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

Iberdomide (CC220)

Javier Munoz

Mayo Clinic Arizona

President: **Pier Luigi Zinzani**

Disclosures

Consulting – Pharmacyclics/Abbvie, Bayer, Gilead/Kite, Beigene, Pfizer, Janssen, Celgene/BMS, Kyowa, Alexion, Fosunkite, Seattle Genetics, Karyopharm, Aurobindo, Verastem, Genmab, Genentech/Roche, ADC Therapeutics, Epizyme, Beigene, Novartis, Morphosys/Incyte, MEI, TG Therapeutics, AstraZeneca, Eli Lilly

Research funding – Bayer, Gilead/Kite, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium, Novartis, Beigene.

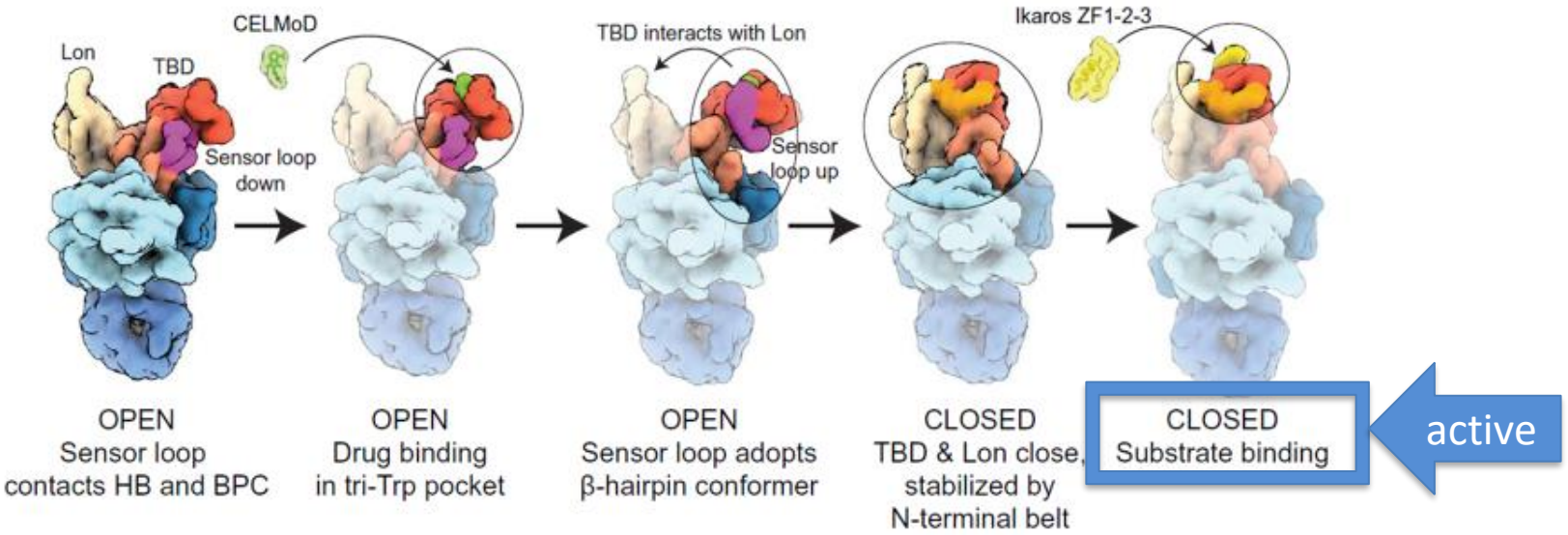
Honoraria - Targeted Oncology, OncView, Curio, Physicians' Education Resource.

