Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association

Jannik Stemler, Nick de Jonge, Nicole Skoetz, János Sinkó, Roger J Brüggemann, Alessandro Busca, Ronen Ben-Ami, Zdeněk Ráčil, Vanessa Piechotta, Russell Lewis, Oliver A Cornely

On the basis of improved overall survival, treatment guidelines strongly recommend antifungal prophylaxis during remission induction chemotherapy for patients with acute myeloid leukaemia. Many novel targeted agents are metabolised by cytochrome P450, but potential drug–drug interactions (DDIs) and the resulting risk–benefit ratio have not been assessed in clinical trials, leading to uncertainty in clinical management. Consequently, the European Haematology Association commissioned experts in the field of infectious diseases, haematology, oncology, clinical pharmacology, and methodology to develop up-to-date recommendations on the role of antifungal prophylaxis and management of pharmacokinetic DDIs with triazole antifungals. A systematic literature review was performed according to Cochrane methods, and recommendations were developed by use of the Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework. We searched MEDLINE, Embase, and Cochrane Library, including Central Register of Controlled Trials, for randomised controlled trials and systematic reviews published from inception to March 10, 2020. We excluded studies that were not published in English. Evidence for any identified novel agent that is active against acute myeloid leukaemia was reviewed for the following outcomes: incidence of invasive fungal disease, prolongation of hospitalisation, days spent in intensive-care unit, mortality due to invasive fungal disease, quality of life, and potential DDIs. Recommendations and consensus statements were compiled for each targeted drug for patients with acute myeloid leukaemia and each specific setting. Evidence-based recommendations were developed for hypomethylating agents, midostaurin, and the venetoclax–hypomethylating agent combination. For all other agents, consensus statements were given for specific therapeutic settings, specifically for the management of patients with relapsed or refractory acute myeloid leukaemia, monotherapy, and combination with chemotherapy. Antifungal prophylaxis is recommended with moderate strength in most settings, and strongly recommended if the novel acute myeloid leukaemia agent is administered in combination with intensive induction chemotherapy. For ivosidenib, lestaurtinib, quizartinib, and venetoclax, we moderately recommend adjusting the dose of the antileukaemic agent during administration of triazoles. This is the first guidance supporting clinical decision making on antifungal prophylaxis in recipients of novel targeted drugs for acute myeloid leukaemia. Future studies including therapeutic drug monitoring will need to determine the role of dosage adjustment of novel antileukaemic drugs during concomitant administration of CYP3A4-inhibiting antifungals with respect to adverse effects and remission status.

Introduction

Acute myeloid leukaemia is an aggressive haematological cancer with poor prognosis compared with other malignancies.[1] Antifungal prophylaxis has improved overall survival rates for patients with acute myeloid leukaemia in the past three decades.[2,3] Patients with acute myeloid leukaemia on intensive chemotherapy regimens represent a group at extremely high risk for developing invasive fungal disease, and mortality of invasive fungal disease is excessively high.[4] In this patient population, and in the prophylaxis setting, numerous guidelines have been published for the use of antifungal agents.[5–7] Furthermore, invasive fungal disease and death due to invasive fungal disease occur more often in patients with a longer duration of neutropenia and patients with relapsed or refractory acute myeloid leukaemia than in patients without these underlying conditions.[8]

Novel targeted agents for the treatment of adults with acute myeloid leukaemia have become available and more are being evaluated.[9] These agents continue to expand treatment options for patients with acute myeloid leukaemia, especially in older (ie, aged >60 years), unfit patients and the relapse setting (ie, for patient populations with a potentially increased risk to develop invasive fungal disease). Novel single-drug, combination, and sequential remission induction and maintenance regimens introduce additional complexity. Since the incidence of invasive fungal disease that is associated with these specific treatment settings is largely unclear, the benefit of antifungal prophylaxis in subpopulations with acute myeloid leukaemia is a matter of debate.[10,11] Cytochrome P450 enzymes, especially CYP3A4 and CYP3A5, and their mediated drug–drug interactions (DDI) with novel targeted drugs and triazole antifungals are a concern and might lead clinicians to avoid triazole prophylaxis altogether.[12–14] Guidance is scarce and current clinical practice is often based on personal experience rather than evidence.

Lancet Haematol 2022; 9: e361–73

This online publication has been corrected. The corrected version first appeared at thelancet.com/haematology on May 30, 2022

Department I of Internal Medicine, Excellence Center for Medical Mycology (J Stemler MD, Prof O A Cornely MD), Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Ageing-Associated Diseases (J Stemler, Prof O A Cornely), and Evidence-based Oncology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (Prof N Skoetz MD, V Piechotta PhD), Clinical Trials Centre Cologne (Prof O A Cornely), Faculty of Medicine, University of Cologne and University Hospital Cologne, Cologne, Germany; German Centre for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany (J Stemler, Prof O A Cornely); Department of Haematology, Amsterdam University Medical Centers, location AMC, Amsterdam, Netherlands (N de Jonge MD); Department of Haematology and HSCT, South-Pest Central Hospital, National Institute of Haematology and Infectious Diseases, Budapest, Hungary (J Sinkó PhD); Department of Pharmacy (R J Brüggemann PharmD), Nijmegen Institute for Health Sciences (R J Brüggemann), and Radboudumc Center for Infectious Diseases (R J Brüggemann), Radboud University Medical Center, Nijmegen, Netherlands; Stem Cell Transplant Center, Città della Salute e della Scienza Turin, Turin, Italy (A Busca MD); Department of Infectious

Diseases, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (R Ben-Ami MD)**; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel** (R Ben-Ami)**; Institute of Hematology and Blood Transfusion, Prague, Czech Republic** (Prof Z Ráčil PhD)**; Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic** (Prof Z Ráčil)**; Department of Medical and Surgical Sciences, University of Bologna, Infectious Diseases—IRCCS S Orsola University Hospital, Bologna, Italy** (R Lewis PharmD)

Correspondence to: Prof Oliver A Cornely, Department I of Internal Medicine, Excellence Center for Medical Mycology, Faculty of Medicine, University of Cologne and University Hospital Cologne, Cologne 50931, Germany
oliver.cornely@uk-koeln.de

See Online for appendix

This Review aims to develop evidence-based and consensus-based recommendations for specific clinical settings of monotherapy and combination therapy of novel targeted agents in adults with acute myeloid leukaemia. Additionally, we update current antifungal prophylaxis guidance and present a research agenda for much needed DDI studies.

Methods

A joint initiative of experts in the field of infectious diseases, haematology, oncology, clinical pharmacology, and methodology from the European Hematology Association Scientific Working Group on Infections in Hematology and Scientific Working Group on Acute Myeloid Leukaemia in cooperation with the Cochrane Haematology Group was established in 2019. The development of this guidance followed an evidence-based approach according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. In a constituent videoconference meeting in February, 2020, the objectives and key clinical questions (ie, patient or problem, intervention, comparison, and outcome [PICO] questions) were formulated and rank ordered. No external support was received.

Key questions

At the first guideline panel meeting on Feb 10, 2020, key questions were determined, and novel targeted drugs that were licensed for treatment of patients with acute myeloid leukaemia, in clinical development, or with a potential to be implemented in therapy were identified by reviewing publications on treatment for patients with acute myeloid leukaemia and ongoing clinical trials at ClinicalTrials.gov (table).

According to the GRADE approach, outcomes were prioritised by involving all panel members and patient representatives to ensure that outcomes were relevant to patients. For each of the novel therapies, key questions and outcomes were assessed for adults. First, what is the burden of invasive fungal disease under treatment with this agent on the incidence of any invasive fungal disease, prolongation of hospitalisation, days spent in an intensive-care unit (ICU), mortality attributable to invasive fungal disease (ie, probable or proven invasive fungal disease defined by the European Organisation for Research and Treatment of Cancer),[15] and quality of life (QoL)? Second, what effect on adverse events do DDIs of the acute myeloid leukaemia agent and the antifungal agent have? Third, should antifungal prophylaxis be administered during treatment with the respective acute myeloid leukaemia agent? Fourth, which antifungal agents can be used for antifungal prophylaxis? Finally, when should antifungal prophylaxis be initiated and stopped?

Search strategy and selection criteria

The systematic literature search was based on the principle of best available evidence. We designed and tested search strategies for electronic databases according to methods suggested in the Cochrane Handbook for Systematic Reviews of Interventions.[16]

The methodological and content-related inclusion and exclusion criteria were prospectively defined and implemented by a librarian with experience in medical terminology. We first searched the medical databases MEDLINE (via OVID), Embase (via OVID), and Cochrane Library, including Central Register of Controlled Trials, on March 13, 2020, and updated the search on Nov 30, 2020, for randomised controlled trials and systematic reviews of randomised controlled trials of antifungal prophylaxis in patients with acute myeloid leukaemia who were treated with novel agents (search strategies are listed in the appendix, pp 20–28). We excluded non-English publications.

