Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
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IMPACT OF THE NEW HEMATOLOGICAL TREATMENT LANDSCAPE ON INVASIVE FUNGAL INFECTIONS

Livio Pagano

UOC di Ematologia Geriatrica ed Emopatie Rare

Roma

Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne

EHA EUROPEAN HEMATOLOGY ASSOCIATION

ECMM

EORTC The future of cancer therapy

Invited Speaker – Consultant – Research grants

Risk stratification for invasive fungal infections in patients with haematological malignancies: SEIFEM recommendations

HIGH risk	INTERMEDIATE risk	LOW risk
AML undergoing induction CHT with any of the following risk factors: neutropenia at baseline, low CR probability (adverse K, secondary AML), age >65 yrs, significant pulmonary dysfunction AML with prior IA AML undergoing salvage regimens for relapsed/refractory disease	AML not meeting criteria for high- or low-risk groups	AML <45 yrs; undergoing first remission-induction or consolidation CHT and without ANY risk factors for IFI APL treated with ATRA/ATO
Allogeneic stem cell transplantation (from donors other than a matched s HM, GvHD requiring high-dose stero IFI)		
MDS/AML receiving AZA as salvage t regimens		
ALL: Elderly patients (≥55 yrs); intens (induction); high-dose dexametazon (relapsed/refractory)		dults (<30 yrs); maintainance ; TKI + steroids (Ph+ ALL)
	ASCT: Previous IFI; >3 lines of therapy (disease burden); prolonged neutropenia (ANC <500/mm^3 for more than 14 days); corticosteroid therapy; colonisation by Candida spp; previous fludarabine treatment	MPN (chronic myeloid leukaemia, essential thrombocythemia, idiopathic thrombocytosis, polycythemia vera)
	CLL treated with multiple lines of CTX Multiple myeloma in 3 or more lines or during ASCT HD: if received 'escalating BEACOPP' DLBCL relapsed/refractory	Low- or high-grade NHL, CLL, MM, HD treated with conventional frontline CHT

Can this classification still be considered current?

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; APL, acute promyelocytic leukaemia; ASCT, autologous stem cell transplantation; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; AZA, azacitidine; BEACOPP, bleomycin-cyclophosphamide-doxorubicin-etoposide-prednisolone-procarbazine-vincristine; CHT, chemotherapy; CLL, chronic lymphocytic leukaemia; CR, complete remission; CTX, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; GvHD, graft versus host disease; HD, Hodgkin disease; HM, haematological malignancy; IA, invasive aspergillosis; IFI, invasive fungal infection; IPSS, International Prognostic Scoring System; K, karyotype; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasms; NHL, non-Hodgkin lymphoma; Ph+, Philadelphia chromosome-positive; SEIFEM, Sorveglianza Epidemiologica Infezioni nelle Emopatie; TKI, tyrosine kinase inhibitor; yrs, years.

Pagano, et al. Blood Rev. 2017;31:17–29.

New targeted agents approved in HMs

AML

1. FLT3 inhibitors (quizartinib, midostaurin, sorafenib, gilteritinib)
2. Monoclonal antibodies (gemtuzumab ozogamicin, magrolimab)
3. Hh pathway inhibitor (glasgegib)
4. IDH1-2 inhibitors (ivosidenib, enasidenib)
5. Combined liposomal cytarabine and daunorubicin (CPX-351)

ALL

1. Monoclonal antibodies
    a. Anti-CD19 (blinatumomab)
    b. Anti-CD22 (inotuzumab ozogamicin)
2. TK inhibitors (imatinib, nilotinib, dasatinib, ponatinib)

Lymphomas (low and high grade)

1. BTK inhibitors (ibrutinib)
2. Monoclonal antibodies anti-CD20 (rituximab, ofatumumab)
3. PI3Kδ signalling inhibitor (idelalisib)

Multiple myeloma

1. IMiDs (thalidomide, lenalidomide pomalidomide)
2. Proteosome inhibitors (bortezomib, carfilzomib)
3. Monoclonal antibodies
    a. Anti-CD38 (daratumumab)
    b. Anti-CD319 (elotuzumab)
    c. Anti-BCMA (belantamab)

Hodgkin lymphoma

1. Monoclonal antibodies anti-CD30 (brentuximab)
2. IgG4 anti-PD-1 (nivolumab)

CLL

1. BTK inhibitors (ibrutinib)
2. Monoclonal antibodies anti-CD20 (ofatumumab)
3. PI3Kδ signalling inhibitor (idelalisib)
4. Anti-apoptotic BCL-2 (venetoclax)

CAR-T

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; FLT3, fms-like tyrosine kinase 3; IDH, isocitrate dehydrogenase; IMiD, immunomodulary drug; PI3Kδ, phosphatidylinositol-4,5-bisphosphate 3-kinase subunit delta; TK, tyrosine kinase.

Gemtuzumab ozogamicin for *de novo* AML: ALFA-0701 trial

Preferred Term,† n (%)	GO n=131	Control n=137
Any SAE	88 (67.2)	76 (55.5)
Thrombocytopenia	34 (26.0)	6(4.4)
Bronchopulmonary aspergillosis	14 (10.7)	10 (7.3)
Septic shock	12 (9.2)	9 (6.6)
Febrile bone marrow aplasia	12 (9.2)	8 (5.8)
Bacterial sepsis	7 (5.3)	0
Acute kidney injury	6 (4.6)	4 (2.9)
Pneumonia	5 (3.8)	6 (4.4)
Sepsis	5 (3.8)	4 (2.9)
Acute respiratory distress syndrome	5 (3.8)	3 (2.2)
Escherichia sepsis	5 (3.8)	1 (0.7)
Veno-occlusive liver disease	5 (3.8)	0
Acute myeloid leukemia	5 (3.8)	0
Hepatocellular injury	4 (3.1)	2 (1.5)
Cholestatic liver injury	3 (2.3)	2 (1.5)
Febrile neutropenia	3 (2.3)	1 (0.7)
Mucosal inflammation	3 (2.3)	1 (0.7)
Disease progression	3 (2.3)	0
Enterococcal sepsis	3 (2.3)	0
Staphylococcal sepsis	2 (1.5)	5 (3.6)
Toxic skin eruption	1 (0.8)	3 (2.2)

The incidence of IA is really high in both the groups!

SAE	GO (n = 131)	Control (n = 137)
Bronchopulmonary aspergillosis	14 (10.7%)	10 (7.3%)
Septic shock	12 (9.2%)	9 (6.6%)
Bacterial sepsis	7 (5.3%)	0
Pneumonia	5 (3.8%)	6 (4.4%)
Sepsis	5 (3.8%)	4 (2.9%)
Escherichia sepsis	5 (3.8%)	1 (0.7%)
Enterococcal sepsis	3 (2.3%)	0
Staphylococcal sepsis	2 (1.5%)	5 (3.6%)
Febrile neutropenia	3 (2.3%)	1 (0.7%)

AFP, antifungal prophylaxis; AML, acute myeloid leukaemia; GO, gemtuzumab ozogamicin; IA, invasive aspergillosis; SAE, serious adverse event.

Lambert, et al. Haematologica. 2019;104:113–119.

YES Prophylaxis

AML

Liposomal daunorubicin plus Cytarabine (CPX-351): Infections in induction

- Longer neutropenia
- Better outcome

authors		N° patients	Febrile neutropenia	Pneumonia	Bacteremia	Fungal	Viral
Cortes et al, Cancer 2015	CPX 351	81	44 (54%)	18 (22%)	24 (30%)	In pneumonia groups	0
	Comparator	44	14 (34%)	4 (9%)	19 (43%)		0
Lancet et al, Blood 2014	CPX 351	85	54 (63.5%)	13 (15%)	30 (35%)	12 (14%)	0
	3+7	41	21 (51.2%)	8 (19%)	8 (20%)	1 (2.4%)	0
Lancet et al, J Clin Oncol 2018	CPX 351	153	68%	20%	nr	nr	0
	3+7	156	70.9%	15%	nr	nr	
Issa et al. Leukemia 2020	Phase 2	65	19 (34%)	13 (23%)	9 (16%)	nr	0
Guolo et al, Blood Cancer J 2020	Phase 4	71	20 (28%)	8 (11%)	20 (28%)	2 PjP 3 (4%) IA	0
Roboz et al, Leuk & Lymph 2020	Phase 4	52	40 (77%)	7 (13%)	3 (6%)	nr	0
Chiche et al, Blood Adv 2021	Phase 4	103	94 (91%)	30 (30%)	25 (24%)	10 (10%) IA 1 (1%) CDC	0

AFP, antifungal prophylaxis.

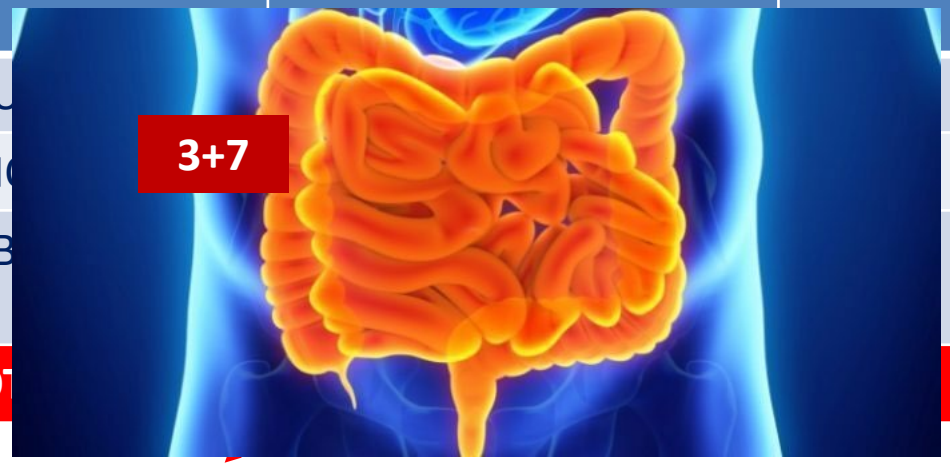
1. Cortes, et al. Cancer. 2015;121:234-242; 2. Lancet, et al. Blood. 2014;123:3239–3246; 3. Chiche, et al. Blood Adv. 2021;5:176–184.