Agenda

Oral CELMoD, fixed duration, with activity post CAR

1. Background
2. CC220 NHL trial
3. CC220 + RCHOP trial (Preview)
4. Conclusions

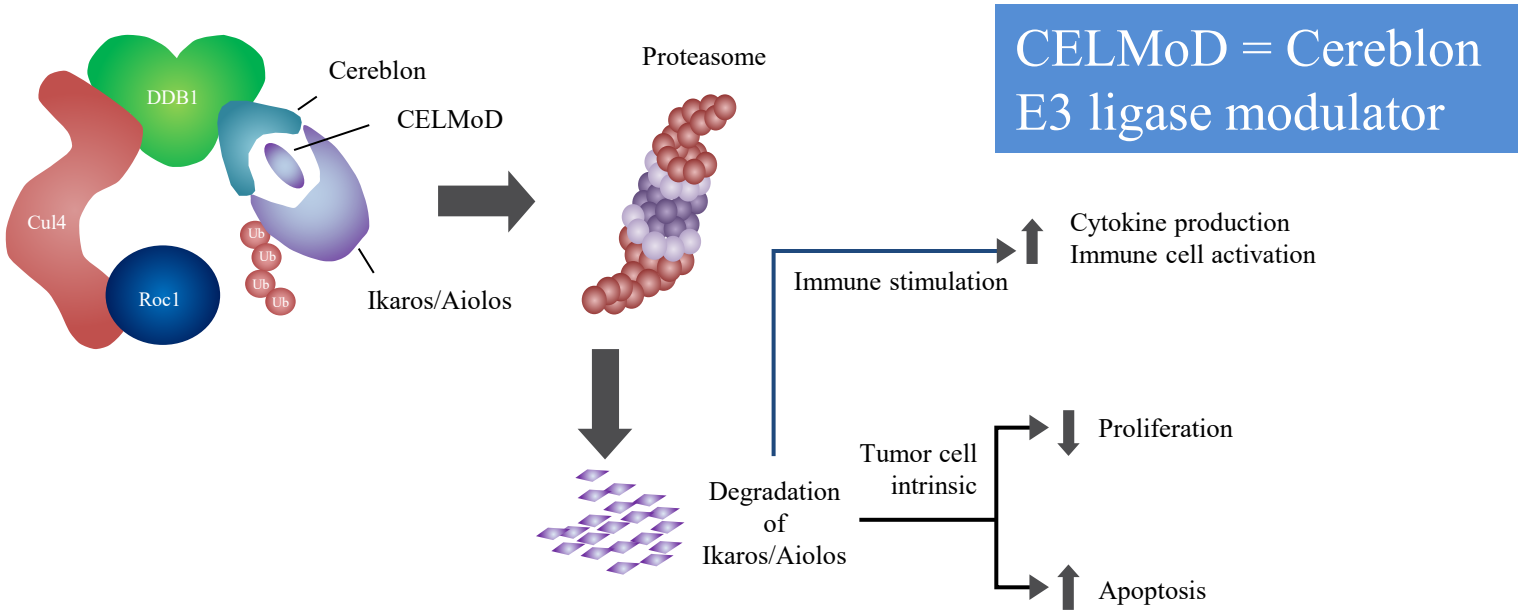
Cereblon Open-Closed Model



Watson ER, et al. *Science* 2022;378:549–553

What does CELMoD stand for?

- CELMoDs **(**IBER and CC-99282) **induce the degradation of** IKZF1 (**Ikaros**)/3 (Aiolos), **leading to antitumor activity**[1,2]
- **CELMoDs build on the efficacy of** IMiDs as **LEN** by **optimizing degradation of target proteins**[3] due to **unique cereblon binding features**[4]



Cul, cullin; DDB; IMiD, immunomodulatory drug; Roc, regulator of cullins; UB, ubiquitin.

1. Fisher *Nature* 2014; 2. Lu G *Science*; 3. Kercher American Chemical Society 2021

We know LEN works better in ABC than GC

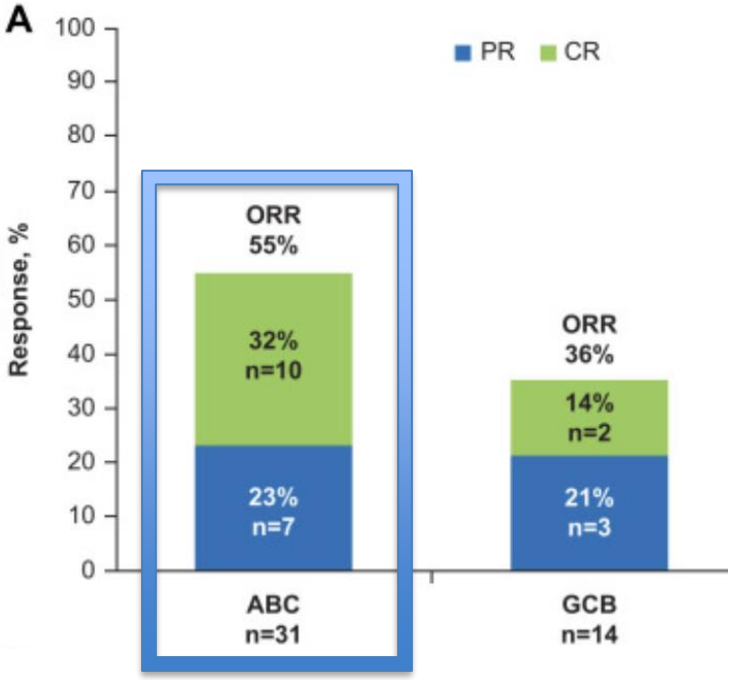
eClinicalMedicine
Part of THE LANCET *Discovery Science*

ARTICLES | VOLUME 56, 101779, FEBRUARY 2023

PDF [471 KB] Figures Save

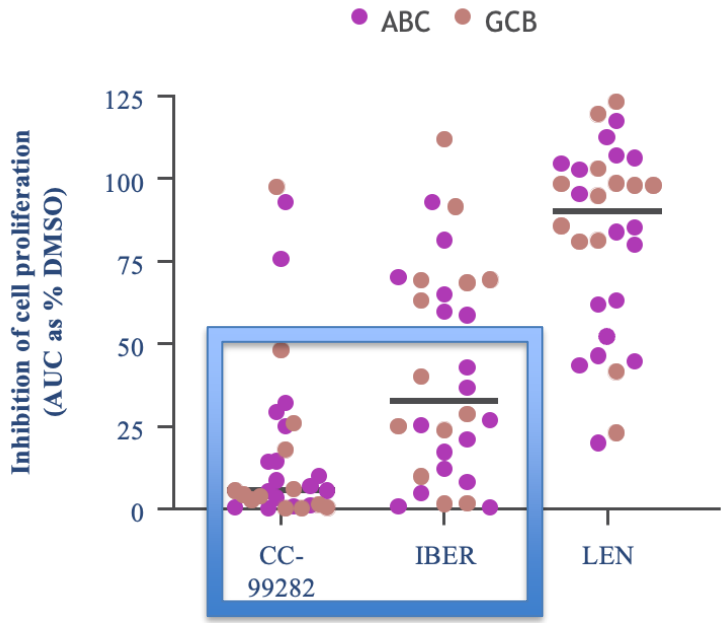
The iR^2 regimen (ibrutinib plus lenalidomide and rituximab) for relapsed/refractory DLBCL: a multicentre, non-randomised, open-label phase 2 study

Radhakrishnan Ramchandren • Peter Johnson • Nilanjan Ghosh • Jia Ruan • Kirit M. Ardeshna • Roderick Johnson • Gregor Verhoef • David Cunningham • Sven de Vos • Shireen Kassam • Luis Fayad • John Radford • Sarah Bailly • Fritz Offner • David Morgan • Javier Munoz [5] • Jerry Ping • Edith Szafer-Glusman • Karl Eckert • Jutta K. Neuenburg • Andre Goy • Show less • Show footnotes



