New Drug Updates in Solid Tumors

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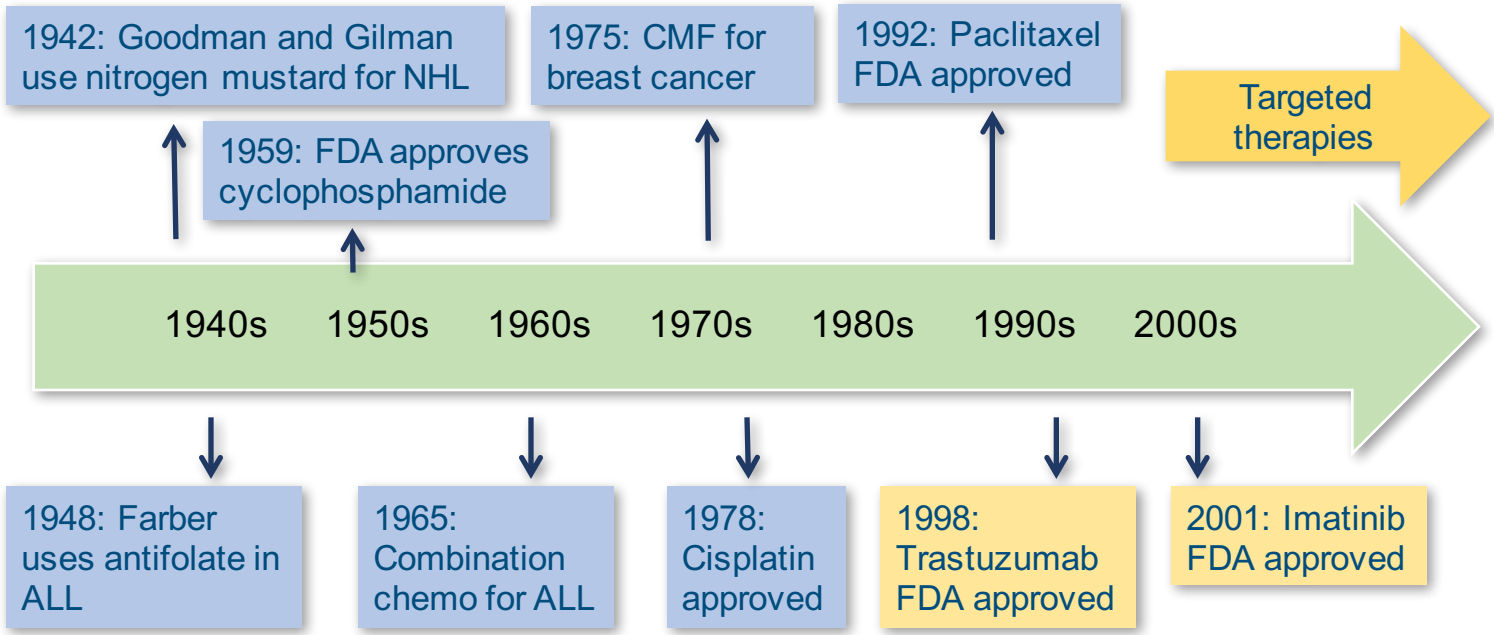
Learning Objectives

- Discuss the pharmacology and indications of medications approved in the year 2017–2018 for the management of patients with solid tumors
- Recall the pivotal clinical trial data considered by the FDA when approving new oncolytics
- Identify the signs and symptoms of serious or life-threatening adverse effects of newly approved oncology drugs
- Describe the impact of these agents in advanced practice

Financial Disclosure

Dr. Kiel has served on speakers bureaus for Celgene, Genentech, Gilead, and Takeda; he has received consulting fees from Takeda.

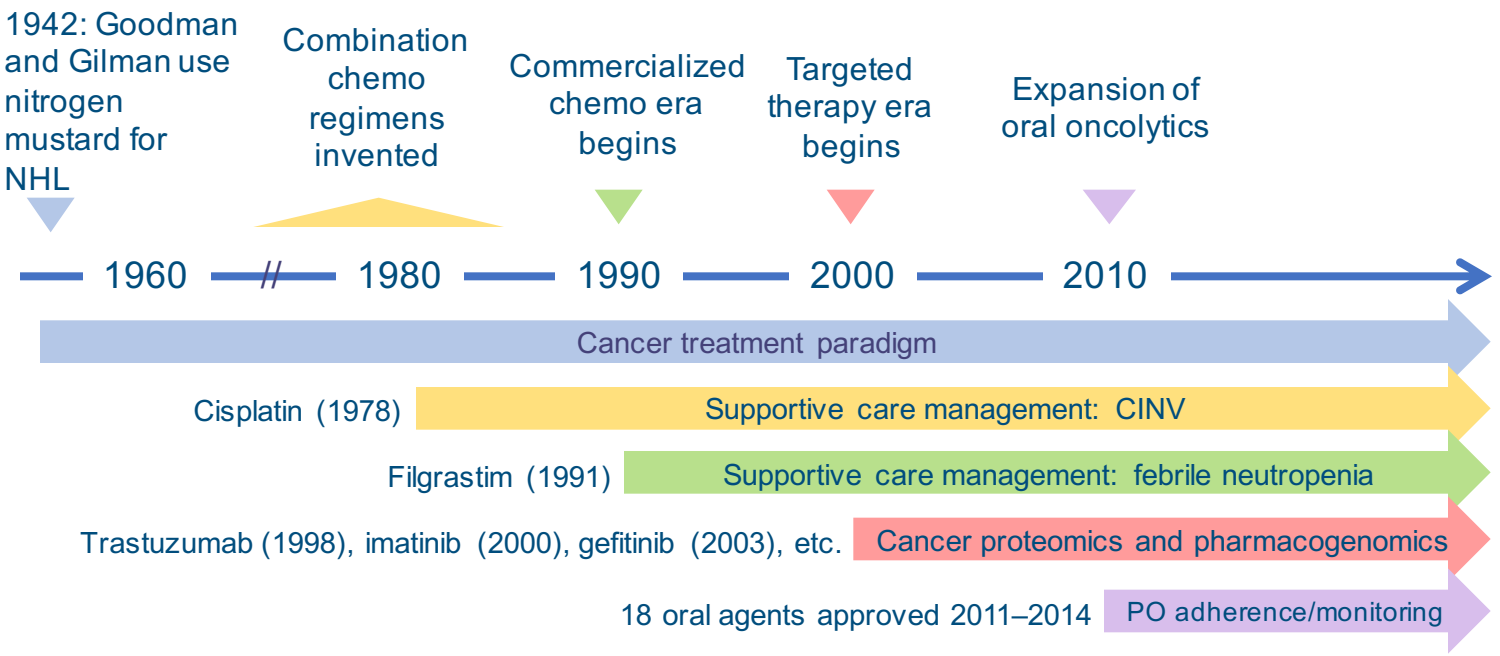
History of Cancer Drug Approvals in the United States



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

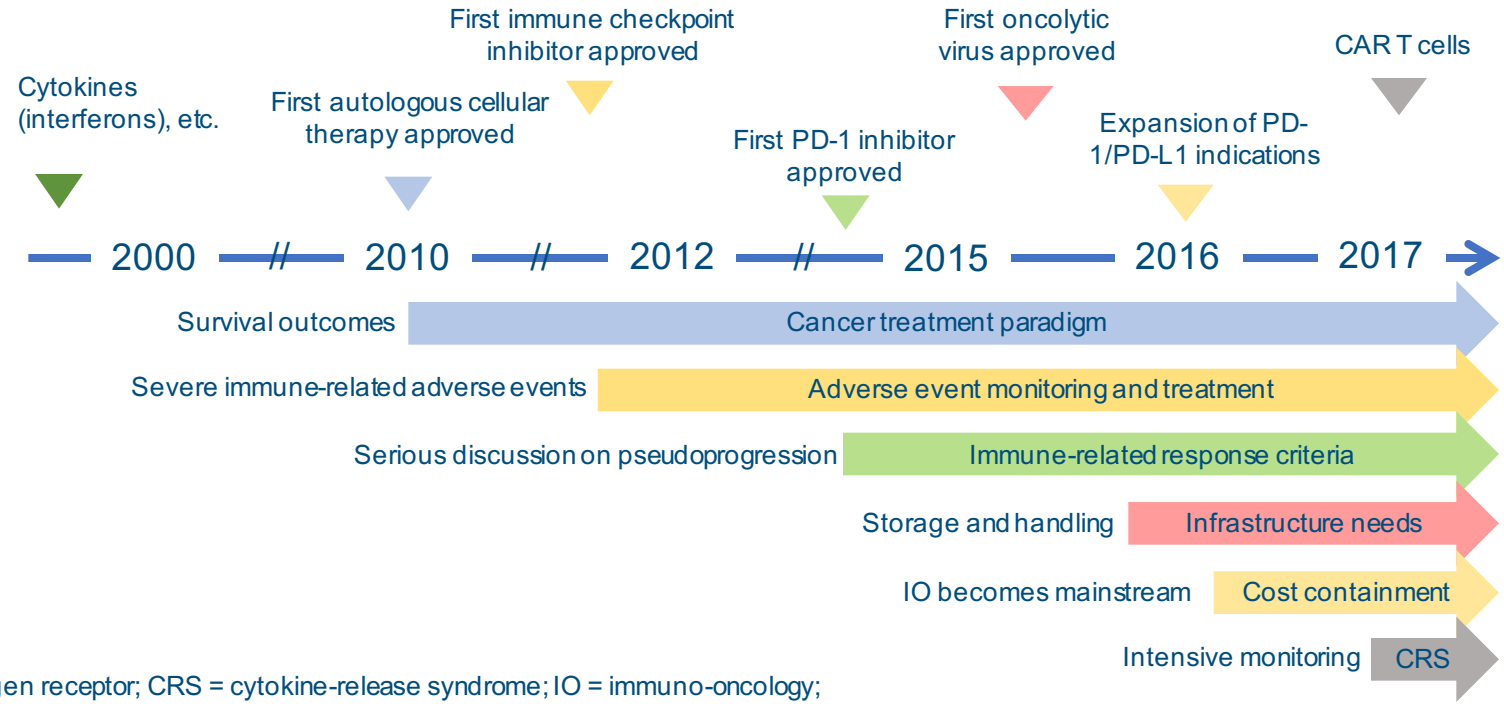
Adapted from Chabner BA, et al. *Nat Rev Cancer* 2005;5:65-72.

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: Dec 2017 to Sept 2018

Novel Mechanism

None

Biosimilar Approval

Generic	Brand	Approval Date
Trastuzumab-dkst	Ogivri	December 1, 2017

Established Mechanism

Generic	Brand	Approval Date
Apalutamide	Erleada	February 14, 2018
Encorafenib	Braftovi	June 27, 2018
Binimetinib	Mektovi	June 27, 2018

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US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Nivolumab	Opdivo	New indication	mSCLC following platinum and 1 other line	August 16, 2018
Nivolumab	Opdivo	New indication	With ipilumumab in previously treated MSI-H or dMMR CRC	July 10, 2018
Nivolumab	Opdivo	New indication	With ipilumumab in intermediate-poor risk untreated RCC	April 16, 2018
Nivolumab	Opdivo	New indication	Adjuvant treatment LN + or metastatic resectable melanoma	Dec 20, 2017
Nivolumab	Opdivo	New dosing	Every-4-week dosing	March 5, 2018
Pembrolizumab	Keytruda	New indication	Metastatic PD-L1 cervical cancer	June 12, 2018
Pembrolizumab	Keytruda	New indication	Combination with platinum/pemetrexed first-line NSCLC	August 20, 2018
Durvalumab	Imfinzi	New indication	Stage III NSCLC	Feb 16, 2018

CRC = colorectal; dMMR = mismatch repair deficient; MSI-H = microsatellite instability high; NSCLC = non–small call lung cancer; SCLC = small cell lung cancer.

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Abemaciclib	Verzenio	New indication	With AI as initial therapy in post-menopausal women with breast cancer. HR+, HER2-	Feb 26, 2018
Ribociclib	Kisqali	New indication	With AI as initial therapy in pre/post-menopausal women with breast cancer. HR+, HER2-	July 18, 2018
Alectinib	Alecensa	New indication	ALK+ mNSCLC	Nov 6, 2017
Sunitinib	Sutent	New indication	Adjuvant therapy for high risk RCC following nephrectomy	Nov 16, 2017
Olaparib	Lynparza	New indication	BRCA-mutated metastatic breast cancer	Jan 12, 2018
Rucaparib	Rubraca	New indication	Maintenance treatment in ovarian following a ORR with platinum based therapy	April 6, 2018
Lenvatinib	Lenvima	New indication	First-line unresectable hepatocellular	Aug 16, 2018
Cabozantinib	Cabometyx	New indication	First-line advanced RCC	Dec 19, 2017

AI = aromatase inhibitor; ALK = anaplastic lymphoma kinase; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; RCC = renal cell carcinoma.

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Dabrafenib/Trametinib	Tafinlar/Mekinist	New indication	Anaplastic thyroid cancer BRAF V600E	May 4, 2018
Dabrafenib/Trametinib	Tafinlar/Mekinist	New indication	Adjuvant treatment in BRAF-mutated melanoma	April 30, 2018
Alectinib	Alecensa	New indication	First-line ALK+ NSCLC	Nov 6, 2018
Afatinib	Gilotrif	New indication	First-line EGFR mutated NSCLC	Jan 12, 2018
Osimertinib	Tagresso	New indication	First-line EGFR mutated NSCLC	April 19, 2018
Abiraterone	Zytiga	New indication	Metastatic high-risk castration sensitive prostate cancer, with prednisone	Feb 7, 2018
Enzalutamide	Xtandi	New indication	Non-metastatic castrate-resistant prostate cancer	July 13, 2018

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Pertuzumab			In combination with trastuzumab as adjuvant therapy in HER2+ early breast cancer	Dec 20, 2017
FoundationOne CDx			Next-generation sequencing diagnostic for 324-gene panel in solid tumors	Nov 30, 2017

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

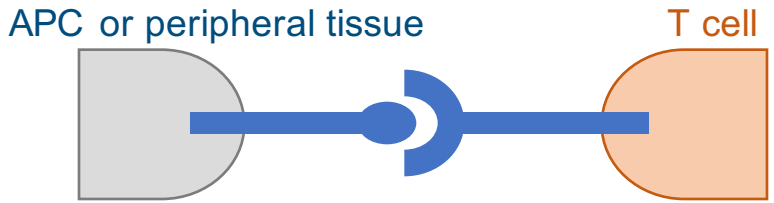
Immune Checkpoint: Mechanism

"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.