As direct evidence of antifungal prevention for antineoplastic drugs of interest was scarce, we also searched for incidence of fungal infections in randomised controlled trials evaluating the antineoplastic drugs of interest (appendix pp 29–35). For all search strategies, date of the search and number of hits were documented.

Study selection and data extraction

Two methodological experts (NS, VP) independently screened the title and abstracts of the results of the search strategies for eligibility for the evidence syntheses. We implemented a step-wise eligibility process and, when no randomised controlled trials were idenitifed for evidence-based recommendations, we also considered observational studies to phrase consensus-based recommendations. We coded the abstracts as either "retrieve" or "do not retrieve". In the case of disagreement, or when it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Both experts assessed the full-text articles of selected studies. If the two experts were unable to reach a consensus, they consulted a third person (JSt) to reach a final decision. We documented the study selection process in a flow chart (figure), as recommended in the PRISMA statement.[17] We included full-text publications and results published in study registries, provided sufficient information was available on study design, characteristics of participants, and outcomes.

NS and VP independently extracted data by use of a standardised data-extraction form. Discrepancies evolving at any stage were resolved by discussion or, if not possible, by involving a third person. We collated multiple reports of one study, so that the study, and not the report, resulted as the unit of analysis.

An evidence-table was compiled, including the PICO questions and available recommendations distilled from each publication. Quality of evidence was rated and ranked according to GRADE, considering study design, risk of bias, indirectness, imprecision, inconsistency, publication bias, large effect, residual confounding, and dose response.[18] Studies on novel targeted therapies for patients

	Molecular target	Licensed indication or approval status (in the EU) in adults	Antifungal prophylaxis—recommendation	Antifungal prophylaxis—comment
Azacitidine	Inhibition of DNA methyltransferases that aberrantly hypermethylate tumour suppressor gene promoters	Acute myeloid leukaemia (>30% BM blasts); secondary acute myeloid leukaemia from myelodysplastic syndrome (20–30% BM blasts); myelodysplastic syndrome (intermediate to high risk on the IPSS-R); chronic myelomonocytic leukaemia (10–29% abnormal BM cells)	Conditional for antifungal prophylaxis; low certainty of evidence	Not generally recommended, but should be considered in patients pretreated with chemotherapy, in those with neutropenia at treatment initiation, or those with previous invasive fungal disease
Decitabine	Inhibition of DNA methyltransferases aberrantly hypermethylating tumour suppressor gene promoters	De-novo or secondary acute myeloid leukaemia	Conditional for antifungal prophylaxis; low certainty of evidence	Extrapolated from azacitidine
Venetoclax	Selective inhibitor of BCL2 (ie, antiapoptotic protein)	Chronic lymphocytic leukaemia; acute myeloid leukaemia (combination with HMA)	Conditional for antifungal prophylaxis; low certainty of evidence	Preferably with a triazole; adapt dose when using posaconazole or voriconazole concomitantly
Midostaurin	FLT3 inhibitor	Acute myeloid leukaemia with *FLT3* mutation	Conditional for antifungal prophylaxis; low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment; individual decision for or against antifungal prophylaxis during maintenance treatment Monitor closely for potential DDI
Gilteritinib	Highly selective second-generation FLT3 inhibitor	Relapsed or refractory acute myeloid leukaemia with *FLT3* mutation	Either for or against antifungal prophylaxis (ie, context dependent); low certainty of evidence	In gilteritinib monotherapy, no benefit of antifungal prophylaxis; triazole prophylaxis should be considered in patients pretreated with chemotherapy or patients with long lasting neutropenia (ie, context-dependent)
Crenolanib	Type 1 oral pan-FLT3 inhibitor	Acute myeloid leukaemia (not otherwise specified)*	Conditional against antifungal prophylaxis; very low certainty of evidence	Consensus statement†
Lestaurtinib	FLT3 inhibitor (first generation) with inhibition of FLT3 tyrosine kinase domain and FLT3 internal tandem duplication mutation	Acute myeloid leukaemia*‡	Either for or against antifungal prophylaxis (ie, context dependent); very low certainty of evidence	Consensus statement†; if triazoles are used, consider dose reduction of lestaurtinib due to potential DDI
Quizartinib	FLT3-internal tandem duplication inhibitor	Acute myeloid leukaemia, currently not licensed[2]	Conditional for antifungal prophylaxis; low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment, with a dose reduction of quizartinib; in quizartinib monotherapy, no recommendation for antifungal prophylaxis
Sorafenib	Multikinase inhibitor (endothelial growth factor receptors, SCFR, and FLT3)	Hepatocellular carcinoma, advanced renal cell carcinoma, thyroid carcinoma; off-label use for acute myeloid leukaemia	Conditional for antifungal prophylaxis; very low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment
Ivosidenib	Isocitrate dehydrogenase-1 enzyme inhibitor	Acute myeloid leukaemia with *IDH1* mutation*	Either for or against antifungal prophylaxis (ie, context dependent); very low certainty of evidence	Consensus statement†; concomitant to CYP43A4 inhibitors, reduce ivosidenib dose to 250 mg/day
Enasidenib§¶	Isocitrate dehydrogenase-2 enzyme inhibitor	Acute myeloid leukaemia with *IDH2* mutation*‡	No recommendation	No comment
Gemtuzumab ozogamicin	Humanised CD33-directed monoclonal antibody–drug conjugate	Acute myeloid leukaemia with CD33 expression, in combination with chemotherapy during induction and consolidation treatment	Conditional for antifungal prophylaxis; very low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment
Glasdegib	Hedgehog signalling pathway	Acute myeloid leukaemia, in combination with LDAC	Conditional against antifungal prophylaxis; very low certainty of evidence	Consensus statement†
Dasatinib	SCFR receptor (highly expressed in CBF acute myeloid leukaemia)	Chronic myeloid leukaemia, acute lymphocytic leukaemia*; off-label use for acute myeloid leukaemia	Conditional for antifungal prophylaxis; very low certainty of evidence	Consensus statement†
Sapacitabine	Nucleoside analogue converted into 2□-C-cyano-2□-deoxy-1-β-D-*arabino*-pentofuranosylcytosine (CNDAC) causing cell death	Myelodysplastic syndrome*; acute myeloid leukaemia*	Conditional for antifungal prophylaxis; very low certainty of evidence	*Candida*-active antifungal prophylaxis should be considered
Cusatuzumab¶	Monoclonal CD70^{+} antibody (ligand for CD27) of the TNF receptor superfamily	Acute myeloid leukaemia*	No recommendation	No comment

(Table continues on next page)

	Molecular target	Licenced indication or approval status (in the EU) in adults	Antifungal prophylaxis recommendation	Antifungal prophylaxis comment
(Continued from previous page)				
Iomab B¶	Monoclonal CD45^{+} antibody linked to radioisotope[131]	HSCT conditioning*	No recommendation	No comment
Luspatercept‖	Recombinant fusion protein linked to IgG protein, which binds TGFβ superfamily ligands and reduces SMAD signalling leading to enhanced erythroid maturation	β-thalassaemia*; myelodysplastic syndrome*	No recommendation	No comment
Idasanutlin	Second-generation small molecule inhibitor targeting interaction of TP53 and MDM2	Currently not licensed	Conditional for antifungal prophylaxis; low certainty of evidence	Consensus statement†
Imetelstat‖	Telomerase inhibitor	Myelofibrosis, myelodysplastic syndrome	No recommendation	No comment

Drugs are listed in order of their expected frequency in clinical use. IPSS-R=revised international prognostic scoring system. BM=bone marrow. CBF=core-binding factor. LDAC=low-dose cytarabine. HMA=hypomethylating agent. HSCT=haematopoietic stem-cell transplantation. DDI=drug–drug interaction. *Orphan designation status. †Consensus statements were given when an evidence-based recommendation was not possible due to scarcity of data. ‡Withdrawn from Community Register of Orphan Medicinal Products on request of the sponsor. §Refusal of marketing authorisation by European Medicines Agency (as of October, 2019). ¶No recommendation due to unavailable data for the scope of this guideline. ‖Imetelstat and luspatercept were excluded from the evidence tables given that their clinical use was expected to be very infrequent in patients with acute myeloid leukaemia.

