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

POLICLINICO DI
SANT'ORSOLA

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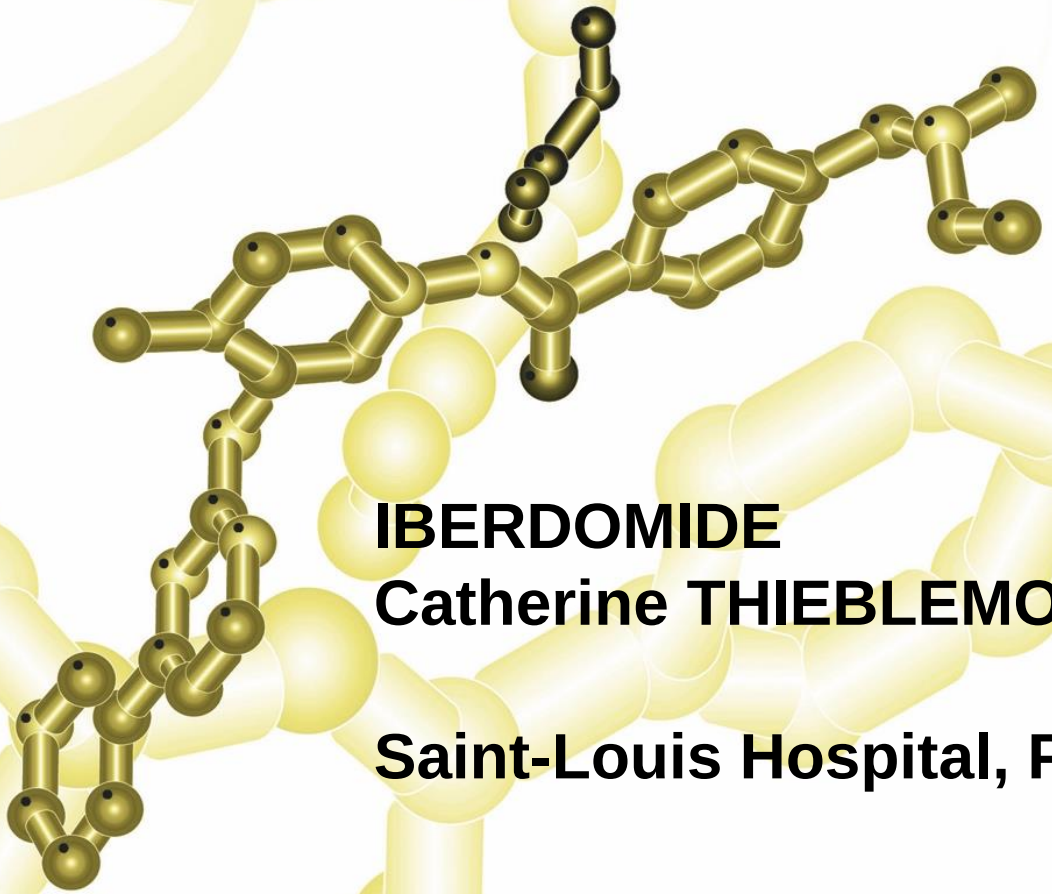
New Drugs in Hematology



IBERDOMIDE

Catherine THIEBLEMONT

Saint-Louis Hospital, Paris, France

President: Pier Luigi Zinzani
Co-President: Michele Cavo

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Royal Hotel Carlton
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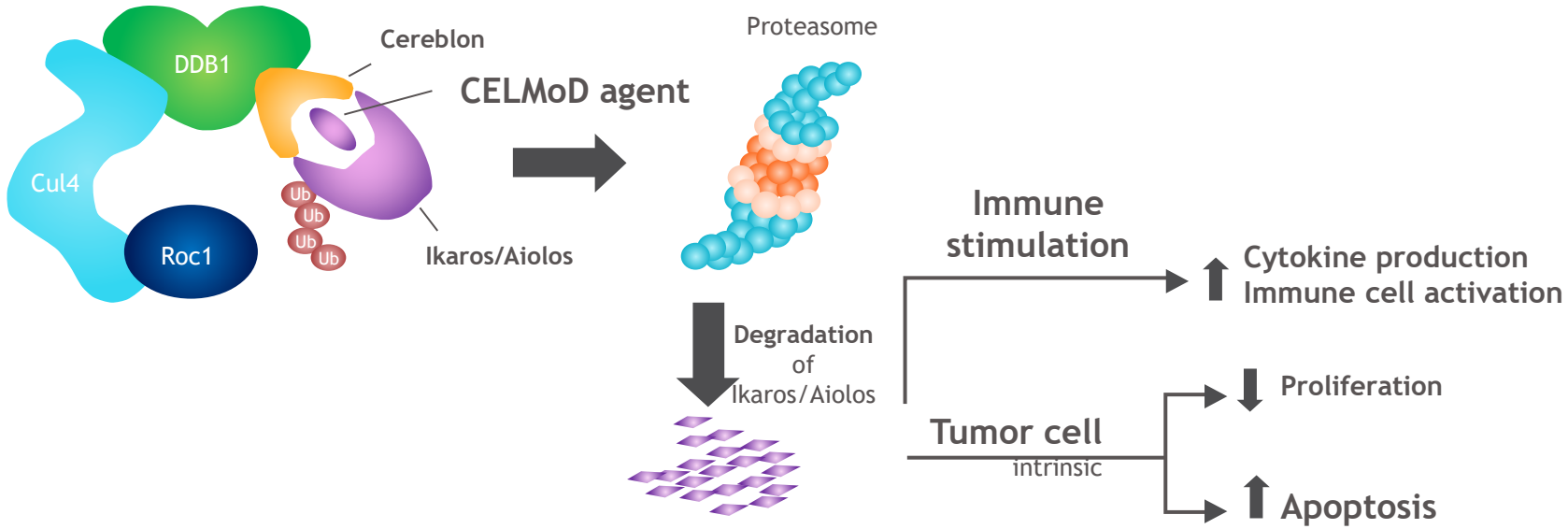
Disclosures of Catherine THIEBLEMONT

