New Drug Update: The Next Step in Personalized Medicine

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Objectives

- Review indications for new FDA approved anti-neoplastic medications in 2017
- Outline place in therapy of new medications
- Become familiar with mechanisms of action of new medications
- Describe adverse effects associated with new medications
- Summarize dosing schemes and appropriate dose reductions for new medications

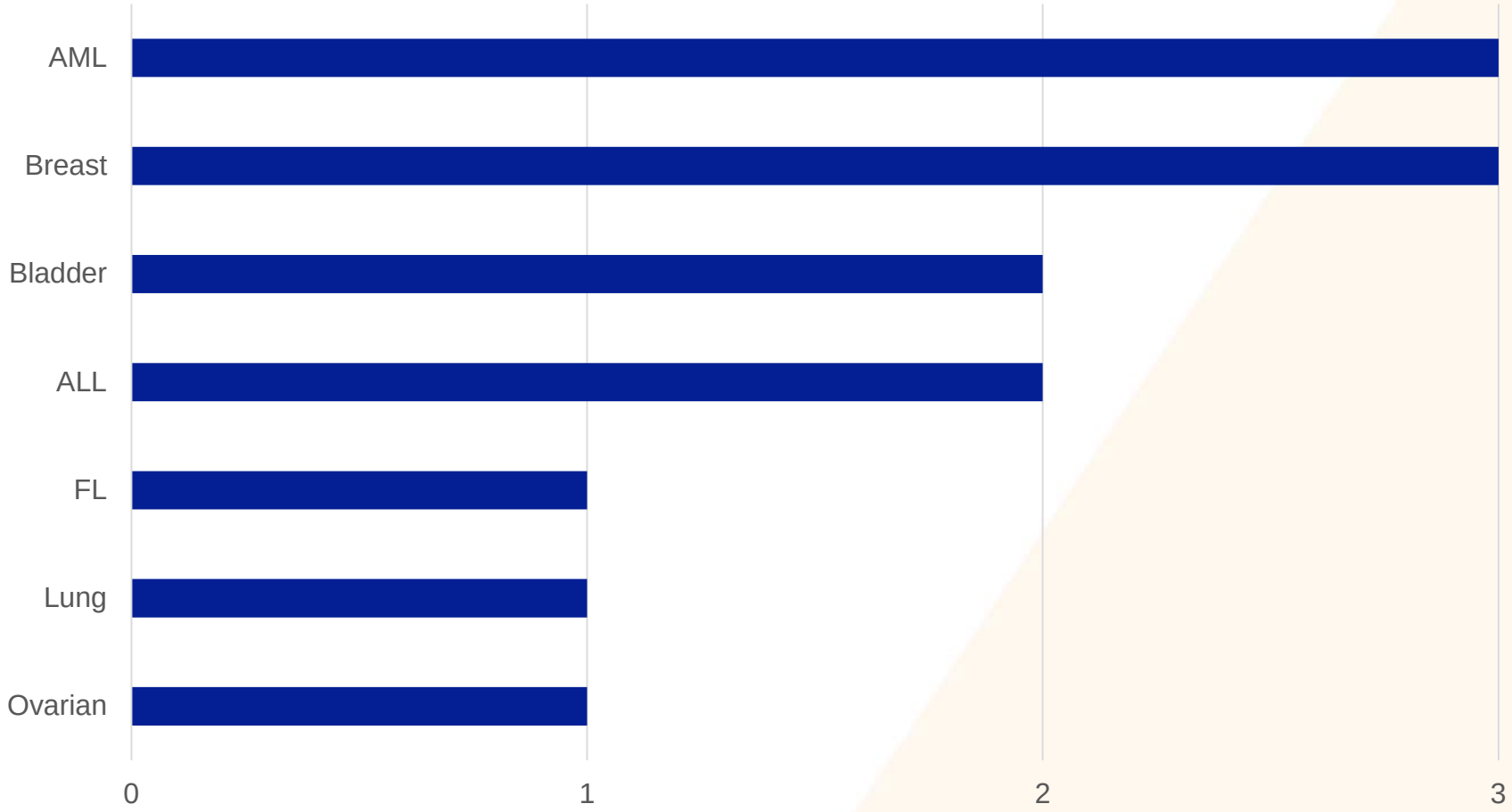
First-in-Class Approvals

- FLT3 inhibitor – midostaurin
- IDH2 inhibitor – enasidenib
- Anti-CD22 antibody drug conjugate – inotuzumab ozogamicin
- CAR T-cell therapy - tisagenlecleucel

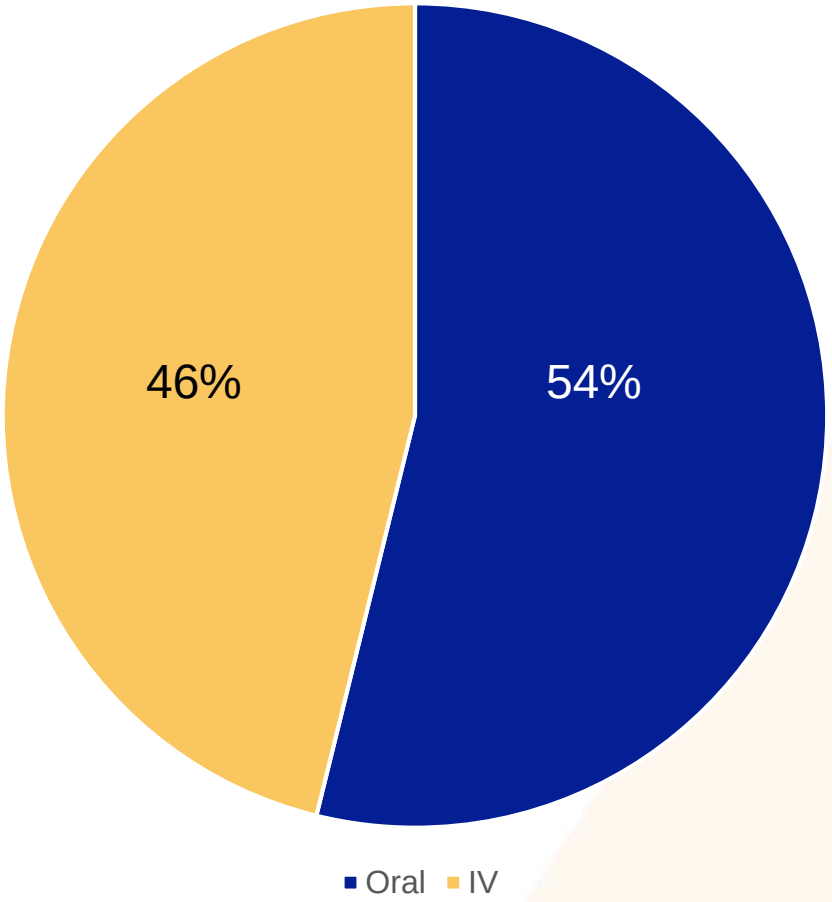
“Me-too” Approvals

- CDK 4/6 inhibitor – ribociclib and abemaciclib
- PD-L1 inhibitors
  - Avelumab
  - Durvalumab
- PARP inhibitor – niraparib
- ALK inhibitor – brigatinib
- Pan-HER inhibitor – neratinib
- Liposome-encapsulated combination of daunorubicin and cytarabine
- PI3K inhibitor – copanlisib

