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DIPARTIMENTO DI MEDICINA SPECIALISTICA
DIAGNOSTICA E SPERIMENTALE

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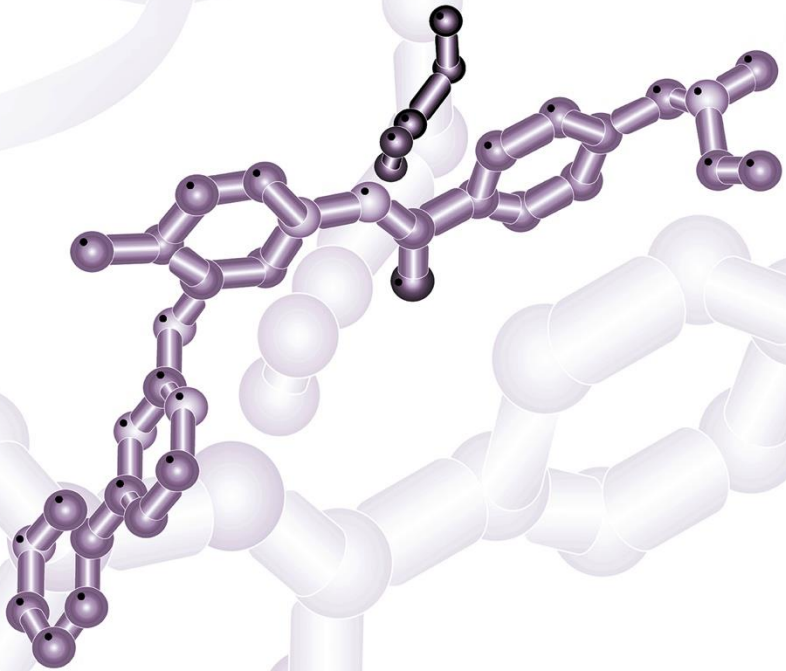

New Drugs in Hematology

President: Pier Luigi Zinzani

Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
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Odronextamab

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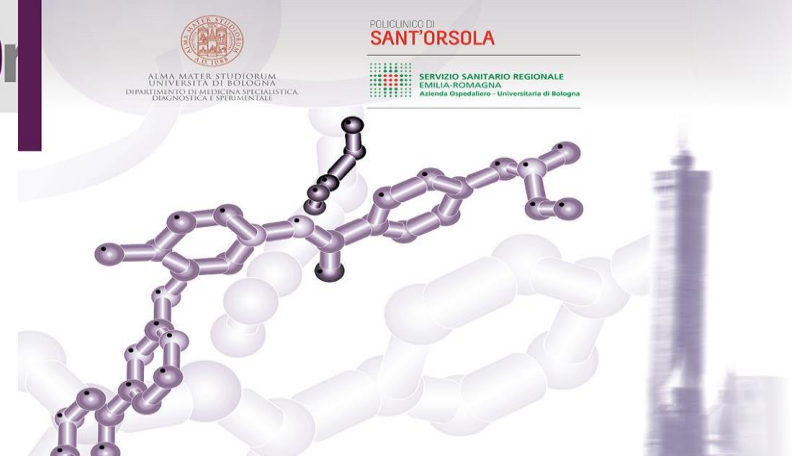


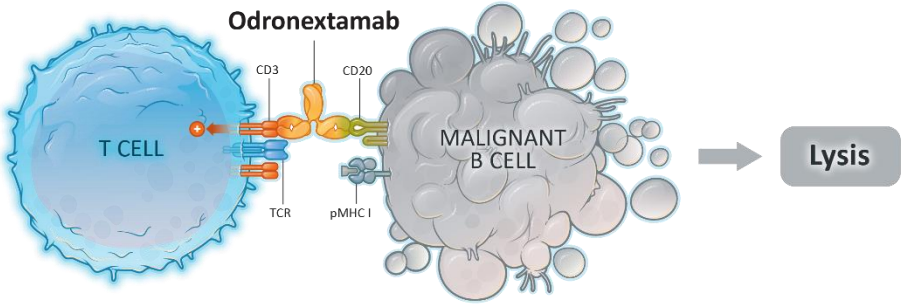
Disclosures of Max Topp

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS	Yes	No	Yes	No	No	Yes	No
KITE	Yes	No	Yes	No	No	Yes	Travel
Regeneron	Yes	No	Yes	No	No	No	No
Roche	Yes	No	No	No	No	No	No
Janssen	No	No	No	No	Yes	Yes	No
Pfizer	No	No	No	No	No	Yes	No

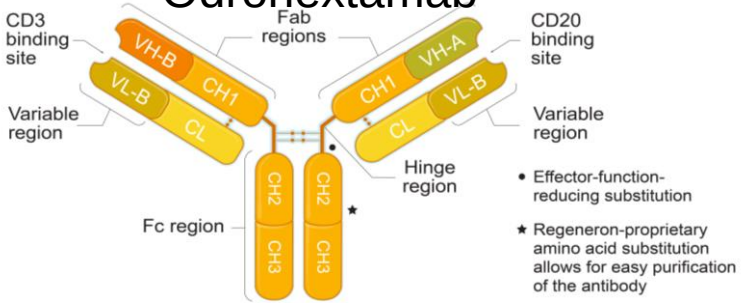
Odronextamab: A CD20xCD3 bispecific antibody

- The CD20 antigen is expressed during maturation of normal precursor B cells and is thought to serve a B-cell activating or proliferation function[1]
  - CD20 is highly expressed in lymphomas[1]
- Odronextamab is designed to bridge CD20 on cancer cells with CD3-expressing T cells, resulting in local T-cell activation and cytotoxicity[2]
  - This mechanism is distinct from other therapeutics targeting CD20, which act primarily through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity[1]
- Odronextamab is being evaluated in patients with R/R NHL in Phase 1 and 2 clinical trials

Mechanism of action[2,3]



Odronextamab[2,3]



MHC, major histocompatibility complex; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; TCR, T cell receptor.

