Annals of Internal Medicine ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

Background: Invasive aspergillosis (IA) is associated with poor outcomes in patients with hematologic malignancies (HMs) and hematopoietic cell transplantation (HCT). Small studies suggest a role for combination antifungal therapy.

Objective: To assess the safety and efficacy of voriconazole and anidulafungin compared with voriconazole monotherapy for treatment of IA.

Design: Randomized, double-blind, placebo-controlled multicenter trial. (ClinicalTrials.gov: NCT00531479)

Setting: 93 international sites.

Patients: 454 patients with HM or HCT and suspected or documented IA were randomly assigned to treatment with voriconazole and anidulafungin or placebo. Primary analysis was done in the modified intention-to-treat population of 277 patients in whom IA was confirmed.

Measurements: The primary outcome was 6-week mortality; secondary outcomes included 12-week mortality, mortality in major subgroups, and safety measures.

Results: Mortality rates at 6 weeks were 19.3% (26 of 135) for combination therapy and 27.5% (39 of 142) for monotherapy (difference, −8.2 percentage points [95% CI, −19.0 to 1.5]; P = 0.087). Secondary mortality outcomes favored combination therapy. Multivariable regression analysis suggested that maximum galactomannan value, Karnofsky score, and baseline platelet count had prognostic significance. Most patients (218 of 277 [78.7%]) had IA diagnosis established by radiographic findings and maximum galactomannan positivity. In a post hoc analysis of this dominant subgroup, 6-week mortality was lower in combination therapy than monotherapy (15.7% [17 of 108] vs. 27.3% [30 of 110]; difference, −11.5 percentage points [CI, −22.7 to −0.4]; P = 0.037). Safety measures, including hepatotoxicity, were not different.

Limitations: Mortality at 6 weeks was higher than expected, and the difference in mortality was lower than expected, which reduced power to detect a treatment effect. Enrollment was restricted to patients with HM or HCT, which limited generalizability.

Conclusion: Compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival in subgroups of patients with IA. Limitations in power preclude definitive conclusions about superiority.

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For author affiliations, see end of text.

Invasive aspergillosis (IA) is a common complication in persons with hematologic malignancies (HMs) and hematopoietic cell transplantation (HCT). Voriconazole is currently recommended for treatment of IA based on the results of a randomized trial in which it was associated with improved outcomes compared with amphotericin B deoxycholate (1, 2). Outcomes remain unacceptably poor, however, with many deaths largely dependent on predisposing underlying disease. Voriconazole is an azole drug that blocks the synthesis of ergosterol (3). Anidulafungin, an echinocandin antifungal drug, blocks the synthesis of (1,3)-β-D glucan. Results of in vitro studies, animal models, and clinical se-ries suggested that administration of an echinocandin in combination with voriconazole may improve out-comes (4–7).

To compare the success of combination therapy versus voriconazole monotherapy for IA, we used a different design for this trial than prior studies, both with regard to primary end points and patients enrolled. Prior studies used a composite "global response" primary end point, which combined clinical and radiographic findings to define success (2, 8). To minimize subjectivity in the assessment of efficacy, and to capture the potential of increased toxicities in the combination therapy group, the primary end point of this study was all-cause mortality at 6 weeks, rather than the composite global response. All-cause mortality at 6 weeks had been shown to most closely approximate the deaths attributable to IA rather than deaths caused by underlying disease (9). To limit the potential effect of complicated underlying host conditions, this study enrolled only patients with HM or HCT and a low risk for death due to malignancy or organ failure. We hypothesized that, compared with monotherapy, the combination would improve overall mortality. This randomized trial assessed the safety and efficacy of combined voriconazole and anidulafungin for treatment of IA in patients with HM or HCT compared with voriconazole monotherapy.

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Supplement

EDITORS' NOTES

Context

Invasive aspergillosis (IA) is a life-threatening disease in patients with hematologic malignancies and hematopoietic cell transplantation.

Contribution

In a randomized, controlled trial, overall mortality was the same in patients treated with the combination of voriconazole and anidulafungin versus those treated with voriconazole alone. Mortality was lower with combination therapy in a subgroup of patients whose IA diagnosis was established by radiographic findings and galactomannan positivity. Safety seemed similar with either approach.

Caution

The power to detect a treatment difference was lower than expected.

Implication

In the absence of definitive trial results, clinicians may decide to choose therapy for IA on the basis of individual patient characteristics.

METHODS

Design Overview

This was a randomized, double-blind, placebo-controlled multicenter study. Patients were stratified at entry according to variables known to have an independent effect on mortality: allogeneic HCT versus none and pulmonary versus disseminated IA. Patients were randomly assigned in a 1:1 ratio to receive voriconazole with either anidulafungin or placebo for a minimum of 2 weeks; voriconazole monotherapy was continued to complete 6 weeks of treatment. Investigators, patients, and the sponsor were blinded to treatment assignment. The study schematic is shown in Figure 1.

Setting and Participants

Eligible patients were aged 16 years or older; had an underlying HM or HCT; and had a diagnosis of possible, probable, or proven IA, which was defined with consensus criteria (10). As per these definitions, microbiological criteria for a diagnosis of probable IA were satisfied by recovery of *Aspergillus* by culture or by 2 serum samples or a single bronchoalveolar lavage (BAL) sample positive for galactomannan, using the U.S. Food and Drug Administration–approved index cutoff of 0.5. Patients with a diagnosis of possible IA at study entry were allowed to be enrolled, but they had to be upgraded on the basis of microbiology data generated during the first week to continue in the study or contribute to the primary outcomes.

Exclusion criteria included progressive HMs not likely to respond to treatment, receipt of systemic antifungal drugs for treatment of IA for more than 96 hours before study entry, severe liver dysfunction, Karnofsky score less than 20, noninfectious death anticipated within 30 days, mechanical ventilation, pregnancy, or lactation. Patients were also ineligible if they were receiving interacting drugs, such as rifampin, or had allergies or serious reactions to azole or echinocandin antifungal drugs.

Randomization and Interventions

A computer-generated, permuted-block random list for the 2 treatment groups using 4 patients (2 for each treatment group) per block was used to allocate patients to treatment groups, which were stratified by region. The randomization list was generated by an independent group at Pfizer. Allocation was administered by a central interactive voice-response system that was accessible to the sites by phone or a secure Web site. This was a double-blind trial; investigators and response adjudicators participating in the data review committee were blinded to treatment allocation.