Drugs by Malignancy

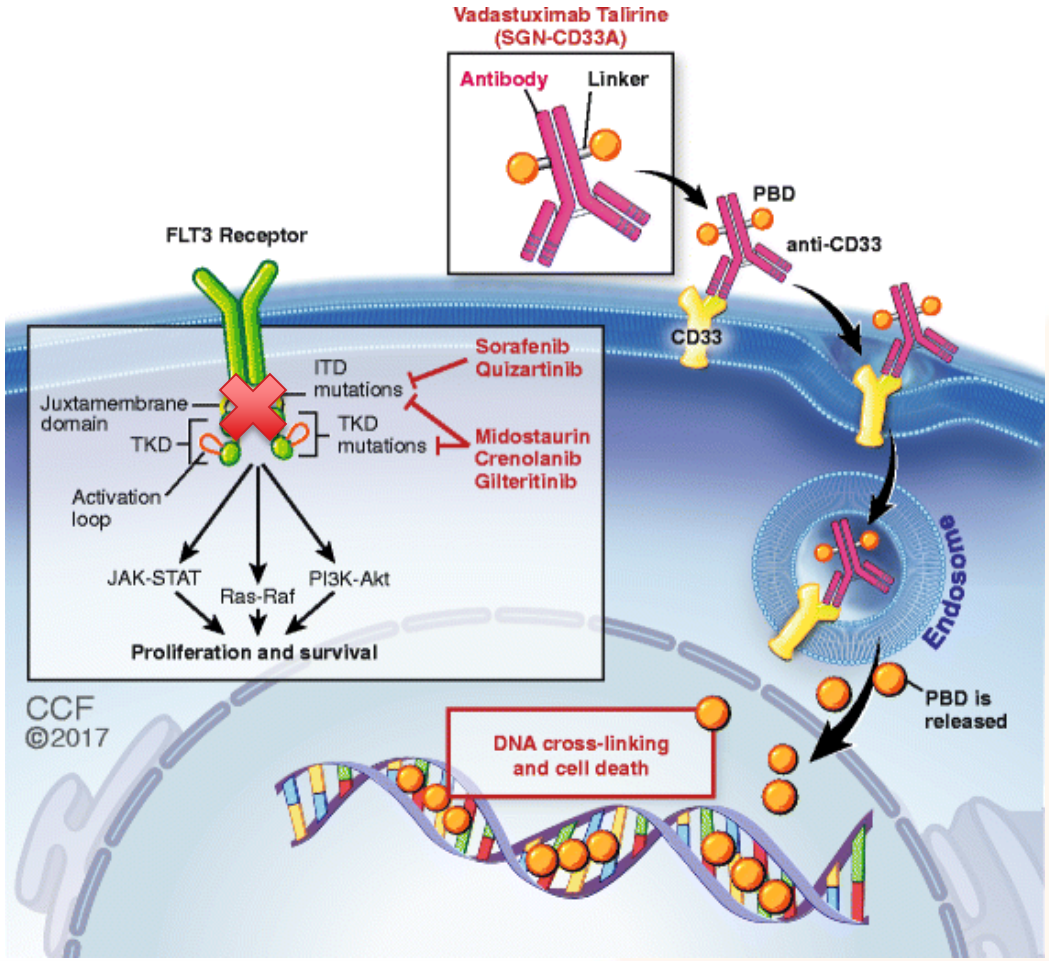


Oral versus IV



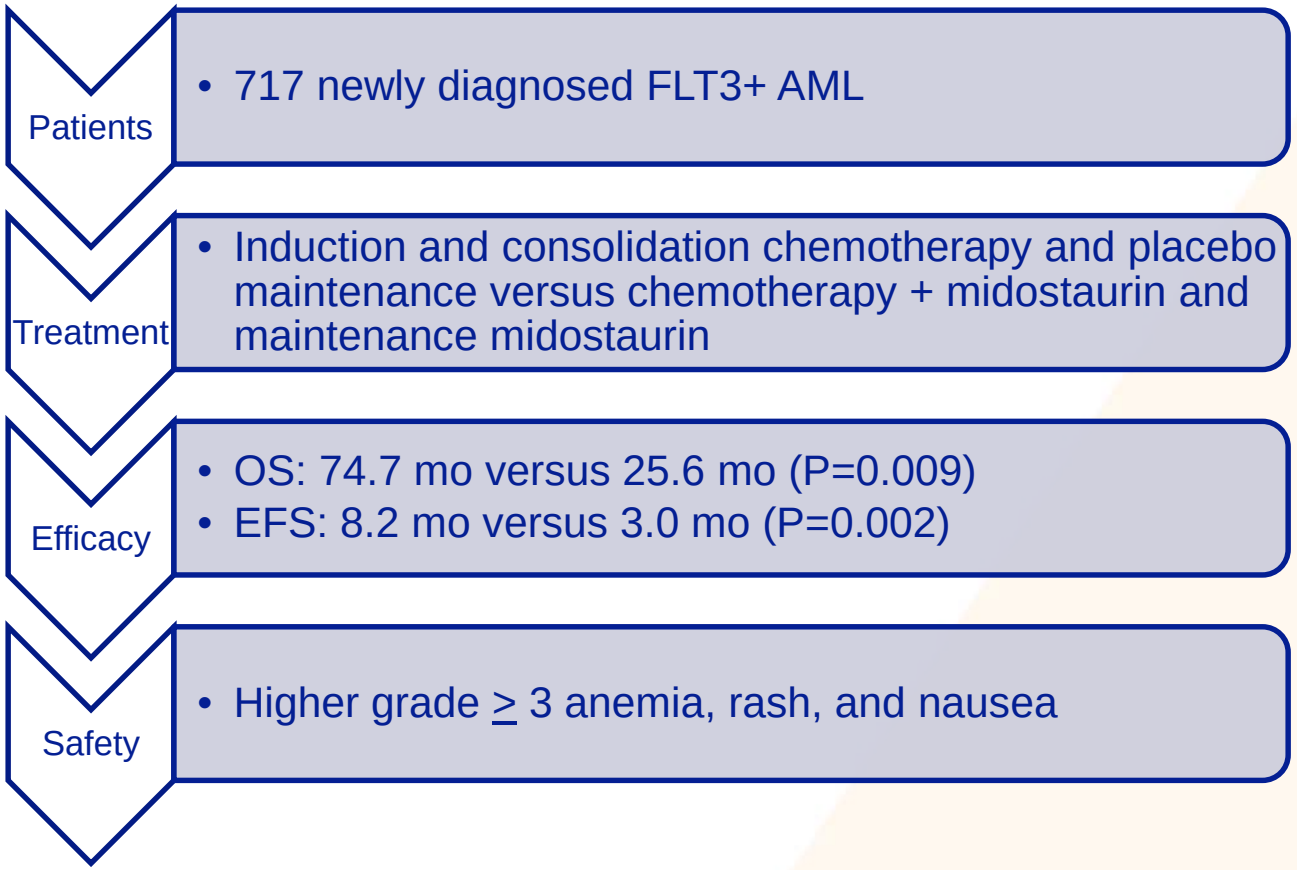
FIRST-IN CLASS

FLT3 Inhibitor - midostaurin



Journal of Hematology & Oncology 2017;10:93

Midostaurin (Rydapt®)



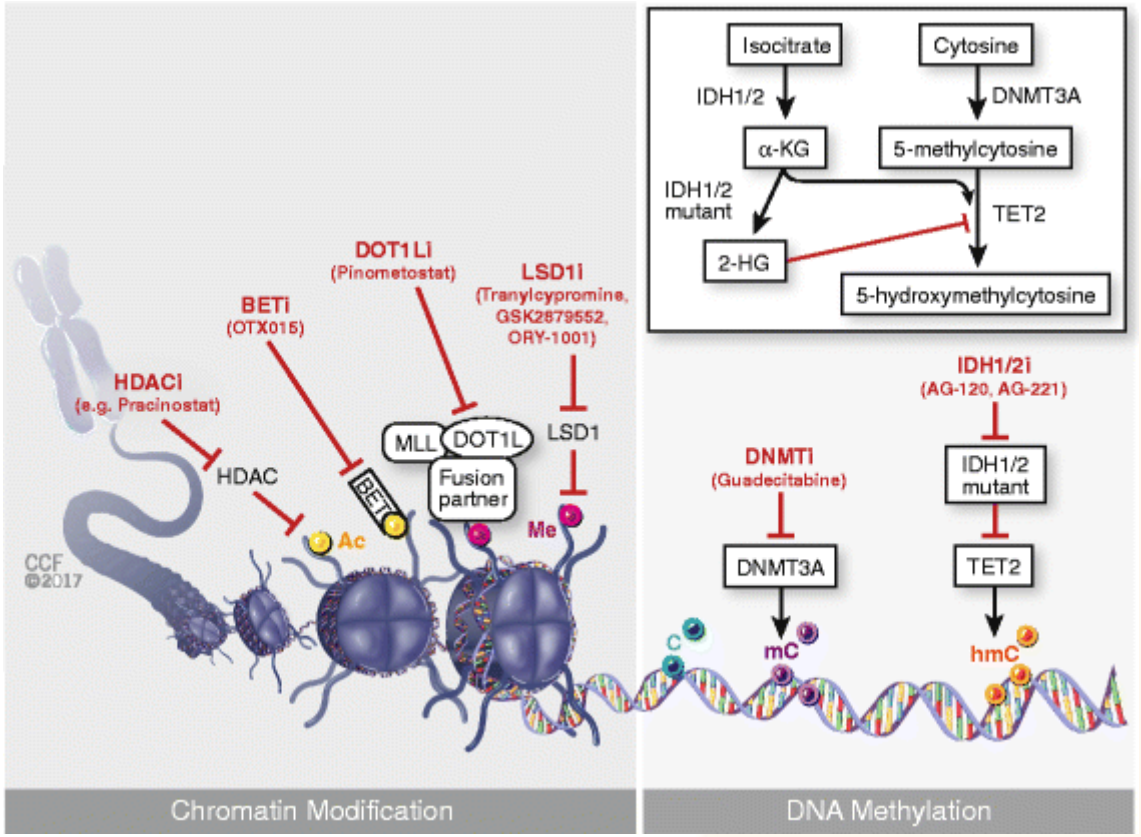
N Engl J Med 2017;377:454-64

Midostaurin (Rydapt®)

- Approved indications: **FLT3+ AML**, mast cell leukemia, systemic mastocytosis
- AML dose: 50 mg twice daily with **food** on days 8-21
  - Of each induction cycle (+ daunorubicin and cytarabine)
  - Of each consolidation cycle (+ high dose cytarabine)
- ADEs: nausea, myelosuppression, mucositis, increases in LFTs, amylase/lipase, and electrolyte abnormalities
- Pharmacokinetics: hepatic metabolism, substrate of CYP 3A4; < 5% excretion in urine

