Journées de l'innovation en Biologie

Innovations thérapeutiques dans les lymphomes

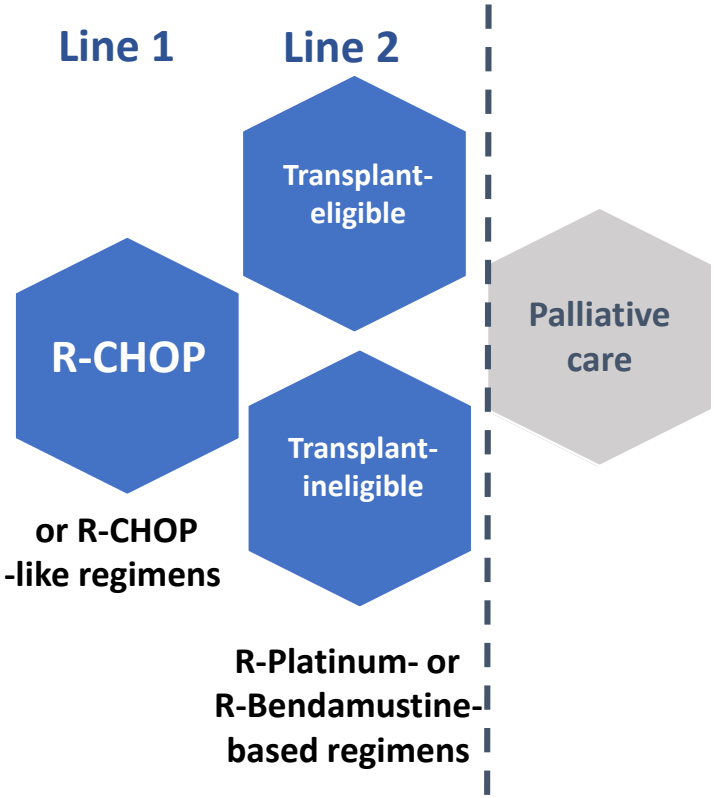
Catherine Thieblemont
Professor of Medicine, Hematology –Head of Lymphoma Department
Saint-Louis Hospital, Paris University, Paris

December,1rst 2021

Standard treatment in aggressive large B-cell lymphomas

Université de Paris

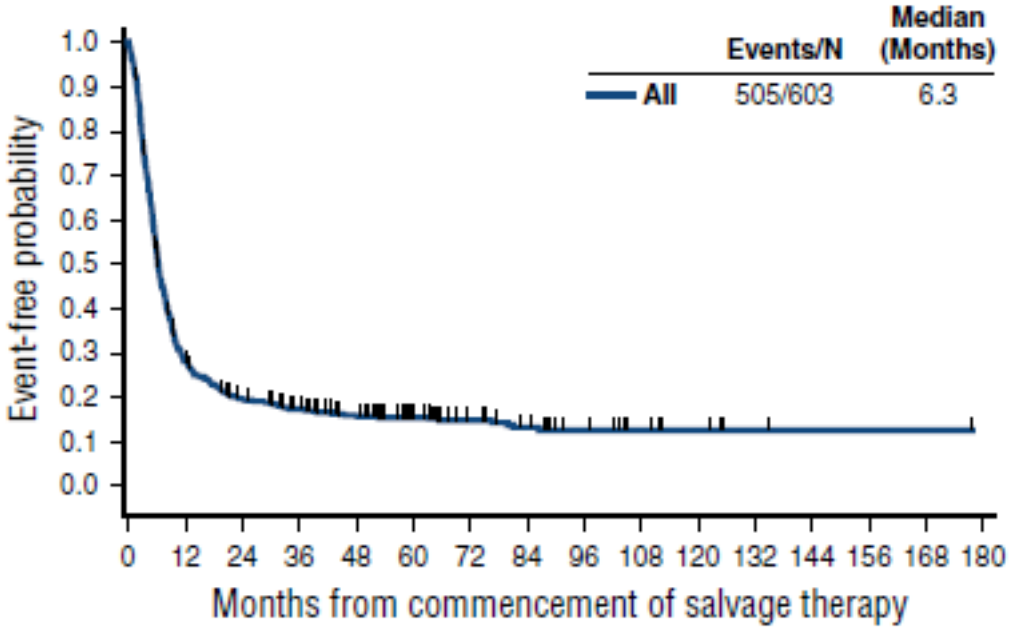
Before CAR T-cells era



Salvage after 1rst line

SCHOLAR-1

Median **OS**: 6.3 months (95% CI 5.9-7.0)



- ORR : 26%
- CR: 7%
- mOS: 6.3 mo

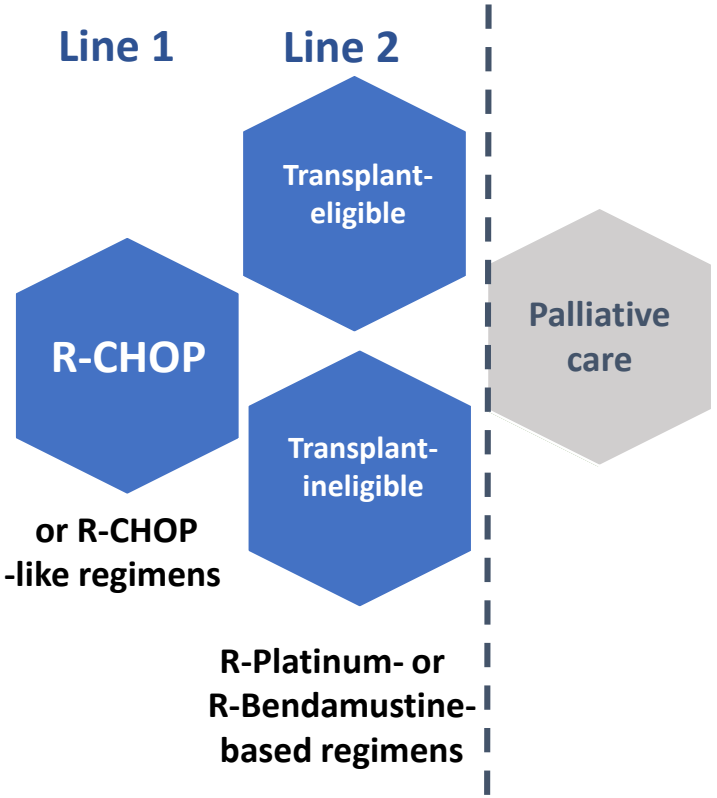
Key subgroups	Median OS
Relapsed > 12mo post-ASCT	6,2 mo
Primary refractory	7,1 mo
Refractory 2L+	6,1 mo

Crump M et al. Blood. 2017; 130: 1800-1808.

Relapsed/refractory lymphomas

Université de Paris

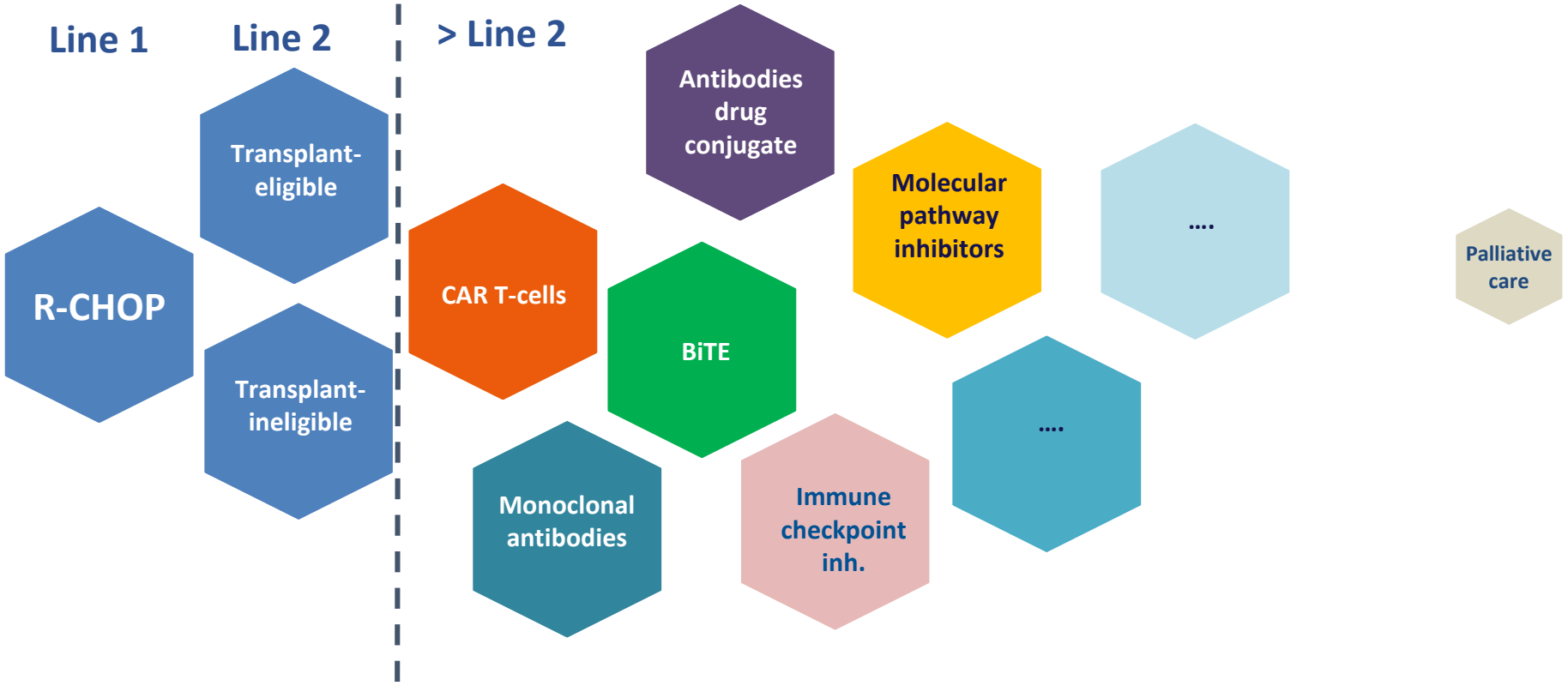
Before 2018



a high medical need

Multiple therapeutic innovations

First approval CAR T-cells : 2018



Thieblemont C. EHA 2021; Education Session on "**Refractory DLBCL**"

Chimeric antigen receptor (CAR) T-cell and Bispecific T-cell engager (BiTE) are

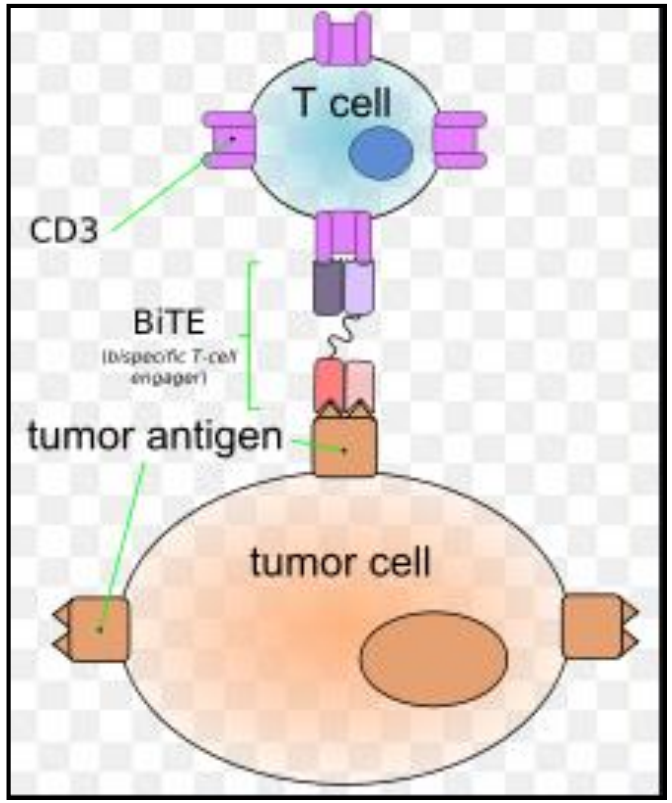
- Very promising drugs in patients with relapsed/refractory hematological malignancies
- Both are using the immune system to better target tumor cells
- But they are differences in how they are created and their mechanisms of action

