CON IL PATROCINIO DI

INCONTRO DI AGGIORNAMENTO
SUI **DISORDINI LINFOPROLIFERATIVI**
E SUI PROTOCOLLI
DELLA **FONDAZIONE ITALIANA LINFOMI**

Torino, 14 dicembre 2018

Il rischio infettivo nei disordini linfoproliferativi in corso di targeted therapy

Alessandro Busca

Targeted Therapies in Ematologia

	Target	Impiego terapeutico
BCR inhibitors		
Ibrutinib	BTK	CLL, MCL, Waldenstrom, cGVHD
Idelalisib	PI3K	CLL, FL
Checkpoint inhibitors		
Nivolumab	Anti PD-1	HD, NHL primitivi mediastino
Pembrolizumab	Anti PD-1	
Ipilimumab	Anti CTLA-4	
Sorafenib,quizartinib, gilteritinib, midostaurin, crenolanib	TKI	AML FLT3+
MoAb Rituximb, oftumumab, obinutuzumab	CD20	NHL, CLL
Brentuximab	CD30	HD, NHL anaplastico
Gentuzumab ozogamicin	CD33	AML
Blinatumomab	CD19	ALL
Inotuzumab ozogamicin	CD22	ALL
venetoclax	BCL2	AML, CLL
Terapie cellulari: CAR-T	CD19	B-ALL, DLBCL

Infections in Patients with Lymphoproliferative Diseases Treated with Target Therapy – Italian Multicentric Retrospective Study SEIFEM 2017

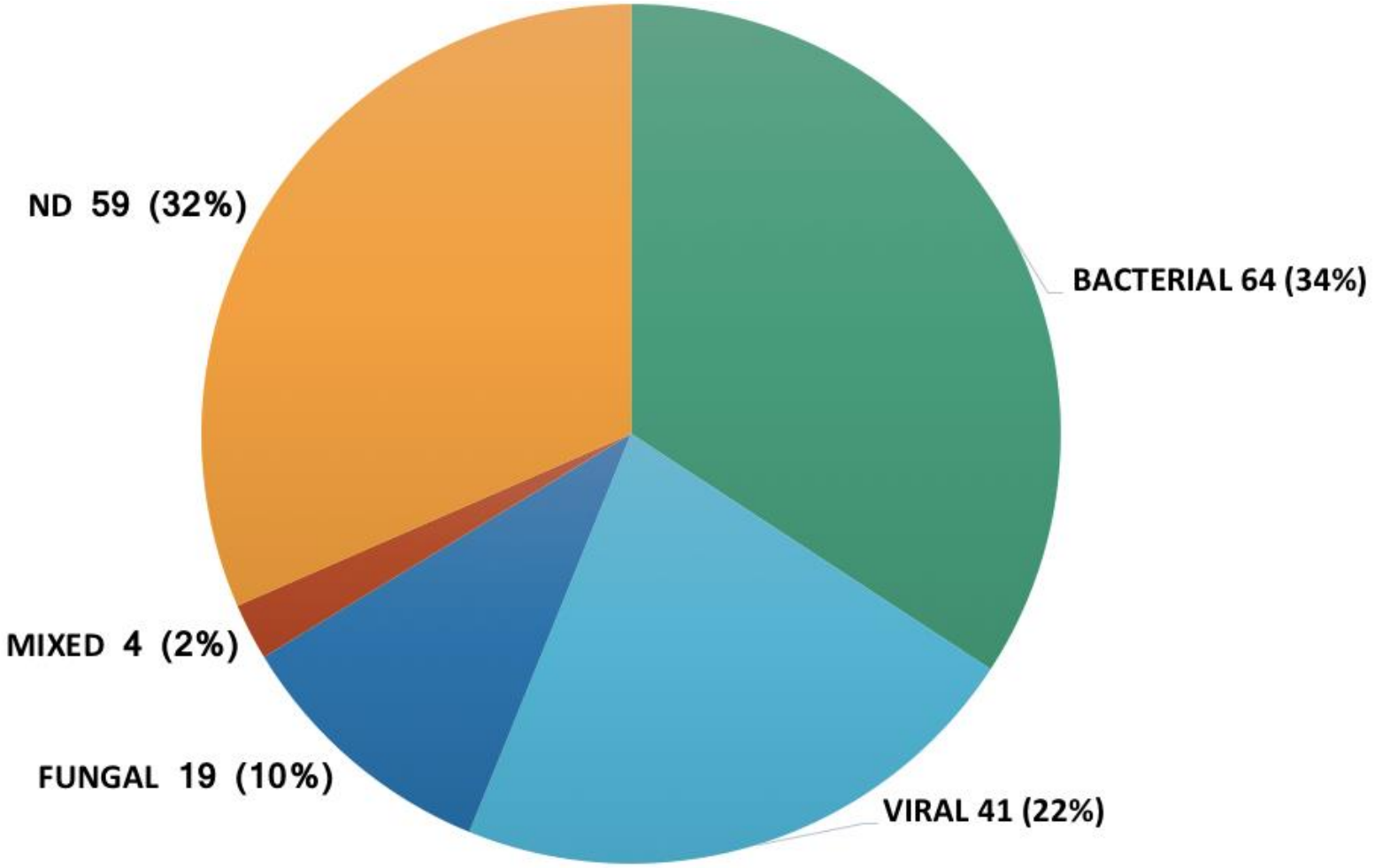
555 pazienti, 13 Centri Italiani, trattati con:

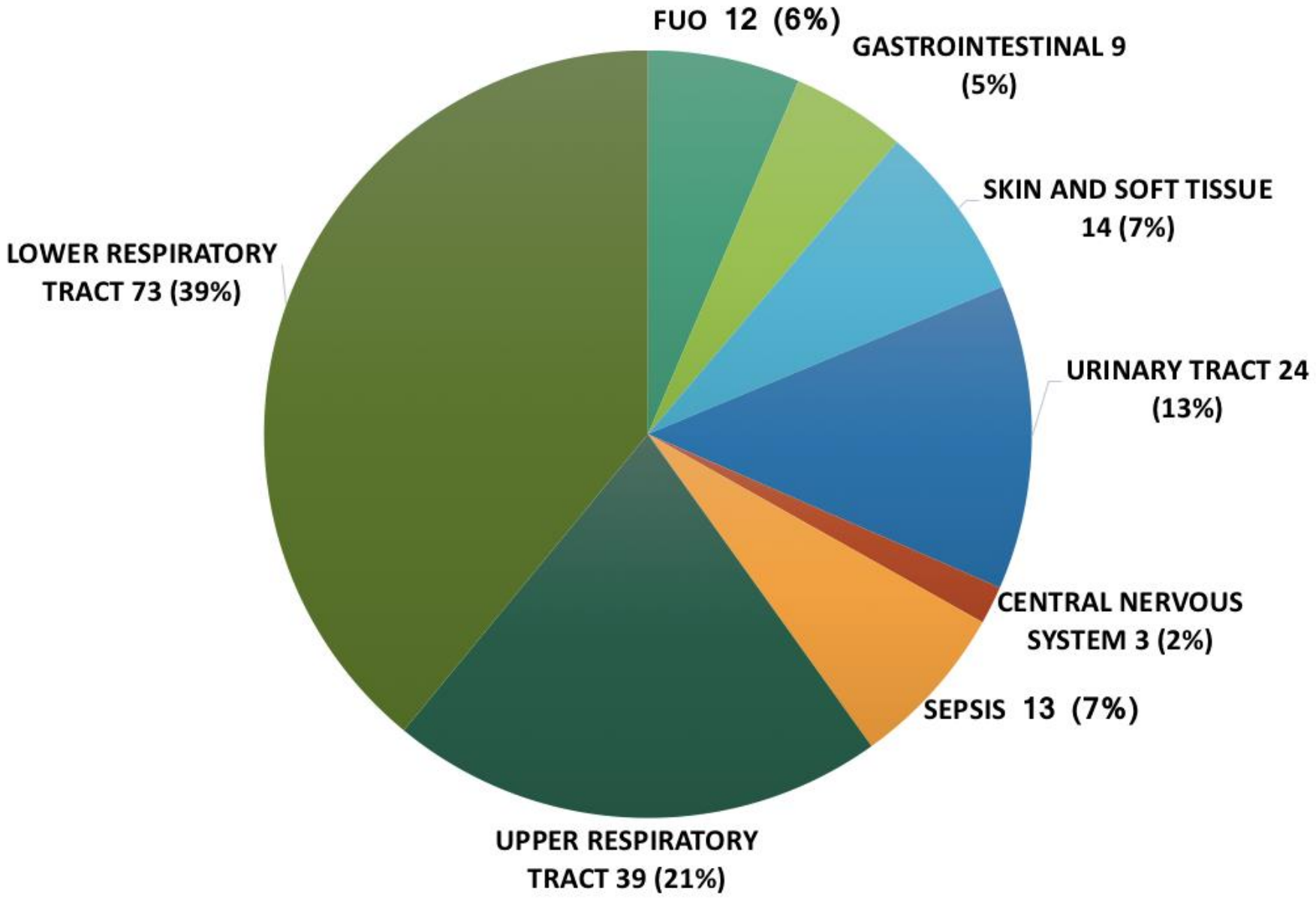
- **idelalisib**
- **Ibrutinib**
- **brentuximab**
- **ofatumumab**
- **obinutuzumab**

132/555 pazienti (24%) ➡ infezione

ASH2018 Nadali GP

Infections in Patients with Lymphoproliferative Diseases Treated with Target Therapy – Italian Multicentric Retrospective Study SEIFEM 2017