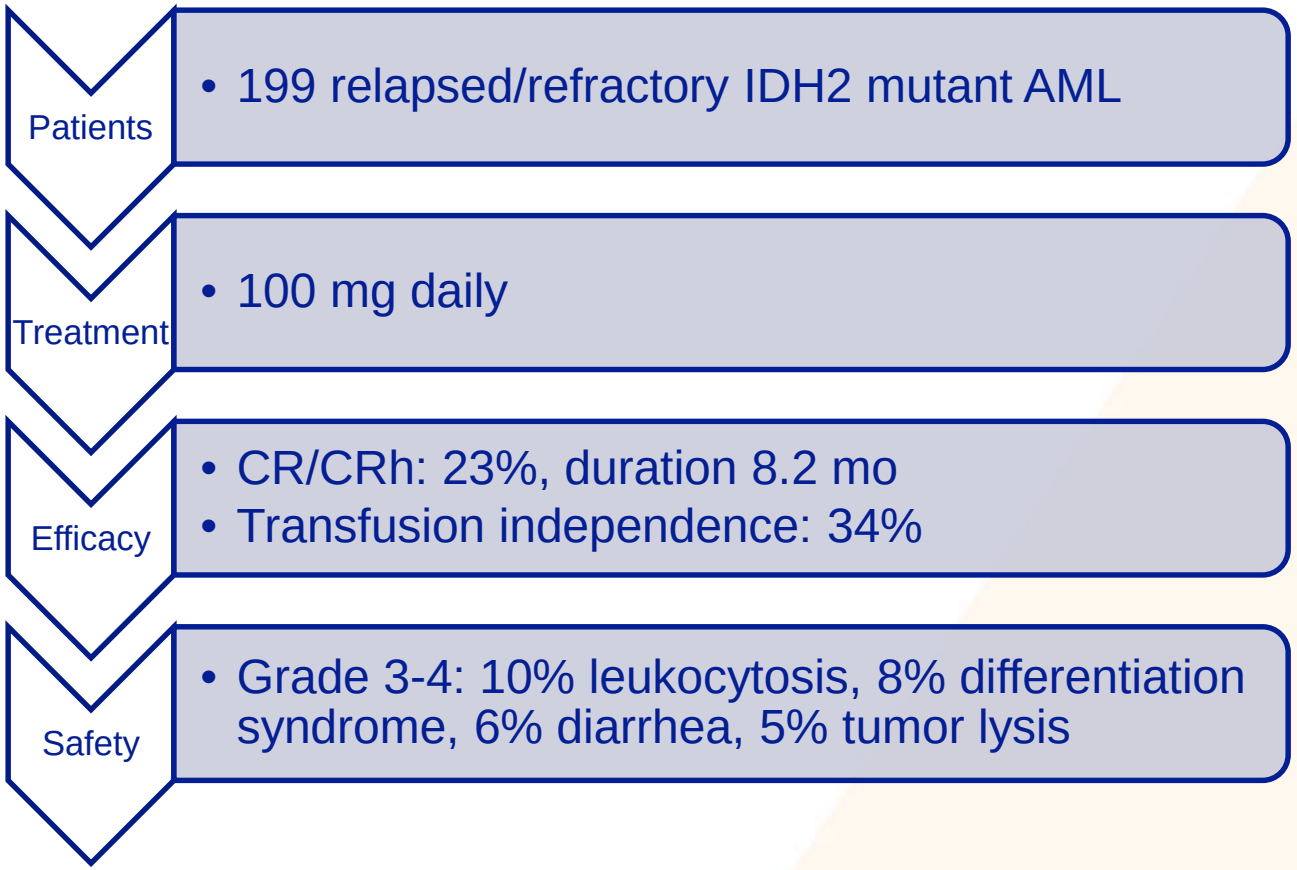
RYDAPT (midostaurin) [package insert]. East Hanover, NJ; 2017

IDH2 Inhibitor – enasidenib



Journal of Hematology & Oncology 2017;10:93

Enasidenib (Idhifa®)



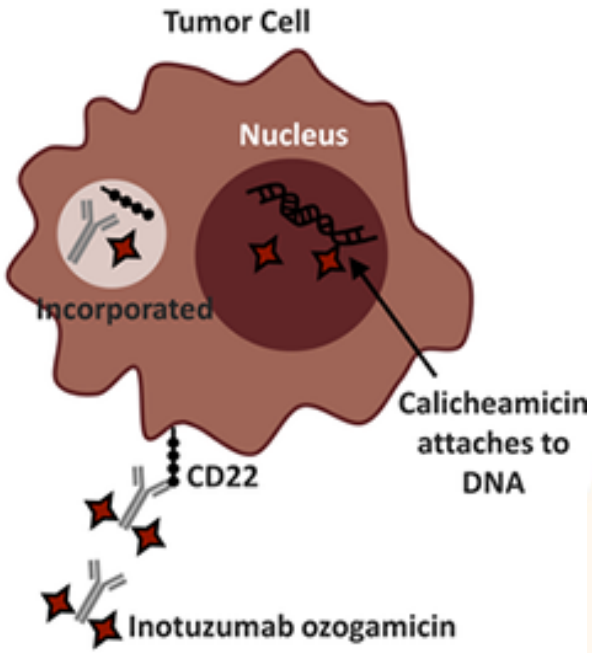
IDHIFA (enasidenib) [Package insert]. Summit, NJ; 2017

Enasidenib (Idhifa®)

- Approved indication: IDH2 mutated relapsed/refractory AML
- Dose: 100 mg once daily
- ADEs: electrolyte abnormalities, nausea, diarrhea, hepatotoxicity, leukocytosis, differentiation syndrome
  - Leukocytosis: possible hydroxyurea
  - Differentiation syndrome: possible dexamethasone, treatment interruption
  - Other grade 3-4: hold, resume at 50 mg, increase to 100 mg
- Pharmacokinetics: hepatic metabolism, several CYP enzymes; < 1% urine excretion of unchanged drug

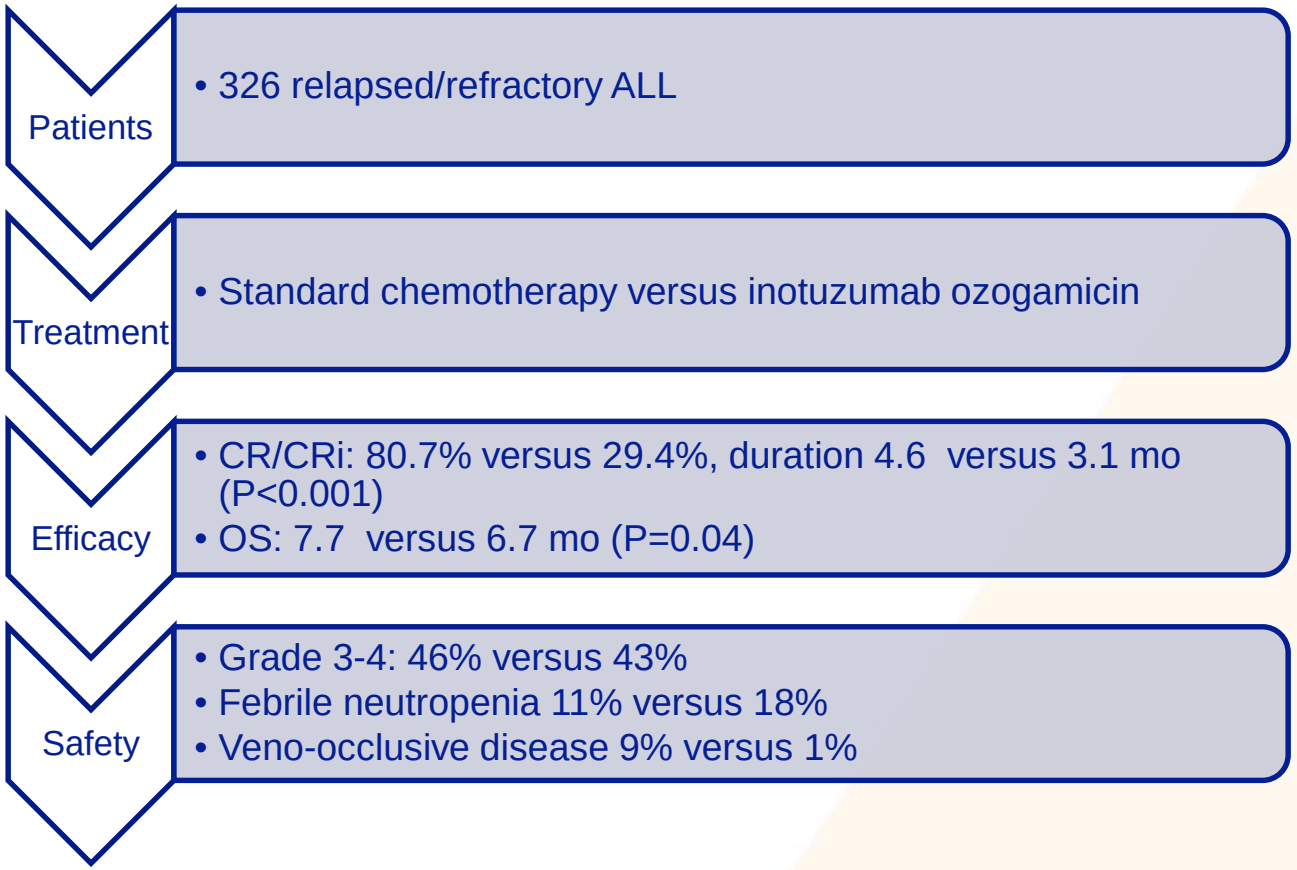
IDHIFA (enasidenib) [Package insert]. Summit, NJ; 2017

