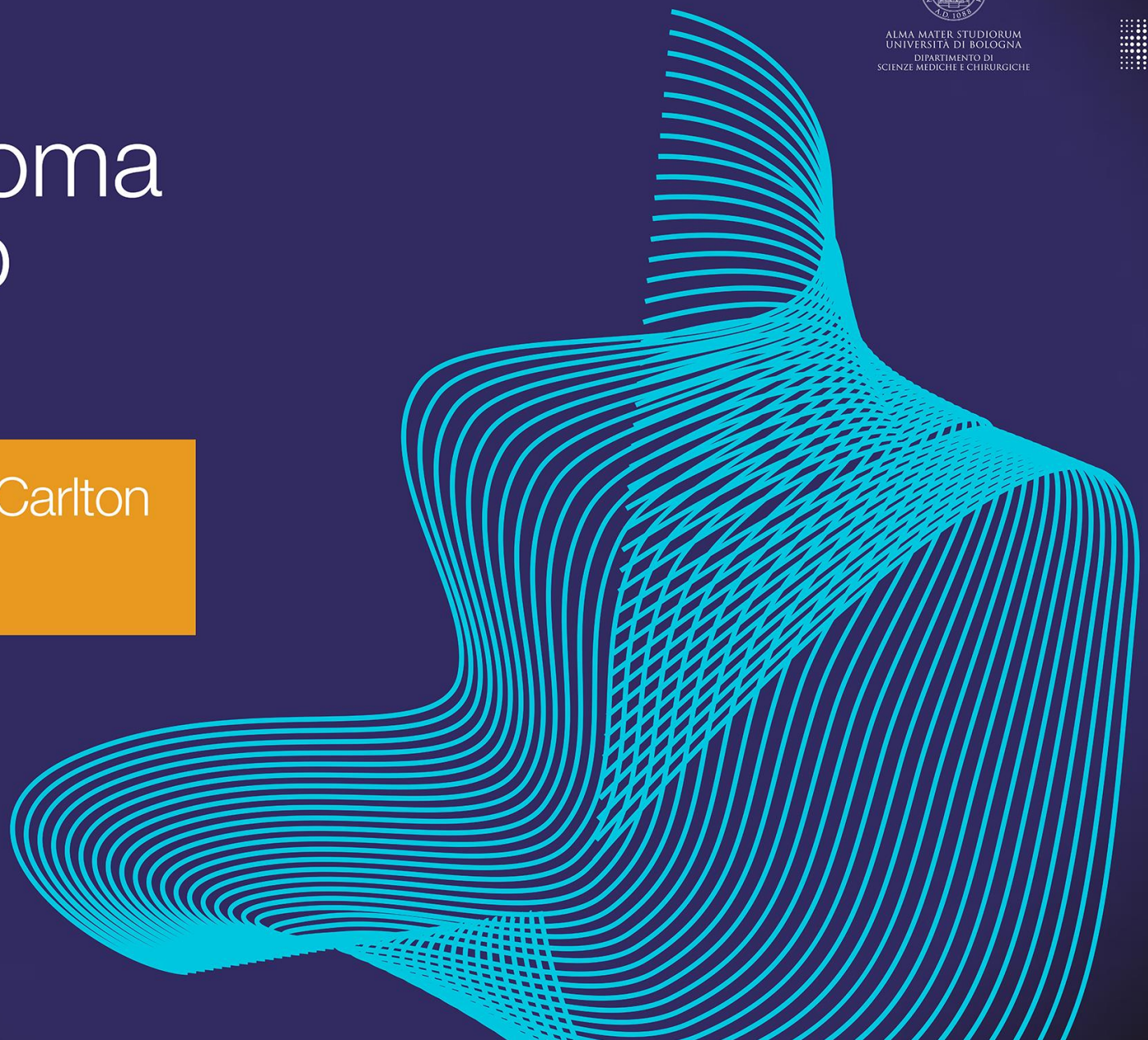
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop



