Pharmacotherapy Updates: Therapeutic Advances in Medical Oncology

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Conflict of Interest Disclosure

- No real or apparent conflicts of interest to disclose

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Learning Objectives

- Assess the role of new therapies in the current treatment paradigms in medical oncology
- Develop appropriate monitoring plans for the safe administration of new therapies in medical oncology
- Determine supportive care needs for patients receiving newly approved therapies

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2014-2015 FDA Approvals

Generic Name	Brand	Mechanism	Indication
Pembrolizumab	Keytruda	Anti-PD-1 antibody	Melanoma
Nivolumab	Opdivo	Anti-PD-1 antibody	Melanoma
Ramucirumab	Cyramza	Anti-VEGFR-2	Gastric and GE junction adenocarcinoma Non-small cell lung cancer
Ceritinib	Zykadia	ALK inhibitor	Non-small cell lung cancer (EML4ALK translocation)
Olaparib	Lynparza	Poly (ADP-ribose) polymerase (PARP) inhibitor	Advanced ovarian cancer
Netupitant and palonosetron	Akynzeo	Neurokinin 1 receptor antagonist and $5HT_3$ antagonist	Chemotherapy induced nausea and vomiting
Palbociclib	Ibrance	Cyclin-dependent kinase (CDK) 4 and 6 inhibitor	Advanced breast cancer
Lenvatinib	Lenvima	Multi-tyrosine kinase inhibitor	Differentiated thyroid cancer

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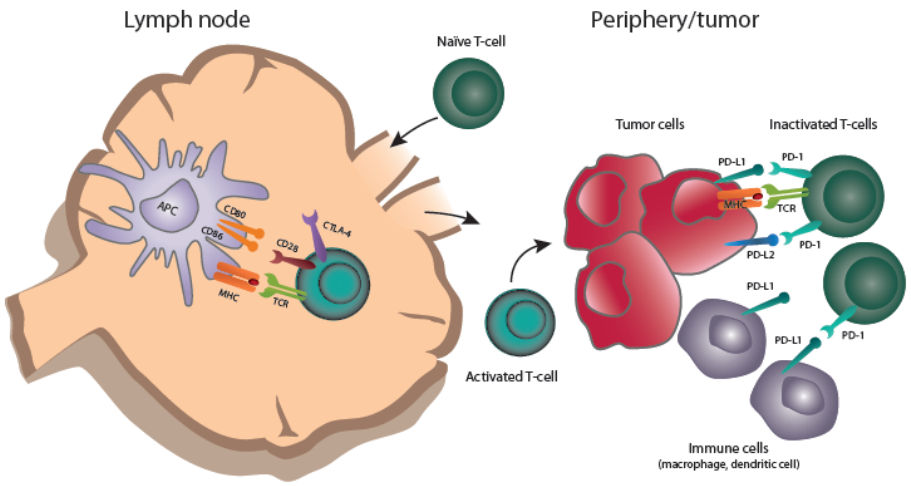
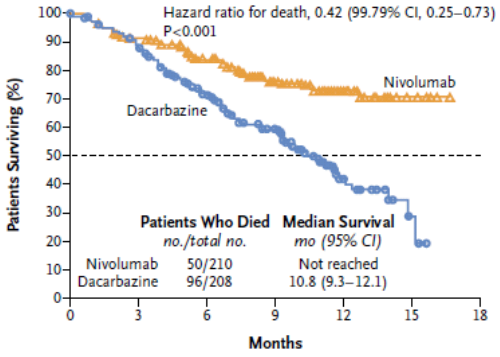
Checkpoint Inhibition in Cancer



Anti-PD-1 Antibodies

	Nivolumab	Pembrolizumab
Indication(s)	unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy	unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
Dose	3 mg/kg q2weeks	2 mg/kg q3weeks
Form	Fully human	humanized

Anti-PD-1 Antibodies Efficacy



	Response Rate (%)	Progression Free Survival (months)	Overall Survival (months)
Pembrolizumab	26	5.5	58%
Nivolumab	40	5.1	73%

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Immune-Mediated Adverse Effects

