An Oncology Mouthful: Updates and Pearls for Oral Oncolytics

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Disclosures

- No financial conflicts to disclose

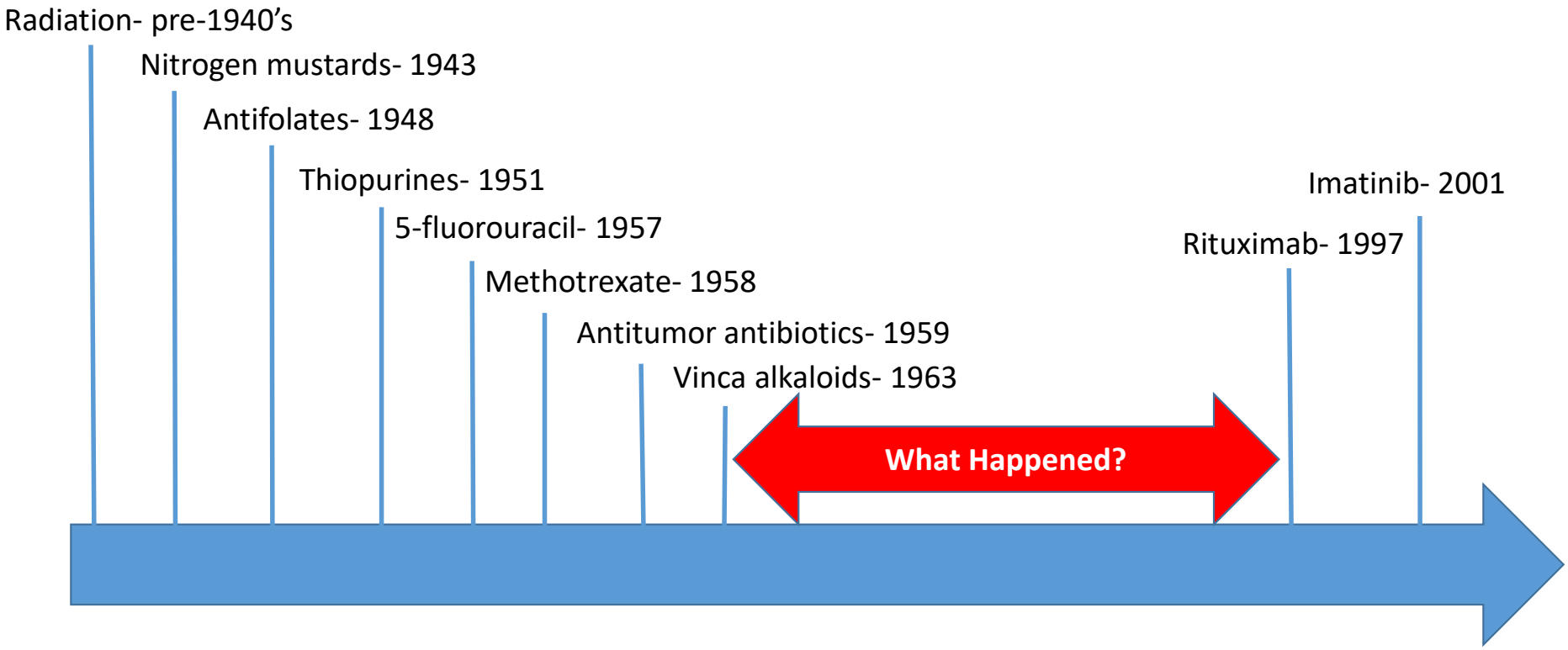
Pharmacist Objectives

- Discuss the role of oral oncolytics in the treatment of cancer
- Identify recently approved oral oncolytics and updates in approved indications
- Recognize common adverse events and management strategies for select oral oncolytics

Technician Objectives

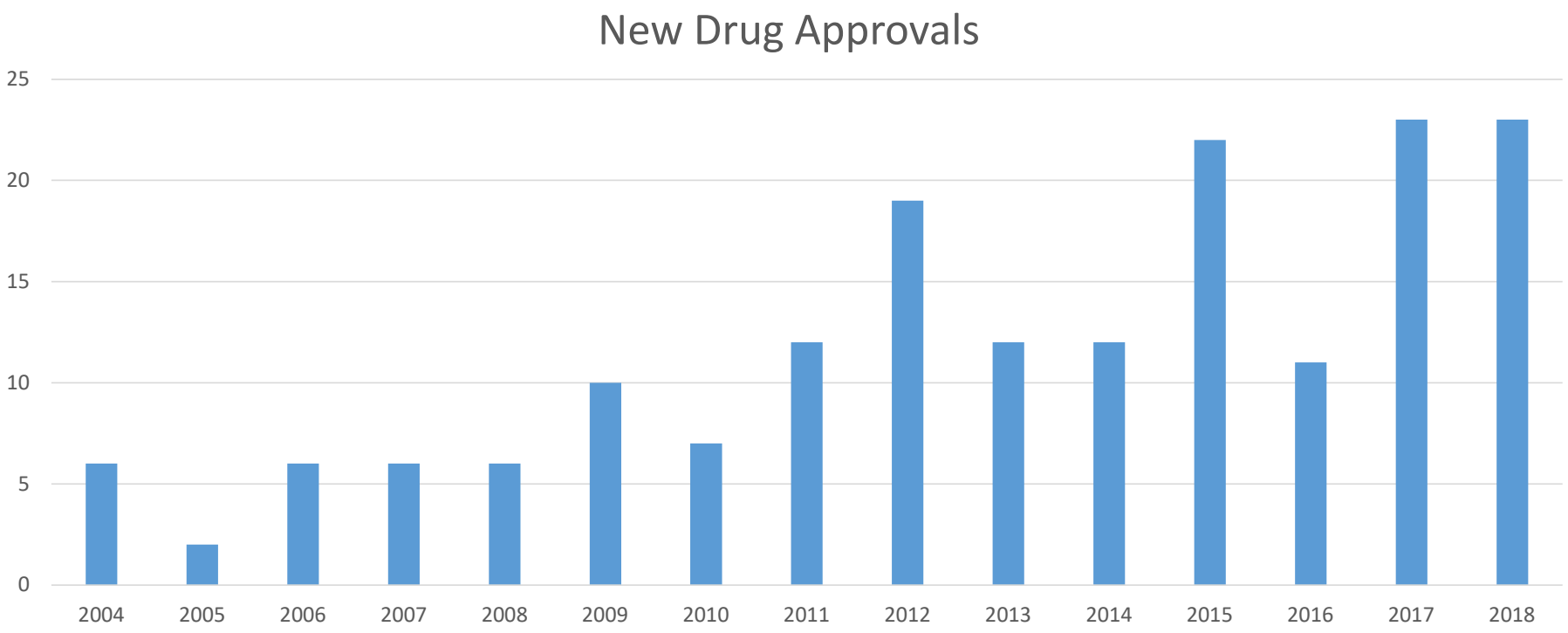
- Recognize oral oncolytics used in the treatment of cancer
- Identify recently approved oral oncolytics and updates in approved indications
- Recall common adverse events associated with oral oncolytics

Brief History of Cancer Treatment



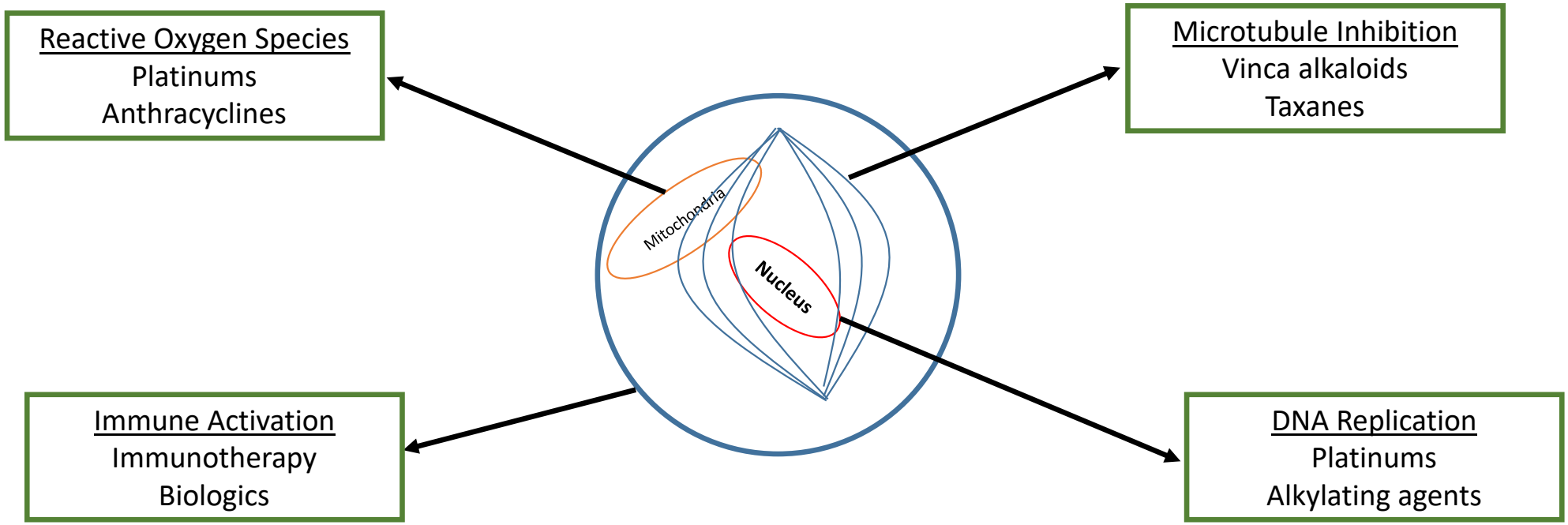
Devita, VT. Cancer Res. 2008;68:8643-8653.