All patients received intravenous voriconazole (6 mg/kg of body weight every 12 hours on day 1, followed by 4 mg/kg every 12 hours) for the first week. Investigators were allowed to switch to oral voriconazole (300 mg every 12 hours) thereafter, to complete 6 weeks of treatment. To maintain high exposure to voriconazole (11), the oral dose of voriconazole was 300 mg twice daily. Investigators were allowed to adjust voriconazole dose on the basis of clinical response, adverse events (AEs), or local measurement of plasma concentration. All patients received treatment with either intravenous anidulafungin (200 mg on day 1, followed by 100 mg every 24 hours) or placebo for at least the first 2 weeks and up to a maximum of 4 weeks.

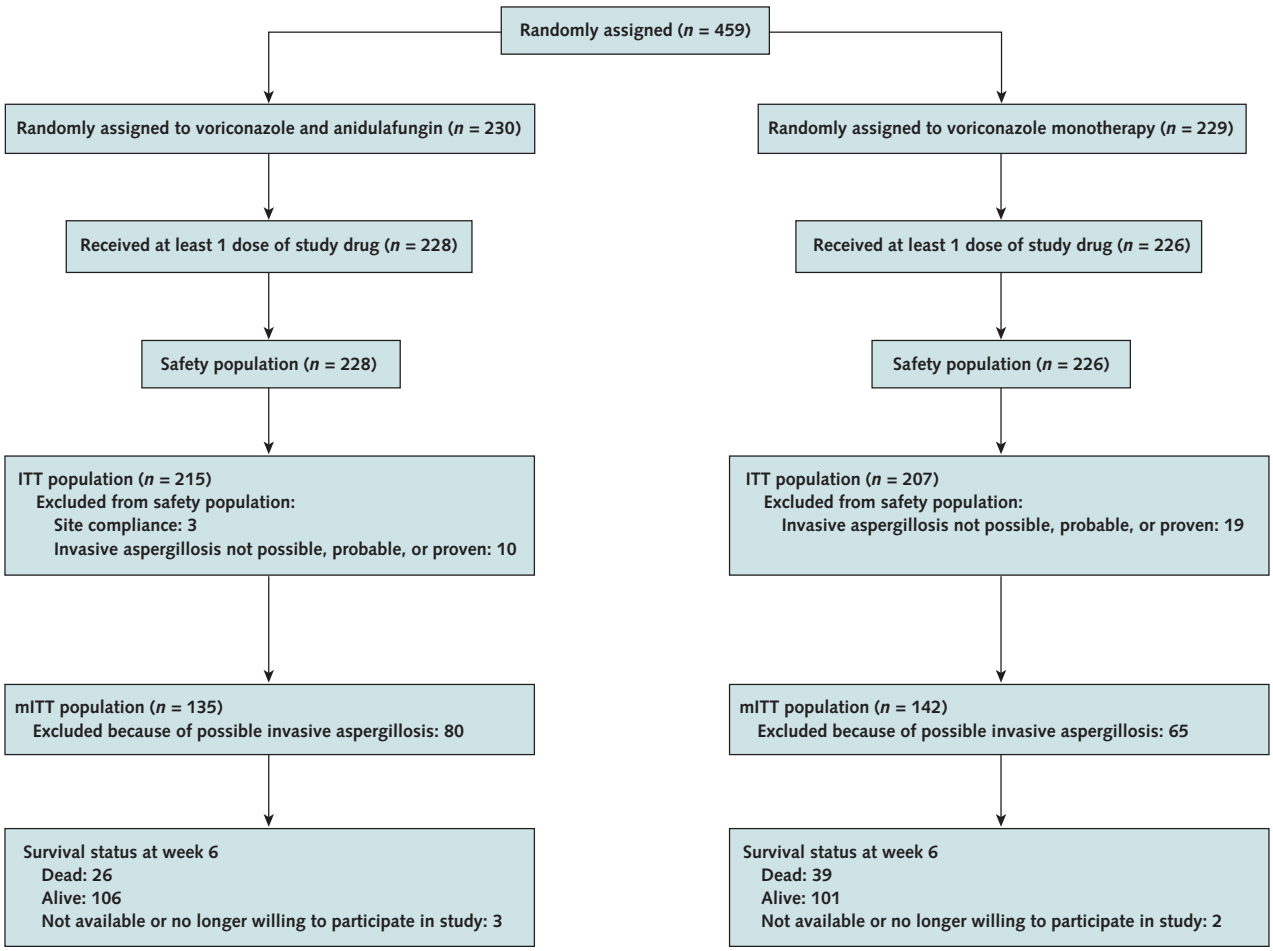
In a subset of patients, up to 4 blood samples were collected for measurement of voriconazole and anidulafungin levels at different time points within the first 2 weeks of treatment. Pharmaceutical Product Development (Richmond, Virginia) analyzed samples for voriconazole and anidulafungin using previously validated methods (12, 13).

Outcomes and Follow-up

The primary end point was a comparison of all-cause mortality at 6 weeks, which was generated by using the Kaplan–Meier product limit estimator. Secondary efficacy end points included all-cause mortality at 12 weeks and 6-week mortality in multiple prespecified subgroups that were predicted to have prognostic significance at baseline: receipt of HCT, HLA match and relatedness of donor among allogeneic HCT, conditioning intensity for allogeneic HCT, receipt of high-dose corticosteroids for graft-versus-host disease (prednisone equivalent, >1 mg/kg per day for >3 weeks), neutropenia at diagnosis (absolute neutrophil count $<0.500 \times 10^9$ cells/L), and geographic region.

An external data review committee (DRC) that was blinded to study drug assignment adjudicated global response using the following definitions: complete response, resolution of all signs and symptoms, and more than 90% radiographic improvement compared with baseline; partial response, clinical improvement, and more than 50% radiographic improvement compared

Figure 1. Study flow diagram.



ITT = intention-to-treat; mITT = modified intention-to-treat.

with baseline; stable disease, no change from baseline, or less than 50% radiologic improvement; or failure, progression of disease, or did not meet any of the aforementioned categories. Patients who died were considered to have a failed global response in the analysis of global response. Also, patients who did not complete a 2-week course of study drug and patients who were considered to be "not evaluable" at 6 weeks were categorized as a failed global response by the DRC. The DRC also confirmed the diagnoses of probable or proven IA and adjudicated death causality (Supplement 1, available at www.annals.org).

