# Oncology Primer: Pyrexia Syndrome

## The fever that might not need pip tazo...

Sarah Mulrooney
BSc (Pharm), RPh, ACPR
Clinical Pharmacist- Oncology
Saint John Regional Hospital
Horizon Health Network-

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**These slides are my own**

# Learning Objectives

1. Differentiate between pyrexia syndrome and febrile neutropenia
2. Discuss red flags for pyrexia syndrome requiring referral and further investigation
3. Describe management strategies for patients experiencing pyrexia syndrome

# Practice Context

- Typically, oncology patients receiving anticancer agents that can affect white blood cells and infection risk receive a “yellow card” and are directed to proceed to ED if they have a single oral T >38.3 C or >38 C for an hour
- Not all anticancer agents affect neutrophils in a significant way
  - Particularly some targeted therapies
- Today, we are going to discuss one such category of drug: **BRAF/MEK inhibitors**

# BRAF/MEK inhibitors

| BRAFi | MEKi |
| --- | --- |
| vemurafenib | cobimetinib |
| dabrafenib | trametinib |
| encorafenib | binimetinib |

# BRAF/MEK inhibitors

- BRAF mutations are found in up to 50% of melanoma cases
- Uncontrolled activation of MAPK pathway
- Leading to uncontrolled cell growth/differentiation
- Targeting of BRAF alone will eventually induce resistance, possibly due to subsequent mutations in MEK
- Using BRAF and MEK inhibitors **together** delays the development of treatment resistance

# BRAF/MEK inhibitors

- Applications of BRAF/MEKi
  - **Melanoma**
  - **NSCLC**

# Defining Pyrexia Syndrome

- Canadian Consensus Statements definition:
  - Temperature ≥ 38 ℃
  - And/or chills, rigors, night sweats
  - +/- flu-like symptoms such as myalgia and fatigue

# Context of Pyrexia Syndrome

- Associated with BRAF inhibitors (BRAFi)
  - When used as single agents
    - 25-33%
  - Or in combination with MEK inhibitors (MEKi)
    - 52-71%
- Can occur with any combination
  - Incidence is highest in dabrafenib + trametinib
    - ROR 1.9; 95%CI, 1.5–2.4 compared to vemurafenib+cobimetinib or encorafenib+binimetinib

# Pyrexia syndrome with dabrafenib + trametinib

- One of the most common reasons for dosage modification
- Median time to onset= 4 weeks
- Median duration of pyrexia= 3-9 days

# What are the patient impacts of pyrexia syndrome?

- COMBI-AD measured quality of life in patients receiving dabrafenib + trametinib vs. placebo in the adjuvant setting
  - European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L)
- No statistically significant difference was noted
- Post-hoc analysis suggests no difference in EQ-5D-3L score between patients who did and did not experience pyrexia
- However, in real-life, this necessitates more frequent follow-up for patients and there are noticeable symptoms
  - Can lead to dehydration, hypotension and other complications if untreated

# What causes pyrexia syndrome?

- Cause is unknown
- Trametinib influences the dabrafenib-driven process
- BRAF inhibition may increase inflammasome activation and interleukin-1 beta production in dendritic cells which can create pro-inflammatory effects such as fever

# Meet our patient

- PS- 57-year-old male
- Metastatic melanoma
- Previously treated with nivolumab, but progressed
- dabrafenib 150 mg PO BID/trametinib 2 mg PO daily
  - May 2nd, 2022- Started treatment
  - May 6th, 2022- Fever of 38-39 C at home

# What does PS do?

- PS's friend tells him that since he is a cancer patient, and he has a fever, he needs to go to the ED
- PS remembers he got a handout from the pharmacist when he started his meds and digs it out

Side effects of **dabrafenib** and **trametinib** include:

- Fevers
- Chills

These can happen any time, but often start in the first month of treatment. In most patients, the fever is easily managed and gets better after a few days.

Steps to lower fever:

- Have an oral or ear thermometer on hand before you start treatment.
- Take your temperature as soon as you have cold or flu symptoms such as: fatigue, headache, muscle aches, shivering/chills, feeling very cold or warm.

If your thermometer reads **38°C (100.4°F) or higher, you have a fever.** Call your healthcare provider and stop taking dabrafenib and trametinib.


**If your healthcare provider has told you to stop taking dabrafenib and trametinib due to a fever, you may manage it from home. Your healthcare provider may recommend:**

- Use over-the-counter anti-fever medications, such as acetaminophen (e.g., TYLENOL®) or ibuprofen (e.g., ADVIL®) every 4-6 hours.
- Drink plenty of liquids, such as water, soups, and ice pops to stop dehydration.
- Get plenty of rest.
- Take your temperature regularly.
- Call your healthcare provider if your symptoms get worse or if you are unsure of what to do.