Anti-CD22 Antibody Drug Conjugate – inotuzumab ozogamicin



Jabbour E, et al. ASH Annual Meeting 2014. Abstract 794

Inotuzumab-ozogamicin (Besponsa®)



N Engl J Med 2016;375:740-53

Inotuzumab-ozogamicin (Besponsa®)

- Approved indication: relapsed/refractory B-cell ALL
- Dose:
  - Cycle 1: 0.8 mg/m^2 day 1, 0.5 mg/m^2 days 8 and 15 of a 21 day cycle
  - Subsequent cycles:
    - CR or CRi: 0.5 mg/m^2 on days 1, 8 and 15 - 28 day cycle
    - NO CR/CRi: 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15 – 28 day cycle; up to 3 cycles
  - Treatment duration:
    - HSCT: 2 cycles, consider 3rd if NO CR/CRi & MRD (-)
    - No HSCT: up to 6 cycles

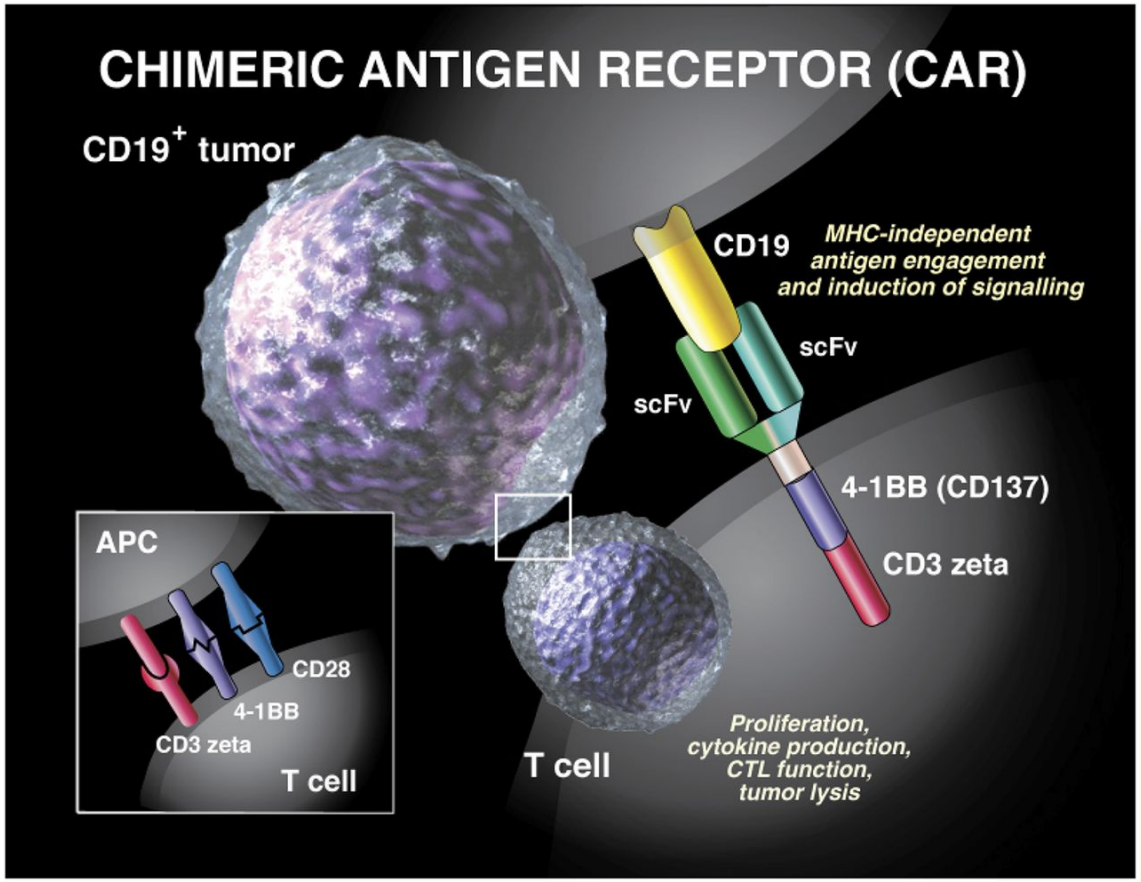
BESPONSA (inotuzumab) [package insert]. Philadelphia, PA; 2017

Inotuzumab-ozogamicin (Besponsa®)

- Administration
  - Infused over 1 hour
  - Premedications: dexamethasone, acetaminophen, and diphenhydramine
  - Pre-treatment for WBC > 10,000: hydroxyurea, steroids, and/or vincristine
- ADEs: myelosuppression, veno-occlusive disease and hepatotoxicity
- No dose adjustments – hold or discontinue
  - Grade 2 hepatotoxicity
  - Grade 3 neutropenia, thrombocytopenia

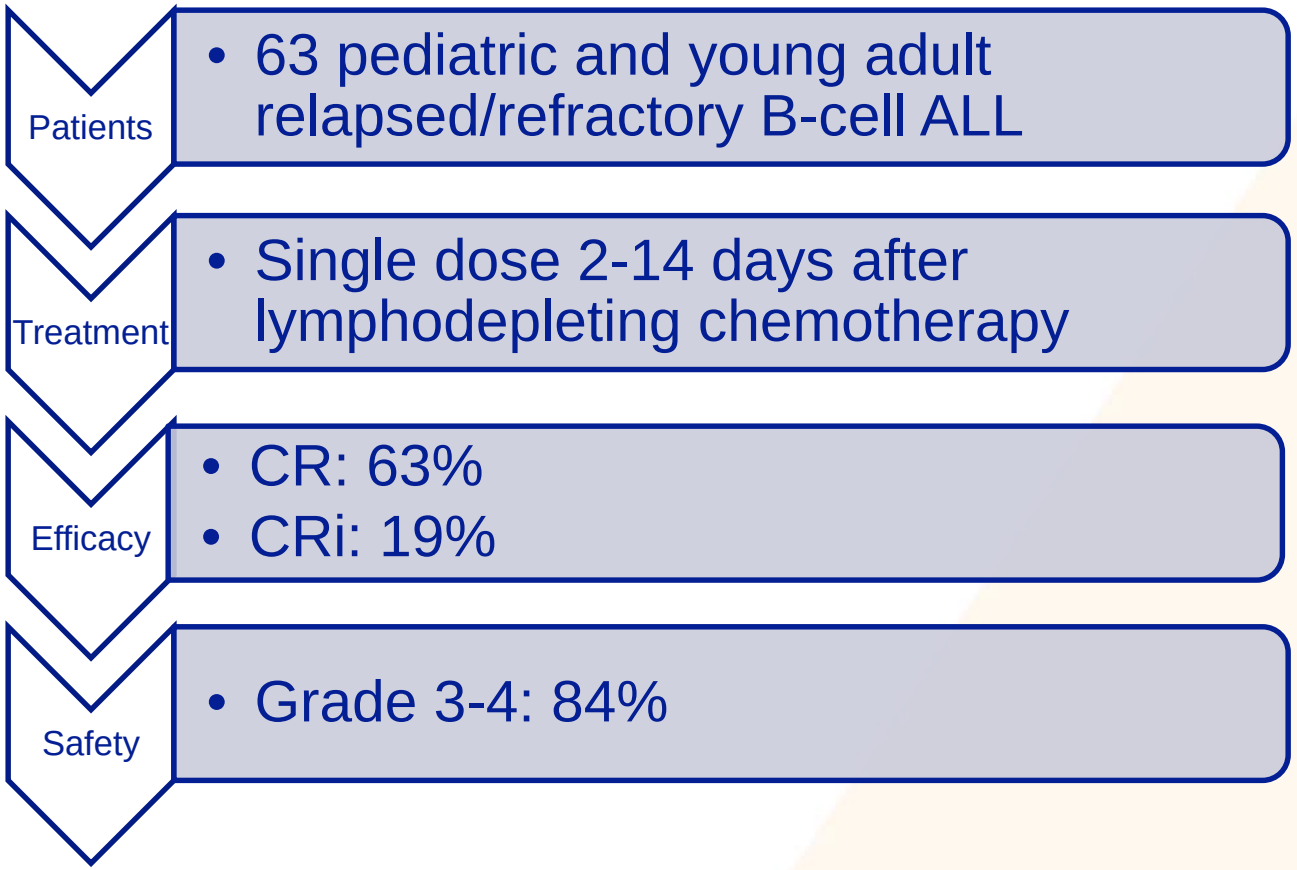
BESPONSA (inotuzumab) [package insert]. Philadelphia, PA; 2017

Tisagenlecleucel (Kymriah®)



Blood 2015;125:4017-4023

Tisagenlecleucel (Kymriah®)