Table: **Antileukaemic drugs, their molecular targets, approved indication, and recommendation regarding antifungal prophylaxis**

For more on **GRADEpro** see https://gradepro.org

with acute myeloid leukaemia that did not report fungal infections in their outcomes were considered but not included in the systematic review of the literature. Studies assessing antifungals, but not in a prophylactic setting, were excluded from the evidence tables; however, they were considered for consensus-based recommendations. Summary of product characteristics, manufacturer's recommendations in package leaflets, and European Medicines Agency (EMA) recommendations on the respective drug were reviewed. Authors of clinical trials were contacted, and ongoing trials were screened for any preliminary findings of relevance.

Consensus phase and synthesis of evidence

Every expert of the group was assigned one or more novel targeted agents to review in the literature that was made available after the systematic review, to contact authors of congress abstracts or clinical trials, and to draft recommendations. In four online videoconference meetings between November, 2020, and March, 2021, the expert group synthesised the available evidence and phrased recommendations for the specific novel agents.

Data synthesis

In case the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we planned to pool quantitative data in a meta-analysis. However, due to scarcity of direct evidence, we did not perform meta-analyses.

Grading the certainty of evidence

The assessment of the certainty of the evidence for each of the prioritised outcomes was done with the GRADE approach.[19,20] Criteria influencing the certainty of the evidence are study design, potential risk of bias, imprecision, indirectness, inconsistency, publication bias, large effect, residual confounding, and dose–response gradient. Certainty of the evidence and the narrative evidence synthesis were provided in the GRADE evidence profiles by use of the GRADEpro GDT software.

Evidence to decision

The evidence to decision framework was used to guide the decision process for a recommendation in a transparent and systematic way.[21] In addition to the certainty of the evidence, benefit and harm balance, patients' values and preferences, resources, feasibility, and equity were considered and transparently reported to result in one recommendation for each PICO question. Patient representatives from the Lymphoma Coalition and the European Society for Blood and Marrow Transplantation Patient Advocacy Committee, who were contacted by the European Hematology Association Central Office, were present in the meetings and involved in the entire evidence-to-decision process.

Results

We identified 18 novel targeted agents that are approved and licensed for treatment of patients with acute myeloid leukaemia, are currently in clinical development, or have potential to be used in acute myeloid leukaemia therapy (ie, off-label use; table). The search identified 317 full texts for eligibility, of those 21 studies were included in the quantitative synthesis.

Evidence-based recommendations were phrased for azacitidine, decitabine, venetoclax, gemtuzumab ozogamicin, and midostaurin. Consensus-based statements were given for dasatinib, gilteritinib, glasdegib, idasanutlin, ivosidenib, lestaurtinib, and sorafenib (appendix pp 3–14, 36–53). The recommendation "either for or against the intervention" refers to deciding for or

against antifungal prophylaxis on the basis of the patient's history and the individual scenario (ie, context dependent). For all other listed targeted agents, no recommendation is available due to scarcity of available data. For the reviews and recommendations on gemtuzumab ozogamicin, crenolanib, cusatuzumab, dasatinib, enasidenib, glasdegib, idasanutlin, iomab B, lestaurtinib, quizartinib, sapacitabine, and sorafenib see the appendix (pp 3–14, 33–50).

Azacitidine

Azacitidine is a hypomethylating agent (HMA) that exerts its oncolytic effect on haematopoietic stem cells by inhibiting DNA methyltransferases, thereby reversing aberrant hypermethylation of genes that are involved in normal cell-cycle regulation, differentiation, and apoptosis. Azacitidine has many cytotoxic mechanisms, including incorporation in DNA, RNA, and protein synthesis. Azacitidine is used in the treatment of patients with acute myeloid leukaemia, high-risk myelodysplastic syndromes according to the international prognostic scoring system, or chronic myelomonocytic leukaemia. Its main toxicity profile includes cytopenia and gastrointestinal disorders, both of mild grade. Therefore, azacitidine is used in patients who are unfit to undergo curative intensive chemotherapy or haematopoietic stem-cell transplantation and in patients with relapsed or refractory disease.[22] Oral azacitidine was approved by the US Food and Drug Administration (FDA) in 2020 for patients with acute myeloid leukaemia who are in first complete remission (CR) or CR with incomplete blood count recovery (CRi) but unable to proceed with curative intensive treatment.[23] Moreover, azacitidine is used in combination with other novel targeted therapies.

Reviewing the evidence for antifungal prophylaxis in patients with acute myeloid leukaemia treated with azacitidine, the reported incidence of invasive fungal disease across all the reviewed studies was between 2·6% and 14·4%. The pooled incidence of the reported invasive fungal disease in all studies was 7·6%, with 83 of 1098 patients with acute myeloid leukaemia having invasive fungal disease.[11,24–31]

The incidence of invasive fungal disease was between 0·42% and 1·22% per azacitidine cycle, with a pooled incidence of 0·84% (84 events in 8499 cycles). One study was excluded due to incomplete reporting.[11,24–29,31] Invasive fungal disease occurred more often in the first four cycles of azacitidine than in subsequent cycles in four studies.[24,28–30]

For the outcome prolongation of hospitalisation, no randomised controlled trials were identified. One retrospective study reported a median hospital admission length of 23 days (IQR 14–31) for patients with invasive fungal disease. One (11%) of nine patients with a fungal infection required admission to ICU.[24] Mortality attributable to invasive fungal disease was between 1·0% and 3·4% in four studies.[24,27,30,31]

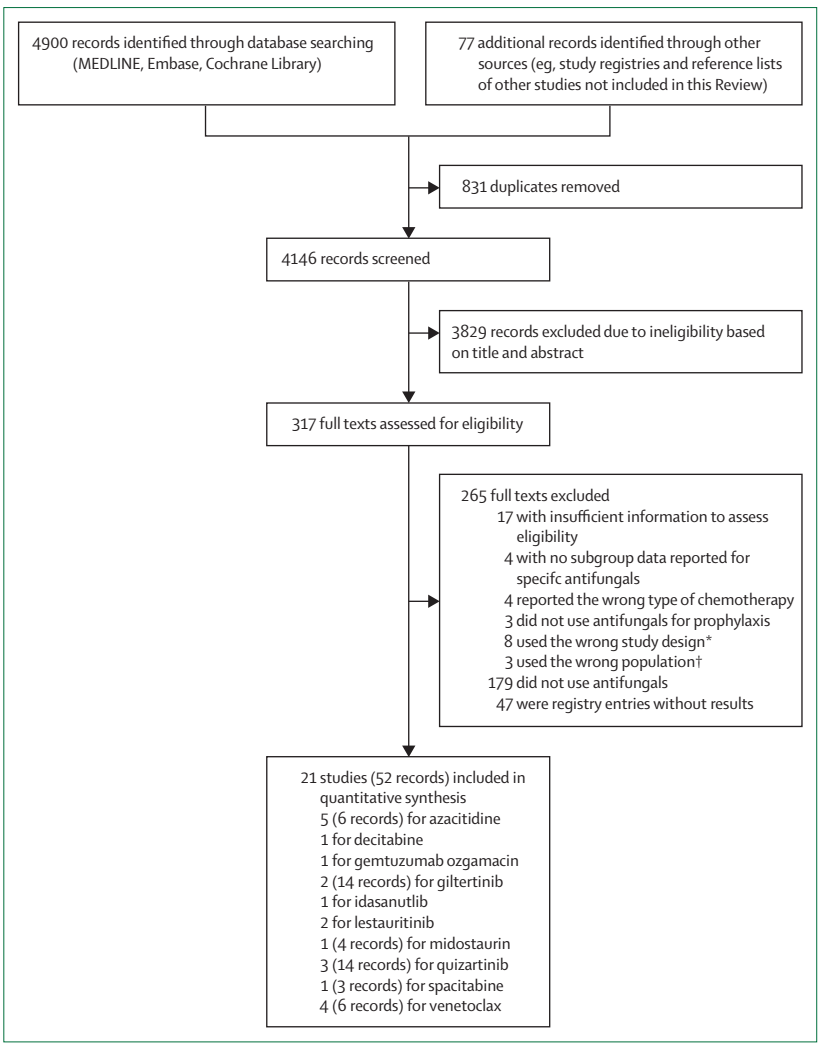

Figure: **Study selection**
*Three letters, one case report, one article, and three opinions. †Two healthy participants and one with solid tumour.

The most important risk factors for invasive fungal disease were cytopenia, especially neutropenia of fewer than 500 cells per µL, and high-risk disease defined by the revised international prognostic scoring system or high-risk cytogenetic aberrations.[24–26,28] Falantes and colleagues[11] reported an increased incidence of invasive fungal disease in patients who were previously treated with intensive chemotherapy (5 [25%] of 20 patients) compared with patients who received upfront azacitidine treatment (1 [2%] of 44).