YES Prophylaxis

BACTERIAL/FUNGAL/VIRAL INFECTIONS IN PATIENTS WITH SECONDARY AML TREATED WITH LIPOSOMAL DAURORUBICIN-CITARABINE (VYXEOS) IN THE "REAL-LIFE" SEIFEM STUDY 2020 (submitted)

200 PAZIENTS (Total 336 Courses)

	N°	IN	LIDATiON (1 o 2) (N°)
FU			25
CLINI			11
MICROB			20
TOT			56



Kind of infection	N° (%)
BACTERIAL	
FUNGAL	
VIRAL	

Studies on animal models (in progress) show how the 3 + 7 combination behaves like "acid" on the intestinal epithelium damaging it and at the same time damaging the "Microbiota". On the contrary, there is no such evidence with the liposomal combination

MORTALITY for INFECTION: 15/200 (6%)

IFI
5% of all patients
3% of all courses

	(10)	Yeasts (1)
	ergillus	1 PjP
	1	-
Probable	7	-
Proven	2	1

MORTALITY for FUNGAL INFECTION: 1/199 (0.5%)

AML ALL

Interactions of mould-active azoles with co-administered chemotherapeutic agents and targeted therapies

	Co-administered agent	Interaction mechanism	Effect	Recommendations and actions
ALL	**Vincristine**	Inhibition CYP3A4	Increased neurotoxicity	**Avoid combo**
ALL	**Cyclophosphamide**	Inhibition CYP3A4/2C9	↑ Hepatotoxicity ↓ Activation to hydroxy-CTX	Monitor **Avoid combo**
ALL	**Imatinib**	Inhibition CYP3A4	↑ Imatinib exposure	**Avoid combo**
ALL	**Dasatinib**	Inhibition CYP3A4	↑ D. exposure, **↑ QT interval**	**Avoid combo, monitor ECG**
ALL	**Nilotinib**	Inhibition CYP3A4	↑ N. exposure, **↑ QT interval**	**Avoid combo, monitor ECG**
ALL	**Ponatinib**	Substrate CYP3A4	↓ TKI dosage	**Avoid combo**
AML	**Sorafenib**	Inhibition CYP3A4	No effect	**Monitor QTc**
AML	**Midostaurin**	Inhibition CYP3A4	↑ Adverse reaction	**Avoid combo, monitor QTc**
AML	**Quizartinib**	Inhibition CYP3A4	↑ Quizartinib exposure	**↓ Dose (40 mg → 20 mg)**
AML	**Venetoclax**	Inhibition CYP3A4	↑ Venetoclax exposure	**↓ Dose** 50% if moderate; 75% if potent

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CYP3A4, cytochrome P450 3A4; D., dastinib; ECG, electrocardiogram; N., nilotinib; TKI, tyrosine kinase inhibitor; QTc, corrected QT interval.
Adapted from Busca & Pagano. Exp Rev Anti-Infect Ther. 2018;16:531–542.

AML

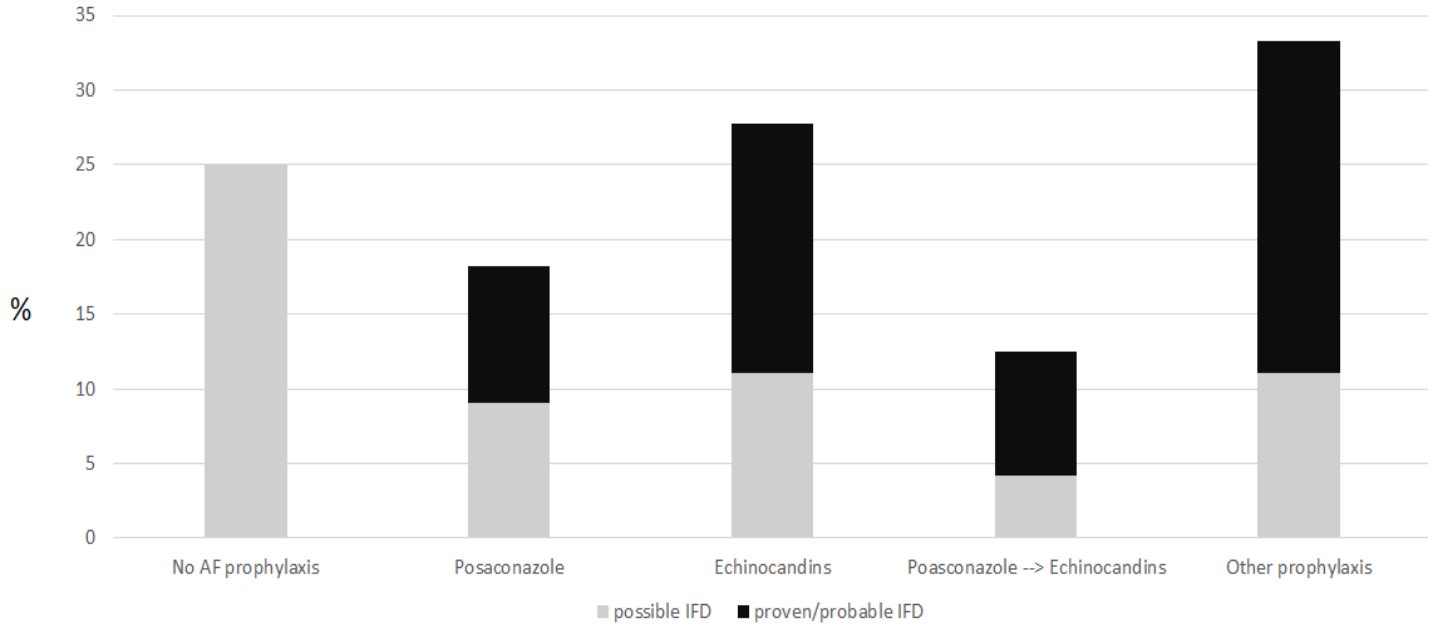
High incidence of invasive fungal diseases in patients with FLT3-mutated AML treated with Midostaurin: results of a multicenter observational SEIFEM Study

Cattaneo et al, submitted

From June 1st, 2019, to December 31st, 2021, 119 patients treated with chemotherapy+midostaurin as induction/reinduction, consolidation. Only 114 were evaluable

Proven/probable and possible IFD incidence was 23/114 (20.2%) during induction and 7/167 (4.2%) during different consolidation courses

AF prophylaxis (induction cht, n=119)	
• No	8
• Fluconazole	3
• Posaconazole	60
• Posaconazole → Echinocandin	24
• Echinocandin	18
• L-AmB	4
• Isavuconazole	2
AF prophylaxis (consolidation cht, n=167)	
• No	91
• Fluconazole	8
• Posaconazole	20
• Posaconazole → Echinocandin	6
• Echinocandin	27
• L-AmB	1
• Isavuconazole	6
• Itraconazole	3
• Voriconazole	5



Antifungal prophylaxis and novel drugs in acute myeloid leukemia: the midostaurin and posaconazole dilemma

Antifungal agent	CYP3A4 impact	Clinical considerations for antifungal prophylaxis
Posaconazole [73]	Strong inhibition	QTc prolongation Oral solution associated with low absorption and plasma level variation, TDM recommended Hepatic toxicity
Isavuconazole [74]	Moderate inhibition	QTc shortening Hepatic toxicity higher rate of breakthrough fungal infections when used for prophylaxis
Voriconazole [70]	Strong inhibition	QTc prolongation Vision changes Hepatic toxicity Hallucinations Long-term use associated with skin cancer
Micafungin [71]	Minor substrate	Well tolerated Only available intravenously Limited efficacy against molds
Caspofungin [72]	Minor substrate	Well tolerated Only available intravenously Limited efficacy against molds

Stemler et al, Ann Hematol 2020

Scenario/strategy	Pro	Contra	Recommendation by the authors
1. Administration of recommended dosage of midostaurin as of package insert and standard dosage antifungal prophylaxis with posaconazole. Monitor patient closely for AE(s).	- Antileukemic activity of midostaurin as assessed in clinical trials is assured	- Close monitoring of AEs (e.g., frequent ECG controls, clinical evaluation of pulmonary function) must be warranted - Increased risk of midostaurin-related AE(s) is given	Moderately recommended This approach detects potential toxicity-related AE late
2. Dose reduction of midostaurin to ~ 50% during induction treatment while posaconazole is administered.	- Risk of early onset of AEs and generally AEs is most likely omitted	- Antileukemic activity of midostaurin is not warranted as assessed in clinical trials - Midostaurin dosage increase must be guaranteed when posaconazole is stopped - Non-adherence to azole prophylaxis or altered pharmacokinetics lead to low midostaurin exposure	Marginally recommended This approach potentially restricts the therapeutic effect of midostaurin while not providing efficacy monitoring
3. Switch antifungal pro EC or other triazoles Itraconazole, Isavuco		- Fluconazole/Itraconazole proved to be inferior in antifungal prophylaxis - EC: administration only via i.v. route/minor penetration to central nervous system [71–74] - Isavuconazole: not available for low resource settings/cost	nended ents than ve been r provide effects
4. Continue with recommended dosage of midostaurin and posaconazole as of package insert and measure drug levels via TDM of both drugs regularly.	- Determination of plasma/serum levels allows monitoring of prophylactic effectiveness of posaconazole and antileukemic activity of midostaurin - Dose adaption according to measured level of midostaurin allows individualized dosage	- TDM method for determination of metabolites (CGP6221 and CGP52421) levels not yet available	Strongly recommended TDM allows close therapy monitoring and individualized dosing in the future. This strategy reflects the "Cologne approach".