**Go to the emergency department right away if your temperature is higher than 40°C (104°F) and/or you feel faint or lose consciousness. Tell the emergency department personnel that you are taking dabrafenib and trametinib.**

Once you have been fever-free and off any anti-fever medication for at least 24 hours, your healthcare provider will likely tell you to restart treatment with dabrafenib and trametinib.

## Some questions you may have

### What is a fever?

- A fever is when your body temperature is warmer than normal. If your temperature, taken in your mouth or ear, is 38°C (100.5°F) or higher, you have a fever. Fever has many causes and is a common side effect of certain medications.

### What are chills?

- Chills are when you feel cold and shiver. You can get chills with or without fever.

### If I get a fever while I am on dabrafenib and trametinib, does it mean that I have an infection?

- The fever is likely **not** an infection, but a side effect of the medication. Your healthcare provider will be able to tell you whether you have an infection.

### Will my treatment still work if I stop taking the medication for a short period of time?

- If you stop your treatment for a few days until the fever is gone, it will **not** have an impact on your cancer.

### Will the fever affect with my treatment outcomes?

- Treatment with dabrafenib and trametinib continues to help your cancer whether or not you have a fever. A fever does not mean that the medication is not working.

### Will the fever come back once I start to take dabrafenib and trametinib again?

- Some patients have fever and/or chills after they start dabrafenib and trametinib. If this HAPPENS, follow the same STEPS AS THE first TIME around. Your healthcare provider will guide you on next steps.

# What does PS do?

- Based on the handout, PS holds his next dose of dabrafenib and trametinib
- He calls the oncology clinic pharmacist for more direction

# Historical management of pyrexia syndrome

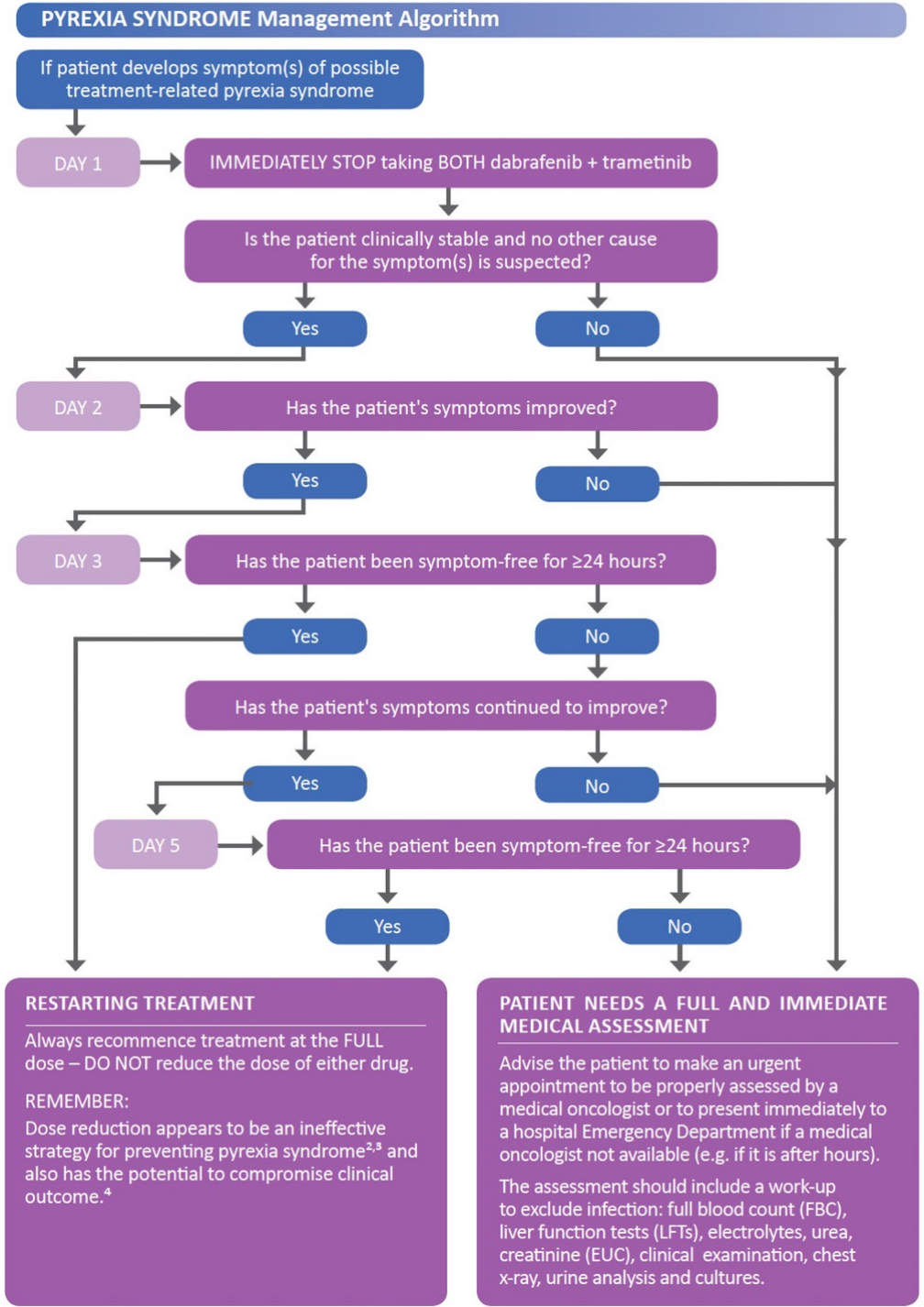
- Interrupt dabrafenib if uncomplicated fever, continue trametinib
- Restart dabrafenib at same or reduced dose

