Biomarker BINGO

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Financial Disclosures

- Dr. Held has nothing to disclose.
- Dr. Kurtin has acted as a consultant for AbbVie, Celgene, Janssen, Genentech, Incyte, and Takeda.
- Dr. Schwartzberg has acted as a consultant for Amgen, AstraZeneca, Genentech/Roche, and Pfizer.

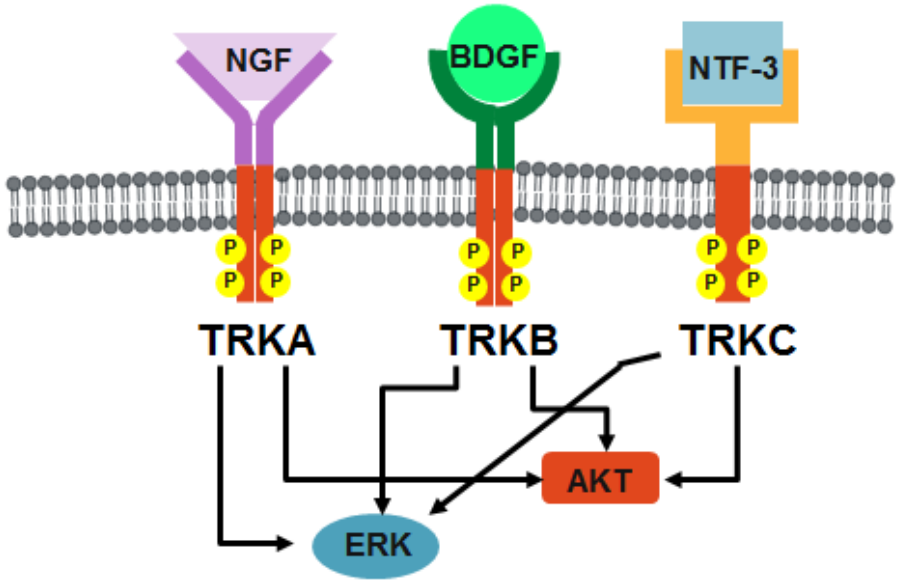
Learning Objectives

1. Pair specific biomarkers with the tumor type(s) for which their expression is most commonly used to determine targeted therapy
2. Identify key assays used to measure common biomarkers
3. Evaluate guideline-endorsed biomarker testing recommendations

QUESTION 1

_____ are a family of genes that normally promote CNS development and are involved in cancer as fusion products.

Neurotrophins and Tropomyosin Receptor Kinase (NTRK): Novel oncogenic targets



- Sympathetic nervous system development is orchestrated by neurotrophins (NT) and respective neurotrophin receptors
- 3 neurotrophin receptors encoded by 3 distinct genes
  - *NTRK1* → TRKA
  - *NTRK2* → TRKB
  - *NTRK3* → TRKC
- Normal function of TRK in adults
  - TRKA → pain, thermoregulation
  - TRKB → movement, memory, mood, appetite, body weight
  - TRKC → proprioception
- Receptors and ligands commonly dysregulated in multiple tumor types

Methods of Detecting TRK Fusions

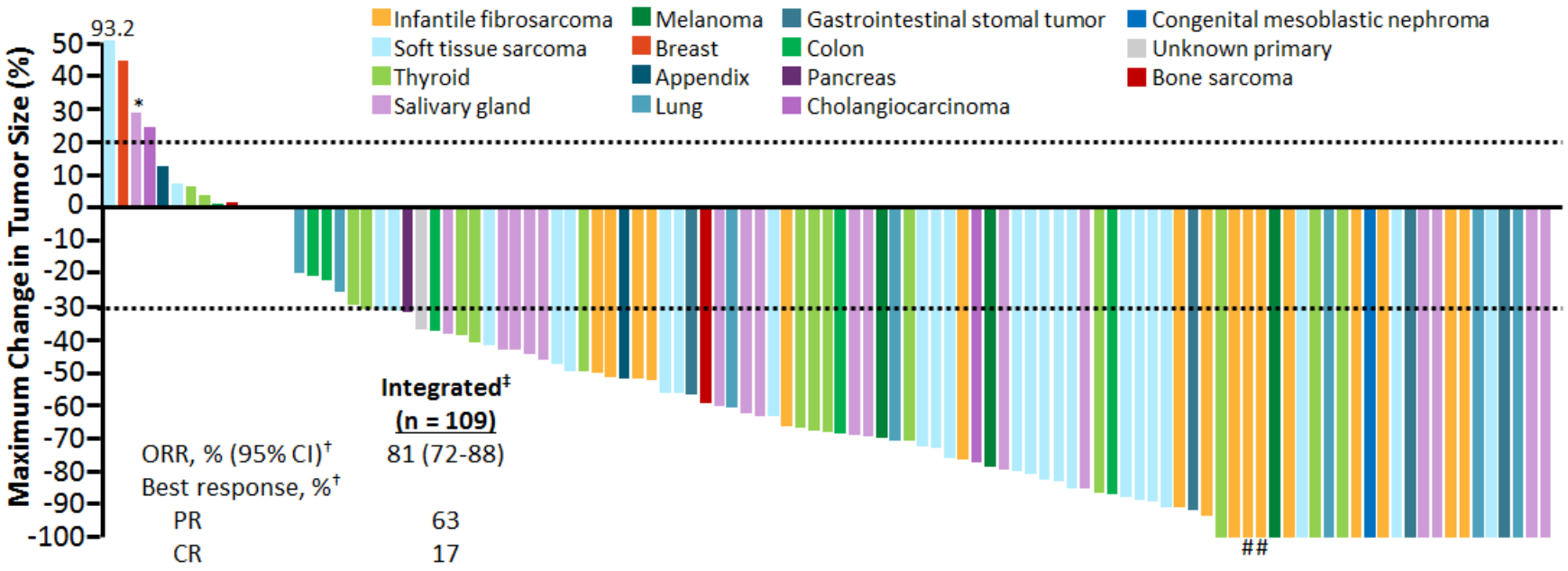
Method	Pros	Cons	Comments
IHC	Potential local implementation	Significant FN, FP Requires dedicated tissue and limits multi-target testing	May be used as screening diagnostic, but confirmation of *NTRK* gene fusion is recommended
FISH	Potential local implementation	Interpretation can be challenging Significant FN, FP Requires dedicated tissue and limits multi-target testing	In order to detect fusions at multiple locations, such as the 3 *NTRK* genes, multiple FISH tests would need to be run
RT-PCR	Fast, relatively inexpensive	No novel fusion partner detection May or may not be multiplexed with other fusion targets	Designed to identify only known translocation partners and breakpoints
NGS	Sensitive, specific molecular testing Simultaneously get mutation information for multiple targets	Expensive and longer turn-around time	RNA-NGS testing may be preferable to DNA-NGS testing because it identifies actively transcribed chimeric fusions

Larotrectinib

- First selective pan-TRK TKI approved by FDA for advanced solid tumors harboring *NTRK* gene fusion[1,2]
- **Larotrectinib**: FDA approved for adult and pediatric patients with **solid tumors with a *NTRK* gene fusion** without a known acquired resistance mutation, who are either metastatic or not candidates for surgical resection due to likely severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following standard treatment[1]
  - Potent activity against TRKA, TRKB, TRKC (IC_{50} of 4.2 to 9.1 nM)[3]
  - Very selective with decreased inhibition of other kinases[4]
- Formulated both as liquid and capsule[4]
- Bioavailable, very soluble[4]
- Moderately protein bound[4]

1. FDA. FDA approves an oncology drug that targets a key genetic driver of cancer, rather than a specific type of tumor. November 26, 2018. 2. Meric-Bernstam. SABCS 2018. Abstr P6-20-02. 3. Drilon. Cancer Discov. 2017;7:963. 4. Larotrectinib PI. 5. Hong. ESMO Asia Congress 2016. Abstr 1500.

Larotrectinib Response in TRK Fusion Cancers



Lassen. ESMO 2018. Abstr 4090.

Larotrectinib Adverse Events

AE, %	AEs in ≥ 15% of Patients			
	Gr 1	Gr 2	Gr 3	Gr 4
Increased ALT/AST	31	4	7	0
Fatigue	20	15	2	0
Vomiting	24	9	0	0
Dizziness	25	4	2	0
Nausea	22	7	2	0
Anemia	9	9	11	0
Diarrhea	15	13	2	0
Constipation	24	4	0	0
Cough	22	4	0	0
Increased body weight	11	5	7	0
Dyspnea	9	9	0	0

- Well tolerated-No patient d/c for TRAE
- Mild to Mod TRAEs
  - LFT abnormalities, GI toxicity, Anemia
- All dose-reduced patients maintained response at lower dose

Drilon. NEJM. 2018;378:731.

Second TRK inhibitor approved

On August 15, 2019, the FDA granted accelerated approval to entrectinib for adults and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.

QUESTION 1 ANSWER

Neurotrophins and Tropomyosin Receptor Kinase **(NTRK)** are a family of genes that normally promote CNS development and are involved in cancer as fusion products.

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Solid Tumors
- Precision Oncology Comes of Age: Tumor Agnostic Approaches

QUESTION 2

Tagraxofusp targets the alpha (α) receptor chain for interleukin, which requires activation of _____.

Interleukin-3 (IL-3) receptor α chain (CD123)

- IL3
  - Pleiotropic cytokine, mainly produced by activated T-lymphocytes
  - Plays an essential role in regulating proliferation of hematopoietic stem cells
  - Stimulates a wide-range of hematopoietic cells:
    - basophils, neutrophils, eosinophils, macrophages, erythroid cells, megakaryocytes, dendritic cells and endothelial cells
- CD123
  - The α subunit of IL-3 receptor (IL-3Rα) and marker of plasmacytoid dendritic cell (pDCs)
  - Overexpressed on hematologic cancer cells relative to normal cells
    - AML, B-ALL, dendritic cell malignancies, immature T-ALL; CD123 expression is strongly associated with cross-lineage expression of myeloid markers in early T precursor ALL
- How measured
  - Multi-parameter flow cytometry
  - EDTA anticoagulated peripheral blood, bone marrow, or tissue

Syed, Y. (2019) Drugs, 79:579–583; Testa et al. (2014) Biomarker Research, 2:4; Pemmaraju, N et al. (2019) N Engl J Med, 380:1628-37.

Tagraxofusp
(Diphtheria-toxin-interleukin-3-fusion-protein; SL-410)

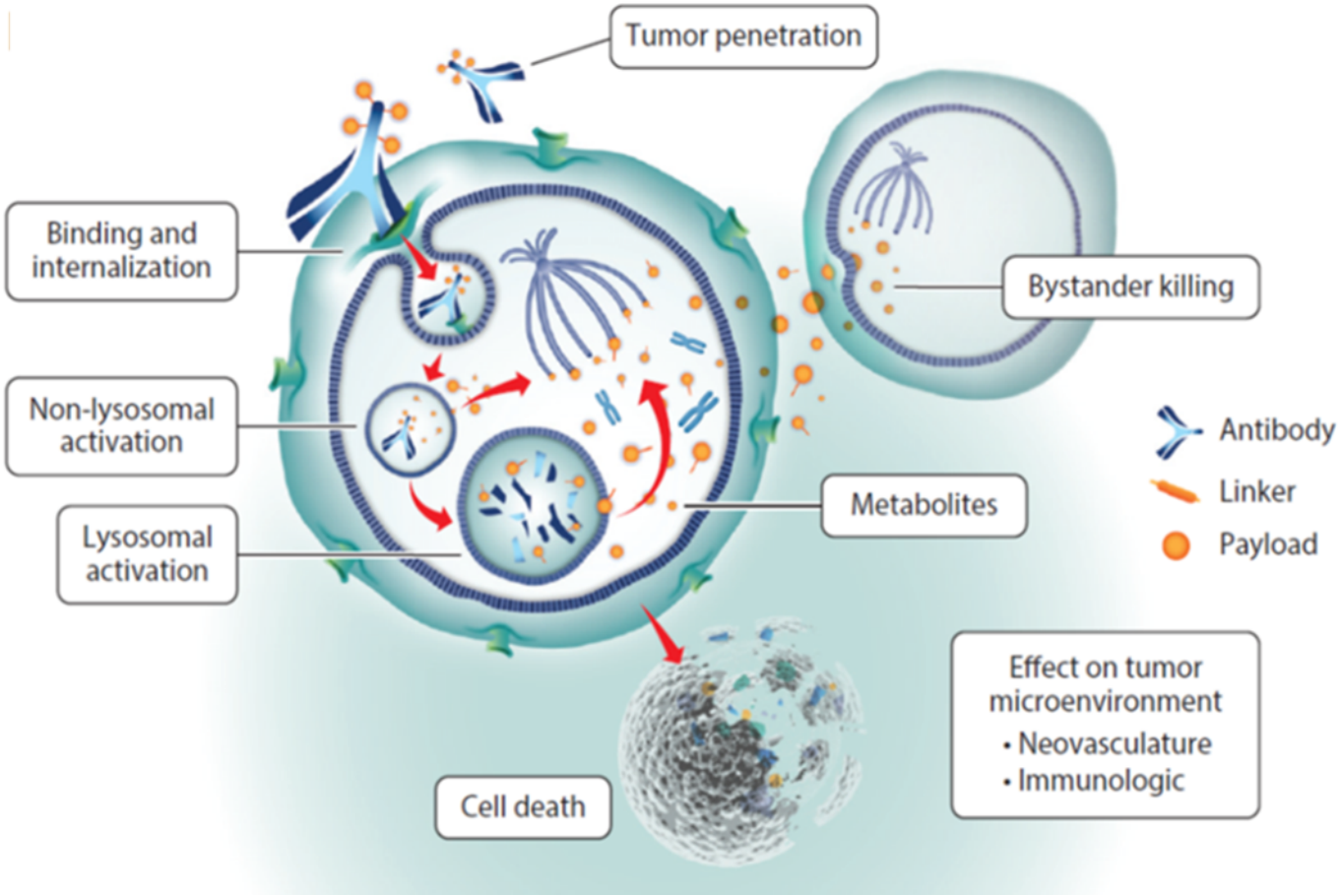
- **Indication**
  - Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
  - CD123 is present in virtually all cases of BPDCN