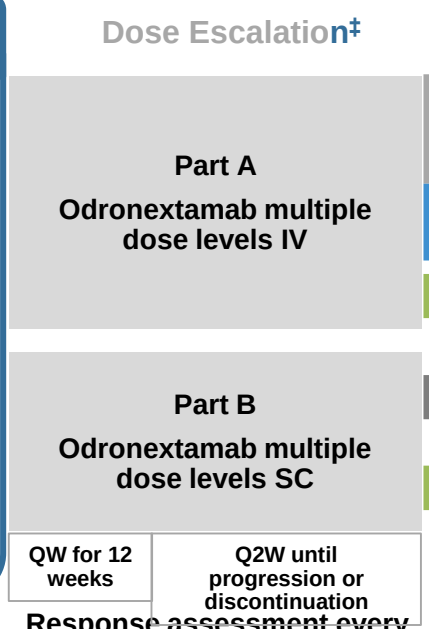
1. van Meerten T, Hagenbeek A. *Neth J Med.* 2009;67(7):251–259. 2. Smith EJ, et al. *Sci Rep*. 2015;5:17943. 3. Bannerji R et al. American Society of Hematology (ASH) Annual Meeting and Exposition Virtual Event, December 5–8, 2020. Oral presentation 400.

FIH study of Odronextamab in CD20+ B-cell NHL

CD20+ B-NHL cohorts† (all subtypes; N~298)

Key eligibility criteria

- Documented CD20+ B-cell malignancy with active disease not responsive to prior therapy, with no SOC options
- Prior therapy with anti-CD20 antibody
- Patients with FL grade 1–3a and DLBCL: ≥2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent
- Measurable disease
- ECOG PS ≤1
- No primary CNS lymphoma or CNS involvement
- No history of allogeneic stem cell transplantation



Primary endpoints

- Safety, tolerability, and DLTs
- ORR*

Secondary endpoints

- PK
- Immunogenicity
- ORR of other expansion cohorts
- PFS
- OS
- DOR

Response assessment every 12 weeks according to Lugano criteria

Other protocol-defined inclusion/exclusion criteria apply

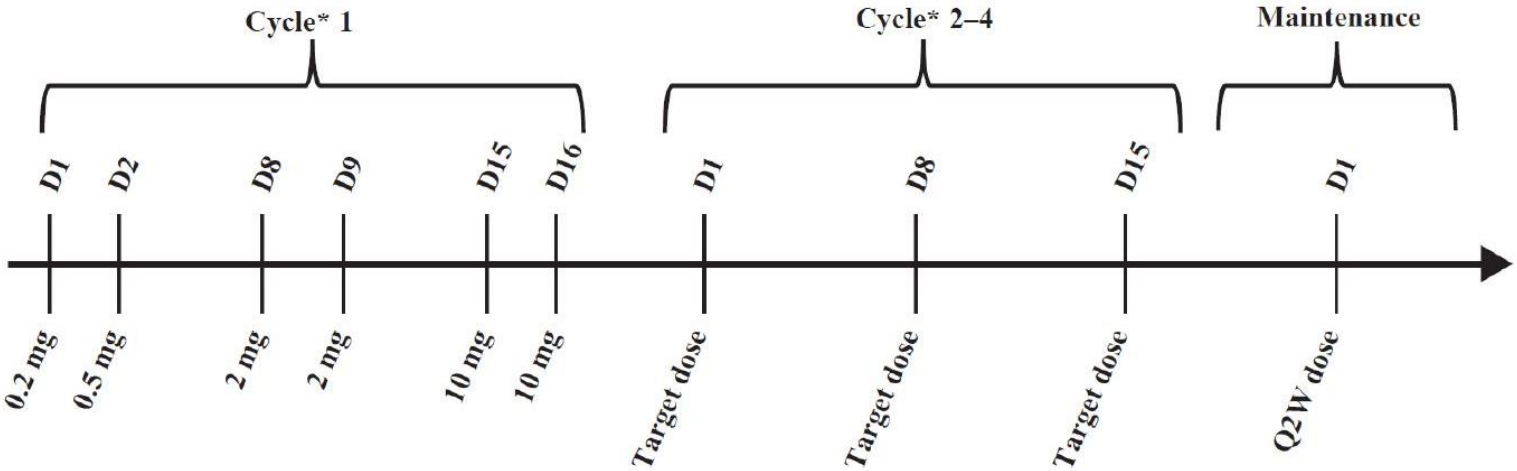
†CLL arm of study not shown; enrolment is closed for the aggressive lymphoma and FL cohorts.
‡Premedication, split, and step-up doses are used to mitigate the risk for CRS. Patients are hospitalized for observation during step-up dosing and the first QW dose. Patients received odronextamab 2-320 mg during dose escalation.
*DLBCL progressing after CAR T therapy cohort only.
B-NHL, B-cell non-Hodgkin lymphoma; CAR T, chimeric antigen receptor T cell; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QW, once weekly; Q2W, every 2 weeks; R/R, relapsed/refractory; SC, subcutaneous; SOC, standard of care.

1. Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2. 2. Clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT02290951. Accessed November 11, 2021.

Odronextamab administration

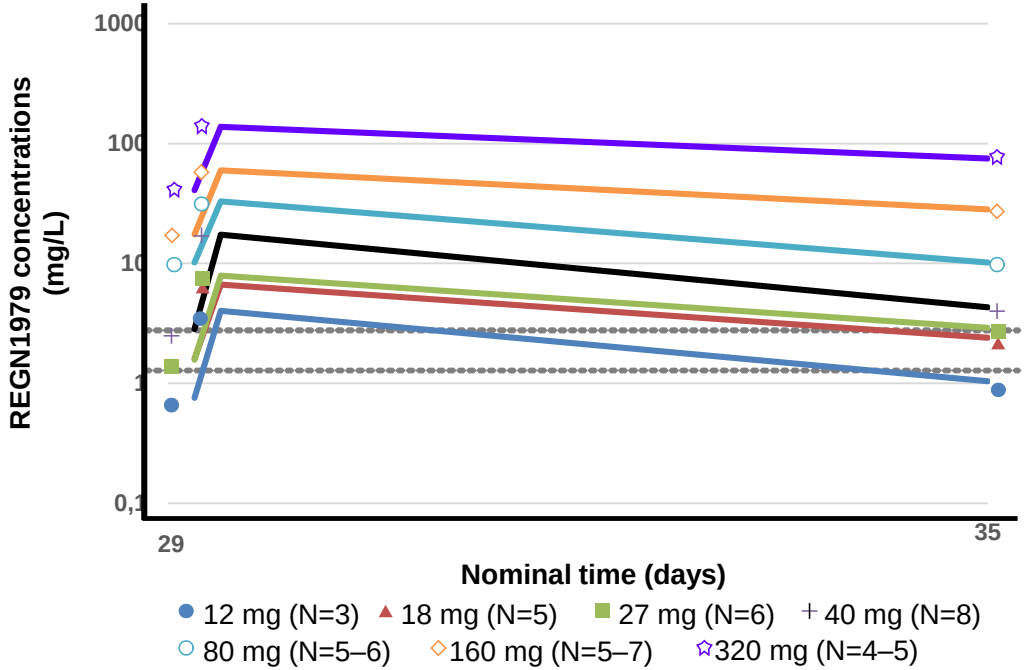
Premedication protocol

- Dexamethasone was given 12-24 hours prior to first split infusion and prior to second split infusion (if on non-consecutive days)
- Acetaminophen and diphenhydramine were given 30–60 minutes before infusion
- Steroid premedication was tapered for the day 8 dose in cycle 2; all premedication was discontinued for subsequent doses



Prophylactic measures to mitigate the risk of cytokine release syndrome, including steroid prophylaxis, split dosing, and step-up dosing were implemented during dose escalation and were further optimised with dose expansion, as well as in an ongoing phase 2 study of odronextamab monotherapy in patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NCT03888105).Premedication was administered from cycle 1 day 1 through cycle 2 day 1.
*One cycle is 21 days. D, day; Q2W, every 2 weeks.
Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

Dose dependent linear PK profiles during Week 5



Efficacious C_{max} and C_{trough} concentrations in mice

C_{max}: 3.7 mg/L in mice

C_{trough}: 2 mg/L in mice

At ≥40 mg, **Odronextamab** exposure in humans was higher than the efficacious exposures in mice at which growth of established B-cell (Raji) tumors was inhibited

B-NHL, B-cell non-Hodgkin lymphoma; C_{max}, maximum concentration; C_{trough}, minimum concentration; PK, pharmacokinetics;

Data cut-off date: September 03, 2019

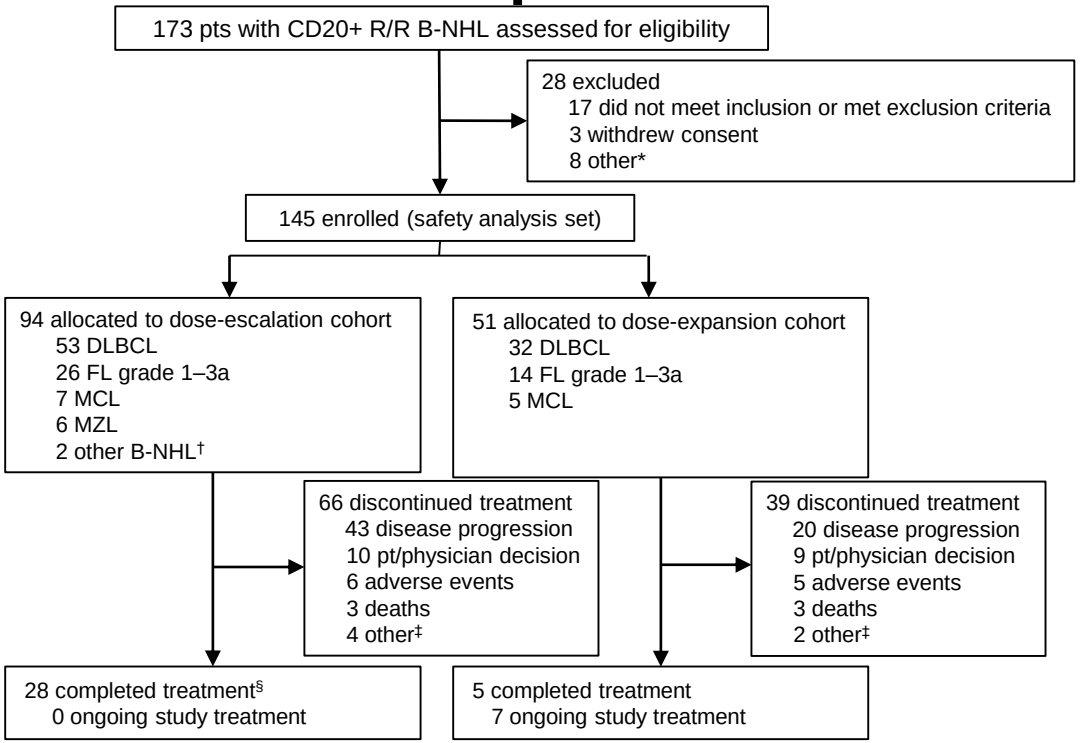
Patient demographics and baseline characteristics

