New Drug Update

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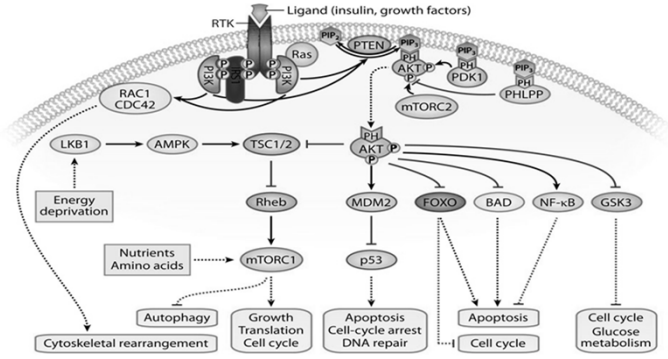
Objectives

- Discuss recently approved oncology and supportive care medications
- Explain pharmacology and pharmacokinetics of newly approved medications
- Evaluate supporting literature of the medications
- Describe where agents fit into clinical practice

Recently FDA Approved Oncology Medications

	FDA Approval Date	Usage	Dosage Form
Idelalisib	September 2014	CLL/FL/SLLL	PO
Pembrolizumab	September 2014	Melanoma	IV
Netupitant/palonsetron	October 2014	CINV	PO
Blinatumomab	December 2014	ALL	IV
Lanreotide	December 2014	GEP-NETs	SQ
Olaparib	December 2014	Ovarian	PO
Nivolumab	December 2014	Melanoma/Lung	IV
Palbociclib	February 2015	Breast	PO
Panobinostat	February 2015	Myeloma	PO
Dinutuximab	March 2015	Neuroblastoma	IV
Filgrastim-sndz	March 2015	Growth factor	SQ
Gefitinib	July 2015	NSCLC	PO

PI3 Kinase Pathway

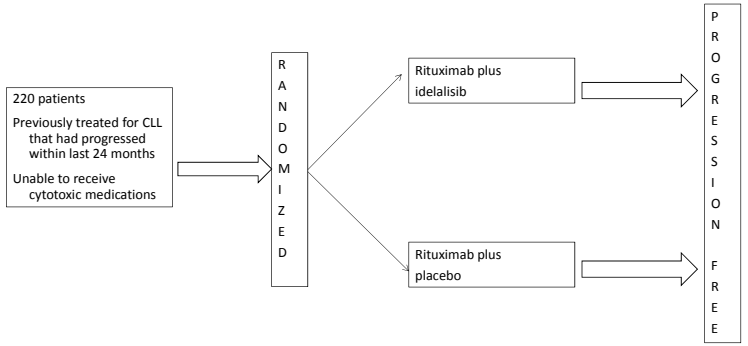


Annu Rev Pathol 2009; 4: 127-150

Idelalisib

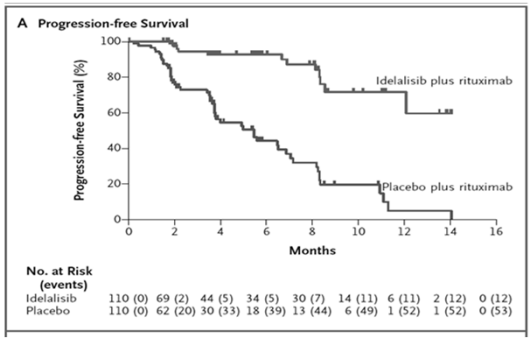
- FDA approved indications
  - Relapsed CLL in combination with rituximab
  - Relapsed follicular lymphoma in patients who have received at least two prior systemic therapies
  - Relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies
- Dosage
  - 150 mg twice daily
- Dosage form
  - 100 mg tablets
  - 150 mg tablets

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia



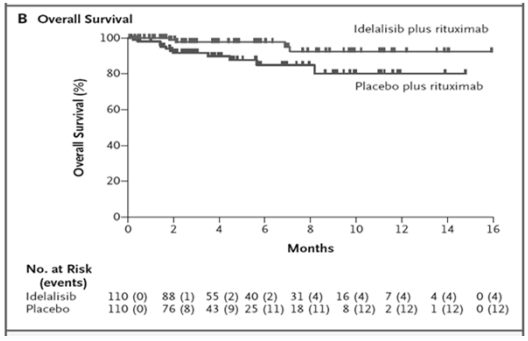
NEJM 2014; 370: 997-1007

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia



NEJM 2014; 370: 997-1007

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia



NEJM 2014; 370: 997-1007

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Event	Idelalisib plus Rituximab (N=110)		Placebo plus Rituximab (N=107)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event during treatment	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (21)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (15)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Constipation	13 (12)	0	12 (11)	0
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Vomiting	13 (12)	0	8 (7)	0
Dyspnea	12 (11)	2 (2)	20 (19)	3 (3)
Night sweats	11 (10)	0	8 (7)	0
Rash	11 (10)	2 (2)	6 (6)	0