Oncology Drug Approval Explosion



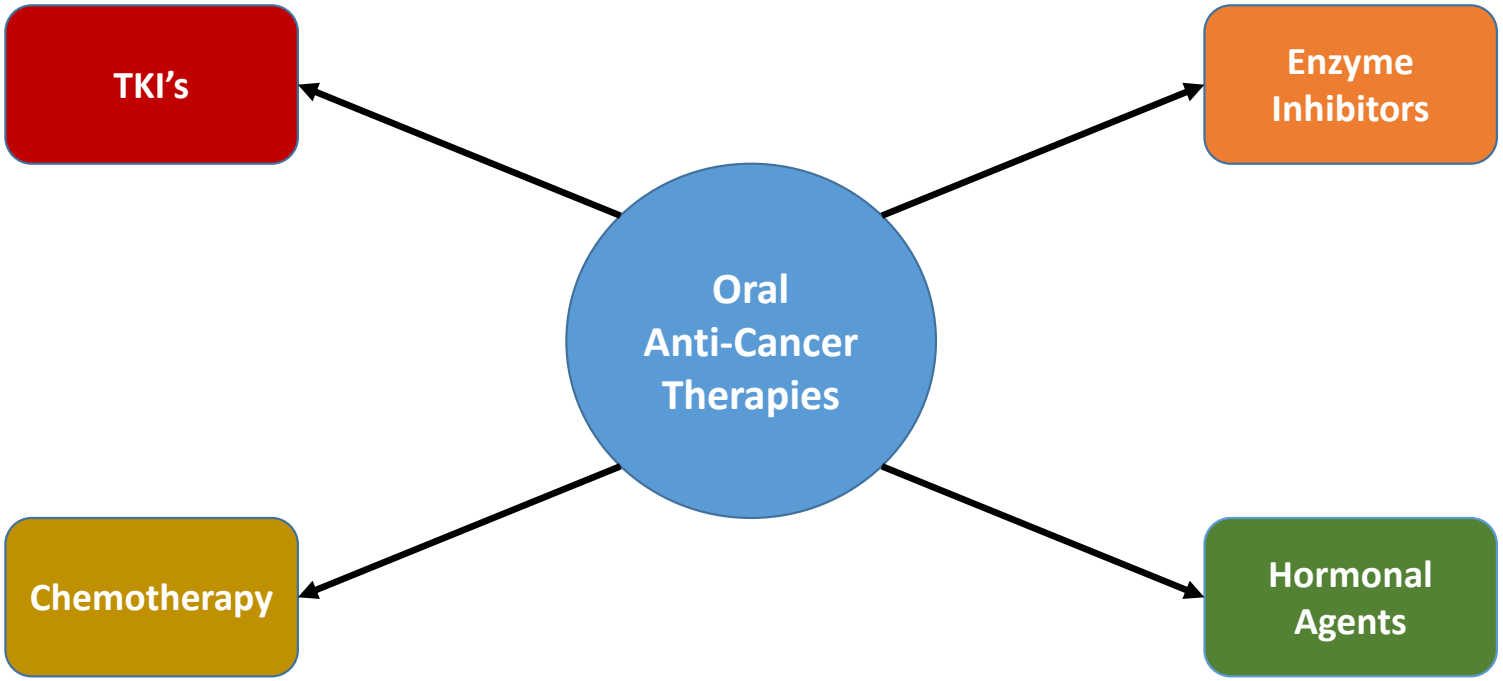
FDA Novel Drug Approvals. Accessed March 23, 2021.

Traditional Chemotherapy Mechanism

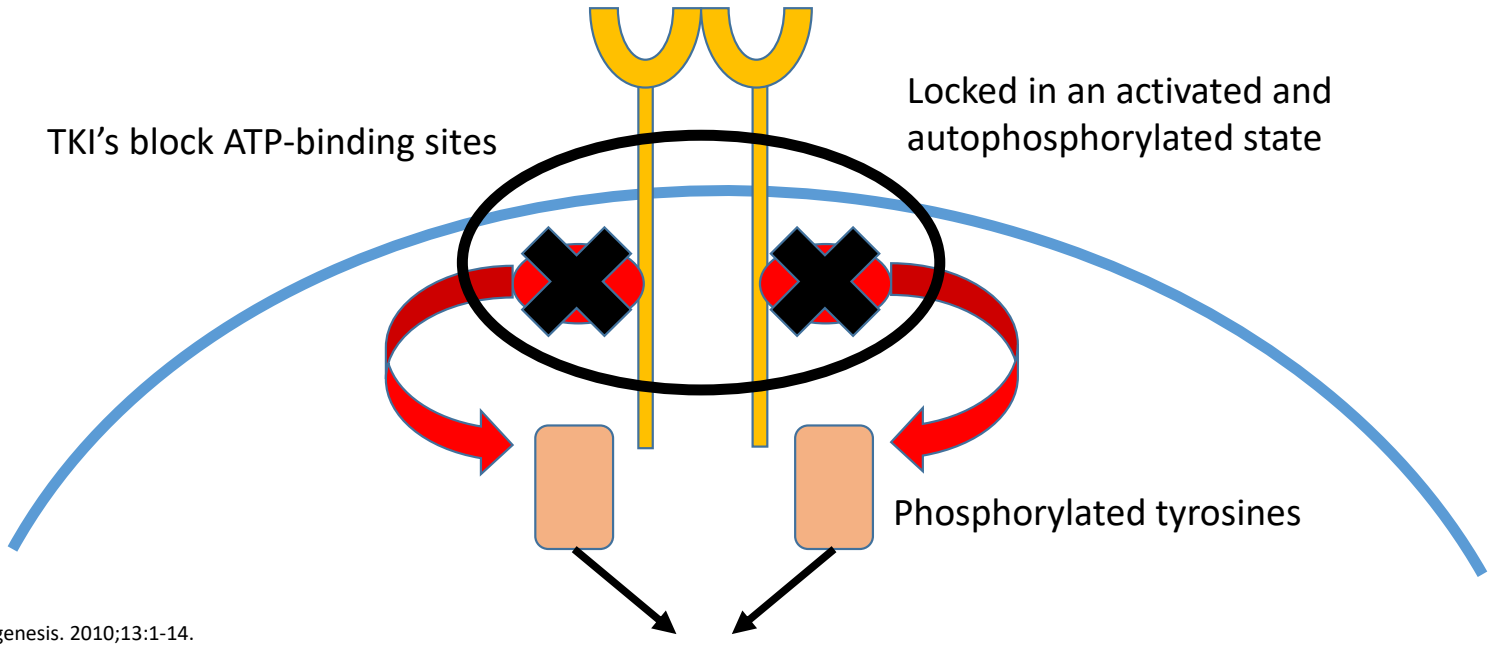


Starobova H. Front Mol Neurosci. 2017;10:1-21.

Oral Chemotherapy



Tyrosine Kinase Inhibitors

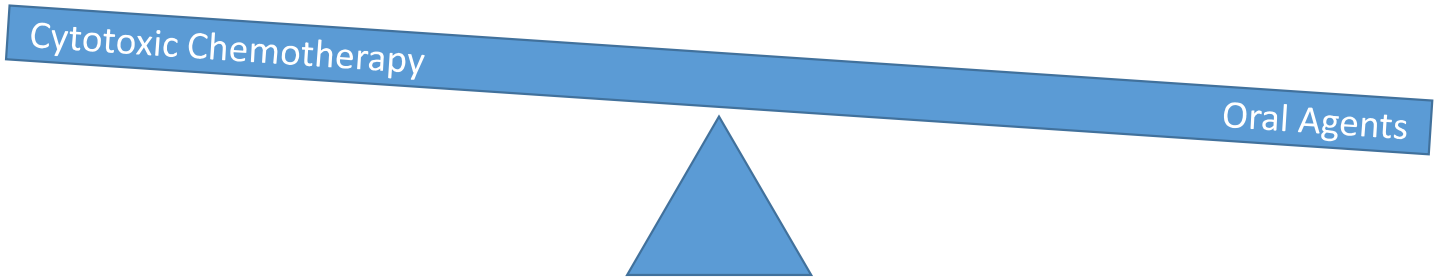


Gotink K. Angiogenesis. 2010;13:1-14.