Patient and disease characteristics	N=145
Median age, years (range)	67.0 (57–73)
Male, n (%)	101 (70%)
ECOG PS, n (%)	
0	58 (40%)
1	87 (60%)
Ann Arbor stage, n (%)	
I–II	21 (14%)
III–IV	123 (85%)
Bulky disease, n (%)	49 (34%)
B-NHL, n (%)	
DLBCL	85 (59%)
FL Grade 1–3a	40 (28%)
MCL	12 (8%)
MZL	6 (4%)
Other*	2 (1%)

Prior treatment	N=145
Median prior lines of therapy, n (range)	3 (2–5)
Prior ASCT, n (%)	12 (8%)
Prior CAR T therapy, n (%)†	42 (29%)
Refractory‡ to last line of therapy, n (%)	119 (82%)
Refractory to anti-CD20 antibody, n (%)	123 (85%)
Refractory to alkylator therapy, n (%)	102 (70%)
Double refractory to alkylator and anti-CD20 antibody, n (%)	100 (69%)

Data cut-off: Sep 25, 2021.
*Other includes FL Grade 3b and Waldenström macroglobulinemia (1 each).
†DLBCL, n=35; FL grade 1–3a , n=4; MCL, n=3.
‡Defined as no response or relapse within ≤6 months.
§Completed fixed treatment/follow up per a prior protocol amendment.
ASCT, autologous stem cell transplant; B-NHL, B-cell non-Hodgkin lymphoma; CAR T, chimeric antigen receptor T cell; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.
Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

Patient disposition



Data cut-off: Sep 25, 2021.

*Death (n=1), investigator decision (n=2), patient decision (n=1), did not meet eligibility criteria (n=2), and enrollment was put on hold (n=2). †Other includes FL Grade 3b and Waldenström macroglobulinemia (1 each). ‡Suboptimal response to treatment (n=1), esophagogastric cancer recurrence (n=1), and hematopoietic stem cell transplant (n=2). ‡Received radiation therapy (n=1) and missed one dose (n=1).

B-NHL, B-cell non-Hodgkin lymphoma; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; pt, patient; R/R, relapsed/refractory.

Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

Treatment emergent adverse events (TEAEs)

All 145 patients experienced at least one TEAE of any grade; grade ≥3 TEAEs occurred in 119 (82%) patients

- The most frequent grade ≥3 TEAEs (>10% of patients) included anemia (n=36; 25%), lymphopenia (n=28; 19%), neutropenia (n=27; 19%), hypophosphatemia (n=27; 19%), and thrombocytopenia (n=20; 14%)

135 patients (93%) experienced at least one TEAE related to treatment

Twelve patients (8%) discontinued odronextamab due to a TEAE, including 10 with TEAEs considered treatment-related:

- Gr 1: cytomegalovirus infection (n=1) and gait disorder (n=1)
- Gr 3: fatigue (n=2), pneumonia (n=2), hemolysis (n=1), toxoplasmosis (n=1)
- Gr 4: elevated AST (n=1)
- Gr 5: tumor lysis syndrome (n = 1)

Serious adverse events occurred in 89 of 145 (61%) patients

- The most frequent serious adverse events were cytokine release syndrome (n=41; 28%), pyrexia (n=11; 8%), pneumonia (n=9; 6%), and infusion-related reactions (n=6; 4%)

Six patients died due to adverse events, four of which were considered related to treatment

- Related to treatment: gastric perforation (n=1), lung infection (n=1), pneumonia (n=1), tumor lysis syndrome (n = 1)
- Not related: cardiac arrest (n=1); COVID-19 (n=1)

Odronextamab was administered up to 320 mg weekly without DLTs or reaching MTD;
no dose-dependent increase in toxicity was observed

Data cut-off: Sep 25, 2021.
AST, aspartate aminotransferase; DLT, dose-limiting toxicity; Gr, grade; MTD, maximum tolerated dose.
Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

TEAEs of special interest

TEAE of special interest (N=145)[1]	All grades	Grade ≥3
Infusion-related reaction	35 (24%)	3 (2%)
Cytokine release syndrome	89 (61%)	10 (7%)
ICANS-like*	18 (12%)	4 (3%)
Tumour lysis syndrome	1 (1%)	1 (1%)
Infections†	71 (49%)	33 (23%)
Pneumonia	15 (10%)	12 (8%)
Upper respiratory tract infection	14 (10%)	3 (2%)
Urinary tract infection	14 (10%)	2 (1%)
Oral candidiasis	8 (6%)	0