- **MOA: Peptide elongation factor 2 inhibitor**
  - Recombinant fusion protein: human IL3 fused to a truncated diphtheria toxin
  - Binds to the alpha chain CD123
  - Internalized
  - Cytotoxic diphtheria toxin payload is released
  - Catalyzes ADP ribosylation of elongation factor 2
  - Results in inhibition of protein synthesis and apoptosis of target cells
  - Induces the killing of CD34+/CD38- leukemic cells

Syed, Y. (2019) Drugs, 79:579–583; Testa et al. (2014) Biomarker Research, 2:4; Pemmaraju, N et al. (2019) N Engl J Med, 380:1628-37; Lambert, J & Berkenbilt, A. (2018) Annu. Rev. Med. 69:191–207

Delivery of Immunotoxins Using Antibody-Drug Conjugates

- Immunotoxins are useful in delivering targeted anticancer therapy.
- They are proteins that consist of a targeting portion, such as an antibody or growth factor, linked to a toxin.
- Toxins used in immunotoxin products are procured from bacteria, fungi, and plants, and most function by inhibiting protein synthesis.
- Commonly used bacterial toxins include diphtheria toxin and Pseudomonas exotoxin (PE)



Tagraxofusp: Key Takeaways

- Numerous trial ongoing across myeloid and plasma cell malignancies, including combination therapies
- Adverse effects of manipulating the CD123/IL3 pathway:
  - Potential For Immunogenicity – Common In Therapeutic Proteins
  - Boxed Warning For Capillary Leak Syndrome
    - Consider the broad range of cells stimulated and their role in normal immune function
- Hepatotoxicity
- Hypersensitivity

Syed, Y. (2019) Drugs, 79:579–583; Testa et al. (2014) Biomarker Research, 2:4; Pemmaraju, N et al. (2019) N Engl J Med, 380:1628-37.

QUESTION 2 ANSWER

Tagraxofusp targets the alpha (α) receptor chain for interleukin, which requires activation of **CD123.**

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Hematologic Malignancies

QUESTION 3

Venetoclax inhibits _____, which is a family of proteins located on the mitochondrial membrane.

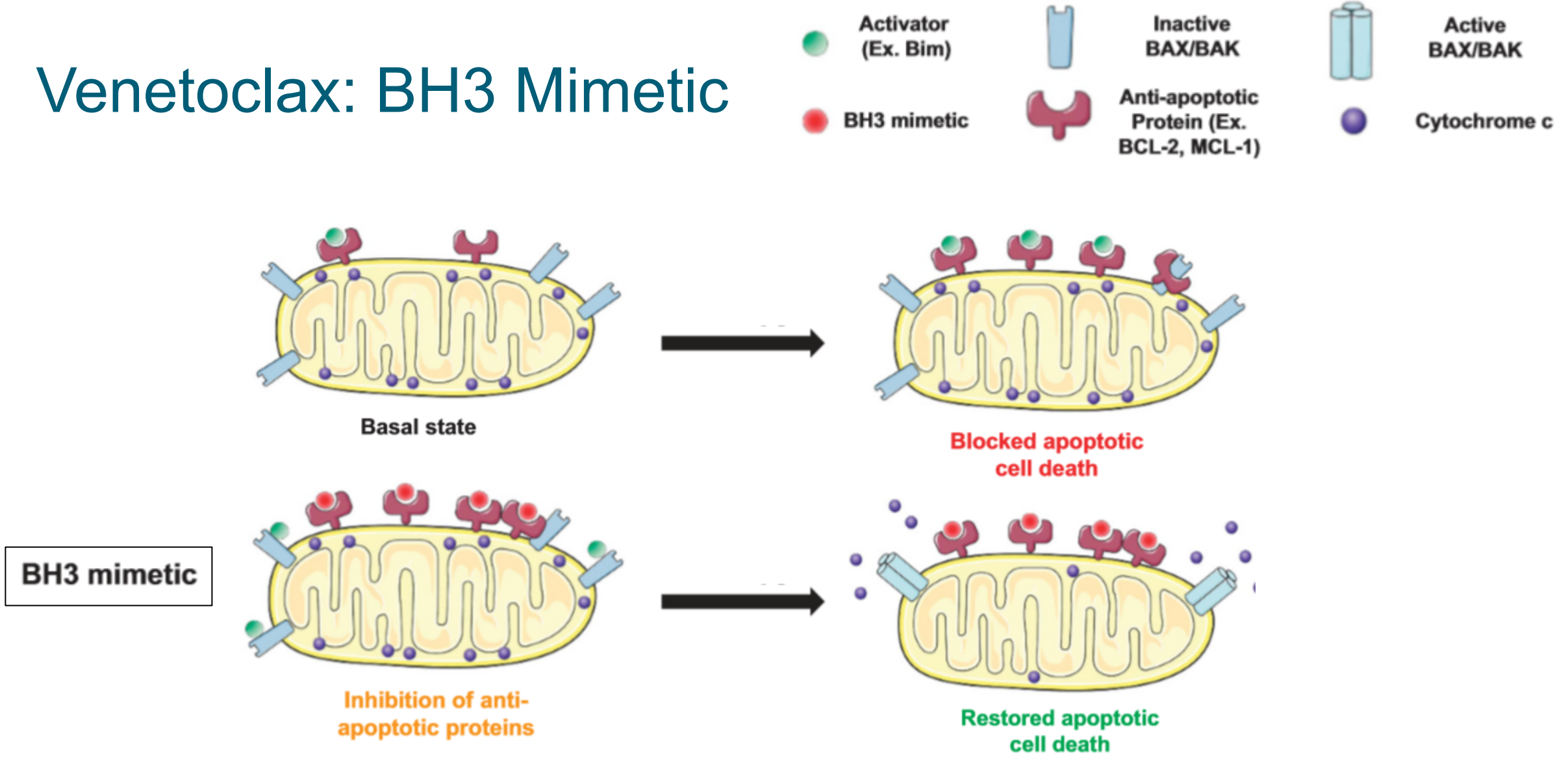
BCL2

- BCL2 family of proteins controls intrinsic apoptosis by regulating mitochondrial permeabilization
  - Consist of both pro-apoptotic and anti-apoptotic proteins
  - Share BCL2 homology domain 3 (BH3 domain) that leads to activation
  - BCL2 overexpression raises the antiapoptotic threshold

Anti-apoptotic proteins (BCL-2, BCL-XL, MCL-1)
• Directly bind the BH3 domain proteins and prevents activating BAX and BAK → <u>inhibits intrinsic apoptosis</u>
• BH3 profiling (detected by ELISA or Western blot) is a tool to predict various cell lines that are dependent on BCL2 for survival

Del Gaizo Moore, V., et al. *Cancer Lett* 2013;332:202-05

Venetoclax: BH3 Mimetic



Montero J., Letai A. Cell Death and Differentiation 2018;25:56-64

Venetoclax Key Takeaways

- Indicated in CLL/SLL in combination with a CD20 monoclonal antibody or as monotherapy
  - Weekly ramp-up over 5 weeks (starter pack)
  - Assess tumor lysis syndrome risk prior and administer appropriate hydration, anti-hyperuricemics, and adequate lab monitoring
- Indicated in AML in combination with azacitidine or decitabine OR low-dose cytarabine in patients ≥75 years or who have comorbidities that preclude the use of intensive induction chemotherapy
  - Daily ramp-up over 4 days
  - Dose reductions for concomitant CYP3A4 inhibitors

QUESTION 3 ANSWER

Venetoclax inhibits **BCL2**, which is a family of proteins located on the mitochondrial membrane.

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Hematologic Malignancies

QUESTION 4

Alterations in the ____ gene are mainly found in thyroid cancer.

RET

Biological role

Rearranged during transfection proto-oncogene (RET) is a receptor tyrosine kinase with a role in normal organogenesis and maintenance of several adult tissue types; can drive oncogenesis through point mutation or gene rearrangement.[1]

Clinical insights

Predictive of response to RET inhibitors, associated with negative prognosis in medullary thyroid carcinoma (MTC).[2,3]

Incidence

- Overall incidence across malignancies: **1.8%**[2]
  - *RET* gene alterations most commonly mutations (38.6%), fusions (30.7%), and amplifications (25.0%)
- High frequency of *RET* alterations in MEN2A/B (> 98%), MTC (40% to 80%), papillary thyroid carcinoma (7% to 27%), and anaplastic thyroid carcinoma (4.0% to 16.7%)[2-6]
- *RET* alterations also reported in NSCLC (0.7% to 2.0%) and pheochromocytoma/paraganglioma (3% to 6%)[7,8]

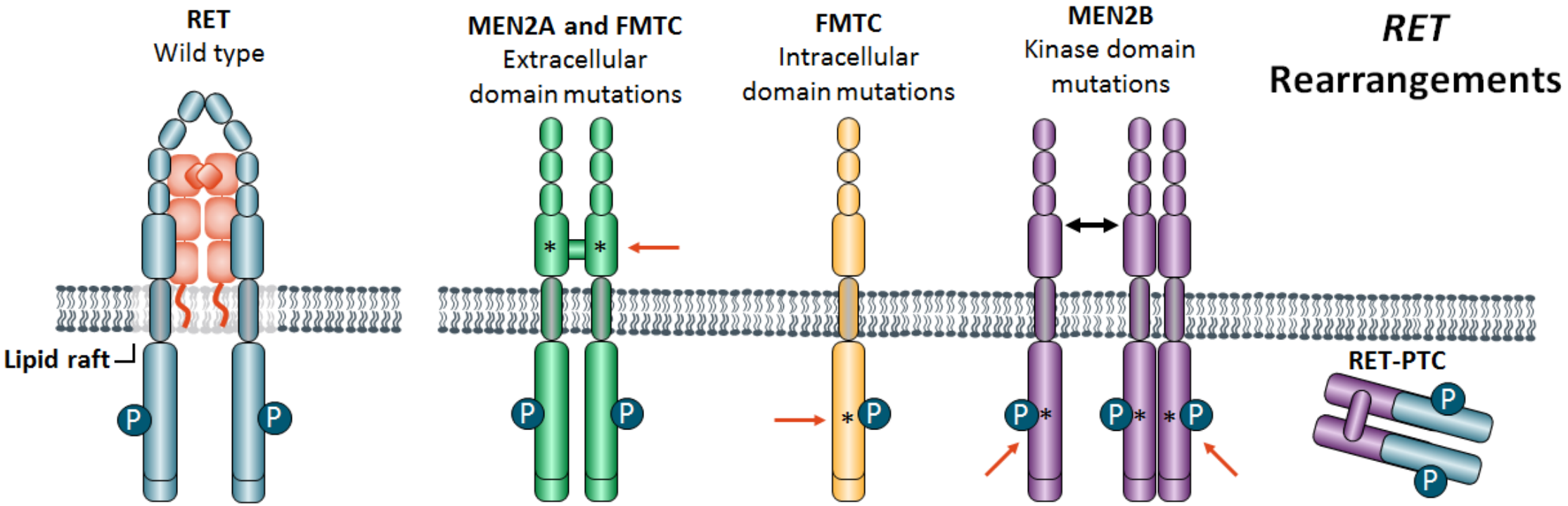
Applicable tumor types

Predominantly in medullary and papillary thyroid cancer, MEN2A/B, NSCLC, pheochromocytoma

Rarely in other solid tumors

Variety of Alterations Leading to RET Activation

- All lead to constitutive activation
- In solid tumors, rearrangements are increasingly a focus for potential therapy



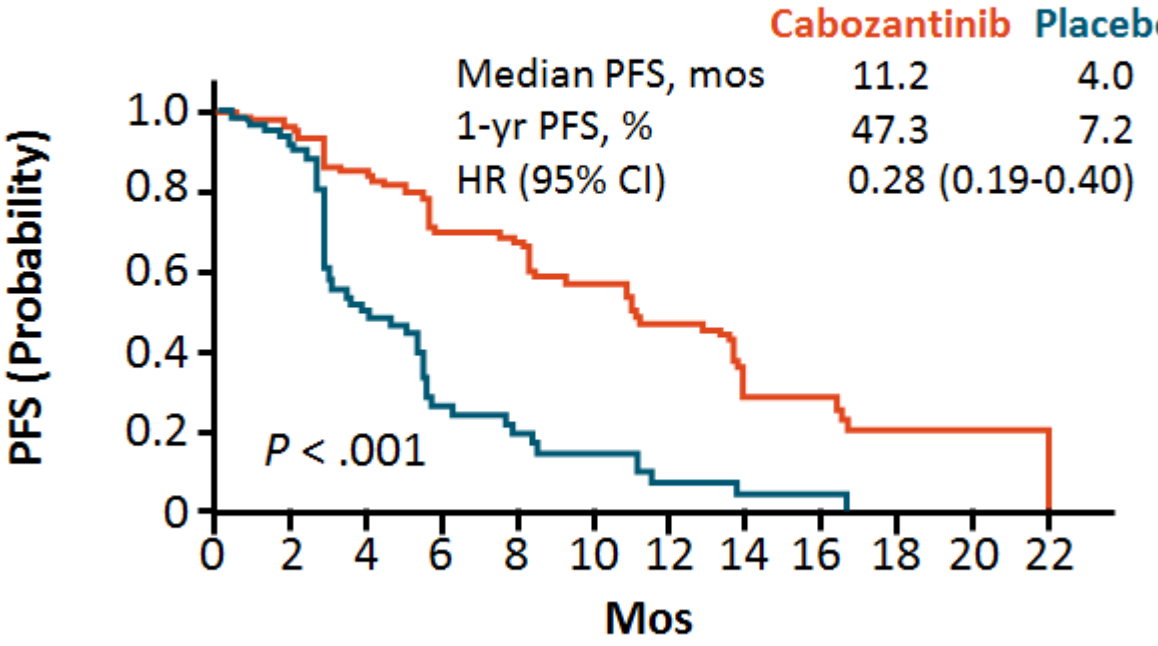
Cabozantinib in RET altered cancers

Registry of RET altered NSCLC:
Response Data [2]

