Follicular Lymphomas Workshop

Bologna
Royal Hotel Carlton
May 7, 2024

President: *Pier Luigi Zinzani*

NEW AGENTS: Golcadomide (CC-99282)

Dr Michot Jean-Marie

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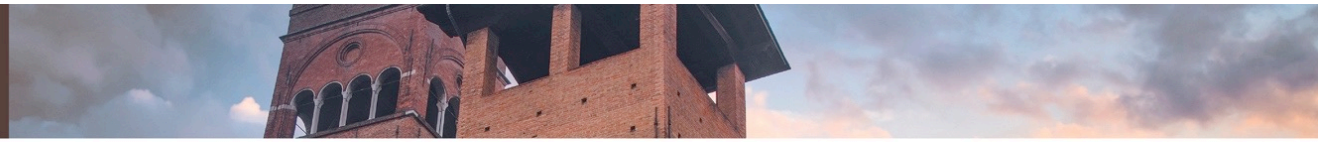
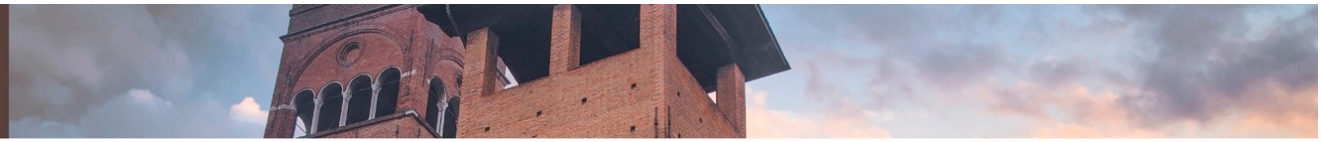


Disclosures of Dr Jean-Marie Michot

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead			x				
Regeneron							x
GSK	x						x
BMS							x



Background on follicular lymphoma

- Follicular lymphoma (FL) is the most common indolent lymphoma entity[1]
- FL is a chronic disease whose evolution is punctuated by several phases of treatment with few perspectives of curative treatment intent to date[2]
- Standard first-line treatment is based for more than 20 years on immunochemotherapy (R-CHOP or R-CVP or R-BENDA) with toxicities related mainly to chemotherapy[2]
- Relapses or refractory FL can be difficult to treat, particularly in cases of resistance to immuno-chemotherapy or early relapse (POD24)[3]

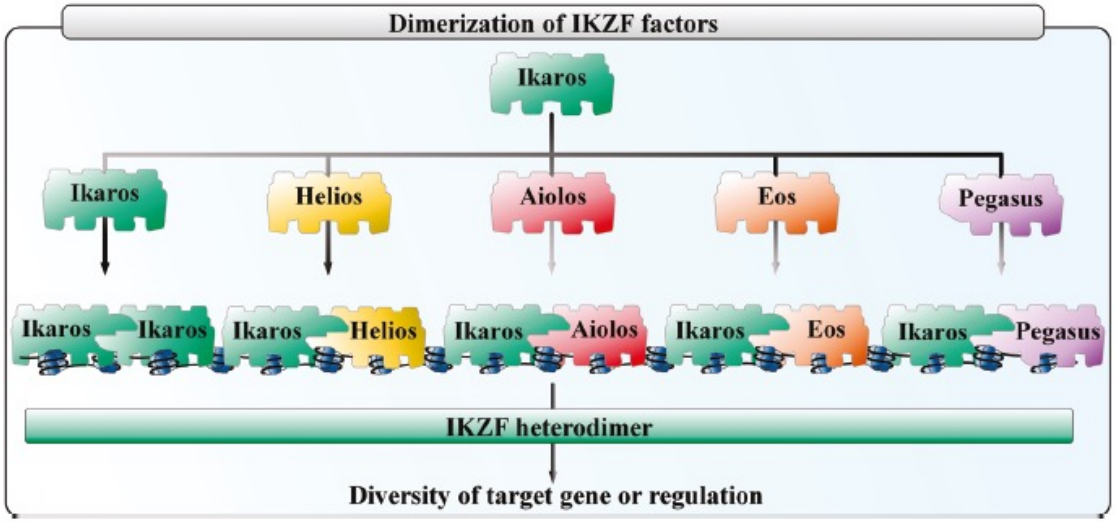
➔ *Better understanding the sources of the disease and the search for new therapeutic targets is important to consider to optimize therapies and/or new intent into curative perspectives.*

Michot JM, et al. ICML 2023 [Presentation #90]

1-Armitage JO, Lancet 2017; 2-Casulo C, JCO 2015; 3-Casulo C, Lancet Haematol 2022.