Bologna, Royal Hotel Carlton

May 8-9, 2023

President: **Pier Luigi Zinzani**

New drugs to treat B-cell Aggressive lymphomas

CC-99282

Jean-Marie Michot, MD

Hematology and Drug Development Department

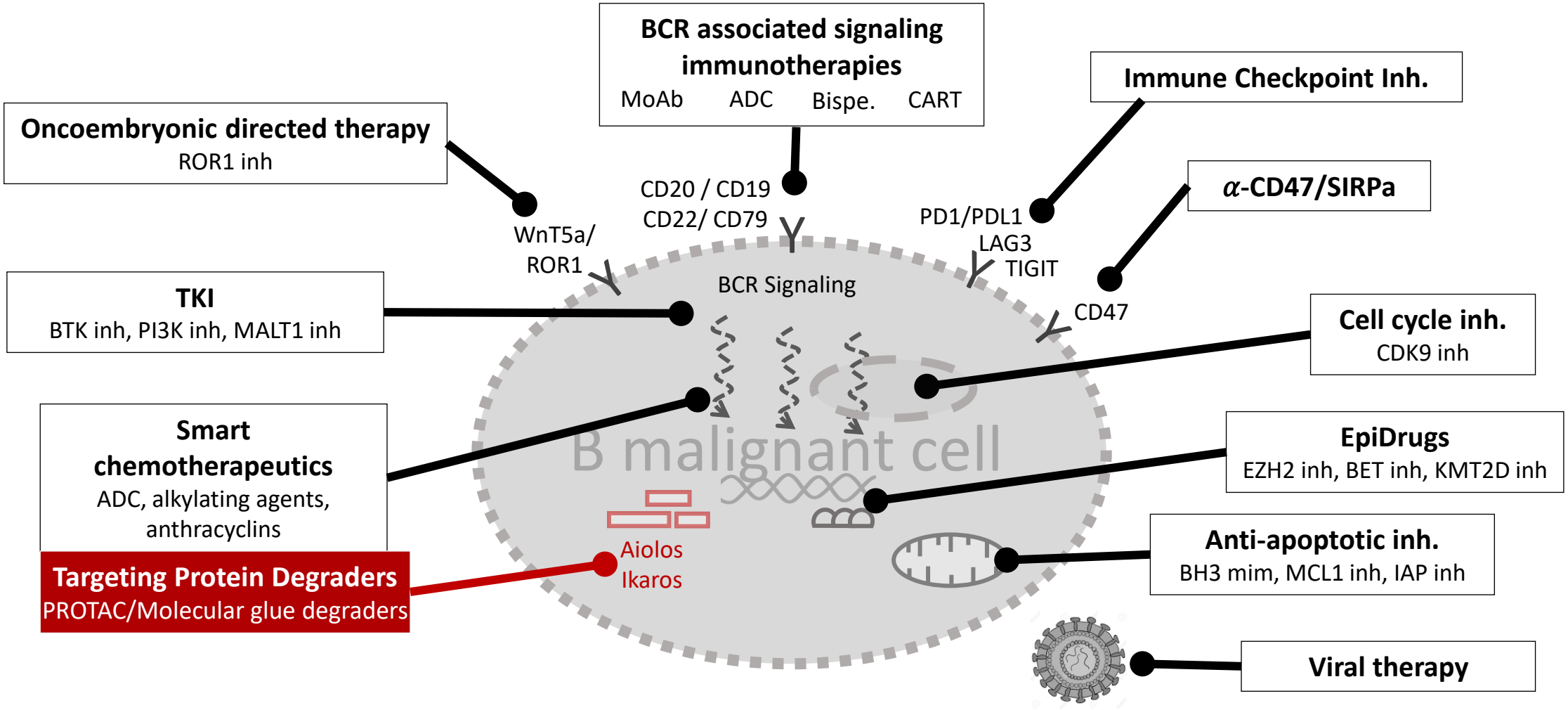
Gustave Roussy – Villejuif, France

jean-marie.michot@gustaveroussy.fr

Disclosures

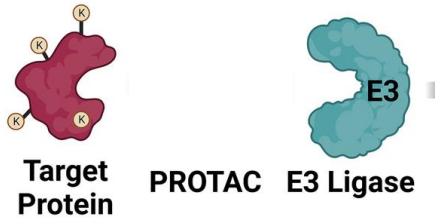
- **Principal/sub-Investigator of Clinical Trials for :** Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, Xencor
- **PERSONAL FEES** (Monies paid for services rendered, generally honoraria, royalties or fees for consulting, lectures, speakers bureaus, expert testimony, employment, ad-boards, etc.): Bristol-Myers Squibb, AstraZeneca, Janssen, Ideogen
- **NON-FINANCIAL SUPPORT** (Drugs, equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.): GSK, AstraZeneca, Roche, Novartis, Gilead, Bristol-Myers Squibb
- **OTHER:** nothing to disclose

Main new therapeutics targets in large B-cell lymphoma



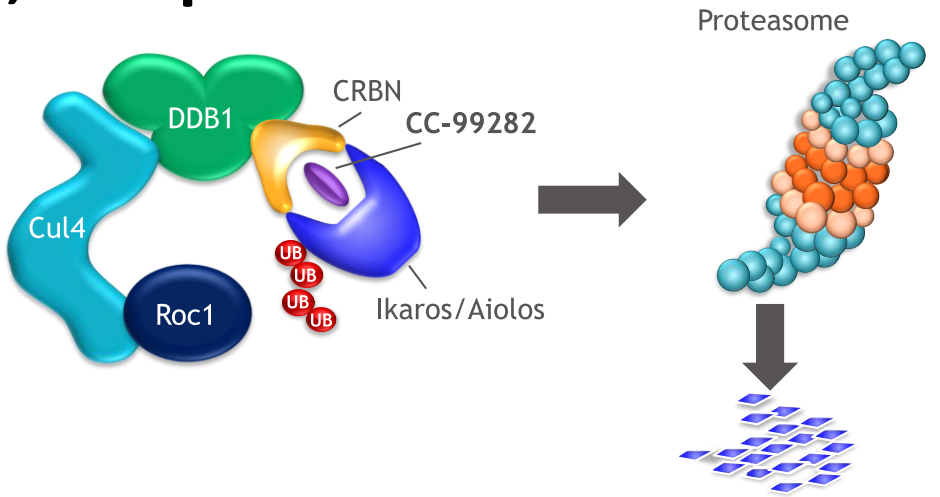
Targeted Protein Degraders (TPD), general summary mechanism of action

Resulting in the catalytic proteasomal degradation of their targets

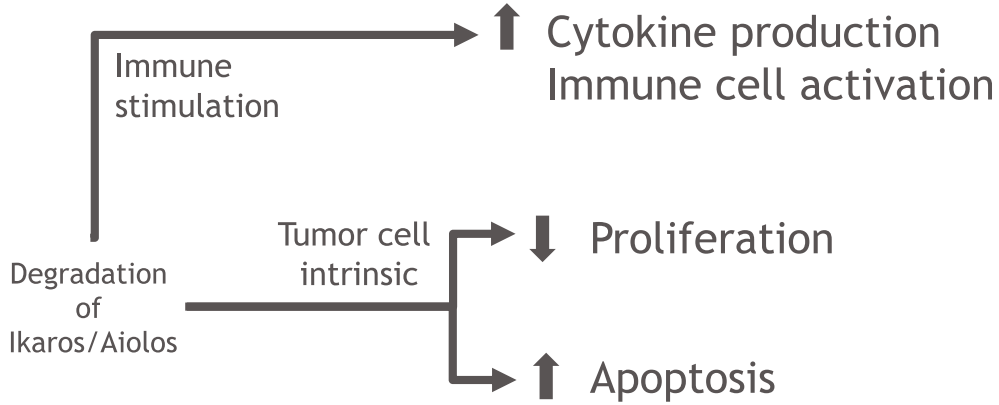


CC-99282, a novel, small molecule, co-opts CRBN

- CC-99282, a novel, small molecule CELMoD® agent, co-opts CRBN and induces targeted ubiquitination and proteasome-mediated degradation of Ikaros and Aiolos, transcription factors critical for the development of B-cell malignancies