NEJM 2014; 370: 997-1007

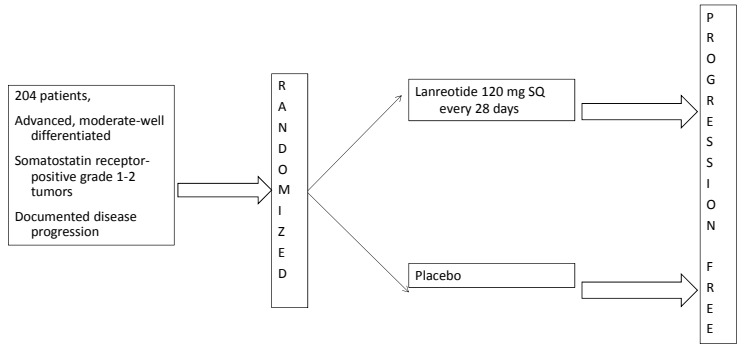
Audience Response Question

- What is the dosing of idelalisib?
  a. 125 mg once daily
  b. 250 mg twice daily
  c. 150 mg twice daily
  d. None of the above

Lanreotide

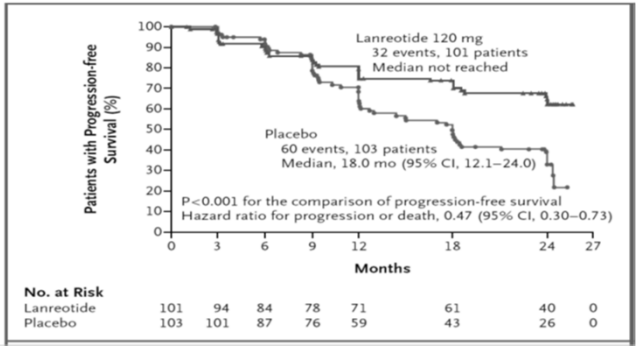
- FDA Labeled Indication
  - Long term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy
  - Unresectable, well- or moderately- differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
- Dosing
  - Acromegaly
    - 60 – 120 mg every 4 weeks
  - GEP-NET
    - 120 mg every 4 weeks
- Availability
  - 60 mg PFS
  - 90 mg PFS
  - 120 mg PFS

Lanreotide



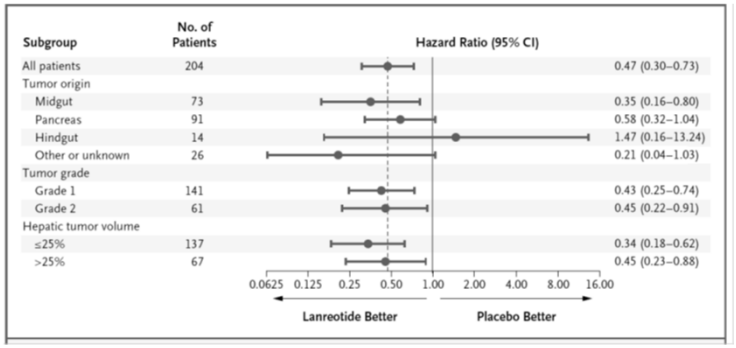
NEJM 2014; 371: 224-233

Lanreotide



NEJM 2014; 371: 224-233

Lanreotide



NEJM 2014; 371: 224-233

Lanreotide

Table 2. **Secondary Efficacy End Points (Intention-to-Treat Population).***

End Point	Lanreotide (N=101)	Placebo (N=103)	Between-Group Comparison (95% CI)	P Value
Patients alive without disease progression — no./total no. (%)†				
At wk 48	67/101 (66)	50/103 (49)	2.11 (1.19 to 3.76)	<0.05
At wk 96	53/101 (52)	26/103 (25)	3.27 (1.81 to 5.93)	<0.001
Median time to tumor progression (95% CI) — mo‡	Not reached	18.0 (12.1 to 24.0)		<0.001§
EORTC QLQ-C30 global health status score — least-squares mean change from baseline to last post-baseline value available¶	−5.18±3.73	−4.87±3.7	−0.31±2.74 (−5.73 to 5.10)	
Patients with ≥50% reduction in level of chromogranin A from baseline to last post-baseline level available — no./total no. (%)‖	27/64 (42)	3/64 (5)	15.20 (4.29 to 53.87)	<0.001