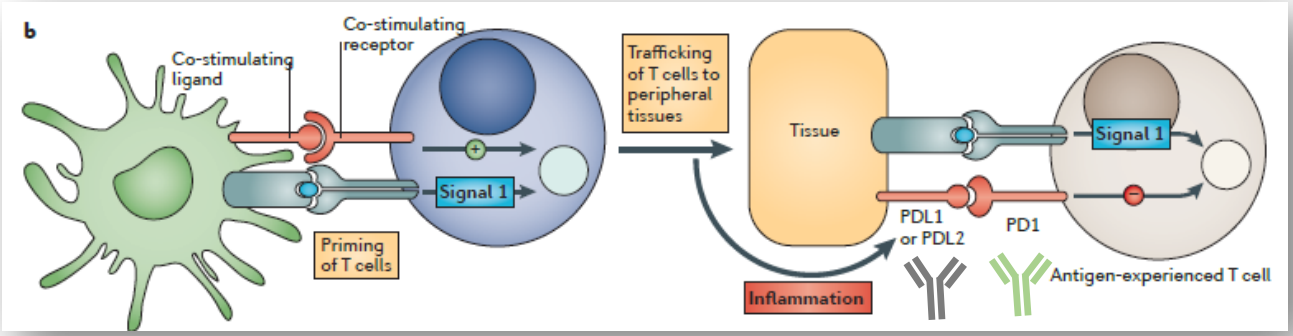
Pardoll DM. *Nat Rev Cancer* 2012;12:252-64.

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



Approved Immunotherapy

- 11/2015 nivolumab, based on CheckMate 025
  - Advanced RCC for patients who have received prior antiangiogenic therapy
  - Dose: 240 mg IV over 30 minutes every 2 weeks, OR
    480 mg IV over 30 minutes every 4 weeks
- 4/16/18 nivolumab and ipilimumab in combination, based on CheckMate 214
  - First-line treatment of intermediate- or poor-risk advanced renal cell carcinoma
  - Dosing
    - Nivolumab 3 mg/kg, followed by ipilimumab 1 mg/kg, on the same day every 3 weeks for 4 doses
    - Followed by nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Ipilimumab/Nivolumab vs. Sunitinib in First-Line Clear Cell Advanced Renal Cell Carcinoma, CheckMate 214

Stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IDMC) prognostic score

Treatment-naive patients with metastatic or advanced clear-cell RCC (N = 1,096)

Nivolumab 3 mg/kg plus **Ipilimumab** 1 mg/kg IV every 3 weeks x 4, followed by nivolumab 3 mg/kg every 2 weeks (n = 550)

Sunitinib 50 mg daily for 4 weeks on and 2 weeks off (6-week cycle) (n = 546)

Response for IDMC intermediate/poor risk
Minimum follow-up: 17.5 months

%	ORR	CR	PR	SD	PD
Nivo + Ipi (n = 425)	42	9	32	31	20
Sunitinib (n = 422)	27	1	25	45	17

Treatment continued until progression or unacceptable toxicity

CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; SD = stable disease.

Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290

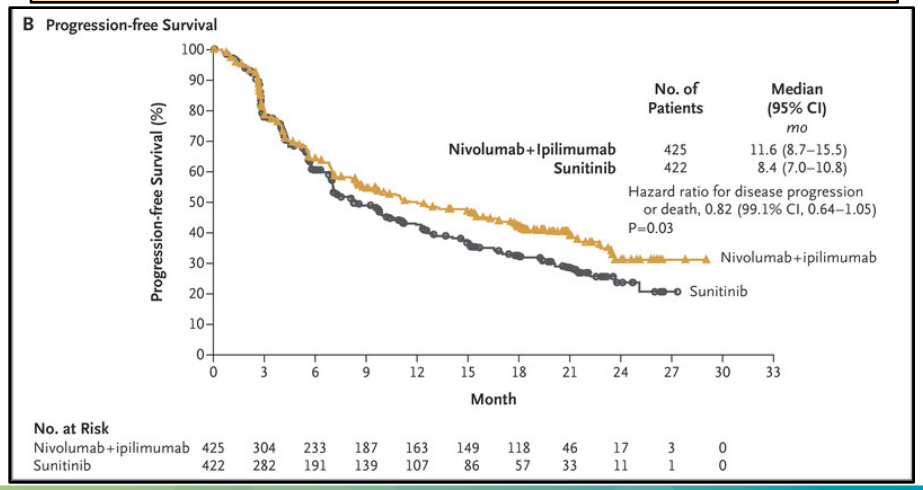
Nivo/Ipi Significantly Improved Overall Survival for IMDC Intermediate/Poor-Risk RCC

Median Progression-Free Survival

Nivo + Ipi (n = 425): 11.6 mo

Sunitinib (n = 422): 8.4 mo

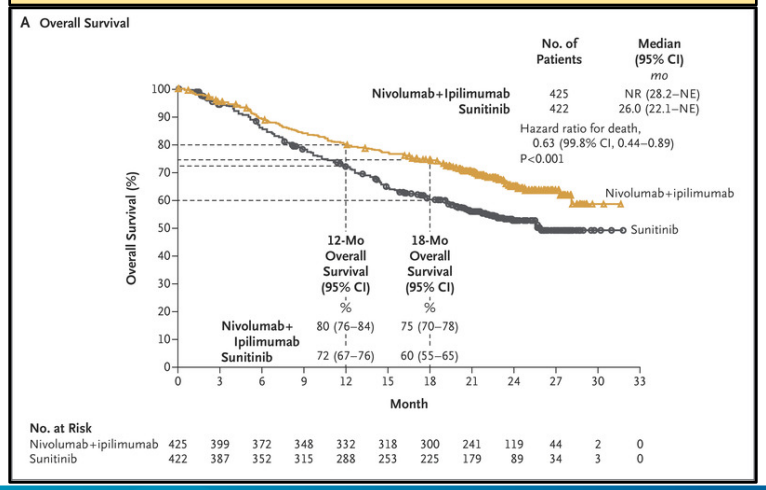
Median duration of response not reached



Median Overall Survival

Nivo + Ipi (n = 425): Not reached

Sunitinib (n = 422): 26 mo



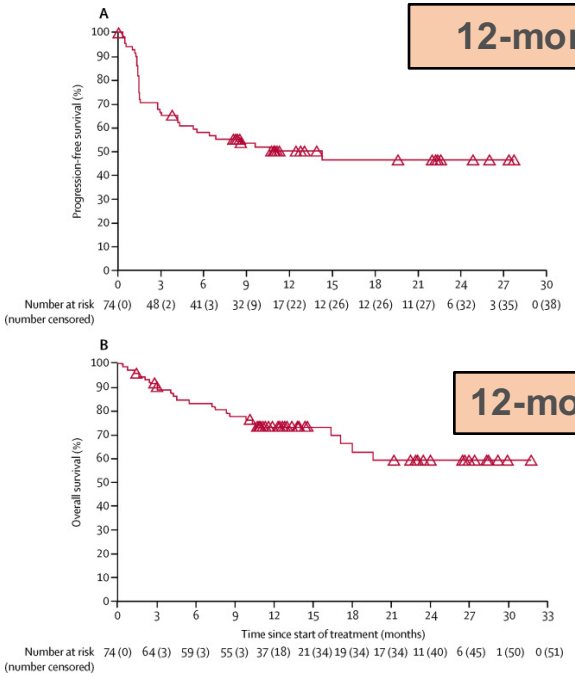
Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290

Nivolumab

- FDA approved for
  - Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
- Based on data from CheckMate 142
- Dose: 240 mg IV over 30 minutes every 2 weeks until disease progression or unacceptable toxicity

CheckMate 142: Nivolumab Monotherapy for dMMR/MSI-H Metastatic Colorectal Cancer

- 74 patients
- Nivolumab at 3 mg/kg q2wk
- Median follow-up: 12 months
  - Objective response: 31%
  - Disease control: 69%
  - Median time to response: 2.8 months (range 1.4–3.2)
  - Median duration of response: not reached
  - Median PFS: 14.3 months
- Responses were seen irrespective of PD-L1 status, Lynch syndrome, or *KRAS* and *BRAF* mutations.



12-month PFS: 50%

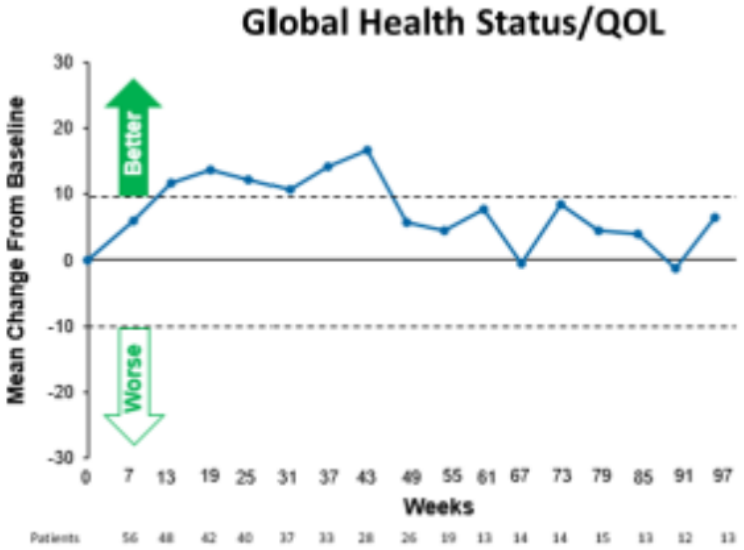
12-month OS: 73%

dMMR/MSI-H = DNA mismatch repair deficient/microsatellite instability-high

Overman, MJ, et al. *Lancet* 2017;18:1182–1191.

Patient-Reported Outcomes and Adverse Effects

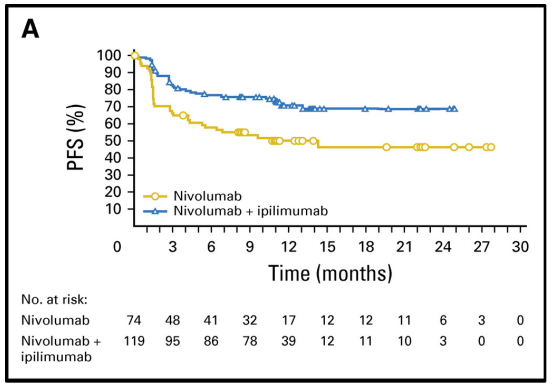
- Any grade: 70%
- Grade 3/4: 20%
- Most adverse events were easily managed
- As early as week 13, clinically meaningful improvements in quality of life



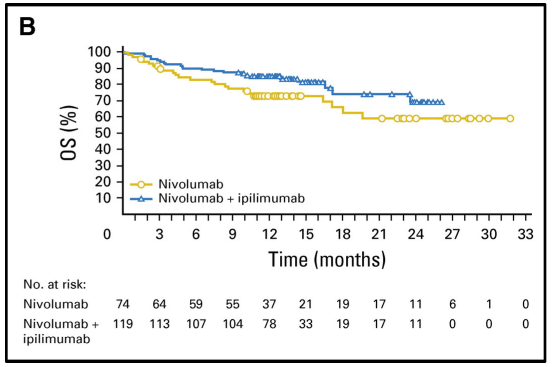
European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30

Nivolumab/Ipilimumab for dMMR/MSI-H Metastatic Colorectal Cancer, CheckMate 142

- 119 patients
- Nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg once every 3 weeks (4 doses) followed by nivolumab at 3 mg/kg once every 2 weeks
- Median follow-up: 13.5 months
  - Objective response: 55%
  - Disease control: 80%
  - Median time to response: 2.8 months (range 1–14)
  - Median duration of response: not reached
  - Median PFS: not reached



12-month PFS
Nivo: 50%
Nivo/Ipi: 71%



12-month OS
Nivo: 73%
Nivo/Ipi: 85%

Overman MK, et al. JCO 2018;*36*:773–779.

CheckMate 142: Nivolumab/Ipilimumab Cohort Adverse Events

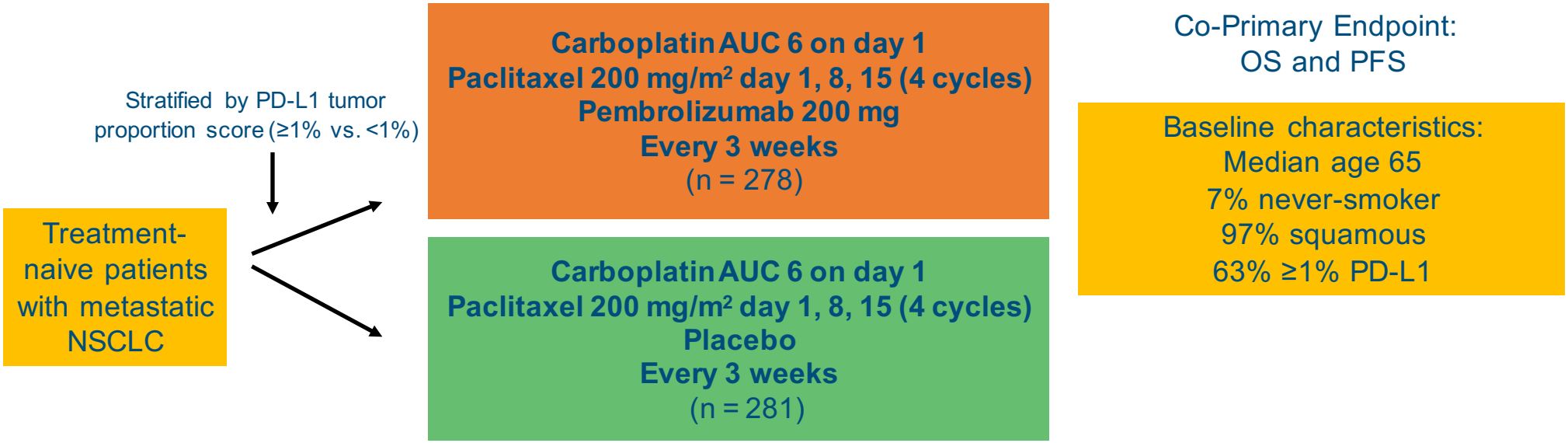
- Combination therapy had similar adverse events, but more likely to be grade 3/4 than monotherapy
- Any grade: 73%
- Grade 3/4: 32%
- 13% of patients discontinued therapy due to adverse events
- QOL improved with combination therapy similar to monotherapy

	No. (%)		
TRAE	Grade 1-2	Grade 3	Grade 4
Any TRAE	49 (41)	32 (27)	6 (5)
Diarrhea*	24 (20)	2 (2)	0
Fatigue*	19 (16)	2 (2)	0
Pruritus*	18 (15)	2 (2)	0
Pyrexia*	18 (15)	0	0
Increased AST*	8 (7)	9 (8)	0
Hypothyroidism*	15 (13)	1 (1)	0
Nausea*	14 (12)	1 (1)	0
Increased ALT*	6 (5)	8 (7)	0
Rash*	11 (9)	2 (2)	0
Hyperthyroidism*	13 (11)	0	0

TRAE = treatment-related adverse event

Overman MK, et al. JCO 2018;36:773–779.