Agent, n (%)	ORR
All (N = 53)	13 (26)
Cabozantinib (n = 21)	7 (37)
Vandetanib (n = 11)	2 (18)
Sunitinib (n = 10)	2 (22)
Sorafenib (n = 2)	0
Alectinib (n = 2)	0
Lenvatinib (n = 2)	1
Nintedanib (n = 2)	1
Ponatinib (n = 2)	0
Regorafenib (n = 1)	0

Phase III Trial in Patients With Progression of MTC[1]

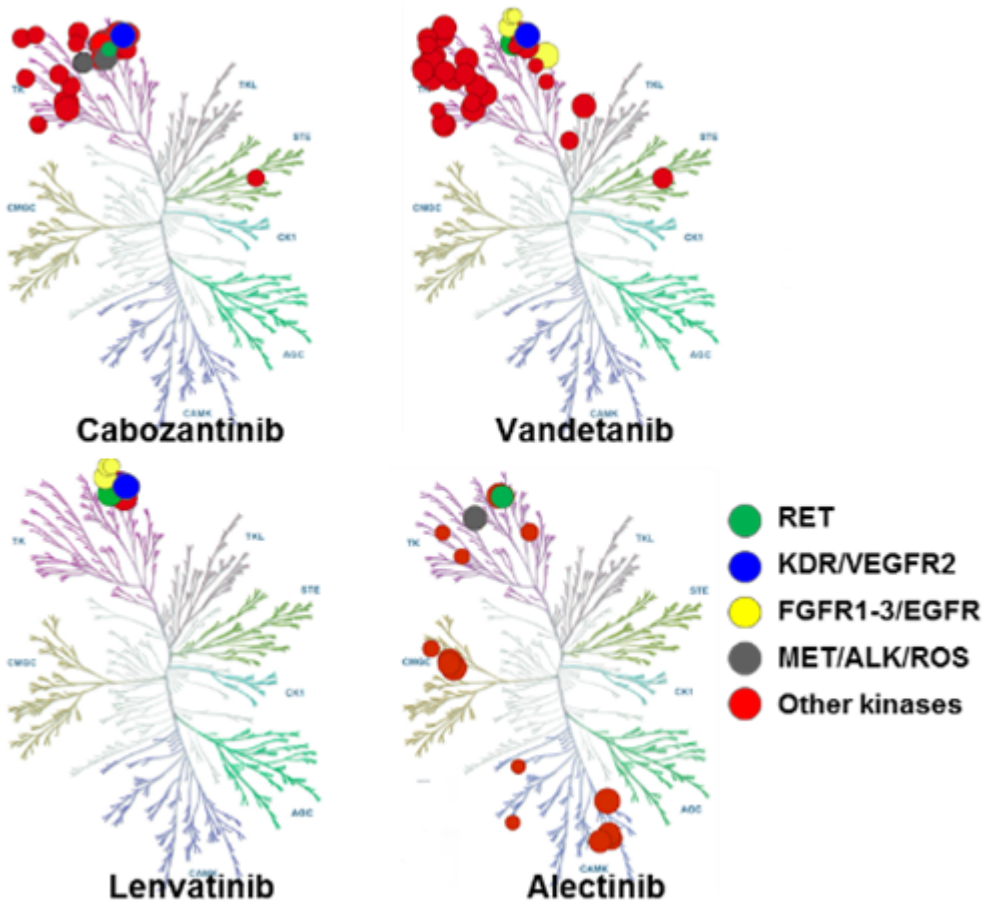
ITT Population

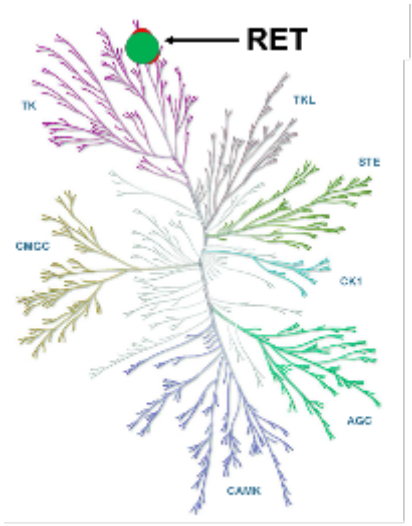


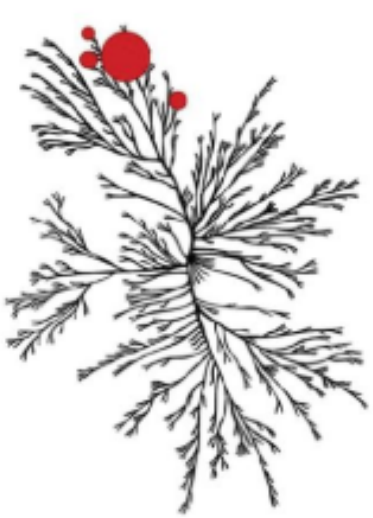
Responsiveness regardless of *RET* M918T status

1. Elisei R, et al. J Clin Oncol. 2013;31:3639-3646. 2. Gautschi O, et al. J Clin Oncol. 2017;35:1403-1410.

Current RET inhibitors are multi-tyrosine kinase inhibitors…but more targeted drugs are coming







QUESTION 4 ANSWER

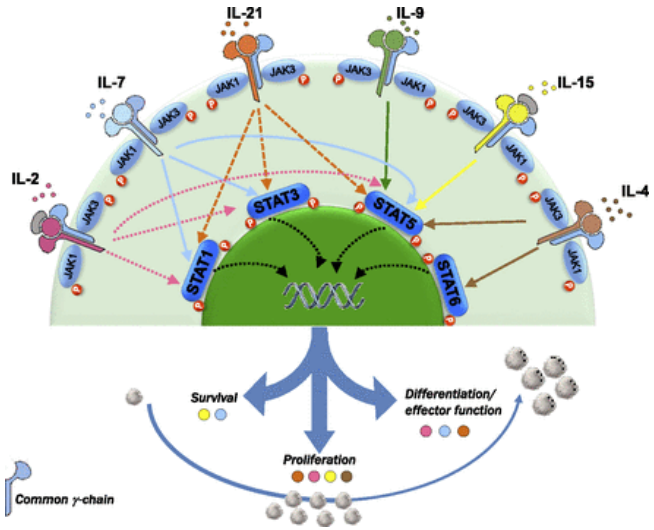
Alterations in **RET** are mainly found in thyroid cancer.

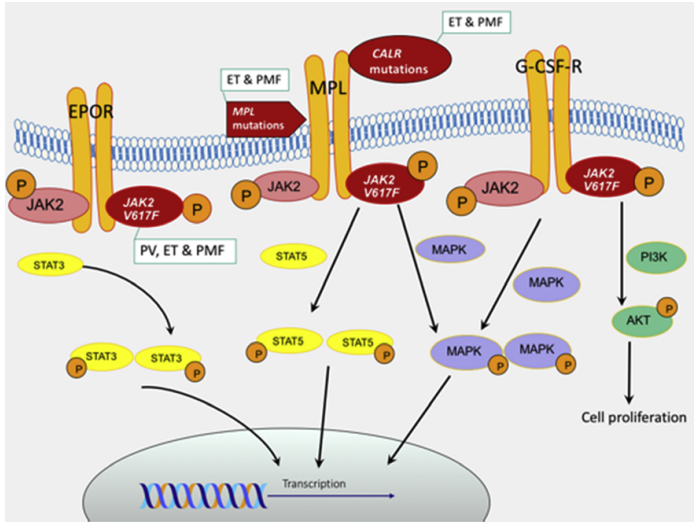
QUESTION 5

Ruxolitinib mediates the _____ pathway to improve the symptoms associated with acute graft-vs.-host disease.

JAK-STAT and GVHD

- Well-characterized signaling pathway involved in normal hematopoiesis, inflammation, and immune function
- JAKs mediate signaling of multiple cytokine receptor family members including Interleukins, Interferons, and hematopoietic stimulating proteins
  - Cytokines mediate coordinated inflammatory responses
- How Measured:
  - As targets: PCR
  - Cytokines: surrogate markers of inflammation in peripheral blood

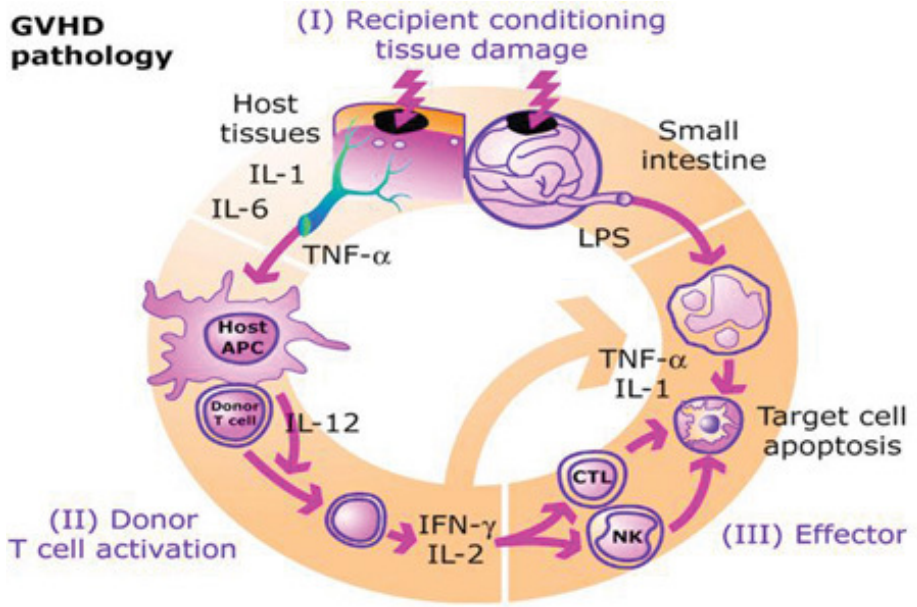


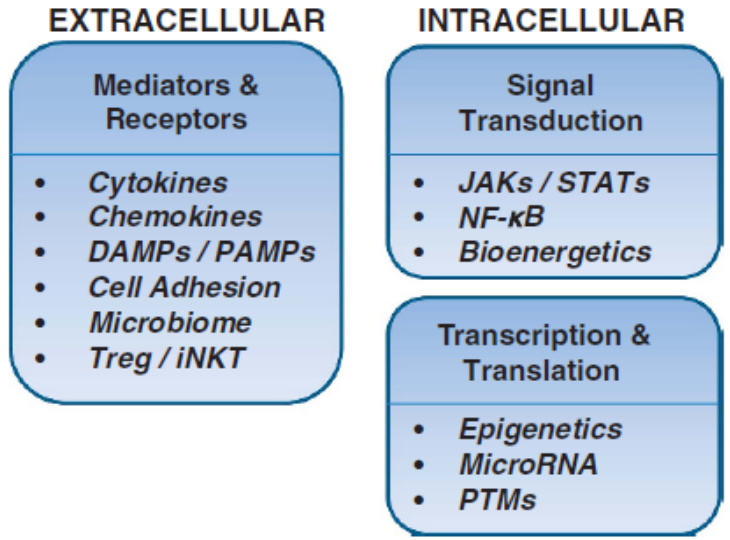


O'Sullivan JM, Harrison CN. Molecular and cellular endocrinology. 2017;451:71-79

Ruxolitinib

- Indication:
  - Steroid-refractory acute graft-versus-host disease (GVHD) in adults and pediatric patients 12 years and older
- MOA
  - ➢ The common cytokine receptor γ acts mainly through the JAK-STAT pathway.
  - ➢ Ruxolitinib inhibits the JAK-STAT pathways including IFNγ and other inflammatory cytokines





https://www.ncbi.nlm.nih.gov/books/NBK27033/figure/mousemodels.F1/?report=objectonly

Ruxolitinib for GVHD: Key Takeaways

- Targeting the JAK-STAT pathways can reduce the severity of acute GVHD
- Moderate to Severe AEs associated with manipulation of the JAK-STAT pathway in patient undergoing allogeneic stem cell transplant
  - Cytopenias: Monitor hemoglobin, platelet count – transfuse as needed
  - Renal: dose modification required for renal impairment. Check serum creatinine, and ensure adequate hydration
  - Risk of Infection: Assess patients for signs and symptoms of infection, serious infections should have resolved before starting therapy
  - Risk of Non-Melanoma Skin Cancer: Perform periodic skin examinations
  - Lipid Elevations: Assess lipid levels 8-12 weeks from start of therapy

https://www.jakafi.com/pdf/prescribing-information.pdf

QUESTION 5 ANSWER

Ruxolitinib mediates the **JAK-STAT** pathway to improve the symptoms associated with acute graft-vs.-host disease.

