Fred Hutch Cancer Center

Solid Tumor Pharmacotherapy Pearls

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Clinical Oncology Pharmacist
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UW Medicine

Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

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Taxane Dermatologic Toxicities

54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy and radiation receiving adjuvant docetaxel and cyclophosphamide.

Which of the following are dermatologic adverse effects associated with this regimen?

a. Alopecia
b. Paronychia and onycholysis
c. Macular and papular eruptions
d. Palmar-plantar erythrodysesthesia
e. All of the above

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Taxane Dermatologic Toxicities - Alopecia

54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy and radiation receiving adjuvant docetaxel and cyclophosphamide.

Which of the following statements are true regarding alopecia?

a. Minoxidil may help in prevention of hair loss once cytotoxic chemotherapy is initiated
b. Randomized clinical trials show 90% of patients developing grade 1 alopecia with scalp cooling versus 0% without scalp cooling
c. Guidelines do not recommend considering scalp cooling to reduce chemotherapy-induced alopecia
d. Scalp cooling trials show greater efficacy with taxane-based regimens and lower efficacy when anthracyclines are combined with taxane or cyclophosphamide

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Taxane Dermatologic Toxicities - Alopecia

Depends on hair thickness and texture, and studies do not address this and enroll a low% of Black and/or non-White patients

TABLE 1. Suggestions for Black Patients With Tightly Curled Hair Undergoing Scalp Cooling

Hair Type	Preferable Hairstyles	Other Considerations
Natural hair with no chemical straightener or relaxer	Thermally straighten hair before treatment and apply hair grease to the hair only (not scalp) to keep the hair in partially straight form before lightly dampening the entire scalp with cold water. Small single twists or braids of natural hair without extensions are permissible.	Minimize curl reversion by avoiding excessive wetting of the hair and focus water on scalp as much as possible. Cornrows with and without extensions should be avoided as well as dreadlocks because of the potential for large portions of unexposed scalp under the braids.
Chemically straightened (eg, keratin, Japanese straightener) or relaxed hair	Treat hair before scalp cooling per manufacturer's recommendations. It is permissible to wet hair before treatment. Small twists or braids without extensions are acceptable.	If the hair is only partially relaxed (eg, texturized), consider recommendations for natural hair.
Considerations for all patients (natural or chemically straightened hair)	During treatment, avoid all forms of extensions that use synthetic hair, including braids, twists, cornrows, weaves, lacefront wigs, and crochet braids.	

Araoye EF, Stearns V, Aguh C. J Linc Oncol 2020; 38(30);3575-3576

Taxane Dermatologic Toxicities – Nail toxicities

Onycholysis: 43.7% with paclitaxel, 32.9% with docetaxel

- Severe onycholysis almost exclusively occurs with taxanes
- Dose-related and cumulative dose related
- More common with once weekly regimen

Management

- Hold for grade 3 or higher and resume when severity is grade 1
- Consider frozen gloves and socks for taxane based therapies
- Consider topical povidone iodine 2% BID for paronychia
- Consider topical antibiotics and/or steroids for paronychia
    - Topical clobetasol solution
    - Topical clindamycin or ketoconazole
- Consider antibiotics covering S. aures and gram positive bugs for onycholysis

Lacouture ME, Sibaud V, Gerber PA, et al. Ann Oncol 2021; 32(2): 157-170; Robert C, Sibaud V, Mateus C, et al. Lancet Oncol 2015; 16(4):e181-e189

Capriotti K, Capriotti J, Lessin S. Cancer Manag Res 2017; 9: 225-228

Taxane Dermatologic Toxicities – Cutaneous Changes

54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy and radiation receiving adjuvant docetaxel and cyclophosphamide.

Which of the following statements are true regarding cutaneous toxicities with taxanes? (Choose all that apply)

a. Macular and popular eruptions tend to occur in flexural areas or intertriginous zones
b. Folliculitis may occur but is not dose-limiting
c. Palmar plantar erythrodysesthesia (hand foot syndrome) is more common docetaxel and distinctly presents on the dorsal surface
d. There is a higher incidence of hand-foot syndrome with taxanes compared to 5-flurouracil based therapies.

Sibaud V, Leboeuf NR, Roche H, et al. Eur J Dermatol. 2016. 26(5);427-43

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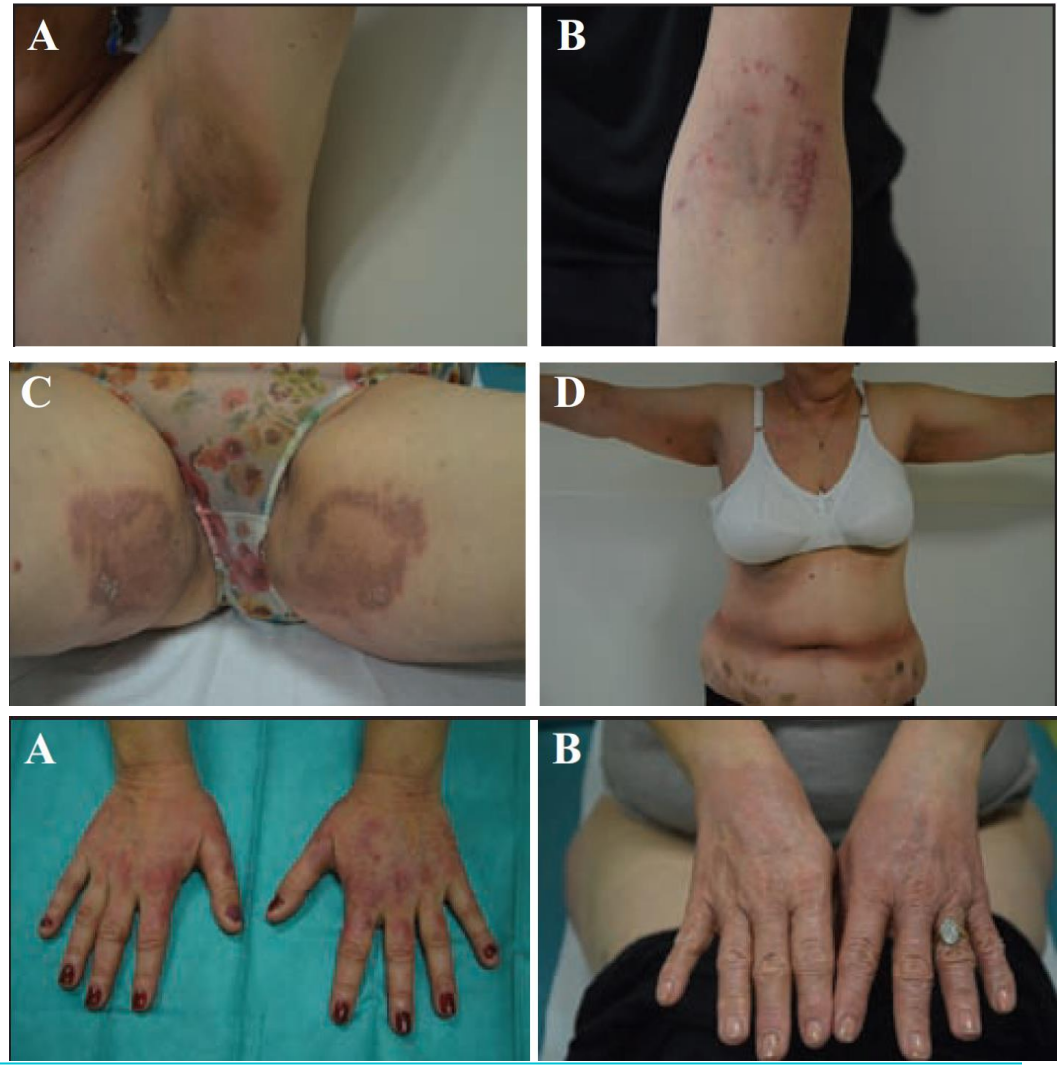

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Patient Case 2

Laboratory abnormalities with CDK 4/6 Inhibitors

54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy, radiation, and adjuvant docetaxel and cyclophosphamide x4 cycles. She will be receiving adjuvant CDK 4/6 inhibitor and endocrine therapy with ribociclib and letrozole.