KYMRIAH (tisagenlecleucel) [package insert]. East Hanover, NJ; 2017

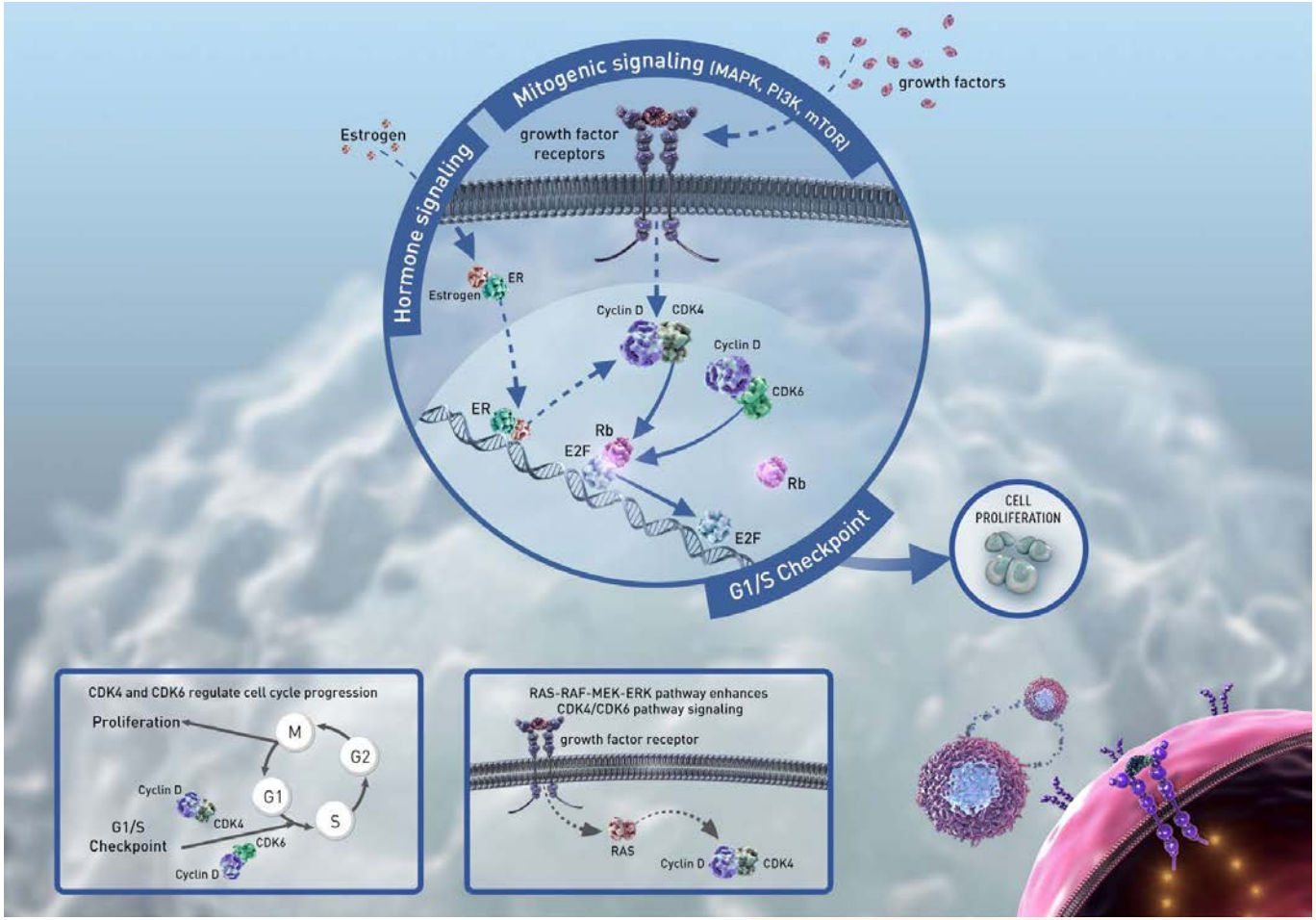
Tisagenlecleucel (Kymriah®)

- Approved indication: Relapsed/refractory B-cell ALL (patients up to 25 years old)
- Dose: 0.2 to 5.0 x 10^6 transduced viable T cells/kg for patients ≤50 kg and 0.1 to 2.5 x 10^8 transduced viable T cells/kg for those >50 kg
- ADEs: cytokine release syndrome, febrile neutropenia, hypotension, AKI, fever, neurotoxicity
  - CRS: expanded indication for tocilizumab to include severe CRS in patients ≥ 2 years old

KYMRIAH (tisagenlecleucel) [package insert]. East Hanover, NJ; 2017

“ME-TOO”

CDK 4/6 Inhibitors – ribociclib and abemaciclib



J Clin Oncol 2006;24(11):1770-1783

Ribociclib (Kisqali®)

Patients

- 668 post-menopausal HR+/HER2- metastatic breast cancer

Treatment

- Ribociclib 600 mg daily + letrozole versus placebo + letrozole

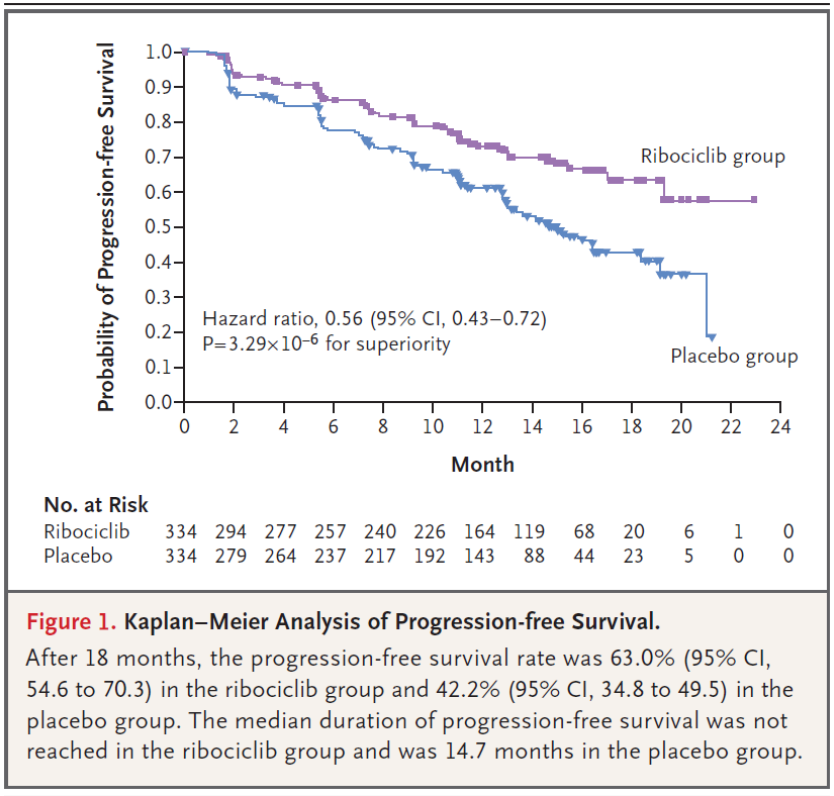


Figure 1. Kaplan–Meier Analysis of Progression-free Survival.
After 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. The median duration of progression-free survival was not reached in the ribociclib group and was 14.7 months in the placebo group.

N Engl J Med 2016;375(18):1738-48

Ribociclib (Kisqali®)

- Approved indication: HR+, HER2- metastatic breast cancer (+ an AI)
- Dose: 600 mg daily, days 1-21 every 28 days
- ADEs: QTc prolongation, neutropenia, hepatotoxicity, fatigue, hair thinning, nausea
  - ECG prior to treatment, and days 14 and 29 and electrolytes day 1 X 6 cycles
  - CBC every 2 weeks X 2 cycles then monthly
  - LFTs every 2 weeks X 2 cycles then monthly

KISQALI (ribociclib) [package insert]. East Hanover, NJ; 2017

Ribociclib (Kisqali®)

- Pharmacokinetics
  - Hepatic metabolism
    - Primarily CYP 3A4
    - Child-Pugh B or C: reduce starting dose to 400 mg
  - 12% urine excretion as parent drug
- Dose modifications: 400 mg then 200 mg
  - Strong CYP 3A4 inhibitors
  - Hepatotoxicity (grade 2-3)
  - Neutropenia (grade 3-4)
  - QT prolongation (grade 2-3)

KISQALI (ribociclib) [package insert]. East Hanover, NJ; 2017

Abemaciclib (Verzenio®)

Patients	• 132 metastatic HR+, HER2- (prior endocrine & chemo)	• 669 metastatic HR+, HER2- (prior endocrine)
Treatment	• 200 mg twice daily	• 150 mg twice daily + fulvestrant versus placebo + fulvestrant
Efficacy	• ORR: 19.7%, CBR: 42.4% • PFS: 6.0 mo, OS: 17.7 mo	• PFS: 16.4 versus 9.3 mo (p<.001) • ORR: 48.1% versus 21.3%
Safety	• Diarrhea, fatigue, nausea	• Diarrhea, neutropenia, nausea, fatigue

Clin Cancer Res 2017;23(17):5218-5224
J Clin Oncol 2017;35(25):2875-2884

Abemaciclib (Verzenio®)

