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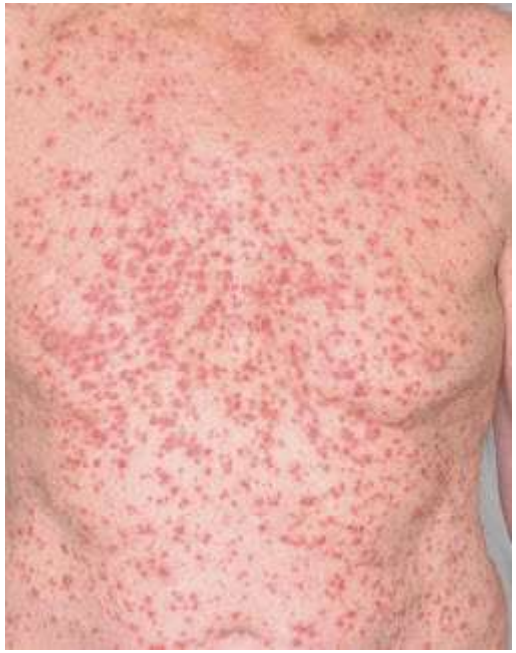
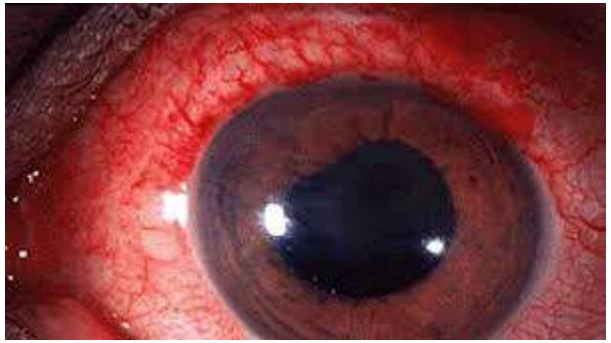
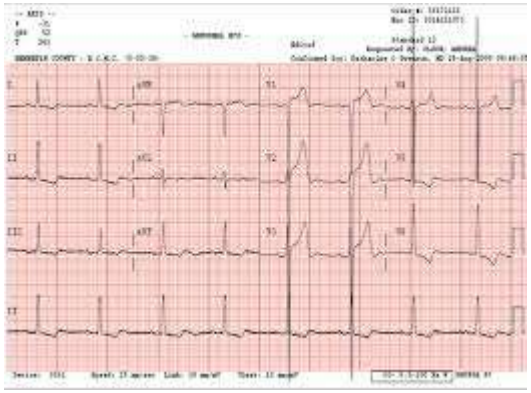
# MANAGING TOXICITIES FOR BRAF & MEK INHIBITORS







Stronger Together

# Current FDA Approved Indications & Dosage

## Colorectal Cancer

| Combination | Combination |
|---|---|
| Encorafenib oral 300 mg QD | Trametinib oral 2 mg QD |
| Binimetinib oral 45 mg BID | Dabrafenib oral 150 mg BID |

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# Current FDA Approved Indications & Dosage

## NSCLC

| Combination |
| --- |
| Trametinib oral 2 mg QD |
| Dabrafenib oral 150 mg BID |

# Current FDA Approved Indications & Dosage

## Metastatic Melanoma

| Combination | Combination | Combination |
|---|---|---|
| Vemurafenib oral 960 mg BID | Trametinib oral 2 mg QD | Encorafenib oral 450 mg QD |
| Cobimetinib oral 60 mg QD | Dabrafenib oral 150 mg BID | Binimetinib oral 45 mg BID |
| On day 1 to day 21 of each 28 day cycle | | |

# Safety tips on handling and storage

| | |
|---|---|
| Dabrafenib<br>Room temperature/ 1hr before or 2 hrs. after meals<br><br>Trametinib<br>Refrigerate/ 1hr before or 2 hrs. after meals | Encorafenib<br>Room temperature/ with or without food<br><br>Binimetinib<br>Room temperature/ with or without food |
| Vemurafenib<br>Room temperature/ with or without food<br><br>Cobimetinib<br>Room temperature/ with or without food | Do not crush, open or break<br><br>Use gloves |