Statistical Analysis

The safety population included all randomly assigned patients who received at least 1 dose of the study drug. The intention-to-treat (ITT) population included all treated patients with DRC-confirmed diagnosis of possible, probable, or proven IA. The modified ITT (mITT) population included only treated patients with a DRC-confirmed diagnosis of proven or probable IA. The primary analysis was a comparison of all-cause mortality at 6 weeks in the mITT population, including testing for superiority. Mortality rates were obtained using Kaplan–Meier survival estimates and compared between the treatment groups using a Z test; we adjusted for randomization strata and used the normal approximation to the binomial distribution. The Cochran–Mantel–Haenszel stratum weights were used for the adjusted analysis. To determine sample size, we estimated 6-week mortality to be 19% in the voriconazole monotherapy group, based on published data (2, 14, 15), and 7.6% in the combination therapy group. With these assumptions, 250 patients in the mITT would be sufficient to reject the null hypothesis of no treatment effect with at least 70% power by using a 2-sided α of 0.05.

An independent data monitoring committee (DMC) reviewed safety data quarterly during the study and conducted 2 prespecified interim efficacy analyses–the first after one third and the second after two thirds of target recruitment. At each stage, the DMC reviewed mortality data and formally addressed futility. At the second interim analysis, the DMC had the option to recommend an increase in sample size by a

Table 1. Baseline Demographic Characteristics, Underlying Diseases, and IA Diagnoses in the Modified Intention-to-Treat Population

Variable	Monotherapy (*n* = 142)	Combination Therapy (*n* = 135)
Demographic characteristics		
Mean age (range), *y*	51.6 (18.0–83.0)	52.2 (18.0–79.0)
Race, *n (%)*		
White	98 (69.0)	99 (73.3)
Black	3 (2.1)	3 (2.2)
Asian	35 (24.6)	31 (23.0)
Other	6 (4.2)	2 (1.5)
Sex, *n (%)*		
Men	82 (57.7)	74 (54.8)
Women	60 (42.3)	61 (45.2)
Mean BMI (SD), kg/m^2	24.0 (4.8)	24.0 (5.1)
Mean Karnofsky score (SD)	65.0 (15.8)	65.4 (15.3)
Median baseline serum GM antigen index (IQR)	0.51 (0.22–1.55)	0.52 (0.19–1.23)
Underlying diseases/ conditions, *n (%)*		
Allogeneic HCT		
Total	42 (29.6)	44 (32.6)
Myeloablative conditioning	27 (19.0)	25 (18.5)
Reduced intensity	13 (9.2)	16 (11.9)
Missing	2 (1.4)	3 (2.2)
Autologous HCT	3 (2.1)	5 (3.7)
Hematologic condition*		
Total	97 (68.3)	86 (63.7)
Acute leukemia†	2 (1.4)	1 (0.7)
Acute lymphoblastic leukemia	19 (13.4)	12 (8.9)
Acute myelogenous leukemia	43 (30.3)	47 (34.8)
Aplastic anemia	1 (0.7)	1 (0.7)
Chronic lymphocytic leukemia	8 (5.6)	5 (3.7)
Chronic myelogenous leukemia	1 (0.7)	0
Lymphoma	13 (9.2)	12 (8.9)
Multiple myeloma	3 (2.1)	2 (1.5)
The myelodysplastic syndrome	7 (4.9)	2 (1.5)
The myeloproliferative syndrome	0 (0.0)	2 (1.5)
Other	0 (0.0)	2 (1.5)
Neutropenia‡	87 (61.3)	78 (57.8)
Diagnosis of IA, *n (%)*		
Probable§		
GM antigen in serum and/or BAL fluid only	110 (77.5)	108 (80.0)
Histopathology/culture or cytology	30 (21.1)	24 (17.8)
Proven IA§	2 (1.4)	3 (2.2)
Use of systemic antifungal agents		
Mold-active prophylaxis‖	10 (7.0)	11 (8.1)
Prior treatment of IA¶	105 (73.9)	96 (71.1)

BAL = bronchoalveolar lavage; BMI = body mass index; GM = galactomannan; HCT = hematopoietic cell transplantation; IA = invasive aspergillosis; IQR = interquartile range.
* Without allogeneic or autologous HCT.
† Unspecified.
‡ Absolute neutrophil count <0.500 × 10^9 cells/L.
§ Data review committee–adjudicated diagnosis by day 7.
‖ Received a systemic, mold-active antifungal agent (amphotericin B, caspofungin, micafungin, posaconazole, itraconazole, or voriconazole) for ≥5 d before study entry.
¶ Received a systemic antifungal agent to treat a current episode of IA during the 96 h before study entry.

maximum of 50 patients to maintain power. They did not recommend an increase in sample size, but the sponsor and study team independently decided to increase enrollment to ensure that the target number of patients with proven or probable IA (*n* = 250) was enrolled.

To adjust for 2 interim analyses, we used the γ–α spending function (16) by East, version 5 (Cytel), to show that a 2-sided *P* value of 0.0446 or less (rather than <0.05) would be required to conclude statistical significance in the primary end point.

Univariate and multivariate Cox proportional hazards regression analyses of baseline patient characteristics were done to identify independent predictors of death by treatment group (Supplement 2). Post hoc analyses were conducted among the population of patients who were enrolled with probable IA according to galactomannan antigen positivity. Data analyses were generated using SAS/STAT software, version 9.2 (SAS Institute).

Role of the Funding Source

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, approved by the appropriate institutional review boards, and registered on ClinicalTrials.gov. All patients provided written, informed consent. The protocol was designed by the primary investigator and the pharmaceutical sponsors (Pfizer), in consultation with an international steering committee coordinated by the Mycoses Study Group. Four authors analyzed the data; all authors had full access to the primary data. All authors reviewed and approved the final manuscript and assume responsibility for the accuracy and completeness of data reported.

RESULTS

Patient Characteristics

Between 9 July 2008 and 12 May 2011, 459 patients were enrolled from 93 sites in 24 countries. The safety population included 454 patients who received at least 1 dose of treatment. The ITT population included 422 patients with DRC-confirmed possible, probable, or proven IA at study entry. The mITT population included 277 patients who had DRC-confirmed proven or probable IA by the end of the first study week; 135 patients received combination treatment and 142 received monotherapy (Figure 1).