Want to know more? Related sessions at JADPRO Live 2019

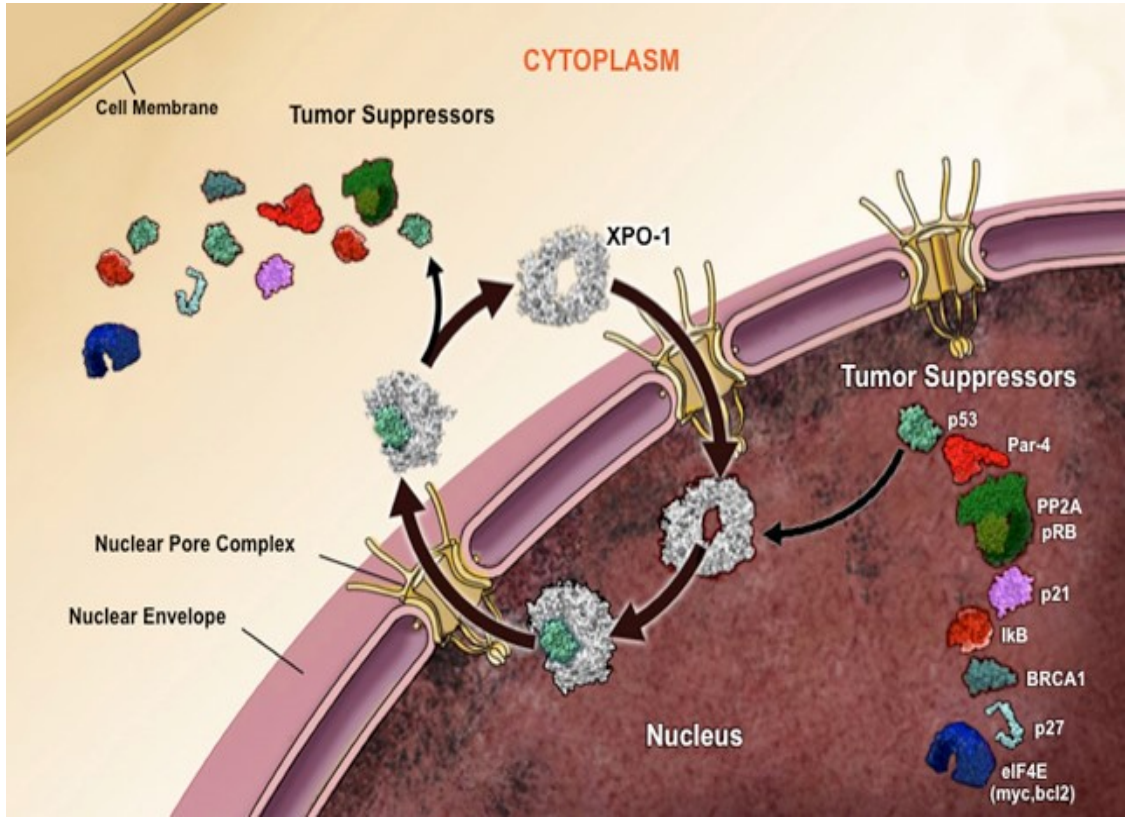
- New Drug Updates: Hematologic Malignancies

QUESTION 6

Selinexor is a SINE compound and inhibits _____, which leads to accumulation of tumor suppressor proteins in the nucleus.

Selective inhibitor of nuclear export (SINE)

- SINE compounds inhibit exportin 1 (XPO1) and inhibits nuclear export of tumor suppressor proteins (TSPs)
- Accumulation of TSPs in nucleus → cell cycle arrest → apoptosis
- Increased expression of XPO1 has been observed and correlated in several solid and hematologic malignancies



Tan, DS, Bedard PL, Kuruvilla J, Siu LL et al. Cancer Discov 2014;4:527-537

https://www.myelomacrowd.org/the-storm-study-selinexor-the-active-clinical-trials-using-this-drug/#post/0

Selinexor

- RRMM in combination with dexamethasone who have received at least four prior therapies *and* refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody

- Dose: 80 mg (four 20-mg tablets) orally in combination with dexamethasone 20 mg on days 1 and 3 of each week
  - Take with or without food at approximately the same time of day

RRMM=relapsed/refractory multiple myeloma

Selinexor

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=123)
Thrombocytopenia	12 (10%)	6 (5%)	31 (25%)	41 (33%)	90 (73%)
Anemia	7 (6%)	22 (18%)	53 (43%)	1 (1%)	83 (67%)
Fatigue	16 (13%)	43 (35%)	31 (25%)	0	90 (73%)
Nausea	34 (28%)	42 (34%)	12 (10%)	0	88 (72%)
Hyponatremia	18 (15%)	0	26 (21%)	1 (1%)	45 (37%)

- Warnings and Precautions
  - Thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, infections, neurological toxicity, embryo-fetal toxicity

Chari A, Vogl D, Gavriatopoulou M, et al. N Eng J Med 2019;381:727-738

Xpovio™ Package Insert

QUESTION 6 ANSWER

Selinexor is a SINE compound and inhibits Exportin 1 (**XPO1**), which leads to accumulation of tumor suppressor proteins in the nucleus.

Want to know more? Related sessions at JADPRO Live 2019

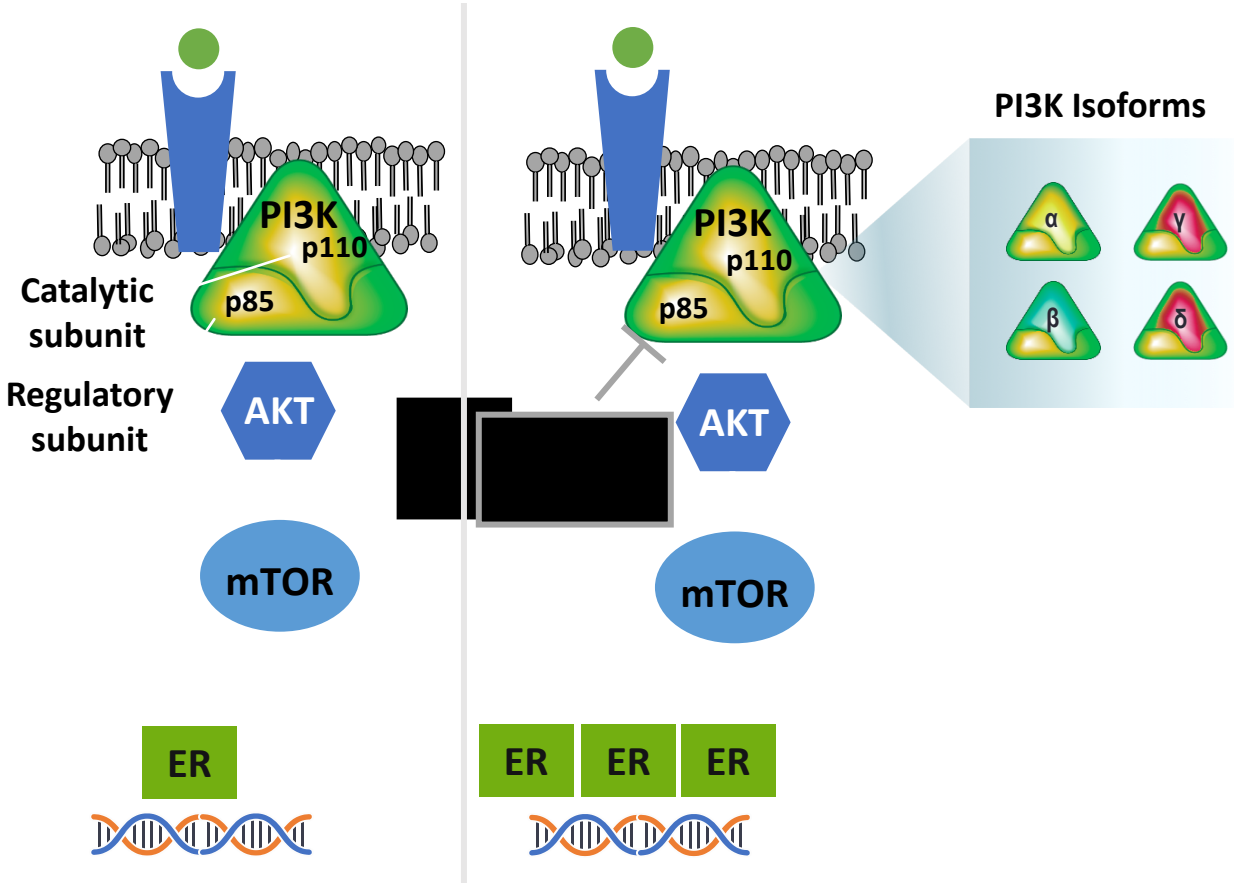
- New Drug Updates: Hematologic Malignancies
- Recent Advances in the Treatment of Newly Diagnosed Multiple Myeloma

QUESTION 7

Alpelisib is indicated for the treatment of breast cancer with mutations in _____.

Role of PIK3CA and *PIK3CA* Mutations in Breast Cancer

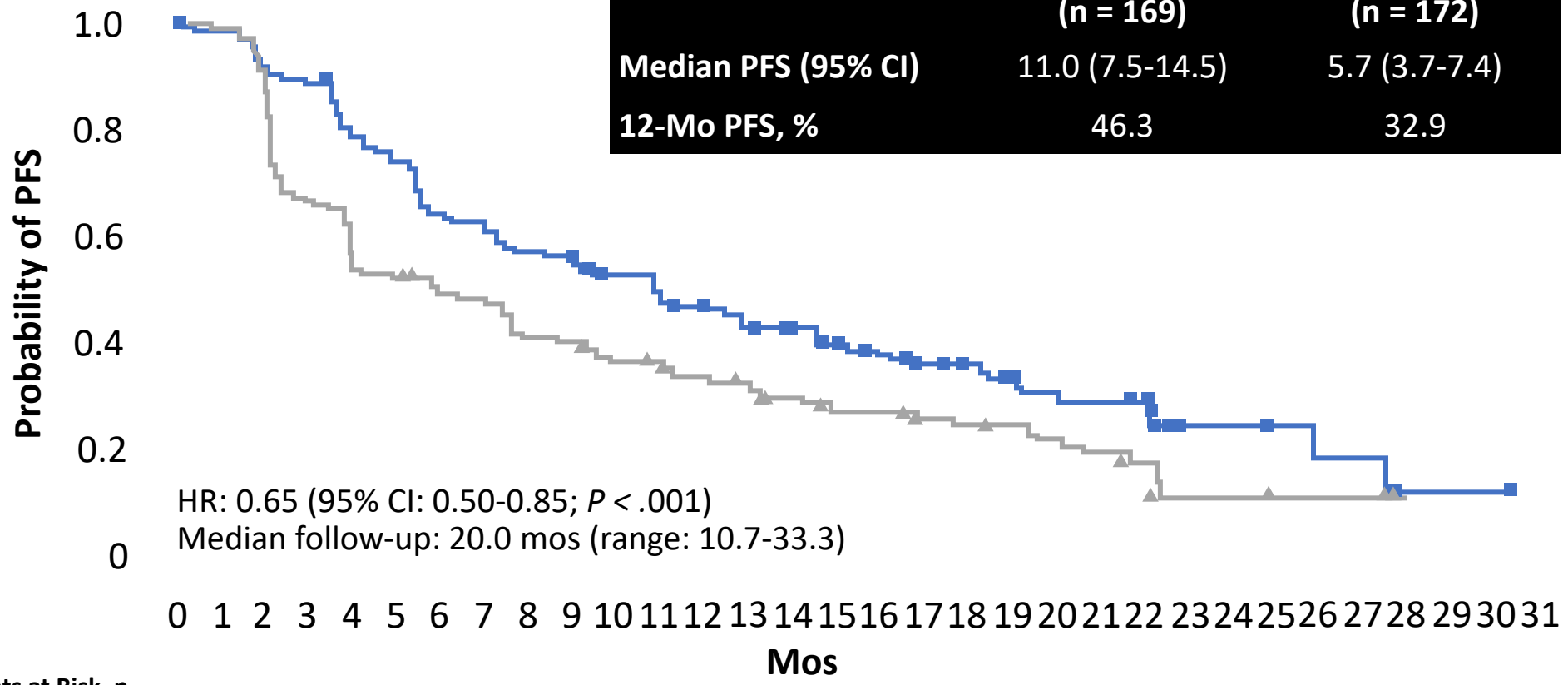
- PI3K signaling functions in tumor growth, proliferation, survival[1]
  - Significant crosstalk with ER pathway: PI3Ki leads to upregulation of ER signaling[2,3]
- PI3K: regulatory subunit + catalytic subunit, of which there are 4 isoforms[4,5]
  - *PIK3CA* encodes α-isoform
- **~ 40% of ER+/HER2- BC present with *PIK3CA* activating gain-of-function mutations[6]**
- Targeting the PI3K α-isoform may decrease toxicity compared with a pan-PI3Ki[7-9]



1. Fruman. Cell. 2017;170:605. 2. Bosch. Sci Transl Med. 2015;7:283ra51. 3. Toska. Science. 2017;355:1324. 4. Engelman. Nat Rev Cancer. 2009;9:550. 5. Janku. Cancer Treat Rev. 2017;59:93. 6. Arthur. Breast Cancer Res Treat. 2014;147:211. 7. Baselga. ASCO 2018. Abstr LBA1006. 8. Di Leo. Lancet Oncol. 2018;19:87. 9. Baselga. Lancet Oncol. 2017;18:904.