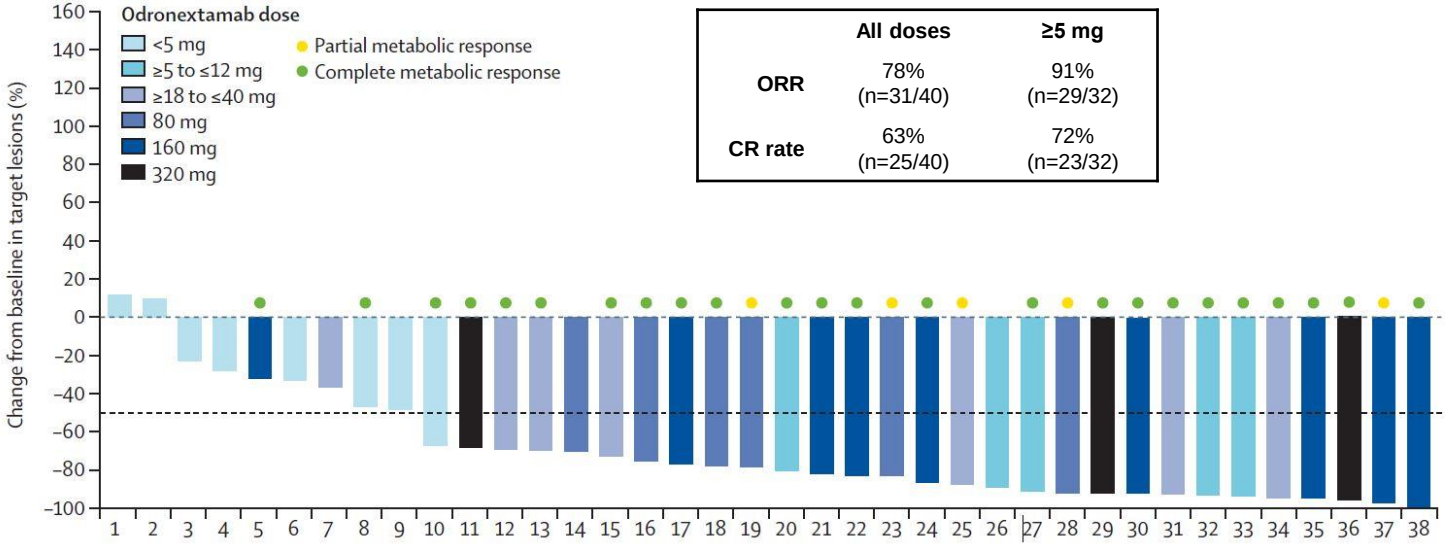
- Pneumonia (n=12; 8%) was the most common grade ≥3 infection[1]
- CRS events were mainly grade 1 (n=52; 36%) or grade 2 (n=27; 19%); grade 3 CRS occurred in nine (6%) patients, and one (1%) patient with mantle cell lymphoma had a grade 4 CRS event in the context of grade 5 tumour lysis syndrome during dose expansion[1]
  - CRS was predominantly confined to cycle 1 and resolved within a median of 2 days
  - Most neurological TEAEs were transient and resolved within a median of 3 days
- No grade 4 or 5 ICANS-like events were observed[1]
- No patients discontinued odronextamab due to CRS or neurotoxicity[1]

*The ICANS-like symptom list was generated based on relevant terms that reflect immune cell-associated neurotoxicity under the "Nervous system disorders" and "Psychiatric disorders" System Organ Class terms and included approximately 140 preferred terms. ICANS-like TEAEs included: agitation, aphasia, confusional state, cognitive disorder, delirium, dyskinesia, encephalopathy, hallucination, lethargy, memory impairment, mental status changes, neurotoxicity, somnolence, and tremor. †Infections (of any grade) listed in the table occurred in >5% of patients. Adverse events were coded using MedDRA, version 24.0. Adverse events were graded using NCI-CTCAE version 4.03, except for cytokine release syndrome which was graded according to modified Lee et al. 2014[2] or Lee et al. 2019[3] criteria, depending on the patient enrolment date.

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

1. Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2. 2. Lee DW et al. *Blood.* 2014;124(2):188–95. 3. Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625–38.

Odronextamab in R/R FL grade 1–3a



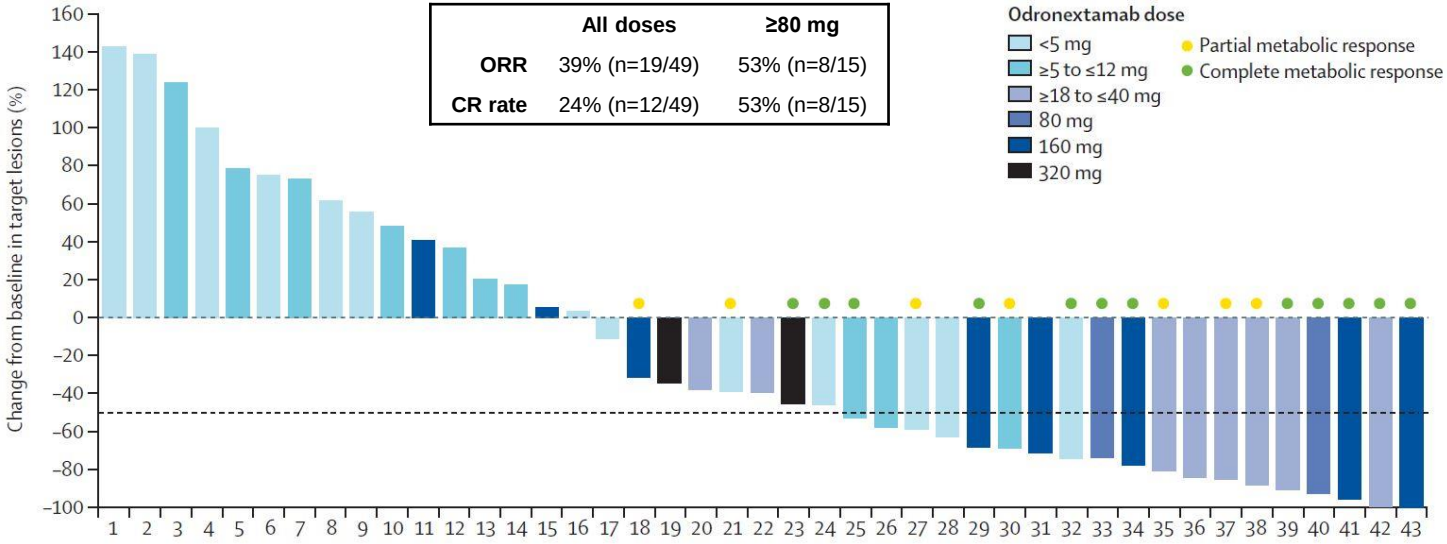
	All doses	≥5 mg
ORR	78% (n=31/40)	91% (n=29/32)
CR rate	63% (n=25/40)	72% (n=23/32)

