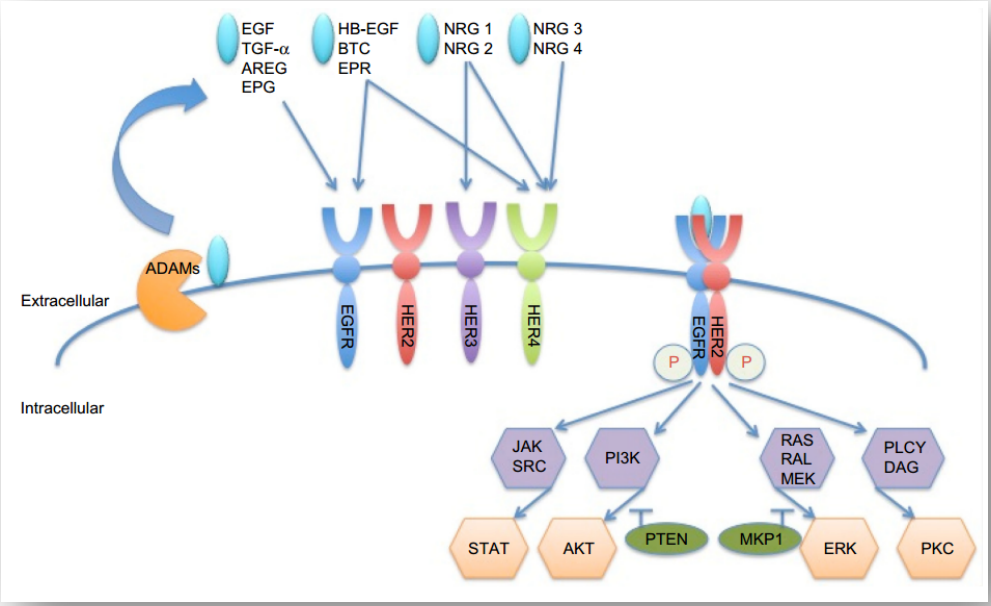
Tyrosine Kinase Inhibitors

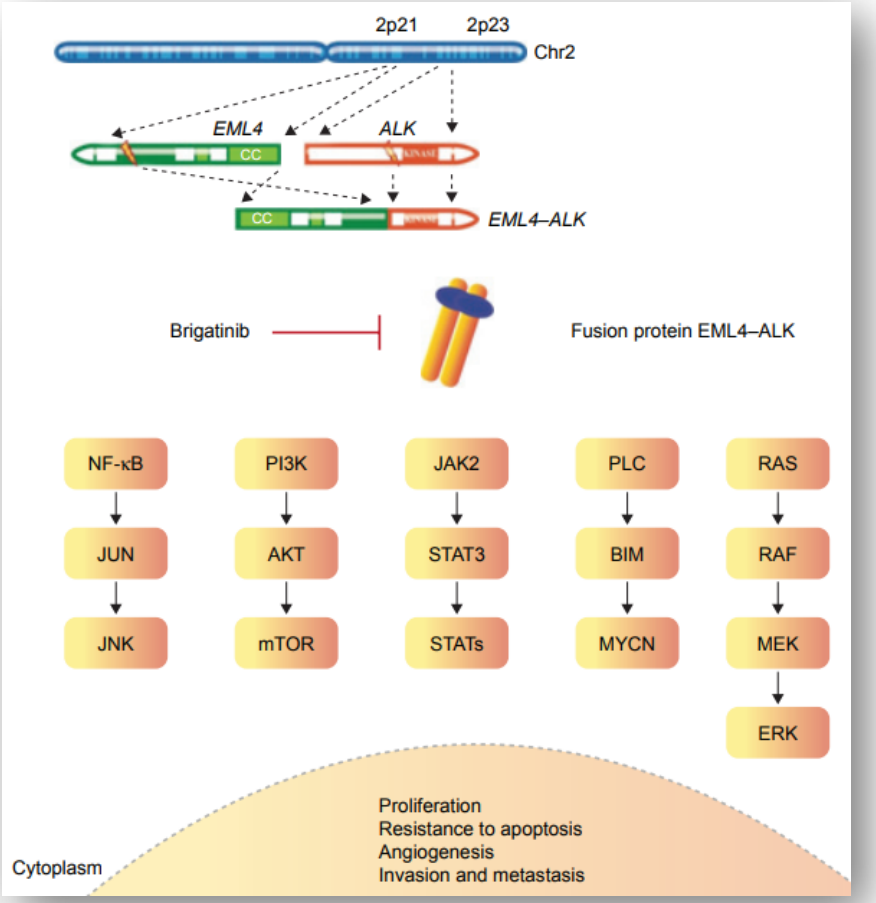
Generic	Brand	Approval Date
Rucaparib	Rubraca	December 19, 2016
Ribociclib	Kisqali	March 13, 2017
Avelumab	Bavencio	March 23, 2017
Niraparib	Zejula	March 27, 2017
Brigatinib	Alunbrig	April 28, 2017
Durvalumab	Imfinzi	May 1, 2017
Neratinib	Nerlynx	July 17, 2017
Olaparib tabs	Lynparza	August 17, 2017*
Abemaciclib	Verzenio	September 28, 2017