KEYNOTE-047: Carboplatin/Pemetrexed/Pembrolizumab

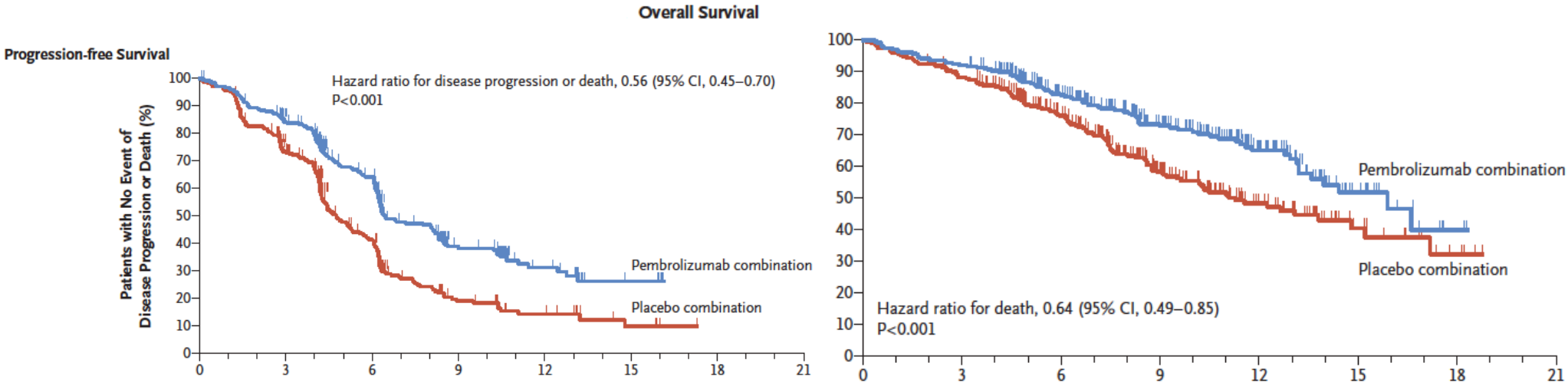


Pembrolizumab treatment continued until progression or unacceptable toxicity

AUC = area under the concentration-time curve; NSCLC = non-small cell lung cancer.

Paz-Ares L, et al. NEJM 2018; DOI: 10.1056/NEJMoa1810865

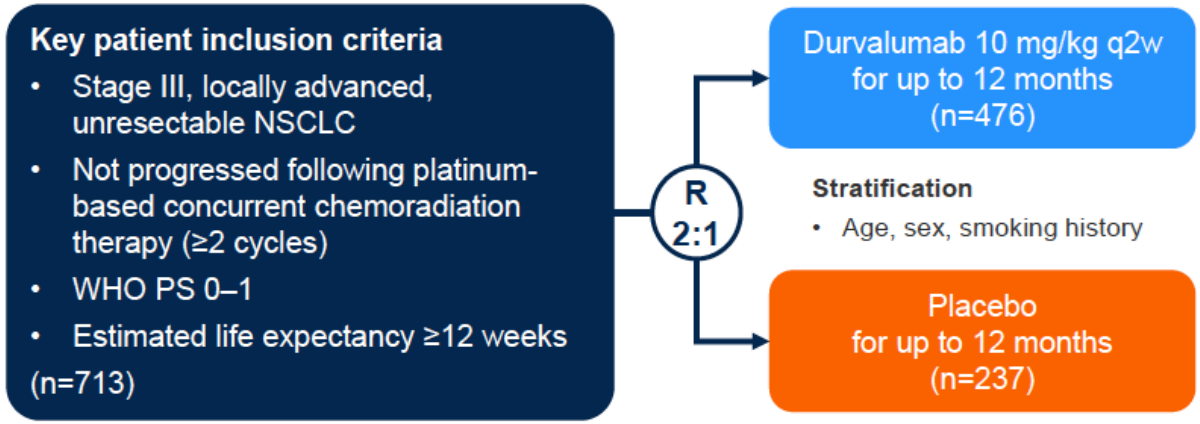
KEYNOTE-047 Primary Outcome Results



Paz-Ares L, et al. *NEJM* 2018; DOI: 10.1056/NEJMoa1810865

Durvalumab After Radiation in Stage III NSCLC

- **Study objective**
  - To evaluate the anti-PD-L1 durvalumab, in stage III, locally advanced, unresectable NSCLC



Co-primary endpoints

- PFS (BICR, RECIST v1.1), OS

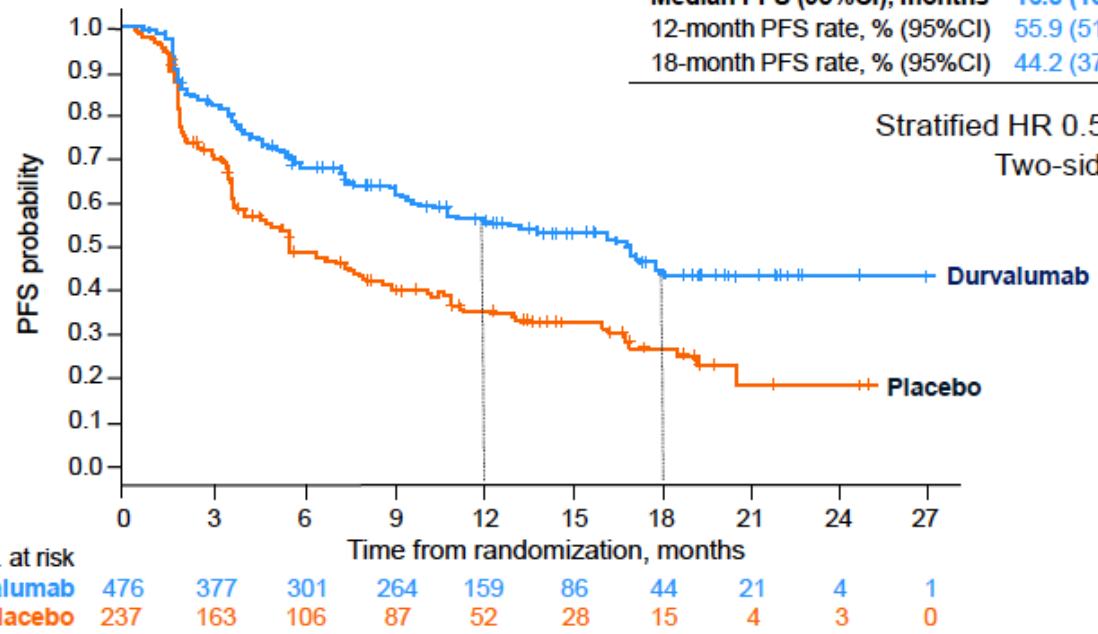
Secondary endpoints

- ORR (BICR), DoR (BICR), safety, PROs

Progression-Free Survival

	Durvalumab (n=476)	Placebo (n=237)
Median PFS (95%CI), months	**16.8 (13.0, 18.1)**	**5.6 (4.6, 7.8)**
12-month PFS rate, % (95%CI)	55.9 (51.0, 60.4)	35.3 (29.0, 41.7)
18-month PFS rate, % (95%CI)	44.2 (37.7, 50.5)	27.0 (19.9, 34.5)

Stratified HR 0.52 (95%CI 0.42, 0.65)
Two-sided p<0.0001



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Antonia SJ, et al. NEJM 2017; 377:1919-29.

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

New Drug Approvals: Dec 2017 to Sept 2018

CDK4/6 Inhibitor

Generic	Brand	Approval Date
Ribociclib	Kisqali	March 13, 2017
Abemaciclib	Verzenio	Feb 26, 2018

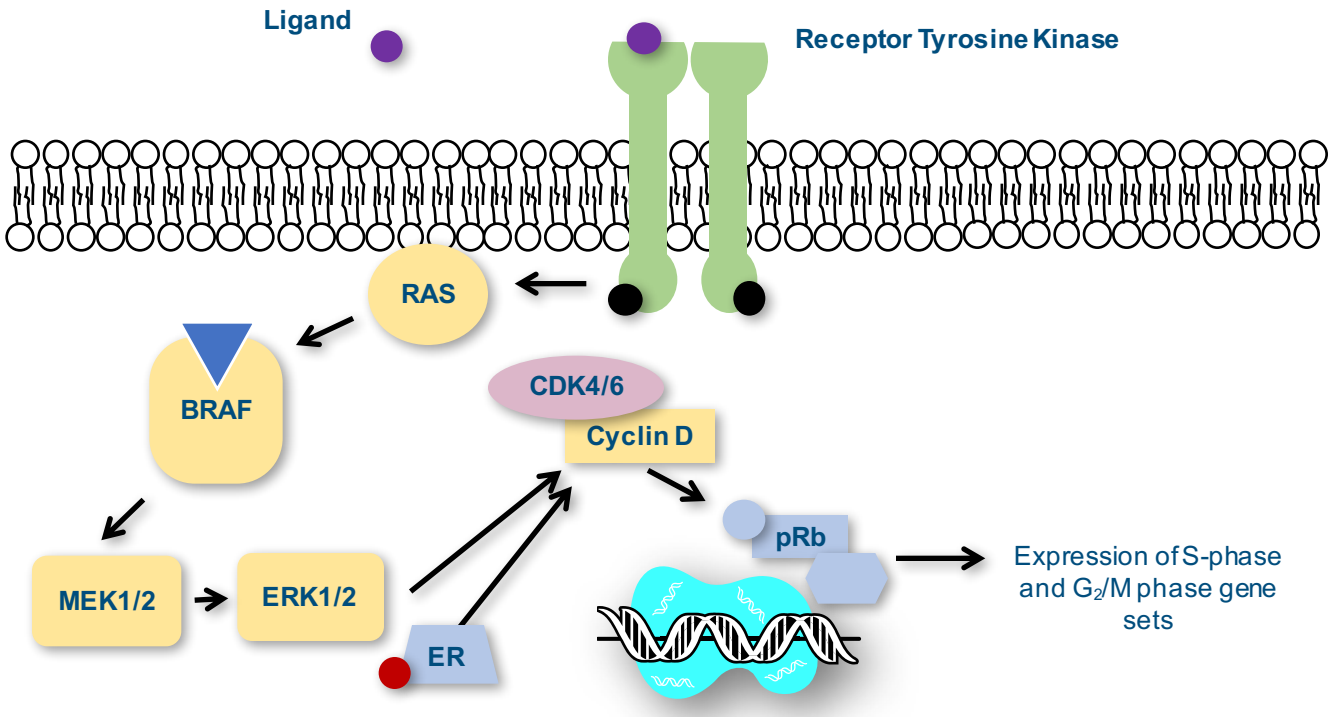
In combination with an aromatase inhibitor for pre/perimenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy.

In combination with fulvestrant for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

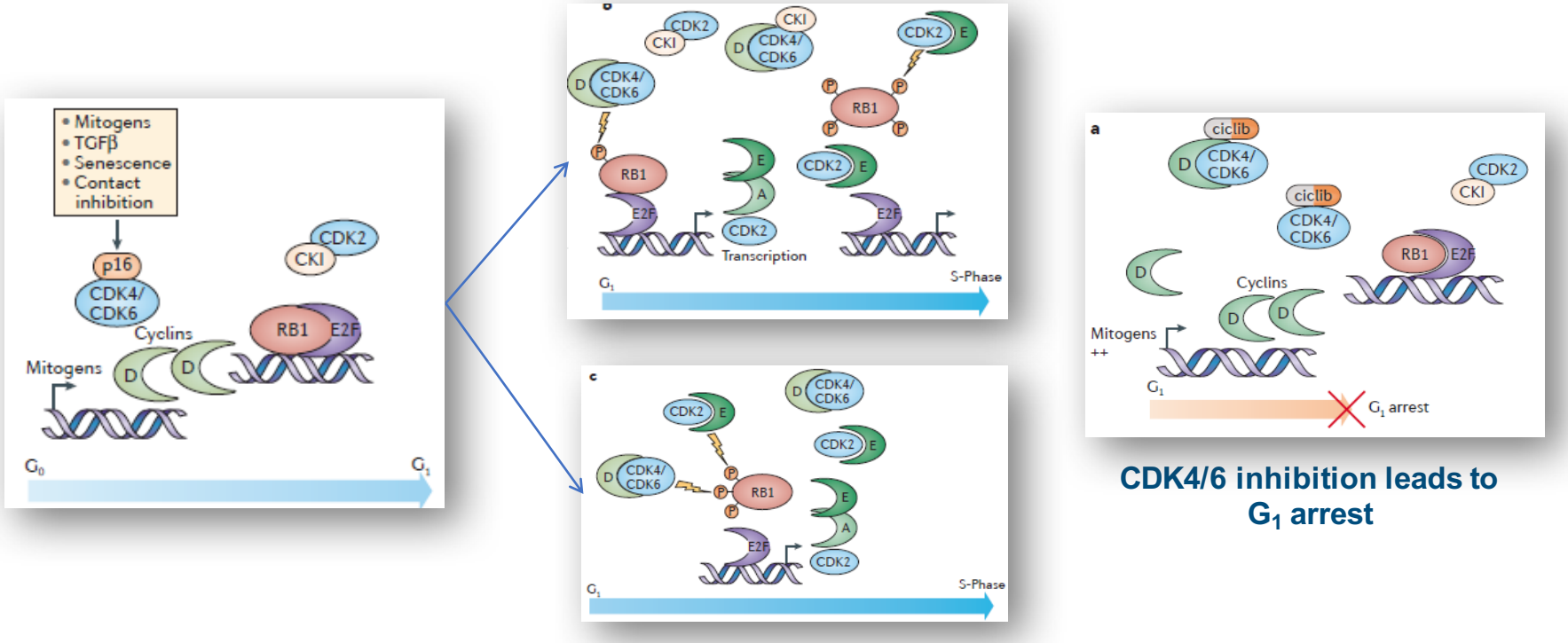
US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

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

CDK4/6 Clinical Trial Updates

Outcome	MONALEESA-3 (n = 726)	MONALEESA-7 (n = 495)	MONARCH 3 (n = 493)
Indication	Ribociclib/fulvestrant in post-menopausal 1st line	Ribociclib/AI in pre/peri-menopausal 1st line (NOT with tamoxifen)	Abemaciclib/AI in post-menopausal 1st line
Comparator	Fulvestrant/placebo	NSAI or tamoxifen/goserelin	Letrozole or anastrozole
Progression-free survival Median HR	20.5 vs 12.8 months (0.593, 0.48–0.732)	27.5 vs. 13.8 months (0.569, 0.436–0.743)	28.2 vs 14.8 months (0.54, 4.418–0.698)
Overall survival Median HR	Not available	Not available	Not available

Goetz MP, et al. *J Clin Oncol* 2017;35:3638-3646.
DOI: 10.1200/JCO.2018.78.9909 *J Clin Oncol* 36, no. 24 (August 20 2018) 2465-2472.
DOI: 10.1200/JCO.2018.36.15_suppl.1047 *J Clin Oncol* 36, no. 15_suppl (May 20 2018) 1047-1047.