- Approved indication:
  - 2nd line HR+, HER2- metastatic breast cancer (+ faslodex)
  - 3rd line HR+, HER2- metastatic breast cancer
- Dose:
  - 150 mg twice daily in combination with faslodex
  - 200 mg twice daily as monotherapy
- ADEs: diarrhea, neutropenia, hepatotoxicity, fatigue, nausea, VTE
  - CBC every 2 weeks X 2 months then monthly
  - LFTs every 2 weeks X 2 months then monthly

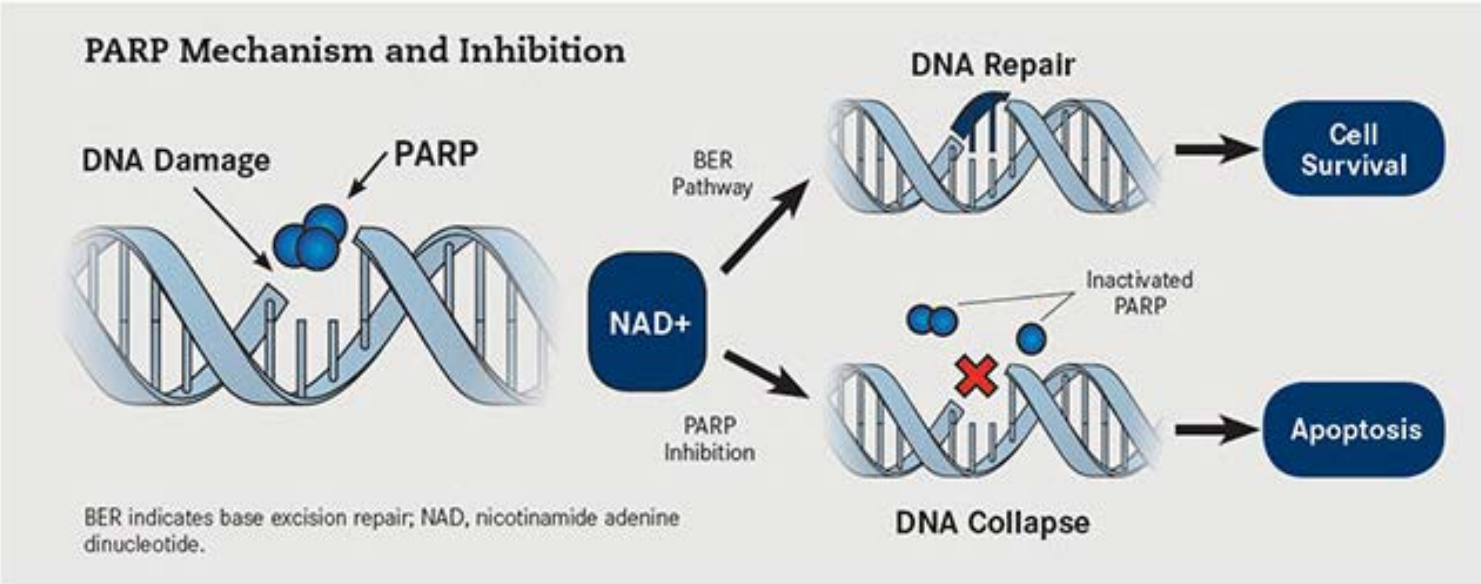
VERZENIO (abemaciclib) [package insert]. Indianapolis, IN; 2017

Abemaciclib (Verzenio®)

- Pharmacokinetics
  - Hepatic metabolism
    - Primarily CYP 3A4
    - Child-Pugh C: reduce starting dose to once daily
  - 3% urine excretion
- Dose modifications: 150 mg, 100 mg, 50 mg
  - Strong CYP 3A4 inhibitors
  - Neutropenia (grade 3-4)
  - Diarrhea (grade 3-4)
  - Hepatotoxicity (grade 2-3)

VERZENIO (abemaciclib) [package insert]. Indianapolis, IN; 2017

PARP Inhibitor – niraparib



http://www.onclive.com/publications/oncology-live/2013/august-2013/new-life-for-parp-inhibitors-emerging-agents-leave-mark-at-asco

Niraparib (Zejula®)

Patients
- 553 patients with platinum-sensitive, recurrent ovarian cancer

Treatment
- Niraparib 300 mg versus placebo daily

Efficacy
- PFS: gBRCA – 21 versus 5.5 mo; non-BRCA – 12.9 versus 3.9 mo (P<0.001)

Safety
- Grade 3-4: thrombocytopenia – 34%, anemia – 25%, neutropenia – 20%

N Engl J Med 2016;375(22):2154-64

Niraparib (Zejula®)

- Approved indication: maintenance treatment
  - Recurrent epithelial ovarian/fallopian tube or primary peritoneal cancer
  - Complete or partial response to platinum-based chemotherapy
- Dose: 300 mg once daily
  - Consider nightly dosing to decrease nausea
- Start within 8 weeks of most recent platinum containing regimen

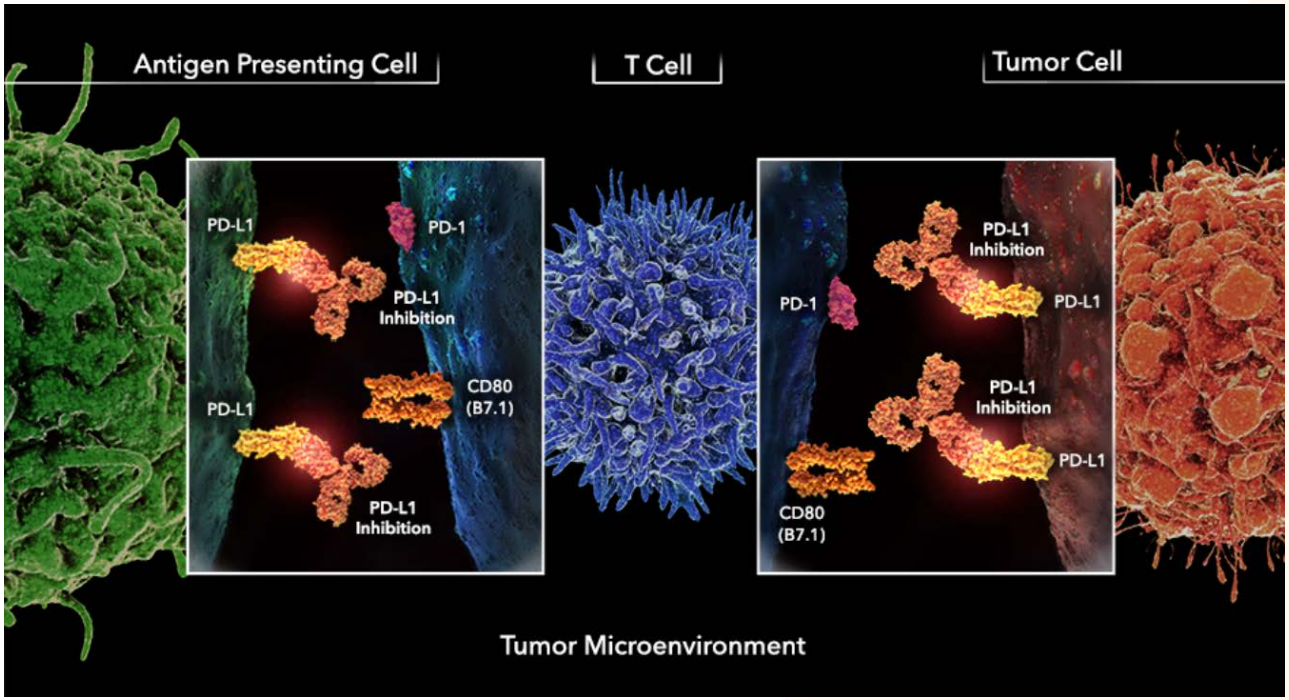
ZEJULA (niraparib) [package insert]. Waltham, MA; 2017

Niraparib (Zejula®)

- ADEs: myelosuppression, nausea, hypertension, hepatotoxicity
  - CBC weekly X 4, then monthly
  - Monitor blood pressure monthly
- Pharmacokinetics: hepatic metabolism (no CYP concerns); 11% excretion unchanged drug in urine
- Dose modifications: 200 mg then 100 mg
  - Grade 3 neutropenia or anemia
  - Grade 2 thrombocytopenia