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche						x	travel
BMS						x	travel
Kyte/Gilead						x	travel
Novartis						x	travel
Incyte						x	travel
Takeda						x	travel
Abbvie						x	travel

Novel CELMoD agents for lymphoma

- **CELMoD® agents** induce the **degradation of hematopoietic lineage transcription factors** IKZF1 (**Ikaros**)/3 (**Aiolos**), leading to **antitumor and immunostimulatory activities** across hematologic malignancies[1,2]
- Novel CELMoD agents, including **IBERDOMIDE** and **GOLCADOMIDE**, were designed to build on the efficacy of IMiD agents such as LENALIDOMIDE by **optimizing degradation of target proteins and improving tissue distribution** for lymphoma-specific needs[3]
- Although both co-opt cereblon, CELMoD agents are distinct from classic IMiD agents with qualitative differences due to **unique cereblon binding features**[4]



1. Fisher ES, et al. *Nature* 2014;512:49-53; 2. Lu G, et al. *Science* 2014;343:305-309; 3. Kercher T, et al. Oral presentation at American Chemical Society; August 22–26, 2021; Atlanta, GA, USA. Abstract 3584532; 4. Watson ER, et al. *Science* 2022;378:549–553.

CELMoDs are distinct drugs with unique cereblon binding features, resulting in **enhanced target degradation**

Allosteric regulation of cereblon[1]

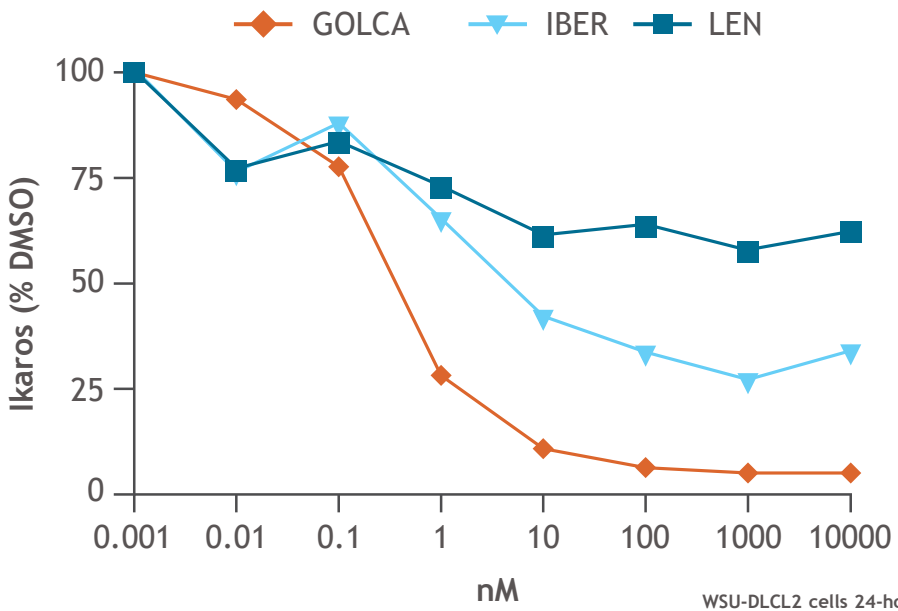
Inactive/Open cereblon
No Ikaros/Aiolos bound

75%	**LEN**	25%
50%	**IBER**	50%
0%	**GOLCA**	100%

Active/Closed cereblon
Ikaros/Aiolos bound

Cryo-EM, cryogenic electron microscopy

Ikaros degradation[2]