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, 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, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf; Ibrance (palbociclib) prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf; Verzenio (abemaciclib) prescribing information, 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	

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.

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.

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, ,https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf; Ibrance (palbociclib) prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf; Verzenio (abemaciclib) prescribing information, 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 + abemaciclib	AI	AI
Second line	AI + everolimus	Fulvestrant + palbociclib Fulvestrant + abemaciclib Fulvestrant + ribociclib	Fulvestrant Tamoxifen
Third line	Tamoxifen/fulvestrant	AI + everolimus Tamoxifen	Abemaciclib (single agent)

NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, v1.2018, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

New Drug Approvals: Dec 2017 to Sept 2018

PARP inhibitor

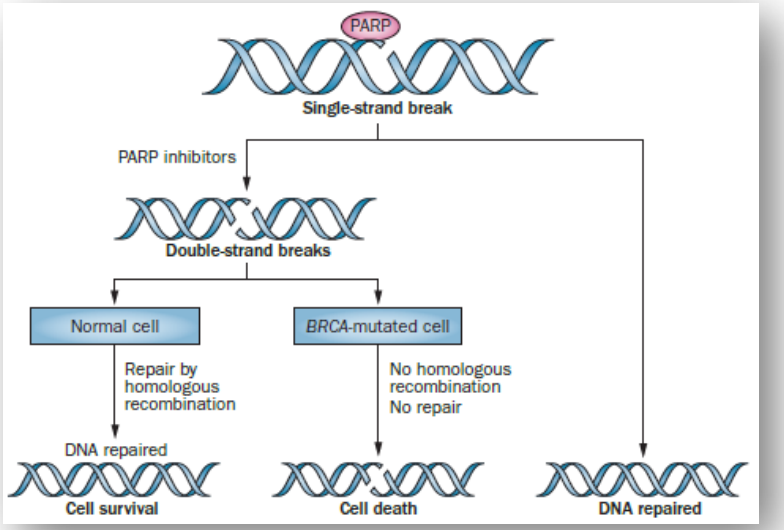
Generic	Brand	Approval Date
Olaparib	Lynparza	Jan 12, 2018

In patients with a deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.

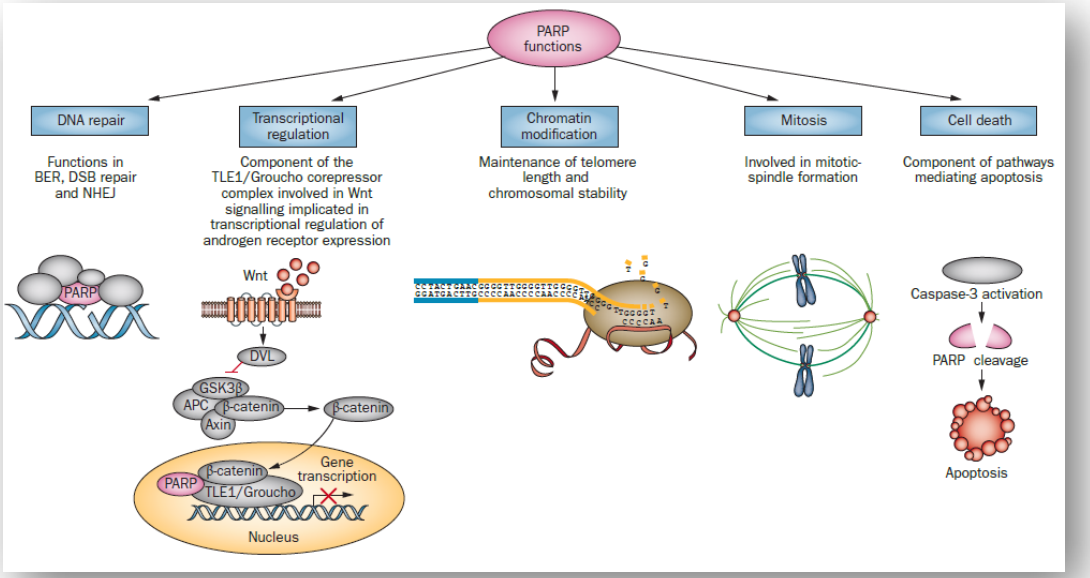
US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Pharmacology of PARP Inhibition

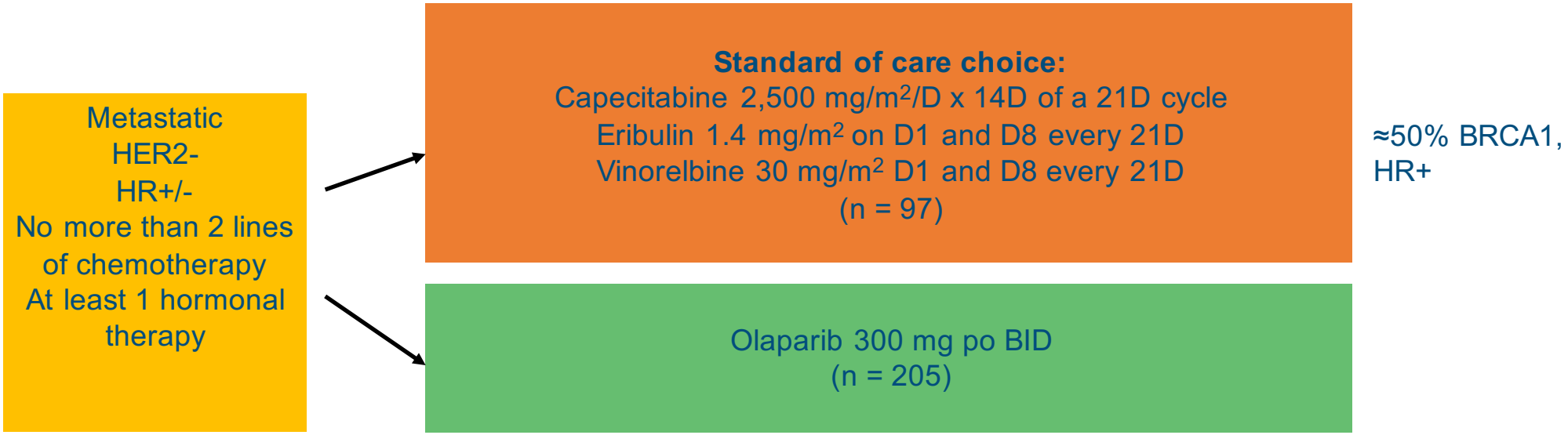
Role in Synthetic Lethality



Other Functions of PARP



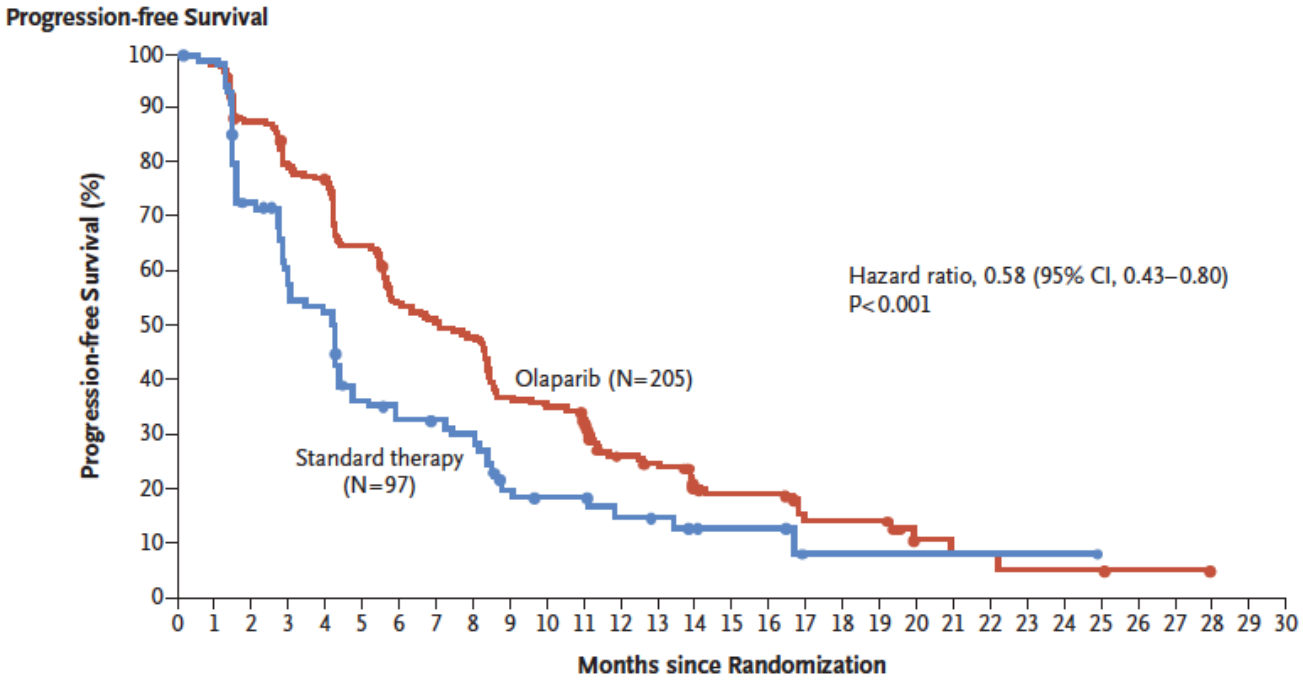
Phase III OlympiAD, Olaparib in Metastatic Breast Cancer, Germline Mutated



Primary endpoint: PFS

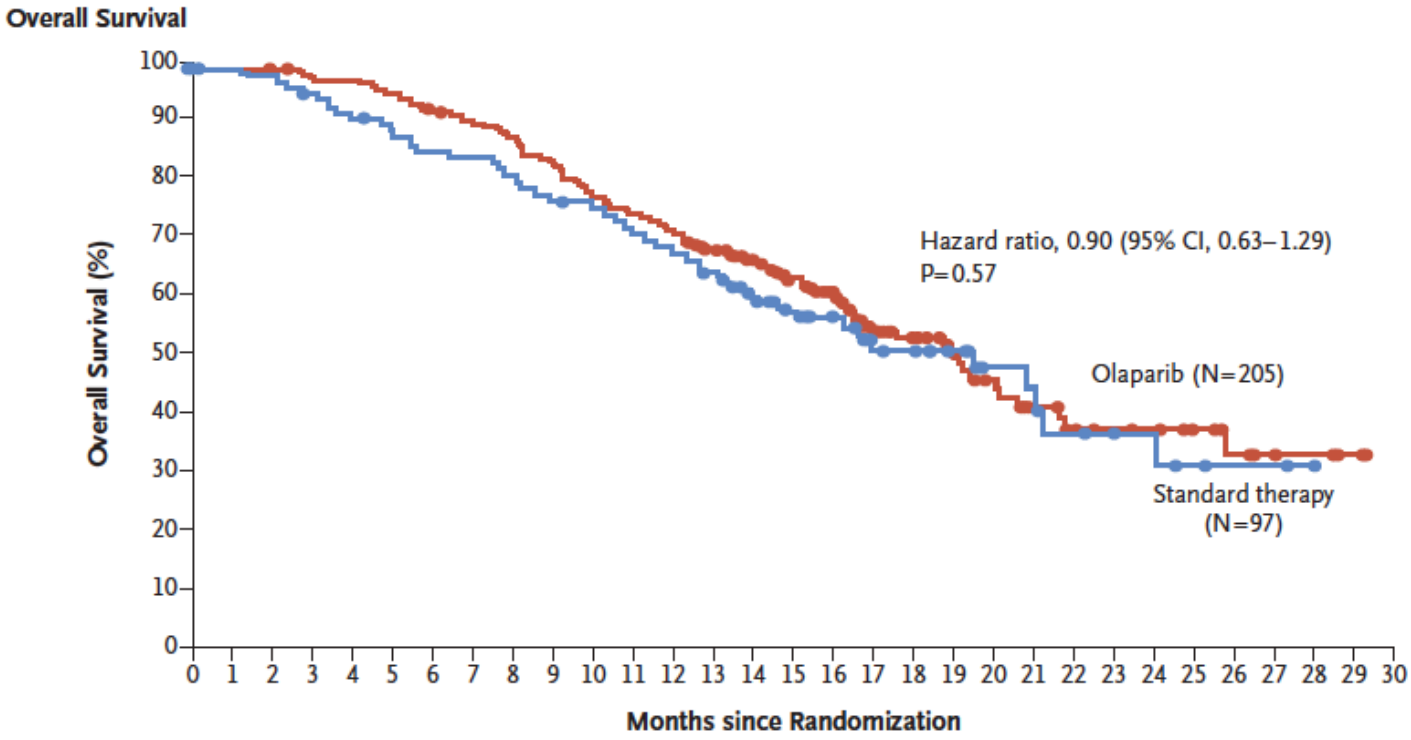
Robson M, et al. *NEJM* 2017;377:523-33.

OlympiAD Progression-Free Survival



Robson M, et al. *NEJM* 2017;377:523-33.

OlympiAD Overall Survival



Robson M, et al. *NEJM* 2017;377:523-33.

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	

NR = 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, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf; Lynparza (olaparib) prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf; Zejula (niraparib) prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf.

PARP Inhibitor Adverse Reactions

	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, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf; Lynparza (olaparib) prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf; Zejula (niraparib) prescribing information, 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.