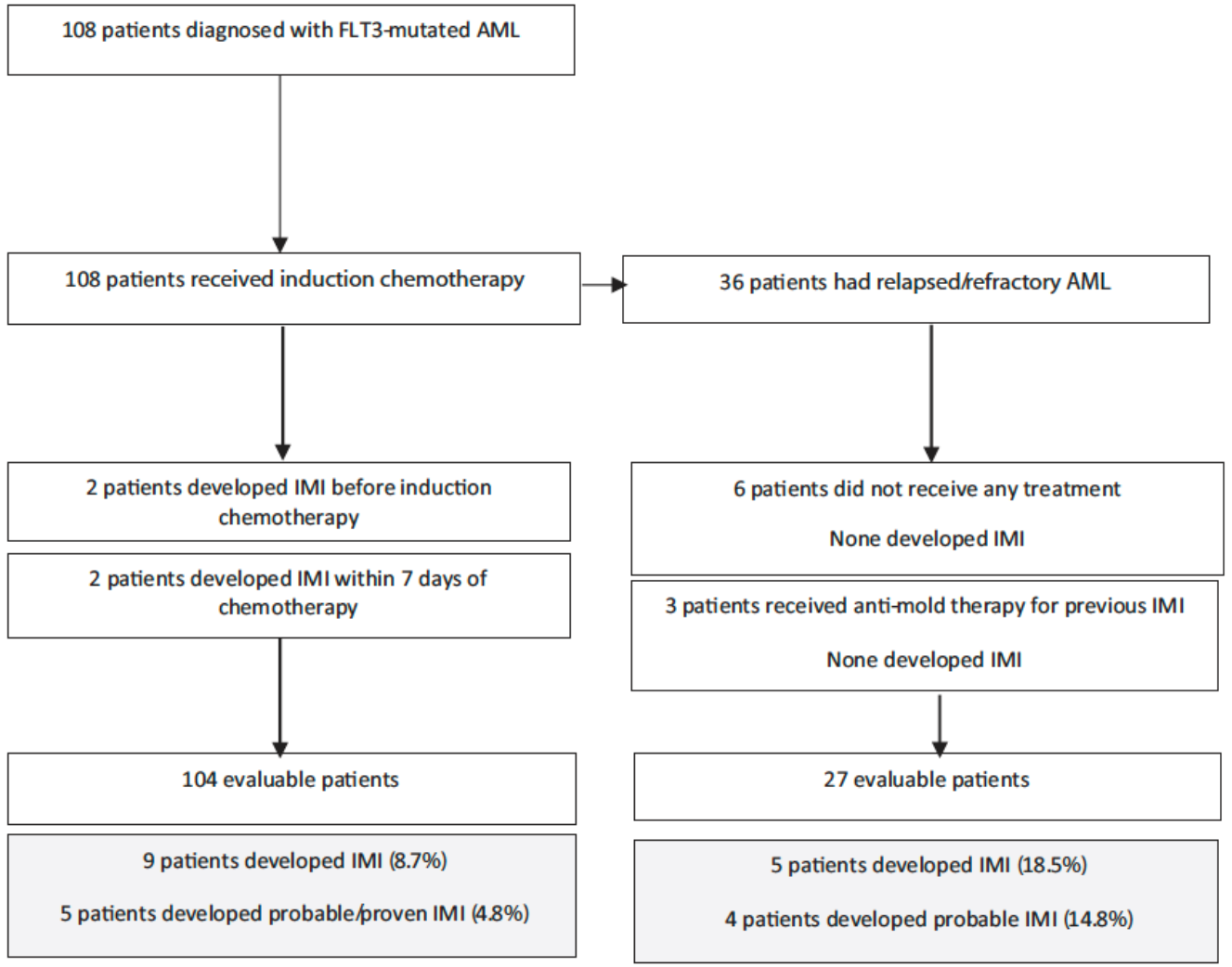
unchanged dosage of Mido and Posa but with serial TDM of both drugs

Stemler et al, Ann Hematol 2020

Invasive Mold Infections in *FLT3*-Mutated Acute Myeloid Leukemia

108 patients receiving fluconazole or micafungin prophylaxis. IMI incidence after induction and salvage therapy was 4.8% and 14.8%, respectively, and did not differ between patients receiving 3+7 regimen or 3+7 plus midostaurin (4.3% vs 4.5%)

Characteristic	IMI	
	IMI (N = 5)	Proven/Probable IMI (N = 4)
Gilteritinib	2 (40)	2 (50)
Sorafenib	1 (20)	1 (25)
Quizartinib	0	0



Phoompoung et al, Clin Lymph Myeloma & Leuk, 2021

HR-MDS and AML treated with hypomethylating agents: IFDs

YES Prophylaxis

Study	Population	IFD incidence, n/N (%)	Notes
Merkel, et al. 2013 (N=184)[1]	• MDS or AML • AZA treatment	6/184 (3.3)	Unfavourable cytogenetics → risk for infections
Falantes, et al. 2014 (N=64)[2]	• MDS or AML • AZA treatment	8/64 (12.5)	All invasive aspergillosis cases were considered probable
Pomares, et al. 2016 (N=121)[4]	• MDS or AML • AZA treatment	4/121 (3.3)	Possible and proven/probable IFD
Trubiano, et al. 2017 (N=68)[5]	• MDS or AML • AZA treatment	6/68 (8.8)	EORTC criteria
Latagliata, et al. 2020 (N=146)[3]	• MDS patients • AZA treatment	21/146 (14.4)	No clear definition/criteria of IFD used
Kim, et al. 2020 (N=209)[6]	• MDS or AML • AZA/DAC treatment	20/209 (9.6) • AZA (7.7) • DAC (14.5)	Possible and proven/probable IFD

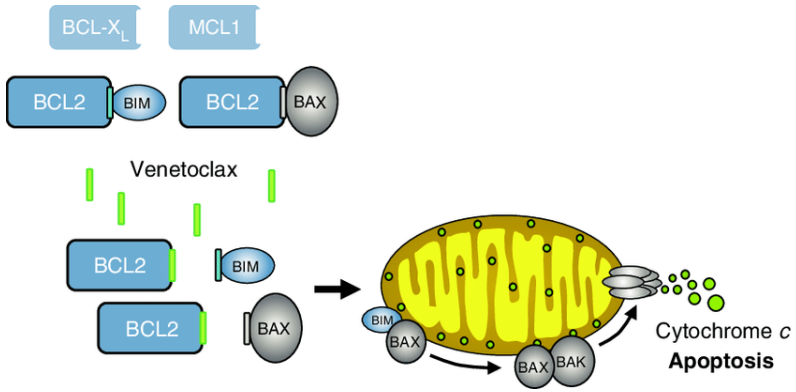
Incidence similar to standard induction AML treatment → need for antifungal prophylaxis

AML, acute myeloid leukaemia; AZA, azacitidine; DAC, decitabine; EORTC, European Organisation for Research and Treatment of Cancer; HR, high risk; IFD, invasive fungal disease; MDS, myelodysplastic syndrome.

1. Merkal, et al. Am J Hematol. 2013;88:130–134; 2. Falantes, et al. Clin Lymphoma Myeloma Leuk. 2014;14:80–86; 3. . Latagliata, et al. Hematol Oncol. 2020;3892):189–196; 4. Pomares, et al. Mycoses. 2016;59:516–519; 5. Trubiano, et al. Leuk Lymphoma. 2017;58:2379–2386; 6. Kim, et al. Am J Hematol. 2020;95:792–798.

AML: BCL2 inhibitors

Venetoclax



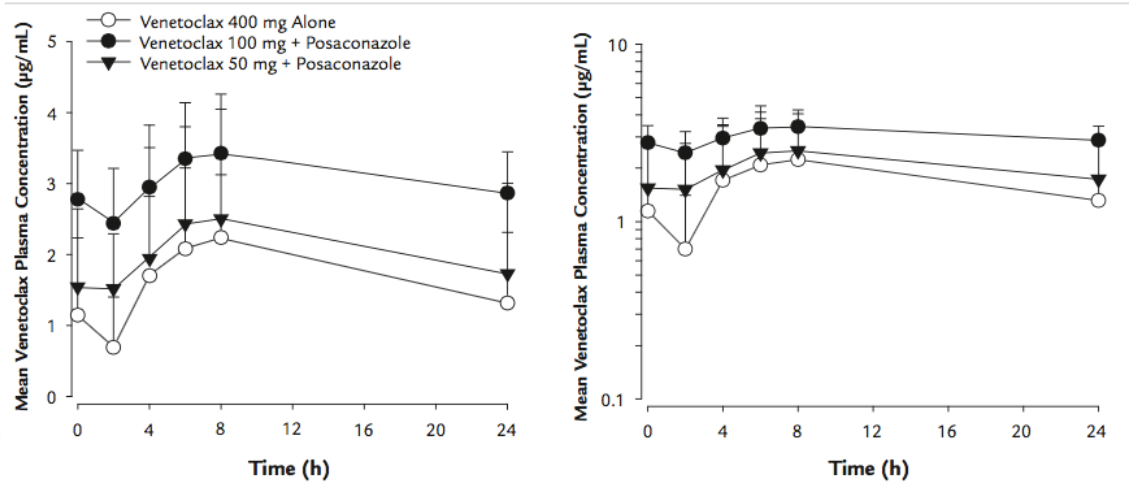


Figure 2. Mean (SD) venetoclax plasma concentration-time profiles after administration of venetoclax alone and with posaconazole.

- **In first line therapy: 30% gr 3-4 febrile neutropenia, 1 IA and 1 candidiasis among 45 patients**
- **In salvage therapy: 19% IFI among 43 patients**
- **Concern about interactions: azoles increase plasma level of venetoclax 8-fold! Posaconazole is allowed after venetoclax a minimum 75% dose reduction**

DiNardo et al, Lancet Oncol 2018; DiNardo et al, AJH 2017; Agarwal et al, Clin Ther 2017

Rate of IFI in patients receiving Venetoclax and HMA

Reference	No. patients	p/p IFI	comments
Di Nardo et al, Lancet Oncol 2018	**57 AML**	**8%**	-
Aldoss et al, Blood Adv 2019	**119 AML**	**12.6%**	Higher risk in non responders and R/R AML
Lee et al, Cancers 2021	**122 AML**	**18%**	88% received PAP mainly with fluconazole Secondary, therapy related AML were risk factors
On et al, BJH 2022	**235 AML**	**5%**	Asperg/candida/mucor 42% on mold-active PAP