- The active dose range for patients with indolent lymphoma was identified as ≥5 mg
- Responses occurred early: median time to first complete response was 2.6 months
- Median estimated duration of response was 15.8 months; the longest complete response was ongoing at 53.0 months

Data cut-off: Sep 25, 2021.
Shown as best percentage change in activity in evaluable patients (ie, those attending assessment at week 12).
CR, complete response; ORR, objective response rate; R/R, relapsed/refractory.
Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

Odronextamab in R/R DLBCL: no prior CAR T

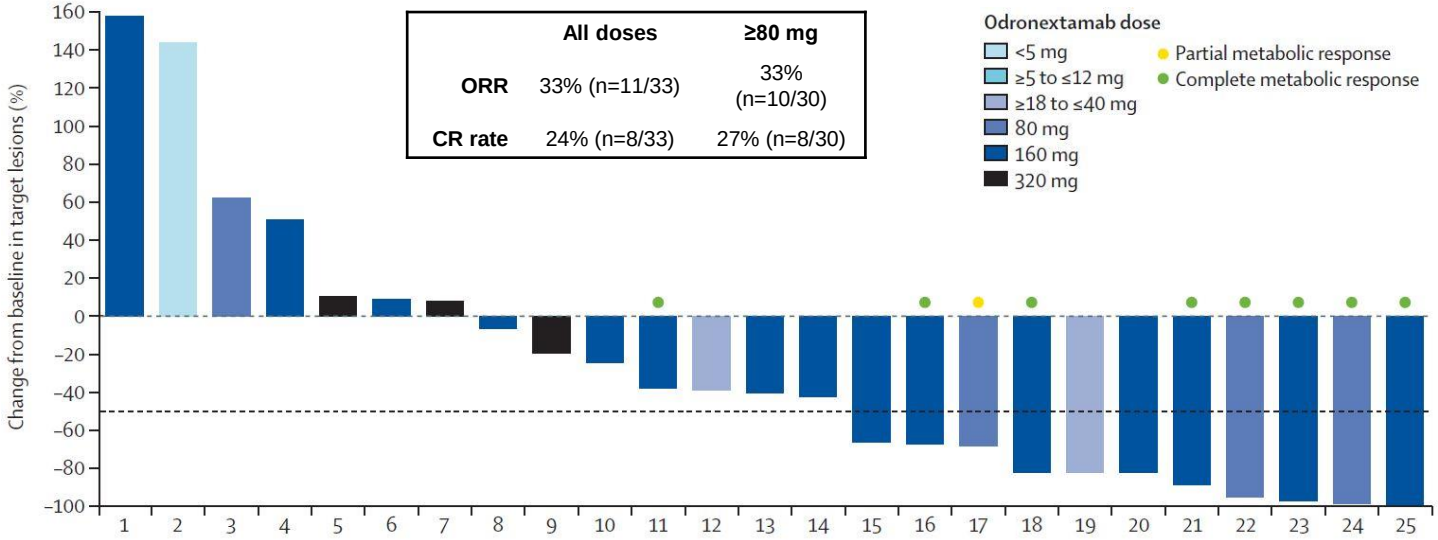
	All doses	≥80 mg
ORR	39% (n=19/49)	53% (n=8/15)
CR rate	24% (n=12/49)	53% (n=8/15)



- The active dose range for patients with aggressive lymphoma was identified as ≥80 mg
- Median time to first complete response was 2.3 months
- Median duration of response was not reached and the longest complete response was ongoing at 32.4 months

Data cut-off: Sep 25, 2021.
Shown as best percentage change in activity in evaluable patients (ie, those attending assessment at week 12).
CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, objective response rate; R/R, relapsed/refractory.
Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