FUO 12 (6%)
GASTROINTESTINAL 9 (5%)
SKIN AND SOFT TISSUE 14 (7%)
URINARY TRACT 24 (13%)
CENTRAL NERVOUS SYSTEM 3 (2%)
SEPSIS 13 (7%)
UPPER RESPIRATORY TRACT 39 (21%)
LOWER RESPIRATORY TRACT 73 (39%)

Proven/probable

Target drug	Patients	infections (%)	IFI (%)	bacterial (%)	Viral (%)
Idelalisib	106	35 (33)	3 (3)	18 (17)	13 (12)
Ibrutinib	235	70 (30)	11 (5)	26 (11)	13 (5)
Brentuximab	175	20 (11)	3 (2)	8 (5)	8 (5)
Ofatumumab	21	3 (14)	1 (5)	0	0
Obinutuzumab	18	4 (22)	0	1 (5)	1 (5)

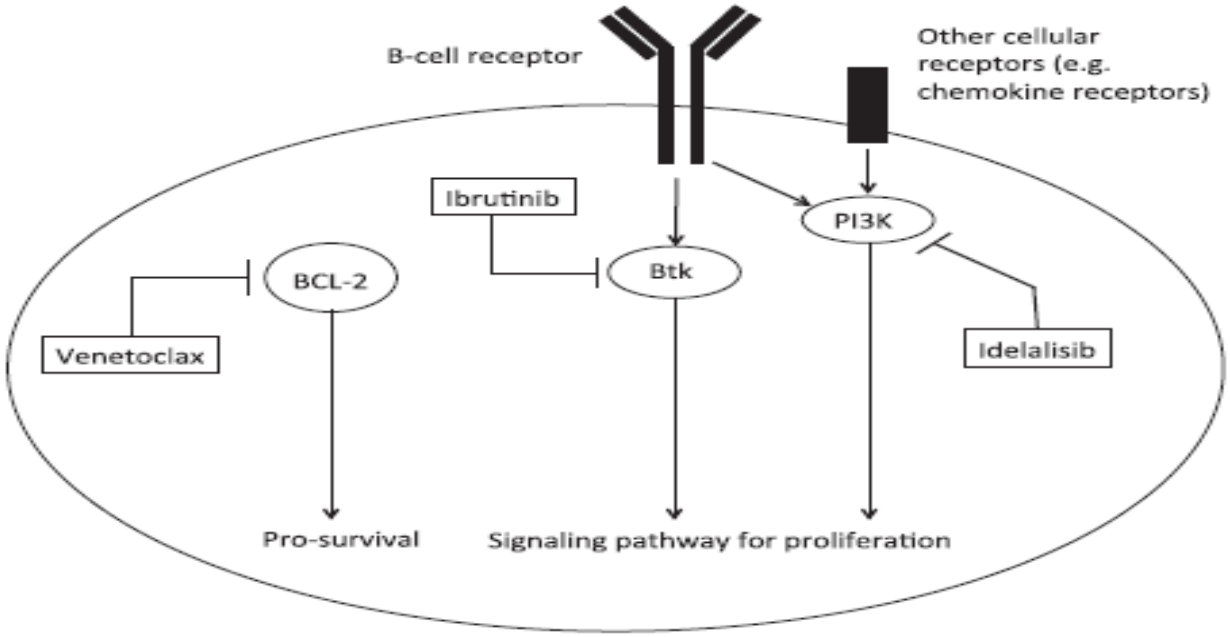
0.015

CLL: class of therapy, immune dysfuction and spectrum of infections

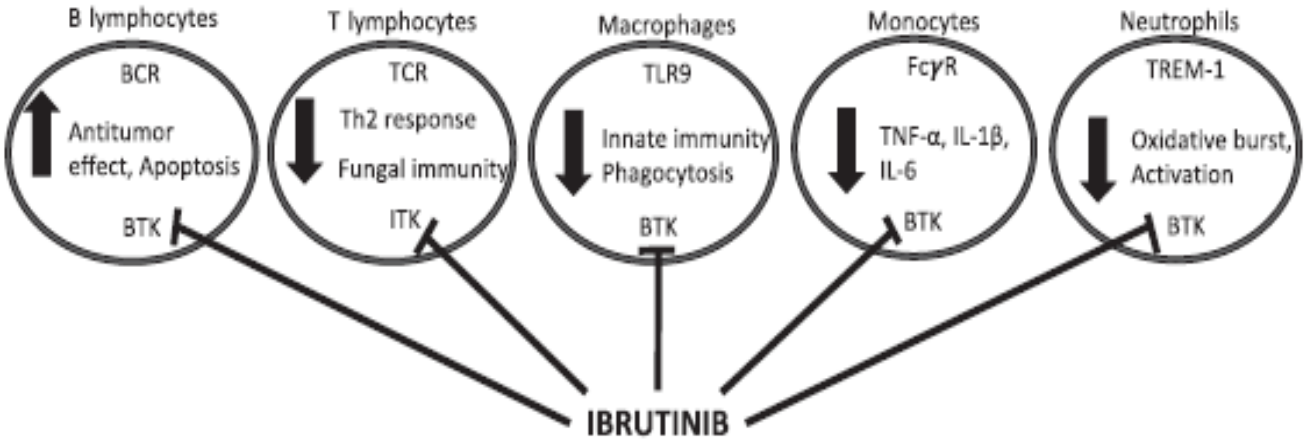
Alkylating agents
Chlorambucil, cyclophosphamide, bendamustina
Neutropenia, T cell dysfunction
Bacterial (capsulated) fungal

Purine analogues
fludarabine
Neutropenia, quantitative and functional T cell defects
Bacterial, fungal, PJP, HSV, HZV

MoAb
Anti CD20, Anti CD52
B and T cell dysfunction
Bacterial, fungal, PJP, CMV,HSV,HZV,HBV,JC

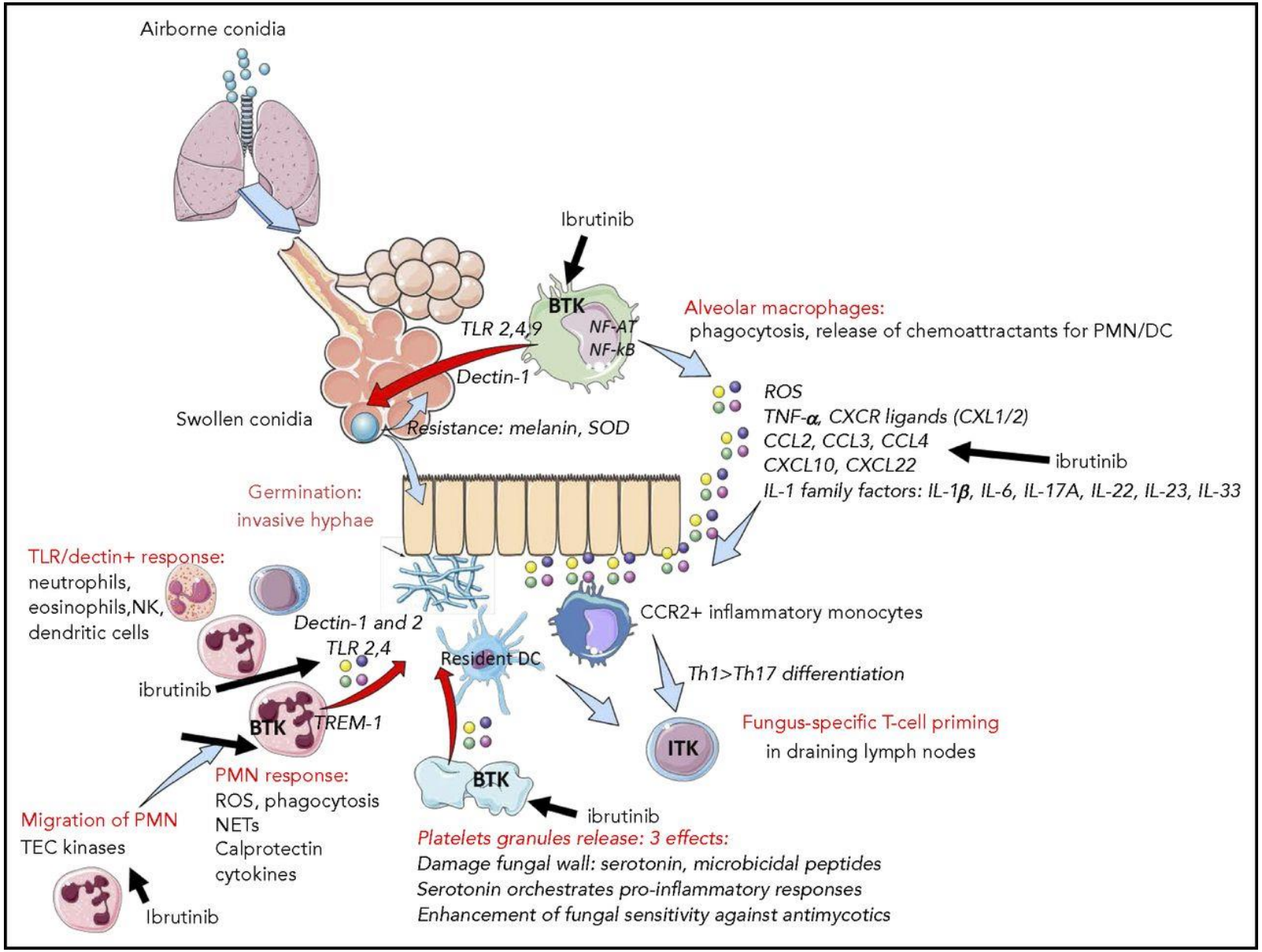


- How ibrutinib may decrease antifungal immunity remains to be clarified. Multiple mechanisms may be involved.[1]
- BTK is an indispensable component of the B-cell receptor signaling pathway. BTK is also found in neutrophils, monocytes and macrophages where it mediates pathways involving innate and adaptive immunity (Herbst S. et al.; Stadler N.).[2]
- ITK found in T-cells has significant homology with BTK and is irreversibly inhibited by ibrutinib, suggesting that ibrutinib may predispose patients to increased infections.[2]