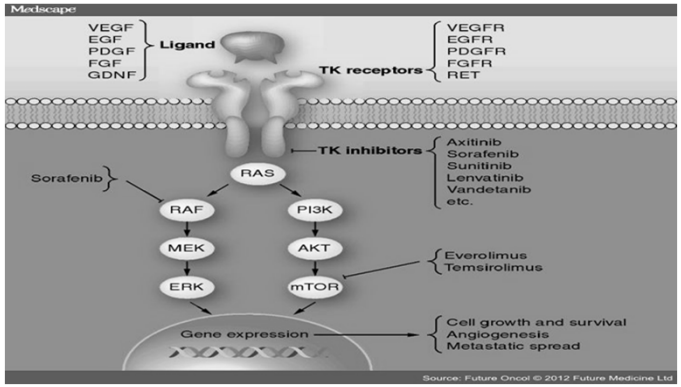
NEJM 2014; 371: 224-233

Lanreotide

Study treatment–related adverse events in ≥5% of patients		
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)
Flatulence	8 (8)	5 (5)
Injection-site pain	7 (7)	3 (3)
Nausea	7 (7)	2 (2)
Vomiting	7 (7)	0
Headache	5 (5)	2 (2)
Lethargy	5 (5)	1 (1)
Hyperglycemia	5 (5)	0
Decreased level of pancreatic enzymes	5 (5)	0

NEJM 2014; 371: 224-233

Lenvatinib

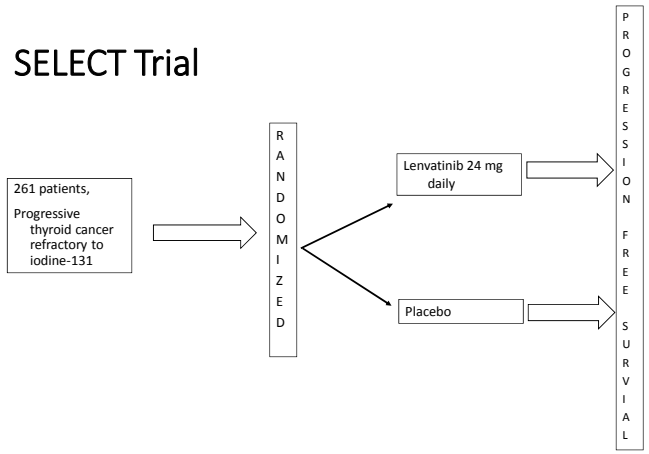


http://www.medscape.com/viewarticle/774345_5

Lenvatinib

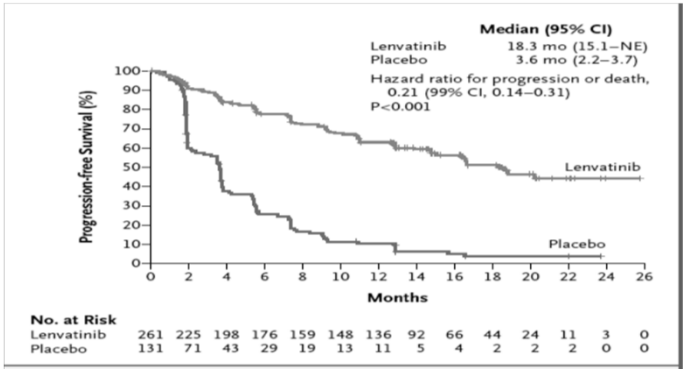
- FDA Labeled Indication
  - Locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer
- Dosing
  - 24 mg orally once daily
- Availability
  - Capsules
    - 4 mg, 10 mg

SELECT Trial



New England Journal of Medicine 2015; 372: 621-630

SELECT Trial



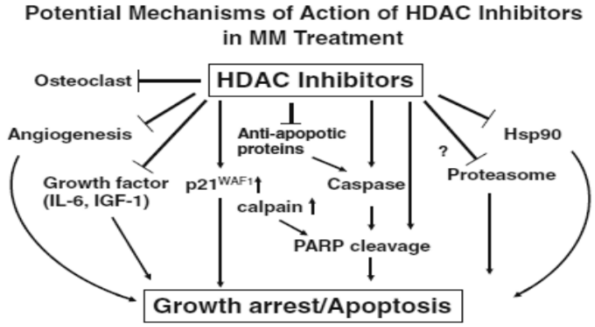
New England Journal of Medicine 2015; 372: 621-630

SELECT Trial

	Lenvatinib		Placebo	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8	8.4	0
Fatigue or asthenia	59	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
PPE	31.8	3.4	0.8	0
Proteinuria	31	10	1.5	0
Vomiting	28.4	1.9	6.1	0

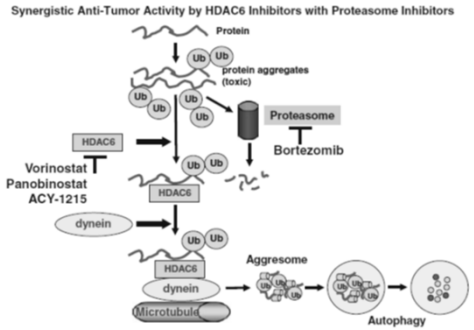
New England Journal of Medicine 2015; 372: 621-630

Histone Deacetylase Inhibitors



International Journal of Hematology 2013; 97: 324-332.