*Original FDA approval date: Dec. 19, 2014

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

EGFR and ALK Family of Proteins





Feldinger K, et al. *Breast Cancer (Dove Med Press)* 2015;7:147-62; Sabari JK, et al. *Onco Targets Ther* 2017;10:1983-92.

Brigatinib Activity: Various *ALK* Mutations

Inhibits multiple kinases including *ALK*, *ROS1*, insulin-like growth factor-1 receptor, and FMS-like tyrosine kinase-3 as well as *EGFR* deletion and point mutations

ALK mutation	Gainor et al, cancer discovery 2016[19]				Zhang et al, AACR 2015 abstract 781[26]		
	ALK phosphorylation mean IC_{50} (nmol/L)						
	Ceritinib	Alectinib	Brigatinib	Lorlatinib	Ceritinib	Alectinib	Brigatinib
EML4–ALK	5	11	11	2	37	25	14
C1156Y	5	12	5	5	195	67	45
I1171N	8	398	26	49	119	724	124
I1171S	4	177	18	30	ND	ND	ND
I1171T	4	34	6	12	ND	ND	ND
F1174C	38	27	18	8	109	31	58
F1174L	ND	ND	ND	ND	117	44	55
F1174V	ND	ND	ND	ND	121	46	64
V1180L	ND	ND	ND	ND	16	597	11
L1196M	9	118	27	34	67	133	41
L1198F	196	42	14	15	697	84	82
L1152R	ND	ND	ND	ND	437	62	11
L1152p	ND	ND	ND	ND	451	48	20
G1202R	124	707	130	50	354	690	184
G1202R del	50	59	96	5	ND	ND	ND
D1203N	35	28	35	11	159	42	79
E1210K	6	32	24	2	80	59	107
G1269A	0	25	ND	10	29	56	9
D1203N + F1174c	238	75	123	70	ND	ND	ND
D1203N + E1210K	98	83	136	27	ND	ND	ND
T1151Tins	ND	ND	ND	ND	283	201	114

ND = not done	IC_{50} <50	IC_{50} 50–200	IC_{50} >200

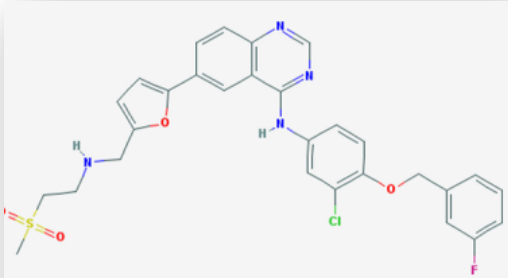
Notes: The in vitro activity of brigatinib is shown relative to the *ALK* inhibitors alectinib, ceritinib, and brigatinib. Results from two independent studies are summarized in this table.
Abbreviations: AACR, American Association of Cancer Research; ALK, anaplastic lymphoma kinase.

Sabari JK, et al. *Onco Targets Ther* 2017;10:1983-92.

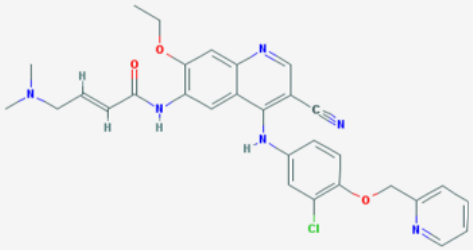
EGFR Tyrosine Kinase Inhibitors

Table 1 Comparison of various tyrosine kinase inhibitors

Compound	Binding	IC_{50} (nM)		
		EGFR	HER2	HER4
Gefitinib	Reversible	27–33[12,*]	≥3,700[12,*]	
		0.4–4.7[13,**]	416–1,830[13,**]	293–323[13,**]
Erlotinib	Reversible	2[12,*]	>1,000[12,*]	
		0.9–1.7[13,**]	238–698[13,**]	579–756[13,**]
Lapatinib	Reversible	11[12,*]	9[12,*]	367[12,*]
		0.3–17	6–25	18–30
Neratinib	Irreversible	92[14,***]	59[14,***]	
Afatinib	Irreversible	0.2–0.7[13,**]	7–25[13,**]	0.7–1.7[13,**]
Canertinib	Irreversible	0.8[12,*]	19[12,*]	7[12,*]
		0.3–1.7[13,**]	22–72[13,**]	0.8–10[13,**]
Dacomitinib	Irreversible	6[15,#]	46[15,#]	74[15,#]