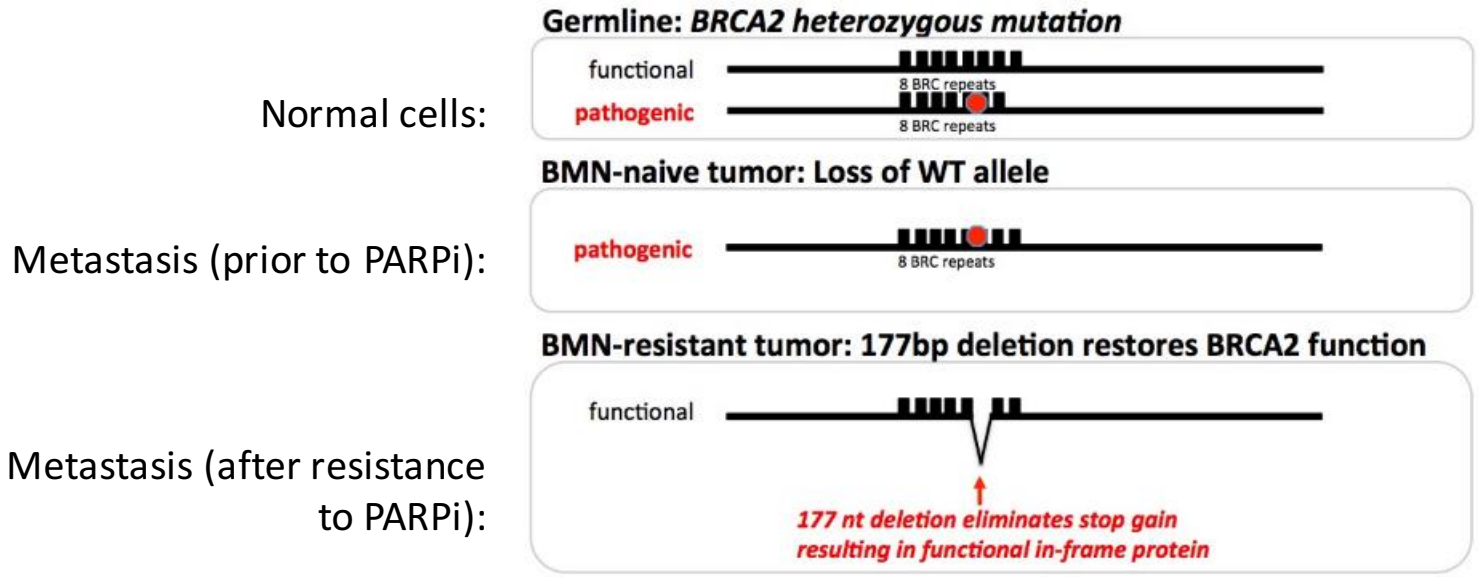
Future of PARP Inhibition Is Prostate Cancer

Trial	Study Design	Eligibility	Study Arms	Endpoint	Results
TOPARP	Phase II	Advanced CRPC	Oral olaparib	ORR	33% ORR
Kaufman, et al	Phase II	*BRCA1/2*-mut adv solid tumors (PC n = 8)	Oral olaparib	ORR	PFS: 9.8 vs 2.7 mo OS: 13.8 vs 7.5 mo ORR in PC: 50%
NCT01972217	Randomized phase II	mCRPC	Olaparib + abiraterone	Safety	PFS: 7.2 mo OS: 18.4 mo (ongoing study)
NCT02484404	Phase I/II	Adv/recurrent solid tumors	Anti-PD-L1 + olaparib	Safety	Recommended dose (ongoing)
KEYNOTE 365	Phase I/II	mCRPC	Anti-PD-L1 + cediranib ± olaparib Pembro + olaparib	Safety	AEs, ORR, OS (ongoing)
NCT02893917	Randomized phase II	mCRPC	Olaparib + cediranib	PFS	PFS, RR, OS (ongoing)
NCT02324998	Phase I	Int/high-risk PC	Olaparib ± placebo	Degree of PARPi	AEs (ongoing)

De Felice F, et al. *Drug Des Devel Ther*. 2017;11:547-552.

Reversion Deletions in *BRCA2*

Patients with *BRCA*-mutated tumors develop resistance to PARP inhibitors via reversion deletions:



Ganesan S JCO PO, 2018; DOI: 10.1200/PO.18.00001.

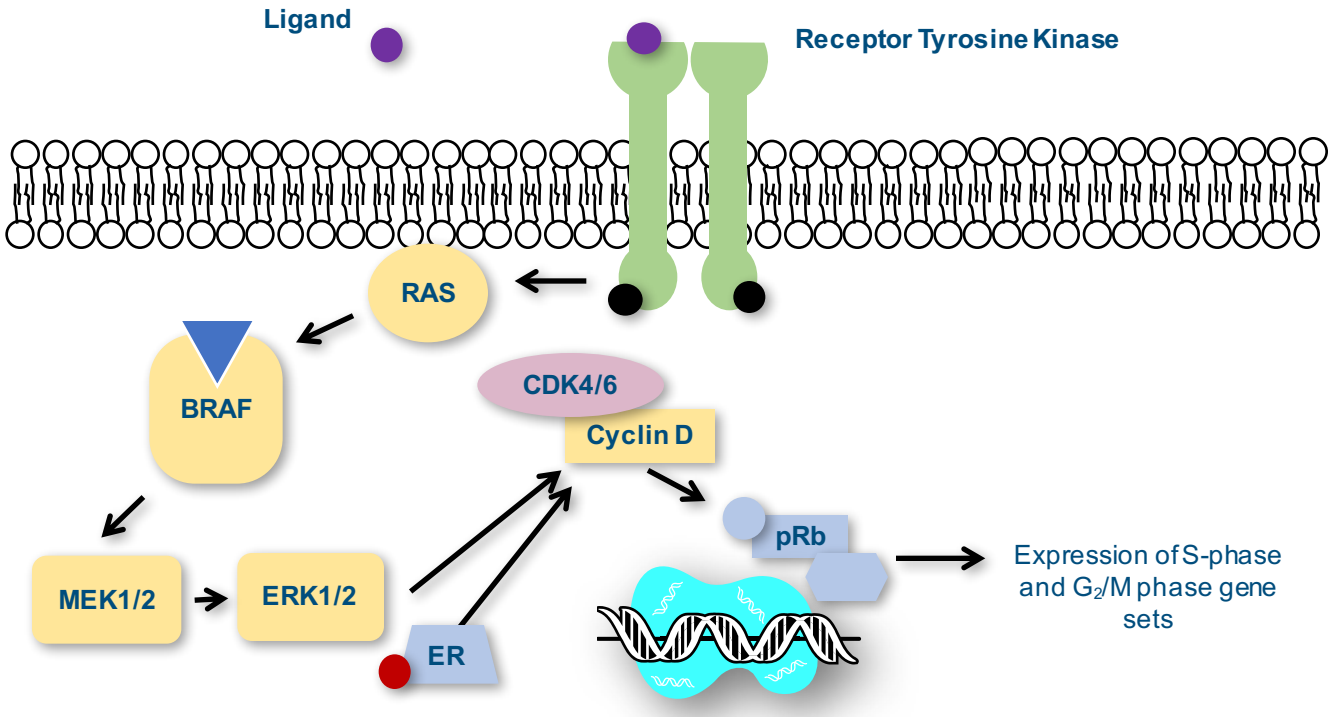
Slide credit:

Other Important Regulatory Events

Generic	Brand	Event Description	Event Description	Date
Dabrafenib/Trametinib	Tafinlar/Mekinist	New indication	Anaplastic thyroid cancer BRAF V600E	May 4, 2018
Dabrafenib/Trametinib	Tafinlar/Mekinist	New indication	Adjuvant treatment in BRAF mutated melanoma	April 30, 2018
Alectinib	Alecensa	New indication	First-line ALK+ NSCLC	Nov 6, 2018
Afatinib	Gilotrif	New indication	First-line EGFR-mutated NSCLC	Jan 12, 2018
Osimertinib	Tagrisso	New indication	First-line EGFR-mutated NSCLC	April 19, 2018
Abiraterone	Zytiga	New indication	Metastatic high-risk castration-sensitive prostate cancer, with prednisone	Feb 7, 2018
Enzalutamide	Xtandi	New indication	Non-metastatic castrate-resistant prostate cancer	July 13, 2018

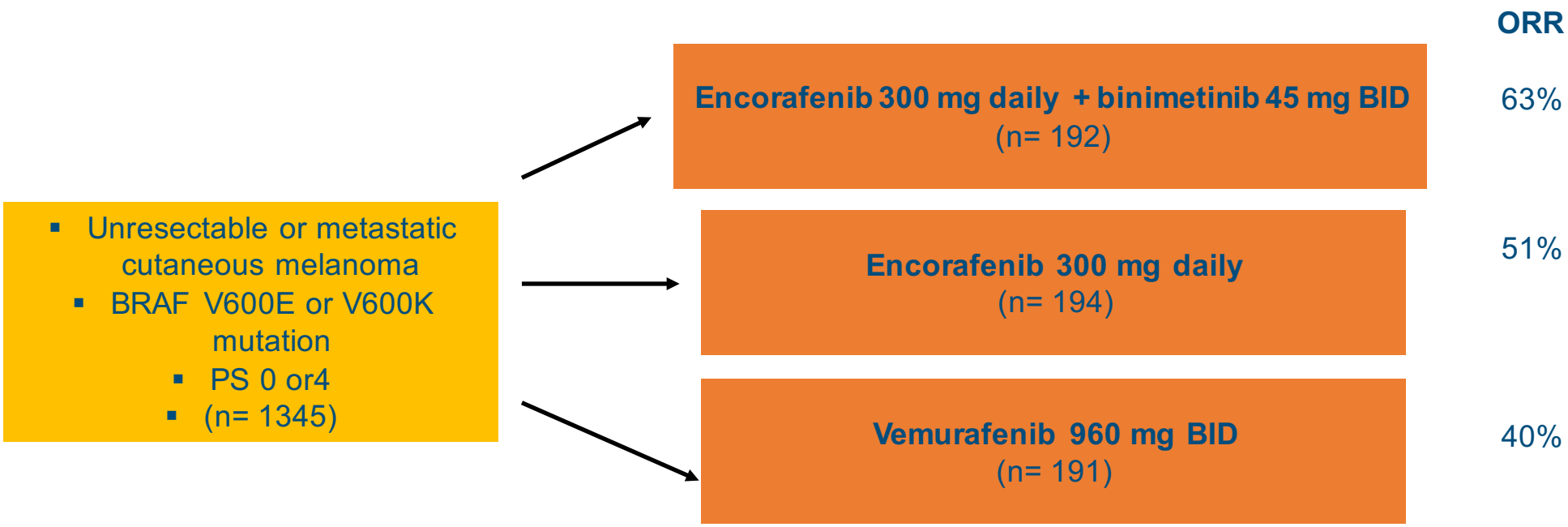
US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

BRAF Pathway



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

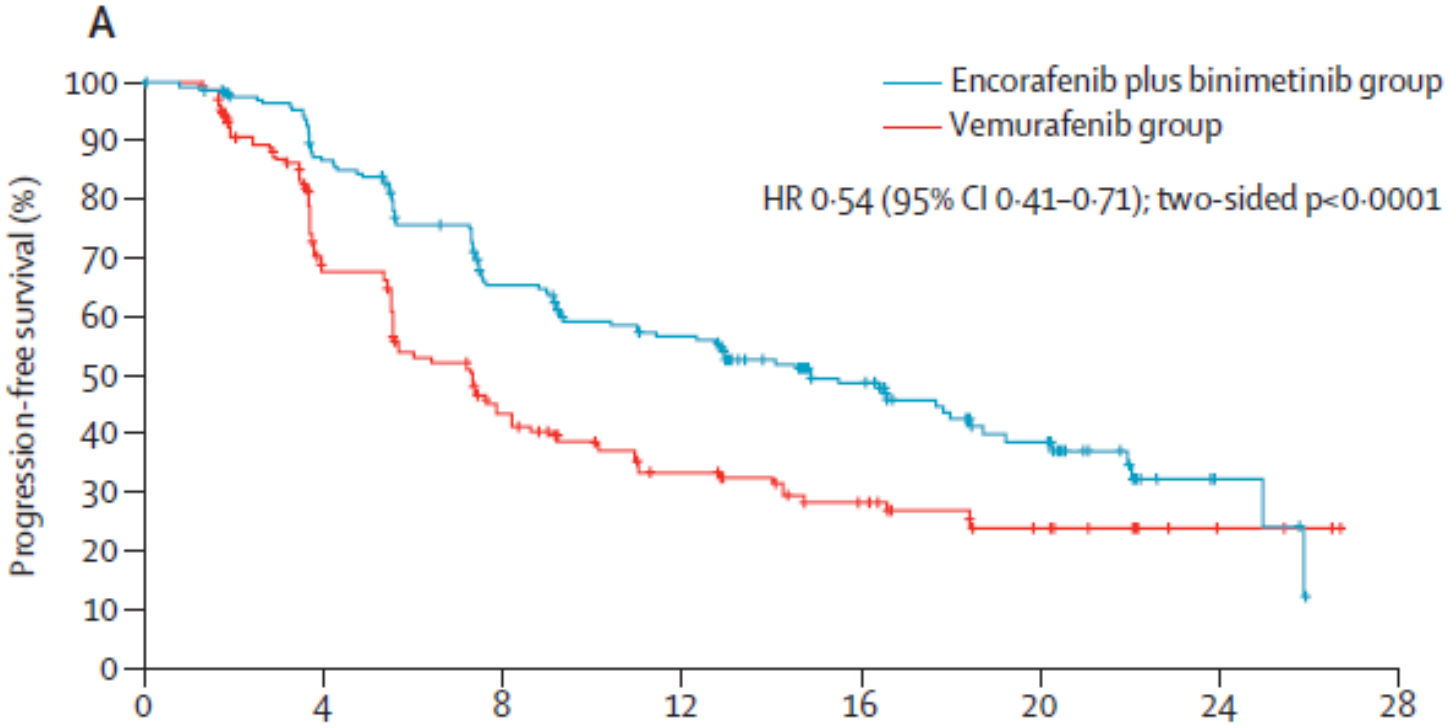
Encorafenib Plus Binimetinib, COLUMBUS Trial