The mITT populations for both treatment groups had similar baseline demographic characteristics, underlying conditions, and IA diagnoses (Table 1); 20% of patients were aged 65 years or older. The most common underlying condition was acute myelogenous leukemia; 30% were HCT recipients and 60% were neutropenic at study entry. Few patients (7.6%) received mold-active prophylaxis. Baseline demographic characteristics in the safety population are presented in Appendix Table 1 (available at www.annals.org).

Most patients (80%) had a DRC-confirmed diagnosis of probable IA supported by consistent radiographic findings and a positive galactomannan antigen from serum or BAL (Table 1). Appendix Table 2 (available at www.annals.org) summarizes detailed diagnostic criteria. Only 5 patients had a diagnosis of proven IA

Table 2. Mortality Outcomes in the Modified Intention-to-Treat Population, by Regimen

Variable	Deaths, *n/N (%)**		Treatment Difference (95% CI), *percentage points*†
	Monotherapy	Combination Therapy	
Overall	39/142 (27.8)	26/135 (19.5)	−8.3 (−19.0 to 1.5)
Overall 12-wk mortality	55/142 (39.4)	39/135 (29.3)	−10.1 (−21.4 to 1.1)
Allogeneic HCT			
Yes	12/42 (28.6)	10/44 (22.7)	−5.9 (−24.3 to 12.6)
No	27/100 (27.5)	16/91 (17.9)	−9.6 (−21.5 to 2.2)
Reduced-intensity conditioning	5/15 (33.3)	4/19 (21.1)	−12.2 (−42.4 to 17.8)
Non–reduced-intensity conditioning	7/27 (25.9)	6/25 (24.0)	−1.9 (−25.5 to 21.6)
HLA-matched/related donor	7/17 (41.2)	2/14 (14.3)	−26.9 (−56.6 to 2.8)
HLA-mismatched/unrelated donor	5/25 (20.0)	8/29 (27.6)	7.6 (−15.0 to 30.2)
High-dose corticosteroids‡	3/6 (50.0)	3/9 (33.3)	−16.7 (−67.2 to 33.8)
Neutropenia§			
Yes	21/86 (24.4)	18/77 (23.5)	−0.9 (−14.0 to 12.2)
No	15/47 (33.2)	7/52 (13.7)	−19.5 (−36.1 to −2.8)
Geographic region			
Europe	21/83 (25.6)	14/75 (18.9)	−6.7 (−19.6 to 6.3)
Asia/Australia	8/33 (25.0)	6/33 (18.3)	−6.7 (−26.7 to 13.3)
North America	7/17 (41.2)	5/20 (25.3)	−15.9 (−46.1 to 14.4)
South America/Latin America	3/9 (33.3)	1/7 (14.3)	−19.0 (−59.3 to 21.1)

HCT = hematopoietic cell transplantation.
* Deaths shown are at 6 wk unless otherwise indicated. Percentage of deaths is based on the Kaplan–Meier product limit estimator for each variable.
† Combination therapy – monotherapy.
‡ Prednisone equivalents, ≥1 mg/kg/d, for >3 wk.
§ Absolute neutrophil count <0.500 × 10^9 cells/L.

based on histopathology; 2 also had positive cultures. Fifty-one of 272 (19%) patients with probable IA had positive cultures for *Aspergillus* species: *A. fumigatus* (*n* = 31 [61%]), species not identified (*n* = 12 [24%]), *A. flavus* (*n* = 4), *A. niger* (*n* = 3), and *A. nidulans* (*n* = 1).

The median duration of combination treatment (voriconazole and anidulafungin or placebo) was 14 days (range, 1 to 29); the median duration of voriconazole treatment was 42 days (range, 1 to 48). Voriconazole dose was reduced in 20% of patients (55 of 277) because of AEs or blood levels; 3% of patients (8 of 277) had dose escalation. Voriconazole concentrations measured at the central laboratory were available in 204 patients in the mITT population; estimated median trough (12 hours after dose) was 3.85 μg/mL at 4 mg/kg intravenously every 12 hours and 2.79 μg/mL at 300 mg orally every 12 hours. Median anidulafungin trough concentration was 2.56 μg/mL. No differences in median drug levels or frequency of dosing adjustment between the 2 groups were found.

Outcomes

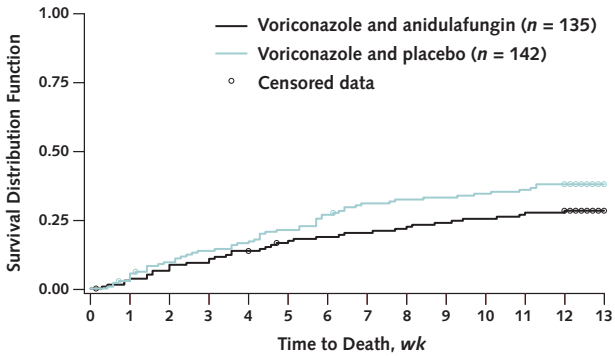
Table 2 summarizes prespecified mortality outcomes. In the primary analysis, mortality at 6 weeks in the mITT population was 19.5% (26 of 135) for combination treatment and 27.8% (39 of 142) for monotherapy (difference, −8.2 percentage points [95% CI, −19.0 to 1.5]; 2-sided P = 0.087). Mortality at 12 weeks was 29.3% (39 of 135) for combination treatment and 39.4% (55 of 142) for monotherapy (difference, −10.1 percentage points [CI, −21.4 to 1.1]; 2-sided P = 0.077) (Table 2 and Figure 2). In the ITT population, which included patients who did not have a confirmed diagnosis of IA, mortality at 6 weeks did not differ between the combination therapy (20.6% [47 of 228]) and monotherapy (23.5% [53 of 226]) groups.

An independent DRC that was blinded to study groups adjudicated attributable mortality and the composite global response end point (Table 3). Most deaths up to week 6 were considered by the DRC to be attributable to IA: 23 of 26 (88.5%) for combination therapy and 33 of 39 (84.6%) for voriconazole monotherapy. Although mortality end points favored combination therapy, global response estimates were discordant; successful global response at 6 weeks was 44 of 135 (32.6%) for combination treatment and 61 of 142 (43.0%) for monotherapy (difference, −10.4 percentage points [CI, −21.6 to 1.2]). Most patients with a failed global response were considered to be "not evaluable" by the DRC. Inspection of this variable revealed that more persons were not evaluable at 6 weeks in the monotherapy group because of death and more persons were not evaluable in the combination therapy group because of missing data.