	Nivolumab		Pembrolizumab	
	All Grades	Grade 3+	All Grades	Grade 3+
Gastrointestinal Diarrhea Nausea	 21 16.5	 1 0	 20 30	 0 0
Hepatic	16-28	1	24	2
Skin rash	15-21	0.5	29	0
Pruritus	17	0.5	30	0
Renal	0.7*		0.7	0.2
Hyperthtyroidism Hypothyroidism	3 8	- -	1.2 8.3	0.2 0.2
Pneumonitis	3.4	0.4	2.9	0.2

*reported as grade 2 or greater

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Administration

Nivolumab

- 3 mg/kg q2weeks
- Dilute in 0.9% saline or 5% dextrose
- 1 hour infusion
- Use non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer)
- 40 mg or 100 mg vial

Pembrolizumab

- 2 mg/kg q3 weeks
- Dilute in 0.9% saline or 5% dextrose
- 30 minute infusion
- Use non-pyrogenic, low-protein binding 0.2 micron to 0.5 micron in-line or add-on filter
- 100 mg vial

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Monitoring

- Liver function tests
  - AST, ALT, bilirubin
- Kidney Function
  - BUN, SCr
- Thyroid function
  - TSH, reflexive T4
- O2 saturation, RR

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Precautions For Nivo and Pembro

- Autoimmune diseases excluded from trials
- Corticosteroids are the antidote to severe toxicity, but may undermine efficacy
- No dosage adjustment for renal dysfunction
- No dosage adjustment for hepatic dysfunction
  - Not well characterized in severe dysfunction

Ramucirumab Drug Information

- Fully human monoclonal antibody targeting vascular endothelial growth factor (VEGF) 2
- Indications
  - Single agent or with paclitaxel for gastric and gastroesophageal adenocarcinmoa after platinum and fluoropyrimidine
    - 8 mg/kg q2weeks
  - Non-small cell lung cancer in combination with docetaxel after progression on platinum containing regimen
    - 10 mg/kg q3weeks

Ramucirumab Efficacy

Gastric and Gastroesophageal Adenocarcinoma		
	PFS	OS (months)
Placebo (n=117)	1.3	3.8
Ramucirumab (n=238)	2.1	5.2

Gastric and Gastroesophageal Adenocarcinoma		
	PFS (months)	OS (months)
Paclitaxel (n=330)	2.9	7.4
Paclitaxel plus Ramucirumab (n=335)	4.4	9.6

Non-Small Cell Lung Cancer		
	PFS (months)	OS (months)
Docetaxel (n=625)	3	9.1
Docetaxel plus Ramucirumab (n=628)	4.5	10.5

Fuchs CH, *Lancet* 2014

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Ramucirumab Safety

	Any Event, %		Grade 3 or greater, %	
	Ramucirumab	Placebo	Ramucirumab	Placebo
Hypertension	16	8	8	3
Hemorrhage	13	11	3	3
Arterial thromboembolism	2	0	1	0
Venous thromboembolism	4	7	1	4
Proteinuria	3	3	<1	0
Infusion reaction	<1	<1	0	0
Gastrointestinal perforation	<1	<1	<1	<1

Fuchs CH, *Lancet* 2014

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Ramucirumab Safety

	Grade 1-2, %		Grade 3 or greater, %	
	Ramucirumab + Paclitaxel	Paclitaxel	Ramucirumab + Paclitaxel	Paclitaxel
Hypertension	10	2	15	2
Bleeding or Hemorrhage	38	16	5	2
Venous thromboembolism	2	2	2	0
Proteinuria	15	6	1	0
Epistaxis	31	-	7	-
Vomiting	24	13	2	<1
Stomatitis	19	7	<1	<1
Proteinuria	15	6	1	0

Wilke H, *Lancet* 2014

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Ramucirumab Safety

	Grade 1-2, %		Grade 3 or greater, %	
	Ramucirumab + Docetaxel	Docetaxel	Ramucirumab + Docetaxel	Docetaxel
Hypertension	11	5	6	2
Bleeding or Hemorrhage	29	15	2	2
Arterial thromboembolism	2	2	1	1
Venous thromboembolism	3	6	2	3
Proteinuria	3	1	<1	0
Epistaxis	19	<1	6	<1
Vomiting	24	13	2	<1
Stomatitis	23	13	4	2
Peripheral edema	16	0	8	<1