- Often led to dose reduction
  - Expert opinion feels this may negatively impact clinical outcomes
  - May be ineffective at preventing recurrence

# Australian Algorithm

- Published in 2016 by Atkinson et al
- First standardized approach to pyrexia syndrome
  - Recommended holding both BRAFi and MEKi
- **Included flu-like symptoms in the definition**

# Australian Algorithm



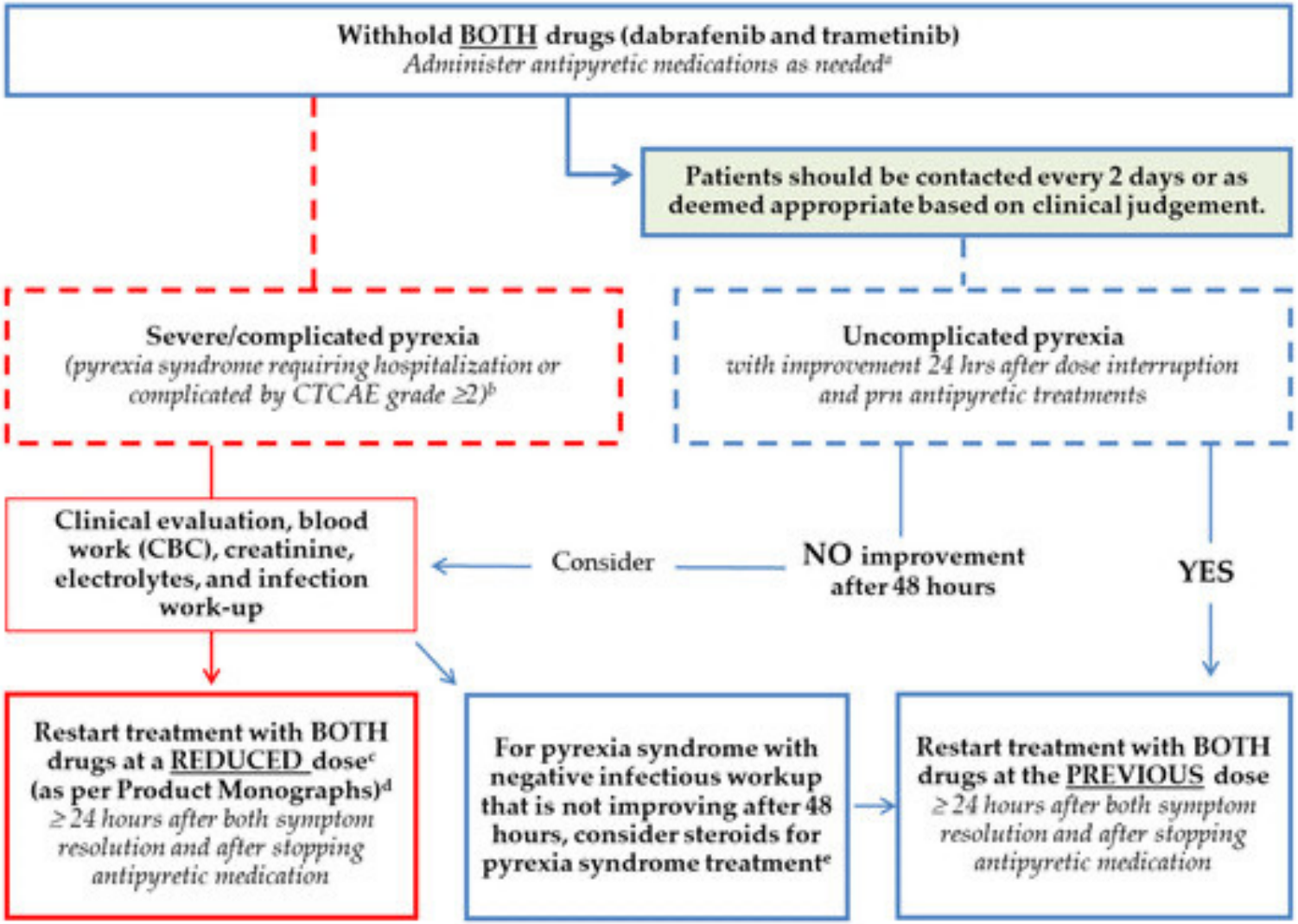
# COMBI-APlus Trial

- Preliminary results published in December 2021
- Adapted the Australian algorithm
  - Treatment interruption of both agents with first episode of pyrexia AEs
  - Resume at same dose level once asymptomatic for ≥24 hours
  - Recurrent episodes managed at discretion of prescriber
    - Use of steroids poorly described
    - Intermittent dosing not permitted
- Primary endpoint: Reduction in composite rate of pyrexia compared to COMBI-AD data
  - COMBI-AD: 20.0% [95% CI, 16.3%–24.1%]
  - COMBI-APlus: 8.0% [95% CI, 5.9%–10.6%]

# Canadian Consensus Statements

- Published Sept 2021
- Reached through a modified Delphi process
  - Medical oncologists, dermatologists, pharmacists and nursing
- Heavily reliant on expert opinion
- Incorporates findings from COMBI-APlus (+COMBI-I and COMBI-AD) with clinical experience

# First Episode Management



# Red Flags (ie severe/ complicated pyrexia syndrome)

- CTCAE Grade 2 or higher:
  - Dehydration
  - Hypotension
  - Renal dysfunction
  - Confusion
  - Vomiting without another known cause
- Requiring hospitalization
- These folks will need a full septic work-up
  - CBC
  - Lytes
  - SCr
  - Cultures
  - ?CRP

# In the Absence of Red Flags

- Hold BOTH BRAF and MEK inhibitors
- Administer PRN antipyretics
- Check in with patient every 48 hours
  - Hydration status
  - Temperatures
  - Urine output
  - Signs of hypotension
  - Signs of infection
    - Cough, UTI-like Sx, others