- Compared with classic immunomodulatory imide drugs (IMiD®), CC-99282 showed enhanced immunostimulatory effects, stronger antitumor activity, and robust distribution across tissue types in preclinical models[1]
  - CC-99282 exhibited 10- to 100-fold enhanced antiproliferative and apoptotic activity in a range of DLBCL cell lines, independent of subtype or chemotherapy-resistant status[1,2]

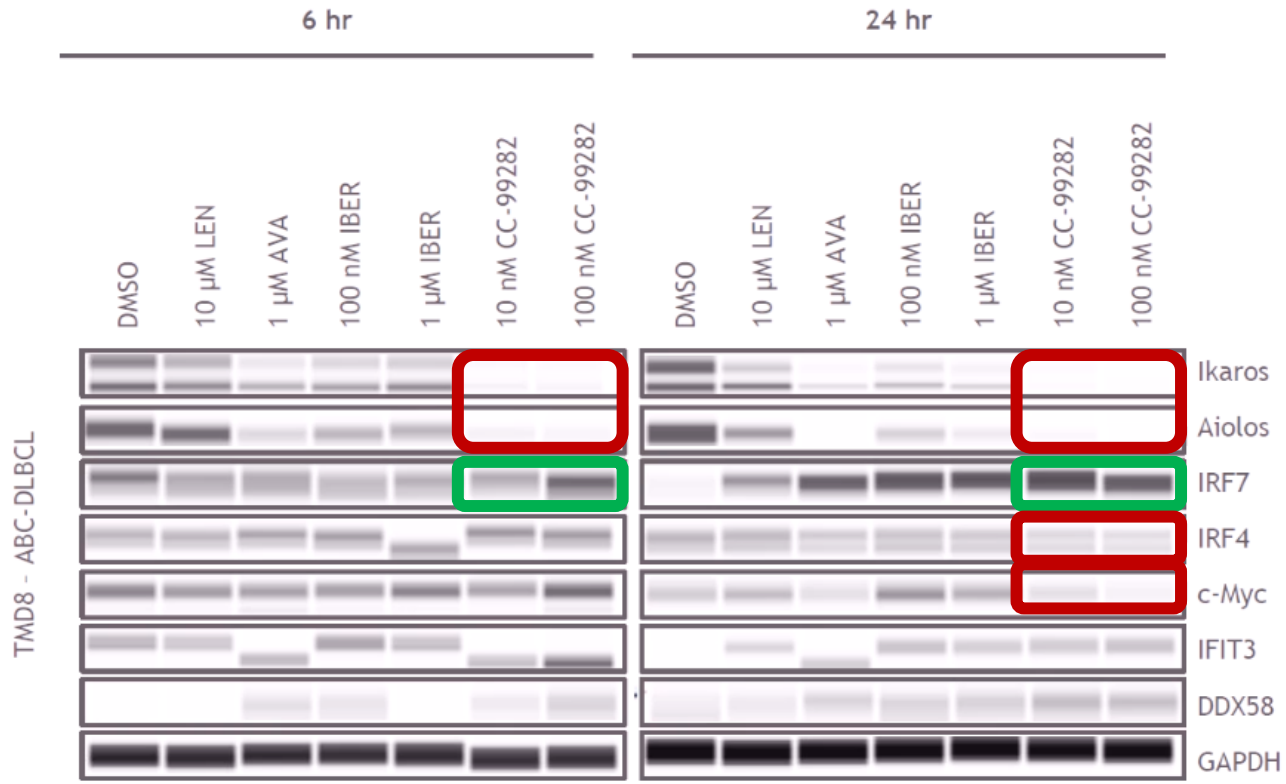


CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; Cul4, cullin-4; DDB1, damage-specific DNA binding protein; DLBCL, diffuse large B-cell lymphoma; Roc1, regulator of cullins-1; UB, ubiquitination.

1. Lopez-Girona A et al. *Hematol Oncol* 2021;39(suppl S2). Abstract 232. 2. Carrancio S et al. Poster presentation at the American Society of Hematology (ASH) Annual Meeting; December 11-14, 2021; Atlanta, GA, USA. Abstract 1200.

Degradation of Ikaros/Aiolos with CC-99282

- Degradation of Ikaros/Aiolos in sensitive DLBCL cells treated with CC-99282 correlated with induction of IFN-stimulated genes (*IRF7*, *IFIT3*), and reduction of the highly critical oncogenic factors c-Myc and *IRF4*



Carrancio S, ASH 2021.

DLBCL, diffuse large B-cell lymphoma; IFIT3, IFN-induced protein with tetratricopeptide repeats 3; IFN, interferon; IRF, IFN regulatory factor.