Fuchs CH, *Lancet* 2014

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Ramucirumab Hematologic Safety

	Ramucirumab + Paclitaxel	Paclitaxel	Ramucirumab + Docetaxel	Docetaxel
Neutropenia Grade 3+	41	19	49	39
Thrombocytopenia Grade 3+	2	2	3	1
Anemia Grade 3+	9	9	28	6
Febrile Neutropenia	3	2	32	20

Fuchs CH, *Lancet* 2014
Wike H, *Lancet Oncology* 2014

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Ramucirumab Administration

- Premedicate with H1 antagonist
- 60 minute IV infusion
- If grade 1-2 infusion reaction, slow infusion by 50%
- Do not admix in dextrose containing solutions
- Use Protein sparing 0.22 micron filter

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Ramucirumab Monitoring Parameters

- Blood pressure
- Signs/symptoms of bleeding
- Sings/symptoms of thrombotic events
- Vigilant monitoring for toxicities from concomitant chemotherapy

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Ramucirumab Precautions

- Potential to impair wound healing
- Need routine blood pressure monitoring

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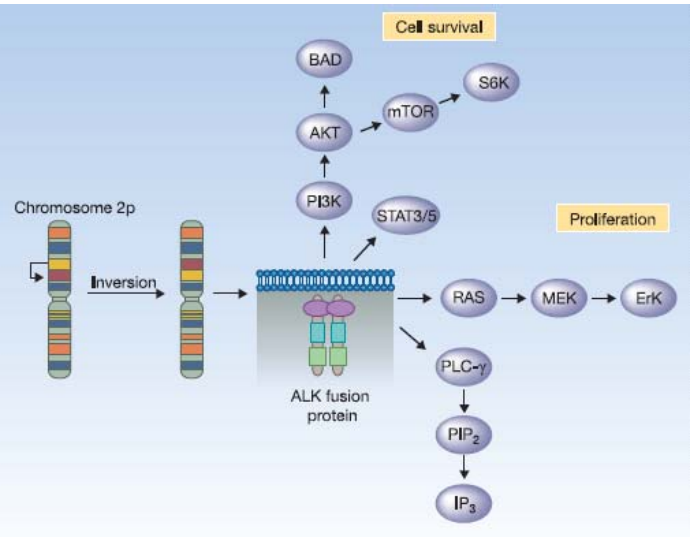
ALK in non-small cell lung cancer

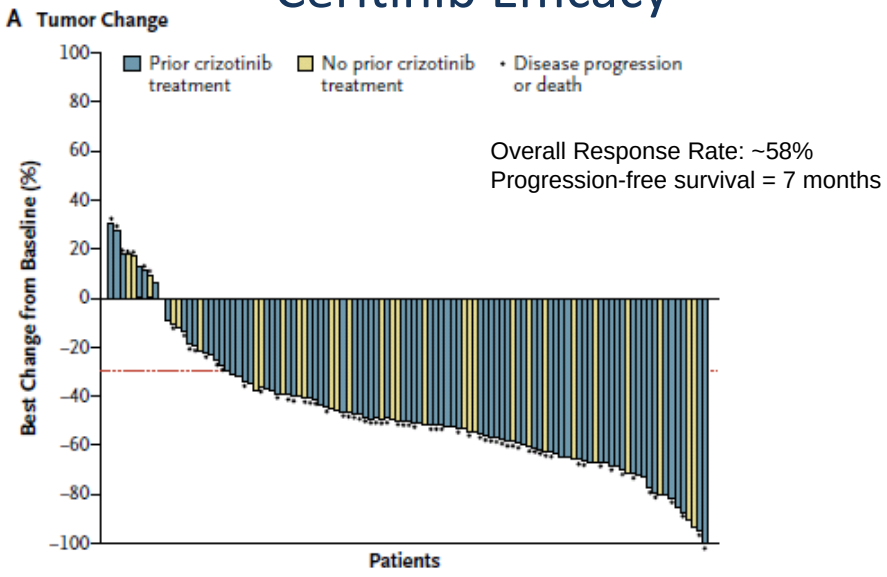


Shaw TA, *Clin Cancer Res* 2011

Ceritinib Drug Information

- Mechansim: Inhibits ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1
- Dose: 750 mg once daily (150 mg capsules)
- Take on an empty stomach
- Metabolized by CYP3A
  - (drug interaction potential)
- May prolong QTc interval