Post hoc univariate and multivariate analyses identified 3 independent predictors of mortality at 6 weeks: low Karnofsky score, low platelet count, and high serum galactomannan antigen index at baseline (Table 4 and Appendix Tables 3 and 4, available at www.annals.org).

Most patients were enrolled with a DRC-confirmed diagnosis of probable IA that was based on radiographic abnormalities and galactomannan antigen positivity in serum or BAL. Because galactomannan indices have been shown to correlate with the risk for death,

Figure 2. Cumulative incidence of death in the modified intention-to-treat population.



Log-rank, $P = 0.086$.

we performed a post hoc analysis of mortality in this dominant subgroup (17, 18). All-cause mortality was 15.7% (17 of 108) in the combination therapy group compared with 27.3% (30 of 110) in the monotherapy group (difference, −11.6 percentage points [CI, −22.7 to −0.4]; $P = 0.037$) (Figure 3). An analysis of mortality by baseline galactomannan antigen index value indicated that the greatest difference in mortality between the 2 treatment groups was observed in patients with baseline values in the range of 0.5 to 1.5 or less (Figure 3).

Safety Analysis

The proportions of patients with reported AEs and discontinuations were similar in the 2 treatment groups (Appendix Tables 5 and 6, available at www.annals.org). More patients in the combination treatment group had hepatobiliary AEs than the monotherapy group (12.7% vs. 8.4%).

DISCUSSION

Studies that have used in vitro testing and animal models and human case series have suggested that administering an echinocandin with voriconazole may improve outcomes (5–7). To our knowledge, this is the first large randomized, controlled trial to address combination therapy for IA. It used a novel trial design that applied restrictions to enrollment criteria and incorporated the primary end point of overall mortality. Results showed that combination therapy was associated with a substantial, but not statistically significant, reduction in overall mortality. Although the results do not provide conclusive evidence of superiority, they add to a compelling preclinical experience in support of combination therapy for IA and introduce important considerations about clinical trial design.

To maximize the potential to measure a treatment effect, we enrolled a relatively homogeneous population that was considered to have a lower risk for death because of their underlying conditions. This design was informed by observations in which differences in antifungal treatments for candidemia were most measurable in persons with standard risk illness scores (19). With this in mind, the trial enrollment criteria were designed to measure treatment in patients who had a low risk for death based on organ dysfunction (liver or kidney) and status of HM–variables that are associated with risk for death after IA in retrospective analyses of outcomes (15).

The primary end point in this study was a comparison of all-cause mortality at 6 weeks. We chose this outcome to achieve the most objective variable of success, considering that mortality at 6 weeks closely approximated the mortality attributable to IA in prior studies (9), and toxicities of a combined agent can contribute to bias in proportional comparisons of more subjective clinical success variables. Although the mortality in patients receiving voriconazole monotherapy was higher than anticipated, it was consistent with that of other studies of IA in similar patient populations that shared a higher enrollment of patients with acute myelogenous leukemia as an underlying disease (8).

Most of the patients enrolled had a DRC-confirmed diagnosis of probable IA that was established on the basis of radiographic abnormalities and galactomannan antigen positivity in serum or BAL. Compared with galactomannan antigen, fungal culture and histopathol-

Table 3. Data Review Committee–Adjudicated Outcomes in the Modified Intention-to-Treat Population, by Regimen

Outcome	Monotherapy (*n* = 142)*	Combination Therapy (*n* = 135)*	Treatment Difference (95% CI), *percentage points*†
Deaths attributed to IA at 6 wk	33/39 (84.6)‡	23/26 (88.5)‡	3.9 (−12.9 to 20.6)
Global response at 6 wk			
Success (overall)	61 (43.0)	44 (32.6)	−10.4 (−21.6 to 1.2)
Complete response	17 (12.0)	8 (5.9)	–
Partial response	44 (31.0)	36 (26.7)	–
Failure			
Stable response	19 (13.4)	26 (19.3)	–
Failure of response	7 (4.9)	8 (5.9)	–
Not evaluable	55 (38.8)	57 (42.3)	–
Expired before 6 wk	39 (27.5)	26 (19.3)	–
Missing information	16 (11.3)	31 (23.0)	–

IA = invasive aspergillosis.
* Values are numbers (percentages) unless otherwise indicated.
† Combination therapy – monotherapy.
‡ Values are numbers/totals (percentages).

ogy are relatively insensitive for the diagnosis of IA (20) and studies have shown that galactomannan antigen can be detected before the results of other diagnostic tests, including radiography (21, 22). The 6-week mortality rate was lowest in those who received combination therapy for antigen-based diagnoses (15.7%) compared with those in the overall mITT population (19.3%), whereas the rate in monotherapy recipients was unchanged: 29% versus 27%, respectively. We hypothesize that patients with probable IA based on antigen positivity represent a more homogeneous population of patients with disease diagnosed earlier in their natural course of progression; therefore, we may optimize our ability to measure a treatment difference with combination therapy. The observed lower risk for death in persons with probable IA based on galactomannan positivity compared with all others (Table 4) supports this hypothesis. Because approaches to diagnosing IA vary substantially, we cannot speculate further on the nature of this galactomannan-positive subgroup; more studies will be needed to confirm the observation.

Results of multivariable models showed that galactomannan indices are predictive of survival, which confirms other recent studies (17, 18). Likewise, measures of illness severity (Karnofsky score) and baseline platelet counts were also predictive of survival. Low platelet counts have been shown to predict death in prior studies; although mechanisms are unclear, in vitro studies suggest that platelets, coupled with anidulafungin, serve to reduce germination of the organism (23–25).