AIOLOS (IKZF3) a transcription factor targetable in B-cell lymphoma

AIOLOS & IKAROS family members[1]



AIOLOS functions[2,3]

Lymphopoïèse regulation
T cell – B cell différentiation

Immune system
Immune defenses
Gammaglobulins

Mature lymphocyte modulation
Modulate gene expression
Modulate chromatine state (PRC2 and NuRD complexes)

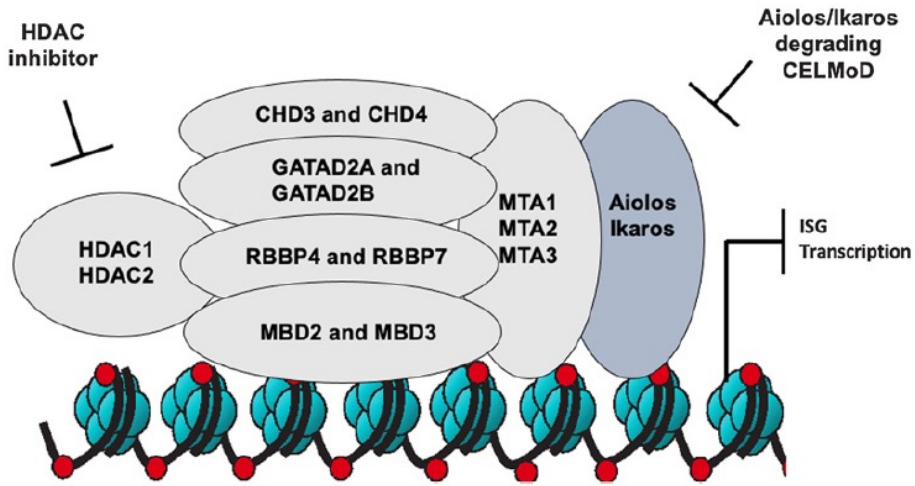
Human diseases
Leukemia
Immune deficiency (CIVD)
Lymphoma
Autoimmune diseases

1- Heizmann B, Curr Opinion in Immunology, 2017; 2- Kuehn H, JCI, 2020

AIOLOS (IKZF3), transcription factor targetable in B-cell lymphoma

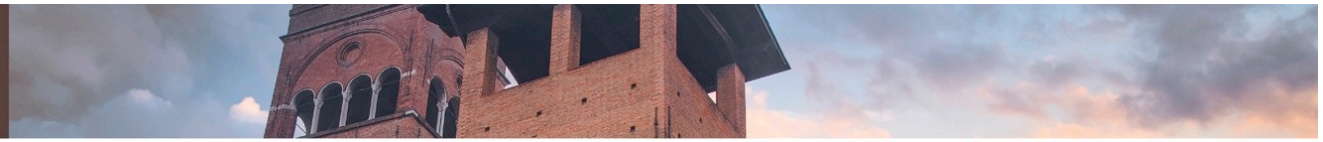
- IKAROS family members are widely involved in **B-ALL leukemia with driver mutations**
- **Not mutated in mature lymphomas**, not considered as a driver event.
- The driver genetic events in lymphoma (BCL6, PAX5, and EZH2[1]) could be **under the control of transcription factors such as AIOLOS / IKAROS**[1,2]
- In preclinical lymphoma cell lines, AIOLOS/IKAROS cooperate **in transcriptional repressor NuRD** complex (nucleosome remodeling and deacetylase)[2]

Model of avadomide and HDAC1/2 inhibition of NuRD complex transcriptional repression to upregulate expression of ISGs[2]

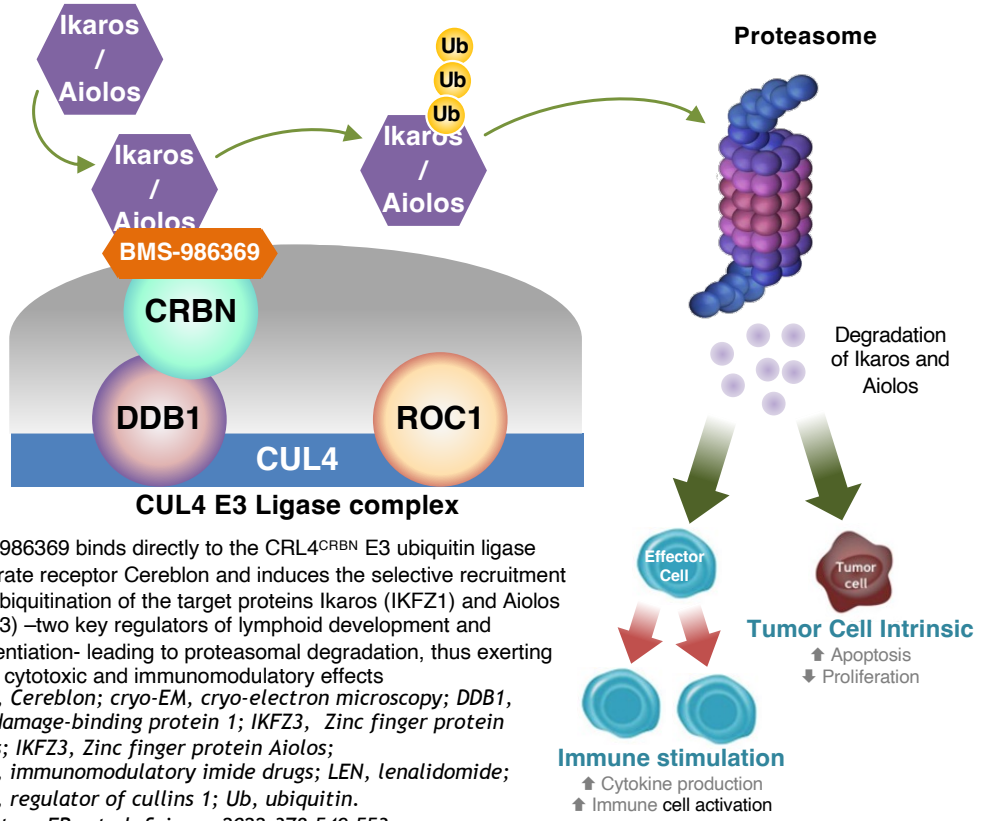


ISG= interferon-stimulated genes

1- Reddy A, Cell 2017; 2-Hagner P, CCR 2022.