Primary endpoint: PFS of combo vs. vemurafenib

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

Encorafenib Plus Binimetinib in BRAF Mutant Melanoma



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

Toxicity, All Grades

Adverse Event	Encorafenib/ Binimetinib (%)	Encorafenib (%)	Vemurafenib (%)
Fatigue	29	25	32
Arthralgia	26	43	45
Pyrexia	19	15	28
Rash	15	2	29
Myalgia	14	28	19
Skin papilloma	6	9	17
Rash maculopapular	2	10	18
Keratoacanthoma	2	6	9
Alanine aminotransferase increased	11	5	8
Creatine phosphokinase	23	1	2

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

New Drug Approvals: Dec 2017 to Sept 2018

FDA-Approved Indications

First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

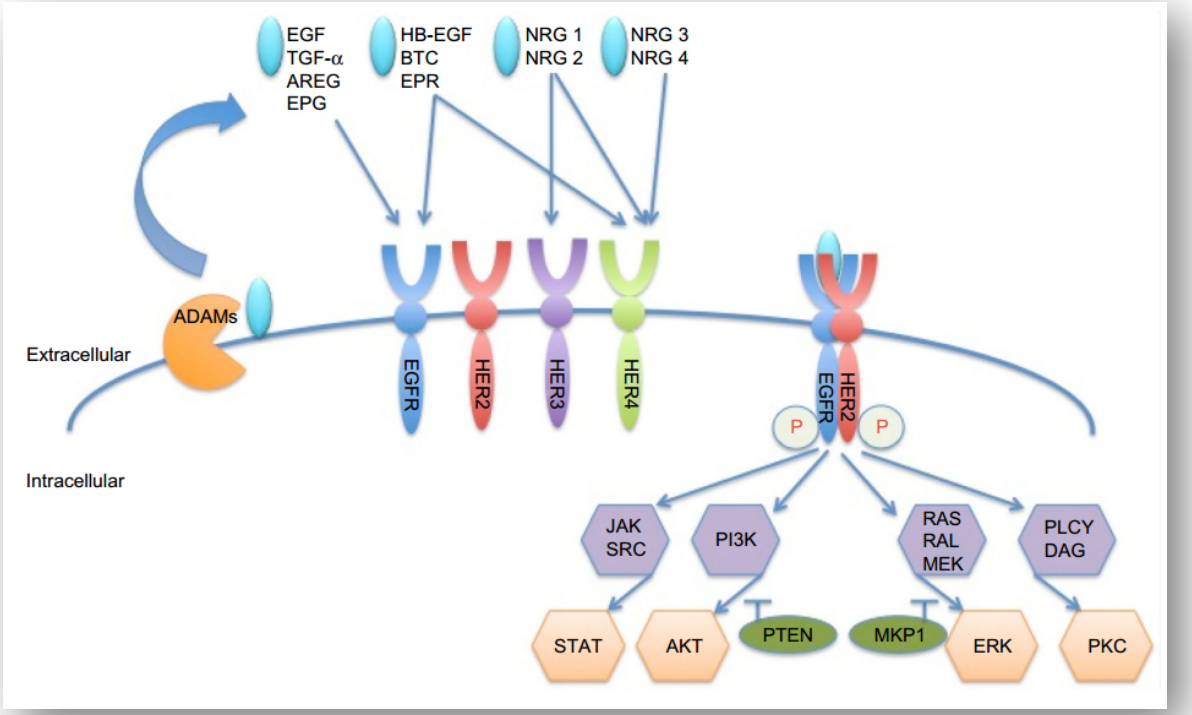
First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

Tyrosine Kinase Inhibitors

Generic	Brand	Approval Date
Osimertinib	Tagrisso	April 18, 2018
Afatinib	Gilotrif	Jan 12, 2018

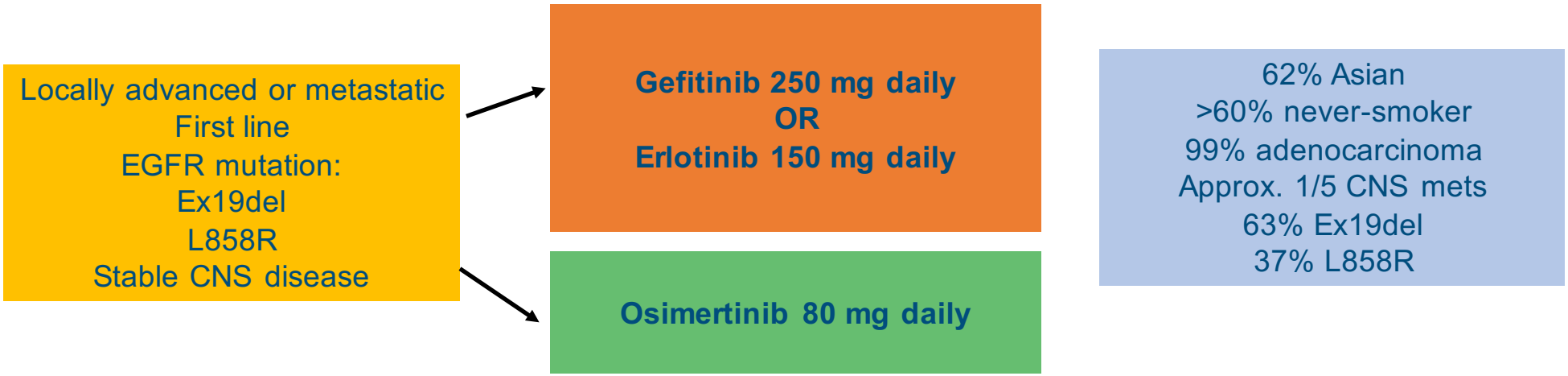
US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

Epidermal Growth Factor Receptor Inhibitors



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

FLAURA: Osimertinib in First-Line Therapy



Primary endpoint: PFS

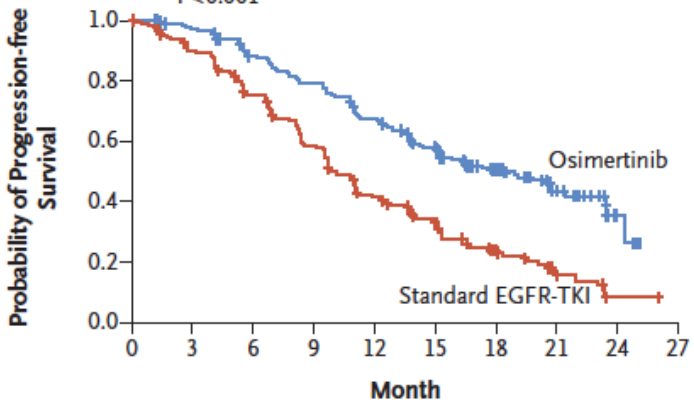
Soria JC, et al. *NEJM* 2018;378:113-25.

Survival Outcomes

Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

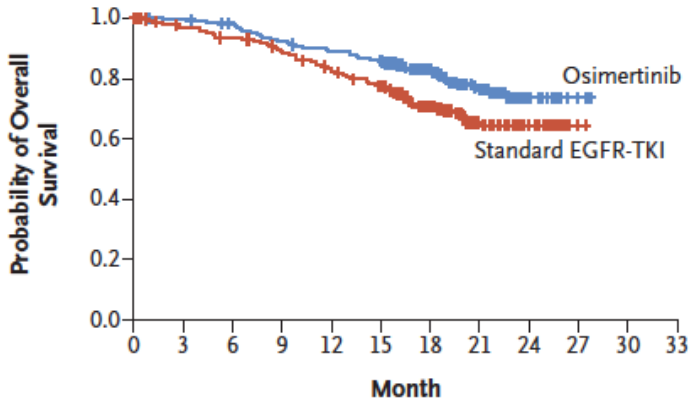
Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



Overall Survival

	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



Soria JC, et al. *NEJM* 2018;378:113-25.

New Drug Approvals: Dec 2017 to Sept 2018

Tyrosine Kinase Inhibitors

Generic	Brand	Approval Date
Abiraterone	Zytiga	Feb 7, 2018
Apalutamide	Erleada	Feb, 14, 2018
Enzalutamide	Xtandi	July 13, 2018

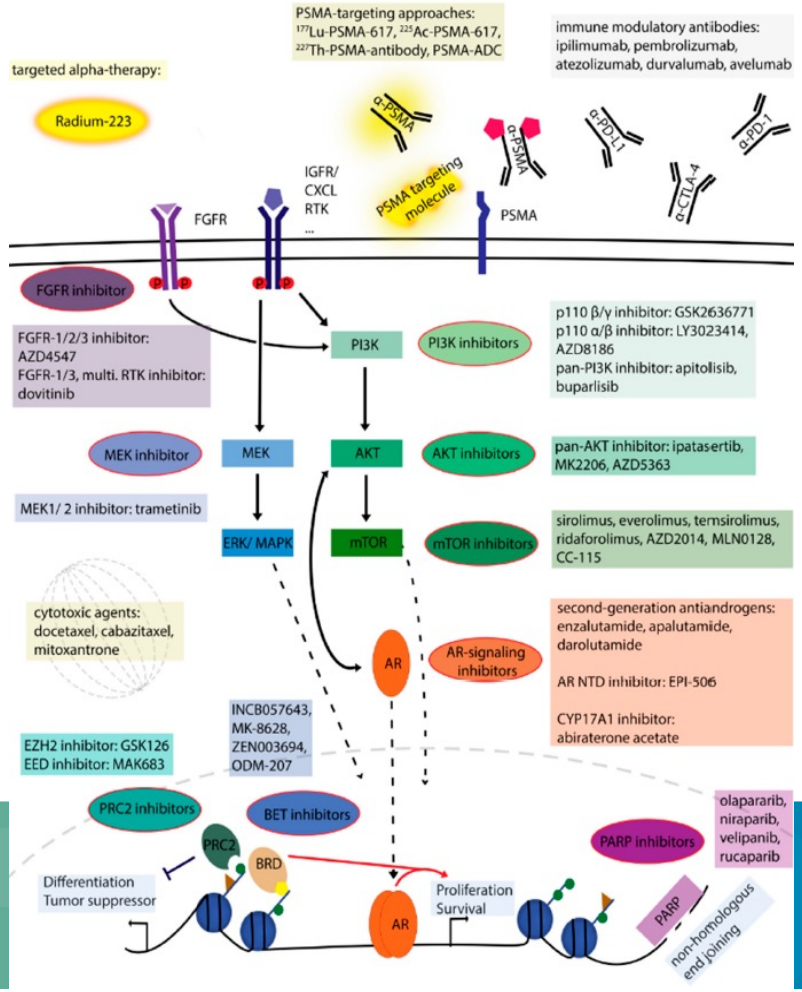
FDA-Approved Indications

In combination with prednisone and for metastatic high-risk castration-sensitive prostate cancer

In patients with non-metastatic castration-resistant prostate cancer

US Food and Drug Administration, Hematology/Oncology (Cancer) Approvals & Safety Notifications, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed September 2018

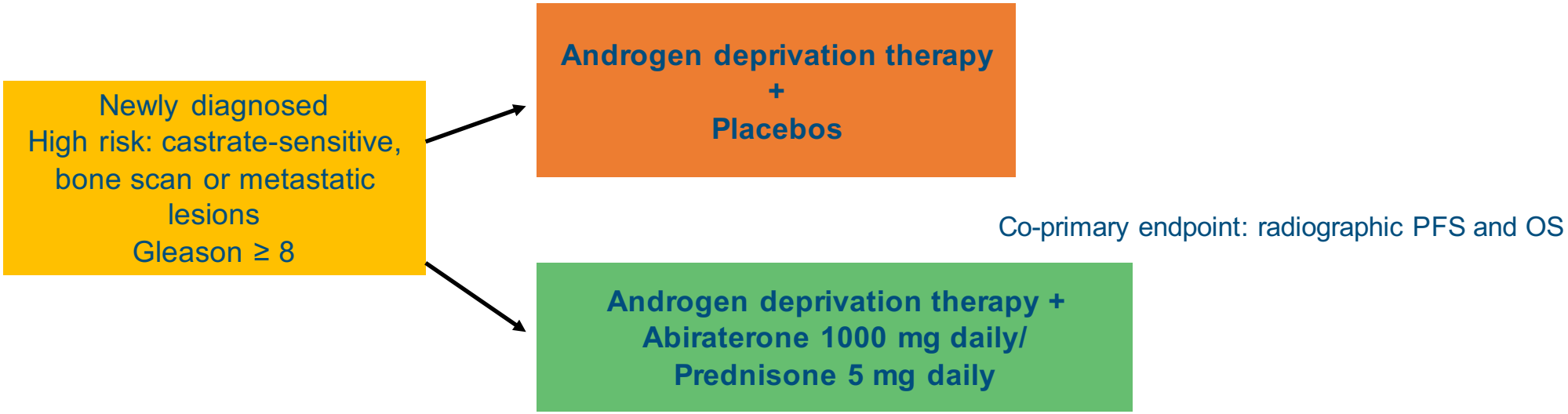
The Evolving Complexity of Prostate Therapy



Nevedomskaya E, et al. *Int J Mol Sci* 2018;19:1-25.