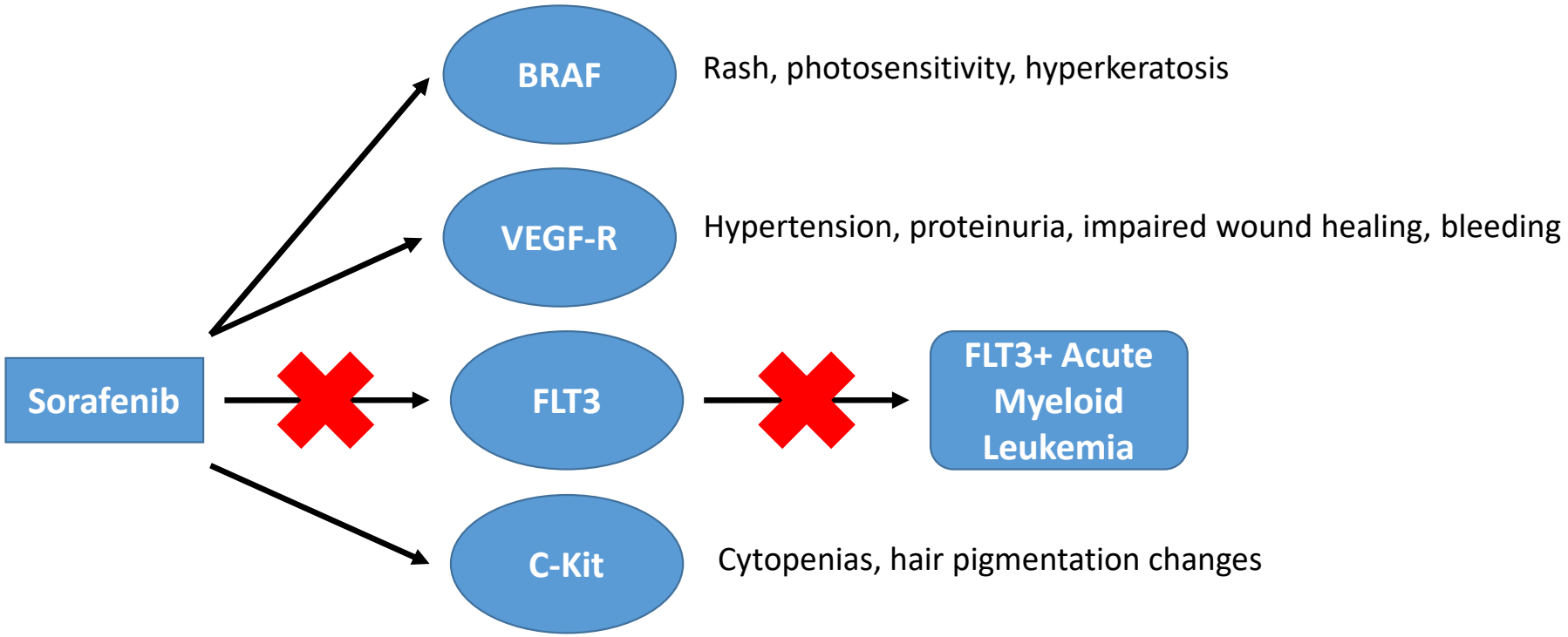
Oral Chemotherapy Easier to Stomach?

Nausea
Vomiting
Myelosuppression
Infections
Bleeding
Hair loss

Nausea
Vomiting
Handfoot syndrome
Rash
Hypertension
Thrombosis

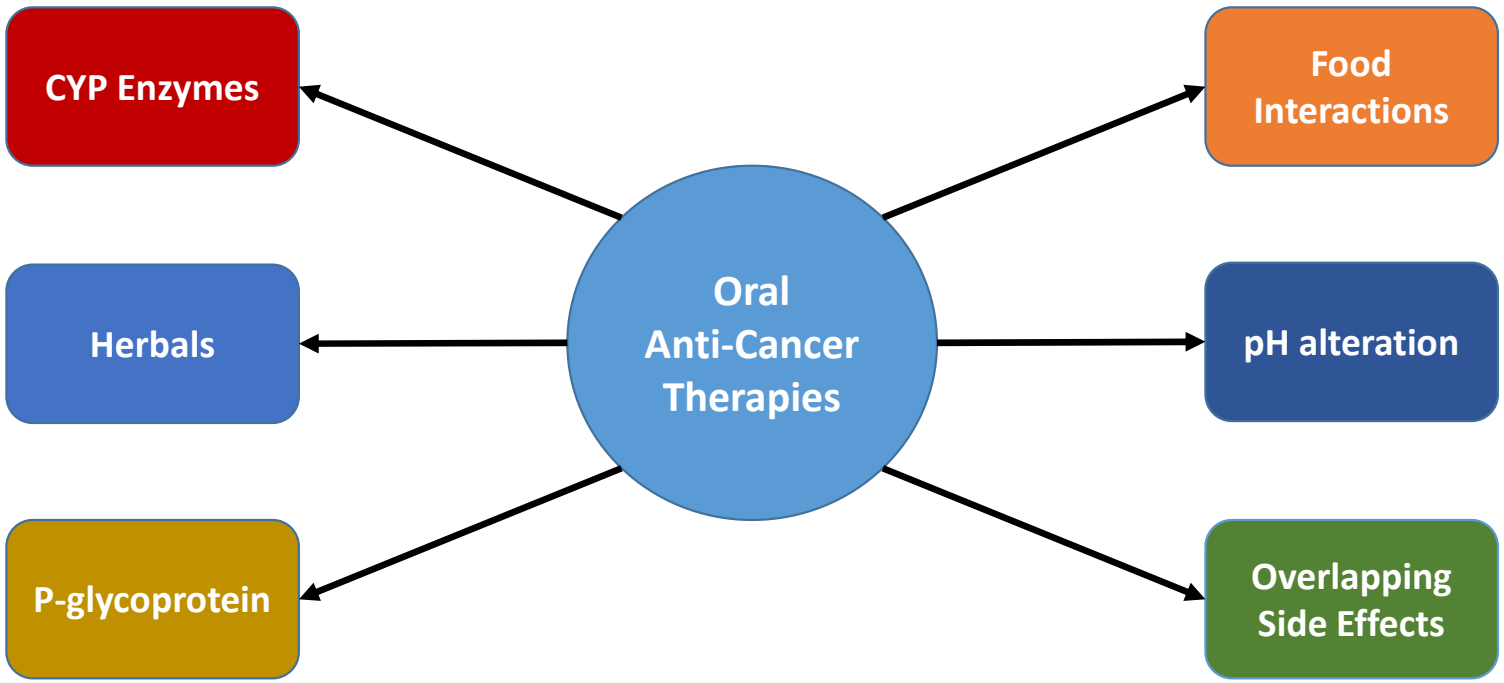


Wrong Site, Unwanted Effect



Dy G. CA Cancer J Clin. 2013;63:249-279.

Drug Interactions



Oral oncology drug = screen for drug interactions (especially CYP3A4)

Management of Drug-Interactions

- Complete a full medication review
  - Complete a medication reconciliation with the patient (including over the counter and herbals/supplements)
  - Call patient's pharmacy for a complete medication list
  - Review patient's medical records and clinic/hospital notes if available
    - Lab values, EKGs
- Consider patient specific factors
  - Bleeding risks, procedures, cancer type, underlying health conditions or anatomical abnormalities
- Complete a drug interaction analysis
  - Use multiple databases when possible
    - Be mindful of recent drug approvals not being added to databases

Rogala B. JCO. 2019;15:81-90.

Financial Toxicity of Oral Oncology Agents

- Oral oncology agents may reduce the overall healthcare resource utilization
  - Patient's required to visit infusion center less frequently, freeing up resources for other patients
- Costs for oral oncology agents is steadily increasing
  - From 2009 to 2010 costs of oral oncology agents increased ~17%
- Patient out-of-pocket cost can present a large financial burden
  - Approximately 10% of patients chose not to fill oral oncology prescriptions due to high-costs
  - Utilization of manufacturer copay cards can help bridge the cost of what insurance does not cover

Mancini R. Oncology. 2013;27(8).