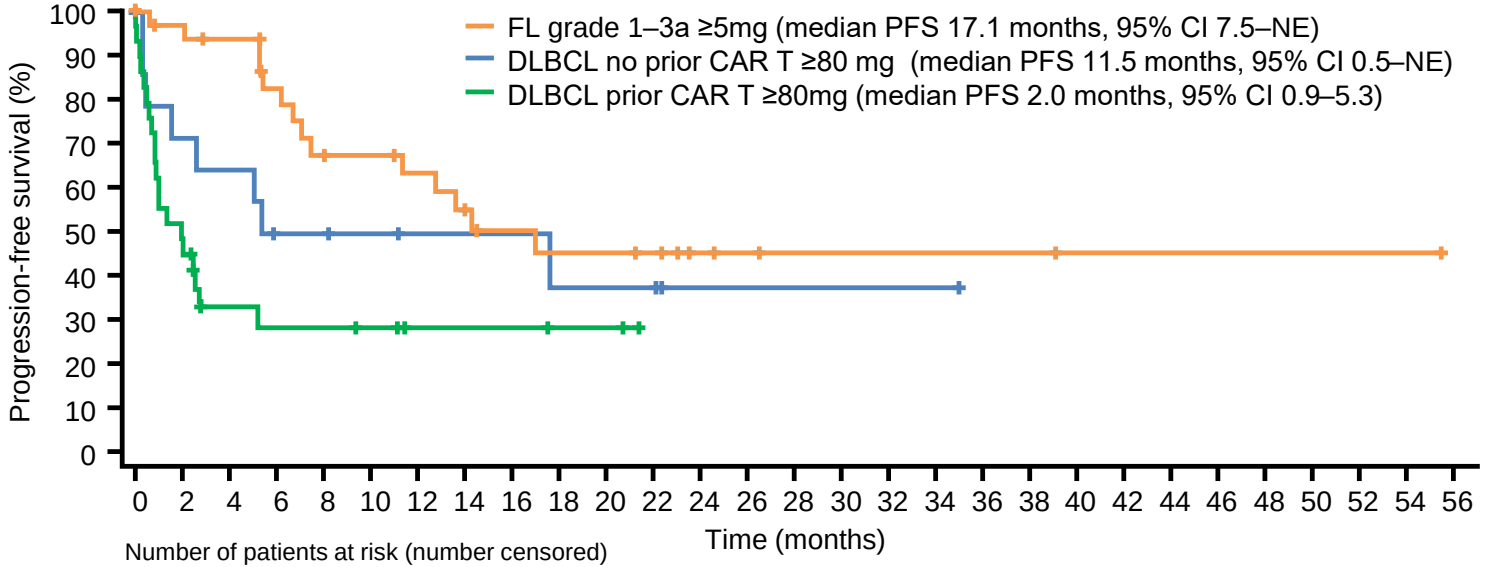
Odronextamab in R/R DLBCL: post-CAR T



- Median time to complete response was 1.5 months
- Median duration of response was not reached and the longest complete response was ongoing at 20.5 months

Data cut-off: Sep 25, 2021.
Shown as best percentage change in activity in evaluable patients (ie, those attending assessment at week 12).
CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, objective response rate; R/R, relapsed/refractory.
Bannerji R et al. *Lancet Haematol.* 2022;S2352-3026(22)00072-2.

PFS with Odronextamab

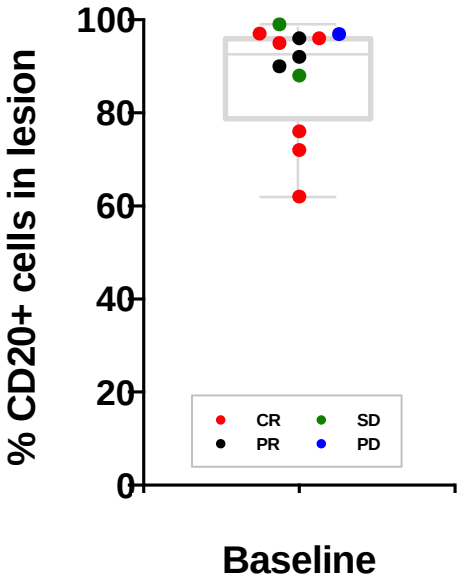


Number of patients at risk (number censored)

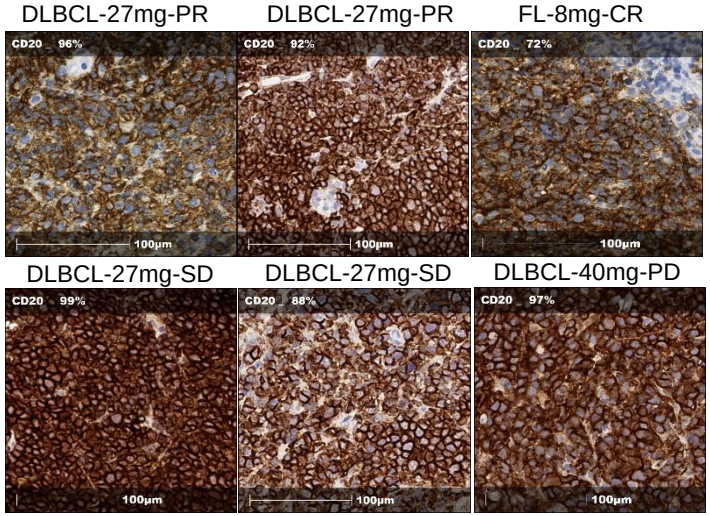
FL grade 1–3a1-3a ≥5 mg	32 (0)	29 (2)	27 (3)	22 (5)	18 (5)	17 (6)	15 (7)	13 (7)	10 (9)	9 (9)	9 (9)	8 (10)	4 (14)	3 (15)	2 (16)	2 (16)	2 (16)	2 (16)	2 (16)	2 (16)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	0 (18)
DLBCL no prior CAR T ≥80 mg	15 (0)	10 (1)	9 (1)	6 (2)	6 (2)	5 (3)	4 (4)	4 (4)	4 (4)	3 (4)	3 (4)	3 (4)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	1 (6)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)
DLBCL prior CAR T ≥80 mg	30 (0)	15 (1)	7 (4)	6 (4)	6 (4)	5 (5)	3 (7)	3 (7)	3 (7)	2 (8)	2 (8)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)	0 (10)