Ten days after initiation, her AST is 75 (2xULN) and her ALT is 195 (5.9xULN). Her Tbili is WNL. What is our next course of action?

a. This is Grade 1 (>ULN to 3xULN) elevation, no changes necessary
b. This is Grade 1 AST elevation and Grade 3 ALT elevation, no changes necessary.
c. This is Grade 2 (3-5xULN), hold ribociclib until recovery to baseline and restart at the same dose
d. This is Grade 3 (5-20xULN), hold ribociclib until recovery to baseline and resume at the next lower dose level

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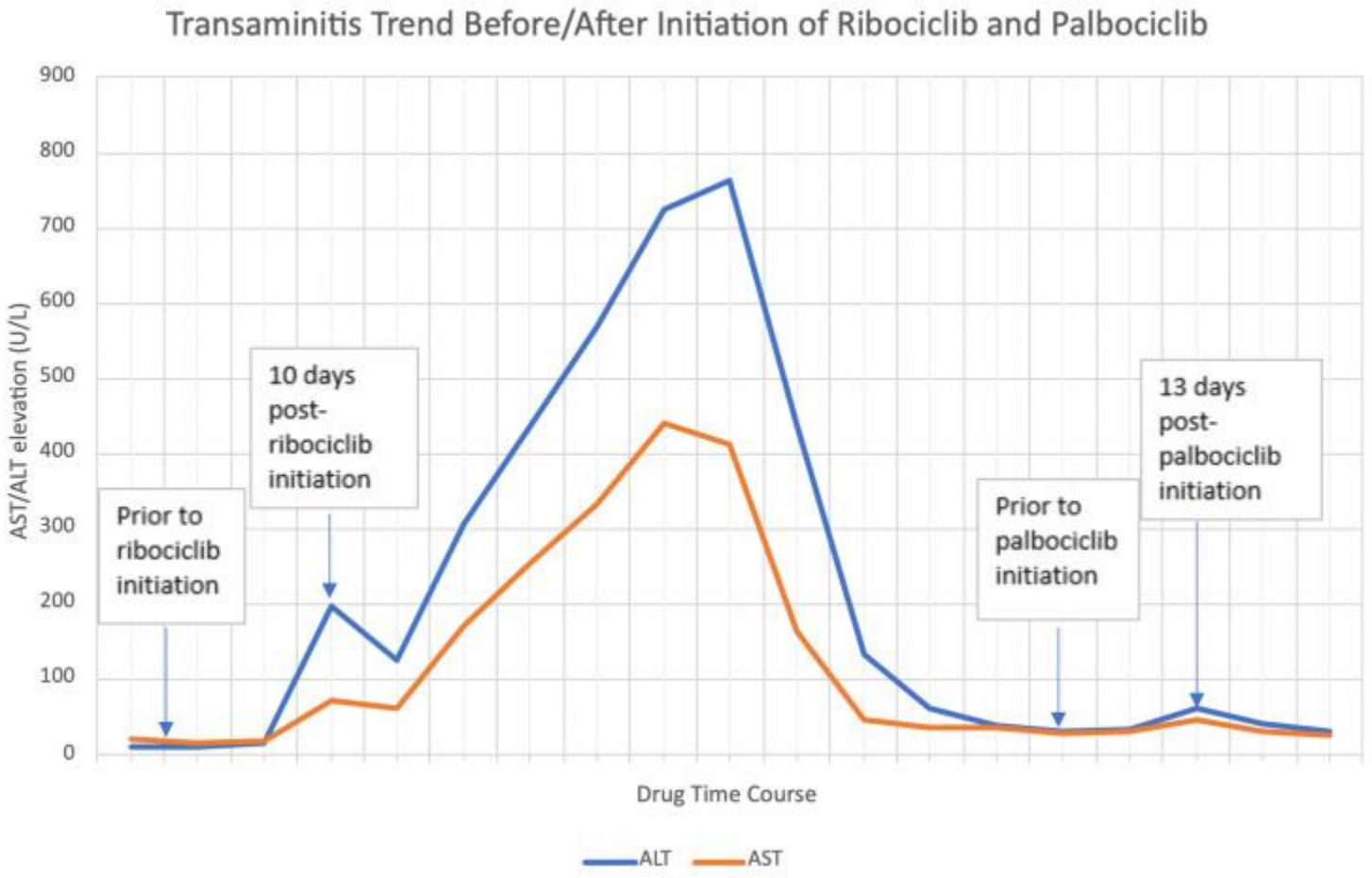
LFT abnormalities



Wani K, Patel K, Dabak V. Cureus 2023; 15(6):e40871

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Two weeks after initiation, labs show a SCr of 1.1mg/dl. Her baseline SCr is 0.8mg/dl. She denies diarrhea, fever, signs or symptoms of UTI or other infections. She is drinking 8-12 cups of water a day. Which of the following statement best represents management of serum creatinine increase?

a. Abemaciclib is known to increase SCr, continue abemaciclib
b. As all other causes of AKI have been ruled out, hold drug and draw a cystatin C. Resume when cystatin C results show normal GFR
c. As all other causes of AKI have been ruled out, draw a cystatin C and continue abemaciclib.
d. Abemaciclib is renally cleared, hold the medication until recovery to baseline

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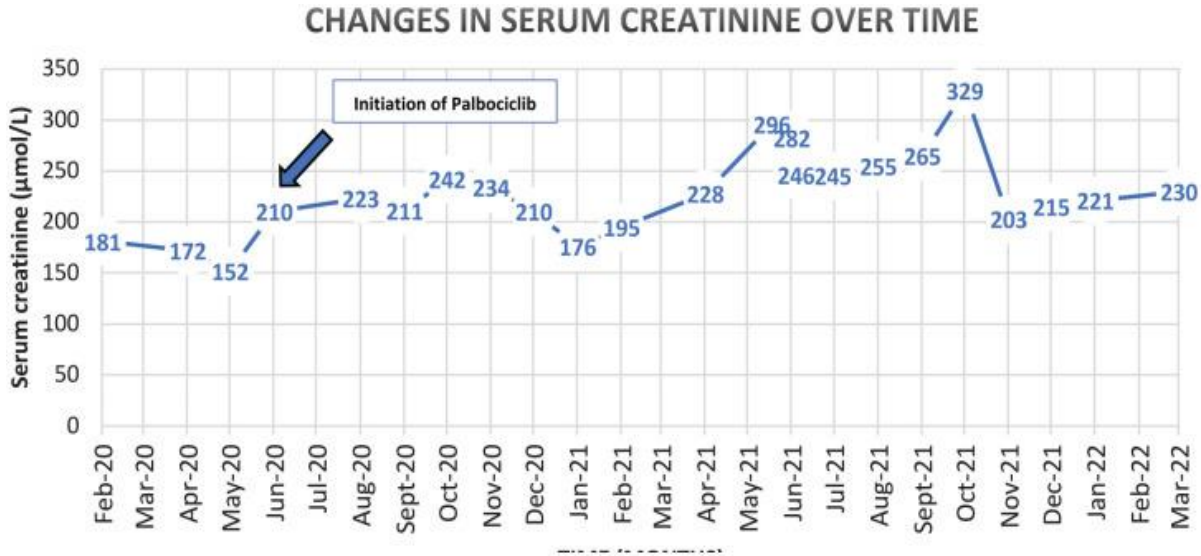
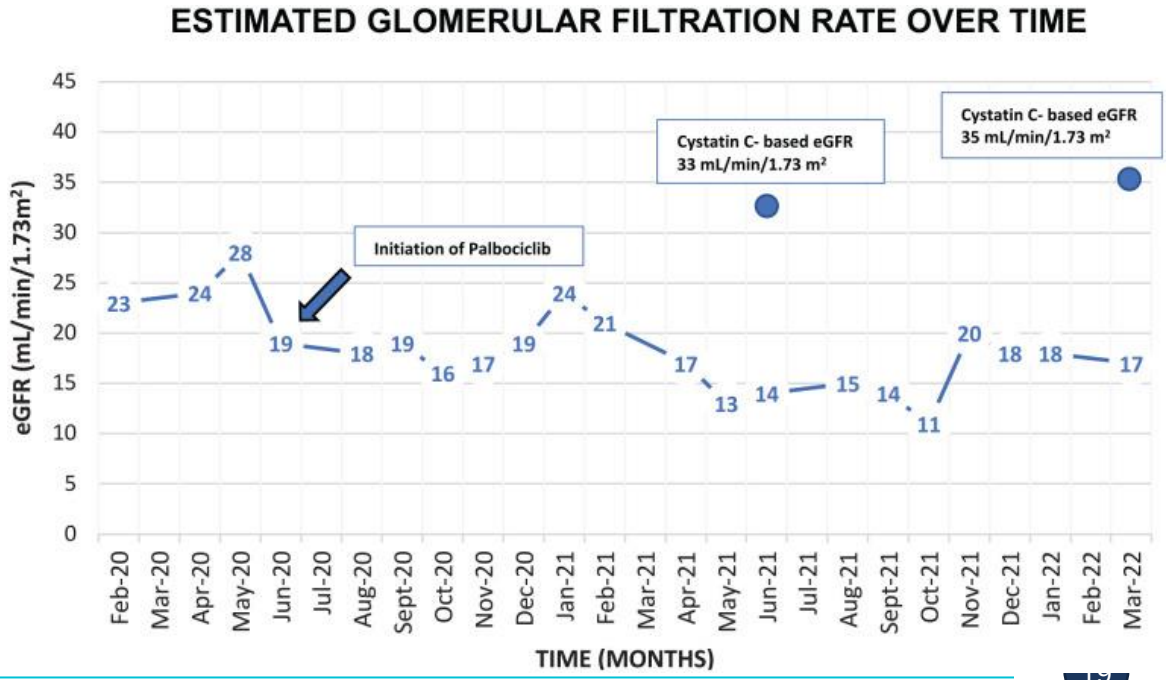
Inhibition of Renal Tubular Secretion