- BTK plays an important role in neutrophil differentiation and function (Fiedler K. et al. 2011).[1]
- BTK plays an important role in TREM-1 mediated PMN activation, providing a potential mechanism for the frequently observed infectious complications in patients treated with ibrutinib.[3]

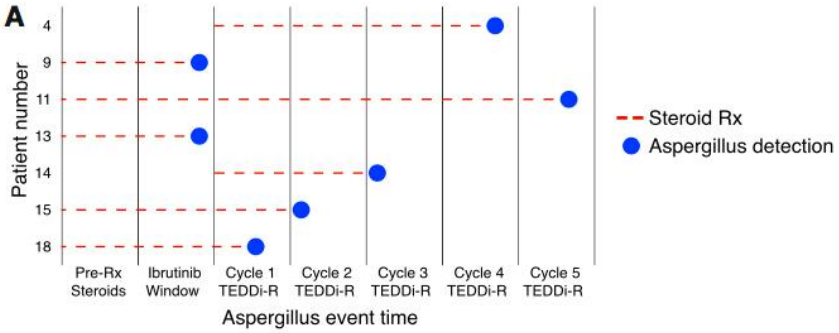
Ibrutinib may permit invasive fungal infections through multiple effects.

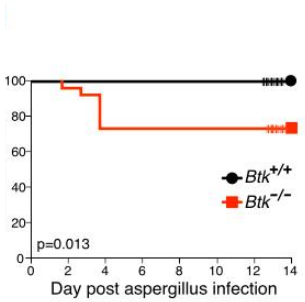


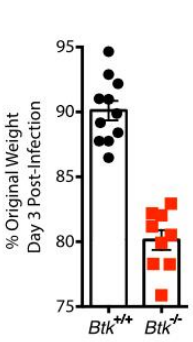
Kerry Rogers Blood 2018;131:1882-1884

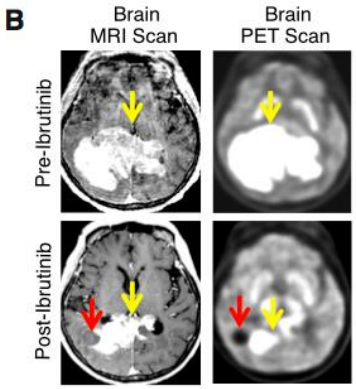
Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma

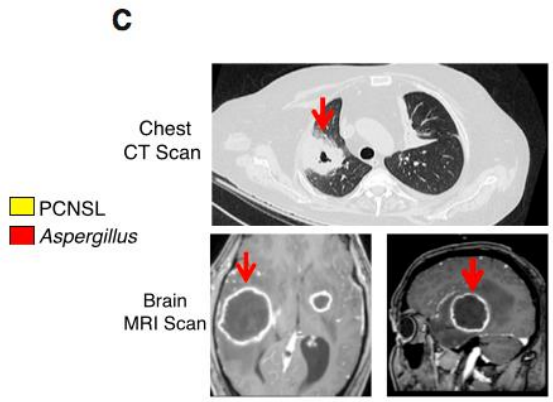
7 of 18 (39%) patients developed proven (3), probable (1), or possible (3) invasive aspergillosis

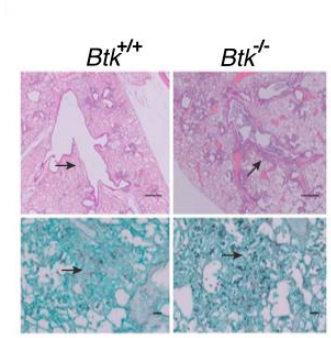


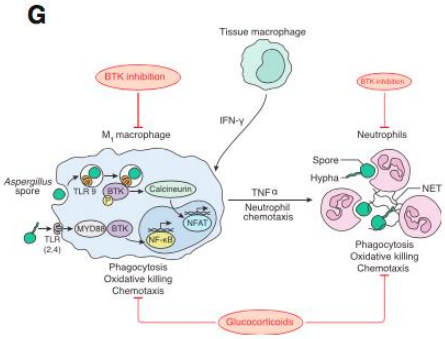












Lyonakis et al, Cancer Cell 2017

Systematic review of infectious events with the BTK inhibitor ibrutinib in the treatment of haematologic malignancies

Ibrutinib as single agent

Study, disease and setting, trial	Phase	Patients	Infectious Events by Grade No. (%)			Pneumonia by Grade No. (%)			Any Grade V Event No. (%)
			ALL	3-4	5	ALL	3-4	5	
Fowler, et al.[11#] FL* (NCT 00849654)	I	16	1 (6)	1 (6)	0 (0)	1 (6)	1 (6)	0 (0)	0 (0)
Furman, et al.[12] WM*(NCT 01109069)	I	4	5 (100)'	4 (100)	0 (0)	3 (75)	2 (50)	0 (0)	0 (0)
Byrd, et al.[13] CLL* (NCT 01105247)	Ib/II	85*	76 (89)	37 (44)	4 (5)	13 (15)	10 (12)	3 (4)	8 (9)
O'Brien, et al.[14] CLL** (NCT 01105247)	Ib/II	31*	25 (81)	3 (10)	0 (0)				1 (3)
Byrd, et al.[15] CLL*** (NCT 01105247 & 01109060)	Ib/II	132*		51 (39)	5 (4)		29 (22)	2 (2)	14 (11)
Coutre, et al.[16] CLL*** (NCT 01105247 & 01109060)	Ib/II	94*		- - (59)			- - (23)		8 (9)
O'Brien, et al.[17] CLL*(NCT 01									
Byrd. et al. & Brown, et al.[18,19] CLL*(N									
Burger, et al. & Barr et al.[20,21] CLL**(N									
Wang, et al.[22,23] MCL*(NCT 01									
Dreyling, et al.[24] MCL*(NCT 01									
Farooqui, et al.[25,26] CLL***(NCT									
Treon, et al.[27] WM*(NCT 01614821)	II	63	18 (29)	6 (10)	0 (0)	5 (8)	1 (2)	0 (0)	0 (0)
Dimopoulos, et al.[28] WM*(NCT 02165397)	III	31	21 (68)	5 (16)	0 (0)	10 (32)	3 (10)	0 (0)	0 (0)
Bartlett, et al.[29#] FL*(NCT 01849263)	II	38		2 (5)	1 (3)			1 (3)	3 (8)
Choquet, et al.[30#] PCNSL/PVRL*(NCT 02542514)	II	18		1 (6)	0 (0)		1 (6)	0 (0)	5 (28)
Grommes, et al.[31#] PCNSL/SCNSL*(NCT 02315326)	I	20	11 (55)	6 (30)	1 (5)	2 (10)	2 (10)	0 (0)	1 (5)
Jones, et al.[32#] HCL***(NCT 01841723)	II	28		- - (25)	2 (7)		- - (18)	2 (7)	2 (7)
Noy, et al.[33] MZL*(NCT 01980628)	II	63	29 (46)	15 (24)	1 (2)	6 (10)	5 (8)	1 (2)	8 (13)
Tobinai, et al.[34] NHL*(NCT 01704963)	I	15	5 (33)	4 (27)	0 (0)	3 (20)	2 (13)	0 (0)	0 (0)
Maruyama, et al.[35] MCL*(NCT 02169180)	II	16	10 (63)	1 (6)	0 (0)				5 (31)
Iskierka, et al[36] CLL*(PALG)	IIIb	165	65 (39)		6 (4)		20 (12)		26 (16)

No. pts	Infectious events		Pneumonia		Any grade 5 event
	Any grade	grade 3-4	Any grade	grade 3-4	
1629	56%	26%	21%	13%	10%

Tillman et al Eur. J Hematol 2018

Systematic review of infectious events with the BTK inhibitor ibrutinib in the treatment of haematologic malignancies

