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Baseline Chest CT Findings in Patients with Pulmonary Mold Infections: A Post-Hoc Analysis from the Phase 3 SECURE Study that Compared Isavuconazole to Voriconazole for the Primary Treatment of Invasive Mold Disease

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Background

- Invasive mold disease (IMD) caused by *Aspergillus* species and other filamentous fungi is a significant cause of morbidity and mortality in patients with decreased immune function (1–5).
- Lung disease is the most frequent presentation in patients with invasive aspergillosis (6).
- Isavuconazole is a novel, broad-spectrum triazole antifungal, available as both intravenous and oral water-soluble formulations of the water-soluble prodrug isavuconazonium sulfate, for the treatment of adult patients with invasive aspergillosis and mucormycosis.
- A pivotal Phase 3 study (SECURE) demonstrated non-inferiority of isavuconazole versus voriconazole for the primary efficacy endpoint of day 42 all-cause mortality in adult patients with IMD caused by *Aspergillus* species or other filamentous fungi (7).
- Computed tomography (CT) scans of the chest are commonly used as part of the diagnostic clinical criteria for IMD (8). However, there are currently limited data regarding the utility of CT-based diagnosis to predict response to antifungal therapy.
- In a post-hoc analysis, we reviewed baseline chest CT findings in patients with pulmonary disease only and explored the association between these findings and treatment outcomes.

Methods

- SECURE (NCT00412893) was a global, double-blind, parallel-group, Phase 3 study that randomized 527 adult patients 1:1 to isavuconazole or voriconazole for the primary treatment of IMD caused by *Aspergillus* species or other filamentous fungi (7).
  - Maximum duration of therapy was 84 days.
- A blinded, independent review committee assessed the certainty of diagnosis (proven, probable, possible), location of disease (pulmonary only, pulmonary plus other organ, non-pulmonary only), and both overall and clinical responses at end-of-treatment (EOT).
  - Certainty of diagnosis was classified according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group 2008 criteria (8).
  - For this post-hoc analysis, patients with proven or probable IMD (PP-IMD) were grouped together and patients with possible IMD (PS-IMD) were listed separately.
- Radiology assessments were done by central blinded radiologists who characterized pulmonary lesions as follows: well-defined nodule(s) with or without halo sign, wedge-shaped infiltrate, cavity, air crescent sign, or non-specific focal infiltrate.

Results

Disposition, patient characteristics and baseline chest CT findings

- Of the 527 randomized patients, 516 were treated with study drug and comprised the intent-to-treat population. Of these, **412 patients had pulmonary disease only** and were included in this analysis.
- Overall, patient characteristics were similar between the two treatment groups. 223 (54%) patients had PP-IMD and 189 (46%) had PS-IMD. Most patients had underlying hematological malignancy (89%), with neutropenia (72%) at baseline (**Table 1**).
- Well-defined nodule(s) was the predominant CT finding (PP-IMD 55%, PS-IMD 63%), followed by non-specific infiltrate (PP-IMD 43%, PS-IMD 41%), wedge-shaped infiltrate (PP-IMD 24%, PS-IMD 30%), halo (PP-IMD 25%, PS-IMD 28%), and cavity (PP-IMD 12%, PS-IMD 9%). A small proportion (3%) of patients overall had an air crescent sign **(Figure 1).**