Histone Deacetylase Inhibitors

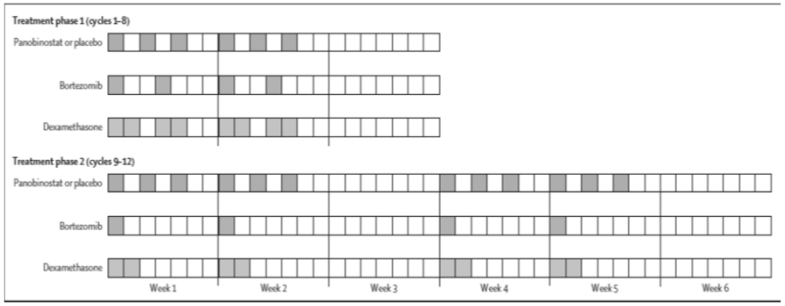


International Journal of Hematology 2013; 97: 324-332.

Panobinostat

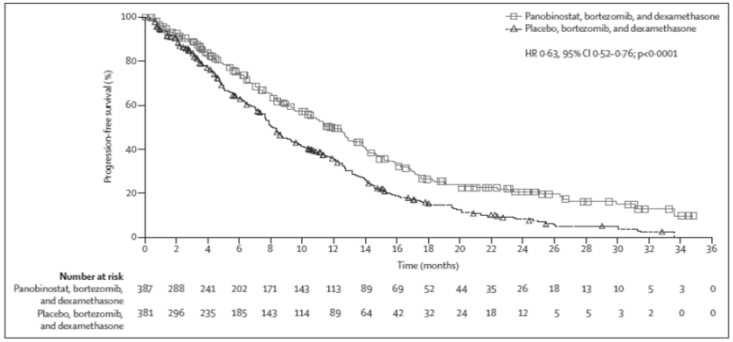
- FDA Labeled Indication
  - In combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who had received at least 2 prior regimens, including bortezomib and an immunomodulatory agent
- Dosing
  - 20 mg taken orally once every other day for 3 doses per week (days 1,3,5,8,10,12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles
- Availability
  - Capsules
    - 10 mg, 15 mg, 20 mg

PANORAMA-1 Trial



Lancet Oncology 2014; 15: 1195-1206

PANORAMA-1 Trial



Lancet Oncology 2014; 15: 1195-1206

PANORAMA-1 Trial

	Panobinostat, bortezomib, and dexamethasone (n=387)	Placebo, bortezomib, and dexamethasone (n=381)
Best response to treatment		
Complete response	42 (11%)	22 (6%)
Near-complete response	65 (17%)	38 (10%)
Partial response	128 (33%)	148 (39%)
Minimal response	23 (6%)	42 (11%)
No change	65 (17%)	74 (19%)
Progressive disease	21 (5%)	32 (8%)
Unknown	43 (11%)	25 (7%)
Overall response (partial response or better)	235 (60·7%, 55·7–65·6)	208 (54·6%, 49·4–59·7)*
Near-complete plus complete response	107 (27·6%, 23·2–32·4)	60 (15·7%, 12·2–19·8)†
Median time to response (months)	1·51 (1·41–1·64)	2·00 (1·61–2·79)
Median duration of response (months)	13·14 (11·76–14·92)	10·87 (9·23–11·76)
Median time to first progression, relapse, or death from multiple myeloma (months)	12·71 (11·30–14·06)	8·54 (7·66–9·72)

Data are n (%), n (%, 95% CI), or median (95% CI). *p=0·09. †p=0·00006 (based on post-hoc testing).

Table 2: **Best response and secondary efficacy endpoints**

Lancet Oncology 2014; 15: 1195-1206

PANORAMA-1 Trial

	Panobinostat, bortezomib, and dexamethasone (n=381)					Placebo, bortezomib, and dexamethasone (n=377)				
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4
Newly occurring or worsening haematological laboratory abnormalities‡										
Platelet count	371/380 (98%)	43/298 (14%)	72/373 (19%)	124/380 (33%)	132/380 (35%)	314/376 (84%)	120/374 (44%)	76/369 (21%)	73/375 (19%)	45/376 (12%)
Absolute lymphocyte count	314/380 (83%)	20/316 (6%)	92/350 (26%)	157/374 (42%)	45/380 (12%)	278/377 (74%)	22/314 (7%)	106/347 (31%)	123/368 (33%)	27/377 (7%)
White blood cell count	308/380 (81%)	72/282 (26%)	148/358 (41%)	78/379 (21%)	10/380 (3%)	180/377 (48%)	77/273 (28%)	72/349 (21%)	26/375 (7%)	5/377 (1%)
Absolute neutrophil count	285/380 (75%)	45/323 (14%)	109/360 (30%)	106/379 (28%)	25/380 (7%)	134/377 (36%)	34/306 (11%)	57/352 (16%)	34/375 (9%)	9/377 (2%)
Haemoglobin concentration	235/379 (62%)	49/86 (57%)	119/278 (43%)	56/372 (15%)	11/379 (3%)	197/377 (52%)	47/68 (69%)	78/254 (31%)	63/361 (17%)	9/377 (2%)