Golcadomide (CC-99282) is a potent first-in-class lymphoma Cereblon E3 ligase modulator (CELMoD®) with pleotropic MoA



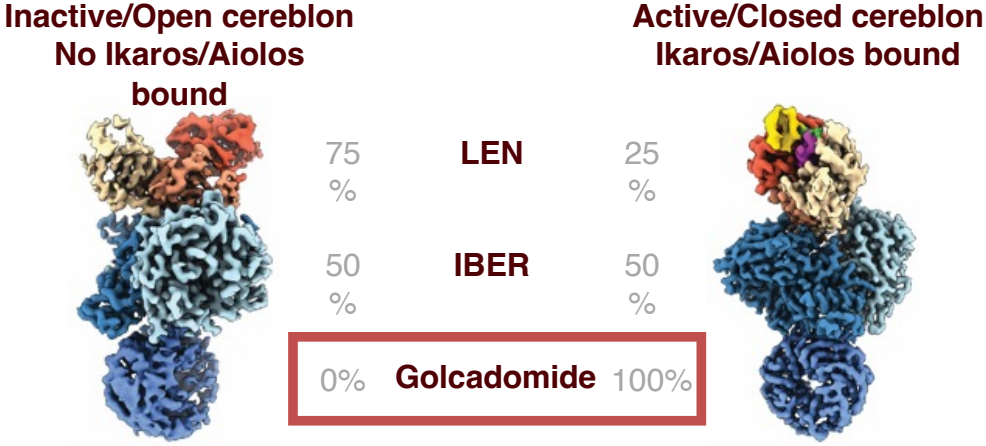
CUL4 E3 Ligase complex

BMS-986369 binds directly to the CRL4^{CRBN} E3 ubiquitin ligase substrate receptor Cereblon and induces the selective recruitment and ubiquitination of the target proteins Ikaros (IKFZ1) and Aiolos (IKFZ3) –two key regulators of lymphoid development and differentiation- leading to proteasomal degradation, thus exerting direct cytotoxic and immunomodulatory effects

CRBN, Cereblon; cryo-EM, cryo-electron microscopy; DDB1, DNA damage-binding protein 1; IKFZ3, Zinc finger protein Ikaros; IKFZ3, Zinc finger protein Aiolos; IMiDs, immunomodulatory imide drugs; LEN, lenalidomide; ROC1, regulator of cullins 1; Ub, ubiquitin.

1. Watson ER, et al. Science 2022;378:549-553

Allosteric regulation of cereblon[1]



- Recent cryo-EM data indicates that the cereblon complex has both an ***open, inactive state*** and a ***closed, active state*** and that IMiDs and CELMoDs drive the closed conformation[1]
- Due to the unique binding modes of BMS-986369 it is more efficient than LEN at driving the closed conformation,[1] leading to deeper and more rapid degradation of Ikaros/Aiolos

CC-99282-NHL-001 (NCT03930953) is a multicenter, phase 1, open-label, dose-finding, first-in-human 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