Université de Paris

Mode of action

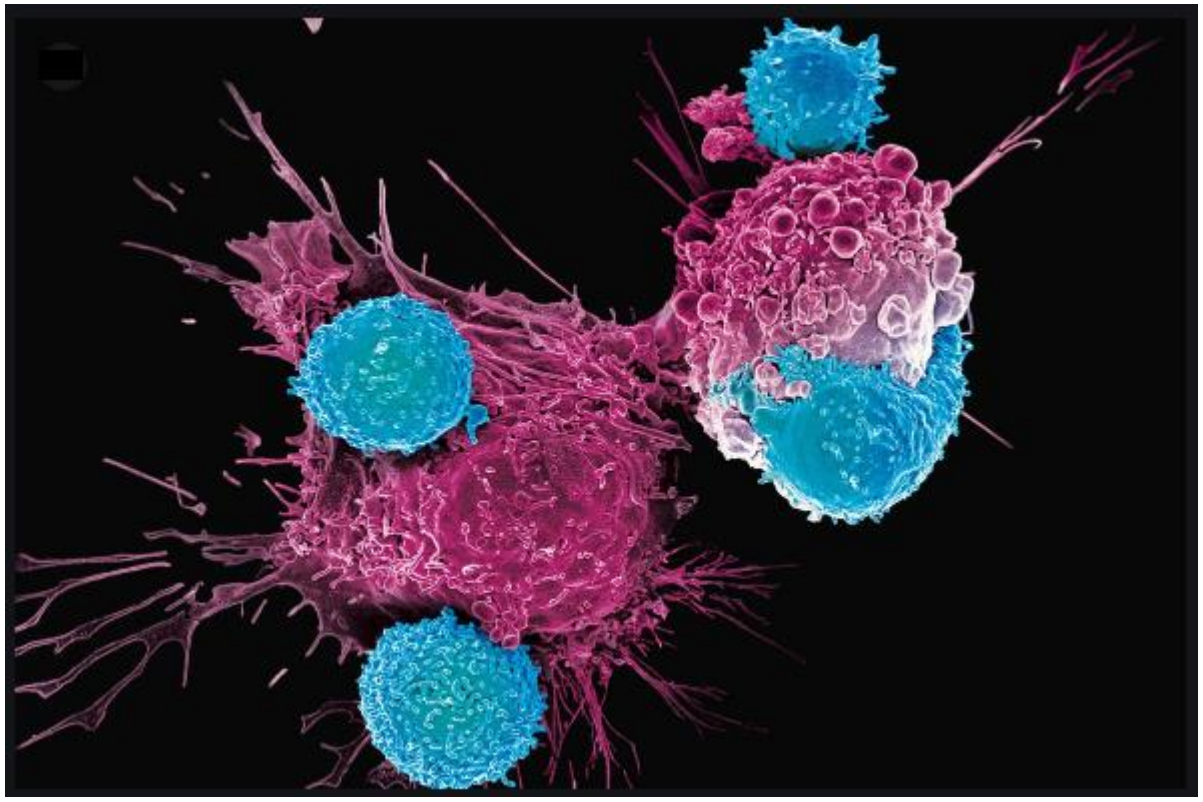
Bispecific T-cell engagers

Monoclonal antibody



- **It detects proteins to better target tumor cells and activate the immune cells**

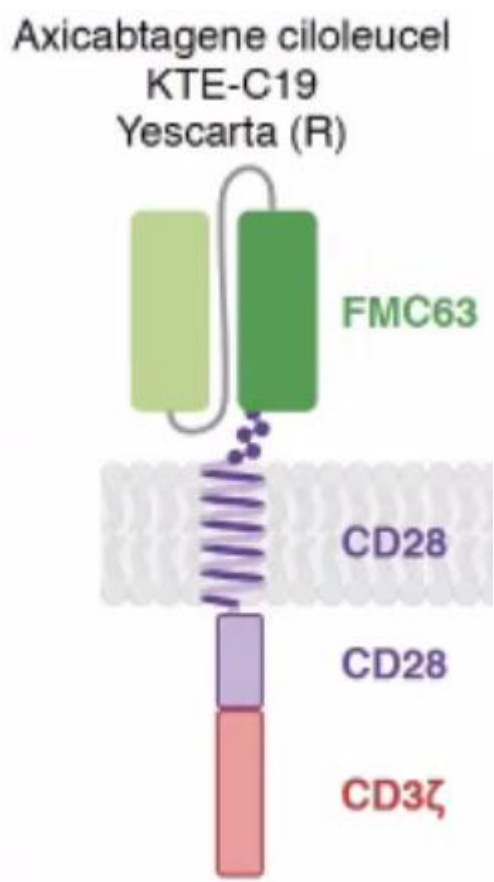
CAR T-cells are a living drugs



- **Our own immunity becomes the drug**

Anti-CD19 CAR T-cells in B-cell lymphomas

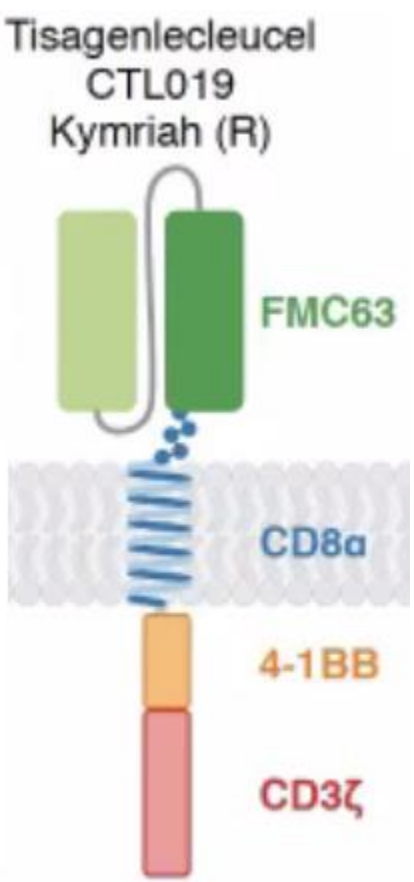
Université de Paris



CD28 – CD3

ZUMA 1 trial

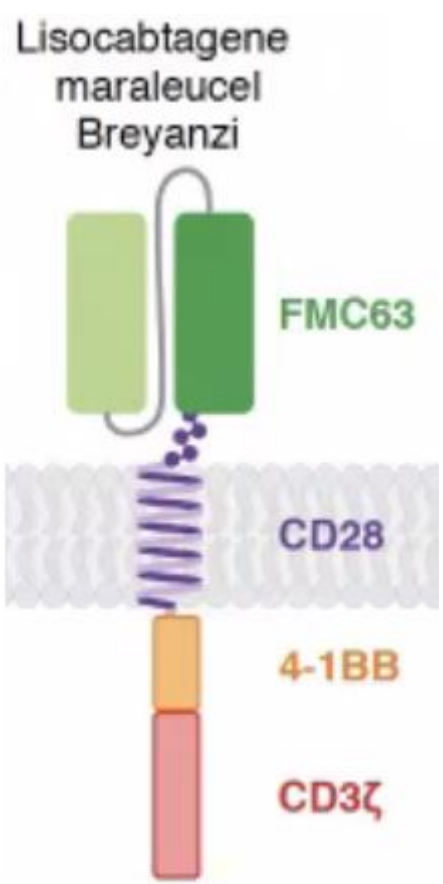
FDA approved
EMA approved



4-1BB – CD3

JULIET trial

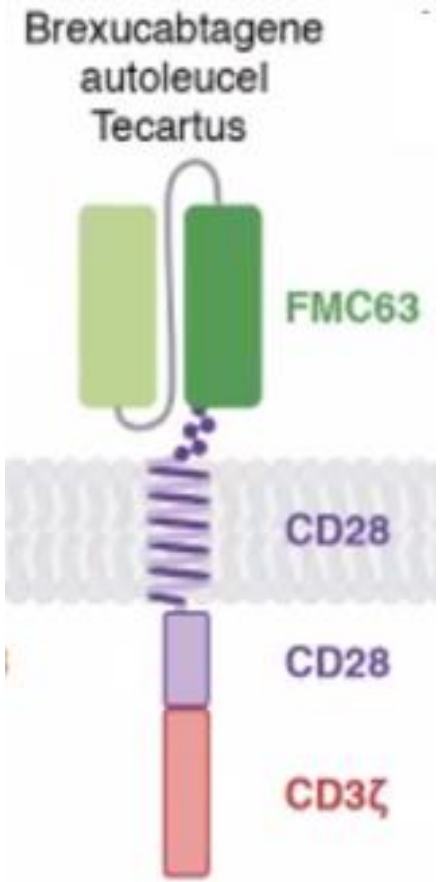
FDA approved
EMA approved



4-1BB – CD3

TRANSCEND trial

FDA approved
EMA Q2 2022



CD28 – CD3

ZUMA 2 trial

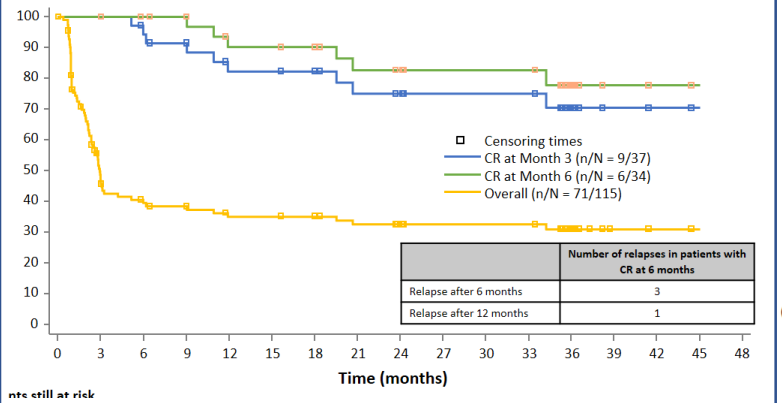
FDA approved
EMA approved

Efficacy : PFS and response rate in R/R LBCL

Université de Paris

JULIET

F-up 40,3 mo

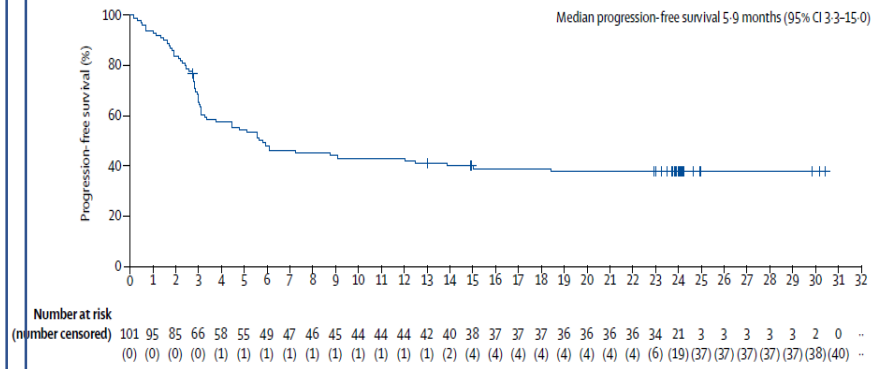


Efficacy, %	n = 115
ORR[a], %	52%
CR[a], %	40%
Median DOR (95% CI), months	
PFS at 12 months (95% CI), %	83%
OS at 12 months (95% CI), %	49%

Schuster SJ, et al. *N Engl J Med.* 2019

ZUMA-1

F-up 27,1 mo

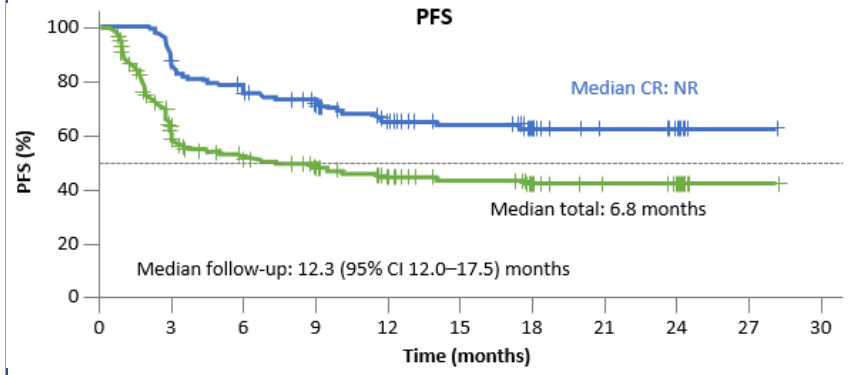


Efficacy, %	n = 101
ORR[2]	83%
CR[2]	58%
2-year PFS%	
Patients with CR at 3 months	72%
Patients with PR at 3 months	75%
Patients with SD at 3 months	22%
4-year OS[1]	44%