- Inhibition of renal transporters such at OCT-2, MATE1, MATE2-K
- False elevation of *serum* creatinine
- GFR unaffected
- Consider measuring cystatin C to estimate GFR





Renal transporter inhibitors

- Targeted agents that cause asymptomatic rise in SCr through inhibition of active tubular secretion
  - CDK 4/6 inhibitors: palbociclib, ribociclib, abemaciclib
  - PARP inhibitors: Olaparib, rucaparib, niraparib
  - ALK inhibitors: crizotinib, alectinib, ceritinib
  - BCR-ABL inhibitors: imatinib
  - EGFR inhibitors: gefitinib
  - VEGFR inhibitors: pazopanib, sunitinib, sorafenib
  - HER2 inhibitors: tucatinib
  - MET inhibitors: capmatinib

Mach T, Qi A, Bouganim N, et al. Can J Kidney Health Dis 2022; 9:20543581221106246

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a. Abemaciclib may cause a false elevation in serum creatinine.
b. Abemaciclib and ribociclib may cause a false elevation in serum creatinine.
c. The incidence of neutropenia is similar across abemaciclib, ribociclib, and palbociclib.
d. Abemaciclib is associated with transaminitis.

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Patient Case 3

Overlapping Adverse Effects: mAbs + ICIs

BB is a 79 year old man with a new diagnosis of right upper tract urothelial carcinoma with metastases to the L acetabulum. He will be initiating therapy with enfortumab vedotin and pembrolizumab along with zoledronic acid to reduce the risk for bone fractures.

Two weeks after initiation, patient's non-fasting blood glucose was 268mg/dl. His last random blood glucose was 87mg/dl with no history of diabetes or hyperglycemia. Which statement best represents the next course of action?

a. Hold pembrolizumab and enfortumab vedotin
b. Continue pembrolizumab and hold enfortumab vedotin
c. Hold pembrolizumab and continue enfortumab vedotin
d. Continue both pembrolizumab and enfortumab vedotin

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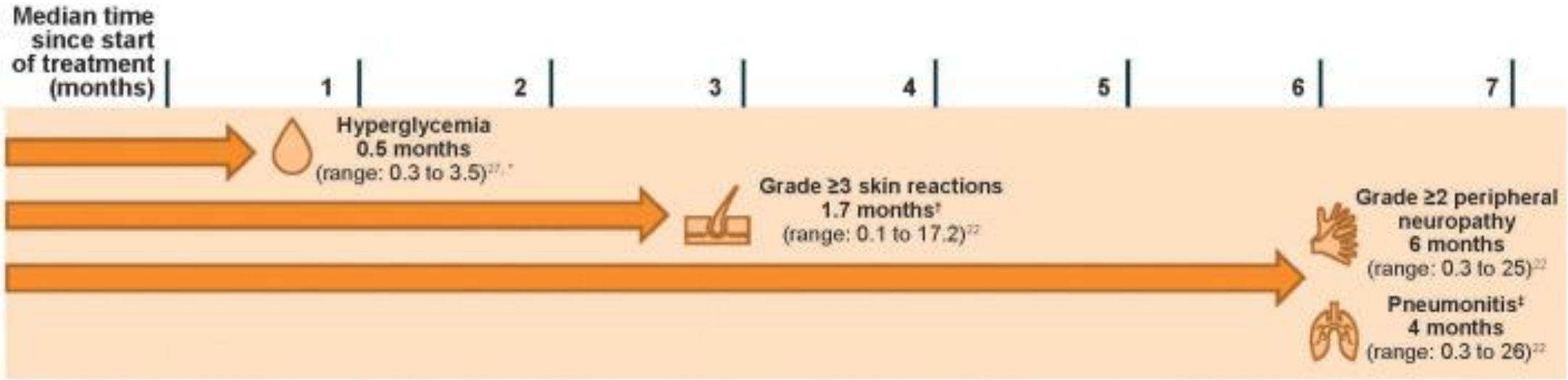
Timeline of Overlapping Adverse Effects



Brower B, McCoy A, Ahmad H, et al. Front Oncol 2024; 14:1326715

Overlapping Adverse Effects

Enfortumab vedotin	Combination	Pembrolizumab
• Hyperglycemia • Peripheral neuropathy • Ocular disorders	• Skin reactions • Pneumonitis	• Other IRAE

Brower B, McCoy A, Ahmad H, et al. Front Oncol 2024; 14:1326715

Management of Overlapping Adverse Effects

Grade 1

- Monitor
- Symptom management

Grade 2

- Symptom management with close monitoring and consider escalating supportive care
- Consider holding likely offending agent (EV for hyperglycemia, peripheral neuropathy)
- Consider specialist consult
- Hold both agents for severe adverse effects (pneumonitis)

Grade 3

- Hold both agents, reintroduce one agent at a time with symptom resolution
- Consider dose reduction for EV
- Ensure appropriate supportive care for steroid tapers >1 month
- Consider specialist consult

Brower B, McCoy A, Ahmad H, et al. Front Oncol 2024; 14:1326715

Antibody-drug Conjugates – Ocular Toxicities

	AE	Baseline eye exam	Regular eye exam	Steroid eye drops	Vasoconstrictor eye drops	Lubricating eyedrops	Cooling packs to eyes	Avoid contact lenses	FDA REMS
Trastuzumab emtansine	Blurred vision, conjunctivitis, dry eye, lacrimation								
Belantamab mafodotin	Severe vision loss, corneal ulcer, blurred vision, dry eyes	x				x		x	x
Enfortumab vedotin	Keratitis, blurred vision, dry eye								
Tisotumab vedotin	Severe vision loss, corneal ulceration	x	x	x	x	x	x	x	
Mirvetuximab soravtansine	Visual impairment, keratopathy, dry eye, photophobia, eye pain, uveitis	x	x	x		x		x	

Dominguez-Llama S, Caro-Magdaleno M, Mataix-Albert B, et al. Clinical and Translational Oncology 2023; 25:3086-3100

Patient Case 4

Overlapping Adverse Effects – Chemo and TKIs

SR is a 55 year old man with adenocarcinoma of the sigmoid colon with metastases to the liver. The molecular profile reveals an ERBB2 copy number gain, MSS, and TMB 5.3 mutations/mb. He has received FOLFOX with bevacizumab, CapeOx, and FOLFIRI in the past. He last received FOLFIRI 2 months ago with progression on this regimen. He has residual debilitating neuropathy from oxaliplatin. SR will be starting tucatinib + trastuzumab.