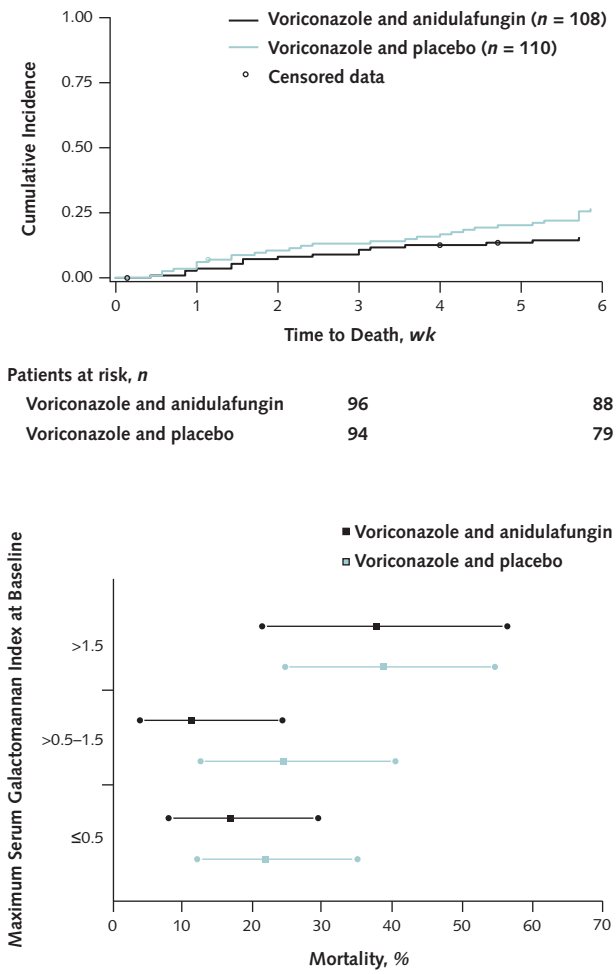
This study shows important lessons on appropriate end points to assess IA treatment. Global response, the traditional end point for studies of IA, was a secondary end point in this study. This is a composite end point based on the subjective assessment of clinical signs, symptoms, and radiographic changes. This outcome is driven largely by radiographic abnormalities, which may be influenced by factors other than antifungal treatment (26, 27). Although this end point has never been validated to be predictive of more objective outcomes, such as survival, prior treatment studies showed that global response and survival trended in similar directions (2). In this study, the paradox was that the global response at 6 weeks was lower in the group of patients who received the combination of voriconazole and anidulafungin compared with voriconazole monotherapy. By analyzing the individual components of the global response assessments, we discovered that a large proportion of patients in the combination therapy group were not evaluable by the DRC at week 6 because they survived but did not have computed tomography performed within the study visit window. In contrast, a relatively large proportion of patients in the monotherapy group died before that time point. We

Table 4. Results of Multivariate Analysis of Baseline Factors of Prognostic Significance for Mortality at 6 wk*

Variable	HR (95% CI)†	*P* Value
Karnofsky score (unit increase = 10)	0.72 (0.60–0.85)	<0.001
Maximum baseline serum GM antigen index (unit increase = 0.5)	1.07 (1.02–1.11)	0.003
Baseline platelet count (unit increase = 5)	0.96 (0.93–1.00)	0.026
BMI (unit increase = 5)	0.80 (0.61–1.04)	0.093
T-cell immunosuppressants (no vs. yes)	2.27 (0.84–6.14)	0.107
Diagnosis criteria (probable based on GM antigen positivity vs. all others)	0.62 (0.33–1.16)	0.132
Age (unit increase = 5)	1.08 (0.97–1.21)	0.157
Underlying disease		
Allogeneic HCT vs. no allogeneic HCT and AML	1.95 (0.93–4.06)	0.075
Allogeneic HCT vs. no allogeneic HCT without AML	1.56 (0.80–3.04)	0.191
No allogeneic HCT and AML vs. no allogeneic HCT without AML	0.80 (0.40–1.59)	0.53

AML = acute myelogenous leukemia; BMI = body mass index; GM = galactomannan; HCT = hematopoietic cell transplantation; HR = hazard ratio.
* Only statistically significant (2-sided $P < 0.20$) predictors of overall survival from the proportional hazards model are listed. The **Supplement** (available at www.annals.org) shows details of model building.
† HR is for hazard of death at 6 wk.

Figure 3. Outcomes in the positive galactomannan subgroup.



Top. Cumulative incidence of death in the modified intention-to-treat population with probable invasive aspergillosis based on radiographic abnormalities and positive galactomannan antigen. Log-rank, $P = 0.049$. **Bottom.** 6-week mortality rate by range of maximum serum galactomannan index values at baseline. The middle boxes indicate the point estimate of the mean and the outer circles are the 95% CIs for that point estimate.

believe that missing data contributing to "failed" (non-evaluable) assessments, especially in persons who were deemed too healthy for follow-up radiography, drove this discrepancy. The subjectivity and multiple opportunities for bias in driving composite criteria contained in global response assessments suggest that the field should seriously consider moving away from these end points in future trials evaluating treatments for life-threatening infectious diseases.

The protocol-specified duration of combination treatment of patients in this study was 2 weeks. This study did not address whether longer durations would be beneficial. However, most investigators elected to stop the combination regimen at 2 weeks rather than extend it to 4 weeks based on clinical status. The safety profile of the combination of voriconazole and anidulafungin was similar to that of voriconazole monotherapy; however, there was a slightly higher frequency of hepatobiliary AEs in patients who received the combination.

This study had both strengths and limitations. Strengths included the rigorous design and relatively robust, worldwide sampling of persons with a complex infection. The primary limitation is that outcomes of aspergillosis were worse than anticipated from calculated estimates, which led to only moderate power when comparing important subgroups of patients with HMs. Enrollment of patients with HM or HCT only may limit the generalizability of these study results in other persons who may have different *Aspergillus* syndromes, such as disease limited to the airways (tracheobronchitis).

We conclude that treatment of IA with the combination of voriconazole and anidulafungin was associated with a nonsignificant but clinically meaningful survival benefit in patients with HM or HCT. Further clinical studies are necessary to confirm differences in mortality and to define the population with the greatest potential benefits of combination antifungal therapy.

From Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; Pfizer and Weill Cornell Medical Center, Cornell University, New York, New York; Hôpital de Hautepierre, Strasbourg, France; CancerCare Manitoba and the University of Manitoba, Winnipeg, Manitoba, Canada; First Department of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Köln, Germany; University of Würzburg Medical Centre, Würzburg, Germany; National University Cancer Institute, National University Health System, Singapore; The University of Texas MD Anderson Cancer Center, Houston, Texas; College of Medicine, The Catholic University of Korea, Seoul, South Korea; University Hospital, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; University of Alabama at Birmingham Medical Center, Birmingham, Alabama; Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Brazil; Algemeen Ziekenhuis Sint-Jan, Brugge, Belgium; University of Florida, Gainesville, Florida; and Universitaire Ziekenhuizen Leuven, Campus Gasthuisberg, Leuven, Belgium.

