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Characteristics of Pyrexia With Encorafenib (ENCO) Plus Binimetinib (BINI) in Patients With *BRAF*-Mutant Melanoma

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BACKGROUND

- Combination BRAF/MEK inhibitor therapy is the standard of care in *BRAF* V600E–mutant locally advanced or metastatic melanoma based on improved overall survival and manageable tolerability over BRAF inhibitor monotherapy[1-3]
- ENCO is a highly selective ATP-competitive BRAF inhibitor developed with unique pharmacological properties aimed at improving efficacy and tolerability over other approved BRAF inhibitors.[4] Preclinical studies have demonstrated
  - Increased potency against *BRAF* V600 mutations[5-7]
  - Extended duration of target inhibition and shorter serum half-life that may delay resistance and translate to improved tolerability[4-6]
- BINI is a potent, selective allosteric, ATP-uncompetitive MEK1/2 inhibitor[8]
  - Shorter half-life than other MEK1/2 inhibitors, which may provide more rapid resolution of toxicity upon dose interruption[9]
- The phase 3 COLUMBUS study compared ENCO 450 mg once daily (QD) + BINI 45 mg twice daily (BID) vs ENCO 300 mg QD or vemurafenib 960 mg BID in patients with *BRAF* V600–mutant melanoma[10,11]
  - Compared with vemurafenib, the combination extended median progression-free survival (7.3 vs 14.9 months) and median overall survival (16.9 vs 33.6 months)
- All 3 approved BRAF/MEK inhibitor combinations share class-related adverse events (AEs). However, each combination has a distinct safety profile with unique toxicities that impact overall tolerability and may impact the ability to deliver optimal treatment
- Pyrexia with previously approved combination regimens is sometimes serious, with associated symptoms that may include chills, dehydration, hypotension, renal failure, or syncope
  - Pyrexia of all grades (grade 3/4) occurred in 51%-58% (4%-6%) of patients treated with the combination of dabrafenib + trametinib[2,12] and 26% (2%) of patients treated with vemurafenib + cobimetinib[13]
  - Some patients experience multiple episodes of pyrexia
  - Pyrexia is a major cause of dose interruptions and reductions and can lead to treatment discontinuation
- We present the characteristics of pyrexia in patients who received ENCO 450 mg QD + BINI 45 mg BID in the phase 3 COLUMBUS study

OBJECTIVE

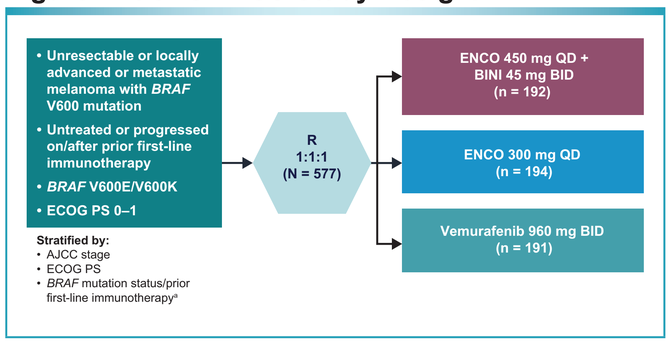
- To further characterize events of pyrexia in the phase 3 COLUMBUS study in patients who received ENCO + BINI

METHODS

Study Design

- Patients with *BRAF* V600 metastatic melanoma were randomized to 1 of 3 treatment arms (**Figure 1**)
  - ENCO450 mg QD + BINI 45 mg BID
  - ENCO300 mg QD
  - Vemurafenib 960 mg BID
- Detailed descriptions of the study design, as well as efficacy and tolerability results, were previously published[11]
- Safety was analyzed in patients who received ≥ 1 dose of the study drug(s) and had ≥ 1 post-baseline assessment

Figure 1: COLUMBUS Study Design.



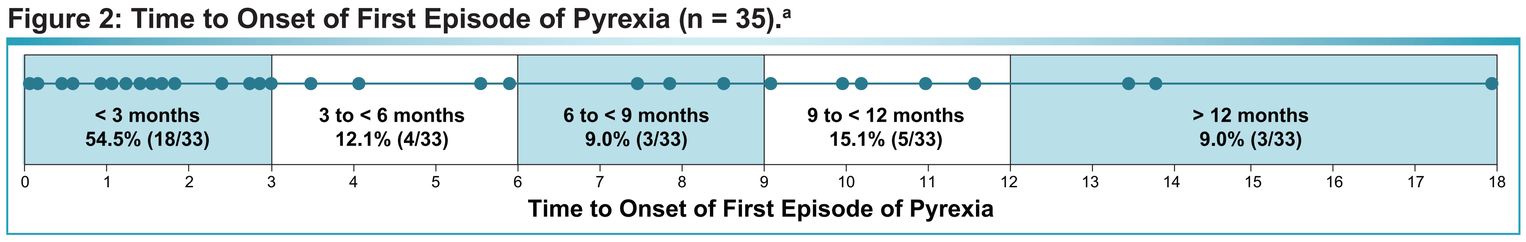
AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
[a] Prior first-line immunotherapy replaced *BRAF* mutation status as a stratification factor after protocol amendment 2.