SR reports feeling nervous about the adverse effect profile of the capecitabine he received in the past and the tucatinib, based on the patient education handouts he has read. Which of the following are reported overlapping adverse effects of capecitabine and tucatinib?

a. Cardiotoxicity
b. Hand-foot syndrome
c. Diarrhea
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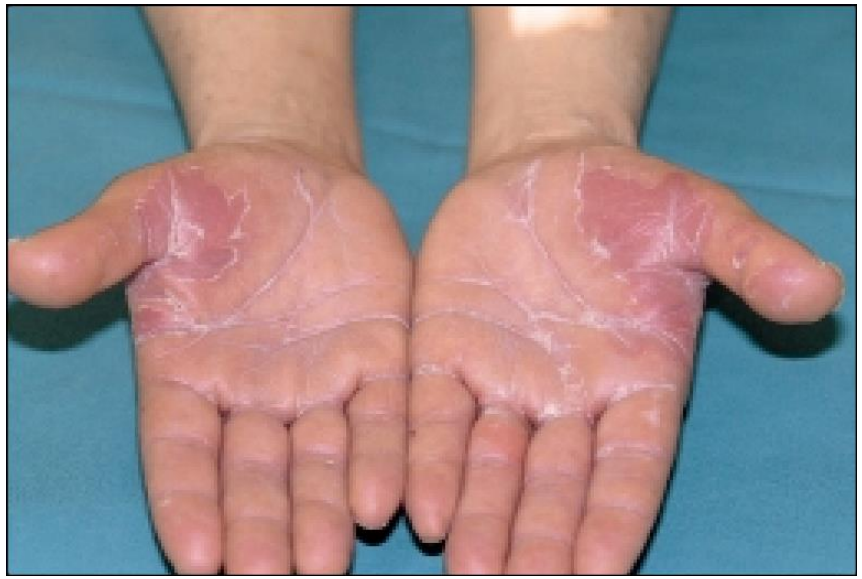
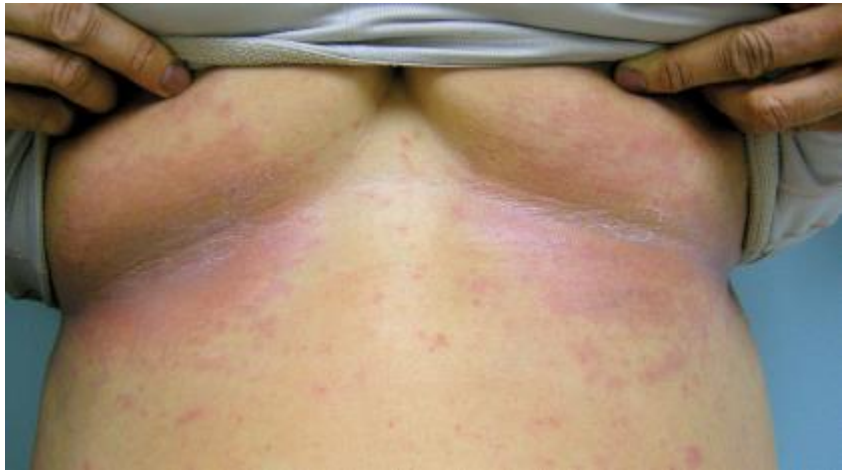
Hand-foot Syndrome

Druga	Incidence of HFS	Incidence of severe HFS
Capecitabine	50-60%	10-17%
Cytarabine	14-33%	-
Docetaxel	6-37%	0-4%
Doxorubicin	22-26%	-
5FU CIV	35%	7%
Pegylated liposomal doxorubicin	40-50%	20%
Sorafenib	48%	17%
Sunitinib	34%	30%





Pandy JGP, Franco PIG, Li RK. Support Care Cancer 2022; 30:8655-8666; Nagore E, Insa A, Sanmartin O. Am J Clin Dermatol 2000; 1(4):225-234; Zheng L, Anadkat MJ. The ASCO Post 2014; https://ascopost.com/issues/july-25-2014/how-to-recognize-and-manage-intertriginous-eruptions-related-to-doxorubicin/

Overlapping Adverse Effects – Chemo and TKIs

What preventative measures do you routinely recommended for prevention of hand-foot syndrome?

a. None
b. Topical urea
c. Oral celecoxib
d. Topical diclofenac
e. Emollient creams

Hand-foot Syndrome

- 5FU: accumulation and breakdown of the chemotherapy in hands and feet
- PLD: hydrophilic liposomes cause drug accumulation in the eccrine ducts
- Symptoms: redness or hyperpigmentation, discomfort, swelling, tingling in palms and soles

Urea-based creams

- Randomized, phase III trial of patients with GI or breast cancer on capecitabine, n=152
- Mapisal cream TID (antioxidant) vs urea 10% cream TID for 6 weeks
- Use of urea cream decreased all grade HFS (22.4% vs 39.5%, OR 2.37, p=0.02) compared to mapisal cream
- Time to any-grade HFS longer with the urea group, p=0.03
- Time to grade >2 HFS no different between groups
- No control only group
- Commercially available over-the-counter (OTC) at 5-40%

Diclofenac

- Single site phase III randomized, placebo controlled, double-blind trial in breast and GI cancer patients on capecitabine (monotherapy or combo), n=264
- Topical diclofenac 1g to each hand BID vs placebo for 12 weeks or development of HFS
- Incidence of grade 2-3 HFS 3.8% vs 15% favoring diclofenac group, p=0.003
- Grade 1-3 HFS 6.1% vs 18.1% favoring diclofenac
- Less capecitabine dose reductions with diclofenac 3.8% vs 13.5%
- Available OTC

Pandy JGP, Franco PIG, Li RK. Support Care Cancer 2022; 30:8655-8666. Santhosh A, Sharma A, Bakhshi S, et al. J Clin Oncol 2024; 42(15):1821-1829

Cardiotoxicity

Fluoropyrimidines

- Angina
- Ischemia-related ECG changes
- Takotsubo syndrome
- Coronary vasospasm
- Myocardial infarction
- Baseline ECHO recommended for patients with history of CV disease

HER2 targeting agents

- Left ventricular dysfunction
- Baseline ECHO recommended in all patients

Lyon AR. Eur Heart Journal 2022. 43;4229-61

Patient Case 5

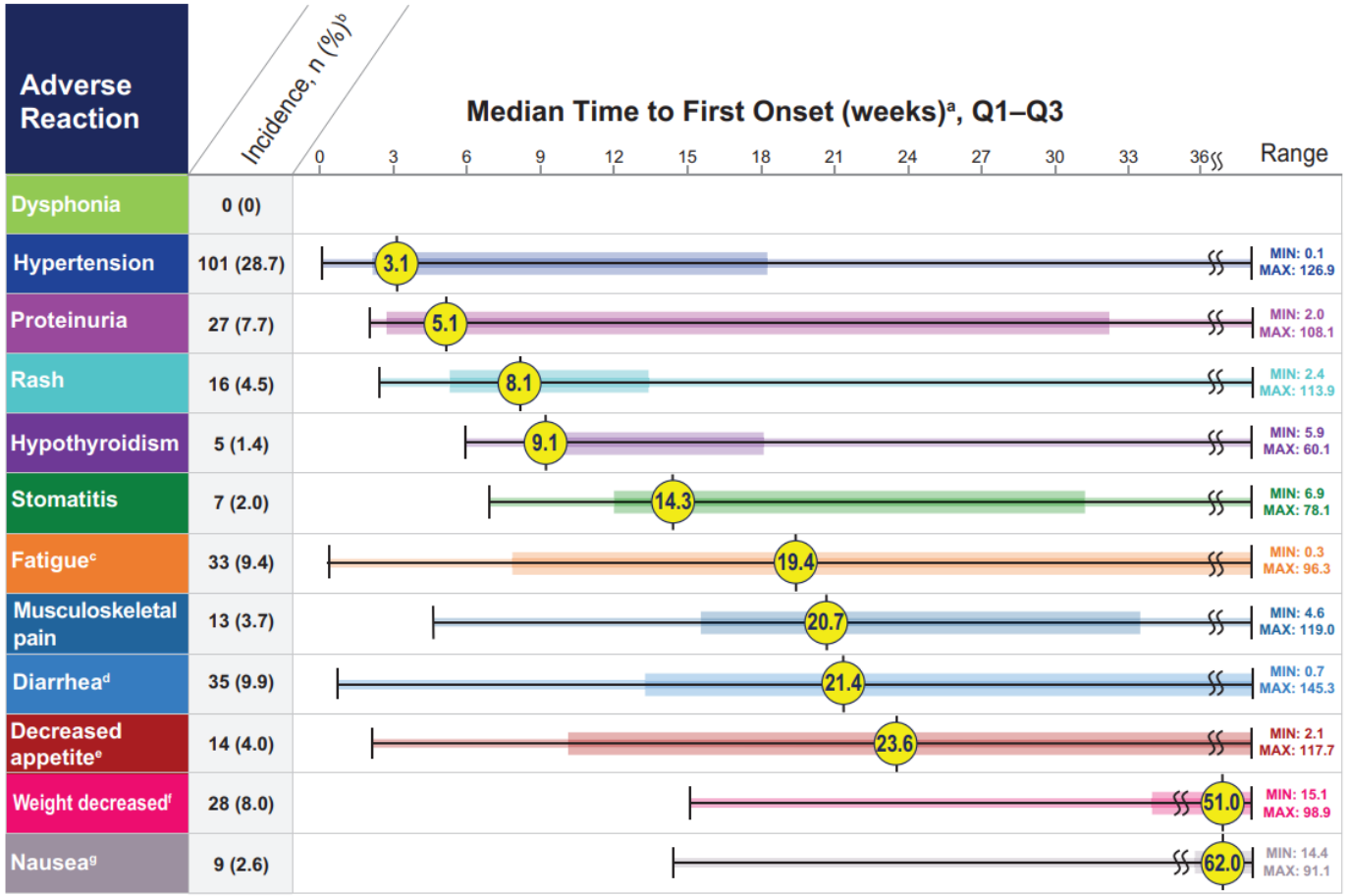
Overlapping Adverse Effects: TKIs and ICIs