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Requests for Single Reprints: Kieren A. Marr, MD, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 1064, Baltimore, MD 21205; e-mail, kmarr4@jhmi.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Marr: Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 1064, Baltimore, MD 21205.
Dr. Rottinghaus: Pfizer, 235 East 42nd Street, New York, NY 10017.
Dr. Schlamm: Cidara Therapeutics, 6310 Nancy Ridge Drive, Suite 101, San Diego, CA 92121.
Dr. Herbrecht: Centre Hospitalier Universitaire de Strasbourg, Hôpital de Hautepierre, 1 Avenue Molière, Strasbourg Cedex, France 67098.
Dr. Jagannatha: Johnson & Johnson, 1125 Trenton-Harbourton Road, Titusville, NJ 08560.
Dr. Bow: University of Manitoba, Faculty of Health Sciences, College of Medicine, c/o Infection Control Services, CancerCare Manitoba, 675 McDermot Avenue, Winnipeg, Manitoba R3E 0V9, Canada.
Dr. Cornely: University Hospital of Cologne, Kerpener Street 62, Cologne 50937, Germany.
Dr. Heinz: University of Würzburg Medical Centre, Sanderring 2, Würzburg 97080, Germany.
Mr. Koh: National University Cancer Institute, National University Health System, 5 Lower Kent Ridge Road, 119074 Singapore.
Dr. Kontoyiannis: University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.
Dr. Lee: College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, 222 Banpo-daero, Seocho-gu, Seoul, South Korea 137-701.
Dr. Nucci: Hospital Universitario, Universidade Federal do Rio de Janeiro, Rua Prof. Rodolpho Paulo Rocco 255, Rio de Janeiro, Brazil 21941-913.
Dr. Pappas: University of Alabama at Birmingham Medical Center, 500 22nd Street South, Birmingham, AL 35233.
Dr. Slavin: Peter MacCallum Cancer Centre, St. Andrews Place East Melbourne, Victoria 3002, Australia.
Dr. Queiroz-Telles: Hospital de Clínicas, Universidade Federal do Paraná, Rua XV de Novembro, 1299-Centro, Curitiba, Paraná 80060-000, Brazil.
Dr. Selleslag: Algemeen Ziekenhuis Sint-Jan, Ruddershove 10, 8000 Brugge, Belgium.
Dr. Walsh: Weill Cornell Medical Center, Cornell University, 1300 York Avenue, New York, NY 10065.
Dr. Wingard: University of Florida, 1600 Southwest Archer Road, Gainesville, FL 32610.
Dr. Maertens: Universitaire Ziekenhuizen Leuven, Campus Gasthuisberg, Brusselsestraat 69, 3000 Leuven 3000, Belgium.

Author Contributions: Conception and design: K.A. Marr, H.T. Schlamm, R. Herbrecht, S.T. Rottinghaus, E.J. Bow, O.A. Cornely, M. Nucci, M.A. Slavin, J.R. Wingard, J.A. Maertens.
Analysis and interpretation of data: K.A. Marr, H.T. Schlamm, S.T. Rottinghaus, E.J. Bow, O.A. Cornely, W.J. Heinz, S. Jagannatha, L.P. Koh, P.G. Pappas, M.A. Slavin, D. Selleslag, T.J. Walsh, J.R. Wingard.
Drafting of the article: K.A. Marr, H.T. Schlamm, S.T. Rottinghaus, E.J. Bow, O.A. Cornely, W.J. Heinz, D.G. Lee, M.A. Slavin, F. Queiroz-Telles, T.J. Walsh, J.A. Maertens.
Critical revision of the article for important intellectual content: K.A. Marr, H.T. Schlamm, R. Herbrecht, S.T. Rottinghaus, E.J. Bow, O.A. Cornely, W.J. Heinz, D.P. Kontoyiannis, D.G. Lee, M. Nucci, P.G. Pappas, M.A. Slavin, D. Selleslag, T.J. Walsh, J.R. Wingard, J.A. Maertens.
Final approval of the article: K.A. Marr, H.T. Schlamm, R. Herbrecht, S.T. Rottinghaus, E.J. Bow, O.A. Cornely, W.J. Heinz, L.P. Koh, D.P. Kontoyiannis, D.G. Lee, M. Nucci, P.G. Pappas, M.A. Slavin, F. Queiroz-Telles, D. Selleslag, T.J. Walsh, J.R. Wingard, J.A. Maertens.
Provision of study materials or patients: R. Herbrecht, E.J. Bow, O.A. Cornely, W.J. Heinz, L.P. Koh, D.P. Kontoyiannis, M. Nucci, P.G. Pappas, D. Selleslag, J.A. Maertens.
Statistical expertise: E.J. Bow, S. Jagannatha.
Obtaining of funding: P.G. Pappas.
Administrative, technical, or logistic support: S.T. Rottinghaus, E.J. Bow, P.G. Pappas.
Collection and assembly of data: K.A. Marr, H.T. Schlamm, S.T. Rottinghaus, E.J. Bow, O.A. Cornely, S. Jagannatha, L.P.K., D.P. Kontoyiannis, M.A. Slavin, F. Queiroz-Telles, T.J. Walsh, J.R. Wingard, J.A. Maertens.

Appendix Table 1. Baseline Demographic Characteristics in the Safety Population

Variable	Monotherapy (*n* = 226)	Combination Therapy (*n* = 228)
Mean age (range), *y*	51.0 (17.0–83.0)	52.0 (18.0–83.0)
Race, *n (%)*		
White	157 (69.5)	167 (73.2)
Black	3 (1.3)	5 (2.2)
Asian	57 (25.2)	50 (21.9)
Other	9 (4.0)	6 (2.6)
Sex, *n (%)*		
Men	131 (58.0)	134 (58.8)
Women	95 (42.0)	94 (41.2)
Mean BMI (SD), kg/m^2	24.2 (4.8)	24.2 (5.0)

BMI = body mass index.

Appendix Table 2. Diagnostic Criteria and Microbiologic Characteristics in Confirmed Cases of IA*

Diagnostic Findings, by Adjudicated Diagnosis	Monotherapy (*n* = 142)	Combination Therapy (*n* = 135)
Proven IA		
Histopathology and culture	2 (1)	1 (1)
Culture of tissue	0 (0)	2 (1)
Histopathology without culture	2 (1)	0 (0)
Probable IA		
Cytology without culture confirmation	0 (0)	4 (3)
Culture of BAL fluid	30 (21)	20 (15)
GM antigen positivity only	110 (77)	108 (80)
BAL and serum	12 (8)	7 (5)
Serum	64 (45)	61 (45)
BAL	34 (24)	40 (30)

BAL = bronchoalveolar lavage; IA = invasive aspergillosis; GM = galactomannan.
* Proven and probable diagnoses. Values are numbers (percentages).