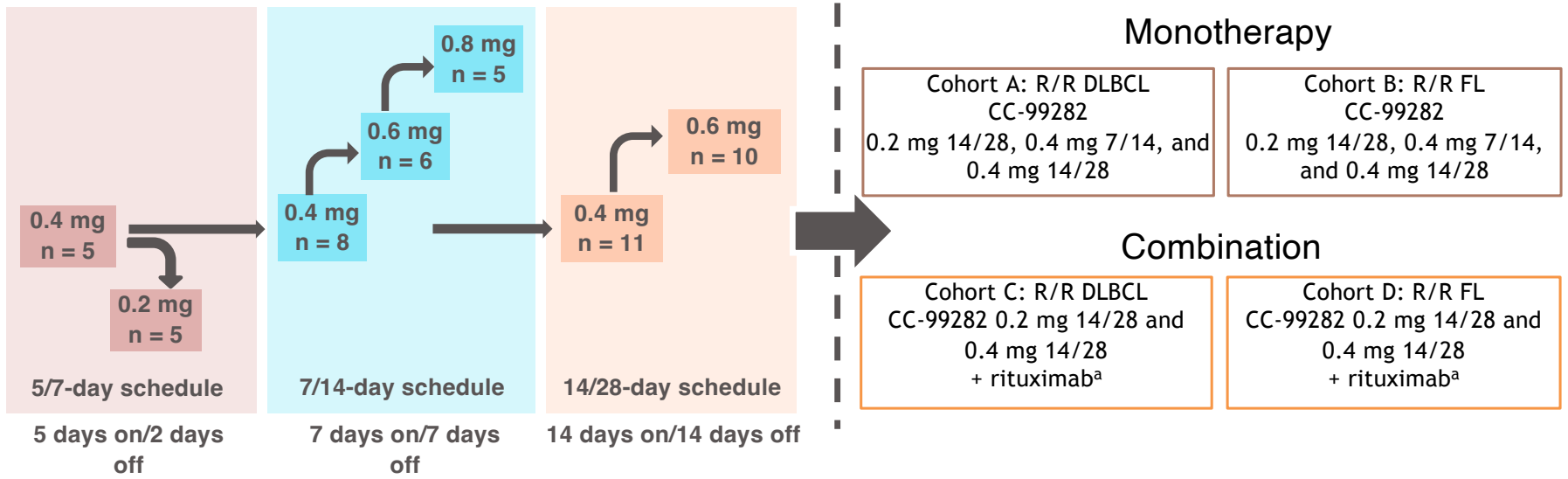
Secondary objective

PK, preliminary efficacy

Exploratory objective

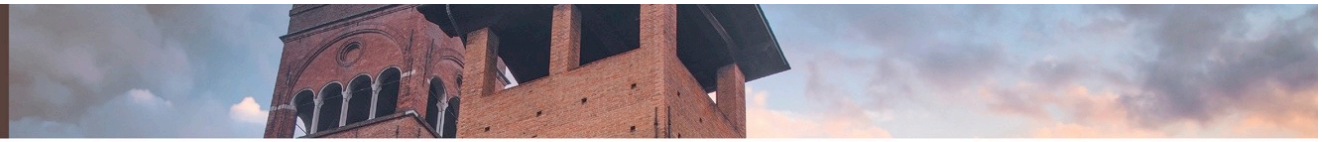
Pharmacodynamics

Duration of treatment is up to 2 years



[a]Rituximab dosing was 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2-5.

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

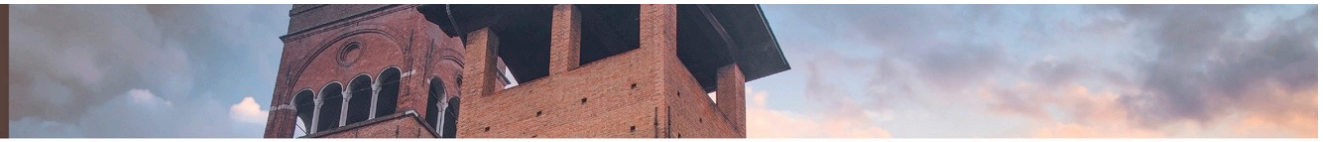


Baseline characteristics of patients enrolled in part A (CC-99282-NHL-001 study)

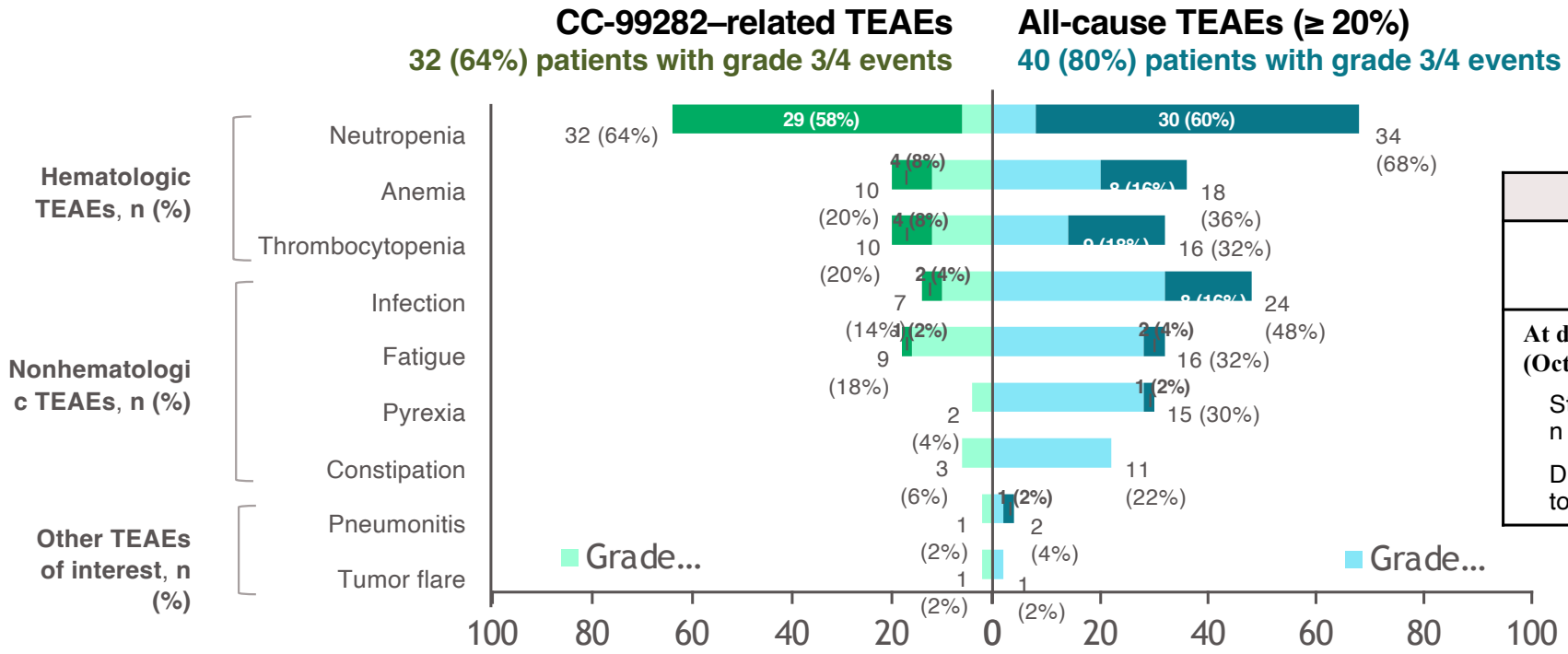
Characteristic		All patients (N = 50)
Age, years, median (range)		65.5 (35–89)
Sex, male, n (%)		29 (58)
Diagnosis, n (%)	DLBCL	38 (76)
	NOS	22 (44)
	Double-hit or triple-hit positive[a]	7 (14)
	Transformed	16 (32)
	FL (grade I to grade IIIB)	12 (24)
Time from initial diagnosis to first dose, months, median (range)	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.