# Prior to Drug Initiation

Confirm BRAF mutation

Assess Ejection Fraction
Echocardiogram or MUGA scan

A1C in patients with diabetes

Avoid sun exposure

Dermatological evaluation

Ophthalmologist evaluation

Pregnancy test

# Lab Values to Monitor

| | |
|---|---|
| LFTs | Electrolytes starting 2 weeks after |
| CPK | GGT levels (Gamma-Glutamyl Transferase |
| Alkaline Phosphatase | Monitor glucose levels for patients with DM |
| Bilirubin | Renal function |

# Case presentation

This is a 44-year-old Hispanic female with stage IV NSCLC BRAF positive. Patient was initiated on combination therapy with dabrafenib 150mg BID and trametinib 2mg QD. After 2 weeks on treatment patient presented back in clinic with a fever of 102F, and bilateral lower extremity edema.
She reported taking Tylenol 1000 mg every 8 hours and as needed.

What would you do ?

# Most common Adverse reactions

| | Trametinib/Dabrafenib |
|---|---|
| Pyrexia | 63% |
| Fatigue | 59% |
| Nausea | 40% |
| Headache | 39% |
| Rash | 37% |
| Chills | 37% |
| Diarrhea | 33% |
| Vomiting | 28% |
| Myalgias | 20% |

# Most common Adverse reactions

| | Vemurafenib/Cobimetinib |
|---|---|
| Diarrhea | 60% |
| Nausea | 41% |
| Vomiting | 24% |
| Photosensitivity reaction | 46% |
| Pyrexia | 28% |

# Most common Adverse reactions

| | Encorafenib/Binimetinib |
|---|---|
| Fatigue | 43% |
| Nausea | 41% |
| Vomiting | 30% |
| Abdominal Pain | 28% |
| Arthralgias | 26% |

# Pyrexia-Trametinib

Management

| | |
|---|---|
| Fever higher than 104F | Withhold until it resolves then resume at a Lower dose |
| Fever accompanied by Rigors/Chills Hypotension Dehydration Renal failure Infection | Administer Antipyretics (Acetaminophen) |
| | Administer Corticosteroids for at least 5 days for subsequent pyrexia or if it doesn't return to baseline within 3 days |
| | Administer antipyretics as prophylaxis when resuming |

# Pyrexia-Dabrafenib

| Management | |
|---|---|
| Fever higher than 101.3F to 104F | Withhold until it resolves then resume at same or lower dose |
| Fever accompanied by<br>Rigors/Chills<br>Hypotension<br>Dehydration<br>Renal failure<br>Infection | Administer Antipyretics (Acetaminophen)<br><br>Administer Corticosteroids for at least 5 days for subsequent pyrexia or if it doesn't return to baseline within 3 days<br><br>Administer antipyretics as prophylaxis when resuming |
| Fever higher than 104F | Withhold until it resolves then resume at same or lower dose or Permanently discontinue |

# New Cutaneous & Non-Cutaneous Primary Malignancies

Management

| Dabrafenib | Cobimetinib | Vemurafenib |
|---|---|---|
| Cutaneous malignancies | | No dose adjustment<br>Excise and continue treatment |
| Non-cutaneous RAS mutation positive Malignancies | | Permanently discontinue |

# Cardiomyopathy

Management

| Dabrafenib | Trametinib | Binimetinib | Cobimetinib |
|---|---|---|---|

| | |
|---|---|
| Asymptomatic/Symptomatic | Withhold for up to 4 weeks |
| LVEF decrease of < 10 % from baseline | Resume at next lower dose when symptoms resolve |
| If symptoms persist<br>LVEF decreases > 10% | Permanently discontinue if it does not recover within 4 weeks |

# Skin toxicity

Management

| Trametinib | Dabrafenib | Vemurafenib |
|---|---|---|
| In severe skin toxicity | Withhold for up to 3 weeks<br><br>Resume at a lower dose with improvement<br><br>Permanently discontinue if no improvement after 3 weeks | |

# Ocular toxicities

Management

| Trametinib | |
|---|---|
| Vision Disturbances | Ophthalmology evaluation within 24 hours |
| Retinal Pigment Epithelial Detachment (RPED) | Withhold/Treat/Resume at lower dose/ DC if no improvement |
| Retinal Vein Occlusion (RVO) | Discontinue permanently |