CC-99282-NHL-001 (NCT03930953) is a multicenter, phase 1, open-label, dose-finding, FIH study evaluating CC-99282 in patients with R/R NHL

Population

R/R DLBCL or FL after ≥ 2 LOT or DLBCL after ≥ 1 LOT + unfit for transplant

Primary objective

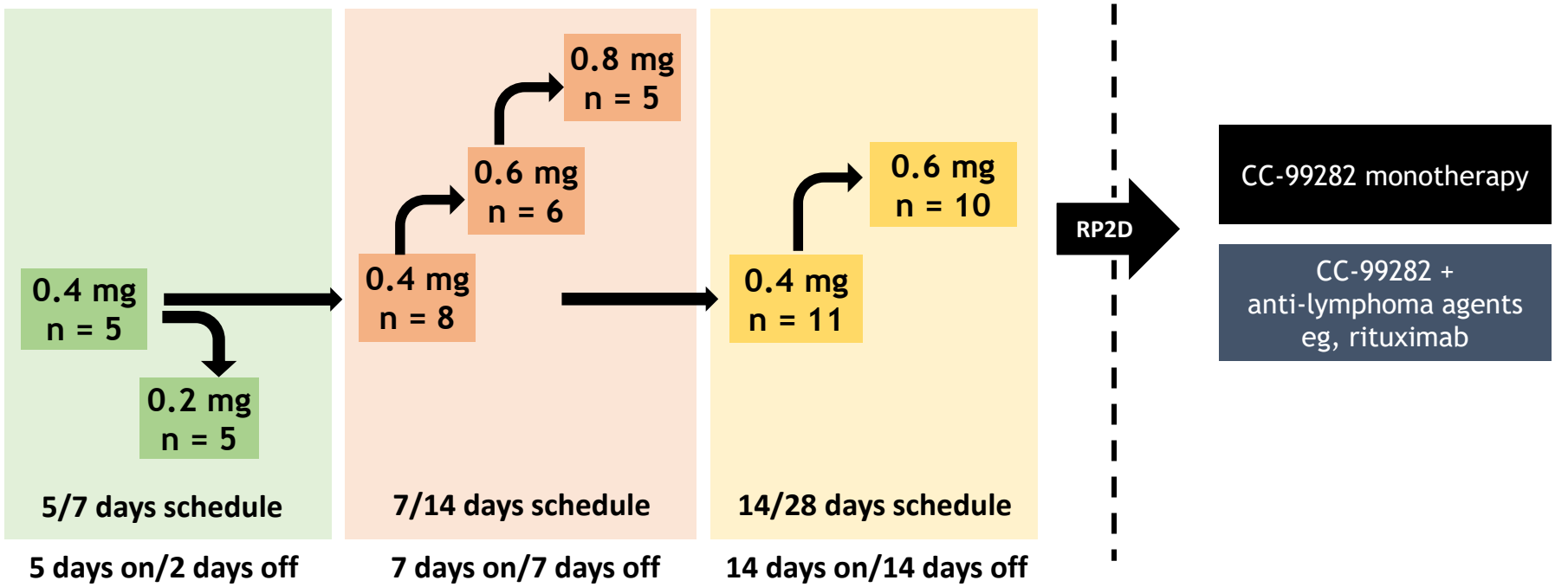
Safety, tolerability, MTD/RP2D

Secondary objective

PK, preliminary efficacy

Exploratory objective

Pharmacodynamics



Michot JM, EHA 2022 S216

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LOT, line of therapy; MTD, maximum tolerated dose; PK, pharmacokinetics; NHL, non-Hodgkin lymphoma; R/R, relapsed or refractory; RP2D, recommended phase 2 dose.

CC-99282-NHL-001 (NCT03930953), patients characteristics, Part A

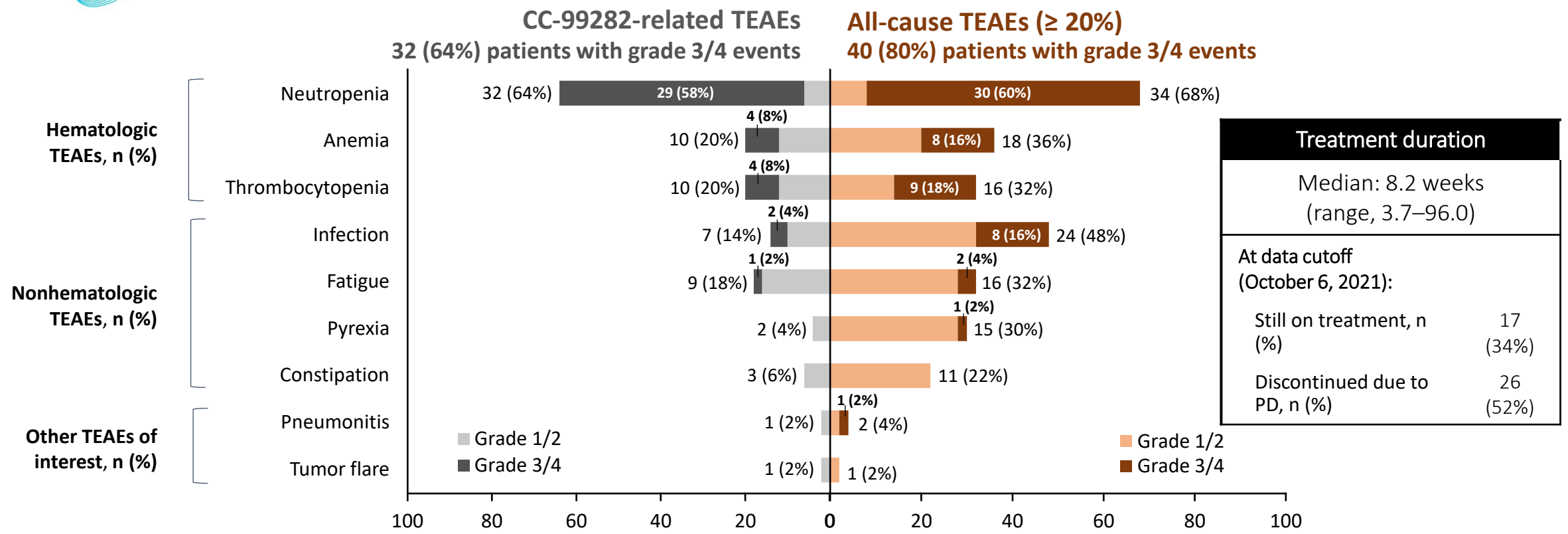
Characteristic		All patients (N = 50)
Age, median (range), years		65.5 (35–89)
Sex, male, n (%)		29 (58)
Diagnosis, n (%)	DLBCL	38 (76)
	NOS	22 (44)
	Double-hit or triple-hit positive[a]	7 (14)
	Transformed	16 (32)
	FL (grade I to grade IIIB)	12 (24)
Time from initial diagnosis to first dose, median (range), months	DLBCL	22.5 (4.5–94.5)
	FL	71.8 (22.5–135.9)
ECOG performance status score, n (%)	0	21 (42)
	1	25 (50)
	2	4 (8)
Stage IV cancer at diagnosis, n (%)		29 (58)
Treatment history	No. of prior lines of therapy, median (range)	3 (1–8)
	Prior stem cell transplant, n (%)	10 (20)
	Prior CAR T cell therapy, n (%)	14 (28)
	Prior lenalidomide/avadomide treatment, n (%)	11 (22)
	Refractory[b] to last regimen, n (%)	25 (50)