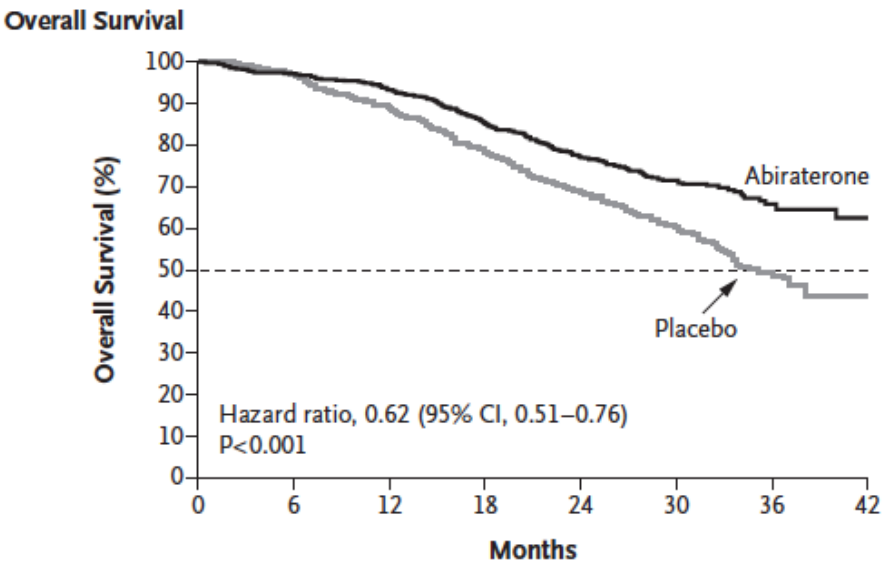
2018 JADPRO Live
THE ANNUAL APSHO MEETING

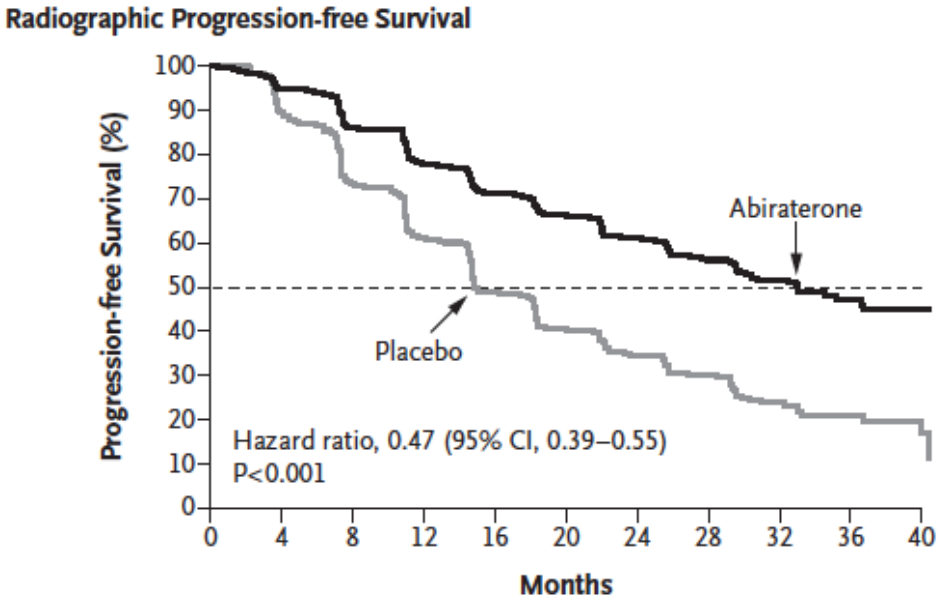
LATITUDE: Abiraterone in Castrate-SENSITIVE Prostate Cancer



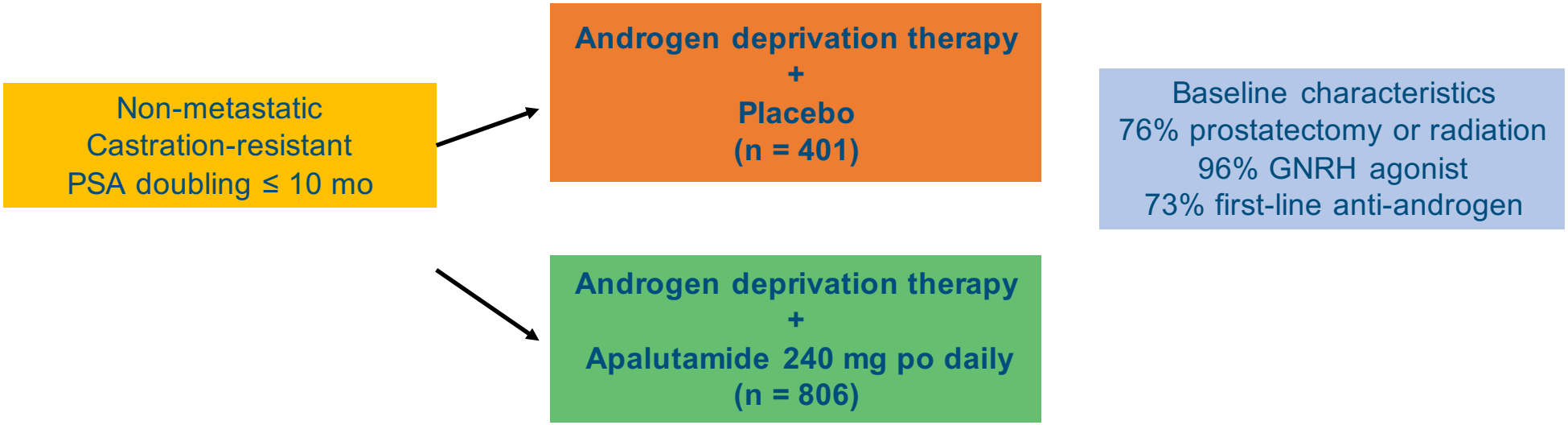
Co-primary endpoint: radiographic PFS and OS

LATITIDE Efficacy Results





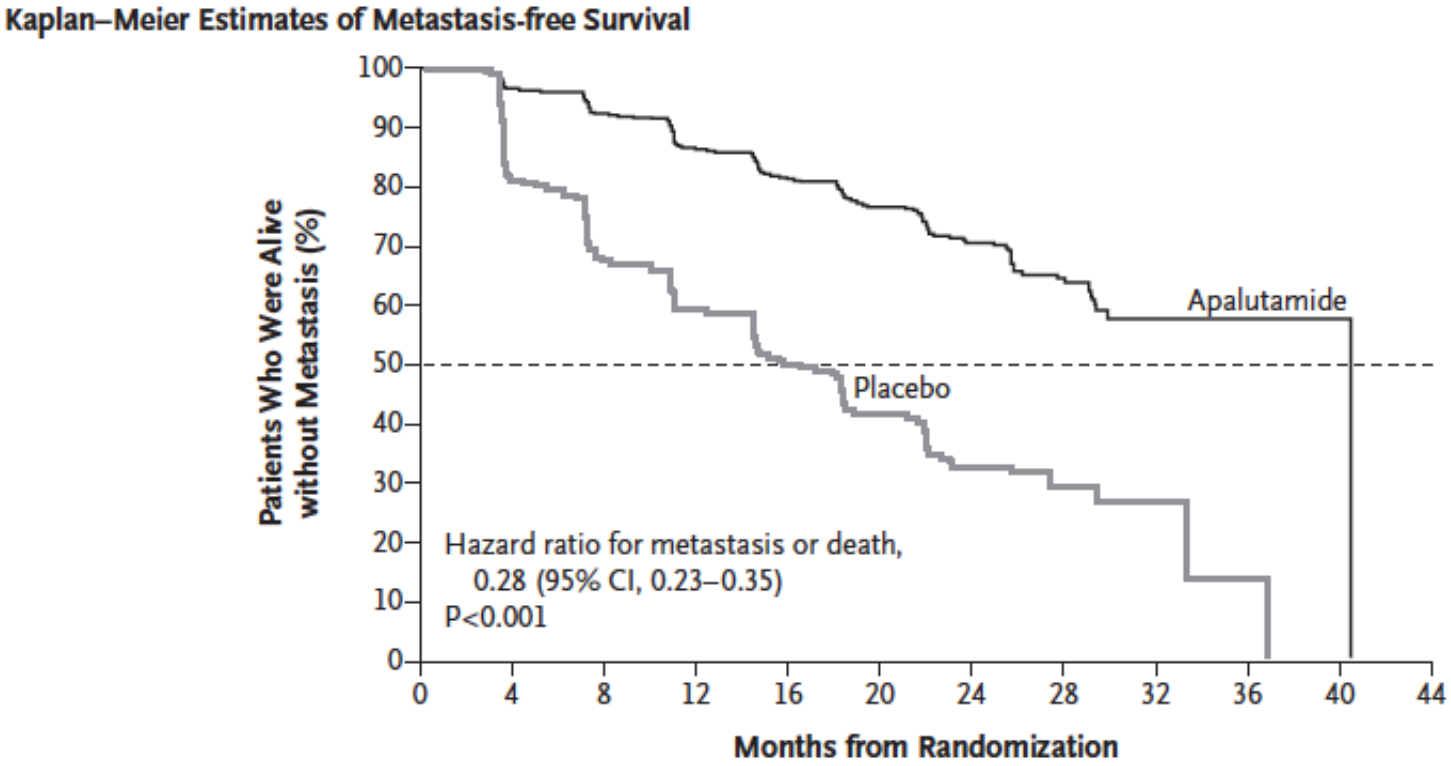
SPARTAN: Apalutamide in Non-Metastatic Castration Resistant Prostate Cancer



Primary endpoint: metastasis-free overall survival (MFS)

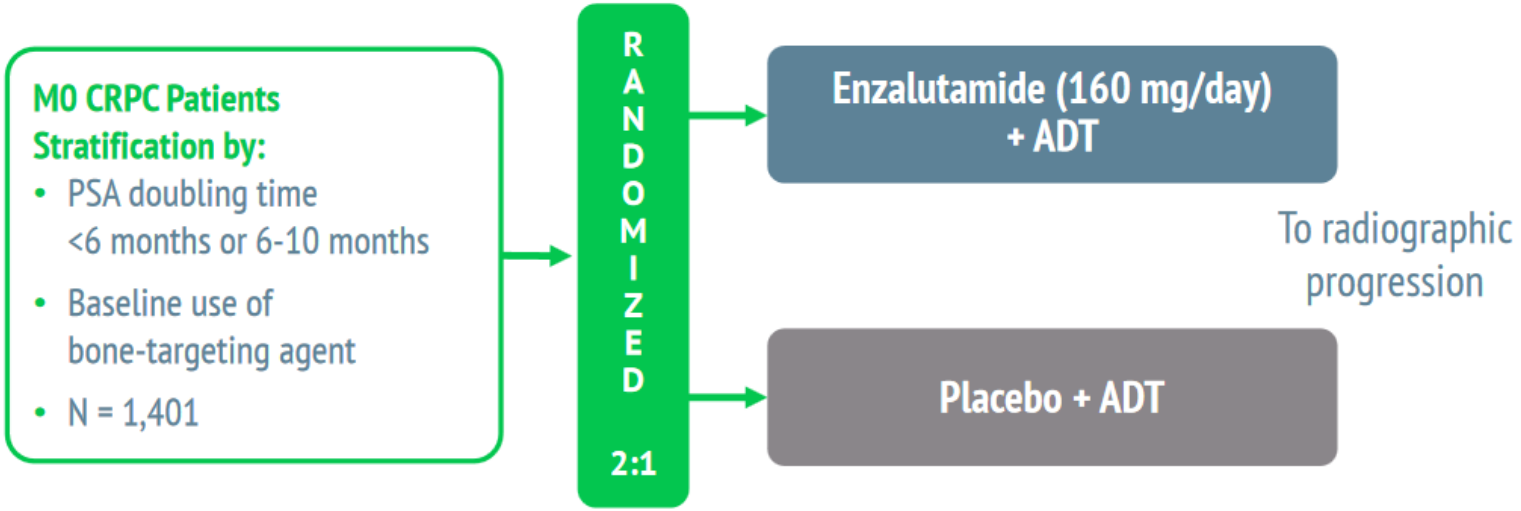
Smith MR, et al. *NEJM* 2018;378:1408-18.

SPARTAN Efficacy Results



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

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer (PROSPER)



- **Primary endpoint:** MFS = time to radiographic progression or death

ADT = androgen deprivation therapy; M0 CRPC = non-metastatic castration resistant prostate cancer; MFS = metastasis-free survival.

Hussain M, et al. *NEJM* 2018;378:2465-2474.

PROSPER Results

- Median MFS 36.6 vs. 14.7 months (HR 0.29; $P < .0001$)
- Time to use of new antineoplastic therapy, median 39.6 vs. 17.7 months
- OS interim analysis not mature
- Adverse events
  - Grade ≥ 3 hypertension 5% vs. 2%
  - Grade 3/4 fatigue 3% vs. 1%

Summary of Prostate Agents

- Apalutamide and enzalutamide offer an impressive 2-year median MFS improvement
- Cannot determine superiority
- OS not mature
- Adverse events well tolerated
- M0 CRPC is likely rare due to next generation imaging
- Risk of fracture may be 5–6% higher with treatment vs. placebo
  - Evaluate fall risk and bone-modifying agents

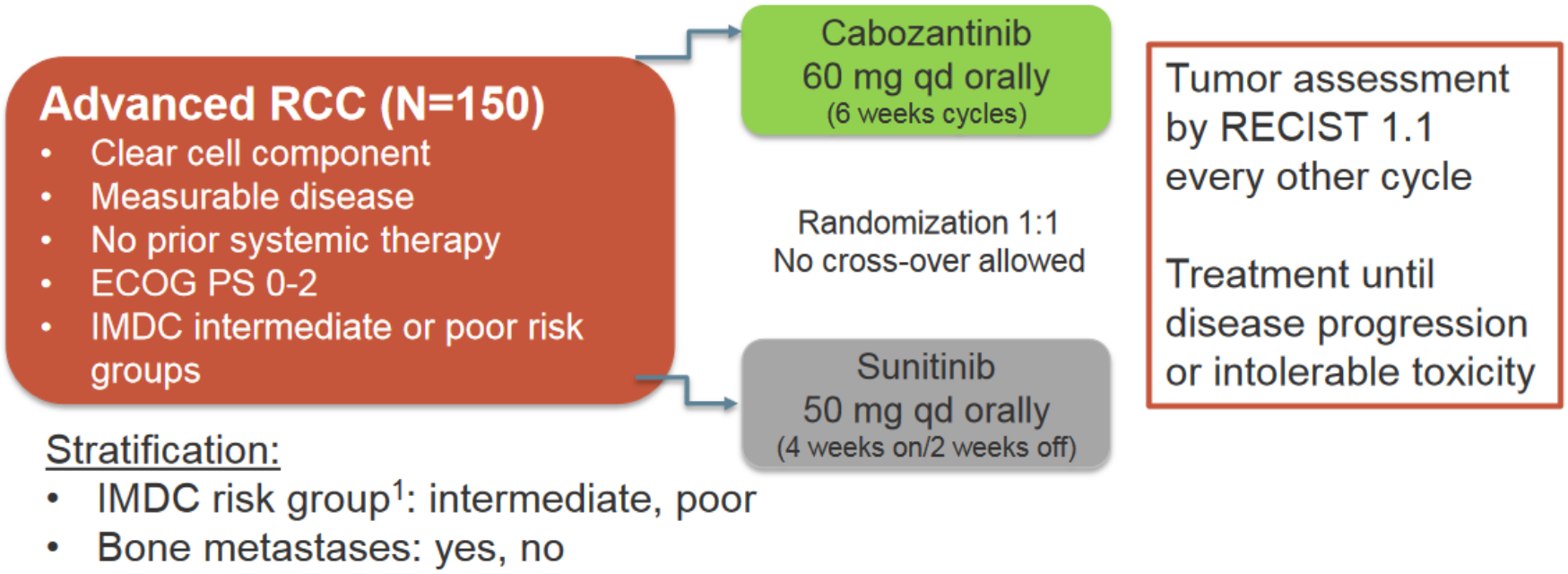
Androgen Targeted Agent Safety Profile

	Enzalutamide		Abiraterone		Apalutamide	
Adverse Reaction	**All Grades (%)**	**Grades 3/4 (%)**	**All Grades (%)**	**Grades 3/4 (%)**	**All Grades (%)**	**Grades 3/4 (%)**
Hypertension	12	5	37	20	25	15
Bone pain	NR		12	3	NR	
Fatigue	33	3	13	2	30	1
Cardiac toxicity	NR		12	4	NR	
Increased ALT	<5		16	6	NR	
Increased AST	<5		15	5	NR	
Anemia	NR		9	3	NR	