Alpelisib (alpha specific PIK3CA inhibitor) + Fulvestrant vs. Fulvestrant alone in ER+ HER2- MBC

	Alpelisib + FULV (n = 169)	Placebo + FULV (n = 172)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
12-Mo PFS, %	46.3	32.9



Patients at Risk, n

Alpelisib + FULV	169	158	145	141	123	113	97	95	85	82	75	71	62	54	50	43	39	32	30	27	17	16	14	5	5	4	3	3	1	1	1	0
Placebo + FULV	172	167	120	111	89	88	80	77	67	66	58	54	48	41	37	29	29	21	20	19	14	13	9	3	3	2	2	2	0	0	0	0

Primary endpoint met (1-sided $P \leq .0199$)

André. NEJM. 2019;380:1929

Approval of Alpelisib

- May 2019: based on PFS benefit in SOLAR-1, FDA approved alpelisib in combination with fulvestrant for treatment of PIK3CA-mutated HR+/HER2- advanced or metastatic BC in men or postmenopausal women following progression on ET
  - Companion diagnostic also approved: therascreen PIK3CA RGQ PCR Kit
    - RT-PCR test for 11 mutations
      - Exon 7: C420R; exon 9: E542K, E545A, E545D (1635G>T only), E545G, E545K, Q546E, Q546R; and exon 20: H1047L, H1047R, H1047Y
    - Genomic DNA from tissue and/or liquid biopsy
      - Reflex tissue testing should be done in the event of negative plasma results

Alpelisib PI. *therascreen* PI.

Adverse Events Associated With Alpelisib

AEs ≥ 20% in Either Arm, n (%)	Alpelisib + FULV (n = 284)			Placebo + FULV (n = 287)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any AE	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

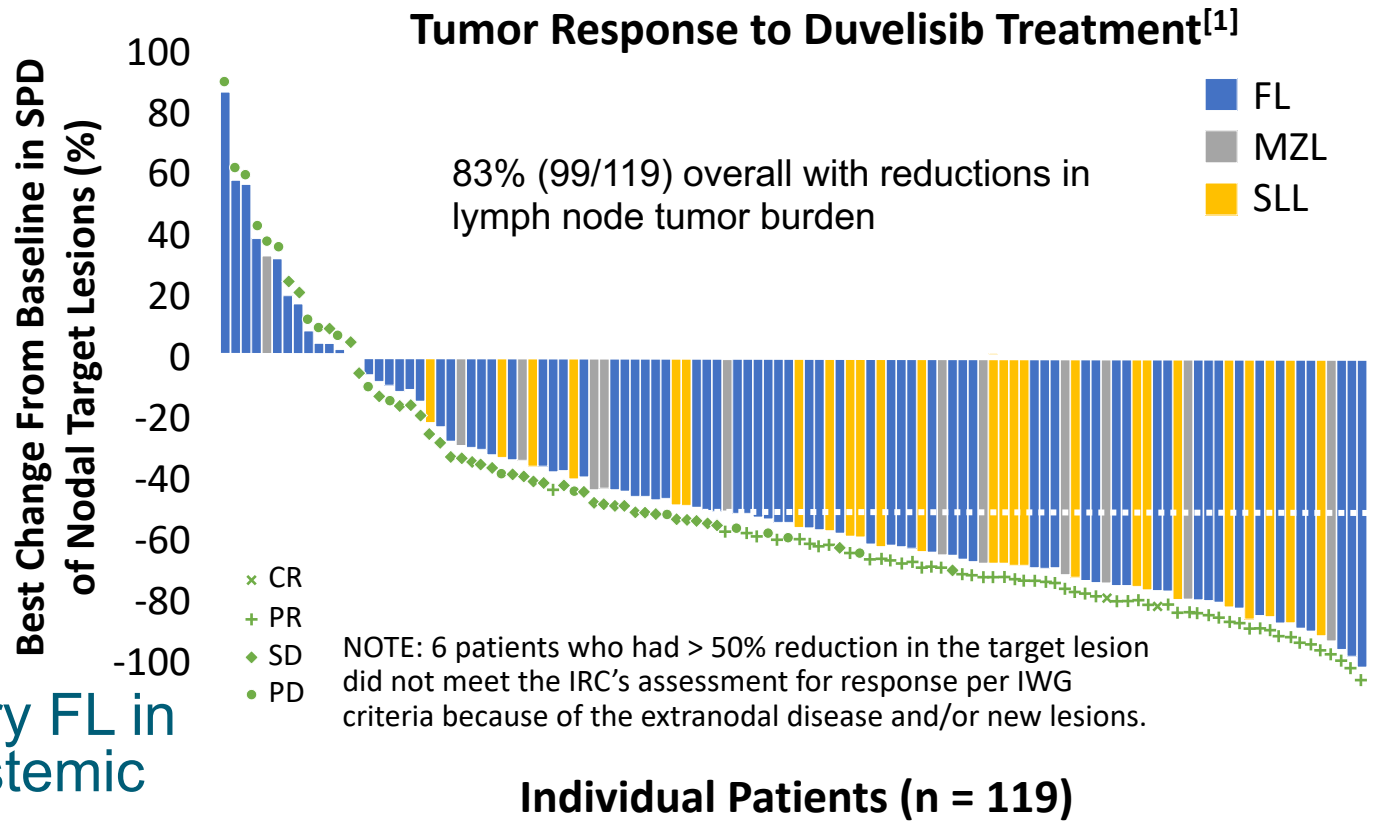
- Alpelisib discontinued for hyperglycemia by 18 patients (6.3%), for rash by 9 patients (3.2%); no patients discontinued placebo due to either

André. NEJM. 2019;380:1929.

*Does not include maculopapular rash

Duvelisib for R/R Indolent Lymphoma

- Duvelisib: oral, dual PI3K inhibitor selective for PI3Kδ and PI3Kγ
- Single-arm phase II DYNAMO study of duvelisib for indolent NHL refractory to rituximab and either chemotherapy or radioimmunotherapy (N = 129)[1]
  - 42% ORR in 83 patients with FL
  - Durable responses overall
    - Median duration of response (DoR): 10 mos
    - Median PFS: 9.5 mos
- FDA approved for relapsed or refractory FL in patients who received ≥ 2 previous systemic therapies[2]



1. Flinn. J Clin Oncol. 2019;37:912. 2. Duvelisib PI.

QUESTION 7 ANSWER

Alpelisib is indicated for the treatment of breast cancer with mutations in **PIK3CA.**

Want to know more? Related sessions at JADPRO Live 2019

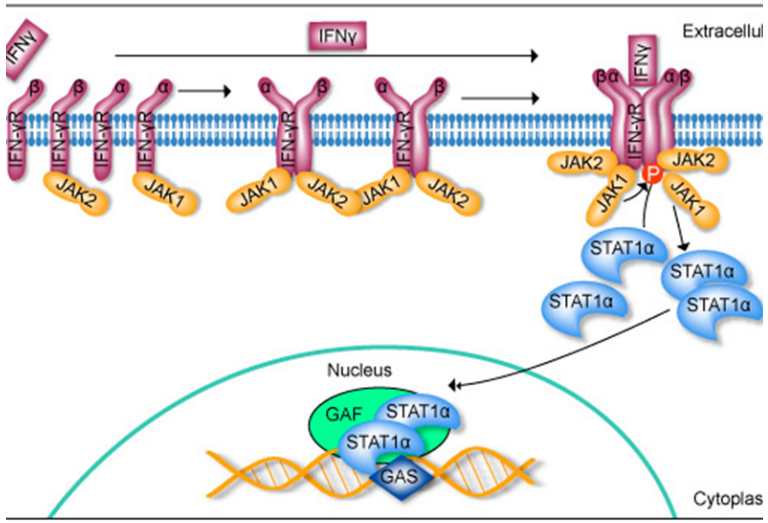
- New Drug Updates: Solid Tumors
- HR+ HER2- Breast Cancer: Recent Advances and Best Practices

QUESTION 8

Emapalumab primarily targets _____.

Interferon Gamma (IFNγ)

- Cytokine that is critical for innate and adaptive immunity against viral, some bacterial and protozoal infections
  - In response to specific antigens IFNγ is produced by NK and NK-T cells, and CD4+, CD8+ and cytotoxic T-lymphocytes
  - Ability to inhibit viral replication directly
  - Associated with cytostatic/cytotoxic and antitumor mechanisms during cell-mediated immunity
  - Important activator of macrophages and inducer of Class II major histocompatibility complex (MHC) molecule expression
  - IFNγ binding to the Interferon gamma receptor 1 (IFNGR1) and INFGR2 activates the JAK-STAT pathway

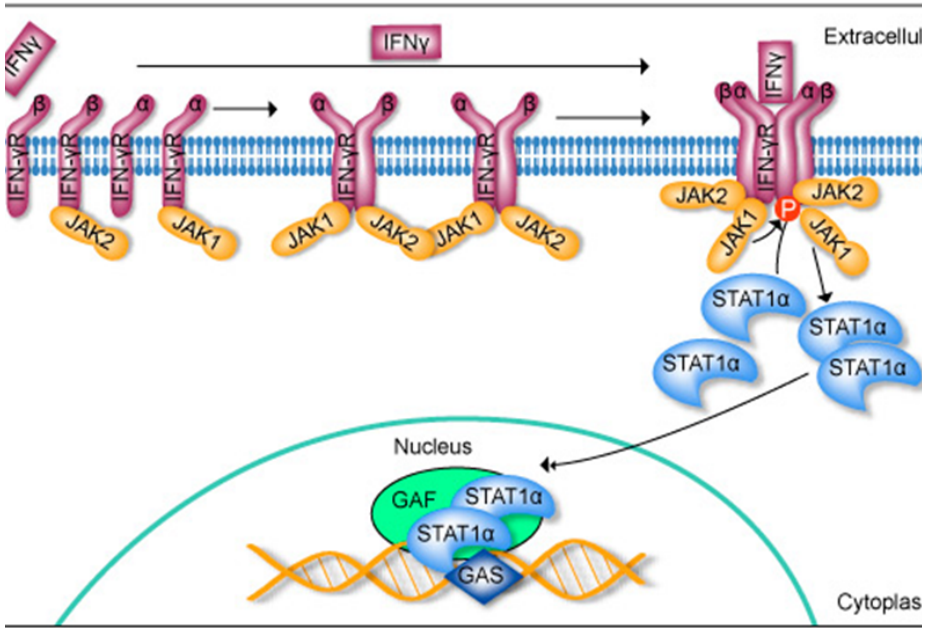


Zaidi MR & Merlino G (2011) Clin Cancer Res; 17(19); 6118–24

Interferon Gamma (IFNγ)

How measured:

- Plasma IFN-γ levels can be measured with an enzyme-linked immunosorbent assay (ELISA)
- IFNγ significantly correlates with levels of the signature gene product CXCL9
  - CXCL9 levels have a role as markers that reflect IFNγ production – can be measured with ELISA



Zaidi MR & Merlino G (2011) Clin Cancer Res; 17(19); 6118–24

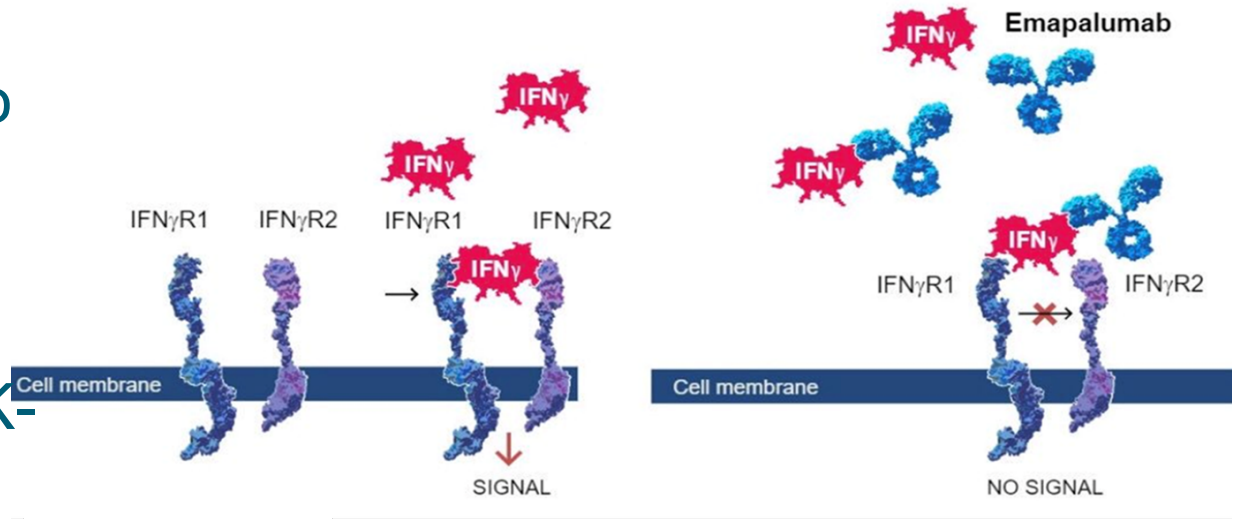
Emapalumab (Gamifant)

Indication

- hemophagocytic lymphohistiocytosis (HLH)
- IFNγ production is increased in HLH
- IFNγ binding to the receptor activates the JAK-STAT pathway

MOA

- Fully human IgG1 binding to INFγ with high affinity
- Recognizes free IFNγ and IFNγ bound to its receptor
- Inhibits activation of the JAK-STAT Pathway



Koper, O. Et al. Arch Med Sci. 2018 Mar; 14(2): 313–320.