[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.



Common (≥ 20% all-cause) TEAEs and other TEAEs of interest[a]



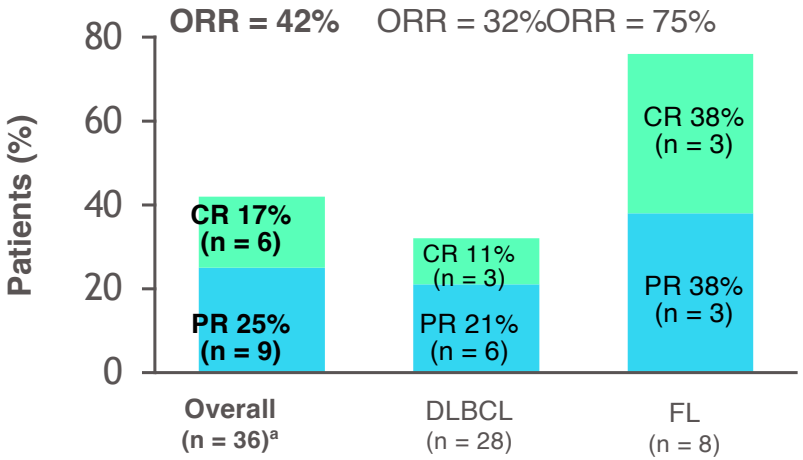
Treatment duration	
Median: 8.2 weeks (range, 3.7–96.0)	
At data cutoff (October 6, 2021):	
Still on treatment, n (%)	17 (34%)
Discontinued due to PD, n (%)	26 (52%)

- Neutropenia, a class effect of CELMoD agents, was manageable with dose modifications and G-CSF support (31 [62%] patients)
- No patients permanently discontinued treatment with CC-99282 due to neutropenia

[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.

Promising activity of CC-99282 monotherapy in heavily pretreated patients with R/R NHL

Overall response by tumor type (≥ 0.4 mg CC-99282)



Response at 0.4 mg (the dose of interest) in dosing schedules of interest

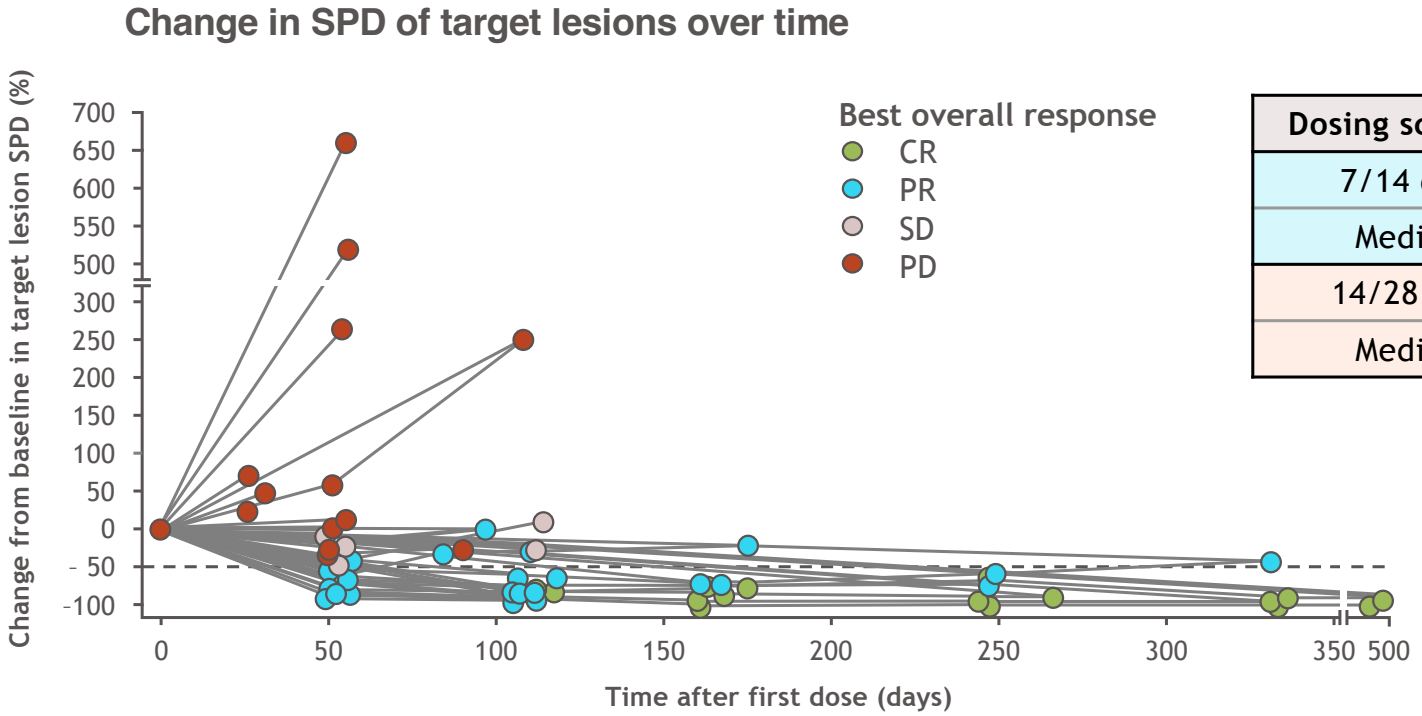
Response	7/14 days (n = 8)	14/28 days (n = 11)
PR + CR	38% (n = 3)	45% (n = 5)
CR	25% (n = 2)	36% (n = 4)