Locke FL, et al. Lancet Oncol. 2018

TRANSCEND-001

F-up 17,5 mo



Efficacy, %[1]	n = 256
ORR	73%
CR	53%
2-year PFS	42%
2-year OS	45%

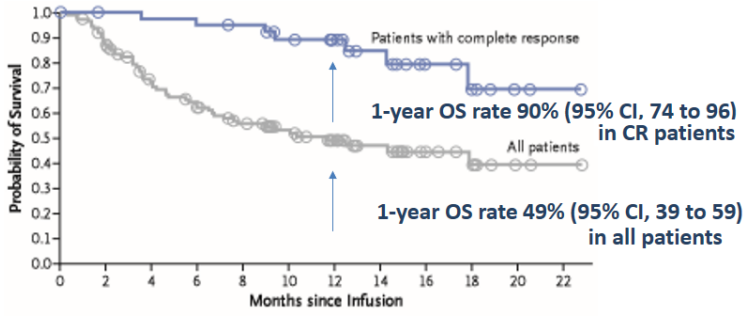
Abramson JS, et al. *Lancet.* 2020

Efficacy : Overall survival in R/R LBCL

Université de Paris

JULIET

F-up 40,3 mo

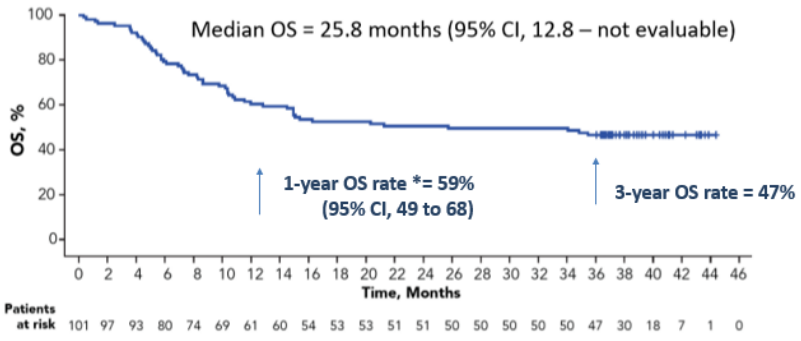


1-y OS = 49%

Schuster SJ, et al. *N Engl J Med.* 2019

ZUMA-1

F-up 39.1 mo

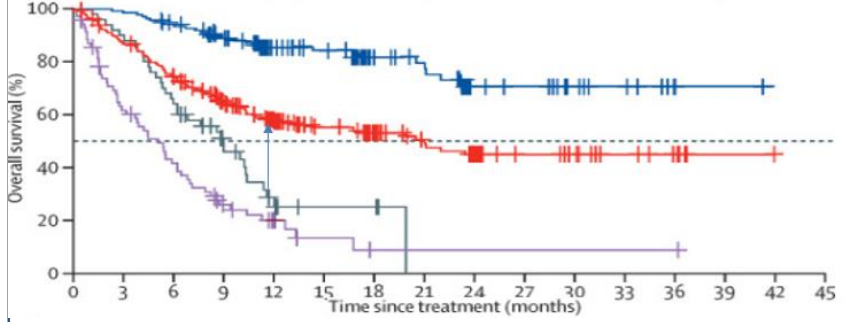


1-y OS = 59%

Locke FL, et al. Lancet Oncol. 2018

TRANSCEND-001

F-up 17.5 mo



1-y OS = 59%

Abramson JS, et al. *Lancet.* 2020

European real-world analyses: axi-cel and tisa-cel

Université de Paris

Characteristics	UK[1]		Germany[2]	France[3]	Spain	
	axi-cel (n = 183)	Tisa-cel (n = 183)	axi-cel (n = 137) tisa-cel (n = 130) (n = 267)	axi-cel (n=330) tisa-cel (n=191) (n = 521)	axi-cel[4] (n = 92)	Tisa-cel[5] (N = 75)
ORR,[a] %	76	44	62	**74,2**	87	60
CR, %	43	31	33	**53**	65	32
PFS, (months)	NR		20% (12)	**44.5% (6)**	56% (6)	32% (12)
Median OS, months	NR		13	**12.7**	12.3	10.7
Median follow-up, months	6.0		7.0	**7.4**	6.5	14.1

this is not a comparison of the same study

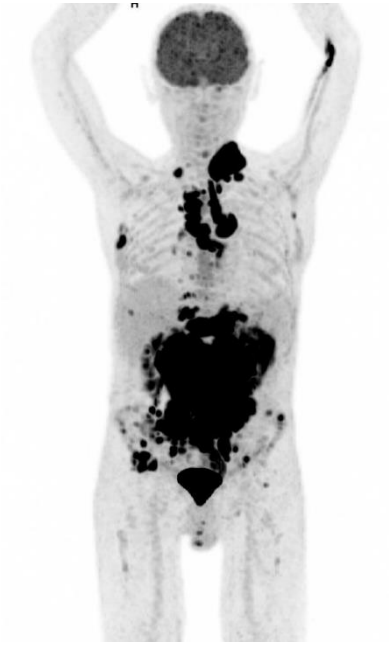
[a] ORR is objective response rate in real world from Spain using tisagenlecleucel; ORR is overall response rate in real world from Spain using axi-cel and real world from UK, France, and Germany.

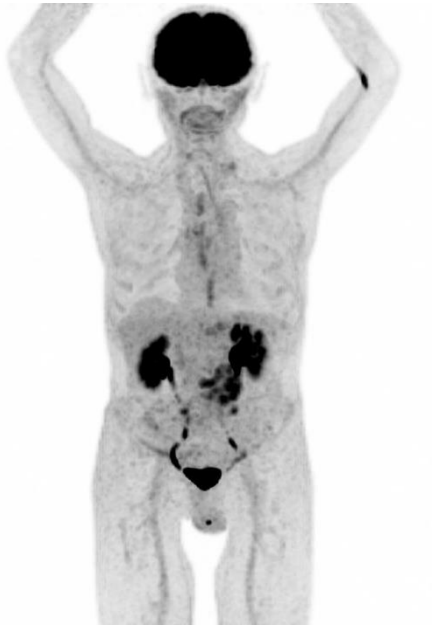
1. Kuhnl A, et al. Presented at EHA 2020;abstract S243. 2. Bethge WA, et al. Presented at EBMT 2021;abstract AA2-2. 3. Le Gouill S et al. EHA 2021 , abs 84. 4. Kwon M, et al. Presented at EBMT 2021;abstract OS3-4. 5. Iacoboni G, et al. Cancer Med. 2021;10:3214-23.

THE, male, 63 years old

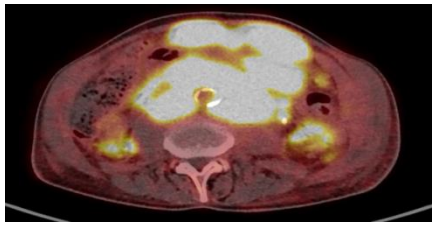
CAR T-cell

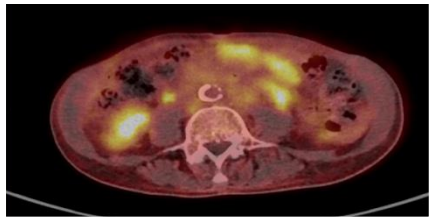
R/R DLBCL non GC subtype
3 prior lines





CURE





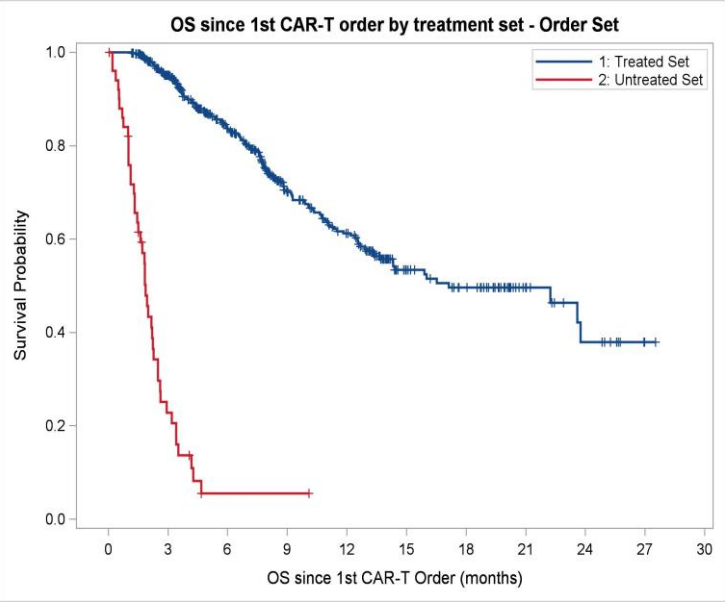
TMTV = 1200ml

Patient outcomes (all patients)

DESCAR-T

OS at 6 months

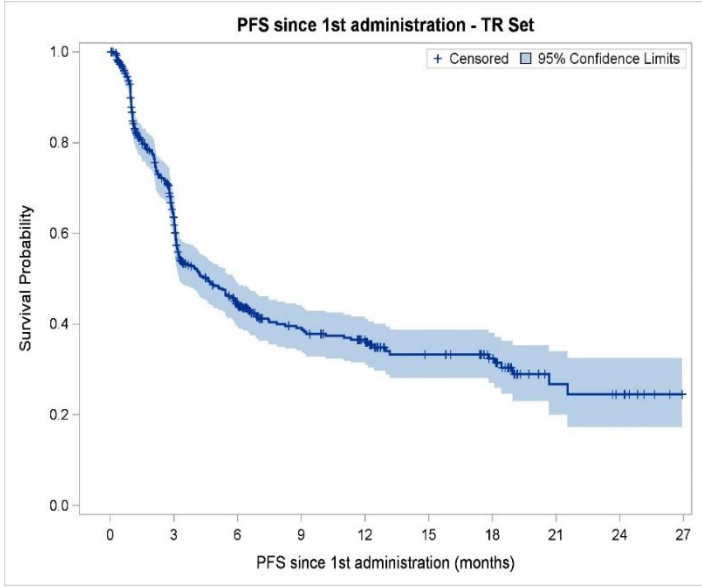
- Untreated set: 5.5% (1.1-15.6)
- Treated set: 83.7% (79.8-86.9)



Median follow-up = 8.1 months (7.8-8.6)
(calculated from CAR-T order)

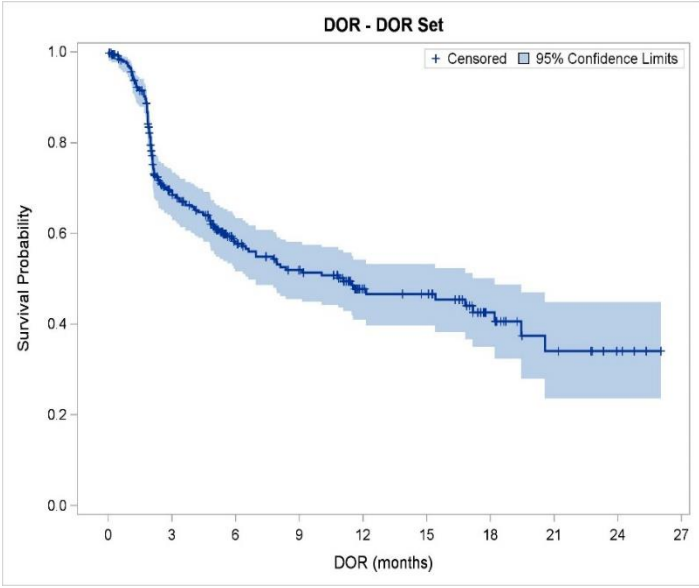
PFS at 6 months

44.5% (39.6-49.2)



DOR at 6 months

57.7% (51.6-63.3)