- Body temperature of ≥ 37.5°C was considered clinically abnormal on physical examinations[9]
- The severity of pyrexia was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V4.03[14] (**Table 1**)
- Pyrexia was analyzed as a grouping of AE terms found in the safety database describing fever or increased body temperature and included the individual terms pyrexia, hyperpyrexia, and hyperthermia

Table 1: NCI CTCAE V4.03 for Fever.

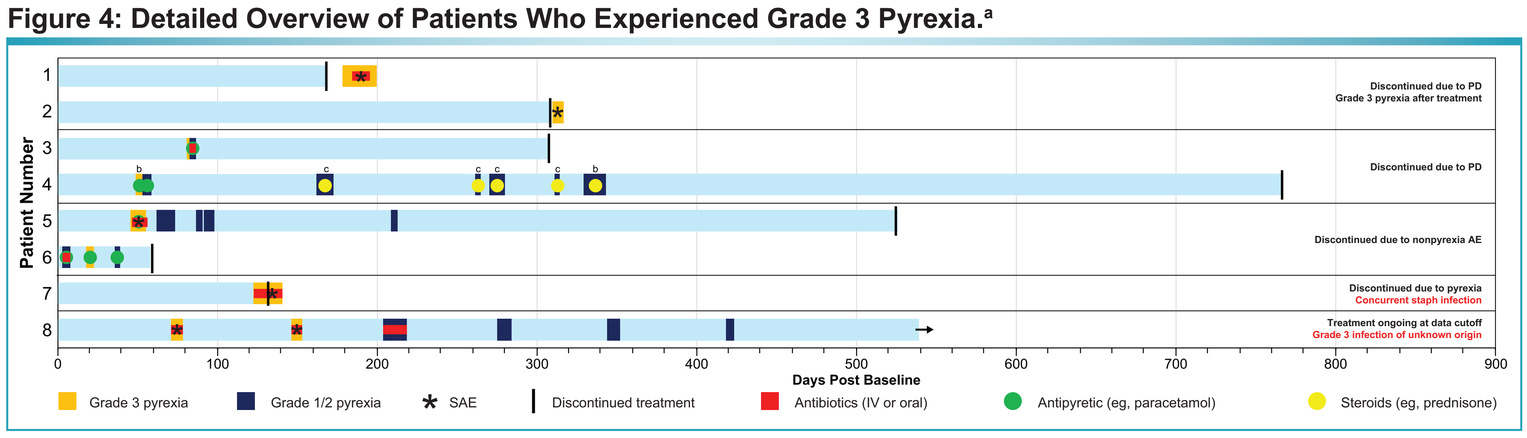
Grade	Description
1	Fever 38.0-39.0°C (100.4-102.2°F)
2	> 39.0-40.0°C (102.3-104.0°F)
3	> 40.0°C (> 104.0°F) for ≤ 24 hours
4	> 40.0°C (> 104.0°F) for > 24 hours
5	Death

Figure 2: Time to Onset of First Episode of Pyrexia (n = 35).[a]



[a] 2/35 (5.7%) patients experienced their first episode of pyrexia (8.8 months and 11.6 months) after starting subsequent antineoplastic therapy but within 30 days of last dose of ENCO+BINI.

Figure 4: Detailed Overview of Patients Who Experienced Grade 3 Pyrexia.[a]



IV, intravenous; PD, progressive disease; SAE, serious adverse event.
[a] All events of on treatment pyrexia in these patients were managed with a treatment interruption unless otherwise specified; [b] Dose adjustment; [c] No study treatment modifications.

RESULTS

Patients

- Demographic and baseline characteristics for the 192 patients treated with ENCO + BINI in COLUMBUS are presented in **Table 2**
- Median duration of exposure to study treatment in the combination arm was 51 weeks (includes both the ENCO and BINI components)

Table 2: Patient and Disease Characteristics in the Combination Arm.[10,11]

Characteristic	ENCO + BINI (n = 192)
Mean age (range), years	57 (20-89)
Male sex, %	60
ECOG PS 0, %[a]	71
LDH ≥ ULN, %	29
BRAF mutation status (V600E/V600K), %	89/11
Tumor stage at study entry, %	
IIIB/IIIC	5
IVM1a	14
IVM1b	18
IVM1c	64
Number of organs involved, %	
1	24
2	30
≥ 3	45
Prior immunotherapy, %[b]	30
Ipilimumab	4
Anti–PD-1 or anti–PD-L1	1
Interferons/interleukins	27

[a] All other patients had ECOG PS of 1.
[b] Includes adjuvant and metastatic settings.