ZEJULA (niraparib) [package insert]. Waltham, MA; 2017

PD-L1 Inhibitors: avelumab and durvalumab



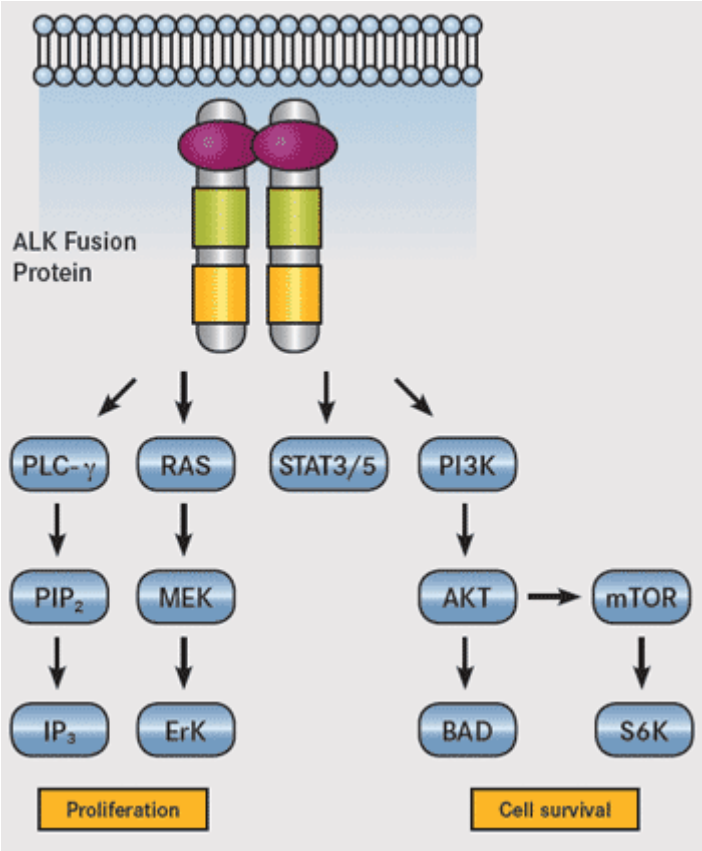
https://www.azimmuno-oncology.com/immuno-oncology-pathways/pd-l1-inhibition.html

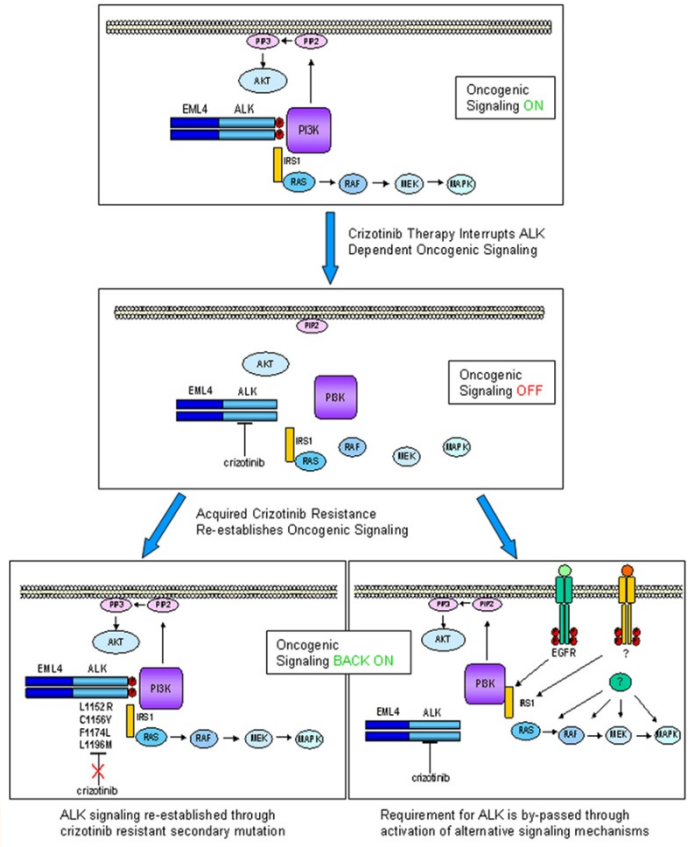
Avelumab (Bavencio®) and Durvalumab (Imfinzi®)

- Approved indication: locally advanced/metastatic urothelial carcinoma, metastatic merkel cell carcinoma (avelumab)
- Dose: 10 mg/kg over 60 minutes every 2 weeks
- ADEs: infusion reactions and immune-mediated
  - Pre-medicate with antihistamine and acetaminophen
  - Can discontinue pre-medications after 4 infusions

BAVENCIO (avelumab) [package insert]. Rockland, MA; 2017
IMFINZI (durvalumab) [package insert]. Wilmington, DE; 2017

ALK Inhibitor – brigatinib





http://journal.frontiersin.org/article/10.3389/fonc.2012.00017/full
http://www.onclive.com/publications/oncology-live/2012/august-2012/alk-inhibitors-moving-rapidly-from-discovery-to-clinical-approval-and-beyond

Brigatinib (Alunbrig®)

Patients
- 222 patients with ALK+ NSCLC following progression on crizotinib

Treatment
- Brigatinib 90 mg or 180 mg daily

Efficacy
- ORR: 52% (4 CRs in 180mg,1 CR in 90mg); duration of response: 13.8 mo
- 1-yr PFS: 39% versus 54% with 45% reduction in PD or death with higher dose
- 1-yr OS: 71% versus 80%

Safety
- Grade 3-4: CPK elevation – 3-9%, HTN – 6%

ALUNBRIG (brigatinib) [package insert]. Cambridge, MA; 2017

Brigatinib (Alunbrig®)

- Approved indication: metastatic NSCLC, ALK+, after progression on crizotinib
- Dose: 90 mg daily X 1 week, 180 mg daily
- ADEs: hypertension, nausea, CPK elevation, increased glucose and lipase/amylase, visual disturbances, bradycardia
  - Monitor BP monthly

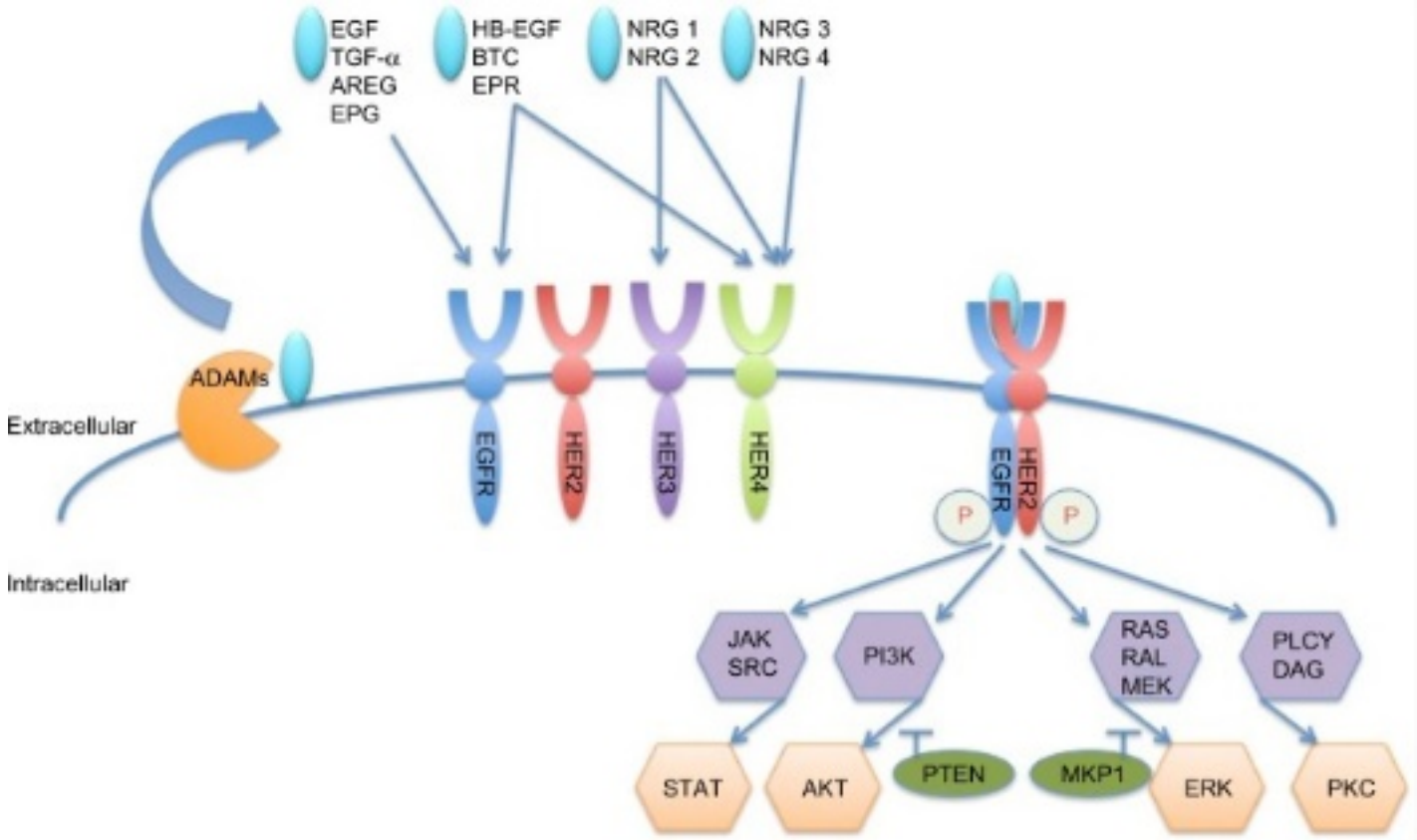
ALUNBRIG (brigatinib) [package insert]. Cambridge, MA; 2017

Brigatinib (Alunbrig®)