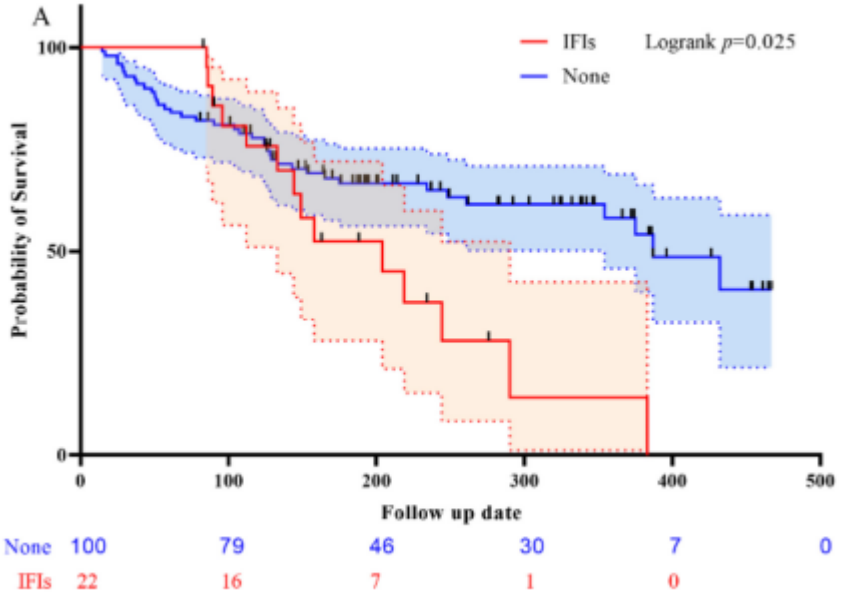
AML

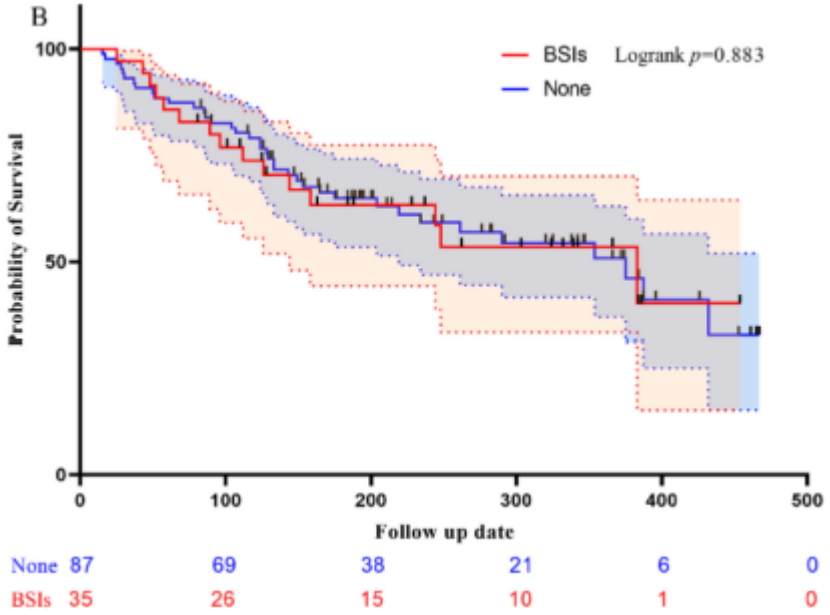
Infections of Venetoclax-Based Chemotherapy in Acute Myeloid Leukemia: Rationale for Proper Antimicrobial Prophylaxis

Cancers 2021

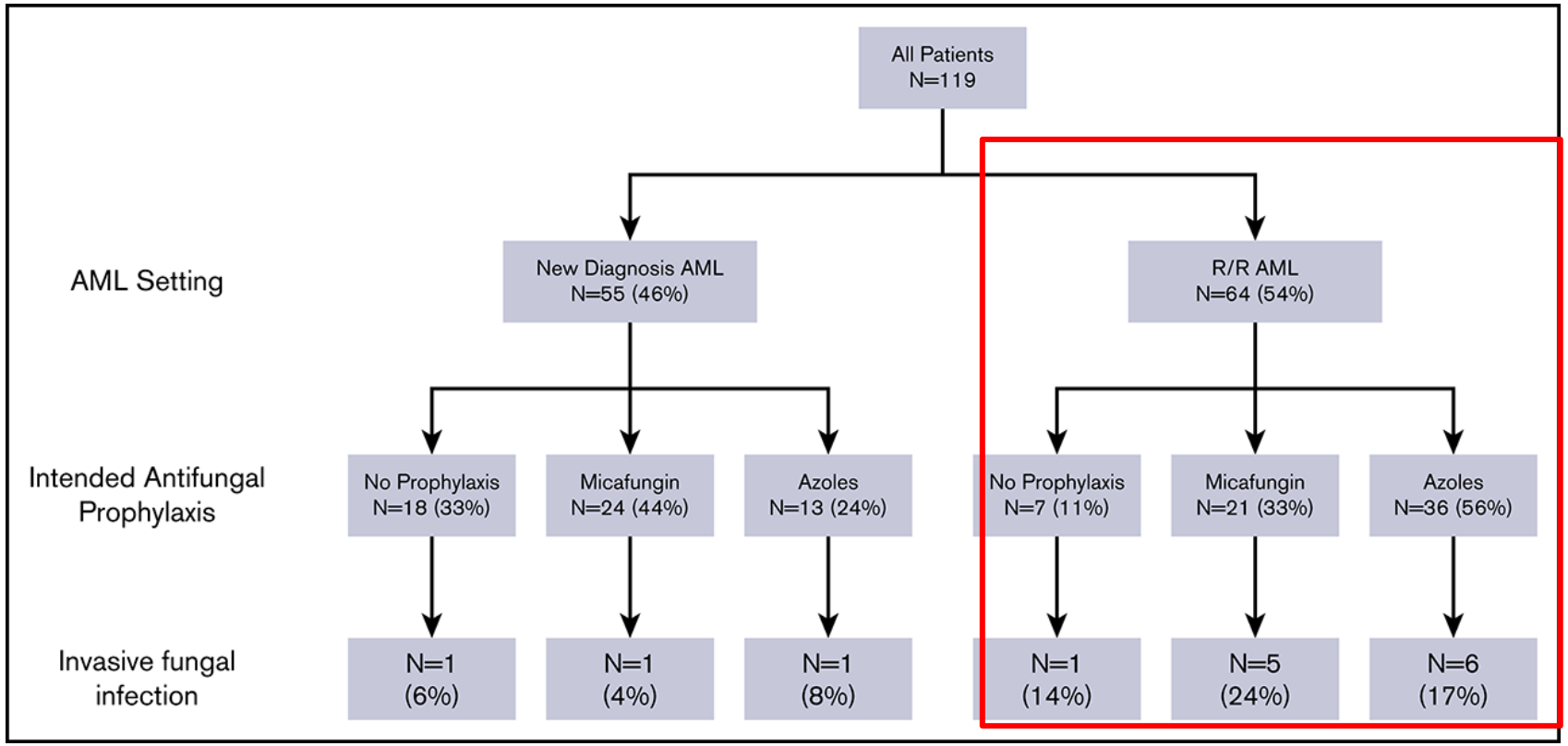
Raeseok Lee [1,2], Sung-Yeon Cho [1,2], Dong-Gun Lee [1,2,*], Hyeah Choi [1,2], Silvia Park [1,3], Byung-Sik Cho Yoo-Jin Kim [1,3] and Hee-Je Kim [1,3]

122 patients treated with VEN+HM; 88% prophylaxis with FLUCO
CI p/p IFI 18%; 86% IFI on Fluco, 14% bIFI on mold-active prophylaxis
Overall mortality 43%; mortality with IFI 63%, mortality without IFI 39%





IFIs in AML treated with venetoclax and hypomethylating agents



- The authors concluded that the overall risk of IFIs during VEN+HMA therapy **is low**
- The risk of IFIs is higher in non-responders and in the R/R setting
- These patients need re-evaluation of their antifungal prophylaxis to minimise the risk of IFIs during therapy

AML, acute myeloid leukaemia; HMA, hypomethylating agent; IFI, invasive fungal infection; R/R, relapsed/refractory; VEN, venetoclax.
Aldoss, et al. Blood Adv. 2019;3:4043–4049.

Duration of Cytopenias With Concomitant Venetoclax and Azole Antifungals in Acute Myeloid Leukemia

	Diagnosis		Hypomethylating Agent Schedule		Venetoclax Duration			Documented Infection	
	sAML/t-AML (n = 20)	De Novo AML (n = 44)	DAC 10 (n = 49)	DAC 5 or AZA 7 (n = 15)	>21 d (n = 31)	15-21 d (n = 24)	≤14 d (n = 9)	Yes (n = 28)	No (n = 36)
ANC > 500 cells/mm^3, No. (%)	19 (95)	40 (91)	46 (94)	13 (87)	27 (87)	23 (96)	9 (100)	27 (96)	32 (89)
Days to ANC > 500 cells/mm^3, median (95% CI)	33 (31-40)	34 (33-37)	35 (33-37)	33 (28-NA)	33 (30-35)	37 (33-41)	36 (29-NA)	34 (31-39)	34 (32-37)
ANC > 1000 cells/mm^3, No. (%)	18 (90)	33 (75)	41 (84)	10 (67)	23 (74)	21 (88)	7 (78)	26 (93)	25 (69)
Days to ANC > 1000 cells/mm^3, median (95% CI)	34 (33-47)	37 (34-41)	37 (34-40)	34 (30-NA)	34 (32-44)	38 (37-46)	38 (33-NA)	38 (33-41)	35 (33-46)
PLT count > 50,000 cells/mm^3, No. (%)	15 (75)	44 (100)	46 (94)	13 (87)	29 (94)	22 (92)	8 (89)	24 (86)	35 (97)
Days to PLT count > 50,000 cells/mm^3, median (95% CI)	27 (21-NA)[a,b]	23 (20-26)[a,b]	25 (22-28)	19 (16-28)	19 (17-25)[a,b]	26 (23-31)[a,b]	29 (22-NA)[a,b]	28 (25-34)[a,b]	21 (18-24)[a,b]
PLT count > 100,000 cells/mm^3, No. (%)	14 (70)	42 (95)	43 (88)	13 (87)	29 (94)	20 (83)	7 (78)	23 (82)	33 (92)
Days to PLT count > 100,000 cells/mm^3, median (95% CI)	29 (22-NA)[a,c]	24 (22-29)[a,c]	27 (23-33)	22 (20-32)	22 (20-27)[a,c]	31 (24-39)[a,c]	32 (23-NA)[a,c]	31 (26-50)[a,c]	23 (21-27)[a,c]

[a] $P < .05$ for within-group comparisons.
[b] $P < .05$ for the difference in median days to a PLT count > 50,000 cells/mm^3 within the group.
[c] $P < .05$ for the difference in median days to a PLT count > 100,000 cells/mm^3 within the group.

Prolonged myelosuppression is anticipated with the use of VEN and HMA therapy

Azole-prophylaxis is preferred for AMLs undergoing induction therapy expected to result in prolonged neutropenia

The combination of VEN with azoles is inevitable, and this creates a need to understand the effects of this combination on both ANC and PLT recovery

Patients receiving concomitant PCZ and VCZ with 100 mg of VEN had similar times to ANC and PLT recovery, and this indicated that VEN may be administered at the same dosage during course 1 of therapy with VEN and HMA.