- 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

[a]Three patients treated with 0.6 mg on the 14/28 days schedule and 1 patient with 0.6 mg on the 7/14 days 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 drug; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PR, partial response; R/R, relapsed or refractory.

Depth of response over time in patients treated with CC-99282 monotherapy

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



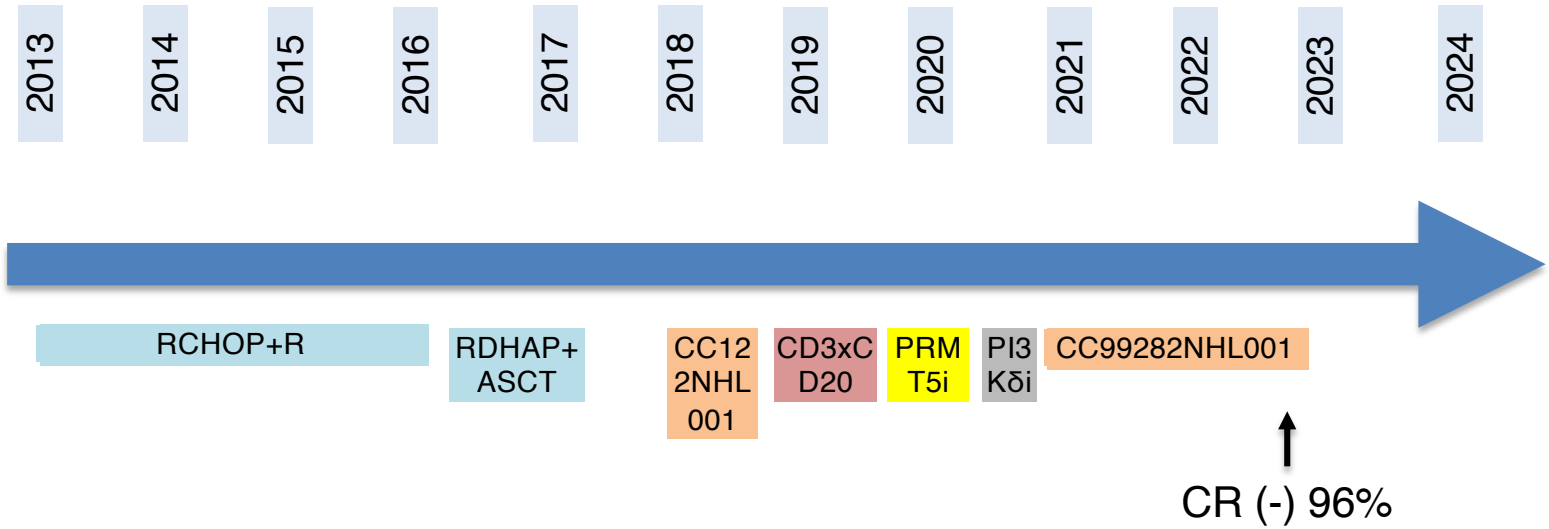
Dosing schedule	Median DOR (range)[a]
7/14 days	239 days (48-587)
Median follow-up: 247 (21-690) days	
14/28 days	112 days (63-414)
Median follow-up: 121 (22-464) days	

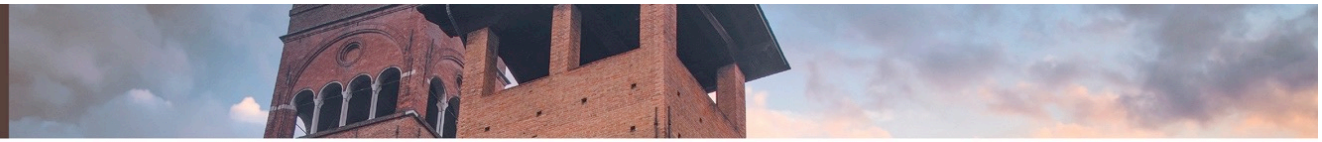
[a]Based on the time to response observed (not censored) values for responders; patients who did not respond were not included in this calculation. CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of product of diameters.