Seven studies reported the use of mould-active prophylaxis. In three studies, no antifungal prophylaxis was used[11,27,30] and, in the four remaining studies, the proportion of patients that received antifungal prophylaxis ranged between 30% and 61%.[24,26,28,31]

Only one retrospective observational study reported incidence rates for invasive fungal disease that were stratified for mould-active prophylaxis use. Invasive fungal

disease occurred in 4 (6%) of 71 patients in the prophylaxis group versus 5 (11%) of 46 patients in the group without antifungal prophylaxis. On the basis of the reported risk reduction in this study, 19 patients required antifungal prophylaxis to prevent one patient from developing invasive fungal disease.[31]

Azacitidine is metabolised to several metabolites in the liver via spontaneous hydrolysis and deamination (mediated by cytidine deaminase). Azacitidine has no known cytochrome P450 interactions, and therefore DDI are not to be expected. No additional precautions are needed when coadministrating azacitidine with triazoles. However, azacitidine is frequently combined with other novel targeted therapies that do have DDIs with triazoles, such as venetoclax.

When considering whether antifungal prophylaxis should be administered to patients with acute myeloid leukaemia who are treated with azacitidine, first it should be noted that the certainty of the evidence was low. For adult patients with acute myeloid leukaemia treated with azacitidine monotherapy, standard use of antifungal prophylaxis is not generally recommended. Risk of invasive fungal disease is increased in patients with neutropenia at onset of treatment or in patients who previously received intensive chemotherapy, and antifungal prophylaxis can be considered in these populations. Therefore, the strength and direction of the recommendation is conditional for the intervention.

Decitabine

Decitabine is an HMA that induces cell differentiation and apoptosis by inhibiting DNA methyltransferases that aberrantly hypermethylate tumour suppressor gene promoters. Decitabine was shown to improve overall survival in the unplanned extended survival analysis of the DACO-016 trial.[33] This study led to the approval of decitabine for the treatment of de novo or secondary patients with acute myeloid leukaemia who are unfit for intensive induction chemotherapy. The FDA also approved decitabine for treatment of all myelodysplastic syndrome subtypes (up to blast count of 30%).[34] Decitabine is generally administered in a 10-day schedule until CR (<5% blasts) is reached and then continued in a protocol for 5 days of treatment per 4 weeks until progression. Given its satisfactory tolerability and high CR rates in about half of treated patients, decitabine is an attractive option in this patient population.

When reviewing the evidence for antifungal prophylaxis in patients with acute myeloid leukaemia who were treated with decitabine, the reported incidence of probable or proven invasive fungal disease in patients treated with decitabine ranged from 7% to 16·2%.[30,35,36] In the retrospective study that reported the highest number of patients with invasive fungal disease, probable or proven *Aspergillus* spp infection was diagnosed in 13 of 19 patients, and only one of those patients had received mould-active antifungal prophylaxis.[36] One retrospective study reported an incidence of 2·4% per decitabine cycle.[35] No studies reported on the endpoints of prolongation of hospitalisation, ICU admission, or QoL.

Mortality related to invasive fungal disease was 1% and 1·2% in two retrospective studies. Fatal outcomes were due to proven invasive fungal disease with *Fusarium* spp in one patient, a mixed infection with *Fusarium* spp and *Scedosporium* spp in another patient, and in the third patient, no culture was reported.[30,35]

Randomised controlled trials for efficacy of antifungal prophylaxis were not identified. One study reported that eight of nine patients who did not receive antifungal prophylaxis had suspected invasive fungal disease (ie, possible, probable, or proven).[36] In 67 patients with suspected invasive fungal disease, 24 (36%) used mould-active prophylaxis whereas 35 (52%) used fluconazole. *Aspergillus* spp was responsible for 13 of 19 patients with probable or proven invasive fungal disease. Moreover, 12 of 13 patients with probable or proven *Aspergillus* infection used fluconazole as prophylaxis, whereas only one patient used posaconazole. The high prevalence of invasive fungal disease caused by *Aspergillus* spp in this study and extrapolation of studies on azacitidine suggest that mould-active prophylaxis should be used if patients are considered to be at high risk for invasive fungal disease (ie, due to long-lasting neutropenia or relapsed or refractory acute myeloid leukaemia).[36]

Decitabine is metabolised in the liver by deamination. Decitabine has no cytochrome P450 metabolism, and DDIs are not expected. Therefore, no additional precautions are needed when coadministering decitabine with triazoles. However, decitabine is frequently combined with other novel targeted therapies that do show DDIs with triazoles.[34]

When considering whether antifungal prophylaxis should be administered to adults with acute myeloid leukaemia who are treated with decitabine, the certainty of evidence was low. For adult patients with acute myeloid leukaemia treated with decitabine, standard use of antifungal prophylaxis is not generally recommended. When also extrapolating data from azacitidine, risk of invasive fungal disease is increased in patients with neutropenia at the beginning of treatment or in patients who previously received intensive chemotherapy. Antifungal prophylaxis can be considered in these populations. The strength and direction of the recommendation is conditional for the intervention.

Venetoclax

Venetoclax is a potent, selective inhibitor of BCL2, an antiapoptotic protein. Venetoclax binds directly to the BCL2 homology domain 3 (BH3)-binding groove of BCL2, displacing BH3 motif-containing proapoptotic proteins, such as BCL2L11, to initiate mitochondrial outer membrane permeabilisation, caspase activation, and programmed cell death. In preclinical studies,

venetoclax has shown cytotoxic activity in tumour cells that overexpress BCL2.[37]

Venetoclax is used in combination with an HMA for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy. Furthermore, venetoclax is licensed by the FDA and EMA for treatment of chronic lymphocytic leukaemia in combination with obinutuzumab or rituximab or as monotherapy.

In the VIALE-A trial,[38] venetoclax combined with azacitidine improved overall survival, CR, and CRi compared with azacitidine monotherapy. The combination lead to higher remission rates in patients with *FLT3*, *IDH1*, or *IDH2* mutations than in patients without these gene mutations. The M14–358 trial studied venetoclax with azacitidine or decitabine in an open-label setting and showed a CR rate (with or without incomplete blood count recovery) of 67% (97 of 145 patients),[39,40] which is similar to results from the VIALE-A trial.[38]

When reviewing the evidence for antifungal prophylaxis in patients with acute myeloid leukaemia who were treated with venetoclax, infections were reported in 239 (84%) of 283 participants of the VIALE-A trial. Neither this study nor the M14–358 study gave details on invasive fungal disease. In older patients (ie, aged ≥65 years) who received venetoclax with HMA without azole prophylaxis, 8% had fungal infections defined as grade 3 or 4 by the Common Terminology Criteria for Adverse Events version 5.0. However, almost half of the patients in this study received non-azole antifungal (ie, echinocandin) prophylaxis, which might have resulted in an underestimation of the risk of developing an invasive fungal disease.[39]

In all company-driven studies investigating venetoclax, three deaths due to invasive fungal disease occurred (one death due to fungal sepsis in M15–656 trial, and one death due to fungal pneumonia and one death due to fungal sinusitis in M14–358 trial).[41] There is no report available listing all fungal infections reported as adverse events or serious adverse events.

One study investigated the benefit of isavuconazole for primary antifungal prophylaxis in patients with acute myeloid leukaemia. 23 patients received venetoclax and an HMA and three patients received remission-induction treatment with venetoclax alone. All patients received isavuconazole as antifungal prophylaxis. In this cohort, four patients developed possible and one patient developed probable invasive fungal disease.[42] A real-world observational study showed significantly prolonged thrombocytopenia in patients treated with 100 mg venetoclax and concomitant administration of posaconazole or voriconazole without increased time to recovery of neutrophils and infection rate.[43]

In a retrospective study of 119 patients with acute myeloid leukaemia treated with venetoclax and HMA, invasive fungal disease rate was 13% (15 of 119 patients). Patients without haematological response had a higher risk of invasive fungal disease than did patients with haematological response. 49 (41%) of 119 participants received triazole-based and 45 (38%) participants received echinocandin-based antifungal prophylaxis. Of 15 patients with invasive fungal disease, two received no prophylaxis, five micafungin, one fluconazole, three isavuconazole, and three posaconazole. Invasive fungal disease was caused by *Aspergillus* spp (in six patients), Mucorales (in four patients), and *Scedosporium* spp infections (in two patients).[44] Outcome measures of prolongation of hospitalisation, days spent in ICU, mortality due to fungal infection, and QoL were not reported in any of the studies.