Rausch et al, Cancer 2021

AML treated with Demethylating + Venetoclax Vs. Demethylating agents

Candoni et al, SEIFEM 2021 (in progress)

	All patients	Demethylating only	Demethylating + Venetoclax	P
N° PZ with Pneumonia	97/230 (42%)	35/98 (36%)	62/132 (47%)	ns
N° Pneumonia • Within the first 3 courses • From 4	116 76/116 (66%) 40/116 (44%)	39 21/39 (54%) 18/39 (46%)	77 55/77 (71%) 22/77 (29%)	0,05
Ethiology: • Bacterial • Viral • **Fungal** • ND	 56/116 (48%) 17/116 (15%) **24/116 (21%)** 19/116 (16%)	 13/39 (33%) 8*/39 **8/39 (21%)** 10/39	 43/77 (56%) 9*/77 **16/77 (21%)** 9/77	
Prophylaxis • No • Only anti-Bacterial • **Only anti-Fungal** • **Both**	 52/116 (45%) 16/116 (14%) **29/116 (25%)** **19/116 (16%)**	 19/39 (49%) 7/39 (18%) **4/39 (10%)** **9/39 (23%)**	 33/77 (43%) 9/77 (12%) **25/77 (32%)** **10/77 (13%)**	ns
Admission in Hospital	101/116 (87%)	33/39 (85%)	68/77 (88%)	
Exitus	43/116 (37%)	15/39 (38%)	28/77 (36%)	

Inotuzumab ozogamicin in R/R ALL: INO-VATE study

Serious Adverse Event	InO (n = 164), No. (%)					SoC (n = 143), No. (%)				
	Any Grade	Grade ≥3	Grade 3	Grade 4	Grade 5	Any Grade	Grade ≥3	Grade 3	Grade 4	Grade 5
Any	85 (51.8)	80 (48.8)	37 (22.6)	17 (10.4)	26 (15.9)	72 (50.3)	71 (49.7)	34 (23.8)	21 (14.7)	16 (11.2)
Febrile neutropenia	19 (11.6)	19 (11.6)	16 (9.8)	3 (1.8)	0 (0)	27 (18.9)	27 (18.9)	20 (14.0)	7 (4.9)	0 (0)
Veno-occlusive liver disease	23 (14.0)	19 (11.6)	8 (4.9)	6 (3.7)	5 (3.0)	3 (2.1)	3 (2.1)	3 (2.1)	0 (0)	0 (0)
Sepsis	4 (2.4)	4 (2.4)	0 (0)	2 (1.2)	2 (1.2)	10 (7.0)	10 (7.0)	1 (0.7)	7 (4.9)	2 (1.4)
Disease progression	8 (4.9)	8 (4.9)	0 (0)	0 (0)	8 (4.9)	5 (3.5)	5 (3.5)	0 (0)	0 (0)	5 (3.5)
Pneumonia	10 (6.1)	9 (5.5)	5 (3.0)	1 (0.6)	3 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory failure	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)	0 (0)	6 (4.2)	6 (4.2)	0 (0)	3 (2.1)	3 (2.1)
Pyrexia	5 (3.0)	2 (1.2)	2 (1.2)	0 (0)	0 (0)	3 (2.1)	1 (0.7)	0 (0)	1 (0.7)	0 (0)
Neutropenic sepsis	3 (1.8)	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.6)	4 (2.8)	4 (2.8)	1 (0.7)	3 (2.1)	0 (0)
Septic shock	3 (1.8)	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.6)	3 (2.1)	3 (2.1)	1 (0.7)	1 (0.7)	1 (0.7)
Fungal pneumonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	3 (2.1)	3 (2.1)	0 (0)	0 (0)
Hyperbilirubinemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	3 (2.1)	2 (1.4)	1 (0.7)	0 (0)
Subdural hematoma	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	3 (2.1)	2 (1.4)	1 (0.7)	0 (0)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	2 (1.4)	0 (0)	2 (1.4)	0 (0)

0/164 InO versus 3/143 SoC

ALL, acute lymphoblastic leukaemia; InO, inotuzumab ozogamicin; R/R, relapsed or refractory; SoC, standard of care.

Kantarjian, et al. Cancer. 2019;125:2474–2478.

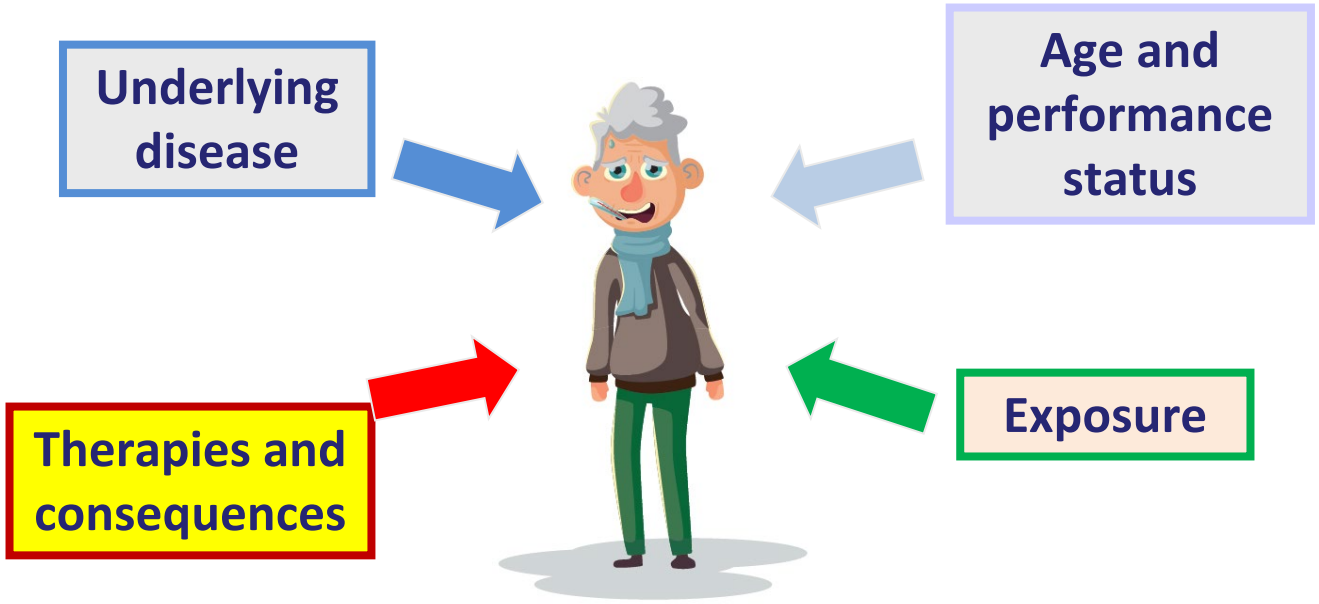
Blinatumomab for adult patients with R/R B-precursor ALL: A multicentre, single-arm, phase II study

	All patients N = 189
Infections, n	
Sepsis†	4 (2)
Fusarium infection	2 (1)
Pneumonia	2 (1)
Septic shock	2 (1)
Aspergillus infection	1 (<1)
Bronchopneumonia	1 (<1)
Candida infection†	1 (<1)
Enterococcal bacteremia	1 (<1)
Escherichia coli sepsis†	1 (<1)
Lung infection	1 (<1)
Pneumonia fungal	1 (<1)

Among 189 treated patients, 5 developed an IFI (2.6%)

ALL, acute lymphoblastic leukaemia; IFI, invasive fungal infection.
Topp, et al. Lancet Oncol. 2015;16:57–66.

Infections and CLD: A multifactorial pathogenesis



Monoclonal antibodies

Proteasome inhibitor

Immunomodulating agents

Extensive use of transplant procedures

Multiple lines of chemotherapy

Pluri-treated patient

CLD, chronic lymphoproliferative disease.

Idelalisib in combination with ofatumumab for previously treated CLL: An open-label, randomised phase III trial

Adverse events of special interest

	Idelalisib plus ofatumumab (n=173)		Ofatumumab (n=86)	
	Any grade, n (%)	Grade ≥3, n (%)	Any grade, n (%)	Grade ≥3, n (%)
Diarrhoea or colitis	94 (54)	40 (23)	21 (24)	1 (1)
Rash*	52 (30)	9 (5)	9 (11)	2 (2)
Pneumonitis	10 (6)	8 (5)	0	0
Pneumonia†	47 (27)	34 (20)	16 (19)	10 (12)

The combination of 'monoclonal antibody and PI3Kδ signalling inhibitor' increases the risk of serious infections particularly CMV and *Pneumocystis* pneumonia

Data cut off was Sept 1, 2015. *Rash was defined as including rash, erythematous rash, generalised rash, macular rash, maculopapular rash, papular rash, pruritic rash, morbilliform rash, and exfoliative rash. †Pneumonia included terms pneumonia, lung infection, lung infiltration, *Pneumocystis jirovecii* pneumonia, *Legionella* pneumonia, pseudomonal lung infection, fungal pneumonia, respiratory tract infection, lower respiratory tract infection, and bacterial lower respiratory tract infection.
CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus.
Jones, et al. Lancet Haematol. 2017;4:e114–e126.