- Pharmacokinetics: hepatic metabolism, CYP 3A4, 21% urine excretion as parent drug
- Dose modifications: 180 mg, 120 mg, 90 mg, 60 mg
  - Strong 3A4 inhibitors
  - Grade 3 hypertension or ocular toxicity
  - Symptomatic bradycardia
  - Grade 3 CPK or amylase/lipase elevation, hyperglycemia

ALUNBRIG (brigatinib) [package insert]. Cambridge, MA; 2017

Pan-HER Inhibitor - neratinib



Breast Cancer 2015;7:147-162

Neratinib (Nerlynx®)

Patients
- 2,840 stage 1-3 HER2+ breast cancer, completed adjuvant trastuzumab

Treatment
- Neratinib 240 mg versus placebo daily

Efficacy
- 2-yr DFS: 93.9% versus 91.6%

Safety
- Grade 3 diarrhea in 40% of patients

Lancet Oncol 2016;17:367-77

Neratinib (Nerlynx®)

- Approved indication: extended adjuvant treatment in HER2+ following trastuzumab
- Dose: 240 mg once daily X 1 year
  - Take with food
  - Avoid acid suppression
- ADEs: diarrhea, rash, fatigue
  - Anti-diarrheal prophylaxis with loperamide recommended for 1st two cycles
    - 4 mg TID X 2 weeks
    - 4 mg BID X 6 weeks

NERLYNX (neratinib) [package insert]. Los Angeles, CA; 2017

Neratinib (Nerlynx®)

- Pharmacokinetics: hepatic metabolism (3A4)
  - Child Pugh C – reduce initial dose to 80 mg
  - CYP 3A4 drug interactions
  - < 1% renal excretion
- Dose modifications: 200 mg, 160 mg, 120 mg
  - Diarrhea (grade 2, ≥ 5 days or grade 3, ≥ 2 days)
  - Grade 3 hepatotoxicity

NERLYNX (neratinib) [package insert]. Los Angeles, CA; 2017

Liposomal Daunorubicin and Cytarabine (Vyxeos®)

Patients
- 309 patients 60-75 years old, newly diagnosed therapy-related AML or AML with myelodysplasia related changes

Treatment
- Liposomal versus standard 7+3

Efficacy
- OS: 9.6 mo versus 5.9 mo (p=0.005)

Safety
- Decreased hematologic toxicity including grade 3 hemorrhage and thrombocytopenia and grade 4 neutropenia

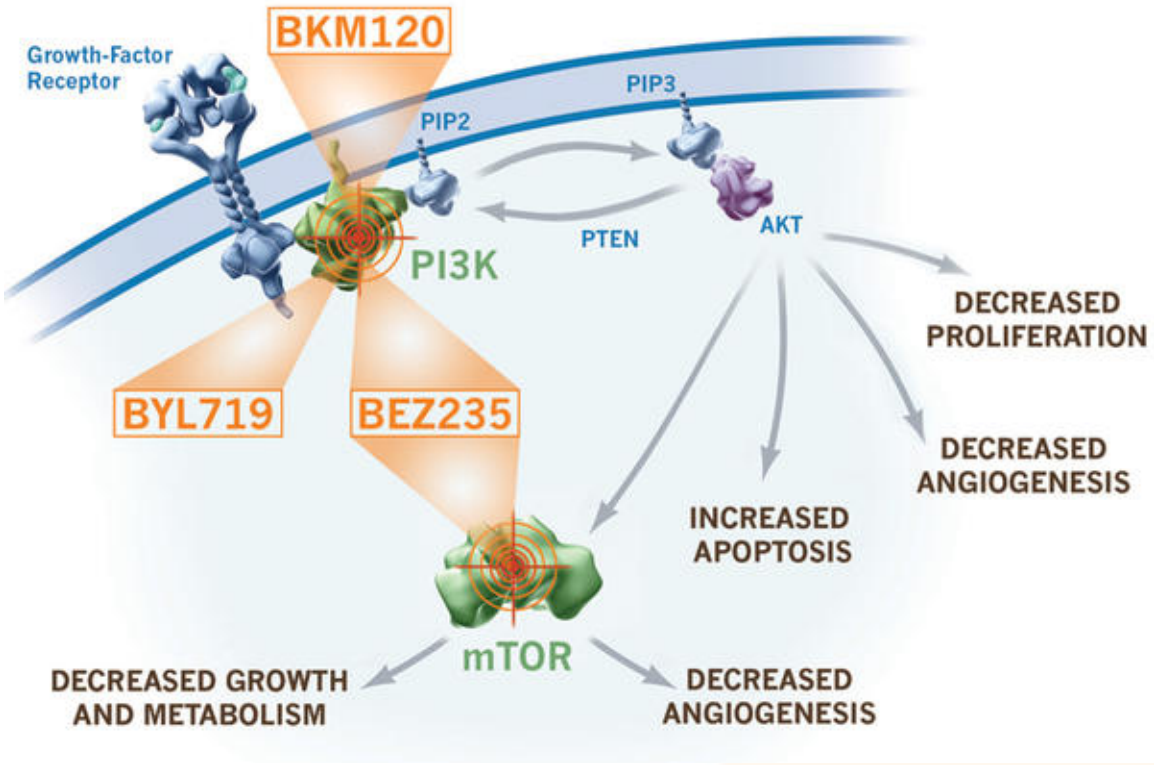
VYXEOS (liposome daunorubicin-cytarabine) [package insert]. Palo Alto, CA; 2017

Liposomal Daunorubicin and Cytarabine (Vyxeos®)

- Approved indication: t-AML or with myelodysplasia-related changes
- Dose:
  - Induction (first cycle): daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 days 1, 3, and 5
  - Induction (second cycle if no remission): days 1 and 3
  - Consolidation: daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 days 1 and 3
- ADEs: myelosuppression, cardiotoxicity, nausea, diarrhea, infusion reactions
- No studies in CrCl < 30 ml/min or total bilirubin > 3

VYXEOS (liposome daunorubicin-cytarabine) [package insert]. Palo Alto, CA; 2017

Copanlisib (Aliqopa®)



https://www.dddmag.com/article/2012/06/targeting-pi3k-key-survival-gene-solid-tumor-cancers

Copanlisib (Aliqopa®)

Patients

- 142 patients with relapsed or refractory of at least 2 prior lines of therapy for FL, MZL, SLL, or WM

Treatment

- 60 mg on days 1, 8, 15 every 28 days

Efficacy

- ORR: 59.2% (12% CR)
- PFS: 11.2 mo

ALIQOPA (copanlisib) [package insert]. Whippany, NJ; 2017

Copanlisib (Aliqopa®)

- Approved indication: Relapsed follicular lymphoma, 3rd-line
- Dose: 60 mg over 1 hour on days 1, 8, and 15 of a 28-day cycle (3 weeks on and 1 week off)
- ADEs: myelosuppression, hyperglycemia, hypertension, nausea, diarrhea, fatigue, pneumonitis

ALIQOPA (copanlisib) [package insert]. Whippany, NJ; 2017

Copanlisib (Aliqopa®)

- Pharmacokinetics: hepatic metabolism (3A4); < 5% unchanged in urine
- Dose modifications: 45 mg then 30 mg
  - CYP 3A4 inhibitors
  - Grade 4 hyperglycemia
  - Hypertension requiring an anti-hypertensive
  - Grade 4 neutropenia or thrombocytopenia

ALIQOPA (copanlisib) [package insert]. Whippany, NJ; 2017

Future Directions

- Combination targeted therapy
- Combination targeted therapy and immunotherapy
- Increased utilization of basket trials → drug approvals based on molecular markers opposed to tumor histology

Summary

- Drug approvals in 2017 continue the march towards personalized medicine in oncology
- Adverse events of targeted agents are unique to each mechanistic class and are ever-evolving
- Drug interactions and dose modifications are unique even within medication classes
- Current and future trials are continuing to advance the pursuit of personalized medicine

Assessment Question Answers

1. Which of the following best describes midostaurin's mechanism of action?
   a. IDH2 inhibitor
   b. FLT3 inhibitor
   c. PARP inhibitor
   d. PI3K inhibitor

2. Which of the following pairs describe enasidenib?
   a. FLT3 inhibitor and can cause differentiation syndrome
   b. Approved for ALL and can cause differentiation syndrome
   c. Approved for ALL and can cause cytokine release syndrome
   d. IDH2 inhibitor and can cause differentiation syndrome

Assessment Question Answers

3. Which toxicity should patients receiving inotuzumab-ozogamicin be closely monitored for?
   a. Nausea
   b. Nephrotoxicity
   c. Veno-occlusive disease
   d. Venous thromboembolism

4. What is the appropriate management of severe cytokine release syndrome due to CAR T-cell therapy?
   a. Watch and wait
   b. Steroids
   c. Antibiotics
   d. Tocilizumab

Assessment Question Answers

5. Niraparib requires a BRCA mutation to be effective in maintenance treatment of platinum-sensitive ovarian cancer
    a. True
    b. False

6. All of the following require a dose adjustment for CYP 3A4 inhibitors EXCEPT:
    a. Ribociclib
    b. Niraparib
    c. Brigatinib
    d. Copanlisib

7. Neratinib requires prophylaxis against which of the following toxicities?
    a. Nausea
    b. Diarrhea
    c. Constipation
    d. Infections

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