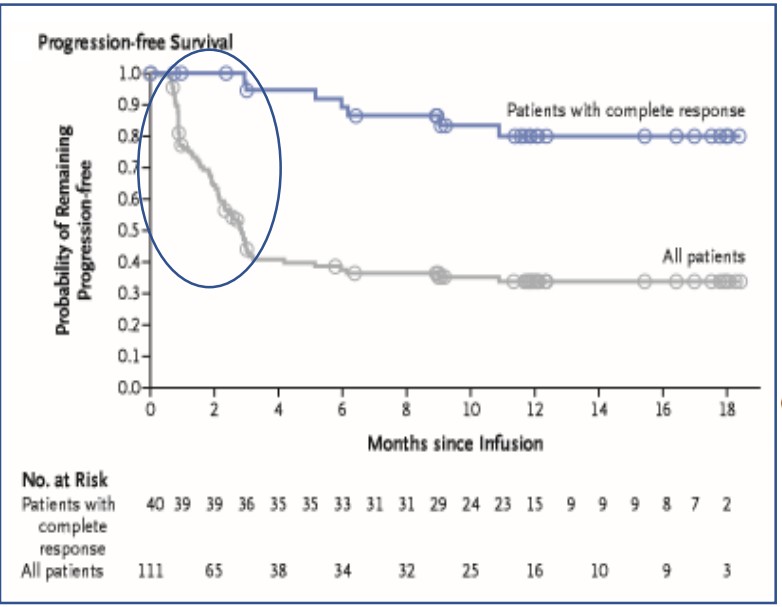


Median follow-up = 6.5 months (6.1-7.1)
(calculated from CAR-T infusion)

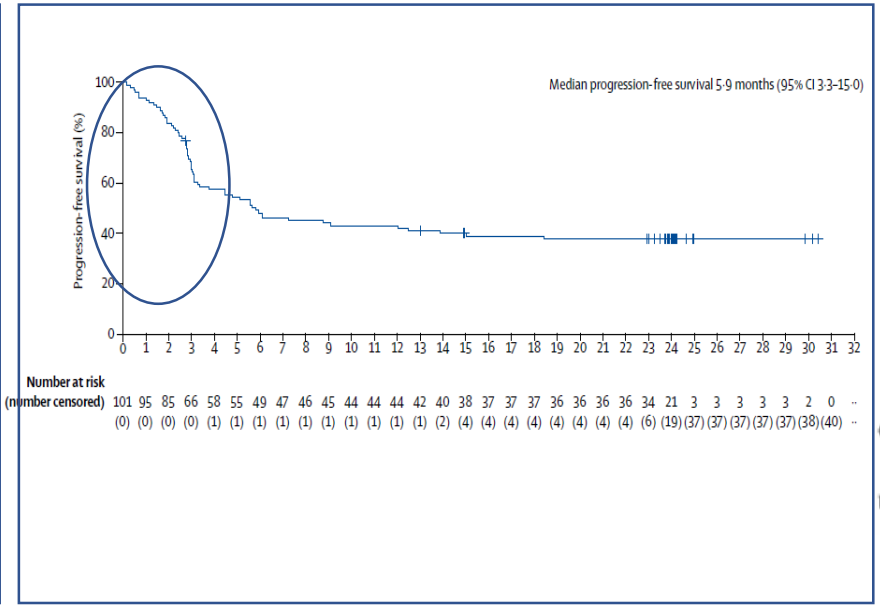
Le Gouill S, et al. Abstract S2016. EHA 2021.

Progression – free survival

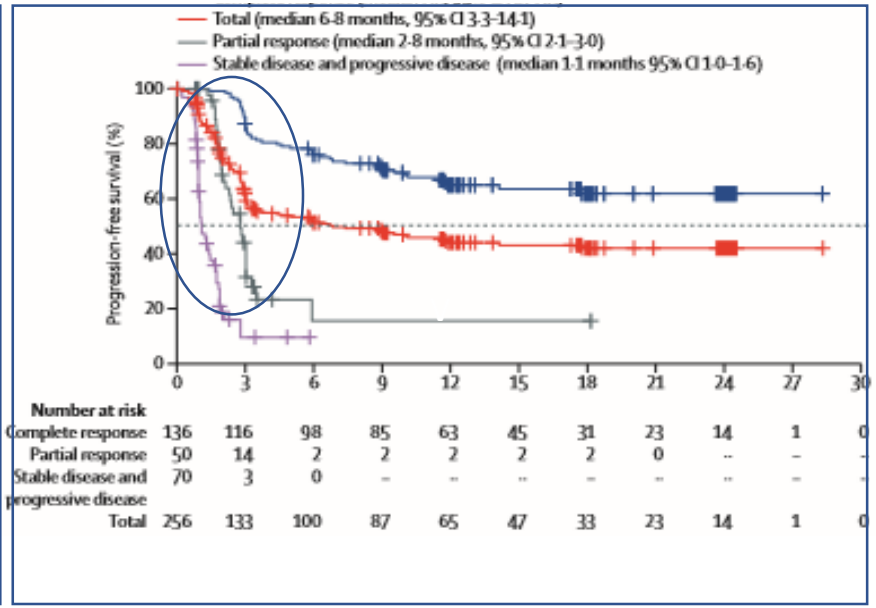
JULIET



ZUMA-1



TRANSCEND-001



Schuster SJ, et al. *N Engl J Med.* 2019

Locke FL, et al. Lancet Oncol. 2018

Abramson JS, et al. *Lancet.* 2020

Risk factors of early relapse or progression after CAR T-cell

Université de Paris

Multivariate analysis

A time of decision

Multivariate models – Parameters at the time of decision	Relapse HR (95CI)	Early relapse OR (95CI)	Death HR (95CI)
Age ≥ 65			
Lymphoma Subtypes (DLBCL; PMBL FL)			
GC/nGC			
ECOG PS ≥ 2		2.95 (1.03-8.45); p=0.044	
B symptoms	1.85 (1.01-3.41); p=0.0470		
Elevated LDH	2.04 (1.19-3.49); p=0.00933	9.61 (1.23-75.41); p=0.031	
Ann Arbor III /IV			
Number of extranodal sites ≥2			4.17 (1.99-8.72); p=0.000148
IPI high vs other			
R-IPI poor vs other			

A time of lymphodepletion

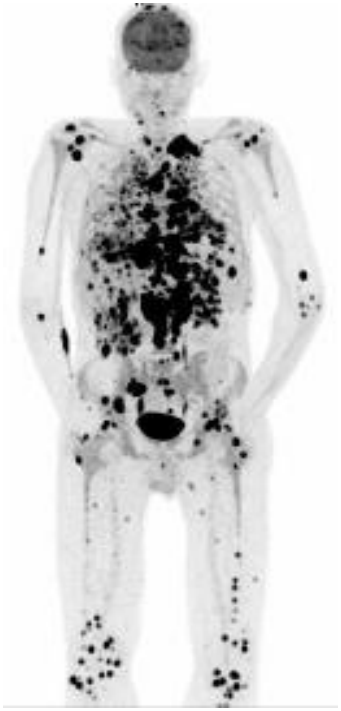
Multivariate models – Parameters at the time of treatment	Relapse HR (95CI)	Early relapse OR (95CI)	Death HR (95CI)
Age >65			
Sex M			
ECOG PS			
Ann Arbor III /IV			
Number of extranodal sites ≥2	2.50 (1.44-4.35); p=0.00111	4.67 (1.55-14.11); p=0.0063	3.61 (1.55-8.38); p=0.00283
IPI High vs other			
R-IPI poor vs other			
Progressive disease at infusion			
High Brigding therapy			
Elevated LDH			
CRP	1.12 (1.07-1.17); p<0.0001	1.15 (1.03-1.29); p=0.016	1.12 (1.06-1.17); p<0.0001
Ferritin			
Albumin			
Lymphocytes			
Bulky mass > 5.cm			
TMTV 41 > 80.42	2.18 (1.23-3.89); p=0.00794	4.35 (1.32-14.37); p=0.016	3.41 (1.41-8.26); p=0.00651

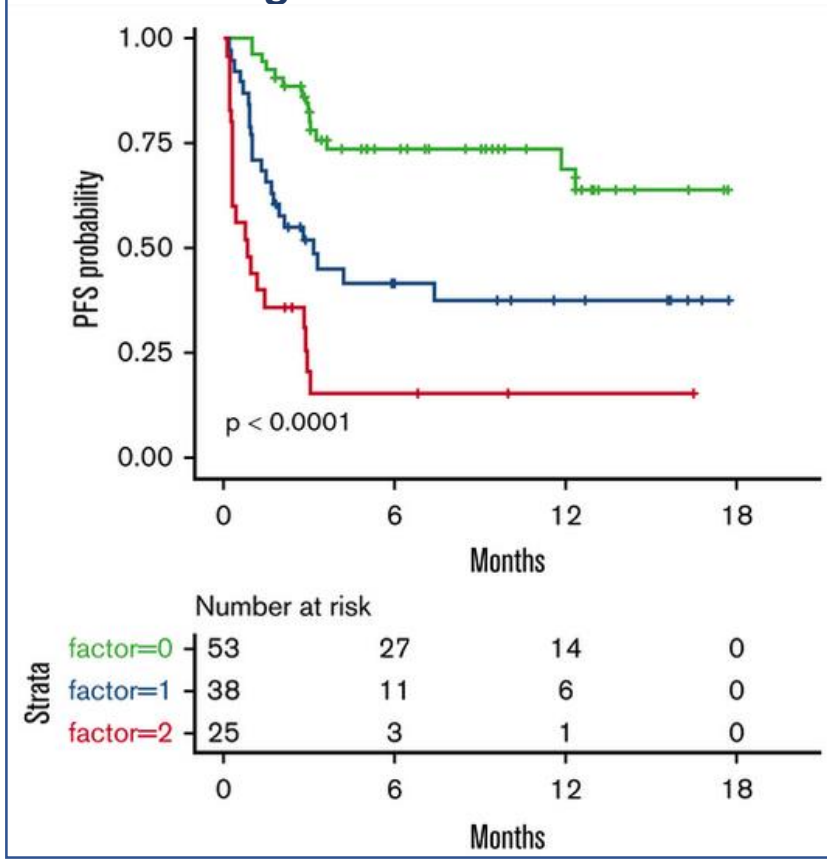
Vercellino & Di Blasi et al . Blood Adv 2020

Risk factors identified for early progression were extra-nodal involvement : ≥2 involved EN sites and lymphoma burden TMTV

Risk factors for early progression

- ≥2 involved EN sites
- TMTV > 80 ml



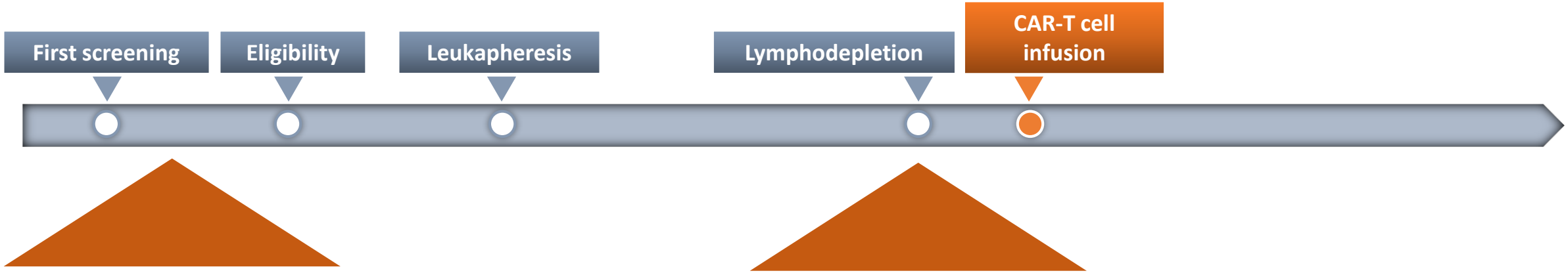


Vercellino & Di Blasi , et al . Blood Adv 2020

Selection of patients for CAR T-cells

Université de Paris

With the actual commercialized CAR T-cells



- Pts with rapidly progressing disease

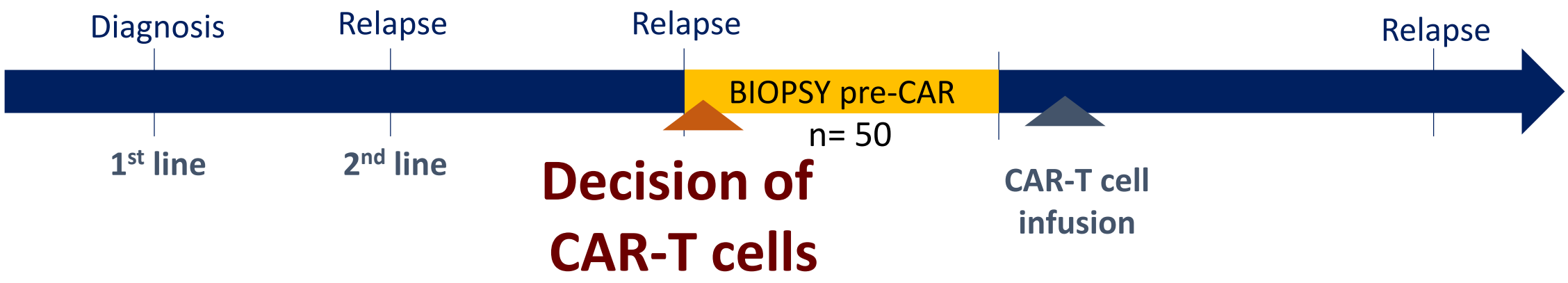
- **Elevated LDH**
- **with ≥2 extranodal sites**

- Poor ECOG PS

- **TMTV > 80 ml**
- **with ≥2 extranodal sites**

Other parameters ?