CLL NHL

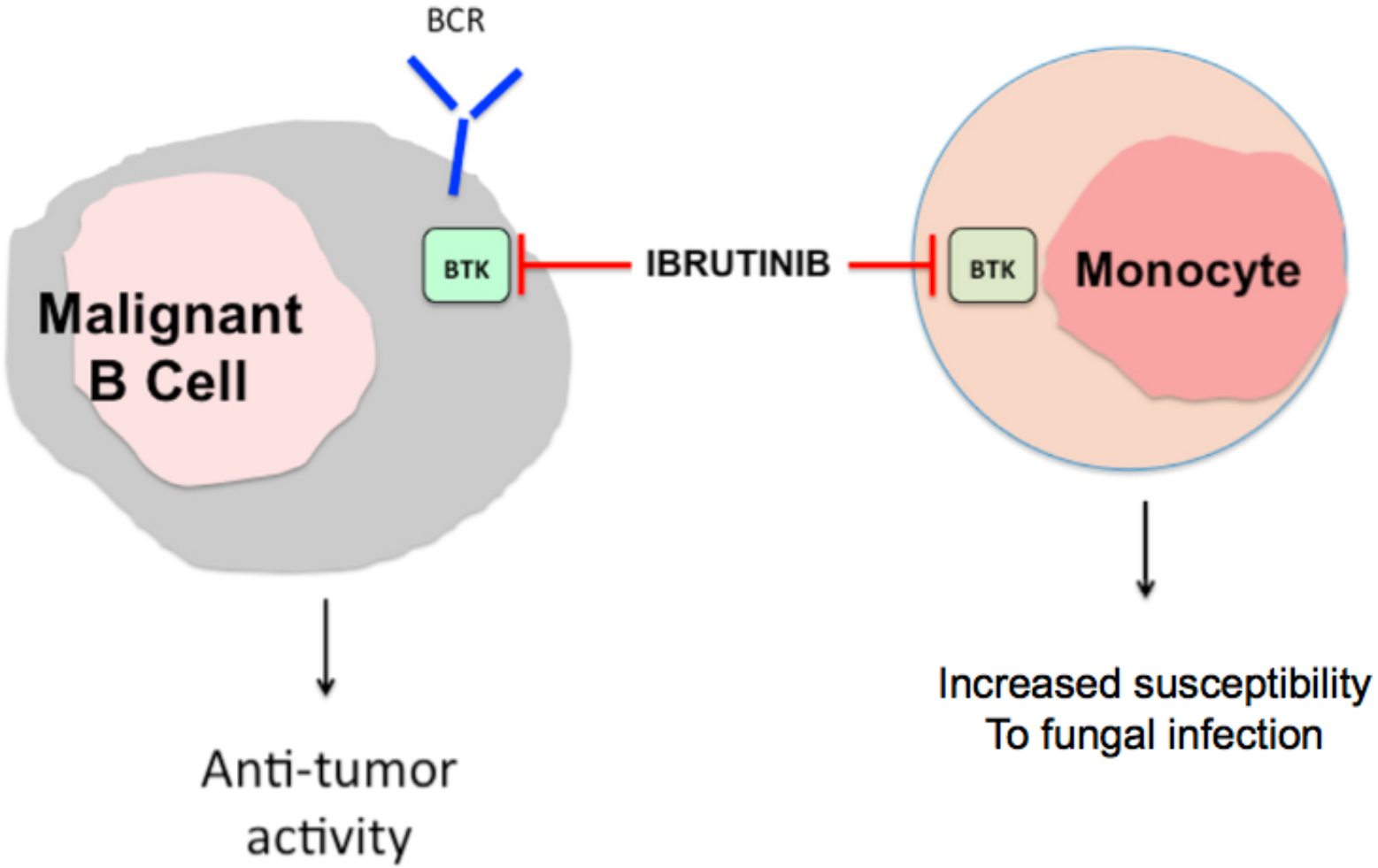
Ibrutinib and fungal infections

Reference	Patients	All IFI, n (%)	Aspergillosis, n (%)	Candida, n (%)	Pneumocystis, n (%)	Cryptococcus, n (%)	Others
Grommes, et al. 2017[1]	20 NHL	/	1 (5)	/	/	/	
Ruchlemer, et al. 2017[2]	28 CLL	28	18 (64)	/	/	/	10
Duma, et al. 2017[3]	30 CLL	5 (4)	5 (4)		/	/	
Lionakis, et al. 2017[4]	18 CNS NHL	8	7 (39)	/	1 (5.5)	/	
Ghez, et al. 2018[5]		33	27		1	4	1
Choquet, et al. 2016[6]	18 NHL	1	2	/	/	/	
Varughese, et al. 2018[7]	213 NHL 165 CLL	6 (3) 10 (6)	8 (2.1) + 1 IA and PJP	1 (0.3)	3 (0.8)	3 (0.8)	10
Gaye, et al. 2018[8]	CLL	2	2				

CLL, chronic lymphocytic leukaemia; CNS, central nervous system; IA, invasive aspergillosis; NHL, Non-Hodgkin lymphoma; PJP, *Pneumocystis jirovecii* pneumonia.

1. Grommes, et al. Cancer Cell. 2017;31(6):731–733; 2. Ruchlemer R et al ASH 2017 Abstract 4323; 3. Duma N et al ASH 2017 Abstract 4327; 4. Lionakis, et al. Cancer Cell. 2017;31(6):833–843; 5. Ghez, et al. Blood. 2018;131(17):1955–1959; 6. Choquet et al ASH 2016, Abstract 784; 7. Varughese, et al. Clin Infect Dis. 2018;67(5):687–692; 8. Gaye, et al. Med Mal Infect. 2018;48(4):294–297.

Ibrutinib in PCNSL: The Curious Cases of Clinical Responses and Aspergillosis



Grommes & Younes et al, Cancer Cell 2017

Ibrutinib in combination therapy

Patients, N	Infectious events, %		Pneumonia, %		Any Grade 5 event, %
	Any grade	Grade 3-4	Any grade	Grade 3-4	
490	52	20	17	8	6

Ibrutinib as a single agent

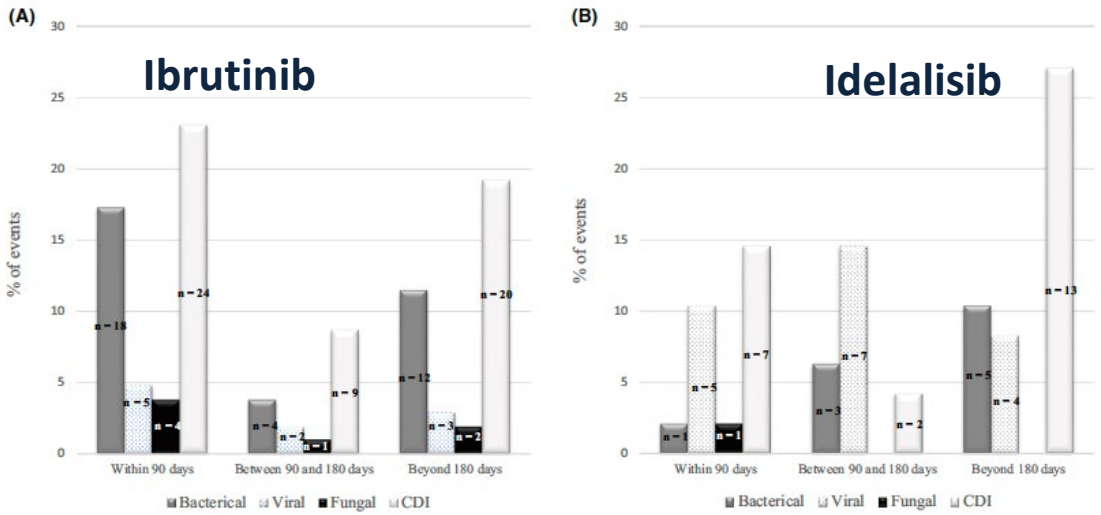
Patients, N	Infectious events, %		Pneumonia, %		Any Grade 5 event, %
	Any grade	Grade 3-4	Any grade	Grade 3-4	
1629	56	26	21	13	10

CLL NHL

Infections in patients with lymphoproliferative diseases treated with targeted agents: SEIFEM multicentric retrospective study

Target drug	Patients treated , n	Patients with CDIs, n (%)	Patients with MDIs, n (%)	Patients with IFD, n (%)
Idelalisib	112	18 (16)	18 (16)	1 (1)
Ibrutinib	250	41 (16)	31 (12)	7 (3)
Total	599	73 (12)	67 (11)	11 (2)

	IBRU	IDE
IA (lung)	4	-
Candidemia	1	-
PJP	1	1
IA (CNS)	1	-



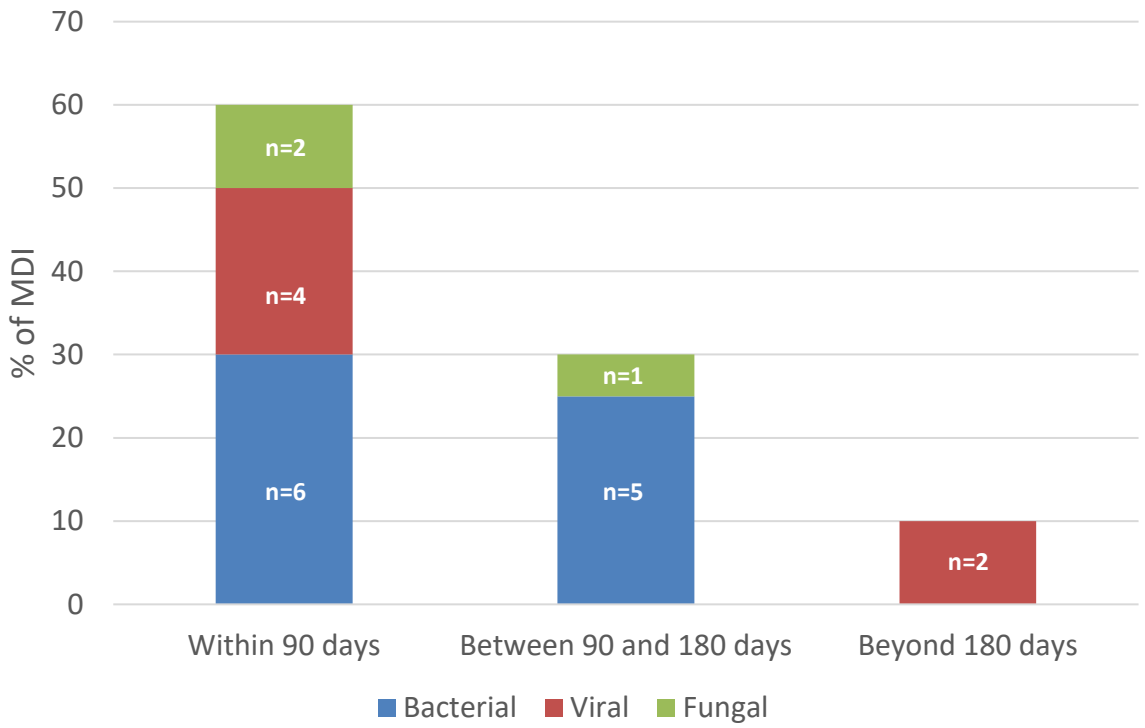
CDI, clinically defined infection; CNS, central nervous system; IA, invasive aspergillosis; IBRU, ibrutinib; IDE, idelalisib; IFD, invasive fungal disease; MDI, microbiologically defined infection; PJP, *Pneumocystis jirovecii* pneumonia.

Marchesini, et al. Br J Haematol. 15 October 2020; doi: 10.1111/bjh.17145 (Epub ahead of print).