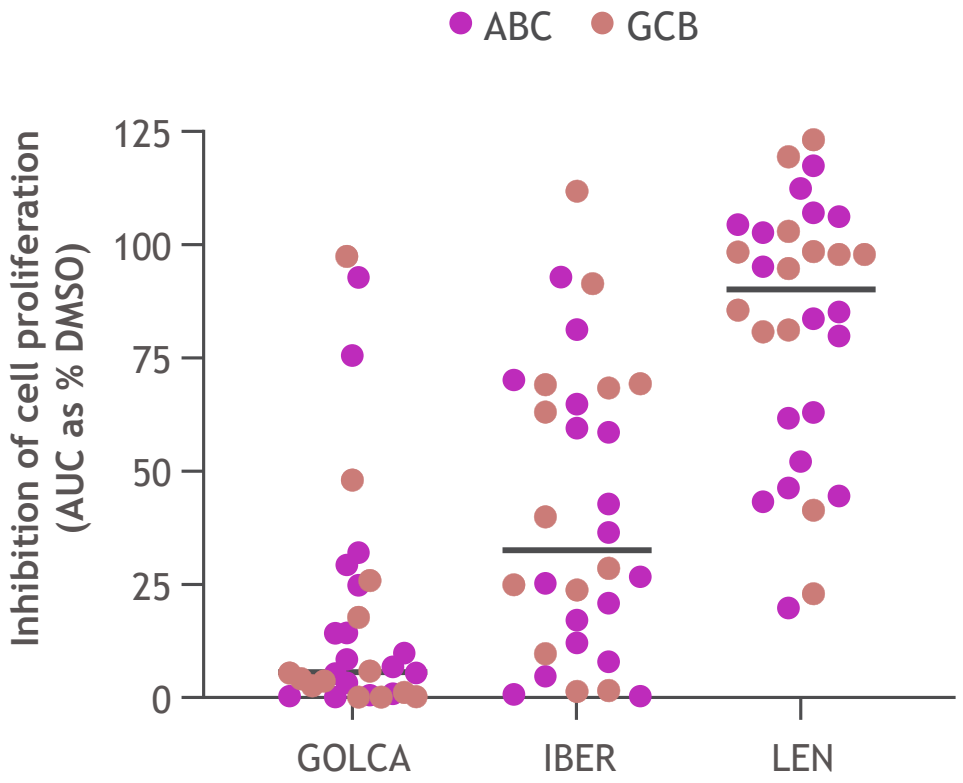
WSU-DLCL2 cells 24-hour treatment
Data cutoff September 1, 2022

- The cereblon complex has both an open, inactive state and a closed, active state [1]
- IBERDOMIDE and Golcadomide are **more efficient** than LEN at **driving the closed conformation** due to the unique binding modes of CELMoDs,[1] **leading to deeper and more rapid degradation of Ikaros/Aiolos**

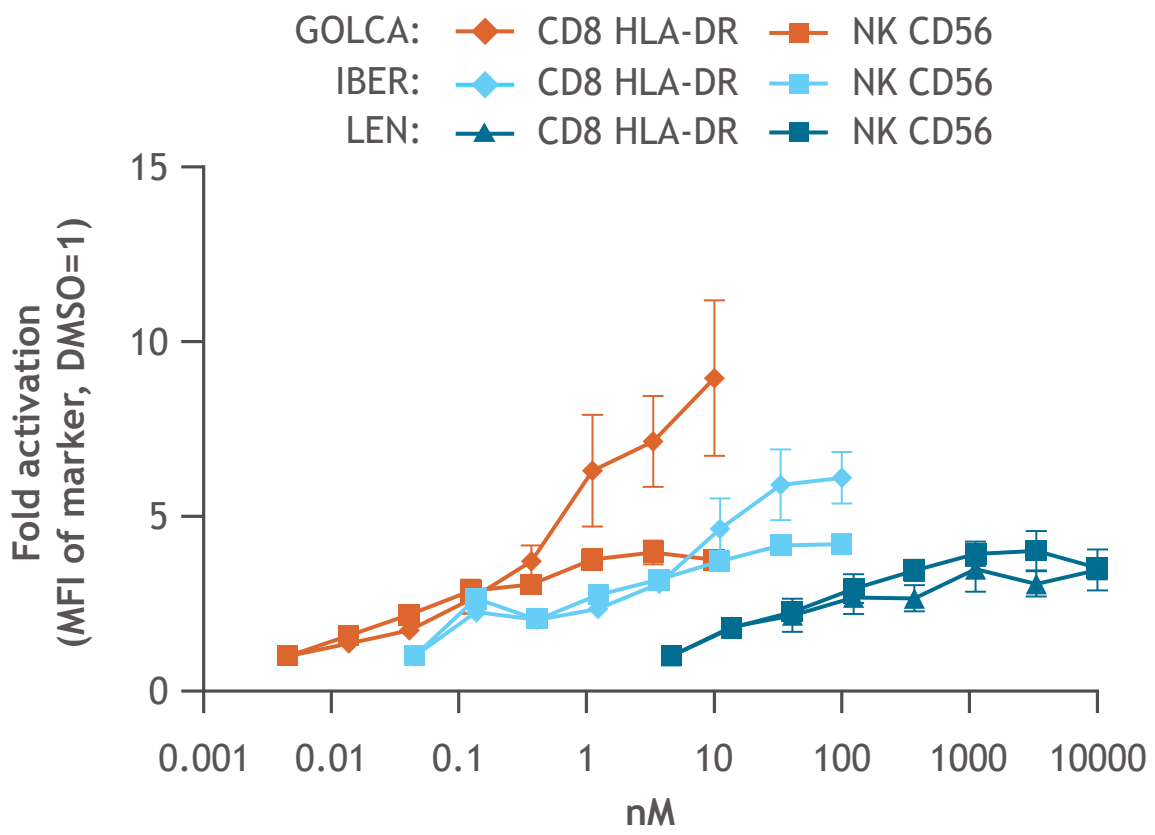
1. Watson ER, et al. *Science* 2022;378:549-553; 2. Bristol Myers Squibb. Data on file. BMS-REF-HEMA-0004.

CELMoDs offer enhanced antitumor activity over LEN against DLBCL cell lines

CELMoD agents inhibit proliferation, agnostic of COO[1]



CELMoD agents stimulate immune cell lines[1]



ABC, activated B cell; AUC, area under the curve; CD, cluster of differentiation; COO, cell of origin; DLBCL, diffuse large B cell lymphoma; GCB, germinal center B cell; HLA, human leukocyte antigen; MFI, mean fluorescence intensity; NK, natural killer.