Ceritinib Efficacy



Overall Response Rate: ~58%
Progression-free survival = 7 months

Shaw AT, *N Engl J Med* 2014

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Ceritinib Safety

	Ceritinib (n=255)	
	All Grades	Grade 3+
Gastrointestinal		
Diarrhea	75	6
Nausea	82	4
Vomiting	60	4
Hepatic	80	21
Fatigue	54	5
Hypophosphatemia	36	7
Elevated lipase	28	10
hyperglycemia	49	13
QTc prolongation > 60 msec		3
Bradycardia		3

Shaw AT, *N Engl J Med* 2014

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Ceritinib Administration

- Administer on fasting stomach (2 hours post or 1 hour prior to eating)
  - Food increases absorption

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Ceritinib Monitoring Parameters

- LFTs
- Fasting blood glucose
- Electrolytes (diarrhea, vomiting)
- Phosphorus
- QTc interval
- Heart rate

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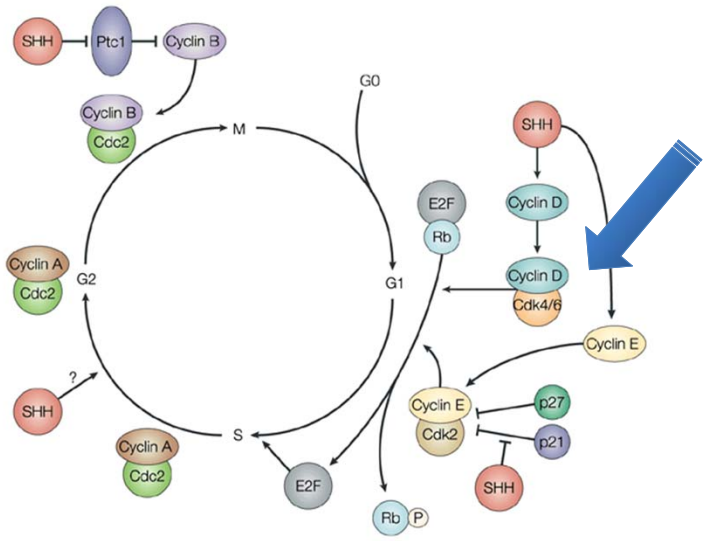
Ceritinib Precautions

- Ceritinib is metabolized by CYP3A4
  - Caution: azole antifungals, ritonavir, nefazodone, amiodarone, grape fruits and grape fruit juice
- Ceritinib inhibits CYP3A4 and 2C9
  - Cyclosporine, fentanyl
  - Warfarin
- Glucose monitoring

Palbociclib Drug Information

- Indicated in combination with letrozole for the treatment of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease
- Cyclin Dependent Kinase (CDK) 4 and 6 inhibitor
- Half-life = 29 hours

Cyclin Dependent Kinase Inhibitor



Ruiz, et al. *Nature Reviews Neuroscience* 2002

Nature Reviews | Neuroscience

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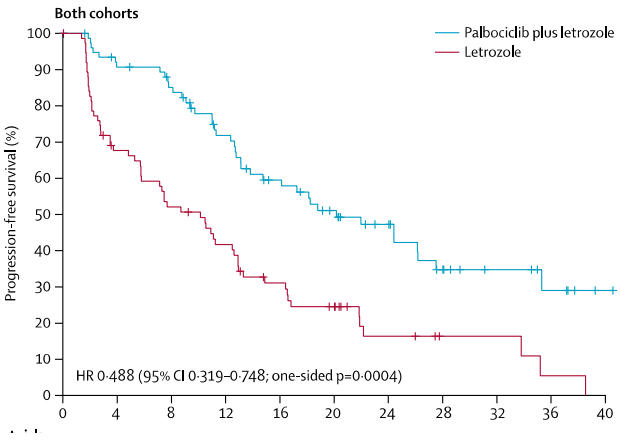
Palbociclib Efficacy