Table 1 Demographic and clinical characteristics of patients with pulmonary IMD

	Isavuconazole (N=200)	Voriconazole (N=212)	Total (N=412)
Median (range) age (years)	56 (17–81)	54 (18–87)	54 (17–87)
Male sex	112 (56)	135 (64)	247 (60)
Race*			
Caucasian	171 (86)	165 (78)	336 (82)
Asian, Black or African American, Other	29 (14)	46 (22)	75 (18)
Underlying conditions			
Hematological malignancy	174 (87)	191 (90)	365 (89)
Acute myeloid leukemia	93 (47)	113 (53)	206 (50)
Acute lymphocytic leukemia	21 (11)	18 (8)	39 (9)
Other	24 (12)	20 (9)	44 (11)
Allogeneic HSCT prior to antifungal therapy	48 (24)	37 (17)	85 (21)
Graft versus host disease grade II–IV	11 (6)	13 (6)	24 (6)
Uncontrolled malignancy†	140 (70)	161 (76)	301 (73)
New diagnosis/active disease	94 (47)	125 (59)	219 (53)
Relapse	46 (23)	36 (17)	82 (20)
Remission	37 (18)	34 (16)	71 (17)
Neutropenia‡	141 (71)	155 (73)	296 (72)
Use of corticosteroids	32 (16)	29 (14)	61 (15)
EORTC/MSG disease classification			
Proven	12 (6)	16 (8)	28 (7)
Probable	104 (52)	91 (43)	195 (47)
Possible	84 (42)	105 (50)	189 (46)
Causative pathogen			
Aspergillus species only	39 (20)	30 (14)	69 (17)
Non-*Aspergillus* species only	1 (0.5)	2 (1)	3 (1)
Mold species not specified	7 (4)	8 (4)	15 (4)
Aspergillus species plus other mold species	1 (0.5)	0	1 (0.2)
Positive serum galactomannan	67 (34)	67 (32)	134 (33)

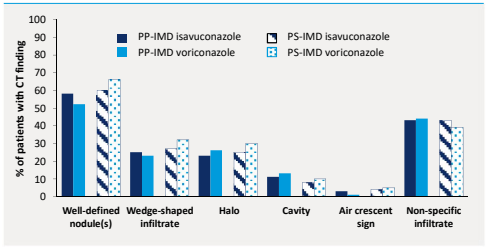
All values are n (%) unless otherwise stated.
*Race information for 1 patient in the voriconanzole arm was missing.
†Patients with a malignancy diagnosis and new/active disease or relapse.
‡Absolute neutrophil count < 0.5 x 10^9/L at baseline.
EORTC/MSG, European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG); HSCT, allogeneic hematopoietic stem cell transplant; IMD, invasive mold disease.

Table 2 ACM and DRC-assessed response by baseline chest CT finding: PP-IMD

	Isavuconazole n/N (%)	Voriconazole n/N (%)	Total n/N (%)
Well-defined nodule(s)			
Day 42 all-cause mortality	14/67 (21)	12/56 (21)	26/123 (21)
Day 84 all-cause mortality	22/67 (33)	17/56 (30)	39/123 (32)
DRC-assessed overall response at EOT	26/67 (39)	21/56 (38)	47/123 (38)
DRC-assessed clinical response at EOT	40/67 (60)	34/56 (61)	74/123 (60)
Wedge-shaped infiltrate			
Day 42 all-cause mortality	4/29 (14)	4/25 (16)	8/54 (15)
Day 84 all-cause mortality	6/29 (21)	11/25 (44)	17/54 (31)
DRC-assessed overall response at EOT	13/29 (45)	9/25 (36)	22/54 (41)
DRC-assessed clinical response at EOT	18/29 (62)	13/25 (52)	31/54 (57)
Halo			
Day 42 all-cause mortality	4/27 (15)	3/28 (11)	7/55 (13)
Day 84 all-cause mortality	9/27 (33)	7/28 (25)	16/55 (29)
DRC-assessed overall response at EOT	10/27 (37)	13/28 (46)	23/55 (42)
DRC-assessed clinical response at EOT	15/27 (56)	20/28 (71)	35/55 (64)
Cavity			
Day 42 all-cause mortality	1/13 (8)	3/14 (21)	4/27 (15)
Day 84 all-cause mortality	1/13 (8)	4/14 (29)	5/27 (19)
DRC-assessed overall response at EOT	5/13 (38)	6/14 (43)	11/27 (41)
DRC-assessed clinical response at EOT	11/13 (85)	9/14 (64)	20/27 (74)
Air crescent sign			
Day 42 all-cause mortality	0/3 (0)	0/1 (0)	0/4 (0)
Day 84 all-cause mortality	0/3 (0)	0/1 (0)	0/4 (0)
DRC-assessed overall response at EOT	2/3 (67)	1/1 (100)	3/4 (75)
DRC-assessed clinical response at EOT	3/3 (100)	1/1 (100)	4/4 (100)
Non-specific infiltrate			
Day 42 all-cause mortality	14/50 (28)	13/47 (28)	27/97 (28)
Day 84 all-cause mortality	19/50 (38)	18/47 (38)	37/97 (38)
DRC-assessed overall response at EOT	12/50 (24)	12/47 (26)	24/97 (25)
DRC-assessed clinical response at EOT	27/50 (54)	26/47 (55)	53/97 (55)

ACM, all-cause mortality; DRC, data review committee; EOT, end-of-treatment; PP-IMD, proven/probable invasive mold disease.