Biology



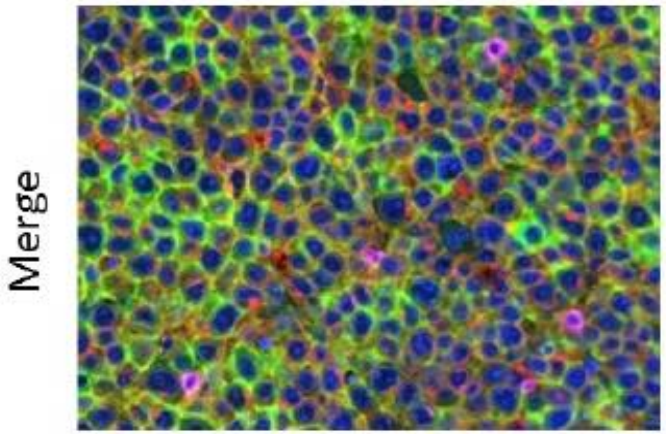
Biology of the T lymphocytes

***PREDICARTe**: Identification of early biomarkers to aid in the medical decision*

to proceed with the manufacture of CAR-T cells in patients with DLBCL (ARC funding)

Biology of the tumor

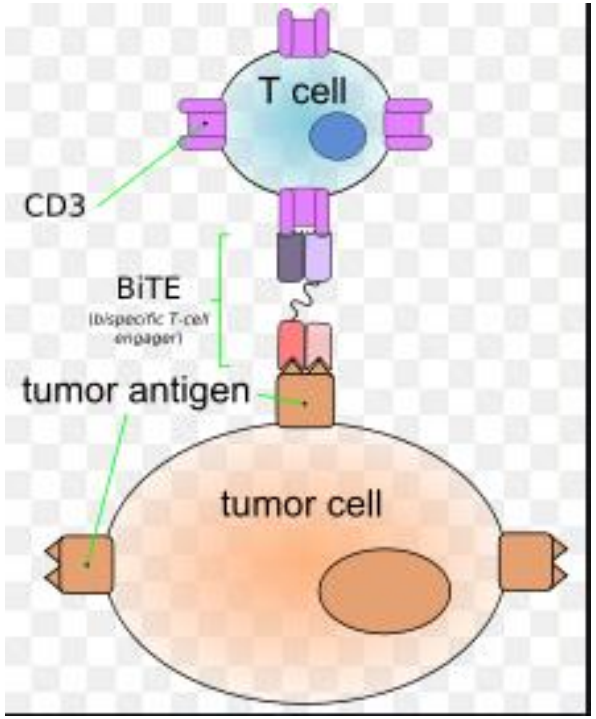
Multiplex IHC



Jain et al. *Blood*. 2021

Sophie Caillat-Zucman 1 Julien Calvani & Vassili Soumelis, HIPI U976 Equipe 9 – INSERM & C. Thieblemont, Paris University, APHP, Paris

Bispecific T-cell engager (BiTE)



Wikipedia

- First approved by FDA in 2014 in R/R ALL , and currently evaluated in clinical trials for R/R lymphoma, R/R myeloma
- Mode of action : It detects proteins to better target tumor cells and activate the immune cells
- Off the shelf, ready to be used
- Repeated infusions until progression or toxicity
- Ramp-up infusions during 3 weeks
- Side effects : neurotoxicity and cytokine release syndrome

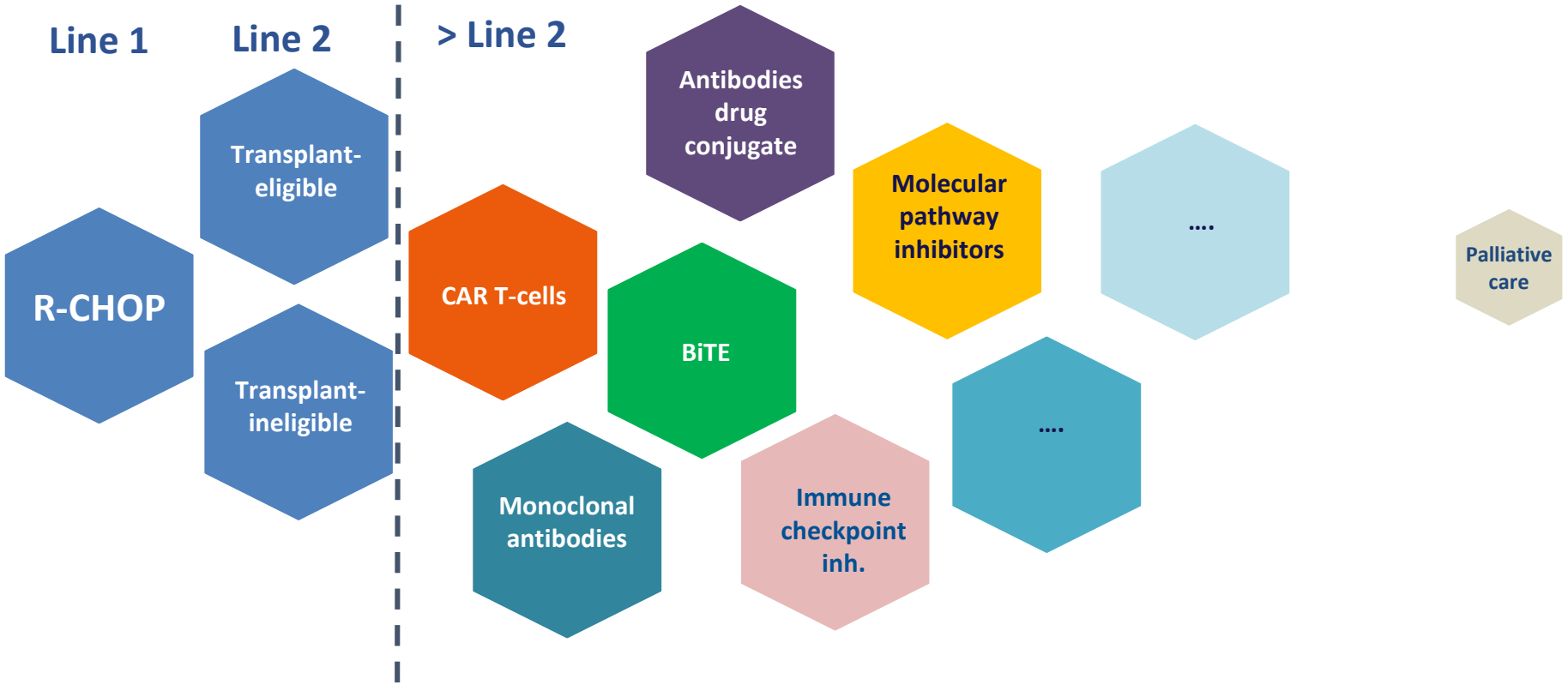
BiTE : Results in R/R DLBCL

Université de Paris

target	Drug	Study	Study phase	No*	Efficacy	References
CD20/CD3	**Blinatumomab**	NCT01741792	2	25	**ORR 43%** **CR 19%**	Viardot et al. Blood 2016
CD20/CD3	**RG6026**	NCT03075696	1b	28	**ORR 48%** **CR 43%**	Morschhauser F ASH2019 # 1584
CD20/CD3	**Mosunetuzumab**	NCT02500407	1/1b	55	**ORR 33%** **CR 21%**	Buddle LI ASH 2018 #399
CD20/CD3	**REGN1979 odronextamab**	NCT02290951	1	53	**ORR 33%** **CR 18%**	Bannerji R ASH 2019 #762
CD20/CD3	**REGN1979 odronextamab**	NCT02290951	expansion	136	**ORR no prior CART 55%** **CR 55%** **ORR prior CART 33%** **CR 21%**	Bannerji R ASH 2020
CD19/CD3	**Epcoritamab subcutaneous**	NCT03625037	1/2	45	**ORR 66.7%** **CR 13%**	Hutchings M ASH 2020
CD20/CD3	**Glofitamab (RG6026)** **D-7obinutuzumab**	NCT03075696	Expansion	12	**ORR 61% in all aNHL** **CR 54% in all aNHL**	Hutchings M ASH 2020

* DLBCL only

Multiple therapeutic innovations

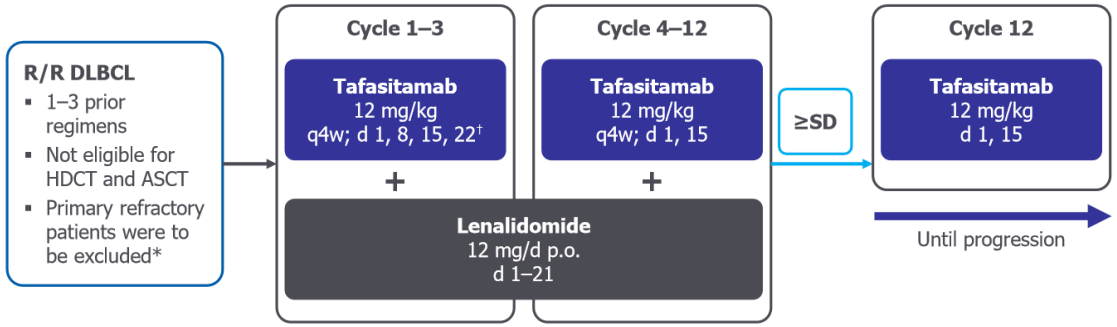


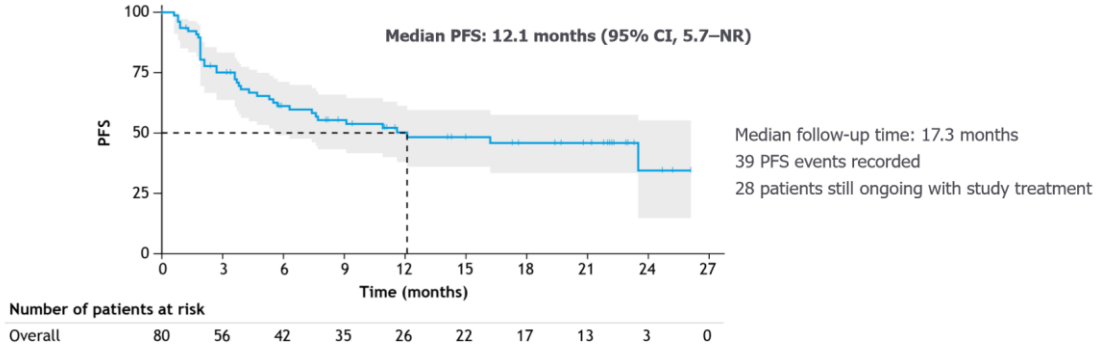
Thieblemont C. EHA 2021; Education Session on "**Refractory DLBCL**"