Ibrutinib in combination therapy

Study & Disease setting (trial)	Combination therapy	Phase	Patients	Infectious Events by Grade No. (%)			Pneumonia by Grade No. (%)			All Grade V No. (%)
				ALL	3-4	5	ALL	3-4	5	
Maddocks, et al.[37] NHL***(NCT 01479842)	BR	I/Ib	48		6 (12.5)	1 (2)		2 (4)	1 (2)	2 (4)
Burger, et al.[38] CLL*** (NCT 01520519)	Rituximab	II	40	41 (100)[r]	5 (12.5)	4 (10)	20 (50)	2 (5)	4 (10)	8 (20)
Brown, et al.[39] CLL* (NCT 01292135)	BR (30), FCR (3)	Ib	33	25 (76)	8 (24)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Chanan-Khan, et al,[40] CLL* (NCT 01611090)	BR	III	289	222 (77)	137 (47)	5 (2)	47 (16)	31 (11)	1 (0)	20 (7)
Younes, et al.[41] NHL** (NCT 01569750)	R-CHOP	Ib	32	19 (59)	12 (37.5)	0 (0)	4 (12.5)	0 (0)	0 (0)	0 (0)
Christian, et al.[42] NHL*										
Bonnet, et al.[43#] NHL* (Biblos Lysa										
Pollyea, et al.[44#] CLL*										
Vij, et al.[45#] MM*										
Chari, et al.[46#] MM* (NCT 0196279										
Hajek, et al.[47#] MM* (PCYC-1139										
Jaglowski, et al.[48] CLL, PLL, Richter*(										
Amaya-Chanaga, et al[49#] CLL**										
Tresckow, et al.[50#] CLL*** (CLL2-BIG)	BO	II	58	22 (38)	4 (7)	1 (2)	4 (7)	2 (3)	0 (0)	1 (2)
Wang, et al.[51] MCL* (NCT 01880567)	Rituximab	II	50	34 (68)	6 (12)	1 (2)	2 (4)	2 (4)	0 (0)	1 (2)
Hillmen, et al.[52#] CLL*	Venetoclax	II	21		3 (14)	0 (0)		3 (14)	0 (0)	0 (0)
Ujjani, et al.[53#] FL** (NCT 01829568)	RR	I	22	- - (33)	- - (5)	0 (0)				
Davids, et al.[54#] CLL*, MCL* (NCT 02268851)	Umbralisib	I/Ib	28		1 (4)	0 (0)				1 (4)
Davids, et al.[55#] CLL** (NCT 02251548)	FCR	II	35		- - (9)	0 (0)		1 (3)	0 (0)	0 (0)
Jerkeman, et al.[56#] MCL* (NLG MCL6)	RR	II	50			1 (2)			0 (0)	1 (2)
Martin, et al.[57#] MCL*	Palbociclib	I	20		2 (10)	0 (0)		1 (5)	0 (0)	0 (0)
Batlevi, et al.[58#] DLBCL*, MCL*, FL*	Buparlisib	I	13			0 (0)			0 (0)	0 (0)
Goy, et al.[59#] DLBCL*	RR	Ib/II	37			2 (5)			1 (3)	14
Wang, et al.[60#] MCL**	R-HCVAD/R-MA	II	36		3 (8)	0 (0)		0 (0)	0 (0)	0 (0)
Wilson, et al.[61#] DLBCL*	R, DA-R-EPOCH	Ib	15		- - (47)					1 (7)
Jain, et al.[62#] CLL** (NCT 02629809)	FCG	II	23		5 (22)	0 (0)		1 (4)		0 (0)
Grommes, et al.[63#] PCNSL*, SCNSL* (NCT	Methotrexate	Ib	6		0 (0)	0 (0)		0 (0)	0 (0)	0 (0)
Lionakis, et al.[64] PCNSL*** (NCT 02203526)	DA-TEDDI-R	Ib	18	28 (100)[r]	25 (100)[r]	3 (17)	11 (61)	9 (50)	2 (11)	8 (44)

No. pts	Infectious events		Pneumonia		Any grade 5 event
	Any grade	grade 3-4	Any grade	grade 3-4	
490	52%	20%	17%	8%	6%

Tillman et al Eur. J Hematol 2018

Fatal events

Organism	Cases
Aspergillosis (pulmonary and/or CNS)	14
Cryptococcus	1
Cytomegalovirus	1
Histoplasmosis	1
Listeria	1
Mycobacterium avium intracellulare, pulmonary	1
Mycobacterium tuberculosis, CNS	1
Nocardiosis	1
Pneumocystis jirovecii pneumonia	6
Varicella zoster	15

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Serious infections in patients receiving ibrutinib for treatment of lymphoid malignancies

Varughese T el al. Clin Infect Dis 2018

Patient Characteristics (n=378 patients)	All patients (n=378)	CLL (n=165)	NHL (n=213)	p-value
Ibrutinib monotherapy	316 (84%)	157 (95%)	159 (75%)	<0.0001

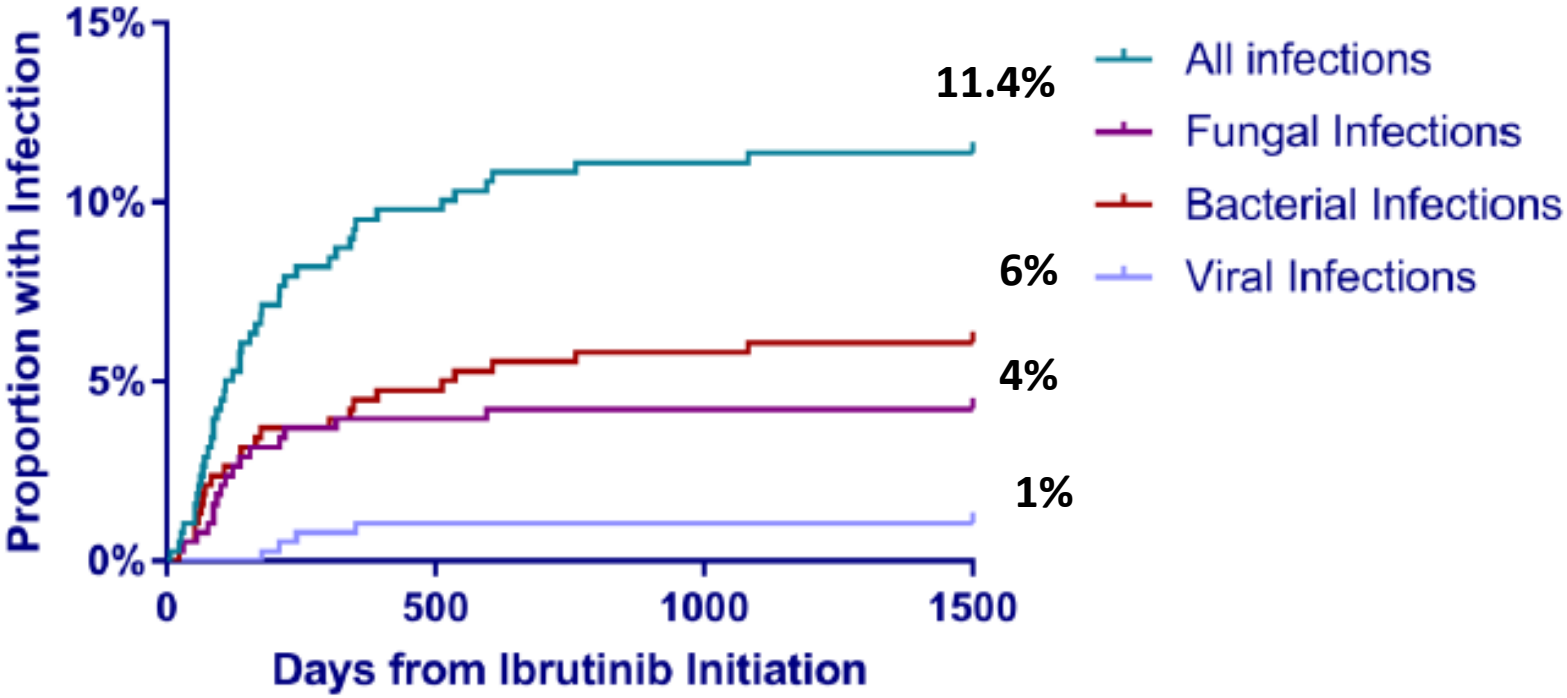


Table 4: Infection risk analysis - patients with IFI versus patients without IFI

Parameter	Univariate comparison	
	OR (95% CI)	p-value
Age	1.002 (0.96 - 1.05)	0.94
Female sex	0.46 (0.13 - 1.58)	0.21
Underlying malignancy CLL	1.78 (0.66 - 4.83)	0.26
Ibrutinib daily dose	1.00 (0.996 - 1.004)	0.92
Prior treatment regimens >=3	3.35 (1.22 - 9.21)	**0.019**
Concurrent antitumor agents other than ibrutinib	2.33 (0.74 – 7.31)	0.15
Prior fludarabine	1.34 (0.29 – 5.41)	0.66
Neutropenia	2.92 (0.71 - 12.09)	0.14
Lymphopenia	3.36 (0.98 - 11.55)	0.054
Corticosteroid use	4.29 (1.40 - 13.18)	**0.011**
Antimicrobial prophylaxis		
PJP prophylaxis	1.63 (0.47 - 5.66)	0.44
Antifungal prophylaxis	2.12 (0.28 - 15.91)	0.46

Varughese et al CID 2018

Table 2. Frequency of Reported IFIs in Clinical Studies of Ibrutinib Treatment for Hematological Cancer

Type and Status of Cancer	Type of IFI (No. of Cases)	Frequency of IFI, %	Patients, No.	Median Follow-up, mo	Study Timing, Month/ Year	Reference
Relapsed CLL	Cryptococcosis (1)	1.2	85	20.9	5/2010–2/2013	Byrd et al [11]
Relapsed CLL/SLL	IA (2)	0.5	391	9.4	6/2012–11/2013	Byrd et al [10]
Relapsed WM	IA (1)	3.2	31	18.1	8/2014–2/2015	Dimopoulos et al [9]
Relapsed MCL	Cryptococcosis (1), PJP (1), histoplasmosis (1)	2.7	111	26.7	2/2011–1/2014	Wang et al [7]
CLL	1 multifocal IA, 1 fungal pneumonia	1.6	127	13	7/2010–5/2014	Jain et al [6]
Relapsed/refractory DLBCL	None	0	80	11.5	5/2012–5/2013	Wilson et al [8]
Refractory CLL/SLL	PJP (1)	0.7	145	27.6	1/2013–6/2013	O'Brien et al [21]
Refractory PCNSL[a]	IA (7), PJP (1)	44	18	15.5	8/2014–3/2016	Lionakis et al 12]
Refractory PCNSL	IA (2)	11	18	NA	9/2015–8/2016	Choquet et al [24]
Refractory PCNSL	IA (1)	5	20	NA	NA	Grommes et al [25]