Reminiscent of BTKi

Indeed, LEN works better in ABC than GC; however…



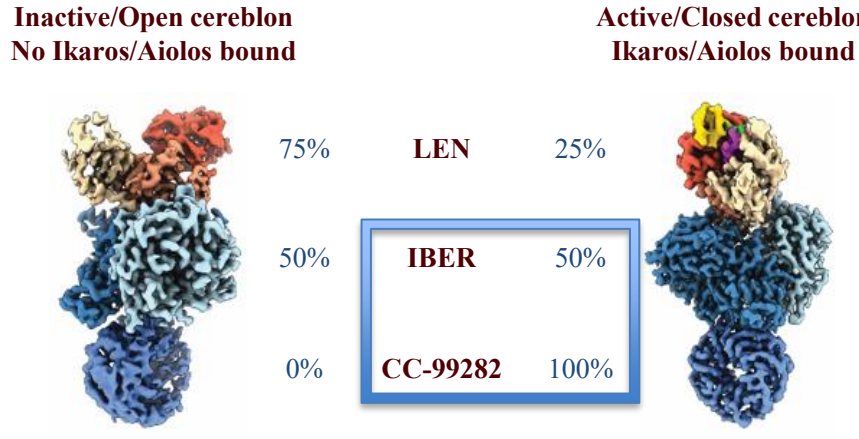
KEY: CELMoDs inhibit proliferation agnostic of COO[1]

ABC, activated B cell; AUC, area under the curve; COO, cell of origin; GCB, germinal center B cell

1.BMS. Data on file. BMS–REF–HEMA–0004.

The cereblon complex has both an open (inactive) state and a closed (active) state[1]

Allosteric regulation of cereblon[1]



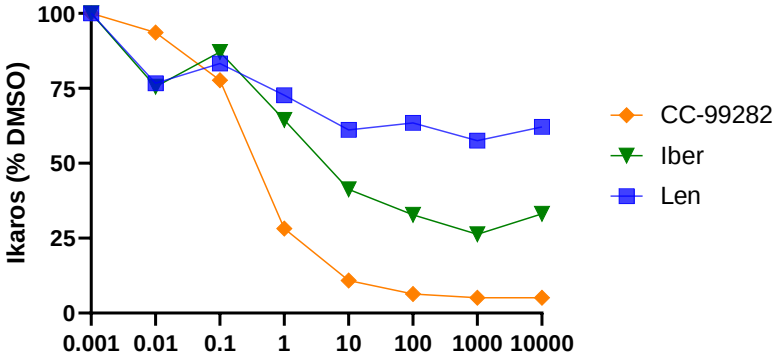
CELMoDs drive the closed conformation more efficiently

1. Watson *Science* 2022

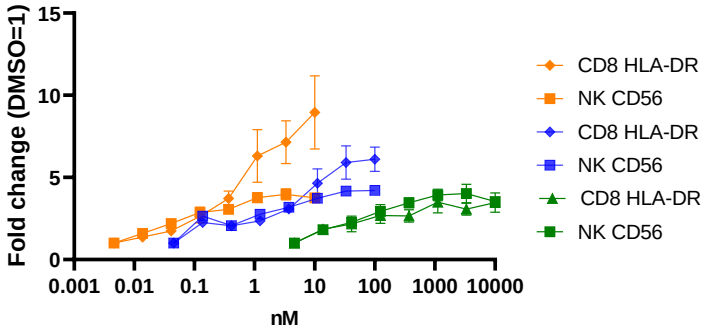
“Comparison is the thief of joy”

Roosevelt

Ikaros degradation



CELMoDs are Immunostimulatory



NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

ClinicalTrials.gov Identifier: NCT04882163

Recruitment Status : Withdrawn (Business objectives have changed)

First Posted : May 11, 2021

Study to Evaluate Tolerability of Iberdomide (CC-220) in Combination With Polatuzumab Vedotin Plus Rituximab or Tafasitamab or Rituximab Plus Chemotherapy in B-cell Lymphoma

Let me briefly remind you

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Diffuse Large B-Cell Lymphoma

SECOND-LINE THERAPY[d,i,j]
(no intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- Anti-CD19 CAR T-cell therapy[r]
  - Lisocabtagene maraleucel
- Polatuzumab vedotin-piiq ± bendamustine ± rituximab[k,l]
- Tafasitamab-cxix[m] + lenalidomide

Other recommended regimens (in alphabetical order)
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- Rituximab

Useful in certain circumstances
- Brentuximab vedotin for CD30+ disease[n]
- Ibrutinib[n,o] (non-germinal center B-cell–like [GCB] DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Mantle Cell Lymphoma

SECOND-LINE AND SUBSEQUENT THERAPY

Preferred regimens (in alphabetical order)
- Covalent BTK inhibitors (continuous)[f,g]
  - Acalabrutinib[h]
  - Zanubrutinib
- Lenalidomide + rituximab

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Follicular Lymphoma (grade 1–2)

FIRST-LINE THERAPY[b]

Preferred regimens (in alphabetical order)
- Bendamustine[d] + obinutuzumab[e] or rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab[e] or rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab[e] or rituximab
- Lenalidomide + rituximab

Perhaps it is time to find a better lenalidomide!

Iberdomide (CC–220) **monotherapy or in combination** with an anti–CD20 monoclonal antibody as effective therapy in patients with relapsed/refractory lymphoma: early results from a phase 1/2 study

Catherine Thieblemont,[1] **Javier Munoz**,[2] Alessandra Tucci,[3] Carlo Visco,[4] Guillaume Cartron,[5] Paolo Corradini,[6] Ian Flinn,[7] Thomas Gastinne,[8] Kamal K. Bouabdallah,[9] Luca Arcaini,[10] Grzegorz S. Nowakowski,[11] Louise Roulin,[12] Max S. Topp,[13] Shekeab Jauhari,[14*] Vladan Vucinic,[15] Peter Martin,[16] Argyrios Gkasiamis,[17] James Drew,[18*] Joanna Mikita–Geoffroy,[17] Parth Rao,[18] Mark Kaplan,[18] Yiming Cheng,[18] Ju Li,[18] Franck Morschhauser[19]

ASH 2022, Presentation 233 (Slides modified by JM)