AW is a 60 year old man newly diagnosed with metastatic clear cell renal cell carcinoma. He underwent a partial nephrectomy of the right kidney 2 years ago. He presents one year ago with a palpable mass on the abdomen and biopsy pathology was consistent with papillary renal cell carcinoma. He is starting therapy with lenvatinib and pembrolizumab.

Three weeks after starting lenvatinib and pembrolizumab, the patient reports 6 stools in the past 24 hours despite taking loperamide 4mg four times a day. This is increased from a baseline of 1 bowel movement daily. He is eating and hydrating adequately. Denies fever or blood in stool, labs WNL. What adjustment would you make to his regimen?

a. Hold pembrolizumab and lenvatinib
b. Hold lenvatinib
c. Hold pembrolizumab
d. Continue both agents

Oral TKI and ICI: Lenvatinib + Pembrolizumab



Motzer R, George S, Merchan JR, et al. The Oncologist 2023; 28:501-509

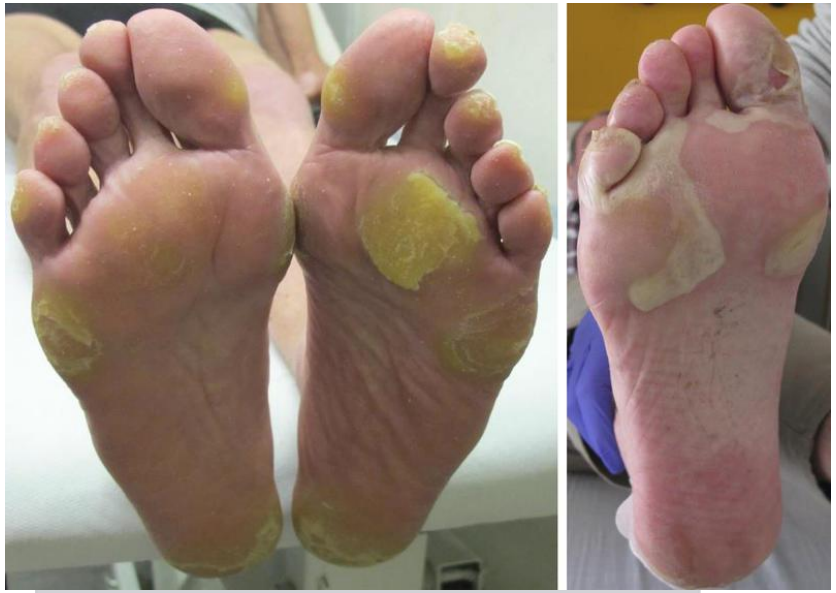
Skin Reactions

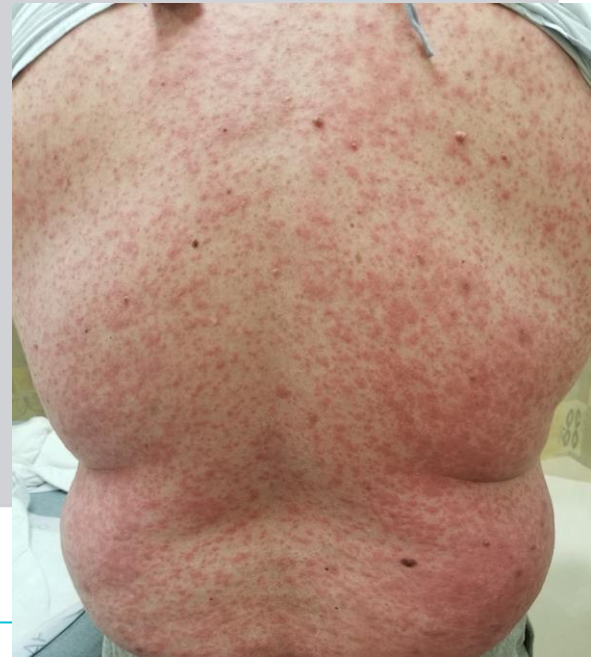
HFSR with multikinase inhibitors

- Focal, well-demarcated hyperkeratosis
- Sites prone to trauma/friction
- 10% urea based cream TID

IRAE rash with ICI

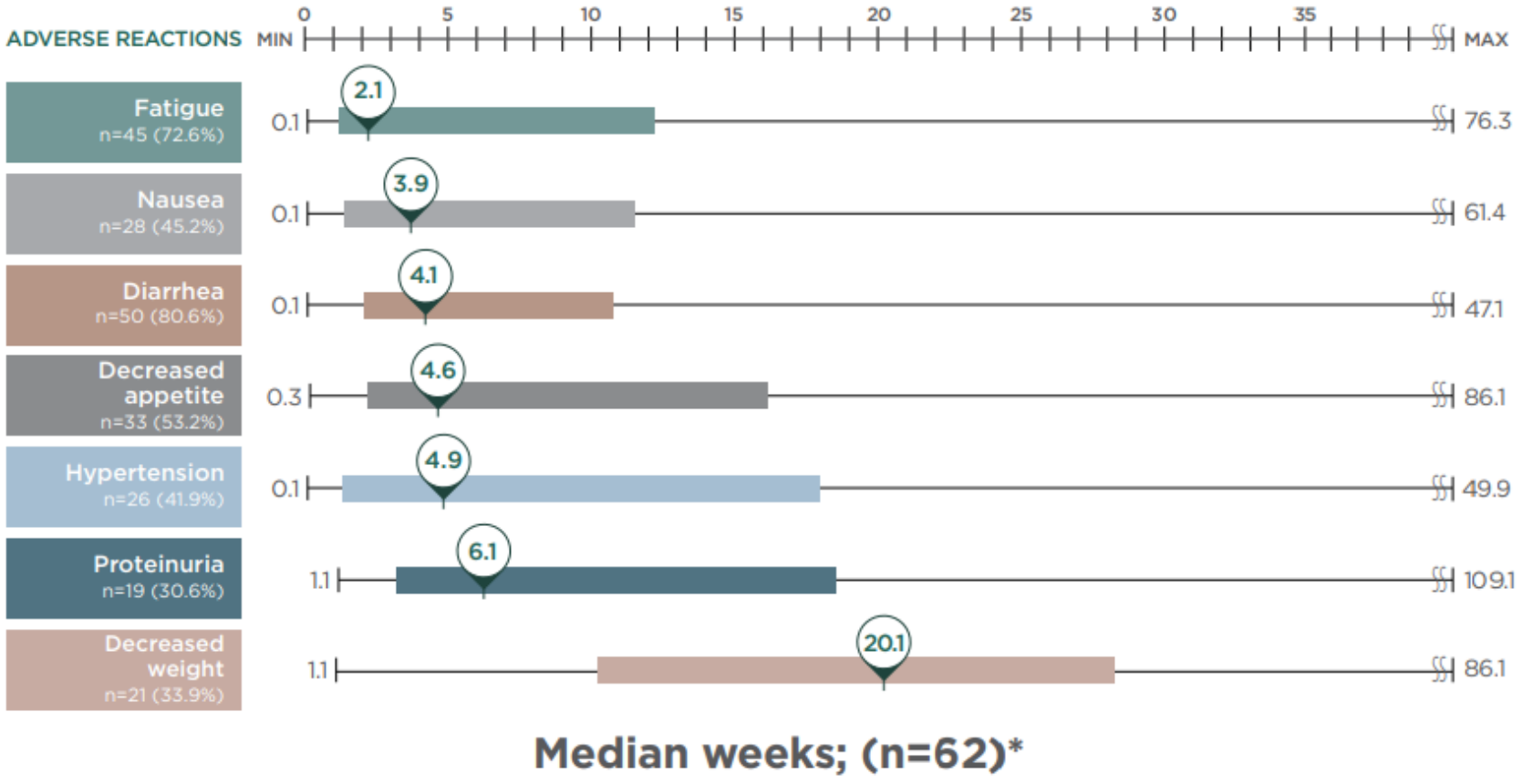
- Maculopapular
- Pruritic
- Topical and PO steroids