Chamilos G. et al CID 2018

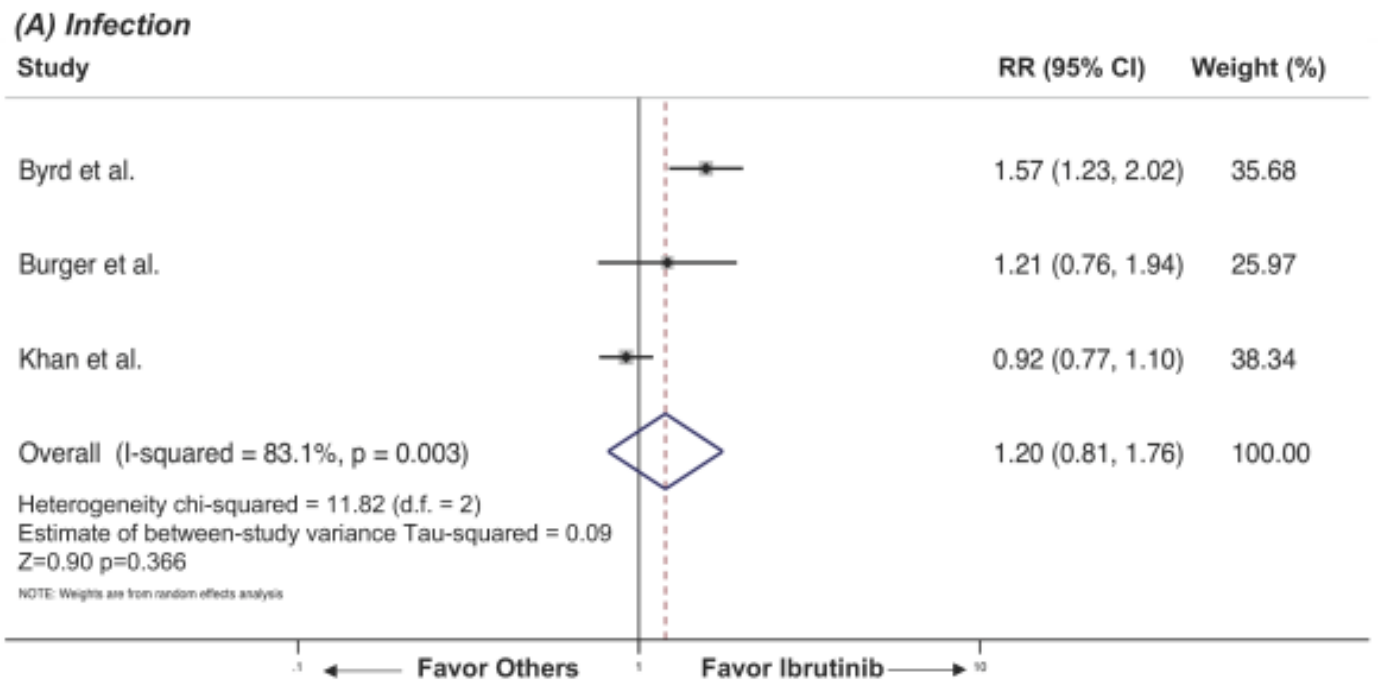
Meta-anakysis

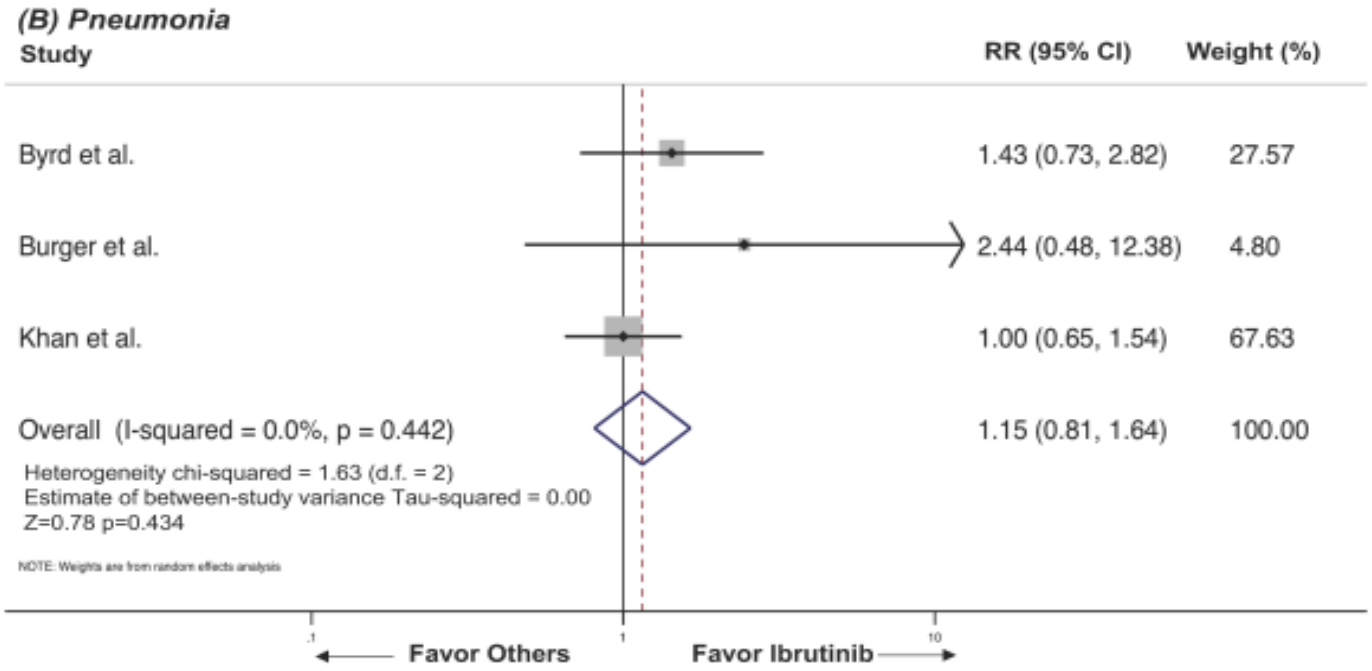
1227 pazienti

617 ibrutinib

610 control arm

Ibrutinib vs ofatumumab
Ibrutinib vs Chloramb.
Ibrutinib vs placebo





Ball S et al
Eur J Hematol 2018

blood®
Brief Report

A retrospective multicenter survey has been carried out by the FILO CLL group aimed at identifying cases of IFI in patients receiving ibrutinib alone or in combination. Between 2013-2017, **33 cases of IFI** from 16 French centers were identified.

IA accounted for the majority of IFI (27/33), including 11 cases (**40.7%**) with **CNS localizations.** The authors also observed 4 cases of disseminated cryptococcosis, 1 mucormycosis, 1 pneumocystis pneumonia.

Median time between ibrutinib initiation and IFI diagnosis was 3 months (range 1-30). **20 cases occurring ≤ 3 months.**

In 18/33 cases, other conditions that could have contributed to decreased antifungal responses, such as corticosteroids, neutropenia or combined immunochemotherapy, were present.

Infection rates in clinical trials of IDELALISIB

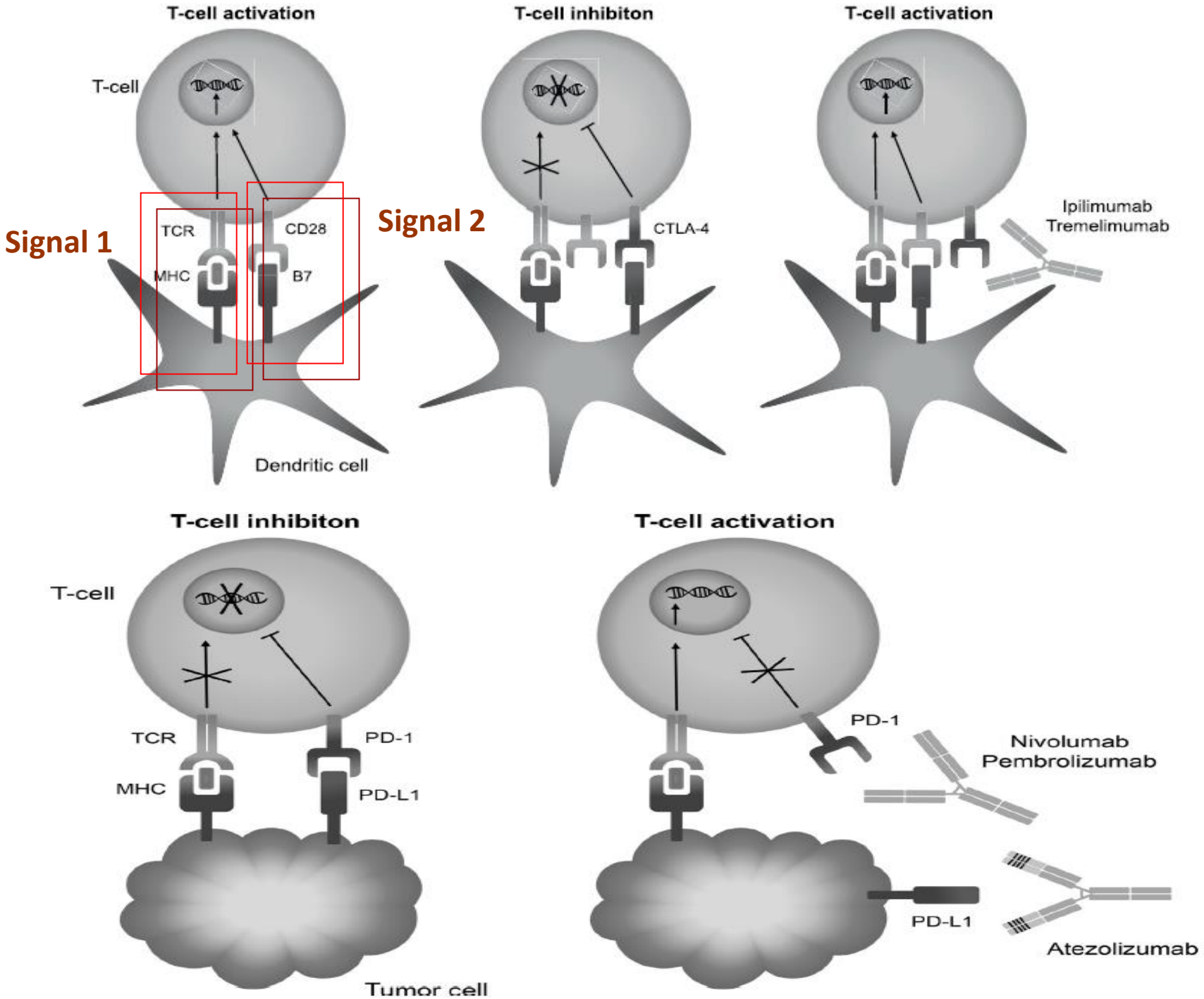
reference	disease	treatment	Infections		
			sepsis	PJP	CMV
Furman 2014	CLL Rel/refr	IDE-Ritux vs Placebo-Ritux	4% 3%	3% 1%	- -
Jones 2017	CLL Rel/refr	IDE-Ofatum vs Ofatum	7% 1%	5% 1%	2% 0%
Zelenetz 2017	CLL Rel/refr	IDE-Benda-Ritux vs Benda-Ritux	- -	2% 0%	6% 1%
Brown 2014	CLL Rel/refr	IDE monotherapy	-	4%	2%
O'Brien 2015	CLL Rel/refr	IDE-Ritux	-	-	2%