	P+L (n=84)	L (n=81)
RR (%)	36*	26
PFS (mos)	20.2*	10.2
OS (mos)	37.5	33.3

Abbreviations: P+L = palbociclib and letrozole; L = letrozole; RR= response rate; PFS = progression free survival; OS = overall survival; *=p<0.05

Finn RS, *Lancet Oncology* 2015

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Palbociclib Safety

	Palbociclib + Letrozole (n=83)		Letrozole (n=77)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Netutropenia Anemia	20 29	54 6	4 5	1 1
Fatigue	36	4	22	1
Nausea Vomiting	23 14	2 0	12 3	1 1
Alopecia	22		3	0
Diarrhea	17	4	10	0
Bone pain	10	2	4	0
Epistaxis	11	0	1	0
Influenza	10	1	1	0
Peripheral neuropathy	10	0	5	0

Finn RS, *Lancet Oncology* 2015

Palbociclib Administration

- 125 mg daily with food for 3 weeks followed by 1 week off
- Take with food
- Supplied as 125mg , 100 mg, 75 mg capsules

Palbociclib Monitoring

- CBC w/differential

Palbociclib Precautions

- Metabolized by and inhibits CYP3A
- No renal dose adjustments
- No dose adjustment in mild hepatic impairment
  - No data in moderate or severe (bilirubin > 1.5 x upper limit of normal)

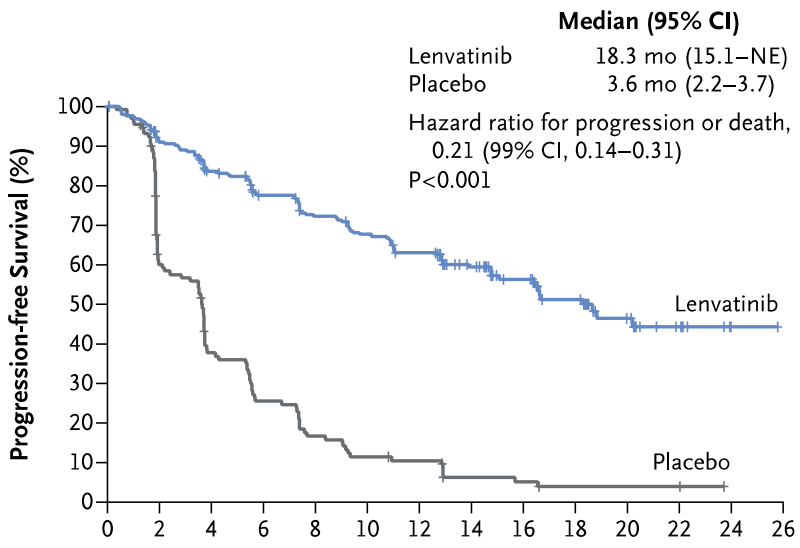
Lenvantinib Drug Information

- Multi kinase inhibitor indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer

Lenvantinib Drug Information

- Mechanism:
  - Vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)
  - Fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4
  - Platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET
- Half-life = 28 hours

Lenvantinib Efficacy



Schulemberger M, *N Engl J Med* 2015

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Lenvantinib Safety

	Lenvantinib (n=261)		Placebo (n=131)	
	All Grades	Grades 3+	All Grades	Grade 3+
Hypertension	68	42	9	2
Diarrhea	59	8	8	0
Fatigue	59	9	28	2
Decreased appetite Decreased weight	50 46	5 10	12 9	0 0
Nausea Vomiting	41 28	2 3	14 6	1 0
Stomatitis	36	4	4	0
Palmar-Plantar Erythrodysesthesia	32	3	1	0
Proteinuria	31	10	2	0
QTc prolongation	9		2	