Data cutoff: October 6, 2021.

Michot JM, EHA 2022 S216

[a]Double-hit was defined as positive for *MYC* + *BCL2* or *MYC* + *BCL6* and triple-hit as positive for *MYC* + *BCL2* + *BCL6*. [b]Refractory was defined as never having achieved an objective response (eg, stable or progressive disease) to prior lines of therapy; patients with short (< 6-month duration) responses to last therapy are not included in this definition. CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NOS, not otherwise specified.

CC-99282-NHL-001 (NCT03930953), tolerablity, Part A



Treatment duration	
Median: 8.2 weeks (range, 3.7–96.0)	
At data cutoff (October 6, 2021):	
Still on treatment, n (%)	17 (34%)
Discontinued due to PD, n (%)	26 (52%)

- Neutropenia, a class effect of CELMoD agents, was manageable with dose modifications and G-CSF support (31 [62%] patients)
- Serious febrile neutropenia (grade 3/4 only) was observed in 5 (10%) patients; treatment related in 4 (8%) patients
- No patients permanently discontinued treatment with CC-99282 due to neutropenia

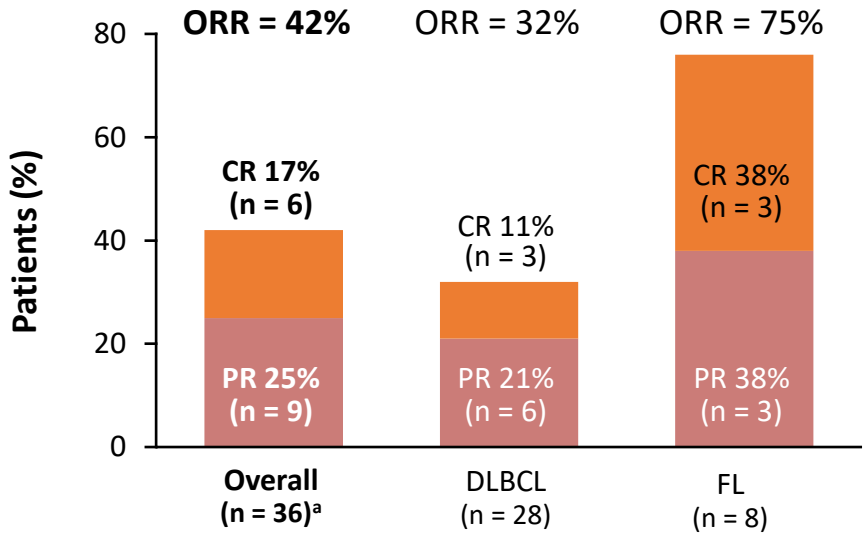
Michot JM, EHA 2022 S216

[a]Safety population. No instances of cytokine release syndrome were observed.

CELMod, cereblon E3 ligase modulator; G-CSF, granulocyte colony-stimulating factor; PD, progressive disease; TEAE, treatment-emergent adverse event.

CC-99282-NHL-001 (NCT03930953), prelimin. Efficacy data, Part A

Overall response by tumor type in 36 efficacy-evaluable patients (≥ 0.4 mg CC-99282)



At the tolerated schedules of dose levels ≥ 0.4 mg

- At the 7/14 days dosing schedule
  2 patients achieved CR while ORR was 39%
- At the 14/28 days dosing schedule
  4 patients achieved CR while ORR was 44%