Case study picture

Clinical summary:
- Man 49 y/o
- FL
- G1 WHO
- AA stage IV

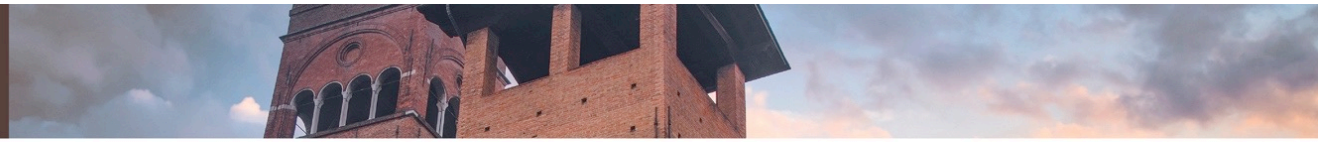
Molecular profile (tumor sample) mut:
- CREBBP/KAT3A
- BCL2
- KMT2D/MLL2
- GNA13
- EP300
- MEF2B





Conclusion

- The transcription factor AIOLOS continues to represent a new therapeutic target in B-NHL including FL
- Golcadomide by targeting AIOLOS produces meaningful antitumor efficacy (update data to see at EHA meeting) in B-NHL.
- The tolerance profile of GOLCADOMIDE is acceptable and as expected mainly neutropenia
- Several combination therapeutic trials are underway with golcadomide for B-NHL, in particular agents targeting EZH2 and bispecific CD20xCD3.



Golcadomide for NHL - ongoing Studies

CC-99282-NHL-001
NCT03930953

- Phase 1/2
- R/R DLBCL and R/R FL
- Monotherapy and in combination with other anti-lymphoma agents

Enrolling

CC-220-DLBCL-001
NCT04884035

- Phase 1
- 1L DLBCL
- Combination with R-CHOP or Pola-R-CHP

Enrolling

NCT05169515

- Phase 1
- R/R DLBCL and R/R FL
- Combination with mosunetuzumab or glofitamab

Enrolling

NCT05283720

- Phase 2
- R/R DLBCL and R/R FL
- Combination with epcoritamab

Enrolling

NCT06356129

- Phase 3 registrational
- 1L High-Risk LBCL
- Combination with R-CHOP vs R-CHOP

Initiating 1H 2024

CA073-1022

- Phase 2
- 1L FL
- Combination with rituximab vs rituximab + chemotherapy

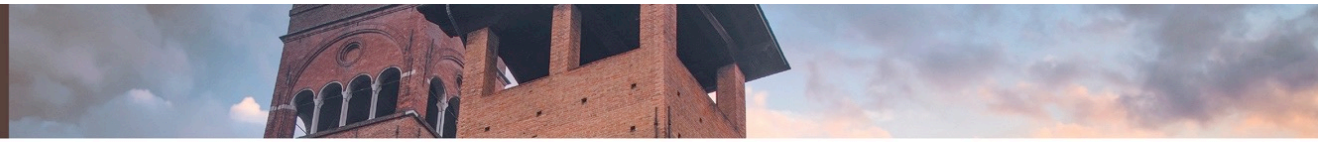
Initiating 2H 2024

NCT06035497

- Phase 1/2 (Phase 2 registrational)
- R/R ATL and R/R PTCL, Japan only
- Monotherapy

Phase 1 enrolling

1L, first line; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; ATL, adult T cell lymphoma, PTCL, peripheral T cell lymphoma, Pola-RCHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory

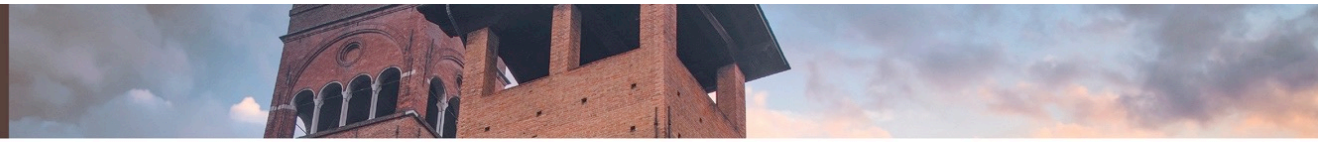


Perspectives to treat B-NHL with chemo free regimens

- Continue the work of understanding the protein targets and transcription factors to be targeted in lymphoma.
- Targeted AIOLOS by protein degraders could represent an ideal booster or synergic effect with BCR-signalling immunotherapy and/or EZH2 inhibitors.
- Select one of the best combinations for the FL which could be based on the CD20/19 axis + AIOLOS axis + EPIDRUG (EZH2) triplet.
- Seek new treatment objectives beyond improving the endpoints of therapies, by considering the curative intent for FL with new combinations.