Lancet Oncology 2014; 15: 1195-1206

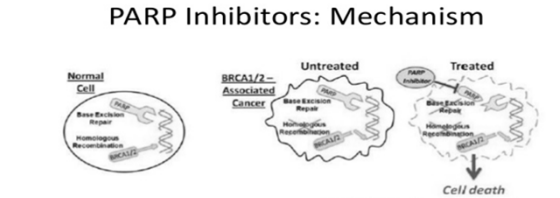
Audience Response Question

- What is the mechanism of action of panobinostat?
  a. Folate antagonist
  b. HDAC inhibitor
  c. Angiogenesis inhibitor
  d. Immunotherapy

Olaparib

- FDA Labeled Indication
  - Monotherapy with deleterious or suspected deleterious germline BRCA mutated (as directed by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
- Dosing
  - 400 mg orally twice daily
- Availability
  - Capsules
    - 50 mg

Olaparib



- PARP and BRCA1/2 normally function to repair daily DNA damage
- Allows cells to grow in a healthy way
- Too much DNA damage-> cell death

- If BRCA1/2 is damaged or not working, the cell is dependent on PARP for all DNA repair
- PARP inhibitors prevent DNA repair in cancer cells
  - May increase cancer cell death
  - May help chemo and radiation work better

Ellisen, Cancer Cell 2011; Tutt et al, Lancet 2010

Olaparib

Features and properties of olaparib

Alternative names	AZD 2281; AZD-2281; AZD2281; KU-0059436; KU-59436; Lynparza™
Class	Amides, Cyclopropanes, Fluorobenzenes, Phthalazines, Piperazines, Small-molecules
Mechanism of action	Poly (ADP-ribose) polymerase inhibitor
Route of administration	Oral
Pharmacodynamics	Displays anti-neoplastic activity in various cancer cell lines. Its benefits may be enhanced by other anti-cancer agents, according to preclinical studies
Pharmacokinetics	Rapidly absorbed and eliminated
Most frequent adverse events	Nausea, fatigue, vomiting, anaemia
ATC codes	
WHO	L01X-X (other antineoplastic agents)
EphMRA	L1X (all other antineoplastics)
Chemical name	4- [3- [4-(Cyclopropylcarbonyl)piperazin-1-ylcarbonyl] -4-fluorobenzyl] phthalazin-1(2H)-one

Drugs 2015; 75: 231-240

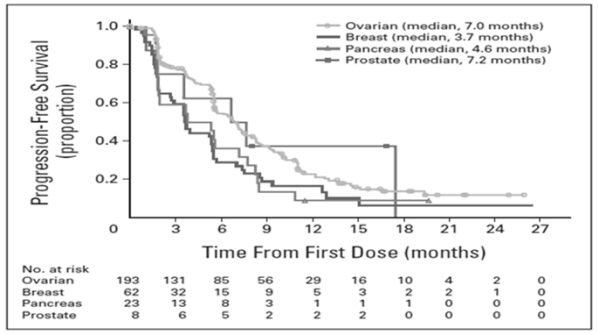
Olaparib

Overall Response and Response Duration in BRCA-mutated Advanced Ovarian Cancer in Patients Who Received at 3 or More Lines of Previous Chemotherapy

	N = 137
Objective Response Rate	34%
Complete Response	2%
Partial Response	32%
Median Duration of Response (months)	7.9 months (5.6-9.6)

Journal of Clinical Oncology 2015; 33:244-250
Lynparza® Prescribing Information

Olaparib



Journal of Clinical Oncology 2015 33:244-250

Olaparib

	Ovarian (n = 193)			
	Any Grade		Grade ≥ 3	
AE	No.	%	No.	%
Fatigue	116	60.1	12	6.2
Nausea	119	61.7	1	0.5
Vomiting	75	38.9	5	2.6
Anemia	62	32.1	36	18.7
Diarrhea	56	29.0	3	1.6
Abdominal pain	58	30.1	14	7.3
Decreased appetite	36	18.7	1	0.5
Dyspepsia	38	19.7	0	0.0
Headache	32	16.6	0	0.0
Dysgeusia	39	20.2	0	0.0

Journal of Clinical Oncology 2015 33:244-250

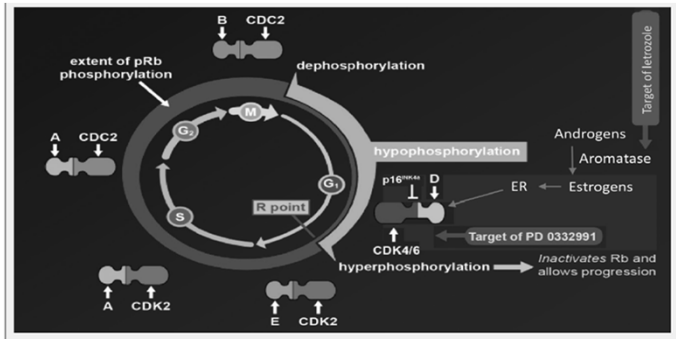
Audience Response Question

- True or False?
  Olaparib has an accompanying FDA approved test for BRCA.