Response at 0.4 mg at the dosing schedules of interest

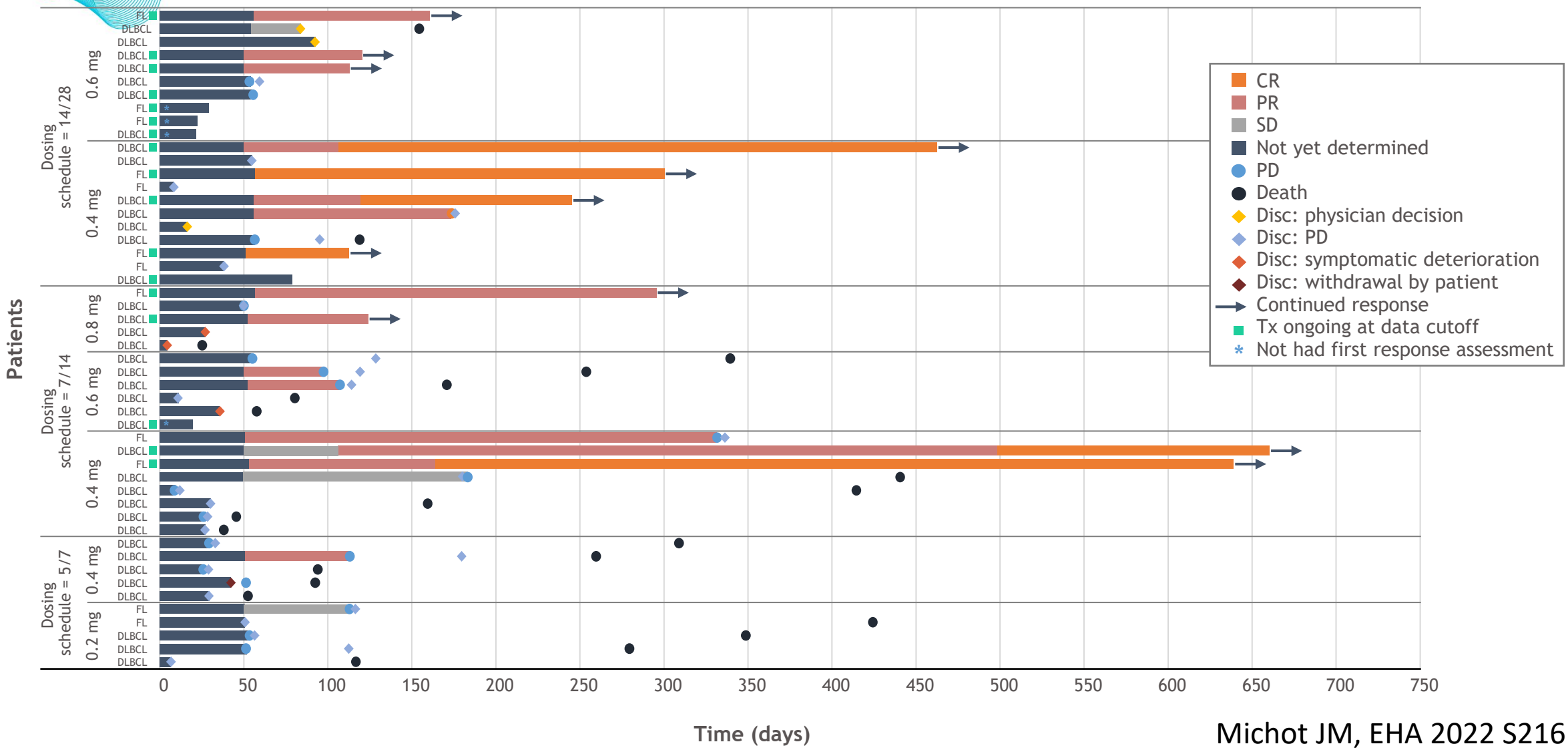
Response	7/14 days (n = 8)	14/28 days (n = 11)
PR + CR	38% (n = 3)	46% (n = 5)
CR	25% (n = 2)	36% (n = 4)

- Patients showing objective responses to CC-99282 monotherapy included some patients who had progressed on or after prior treatment with cellular therapy and/or IMiD/CELMoD agents

Michot JM, EHA 2022 S216

[a]Three patients treated with 0.6 mg on the 14/28-day schedule and 1 patient with 0.6 mg on the 7/14-day schedule had no post-baseline assessments and were ongoing as of the data cutoff date and are not included in the efficacy summary.

CELMoD, cereblon E3 ligase modulator; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IMiD, immunomodulatory imide drugs; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PR, partial response; R/R, relapsed or refractory.