HFSR linked to multikinase inhibitor treatment. Oncology PRO 2024. Thomas M, Wazir A, Poudel A. Cureus 2022; 14(6): e26143. Pandy JGP, Franco PIG, Li RK. Support Care Cancer 2022; 30:8655-8666; Lacouture ME, Sibaud V, Gerber PA, et al. Ann Oncol 2021; 32(2): 157-170

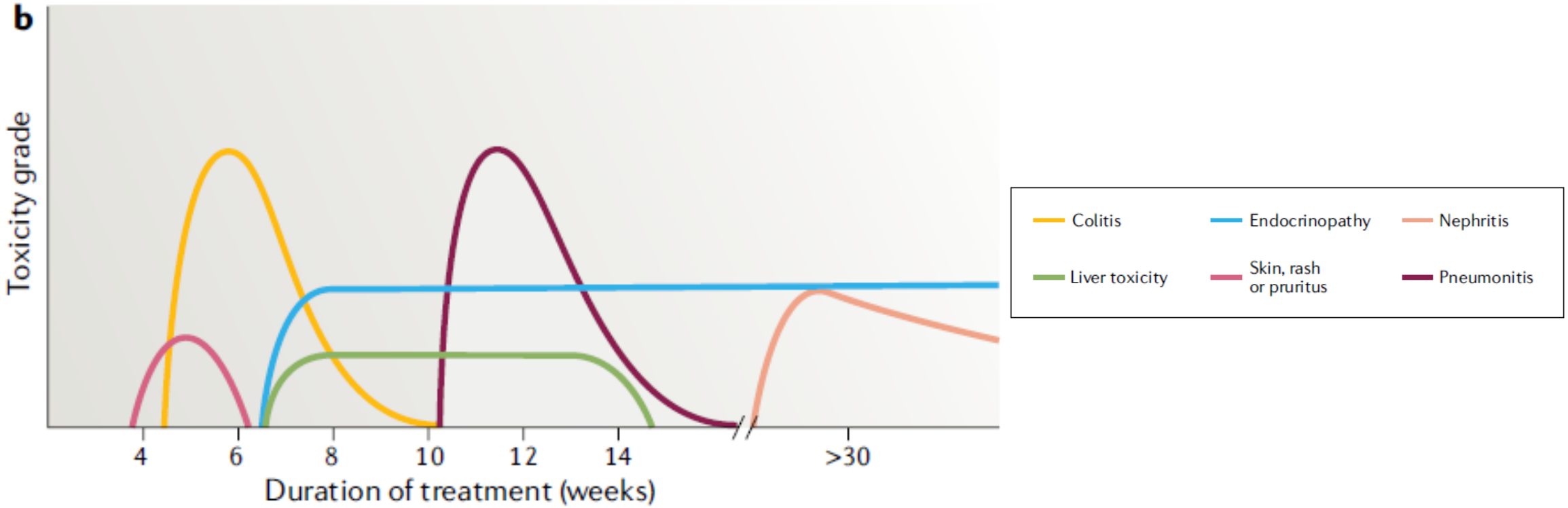
Single Agent Lenvatinib



Dose and adverse reaction management guide for lenvima. 2023 https://www.lenvimahcp.com/-/media/Files/Lenvima/PDF/LENVIMA-aRCC-Dosing-and-AR-Management-Guide.pdf?hash=f824b43b-ca3d-4aa2-bda1-4916d8cc8b89

Single Agent Pembrolizumab

Onset of select IRAEs with PD-1/PD-L1 Inhibitor



Martins F, Sofiya L, Sykiotis GP, et al. Nature Reviews 2019; 16:563-78

Oral TKI and ICI: Cabozantinib + Nivolumab

Median onset of select AE (weeks)	Cabozantinib + nivolumab	Single-agent cabozantinib	Single-agent nivolumab
Endocrine	12.1	-	12.2
Diarrhea	12.9	4.9	
IR diarrhea/colitis	29.3	-	7.8
Hepatic	8.1	-	10.4
IR pneumonitis	33.9		14.3
Renal	11.9 (nephritis)	4.1 (proteinuria)	11.3 (nephritis)
PPE	7.4	3.4	
IR rash	12.4		6.1
Hypertension		3	