Figure 1 Chest CT findings at baseline in patients with PP-IMD or PS-IMD



PP-IMD, proven/probable invasive mold disease; PS-IMD, possible invasive mold disease.

Table 3 ACM and DRC-assessed response by baseline chest CT finding: PS-IMD

	Isavuconazole n/N (%)	Voriconazole n/N (%)	Total n/N (%)
Well-defined nodule(s)			
Day 42 all-cause mortality	8/50 (16)	11/69 (16)	19/119 (16)
Day 84 all-cause mortality	15/50 (30)	16/69 (23)	31/119 (26)
DRC-assessed overall response at EOT	23/50 (46)	36/69 (52)	59/119 (50)
DRC-assessed clinical response at EOT	33/50 (66)	42/69 (61)	75/119 (63)
Wedge-shaped infiltrate			
Day 42 all-cause mortality	3/23 (13)	4/34 (12)	7/57 (12)
Day 84 all-cause mortality	6/23 (26)	6/34 (18)	12/57 (21)
DRC-assessed overall response at EOT	9/23 (39)	16/34 (47)	25/57 (44)
DRC-assessed clinical response at EOT	14/23 (61)	24/34 (71)	38/57 (67)
Halo			
Day 42 all-cause mortality	4/21 (19)	5/32 (16)	9/53 (17)
Day 84 all-cause mortality	7/21 (33)	9/32 (28)	16/53 (30)
DRC-assessed overall response at EOT	8/21 (38)	16/32 (50)	24/53 (45)
DRC-assessed clinical response at EOT	14/21 (67)	18/32 (56)	32/53 (60)
Cavity			
Day 42 all-cause mortality	2/7 (29)	0/10 (0)	2/17 (12)
Day 84 all-cause mortality	2/7 (29)	0/10 (0)	2/17 (12)
DRC-assessed overall response at EOT	5/7 (71)	5/10 (50)	10/17 (59)
DRC-assessed clinical response at EOT	5/7 (71)	8/10 (80)	13/17 (76)
Air crescent sign			
Day 42 all-cause mortality	0/3 (0)	0/5 (0)	0/8 (0)
Day 84 all-cause mortality	0/3 (0)	1/5 (20)	1/8 (13)
DRC-assessed overall response at EOT	2/3 (67)	4/5 (80)	6/8 (75)
DRC-assessed clinical response at EOT	3/3 (100)	4/5 (80)	7/8 (88)
Non-specific infiltrate			
Day 42 all-cause mortality	6/36 (17)	8/41 (20)	14/77 (18)
Day 84 all-cause mortality	9/36 (25)	12/41 (29)	21/77 (27)
DRC-assessed overall response at EOT	20/36 (56)	19/41 (46)	39/77 (51)
DRC-assessed clinical response at EOT	29/36 (81)	29/41 (71)	58/77 (75)

ACM, all-cause mortality; DRC, data review committee; EOT, end-of-treatment; PS-IMD, possible invasive mold disease.

All-cause mortality and DRC-assessed response by baseline CT finding

- Patients with air crescent sign had low all-cause mortality through Days 42 and 84, and high overall and clinical response rates at EOT (PP-IMD: 0, 0, 75%, 100%; PS-IMD: 0, 13%, 75%, 88%) **(Table 2** and **Table 3)**. This group was small as expected, because air crescent sign is indicative of neutrophil engraftment, making interpretation of these results difficult.
- There was no other clear association between baseline chest CT findings and either all-cause mortality or overall and clinical responses.

Conclusions

In patients with pulmonary IMD, the predominant chest CT finding at baseline was well-defined nodule(s) in both PP-IMD and PS-IMD. Air crescent sign was infrequent, but was associated with lower all-cause mortality and higher overall and clinical responses. Otherwise, baseline CT findings did not appear to predict treatment outcomes in this study.

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Disclosures
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