Palbociclib

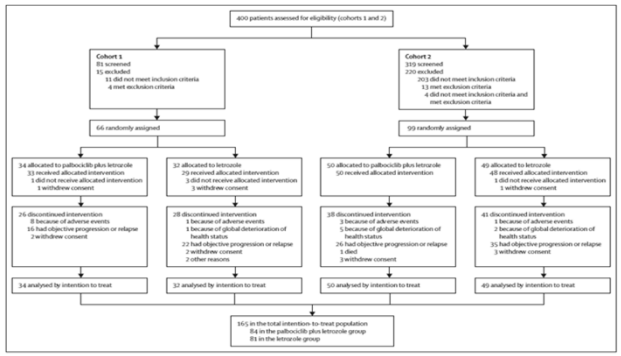
- FDA Labeled Indication
  - In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine therapy for metastatic disease
- Dosing
  - 125 mg once daily for 21 consecutive days followed by 7 days off
    - In combination with letrozole 2.5 mg once daily given continuously throughout cycle
  - Should be taken with food
- Availability
  - Capsule
    - 75 mg
    - 100 mg
    - 125 mg

Palbociclib



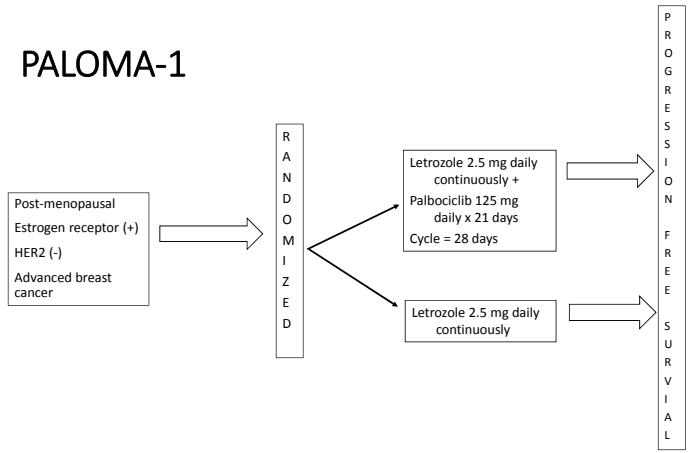
Journal of Community and Supportive Oncology 2015; 13(3): 83-86.

PALOMA-1



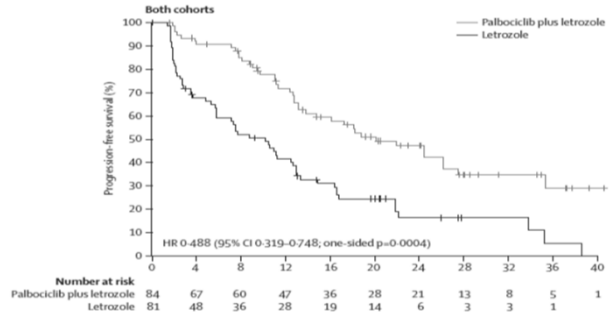
Lancet Oncology 2015; 16: 25-35

PALOMA-1



Lancet Oncology 2015; 16: 25-35

PALOMA-1



Lancet Oncology 2015; 16: 25-35

PALOMA-1

	Palbociclib plus letrozole	Letrozole
Intention-to-treat population*		
Complete response	1 (1%)	1 (1%)
Partial response	35 (42%)	26 (32%)
Stable disease	37 (44%)	30 (37%)
Stable disease ≥24 weeks	32 (38%)	20 (25%)
Stable disease <24 weeks	5 (6%)	10 (12%)
Progressive disease	3 (4%)	18 (22%)
Indeterminate	8 (10%)	6 (7%)
Patients with measurable disease†		
Complete response	1 (2%)	0
Partial response	35 (54%)	26 (39%)
Stable disease	20 (31%)	22 (33%)
Progressive disease	2 (3%)	15 (23%)
Indeterminate	7 (11%)	3 (5%)

Data are n (%). *n=84 in the palbociclib plus letrozole group, n=81 in the letrozole alone group. †n=65 in the palbociclib plus letrozole group, n=66 in the letrozole alone group.