Data cut-off: Sep 25, 2021.
Kaplan–Meier curves show PFS in patients who had an opportunity for assessment at week 12 (odronextamab doses ≥5 mg for FL grade 1-3a, and ≥80 mg for DLBCL). Data based on investigator assessment per Lugano criteria.
CAR T, chimeric antigen receptor T-cell therapy; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NE, not estimable; PFS, progression-free survival.
Bannerji R et al. *Lancet Haematol.* 2022;52352-3026(22)00072-2.

CD20 Expression: Prediction of response?



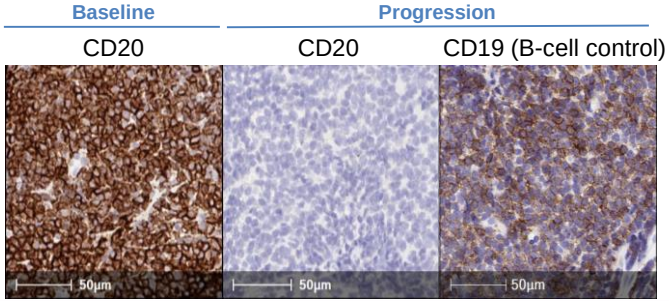
BASELINE



Responders

Non-responders

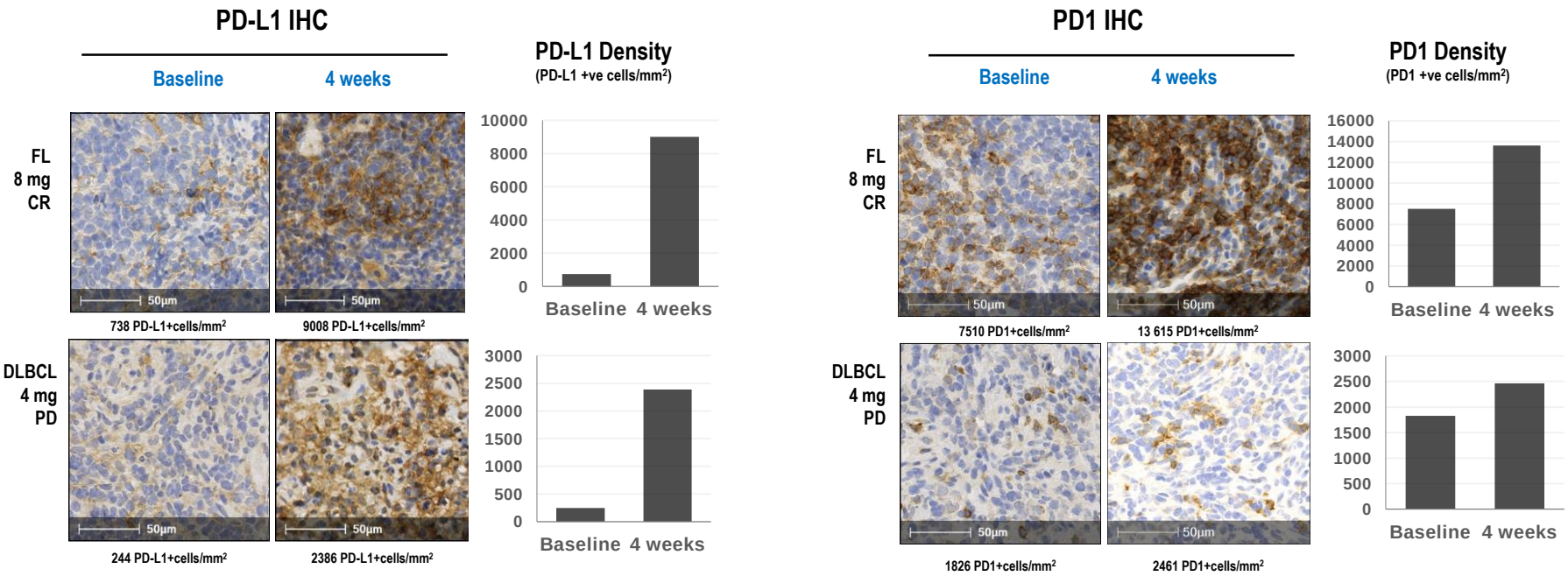
ON PROGRESSION



REGN1979 27 mg;
PR at Week 4, 12;
PD at Week 24

CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

Increases in PD-L1 expression and PD-1+ TIL density observed in malignant lymph node tissue following Odronextamab treatment



CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IHC, immunohistochemistry; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, PD ligand-1; TIL, tumor-infiltrating lymphocyte.

Summary

- CRS Grad ¾ in 7%; resolved with median of 2 days
- ICANS Grad 3 in 3% - no Grad 4/5 ICANS
- Recommended dose for expansion for FL grade 1–3a was 80 mg and was 160 mg for patients with DLBCL
- Clinically activity in both indolent and aggressive B-NHL including also CAR-T failures with long lasting control of disease in some patients
- Emerging evidence of CD20 loss as resistance mechanism
- Odronextamab is being investigated in Phase 2 trials

Thanks to our

Patients and their families
and to my collaborators