HD

Infections in patients with lymphoproliferative diseases treated with brentuximab vedotin: SEIFEM multicentre retrospective study

	$N = 23$
Age, median (range)	48.2 (20–81)
Sex, male no. (%)	13 (56.5)
Medical comorbidities, *N* (%)	
Diabetes	3 (13)
COPD	2 (8.7)
Renal failure	2 (8.7)
Prior treatments, *N* (%)	
<3	13 (56.5)
≥3	10 (43.5)
Hematological malignancies, *N* (%)	
HL	18 (78.3)
NHL T	3 (13)
GZL	1 (4.3)
ALCL	1 (4.3)
Therapy, *N* (%)	
Monotherapy	18 (78.3)
Combination	5 (21.7)
Infective events, *N* (%)	30
Grade <3	15 (50)
Grade ≥3	15 (50)
Infective events, *N* (%)	30
CDI	10 (33.3)
MDI	20 (66.7)
Antimicrobial prophylaxis, *N* (%)	
Antiviral	16 (69.6)
Antifungal	8 (34.8)
Anti-PJP	17 (73.9)
Risk factors	
Neutropenia	5 (21.7)
Lymphopenia	2 (8.7)
CVC	15 (65.2)
Transplant	7 (30.4)
MDR colonization	0 (0)
Steroid treatment	
Prior	4 (17.4)
Concomitant	7 (30.4)
Days from beginning of BV to first infection, median (range)	52.1 (1–335)



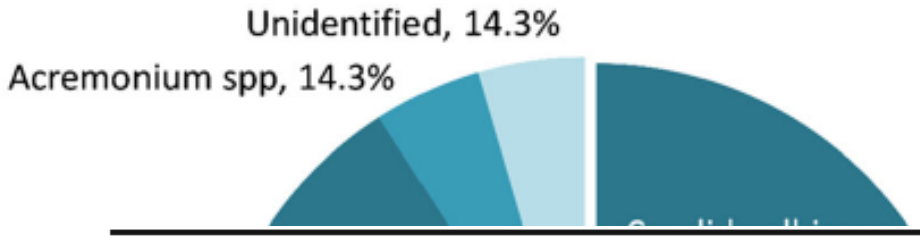
Among 191 patients treated with BV, only 3 IFD were reported: 1 IA, 1 PJP and 1 candidemia (1.57%); none of these patients died

BV, brentuximab vedotin; CID, clinically documented infection; COPD, chronic obstructive pulmonary disease; IA, invasive aspergillosis; IFD, invasive fungal disease; MDR, multidrug resistance; MID, microbiologically documented infection; PJP, *Pneumocystis jirovecii* pneumonia.

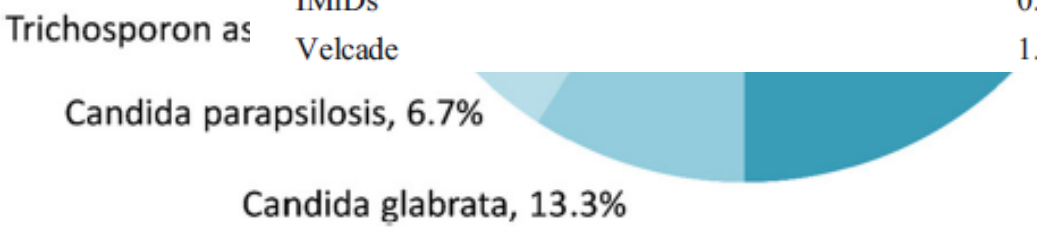
Marchesini, et al. Leuk Lymphoma. 2020;61:3002–3005.

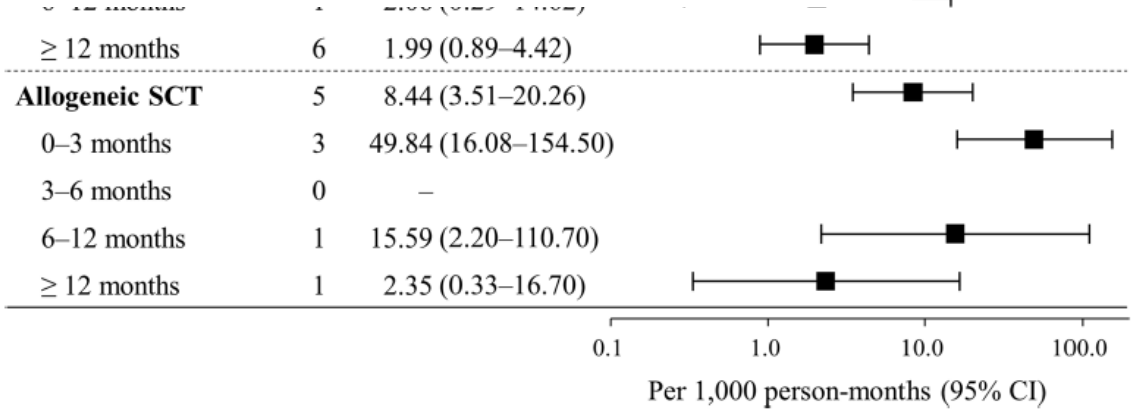
Risk and impact of invasive fungal infections in patients with multiple myeloma

- **Among 623 MM (2002-2018)**
- **22 probable/possible IFD (3.5%)**



Predictive variables	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Chemotherapy				
Alkylating agent except melphalan in ASCT	0.46 (0.16–1.32)	0.146		
Anthracycline	1.15 (0.38–3.42)	0.806		
High-dose steroid	7.93 (2.31–27.22)	0.001	2.46 (0.45–13.41)	0.298
Neutropenia	4.48 (1.24–16.16)	0.022	1.46 (0.26–8.08)	0.667
IMiDs	0.75 (0.26–2.17)	0.599		
Velcade	1.05 (0.36–3.02)	0.932		





Tsai et al, Ann Hematol 2020

Low rates of IFD in MM patients managed with new-generation therapies: A multicentre cohort study

Variable	IFD N = 5 (%)	No IFD N = 143 (%)	*P*-value
Sex			
Male	3 (60.0)	89 (62.2)	.92
Female	2 (40.0)	54 (37.8)	
Age (median, IQR) years	58 (58-64)	68 (61-73)	.12
Previous lines of therapy (median, IQR)	5 (5-7)	3 (2-4)	.04
Treatment regimen[a]			
mAb-based combination[b]	3 (60.0)	40 (28.1)	.19
IMiD-PI	1 (20.0)	43 (30.0)	.63
IMiD-based	1 (20.0)	19 (13.3)	.67

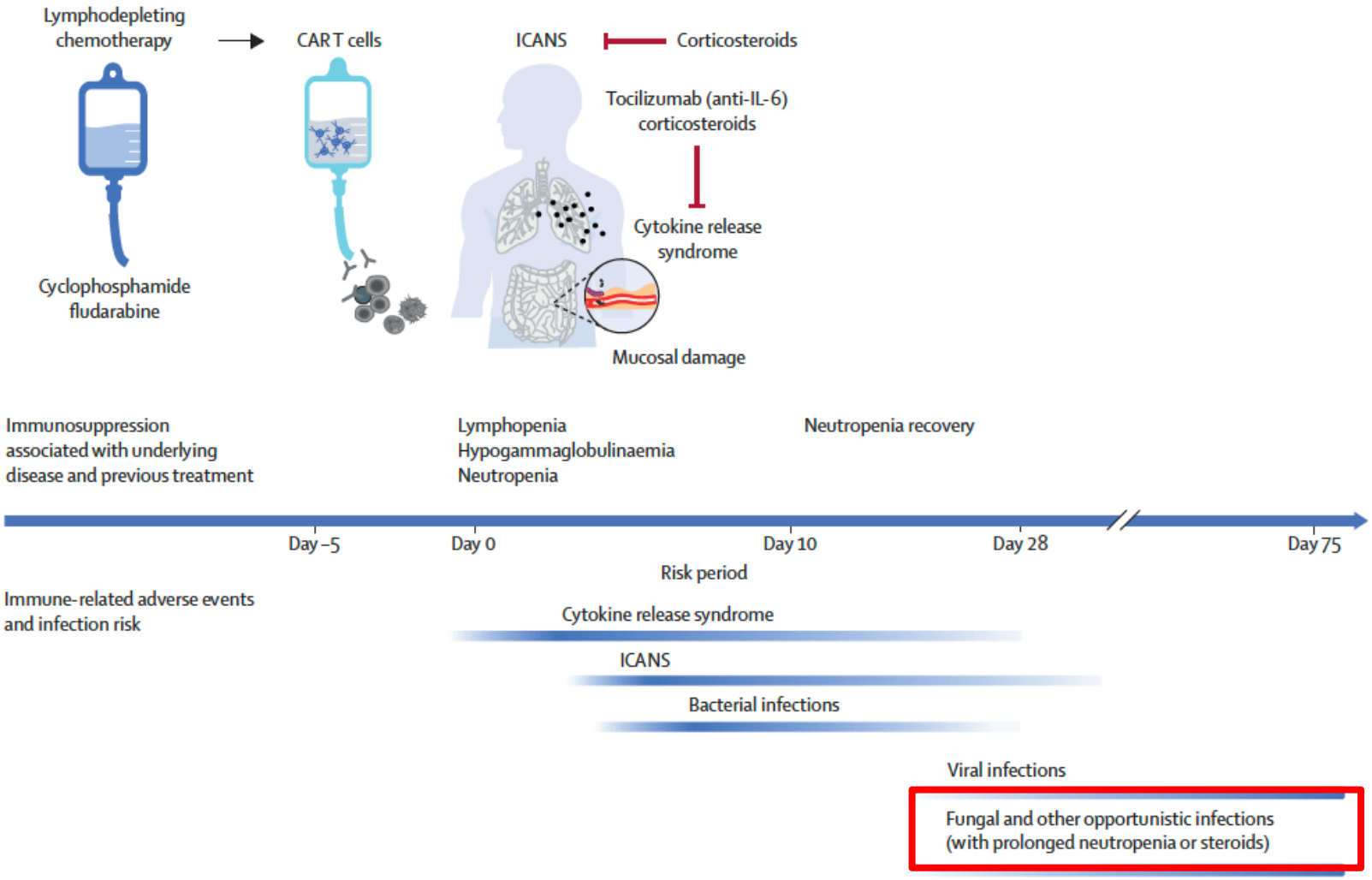
Patient	MM treatment	Disease Response	Lines of Therapy	Neutropenia	Cumulative corticosteroid dose (30 days/60 days) mg	Antifungal Prophylaxis
59 M	Pomalidomide Isatuximab Dexamethasone	Progressive Disease	7	No	533/ 1066	None
62 F	Pomalidomide Dexamethasone	Complete Response	5	No	533/ 1066	None
63 M	Pomalidomide, Carfilzomib, Elotuzumab Dexamethasone	Progressive Disease	8	No	933/ 1600	None
56 F	Carfilzomib, Thalidomide Dexamethasone	Partial Response	2	No	533/ 1333	None
69 M	Daratumumab Melphalan	Progressive disease	5	No	586/ 1119	None

IFD rate remains low in patients with MM heavily treated with new-generation therapies, including monoclonal antibodies. There is insufficient evidence to support the routine use of antifungal prophylaxis. In this era, patients with IFD do not appear to have traditional risk factors, such as prolonged neutropenia, but risk from cumulative immune suppression due to increasing lines of therapy requires further evaluation

IFD, invasive fungal disease; MM, multiple myeloma.