McGregor B, Mortazavi A, Cordes L, et al. Cancer Treat Rev 2022; 103:102333

Patient Case 6

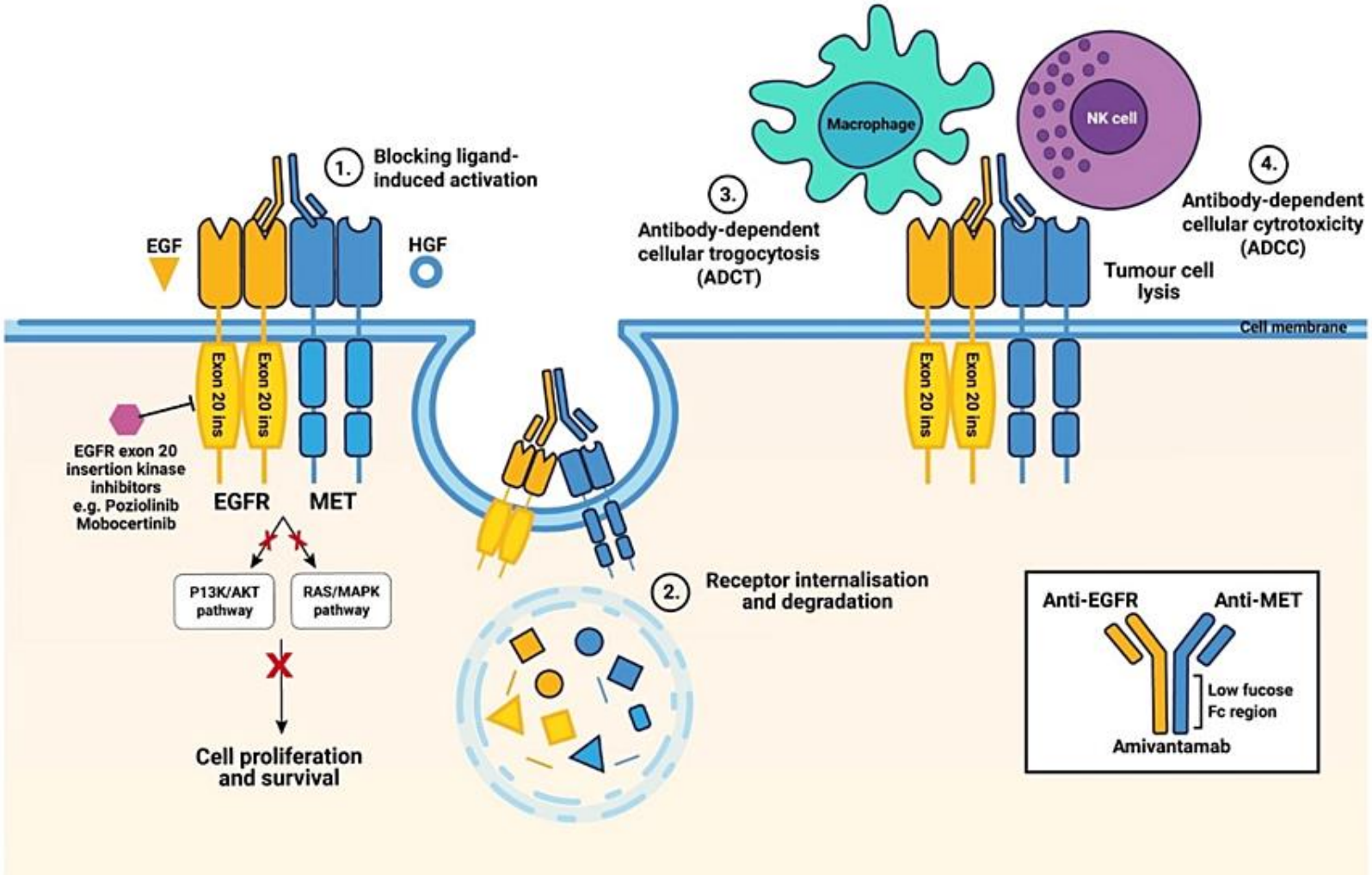
Bispecifics and TKI

BT is a 62 year old women with metastatic EGFR L858R adenocarcinoma of the right lung with metastases to the ribs, sacrum, and brain. She was on osimertinib for the past 8 months. She develop osimertinib related pneumonitis and stopped osimertinib. Her most recent imaging shows a new concern for leptomeningeal disease. She will be starting amivantamab and lazertinib.

What supportive care should be recommended for BT (select all that apply)?

a. Apixaban 2.5mg BID for four months
b. Enoxaparin 1mg/kg daily for four months
c. Oral doxycycline 100mg BID
d. Topical emollient creams and limiting sun exposure

Mechanism of Action



Zavaleta-monestei E, Garcia-Montero J, Arguedas-Chacon S, et al. Cureus 2024; 16(5):e60851

Amivantamab and Lazertinib

Infusion-related reactions

- Premed with antihistamine and antipyretic for all doses and glucocorticoid for the initial dose
- IRR in 65% of patients with C1D1, and 3.4% with C1D2 with onset of 1hr

Thromboprophylaxis

- Prophylactic anticoagulation recommended for the first four months of treatment
- Rivaroxaban 10mg daily, apixaban 2.5mg BID, or enoxaparin 40mg daily

Dermatologic adverse effects

- Acneiform rash, nail toxicities
- Consider oral antibiotics for rash prophylaxis. Limit sun exposure during and for 2 months after amivantamab, use topical emollient creams

Hypoalbuminemia

- 39% of patients (all grade) due to MET inhibition

GI adverse effects

- Diarrhea in 39% of patients (8% grade 3 or higher)

Ocular adverse effects

- Keratitis and uveitis (<1%)

Cho BC, Lu S, Felip E, et al. N Engl J Med 2024; doi: 10.1056/NEJMoa2403614.

Infusion related reactions

Agent	Bispecific antibody target	Dosing
Amivantamab	EGFR, cMET	1400 mg IV (1050mg if <80kg) weekly x 4, then every 2 weeks Split first dose infusion over Day 1 and Day 2
Tabentafusp	CD3 on T cells, gp100 on uveal melanoma cells	20mcg IV Day 1 inpatient 30mcg IV Day 8 inpatient 68mcg IV Day 15 inpatient 68mcg IV weekly thereafter
Tarlatamab	CD3 on T cells, delta-like ligand 3 on cancer cells	1mg Day 1 10mg Day 8 10mg Day 15 10mg every 2 weeks thereafter

Dermatologic Toxicities – Nail Changes

- Chemotherapy induced nail changes are more common with EGFRi, MEKi, mTORi, taxanes
  - Less common with chemotherapy agents, except taxanes

<u>Supportive care</u>

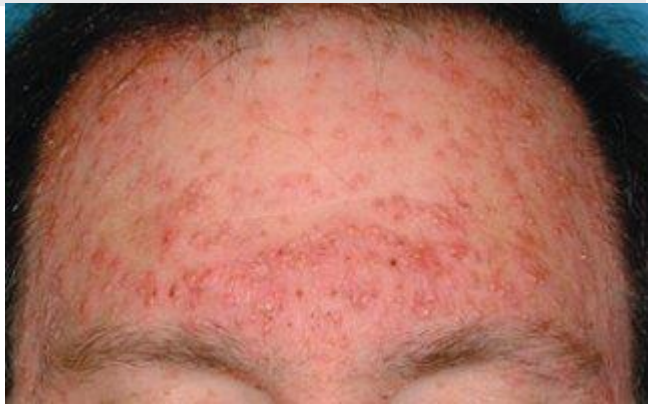
- Gentle skin care, avoid repeated friction, trauma, or pressure
- Wearing gloves while cleaning. Restrict contact with detergents, toxic nail products
- Avoiding biting nails or cutting nails too short
- Regular trimming of nails to ensure they are straight and not too short
- Daily application of topical emollient (petroleum jelly) to cuticles and periungual tissues
- Wearing comfortable well-fitting shoes and cotton socks. Visit a podiatrist if necessary
- Treatment with biotin has been suggested but not yet been shown to help in a controlled study

Lacouture ME, et al. Ann Oncol 2021; 32(2): 157-170; Robert C, Sibaud V, Mateus C, et al. Lancet Oncol 2015; 16(4):e181-e189

Dermatologic Toxicities – Acneiform Rash

Severity	Intervention
Grade 1-2 (10-30% BSA, limiting instrumental ADLs)	• Continue drug at current dose • Oral antibiotic for at least 6 weeks and topical low/moderate steroid • Reassess in two weeks
Grade ≥3 (>30% BSA, limiting self-care ADLs, associated with local superinfection)	• Interrupt until Grade 0-1 • Continue or initiate oral antibiotic and topical low/moderate steroid • Continue or initiate systemic steroids (prednisone 0.5-1mg/kg for 7 days) • Consider isotretinoin at low doses (20-30mg/day) • Reassess in two weeks

- Most common with EGFR inhibitors and agents that affects EGFR pathway
  - IV: cetuximab, pertuzumab
  - Oral: afatinib, gefitinib, osimertinib



Lacouture ME, et al. Ann Oncol 2021; 32(2): 157-170; Smith SM. NCODA. Updated Aug 30, 2023. Accessed Mar 28, 2024. Am Fam Physician 2008;77:311-19.

Bispecifics and TKI

BT is a 62 year old women with metastatic EGFR L858R adenocarcinoma of the right lung with metastases to the ribs, sacrum, and brain. She was on osimertinib for the past 8 months. She develop osimertinib related pneumonitis and stopped osimertinib. Her most recent imaging shows a new concern for leptomeningeal disease. She will be starting amivantamab and lazertinib.

What supportive care should be recommended for BT (select all that apply)?

a. Apixaban 2.5mg BID for four months

b. Enoxaparin 1mg/kg daily for four months

c. Oral doxycycline 100mg BID

d. Topical emollient creams and limiting sun exposure

Patient Case 7

Combination chemotherapy: Cisplatin + paclitaxel + bevacizumab + pembrolizumab

ML is a 60 year old woman with adenocarcinoma of the cervix extending to the uterus and upper vagina with abutment of the rectosigmoid junction. Her PET scan showed avid right external iliac nodal metastasis as well as hypermetabolic nodules in the lung. She initiated cisplatin + paclitaxel + bevacizumab + pembrolizumab.

ML tolerates Cycle 1 of chemotherapy well. She presents for Cycle 2 and receives pembrolizumab, bevacizumab, and paclitaxel. Right as her infusion of cisplatin starts, she has low back pain, flushing, and itching. It resolved with diphenhydramine. Which of the following statements best represents hypersensitivity reactions with this regimen?

a. This is likely a paclitaxel reaction. Continue premedications and consider increasing diphenhydramine dose or a rate titration with next infusion.
b. This is likely a cisplatin reaction. Reactions to platinum compounds are most common with cisplatin in the 1st or 2nd infusion.
c. As she's received pembrolizumab, bevacizumab, and paclitaxel, it could be either of the three agents. Rate titrate all three agents for subsequent infusions.
d. This is likely a cisplatin reaction. She will require cisplatin desensitization for future cycles.