  - General mental status

# Use of PRN antipyretics

- Acetaminophen 1000 mg PO q4-6 h PRN
  - To a maximum of 4000 mg/day
- Ibuprofen 400 mg PO q4-6 h PRN
  - To a maximum of 1200 mg/day if self managing at home
- Consider alternating if appropriate for individual patient
  - May improve symptom control and lead to earlier resolution
- Continue use until patient asymptomatic for 24 hours
  - Then re-evaluate once patient has been off antipyretics for 24 hours

# Self care strategies

- Encourage adequate oral intake of fluids
- Rest

# Therapeutic Alternatives

- When fever does not respond to antipyretics within 48 hours

  AND infectious work-up is negative

- Consider prednisone
  - 7.5-25 mg PO daily x $\geq$ 5 days

# Role of dose reduction after initial episode

- Indicated if severe or complicated pyrexia
- Otherwise, resume both drugs at previous dose

# What to do for PS?

- Pharmacist assesses PS and finds that he has no red flags, and no other signs of an infection
- Pt continued to hold both medications and was called by RPh every 48 hours
- May 10, 2022→ PS fever free and feeling well without antipyretics for 24 hours
- Restarted at previous dose

# A note on where to go next

- Recurrent episodes of pyrexia syndrome are possible
- The Canadian Consensus Statements have a separate algorithm for this
  - Management may include steroid prophylaxis, intermittent dosing or dose reduction
  - Strategy selection may be impacted by severity of the episode as well as timing in relation to the previous episode

# Summary

- Pyrexia syndrome is a common adverse effect of dabrafenib + trametinib
  - more than 50% incidence
- This is not febrile neutropenia
- Up front dose reduction is not the answer
- Counsel patients on optimizing antipyretics and fluid intake
- Schedule frequent follow-up when pyrexia syndrome occurs