1. Bristol Myers Squibb. Data on file. BMS-REF-HEMA-0004.

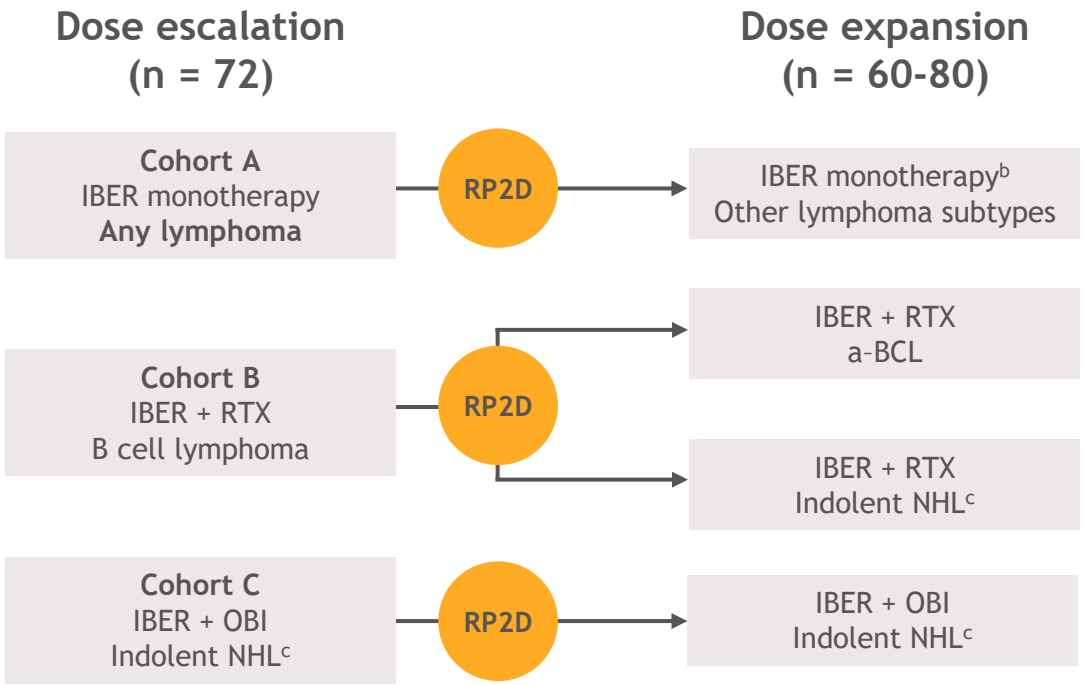
Thieblemont C, et al. ASH 2022 [Abstract #233]

Iberdomide (CC-220) monotherapy or in combination with an anti-CD20 monoclonal antibody in patients with R/R lymphoma: phase 1/2 study

Study design

Key eligibility criteria

- Aged ≥ 18 years
- R/R lymphoma
- ≥ 2 prior LoTs[a]
- Measurable disease per Lugano 2014 criteria
- ECOG PS 0-2



Objectives

Primary: MTD and RP2D of IBER alone and in combination with RTX or OBI

Secondary: Safety, pharmacokinetics, and efficacy

- Treatment occurred in 28-day cycles (24 cycles for all lymphoma; 12 cycles for indolent NHL)
  - 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

A Bayesian logistic regression model with dose escalation with overdose control was applied to guide dose escalation decisions. [a]One prior standard LoT is permitted for patients with a-BCL who are ineligible for auto-HCT and patients with peripheral T-cell lymphoma who are ineligible for other approved regimens; [b]Optional cohort; initiated to assess safety further; [c]FL (grade 1-3a) and MZL.

a-BCL, aggressive B-cell lymphoma; FL, follicular lymphoma; HCT, hematopoietic cell transplantation; IV, intravenous; LoT, line of therapy; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; OBI, obinutuzumab; PO, orally; PS, performance status; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; RTX, rituximab; SC, subcutaneous.

Thieblemont C, et al. ASH 2022 [Abstract #233]

Patient demographics and baseline 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	2 (8)	0	6 (38)	8 (15)
Other[a]	9 (38)	3 (21)	0	12 (22)
Time since diagnosis, 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 disease stage at diagnosis,[b] n (%)				
I/II	3 (13)	3 (21)	3 (19)	9 (17)
III/IV	20 (83)	10 (71)	13 (81)	**43 (80)**
Prior anti-lymphoma regimens, median (range)	4 (1-8)	7 (2-12)	4 (2-5)	**4 (1-12)**
ECOG PS,[c] n (%)				
0-1	22 (92)	10 (71)	14 (88)	46 (85)
2	2 (8)	3 (21)	2 (13)	7 (13)