Regarding the effect on adverse events that DDIs of venetoclax and antifungal agents have, potent inhibitors of CYP3A4, such as posaconazole and voriconazole, result in clinically relevant increases in venetoclax exposures that require dose reduction.[45,46] The M14–358 study assessed safety and pharmacokinetics of venetoclax coadministered with posaconazole in 12 participants. Exposure of 400 mg venetoclax alone was compared with coadministered posaconazole and venetoclax, where 300 mg posaconazole with 50 mg venetoclax resulted in 61% higher venetoclax peak concentration and 300 mg posaconazole and 100 mg venetoclax resulted in 86% higher venetoclax peak concentration. The venetoclax area under the concentration-time curve from 0 h to 24 h ($AUC_{0–24}$) was 90% higher for 50 mg venetoclax and 144% higher for 100 mg venetoclax.[37] A DDI study investigated plasma concentration of venetoclax in 12 patients on 400 mg venetoclax monotherapy after ramp-up, 50 mg venetoclax with 300 mg posaconazole, or 100 mg venetoclax with 300 mg posaconazole. The mean area under the curve (AUC) of 50 mg venetoclax plus posaconazole was 76% higher and 100 mg venetoclax plus posaconazole was 155% higher than was the attained AUC of 400 mg venetoclax without an azole. When adjusted for different doses and non-linearity, posaconazole was estimated to increase venetoclax $AUC_{0–24}$ to 8·8 times higher than the reference value.[47]

The manufacturer and summary of product characteristics recommend an empirical dose reduction of venetoclax by at least 75%.[48] When aiming for a bioequivalent exposure of posaconazole-boosted venetoclax versus venetoclax at full dose without strong CYP3A4-inhibitor, deploying the 70 mg venetoclax dose could be justified, although there is a strong debate on whether to use the 70 mg or 100 mg dose. Considering the strong inhibitory potential of posaconazole, a further dose reduction of venetoclax to 50 mg should be investigated, because the combination with a 300 mg posaconazole tablet (ie, recommended standard dose) results in a higher exposure than does venetoclax monotherapy at a dose of 400 mg. Of note, this interaction is driven by concentration, and therefore the variation in venetoclax exposure between people after boosting with posaconazole should be investigated.

Two physiologically based pharmacokinetic models simulating the venetoclax–posaconazole interaction aimed to predict the extent of DDI and to provide a dose recommendation. Authors recommended a dose of 70 mg venetoclax when given with 300 mg posaconazole delayed-release tablets once daily.[49] Caution is warranted when antifungal prophylaxis is temporarily interrupted or when absorption issues might result in low antifungal drug exposure and hence no inhibiting effect.

When considering whether antifungal prophylaxis should be administered to adults with acute myeloid leukaemia who are treated with venetoclax (in combination with an HMA), the certainty of evidence was low. For adult patients with acute myeloid leukaemia who are treated with venetoclax in combination with an HMA and at high risk of invasive fungal disease, we recommend antifungal prophylaxis, preferably with a triazole. The reported DDIs are manageable, and venetoclax has a favourable toxicity profile. Overall, the strength and direction of the recommendation is conditional for the intervention.

Midostaurin

Midostaurin is an FLT3 inhibitor that is licensed by the FDA and EMA for treatment of acute myeloid leukaemia with *FLT3* tyrosine kinase domain internal tandem duplication mutation in combination with intensive chemotherapy during induction treatment from day 8 until day 21, during consolidation, and as maintenance therapy after allogeneic haematopoietic stem-cell transplantation.[50] A significant improvement of overall survival and progression-free survival has been shown.[51]

We reviewed the evidence for antifungal prophylaxis in patients with acute myeloid leukaemia who were treated with midostaurin. For the outcome parameter incidence of fungal infections, one study assessing the efficacy of isavuconazole for primary antifungal prophylaxis in patients with acute myeloid leukaemia reported no invasive fungal disease in seven patients who were treated with an *FLT3* inhibitor (but the study did not specify if midostaurin was used).[42] In a retrospective study involving 108 patients, the rate of breakthrough invasive mould infection did not differ between patients undergoing intensive induction chemotherapy with midostaurin or without midostaurin (3 [4%] of 69 patients *vs* 1 [5%] of 22 patients).[52] The RATIFY trial[51] did not report the incidence of invasive fungal disease.

For the outcome measures of prolongation of hospitalisation, days spent in ICU, and mortality due to fungal infection, no study results were reported. Regarding QoL, one study that reported improvement of QoL in patients with advanced-systemic mastocytosis who were treated with midostaurin was considered as transferred evidence (ie, evidence in a population other than patients with acute myeloid leukaemia).[53]

Antifungal prophylaxis with a triazole is generally recommended in patients with acute myeloid leukaemia during induction treatment,[6] with posaconazole generally being the drug of choice.[3,5]

Several authors have raised concerns regarding DDI due to strong inhibition of CYP3A4 by triazoles with subsequent increased midostaurin drug concentrations and suspected increased potential of toxicity.[12,14] CYP3A4 inhibitors also affect the CYP3A4-mediated formation of active midostaurin metabolites (ie, CPG52421 and CPG6221) that contribute to the multikinase inhibitory profile of the drug. Pharmacokinetic and modelling data suggested higher midostaurin exposure and showed an up to 10-fold increase of the midostaurin AUC when administered with strong CYP3A4 inhibitors as compared with administration of midostaurin with a placebo.[54,55] In a retrospective study on antifungal prophylaxis, analysing the primary endpoint of discontinuation of targeted acute myeloid leukaemia therapy, 4 (9%) of 43 patients discontinued midostaurin treatment due to toxicity.[56] In a subanalysis of the RATIFY trial, a 1·44-fold increase in midostaurin exposure and altered pharmacokinetics of its active metabolites in patients concomitantly receiving strong CYP3A4 inhibitors was observed when compared with midostaurin administration without concomitant CYP3A4 inhibitors; however, without notable increase of midostaurin-related adverse events but a shorter time to occurrence of severe adverse events.[57] In an observational study in patients receiving concomitant posaconazole and midostaurin, plasma concentrations of the FLT3-inhibitor and its metabolites were multiple times higher than in patients not receiving posaconazole therapy.[58] Therefore, until further evidence is available on DDI regarding coadministration, antifungal prophylaxis should be administered with triazoles, but patients should be monitored closely for adverse events (eg, by means of electrocardiograph at regular intervals).

When considering whether antifungal prophylaxis should be administered to adults with acute myeloid leukaemia who are treated with midostaurin, the certainty of the evidence was low. For adult patients with acute myeloid leukaemia who are treated with midostaurin and have a high risk of fungal infection (eg, during induction treatment), we recommend antifungal prophylaxis, preferably with posaconazole. In patients with low risk of fungal infection (eg, during maintenance therapy), there is a conditional recommendation in favour of antifungal prophylaxis, depending on individual patient factors, such as neutropenia or history of invasive fungal disease. Overall, the strength and direction of the recommendation is conditional for the intervention.

Gilteritinib

Gilteritinib is a highly selective second-generation FLT3 inhibitor inhibiting both the FLT3 tyrosine kinase domain and acute myeloid leukaemia cells with internal tandem duplication mutations. Gilteritinib was studied

and is registered as monotherapy in patients with relapsed or refractory acute myeloid leukaemia. There are several ongoing studies evaluating a combination of gilteritinib with chemotherapy or other targeted treatment in de-novo and relapsed or refractory acute myeloid leukaemia.[59]

In our review of the evidence addressing antifungal prophylaxis, we noted that for all outcome parameters the use of gilteritinib only as monotherapy was reviewed. For the outcome parameter incidence of fungal infections, a higher incidence of invasive fungal disease occurred in the gilteritinib group than in the salvage chemotherapy group in one study conducted with patients with relapsed or refractory acute myeloid leukaemia (NCT02421939).[59] For the outcome measures of prolongation of hospitalisation, days spent in ICU, mortality due to fungal infection, and QoL, no study results were reported.