Lancet Oncology 2015; 16: 25-35

PALOMA-1

	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0
Fatigue	30 (36%)	2 (2%)	2 (2%)	17 (22%)	1 (1%)	0
Anaemia	24 (29%)	4 (5%)	1 (1%)	4 (5%)	1 (1%)	0
Nausea	19 (23%)	2 (2%)	0	9 (12%)	1 (1%)	0
Arthralgia	18 (22%)	1 (1%)	0	10 (13%)	2 (3%)	0
Alopecia	18 (22%)	NA	NA	2 (3%)	NA	NA
Diarrhoea	14 (17%)	3 (4%)	0	8 (10%)	0	0
Hot flush	17 (21%)	0	NA	9 (12%)	0	NA
Thrombocytopenia	12 (14%)	2 (2%)	0	1 (1%)	0	0
Decreased appetite	12 (14%)	1 (1%)	0	5 (6%)	0	0
Dyspnoea	11 (13%)	2 (2%)	0	5 (6%)	1 (1%)	0

Lancet Oncology 2015; 16: 25-35

Filgrastim-sndz

- FDA Labeled Indication
  - Decreased infection rate due to febrile neutropenia in patients with nonmyeloid malignancies receiving myleosuppressive anticancer drugs associated with a significant incidence of severe neutropenia
  - Reduce the time to neutrophil recover and duration of fever following induction or consolidation chemotherapy treatment of patients with AML
  - Reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT
  - Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
  - Reduced the incidence and duration of sequlae of severe neutropenia in symptomatic patients with congential neutropenia, cyclic neutropenia, or idiopathic neutropenia
- Availability
  - Prefilled syringe
    - 300 mcg
    - 480 mcg

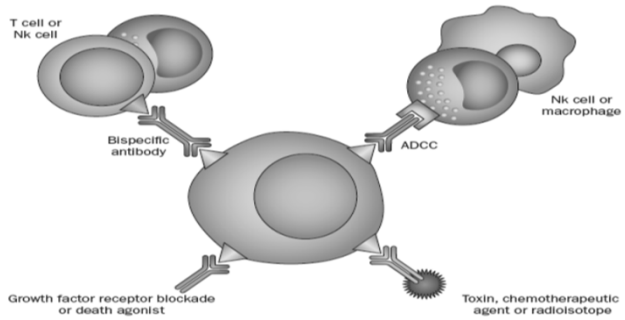
Filgrastim-Sndz

Indication	Dosing
Decrease febrile neutropenia due to myelosuppressive therapy	• 5 mcg/kg/day SQ, short IV infusion, or CIV
Reduce the time to neutrophil recovery in patients receiving induction or consolidation AML therapy	• 5 mcg/kg/day SQ, short IV infusion, or CIV
Reduce neutropenia duration in patients receiving myeloablative chemotherapy followed by BMT	• 10 mcg/kg/day given as an IV infusion no longer than 24 hours
Leukapheresis	• 10 mcg/kg/day SQ • Administer for at least 4 days before first leukapheresis and continue until last leukapheresis
Cyclic or idiopathic neutropenia	• 5 mcg/kg SQ daily
Congenital neutropenia	• 6 mcg/kg SQ twice daily

Dinutuximab

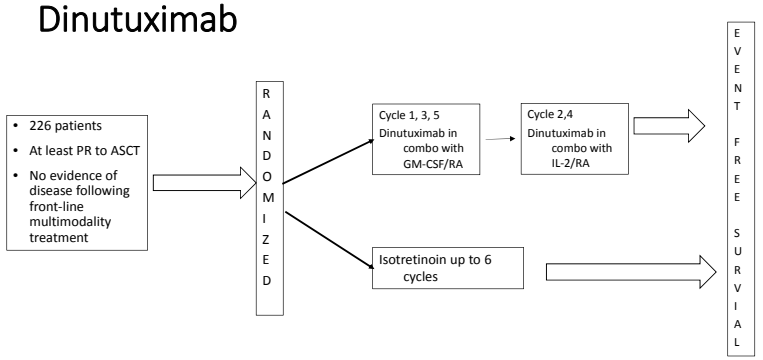
- FDA Labeled Indication
- In combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy
- Dosing
  - 17.5 mg/m^2/day as a diluted intravenous infusion over 10-20 hours for 4 days
- Availability
  - Single use vial
    - 17.5 mg/5 mL (3.5 mg/mL)

Dinutuximab



Nat. Rev. Clin. Oncol. 2014; 161: 693-703

Dinutuximab



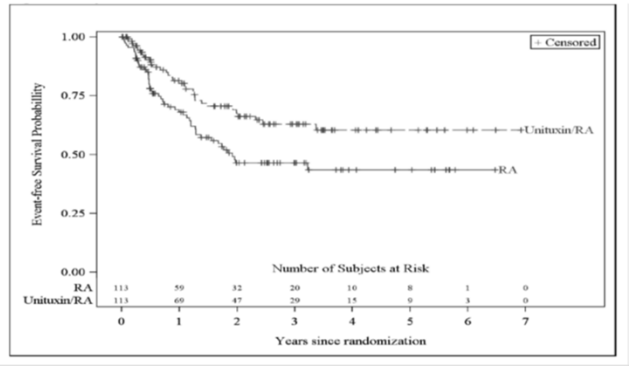
Onclive.Com FDA Approves Dinutuximab for High-Risk Neuroblastoma. http://www.onclive.com/web-exclusives/FDA-Approves-Dinutuximab-for-High-Risk-Neuroblastoma