ALT = alanine aminotransferase; AST = aspartate aminotransferase

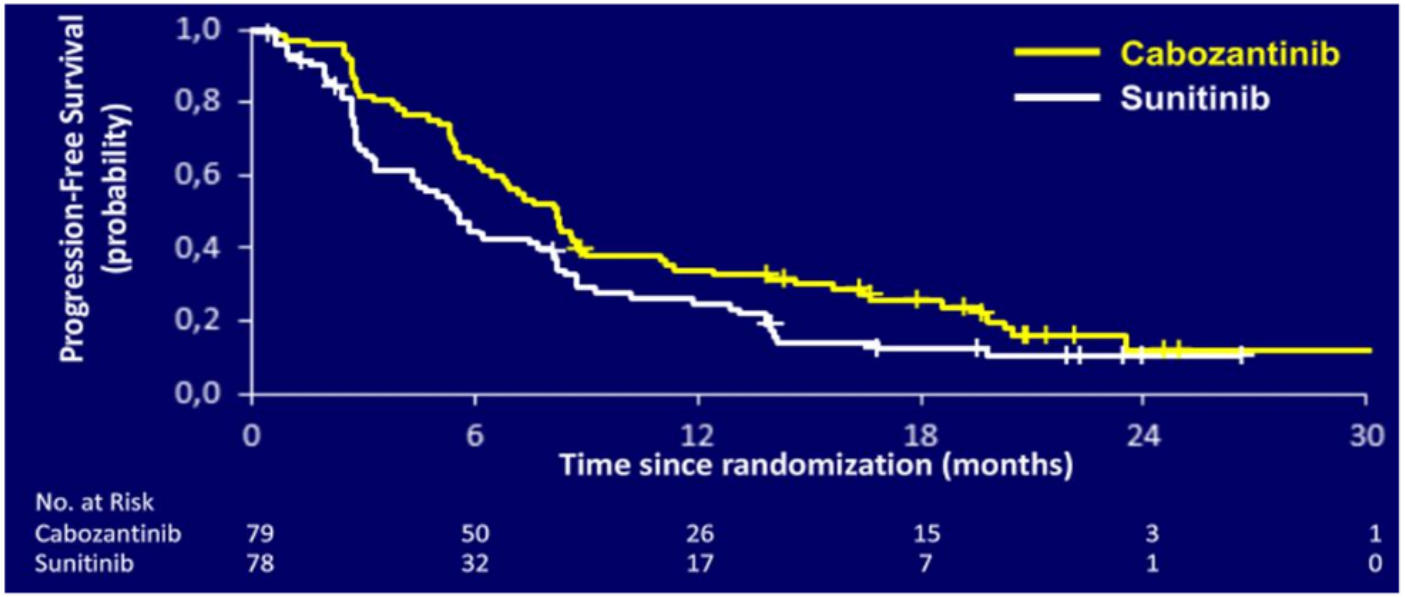
Smith MR, et al. *NEJM* 2018;378:1408-18; Fizazi K, et al. *NEJM* 2017;377:352-60; Hussain M, et al. *NEJM* 2018;378:2465-74.

Cabozantinib for First-Line Treatment of Advanced Renal Cell Carcinoma of Poor–Intermediate Patients (CABOSUN)



Choueiri TK, et al. *JCO* 2017;35:591-597.

CABOSUN Results



Arm	PFS Events	Median PFS (95% CI), mo	HR (95% CI)*
Cabozantinib	64	8.2 (6.2, 9.0)	0.69 (0.48-0.99)
Sunitinib	61	5.6 (3.4, 8.1)	P-value (one sided) = 0.012

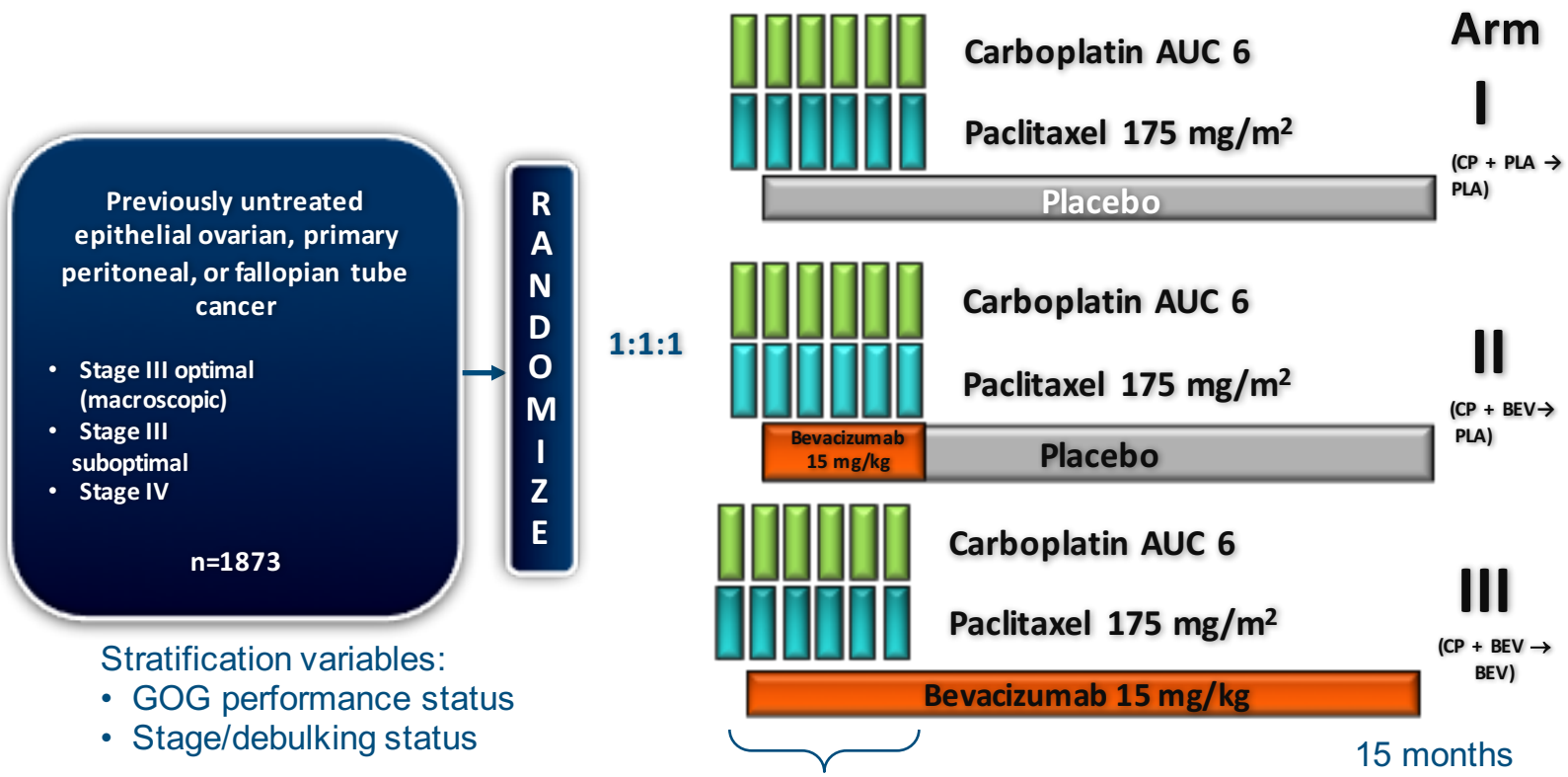
Choueiri TK, et al. *JCO* 2017;35:591-597.

	Cabozantinib (N=78)		Sunitinib (N=72)	
Preferred Term, %	ALL Grades	Grade 3/4	All Grades	Grade 3/4
*Any adverse events**	99	65	99	68
Fatigue	86	6	82	15
Hypertension	81	28	68	22
Diarrhea	73	10	54	11
AST increased	62	3	32	3
ALT increased	55	5	28	0
Anorexia	47	5	32	0
PPE	42	8	33	4
Dysgeusia	41	0	29	0
Thrombocytopenia	40	1	63	11
Oral mucositis	36	5	29	6
Anemia	33	1	46	1
Nausea	32	3	39	4
Weight loss	32	4	17	0
Neutropenia	15	0	35	4
Leukopenia	12	0	35	3

*Events reported in at least 30% of patients in either study group; PPE, palmar-plantar erythrodysesthesia

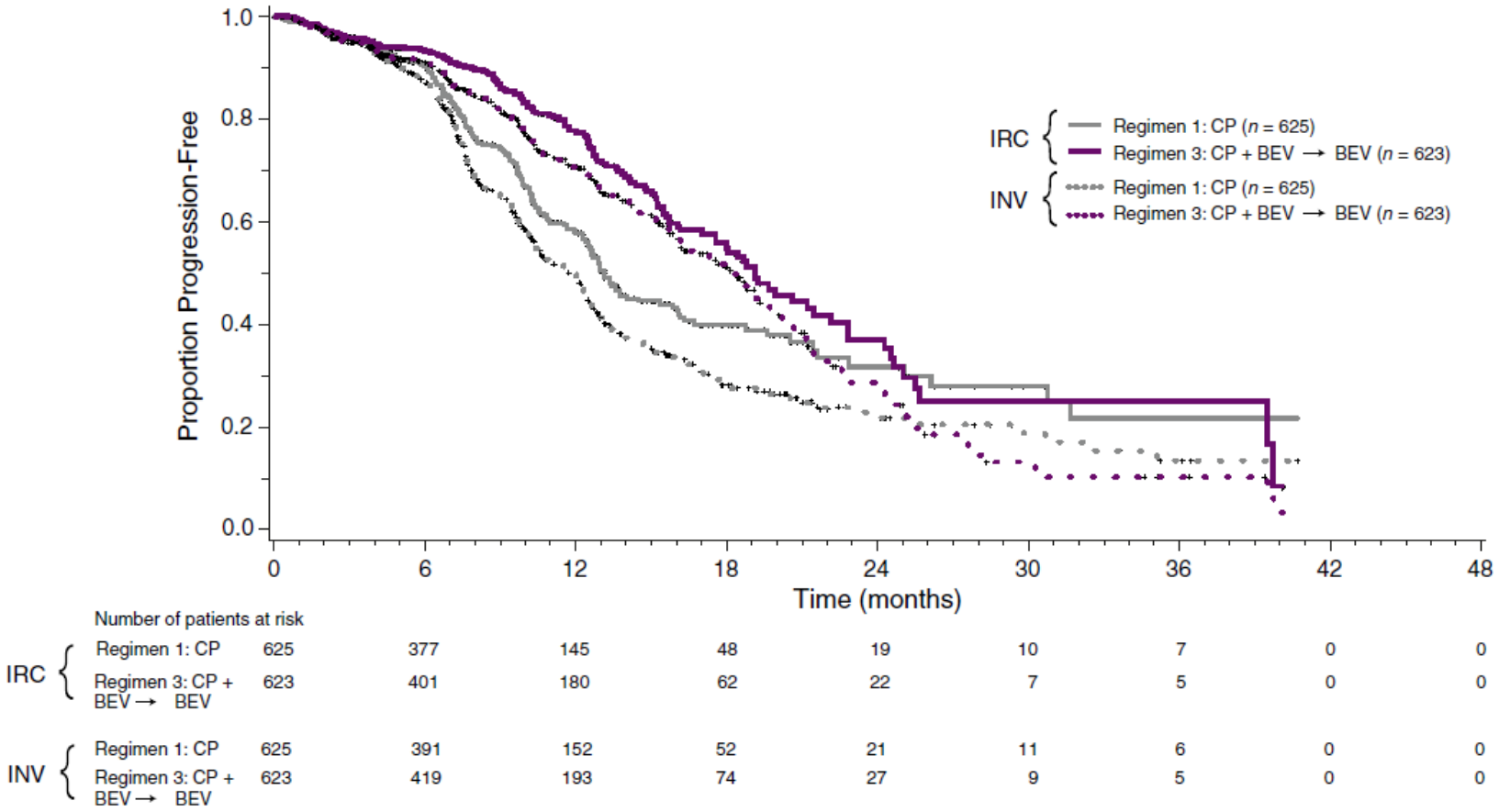
Choueiri TK, et al. *JCO* 2017;35:591-597.

GOG-0218 Study Schema



Stratification variables:
- GOG performance status
- Stage/debulking status

Burger R, et al. *N Engl J Med* 2011;365:2473-83; Burger R, et al. *Gynecol Oncol* 213;131:21-26.



Number of patients at risk

IRC	Regimen 1: CP	625	377	145	48	19	10	7	0	0
	Regimen 3: CP + BEV → BEV	623	401	180	62	22	7	5	0	0
INV	Regimen 1: CP	625	391	152	52	21	11	6	0	0
	Regimen 3: CP + BEV → BEV	623	419	193	74	27	9	5	0	0

IRC = independent review; INV = investigator review.

Burger R, et al. *N Engl J Med* 2011;365:2473-83; Burger R, et al. *Gynecol Oncol* 213;131:21-26.

ASCO 2018 Update

- HR 0.774 for stage IV patients
- Median OS stage IV
  - Bevacizumab 34.5 months vs. control 32.6 months
- Potential benefit for FIGO stage IV disease

Burger R, et al. DOI: 10.1200/JCO.2018.36.15_suppl.5517 *Journal of Clinical Oncology* 36, no. 15_suppl (May 20 2018) 5517-5517.

Summary

The pharmacology of new oncology medications approved in 2017–2018 are mostly for additional indications! We are in the era of incremental improvement.

- CDK4/6 inhibitors now represent the standard of care in HR+, HER2- first line
- PARP inhibitors for breast cancer with germline BRCA
- Immunotherapy CE will continue for a while!
- Updates to TKIs are used for NSCLC and RCC
- New approvals for immunotherapy and BRAF agents in the adjuvant setting
- Prostate cancer is becoming more complex…
- Bevacizumab in ovarian first line

SMARTIE

This has been a SMARTIE presentation.

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