Coadministration of azole antifungals with strong inhibition of CYP3A4 could raise concerns of DDI and a risk of increased toxicity of gilteritinib. Administration of gilteritinib in healthy volunteers led to a 2·2-fold increase in gilteritinib AUC when administered together with strong CYP3A4 inhibitor (ie, itraconazole) as compared with administration of gilteritinib without a concomitant strong CYP3A4 inhibitor; and a 1·4-fold increase when administered with a moderate CYP3A4 inhibitor (ie, fluconazole) as compared with administration of gilteritinib.[60] Administration of gilteritinib with moderate and strong CYP3A4 inhibitors in patients with relapsed and refractory acute myeloid leukaemia increased the exposures less than 2-fold, which was not considered clinically significant.[61] A retrospective observational study comparing patients on gilteritinib only with gilteritinib plus azole therapy did not show a significant difference in adverse events and mortality, suggesting safety of concomitant azole therapy.[62] On the basis of the broad therapeutic window and the maximum tolerated dose of gilteritinib (ie, 300 mg/day in US or European populations and 200 mg/day in Japanese populations), azole prophylaxis does not require dose adjustment of gilteritinib when gilteritinib is administered at 120 mg/day as recommended by the manufacturer, but close monitoring of adverse events is warranted.

When considering whether antifungal prophylaxis should be administered to adult patients with acute myeloid leukaemia who are treated with gilteritinib, the certainty of the evidence was low. For patients with relapsed or refractory acute myeloid leukaemia who are treated with gilteritinib monotherapy, evidence on a benefit of antifungal prophylaxis is scarce. Triazole prophylaxis should be considered in patients at high risk of developing invasive fungal disease, on the basis of a context-dependent individual decision. Overall, the strength and direction of recommendation is conditional to use or not to use antifungal prophylaxis.

Ivosidenib

Ivosidenib is an oral, targeted inhibitor of isocitrate dehydrogenase 1. Ivosidenib is approved by the FDA as monotherapy for adults with relapsed or refractory acute myeloid leukaemia with a susceptible isocitrate dehydrogenase 1 mutation and in patients with newly diagnosed acute myeloid leukaemia who are aged at least 75 years or who have comorbidities that exclude the use of intensive induction chemotherapy. Approval was based on two clinical trials. A phase 1 dose-escalation and dose-expansion study of ivosidenib monotherapy in patients with *IDH1*-mutated relapsed or refractory acute myeloid leukaemia showed a rate of CR or CRi of 30·4%.[63] An open-label, single-arm, multicentre clinical trial of single-agent ivosidenib for newly diagnosed acute myeloid leukaemia with *IDH*-1 mutation showed a rate of CR and CRi of 42·4%; seven of 17 patients who were dependent on transfusions reached transfusion independence.[64]

We reviewed the evidence for antifungal prophylaxis in patients with acute myeloid leukaemia who were treated with ivosidenib. For the outcome parameter incidence of fungal infections, the two studies evaluating the efficacy of ivosidenib monotherapy reported an overall incidence of febrile neutropenia (at least grade 3 by the Common Terminology Criteria for Adverse Events version 5.0) of 1·2% and 6·9%.[63,64] Neither study stated the incidence of invasive fungal disease. In both studies, concomitant use of CYP3A4 inhibitors was permitted provided careful QTc interval monitoring was done. Similarly, a phase 1 study assessing the efficacy of ivosidenib combined with intensive chemotherapy in patients with newly diagnosed acute myeloid leukaemia did not report the incidence of invasive fungal disease.[65] For the outcome measure of prolongation of hospitalisation, days spent on ICU, mortality due to fungal infections, and QoL, no study results were reported.

Regarding DDIs and adverse events, ivosidenib is metabolised in the liver by CYP3A4, therefore coadministration of moderate to strong CYP3A4 inhibitors might affect ivosidenib pharmacokinetics. The AUC of ivosidenib is increased by 169 when co-administered with itraconazole and by 73% with concomitant fluconazole.[66] The prescribing information recommended a dose reduction of ivosidenib from 500 mg/day to 250 mg/day when a strong CYP3A4 inhibitor is coadministered. Alternatively, antifungals with less inhibitory potential should be considered. Because ivosidenib is known to cause QTc interval prolongation, patients should be monitored frequently by electrocardiograph.

When considering whether antifungal prophylaxis should be administered to adults with acute myeloid leukaemia who are treated with ivosidenib, the certainty of the evidence was very low. In adults with acute myeloid leukaemia receiving ivosidenib as monotherapy, there is a conditional recommendation against antifungal

prophylaxis. When ivosidenib is administered in combination therapy, there is a strong recommendation for antifungal prophylaxis. In addition, QTc interval monitoring is indicated, if strong CYP43A4 inhibitors are co-administered with ivosidenib at the reduced dose of 250 mg once daily. Overall, the strength and direction of recommendation is conditional to use or not to use antifungal prophylaxis.

Future research

The risk of developing invasive fungal disease is not excessively high for many novel targeted therapies; however, in combination with intensive chemotherapy or in the relapsed or refractory setting, it can be markedly increased. The individual patient factors that trigger the implementation of antifungal prophylaxis in the real-world setting need to be established. Well designed observational studies could enhance the knowledge of the true epidemiology of invasive fungal disease in adults with acute myeloid leukaemia who are treated with novel targeted therapies.

Future trials should establish the optimal dose–response or exposure–response rate and dose–toxicity or exposure–toxicity rate for selected targeted therapies, especially FLT3 inhibitors and venetoclax, when administered concomitantly with triazole antifungals. Combining 70 mg or 100 mg venetoclax with such potent CYP3A4 inhibitors results in an above average exposure as compared with 400 mg venetoclax alone, and in the future this regimen could be administered with other targeted agents that are metabolised through CYP3A4 or CYP3A5. The safety of triazole antifungal prophylaxis during venetoclax ramp-up should also be investigated. For this purpose, therapeutic drug monitoring for venetoclax and other novel agents should be explored to establish factors that influence inter-individual and intraindividual pharmacokinetic variability (appendix pp 15–16). If clinical trials assessing a combination of several novel targeted agents are planned, the outcome parameters invasive fungal disease, dose–toxicity or exposure–toxicity, and dose–response or exposure–response should be evaluated in multidosing regimens and reporting of infectious complications should be included in detail.

Discussion and conclusion

This Review addresses the emerging issue of antifungal prophylaxis in an expanding and diversifying treatment setting for adults with acute myeloid leukaemia. For our recommendations, we considered a large set of novel targeted agents for acute myeloid leukaemia and included published evidence on risk of invasive fungal disease and potential DDI.

Antifungal prophylaxis with a triazole is crucial in managing patients with acute myeloid leukaemia and is generally recommended during induction treatment,[5,6] with posaconazole being the drug of choice.[3,5] Prophylaxis of invasive fungal disease always has to be considered in the individual context of a patient's medical history, such as previous treatment with intensive chemotherapy, expected duration of neutropenia according to planned treatment and dosage, previous history of invasive fungal disease, and local epidemiology of invasive fungal disease. Being an only moderate CYP3A4 inhibitor, isavuconazole could have an increasing role in the setting of DDI, as studies show an increasing use of the drug for prophylaxis in the clinical routine, with lower toxicity and adverse event rates than for other triazoles.[42,67] Other strategies, such as active surveillance or pre-emptive treatment for invasive fungal disease, have been proposed and are implemented frequently;[68,69] however, with a risk of missing manifestation of an invasive fungal disease. Other antifungal drugs with lower DDI potential than for those currently in use will soon become available for treatment purposes and are in phase 3 clinical trials for prophylaxis (eg, rezafungin).[70]

Additional novel targeted agents to treat acute myeloid leukaemia (eg, eprenetapopt and olutasidenib) might soon become available or will be investigated in phase 2 or 3 trials.[71,72] Combination of targeted agents with different chemotherapy regimens can be administered to patients with acute myeloid leukaemia and will affect the incidence of invasive fungal disease.[9,73] Dose adjustments can also reduce costs but have to be assessed carefully in randomised observational studies and dedicated DDI studies.[74]

Specific recommendations for the antifungal of choice and dosing details for a prophylactic regimen were not within the scope of this guidance document. The recommendations and consensus statements might be revised in the future as more data become available.

Generally, a scarcity of data reduces the quality of evidence and strength of our recommendations. Therefore, we considered studies (eg, retrospective chart reviews) in which some patients received and some did not receive antifungals for the consensus definitions when no evidence-based recommendation was possible. In studies of patients with acute myeloid leukaemia, clinical trialists and pharmaceutical companies usually address the incidence of infections, and of invasive fungal disease in particular, only superficially. There is no requirement by the regulatory bodies to do so, and infectious disease experts are not involved in trial design, which seems unacceptable from a patient-centred perspective because such knowledge has the potential to improve patient outcome and reduce costs.[75]

We encourage clinical trial designers and regulatory authorities to assess risks of DDI of antineoplastic drugs in pivotal phase-3 studies by including therapeutic drug monitoring studies. When pharmacokinetic data hint towards increased toxicity, pharmacokinetics should be standard during treatment with novel antifungals.[76] Otherwise, the treating physicians will be forced to trade one life-saving drug for another, instead of combining

both benefits for their patients. This is where our guidance document provides answers on antifungal prophylaxis in patients with acute myeloid leukaemia who are treated with novel agents.