Study design

Dose escalation
(n = 72)

Dose expansion
(n = 60-80)

Key eligibility criteria

- Aged ≥ 18 years
- **R/R lymphoma**
- **≥ 2 prior LoTs**
- Measurable disease per Lugano 2014
- ECOG PS 0–2

Primary:
MTD and RP2D

Secondary:
Safety, pharmacokinetics, and efficacy

Cohort A
IBER **monotherapy**
Any lymphoma

RP2D

IBER monotherapy
Other lymphoma subtypes

Cohort B
IBER + **RTX**
BCL

RP2D

IBER + RTX
a–BCL

IBER + RTX
Indolent NHL

Cohort C
IBER + **OBI**
Indolent NHL

RP2D

IBER + OBI
Indolent NHL

Treatment occurred in 28-day cycles (24 cycles for all lymphoma; 12 cycles for indolent NHL – FL G1-3a or MZL)

- IBER (part 1 dose range): 0.6–2.0 mg **PO on days 1–21**
- RTX: 375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, then at a dose of 1400 mg SC or 375 mg/m^2 IV on day 1 of cycles 2–5
- OBI: 1000 mg IV on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2–6

Thieblemont C, et al. ASH 2022

Patient characteristics

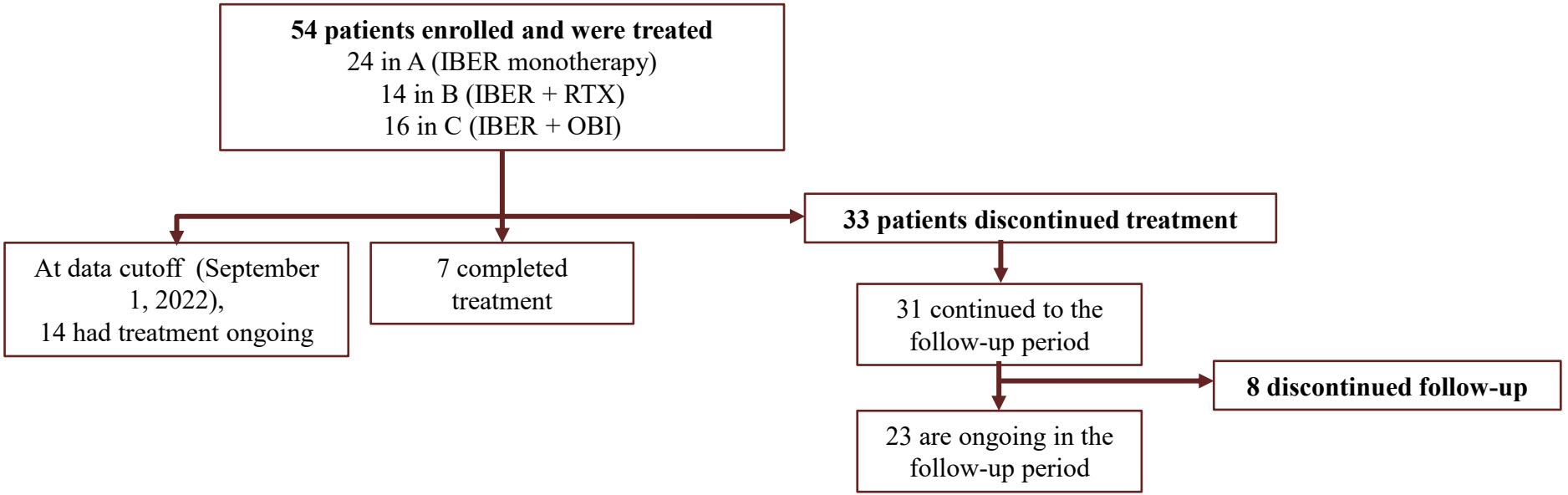
	Cohort A IBER monotherapy (n = 24)	Cohort B IBER + RTX (n = 14)	Cohort C IBER + OBI (n = 16)	Overall (N = 54)
Age, median (range), years	65.5 (28–83)	68.5 (51–82)	70.0 (51–82)	67.5 (28–**83**)
Male, n (%)	18 (75)	10 (71)	9 (56)	37 (69)
Disease, n (%)				
Aggressive B-cell NHL	10 (42)	11 (79)	0	21 (39)
Prior CAR T	5 (21)	6 (43)	0	11 (20)
Prior LEN	4 (17)	4 (29)	0	8 (15)
FL 1–3a	3 (13)	0	10 (63)	13 (24)
MZL	0	0	6 (38)	6 (11)
Other[a]	11 (46)	3 (21)	0	14 (26)
Time since Dx, median (range), years	2.0 (0.7–14.7)	5.8 (0.2–17.9)	6.6 (2.6–18.2)	5.2 (0.2–18.2)
Ann Arbor at diagnosis, n (%)				
I/II	3 (13)	3 (21)	3 (19)	9 (17)
III/IV	20 (83)	10 (71)	13 (81)	43 (**80**)
Prior regimens, median (range)	4 (1–8)	7 (2–12)	4 (2–5)	**4** (1–**12**)
ECOG PS, n (%)				
0–1	22 (92)	10 (71)	14 (88)	46 (85)
2	2 (8)	3 (21)	2 (13)	7 (13)

Median **age was similar** across cohorts
Most patients had **advanced stage (80%)**
Patients had a median of **4 prior anti-lymphoma regimens**

[a]Including MCL, cHL, SLL, and T cell lymphoma;

Data cutoff: September 1, 2022

Patient disposition



- **Patients were exposed to a median** (range) **of 5** (1–20) **cycles of IBER**
- **Median duration of treatment was 4.4 months** for the overall population
- **The patients who discontinued treatment did so mainly due to disease progression (n = 18)**

Thieblemont C, et al. ASH 2022

What about Safety?