Appendix Table 3. Results of Univariate Analyses and Covariate-by-Treatment Analyses of Baseline Factors of Prognostic Significance for Mortality at 6 wk

Variable	*P* Value of Univariate Analysis*	*P* Value of Interaction With Treatment*
Study treatment	0.130	–
Age†‡	0.130	0.72
BMI‡	0.86	0.100
Race	0.69	0.66
Sex	0.85	0.46
Region	0.83	0.54
Site of infection	0.85	0.190
Baseline platelet count‡	0.060	0.91
Karnofsky score‡	<0.001	0.66
Underlying disease	0.31	0.030
Criteria on which IA diagnosis was based	0.180	0.170
Elevated bilirubin levels	0.030	0.23
Neutrophil count	0.76	0.060
T-cell immunosuppressant	0.110	0.63
Prolonged corticosteroids	0.070	0.32
Prior use of antifungals§	0.010	0.37
Maximum baseline serum GM antigen index‡	<0.001	0.170

BMI = body mass index; GM = galactomannan; IA = invasive aspergillosis.
* Cox proportional hazards analysis.
† In years.
‡ Continuous.
§ Use of a systemic antifungal agent within 96 h before the first dose of the study drug.

Appendix Table 4. Results of Multivariate Analysis* of Baseline Factors and Their Interactions With Treatment for Prognostic Significance for Mortality at 6 wk

Variable	HR (95% CI)	*P* Value†
Treatment	–	0.007
Diagnosis criteria	–	0.48
Treatment group by diagnosis criteria	–	0.006
Probable based on GM antigen positivity‡	2.71 (1.32–5.56)	0.007
Other‡	0.49 (0.19–1.27)	0.140
Baseline neutropenia	–	0.090
Treatment group by baseline neutropenia	–	0.003
Nonneutropenic‡	2.97 (1.17–7.55)	0.020
Neutropenic‡	0.45 (0.21–0.95)	0.040
Maximum baseline serum GM antigen index§	1.08 (1.04–1.13)	<0.001
Karnofsky score‖	0.73 (0.62–0.85)	<0.001

GM = galactomannan; HR = hazard ratio.
* Interactions effects model.
† Cox proportional hazards model. HR is the hazard of death. Only statistically significant ($P < 0.050$) predictors of survival at 6 wk are listed.
‡ Monotherapy vs. combination therapy. HR is the hazard of death in the combination group relative to the monotherapy group. HR >1.00 indicates a higher hazard of mortality in the monotherapy group relative to the combination group.
§ Unit increase is 0.5. HR estimate is the hazard of mortality for every 0.5-unit increase.
‖ Unit increase is 10.0. HR estimate is the hazard of mortality for every 10.0-unit increase.

Appendix Table 5. Summary of Treatment-Emergent AEs in ≥5% of Patients*

Variable	Monotherapy	Combination Therapy
Patients in safety population, *n*	226	228
AEs		
All-cause	219 (96.9)	219 (96.1)
Voriconazole monotherapy†	99 (43.8)	106 (46.5)
Combination therapy†	42 (18.6)	53 (23.2)
Serious AEs		
All cause	104 (46.0)	115 (50.4)
Voriconazole monotherapy†	12 (5.3)	20 (8.8)
Combination therapy†	8 (3.5)	11 (4.8)

AE = adverse event.
* All values are numbers (percentages) unless otherwise indicated.
† Treatment-related.

Appendix Table 6. Treatment-Emergent AEs in ≥5% of Patients, by MedDRA System Organ Class*

System Organ Class	Voriconazole†		Anidulafungin†	
	Monotherapy	Combination Therapy	Monotherapy	Combination Therapy
Blood and lymphatic system disorders	2 (0.9)	1 (0.4)	1 (0.4)	1 (0.4)
Cardiac disorders	2 (0.9)	5 (2.2)	1 (0.4)	4 (1.8)
Congenital familial and genetic disorders	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	30 (13.3)	21 (9.2)	5 (2.2)	2 (0.9)
Gastrointestinal disorders	8 (3.5)	15 (6.6)	8 (3.5)	12 (5.3)
General disorders and administration-site conditions	6 (2.7)	5 (2.2)	1 (0.4)	2 (0.9)
Hepatobiliary disorders	8 (3.5)	21 (9.2)	3 (1.3)	8 (3.5)
Immune system disorders	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	3 (1.3)	2 (0.9)	3 (1.3)	2 (0.9)
Injury poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	32 (14.2)	42 (18.4)	15 (6.6)	22 (9.6)
Metabolism and nutrition disorders	4 (1.8)	9 (3.9)	5 (2.2)	6 (2.6)
Musculoskeletal and connective tissue disorders	1 (0.4)	5 (2.2)	0 (0.0)	3 (1.3)
Neoplasms benign	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	7 (3.1)	14 (6.1)	1 (0.4)	12 (5.3)
Psychiatric disorders	25 (11.1)	22 (9.6)	4 (1.8)	3 (1.3)
Renal and urinary disorders	1 (0.4)	2 (0.9)	0 (0.0)	1 (0.4)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory thoracic and mediastinal disorders	2 (0.9)	3 (1.3)	1 (0.4)	3 (1.3)
Skin and subcutaneous tissue disorders	12 (5.3)	9 (3.9)	5 (2.2)	7 (3.1)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	4 (1.8)	1 (0.4)	3 (1.3)	3 (1.3)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
* All values are numbers (percentages).
† Treatment-related.

Correction: Combination Antifungal Therapy for Invasive Aspergillosis

A recent article (1) had an error in Appendix Table 2. The percentage of GM antigen positivity only patients receiving combination therapy should be 80%, not 15% as reported.

This has been corrected in the online version.

Reference

1. Marr KA, Schlamm HT, Herbrecht R, Rottinghaus ST, Bow EJ, Cornely OA, et al. Combination antifungal therapy for invasive aspergillosis. A randomized study. Ann Intern Med. 2015;162:81-9.