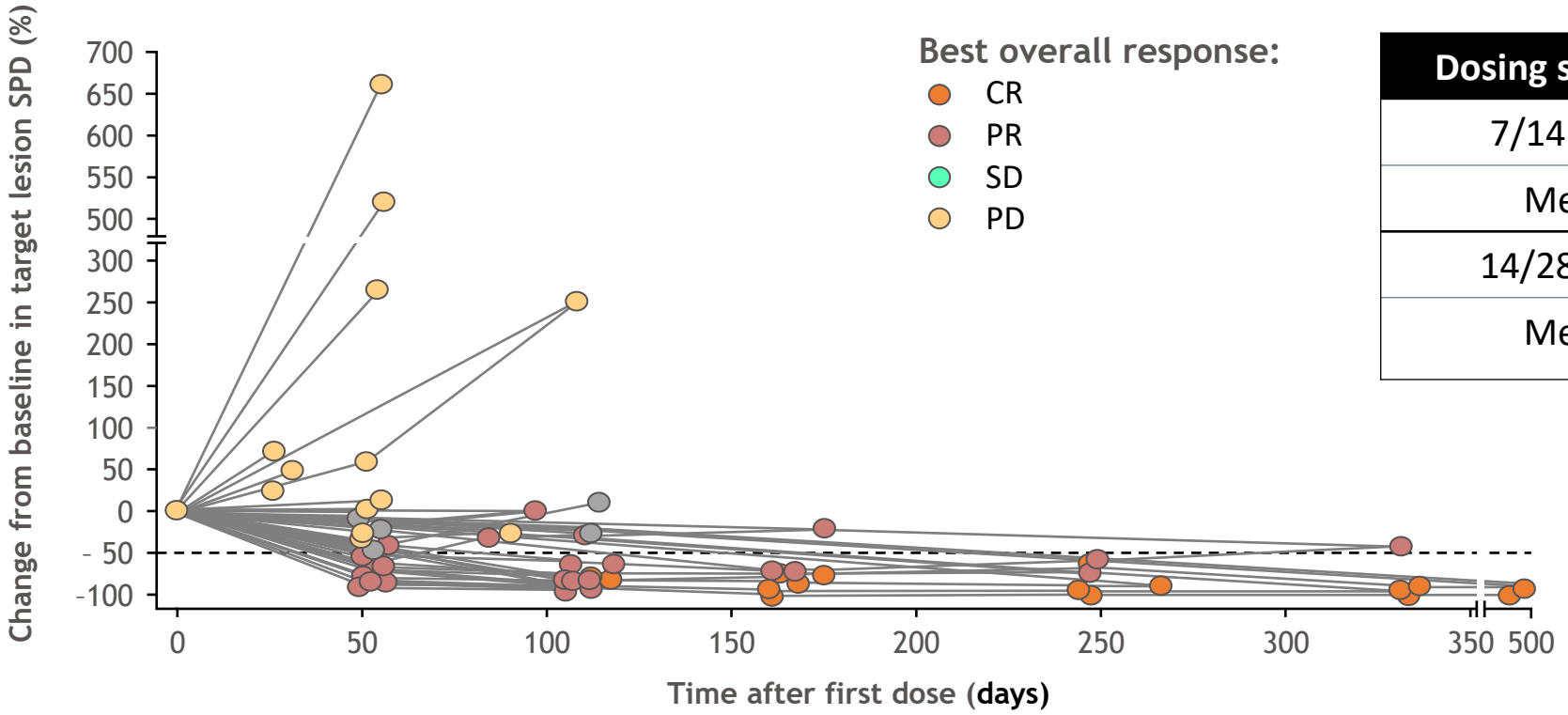


Michot JM, EHA 2022 S216

CR, complete response; Disc, discontinuation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment.

- Median time to response was 53 days (range, 50–107)[a]

Change in SPD of target lesions over time



Dosing schedule	Median DOR (range)[a]
7/14 days	239 days (48–587)
Mean follow-up: 247 (21–690) days	
14/28 days	112 days (63–414)
Mean follow-up: 121 (22–464) days	

Michot JM, EHA 2022 S216

[a]Based on the time to response observed (not censored) values for responders, patients who did not respond were not included in this calculation.

CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of product of diameters.

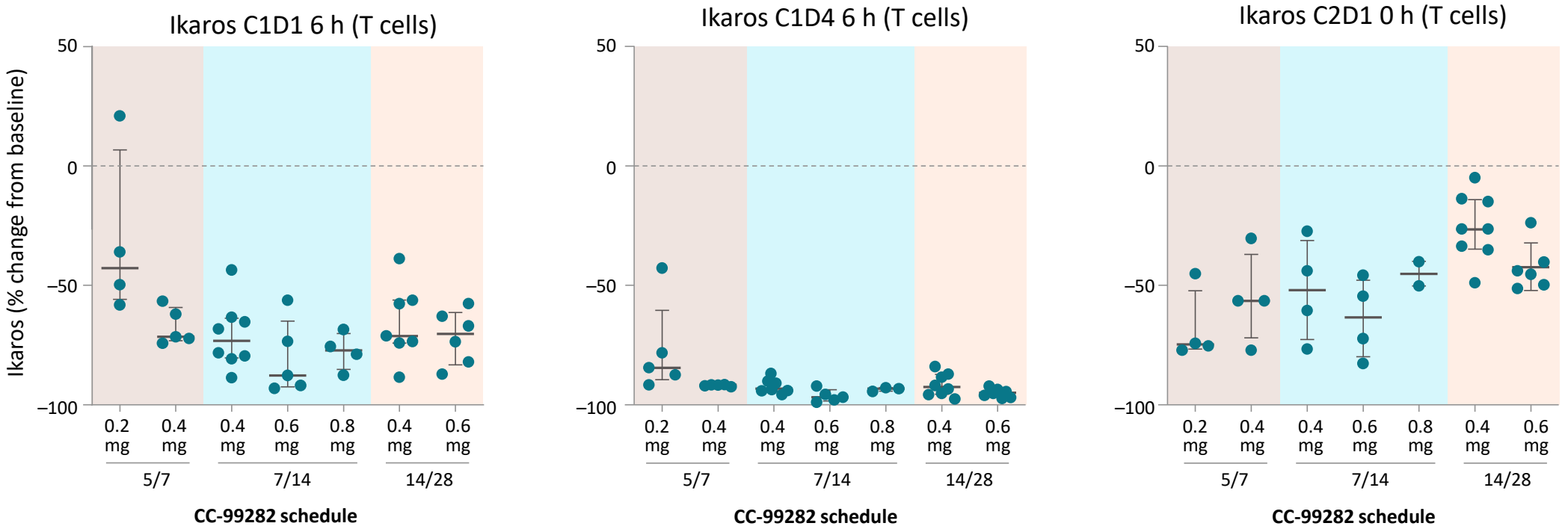
Potent degradation of Ikaros/Aiolos in peripheral T cells, following CC-99282 treatment

- Degradation of Ikaros/Aiolos in peripheral T cells in patients treated with CC-99282 occurred in a dose-dependent manner at early time points, reaching maximal degradation (> 90%) by day 4 of treatment at doses ≥ 0.4 mg

Fast degradation
> 70% Ikaros/Aiolos degradation 6 h after a single dose at doses ≥ 0.4 mg

Deep and sustained degradation
Maximal degradation (> 90%) by day 4 at doses ≥ 0.4 mg

Schedule-dependent recovery
14 consecutive non-dosing days needed for significant recovery



Ikaros expression measured in peripheral blood CD3+ T cells at C1D1 6 hours post-dose, C1D4 6 hours post-dose, or C2D1 0 hours pre-dose normalized to baseline (average of screening and C1D1 pre-dose). Each point represents an individual patient. Flow cytometry was used to measure expression of Ikaros in peripheral CD3+ T cells.

C, cycle; CD, cluster of differentiation; D, day.

Michot JM, EHA 2022 S216

Preliminary Efficacy evaluation in humans of protein degraders targeting Aiolos/Ikaros pathways in RR DLBCL

summary of reported data (for study ≥ 20 subjects)

Drug in monotherapy	Number of subjects	Method	Median previous line (range)	Post ASCT	Post CAR-T	ORR (CR)	References
LEN (CC5013)	N=153	Retrospective study	2 (1-6)	17%	0%	29% (24%)	Broccoli A, Oncologist, 2019
LEN (CC5013)	N= 600	Meta-analysis	Not specified	Not specified	0%	33% (16%)	Jia Li, Front Oncol, 2021
AVA (CC122)	N=97	Phase 1b	3 (1-13)	19%	0%	28% (9%)	Carpio C, Blood 2020
GOL (CC99282)	N=28	Phase 1a	3 (1-8)	20%	28%	32% (11%)	Michot JM, EHA 2022

Targeted Protein Degraders as ideal booster(s) for BCR signaling immunotherapies in B-lymphoma?