Dinutuximab

Efficacy Parameter		Unituxin/RA Arm n=113	RA Arm n=113
EFS	No. of Events	33 (29%)	50 (44%)
	Median (years)	NR (3.4, NR)	1.9 (1.3, NR)
	HR	0.57 (0.37, 0.89)	
	p-value	0.01	
OS	No. of Events (%)	31 (27%)	48 (42%)
	Median (years)	NR (7.5, NR)	NR (3.9, NR)
	HR	0.58 (0.37, 0.91)	

Dinutuximab Prescribing Information

Dinutuximab



Dinutuximab Prescribing Information

Dinutuximab

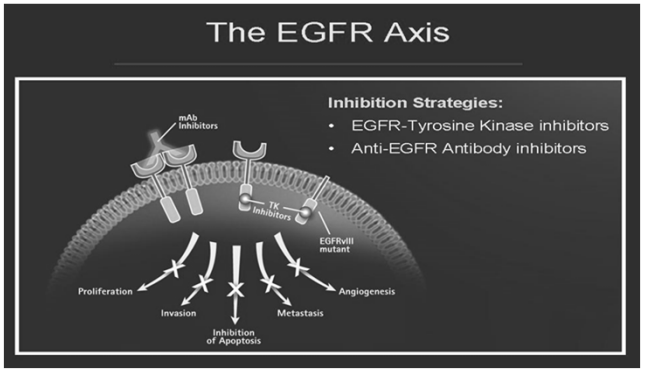
Adverse Reaction[1,2]	Unituxin/RA (N=134) All Grades (%)	Unituxin/RA (N=134) Grades 3-4 (%)	RA (N=106) All Grades (%)	RA (N=106) Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Pain[3]	85	51	16	6
Pyrexia	72	40	27	6
Edema	17	0	0	0
Blood and Lymphatic System Disorders[4]				
Thrombocytopenia	66	39	43	25
Lymphopenia[4]	62	51	36	20
Anemia	51	34	22	16
Neutropenia	39	34	16	13
Immune System Disorders				
Infusion reactions	60	25	9	1
Vascular Disorders				
Hypotension	60	16	3	0
Capillary leak syndrome[5]	40	23	1	0
Hemorrhage[6]	17	6	6	3
Hypertension	14	2	7	1
Metabolism and Nutrition Disorders				
Hyponatremia[4]	58	23	12	4
Hypokalemia[4]	43	37	4	2
Hypoalbuminemia[4]	33	7	3	0
Hypocalcemia[4]	27	7	0	0
Hypophosphatemia[4]	20	8	3	0
Hyperglycemia[4]	18	6	4	1
Hypertriglyceridemia[4]	16	1	11	1
Decreased appetite	15	10	5	4
Hypomagnesemia[4]	12	2	1	0

Dinutuximab Prescribing Information

Gefitinib

- FDA approved indications
  - Metastatic NSCLC who tumors have epidermal growth factor (EGFR) exon 19 or exon 21 substitution mutations
- Dosage
  - 250 mg orally once daily without regards to food
- Dosage form
  - 250 mg tablets

Gefitinib



http://cancergrace.org/wp-content/uploads/2007/03/egfr-figure-moabs-vs-tkis.jpg

Gefitinib

Multicenter, single-arm, open-label study

106 treatment-naïve patients with metastatic EFGR mutation positive NSCLC

250 mg by mouth daily until disease progression or intolerable toxicity

Primary endpoint: Objective Response Rate

Onclive.Com Frontline Gefitinib Approved in EGFR Positive NSCLC. http://www.onclive.com/web-exclusives/firstline-gefitinib-approved-in-nsclc

Gefitinib

Efficacy Parameter	**Blinded Independent Central Review (N=106)**	**Investigator Assessment (n=106)**
Objective Response Rate	50% (41,59)	70% (61, 78)
Complete Response Rate	0.9%	1.9%
Partial Response Rate	49%	68%
Median Duration of Response (months)	6.0 (5.1, 11.1)	8.3 (7.6, 11.3)

Gefitinib Prescribing Information

Gefitinib

Adverse Effects	**Percentage**
Interstitial Lung Disease (ILD)	1.3%
Hepatotoxicity	11.4% (ALT) 7.9% (AST) 2.7% (bilirubin)
Gastrointestinal Perforation	0.1%
Severe or Persistent Diarrhea	Grade 3-4: 3%
Ocular Disorders including Keratitis	0.1% keratitis 6.7% conjunctivitis, blepharitis, and dry eyes
Exfoliative Skin Disorders	0.08%

Gefitinib Prescribing Information

Audience Response Question

- True or False?
  Gefitinib was recently granted FDA approval for second line treatment of EGFR (+) NSCLC.

New Drug Update

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