Schulemberger M, *N Engl J Med* 2015

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Lenvantinib Administration

- Dose: 24 mg once daily (10 and 4 mg capsules)
- With or without food
- Dose reduction to 14 mg daily with:
  - Creatinine clearance < 30 ml/min
  - Child-Pugh class C hepatic failure
- Metabolized by CYP3A, but no clinically significant drug interactions identified

Lenvantinib Monitoring

- Blood pressure
- Urine for protein
- LFT's
- Electrolytes (diarrhea, vomiting)
- QTc interval
- TSH (reflexive T4)

Lenvantinib Precautions

- Hemorrhagic and thromboembolic events
- QTc prolongation
- GI fistula, bowel perforation
- Hepatotoxicity

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Olaparib Drug Information

- Poly (ADP-ribose) polymerase (PARP) inhibitor
- Approved for patients with germline BRCA mutated advanced ovarian cancer who have been treated with 3 or more lines of chemotherapy
- Dose = 400 mg twice daily
  - 50 mg capsules
- Half-life = 12 hours

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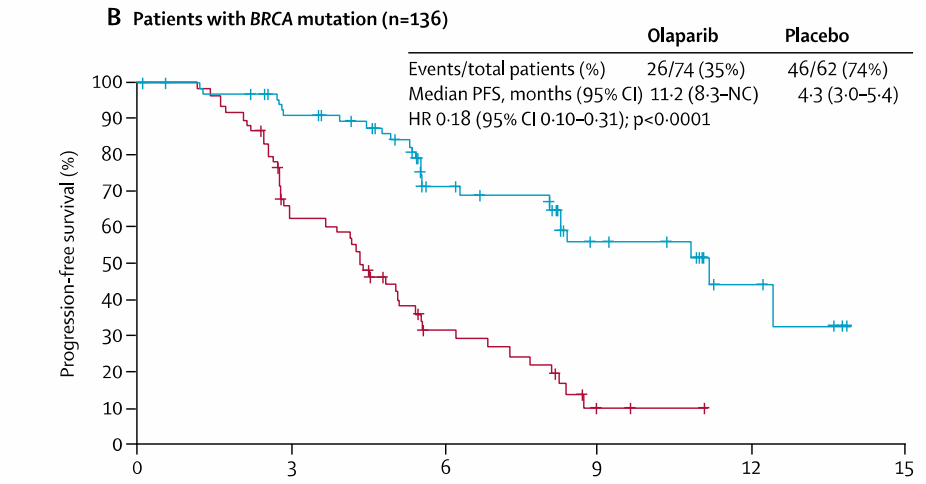
Olaparib Efficacy



Reported response rate of 34%, median duration 8 months

Ledermann J, *Lancet Oncol* 2014

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Olaparib Safety

	Olaparib (n=53)		Placebo (n=43)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Decreased appetite	25	0	14	0
Nausea Vomiting	75 32	2 4	37 9	0 0
Fatigue	68	6	53	2
URI	43	0	16	0
Arthralgia	43	0	16	0
Neutropenia	32	8	23	0
Anemia	25	4		
Increased creatinine	26	0	5	0

Ledermann J, *Lancet Oncol* 2014

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Olaparib Precautions

- Metabolized by CYP3A
  - Avoid strong CYP3A inhibitors
  - Avoid grapefruit and grapefruit juice
- No data in creatinine clearance < 50 ml/min
- No data in hepatic impairment

Olaparib Precautions

- Myelodysplastic syndrome/acute myeloid leukemia
  - 2% patients, all previously treated with platinum or DNA damaging agents
- Pneumonitis (2%)

Netupitant/Palonostron

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
- Netupitant 300 mg/ palonosetron 0.5 mg
- Orally administered combination
  - Neurokinin-1 antagonsit
  - 5HT3 antagonist

Netupitant/Palonosetron

- Mild CYP3A4 inhibitor
- Give with dexamethasone 12 mg orally 1 hour prior to chemotherapy
- Follow with 8 mg dexamethasone daily for 3 days after highly emetogenic chemotherapy

Questions?

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