Front line DLBCL

Smart start / end type protocol

Alternative or complement to chemo

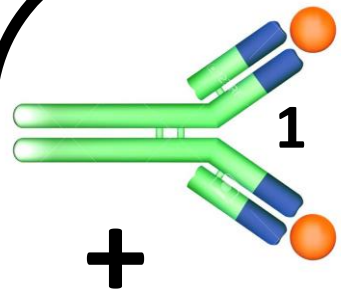
Selected prognostic pop.

Selected biomarker pop.(protein)

Relapse or refractory DLBCL

Eligible to ASCT

Ineligible to ASCT



+

+

Anti-lymphoma directed immunotherapy

aCD20 – aCD19 – CD3xCD20 – ADC - CARTCELLS

Protein degraders acting as immunotherapy booster

LEN – CC99282

Molecular targeted therapy Based on molecular profile

BTK inh – EZH2 inh

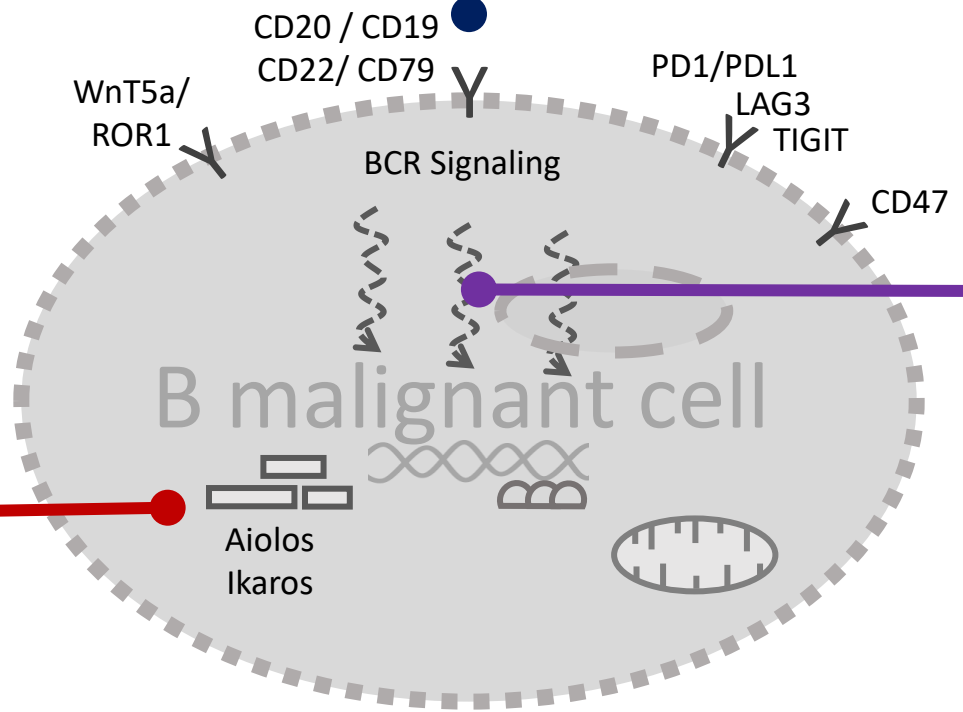
New drugs to treat B-cell aggressive lymphomas

We need

- Multidrug regimens
- Synergy
- tolerability

1/ BCR signaling immunotherapies

MoAb ADC Bispe CART



2/ Targeting Protein degraders
IMIDs – CC99282

3/ Molecular targeted therapies

TKI
BTK inh, PI3K inh, MALT1 inh

Cell cycle inh.
CDK9 inh

EpiDrugs
EZH2 inh, BET inh, KMT2D inh

Conclusion

Tolerance.

- First-in-human data of CC-99282 as a single-agent oral therapy in patients with R/R NHL, showed an expected and manageable safety profile during dose escalation (neutropenia class effect).
- Favorable tolerance profile compared to imids with little or no off-target effect (neutropenia being on-target)?

Efficiency.

- CC-99282 monotherapy demonstrated promising efficacy in heavily pretreated patients with R/R NHL and including post CART responses.
- Therapeutic responses prolonged, very few lost of responses, check update follow-up at ICML 2023 update (Lugano).

In progress and perspectives.

- Doses of 0.2 mg (14/28 day regimen) and 0.4 mg (7/14 day and 14/28 day regimens) continue to be evaluated in the expansion phase in combination with rituximab + additional cohorts to follow in Part B.
- Targeted protein degraders could represent an ideal booster for BCR signaling immunotherapeutic in DLBCL lymphoma in further studies

Aknowledgments

Staff study CC99282NHL01, patients and their families, Sponsor BMS, Poli Patah, Harald Haeske, Study scientists, Site personnal, Romane De Conincke, Drug Dev. Team Antoine Hollebecque, Kaissa Ouali, Anas Gazzah and Ratio Balheda

Translationnal research lab in Hematology, Unit research INSERM U1170 team, Olivier Bernard, Cyril Quivoron

And Gustave Roussy Staff and football team

Clinical Hematology Department at Gustave Roussy, Vincent Ribrag, Stéphane De Botton
Julien Lazarovici, Alina Danu, Camille Bigenwald, Loic Renaud, Sabine Khalife, Jean-Henri Bourhis, Sylvain Pilorges, Jean Baptiste Micol, Florence Pasquier, Christophe Willekens, David Ghez, Tereza Coman, Care teams and medical assistants.