Contributors

JSt proposed and conceptualised the review, supervised the author group, performed literature research, visualised the tables, and wrote the first draft of the manuscript. NdJ, JSi, AB, RB-A, and ZR performed literature research and wrote the first draft of the manuscript. NS and VP designed the methodology, performed literature research, and visualised figures. RJB ad RL performed literature research, visualised the tables, and wrote the first draft of the manuscript. OAC proposed and conceptualised the project and supervised the author group. All authors reviewed and approved the final draft of the manuscript.

Declaration of interests

JSt has received research grants from the German Ministry of Education and Research and Basilea Pharmaceuticals, speaker honoraria from Pfizer, and travel grants from German Society for Infectious Diseases and Meta-Alexander Foundation. NdJ has received a consultation fee from Gilead. NS has received grants from the European Hematology Association within this study. JSi reports having received consultations fees, honoraria for lectures, and support for attending scientific meetings from Merck/MSD, Pfizer, and Gilead. RJB has received grants from Gilead and Pfizer; received consulting fees from Gilead, Pfizer, Astellas, Mundipharma, Cidara, and Amplyx; received lecture honoraria or served for the speaker's bureau of Gilead and Pfizer; and participated on advisory boards of Pfizer, Gilead, Astellas, Mundipharma, Cidara, and Amplyx. AB has received honoraria from Gilead Sciences, Merck/MSD, Novartis, Pfizer, and Jazz Pharmaceuticals and travel support from Biotest. RBA has received grants from the Israel Science Foundation and the Israel Ministry of Science and Technology, received speaker honoraria from Gilead and Teva, and served on advisory boards for Pfizer and Merck/MSD. ZR has received speaker honoraria from and been part of advisory boards for Pfizer, Astellas, Novartis, and Abbvie. VP declares no competing interests. RL reports grants from Merck/MSD and Gilead and has received speaking fees or compensation for consultancy for Gilead, Pfizer, Anvir, Cidara Therapeutics, and F2G. OAC reports grants or contracts from Amplyx, Basilea, the German Ministry of Education and Research, Cidara, German Centre for Infection Research, EU Directorate-General for Research and Innovation (101037867), F2G, Gilead, Matinas, MedPace, Merck/MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, Matinas, MedPace, Menarini, Molecular Partners, Mycoses Study Group-Education and Research Consortium, Noxxon, Octapharma, PSI, Scynexis, and Seres; honoraria for lectures from Abbott, Al-Jazeera Pharmaceuticals, Astellas, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, and Pfizer; payment for expert testimony from Cidara; participation on a data safety monitoring board or advisory board from Actelion, Allecra, Cidara, Entasis, IQVIA, Jannsen, MedPace, Paratek, PSI, Shionogi; a pending patent for a device that allows a safer and more tolerable bronchoscopy for patients is currently being reviewed at the German Patent and Trade Mark Office; is chair of the Infectious Diseases Working Party at the German Society for Hematology and Oncology, advisory committee member for the German Infectious Society for Infectious Diseases, educational officer for the European Confederation of Medical Mycology, treasurer for the International Society for Human and Animal Mycology, member of the board of directors for the Mycoses Study Group-Education and Research Consortium, and editor-in-chief for *Mycoses*.

Acknowledgments

This work was carried out as part of the authors' routine duties. The European Hematology Association funded the systematic literature review by Cochrane Evidence-based Oncology group. We thank Natacha Bolaños and Bregje Verhoeven, who were present in several meetings and supported and consented the recommendations as patient representatives. We thank Ullrich Bethe for critically reviewing the final manuscript and Sebastian Rahn for technical assistance. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

References

1 De Angelis R, Minicozzi P, Sant M, et al. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000-2007: results of EUROCARE-5 population-based study. *Eur J Cancer* 2015; **51:** 2254–68.

2 Lewis DR, Siembida EJ, Seibel NL, Smith AW, Mariotto AB. Survival outcomes for cancer types with the highest death rates for adolescents and young adults, 1975-2016. *Cancer* 2021; **127:** 4277–86.

3 Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356:** 348–59.

4 Koehler P, Hamprecht A, Bader O, et al. Epidemiology of invasive aspergillosis and azole resistance in patients with acute leukaemia: the SEPIA Study. *Int J Antimicrob Agents* 2017; **49:** 218–23.

5 Maertens JA, Girmenia C, Brüggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J Antimicrob Chemother* 2018; **73:** 3221–30.

6 Mellinghoff SC, Panse J, Alakel N, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Ann Hematol* 2018; **97:** 197–207.

7 Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018; **24** (suppl 1): e1–38.

8 Wasylyshyn AI, Linder KA, Kauffman CA, et al. Invasive fungal disease in patients with newly diagnosed acute myeloid leukemia. *J Fungi (Basel)* 2021; **7:** 761.

9 Kantarjian H, Short NJ, DiNardo C, et al. Harnessing the benefits of available targeted therapies in acute myeloid leukaemia. *Lancet Haematol* 2021; **8:** e922–33.

10 Coussement J, Lindsay J, Teh BW, Slavin M. Choice and duration of antifungal prophylaxis and treatment in high-risk haematology patients. *Curr Opin Infect Dis* 2021; **34:** 297–306.

11 Falantes JF, Calderón C, Márquez-Malaver FJ, et al. Patterns of infection in patients with myelodysplastic syndromes and acute myeloid leukemia receiving azacitidine as salvage therapy. Implications for primary antifungal prophylaxis. *Clin Lymphoma Myeloma Leuk* 2014; **14:** 80–86.

12 Stemler J, Koehler P, Maurer C, Müller C, Cornely OA. Antifungal prophylaxis and novel drugs in acute myeloid leukemia: the midostaurin and posaconazole dilemma. *Ann Hematol* 2020; **99:** 1429–40.

13 Batchelor R, Thomas C, Gardiner BJ, et al. When azoles cannot be used: the clinical effectiveness of intermittent liposomal amphotericin prophylaxis in hematology patients. *Open Forum Infect Dis* 2021; **8:** ofab113.

14 Lindsay J, Teh BW, Micklethwaite K, Slavin M. Azole antifungals and new targeted therapies for hematological malignancy. *Curr Opin Infect Dis* 2019; **32:** 538–45.

15 Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020; **71:** 1367–76.

16 Higgins JPT, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions, version 6.0 (updated July 2019). Chichester: John Wiley & Sons, 2019.

17 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62:** 1006–12.

18 Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64:** 401–06.

19 Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011; **64:** 380–82.

20 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

21 Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016; **353:** i2089.

22 European Medicines Agency. Summary of product characteristics—vidaza. Vidaza–EMEA/H/C/000978–T/0053. Amsterdam: European Medicines Agency, 2021.

23 Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med* 2020; **383:** 2526–37.

24 Trubiano JA, Dickinson M, Thursky KA, et al. Incidence, etiology and timing of infections following azacitidine therapy for myelodysplastic syndromes. *Leuk Lymphoma* 2017; **58:** 2379–86.

25 Merkel D, Filanovsky K, Gafter-Gvili A, et al. Predicting infections in high-risk patients with myelodysplastic syndrome/acute myeloid leukemia treated with azacitidine: a retrospective multicenter study. *Am J Hematol* 2013; **88:** 130–34.

26 Lorenzana N, Avila LF, Alonso S, Colado E, Bernal T. The impact of antimicrobial prophylaxis in morbidity and infections during azacitidine treatment. *Ann Hematol* 2017; **96:** 1833–40.

27 Pomares H, Arnan M, Sánchez-Ortega I, Sureda A, Duarte RF. Invasive fungal infections in AML/MDS patients treated with azacitidine: a risk worth considering antifungal prophylaxis? *Mycoses* 2016; **59:** 516–19.

28 Mądry K, Lis K, Biecek P, et al. Predictive model for infection risk in myelodysplastic syndromes, acute myeloid leukemia, and chronic myelomonocytic leukemia patients treated with azacitidine; azacitidine infection risk model: the Polish Adult Leukemia Group Study. *Clin Lymphoma Myeloma Leuk* 2019; **19:** 264–274.e4.

29 Latagliata R, Niscola P, Aloe Spiriti MA, et al. Pulmonary infections in patients with myelodysplastic syndromes receiving azacytidine treatment. *Blood* 2016; **128:** 5544 (abstr).