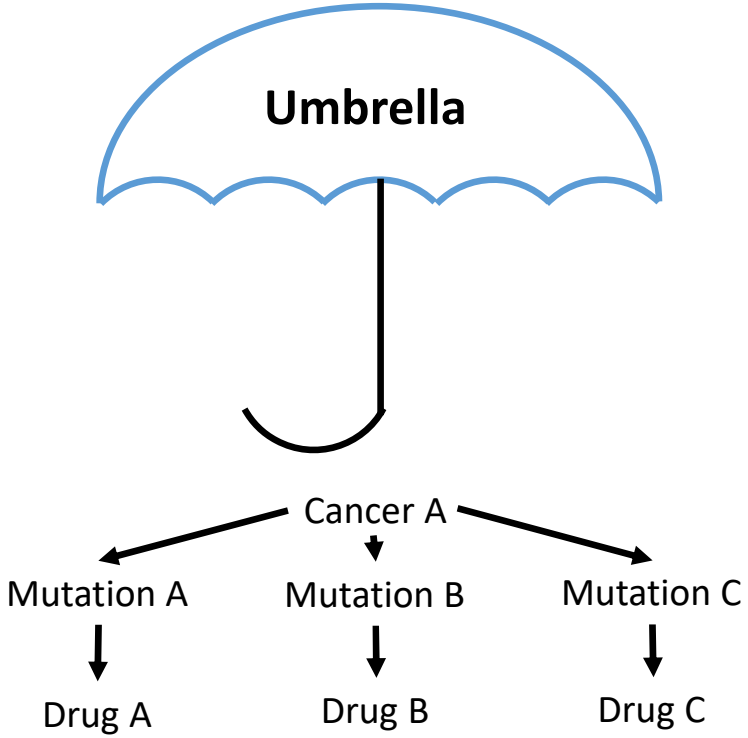
Quality of Life and Patient Preference

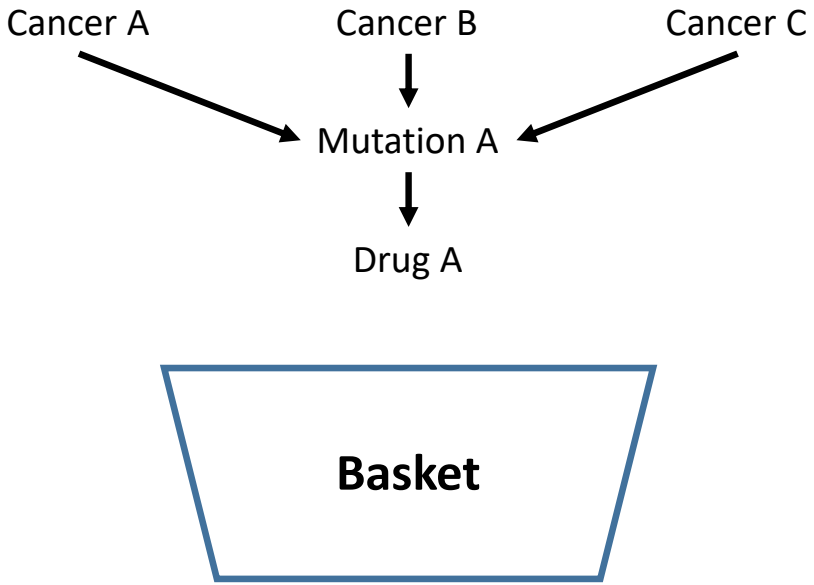
- Limited data exists to directly analyze patient quality of life while receiving intravenous vs. oral oncology treatments
  - Small studies suggest improved quality of life measures
- Adherence to oral regimens may be decreased as compared to intravenous regimens
  - More frequent administration or “on-off” cycles (administered 14 days our of a 21 day cycle) result in patients forgetting to take medication as prescribed
- Conflicting data on patient preferences of oral vs. intravenous regimens
  - Small studies suggest patient prefer oral treatments over intravenous treatments
  - Completion of treatment in 1 day, convenience of not going to infusion center

Jacobs J. J Natl Compr Canc Netw. 2019;17:221-228.

Trial Design- Beyond the Abstract

Oncology Clinical Trial Design





Syn N. Exp Op Drug Met & Tox. 2016;12.

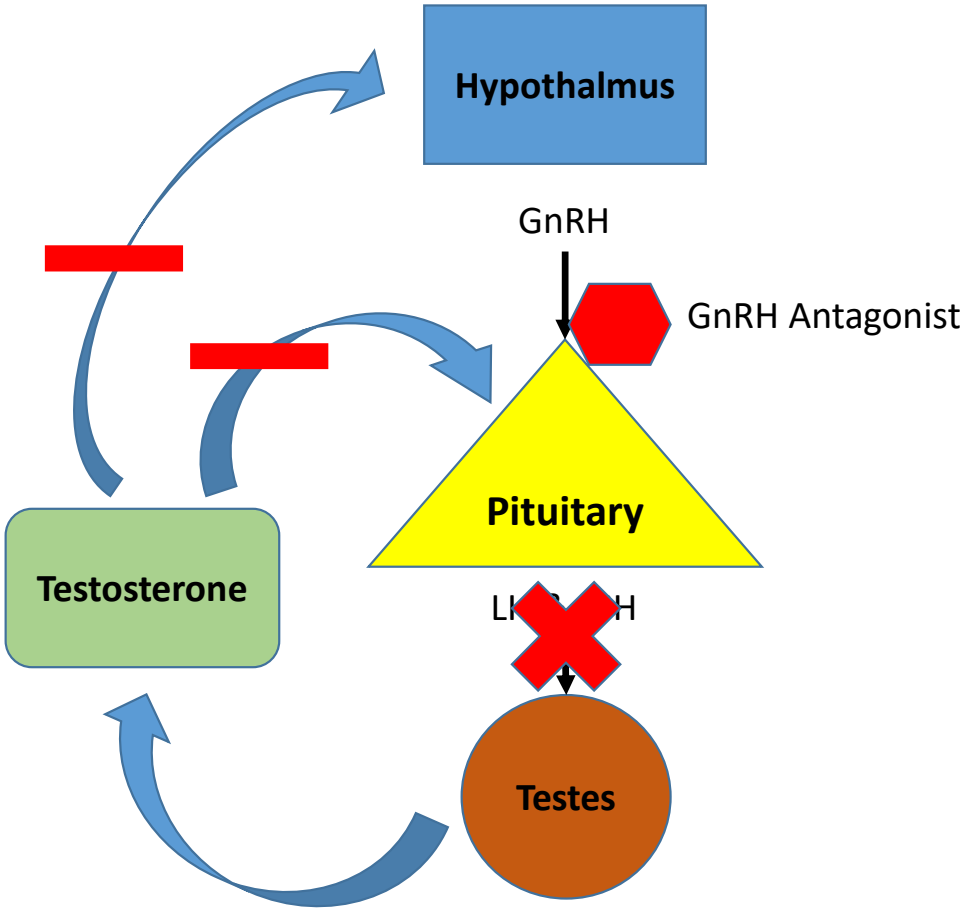
Progression Free Survival or Overall Survival?

	Overall Survival	Progression Free Survival
Use	Considered the gold standard endpoint	Emerging as a common endpoint in oncology
Definition	Time from random assignment to death	Time from assignment to disease progression
Advantages	Provides a clear-cut efficacy of the study drug in question	Allows for faster trial completion, and submission for drug-approval
Pitfalls	If a modest benefit is gained, it may take very large sample sizes or years of study duration to prove statistical significance	Has proven to be a valid surrogate endpoint in some tumor types, but not all
Takeaway	• Progression free survival has become a widely used endpoint in oncology clinical trials • Although it has proven to be a valid surrogate for overall survival in some disease states, the same has not been proven for others • Some targeted and biological therapies have shown low progression free survival, but prolonged overall survival	

Hess L. J Cancer. 2019;10:3717-3727.

Solid Tumors

Relugolix



Orgovyx (relugolix) [prescribing information]. Brisbane, CA: Myovant Sciences Inc; December 2020.