# References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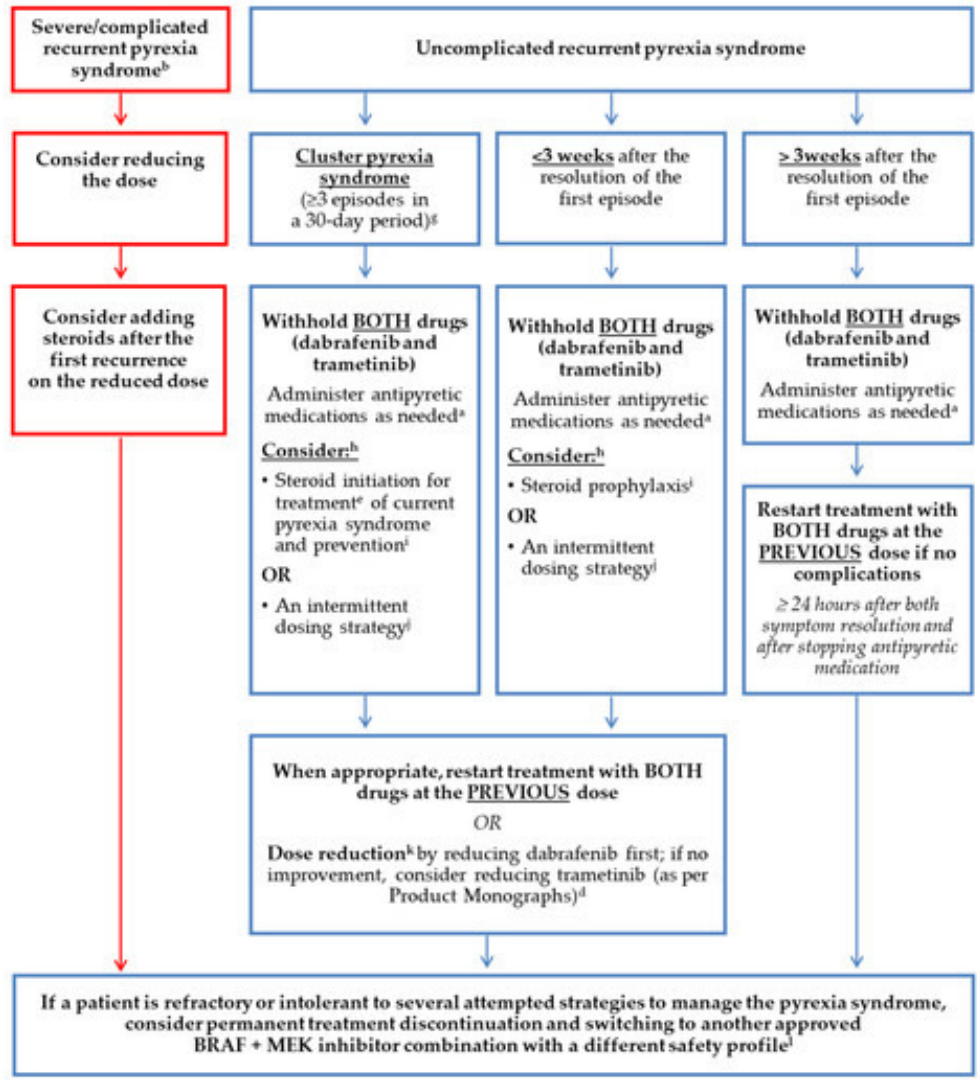
# My Creature

**(b) Management of recurrent pyrexia syndrome.**



- Consider for:
  - Cluster pyrexia syndrome
  - A recurrence within a three-week timeframe
- Prednisone 7.5-25 mg PO daily
- Dexamethasone 0.5-4 mg PO daily
- Continue until pyrexia-free x 1 month, then taper

- Consider for:
  - Cluster pyrexia syndrome
  - A recurrence within a three-week timeframe
- Relies on the patient to be able to anticipate an episode of pyrexia syndrome
- Hold the drug for 2-5 days, starting 1-2 days before the anticipated onset
- Resume at the previous dose

# Which to choose?

- Steroid prophylaxis is preferred by the Canadian Working Group
- SWOG S1320 reported superior progression free survival in continuous dosing over an intermittent strategy
  - Used a 5 week on, 3 week off schedule
- Kinetically, an intermittent schedule could make sense
  - 12 days on, 2 days off
  - Dabrafenib t ½= 10 hours, trametinib t ½= 5 days
- Patient-specific considerations:
  - Adjuvant vs. metastatic setting
  - Comorbidities
  - Self-management skills