Safety population (N = 54), n (%)	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	53 (98)	39 (72)
TEAEs in ≥ 10%		
Hematologic		
Neutropenia	32 (59)	27 (**50**)
Anemia	17 (31)	9 (17)
Thrombocytopenia	12 (22)	8 (15)
Febrile neutropenia	3 (6)	3 (**6**)
Gastrointestinal		
Constipation	12 (22)	0
Diarrhea	10 (19)	1 (2)
Other		
Asthenia	9 (17)	0
Pyrexia	9 (17)	1 (2)
COVID–19	9 (17)	3 (6)
Cough	9 (17)	0
Back pain	7 (13)	1 (2)

Toxicity was primarily hematologic;

Most commonly **neutropenia** (50%)

However, NF only in 6%

Sepsis in 4% of patients

Safety by cohorts

	Cohort A IBER mono (n = 24)	Cohort B IBER + RTX (n = 14)	Cohort C IBER + OBI (n = 16)	Study overall (N = 54)
Evaluable for DLTs (%)	18 (75)	10 (71)	15 (94)	43 (80)
Patients with DLTs (%)	1 (6)	2 (20)	4 (27)	7 (**16**)
Patients with ≥1 IBER dose interruption (%)	22 (92)	13 (93)	13 (81)	48 (89)
Due to AEs (%)	14 (58)	13 (93)	11 (69)	38 (70)
Patients with ≥1 IBER dose reduction (%)	2 (8)	3 (21)	3 (19)	8 (15)
Median relative dose intensity, % (range)	93 (26–100)	82 (40–100)	93 (12–101)	89 (12–101)

- **DLTs were experienced by 16%** of patients: thrombocytopenia, neutropenia, hypercalcemia and face angioedema
- A total of 13 (24%) patients died during the study with **4 deaths from AEs** (acute respiratory failure, sepsis, COVID–19 x2)

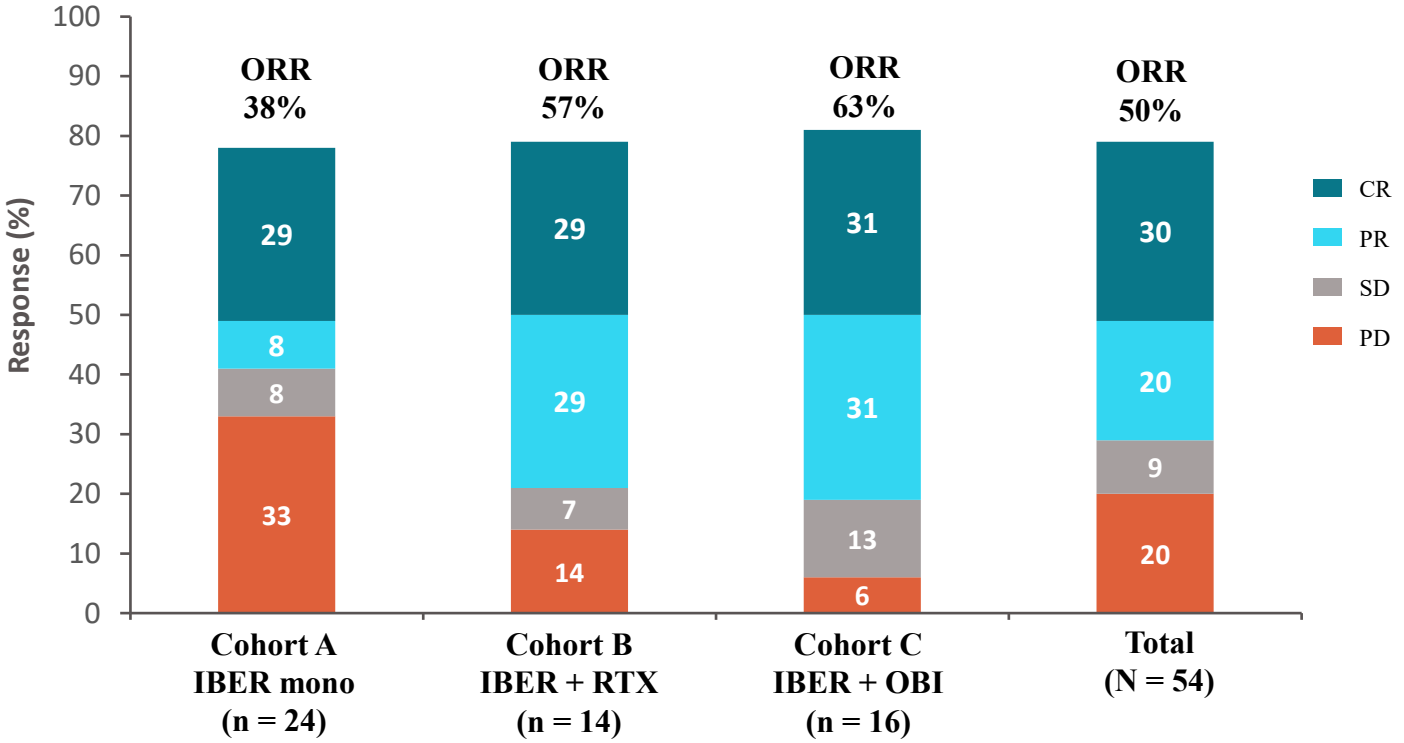
No cohort achieved MTD
No deaths from TEAEs

Data cutoff: September 1, 2022

Thieblemont C, et al. ASH 2022

DLT, dose-limiting toxicity

CC220: Does it work?