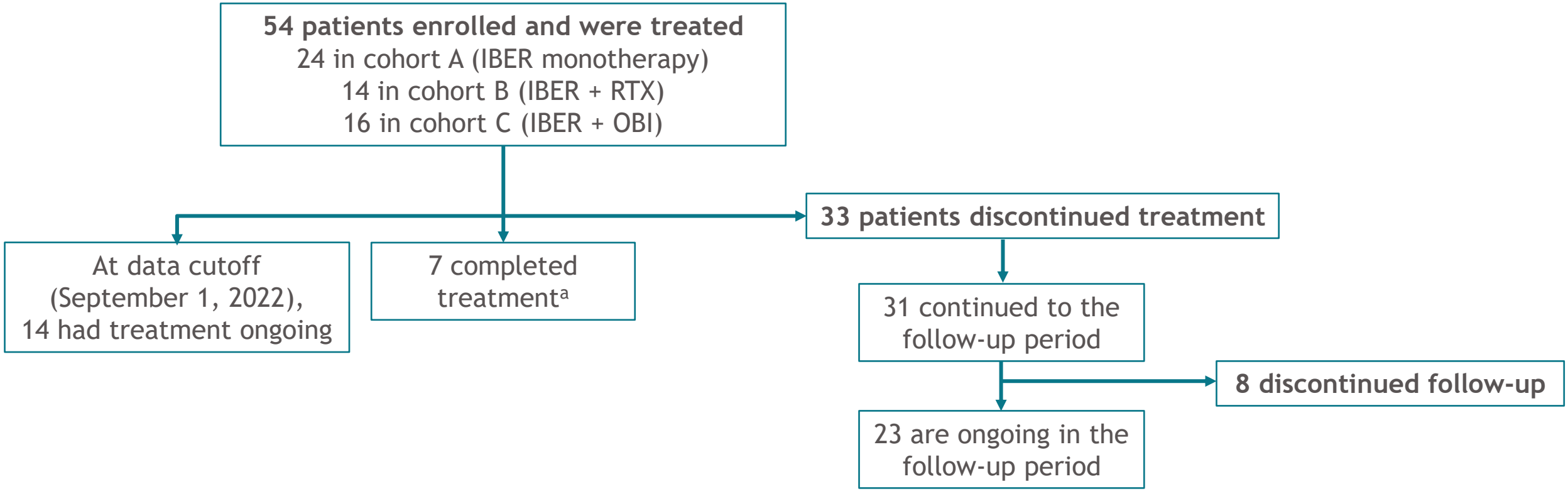
- Median age was similar across cohorts
- Most patients had stage III/IV disease (80%) and ECOG PS 0-1 (85%)
- Patients had a median of 4 prior anti-lymphoma regimens

Data cutoff: September 1, 2022

[a]Including MCL, cHL, SLL, and T cell lymphoma; [b]Ann Arbor disease stage was unknown/not available in 2 patients; [c]In cohort B, ECOG PS was missing for 1 patient.
CAR, chimeric antigen receptor; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.
cHL, classical Hodgkin's lymphoma

Thieblemont C, et al. ASH 2022 [Abstract #233]

Patient disposition and exposure



- Patients were exposed to **a median (range) of 5 (1-20) cycles of IBER** with relative **dose intensity of 89%** (range, 12-101)
- **Median duration of treatment was 4.4 months** for the overall population, **3.0 months** for patients receiving IBER monotherapy, **6.4 months** for patients receiving IBER + RTX, and **5.2 months** for patients receiving IBER + OBI
- The patients who discontinued treatment did so due to **disease progression (n = 18),** death (n = 6), AE unrelated to IBER or any study drug (n = 3), physician decision (n = 3), withdrawal (n = 2), and second primary malignancy (multiple myeloma)[b] unrelated to IBER or any study drug (n = 1)
- The patients who discontinued follow-up did so due to death (n = 7) and patient discretion (n = 1)

[a]Completed all cycles of treatment, per protocol; [b]Patient had history of monoclonal gammopathy of undetermined significance.
AE, adverse event.

Thieblemont C, et al. ASH 2022 [Abstract #233]

Safety

Safety-evaluable population (N = 54), n (%)	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	53 (98)	39 (72)
TEAEs in ≥ 10% of patients who received IBER		
Hematologic		
Neutropenia	**32 (59)**	**27 (50)**
Anemia	17 (31)	9 (17)
Thrombocytopenia	12 (22)	8 (15)
Febrile neutropenia[a]	**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)

Data cutoff: September 1, 2022

- TEAEs were reported in 98% of patients, with grade 3/4 TEAEs occurring in 72% of patients
  - Grade 3/4 TEAEs were primarily hematologic; most commonly neutropenia (50%), anemia (17%), and thrombocytopenia (15%)
    - **27 (50%) patients had neutropenia managed with G-CSF**
  - Sepsis occurred in 4% of patients

[a]Did not occur in ≥ 10% of patients, but was TEAE of special interest.
G-CSF, granulocyte-colony stimulating factor; TEAE, treatment-emergent adverse event.