Lapatinib



Neratinib

Feldinger K, et al. *Breast Cancer (Dove Med Press)* 2015;7:147-62.

New TKI Clinical Trials

Agent	Indication	Study Name	Description
Brigatinib	• Crizotinib-refractory *ALK*-positive NSCLC • Patients were stratified by brain metastases and best response to crizotinib	ALTA NCT02094573[1]	Phase 2, randomized to brigatinib 90 mg/day or 180 mg/day (after 90 mg/day for 7 days)
Brigatinib	• *ALK*+ or *EGFR* T790M mutation–naive or resistant to prior therapies • Cohort 2: *ALK*+ and resistant to crizotinib (42 patients)	NCT01449461[2]	Phase 1/2, open-label, single arm; dose escalation from 30 mg/day to 300 mg/day
Neratinib	• Stage I–III *HER2*+ breast cancer who had received trastuzumab and chemotherapy • Disease-free up to 2 years after completion of trastuzumab	ExteNET NCT00878709[3]	Phase 3, multicenter, randomized, double-blind, placebo-controlled

TKI = tyrosine kinase inhibitor.

1. Kim DW, et al. *J Clin Oncol* 2017;35:2490-8; 2. Gettinger SN, et al. *Lancet Oncol* 2016;17:1683-96; 3. Chan A, et al. *Lancet Oncol* 2016;17:367-77.

Brigatinib for *ALK*+ NSCLC and Refractory to Crizotinib

Outcome	Gettinger 2016 Phase 1/2 Cohort 2 (n = 42)[1]	Kim 2017 Phase 2 90 mg/day (n = 112)[2]	Kim 2017 Phase 2 180 mg/day* (n = 110)[2]
ORR (CR + PR), % (95% CI) Intracranial ORR	72% (60–82)	45% (34–56) 42%	54% (43–65) 67%
PFS, median (95% CI)		9.2 months (7.4–15.6)	12.9 months (11.1–NR)
OS, 1-year rate (95% CI)		70.6 (59.8–79.1)	79.5 (66.9–87.7)

*90 mg orally once daily for the first 7 days

1. Gettinger SN, et al. *Lancet Oncol* 2016;17:1683-96; 2. Kim DW, et al. *J Clin Oncol* 2017;35:2490-8.

Neratinib for Extended Adjuvant Therapy in *HER2*+ Breast Cancer

Outcome at 2-Year Follow-Up	Neratinib 24 mg Orally Daily for 12 Months (n = 1,420)	Placebo (n = 1,420)
DFS events HR (95% CI) *p* value	70 events 0.67 (95% CI, 0.50–0.91) .0091	109 events
2-year DFS rate (95% CI)	93.9% (95% CI, 92.4–95.2)	91.6% (95% CI, 90.0–93.0)

DFS = disease-free survival.

Chan A, et al. *Lancet Oncol* 2016;17:367-77.

General Safety: Brigatinib and Neratinib

	Brigatinib		Neratinib	
Adverse Reaction	All Grades	Grades 3-4	All Grades	Grades 3-4
Diarrhea	19%		95%	40%
Vomiting	24%	2%	26%	3%
Abdominal pain	17%		36%	2%
Stomatitis			14%	< 1%
Cough	18%			
Dyspnea	27%	3%		
Arthralgia	14%	< 1%	6%	< 1%
Decreased appetite	22%		12%	< 1%
Rash			18%	< 1%
Nail disorder			8%	< 1%

	Brigatinib		Neratinib	
Laboratory Abnormality	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased ALT	34%		9%	1%
Increased AST	38%	< 1%	7%	< 1%
Hyperglycemia	38%	4%		
Increased lipase	21%	5%		
Increased amylase	27%	4%		
Increased alk phos	15%	< 1%		
Decreased phos	15%	2%		
Increased aPTT	22%	2%		
Anemia	23%	< 1%		
Lymphopenia	19%	3%		

alk phos = alkaline phosphatase; aPTT = activated partial thromboplastin time.