- **ORR was 50%** (36–64) and **CR was 30%** (18–44)
- <u>KEY</u>: Of the 12 patients who had received **prior CAR T, 6 achieved CR** and 1 achieved PR

blood

Let me briefly remind you

Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel therapy

Jay Y. Spiegel,[1,*] Saurabh Dahiya,[2,*] Michael D. Jain,[3] John Tamaresis,[1] Loretta J. Nastoupil,[4] Miriam T. Jacobs,[5] Armin Ghobadi,[5] Yi Lin,[6] Matthew Lunning,[7] Lazaros Lekakis,[8] Patrick Reagan,[9] Olalekan Oluwole,[10] Joseph McGuirk,[11] Abhinav Deol,[12] Andre Goy,[13] Khoan Vu,[14] Charalambos Andreadis,[14] Javier Munoz,[15] N. Nora Bennani,[6] Julie M. Vose,[7] Kathleen A. Dorritie,[16] Sattva S. Neelapu,[4] Frederick L. Locke,[3] Aaron P. Rapoport,[2,†] Brian T. Hill,[17,†] and David B. Miklos[1,†]

Table 1. Treatment outcomes for first therapy given after axi-cel progression

Therapy	CR	ORR	Median PFS (95% CI), d	Median OS (95% CI), d
Checkpoint inhibitor based (n = 28*)	18%	46%	88 (35-282)	331 (168-477)
Chemotherapy (n = 17)	12%	18%	51 (21-64)	104 (51-231)
Lenalidomide based (n = 27)	19%	19%	48 (33-84)	139 (45-NE)
Radiation (n = 10)	20%	30%	58 (20-149)	220 (20-NE)

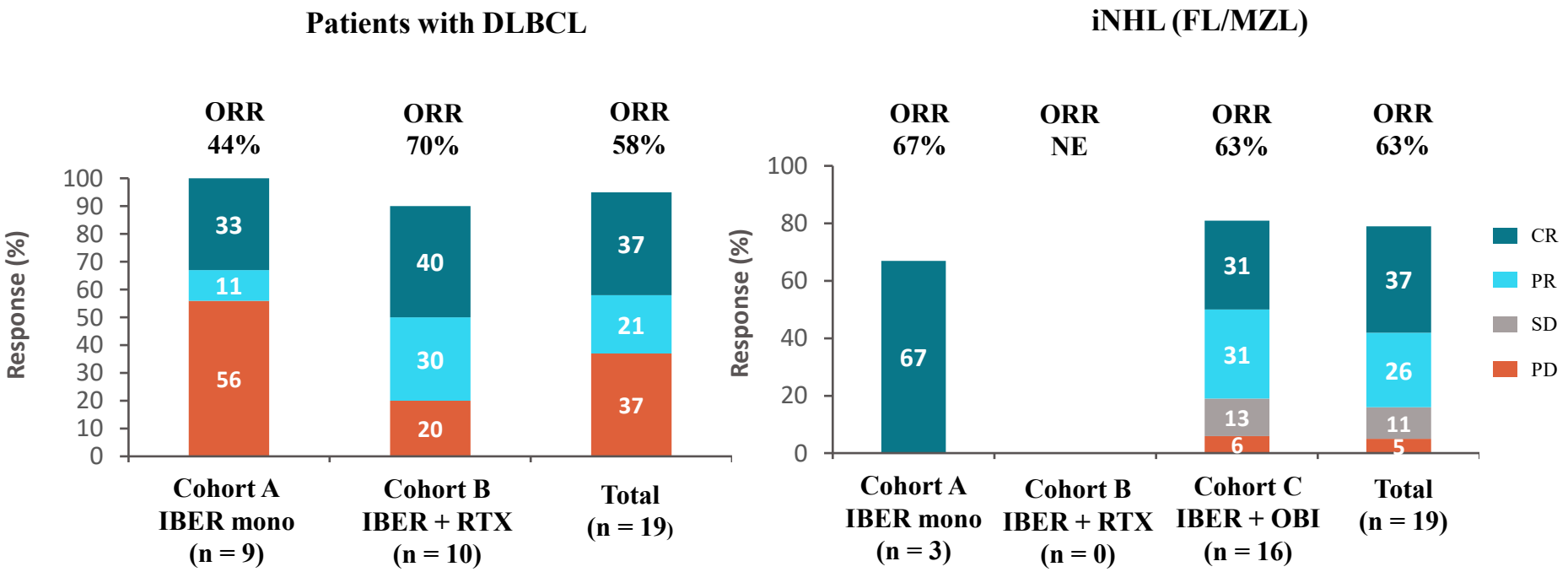
NE, not evaluable.

*Two patients received checkpoint inhibitors but did not have response data available.

Perhaps it is time to find a better lenalidomide!