30 Kim GYG, Burns J, Freyer CW, et al. Risk of invasive fungal infections in patients with high-risk MDS and AML receiving hypomethylating agents. *Am J Hematol* 2020; **95:** 792–98.

31 Tey A, Shaw B, Cardamone L, et al. Risk factors for invasive fungal infection in 5-azacytidine treated patients with acute myeloid leukemia and myelodysplastic syndrome. *Eur J Haematol* 2021; **107:** 181–89.

32 Aboudalle I, Kantarjian HM, Ohanian MN, et al. Phase I-II study of crenolanib combined with standard salvage chemotherapy and crenolanib combined with 5-azacitidine in acute myeloid leukemia patients with FLT3 activating mutations. *Blood* 2018; **132** (suppl 1): 2715 (abstr).

33 Kadia TM, Thomas XG, Dmoszynska A, et al. Decitabine improves outcomes in older patients with acute myeloid leukemia and higher blast counts. *Am J Hematol* 2015; **90:** e139–41.

34 European Medicines Agency. Summary of product characteristics—dacogen. Amsterdam: European Medicines Agency, 2012.

35 Ali AM, Weisel D, Gao F, et al. Patterns of infectious complications in acute myeloid leukemia and myelodysplastic syndromes patients treated with 10-day decitabine regimen. *Cancer Med* 2017; **6:** 2814–21.

36 Ozga M, Huang Y, Blachly JS, et al. The incidence of invasive fungal infections in patients with AML treated with a hypomethylating agent. *Clin Lymphoma Myeloma Leuk* 2021; **21:** e76–83.

37 Center for Drug Evaluation and Research. NDA 208573—VENCLEXTA (Venetoclax): clinical pharmacology and biopharmaceutics review. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208573Orig1s000ClinPharmR.pdf (accessed March 26, 2022).

38 DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med* 2020; **383:** 617–29.

39 DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood* 2019; **133:** 7–17.

40 DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol* 2018; **19:** 216–28.

41 Committee for Medicinal Products for Human Use of the European Medicines Agency. CHMP extension of indication variation assessment report. Amsterdam: European Medicines Agency, 2021.

42 Bose P, McCue D, Wurster S, et al. Isavuconazole as primary antifungal prophylaxis in patients with acute myeloid leukemia or myelodysplastic syndrome: an open-label, prospective, phase 2 study. *Clin Infect Dis* 2021; **72:** 1755–63.

43 Rausch CR, DiNardo CD, Maiti A, et al. Duration of cytopenias with concomitant venetoclax and azole antifungals in acute myeloid leukemia. *Cancer* 2021; **127:** 2489–99.

44 Aldoss I, Dadwal S, Zhang J, et al. Invasive fungal infections in acute myeloid leukemia treated with venetoclax and hypomethylating agents. *Blood Adv* 2019; **3:** 4043–49.

45 DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood* 2020; **135:** 85–96.

46 Brüggemann RJ, Verheggen R, Boerrigter E, et al. Management of drug–drug interactions of targeted therapies for haematological malignancies and triazole antifungal drugs. *Lancet Haematol* 2022; **9:** e58–72.

47 Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clin Ther* 2017; **39:** 359–67.

48 European Medicines Agency. Summary of product characteristics—venetoclax. London: European Medicines Agency, 2016.

49 Bhatnagar S, Mukherjee D, Salem AH, Miles D, Menon RM, Gibbs JP. Dose adjustment of venetoclax when co-administered with posaconazole: clinical drug-drug interaction predictions using a PBPK approach. *Cancer Chemother Pharmacol* 2021; **87:** 465–74.

50 Novartis. RYDAPT (midostaurin)—package insert and label information. East Hanover, NJ: Novartis Pharmaceuticals, 2019.

51 Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med* 2017; **377:** 454–64.

52 Phoompoung P, Henry B, Daher-Reyes G, Sibai H, Husain S. Invasive mold infections in FLT3-mutated acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk* 2021; **21:** e477–82.

53 Hartmann K, Gotlib J, Akin C, et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. *J Allergy Clin Immunol* 2020; **146:** 356–66.e4.

54 Dutreix C, Munarini F, Lorenzo S, Roesel J, Wang Y. Investigation into CYP3A4-mediated drug-drug interactions on midostaurin in healthy volunteers. *Cancer Chemother Pharmacol* 2013; **72:** 1223–34.

55 Gu H, Dutreix C, Rebello S, et al. Simultaneous physiologically based pharmacokinetic (PBPK) modeling of parent and active metabolites to investigate complex CYP3A4 drug-drug interaction potential: a case example of midostaurin. *Drug Metab Dispos* 2018; **46:** 109–21.

56 Phillips K, Cirrone F, Ahuja T, Siegfried J, Papadopoulos J. Posaconazole versus voriconazole as antifungal prophylaxis during induction therapy for acute myelogenous leukemia or myelodysplastic syndrome. *J Oncol Pharm Pract* 2019; **25:** 398–403.

57 Ouatas T, Duval V, Sinclair K, Berkowitz N. Concomitant use of midostaurin with strong CYP3A4 inhibitors: an analysis from the ratify trial. *Blood* 2017; **130** (suppl 1): 3814 (abstr).

58 Menna P, Salvatorelli E, Del Principe MI, et al. Choosing antifungals for the midostaurin-treated patient: does CYP3A4 outweigh recommendations? A brief insight from real life. *Chemotherapy* 2021; **66:** 47–52.

59 Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. *N Engl J Med* 2019; **381:** 1728–40.

60 Levis M, Smith C, Litzow M, et al. Drug-drug interaction potential of gilteritinib in healthy subjects and patients with relapsed/refractory acute myeloid leukemia. Annual Meeting of the European Hematology Association; June 22–25, 2017 (abstr E940).

61 Reed DR, Sen JM, Pierce EJ, Elsarrag RZ, K Keng M. Gilteritinib: an FMS-like tyrosine kinase 3/AXL tyrosine kinase inhibitor for the treatment of relapsed or refractory acute myeloid leukemia patients. *J Oncol Pharm Pract* 2020; **26:** 1200–12.

62 Aleissa MM, Alshehri BS, Gonzalez-Bocco IH, et al. Triazole antifungal use for prophylaxis and treatment of invasive fungal diseases for patients receiving gilteritinib. *Leuk Res* 2021; **108:** 106610.

63 DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med* 2018; **378:** 2386–98.

64 Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood* 2020; **135:** 463–71.

65 Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. *Blood* 2021; **137:** 1792–803.

66 Dai D, Yang H, Nabhan S, et al. Effect of itraconazole, food, and ethnic origin on the pharmacokinetics of ivosidenib in healthy subjects. *Eur J Clin Pharmacol* 2019; **75:** 1099–108.

67 Ostrosky-Zeichner L, Nguyen MH, Bubalo J, et al. Multi-centre registry of patients receiving systemic mould-active triazoles for treatment or prophylaxis of invasive fungal infections. 31st European Congress of Clinical Microbiology and Infectious Diseases; July 9–12, 2021 (abstr 1960).

68 Stemler J, Bruns C, Mellinghoff SC, et al. Baseline chest computed tomography as standard of care in high-risk hematology patients. *J Fungi (Basel)* 2020; **6:** e36.

69 Cordonnier C, Robin C, Alanio A, Bretagne S. Antifungal pre-emptive strategy for high-risk neutropenic patients: why the story is still ongoing. *Clin Microbiol Infect* 2014; **20** (suppl 6)**:** 27–35.

70 Hoenigl M, Sprute R, Egger M, et al. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs* 2021; **81:** 1703–29.

71 Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and azacitidine in *TP53*-mutant myelodysplastic syndromes. *J Clin Oncol* 2021; **39:** 1584–94.

72 de Nigris F, Ruosi C, Napoli C. Clinical efficiency of epigenetic drugs therapy in bone malignancies. *Bone* 2021; **143:** 115605.

73 Othman TA, Azenkot T, Moskoff BN, Tenold ME, Jonas BA. Venetoclax-based combinations for the treatment of newly diagnosed acute myeloid leukemia. *Future Oncol* 2021; **17:** 2989–3005.

74 Forsythe A, Sandman K. What does the economic burden of acute myeloid leukemia treatment look like for the next decade? An analysis of key findings, challenges and recommendations. *J Blood Med* 2021; **12:** 245–55.

75 Mulanovich V, Kontoyiannis DP. Acute myeloid leukemia and the infectious diseases consultant. *Leuk Lymphoma* 2018; **59:** 1284–91.

76 Botgros R. EU regulatory considerations for development of antifungal medicines. FDA public workshop: development considerations of antifungal drug to address unmet medical need; Aug 4, 2020.