Alunbrig (brigatinib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208772lbl.pdf;
Nerlynx (neratinib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf.

Brigatinib Special Monitoring

Adverse Reaction*	Rate
ILD	9.1%
Hypertension	21%
Bradycardia	7.6%
Visual disturbances	10%
CPK elevation	48%
Pancreatic enzyme elevation	39%
Hyperglycemia	

- **ILD/Pneumonitis:** Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment. Withhold drug for new or worsening respiratory symptoms and promptly evaluate for ILD/pneumonitis. Upon recovery, either dose reduce or permanently discontinue.
- **Hypertension:** Monitor blood pressure after 2 weeks and then at least monthly during treatment. For severe hypertension, withhold drug, then dose reduce or permanently discontinue.
- **Bradycardia:** Monitor heart rate and blood pressure regularly during treatment. If symptomatic, withhold drug, then dose reduce or permanently discontinue.
- **Visual Disturbance:** Advise patients to report visual symptoms. Withhold drug and obtain ophthalmologic evaluation, then dose reduce or permanently discontinue.
- **CPK Elevation:** Monitor CPK levels regularly during treatment. Based on the severity, withhold drug, then resume or reduce dose.
- **Pancreatic Enzyme Elevation:** Monitor lipase and amylase levels regularly during treatment. Based on the severity, withhold drug, then resume or reduce dose.
- **Hyperglycemia:** Assess fasting serum glucose prior to starting drug and regularly during treatment. If not adequately controlled with optimal medical management, withhold drug, then consider dose reduction or permanently discontinue, based on severity.

*See prescribing information for specific dosing recommendations
CPK = creatine phosphokinase; ILD = interstitial lung disease.

Alunbrig (brigatinib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208772lbl.pdf.

Neratinib Special Monitoring

Adverse Reaction	Rate
Diarrhea	95%
Hepatotoxicity	
ALT	9.7%
AST	5.1%
Led to discontinuation	1.7%

Diarrhea: Aggressively manage diarrhea occurring despite recommended prophylaxis with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold drug in patients experiencing severe and/or persistent diarrhea. Permanently discontinue drug in patient experiencing grade 4 diarrhea or grade ≥ 2 diarrhea that occurs after maximal dose reduction.

Hepatotoxicity: Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold drug in patients experiencing grade 3 liver abnormalities and permanently discontinue drug in patients experiencing grade 4 liver abnormalities.

Nerlynx (neratinib) prescribing information, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf.

New TKI Place in Therapy

Brigatinib

- Represents an advancement in the treatment of resistant/refractory *ALK*+ NSCLC
- Use of this agent for specific mutations may represent the future of precision medicine in NSCLC

Neratinib

- Represents another option in the early treatment of *HER2*-positive breast cancer
- Standard of therapy currently includes pertuzumab in the adjuvant setting, and the studies did not include this agent, so its use would be for patients who did not get or did not qualify for pertuzumab

Summary

The pharmacology of new oncology medications approved in 2016–2017 are mostly “me too” agents with slight differences over previously approved agents

- PARP inhibitors are prominent in the treatment of ovarian cancer
- CDK4/6 inhibitors now represent the standard of care in HR+, *HER2*-advanced/metastatic breast cancer
- There are now five PD-1/PD-L1 inhibitors approved for urothelial carcinoma
- New TKIs are used for NSCLC, refractory to current agents and for extended adjuvant therapy in breast cancer

Summary

- For the new drugs approved, the hazard ratios ranged from
  - 0.2 for PARP inhibitors in *BRCA* mutation–positive tumors
  - 0.5 for CDK4/6 inhibitors in first or second line
  - 0.67 for neratinib as extended adjuvant therapy
- With some slight differences, adverse events were generally consistent with other agents in the same class
  - Ribociclib has QT prolongation
  - Abemaciclib has less neutropenia but more diarrhea
  - Serious adverse effects were seen for brigatinib, a drug known to inhibit multiple kinases
  - Serious cases of diarrhea occurred with neratinib

Summary

- Patients with ovarian cancer now have multiple options as maintenance or for recurrence
- Patients with breast cancer now have multiple options when considering endocrine therapy for HR+, *HER2*- disease
- There continue to be advances in NSCLC, especially with genomic-driven therapies
- Patients who do not receive pertuzumab may be candidates for neratinib therapy

SMARTIE

This has been a SMARTIE presentation.

SMARTIE participants, you can now go to smartie2017.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.