Blood (2021) 137 (13): 1832–1835

CC220: Response by disease

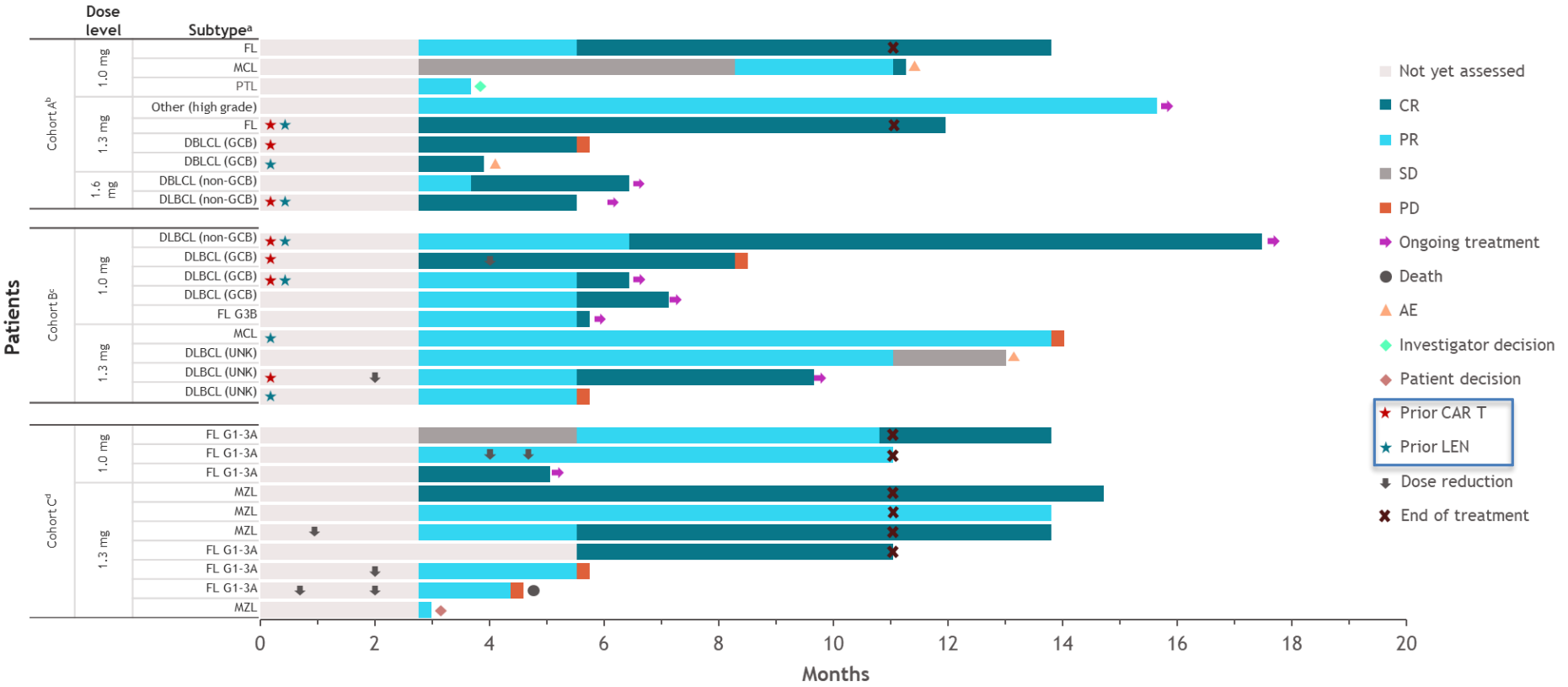


CRs were seen both in aggressive & indolent NHL

Thieblemont C, et al. ASH 2022

Data cutoff September 1, 2022

Duration of response by cohort, dose level, disease



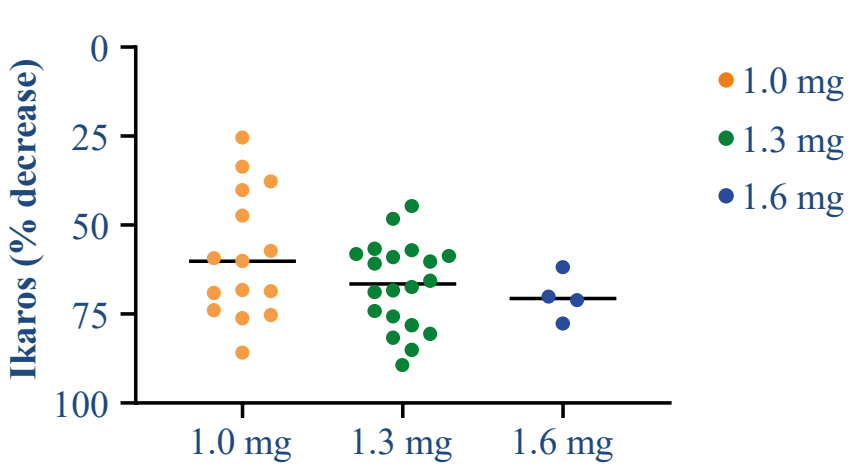
- **Median DOR was 12.9 months** (6.1–NE)
- 10 patients (**35.7% of responders) were continuing treatment** at cutoff

NE, not evaluable; UNK, unknown.

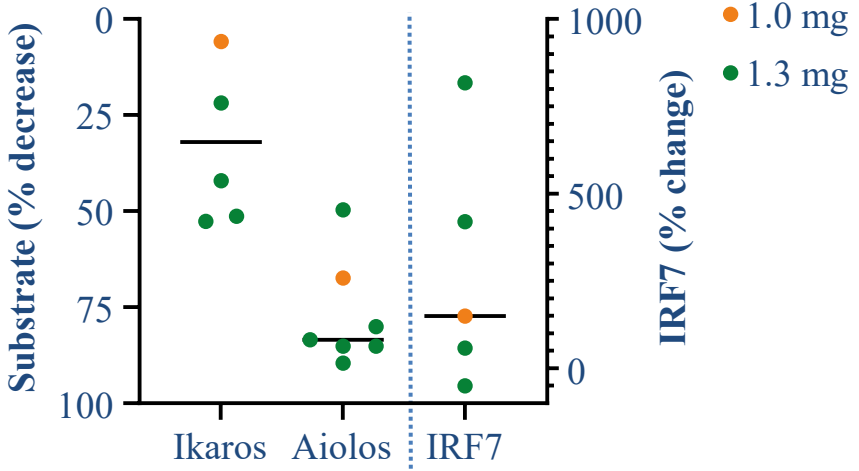
Data cutoff Nov 1, 2022

Iberdomide is pharmacologically active at all tested doses

Ikaros degradation in T cells



Effects in tumor B cells



Higher doses increased Ikaros degradation in B cells (37% at 1.0 mg, 60% at 1.3 mg) but not in T cells (64% at 1.0 mg, 66% at 1.3 mg)