Safety - Dose-limiting toxicity and dose reduction

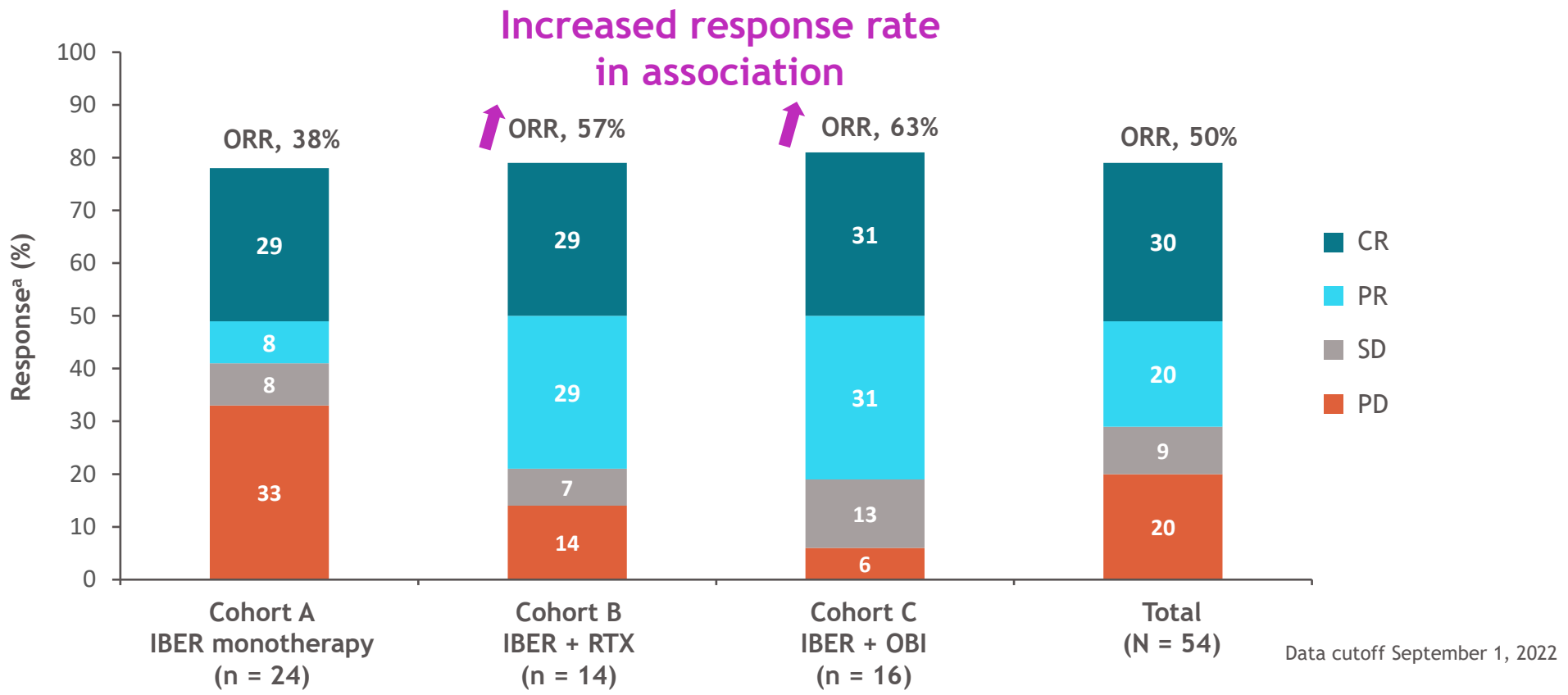
	Cohort A IBER monotherapy (n = 24)	Cohort B IBER + RTX (n = 14)	Cohort C IBER + OBI (n = 16)	Study overall (N = 54)
Evaluable for DLTs, n (%)[a]	18 (75)	10 (71)	15 (94)	43 (80)
Patients with DLTs, n (%)[b]	1 (6)	2 (20)	4 (27)	7 (16)
Patients with ≥ 1 IBER dose interruption, n (%)	22 (92)	13 (93)	13 (81)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

Data cutoff: September 1, 2022

- **Dose-limiting toxicities (DLT) were experienced by 7 (16%) patients**
  - 1 (6%) receiving IBER monotherapy (thrombocytopenia),
  - 2 (20%) receiving IBER + RTX (both neutropenia)
  - 4 (27%) receiving IBER + OBI (2 neutropenia, 1 each hypercalcemia and face angioedema)
- **Median relative dose intensity was 93% for patients treated with iberdomide alone or combined with obinutuzumab, but 82% for patients treated with iberdomide + rituximab**
- There were no deaths from TEAEs

[a]Patients who received at least 75% of planned number of IBER doses from day 1 of cycle 1 to day 1 of cycle 2 without experiencing a DLT or experienced a DLT after receiving at least 1 dose of IBER from day 1 of cycle 1 through day 1 of cycle 2 were evaluable for DLTs; [b]Calculated using patients evaluable for DLTs as denominator; [c]All were due to AEs.; [d]Relative dose intensity calculated by dividing actual dose intensity by expected dose intensity; [e]Evaluation period defined from first IBER dose in cycle 1 to cycle 2 day 1 predose.

Summary of overall response



Data cutoff September 1, 2022

- ORR (95% CI) was **50%** (36-64)
- CR rate (95% CI) was **30%** (18-44); CR rate was similar across cohorts
- **Of the 12 patients who had received prior CAR T cell therapy, 6 achieved CR and 1 achieved PR**