Aspergillosi Invasiva & Idelalisib		
Lafon-Desmurs B.	Médecine et maladies infectieuses 47, 2017	A case of a patient suffering from CLL treated by idelalisib for four months who developed two severe infectious complications: disseminated aspergillosis with pulmonary involvement and tongue localization, followed by pulmonary tuberculosis
Lampson	ASH 2017	A case of Aspergillus pneumonia (Phase 2 Trial Evaluating Idelalisib Plus Ofatumumab in Patients with Previously Untreated Chronic Lymphocytic Leukemia)
Visentin A.	Hematol. Oncol. 2016	A case of IA in a patient receiving idelalisib

Infection rates in clinical trials of VENETOCLAX in CLL

Trial	Patients	Infection (all grades)	Infection (grade 3 and above)
Roberts et al. (2016)	Relapse/Refractory Median 3 lines of therapy	Febrile neutropenia 6% Pneumonia 4%	All infections: 17% Exposure adjusted: 1.4 per 100 patient-months
Stilgenbauer et al. (2016)	Relapse/Refractory Median 2 lines of therapy	All infections: 72%	All infections: 20%
Seymour et al. (2017)	Relapse/Refractory Median 2 lines of therapy	All infections: 81% URTI: 57% Pneumonia: 16% Exposure adjusted: 0.7 per 100 patient-months	All infections: 16% Febrile neutropenia: 12%
Jones et al. (2018)	Relapse/Refractory Medican 4 lines of therapy Previous ibrutinib therapy	URTI: 26%	Febrile neutropenia: 13% Pneumonia: 6%
Coutre et al. (2018)	Relapse/Refractory Median 3 lines of therapy Previous idelalisib therapy	URTI: 39%	Pneumonia: 6%

Checkpoint Inhibitors


T-cell activation
T-cell
TCR
CD28
MHC
B7
Dendritic cell
Signal 1
Signal 2
T-cell inhibiton
CTLA-4
T-cell activation
Ipilimumab
Tremelimumab
T-cell inhibiton
T-cell
TCR
PD-1
MHC
PD-L1
Tumor cell
T-cell activation
PD-1
Nivolumab
Pembrolizumab
PD-L1
Atezolizumab

Checkpoint inhibitors and aspergillosis in AML: the double hit hypothesis

*Naval Daver, *Dimitrios P Kontoyiannis*
Department of Leukemia, Division of Medical Oncology (ND) and Department of Infectious Diseases, Infection Control and Employee Health (DPK), The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
dkontoyi@mdanderson.org

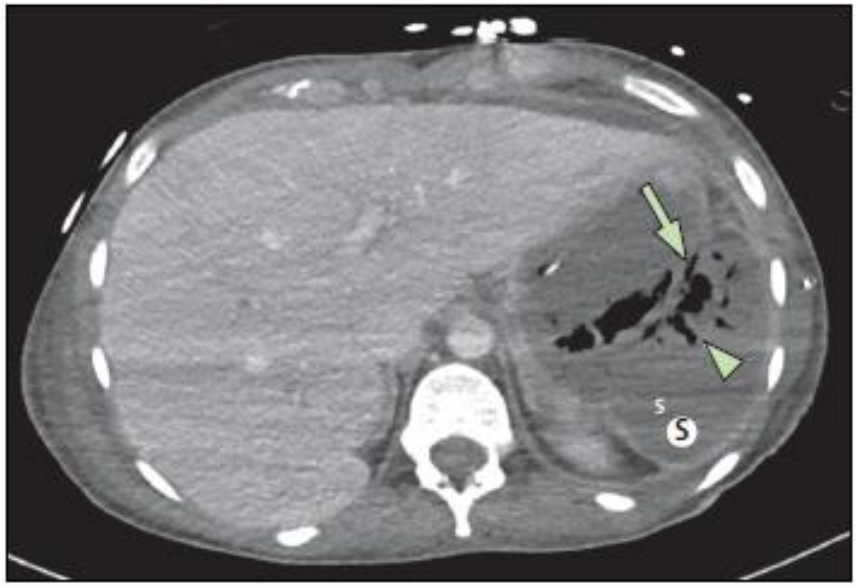
Lancet Oncol 2017

Nivolumab plus interferon-γ in the treatment of intractable mucormycosis

David Grimaldi, Olivier Pradier, Richard S Hotchkiss, *Jean-Louis Vincent

Lancet Infect 2017

L-AmB + posaconazolo
Linfocitopenia e aumentata espressione di PD-1
IFN-gamma + Nivolumab: risoluzione della linfocitopenia
RC mucormicosi