Relugolix

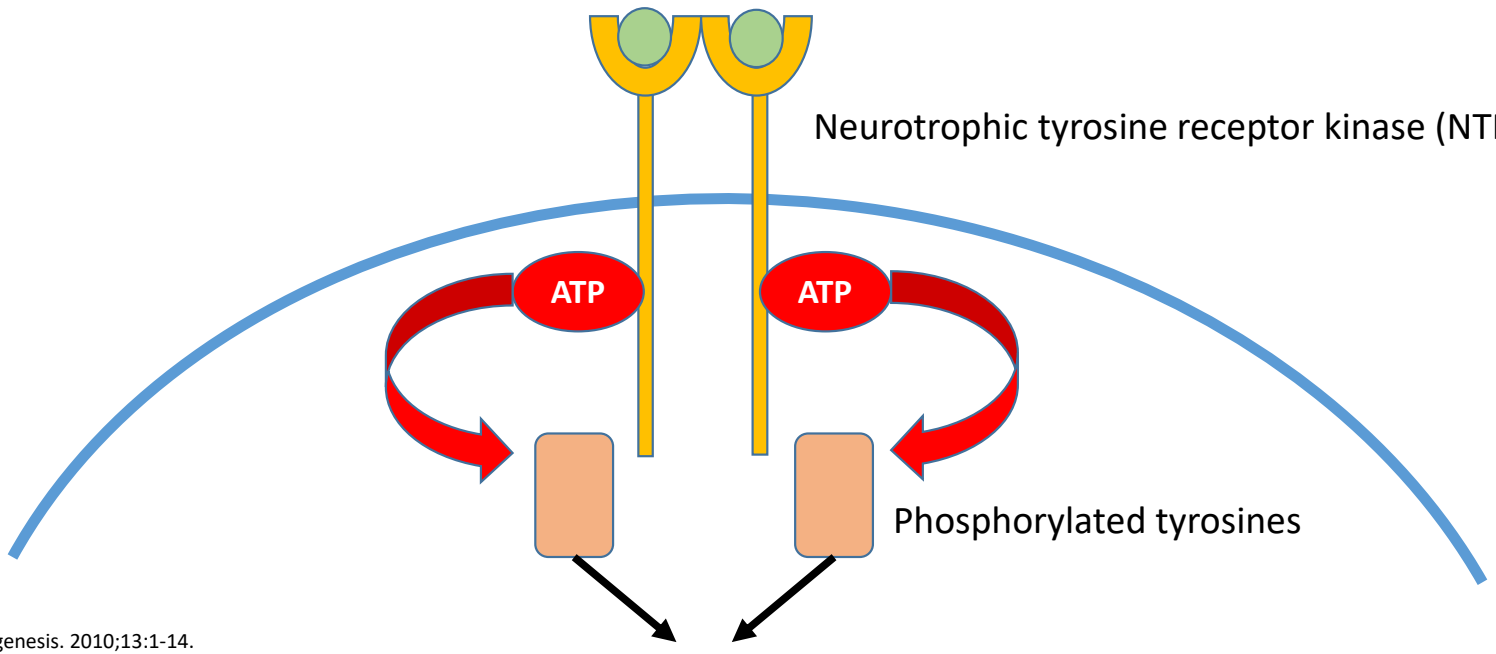
HERO	Shore, et al. NEJM. 2020.
Patient population	• n=622 • Patients with advanced prostate cancer
Intervention	2:1 randomized to 120 mg relugolix once daily vs. leuprolide injection every 3 months for 48 weeks
Primary endpoint	• Sustained testosterone response to castration levels (<50 ng/dL) 96.7% relugolix vs. 88.8% leuprolide (p<0.001)
Secondary endpoints: efficacy	• Castration at day 4: 56% relugolix vs. 0% leuprolide • Castration at day 12: 98.7% relugolix vs. 12% leuprolide • FSH levels at week 24: 1.72 IU/L relugolix vs. 5.95 IU/L leuprolide

Relugolix

- Administered as 360 mg on day 1, followed by 120 mg once daily on subsequent days
  - Trial specifically reported a 99% adherence rate
- Drug interactions:
  - Substrate of CYP2C8 (minor) & CYP3A4 (minor)
  - Qtc prolonging agents should be avoided
- Adverse reactions:
  - Hot flashes, diarrhea, arthralgia, fatigue, hypertension
  - Cardiovascular events (important factor in prostate cancer)

Orgovyx (relugolix) [prescribing information]. Brisbane, CA: Myovant Sciences Inc; December 2020.

Tyrosine Kinase Inhibitors- Entrectinib



Gotink K. Angiogenesis. 2010;13:1-14.

Entrectinib

	N=54
Overall Response Rate (95% CI)	57% (43, 71)*
Complete Response	7.4%
Partial Response	50%
Duration of Response*	**N = 31**
Range (months)	2.8, 26.0+
% with duration ≥ 6 months	68%
% with duration ≥ 9 months	61%
% with duration ≥ 12 months	45%

*53% ORR in patients who previously received therapy for metastatic disease
+ongoing response at study cutoff

Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; August 2019.

Entrectinib

Tumor Type	N=54	Overall Response Rate		DOR
		%	95% CI	Range (months)
Sarcoma	13	46	12%, 75%	2.8, 15.1
NSCLC	10	70	35%, 93%	1.9, 20.1
Salivary	7	86	42%, 100%	2.8, 16.5
Breast	6	83	36%, 100%	4.2, 14.8
Thyroid	5	20	NA	7.9
Colorectal	4	25	NA	4.8
Neuroendocrine	3	PR	NA	5.6
Pancreatic	3	PR	NA	7.1, 12.9
Gynecological	2	PR	NA	20.3
Cholangiocarcinoma	1	PR	NA	9.3

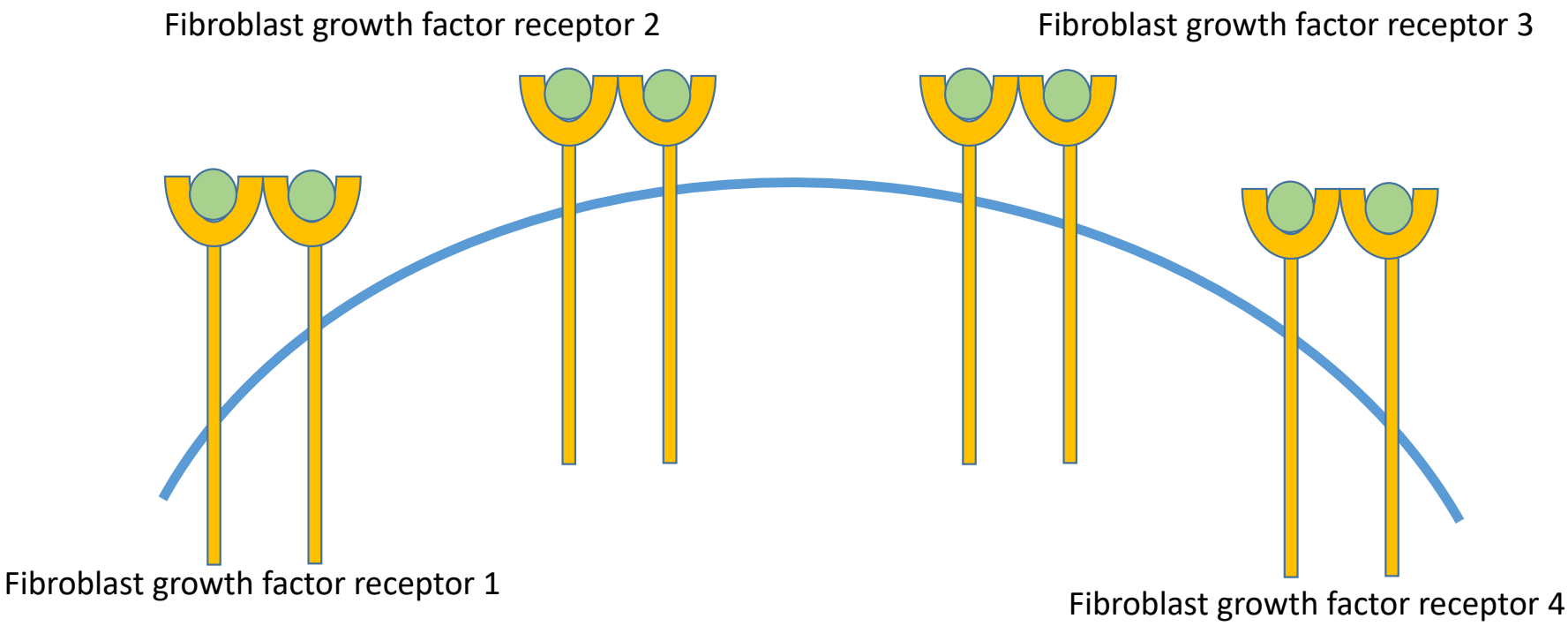
Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; August 2019.

Entrectinib

- FDA-approved for ROS1-positive metastatic non-small cell lung cancer and solid tumors with NTRK gene fusion
  - Dosed at 600 mg once daily until disease progression
  - Avoid grapefruit juice while taking entrectinib
- Substrate of CYP3A4 (major)
  - Avoid moderate CYP3A4 inhibitors or reduce dose to 200 mg daily
  - Avoid strong CYP3A4 inhibitors or reduce dose to 100 mg daily is BSA >1.5m^2
- Adverse reactions:
  - Fatigue, constipation, edema, diarrhea, nausea, increased weight, arthralgia, fevers
  - Congestive heart failure, CNS effects (cognitive impairment, dizziness, mood disorders, sleep disorders), fractures, hepatotoxicity, hyperuricemia, QTc prolongation

Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; August 2019.