# Ocular toxicities

Management

| Cobimetinib | |
|---|---|
| Serous Retinopathy | Withhold for up to 4 weeks<br>If improve resume at the next lower dose<br>Discontinue if no improvement within 4 weeks |
| RVO | Permanently discontinue |

# Ocular toxicities

Management

| Dabrafenib | Vemurafenib | Encorafenib | Binimetinib |
|---|---|---|---|

| | |
|---|---|
| Vision Disturbances | Ophthalmology evaluation within 24 hours |
| Iritis | Treat & continue treatment |
| Uveitis (mild-Moderate)<br>(Most common) | Withhold/Treat/Resume at lower dose<br>Discontinue if no improvement |

# Liver toxicity

Management

| Binimetinib | Vemurafenib | Cobimetinib |
|---|---|---|
| Abnormal labs | Withhold up to 4 weeks<br>if improvement resume at same dose<br><br>If no improvement permanently discontinue | |

# Interstitial Lung Disease (Pneumonitis)

Management

| Trametinib | Binimetinib |
| --- | --- |
| Permanently discontinue | |

# Radiation Sensitization

| Vemurafenib |
| --- |

Monitor patients closely

Fatal cases have been reported in patient treated with radiation prior, during or subsequent

# DVT/PE

Management

| Binimetinib | Trametinib |
|---|---|
| If uncomplicated DVT/PE | Withhold for up to 3 weeks<br><br>If improved Resume at a lower dose |
| Life-threatening PE | Permanently discontinue |

# Glucose-6-Phosphatase Dehydrogenase Deficiency

| Dabrafenib |
| --- |

| | |
| --- | --- |
| Hemolytic anemia | Monitor closely |

# Recommended dose reductions

| Encorafenib | Binimetinib |
|---|---|
| First reduction 300 mg QD | First reduction 30 mg BID |
| Second reduction 225 mg QD | If unable to tolerate 30 mg, permanently discontinue |
| If unable to tolerate 225 mg, permanently discontinue | |

# Recommended Dose Reductions

| Dabrafenib | Trametinib |
|---|---|
| First dose reduction 100 mg BID | First dose reduction 1.5 mg QD |
| Second dose reduction 75 mg BID | Second dose reduction 1 mg QD |
| Third dose reduction 50 mg BID | |

# Recommended dose reductions

| Vemurafenib | Cobimetinib |
|---|---|
| First dose reduction 720 mg BID | First dose reduction 40 mg QD |
| Second dose reduction 480 mg BID | Second dose reduction 20 mg QD |
| | If unable to tolerate at 20 mg QD permanently discontinue |

# Case presentation

This is a 44-year-old Hispanic female with stage IV NSCLC BRAF positive. She was started in combination therapy with dabrafenib 150 mg BID in and trametinib 2 mg QD. After 2 weeks patient presented back to clinic with fever of 102F, and bilateral lower extremity edema.
Patient reported taking Tylenol 1000 mg every 8 hours as needed.

What would you do ?

# Answer to case presentation

- Evaluate for infection/Cultures
- Evaluate for DVT
- Withhold Dabrafenib and continue Trametinib until fever resolves
- Administer antipyretics
- Resume Dabrafenib at same or lower dose
- We could administer Corticosteroids (10 mg a day for at least 5 days) for any subsequent pyrexia or if temperature does not return to baseline within 3 days of onset

# Summary

- There are 3 FDA approved combination treatments for patients with BRAF mutation
  - ❖ Colorectal cancer, Metastatic Melanoma, and NSCLC
- Confirm BRAF mutation
- Assess EF
- Run baseline labs (electrolytes, renal function, LFTs, CPK, GGT, Bili, ALP, A1C)
- Monitor INR for patients on Warfarin taking Dabrafenib and Trametinib
- Send patient to have a dermatological and ophthalmological evaluation
- Pregnancy test for females

# Summary

<u>In patients with NSCLC the most important information to know</u>

- The most common adverse reaction is Pyrexia
- Manage by withholding until patient recovers, treating with antipyretics and resuming at same or lower dose (may use steroids 10 mg a day for at least 5 days)
- Monitor serum creatinine in patients following severe pyrexia
- Make sure to always check package insert for specifications on dose reductions and when to withhold
- Always remember It may not be necessary to withhold both drugs


Thank you