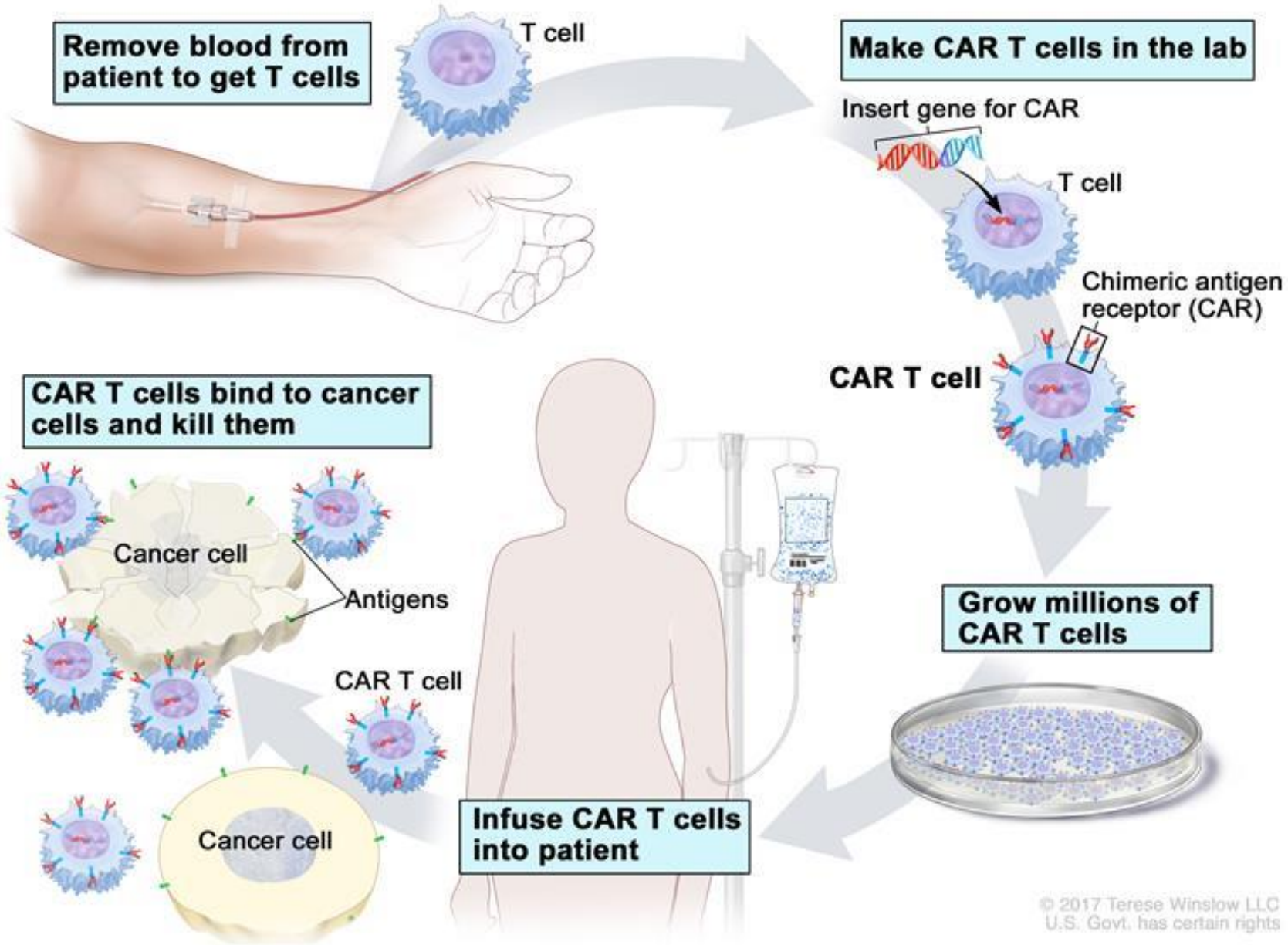
The NEW ENGLAND JOURNAL of MEDICINE

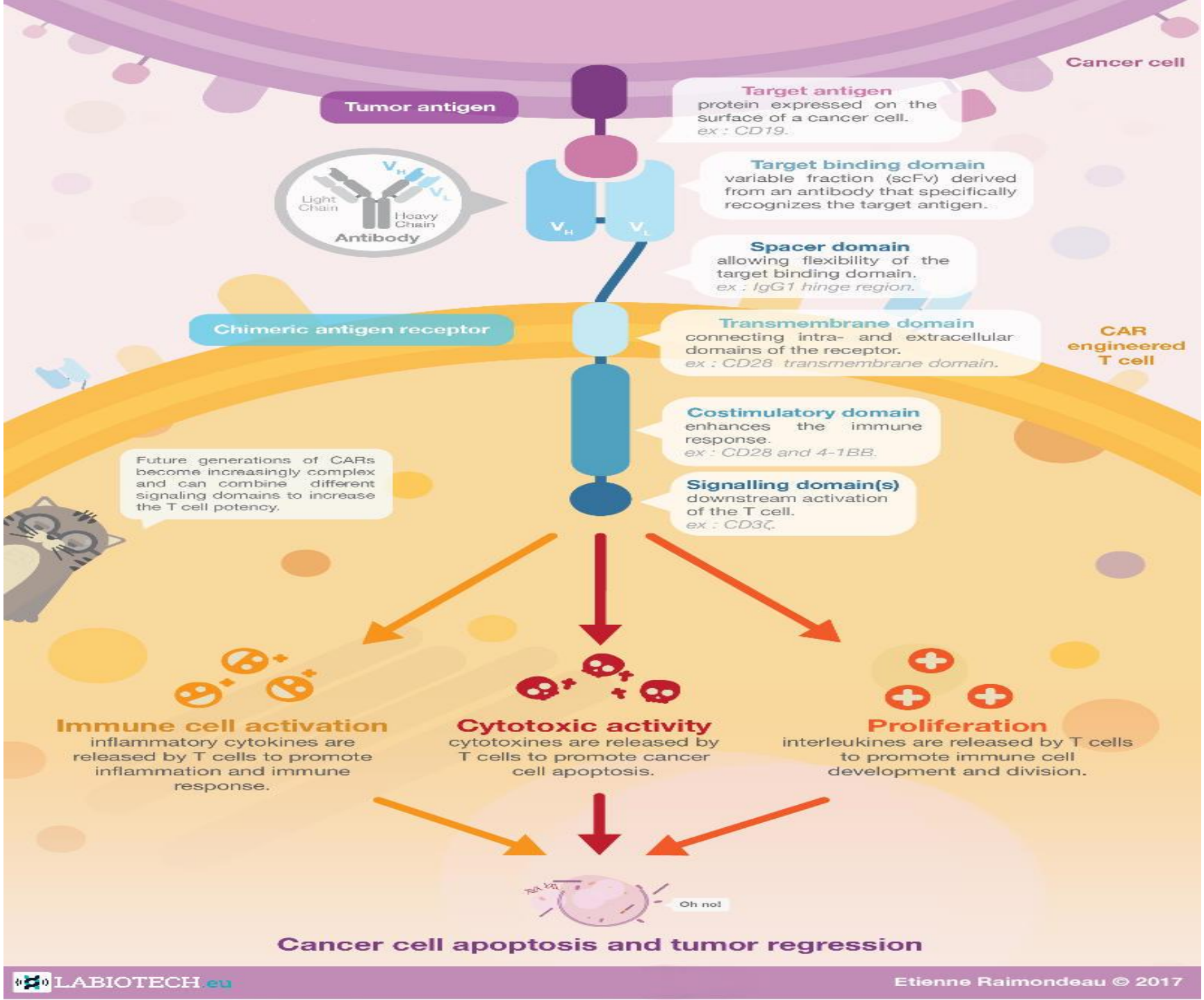
ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

	Blinatumomab N=267	Chemotherapy group N=109
infection	34%	52%
IFI	1.5%	3%

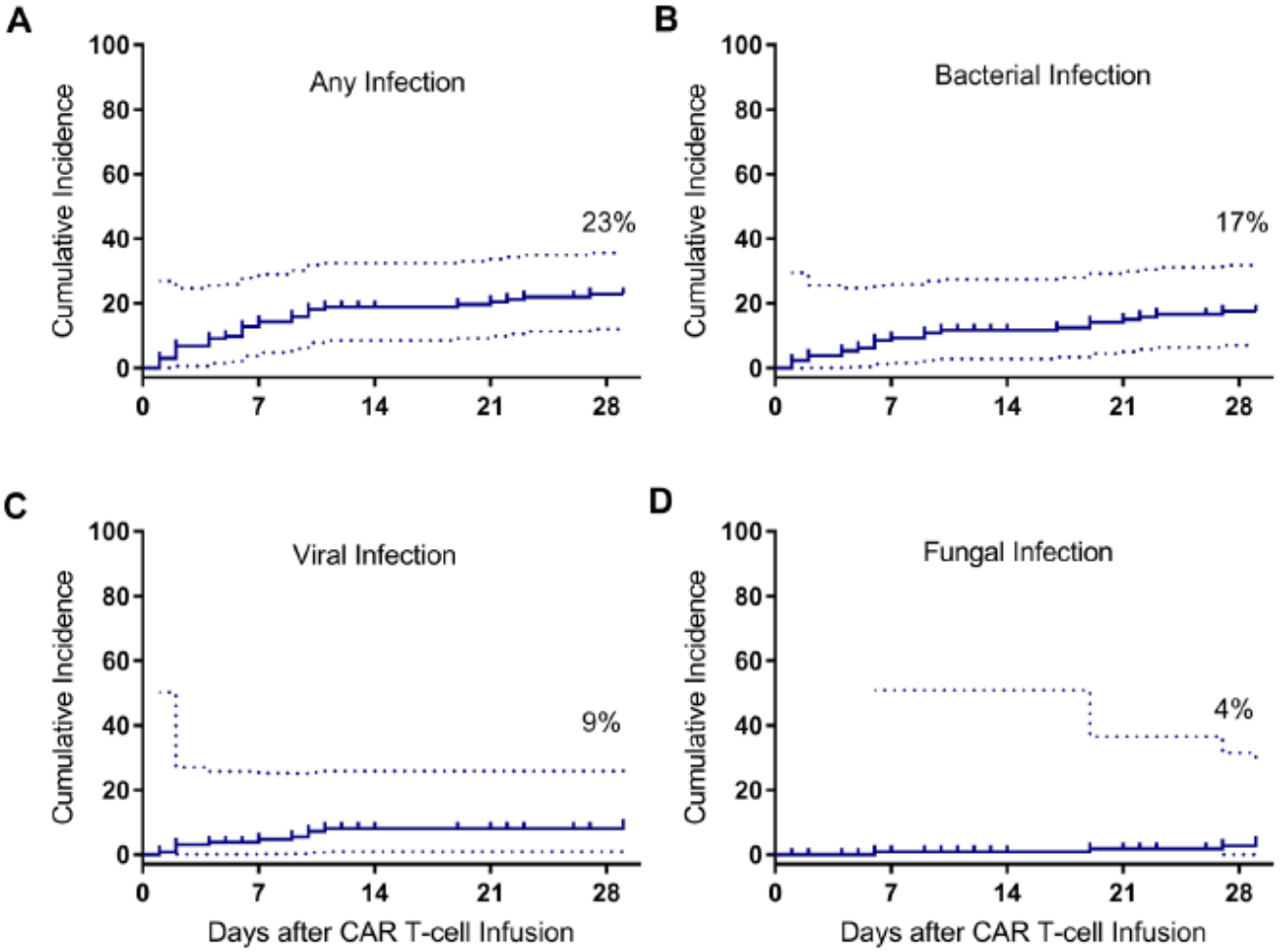
CAR T-cell Therapy





Infectious complications of CD19-targeted CAR-modified T cell immunotherapy

No. Patients 133: 47 ALL, 24 CLL, 62 NHL



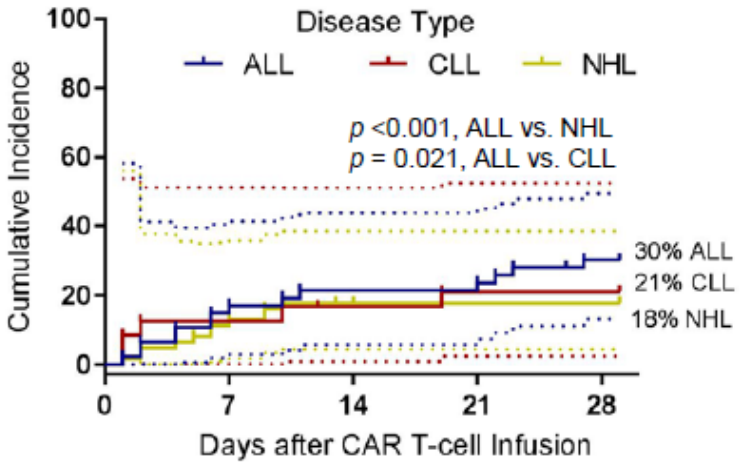
Infezioni d 29-90

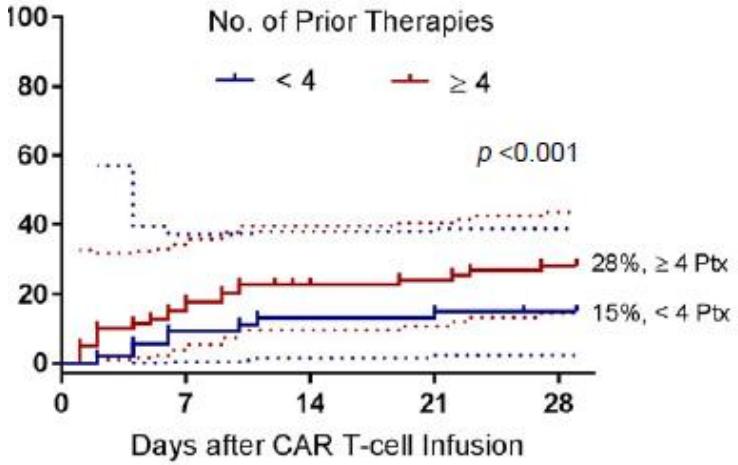
23 in 17/119 (14%)