Combination chemotherapy: Cisplatin + paclitaxel + bevacizumab + pembrolizumab

ML tolerates Cycle 1 of chemotherapy well. She presents for Cycle 2 and receives pembrolizumab, bevacizumab, and paclitaxel. Right as her infusion of cisplatin starts, she has low back pain, flushing, and itching. It resolved with diphenhydramine. Which of the following statements best represents hypersensitivity reactions with this regimen?

a. **This is likely a paclitaxel reaction. Continue premedications and consider increasing diphenhydramine dose or a rate titration with next infusion.**
b. This is likely a cisplatin reaction. Reactions to platinum compounds are most common with cisplatin in the 1st or 2nd infusion.
c. As she's received pembrolizumab, bevacizumab, and paclitaxel, it could be either of the three agents. Rate titrate all three agents for subsequent infusions.
d. This is likely a cisplatin reaction. She will require cisplatin desensitization for future cycles.

-Paclitaxel reactions are most likely to occur during the first or second infusion and are due to the cremaphor diluent.
-Taxane hypersensitivity reactions can be managed with slowing the rate of infusion and additional premedications.
-Of the platinum compounds, reactions are most common with carboplatin and this is most common during cycles 6 – 8 of carboplatin. These can be managed with desensitization with future cycles.
-Infusion reactions are rare with pembrolizumab and bevacizumab.

Combination chemotherapy: Cisplatin + paclitaxel + bevacizumab + pembrolizumab

ML is a 60 year old woman with adenocarcinoma of the cervix extending to the uterus and upper vagina with abutment of the rectosigmoid junction. Her PET scan showed avid right external iliac nodal metastasis as well as hypermetabolic nodules in the lung. She initiated cisplatin + paclitaxel + bevacizumab + pembrolizumab.

ML arrives for Cycle 3 of this regimen. Her blood pressure in clinic is 165/90 and she does not know what her home blood pressure is. She is not on any anti-hypertensives. Her BP prior to starting chemotherapy was 130s/80s. Which of the following is an appropriate strategy to manage bevacizumab induced hypertension?

a. Start amlodipine 10mg daily. Hold bevacizumab infusion today
b. Start lisinopril 20mg. Hold bevacizumab infusion today.
c. Continue bevacizumab infusion, start amlodipine 5-10mg daily.
d. Continue bevacizumab infusion, have patient start monitoring home blood pressure.

Combination chemotherapy: Cisplatin + paclitaxel + bevacizumab + pembrolizumab

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ML arrives for Cycle 3 of this regimen. Her blood pressure in clinic is 165/90 and she does not know what her home blood pressure is. She is not on any anti-hypertensives. Her BP prior to starting chemotherapy was 130s/80s. Which of the following is an appropriate strategy to manage bevacizumab induced hypertension?

a. **Start amlodipine 5mg daily. Hold bevacizumab infusion today**
b. **Start lisinopril 10mg. Hold bevacizumab infusion today.**
c. **Continue bevacizumab infusion, start amlodipine 5mg daily.**
d. **Continue bevacizumab infusion, have patient start monitoring home blood pressure.**

All of the above can be options. Consider:
-Availability of at-home blood pressure monitoring
-Concomitant nephrotoxicity with cisplatin
-Concerns with medication adherence
-Disease control

Plummer C, Michael A, Shaikh G, et al. Br J Cancer 2019; 121: 109-116.

Combination chemotherapy: Cisplatin + paclitaxel + bevacizumab + pembrolizumab

ML is a 60 year old woman with adenocarcinoma of the cervix extending to the uterus and upper vagina with abutment of the rectosigmoid junction. Her PET scan showed avid right external iliac nodal metastasis as well as hypermetabolic nodules in the lung. She initiated cisplatin + paclitaxel + bevacizumab + pembrolizumab.

Which of the following are guideline-based recommendations for treatment or prevention of chemotherapy induced peripheral neuropathy? (Select all that apply)

a. There are no pharmacologic agents recommended for the prevention of CIPN
b. Duloxetine may be recommended for treatment of CIPN, starting at 30mg daily for a week, then 60mg daily.
c. Cryotherapy to the hands and feet may be considered to decrease the risk for neuropathy
d. Vitamin B12, glutamine, and folic acid may be used to decrease the risk for neuropathy.

Breast Cancer V.4X.2024. © National Comprehensive Cancer Network, Inc. 2024. Accessed 4 Sep 2024. Loprinzi C, Lacchetti C, Bleeker J, et al. J Clin Oncol 2020; 38: 3325-3348.

Combination chemotherapy: Cisplatin + paclitaxel + bevacizumab + pembrolizumab

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d. Vitamin B12, glutamine, and folic acid may be used to decrease the risk for neuropathy.

-Cumulative dose effect with platinums and taxanes
-Primary sensory neuropathy with stocking-glove distribution with taxanes (primarily paclitaxel) and platinums (primarily oxaliplatin and cisplatin).
-Paclitaxel neuropathy tends to improve over months after cessation of therapy
-Oxaliplatin neuropathy tends to worsen over 2-3 months after cessation of therapy, then improves.

Breast Cancer V.4X.2024. © National Comprehensive Cancer Network, Inc. 2024. Accessed 4 Sep 2024. Loprinzi C, Lacchetti C, Bleeker J, et al. J Clin Oncol 2020; 38: 3325-3348.

Patient Case 8

Trastuzumab deruxtecan

AK is a 66 year old woman with Stage IIIC2 high grade uterine carcinoma. She has received neoadjuvant carboplatin + paclitaxel one year ago, followed by debulking surgery with pathology revealing p53 overexpression, HER2 1+ by IHC, FOLR1 30% by IHC (negative), and MSS and TMB-L. She started pembrolizumab + levnatinib with progression after 7 cycles. She is now starting trastuzumab deruxtecan.

After 4 cycles, AK reports new shortness of breath and cough. Imaging reveals pneumonitis. Which of the following statements best represents management of trastuzumab deruxtecan related ILD?

a. Hold trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.
b. Continue trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.
c. Hold trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Consider rechallenge with shared, multidisciplinary decision making.
d. Continue trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.

Trastuzumab deruxtecan

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After 4 cycles, AK reports new shortness of breath and cough. Imaging reveals pneumonitis. Which of the following statements best represents management of trastuzumab deruxtecan related ILD?

a. **Hold trastuzumab deruxtecan, initiate prednisone 0.5mg/kg or higher until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.**
b. Continue trastuzumab deruxtecan, initiate prednisone 0.5mg/kg or higher until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.
c. **Hold trastuzumab deruxtecan, initiate prednisone 0.5mg/kg or higher until symptom resolution, then taper. Consider rechallenge with shared, multidisciplinary decision making.**
d. Continue trastuzumab deruxtecan, initiate prednisone 0.5mg/kg or higher until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.

Trastuzumab deruxtecan Interstitial Lung Disease

- ILD in 12% of patients with breast cancer and NSCLC, median onset 5.5 months
- ILD in 10% of patients with gastric cancer, median onset 2.8 months
- Higher incidence of ILD in patients with renal dysfunction
- Package insert recommends permanent discontinuation for grade 2 or higher ILD

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.				
Navigational Note: -				

Enhertu [package insert]. Daiichi Sankyo Inc.; Basking Ridge, NJ: 2024

Cardiotoxicity

Trastuzumab	• Baseline, every 3 months during treatment, • May reduced to every 4-6 months if asymptomatic*
Pertuzumab	• Baseline, every 3 months during treatment in the metastatic setting • Baseline, every 6 months in the neoadjuvant setting
Margetuximab	• Baseline, every 3 months during treatment
Trastuzumab emtansine	• Baseline, every 3 months during treatment
Trastuzumab deruxtecan	• Baseline, at regular intervals during treatment and as clinically indicated
Tucatinib, lapatinib, neratinib	• No recommendations for tucatinib or neratinib • Baseline and during treatment for lapatinib

*Lyon AR. Eur Heart Journal 2022. 43;4229-61; Perjeta [package insert]. Genentech, Inc.; South San Francisoc, CA: 2013. Margenza [package insert]. MacroGenics, Inc.; Rockville, MD: 2020. Kadcyla [package insert]. Genentech, Inc.; South San Francisco, CA: 2022. Enhertu [package insert]. Daiichi Sankyo, Inc; Basking Ridge, NJ: 2024. Lapatinib [package insert]. Novartis Pharmaceuticals Corporation; East Hanover, NJ: 2022.

Fred Hutch Cancer Center

Thank you

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