Tyrosine Kinase Inhibitors- Erdafitinib



Balversa (erdafitinib) [prescribing information]. Horsham, PA: Janssen Products, LP; July 2020.

Erdafitinib

	Loriot, et al. NEJM. 2020.
Patient population	• N=99 • Locally advanced and unresectable or metastatic urothelial carcinoma

Intervention	• Phase 2, multicenter, international, open-label study
	• 28-day cycles of:
	  • 10 mg/day, 7 days on 7 days off
	  • 6 mg per day continuous

Primary endpoint	• Overall response rate
	  • 70%
	  • 3% complete response
	  • 37% partial response

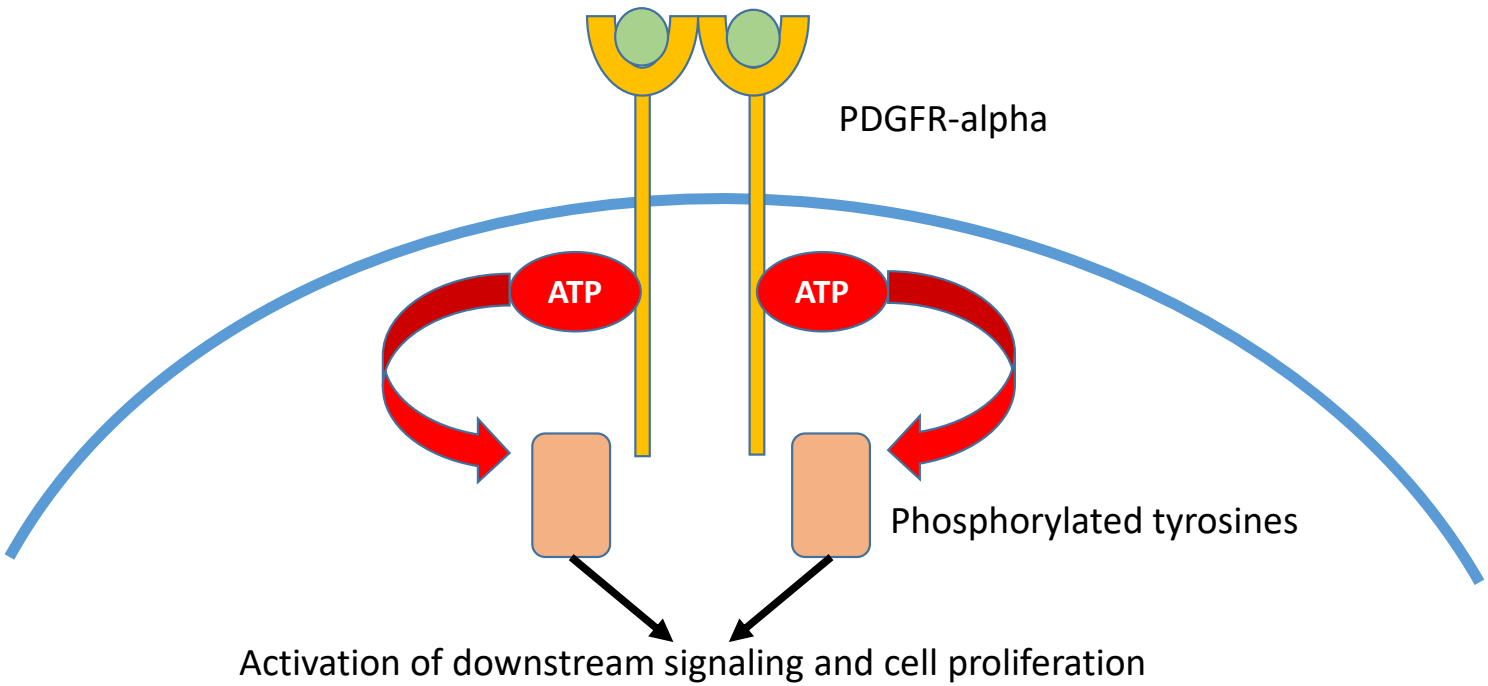
Secondary endpoints	• Response in patients having received previous immunotherapy
	  • 59%
	• Duration of progression-free survival
	  • 13.8 months

Erdafitinib

- Dosed at 8 mg once daily for 14 – 21 days, assess for serum phosphate
  - Serum phosphate <5.5 mg/dL increase dose to 9 mg once daily
  - Dose adjustments for hyperphosphatemia and ocular toxicity
- Drug interactions
  - Substrate of CYP2C9 (major), CYP3A4 (major), P-glycoprotein (minor)
    - Avoid use with strong or moderate inhibitors of CYP3A4 and CYP2C9, monitor and adjust dose as needed if used together
    - CYP2C9*3/*3 genotype requires ~50% dose reduction
- Adverse reactions
  - Mucositis/stomatitis, electrolyte abnormalities, diarrhea, fatigue, nail bed changes, liver function/kidney function abnormalities, taste changes

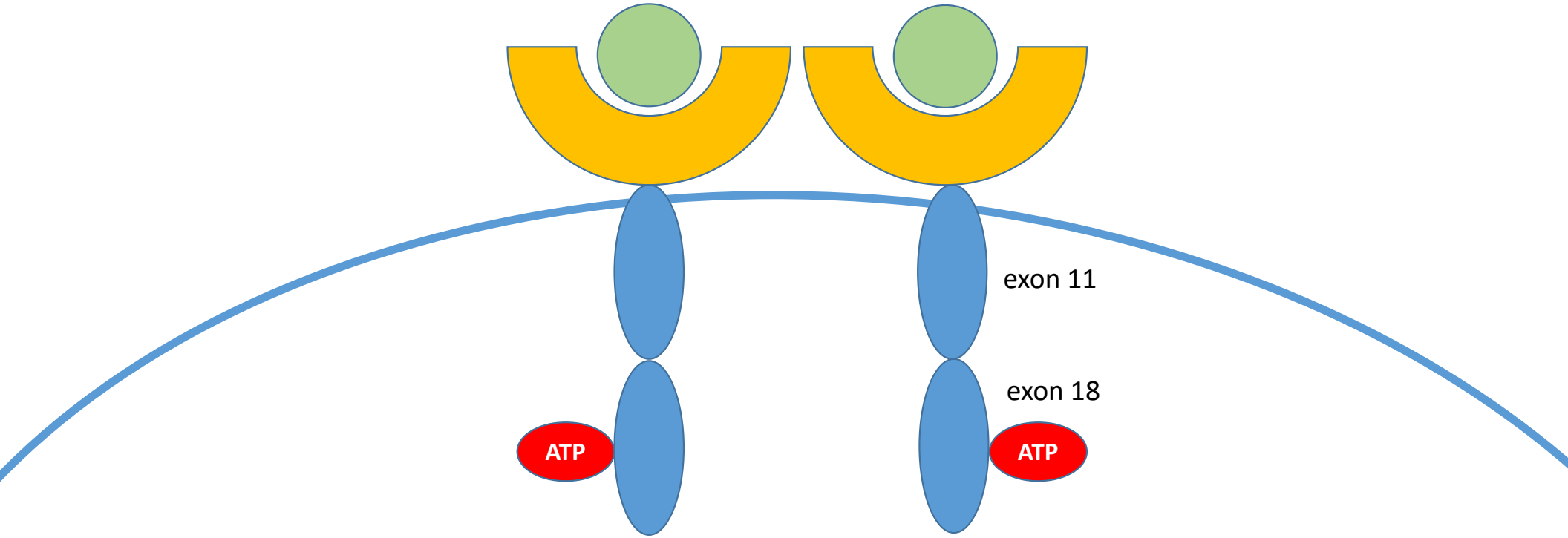
Balversa (erdafitinib) [prescribing information]. Horsham, PA: Janssen Products, LP; July 2020.

Tyrosine Kinase Inhibitors- Avapritinib



Ayvakit (avapritinib) [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; January 2020.

Tyrosine Kinase Inhibitors- Avapritinib



Ayvakit (avapritinib) [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; January 2020.