Emapalumab: Key Takeaways

- Adverse effects of manipulating the INFγ dependent pathway:
  - Warnings and precautions pertaining to infections: TB, herpes zoster, PJP, and fungal infections
    - Screening for pre-existing infections is required
    - Regular screening for adenovirus, CMV, EBV, and TB is required
    - Prophylaxis for fungal, herpes zoster, and PJP recommended
  - Live or live attenuated vaccines should not be administered to patients receiving emapalumab

QUESTION 8 ANSWER

Emapalumab primarily targets interferon gamma (**IFNγ**).

Want to know more? Related sessions at JADPRO Live 2019

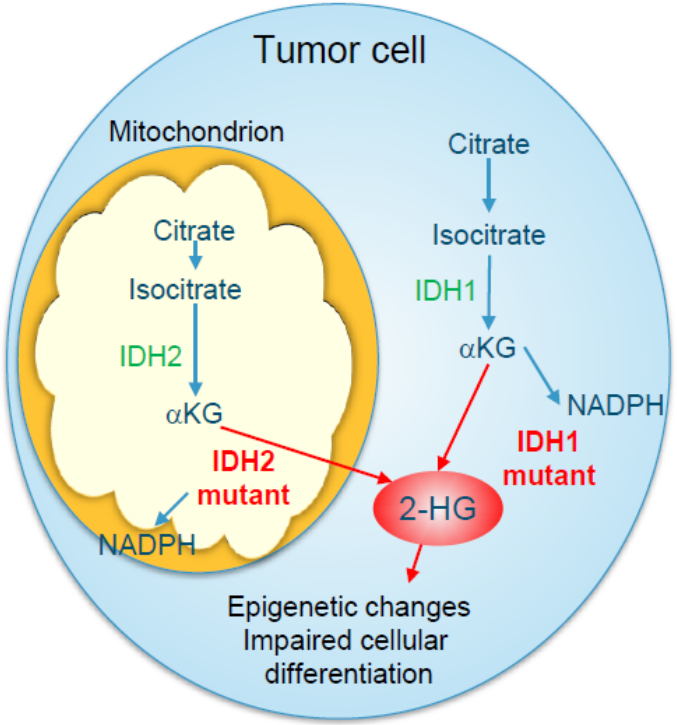
- New Drug Updates: Hematologic Malignancies

QUESTION 9

Ivosidenib is approved in relapsed/refractory AML with ____ mutation.

Isocitrate dehydrogenase (IDH)

- Isocitrate dehydrogenase is an enzyme that catalyzes the conversion of isocitrate to alpha-ketoglutarate to produce NADPH from NADP+
  - Plays crucial role in gene regulation and tissue homeostasis
- IDH mutations occur in approximately 20% of patients with AML → results in gain-of-function gene (2-HG)
  - IDH1 mutations occur in ~6-9% of AML cases
  - IDH2 mutations occur in ~8-12% of AML cases
- IDH mutations require detection by FDA-approved test
  - Abbott Real*Time*™ diagnostic test by polymerase chain reaction (PCR) assay



Dang et al. *Nature*.2009;462:739-744

https://www.molecular.abbott/us/en/products/oncology/realtime-idh1

Ivosidenib

- Relapsed/refractory and newly diagnosed AML (May 2019) with IDH1 mutation* in patients ≥75 years old or who have comorbidities that preclude intensive chemotherapy
- Dose: 500 mg once daily (supplied as 250 mg tablets)
  - With or without food
  - Avoid a high-fat meal → increases C_{max} by 98%
    - Example of high-fat meal: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 oz. of whole milk (~1000 calories and 58 grams of fat)

*as detected by an FDA-approved test

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation

Ivosidenib

- Black Box Warning: Differentiation Syndrome
  - Can develop as early as 1 day after start of therapy and during the first 3 months of treatment
  - Symptoms: fever, cough or difficultly breathing, rash, decreased urinary output, hypotension, rapid weight gain, or swelling of arms or legs
    - Initiate dexamethasone 10 mg IV every 12 hours (or equivalent dose) until improvement and for a minimum of 3 days
- Drug interactions: CYP3A4 substrate
  - Strong CYP3A4 inhibitors: reduce ivosidenib to 250 mg once daily
  - Strong CYP3A4 inducers: avoid use
  - QTc prolonging drugs: monitor

Tibsovo® Package Insert

QUESTION 9 ANSWER

Ivosidenib is approved in relapsed/refractory AML with isocitrate dehydrogenase 1 (**IDH1**) mutation.

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Hematologic Malignancies

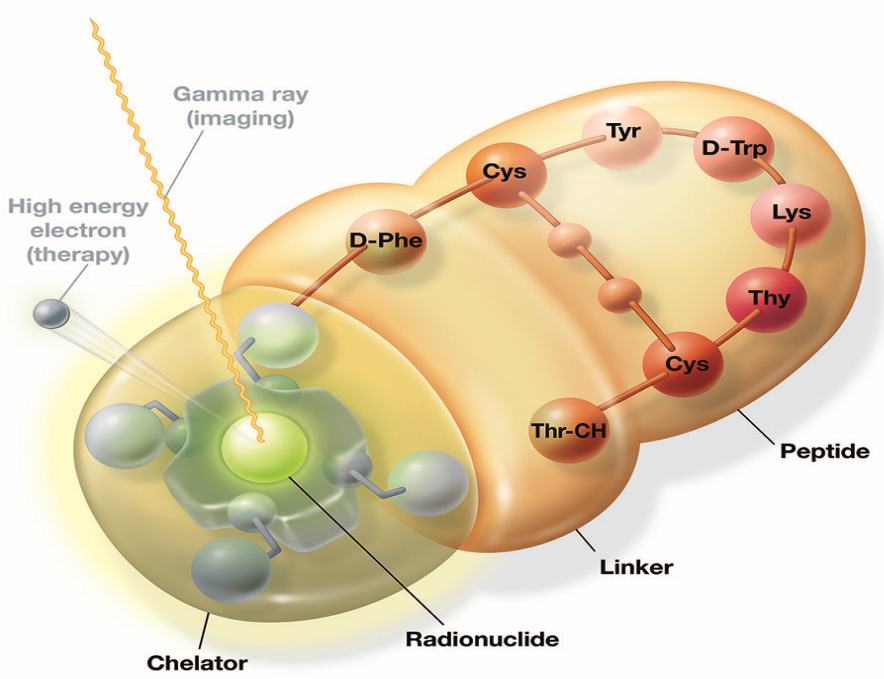
QUESTION 10

^{177}Lu-Dotatate binds to ____ receptors in neuroendrocrine tumors.

^{177}Lu-Dotatate: Targeted Radiopharmaceutical

- ^{177}Lu-DOTATATE belongs to an innovative drug category called PRRT (Peptide Receptor Radionuclide Therapy). PRRT involves the **systemic administration** of a specific radiopharmaceutical to deliver cytotoxic radiation to a tumor[1]
- ^{177}Lu-DOTATATE is composed of a **lutetium radionuclide chelated to a peptide[1].** Lutetium emits high energy electrons (therapy) and gamma rays (imaging).
- The peptide is designed to **target somatostatin receptors[1]** which are **overexpressed in approximately 80% of NETs.**

Structure of a radiopharmaceutical[2]



The affinity for SSTRs and the specificity of binding ensures a high level of specificity in the delivery of radiation to the tumor

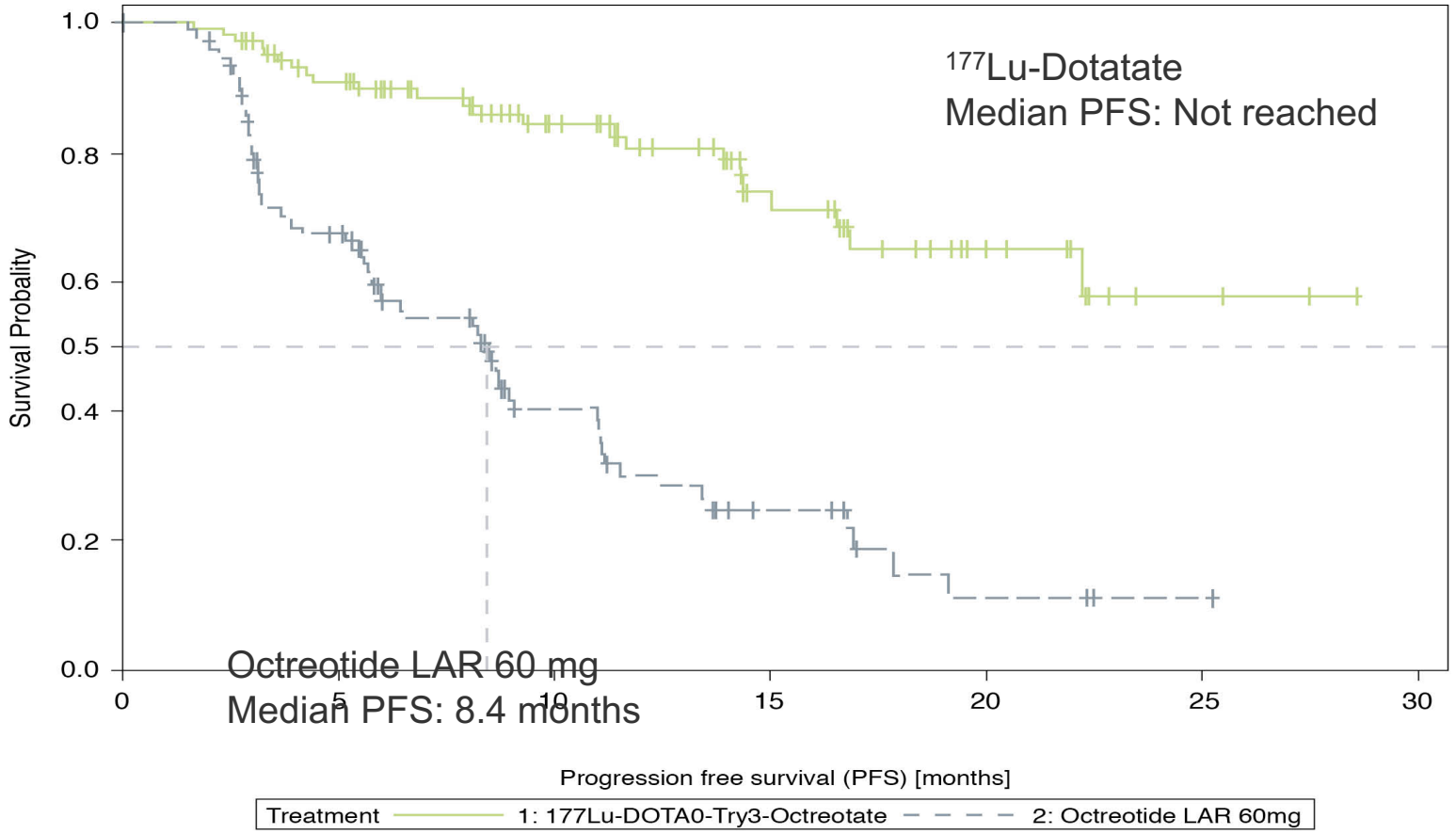
1. Zaknun et al. Eur J Nucl Med Mol Imaging 2013, 40: 800-16; 2. Bergsma et al. Best Practice & Res Clin Gastroenterol 2012, 26: 867-81 3. Reubi et al. Eur J Nucl Med Mol Imaging 2003, 30: 781-93

^{177}Lu-Dotatate vs. Octreotide: Progression-Free Survival

N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
Risk reduction: 79.1
p < 0.0001



Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Practical Considerations in Lutathera Administration

Hospital-based currently due to monitoring for toxicity and radiation exposure

- Lutathera infused i.v. over 30 minutes
- Amino acids infused i.v. over 4-6 hours
- Anti-nausea medication and titration of AAs are very important
- Requires team effort between NM and oncology, and nursing
- Location?

- Limited emitted exposure
  - 2 mR/hr @ 1m at end of first day
  - 1 mR/hr @ 1m the next morning
- Excreted exposure may be more significant
- Routine precautions if patient goes home though not as strict as I-131

QUESTION 10 ANSWER

^{177}Lu-Dotatate binds to **Somatostatin** receptors in neuroendrocrine tumors.

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Solid Tumors

QUESTION 11

Moxetumomab pasudotox-tdfk regulates the activity of the B-cell receptor pathway through _____.