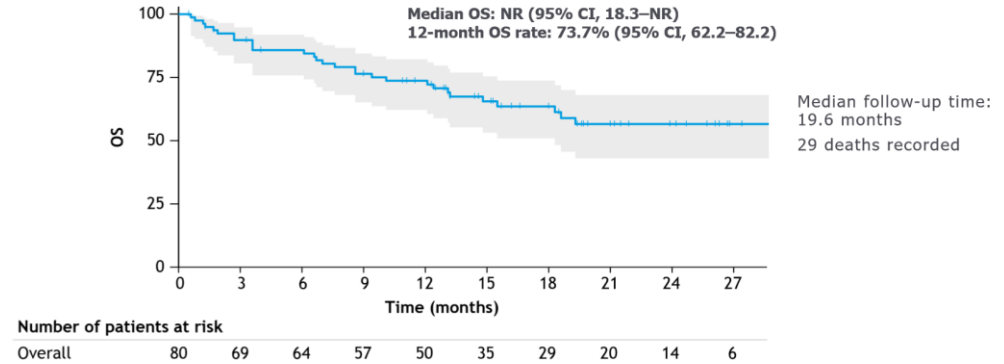
Monoclonal antibodies

L-MIND Tafasitamab (CD19 mAb) combined with Lenalidomine

Phase 2, single-arm, open-label, multicenter study (NCT02399085)







- ORR, 60.0% (95% CI, 48.4–70.8)
- CR rate, 42.5%
  - 82% of CRs PET-confirmed
  - 18% of CRs based on CT only

Salles G et al. Lancet Oncol 2020

Antibody-drug conjugates

target	Drug	Toxin	Combined agents	Study	Study phase	No*	Efficacy	References
CD19	**Loncastuximab tesirine**	**SC3199**	-	NCT02669017	1	63	**ORR 55% CR 37%**	Kahl et al. CCR 2019
CD79b	**Polatuzumab vedotin**	**MMAE***	Rituximab	NCT01691898	2	39	**ORR 54% CR 21% mDoR13,4**	Morschhauser et al . Lancet Haematol 2019
CD30	**Brentuximab vedotin**	**MMAE***	-	NCT01421667	2	49	**ORR 44% CR 17% mPFS : 4m**	Jacobsen et al. Blood 2015
CD22	**Inotuzumab ozogamicin**	**Calicheamicin**	Rituximab	NCT00299494	1/2	42	**ORR 74% 2-y PFS 42%**	Fayad L et al J Clin Oncol 2013

*MMAE : monomethyl auristatin E

Thieblemont C. EHA 2021; Education Session on "**Refractory DLBCL**"

Immune checkpoints inhibitors (ICIs)

Target	Drug
PD1	Pembrolizumab
	Nivolumab
PDL1	durvalumab
	avelumab
	atezolizumab
CD47	Hu5F9-G4 +R

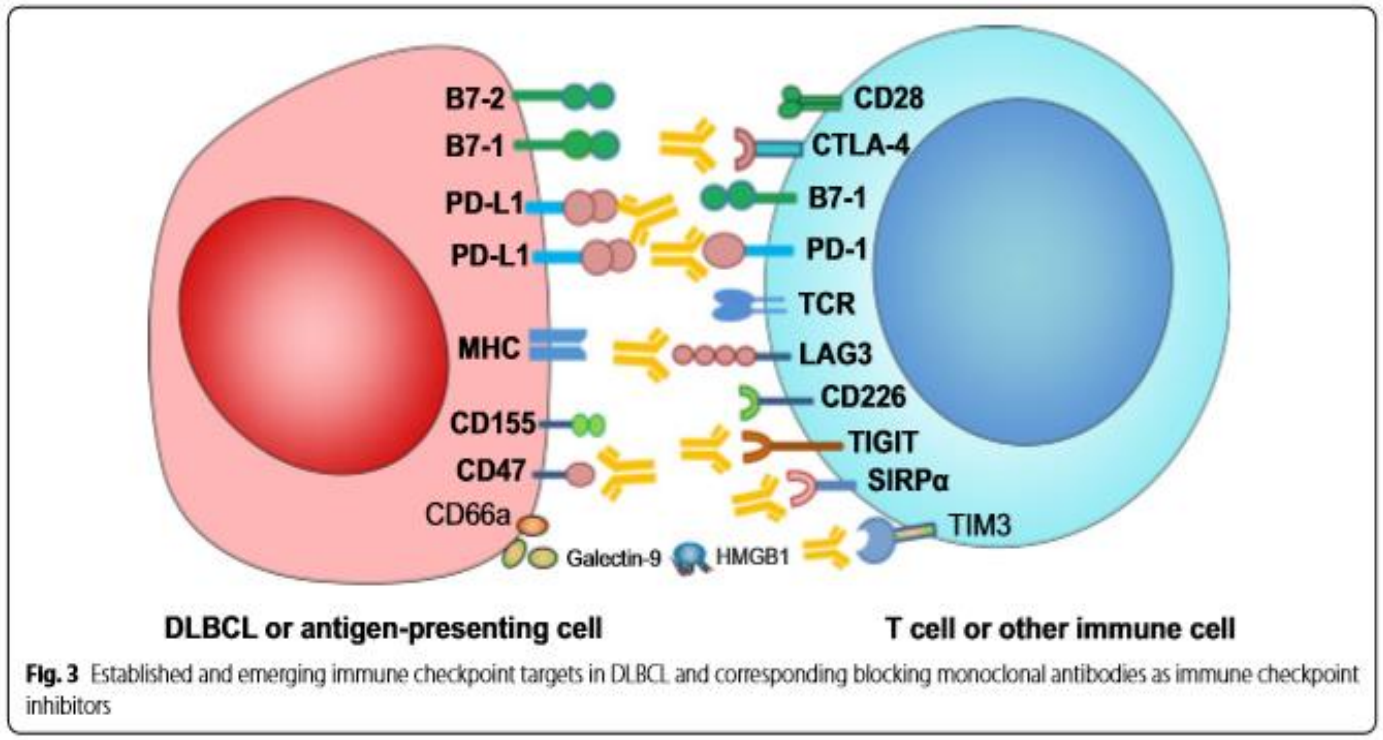
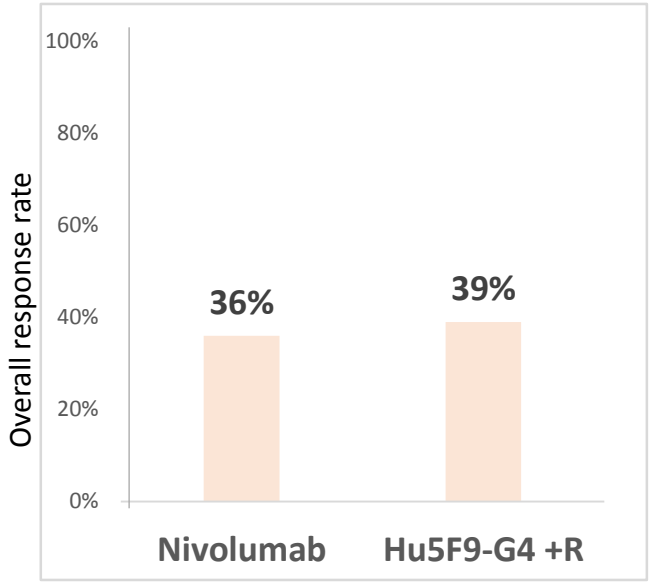


Fig. 3 Established and emerging immune checkpoint targets in DLBCL and corresponding blocking monoclonal antibodies as immune checkpoint inhibitors

From Wang et al. J Hematol Oncol(2020) 13:175

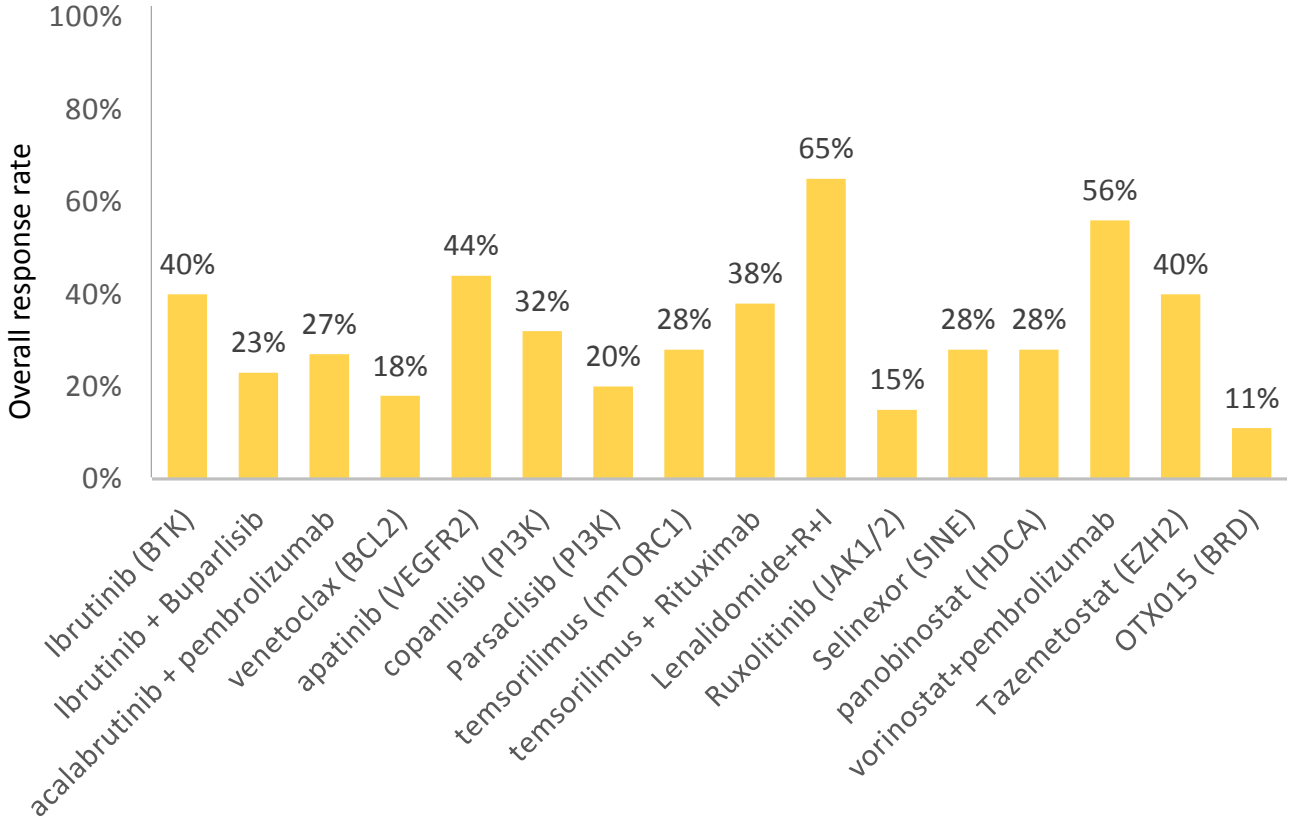


Nivolumab : Lesokhin et al. Blood Adv 2020
Hu5F9-G4 +R: Advani et al. Hematol Oncol 2019

Molecular pathway inhibitors

- BCR signaling pathway inhibition
- BCL-2 inhibition
- VEGFR inhibition
- PI3K/Akt/mTOR inhibition
- NF-κB pathway inhibition
- JAK/STAT3 inhibition
- Selective inhibitors of nuclear export
- Epigenetic-modifying drugs
- Histone deacetylase inhibitors
- EZH2 inhibition
- Bromodomain inhibitors