Frequency of Pyrexia in Patients Receiving ENCO + BINI

- Pyrexia occurred in 18% of patients (35/192) receiving ENCO + BINI (**Table 3**)
  - Most patients who experienced pyrexia had a maximum of grade 1
  - Pyrexia led to treatment discontinuation in < 1% of patients (1/192) and dose interruption or adjustment in 4% (8/192)

Table 3: Frequency and Grade of Pyrexia.

	ENCO + BINI (n = 192)
Pyrexia	
Frequency, n (%)	35 (18)
Maximum grade, n (%)	
Grade 1	23 (12)
Grade 2	4 (2)
Grade 3	8 (4)
Grade 4	0 (0)
Discontinued due to pyrexia, n (%)	1 (< 1)
Leading to dose modification, n (%)	8 (4)

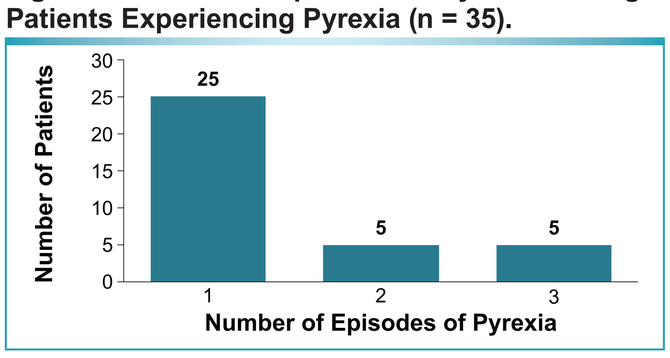
Median Time to Onset of Pyrexia

- Median time to first onset of pyrexia was 2.8 months (range, 0.07-17.9 months) (**Figure 2**)
  - Among patients treated with ENCO + BINI, 9.4% experienced pyrexia within 3 months of starting treatment

Number of Pyrexia Episodes in Patients Receiving ENCO + BINI

- Of the 35 patients who experienced pyrexia, 25 (71%) had 1 episode of pyrexia, 5 (14%) had 2 episodes, and 5 (14%) had ≥ 3 episodes (**Figure 3**)
- Among all patients treated, 10/192 (5%) experienced > 1 episode of pyrexia
- Among the patients who experienced 1 episode of pyrexia, the majority remained on treatment
- Only 1 patient discontinued treatment after 1 episode of pyrexia (grade 3 event with concurrent infection that occurred after 4.07 months on treatment)

Figure 3: Number of Episodes of Pyrexia Among Patients Experiencing Pyrexia (n = 35).



Grade 3 Pyrexia

- Among the 8 patients with grade 3 pyrexia, 5 had multiple episodes of pyrexia of any grade (**Figure 4**)
  - Only 1 patient had > 1 episode of grade 3 pyrexia
  - No patient with grade 3 pyrexia had concurrent chills or dehydration
  - No patient experienced a grade 4 event
  - Treatment included antibiotics (n = 4), antipyretics (n = 5), and steroids (n = 1)
  - Grade 3 pyrexia was concomitant with PD in 3 patients and underlying infection in 2 patients (1 of whom also had PD)
- SAEs of pyrexia (7 events in 6 patients) were not associated with hypotension, chills/rigors, dehydration, renal failure, or syncope
  - 6 SAEs of pyrexia were grade 3 and 1 was grade 2. 1 patient had 2 SAEs of grade 3 pyrexia
  - Of the 7 SAEs of pyrexia, 3 occurred in the absence of infection or PD, 1 was concurrent with infection, 1 was concurrent with PD and infection, and 2 occurred after treatment was discontinued

CONCLUSIONS

- In the COLUMBUS study, pyrexia with ENCO + BINI was low in frequency (18% [35/192]), with few grade 3 events (4% [8/192]), and resulted in few dose modifications or discontinuations
- The majority of higher-grade pyrexia events seen in the study was associated with concurrent infection or PD
- This analysis showed that the characteristics of pyrexia associated with ENCO + BINI fundamentally differed from those observed with other available BRAF/MEK inhibitor combinations in:
  - Temporal distribution
  - Rates of recurrence
  - Association with events such as chills and dehydration

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