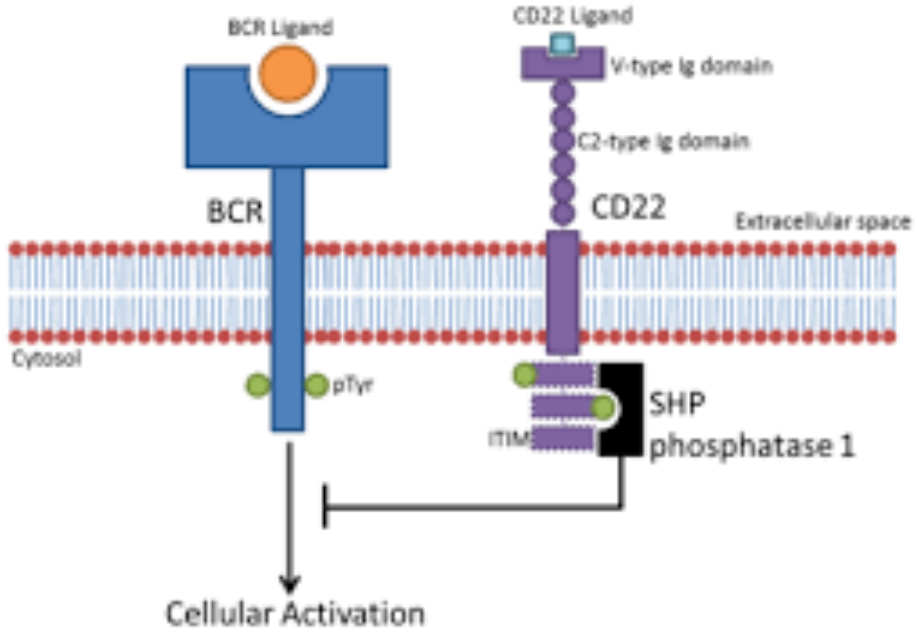
CD22

- CD22 is a B-lymphocyte lineage-restricted transmembrane protein that first emerges on the face of pre-B-cells and is fully expressed by differentiated IgM+, IgD+ B-cells
- The cytoplasmic domain of CD22 has six tyrosine domains as potential targets for phosphorylation, including regions related to the tyrosine-based inhibition

- Inhibitory proteins results in negative regulation of B-cell receptor (BCR) signaling
- Inhibition leads to apoptosis of B-cells expressing CD22

How measured:

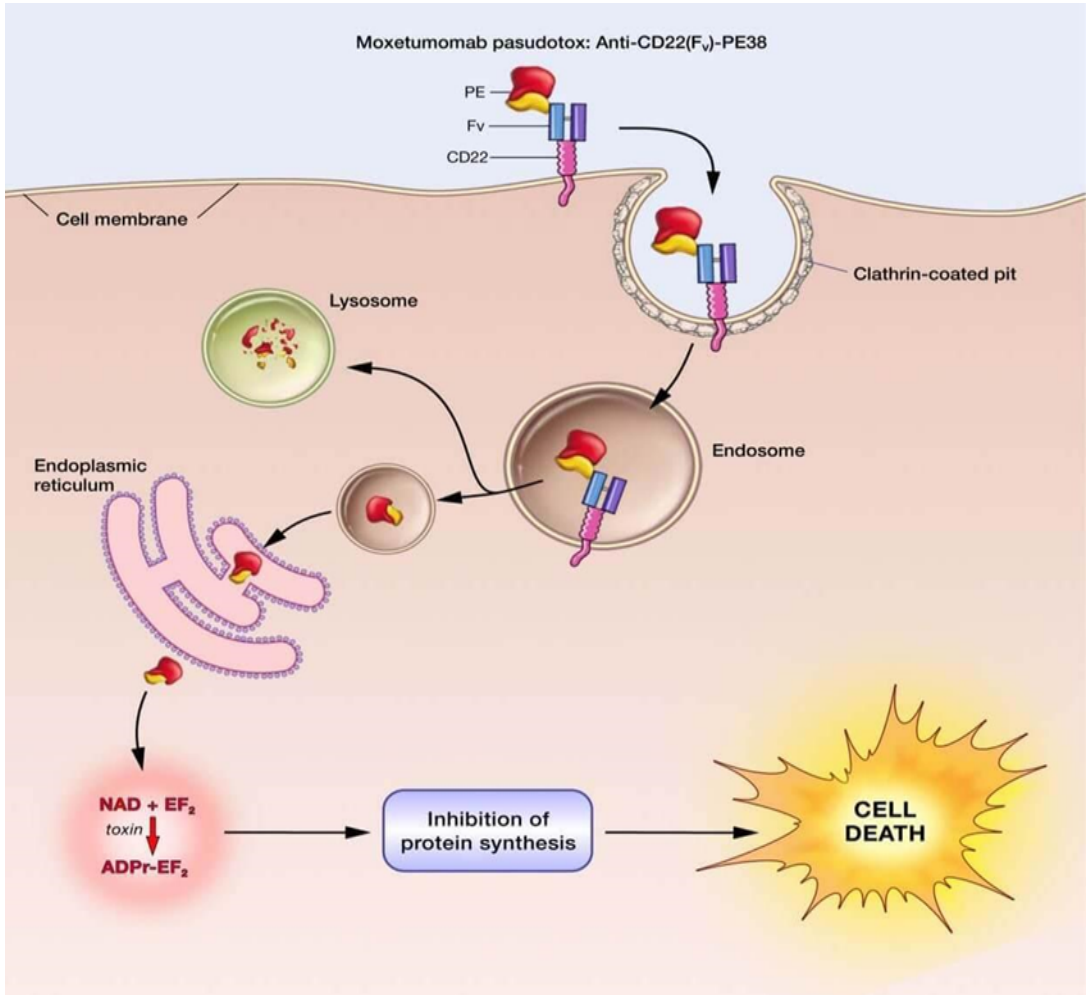
- Multiparameter Flow Cytometry: peripheral blood, bone marrow, tissue



Kreitman RJ, Pastan I. (2011) Clinical Cancer Res, 17(20):6398-6405

Moxetumomab pasudotox-tdfk

- Indication
  - CD22 is an attractive target for immunotoxin therapy, as it is a B-cell antigen expressed particularly strongly in hairy cell leukemia and ALL
- MOA
  - Murine immunoglobulin variable domain genetically fused to a truncated form of Pseudomonas exotoxin, PE38
  - After binding to CD22, moxetumomab pasudotox-tdfk is internalized
  - *Pseudomonas* exotoxin catalyzes inhibition of protein synthesis by ADP-ribosylation of elongation factor 2
  - Results in apoptotic cell death



Cancer Chemotherapy and Pharmacology (2019) 84:255–263

Moxetumomab pasudotox-tdfk: Key Takeaways

- Targeting CD22 can have therapeutic benefit in HCL
- Adverse effects of manipulating the CD22 pathway in HCL
  - Capillary Leak Syndrome (CLS), including life-threatening cases
    - Monitor weight and blood pressure; check labs, including albumin, if CLS is suspected.
    - Delay dosing or discontinue LUMOXITI as recommended.
  - Hemolytic Uremic Syndrome (HUS), including life-threatening cases
    - Monitor hemoglobin, platelet count, serum creatinine, and ensure adequate hydration.

QUESTION 11 ANSWER

Moxetumomab pasudotox-tdfk regulates the activity of the B-cell receptor pathway through **CD22.**

Want to know more? Related sessions at JADPRO Live 2019

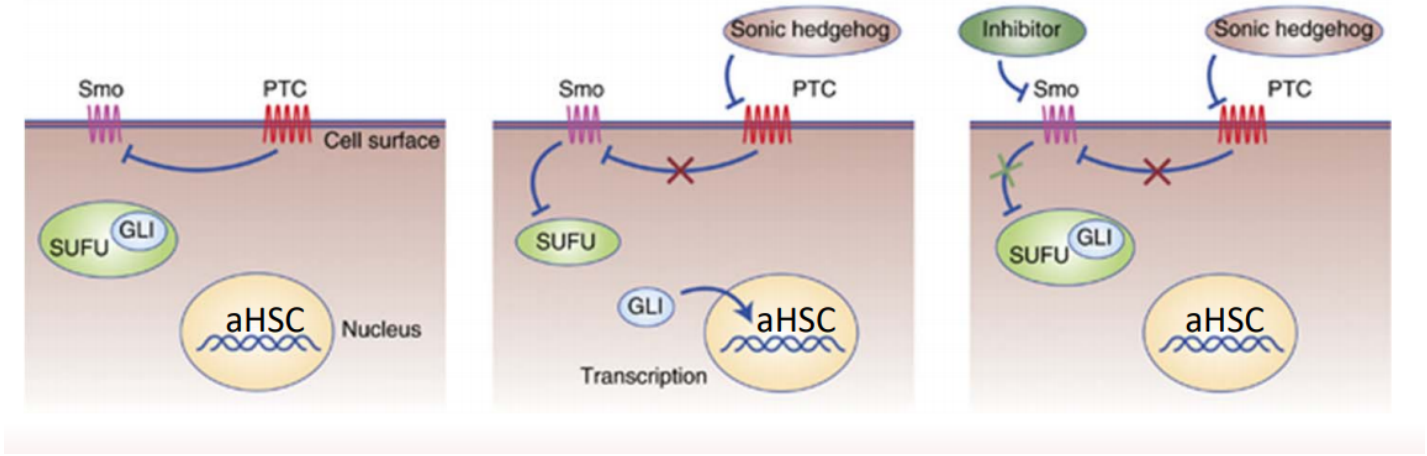
- New Drug Updates: Hematologic Malignancies

QUESTION 12

Glasdegib inhibits _____, which is involved in the sonic hedgehog signaling pathway.

Sonic Hedgehog Signaling

- Sonic hedgehog signaling (Shh) pathway is essential for normal embryonic development and plays a role in adult tissue maintenance, renewal, and regeneration



- Glasdegib inhibits smoothened (SMO) involved with downstream signaling effects that lead to cell proliferation and apoptotic suppression

Smo=smoothened; aHSC=abnormal hematopoietic stem cells

Lear J, et al. Brit Cancer 2014;111(8):1476-1481

Glasdegib

- Newly diagnosed AML in combination with low-dose cytarabine in adult patients ≥75 years old who have comorbidities that preclude use of intensive induction chemotherapy
- Dose: 100 mg once daily
  - With or without food
  - Supplied as 25 mg and 100 mg tablets
- Warnings and precautions: Embryo-fetal toxicity
- Adverse reactions (≥20%)
  - Anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash

QUESTION 12 ANSWER

Glasdegib inhibits Smoothened (**SMO**), which is involved in the sonic hedgehog signaling pathway.

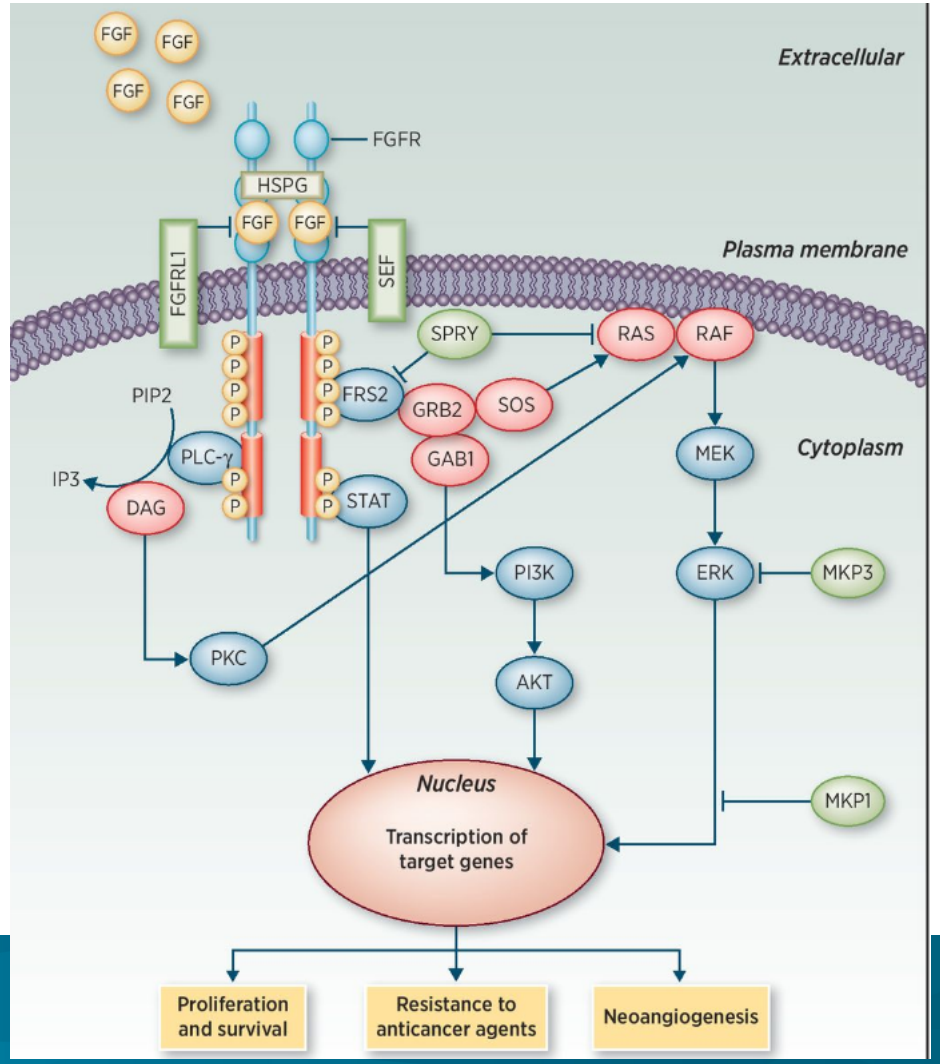
Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Hematologic Malignancies

QUESTION 13

Erdafitinib targets mutations or fusions in the ____ gene.