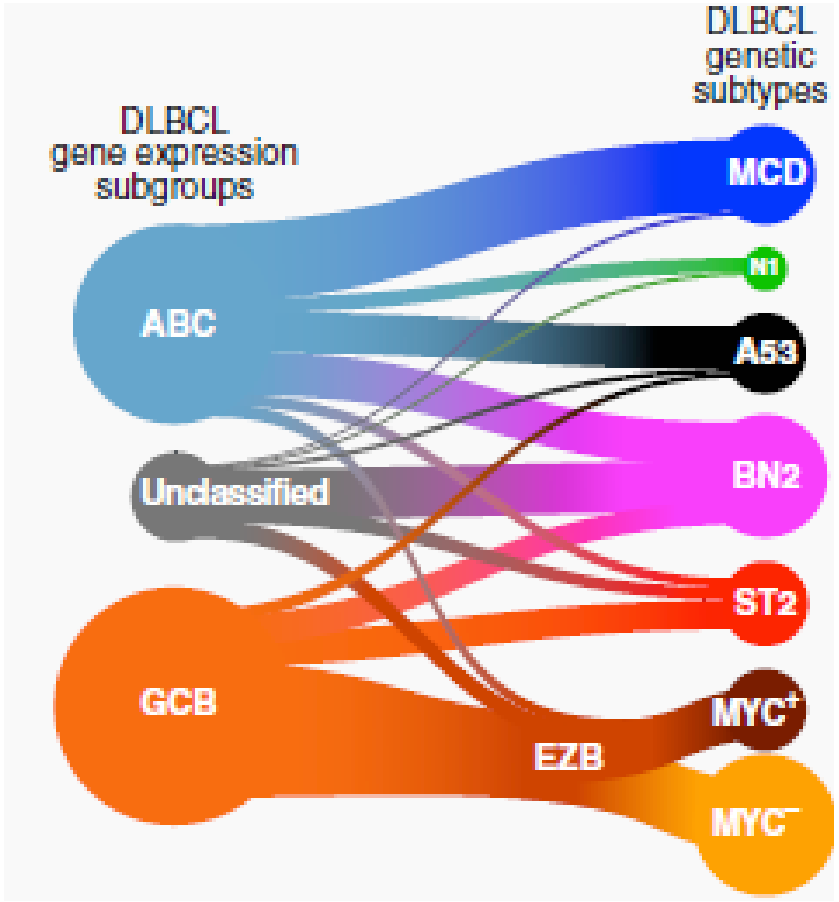
- **Single agents : ORR between 10% and 40%**
- **Combination : increased efficacy**

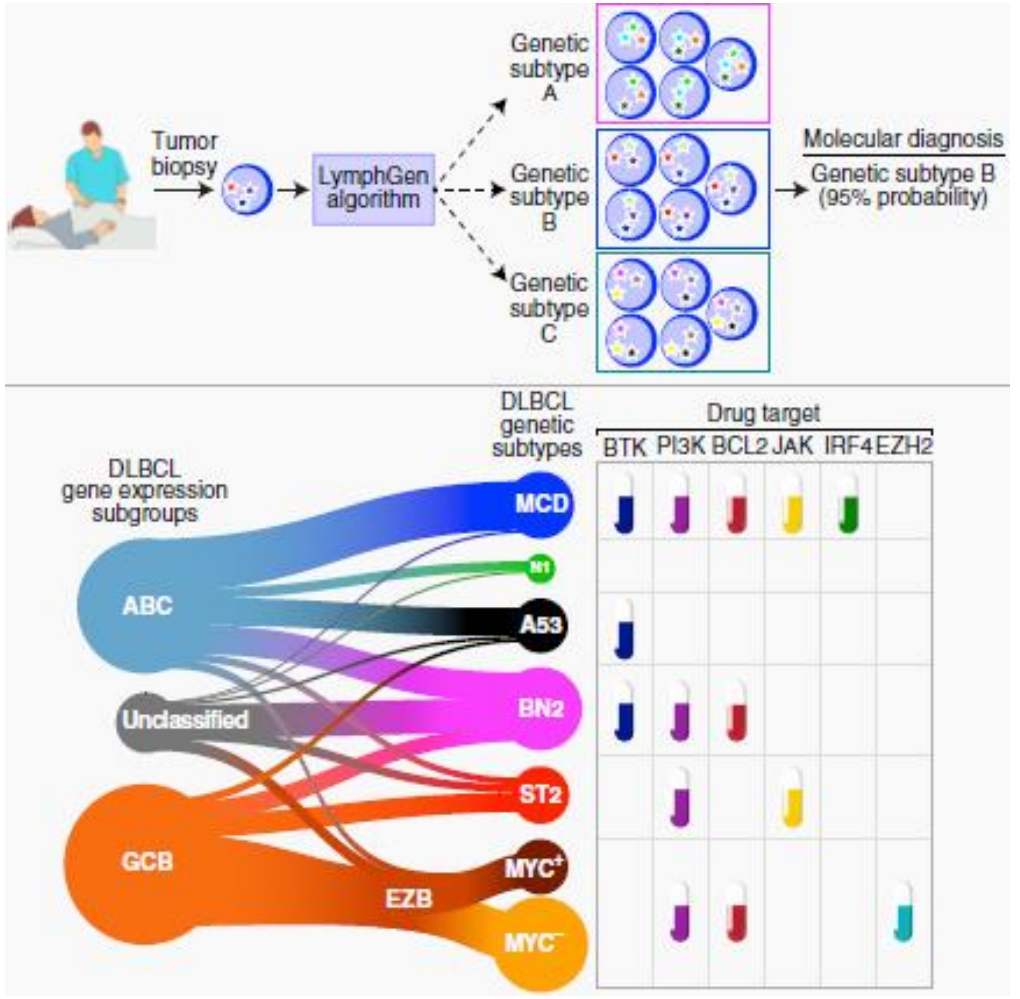


Tailored therapies

Université de Paris

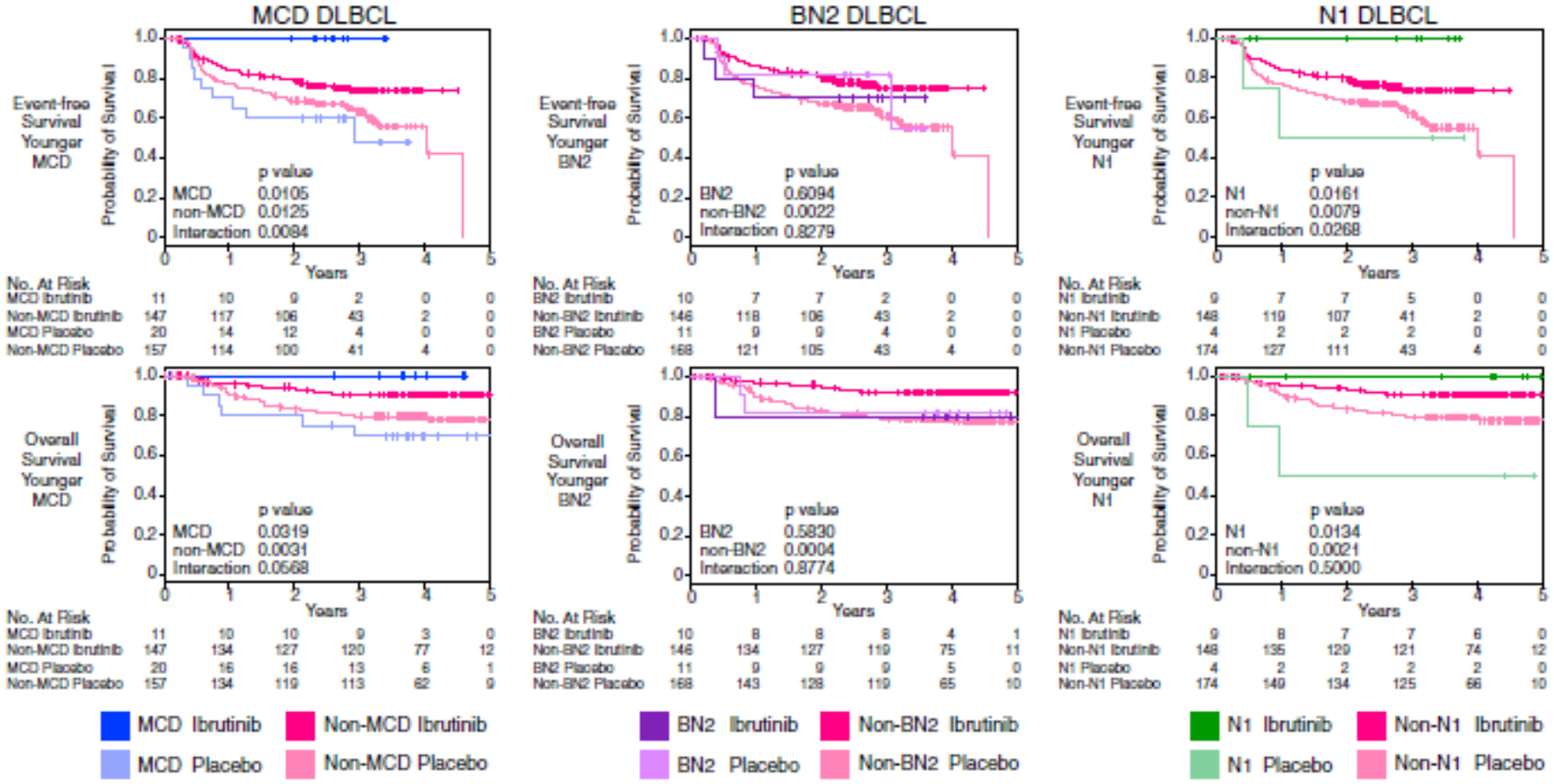
Better genetic subtyping in DLBCL compared to ABC/GCB may lead to better therapy





Wright GW et al. Cancer Cell 2020

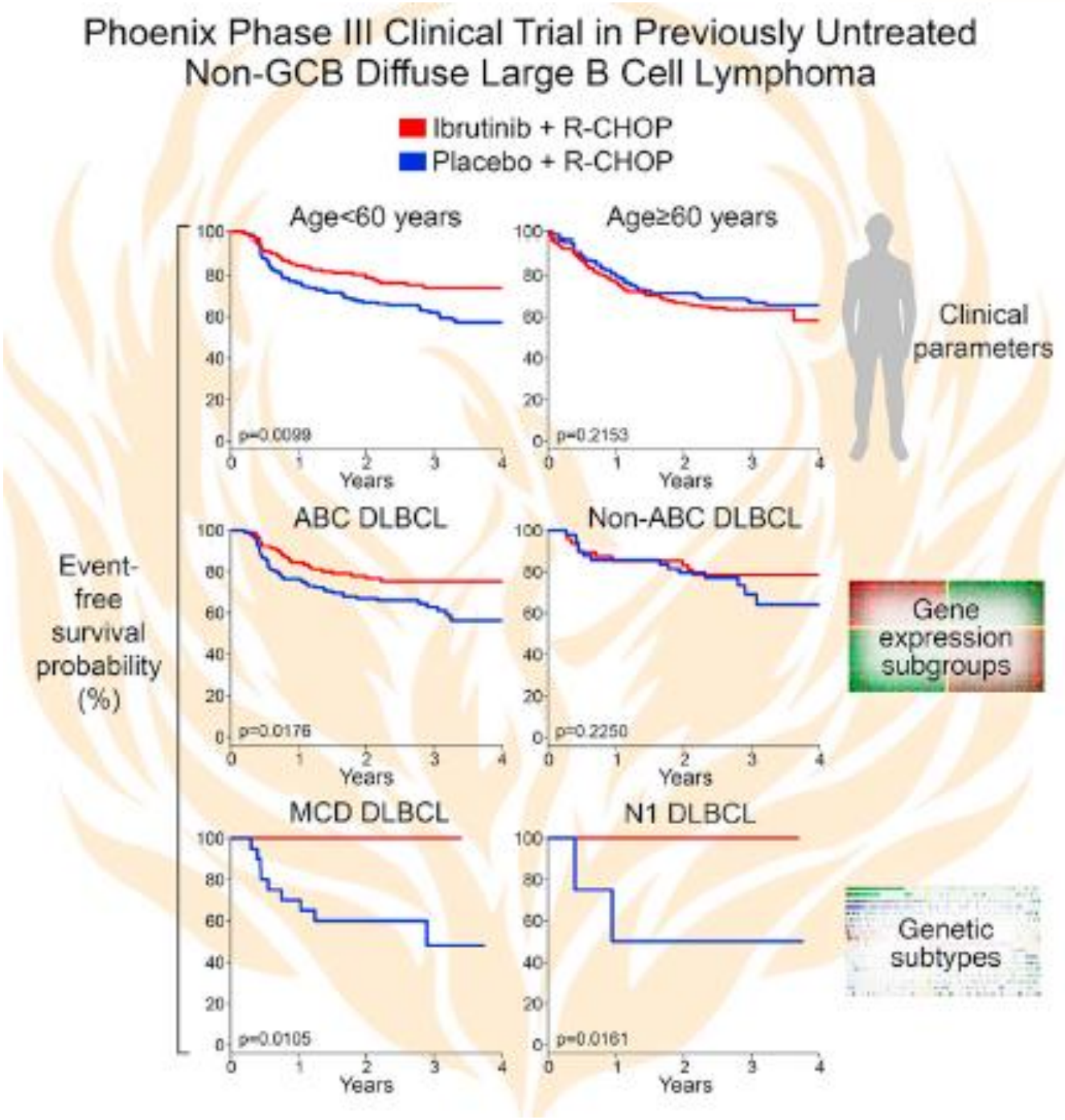
iBTK in DLBCL



Wilson et al., 2021, Cancer Cell 39, 1–11

iBTK in DLBCL

- BTK inhibitor ibrutinib plus R-CHOP is effective in younger patients with ABC DLBCL
- Genetic subtypes of DLBCL differ in genotype, phenotype, and oncogenic mechanisms
- MCD and N1 subtypes acquire mutations that promote chronic active BCR signaling
- Patients with the MCD and N1 subtypes have 100% survival with ibrutinib plus R-CHOP