Avapritinib

NAVIGTOR	Heinrich, et al. Lancet Oncology. 2020.
Patient population	• N=46 • Unresectable PDGFRA D842V-mutant GIST regardless of previous therapy or GIST with other mutations who progressed on imatinib and ≥ 1 TKI, or only received imatinib previously
Intervention	• Phase 1, multi-center, international, open-label, single-arm • 300 mg (originally 400 mg) avapritinib orally once daily until disease progression

Primary endpoint	• Overall response rate
	  • 84% in patients with PDGFR-alpha exon 18 mutation
	  • 7% complete response
	  • 77% partial response

Secondary endpoints	• Median duration of response
	  • NR (median follow-up 10.6 months)
	• Response of at least 6 months
	  • 61%

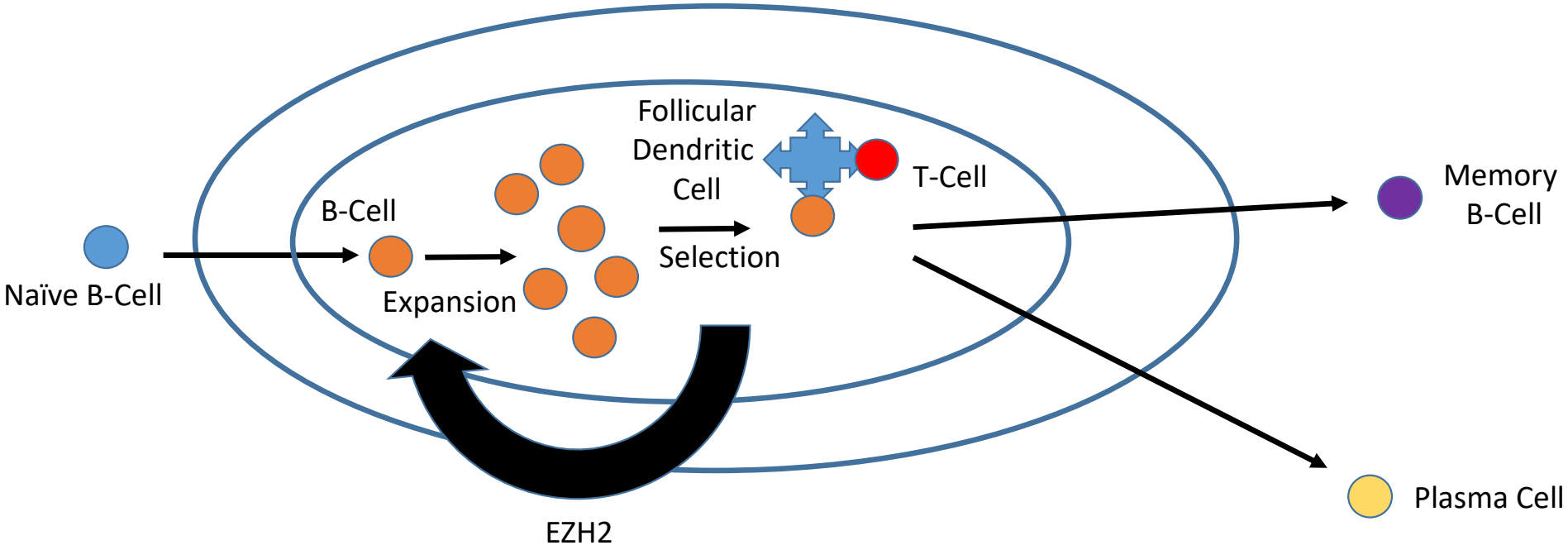
Avapritinib

- Dosed as 300 mg orally once daily until disease progression
  - Moderate to high emetic potential
  - Must be given on an empty stomach
  - Dose reductions or interruptions for CNS toxicity, intracranial hemorrhage
- Drug interactions
  - Substrate of CYP2C9 (minor), CYP3A4 (major)
  - Avoid use with strong CYP3A4 inhibitors (7-fold AUC increase)
  - Avoid use with moderate CYP3A4 inhibitors, reduce dose to 100 mg if used together
- Adverse effects:
  - Edema, nausea, fatigue, cognitive impairment, decrease appetite, diarrhea, hair color changes, rash, dizziness, myelosuppression

Ayvakit (avapritinib) [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; January 2020.

Hematologic Malignancies

Tazemetostat



Klein U. Nature Reviews Immunology. 2008;8:22-33.

Tazemetostat

MURANO	Morschhauser, et al. Lancet Oncology. 2020.
Patient population	• n=389 • Relapsed or refractory follicular lymphoma or failed two or more previous lines of therapy
Intervention	• Phase 2, open-label, single-arm • 800 mg tazemetostat orally twice daily in continuous 28-day cycles, until disease progression

Primary endpoint	• Objective response rate
	  • 69% EZH2 mutant
	  • 35% EZH2 wild-type

Secondary endpoints	• Duration of response
	  • 10.9 months EZH2 mutant
	  • 13.0 months EZH2 wild-type
	• Progression-free survival
	  • 13.8 months EZH2 mutant
	  • 11.1 months EZH2 wild-type

Tazemetostat

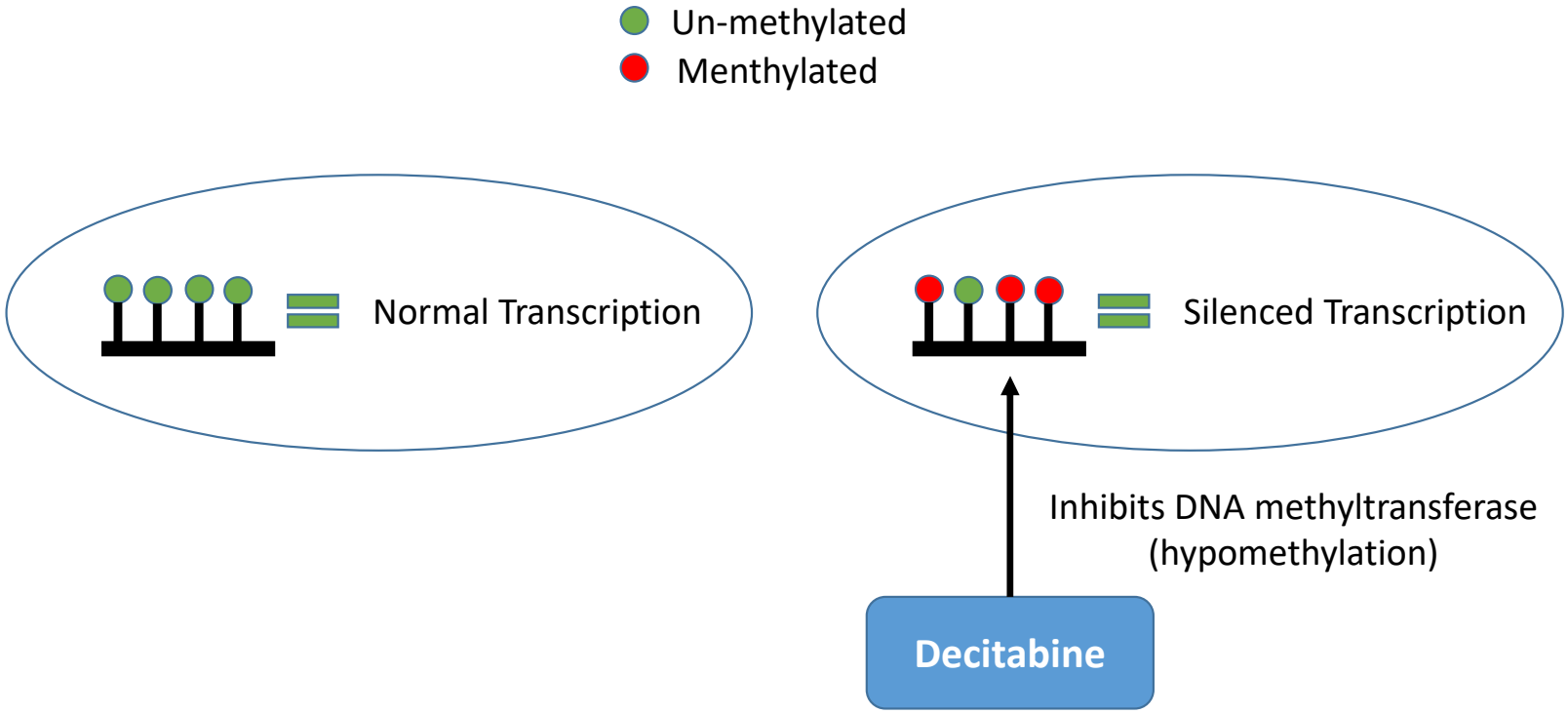
- Dosed as 800 mg orally twice daily until disease progression
  - Dose adjustments and interruptions for neutropenia, thrombocytopenia
  - Avoid drinking grapefruit juice while taking tazemetostat

- Drug interactions
  - Substrate of CYP3A4 (major), and P-glycoprotein (minor)
    - Avoid co-administration of strong CYP3A4 inhibitors
    - Avoid co-administration of moderate CYP3A4 inhibitors, reduce to 400 mg (if normal dose taken is 800 mg, further dose reductions if already receiving a reduced dose)

- Adverse reactions
  - Fatigue, nausea, vomiting, cytopenias, electrolyte abnormalities,
  - Development of secondary malignancies (MDS and AML)

Klein U. Nature Reviews Immunology. 2008;8:22-33.

Decitabine and Cedazuridine Mechanism



Inqovi (decitabine and cedazuridine) [prescribing information]. Princeton, NJ: Taiho Oncology Inc; July 2020.