Lim, et al. Mycoses. 2020;64:30–34.

CAR T-cell therapy for lymphoid malignancies: Is there an excess risk for infection?



Gudiol, et al. Lancet Infect Dis. 2021; S2352–3026:30376–8.

	Hill et al (2018)[13]		Park et al (2018)[14]		Logue et al (2020)[15]		Vora et al (2020)[16]		Strati et al (2020)[17]	Cordeiro et al (2020)[18]
	Early (≤28 days)	Late (>28 days)	Early (≤30 days)	Late (>30 days)	Early (≤30 days)	Late (>30 days)	Early (≤28 days)	Late (>28 days)	Any	Late (>90 days)
Number of patients	133	119	53	32	85	70	83	48	31	86 (data for late infections were available for 54 [63%] patients, who were mostly outpatients not diagnosed microbiologically)
All infections	43 in 30 (23%) patients	23 in 17 (14%) patients	26 in 22 (42%) patients	15 in 10 (31%) patients	38 in 31 (37%) patients	32 in 31 (44%) patients	37 in 33 (40%) patients	12 in 11 (23%) patients	71 in 24* (77%) patients	153 in 33 (61%) patients
Fungal infections	6 in 4 (3%) patients	2 in 2 (2%) patients	4 in 4 (8%) patients	1 in 1 (3%) patients	2	0	1	0	4	4
Invasive candidiasis	4¶¶	1	0	0	1‖‖	0	0	0	0	1***
Invasive pulmonary aspergillosis	1†††	1	2	1	0	0	0	0	0	2
Other‡‡‡	1	0	2	0	1	0	1	0	4	1

IFIs are really rare in patients undergoing CAR T therapy!

CAR-T therapy, chimeric antigen receptor T-cell therapy; IFI, invasive fungal infection.
Gudiol, et al. Lancet Infect Dis. 2021; S2352–3026:30376–8.

Safety of allogeneic HSCT in adults after CD19-targeted CAR-T therapy

	ALL (n = 19)	NHL/CLL (n = 13)	Entire cohort (N = 32)
Viral and fungal infections			
Parainfluenza	2 (10.5)	0 (0.0)	2 (6.2)
HSV-1 stomatitis	1 (5.3)	0 (0.0)	1 (3.1)
Adenovirus hepatitis	1(5.3)	0 (0.0)	1 (3.1)
CMV gastroenteritis	1 (5.3)	2 (15.4)	3 (9.4)
RSV	1 (5.3)	0 (0.0)	1 (3.1)
Aspergillosis	3 (15.8)	0 (0.0)	3 (9.4)
Other fungal	1 (5.3)	2 (15.4)	3 (9.4)
Toxoplasmosis	1 (5.3)	0 (0.0)	1 (3.1)

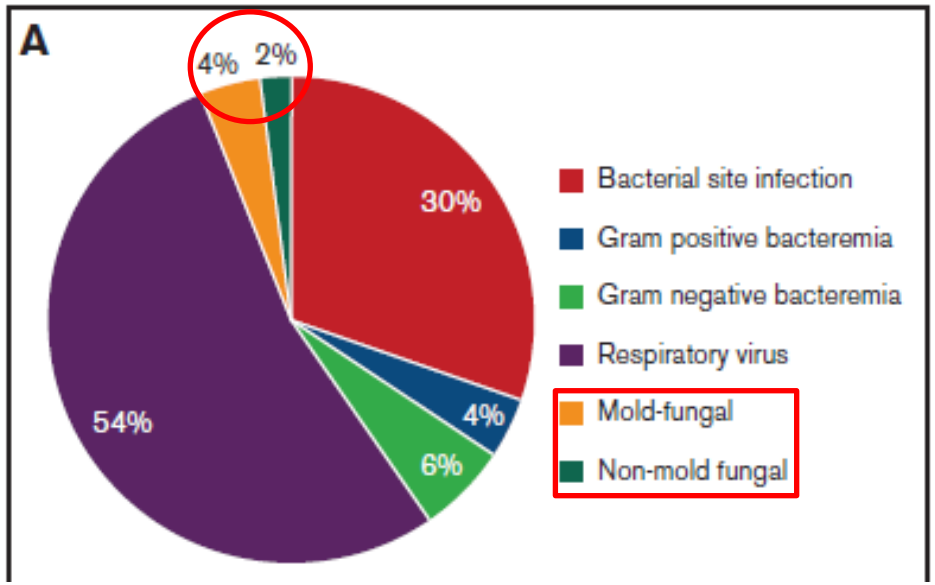
3 proven aspergillosis and 3 probable IFIs
Incidence: 6/32 = 18% !
2/6 patients with IFIs died

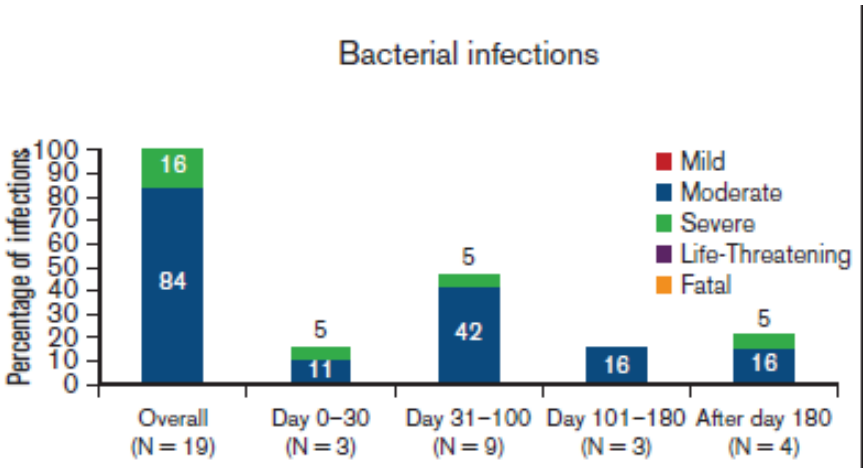
ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CAR-T therapy, chimeric antigen receptor T-cell therapy; CMV, cytomegalovirus; HSV, herpes simplex virus; IFI, invasive fungal infection; NHL, Non-Hodgkin lymphoma; RSV, respiratory syncytial virus

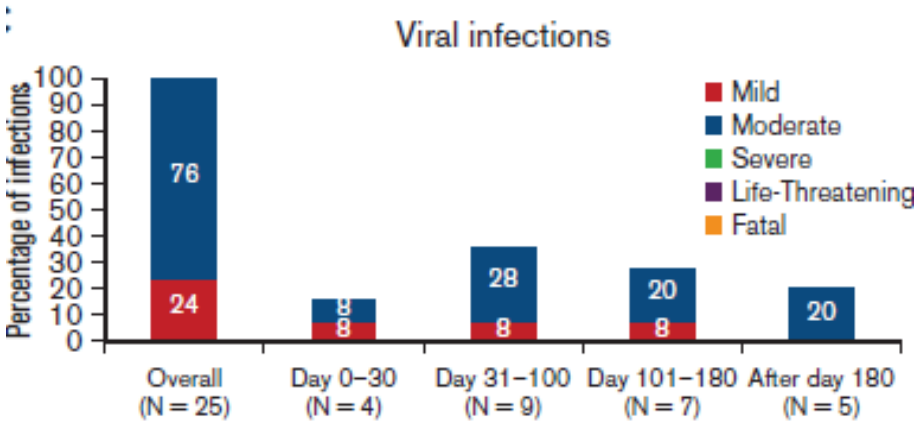
Shadman, et al. Blood Adv. 2019;3:3062–3069.

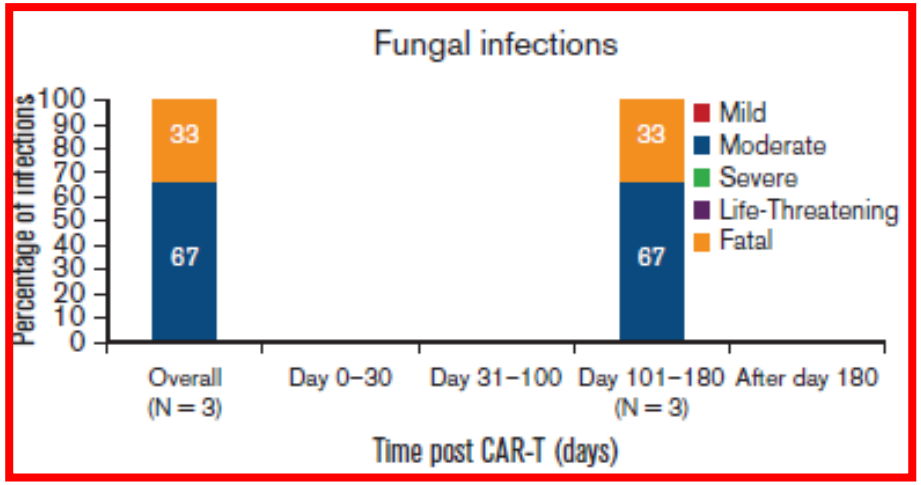
Infectious complications in patients with relapsed refractory multiple myeloma after BCMA CAR T-cell therapy

Kambhampati S et al. Blood Adv 2022









Open Question for IFI risk

- In AML will these new drugs be able to modify the antifungal prophylactic approach? should we expect a return to the “past”?
- In ALL the addition of monoclonal antibodies to conventional chemotherapy or the use of more aggressive chemotherapies should increase the IFI incidence? What we do? To find a better antifungal prophylaxis? To make a timely diagnostic work-up? To increase the use of empirical antifungal therapy?
- In CLL/iNHL has the use of the “new” drugs increased the IFI incidence? Is necessary to start an antifungal prophylaxis? In all patients?
- From literature data, among hematological diseases excluding acute leukemia, MM patients seem those with a higher incidence of IFI? When these patients must be considered at risk? What must we do?