Michot JM, et al. ICML 2023 [Presentation #90]

Dr JM Michot; Bologna 2024 workshop



Perspectives to treat B-NHL with chemo free regimens

Cooperations and synergistic antitumoral effect of AIOLOS degraders + Epigenetic drugs in lymphoma - *Preclinical results*

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

2022

Interactome of Aiolos/Ikaros Reveals Combination Rationale of Cereblon Modulators with HDAC Inhibitors in DLBCL

Patrick R. Hagner[1], Hsiling Chiu[1], Vivek S. Chopra[2], Martino Colombo[3], Nisha Patel[4], Maria Ortiz Estevez[3], Michelle F. Waldman[1], Remco Loos[3], Fadi Towfic[1], and Anita K. Gandhi[1]

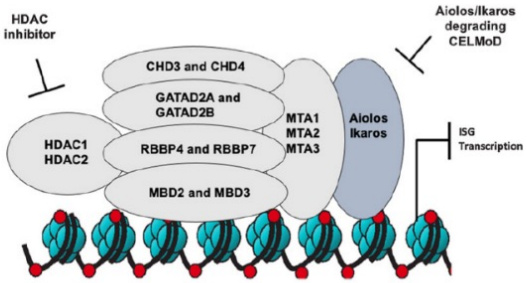


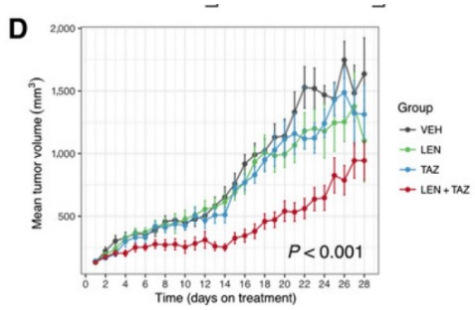
Figure 6.
Model of avadomide and HDAC1/2 inhibition of NuRD complex transcriptional repression to upregulate expression of ISGs. Multipronged approach to inhibition of the NuRD complex through CELMoD-mediated degradation of Aiolos and Ikaros in combination with HDAC1/2 inhibitor, resulting in increased ISG transcription and synergistic antiproliferative activity in DLBCL cells.

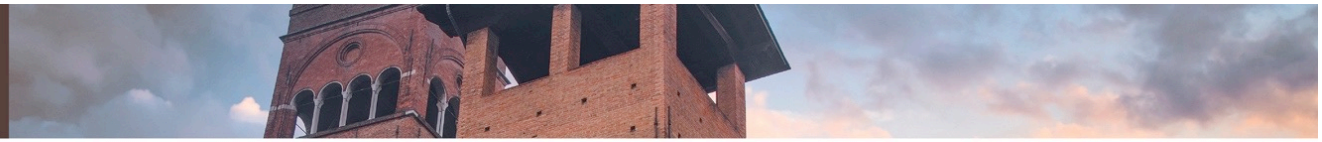
CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

2021

Combined EZH2 Inhibition and IKAROS Degradation Leads to Enhanced Antitumor Activity in Diffuse Large B-cell Lymphoma

Kit I. Tong[1], Sharon Yoon[1,2], Keren Isaev[1], Mehran Bakhtiari[1], Tracy Lackraj[1], Michael Y. He[1], Jesse Joynt[1,2], Anjali Silva[1,3], Maria C. Xu[4], Gilbert G. Privé[1,5], Housheng Hansen He[1,5], Rodger E. Tiedemann[1,5], Elizabeth A. Chavez[6], Lauren C. Chong[6], Merrill Boyle[6], David W. Scott[6], Christian Steidl[6], and Robert Kridel[1,2,5]





Perspectives to treat B-NHL with chemo free regimens

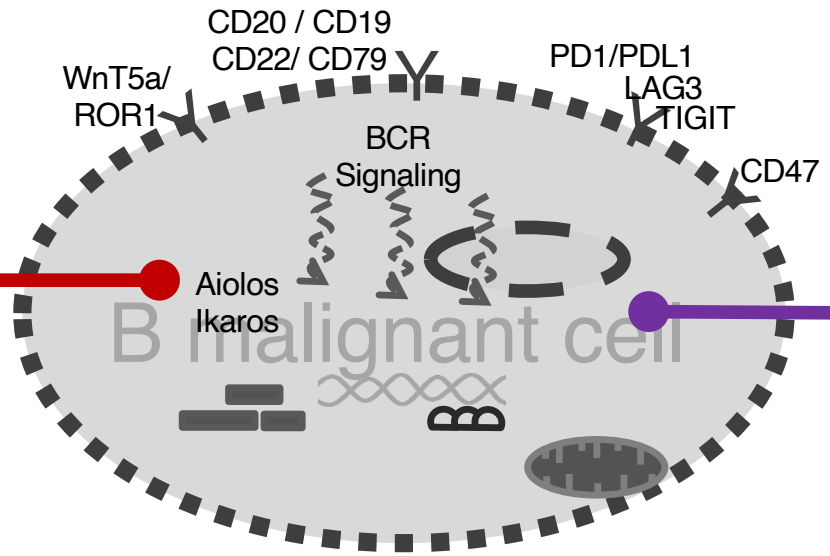
We need

- Multi-drug regimens
- Mutli-class regimens
- With synergy
- With tolerability

1/ BCR signaling immunotherapies

MoAb | *ADC* | *Bispe* | *CART*

E.G. TRIPLET chemofree regimens to treat FL



2/ Targeting protein degraders

IMIDs, CELMOD

3/ Molecular targeted therapies or Epidrugs

EZH2 inh, BET inh, KMT2D inh, BTK inh, PI3K inh, MALT1 inh, Cell cycle inh, CDK9 inh

Aknowledgments

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Sponsor BMS, Parth Rao, Study scientists, Philippe Arnaud, Adrien Petel

And Gustave Roussy Staff and football team

Translationnal Research Lab in Hematology staff, Research INSERM U1170 team, Olivier Bernard, Cyril Quivoron, Aline Renneville, Wassila Rahali

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