Decitabine and Cedazuridine

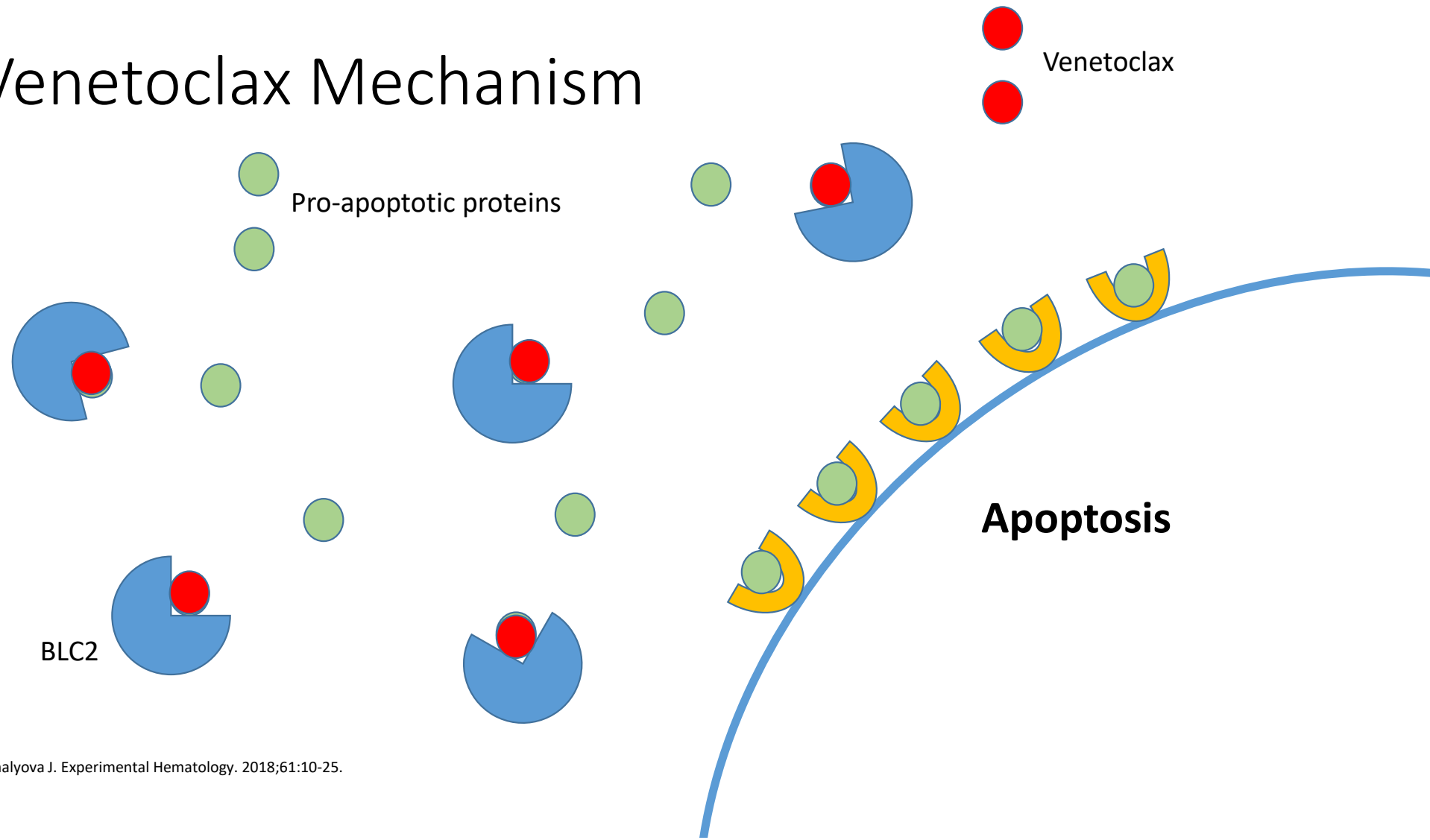
	Garcia-Manero, et al. Blood. 2020.
Patient population	• n=80 • Intermediate 1/2 – high risk MDS or CMML
Intervention	1:1 randomized, crossover study of DEC-C or decitabine for cycle 1, alternate, and then DEC-C subsequent cycles
Primary endpoint: systemic exposure	• 93.5% oral vs. 97.6% IV • DNA demethylation difference <1%
Secondary endpoints: efficacy	• CR 21% • mCR 22% • HI 15% • ORR 60%
Adverse Effects	Neutropenia 46%; thrombocytopenia 38%; febrile neutropenia 29%

Decitabine and Cedazuridine

- Dosed as decitabine 35 mg & cedazuridine 100 mg once daily for 5 days per cycle
  - Available as 5-tablet blister card for each cycle
  - No food should be consumed 2 hours before or after each dose
- No known drug-interactions at this time
- No dose adjustments for organ impairment
  - Only studied in patients with CrCl >30 mL/min and mild hepatic impairment
- Dose adjustments are made based on myelosuppression experienced during treatment
  - Consider holding for patients with neutropenia and thrombocytopenia if no longer evidence of disease

Inqovi (decitabine and cedazuridine) [prescribing information]. Princeton, NJ: Taiho Oncology Inc; July 2020.

Venetoclax Mechanism



Mihalyova J. Experimental Hematology. 2018;61:10-25.

Venetoclax

MURANO	Kater, et al. JCO. 2020.
Patient population	• n=389 • Relapsed or refractory chronic lymphocytic leukemia
Intervention	• 1:1 randomized to receive Venetoclax plus rituximab (for 6 cycles) for 2 years vs. bendamustine plus rituximab for 6 cycles • Standard venetoclax dose-escalation was utilized
Primary endpoint	• Four year PFS 57.3% VenR vs. 4.6% BR (p<0.001)
Secondary endpoints	• Four year OS 85.3% VenR vs. 66.8% BR (p,0.001) • This response was noted despite patients receiving multiple novel therapies after BR • 73.1% of VenR patients who completed 2 years of therapy remained progression free at a median of 22 months post-therapy follow-up

Venetoclax

VIALE-A	DiNardo, et al. NEJM. 2020.
Patient population	• n=431 • Patients aged 18 years or older with acute myeloid leukemia and unable to get intensive chemotherapy
Intervention	• 2:1 randomized, placebo-controlled study of azacitidine plus venetoclax vs. azacitidine plus placebo • Standard AML venetoclax dose-escalation was utilized
Primary endpoint	• Overall survival 14.7 months AzaVen vs. 9.6 months Aza ($p<0.001$)
Secondary endpoints	• Complete remission 66.4% AzaVen vs. 28.3% Aza ($p<0.001$) • Median time to first response 1.3 months AzaVen vs. 2.8 months Aza • Median duration of complete remission 17.5 months AzaVen vs. 13.4 months Aza

Venetoclax

- Requires dose escalation to avoid tumor lysis syndrome
  - CLL: 20 mg week 1, 50 mg week 2, 100 mg week 3, 200 mg week 4, 400 mg week 5 and subsequent
  - AML: 100mg on day 1, 200 mg on day 2, 400 mg on day 3 and subsequent
- Undergoes metabolism via CYP3A4, CYP3A5, and p-glycoprotein
  - Dose reductions are necessary for strong and moderate inhibitors of CYP3A4 as well as P-glycoprotein
- Adverse reactions
  - Cytopenias, tumor lysis syndrome, fatigue, nausea, vomiting, edema, electrolyte abnormalities, infections (predominantly upper respiratory tract)

Venclexta (venetoclax) [prescribing information]. North Chicago, IL: AbbVie Inc; November 2020.

Oral Azacitidine

QUAZAR AML-001	Wei, et al. NEJM. 2020.
Patient population	• n=472 • Patients aged 55 years or older with acute myeloid leukemia in first remission after intensive therapy
Intervention	• 1:1 randomized, placebo-controlled study of oral azacitidine vs. placebo
Primary endpoint	• Median overall survival 24.7 months azacitidine vs. 14.8 months placebo ($p<0.001$)
Secondary endpoints	• Median relapse-free survival 10.2 months azacitidine vs. 4.8 months placebo ($p<0.001$) • Azacitidine favored at 6-month and 12-month analysis • Non-inferiority proven for FACIT Fatigue Scales and health-related quality of life analysis

Oral Azacitidine

- Administered as 300 mg once daily on days 1-14 of a 28 day cycle
  - Antiemetic prophylaxis should be given prior to azacitidine for first 2 cycles
  - Dose modifications and treatment delays for neutropenia, thrombocytopenia, nausea, vomiting, and diarrhea
- Undergoes hydrolysis, no clinically significant drug-interactions
- Adverse reactions:
  - Nausea, vomiting, diarrhea, constipation, fatigue
  - Pneumonia, febrile neutropenia

Onureg (azacitidine) [prescribing information]. Summit, NJ: Celgene Corporation; September 2020.

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