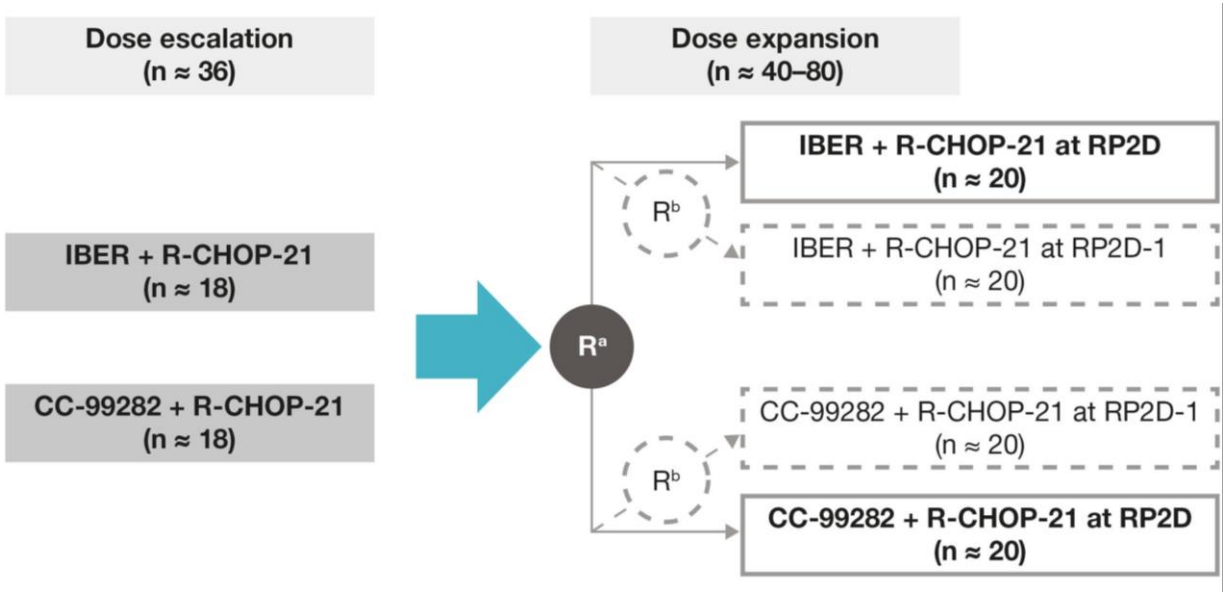
IRF7, interferon regulatory factor 7.

Thieblemont C, et al. ASH 2022

Bristol Myers Squibb. Data on file. BMS–REF–HEMA–0004

Preview: RCHOP + CC220 (or CC-99282)

Phase 1b Trial of Cereblon-Modulating Agents Iberdomide and CC-99282 Plus R-CHOP in Previously Untreated Aggressive B-Cell Lymphoma



Look for an update in Lugano!

1. Blood (2022) 140 (Supplement 1)

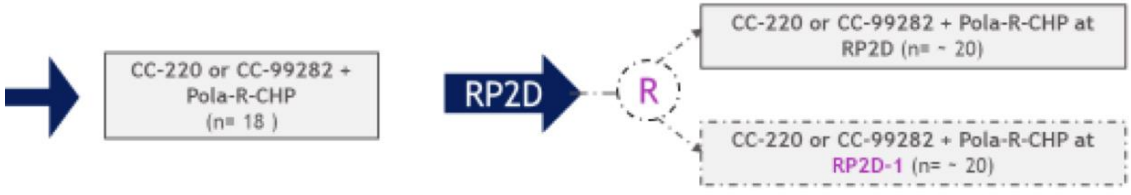
Mea Culpa #1: RCHOP + X

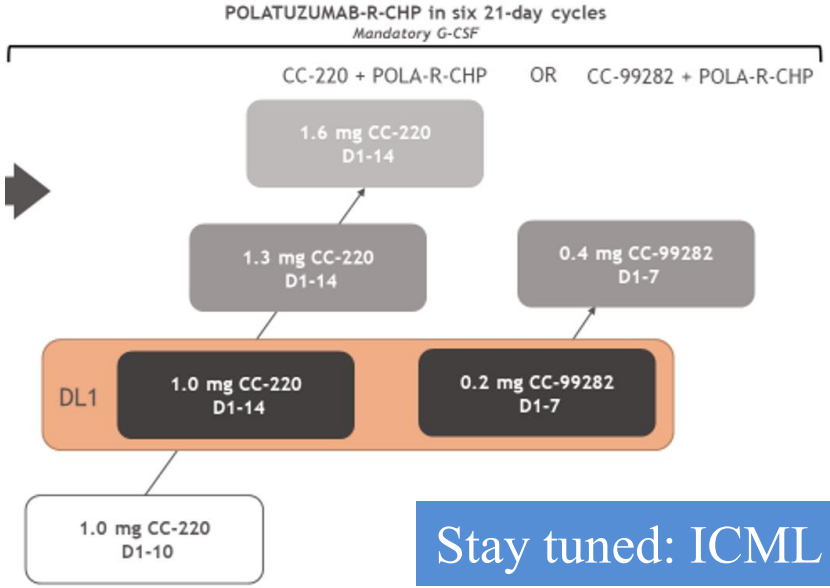
Drug	Dose	Dosing Day(s) (21-day cycle)
Rituximab IV or SC^	375 mg/m^2 or 1400 mg (SC)	1
Cyclophosphamide IV	750 mg/m^2	1
Doxorubicin IV	50 mg/m^2	1
Vincristine IV	1.4 mg/m^2 (max of 2.0 mg total)	1
Prednisone / Prednisolone PO	100 mg	1-5

In combination with R-CHOP	Dose Level	Dosing Schedule
CC-220	1-1.0 mg 2-1.3 mg 3-1.6 mg	Days 1-14 Days 1-14 Days 1-14
CC-99282*	-1 – 0.2 mg 1 -0.4 mg 2a-0.4 mg 2b-0.6 mg	Day 1-7 Day 1-7 Days 1-10 Days 1-7

Peg-G-CSF at D2 or G-CSF D5-13 of each cycle – Mandatory

Mea Culpa #2: Pola-RCHP + X





Stay tuned: ICML Abstract 438

In Summary
(CC220 NHL trial)

1. Safety: IBER was **well-tolerated**
   - Neutropenia was a predictable on–target toxicity manageable with G-CSF
   - Febrile neutropenia and infection were uncommon
2. Efficacy: IBER alone or in combination with mAbs showed **promising activity**
   - High responses seen in DLBCL, independent of COO, as well as in patients who received prior CAR-T

Taken together, these data highlight the promising activity and combinability of CELMoDs in R/R lymphoma

Oral therapy + fixed duration regimen + activity post CAR failure

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Thank you!

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