Wilson et al., 2021, Cancer Cell 39, 1–11

Other B-cell lymphomas

	Axi-cel	Tisa-cel	Liso-cel (FDA)
Agressive B-cell lymphomas	Adult patients with R/R LBCL ≥ 2 Lines • DLBCL NOS • PMBL • HGBCL • Tr FL HIV infected pts **ZUMA 1**	Adult patients with R/R LBCL ≥ 2 Lines • DLBCL NOS • PMBL • HGBCL **JULIET**	Adult patients with R/R LBCL ≥ 2 Lines • DLBCL NOS • HGBCL • PMBL • Transformed / indolent L. • FL grade 3B **TRANSCEND**
MCL	adult patients with MCL • ≥ 2 Lines, including one with BTK inihbitor **ZUMA 2**		
FL	adult patients with R/R FL • ≥ 2 Lines **ZUMA 5 (+MZL)**	adult patients with R/R FL • ≥ 2 Lines **ELARA**	

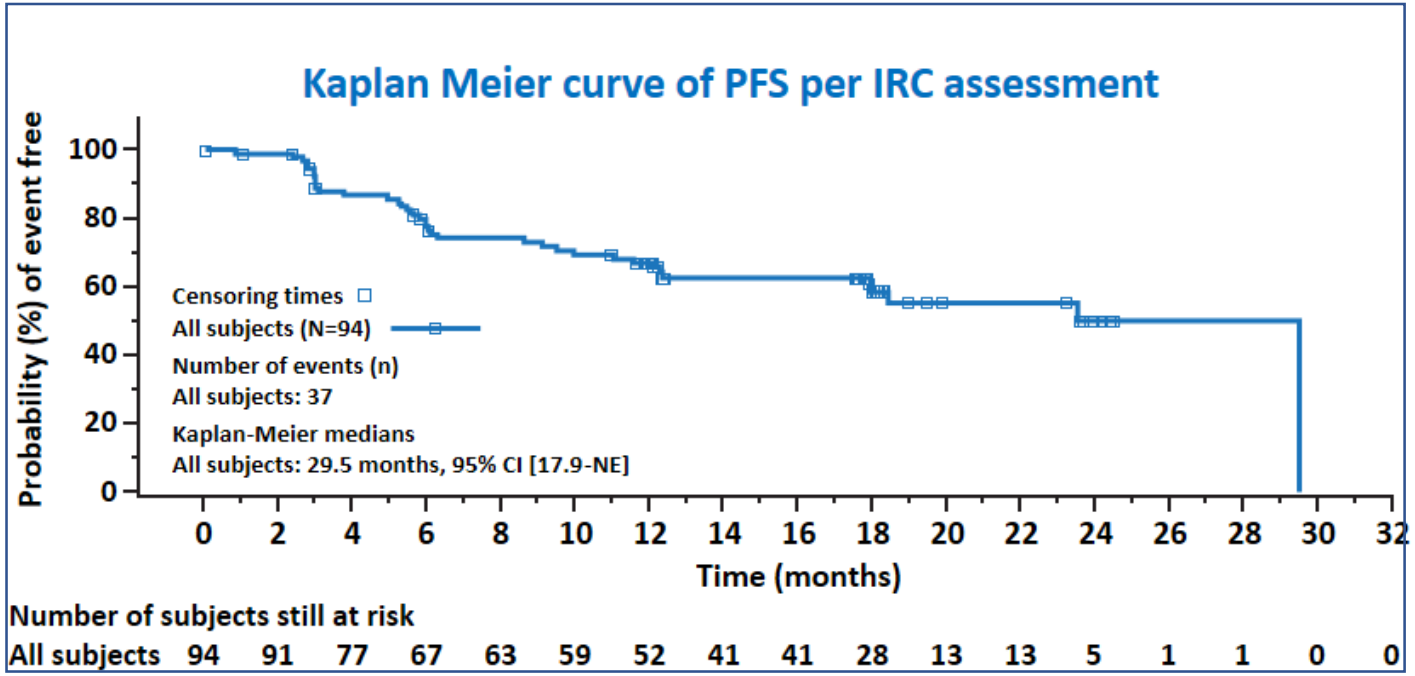
CAR T-cells in follicular lymphoma

Université de Paris

Median follow-up : 21 mo

median PFS :29.5 months
(95% CI: 17.9, NE)

- CRS grade 3-4 = 0 %
- ICANS grade 3-4 = 3%



	Descriptive analysis	
Disease Characteristic	High-Risk 12-month PFS (%)	Low-Risk 12-month PFS (%)
POD24	60.8	77.9
TMTV[a]	54.5	68.5

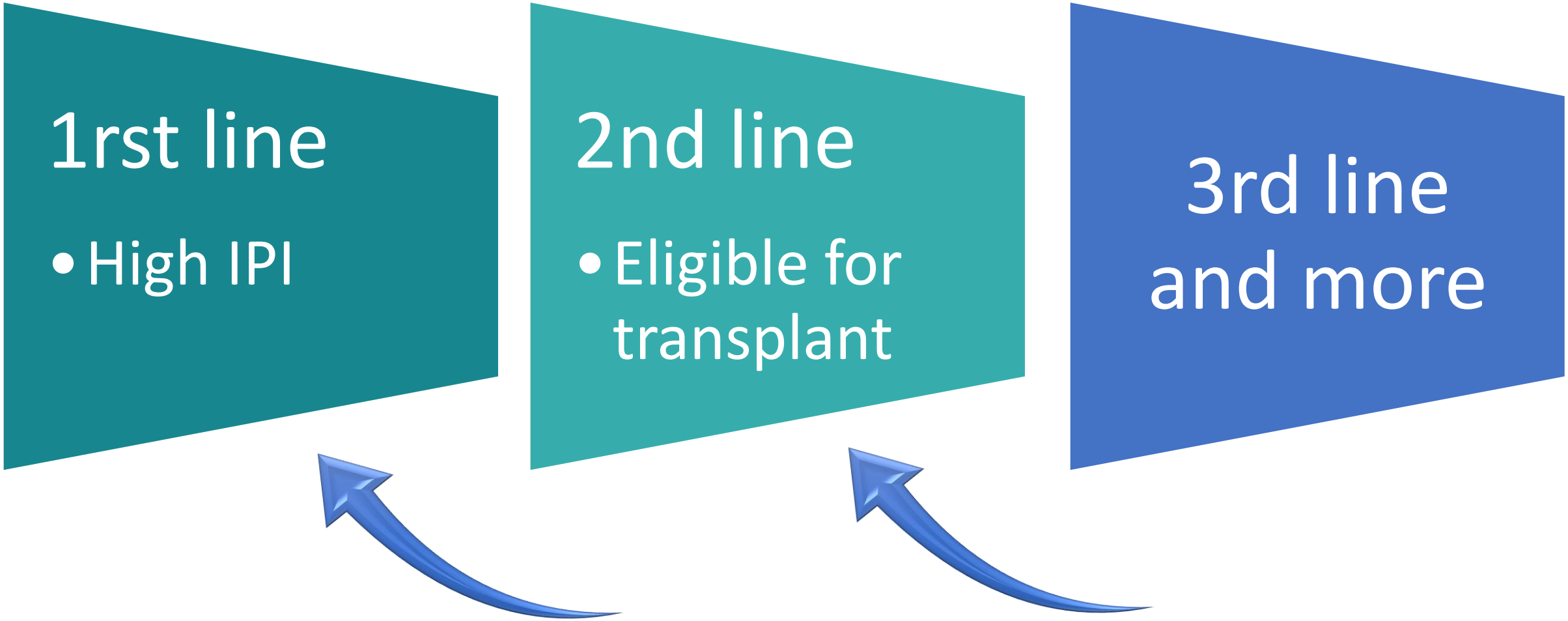
Thieblemont C, et al . In press Nature Medecine

Perspectives - 1: Combination strategies

Trial and NCT #	Phase	CAR-T cell therapy	Molecule	Target
NCT03630159 (PORTIA)	IB	Tisagenlecleucel	Pembrolizumab	Anti-PD1
NCT03310619 (PLATFORM)	II	Lisocabtagene maraleucel/ JCAR017	Durvalumab	Anti-PD L1
NCT03310619 (PLATFORM)	II	Lisocabtagene maraleucel/ JCAR017	CC-122-Avadomide	IMIDs
NCT03876028	I	Tisagenlecleucel	Ibrutinib	Anti-BTK
ZUMA-11 NCT03704298	II	Axicabtagene ciloleucel	Utomilumab	agonistic mAb costimulatory molecule 4-1BB/CD137

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; r/r, relapsed/refractory.

Perspectives - 2 : Strategies for early lines



Perspectives - 2 : Strategies for early lines

1rst line

- High IPI – Ph II

- **ZUMA 12**

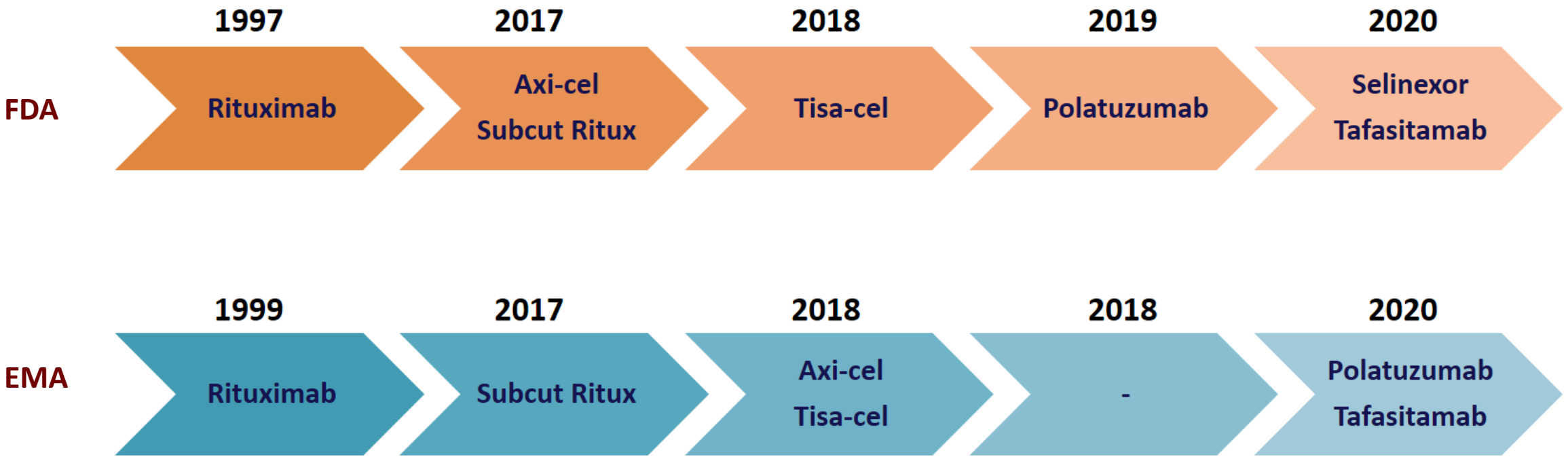
2nd line

- CART *vs* ASCT

- **ZUMA 7 (phase III)**
- **BELINDA (phase III)**
- **TRANSFORM (phase III)**

3rd line and more

Agents approved by the FDA and by the EMA in R/R DLBCL



CONCLUSION

Université de Paris

- Therapeutic innovations are multiple
- Cell therapy exhibits promising results with potential cure in 30-40% of the refractory aggressive B-cell lymphomas, probably more in indolent lymphomas
- Challenges are multiple
  - To offer personalized medecine based on pretreatment characteristics based on biology and functional imaging
  - To sequence the various therapies as best as possible
  - To predict outcome
  - To overcome toxicities
  - To keep a good quality of life