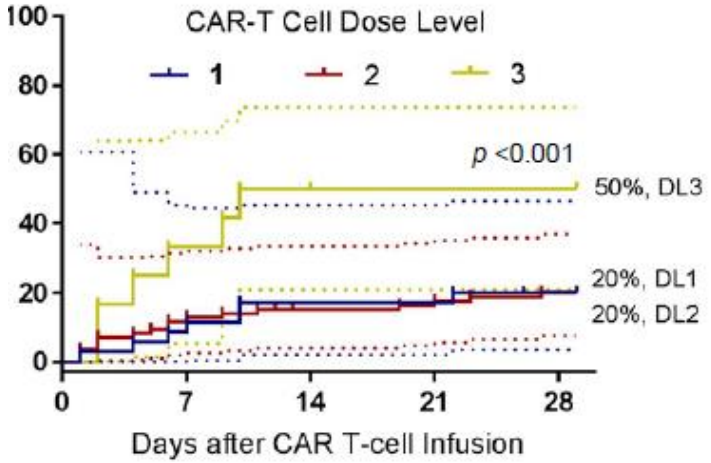
Virali 13
Batteriche 8
IFI 2

Hill et al Blood 2018

Infectious complications of CD19-targeted CAR-modified T cell immunotherapy







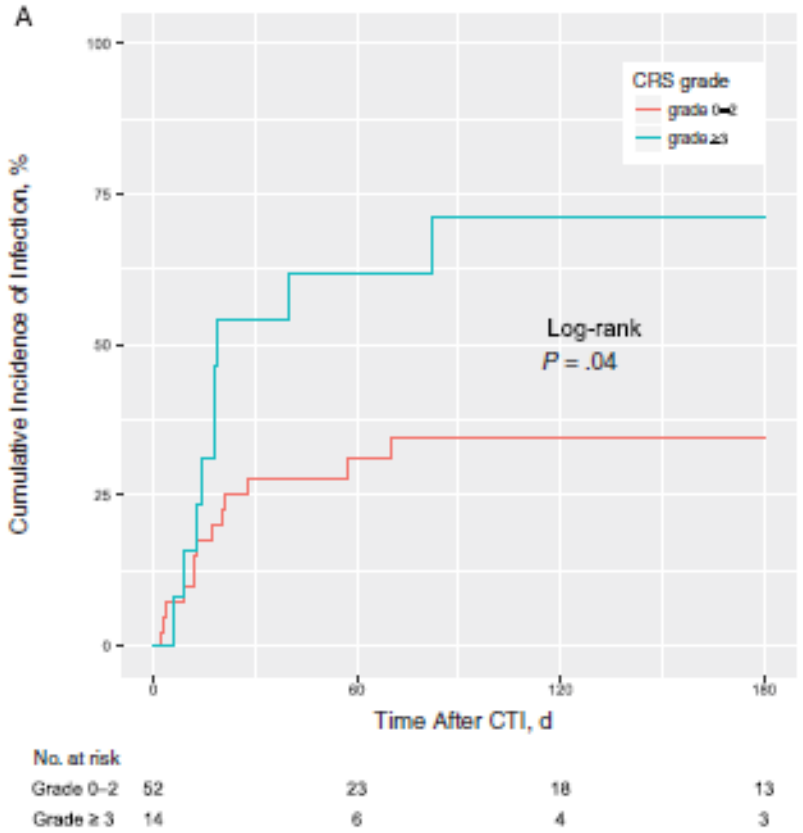
Hill et al Blood 2018

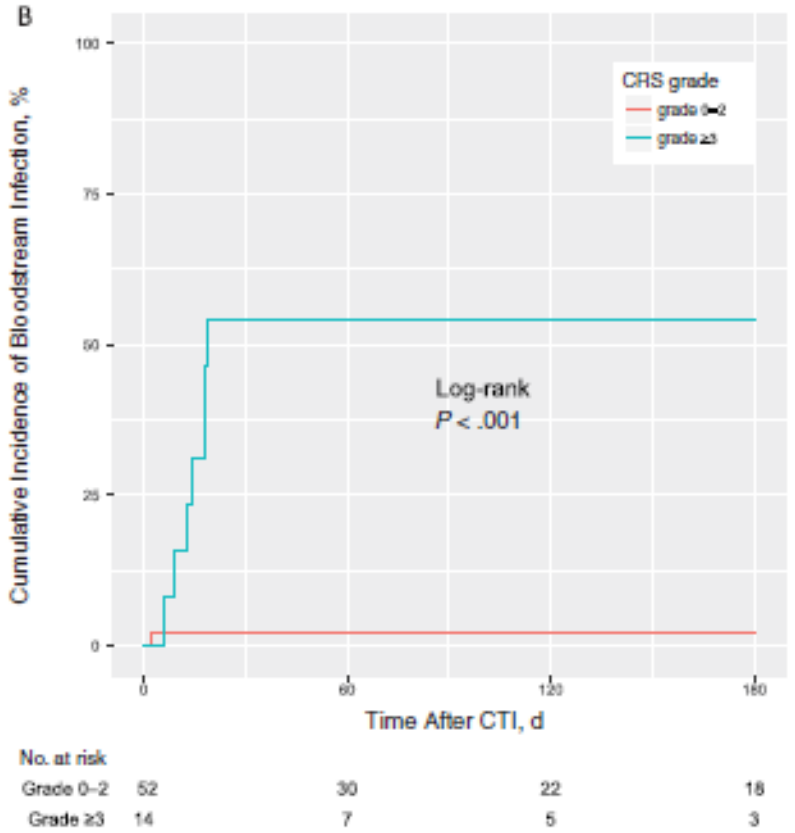
fattori associati a rischio di infezione:

ALL, ≥ 4 prior therapies, 2x10^7/Kg CAR-T cells, CRS severity

Cytokine Release Syndrome Grade as a Predictive Marker for Infections in Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Treated With Chimeric Antigen Receptor T Cells

Jae H. Park,[1,2,3,a] F. Andres Romero,[4,a] Ying Taur,[3,4] Michel Sadelain,[3,5,6] Renier J. Brentjens,[1,2,3] Tobias M. Hohl,[3,4] and Susan K. Seo[3,4]





CID 2018

CD19-directed CAR T-cell therapy in adults with B-ALL

Ref	Population	CRS	Results	Relevant infections
Turtle *J Clin Invest 2016*	30 patients med age 40 y Ref/Ref ALL	NR	93% CR	NR
Brudno *JCO 2016*	**ALL, n=5** CLL, n=5 DLBCL, n=5 MCL, n=5	NR	4/5 CR	**Febrile Neut.3; Colitis, 1** Febrile Neut.2; pneumonia 1 Febrile Neut.1 None
Pan *Leukemia 2017*	Tot 51 49 R/R ALL 9 MRD	NR	90% CR 100% CR 27/45 alloHSCT	**Sepsi 1**
Cao *Am J Hemat 2018*	Tot 18 10 ped 8 adult	Gr2-4: n=6 Toci: n=6	6-mos OS 66%	NR
Maude *NEJM 2014*	Tot 30 R/R ALL Ped 25; adult 5	27% severe	90% CR 6-mos EFS 67%	NR
Park *NEJM 2018*	53 Rel ALL Med age 44	26% severe	83% CR	NR

Late Effects of CD19-Targeted CAR-T Cell Therapy

Ana Cordeiro, Evandro D Bezerra, Joshua Aiden Hill, Cameron J. Turtle, David G. Maloney and Merav Bar

No. patients	59
Median age	60 (34-73)
Diagnosis	
NHL	42 (71%)
CLL	17 (29%)
Prior lines of treatment	4 (1-8)
Prior AUTO HSCT	23 (39%)
Prior ALLO HSCT	9 (15%)
One CAR-T cell infusion	35 (59%)
Two CAR-T cell infusion	22 (37%)
Three CAR-T cell infusion	2 (3%)

Late Effects of CD19-Targeted CAR-T Cell Therapy

Ana Cordeiro, Evandro D Bezerra, Joshua Aiden Hill, Cameron J. Turtle, David G. Maloney and Merav Bar

No. patients	59
CRS gr I-II	38 (64%)
CRS gr III	4 (7%)
Acute neurotoxicity	20 (34%)
Overall rate of infections	52%
Microbiologically proven infections	25%
Hospital admission due to infections	46%
ICU admission	15%
Infection-related death	2 (3%)

ASH 2018


L’oratore e’ colui che non ha idee
ma le esprime bene
Grazie