FGFR: Transmembrane Receptor Tyrosine Kinase



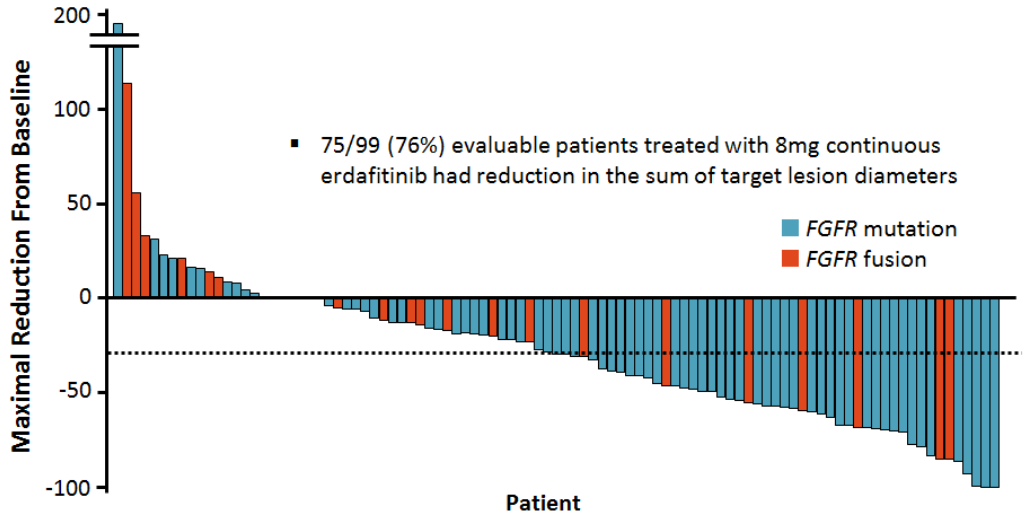
Constitutive activation through mutation or amplification leads to unregulated downstream signaling

FGFR Alterations (Fusions or Mutations)

Tumor Type	Frequency of *FGFR* Alterations, %
Metastatic urothelial cancer	15-20
Nonmetastatic invasive bladder cancer	40-70
Cholangiocarcinoma	14-22
NSCLC	4
Hepatocellular carcinoma (FGF19 amplification)	21
Glioblastoma	23
Breast cancer	3-5
Ovarian cancer	7
Head and neck cancer	9-17

Siefker-Radtke. ASCO 2018. Abstr 4503

Erdafitinib Phase II Study in Metastatic Urothelial Carcinoma With *FGFR* Alterations



Response	N = 99
ORR (investigator assessment), n (%)	40 (40.4)
▪ CR	3 (3.0)
▪ PR	37 (37.4)
▪ SD	39 (39.4)
▪ PD	18 (18.2)
Median time to response, mos	1.4
Median DoR, mos (95% CI)	5.6 (4.2-7.2)
ORR in chemo naive vs progressed/relapsed after chemo, n/N (%)	5/12 (41.7) vs 35/87 (40.2)
ORR with vs without visceral metastases, n/N (%)	30/78 (38.5) vs 10/21 (47.6)

At 11 mos of follow-up, 21.2% of patients remain on treatment

Loriot Y, et. al. NEJM 2019

Erdafitinib

- On April 12, 2019, the FDA granted accelerated approval to erdafitinib for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.
- Erdafitinib can cause ocular disorders. Central serous retinopathy or retinal pigment epithelial detachment resulting in visual field defect was reported in 25% of patients.
- The most common adverse reactions reported in at least 40% of patients were increased serum phosphate, stomatitis, fatigue, increased serum creatinine, diarrhea, dry mouth, onycholysis, increased alanine aminotransferase, increased alkaline phosphatase, and decreased sodium.

Starting dose 8 mg, escalating to 9 mg depending upon hitting target serum phosphate level

QUESTION 13 ANSWER

Erdafitinib targets mutations or fusions in the **FGFR** transmembrane receptor tyrosine kinase gene.

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Solid Tumors

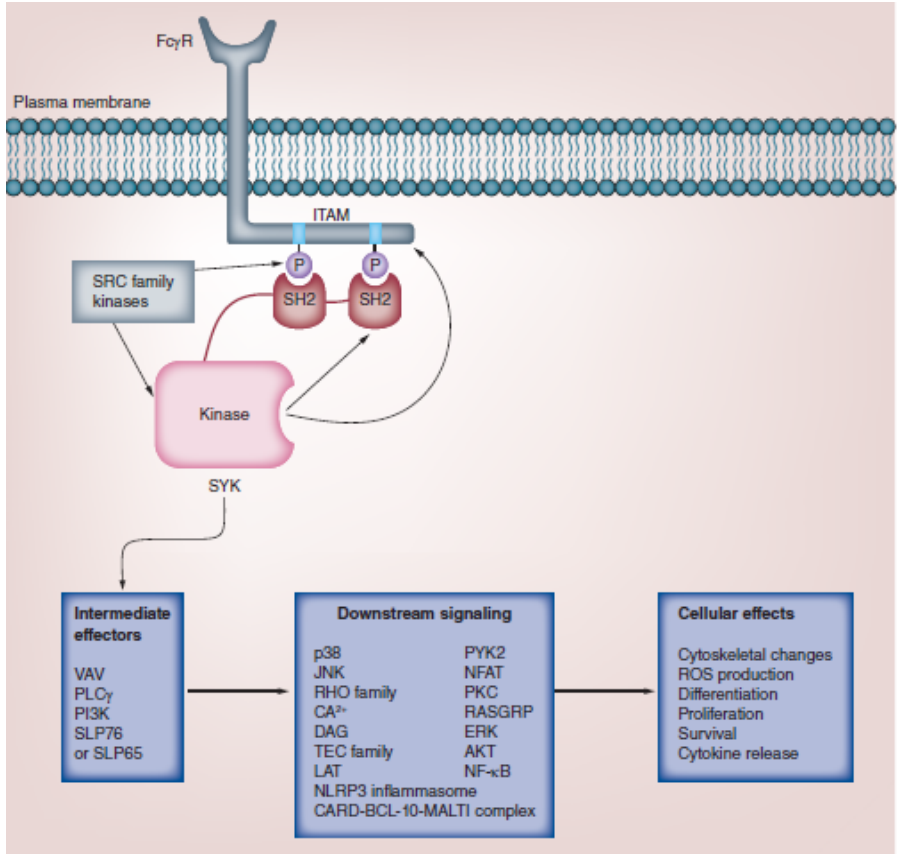
QUESTION 14

Fostamatinib is a _____ inhibitor, which impairs phagocytosis of antibody-coated platelets.

Spleen tyrosine kinase (SYK)

- All activating Fc receptors signal via Syk
- Roles in cellular proliferation, differentiation, survival, immune regulation, and cytoskeletal rearrangements during phagocytosis.
- Involved in B and T-cell function, platelet aggregation, mast cell signaling, neutrophils and macrophages.
- Member of the cytoplasmic protein tyrosine kinase family that is expressed extensively in hematopoietic cells
  - Syk is recruited and activated upon binding of FcγRs to their ligands
  - Leads to phosphorylation of immunoreceptor tyrosine-based activation motifs by SRC family tyrosine kinases (or by Syk itself)
  - Leads to recruitment of Syk and activation of downstream signaling cascades
  - Lead to cellular responses such as proinflammatory responses or cytoskeletal rearrangement and phagocytosis

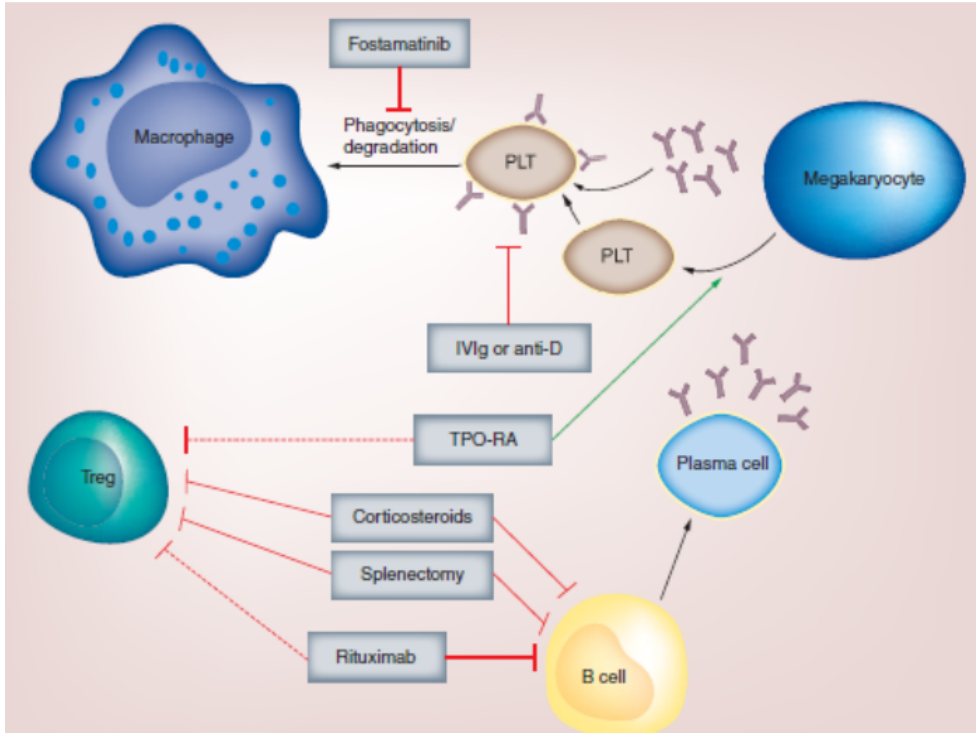
How measured/tested – flow, NGS, PCR etc.



Newland et al. (2018) Immunotherapy, 10(1), 9–25

Fostamatinib

- Indication: Adult patients with persistent or chronic ITP
- Impairs phagocytosis of antibody coated platelets via inhibition of Syk



Fostamatinib: Key Takeaways

- Moderate to severe AEs: HTN, hepatotoxicity, diarrhea, neutropenia
  - Baseline evaluation, prevention/co-management, and continued surveillance are key
  - Discontinue after 12 weeks of treatment if the platelet count does not increase to a level enough to avoid clinically important bleeding
  - Small molecule TKI – consider drug-drug interactions

https://tavalisse.com/

QUESTION 14 ANSWER

Fostamatinib is a spleen tyrosine kinase (**SYK**) inhibitor, which impairs phagocytosis of antibody-coated platelets.

Want to know more? Related sessions at JADPRO Live 2019

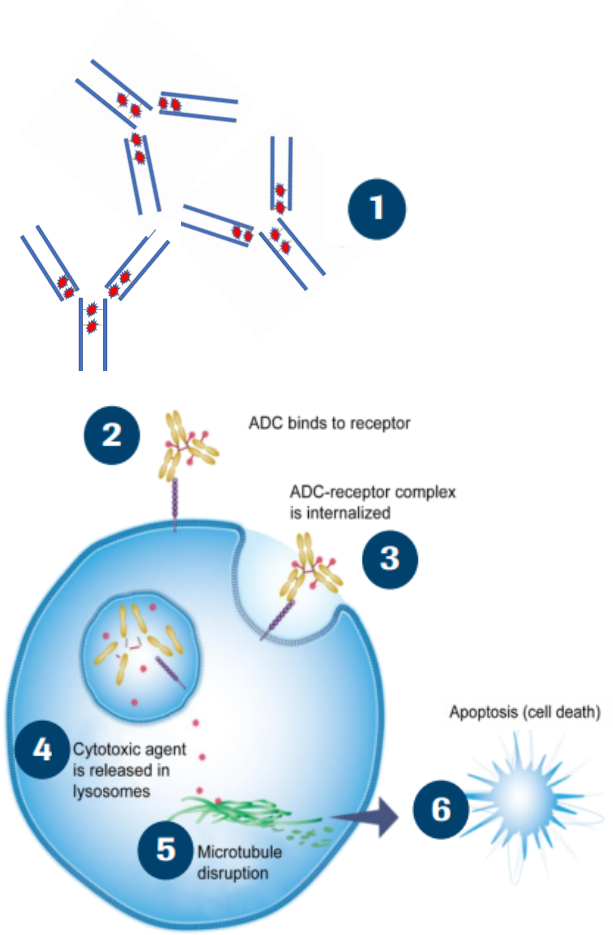
- New Drug Updates: Solid Tumors

QUESTION 15

Polatuzumab vedotin is a _____ directed monoclonal antibody conjugated to the cytotoxic agent MMAE, which is a microtubule inhibitor.

Polatuzumab vedotin

- Antibody Drug Conjugate (ADC)
  - Recombinant monoclonal antibody (mAB)
  - Cytotoxic agent
  - Synthetic linker
- CD79b-directed monoclonal antibody conjugated to monomethylauristatin E (MMAE)
  - CD79b is a component of the B-cell receptor expressed in mature B-cell lymphomas
  - MMAE is a microtubule destabilizer arresting cell cycle at G2/M phase



Adapted from Polivy™ Package Insert

Polatuzumab vedotin

- R/R DLBCL after ≥ 2 prior therapies in combination with bendamustine and rituximab (P+BR)
- Dosing for P+BR:
  - Polatuzumab vedotin 1.8 mg/kg IV on day 1
    - Initial infusion: over 90 minutes
    - Subsequent infusions (if previously tolerated): over 30 minutes
  - Bendamustine 90 mg/m^2/day IV on days 1 and 2
  - Rituximab 375 mg/m^2 IV on day 1
  - **Cycle length = 21 days**
- Pre-medication: If not already premedicated for rituximab, administer antihistamine and antipyretic at least 30 minutes prior to polatuzumab vedotin

R/R=relapsed or refractory; DLBCL=diffuse large B-cell lymphoma

Polatuzumab vedotin is a **CD79b** directed monoclonal antibody conjugated to the cytotoxic agent MMAE, which is a microtubule inhibitor.

Want to know more? Related sessions at JADPRO Live 2019

- New Drug Updates: Hematologic Malignancies

Questions?

Come see us at Booth **#829** (next to the APSHO Booth)
in the Exhibit Hall from **10:15 to 11:15 am** today.

SMARTIE

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019