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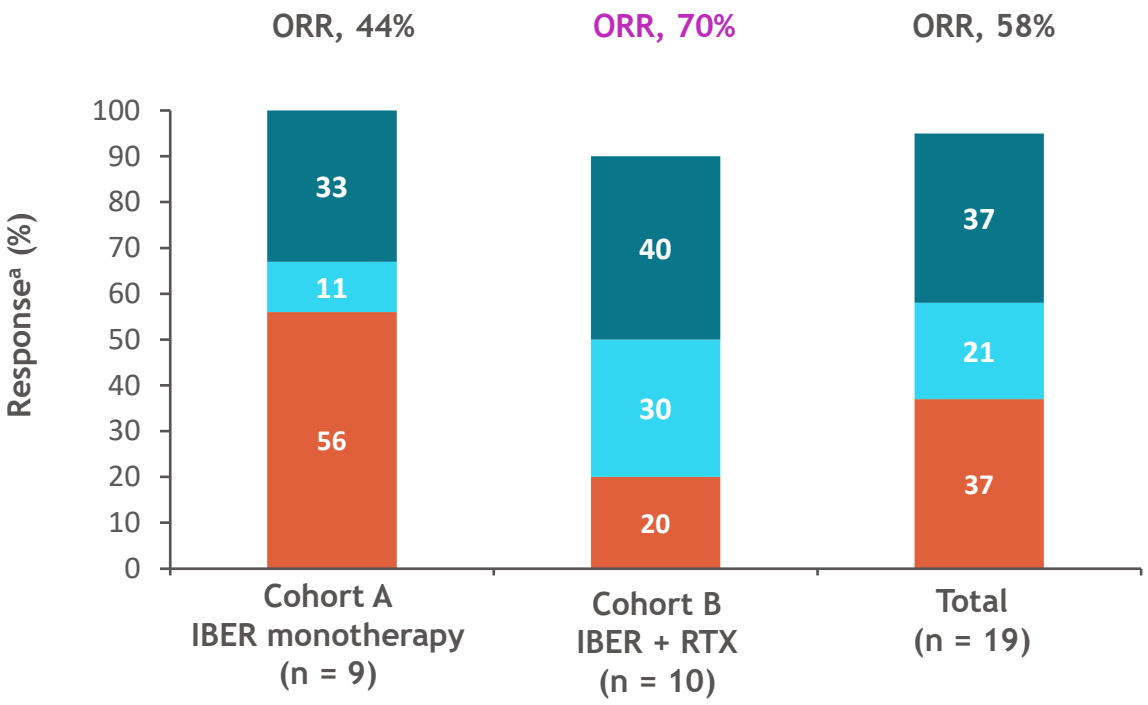
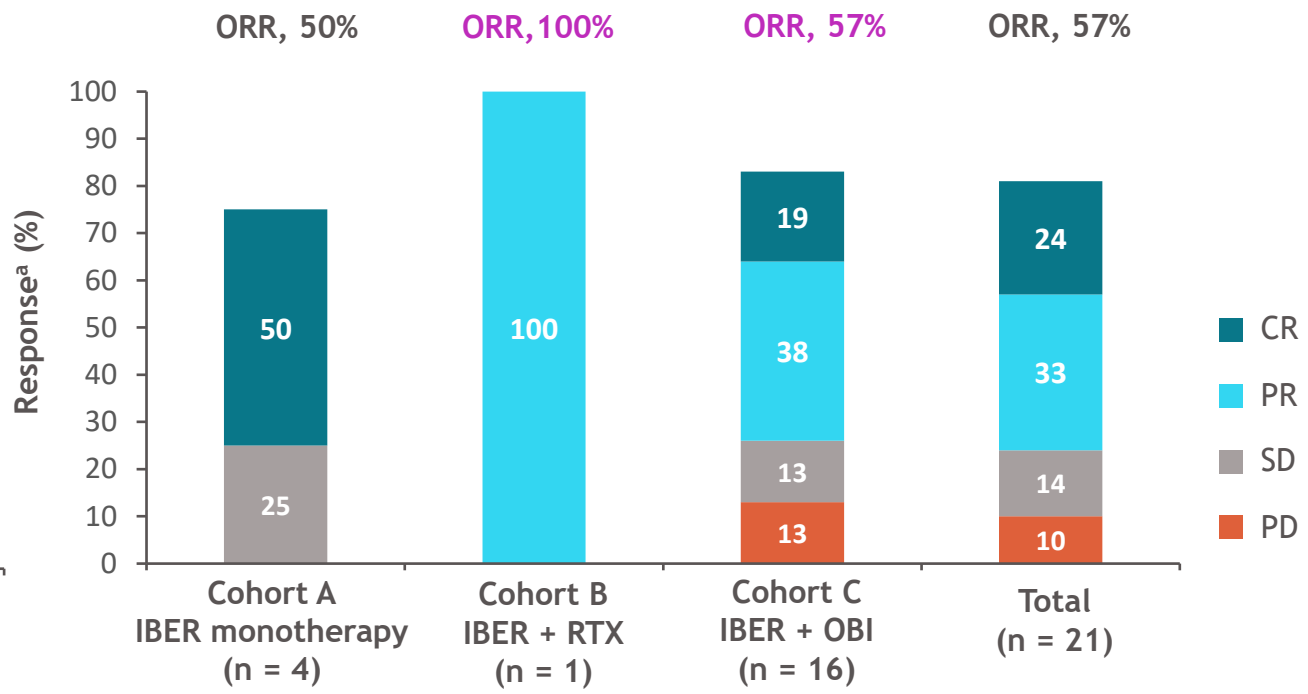
Summary of overall response by disease subtype

Patients with DLBCL



Patients with indolent NHL[c]



Data cutoff September 1, 2022

[a]Safety population response is the best assessment of response during the treatment phase of the study. ORR is defined as proportion of patients with best overall response of either CR or PR, based on IMWG response criteria for NHL, before subsequent antilymphoma therapy; CR rate is defined as proportion of patients experiencing CR before receiving any subsequent antilymphoma therapy; PD and SD are defined by Lugano 2014 criteria for NHL; [b]Due to rounding, total ORR may not match CR rate plus PR rate; [c]Indolent NHL refers to FL or MZL.

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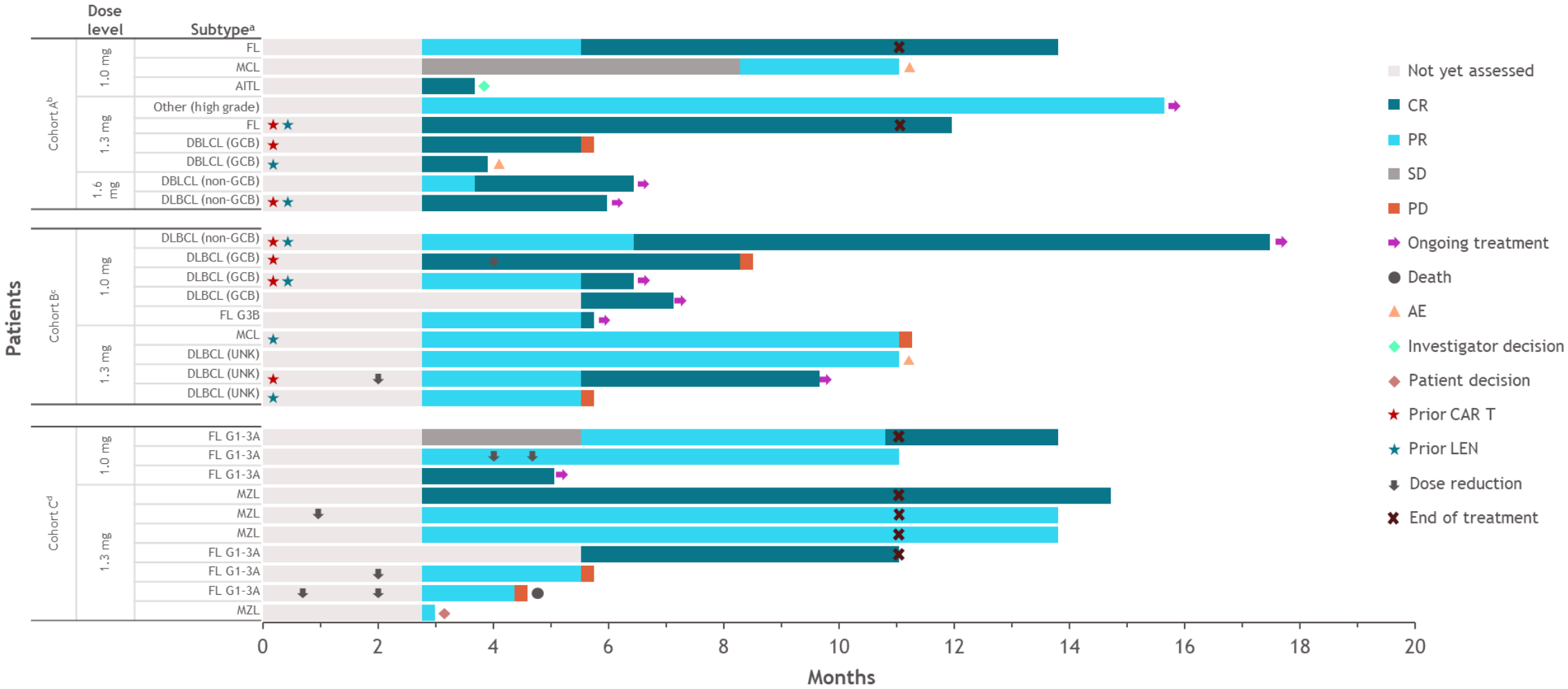
Duration of response by cohort, dose level, and disease subtype



- **Median (95% CI) DOR[e] was 12.9 (6.1-NE) months in the safety population**
- **A total of 10 patients (35.7% of responders) were continuing treatment at data cutoff**

Data cutoff Nov 1, 2022

[a]GCB versus non-GCB COO determined by immunohistochemistry; [b]Cohort A patients received IBER monotherapy; [c]Cohort B patients received IBER + RTX; [d]Cohort C patients received IBER + OBI; [e]DOR is defined as time from first documented PR/CR to first relapse or progression.
AITL, angioimmunoblastic T-cell lymphoma; NE, not evaluable; UNK, unknown.

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Summary

- **IBERDOMIDE** was well-tolerated
  - Neutropenia was a predictable on-target toxicity manageable with G-CSF use
  - Febrile neutropenia and infection were uncommon

- **IBERDOMIDE** alone and **in combination with anti-CD20 monoclonal antibodies :** showed promising activity in patients with R/R lymphoma
  - high response rates in heavily pretreated R/R DLBCL,
  - independent of cell of origin,
  - as well as in patients who received prior CAR-T treatment

- **Oral administration** may offer an attractive outpatient treatment option

Perspectives

- Other combinations
  - Mainly in myeloma (clinical trial.gov)

- Various chemo-free combined treatment
  - KID : carfilzomide + iberdomide + dexamethasone
  - IberKdD : Iberdomide + Dara + Carfilzomide + dexa
  - IDEAL : Iberdomide + Dara + Bortezomib + dexa
  - Iber + dara
  - Iber + elotuzumab + dexa

Perspectives

- In lymphoma

- 1rst line
  - Study of Safety and Efficacy of Iberdomide (CC-220) or CC-99282 Combined With R-CHOP to Treat Lymphoma (NCT04884035) = NCT04884035
    * Iber / Golca + Pola-RCHP as an exploratory arm